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Original Research

BRCA screening, treatment patterns and response among patients with ovarian cancer in the second line treatment setting: results from a real world survey

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Abstract

Objective: Although *BRCA* gene testing of patients diagnosed with ovarian cancer (OC) is now recommended, the level of testing undertaken in various countries is largely unknown. This study describes *BRCA* mutation screening patterns and results, demographics, clinical characteristics and the use of poly (ADP-ribose) polymerase inhibitors (PARPi) as maintenance treatment within a real-world sample of patients with advanced OC in the second-line (2L) treatment setting. **Methods**: Data were collected using the Adelphi Real World OC Disease Specific Programme (DSP)™, a point-in-time survey of physicians and their consulting patients with OC in clinical practice, undertaken across Europe (EU5: France, Germany, Italy, Spain and United Kingdom) and the United States (US) between December 2017–March 2018. Physicians completed a detailed patient record form for their next eight consecutively consulting patients, capturing data on their clinical history and treatment. All analysis was descriptive. **Results**: Of 1315 patients identified, 1096 (83%) were receiving 2L treatment and 219 (17%) were receiving 2L maintenance treatment; either PARPi (olaparib, rucaparib or niraparib, n = 103) or a non-PARPi (n = 116). *BRCA* screening rates varied between countries, increased with each line of therapy and were higher in the EU5 (55%) than the US (44%). 28% of patients receiving 2L treatment had a *BRCA1/2* mutation. Patients receiving PARPi maintenance treatment had better Eastern Cooperative Oncology Group (ECOG) performance status, higher *BRCA* screening rates and higher proportions of serous epithelial OC than those receiving 2L treatment or non-PARPi maintenance. Common reasons for choosing 2L treatments were progression-free/overall survival benefit and improvement of quality of life. **Conclusions**: Despite guidelines recommending *BRCA* testing in patients with OC, many OC patients undergoing 2L treatment were not screened for *BRCA* mutations. Decisions related to PARPi use in 2L maintenance appeared to be driven by *BRCA* status, histology and response to first-line treatment.

Keywords: *BRCA*; chemotherapy; second-line; maintenance; ovarian cancer; real-world; PARP inhibitors

1. Introduction

Ovarian cancer (OC) most commonly affects older, postmenopausal women, with >80% of women diagnosed with OC being >50 years old [1]. Globally, OC is the fifth most common type of cancer in women and the fourth most common cause of cancer death in women [1]. Worldwide, there were an estimated 314,000 new cases of OC and 207,000 OC-related deaths in 2020 [2].

BRCA mutation status is important when considering treatment options in advanced OC, particularly in those patients with a familial history of breast and OC [3]. Around 20% of high-grade serous OCs harbour germline or somatic *BRCA* mutations [4]. Although *BRCA* testing of patients diagnosed with OC is recommended [5,6], the level of testing undertaken in various countries is largely unknown.

The recommended first-line (1L) treatment for advanced OC in 2018 was surgical cytoreduction followed by carboplatin/paclitaxel chemotherapy [5,7]. However, disease progression occurs in around 70% of patients within 3 years of receiving treatment, with the probability of response to second-line (2L) and subsequent lines of therapy depending largely on the progression-free period during or following the previous course of chemotherapy [1]. A further course of chemotherapy, usually single-agent carboplatin, may be prescribed as 2L therapy in patients who are platinum-sensitive at relapse. Treatment options for platinum-resistant or platinum-refractory patients are more limited; these patients usually receive non-platinum chemotherapy.

In recent years, several poly (ADP-ribose) polymerase inhibitors (PARPi) have received approval in Europe and the United States (US) [8], with the National Comprehensive Cancer Network guidelines recommending considering maintenance therapy with a PARPi in platinum-sensitive patients with relapsed OC, regardless of *BRCA* mutation status [6].

In the NOVA trial, the PRIMA trial and the QUADRA study, niraparib was shown to improve progression-free survival (PFS) in advanced OC across a broad range of patient groups [9–11]. In the ARIEL3 trial, rucaparib significantly improved PFS in platinum sensitive, recurrent (PSR) patients, indicating its utility as maintenance treatment in platinum-sensitive OC following a complete or partial response to 2L or later platinum-based chemotherapy [12]. Both rucaparib and niraparib have been approved for treatment of OC across a range of clinical settings in both the US and Europe [7].

