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Research Report

Re-treatment with PARPi in patients with recurrent epithelial ovarian cancer: A single institutional experience

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ABSTRACT

Introduction: We aimed to evaluate real-life experiences with the re-challenge of poly(ADP-Ribose)Polymerase (PARP) inhibitors (PARPi) after a prior PARPi therapy in patients with recurrent EOC.

Methods: A retrospective descriptive study was conducted at a tertiary care center of excellence for ovarian cancer. Demographic, pathological, and therapeutic data were collected for patients with recurrent epithelial ovarian cancer who were re-treated with PARPi in their therapy course.

Results: Twenty-nine patients were included in the study. Twenty-six patients received the second PARPi as maintenance therapy after two different lines of therapy and three patients received the second PARPi as upfront therapy after progression. Most of the patients (57.7%) were exposed to first PARPi after a second-line therapy. The median progression-free survival under the first and second PARPi therapy was estimated at 15 and 7 months respectively. PFS under the second PARPi after platinum-based chemotherapy was better after a complete remission with a median PFS of 8.5 months, compared to patients with partial remission (5.5 months). A better PFS was noted in case of negative *BRCA* status under the second PARPi therapy (median PFS of 7.4 vs. 4.5 months, $p = 0.11$). The second PARPi therapy was mainly discontinued due to disease progression (84.6% of the cases). Discontinuation of treatment with the second PARP due to toxicity was needed in one case who developed a myelodysplastic syndrome.

Conclusion: Real-life data support prospective evidence that patients with recurrent EOC may derive benefit of the re-treatment with PARPi in case of clear response to the last platinum-based therapy.

1. Introduction

Platinum-based chemotherapy is one of the cornerstones in the medical treatment of epithelial ovarian cancer (OC). Moreover, maintenance therapy with antiangiogenetic agents have evolved rapidly in the last two decades and play a pivotal role in the treatment of the deadliest gynecological malignancy (Perren et al., 2011; Burger et al., 2011; Aghajanian et al., 2012; Pujade-Lauraine et al., 2014; Heitz et al., 2012). The introduction of a new class of drugs that target the ability of cancer cells to repair DNA single-strand breaks, the poly(ADP-Ribose) Polymerase (PARP) inhibitors (PARPi), reached clinical development later (Gelmon et al., 2011). Study 19 was the first randomized trial to show the efficacy of olaparib maintenance therapy in relapsed platinum-sensitive high-grade serous OC. Patients with a treatment free interval of more than 6 months after a platinum-based chemotherapy and a response to a platinum-based re-induction chemotherapy had to have a partial, or complete response. 265 patients were randomized to 400 mg olaparib (capsules) BID or placebo until progressive disease. Median progression-free survival (PFS) of patients receiving olaparib was 8.4 months, and median survival of patients receiving placebo was 4.8 months (Ledermann et al., 2012). After that, the SOLO-2 trial showed a prolonged PFS by 13.6 months in patients with *BRCA1* or *BRCA2*

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mutations who were treated with 300 mg olaparib (tablets) BID maintenance therapy compared to placebo (Pujade-Lauraine et al., 2017). Moreover, efficacy of other PARPi, such as niraparib and rucaparib, was evaluated in the NOVA and ARIEL3 phase III trials, respectively, showing benefit in terms of progression-free survival when used as maintenance treatment after platinum-based chemotherapy (Mirza et al., 2016; Coleman et al., 2017). Furthermore, PARPi efficacy with olaparib, niraparib and rucaparib has been evaluated in several other settings, namely in the treatment (not maintenance) of heavily pretreated patients with platinum-resistant and/or – sensitive OC (Oza et al., 2017; Penson et al., 2020; Moore et al., 2019). Inspired by these findings in the recurrent setting, several first-line trials with PARPi as maintenance therapy were initiated. The use of olaparib maintenance showed a substantial benefit in progression-free survival among women with newly diagnosed advanced OC and a *BRCA1/2* mutation (Moore et al., 2018), while niraparib expanded the option of maintenance treatment with PARPi to include *BRCA1/2* wild type patients (González-Martín et al., 2019). The PAOLA-1 trial has shown superiority of adding olaparib to bevacizumab maintenance therapy after a first-line standard therapy in patients with homologous recombination (HR)-deficient tumors (Ray-Coquard et al., 2019).

