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ORIGINAL ARTICLE

Real-world outcomes of PARP inhibitor maintenance in advanced ovarian cancer: a focus on disease patterns and treatment modalities at recurrence

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Available online xxx

Background: The utilization of poly-ADP-ribose polymerase (PARP) inhibitors (PARPi) as a first-line maintenance therapy for advanced ovarian cancer has increased significantly, with ∼80% of patients potentially eligible. This expansion has led to a rise in the population experiencing platinum-sensitive recurrence, yet data on first recurrence during PARPi are limited. This real-world study from a high-volume referral center aims to elucidate recurrence rates, disease distribution, and treatment modalities at the time of progression in PARPi-treated patients.

Materials and methods: We analyzed our prospectively maintained database to identify patients receiving first-line PARPi maintenance from January 2019 to December 2022 at our institution.

Results: A total of 373 cases were identified, 51.5% of which had a *BRCA* mutation. With a median follow-up of 38 months, 44.8% of patients experienced recurrence, with 90.3% having a platinum-free interval exceeding 6 months. Recurrences were oligometastatic in 44.9% of cases, with *BRCA* mutations strongly predicting this pattern (hazard ratio 3.014, confidence interval 1.486-6.113, $P = 0.002$). The median progression-free survival was 39 months, significantly longer for *BRCA*-mutated and homologous recombination deficiency-positive patients. Over one-third of platinum-sensitive recurrent patients were candidates for local treatments, and PARPi administration was prolonged in 53.7%.

Conclusions: Despite the notable survival improvement, a significant proportion of the population will experience a platinum-sensitive recurrence on PARPi, for which local treatments are often a viable option. Our study highlights the need for further research to determine whether the ablation of oligometastatic sites has a significant impact on post-recurrence survival and to identify if there are patient categories that would benefit from personalized follow-up due to their susceptibility to oligometastatic recurrences and local treatments.

Key words: ovarian cancer, PARP inhibitors, recurrence, oligometastatic, secondary cytoreduction, stereotactic brachytherapy

INTRODUCTION

Remarkable advancements in surgical techniques and medical treatment in the past 20 years have delayed disease progression and prolonged overall survival for advanced ovarian cancer patients.[1]

Data supporting poly-ADP-ribose polymerase inhibitors (PARPi) use in the first-line maintenance setting come from several randomized controlled trials showing significant improvements in progression-free survival (PFS). However, these trials differ considerably in terms of their control arms (placebo or active intervention), patient populations (platinum response rates and residual disease), and planned duration of treatment.[2,3]

As a matter of fact, the 3-year PFS reported in these trials ranges between 12% and 60%,[2-4] confirming that relapse still represents a major problem for patients diagnosed with advanced ovarian cancer.

Nowadays, PARPi have been largely introduced in clinical practice and a large real-world study has suggested that up

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to 79% of patients with primary advanced ovarian cancer would be potentially eligible for PARPi maintenance treatment, according to current European reimbursement policies.[5]

Therefore, the use of PARPi in first-line maintenance has introduced a new and potentially larger category of platinum-sensitive recurrent patients, which represents a challenge for oncologists worldwide. Indeed, the effect of PARPi on the disease presentation upon recurrence and post-recurrence survival outcomes remains largely unexplored. This aspect has the potential to influence treatment decisions for subsequent therapies, including local treatments such as secondary cytoreductive surgery (SCS)[6] and/or infield radiotherapy.[7] There are currently few experiences in the literature describing the outcomes of first-line PARPi use in clinical scenarios outside the stringent selection criteria of clinical trials.[8]

This study aims to provide data on recurrence rate, disease presentation, and treatment modalities at the time of progression in patients treated with first-line PARPi at a single tertiary referral center for ovarian cancer care.

MATERIALS AND METHODS

This observational, longitudinal, medical chart review study collected real-world data from consecutive ovarian cancer patients who received first-line PARPi maintenance treatment at the Gynecologic Oncology Unit, Fondazione Policlinico Universitario A. Gemelli, Rome, from January 2019 until December 2022. All patients showed either clinical complete or partial response after six cycles of platinum-based chemotherapy. Patients who received bevacizumab combined with PARPi as maintenance were excluded from the present analysis. The flow chart of the study population is reported in Figure 1.