In the PAOLA-1 trial published in 2019, olaparib was shown to significantly improve PFS in patients with homologous recombination deficiency positive (HRD+) status when added to bevacizumab maintenance treatment following platinum-based 1L chemotherapy [13,14]. Maintenance treatment with olaparib has shown improvement in PFS in platinum-sensitive women with a *BRCA1/2* mutation in the SOLO1 trial for 1L maintenance published in 2018 (hazard ratio (HR) 0.30; 95% confidence interval (CI), 0.23 to 0.41; $p < 0.001$) [15] and in the SOLO2 trial in 2L maintenance treatment following relapse published in 2017 (PFS; 19.1 *vs* 5.5 months, HR; 0.30, 95% CI 0.22–0.41, $p < 0.0001$) [16]. In the SOLO3 trial published in 2020, olaparib improved PFS in PSR patients with *BRCA1/2* mutations who had received at least two prior lines of platinum-based chemotherapy (PFS; 13.4 *vs* 9.2 months HR; 0.62; (95% CI, 0.43 to 0.91); $p = 0.013$) [17].

The PSR setting has become an important focus of research. Understanding current *BRCA* screening rates in OC on a wider geographical scale, and how these relate to real-world treatment patterns in the context of an increasing variety of newly-introduced therapies could provide interesting insights. Therefore, the objective of this study was to describe *BRCA* screening patterns and results, patient demographics and clinical characteristics, the use of PARPi as maintenance treatment and subsequent treatment response within a real-world sample of patients with advanced OC in the 2L treatment setting.

2. Materials and methods

2.1 Study design

Data were collected using the Adelphi Real World Advanced OC Disease Specific Programme (DSP)™ in Europe (EU5 — France, Germany, Italy, Spain and United Kingdom (UK)) and the US between December 2017 and March 2018. DSPs are large, point-in-time, non-interventional multi-country surveys of physicians and their consulting patients conducted in real-world clinical practice. This methodological approach is well established and has been used extensively across multiple therapy areas. The full DSP methodology has been previously published in detail [18], has been validated against external data sources [19], and has demonstrated the power of trend data over time [20].

The DSP collects data from physicians, including perceptions and workload using physician surveys, and data related to individual patients via patient record forms. Data collected includes both subjective (opinion-based) and objective variables, clinical information about individual patients, their disease and treatment.

2.2 Ethics approval and consent to participate

Data collection was undertaken in line with European Pharmaceutical Marketing Research Association [21] guidelines, and as such did not require ethics committee approval. Each survey was performed in full accordance with relevant legislation at the time of data collection, including the US Health Insurance Portability and Accountability Act 1996 [22], and Health Information Technology for Economic and Clinical Health Act legislation [23], as well as in accordance with the Declaration of Helsinki. Using a check box, physicians and patients provided informed consent to take part in the survey. Data were collected in such a way that patients and physicians could not be identified directly; all data were aggregated and de-identified before receipt.

2.3 Data collection

A geographically diverse sample of physicians were recruited by field-based interviewers, and were identified from publicly available lists of healthcare professionals. Physicians were eligible to participate if they qualified as a medical/clinical oncologist or gynecologist between 1983 and 2013, saw at least 10 patients with advanced OC in a typical month and were personally responsible for treatment decisions for patients with advanced OC. Physician participation was financially incentivized, with reimbursement upon survey completion according to fair market research rates.

Once recruited to the study, participating physicians completed a detailed electronic patient record form for their next eight consecutively consulting patients who met the eligibility criteria, to mitigate against recruitment bias. Data were recorded at time of consultation, to mitigate against recall bias. All patients were $\geq$18 years old, with histologically confirmed epithelial ovarian, fallopian tube or peritoneal cancer (including malignant Müllerian tumors with high grade serous component) at stage II–IV OC and receiving systemic treatment at the point of data collection.

Of the eight consecutive patients included in the study, physicians were asked to ensure that the proportion of patients recruited met the following criteria; three patients were receiving 1L treatment (consolidation or maintenance) at point of data abstraction, one patient was receiving 2L or later treatment at point of data abstraction having previously received bevacizumab at 1L maintenance, and four patients were known to be on 2L or later treatment at data abstraction having received a platinum-based regimen at 1L. Physicians were asked to recruit the next sequential patient who met the various inclusion criteria above, in order

to recruit as broad a patient cohort as possible whilst minimizing selection bias. Consulting patients were enrolled in the study, therefore alive at the point of data capture. As a result, the DSP did not capture survival data.

2.4 Study variables

Information captured in the patient record form included demographics, clinical characteristics, *BRCA* testing details and findings (*BRCA* testing, either germline or somatic, undertaken at any time point), current treatment for OC and treatment history (including reasons for treatment choices and treatment response). Physicians were asked to record whether patients were complete responders, partial responders or had stable disease following completion of treatment regimen, as well as recording any reasons for treatment failure.

