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ORIGINAL RESEARCH

Management and Clinical Outcomes of Patients with Advanced Ovarian Cancer in Routine Clinical Practice in Spain: The OVOC Study

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ABSTRACT

***Introduction*:** The OVOC study was carried out to evaluate the management and clinical evolution of patients with advanced ovarian cancer (AOC) in routine clinical practice in Spain.

***Methods*:** A retrospective study was made in women diagnosed with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer (FIGO IIIB-IV) who had received at least one line of treatment between 2013 and 2016, before the establishment of poly ADP ribose polymerase (PARP) inhibitors as first-line treatment.
***Results*:** A total of 400 patients (median age: 61.7 years; FIGO IIIC: 60.0%; high-grade serous carcinoma: 75.0%) received a median of two therapy lines. Primary and interval debulking surgery was performed in 37.0% and 54.3% of the patients. Germline *BRCA1* and *BRCA2* mutations were found in 16.2% and 12.0% of the patients. The median progression-free survival

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(PFS) from the start of the first-/second-/third-line of treatment was 14.2/8.7/4.5 months. The median treatment-free interval (TFI) to the start of the second line was 9.9 months. The median overall survival (OS) was 42.6 months. At first relapse, 65.9% of the patients were platinum-sensitive and 34.1% platinum-resistant. Biologic therapies were administered in 25.2% of the platinum-sensitive and 16.2% of the platinum-resistant patients. Patients harboring *BRCA* mutations had a lower risk of progression/relapse after the first (*BRCA1* and *BRCA2* mutation versus native: $p<0.0001$) and second line (*BRCA1* and *BRCA2* mutation versus native: $p=0.021$ and $p=0.037$, respectively). Patients with *BRCA2* mutations had a lower mortality risk than those without ($p=0.015$). The median PFS was significantly higher in patients receiving targeted therapy in the first (17.4 versus 11.6 months; $p=0.039$) and second line (11.1 versus 7.8 months; $p<0.001$).

***Conclusion*:** This study provides real-world data on therapeutic management and outcomes in AOC patients in Spain. A longer PFS was achieved in patients receiving targeted therapies. *BRCA1/2* mutations were a favorable prognostic factor for PFS and *BRCA2* mutation for OS.

Keywords: Advanced ovarian cancer; Treatment patterns; Clinical outcomes; Biologic therapies

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Key Summary Points

Why carry out this study?

Patients with advanced ovarian cancer are at a high risk for disease progression or death.

Understanding real-world clinical treatment strategies, their evolution, and their associated outcomes in patients with advanced ovarian cancer is crucial to adopt optimal treatment decisions.

What was learned from the study

The study found neoadjuvant chemotherapy as well as platinum-based chemotherapy following primary debulking surgery as the most common first-line treatments, with platinum-based chemotherapy as the cornerstone second-line treatment. Targeted therapies were used in around a third of patients in first-line settings and a quarter in the second-line in real-world clinical practice between 2013 and 2016.

Patients receiving targeted therapy in both the first-line setting and after first relapse experienced a significantly longer progression-free survival (PFS), confirming, in real-world practice, the benefit of incorporating targeted therapies into treatment strategies.

The study suggests the importance of BRCA mutation status in the selection of therapy and predicting patient outcomes, as indicated in current clinical guidelines. *BRCA* mutations were associated with a longer PFS and overall survival (OS), reinforcing the need for *BRCA* testing to guide treatment decisions.

INTRODUCTION

Ovarian cancer (OC) constitutes the leading cause of death from gynecologic malignancies in developed countries [1]. The reasons behind the high mortality are related to the late-stage

presentation of the disease, occurring in nearly 80% of the patients [2].

The traditional standard of care for the first-line treatment of advanced OC (AOC) has been the combination of primary debulking surgery (PDS) with adjuvant chemotherapy based on platinum and taxanes [3, 4]. In patients with AOC who are not candidates for PDS because of advanced age, frailty, compromised performance status, or comorbidities, or who have a low likelihood of achieving complete cytoreduction, neoadjuvant chemotherapy (NAC) preceding interval debulking surgery (IDS) has been recommended [3–7].

Despite notable improvements in surgery procedures and the optimized use of available agents, approximately 70–80% of all patients with AOC experience disease recurrence [8–12]. Following recurrence, the patients are rarely cured [13, 14]. This recurrence is primarily attributed to the development of chemotherapy resistance [15]. Traditionally, the selection of successive lines of treatment has arbitrarily relied on the length of the platinum-free interval (PFI) [3, 16]. According to the latest recommendations, treatment selection should consider tumor-associated characteristics and individual patient-related factors such as clinicopathologic parameters, the nature and severity of symptoms, performance status, molecular results, the type and number of previously administered treatments, or the presence of residual toxicities [3, 4, 17].

In the last decade, alongside the initiation of this study, newly developed targeted drugs, such as the antiangiogenic monoclonal antibody bevacizumab or the Poly ADP ribose polymerase (PARP) inhibitors, have emerged as promising treatment options in all phases of the disease. Bevacizumab in combination with chemotherapy has demonstrated its efficacy in improving progression-free survival (PFS) in different phase III clinical trials in treatment-naïve, recurrent platinum-sensitive, and platinum-resistant patients with AOC [18–20]. Consequently, the latest clinical guidelines have incorporated bevacizumab-containing regimens as viable options across all lines of treatment [3, 4], underscoring the therapeutic significance attributed to this antiangiogenic agent. In parallel, PARP inhibitors have emerged as effective maintenance therapy in first-line [21, 22] and recurrence settings in all patients with OC, especially in those harboring mutations in the *BRCA1/2* genes [23].