Cases were retrieved from our prospectively collected and maintained REDCAP database. All patients signed an informed consent to collect their data for scientific purposes. The Institutional Review Board approved the study (Protocol N. 0003205/24). We used the European Society for Medical Oncology (ESMO)-GROW (Guidelines for Reporting Oncology real-World evidence) checklist when writing our report.[9]

All clinicopathological data, tissue, and/or germline *BRCA* and homologous recombination deficiency (HRD) status were collected.

Patients were followed up during maintenance with physical examination, computed tomography (CT) scan, and cancer antigen 125 (CA 125) serum levels, each 6 months for 2-3 years.[10]

Platinum sensitivity was defined as recurrence after a time $\geq$6 months from the completion of primary platinum-based chemotherapy. RECIST1.1 criteria were used to mark the recurrence/progression. Every patient underwent a multidisciplinary discussion at tumor boards to define treatment strategy at recurrence. An [^{18}F]2-fluoro-2-deoxy-D-glucose positron emission tomography integrated with CT (18F-FDG—PET—CT) scan was required for all patients eligible for local treatments and for those in whom there were uncertainties on traditional CT scan findings.

The site of recurrence was classified according to the number of nodules, as discrete/oligometastatic ($\leq$5 nodules) or diffused (>5 nodules).[11]

Treatment modalities for a platinum-sensitive recurrence included (i) second-line chemotherapy alone and (ii) local treatment [either SCS or stereotactic radiotherapy (SBRT)]. All patients receiving local treatment were offered to continue maintenance treatment or to start a second-line chemotherapy, according to the ESMO-ESGO (European Society of Gynaecological Oncology)-ESP (European Society of Pathology) consensus conference.[12] No treatment was also an option based on patients' preference and conditions.

For cases in which SCS was deemed feasible at preoperative assessment, a diagnostic laparoscopy was carried out to exclude the presence of miliary carcinomatosis, followed by immediate secondary cytoreduction, according to the algorithm proposed by our institution.[13] For patients undergoing SCS, none of them received neoadjuvant chemotherapy before surgery.

Residual tumor was recorded at the end of surgery, and complete cytoreduction was defined as no visible residual disease.

Selected patients underwent stereotactic body radiotherapy, either because of lesion location or because they refused or were unfit for surgery. No PARPi discontinuation was required,[14] and PARPi maintenance could be continued until further progression of the disease. According to the target sites, the stereotactic body radiotherapy dose ranged between 25 Gy and 50 Gy delivered to all active metastatic lesions as per diagnostic imaging using a 5-day treatment schedule. Image-guided radiotherapy was used throughout all treatment fractions.

For patients undergoing follow-up after local treatments for recurrent disease under PARPi, traditional schedule consisted of a clinic visit at 4-month intervals for the first 2 years, at 6-month intervals for the next 3 years, and then annually. A general clinical and gynecological examination (including a transvaginal ultrasonographic scan) and measurement of CA 125 serum levels were carried out. Imaging diagnostics with CT scan were recommended at 6-month intervals for the first 3 years.

For survival analysis, we considered patients with progression/death at any time after recurrence diagnosis and women with at least 12 months of observation if they had no registered event. PFS was defined as the time elapsed between the last administration of first-line chemotherapy and the date of disease recurrence, progression, last follow-up, or patient's death, whichever comes first.

Statistical analysis

Statistical analysis was carried out using Statistical Package for Social Science software, Version 25, and R-Studio 0.98.1091 software. Chi-square or Fisher's exact test was used for the comparison of categorical items while differences in quantitative variables were assessed by the