Patients were classified as platinum-sensitive if disease progression was noted >6 months after 1L platinum treatment, platinum-resistant if disease progression was noted 0–6 months after 1L platinum treatment or platinum-refractory if disease progression was noted during 1L platinum treatment.

2.5 Analysis

Patients were included in the main analysis if they were receiving 2L treatment at the time of data collection, including 2L maintenance treatment. All analyses were descriptive, with statistics calculated for patient demographics, clinical characteristics, treatment patterns, 1L treatment response and reasons for choice of 2L maintenance therapy. Mean, standard deviation and range were calculated for continuous variables, and frequency counts and percentages for categorical variables. All analyses were conducted in Survey Reporter.

3. Results

3.1 Participants

A total of 340 physicians participated in the study (EU5: 228 (France: 50, Germany: 50, Italy: 46, Spain: 46, UK: 36), US: 112). Data were collected for 1315 patients who were receiving 2L treatment (Table 1). Of these, 1096 (83%) patients were receiving 2L treatment and 219 (17%) patients were receiving 2L maintenance treatment, which consisted of a PARPi (olaparib, rucaparib or niraparib) in 103 (47%) patients and a non-PARPi in 116 (53%) patients.

Just over three-quarters of patients (76%) were from the EU5, with the largest EU sample from Germany (17%) and the smallest from the UK (12%), and around a quarter of patients were from the US (24%). Patients were of similar age (mean age $\pm$ standard deviation (SD): 63.2 $\pm$ 9.6 years), regardless of the 2L treatment regimen they were receiving (Table 1).

At the time of data collection, there was little difference in stage of disease in patients receiving PARPi maintenance treatment compared to those receiving 2L treatment or non-PARPi maintenance treatment (Stage III, 27% *vs* 24% or 35%; Stage IVa, 18% *vs* 18% or 28%; Stage IVb, 54% *vs* 57% or 31%, respectively). However, PARPi maintenance treatment was associated with a better Eastern Cooperative Oncology Group (ECOG) performance status *vs* 2L treatment or non-PARPi maintenance treatment (ECOG 0–1, 79% *vs* 69% or 49%; ECOG $\geq$2, 19% *vs* 29% or 50%, respectively) (Table 1).

The most common OC histology in all treatment groups was serous epithelial OC (overall, 63%). There were differences across treatment groups in the proportions of patients with each histology, with the highest proportion of patients receiving PARPi maintenance treatment having serous epithelial OC (Table 1). A higher proportion of patients receiving PARPi maintenance treatment had a family history of OC (27%) compared to patients from the other two treatment groups (2L treatment, 8%; non-PARPi maintenance treatment, 9%) (Table 1).

3.2 Treatment at 1L setting

Of all patients receiving 2L treatment at the time of data collection, the majority (95%) of patients had received platinum-based chemotherapy in the 1L treatment setting; almost all (99%) patients receiving PARPi at 2L maintenance received a platinum-containing regimen at 1L compared with around three-quarters (72%) of patients who were receiving 2L maintenance with a treatment other than a PARPi (Table 2).

1L maintenance treatment was received by just under half (44%) of all patients undergoing 2L treatment, with the most common maintenance treatment overall being a bevacizumab-containing regimen (87%), although this was only received by just over half of the patients (57%) receiving non-PARPi 2L maintenance treatment. At 1L treatment stage, 28 (5%) patients received a PARPi-based maintenance treatment, with all but three of these receiving olaparib (Table 2).

3.3 1L treatment response

The most common response to 1L treatment across patients at 2L treatment stage in both the EU5 and US was completion of the treatment course with the patient showing a complete response to 1L treatment. Patients who were receiving a PARPi at 2L maintenance included a higher proportion of patients showing complete response to 1L treatment (EU5: 79%, US: 55%) compared to those receiving non-PARPi 2L maintenance treatment (EU5: 33%, US: 7%) (Table 3).

For those patients receiving 2L maintenance treatment with therapy other than a PARPi, the most common response to 1L treatment was partial response on completion of the treatment course (Table 4). Country differences were observed between patients from the EU5 and US in 1L treatment responses, with 93% and 51% of EU5 and US patients, respectively, who were receiving a non-PARPi maintenance

Table 1. Patient demographics and clinical characteristics.

