

Health-Related Quality of Life in PARP-Inhibitor Olaparib Maintenance in Ovarian Cancer Patients: Real World Data and Experience of a Single-Center in China

Yi Jiang

The first affiliated hospital of nanjing medical university

Huangyang Meng

The first affiliated of Nanjing Medical University

Xinjia Ruan

Research center of biostatistics and computational pharmacy

Lin Yuan

The first affiliated hospital of nanjing medical university

Chengyan Luo

The First Affiliated Hospital of Nanjing Medical University

Yicong Wan

The first affiliated hospital of nanjing medical university

Wenjun Cheng (✉ wenjunchengdoc@163.com)

Jiangsu Province Hospital and Nanjing Medical University First Affiliated Hospital

<https://orcid.org/0000-0002-3872-4384>

Research

Keywords: Germline BRCA mutation, epithelial ovarian cancer, quality of life (QOL), Olaparib

Posted Date: August 6th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-751531/v1>

License:  This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Objectives:

To preliminarily explore the germline BRCA1/2 gene mutation status of patients with epithelial ovarian cancer (EOC), analyze the relationship with clinicopathological characteristics and the impact on survival and prognosis. Then examine the BRCA1/2 gene sequence mutation rate and the QOL of ovarian cancer patients with oral Olaparib in a single-center of China.

Methods:

A retrospective analysis of the survival and prognostic factors of 82 ovarian cancer patients who had undergone genetic testing in the Department of Gynecology, the First Affiliated Hospital of Nanjing Medical University from 2015 to 2018. These patients also underwent germline BRCA1/2 genetic testing. Then, we use the Quality of Life Questionnaire (QLQ-C30) and the Quality of Life Ovarian Cancer 28 Questionnaire (QLQ-OV28) to determine the relationship between quality of life (QOL) in each category, and key demographic and clinical factors.

Results:

The total mutation rate of BRCA1/2 was 30.48%, among which the pathogenic mutation rate of BRCA1 was 20.73%, and the pathogenic mutation rate of BRCA2 was 9.75% in our single-center. A total of 18 pathogenic mutation sites and 2 mutation sites of unknown significance were found. Olaparib as maintenance therapy was significantly associated with better QOL on all **functioning domains** and several **symptom domains**. The patients without Olaparib maintenance therapy may experience deteriorating QOL in several domains.

Conclusions:

Patients with EOC have a higher frequency of BRCA1/2 gene mutation rate, which is related to the malignant biological behavior of the tumor. Patients with BRCA1/2 gene mutation may have a better prognosis. Olaparib maintenance therapy is associated with better QOL and higher QOL in several domains in single center of Chinese.

Introduction

Epithelial ovarian cancer (EOC) is the gynecological malignant tumor with the highest fatality rate. At the time of treatment, patients are often at an advanced stage. Despite satisfactory primary debulking surgery (PDS) combined with platinum-based chemotherapy, 70% of patients still relapse within two years [1–2]. In recent years, the latest biological knowledge has shown that almost half of advanced ovarian cancers exhibit changes in homologous recombination (HR), which is a high-fidelity double-strand break (DSB) DNA repair mechanism that starts during cell replication [3–4]. These alterations can lead to HR Deficiency (HRD), resulting in lack of DNA integrity, and a better response to DNA damaging

agents, such as platinum compounds [5]. Among these alterations, BRCA1 and BRCA2 mutations account for 22.6% of HGSOC mutations. Patients with these mutations are highly responsive to platinum, and have been treated with PolyADP Ribose Polymerase inhibitors (PARPis) to discover this biological characteristic. The inhibitors causes HRD cell apoptosis based on a synthetic lethal mechanism [6–9]. In vitro, studies have shown that BRCA1/2 mutated cell lines are sensitive to PARPis. Clinical trials have confirmed that although interesting activities are also observed in BRCA wild-type ovarian cancers, patients with BRCA1/2 mutations show the greatest benefit of PARPis [8–10].