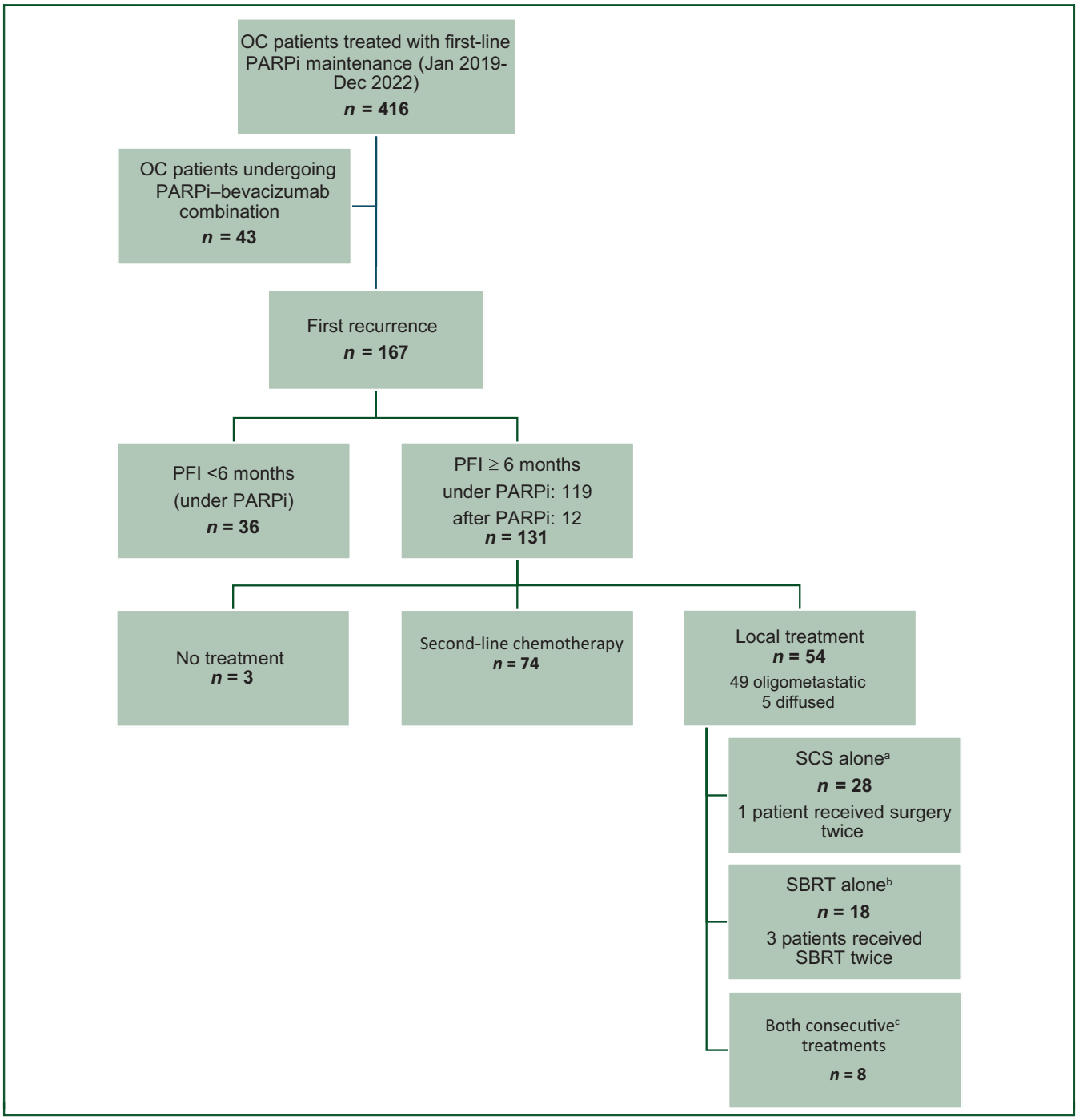

Figure 1. Flow chart of the patient population. Numbers refer to patients, not to treatments.
OC, ovarian cancer; PARPi, poly-ADP-ribose polymerase inhibitors; PFI, platinum-free interval; SBRT, stereotactic brachytherapy; SCS, secondary cytoreductive surgery.
[a]Two consecutive surgeries in one patient.
[b]Two consecutive SBRT in three patients.
[c]Surgery as the first approach followed by SBRT at subsequent recurrence in five patients; SBRT as the first approach followed by surgery at subsequent recurrence in three patients.