	Total (n = 1315)	Receiving 2L treatment (n = 1096)	Receiving 2L maintenance (n = 219)	
			Receiving PARPi 2L maintenance treatment (n = 103)	Receiving non-PARPi 2L maintenance treatment (n = 116)
Geographic region, n (%)				
France	216 (16)	174 (16)	26 (25)	16 (14)
Germany	222 (17)	191 (17)	13 (13)	18 (16)
Italy	193 (15)	152 (14)	11 (11)	30 (26)
Spain	209 (16)	183 (17)	17 (17)	9 (8)
UK	162 (12)	159 (15)	3 (3)	0
EU5	1002 (76)	859 (78)	70 (68)	73 (63)
US	313 (24)	237 (22)	33 (32)	43 (37)
Age, years*				
n	1305	1087	103	115
Mean (SD)	63.2 (9.6)	63.8 (9.5)	61.8 (8.4)	58.9 (11.1)
Min, max	28, 89	28, 89	37, 80	35, 88
OC stage at data collection, n (%)				
Stage II	20 (2)	14 (1)	0	6 (5)
Stage III	329 (25)	260 (24)	28 (27)	41 (35)
Stage IVa**	254 (19)	202 (18)	19 (18)	33 (28)
Stage IVb**	712 (54)	620 (57)	56 (54)	36 (31)
Histology, n (%)				
Serous epithelial OC	827 (63)	697 (64)	76 (74)	54 (47)
Mucinous epithelial OC	143 (11)	108 (10)	10 (10)	25 (22)
Endometrioid epithelial OC	97 (7)	83 (8)	5 (5)	9 (8)
Clear cell epithelial OC	112 (9)	102 (9)	4 (4)	6 (5)
Undifferentiated epithelial OC	69 (5)	59 (5)	1 (1)	9 (8)
Fallopian tube cancer	28 (2)	16 (1)	5 (5)	7 (6)
Peritoneal cancer	36 (3)	29 (3)	1 (1)	6 (5)
Other	3 (<1)	2 (<1)	1 (1)	0
ECOG performance status at data collection, n (%)				
0–1	892 (68)	754 (69)	81 (79)	57 (49)
≥2	398 (30)	320 (29)	20 (19)	58 (50)
Unknown/Not assessed	25 (2)	22 (2)	2 (2)	1 (1)
Family history of OC, n (%)				
Yes	127 (10)	88 (8)	28 (27)	11 (9)
No	1050 (80)	904 (82)	68 (66)	78 (67)
Unknown	138 (10)	104 (9)	7 (7)	27 (23)

*Patients <90 years old.

**Stage IVa = pleural effusion only; Stage IVb = any metastasis other than pleural effusion.

Percentages rounded to nearest whole number, therefore percentages may not add up to 100%. Abbreviations: 2L, second-line treatment; BRCA, BReast CAncer gene; ECOG, Eastern Cooperative Oncology Group; EU5, United Kingdom, France, Germany, Spain and Italy; Min, minimum; Max, maximum; OC, ovarian cancer; PARPi, poly (ADP-ribose) polymerase inhibitor; SD, standard deviation; UK, United Kingdom; US, United States.

Table 2. Treatment received at 1L and 2L setting in patients currently receiving 2L treatment.

	Total (n = 1315)	Receiving 2L treatment (n = 1096)	Receiving 2L maintenance (n = 219)	
			Receiving PARPi 2L maintenance treatment (n = 103)	Receiving non-PARPi 2L maintenance treatment (n = 116)
1L treatment, n (%)				
Platinum-based chemotherapy	1244 (95)	1059 (97)	102 (99)	83 (72)
Bevacizumab-containing regimen	303 (23)	257 (23)	26 (25)	20 (17)
Olaparib-containing regimen	6 (<1)	5 (<1)	1 (1)	0
Rucaparib-containing regimen	4 (<1)	2 (<1)	0	2 (2)
Niraparib-containing regimen	6 (<1)	2 (<1)	0	4 (3)
Received 1L maintenance treatment, n (%)	585 (44)	466 (43)	50 (49)	69 (59)
1L maintenance treatment, n (%)*				
Platinum-based chemotherapy	85 (15)	42 (9)	7 (14)	36 (52)
Bevacizumab-containing regimen	508 (87)	422 (91)	47 (94)	39 (57)
Olaparib-containing regimen	25 (4)	24 (5)	1 (2)	0
Rucaparib-containing regimen	2 (<1)	1 (<1)	0	1 (1)
Niraparib-containing regimen	1 (<1)	1 (<1)	0	0
2L treatment, n (%)**				
Platinum-based chemotherapy	770 (59)	625 (57)	88 (85)	57 (49)
Bevacizumab-containing regimen	227 (17)	195 (18)	15 (15)	17 (15)
Olaparib-containing regimen	43 (3)	37 (3)	3 (3)	3 (3)
Rucaparib-containing regimen	8 (1)	4 (<1)	1 (1)	3 (3)
Niraparib-containing regimen	13 (1)	12 (1)	0	1 (1)
Received 2L maintenance treatment, n (%)	219 (17)	N/A	103 (100)	116 (100)
2L maintenance treatment, n (%)***				
Platinum-based chemotherapy	44 (20)	N/A	3 (3)	41 (35)
Bevacizumab-containing regimen	49 (22)	N/A	0	49 (42)
Olaparib-containing regimen	69 (32)	N/A	69 (67)	0
Rucaparib-containing regimen	5 (2)	N/A	5 (5)	0
Niraparib-containing regimen	29 (13)	N/A	29 (28)	0

*% based on those who received 1L maintenance treatment.