The expansion of treatment options has increased the intricacy of managing this heterogeneous condition. Thus, there is no single best treatment algorithm, and a considerable variation in treatment patterns is recognized based on the disease characteristics and the patient preferences [17].

The present retrospective observational study sought to describe real-world treatment strategies and the factors associated with treatment selection and clinical outcomes in patients with AOC in Spain between 2013 and 2016. When the study started, bevacizumab was the only targeted therapy available for clinical use in OC (approved in Europe in December 2011), and some uncertainties about its use were under discussion, including dose selection, the optimal duration of treatment, and its role in second-line treatment [24]. In addition, PARP inhibitors were approved in Europe in 2014. The OVOC study aimed to describe the evolving landscape of AOC management during the incorporation of targeted therapies into the clinical practice, considering the multifaceted aspects that influence therapeutic decision-making in clinical practice.

METHODS

Study Design and Patients

The OVOC was a multicenter, retrospective observational study conducted at 27 Spanish hospitals. Hospitals were selected to ensure adequate patient volume for recruitment and broad geographical representation across Spain. Eligible patients were women aged ≥ 18 years and diagnosed with advanced (FIGO [Fédération Internationale de Gynécologie et d'Obstétrique] stage IIIB, IIIC, and IV) epithelial ovarian, fallopian tube, or peritoneal cancer between 1 January 2013 and 31 December 2016, who had

received at least one line of treatment for the management of their advanced disease. Patients with any medical or psychologic condition compromising their ability to understand and voluntarily sign the consent (in the case of alive patients) were excluded. Written informed consent was obtained from all patients before their inclusion in the study. The present study identified with the code ML40141 was approved by the Ethics Committee of Hospital Universitari Doctor Josep Trueta de Girona in Spain during the meeting held on 17 July 2018. The study was performed following the Declaration of Helsinki (1964 and its later amendments).

Study Endpoints

The primary objective of the OVOC study was to describe treatment strategies received by line of therapy in patients with AOC between 2013 and 2016 in a real-world setting in Spain. For this purpose, treatment strategies (including type, setting, and schedule) used for AOC management in the first, second, and later lines of treatment received from recurrence, progression, or treatment discontinuation for any reason until death, loss to follow-up, or study initiation, whichever came first, were assessed. Secondary endpoints included factors associated with treatment selection, clinical outcomes in terms of PFS, treatment-free interval (TFI), PFI, and overall survival (OS), prognostic factors associated with PFS and OS, the proportion of patients with platinum-sensitive or platinum-resistant disease, treatment strategies used in each subgroup, and associated clinical outcomes in the first line and after first recurrence.

Platinum-sensitive patients were defined as those who responded to first-line platinum treatment (complete response [CR] or partial response [PR]) and had PFI ≥ 6 months. Patients who relapsed within 6 months after the last platinum treatment were classified as platinum-resistant. Those relapsing within 4 weeks after the last platinum treatment were considered platinum-refractory patients.

In this study, molecularly targeted therapies refer to antiangiogenic agents (such as bevacizumab) and PARP inhibitors (such as olaparib, niraparib, and rucaparib).

Statistical Analysis

A descriptive statistical analysis was performed to describe treatment strategies used for AOC management under real-world conditions in Spain. Measures of central tendency and dispersion (mean ± standard deviation [SD], median, and interquartile range [IQR]) were used to describe quantitative variables and counts, and percentages were calculated to report qualitative variables. Exploratory subgroup analyses were performed comparing categorical variables using the chi-squared or the Fischer exact test, as applicable. Continuous variables that did not follow a parametric distribution were compared using the Mann-Whitney *U*-test.

Time-to-event variables were estimated using the Kaplan-Meier method. Median PFS and OS and 95% confidence intervals (CI) were calculated. Differences between treatment groups were compared with an exploratory subgroup analysis using the stratified log-rank test. The probability of PFS and OS were estimated using the Kaplan-Meier method. PFS was defined as the time from the start of the first-, second-, or third-line treatment to disease progression, recurrence, relapse, or patient death. TFI was the time between the end of the first treatment and the start of a second-line therapy. PFI was calculated as the time elapsed between the last cycle of platinum-based treatment in the first-line setting and the evidence of disease progression, relapse or recurrence, or the start of a new regimen. OS was measured from AOC diagnosis to death for any reason. Although it was not initially planned in the study protocol, the tumor response according to RECIST to first-, second-, and third-line treatment was also evaluated.

A multivariate logistic regression analysis was performed to identify independent factors associated with the most frequent (> 15%) treatment strategies used in the first and the second line. Odds ratio and 95% CI were calculated. The covariates assessed as potential

factors associated with first- and second-line treatment strategy were age at diagnosis, year of diagnosis, Eastern Cooperative Oncology Group (ECOG) performance status at diagnosis, symptoms of disease, FIGO stage, histology, histologic grade, germline *BRCA* mutational status at diagnosis, surgical outcome, TFI, and PFI. A multivariate COX regression analysis was performed to determine potential prognostic factors associated with PFS in the first- and the second-line setting and OS. Variables with a statistical significance $p<0.2$ in the univariate model were analyzed in a multivariate model with stepwise selection. Hazard ratio and 95% CI were calculated. The covariates assessed as potential factors were age, ECOG performance status at diagnosis, FIGO stage, histology, histologic grade, germline *BRCA* mutational status, surgical outcome, type of surgery, response to prior line of treatment (RECIST criteria), and TFI.