Given the high efficacy of PARPi after response to platinum-based chemotherapy in terms of prolonging PFS -independently of the treatment line-, increasing demand led to the question whether re-inducing a therapy with PARPi after a prior PARPi maintenance therapy is effective and safe. Prospective data from the OReO/ENGOT OV-38 trial (NCT03106987) have been presented recently and showed that patients may derive benefit from a re-treatment with olaparib after response to platinum-based chemotherapy (Pujade-Lauraine et al., 2021). In this retrospective study, we sought to illustrate our experience in the re-treatment with PARPi in treating recurrent OC at our tertiary care center.

2. Methods

A retrospective chart review at our tertiary gyneco-oncologic unit, an ESGO accredited center of excellence for advanced ovarian cancer (OC) surgery, was undertaken. The medical records of all patients with epithelial OC treated between December 2014 and July 2021 who had experienced recurrent disease and received maintenance therapy with a PARPi in their treatment course were reviewed. Patients who received PARPi therapy in two different treatment lines were included. Demographic, pathological, and therapeutic data were collected for each patient. The primary outcomes were the type of the first and second PARPi, duration of treatment with PARPi, reasons for discontinuation of the therapy, toxicity under PARPi treatment and PFS. The serologic (CA125-level) and radiologic disease status before and after each PARPi therapy were included based on GCIG criteria for CA125 and according to RECIST 1.1 criteriafor tumor assessment. The *BRCA-1/2* status, germline or somatic, was also retrieved. HRD status was not available for the whole cohort as all patients had their first diagnosis before routine HRD testing was implemented. We looked for each patient if she fulfilled the OReO criteria or not. In the OReO trial, patients in the *BRCA-1/2* positive cohort should have received the first PARPi for at least 18 months after first-line chemotherapy, or at least 12 months after second-line or later chemotherapy. In the BRCA-1/2 negative cohort, patients should have had a prior PARPi exposure for at least 12 months after first-line or at least 6 months after second-or later line therapy. An approval from the ethical committee was not mandatory due to the study's retrospective design of anonymized data.

3. Results

Twenty-nine patients were included in the study. We identified 26 patients who received at least two lines of platinum-based treatment and received PARPi as maintenance therapy after two different lines of chemotherapy. Three patients in our cohort received the second PARPi as upfront therapy after progression under the last therapy line. Demographic information including stage at diagnosis, histology, receipt of neoadjuvant versus primary debulking surgery, and BRCA status are provided in Table 1. In Table 2, we listed the patients' characteristics concerning the type of PARPi, time of initiation, therapy duration, reasons for treatment discontinuation and evaluation of fulfillment of OReO criteria among the whole cohort. The median age of the patients was 52 years (range: 37–76). 93.1% of the patients had high-grade serous adenocarcinoma. Genetic analysis was performed in 93.1% of the cases. Nine patients harbored a *BRCA-1* germline mutation, while only one patient had a *BRCA-2* germline mutation. Additional three patients were diagnosed with a somatic *BRCA-1* mutation. Six patients had a previous/metachronous malignancy in their medical history: breast cancer (5 cases), colon cancer (one case).

Most patients received their first PARPi after two lines of therapy (range, 1–4). Five, fifteen, five and one patients received the first PARPi treatment after 1st, 2nd, 3rd and 4th line therapy, respectively. 57.7% of the patients had a complete serological remission, and 38.5% of the patients presented with a complete radiological remission, while 57.7% had a partial radiological response before initiating the therapy with the first PARPi. 14 out of 26 patients (53.8%) received olaparib, and 12 (46.2%) received niraparib as the first PARPi. Reasons for the discontinuation of treatment with first PARPi were: progressive disease (88.8%, 23 out of 26 cases), and maximal planned cycles reached (3.8%, 1 case - first line maintenance). Two patients discontinued their first PARPi therapy because of toxicities: one because of fatigue and the second due to severe thrombocytopenia. Median duration of first PARPi maintenance therapy was 12 months (range, 4–28). The median progression-free survival under the first PARPi therapy was estimated at 15 months [95% confidence interval (CI), 10–20].