Olaparib (Lynparza™) is a PARP inhibitor that can induce synthetic lethality in BRCA1/2-deficient tumor cells [11–12]. According to previous research results, Olaparib is the effectiveness treatment for platinum-sensitive high-grade serous recurrent ovarian cancer (HSROC). Study 19 (NCT00753545) is a Phase II trial to assess the efficacy and safety of Olaparib maintenance monotherapy in platinum-sensitive HSROC patients, the data from which showed a significant improvement in PFS in the Olaparib-treated group relative to the placebo group (hazard ratio (HR) 0.35, 95% confidence interval (CI) 0.25–0.49; $p < 0.0001$) [13]. SOLO2 (Study of Olaparib in Ovarian cancer) is the Phase III trial (NCT01874353), which aimed to concluded the PFS in the Olaparib-treated group compared to the placebo group (HR 0.30, 95% CI 0.22–0.41; $p < 0.0001$) among the patients with platinum-sensitive HSROC and a BRCA1/2 mutation (BRCAm) as maintenance monotherapy [14].

Olaparib is an oral inhibitor of PARP 1, PARP 2, and PARP 3 [15–16]. It was approved by EMA in 2014 for platinum-sensitive relapsed ovarian cancer patients with BRCA mutations (germ cells and/or somatic cells). This approval was based on results from Study 19, a randomized, placebo controlled phase II trial [10, 13, 17–18] that was confirmed by SOLO2 trial, an international, multicentre, phase III randomized, double blind, placebo controlled trial [14]. In this latter trial patients receiving Olaparib maintenance therapy achieved an improvement of 13.6 months in PFS (19.1 vs 5.5 months in placebo arms, HR 0.30 $p < 0.0001$) [19].

Although there are many real-world research results on the adverse reactions of PARPi, the quality of life of patients after oral administration of PARPi is rarely reported. This study conducted EORCT-Q30 and QLQ-OV28 questionnaire surveys on 42 patients who took PARPi drugs orally, hoping to analyze the safety and effectiveness of the drugs. Although there are many real-world research results on the adverse reactions of PARPi, there are few reports on the quality of life of patients after oral administration of PARPi. This study conducted EORCT-Q30 and QLQ-OV28 questionnaire surveys on 42 patients taking PARPi drugs, hoping to analyze the safety and effectiveness of the drugs.

Methods

Patients

This study is a retrospective analysis of patients with epithelial ovarian cancer who were treated in the Gynecology Department, the First Affiliated Hospital of Nanjing Medical University from January 2015 to January 2020 and met the following conditions: 1) After surgery or biopsy in our hospital patients with epithelial ovarian cancer diagnosed by histopathology; 2) Gene detection results of high-throughput second-generation sequencing technology have been available. All patients signed an informed consent form. A total of 82 ovarian cancer patients underwent cytoreductive surgery and chemotherapy at the Gynecology Department of The First Affiliated Hospital of Nanjing Medical University from June, 2015 to December, 2018. We enrolled demographic and clinical information of the participants by reviewing medical records and interviewing patients, such as age, marital status, education, menstrual history.

QOL evaluation

We employed two common questionnaires to estimate the QOL of study participants. They were Quality of Life Questionnaire (QLQ-C30) and the simplified Chinese version of the Quality of Life Ovarian Cancer 28 Questionnaire (QLQ-OV28) questionnaire, the first of which was the simplified Chinese version (3.0) of the European Organization for Research and Treatment [EORTC] 30-Item Core, and the second of which was specific to ovarian cancer. Previous studies have shown that both types of questionnaires have good reliability, validity, feasibility and responsiveness [20]. We strictly follow the steps prescribed by the EORTC QOL group to score and calibrate the questionnaire. QLQ-C30 has a higher function and overall health score, and QLQ-OV28 has a higher sexual function score, indicating that the higher the QOL score, the more severe the individual's symptoms [21-22].

Statistical analysis

Baseline characteristics were analyzed according to descriptive statistics. Continuous variables were described with median values and interquartile range; categorical variables were described in terms of absolute numbers and proportion over the total number of patients analyzed.