The Statistical Package for the Social Sciences (SPSS) software (v22.0) was used to carry out the data analyses.

RESULTS

Patient Sociodemographic and Clinical Characteristics

Between December 2018 and June 2019, a total of 406 women diagnosed with AOC from 2013 to 2016 were included in the study. The evaluable population comprised a total of 400 patients. The clinical and sociodemographic characteristics of the patients are shown in Table 1.

Treatment Strategies and Factors Associated with Treatment Selection

The patients received a median of two (quartile [Q]1–Q3: 1–3) lines of treatment for their advanced disease: 32.8% ($n=131$) were treated with only one line of treatment, while 24.0% ($n=96$), 18.3% ($n=73$), and 23.8% ($n=95$) received two, three, and four or more treatment lines, respectively.

Most patients underwent surgery ($n=338$, 84.5%); PDS was performed in 148 (37.0%) patients and IDS in 217 (54.3%). Surgery-related data are shown in Table S1. A total of 187 (47.8%) patients had completed neoadjuvant treatment, which was based on platinum in 182 patients (97.3%) and contained bevacizumab in 26 (13.9%) patients. Neoadjuvant treatment strategies are shown in Table S2.

The most frequent regimens used by line of therapy are detailed in Table 2 and Table S3. As first-line therapy, most patients received platinum-based chemotherapy ($n=377$, 95.7%). The most frequent regimens were neoadjuvant chemotherapy (39.5% of the patients) and platinum-based chemotherapy following PDS (24.0%). Platinum-based chemotherapy was the prevailing second-line treatment strategy (37.0% of the patients). Chemotherapy combined with bevacizumab was administered as a second-line treatment to 17.4% of the patients with recurrent disease.

Multivariate logistic regression analysis identified independent factors associated with the most frequent treatment strategies and is detailed in Table 3. Patients with a longer TFI were more likely to have received platinum-based chemotherapy following PDS as first-line therapy. FIGO stage IIIC, IVA, and IVB at diagnosis were independent factors for selecting neoadjuvant chemotherapy. Individuals harboring mutated *BRCA1* were less prone to receive platinum-based chemotherapy without targeted agents as their second-line treatment, while a higher likelihood of receiving this therapy was observed in patients with an extended PFI.

Clinical Outcomes and Prognostic Factors

The median PFS since first-, second-, and third-line treatment initiation was 14.2 (95% CI: 12.6–15.8), 8.7 (95% CI: 7.7–9.7), and 4.5 (95% CI: 3.8–5.3) months, respectively (Fig. 1). The median TFI was 9.9 (95% CI: 7.9–11.9) months, the median PFI was 10.9 (95% CI: 9.5–12.3), and the median OS was 42.6 (95%

Table 1 Patient sociodemographic and clinical characteristics at diagnosis

	Value
Patient characteristics	
Age (years), median (Q1–Q3)	61.7 (53.8–70.0)
Race, *n* (%)	
White	393 (98.3)
Black	1 (0.3)
Asian	1 (0.3)
Hispanic	2 (0.5)
Time from diagnosis to study inclusion (*n* = 156) (years), median (Q1–Q3)	4.0 (3.2–5.0)
Comorbidities[a], *n* (%)	234 (58.5)
Cardiovascular disease	133 (56.8)
Endocrine disorder	116 (49.6)
Neurologic/psychiatric disorder	62 (26.5)
Symptoms[a], *n* (%)	340 (85.0)
Abdominal pain	228 (67.1)
Bloating	94 (27.6)
Fatigue	52 (15.3)
Personal/family history of breast cancer (*n* = 387/374)	20 (5.2)/96 (25.7)
Family history of ovarian cancer (*n* = 367)	38 (10.4)
ECOG performance status (*n* = 311)	
0–1	268 (86.2)
2	36 (11.6)
≥ 3	7 (2.3)
Data related to ovarian cancer	
FIGO staging at diagnosis, *n* (%) (*n* = 395)	
IIIB	45 (11.4)
IIIC	237 (60.0)
IVA	72 (18.2)
IVB	41 (10.4)
Primary tumor site, *n* (%)	
Ovary	350 (87.5)
Peritoneum	35 (8.8)
Fallopian tube	10 (2.5)
Tumor histology[b], *n* (%)	
High-grade serous carcinoma	300 (75.0)
Clear cell carcinoma	20 (5.0)
Endometrioid carcinoma	16 (4.0)
Adenocarcinoma	14 (3.5)
Low-grade serous carcinoma	12 (3.0)
Mucinous carcinoma	8 (2.0)
Other	53 (13.3)
Metastatic disease[c], *n* (%)	375 (93.8)
Visceral metastases, *n* (%)	83 (20.8)
Liver[d]	37 (44.6)
Lung[d]	24 (28.9)
Non-visceral metastases, *n* (%)	353 (88.3)
Peritoneum[e]	307 (87.0)
Lymph nodes[e]	139 (39.4)
Pleura[e]	67 (19.0)
Germline *BRCA* testing, *n* (%)	216 (54.0)
BRCA wild type[f]	143 (66.2)
BRCA1 mutated[f]	35 (16.2)
BRCA2 mutated[f]	26 (12.0)
Result not available[f]	12 (5.6)

BRCA Breast Cancer Associated genes, *ECOG* Eastern Cooperative Oncology Group, *FIGO* Fédération Internationale de Gynécologie et d'Obstétrique, *Q* quartile. [a]Comorbidities or symptoms in > 15% of patients. [b]Multiple response option, patients may have more than one histologic type. [c]Metastases in > 20% of patients with metastatic disease. [d]*n* = 83. [e]*n* = 353. [f]*n* = 216

CI: 38.1–47.1) months. A total of 236 (59.0%) patients had already died at study initiation,

mainly because of disease progression (89.0%, $n=210$), and 156 (39.0%) were alive.