Twenty-six patients received the second PARPi as a maintenance therapy after a response to a previous systemic therapy. As a second PARPi 13 patients received olaparib, 11 patients niraparib and two rucaparib. 30.8% of the patients (8 out of 26) presented with complete radiological response before starting with the second PARPi. Seven, thirteen and four patients received the second PARPi treatment after two, three and four lines of therapy, respectively. Twenty-two patients (84.6%) received the 2nd PARPi treatment after the next subsequent therapy line after progression on PARPi. The median duration of treatment with the second PARPi therapy was five months (range: 1–12). Dose reduction of the second PARPi therapy was needed in three cases. The reasons for the dose reduction were: thrombocytopenia and anemia. Discontinuation of treatment with the second PARPi due to toxicity was needed only in one case. This patient developed a myelodysplastic syndrome (MDS). This patient developed MDS after three courses of

Table 1
Patients characteristics.

Patient characteristics	n = 29
Median age of diagnosis	52 years (range: 37-76)
Stage	
II	4
III	14
IV	11
Histology	
High grade serous	27
Endometrioid	1
Mixed	1
BRCA status	
gBRCA1 +	9
gBRCA2 +	1
tBRCA1 +	3
tBRCA2 +	0
Cytoreduction	
Primary	23
Interval	4
none	2

Table 2
Type of PARPi, time of initiation, therapy duration, reasons for treatment discontinuation and evaluation of fulfillment of OReO criteria among the whole cohort.

Patient number	Age at first diagnosis (years)	Type of PARPi 1	Setting	Duration of therapy with 1. PARPi (months)	Reasons for discontinuation of treatment	Duration between first and second PARPi (months)	Type of PARPi 2	Setting	Duration of therapy with 2. PARPi (months)	PFS after 2nd PARPi exceeding the time of PFS after 1st PARPi	Reasons for discontinuation of treatment	OReO criteria fulfilled
1	50	Olaparib	Maintenance after 2nd line	20	Progressive disease	6	Niraparib	Maintenance after 3rd line	2	no	Progressive disease	yes
2	51	Niraparib	Maintenance after 3rd line	18	Progressive disease	7	Rucaparib	Maintenance after 4th line	3	no	Progressive disease	yes
3	52	Niraparib	Maintenance after 2nd line	8	Progressive disease	5	Olaparib	Maintenance after 3rd line	6	no	Progressive disease	yes
4	60	Olaparib	Maintenance after 3rd line	2	Progressive disease	8	Rucaparib	Upfront therapy as 5th line	4	yes	Progressive disease	no
5	44	Niraparib	Maintenance after 2nd line	16	Progressive disease	9	Olaparib	Maintenance after 3rd line	8	No	Progressive disease	yes
6	50	Olaparib	Maintenance after 3rd line	25	Progressive disease	9	Rucaparib	Upfront therapy as 5th line	6	No	Progressive disease	no
7	54	Olaparib	Maintenance after 2nd line	24	Progressive disease	15	Rucaparib	Maintenance after 4th line	4	No	Progressive disease	yes
8	38	Niraparib	Maintenance after 1st line	12	Progressive disease	6	Niraparib	Maintenance after 2nd line	1	No	Progressive disease	no
9	54	Niraparib	Maintenance after 2nd line	13	Progressive disease	6	Olaparib	Maintenance after 3rd line	8	No	Progressive disease	yes
10	67	Olaparib	Maintenance after 1st line	5	Progressive disease	8	Niraparib	Maintenance after 2nd line	ongoing (since 5 months)	No	Ongoing	no
11	65	Niraparib	Maintenance after 2nd line	17	Progressive disease	20	Niraparib	Maintenance after 4th line	5	No	Progressive disease	yes
12	51	Olaparib	Maintenance after 1st line	27	Progressive disease	6	Niraparib	Upfront therapy as 3rd line	2	No	Progressive disease	no
13	48	Niraparib	Maintenance after 1st line	20	Progressive disease	9	Olaparib	Maintenance after 2nd line	3	No	Progressive disease	yes
14	76	Niraparib	Maintenance after 2nd line	4	Toxicity (thrombocytopenia CTCAE II, planned hip replacement surgery)	12	Olaparib	Maintenance after 3nd line	10	Yes	Progressive disease	no
15	49	Olaparib	Maintenance after 3nd line	18	Progressive disease	9	Olaparib	Maintenance after 4th line	10	No	Progressive disease	yes
16	37	Olaparib	Maintenance after 2nd line	28	Progressive disease	7	Olaparib	Maintenance after 3nd line	8	No	Progressive disease	yes
17	51	Olaparib	Maintenance after 2nd line	7	Drug intolerance (fatigue CTCAE II)	39	Niraparib	Maintenance after 3nd line	4	no	Toxicity (myelodysplatic syndrome)	no
18	48	Niraparib	Maintenance after 2nd line	4	Progressive disease	1	Niraparib	Re-induction with PARPi after local therapy of recurrence	5	yes	Progressive disease	no
19	38	Niraparib	Maintenance after 2nd line	8	Progressive disease	7	Olaparib	Maintenance after 3nd line	5	no	Progressive disease	no
20	42	Olaparib	Maintenance after 3rd line	8	Progressive disease	1	Olaparib	Re-induction with PARPi after local therapy of recurrence	2	no	Progressive disease	no
21	57	Olaparib	Maintenance after 2nd line	10	Progressive disease	5	Niraparib	Maintenance after 3nd line	3	no	Progressive disease	yes