Health-related quality of life

We used the QLQ-C30 (version 3.0) to assess Health-related quality of life (HRQoL) [23]. This questionnaire not only contains five functional scales regarding physical, role, cognitive, emotional and social functioning and a global health status scale, but also comprises symptom scales on fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea and financial problems. Each item is scored on a 4-point scale ranging from 1: not at all, to 4: very much. All scale scores were linearly transformed to a 0–100 score [24]. The higher the score on the functional scale and overall health status/QOL, represent the better HRQoL, while the higher the score on the symptom scale, the worse the HRQoL.

Results

Analysis of patient's germline BRCA gene mutation

A total of 82 patients with epithelial ovarian cancer were enrolled, and 25 cases of BRCA1/2 pathogenic mutations were found, with a total mutation rate of 30.48%. Among them, 17 cases of BRCA1 pathogenic mutation, the mutation rate was 20.73%. There were 8 cases of BRCA2 pathogenic mutation, the mutation rate was 9.75%. A total of 13 pathogenic mutations in BRCA1 were detected, including c.2160delA, c.3770_3771delAG, c.5470_5477delATTGGGCA, c.3255_3259del (p.Leu1086fs), c.3294del (p.Pro1099fs), c.4782del (p.Ser1595fs), c.587dupA (p.Tyr196fs), c.4065_4068delTCAA, c.4132delG these 9 sites are frame-shift mutations, followed by c.3967C>G, c.1115G>A, c.4801A>T, C.6528C >G is a missense mutation. A total of 7 pathogenic mutations were detected in BRCA2, c.1495C>T, c.6528C>G, c.2041G>A, c.4593dupA were missense mutations, c.1499del (p.Gly500fs), c.3770_3771del (p.Glu1257fs), c.6405_6409delCTTAA were frame-shift mutations. The clinical significance of c.4132delG locus and C.6528C>G locus is unknown and there is no literature report, which may have potential research value (**Table 1**).

Demographic and clinical information

Detailed information concerning age, meno information, pathological type, FIGO stage *et al.* are shown in **Table 2**. Our results showed that the 82 cases were all patients with epithelial ovarian cancer, including 12 (14.6%) cases of stage I-II, 70 (86.4%) cases of stage III-IV; among the pathological factors, 74 (90.2%) cases of serous cancer, 8 (9.8%) cases of non-serous cancer, specifically: 5 cases of clear cell carcinoma, 3 cases of endometrioid carcinoma; 42 cases of neoadjuvant chemotherapy patients, all of whom were stage IIIC and IV. After follow-up, 63 (76.8%) of 82 patients were platinum-sensitive; 19 (23.2%) were platinum-resistant or refractory; confirmed by imaging or postoperative pathology, 34 (41.5%) patients with lymph node metastasis; 49 (59.8%) patients had greater omental metastasis; 31 (37.8%) patients had diaphragmatic top metastasis; 21 (25.6%) patients had colorectal invasion; preoperative CA125 value>500 U/mL 51 (62.2%) cases. There was no significant difference in clinical factors such as age of onset and menstrual status between the two groups of patients ($P>0.05$), and they were comparable. The pathogenic mutation status of BRCA1/2 gene is related to pathological type, platinum sensitivity, neoadjuvant chemotherapy, and the difference between groups is statistically significant ($P<0.05$) (**Table 2**). Among the patients undergoing germline BRCA mutation gene detection, a total of 42 patients were treated with Olaparib orally, and 40 patients were selected as the control group.

Olaparib status and QOL

All 82 patients completed the QLQ C30 and QLQ OV28 questionnaires at the time of initial enrollment. **Table 3** shows the QOL scores of patients with different Olaparib strata. At the early stage of the enrollment survey, the overall health score of QLQ-C30 was very low. The lowest scores are social function and cognitive function. In terms of symptoms, financial difficulties are the most serious. The QLQ-OV28 sexual score was the lowest. Among these 44/82 patients, 35/71 (86.5%) reported complete loss of interest in sex, and the remaining 7/11 (13.4%) reported low interest in sex. A total of 38/75 patients (91.4%) reported no sexual activity at all. Only 6/11 patients reported that they had sexually

activity, but all said that they rarely experienced sexual enjoyment. We used linear regression models to establish the correlation between Olaparib status and QOL at the time of initial enrollment (**Table 3**).