Multivariate Cox regression analysis identified that patients with an ECOG performance status of 1 or 2 were at higher risk of progression in the first-line setting, and upfront surgery reduced the risk of progression (Table 4). The absence of complete response to first-line treatment was associated with an increased risk of progression after second-line treatment. Progression was less likely to happen in patients harboring *BRCA1* and *BRCA2* mutations at diagnosis, after both first- and second-line treatment.

Patients with FIGO stage IVA and IVB at diagnosis and patients with platinum-resistant disease were significantly associated with a higher risk of death. The presence of mutated *BRCA2* at diagnosis was associated with increased OS (Table 4).

According to the RECIST, CR was achieved by 40.4% and 14.0% of the patients in the first and second line, while 5.4% obtained a CR in the third-line setting. Progressive disease (PD) occurred in 9.6% of the patients receiving first-line treatment, while 21.9% and 36.5% had PD after the second and third lines of treatment (Fig. S1). Among patients for whom radiologic tumor response to neoadjuvant treatment was available ($n=173$), 81.3% achieved PR, and 5.3% reached CR.

Platinum Resistance

Among the patients with disease progression after response (CR or PR) to first-line treatment ($n=299$), 197 (65.9%) patients had platinum-sensitive OC and 102 (34.1%) platinum-resistant OC (42 [41.2%] had platinum-refractory disease). Treatment patterns and outcomes of platinum-sensitive and platinum-resistant patients are described in Table S4. Of note, platinum-based chemotherapy was administered as a second-line treatment strategy to 50.4% of platinum-sensitive patients and 13.5% of platinum-resistant ($p<0.001$). Of the latest, 60.0% achieved stable disease, 20.0% PR, and 10.0% CR, and 10.0% progressed after second-line treatment.

Use of Targeted Therapies and Outcomes

Regimens based on targeted agents were administered to 33.8% of the patients in the first-line setting, with bevacizumab being used in 30.9% (Table S2).

Targeted agents were administered to 26.0% of the patients in the second-line setting; 25.2% of the patients with platinum-sensitive, 25.0% with platinum-refractory, and 16.2% with platinum-resistant disease received targeted therapy in the second-line setting (Tables S2 and S4). Bevacizumab was used in 18.0% of the patients in second-line. The use of targeted-based therapies as second-line treatment was significantly associated with the mutational status of *BRCA* genes; 47.6% of the patients with platinum-sensitive disease and with mutated *BRCA* gene (*BRCA1* mutated: 50.0%; *BRCA2* mutated: 42.9%) were treated with targeted agents compared to 16.9% of the patients with wild-type *BRCA* ($p=0.008$).

In the third-line setting, targeted-based regimens were used in 14 (19.4%) platinum-sensitive and 6 (28.6%) platinum-refractory patients.

PFS of the patients who received targeted therapy as first-line treatment (17.4 [95% CI: 15.1–19.7] months) was significantly longer than in those patients who did not receive first-line targeted treatment (11.5 [95% CI: 9.9–13.2] months; $p=0.039$) (Fig. 1). The median PFS since second-line treatment was 11.1 (95% CI: 9.3–12.9) months in patients receiving targeted therapy in the second-line setting versus 7.8 (95% CI: 6.1–9.4) months in patients who did not receive targeted therapy as second-line treatment ($p<0.001$).

DISCUSSION

The present study provides a comprehensive analysis of the clinical characteristics, treatment patterns, and outcomes in a cohort of 400 evaluable women with AOC in Spain between 2013 and 2016. The findings shed light on several aspects of ovarian cancer management,

Table 2 First- and second-line treatment strategies

	N (%)
First-line treatment strategies	
PDS followed by platinum-based chemotherapy[(a)]	96 (24.0)
PDS followed by targeted agents plus any chemotherapy	46 (11.5)
Platinum-based chemotherapy[(b)]	49 (12.3)
Targeted agents plus any chemotherapy[(c)]	19 (4.8)
Neoadjuvant chemotherapy[(d)]	158 (39.5)
Neoadjuvant targeted agents	29 (7.2)
Second-line treatment strategies	
Platinum-based chemotherapy[(e)]	98 (37.0)
Chemotherapy plus bevacizumab	46 (17.4)
Chemotherapy followed by any PARP inhibitor[(f)]	16 (6.0)

PDS primary debulking surgery, *PARP* Poly ADP ribose polymerase. [(a)]Patients treated with targeted agents as first-line treatment are excluded; [(b)]patients who underwent upfront surgery or received neoadjuvant treatment or targeted agents as first-line treatment are excluded; [(c)]patients who underwent upfront surgery or received neoadjuvant treatment are excluded; [(d)]patients who received targeted agents as neoadjuvant treatment are excluded; [(e)]patients who underwent surgery after the first-line treatment or received targeted agents as second-line treatment are excluded; [(f)]PARP inhibitors: olaparib, rucaparib, or niraparib

including surgery, neoadjuvant therapy, treatment selection factors, clinical outcomes, and the incorporation of targeted therapies into clinical practice at the time when these patients underwent ovarian cancer treatment.