(*continued on next page*)

Table 2 (*continued*)

Patient number	Age at first diagnosis (years)	Type of PARPi 1	Setting	Duration of therapy with 1. PARPi (months)	Reasons for discontinuation of treatment	Duration between first and second PARPi (months)	Type of PARPi 2	Setting	Duration of therapy with 2. PARPi (months)	PFS after 2nd PARPi exceeding the time of PFS after 1st PARPi	Reasons for discontinuation of treatment	OReO criteria fulfilled
22	58	Niraparib	Maintenance after 2nd line	28	Progressive disease	6	Olaparib	Maintenance after 3nd line	ongoing (since 12 months)	no	Ongoing	yes
23	51	Olaparib	Maintenance after 1st line	24	Maximal number of cycles	12	Olaparib	Maintenance after 2nd line	6	no	Progressive disease	yes
24	53	Olaparib	Maintenance after 1st line	12	Progressive disease	7	Niraparib	Maintenance after 2nd line	ongoing (since 4 months)	no	Ongoing	yes
25	61	Olaparib	Maintenance after 2nd line	13	Progressive disease	7	Niraparib	Maintenance after 3nd line	3	no	Progressive disease	yes
26	63	Olaparib	Maintenance after 2nd line	11	Progressive disease	1	Olaparib	Re-induction with PARPi after local therapy of recurrence	12	yes	Progressive disease	no
27	56	Niraparib	Maintenance after 3rd line	4	Progressive disease	1	Niraparib	Re-induction with PARPi after local therapy of recurrence	7	yes	Progressive disease	no
28	52	Niraparib	Maintenance after 4th line	6	Progressive disease	15	Olaparib	Maintenance after 6th line	5	no	Progressive disease	no
29	52	Olaparib	Maintenance after 3rd line	19	Progressive disease	14	Niraparib	Maintenance after 5th line	3	no	Progressive disease	yes

carboplatin and two PARPi treatments with olaparib and niraparib, which lasted 7 and 4 months, respectively. She died 4 months after the diagnosis of MDS. Otherwise, treatment with the second PARPi was mainly discontinued because of disease progression under the maintenance treatment. Median progression-free survival after the second PARPi was 7 months [95% confidence interval (CI), 5.2–8.8]. Assuming a therapy interval $\geq$ 6 months to be of clinical benefit, 11 out of 26 patients achieved this result. Four patients (15.4%) experienced a better or similar PFS under the second PARPi maintenance therapy than with the first PARPi, with PFS of 4 and 7, 6 and 8, and in two patients 12 and 12 months, respectively. One patient received rucaparib treatment as 2nd PARPi and she experienced a comparable PFS as after 1st PARPi maintenance therapy (2 and 4 months, respectively).

A better PFS to first PARPi maintenance therapy was observed in case of complete response compared to partial response after systemic therapy (median PFS of 16 vs. 12 months); however, the difference was not statistically significant ($p = 0.208$) (Fig. 1). The PFS under the second PARPi was better after a complete remission with a median PFS of 8.5 months, compared to patients with partial remission (5.5 months) after platinum-based chemotherapy, and was 3.3 months with upfront therapy ($p = 0.011$) (Fig. 2). Patients with a *BRCA* mutation had a longer PFS with PARPi maintenance therapy after the first therapy compared to patients without a *BRCA* mutation (median PFS of 18 vs. 12 months, $p = 0.15$) (Fig. 3). Under the second PARPi therapy, we noted a better PFS in case of negative *BRCA* status (7.4 vs. 4.5 months) but this difference was statistically not significant ($p = 0.11$) (Fig. 4). Of the 26 patients with 2nd PARPi maintenance therapy, 15 patients met the inclusion criteria of the OReO trial. Median PFS of 2nd PARPi treatment was 5 months in both groups of patients who fulfilled, and not fulfilled inclusion criteria.