Our results showed that patients without Olaparib status fared worse with respect to physical functioning ($P = 0.038$), role functioning ($P = 0.010$), cognitive functioning ($P = 0.005$), emotional functioning ($P = 0.006$) and social functioning ($P < 0.0001$). The results showed that patients without Olaparib performed worse in terms of physical function ($P = 0.038$), role function ($P = 0.010$), cognitive function ($P = 0.005$), emotional function ($P = 0.006$), and social function ($P < 0.0001$).

Patients suffered more severe symptoms of constipation ($P = 0.001$), poor body image ($P = 0.003$), poor attitude toward treatment and disease ($P < 0.0001$), and other chemotherapy side effects ($P = 0.020$). They suffered from more severe constipation symptoms ($P = 0.001$), poor body image ($P = 0.003$), poor attitudes towards treatment and disease ($P < 0.0001$), and other side effects of chemotherapy ($P = 0.020$).

There were 82 patients that completed both the baseline and follow-up surveys and changes in QOL outcomes were determined for this group. 42 patients completed the baseline and follow-up surveys, and determined the changed outcomes in QOL results for this group.

Our research results show that the physical, role function and cognitive function as well as the range of nausea and vomiting, insomnia, loss of appetite and other side-effects were significantly worsened (**Table 3**). Then, we identified patients with deteriorating QOL who had lower scores in terms of functional domain, global health, and sexual function; or increased other symptom domains during follow-up (**Table 3**).

We applied a logistic regression model to determine whether Olaparib status can predict the risk of QOL deterioration. Our results show that patients without Olaparib had a significantly higher risk of deterioration in their quality of life in terms of physical function ($P = 0.001$), role function ($P = 0.0140$), emotional function ($P = 0.021$), pain ($P = 0.010$), and financial difficulties ($P = 0.003$) (**Table 3**).

Discussion

In recent years, many studies have revealed the important role of BRCA1/2 in the mechanism of DNA damage repair. BRCA1/2 mutation induces synthetic lethality in cells with potential HRD (homologous recombination defect). Single nucleotide polymorphisms and mutations of BRCA gene are the main causes of abnormal structure and function of BRCA gene [25]. At present, patients with ovarian cancer with BRCA1/2 mutations, especially those with advanced recurrence of ovarian cancer, often take personalized treatment measures [26]. In addition to surgery and chemotherapy, oral PARPi drugs are more likely to be used as first-line maintenance therapy or chemotherapy to achieve CR/PR maintenance after recurrence. Although the status of BRCA1/2 mutation is important for clinical decision-making and prognosis of ovarian cancer, China is still in the exploratory stage, and more multi-center clinical studies are needed to enter clinical practice.

This study describes the BRCA mutation status of 82 patients with epithelial ovarian cancer undergoing genetic testing, the relationship with common clinicopathological factors, and the positive impact on the prognosis. In our study, the total mutation rate was 30.48%, among which the BRCA1 mutation rate was 20.73%, and the BRCA2 mutation rate was 9.75%. In collaboration with Shan-Mughapriya's studies on ovarian cancer patients from different regions and races were conducted and the results of the systematic analysis were basically consistent (the gene mutation rates of BRCA1 and BRCA2 are 1.1%~39.7% and 0~13.9%, respectively) [25]. BRCA1/2 gene mutation types include frameshift mutations, nonsense mutations, missense mutations, synonymous mutations and splicing mutations. Among them, there are three types of frameshift mutations, nonsense mutations and splicing mutations, and their common feature is the early termination of protein coding synthesis [26]. In this study, BRCA1 detected a total of 9 frameshift mutations and 4 missense mutations, and BRCA2 detected a total of 3 frameshift mutations and 4 missense mutations. Frameshift mutations can cause BRCA to appear stop codons in advance, form a truncated protein or change the primary structure of the protein, thereby causing BRCA protein dysfunction. Missense mutations can cause changes in amino acid coding. According to current data, these mutations can affect the function of BRCA protein and lead to the development of ovarian cancer. However, the clinical significance of c.4132delG locus and C.6528C>G locus is unknown, and there is no literature report. It needs to be studied in future work.