While most patients with AOC achieve remission with first-line treatment, AOC recurs in 70–85% of all patients [3, 8–12]. Although the patients are rarely cured after recurrence, successive lines of therapies can provide significant clinical responses [13, 14]. In this study, patients with AOC received a median of two lines of treatment. Thus, this cohort did not undergo extensive therapeutic interventions.

The standard front-line treatment for OAC has traditionally involved cytoreductive surgery, aiming for no residual disease (R0), followed by platinum-based chemotherapy. In this study, 24.0% of the patients received cytoreductive surgery followed by platinum-based chemotherapy as first-line treatment, aligning with the prevailing standard for advanced disease treatment at the start of the treatments in this study. Interestingly, those receiving this regimen were more likely to exhibit extended TFI, reaffirming this strategy as the standard of care. However, a potential bias due to the selection of fitter patients for this approach cannot be ruled out.

Additionally, our observations revealed that 39.5% of the patients received IDS combined with NAC, which serves as an alternative treatment strategy for individuals who may not be suitable candidates for PDS [3, 4]. Accordingly, patients presenting a more aggressive FIGO stage (IIIC, IVA, and IVB) at diagnosis were more likely to receive NAC in the first-line treatment.

The results from this study indicate that most of the patients received surgery (84.5%) and platinum-based chemotherapy (95.7%) during first-line treatment, as previously reported in real-world retrospective studies conducted in the USA, France, Italy, Germany, UK, Spain, Greece, Canada, Portugal, South Korea, and Romania in patients diagnosed with AOC between 2012 and 2019 [25–30].

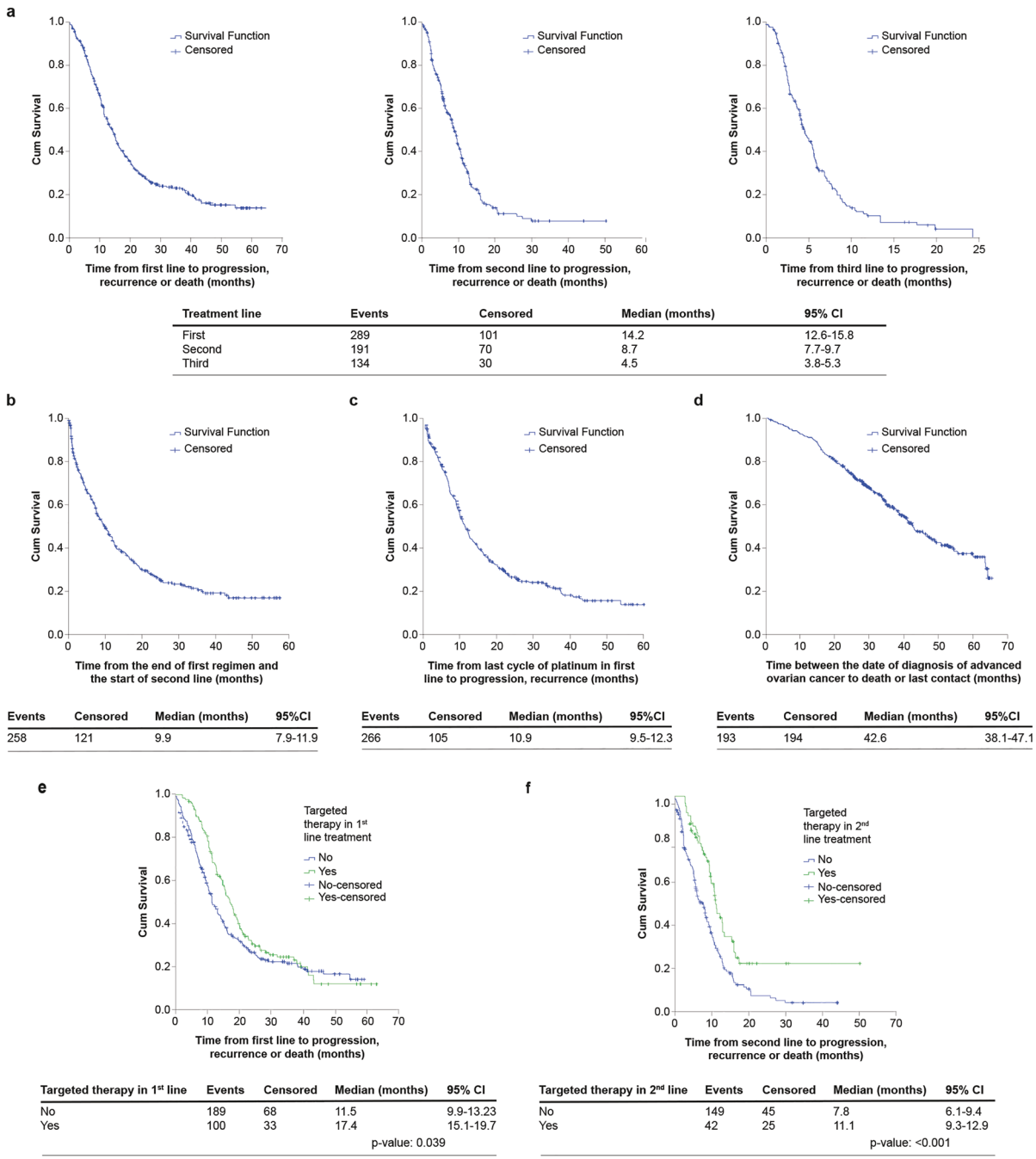
The addition of bevacizumab to chemotherapy has emerged as an effective option in the first-line treatment setting [18, 31, 32]. Spanish guidelines at the initiation of the OVOC study already recommended the administration of bevacizumab with the initial chemotherapy followed by a maintenance period of bevacizumab in patients with R0 after standard surgery [24]. However, bevacizumab was the only targeted therapy available for clinical use in OC (approved in Europe in 2011), and some uncertainties about its use were under discussion [24]. In addition, PARP inhibitors were approved in Europe in 2014. In this context, our study shows that targeted agent-based regimens were used in 33.8% of the patients in the first-line setting, with bevacizumab being administered in 92% of the patients receiving targeted therapy.