Three patients with BRCA mutations received the second PARPi as a therapy after disease progression (rucaparib in two cases and niraparib in one case). All of them had a germline *BRCA*-1 mutation. In both cases, rucaparib was a therapy as a fifth line with a PFS of 4 and 6 months, respectively, niraparib was applied as a third line therapy and the PFS was estimated at 2 months.

4. Discussion

In the present analysis, we observed that there is a small group of patients with recurrent high-grade ovarian cancer (OC), who might derive benefit from an exposure to a PARPi, although they were treated with a PARPi earlier in their disease course. This re-treatment with PARPi seems to be safe, as we did not observe excessive toxicities in the 29 patients treated at our department, except one patient who developed myelodysplastic syndrome.

The efficacy of re-treatment with DNA damaging agents in recurrent OC has been evaluated in earlier phase III trials. Re-challenge with Bevacizumab in combination with platinum-based doublets was evaluated in the MITO16B-MaNGO OV2B-ENGOT OV17 trial. The re-challenge with bevacizumab was associated with a significantly prolonged PFS (11.8 vs. 8.8 months, HR 0.51, 95 %CI: 0.41–0.64, $p < 0.001$) compared to placebo (Pignata et al., 2021). The introduction of PAPRi maintenance therapy after response to platinum-based chemotherapy has firstly changed the landscape of treatment of platinum-eligible recurrent ovarian cancer tremendously. Recently, the American Society of Clinical Oncology (ASCO) recommended PARPi maintenance therapy in many patients with high-grade ovarian cancer following successful 1st-line chemotherapy with carboplatin and paclitaxel and facultatively in combination with bevacizumab (Tew et al., 2020). Due to the fact, that PARPi maintenance therapy is very effective, if given for the first time- irrespectively of the line of treatment- it was an unmet medical need to investigate whether re-treatment with PARPi could again improve survival of patients. Therefore, the OReO study, a phase IIIb randomized controlled trial was conducted and results were presented recently. It could be shown, that re-challenge with maintenance olaparib provided a statistically significant improvement in PFS

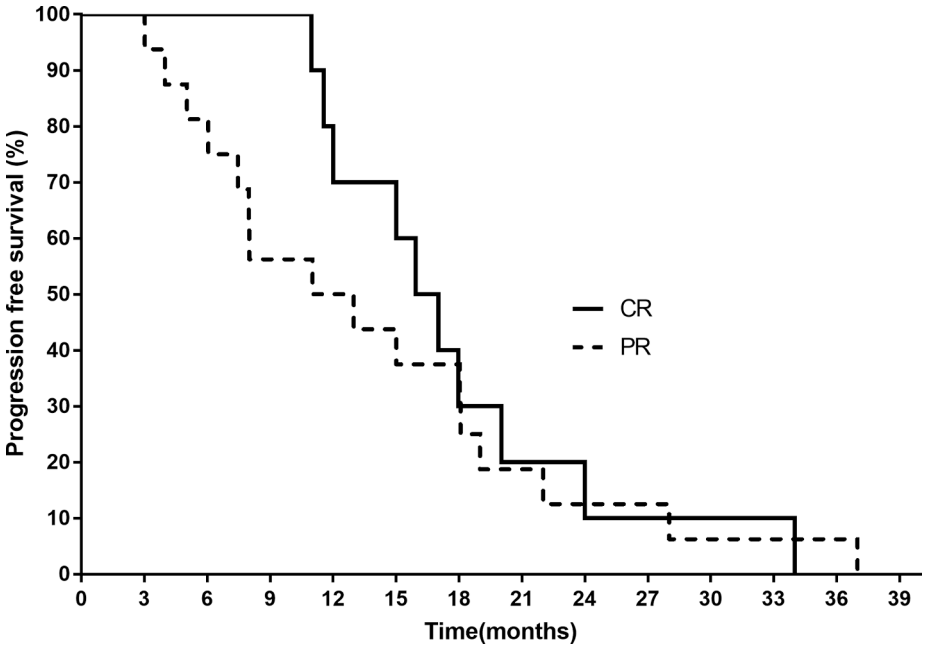

Fig. 1. Progression-free survival under first PARPi therapy in case of complete remission (CR) or partial remission (PR) after a systemic therapy.