There are several articles reporting the effectiveness and safety of Olaparib in patients with HSROC [15-16,19], but there are no research reports on QOL in patients with Olaparib. To the best of our knowledge, this study represents the first investigation of the QOL of ovarian cancer patients who taken Olaparib. Our study included 42 Olaparib patients and 40 ovarian cancer patients without Olaparib.

We currently know that Olaparib and other PARPis maintenance treatment can significantly improved the overall PFS of platinum-sensitive relapsed ovarian cancer patients according to registrative clinical trials. Study 19 is a randomized, double-blind, placebo-controlled, multi-center Phase II clinical study designed to evaluate the efficacy and safety of Olaparib versus placebo in patients with recurrent high-grade serous ovarian cancer. The results indicated that patients receiving Olaparib 400mg twice a day as maintenance therapy had a longer PFS (8.4 vs 4.8 months in placebo arm with HR of 0.35 P < 0.001) with a greater benefit in BRCA (germline and somatic) mutated subgroup (11.2 vs 4.3 months HR 0.18 P < 0.0001) [10,13,17,18].

The results of the SOLO-2 phase III clinical study showed that patients with BRCA-mutated platinum-sensitive relapsed ovarian cancer who received Olaparib tablets (300mg twice a day) had significantly prolonged PFS compared with placebo. The study reached the main study endpoint: the investigator assessed PFS (median PFS 19.1 months vs 5.5 months) and had low toxicity and high safety [14,19].

After these results Olaparib has been rapidly introduced in everyday practice, modifying treatment algorithms. Nevertheless, in SOLO2 and Study 19 trial, as usually in all registrative trials [13], Olaparib was administered to very selected patients from highly experienced providers with very straight rules, time lines and schedules per protocol. This improved PFS obtained in an ideal setting needs external validity in

a less selected population. The results of the highly anticipated 5-year follow-up of the SOLO1 study were announced on ESMO 2020. The results showed that mPFS in the Olaparib group lasted up to 56 months, reduced the risk of disease progression or death by 67%, and 48% of patients had no disease progression in 5 years. These patients may have achieved clinical "cure".

And we still need real world studies to define if drugs are effective in real world setting. Few results from Olaparib real world use have been reported, with short follow up [27-28] or small population [29], lacking essential clinical information like BRCA status [30] and focusing above all on safety. This is the first QOL study on patients with ovarian cancer undergoing maintenance treatment with oral olaparib in China. Our real-world experience of the QOL of Olaparib maintenance treatment in HSROC patients with BRCA1/2 mutation is consistent with that reported in previous studies [15-16,19] with tolerable toxicity profiles. Our results can be compared to those of Study 19, a phase II trial of Olaparib capsules as maintenance monotherapy in patients with platinum-sensitive HSROC, as we used the same indications and regimen (capsule 400 mg bid). The use of Olaparib in China was permitted based on the results of NCCN guideline and it is mandatory for physicians in China to follow the recommendations and guidelines of NCCN.

Limitations: first of all, because this study is based on ovarian cancer patients undergoing oral maintenance treatment with Olaparib in our center, the detection time is close to the follow-up end point, and there is obvious survivor bias. Therefore, the overall survival time OS data analyzed in this study is short. In subsequent studies, we can increase the overall survival rate statistics in the process of expanding the sample size. Secondly, the sample size of this study is small, and it is only a preliminary exploratory study. The conclusions obtained and their specific related mechanisms need to be further confirmed.