**% based on those who were receiving 2L treatment at data collection or received 2L treatment (and progressed to 2L maintenance).

***% based on those receiving 2L maintenance treatment.

Percentages rounded to nearest whole number, therefore percentages may not add up to 100%. Abbreviations: 1L, first-line treatment; 2L, second-line treatment; PARPi, poly (ADP-ribose) polymerase inhibitor.

Table 3. Response to 1L treatment in patients now recieving 2L treatment in the EU5 and US.

	EU5			US		
	Receiving 2L treatment (n = 859)	Receiving 2L PARPi maintenance (n = 70)	Receiving 2L non-PARPi maintenance (n = 73)	Receiving 2L treatment (n = 237)	Receiving 2L PARPi maintenance (n = 33)	Receiving 2L non-PARPi maintenance (n = 43)
Regimen completed — Response (n, %)						
Complete/Partial response/Stable disease	693 (81)	66 (94)	68 (93)	191 (81)	31 (94)	22 (51)
Complete response	397 (46)	55 (79)	24 (33)	102 (43)	18 (55)	3 (7)
Partial response	217 (25)	11 (16)	42 (58)	68 (29)	9 (27)	14 (33)
Stable disease	79 (9)	-	2 (3)	21 (9)	4 (12)	5 (12)
Reasons for treatment failure (n, %)						
Disease progression	138 (16)	2 (3)	3 (4)	37 (16)	-	11 (26)
Unacceptable tolerability	19 (2)	2 (3)	2 (3)	3 (1)	1 (3)	2 (5)
Unacceptable impact on patient's QoL	8 (1)	-	-	2 (1)	-	2 (5)
Patient request to stop treatment	8 (1)	1 (1)	-	13 (5)	1 (3)	8 (19)
Other	3 (0)	-	1 (1)	-	-	-

Percentages rounded to nearest whole number, therefore percentages may not add up to 100%.

Abbreviations: 1L, first-line treatment; 2L, second-line treatment; PARPi, poly ADP ribose polymerase inhibitor; QoL, quality of life.

Table 4. *BRCA* screening rates and test results in patients recieving 2L treatment.

	All 2L patients (n = 1315)		Total 2L treatment patients (n = 1096)		Receiving 2L maintenance (n = 219)			
					Total 2L maintenance PARPi patients (n = 103)		Total 2L maintenance non-PARPi patients (n = 116)	
	EU5 (n = 1002)	US (n = 313)	EU5 (n = 859)	US (n = 237)	EU5 (n = 70)	US (n = 33)	EU5 (n = 73)	US (n = 43)
Patients screened for *BRCA* (n, %)	554 (55)	138 (44)	465 (54)	103 (43)	61 (87)	25 (76)	28 (38)	10 (23)
Of those tested, % *BRCA* +ve (n, %)	154 (28)	43 (31)	102 (22)	22 (21)	49 (80)	11 (44)	3 (11)	10 (100)

% based on those tested. Percentages rounded to nearest whole number. Abbreviations: 2L, second-line treatment; +ve, positive; *BRCA*, Breast Cancer gene; EU5, United Kingdom, France, Germany, Spain and Italy; PARPi, poly ADP ribose polymerase inhibitor; US, United States.

treatment at 2L, having a complete/partial response or stable disease following 1L treatment (Table 3). Overall, 35% of all patients included in this analysis were defined as platinum-sensitive, 14% as platinum-resistant and 14% as platinum-refractory. Platinum sensitivity differed markedly between patients receiving PARPi and non-PARPi maintenance treatment at 2L, with 53% and 16% of these patients classified as platinum-sensitive, respectively.

3.4 2L treatment and reasons for choice of 2L maintenance treatment

Of patients receiving 2L non-maintenance treatment (n = 1096), at the time of data collection, 57% of patients were receiving a platinum-containing regimen, compared with 85% of patients receiving PARPi-based 2L maintenance treatment (n = 103) (Table 2).