Mann–Whitney test. All *P* values reported are two-sided and a $P < 0.05$ was considered statistically significant. Medians and life tables were computed using the product limit estimate by the Kaplan–Meier method, and the log-rank test was used to assess statistical significance. Median follow-up time was calculated by the reverse Kaplan–Meier method. A logistic regression model in the recurrent subgroup was applied to identify factors associated with oligometastatic recurrence. We included in the analysis all clinicopathological variables that we considered potentially involved in determining an oligometastatic disease presentation at recurrence, including *BRCA* status. We used a Cox regression model in the entire population to identify prognostic factors associated with PFS. We included all factors deemed relevantly linked to influencing survival based on existing literature. For the

multivariate analysis, we incorporated factors with a *P* value below 0.100 and those considered clinically significant for the study.

RESULTS

We identified 416 patients who received first-line maintenance therapy with PARPi at our center in the study period. Among them, 43 patients received a combination therapy with olaparib and bevacizumab and were therefore excluded from the final analysis (Figure 1). The baseline characteristics of the entire population undergoing first-line PARPi treatment ($n = 373$) are presented in Table 1. More than half of the population carried a somatic or germline *BRCA* mutation (51.5%). Additionally, 28 out of 75 women tested were found HRD positive/*BRCA* wild-type (*BRCA-wt*) on their tumor tissue. Neoadjuvant chemotherapy was administered in 46.9% of cases, with an overall rate of complete cytoreduction of 89.5%.

At the date of April 2024, with a median follow-up of 38 months [95% confidence interval (CI) 36.1-39.9 months], 167 of 373 patients (44.8%) experienced a recurrence, and among them 69 patients died of disease (18.5%). One more patient died of other causes, without evidence of recurrence (0.3%). Most of the patients recurred during maintenance (155 of 167, 92.8%) (Figure 1); the PFS was <6 months in 36 patients (9.7%), between 6 and 12 months in 53 patients (14.2%), and ≥12 months for 78 patients (20.9%). Data on disease status since the last cycle of chemotherapy are shown in Figure 2.

Table 1. Baseline characteristics of patients treated with first-line PARPi maintenance treatment

Characteristics		Overall $N = 373$
Median age (years, range)		58.4 (35-86)
BRCA status, *n* (%)	*BRCAm*	192 (51.5)
	BRCA-wt/VUS	181 (48.5)
HRD status in *BRCA-wt* population,[a] *n* (%)	*BRCA-wt*-HRDpos	28 (15.5)
	BRCA-wt-HRDneg	47 (26.0)
	BRCA-wt-HRDunk	106 (58.6)
Stage at diagnosis, *n* (%)	III	272 (72.9)
	IV	101 (27.1)
Histology, *n* (%)	HGSC	365 (97.9)
	Non-HGSC	8 (2.1)
Residual tumor, *n* (%)	CGR	334 (89.5)
	No CGR	32 (8.6)
	Missing	7 (1.9)
Primary treatment, *n* (%)	PCS	198 (53.1)
	NACT	175 (46.9)
PARPi, *n* (%)	Olaparib	189 (50.7)
	Niraparib	146 (39.1)
	Rucaparib	38 (10.2)

BRCAm, *BRCA*-mutated; *BRCA-wt*, *BRCA* wild-type; CGR, complete gross resection; HGSC, high-grade serous cancer; HRD, homologous recombination deficiency; HRDneg, homologous recombination deficiency-test negative; HRDpos, homologous recombination deficiency-test positive; HRDunk, homologous recombination deficiency-test not carried out; NACT, neoadjuvant chemotherapy; PARPi, poly-ADP-ribose polymerase inhibitors; PCS, primary cytoreductive surgery; VUS, variant of unknown significance.
[a]HR test results were available for 75 patients at the time of the analysis.

Pattern of disease distribution and treatment at recurrence

Among 167 patients with disease recurrence, 75 patients (44.9%) experienced relapse with less than five lesions visualized on [^{18}F]-FDG—PET—CT, while 92 patients (55.1%) had recurrent disease with either five or more nodules or peritoneal carcinomatosis. Among *BRCA*-mutated (*BRCAm*) patients, 64.5% of recurrences presented as oligometastatic, whereas in the *BRCA-wt/VUS* (variant of uncertain significance) group, this percentage was 33.3% ($P < 0.001$). In logistic regression analysis for the risk of oligometastatic recurrence, patients with *BRCA* mutations were associated with a probability more than three times higher than patients without mutations to develop oligometastatic disease [hazard ratio (HR) 3.014, 95% CI 1.486-6.113, $P = 0.002$] (Table 2).