List Of Abbreviations

Epithelial ovarian cancer

EOC

Primary Debulking Surgery

PDS

Homologous Recombination

HR

Double-strand break

DSB

HR Deficiency

HRD

PolyADP Ribose Polymerase inhibitors

PARPis

High-grade serous recurrent ovarian cancer

HSROC

confidence interval

CI
Quality of Life Questionnaire
QLQ
Quality of Life Ovarian Cancer 28 Questionnaire
QLQ-OV28
European Organization for Research and Treatment
EORCT
Health-related quality of life
HRQoL

Declarations

Ethics approval and consent to participate

All patients signed informed consent before using clinical specimens. The use of specimens for this study has been proved by the ethics committee of the First Affiliated Hospital with Nanjing Medical University.

Consent for publication

Not applicable

Availability of data and materials

They could be achieved upon reasonable request to the authors.

Competing interests

The authors declare that they have no competing interests.

Funding

This work was supported by the National Natural Science Foundation (81872119), the National Natural Science Youth Foundation (81702566) and 333 High-level Talents Training Project in Jiangsu Province, China (RS19).

Authors' contributions

Authors Wenjun Cheng designed the project. Yi Jiang and Huangyang Meng contributed to preparing the main manuscript equally. Xinjia Ruan was responsible for the data analysis. Lin Yuan and Chengyan Luo were responsible for clinical data collection and performing clinical validation. Shulin Zhou, Guodong Sun and Yicong Wan were responsible for proofreading. All authors reviewed the manuscript.

Acknowledgement

We thank all members of the Cheng's laboratory for their advice and technical assistance.

Conflict of Interest

The authors declare that they have no competing interests.

References

1. Colombo N, Sessa C, Bois AD, Ledermann J, McCluggage WG, McNeish I, et al. ESMO-ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease. *Int J Gynecol Cancer* 2019; 02:1–33.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin*. 2019;01:1–28.
3. Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. *Nature*. 2011;474:609–15.
4. Pal T, Permuth-Wey J, Betts JA, Krischer JP, Fiorica J, Arango H, et al. BRCA1 and BRCA2 mutations account for a large proportion of ovarian carcinoma cases. *Cancer*. 2005;104:2807–16.
5. Pennington KP, Walsh T, Harrell MI, Lee MK, Pennil CC, Rendi MH, et al. Germline and somatic mutations in homologous recombination genes predict platinum response and survival in ovarian, fallopian tube, and peritoneal carcinomas. *Clin Cancer Res*. 2014;203:764–75.
6. Bryant HE, Schultz N, Thomas HD, Parker KM, Flower D, Lopez E, et al. Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. *Nature*. 2005;434:913–7.
7. Mittica G, Ghisoni E, Giannone G, Genta S, Aglietta M, Sapino A, et al. PARP inhibitors in ovarian cancer. *Recent Pat Anticancer Drug Discov*. 2018;13:392–410.
8. Farmer H, McCabe N, Lord CJ, Tutt AN, Johnson DA, Richardson TB, et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. *Nature*. 2005;434:917–21.
9. Scott CL, Swisher EM, Kaufmann SH. Poly (ADP-ribose) polymerase inhibitors: recent advances and future development. *J Clin Oncol*. 2015;33:1397–406.
10. Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, et al. Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial. *Lancet Oncol*. 2014;15:852–61.
11. Evers B, Drost R, Schut E, de Bruin M, van der Burg E, Derksen PW, et al. Selective inhibition of BRCA2-deficient mammary tumor cell growth by AZD2281 and cisplatin. *Clin Cancer Res*. 2008;1412:3916–25.
12. Rottenberg S, Jaspers JE, Kersbergen A, van der Burg E, Nygren AO, Zander SA, et al. High sensitivity of BRCA1-deficient mammary tumors to the PARP inhibitor AZD2281 alone and in combination with platinum drugs. *Proc Natl Acad Sci USA*. 2008;105:17079–84.
13. Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. *N Engl J Med*. 2012;366:1382–92.