Table 3 Factors associated with treatment selection in the first- and the second-line setting

Treatment line	Factor	B	*P* value	OR	95% CI	
					Lower	Upper
First line						
PDS followed by platinum-based chemotherapy[a]	Age at diagnosis (continuous variable)	− 0.044	< 0.001	0.957	0.934	0.981
	Abdominal pain (yes/no)	− 0.575	0.043	0.563	0.322	0.982
	FIGO stage IIIC at diagnosis (reference category: IIIB)	− 0.958	0.010	0.384	0.185	0.795
	FIGO stage IVA at diagnosis (reference category: IIIB)	− 3.374	< 0.001	0.034	0.008	0.151
	FIGO stage IVB at diagnosis (reference category: IIIB)	− 2.540	< 0.001	0.079	0.019	0.322
	Clear cell carcinoma (reference category: no)	1.423	0.017	4.149	1.293	13.311
	TFI (continuous variable)	0.116	< 0.001	1.123	1.064	1.185
	PFI since first-line (continuous variable)	− 0.098	< 0.001	0.907	0.859	0.956
Neoadjuvant chemotherapy[b]	Dyspnea (yes/no)	0.806	0.033	2.238	1.066	4.699
	FIGO stage IIIC at diagnosis (reference category: IIIB)	1.376	0.002	3.959	1.687	9.291
	FIGO stage IVA at diagnosis (reference category: IIIB)	1.260	0.009	3.524	1.365	9.100
	FIGO stage IVB at diagnosis (reference category: IIIB)	0.908	0.089	2.480	0.872	7.055
	High-grade serous carcinoma (reference category: no)	0.578	0.026	1.783	1.072	2.964
Second line						
Platinum-based chemotherapy[c]	*BRCA1* mutated at diagnosis (reference category: *BRCA* wild type)	− 1.224	0.032	0.294	0.096	0.901
	PFI since first-line (continuous variable)	0.047	0.025	1.049	1.006	1.093

BRCA Breast Cancer Associated genes, *CI* confidence interval, *FIGO* Fédération Internationale de Gynécologie et d'Obstétrique, *OR* odds ratio, *PFI* platinum-free interval, *TFI* treatment-free interval. [a]Patients treated with targeted agents as first-line treatment are excluded; [b]patients who received targeted agents as neoadjuvant treatment are excluded; [c]patients who underwent surgery after the first-line treatment or received targeted agents as second-line treatment are excluded

Consequently, bevacizumab was the most consistently used additional agent combined



Treatment line	Events	Censored	Median (months)	95% CI
First	289	101	14.2	12.6-15.8
Second	191	70	8.7	7.7-9.7
Third	134	30	4.5	3.8-5.3

Events	Censored	Median (months)	95%CI
258	121	9.9	7.9-11.9

Events	Censored	Median (months)	95%CI
266	105	10.9	9.5-12.3

Events	Censored	Median (months)	95%CI
193	194	42.6	38.1-47.1

Targeted therapy in 1st line	Events	Censored	Median (months)	95% CI
No	189	68	11.5	9.9-13.23
Yes	100	33	17.4	15.1-19.7
			p-value: 0.039	

Targeted therapy in 2nd line	Events	Censored	Median (months)	95% CI
No	149	45	7.8	6.1-9.4
Yes	42	25	11.1	9.3-12.9
			p-value: <0.001	

Fig. 1 Progression-free survival since first-, second-, and third-line treatment (**a**), treatment-free interval (TFI) (**b**), platinum-free interval (PFI) (**c**), overall survival (OS) (**d**), and PFS according to the use of targeted therapy in first- (**e**) and second-line settings (**f**)

with chemotherapy during the first-line treatment of OC. Similar results were found in a later real-world study using data from the USA and five European countries (France, Germany, Italy, Spain, and UK) from 2017 to 2018, accounting for 26% bevacizumab-containing regimens and 1% a PARP inhibitor-containing regimen as first-line [30]. Another real-world study from 2018