Among the 131 platinum-sensitive patients, only three (2.2%) did not undergo further treatment due to poor clinical conditions ($n = 2$) and patient's choice ($n = 1$). Second-line chemotherapy was the treatment of choice in 74 cases (56.6%), while 54 patients (41.2%) received local treatment (28 SCS and 18 SBRT) (Figure 1). Local treatment was repeated on subsequent recurrences during PARPi administration in 12 women: (i) 8 patients had consecutively both approaches (5 SCS first and then SBRT; 3 SBRT first and then SCS), and (ii) 4 patients repeated the same treatment (SBRT in 3 cases and secondary and tertiary cytoreduction in 1 patient). Therefore, 54 patients treated with local approaches received a total number of 37 surgeries and 29 radiotherapies at the time of their recurrences.

A complete gross resection (CGR) of recurrent disease was achieved in all patients selected for SCS.

Overall, the administration of PARPi was continued in 53.7% of patients who received local treatment for oligometastatic disease. Following local treatment, patients in the surgery group more frequently received second-line adjuvant chemotherapy (61.3%) and, to a lesser extent, prolonged PARPi therapy (38.7%). In contrast, none of the patients treated with radiotherapy received adjuvant chemotherapy; however, prolonged PARPi administration was adopted in 73.9% of these cases, while 26.1% were managed with active surveillance (Table 3).

The median duration of extended PARPi administration was ∼7 months (95% CI 3.7-10.3 months), 8 months (95% CI 4.4-11.6 months) for the radiotherapy group and 7 months (95% CI 3.0-11.1 months), for the surgery group, $P = 0.963$.

One-third of the patients with oligometastatic disease were approached by minimally invasive surgery. Details on treatments and surgical modalities for oligometastatic recurrent patients are reported in Table 3.

The 36 platinum-resistant patients were mainly treated with second-line chemotherapy ($n = 30$), whereas a local treatment was offered in five cases: three patients received a secondary cytoreduction and two were treated with radiotherapy.