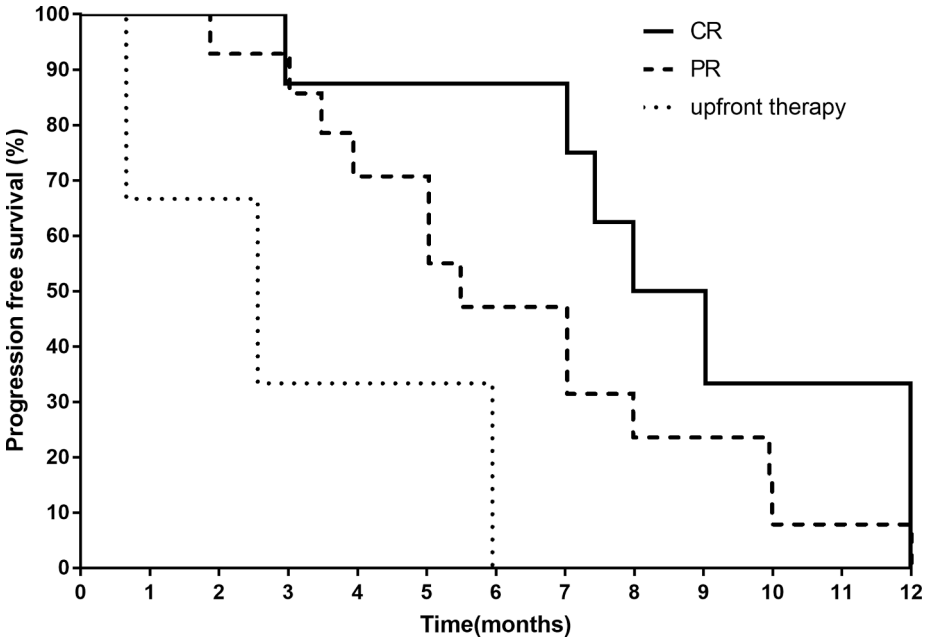

Fig. 2. Progression-free survival under second PARPi therapy in case of complete remission (CR), partial remission (PR), and as upfront therapy.

compared with placebo, regardless of *BRCA* mutational status: 4.3 vs. 2.8 months (HR 0.57 (95% CI 0.37–0.87); p = 0.022) in the *BRCAm* cohort and 5.3 vs. 2.8 months (HR 0.43 (95% CI 0.26–0.71); p = 0.0023) in the non-*BRCAm* cohort (Pujade-Lauraine et al., 2021). Our real-life data are in line with the general paradigm established by the OReO trial, that there are patients who benefit from re-exposure to PARPi. In comparison to the data of the OReO trial, patients in our cohort with and without *BRCA* mutations had a median PFS of 4.5 months and 7.4 months, respectively. Setting a therapy duration with second PARPi of $\geq$ 6 months to be considered efficient, our cohort's clinical benefit rate is then estimated at 38.5% (11 out of 26 patients). Obviously, we did not have any controlled comparisons to evaluate efficacy of 2nd PARPi treatment. However, as the chemotherapy-free intervals shorten from treatment-line to treatment line (Hanker et al., 2012), an equal, or a longer chemotherapy-free interval in a later treatment line, in comparison to the chemotherapy-free interval of an earlier treatment line could serve of an indicator for treatment efficacy. Applying the latter method to our cohort of patients, we found 5 of 29 patients (17.2%) experiencing a benefit of the 2nd PARPi exposure. Noteworthy, all those 5 patients did not meet the -strict- OREO inclusion criteria. Thus, on the one hand there is the cohort of patients who derived benefit from 2nd PARPi treatment proven by the OReO trial. Actually, our data add some evidence, that there is another group of patients, who might derive benefit from 2nd PARPi exposure beyond the OReO criteria. We compared our findings to earlier results published by Essel et al. who suggested a possible efficacy for repeat PARPi monotherapy utilization (Essel et al.,