Table 4 Factors associated with clinical outcomes

Outcome	Treatment line	Factor	B	*P* value	OR	95% CI	
						Lower	Upper
PFS	First line	ECOG PS 1 (reference category: ECOG 0)	0.617	0.006	1.853	1.197	2.869
		ECOG PS 2 (reference category: ECOG 0)	1.011	0.011	2.749	1.255	6.019
		BRCA1 mutated at diagnosis (reference category: *BRCA* wild type)	− 1.064	< 0.001	0.345	0.187	0.639
		BRCA2 mutated at diagnosis (reference category: *BRCA* wild type)	− 1.442	< 0.001	0.237	0.115	0.487
		Upfront surgery (reference category: no surgery upfront or after neo-treatment)	− 0.869	0.016	0.419	0.206	0.853
PFS	Second line	*BRCA1* mutated at diagnosis (reference category: *BRCA* wild type)	− 0.939	0.021	0.391	0.177	0.866
		BRCA2 mutated at diagnosis (reference category: *BRCA* wild type)	− 1.229	0.037	0.292	0.092	0.931
		PR with first-line treatment (reference category: CR)	0.518	0.039	1.679	1.025	2.750
		PD with first-line treatment (reference category: CR)	1.333	< 0.001	3.792	1.782	8.068
OS	–	FIGO stage IVA at diagnosis (reference category: IIIB)	1.573	0.016	4.819	1.340	17.338
		FIGO stage IVB at diagnosis (reference category: IIIB)	2.210	0.002	9.112	2.310	35.945
		BRCA2 mutated at diagnosis (reference category: *BRCA* wild type)	− 2.527	0.015	0.080	0.010	0.609
		Platinum resistance (reference: platinum-sensitive)	1.636	< 0.001	5.135	2.685	9.821

BRCA Breast Cancer Associated genes, *CI* confidence interval, *CR* complete response, *ECOG PS* Eastern Cooperative Oncology Group performance status, *FIGO* Fédération Internationale de Gynécologie et d'Obstétrique, *OR* odds ratio, *OS* overall survival, *PD* progressive disease, *PR* partial response, *PFS* progression-free survival, *TFI* treatment-free interval

to 2019 found higher proportions of patients treated with angiogenesis inhibitors at first line (47.3% of the patients received chemotherapy and angiogenesis inhibitors) [27]. Overall, this evidence shows the increasing use of targeted therapies in real-world settings as recommended by current guidelines and consensus [3, 33].

Managing patients with recurrent disease represents a challenge for clinicians, given the inherent heterogeneity of the disease and the diversity of clinical scenarios. Traditionally, the selection of successive lines of treatment has arbitrarily relied on the length of the PFI [3, 16]. According to this approach, most patients with OC have platinum-sensitive disease (PFI ≥ 6 months) after the first recurrence [34]. Indeed, 65.9% of the patients showed platinum-sensitive disease after first-line treatment in the present study. The standard therapy for these patients at the time the study started consisted of retreatment with a platinum-containing regimen [24, 35]. Accordingly, the preferred

second-line treatment in this study was platinum-based chemotherapy, administered to 37.0% of the patients with recurrent disease and 50.4% of the patients with platinum-sensitive disease. In agreement, before bevacizumab approval, from 2008 to 2010, 69% of patients with recurrent disease received second-line chemotherapy, according to a Spanish retrospective observational real-world study including 277 patients diagnosed with AOC [36]. In this line, we found that patients with an extended PFI had a higher likelihood of receiving platinum-based chemotherapy as second-line treatment, aligning with the historical recognition of PFI as a leading factor guiding therapeutic decisions in managing recurrent OC. Of note, the use of platinum-based chemotherapy in our study declined as patients relapsed, as previously reported in real-world studies [25, 27]. Since patients with platinum-resistant disease are unlikely to respond to additional platinum-based treatments, platinum rechallenge therapy should not be considered as an option when progression occurs in these individuals [3, 37]. Nevertheless, our findings reveal that approximately 13.5% of the patients with platinum-resistant disease were subjected to retreatment with platinum-based regimens following first recurrence, of whom 60.0% achieved stable disease, 20.0% PR, 10.0% CR, and 10.0% PD after the second-line treatment.

According to the latest recommendations, treatment selection after recurrence should consider tumor-associated characteristics and individual patient-related factors such as clinicopathologic parameters, the nature and severity of symptoms, performance status, molecular results, the type and number of previously administered treatments, or the presence of residual toxicities [3, 4, 17, 33]. Current guidelines acknowledge that platinum-containing regimens can still be the best option for certain patients with recurrent disease [3]. Nevertheless, new evidence supports that platinum-based combination with bevacizumab and platinum-based combination followed by PARPi are optimal options [3]. Thus, targeted agents have emerged as a promising treatment option. For instance, combining bevacizumab with chemotherapy has proven beneficial in terms of PFS and OS in patients with platinum-resistant disease [20, 38]. Indeed, bevacizumab is indicated for the front-line treatment of AOC and in platinum-sensitive recurrent and platinum-resistant recurrent settings for epithelial ovarian cancer, according to its summary of product characteristics (SmPC) [39]. Our study reveals that the combined regimen of chemotherapy with bevacizumab was the second most frequently used second-line treatment, administered to approximately 17.4% of the patients. Chemotherapy followed by any PARP inhibitor was administered to 6.0% of patients. Similar results were reported in the real-world study carried out by Hall et al. [30] for France, Germany, Italy, and Spain, but not for the USA and UK, which had a similar frequency with olaparib monotherapy. Of note in our study, the use of targeted therapy in the second-line setting was similar in patients with platinum-sensitive (25.2%) and platinum-refractory (25.0%) disease but tended to be lower in patients with platinum resistance (16.2%).

Our findings show that the proportion of patients undergoing second-line therapy with a bevacizumab-based regimen (18.0%) represented nearly half of those who received bevacizumab in the first-line setting (30.9%), suggesting that at the time of this study, bevacizumab was preferably used in the first-line setting. These findings align with real-world evidence from the EpOCa study in Greece [27] and from the study carried out by Hall et al. in France, Germany, and Italy [30]. Interestingly, data from Spain from the former study showed a higher prevalence of bevacizumab-containing regimens in the second-line setting (16% versus 31%). However, 39% of the overall population received first-line maintenance therapy, with 73% of those regimens containing bevacizumab [30]. These results highlight the growing recognition of the role of maintenance therapy in delaying disease progression in recent years [12, 40, 41]. In our study, only 2.5% of the patients were retreated with bevacizumab in the second-line setting after receiving first-line bevacizumab-based therapy. It is important to underscore that bevacizumab is approved in recurrent OC for patients who have not previously received this targeted agent.