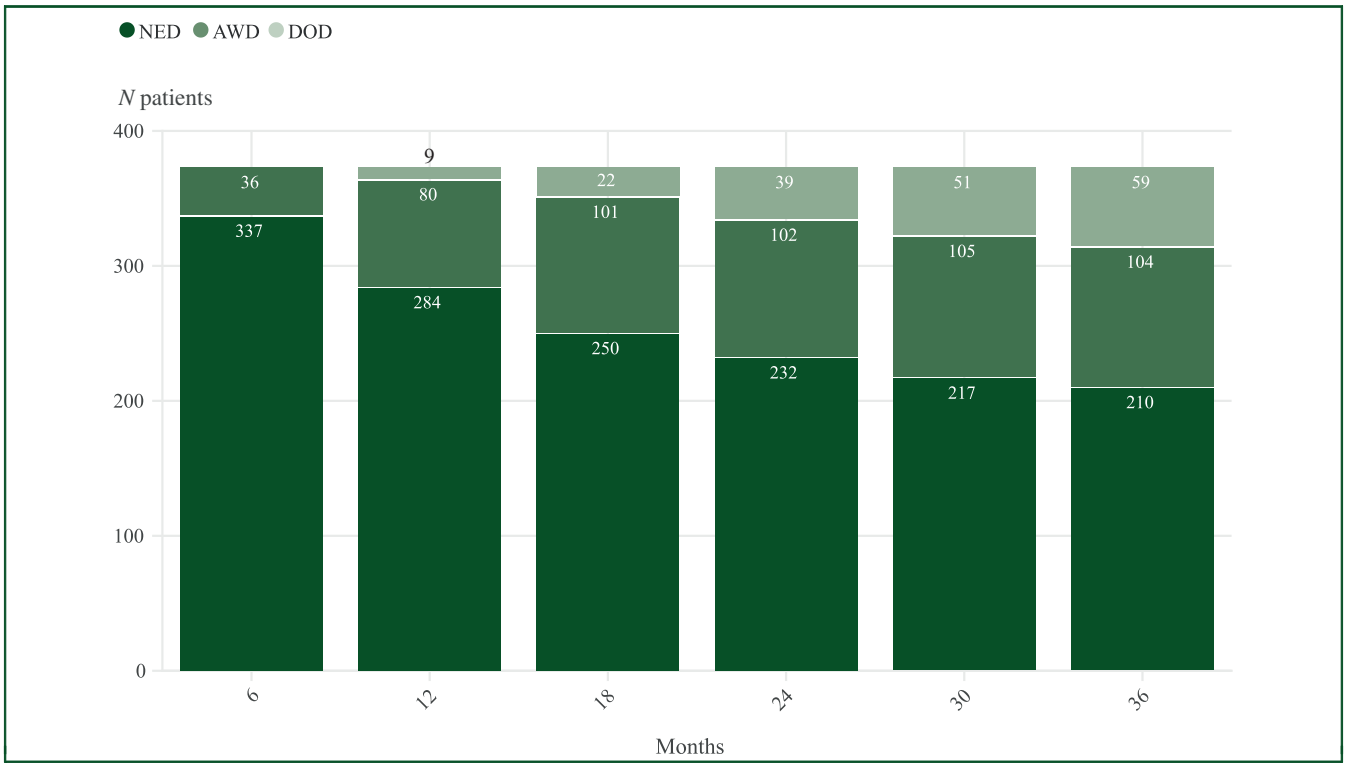

Figure 2. Data on disease status since the last cycle of chemotherapy.
AWD, alive with disease; DOD, dead of disease, NED, non-evidence of disease.

Survival analysis

The median PFS in the overall population was 39 months (95% CI 27.5-50.5 months) (Supplementary Figure S1A and B, available at https://doi.org/10.1016/j.esmoop.2024.104119).

We also observed that patients with an oligometastatic pattern of recurrence tended to experience later recurrences (median PFS 13 months, 95% CI 10.2-15.8 months, for the oligometastatic group versus 9 months, 95% CI 7.3-10.7 months, for the diffuse group, $P = 0.004$)

Table 2. Logistic regression for oligometastatic pattern of recurrence

	Univariate HR (95% CI)	*P*	Multivariate HR (95% CI)	*P*
BRCA status				
BRCA-wt/VUS	1			
BRCAm	3.636 (1.880-7.034)	**<0.001**	3.014 (1.486-6.113)	**0.002**
Histotype				
HGSC	1			
Non-HGSC	1.233 (0.170-8.966)	0.836		
Primary treatment				
PCS	1			
NACT	0.735 (0.396-1.362)	0.328		
Residual tumor				
CGR	1			
No CGR	0.896 (0.272-2.949)	0.856		
Stage at diagnosis				
III	1			
IV	0.902 (0.464-1.751)	0.760		
Platinum-free interval, months				
<6	0.386 (0.169-0.882)	**0.024**	0.567 (0.235-1.365)	0.205
6-11	0.432 (0.211-0.885)	**0.022**	0.642 (0.295-1.396)	0.263
>12	1			
CA 125 serum levels at recurrence (UI/ml)				
<35	1			
>35	0.783 (0.398-1.544)	0.481		

P-values < 0.05 are highlighted in bold.
BRCAm, *BRCA*-mutated; *BRCA-wt*, *BRCA* wild-type; CA 125, cancer antigen 125; CI, confidence interval; CGR, complete gross resection; HGSC, high-grade serous cancer; HR, hazard ratio; NACT, neoadjuvant chemotherapy; PCS, primary cytoreductive surgery; VUS, variant of unknown significance.

Table 3. Disease location of oligometastatic recurrences according to the treatment strategy

Disease location	All	Local treatment		Systemic treatment
		SCS	SBRT	
	$N = 75$[a]	$n = 31$[b]	$n = 23$[c]	$n = 20$
Lymph nodes, *n* (%)	32 (42.7)	MIS 3 (30) Open 8 (38.1)	16 (69.6)	5 (25.0)
Peritoneum, *n* (%)	21 (28.0)	MIS 5 (50) Open 7 (33.3)	2 (8.7)	7 (35.0)
Mixed + other sites,[d] *n* (%)	22 (29.3)	MIS 2 (20) Open 6 (28.6)	5 (21.7)	8 (40.0)
PARPi prolongation	29 (53.7)[e]	12 (38.7)	17 (73.9)	0 (0)

MIS, minimally invasive surgery; PARPi, poly-ADP-ribose polymerase inhibitors; SBRT, stereotactic brachytherapy; SCS, secondary cytoreductive surgery.
[a]One patient (mixed + other site group) did not receive any further treatment.
[b]Five patients received radiotherapy after surgery on subsequent recurrence.
[c]Three patients received surgery after radiotherapy on subsequent recurrence.
[d]Brain, chest, liver, abdominal wall.
[e]Percentage is calculated on patients receiving local treatment ($n = 54$).