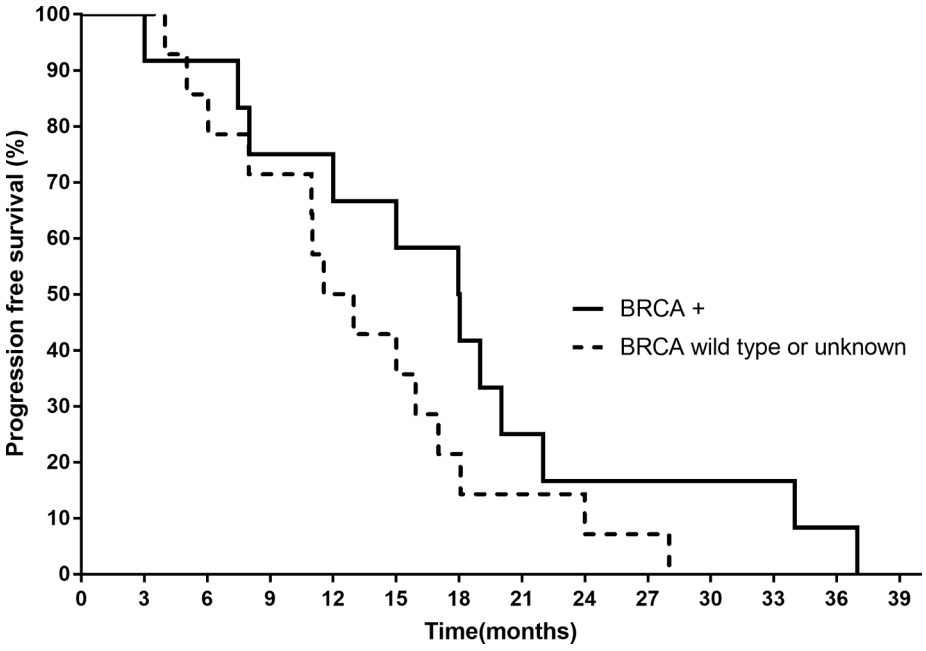

Fig. 3. Progression-free survival under first PARPi therapy according to *BRCA* status.

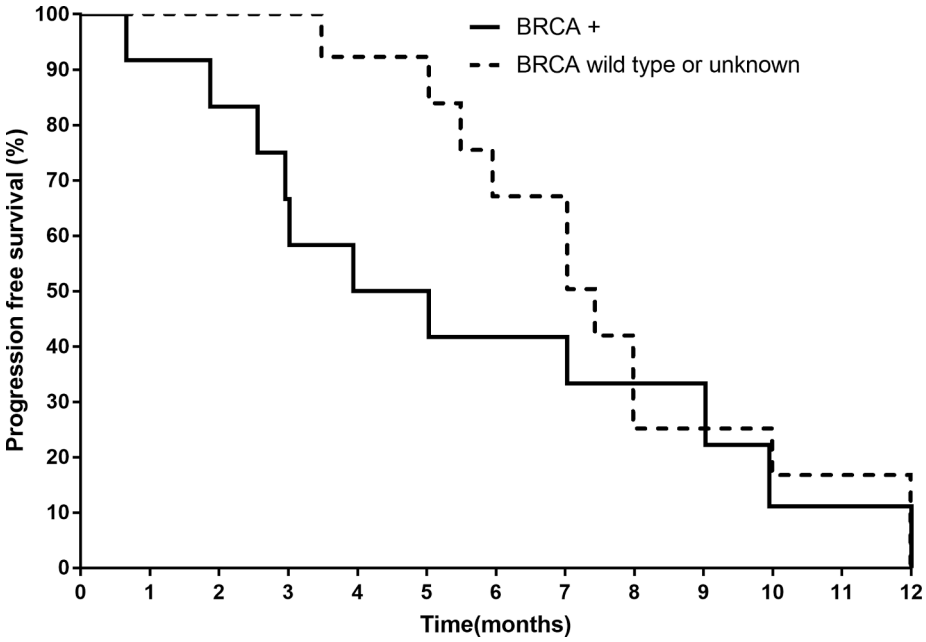

Fig. 4. Median progression-free survival under second PARPi therapy according to *BRCA* status.

2021). In their multi-institutional series of 22 patients, they did not publish any PFS data but they reported the type of response after the second PARPi: 3 with partial remission, 13 with stable disease, and 3 with progressive disease. However, in their cohort, the second PARPi was used as maintenance therapy only in three patients which makes a comparison with the OReO results difficult. Also, the authors noted that patients with *BRCA* associated tumors whose disease did not progress during first PARPi as part of frontline therapy experienced benefit from re-treatment with a PARPi. Another cohort of patients with PARPi retreatment were reported from the QUADRA trial. In a subgroup analysis of 37 patients who received niraparib in the 4th or more therapy line after prior PARPi therapy the overall response rate was 6%, and the clinical benefit rate at 16 weeks was 20%, indicating some signal of disease control (Rimel et al., 2020).