When physicians were asked to record their reasons for treatment choices at different lines of treatment, the most common reasons for choosing maintenance treatment were progression-free/overall survival benefit (60%/40%) and maintenance or improvement of quality of life (32% and 19%). The proportions of physicians indicating reasons for their choice of 2L maintenance treatment were generally similar between PARPi-containing and non-PARPi 2L regimens (predominantly either platinum-based chemotherapy or bevacizumab, as summarized in Table 2); however, differences were observed for PFS benefit (69% and 53%, respectively), manageable side effect profile (42% and 21%, respectively) and high response rate (35% and 24%, respectively) (data not shown).

3.5 BRCA screening rates and test results in patients at 2L treatment stage

Of all 2L patients (n = 1315), 692 patients had their *BRCA* status tested, with screening rates slightly higher in the EU5 than the US (55% *vs* 44%, respectively). Higher proportions of patients from both the EU5 and the US receiving a PARPi at 2L maintenance were tested for *BRCA* (87% and 76%, respectively) compared to those who were receiving 2L treatment (54% and 43%, respectively) or 2L maintenance that was not PARPi-based (38% and 23%, respectively) (Table 4). Of all 2L tested patients (n = 692), 28% of patients receiving 2L treatment tested positive for a *BRCA1/2* mutation, while test results for those receiving maintenance treatment varied between treatments and regions. Of those tested for *BRCA* and who were receiving PARPi 2L maintenance treatment (n = 103), positive results were obtained for 80% and 44% of EU5 and US patients, respectively. Of those tested for *BRCA* and who were receiving non-PARPi 2L maintenance treatment (n = 106), 11% and 100% of EU5 and US patients, respectively, had a positive test (Table 4). Of 2L maintenance patients receiving a PARPi, 27% of patients had a family history of OC and 93% of these patients had a positive *BRCA* status.

3.6 BRCA screening rates and test results by line of therapy at data collection and country (all patients)

When the *BRCA* screening rates by line of therapy and country were examined, it was found that the *BRCA* screening rate increased as the line of therapy progressed from 1L to 2L and to third-line treatment and beyond (3L+) (Table 5). The highest rates of testing were observed in Spain (60% at 1L and 66% at 2L). Both Italy (39% at both 1L and 2L) and the UK (24% at 1L and 40% at 2L) were below the EU5 average (45% at 1L and 55% and 2L, respectively). When comparing the EU5 and the US, there was little difference in *BRCA* testing rates at 1L (45% *vs* 46%, respectively); however, a greater proportion of EU5 patients were tested at 2L compared to the US cohort (55% *vs* 44%, respectively).

4. Discussion

In this real-world study, we explored demographics, clinical characteristics, BRCA screening patterns and results, treatment patterns and response in a sample of 1315 patients with advanced OC receiving 2L treatment from five European countries and the US. At the time this study was undertaken (Dec 2017–Mar 2018), the recommended 1L treatment for advanced OC was surgical cytoreduction followed by carboplatin/paclitaxel chemotherapy [5,7], with PARPi maintenance therapies only recently being approved in certain settings. Compared to patients receiving non-PARPi-based 2L maintenance treatment (n = 116), the 103 patients receiving 2L maintenance treatment containing one of the approved PARPi therapies (olaparib, rucaparib or niraparib) included in our study had a more advanced stage of OC. Those receiving PARPi more frequently presented with serous epithelial OC and with a family history of OC, and were more frequently tested for, and had, *BRCA* mutations; had received platinum-based chemotherapy at 1L and 2L treatment stage; and were classified as platinum-sensitive.

PARPi have been shown to improve PFS in PSR OC, as demonstrated in clinical trials for niraparib [9–11], rucaparib [12] and olaparib [14–16], and are of particular benefit in patients with *BRCA* mutations who are at higher risk of developing OC [24], with the combination of PARPi in patients with *BRCA1/2* deficiency resulting in tumour cell death [25]. In this study, a higher proportion of patients from both the EU5 and the US receiving a PARPi at 2L maintenance were tested for *BRCA* (87% *vs* 76%, respectively) compared to those who were receiving 2L treatment (54% *vs* 43%, respectively) or non-PARPi-based or 2L maintenance (38% *vs* 23%, respectively). Of those tested for *BRCA* and who were receiving PARPi 2L maintenance treatment (n = 103), positive results were obtained for 80% and 44% of EU5 and US patients, respectively. Of those tested for *BRCA* and who were receiving non-PARPi 2L maintenance treatment (n = 106), 11% and 100% of EU5 and US patients, respectively, had a positive test.

Table 5. *BRCA* screening rates and results by line of therapy at data collection and country.