(Supplementary Figure S1C, available at https://doi.org/10.1016/j.esmoop.2024.104119).

At multivariate analysis, *BRCA* mutation (HR 0.362, 95% CI 0.263-0.498, $P < 0.001$), FIGO stage III (HR 1.467, 95% CI 1.053-2.044, $P = 0.023$), and primary cytoreductive surgery (HR 2.014, 95% CI 1.477-2.745, $P < 0.001$) retained their favorable prognostic value for prolonged PFS (Supplementary Table S1).

DISCUSSION

Summary of main results

In this paper, we describe the course of advanced ovarian cancer patients undergoing PARPi administration at first-line treatment in a real-word setting. Women were treated according to the local European regulatory system and decisions were taken at the local tumor board. All data have been prospectively registered, randomly quality-checked, and maintained in our hospital database and therefore, they represent an accurate source of information for a glimpse of reality, where different options can be offered to each single patient.

Results in the context of the literature

A 93.2% rate of oligometastatic progression was reported by Kamrava et al.[15] in a subgroup analysis of the PRIMA study, which is much higher than our 45%. However, differently from our study, only patients with a complete response to therapy at the end of the treatment were selected in the subgroup analysis from the PRIMA trial. Given the high rate of incomplete cytoreduction (47%), this method may have selected a more platinum-sensitive population with a different propensity to develop oligometastatic disease.

All other data available on recurrence patterns during PARPi treatment demonstrated lower rates of oligoprogression (16%-34%), though these findings are limited by the inclusion of patients treated with PARPi beyond the first-line setting.[7,16-19]

Also, the pattern of oligometastatic disease is different from the one reported by Kamrava et al., with a higher rate of lymph nodal disease in our series, which can be explained with our 90% CGR without lymphadenectomy.[20,21]

In the present series, *BRCAm* patients showed three-times higher chances of oligometastatic recurrence than *BRCA-wt*. A better control by PARPi in tumors with HRD could explain a greater tendency to develop isolated resistant clones that manifest as oligoprogressive recurrence. This finding partially contrasts with the report by Kamrava et al., which does not show differences in disease distribution based on *BRCA* status but indicates a lower number of lesions in HRD-positive patients.[15] Again, the different selection of patients, with a much lower number of *BRCAm* patients (33.1% versus 51.1%), and the different number of patients tested for HRD in the two studies may partially explain this discrepancy.

In line with the most recent trends,[14,16] we demonstrate that almost 40% of platinum-sensitive recurrent patients may be treated with local treatment and around 54% of them may continue their PARPi maintenance. As in other series,[17] radiotherapy has been primarily chosen to manage nodal disease (69.6%), while surgery was more commonly indicated for cases with peritoneal and parenchymal disease (64.5%). Of note, this is the first report of minimally invasive surgery in 10 patients with recurrence under PARPi maintenance. Also, we report a 24% repeated local treatment. The survival benefit of this approach still needs to be confirmed, but due to the short follow-up and low number in our series it is beyond the purpose of this study.

The 69.3% PFS at 3 years observed in our *BRCAm* population aligns with the 60% PFS observed in the experimental arm of the SOLO-1 trial, but it is higher than 47% and 50% reported in the PRIMA and VELIA studies,[22-24] respectively. Similarly, the 2-year PFS of 77.6% in the same population is higher than 68% and 60% observed in the ATHENA-MONO and PRIME trials, respectively.[4,25]

The 3-year PFS rate in the *BRCAm* population compared with the SOLO-1 study is particularly valuable considering the higher rates of neoadjuvant chemotherapy administered (46.9% versus 36%) and of FIGO stage IV (27.1% versus 15%)[26] in our study, and can be explained by the high rate of complete cytoreductions.