Six patients experienced the same hematologic toxicity after restarting a therapy with PARPi, knowing that five of them received by the second treatment another PARPi molecule. Discontinuation due to toxicities was necessary only in one case and because of de novo myelodysplastic syndrome. However, this occurred just 4 months after initiation of the second PARP-inhibitor which makes it questionable if the MDS was attributed only to the second PARP-inhibitor or the cumulative treatment. Parallel to our findings, in the OReO trial, grade ≥ 3 adverse events (AEs) occurred in 15% of olaparib arm vs 5% of placebo in the *BRCAm* cohort and 21% vs 8% of non-*BRCAm* patients. 3% of *BRCAm* and 1% non-*BRCAm* patients discontinued olaparib because of an AE.

Data of the OReO trial indicates, that approximately 50% of patients

included to the trial did not derive any benefit from 2nd PARPi therapy, despite strict inclusion criteria. In our-very different-cohort, ~80% of patients derived no benefit of 2nd PARPi therapy. These patients didn't fulfill the OReO criteria. Those who benefited were BRCA1/2-positive in three cases and -negative in two cases. Three out of five patients who truly benefited also received a local surgical therapy of recurrence, which might have improved the response after the second PARPi exposure. Thus, an emergence of PARPi resistance may explain the lack of response to PARPi re-exposure and several resistance mechanisms have been described in literature. Secondary somatic reversion mutations in *BRCA1/2* genes will restore the homologous recombination function in the tumor cells. Also, the loss or diminished expression of PARP-1 in tumor cells, low expression levels of the TP53-binding protein 1 (53BP1), and upregulation of P-glycoprotein are correlated with poorer response to PARPi (Klotz and Wimberger, 2020). Indeed, a recent prospective report demonstrated that the presence of a BRCA reversion mutation predicts for a primary resistance to rucaparib (Kristeleit et al., 2021). In another paper, Nesic et al. demonstrated that an acquired *RAD51C* promotor methylation loss could cause a PARPi resistance in high-grade serous ovarian cancer (Nesic et al., 2021). New therapies targeting these mechanisms will be needed in the future to enhance the PARPi efficacy. In a phase II non-comparative study, Westin et al. recently showed efficacy of adavosertib given alone or in combination with olaparib in patients with PARPi-resistant OC. Actually, adavosertib inhibits the WEE2, which phosphorylates and inhibits cyclin-dependent kinases 1 and 2 and is involved in regulation of the intra-S and G2/M cell cycle checkpoint arrest for premitotic DNA repair (Westin et al., 2021). Earlier, Lheureux et al. reported that the cediranib-olaparib combination showed some activity after progression on prior PARPi. They also identified genomic mechanisms of resistance to PARPi: again reversion mutations in BRCA1, BRCA2, or RAD51B (19%); CCNE1 amplification (16%); ABCB1 upregulation (15%); and SLFN11 downregulation (7%) (Lheureux et al., 2020). Maybe it is worth considering new clinical trials studying the efficacy of PARPi-combination therapy, with the purpose to harbor or reverse PAPRi resistance, particularly as re-challenge efficacy rates are still modest.

But what are the clinical consequences of the before said? Patients who meet the inclusion criteria of the OReO trial can again be given olaparib as maintenance therapy. Patients should be explained, that approximately 50% of patients will derive benefit from a treatment. In addition, further trials should be undertaken to understand the mechanisms of PARP resistance and to identify patients who may derive benefit of 2nd PARPi treatment. Patients who do not meet the inclusion criteria of OReO are not candidates for a routine PARPi rechallenge. If patients understand the limitations (approximately 20% of patients might derive benefit from a treatment) and risks of PARPi rechallenge and follow-up split imaging is scheduled in three months intervals, PARPi rechallenge might be an option.

The limitation of our study is the retrospective design, which is prone to several bias. However, it is the largest retrospective series covering the question of 2nd PARPi therapy published until now.

In conclusion, re-challenge with PARPi can be offered to patients with recurrent EOC after a complete or partial response to the last systemic platinum-based therapy regardless of *BRCA*-status. We could not demonstrate a clear benefit in a rather small number of patients with PARP re-treatment. However, our findings suggest that there might be also another group of patients beyond defined OReO criteria that might be eligible for second PARPi therapy. In fact, parameters to identify patients who will derive most benefit from re-treatment with PARPi are highly needed.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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