Our results indicate that the use of targeted therapy as second-line treatment varied significantly based on the mutational status of the *BRCA* gene. While nearly 50% of the patients with platinum-sensitive disease with *BRCA* gene mutations received targeted therapy as second-line treatment, only 16.9% of those with *BRCA* wild-type patients received such therapy. Additionally, our findings identified germline *BRCA1* mutational status as an independent factor influencing the selection of platinum-based chemotherapy regimens (not containing targeted therapies) as second-line treatment. These results are consistent with current guidelines emphasizing the significance of *BRCA1/2* mutations as validated biomarkers guiding the use of PARP inhibitors [3]. The findings underscore the potential impact of genetic factors on treatment choices besides chemotherapy. Indeed, several genes have been found mutated in ovarian cancer [42]. Besides *BRCA1/2* mutations, several other genes associated with homologous recombination repair deficiency (HRD), such as *CHEK2*, *RAD51*, *BRIP1*, and *PALB2*, have been described [42, 43]. In addition, mutations in genes encoding proteins in other pathways, such as the RAS-RAF-MEK-ERK pathway, have also been detected in OC [42, 44]. These molecular insights are directly influencing therapeutic strategies. For instance, patients with positive results for HRD can also benefit from maintenance therapy with PARP inhibitors [43, 45]. Moreover, several therapeutic molecular inhibitors of these pathways have been developed and are currently assessed in clinical trials [44]. The expanding understanding of the molecular landscape of ovarian cancer facilitates the development of personalized treatment approaches.

The median PFS in the first-line setting was 14.2 months. Most patients in this context underwent PDS followed by platinum-based chemotherapy or IDS after neoadjuvant treatment followed by platinum-based chemotherapy. The observed PFS in this real-world study aligned with the data reported in the GOG-0218 study, ranging from 10.3 months in patients treated with paclitaxel and carboplatin to 14.1 months in patients treated with the combination of chemotherapy and bevacizumab [31]. Due to the observational nature of this study, direct comparisons with phase III trials should be regarded as purely descriptive. The observational EpOCa study, conducted in Greece with 154 patients with AOC, reported a PFS of 18.2 months [27]. However, that study had a higher rate of first-line targeted therapy (approximately 50% of patients) than ours (33.8%). Notably, our study revealed a significantly longer PFS (17.4 months) among patients who received targeted therapy in the first-line setting (92% of them received bevacizumab) compared to those who did not (11.55 months; $p = 0.039$). This observation aligns with the findings of the GOG-0218 and ICON-7 trials, as well as the EpOCa study and the study of Fukuda et al., which demonstrated that the addition of bevacizumab to paclitaxel plus carboplatin resulted in a statistically significantly improvement in PFS or disease-free survival [18, 27, 31, 32].

A median PFS of 8.7 months was observed following initiation of second-line treatment in this study, consistent with the median post-progression survival of 9.7 months observed across 22 phase III randomized controlled trials focusing on second-/third-line chemotherapy treatment for patients with AOC [46]. This finding also aligns with the estimated PFS for the second-line treatment setting in the observational EpOCa study (8.8 months) [27]. As seen in the first-line setting, a significantly longer PFS is achieved among patients receiving targeted therapy after the first relapse ($p < 0.001$).

Our findings reveal that individuals carrying *BRCA1* and *BRCA2* mutations experience a diminished probability of disease progression, recurrence, or mortality compared to those with wild-type variants. These results are in line with the outcomes of a meta-analysis including 14 studies in ovarian cancer emphasizing a more favorable prognosis in terms of both PFS and OS in women with *BRCA1/2* mutations, irrespective of grade, tumor stage, or histologic subtype [47].

Overall, the discrepancies observed between clinical practice at the start of the study and current guidelines represent a significant opportunity to improve the clinical outcomes of patients

with AOC by implementating effective targeted therapies recommended by these guidelines.

This study has limitations that should be acknowledged. The findings need to be interpreted in the context of the targeted agents that were available at the time when the patients underwent OC treatment. It is crucial to acknowledge that the landscape of OC therapy has evolved in recent years with the integration of new targeted agents into the treatment arsenal. In addition, the retrospective design of the study dictated data availability, implying data generation according to routine clinical practices and a lack of systematic collection.

CONCLUSIONS

This study comprehensively examines patient characteristics, treatment patterns, and outcomes in women with AOC in Spain between 2013 and 2016 during the incorporation of targeted therapies into the clinical practice. Neoadjuvant chemotherapy and platinum-based chemotherapy following PDS were found to be the most frequently used first-line treatment strategies and platinum-based chemotherapy the prevailing second-line treatment strategy in the real world. Targeted agents were administered to one-third of the patients in the first-line setting and a quarter of the patients in the second-line setting. A longer PFS was achieved among patients receiving targeted therapy in the first-line setting and after first relapse. This study also shows that *BRCA* mutation status is an independent prognostic factor for PFS and OS in real life. The findings contribute valuable information to the existing literature, guiding clinicians in optimizing treatment decisions to further enhance the management of this challenging disease.

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Declarations

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