The high percentage of *BRCAm* patients presented in this study is related to the higher prevalence of *BRCA* mutation in the Italian population[27] and the national prescription regulations, as olaparib has been licensed since 2019 for *BRCAm* patients only, while niraparib since 2020 for all patients.

No detailed data on HRD-positive/*BRCA-wt* and HRD-negative populations can be shown in our study due to the lack of testing in almost half of the remaining patients and short follow-up time.

Another finding in our study is the rate of ~10% of platinum-resistant patients, which is significantly reduced compared with the pre-PARPi era, as reported in a multicenter European real-world study on 1119 patients, with a platinum-resistant recurrence rate of 28.1%.[7] Again, our

result is consistent with data from randomized trials on PARPi where the rate of early recurrences/progressions ranges from 5% to 25% in the experimental arm, according to *BRCA* and HRD status.[22]

Strengths and weaknesses

There are several limitations to acknowledge in this study. Firstly, its retrospective nature and the sample size may have led to selection biases and reduced statistical power. The absence of the HRD test, routinely carried out for advanced ovarian tumors at our institution only since 2022, prevented us from stratifying the *BRCA-wt* population based on HR status. Despite this, our findings appear consistent with those reported in principal randomized clinical trials currently available.

Given the relatively short follow-up period, analysis of post-recurrence survival was not included in this study. The relatively limited follow-up may have selected a subset of the population with early recurrence after PARPi treatment, which might not be representative of the entire population. Lastly, this study focused on PARPi monotherapy, excluding patients on combination therapy with bevacizumab to maintain data homogeneity. The limited sample size for combination therapy ($n = 43$) further supported this choice.

However, this is the largest study conducted at a single tertiary reference center to describe a real-life scenario of the efficacy of PARPi in the frontline setting and the characteristics of 'post-PARPi' recurrence. Because of this, we can offer specific insights on the type of treatment following recurrence.

Implications for practice and future research

There are still some unanswered questions that need to be addressed in the ovarian cancer population under maintenance treatment. We do not know whether (i) there is a positive impact of prolongation of platinum-free interval throughout the removal of oligometastatic disease on subsequent treatment; (ii) there is an option for different follow-up strategies in different group categories (i.e. *BRCAm* patients); or (iii) there is a difference in terms of the pattern of recurrence for patients undergoing combination of PARPi and bevacizumab.

Finally, results from new surgical and SBRT trials including patients undergoing PARPi maintenance (i.e. KGOG 3067/SOCCER-P trial, MITO RT3/RAD, SOPRANO trial[28-30]) are awaited.

Conclusions

Our study demonstrates that data from randomized trials on PARPi maintenance in the first-line setting are applicable to the real-world setting in a similar fashion. The analysis of these data aims not to replace the results of a randomized trial but to provide a different perspective, unrestricted by stringent inclusion criteria, offering clinicians practical prognostic insights applicable to the daily clinical setting.

In these patients, we expect 45% recurrences at 3 years, mainly under PARPi treatment, of which 10% are platinum-resistant tumors.

Forty-five percent of the patients will have an oligometastatic recurrence, mainly located in the lymph nodes, and can receive local treatment (either SCS or SBRT) in 40% of the cases. One-third can undergo successful minimally invasive surgery. *BRCA* status is one of the strongest determinants of oligometastatic disease.

ACKNOWLEDGEMENTS

Authors would like to acknowledge the Italian Ministry of Health - Ricerca Corrente 2025.

FUNDING

None declared.

DISCLOSURE

CM received funding from Clovis, PharmaMar, GSK, AstraZeneca, MSD, Roche. VS received funding from AstraZeneca, Novocure, GSK, MSD, PharmaMar. GS received funding from Merck, Clovis, Roche, Novartis, Immunomedics, Tesaro, Myriad, Amgen, Seagen, ECS PROGASTRIN, LEK, Daiichi Sankyo Europe GmbH, Bayer, Eisai, Covidien, AstraZeneca, MSD, Olympus, Baxter, Intuitive, GSK. AF received funding from AstraZeneca, PharmaMar, GSK, Johnson&Johnson, Menarini, AstraZeneca, MSD. All other authors have declared no conflicts of interest.

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