	Base	France	Germany	Italy	Spain	UK	EU5	US
1L treatment at data collection, n	1004	154	150	135	136	143	718	286
Tested, n (%)	456 (45)	76 (49)	78 (52)	53 (39)	82 (60)	35 (24)	324 (45)	132 (46)
Not tested, n (%)	548 (55)	78 (51)	72 (48)	82 (61)	54 (40)	108 (76)	394 (55)	154 (54)
Of those tested - Positive, n (%)	108 (24)	13 (17)	22 (28)	9 (17)	22 (27)	2 (6)	68 (21)	40 (30)
Of those tested — Negative, n (%)	273 (60)	34 (45)	55 (71)	24 (45)	51 (62)	21 (60)	185 (57)	88 (67)
Of those tested — Results unknown, n (%)	75 (16)	29 (38)	1 (1)	20 (38)	9 (11)	12 (34)	71 (22)	4 (3)
2L treatment at data collection, n	1315	216	222	193	209	162	1002	313
Tested (n, %)	692 (53)	130 (60)	147 (66)	76 (39)	137 (66)	64 (40)	554 (55)	138 (44)
Not tested (n, %)	623 (47)	86 (40)	75 (34)	117 (61)	72 (34)	98 (60)	448 (45)	175 (56)
Of those tested - Positive (n, %)	197 (28)	29 (22)	47 (32)	19 (25)	47 (34)	12 (19)	154 (28)	43 (31)
Of those tested — Negative (n, %)	466 (67)	92 (71)	96 (65)	52 (68)	83 (61)	49 (77)	372 (67)	94 (68)
Of those tested — Results unknown (n, %)	29 (4)	9 (7)	4 (3)	5 (7)	7 (5)	3 (5)	28 (5)	1 (1)
3L+ treatment at data collection, n	177	37	28	35	16	30	146	31
Tested, n (%)	119 (67)	29 (78)	18 (64)	21 (60)	11 (69)	22 (73)	101 (69)	18 (58)
Not tested, n (%)	58 (33)	8 (22)	10 (36)	14 (40)	5 (31)	8 (27)	45 (31)	13 (42)
Of those tested — Positive, n (%)	42 (35)	9 (31)	9 (50)	7 (33)	1 (9)	8 (36)	34 (34)	8 (44)
Of those tested — Negative, n (%)	72 (61)	17 (59)	8 (44)	14 (67)	9 (82)	14 (64)	62 (61)	10 (56)
Of those tested — Results unknown, n (%)	5 (4)	3 (10)	1 (6)	-	1 (9)	-	5 (5)	-

Percentages rounded to nearest whole number, therefore percentages may not add up to 100%.

Abbreviations: 1L, first-line treatment; 2L, second-line treatment; 3L+, third-line treatment and beyond; EU5, United Kingdom, France, Germany, Spain and Italy; UK, United Kingdom; US, United States.

BRCA testing can inform treatment decisions in OC. While it is well established that carriers of *BRCA* mutations are at increased risk of OC, there is also evidence for better prognosis in OC patients who carry germline *BRCA* mutations compared with those without [26]. However, as this study was a point-in-time survey, we did not capture information relating to long-term survival and prognosis. It has been previously reported that only one-third of 6,001 women diagnosed with OC in California and Georgia between 2013 and 2014 underwent genetic testing [27]. In this study, we found that *BRCA* screening rates were higher than previously reported; with rates slightly higher in the EU5 than the US (55% *vs* 44%, respectively). We also found that the *BRCA* screening rate increased as the line of therapy progressed from 1L to 2L (45% *vs* 53%, respectively) and 28% of patients receiving 2L treatment tested positive for a *BRCA1/2* mutation, in line with the values previously reported in the literature [4]. In 2L maintenance patients receiving a PARPi, 27% of patients had a family history of OC, and of these, 93% of patients had a positive *BRCA* status. *BRCA* testing of all patients diagnosed with OC is now recommended in clinical practice [5,6]. It is important to acknowledge the role that financial burden may play in relation to *BRCA* testing rates and choice of 2L maintenance treatment. While the cost of *BRCA* testing may be relatively inexpensive, treatment options available at 2L and beyond may not be accessible or affordable to patients without insurance coverage, or where reimbursement is onerous. While this is not expected to be a major factor in Europe, In the US where insurance coverage status can vary, physicians and their consulting patients may decide not to undertake *BRCA* testing, despite updated clinical guidance, due to the potential cost implications for the patient with respect to future treatment options.