14. Pujade-Lauraine E, Ledermann JA, Selle F, GebSKI V, Penson RT, Oza AM, et al. SOLO2/ENGOT-Ov21 investigators, Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): A double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncol.* 2017;189:1274–84.
15. Wahlberg E, Karlberg T, Kouznetsova E, Markova N, Macchiarulo A, Thorsell AG, et al. Family-wide chemical profiling and structural analysis of PARP and tankyrase inhibitors. *Nat Biotechnol.* 2012;30:283–8.
16. Lynparza [package insert]. astra zeneca. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208558s001lbl.pdf, 2018.
17. Ledermann JA, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, et al. Overall survival in patients with platinum-sensitive recurrent serous ovarian cancer receiving olaparib maintenance monotherapy: an updated analysis from a randomised, placebo-controlled, double-blind, phase 2 trial. *Lancet Oncol.* 2016;17:1579–89.
18. Friedlander M, Matulonis U, Gourley C, du Bois A, Vergote I, Rustin G, et al. Long-term efficacy, tolerability and overall survival in patients with platinum sensitive, recurrent high-grade serous ovarian cancer treated with maintenance olaparib capsules following response to chemotherapy. *Br J Cancer.* 2018;119:1075–85.
19. Penson R, Kaminsky-Forrett M, Ledermann J, Brown C, Plante M, Korach J, et al. Efficacy of olaparib maintenance therapy in patients with platinum sensitive relapsed ovarian cancer by number of lines of prior chemotherapy: phase III SOLO2 trial (ENGOT Ov-21). *Ann Oncol.* 2017;14:330–54.
20. Paradowski J, Tomaszewski KA, Bereza K, Tomaszewska IM, Pasternak A, Paradowska D, et al. Validation of the polish version of the EORTC QLQ-OV28 module for the assessment of health-related quality of life in women with ovarian cancer. *Expert Rev Pharmacoecon Outcomes Res.* 2014;14:157–63.
21. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst.* 1993;85:365–76.
22. Greimel E, Bottomley A, Cull A, Waldenstrom AC, Arraras J, Chauvenet L, et al. EORTC Quality of Life Group and the Quality of Life Unit, An international field study of the reliability and validity of a disease-specific questionnaire module (the QLQ-OV28) in assessing the quality of life of patients with ovarian cancer. *Eur J Cancer.* 2003;39:1402–8.
23. Giesinger JM, Kieffer JM, Fayers PM, Groenvold M, Petersen MA, Scott NW, et al. EORTC Quality of Life Group, Replication and validation of higher order models demonstrated that a summary score for the EORTC QLQ-C30 is robust. *J Clin Epidemiol.* 2016;69:79–88.
24. Fayers PM, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A, et al. In: Brussels, editor. EORTC QLQ-C30 scoring manual. edition r. EORTC; 2001.
25. George SH, Shaw P. BRCA and Early Events in the Development of Serous Ovarian Cancer. *Front Oncol.* 2014;4:1–8.

26. Seo JH, Jeong SY, Kim MS, Kang JH, Paik ES, Lee YY, et al. Prevalence and oncologic outcomes of BRCA1/2 mutation and variant of unknown significance in epithelial ovarian carcinoma patients in Korea. *Obstet Gynecol Sci.* 2019;62:411–9.
27. Mahajan R. Real world data: additional source for making clinical decisions. *Int J Appl Basic Med Res.* 2015;5:82.
28. De La Motte Rouge T, Pautier P, Alexandre P, Ray-Coquard I, Cottu P, Rodrigues M, et al. 2755 POSTER first real life data on olaparib in BRCA1/2 mutated platinum-sensitive relapsed epithelial ovarian cancer in France: analysis of 52 patients enrolled in the French temporary authorization for use (ATU). *Eur J Cancer.* 2015;51:548–9.
29. Orbegoso Aguilar MA, Dumas L, Davies E, Gore M, George A. S.B.. 273P Olaparib maintenance treatment, the Royal Marsden experience. *Ann Oncol.* 2018;29:suppl–9.
30. Eriksson I, Wettermark B, Bergfeldt K. Real-world use and outcomes of olaparib: a population-based cohort study. *Target Oncol.* 2018;13:725–33.

Tables

Due to technical limitations, table 1,2,3 is only available as a download in the Supplemental Files section.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Table1.pdf](#)
- [Table2.pdf](#)
- [Table3.pdf](#)