These findings are of particular relevance as they demonstrate the issue of testing inertia. Despite updated testing recommendations and the availability of new treatment regimens, there is a lag in physician uptake of these principles, indicating the importance of physician education surrounding new clinical practices. With further advances in biomarker-driven treatments, access to testing needs to be improved in order to enable patients to benefit from the most effective and appropriate treatments. As acceptance of this guidance filters down to clinical practice and treatment options in advanced OC develop, it would be expected that the screening rates reported in this study will increase further, and should be monitored closely in future studies.

In addition to testing for *BRCA* mutations, recent research has suggested HRD+ as an alternative biomarker for OC that might benefit from PARPi treatment. Homologous recombination is a DNA repair pathway, and approximately 13% of OCs harbor HRD+ attributable to germline

BRCA1/2 mutations and 50% harbor HRD+ in the absence of germline *BRCA1/2* mutations [28,29]. Further investigations to verify if an HRD+ test may be useful to select platinum-resistant tumors that may benefit from PARPi therapy are needed [29].

Our study had a number of limitations. The study was descriptive and not designed to formally compare treatment options. The sample was not a truly random sample but a convenience sample from physicians likely to practice in specialized centers. While minimal inclusion criteria governed the selection of the participating physicians, participation was influenced by willingness to complete the survey. Physicians are asked to provide data for a consecutive series of patients to avoid selection bias, but no formal patient selection verification procedures are in place. As data were only included for patients who consulted during the data collection period, patients who consulted more frequently might have been over-represented, and patients with very severe disease being treated as hospital inpatients not represented. Recall bias is a common limitation of surveys, however the data for these analyses were collected at the time of each patient's appointment which is expected to reduce the likelihood of this occurring. As with all studies of this type, findings depend on the accurate reporting of the participating physicians. Despite such limitations, real-world studies provide insights into current clinical practice. The methodological approach reported in this study is well established and has been used extensively across multiple therapy areas. The full DSP™ methodology has been previously published in detail [18], has been validated against external data sources [19], and has demonstrated the power of trend data over time [20].

5. Conclusions

In conclusion, our study showed low levels of testing for *BRCA* mutations in this population of patients with advanced OC receiving 2L treatment, despite recent guidelines recommending testing. *BRCA* screening rates varied between countries, increased with each line of therapy and were higher in the EU5 (55%) than the US (44%). PARPi are of benefit in OC patients with platinum-sensitive relapse, and in particular those with *BRCA* mutations. In this study, 28% of patients receiving 2L treatment had a *BRCA1/2* mutation. 94% of patients who were receiving a PARPi in the 2L maintenance setting had a complete response, partial response or stable disease as a result of their 1L treatment. Patients who were receiving a PARPi in the 2L maintenance setting were more often tested for *BRCA* mutations compared to other treatment groups, and a higher proportion of those tested were positive, suggesting that decisions regarding PARPi use in the 2L maintenance setting were driven by patients' *BRCA* status, histology and response to 1L treatment.

Author contributions

All authors were involved in (1) conception or design, or analysis and interpretation of data; (2) drafting and revising the article; (3) providing intellectual content of critical importance to the work described; and (4) final approval of the version to be published. MM contributed to conceptualization, formal analysis, funding acquisition, visualization, writing of the original draft and reviewing and editing of the manuscript. JH contributed to conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, supervision, validation, visualization, and reviewing and editing of the manuscript. RM contributed to conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, supervision, validation, visualization, and reviewing and editing of the manuscript. KK contributed to conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, supervision, validation, visualization, and reviewing and editing of the manuscript KM contributed to conceptualization, funding acquisition, visualization, writing of the original draft and reviewing and editing of the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Using a check box, physicians and patients provided informed consent to take part in the survey. Data were collected in such a way that patients and physicians could not be identified directly; all data were aggregated and de-identified before receipt. Data collection was undertaken in line with European Pharmaceutical Marketing Research Association guidelines and as such did not require ethics committee approval. Each survey was performed in full accordance with relevant legislation at the time of data collection, including the US Health Insurance Portability and Accountability Act 1996, and Health Information Technology for Economic and Clinical Health Act legislation, and the Declaration of Helsinki.

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Conflict of interest

MJM is employed by Merck Sharp & Dohme Corp. (MSD), a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. KM is employed by AstraZeneca. JPH is employed by Adelphi Real World, and declares no additional competing interests. RM and KK were employed by Adelphi Real World at the time this study was undertaken, and declare no additional competing interests. Data collection was undertaken by Adelphi Real World as part of an independent survey; the Adelphi Advanced Ovarian Cancer Disease Specific Programme (DSP). The DSP is a wholly-owned Adelphi product, all data are the intellectual property of Adelphi Real World.

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