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Real-world bevacizumab utilization and outcomes among women with ovarian cancer in Europe and the United States

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Objective: To investigate real-world utilization of bevacizumab and treatment outcomes in patients with advanced ovarian cancer (OC) in Europe (EU5 - France, Germany, Italy, Spain, United Kingdom) and the United States (US). *Methods*: Data were derived from the Advanced Ovarian Cancer Disease Specific Programme™ - a point-in-time, independent survey conducted between November 2017–March 2018. Physicians provided data for 8 consecutive eligible patients; patients were included if their first-line (1L) treatment consisted of chemotherapy with no maintenance (chemotherapy only) or chemotherapy plus bevacizumab and bevacizumab maintenance (chemotherapy + bevacizumab). All analyses were descriptive. *Results*: Data on 1498 patients were analysed. At 1L, 82% received chemotherapy only and 18% received chemotherapy + bevacizumab; 63% had completed 1L, of which 38% were BReast CAncer (*BRCA*) gene wildtype. Bevacizumab was used by 20% of US patients and 11% of EU5 patients. Patients who received 1L chemotherapy + bevacizumab were more likely to have tumour response (96% vs 79%), be platinum sensitive (58% vs 35%) and initiate platinum chemotherapy at second-line (2L) (72% vs 58%) compared with patients who received chemotherapy only. Treatment response (85% vs 83%) and platinum sensitivity (51% vs 40%) were similar in patients with *BRCA* wildtype compared with the total study population. Benefits observed with chemotherapy + bevacizumab compared to chemotherapy alone were consistent, regardless of *BRCA* status. *Conclusion*: Despite the benefits observed with 1L chemotherapy + bevacizumab, relatively low proportions of patients received this regimen and treatment patterns between the US and EU5 were not uniform, in part due to differences in timings of approvals and reimbursement across territories.

Keywords

Bevacizumab; Chemotherapy; First-line; Maintenance; Ovarian cancer; Real-world

1. Introduction

Ovarian cancer (OC) is the leading cause of death from gynecologic cancers, with more than two-thirds of patients presenting with advanced disease [1]. The highest incidence rates for OC are observed in developed parts of the world [2]. An estimated 295,000 newly diagnosed cases of OC and 185,000 OC-related deaths occurred worldwide in 2018 [3], with the American Cancer Society approximating there will be 21,750 newly diagnosed cases and 13,940 OC-related deaths in the United States (US) in 2020 [4]. The recommended treatment for advanced OC in the first-line (1L) setting is surgical cytoreduction followed by chemotherapy (with carboplatin and paclitaxel the standard of care) [1, 5]. A number of targeted treatments are also available. The poly adenosine diphosphate (ADP-ribose) polymerase inhibitors (PARPi) niraparib [6–8], rucaparib [9] and olaparib [10–12] have been shown to improve progression-free survival (PFS) in OC, and are approved for use in Europe and the US across a range of settings [13].

A standard of care option presented in international guidelines is the anti-angiogenetic agent, bevacizumab, plus chemotherapy, followed by bevacizumab as maintenance treatment [1, 5, 14]. Bevacizumab was approved for use in OC in Europe in 2011 following the results of two trials. In the ICON-7 trial, the addition of bevacizumab to carboplatin/paclitaxel significantly increased PFS [15], although no differences in overall survival (OS) were observed following long-term follow-up [16]. In the GOG-0218 trial, addition of bevacizumab to carboplatin/paclitaxel significantly extended PFS, but was not associated with a significant difference in OS [17]. Approval of bevacizumab for OC in the US was obtained in 2018 [18], following the availability of extended OS results from GOG-0218, which showed patients with stage IV disease had an increase in OS following addition of bevacizumab, although the difference was not statistically significant [19].

In addition to the different timelines for regulatory approval of bevacizumab in Europe and the US, its reimbursement status varies across European countries. In the US, reimbursement of bevacizumab is covered by Medicare. Reimbursement within national health service frameworks has been approved in France, Germany and Italy. In the United Kingdom (UK), the National Institute for Health and Care Excellence does not recommend bevacizumab, but its use is funded via the National Cancer Drugs Fund [20]. This variation in both timing of approval and reimbursement status

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make real-world data on patterns of bevacizumab use of interest; real-world evidence is valuable in decision-making [21], but data describing treatment patterns in patients with OC are scarce. Recent and future approvals of biosimilars may impact the use of bevacizumab in OC patients.

Given the changing treatment landscape in OC, the objective of this study was to describe the real-world utilization of bevacizumab and outcomes of treatment in the 1L setting among advanced OC patients in France, Germany, Italy, Spain, the UK (EU5) and the US.

2. Methods

2.1 Study design and data collection

The data presented in this study were derived from the Adelphi Real World Advanced Ovarian Cancer Disease Specific Programme (DSP)™ — an independent, point-in-time, non-interventional patient record-based survey of physicians and their consulting patients with advanced OC. The survey was conducted in Europe (EU5 - France, Germany, Italy, Spain, United Kingdom) and the United States (US) between November 2017 and March 2018. The full DSP™ methodology has been published in detail [22], has been validated against external data sources [23], and has demonstrated the power of trend data over time [24]. Data collection was undertaken in line with European Pharmaceutical Marketing Research Association guidelines [25] and according to relevant legislation at the time [26, 27], therefore did not require ethical approval.

A geographically diverse sample of physicians were recruited by local field-based interviewers, and were identified from publicly available lists of healthcare professionals. Physicians were eligible to participate if they qualified as a medical oncologist or gynecologist between 1983 and 2013, were personally responsible for treatment decisions for patients with advanced OC, saw at least 10 patients with advanced OC in a typical month, and agreed to all DSP™ requirements [22]. Using a check box, physicians and patients provided informed consent for use of their anonymized and aggregated data for research and publication in scientific journals. 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. 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 and receiving systemic treatment at the time 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: 3 patients on their 1L drug treatment (consolidation or maintenance); 1 patient on their second-line (2L) or later line drug treatment, having received bevacizumab at 1L maintenance; and 4 patients on their 2L or later line drug treatment, having received a platinum-based regimen at 1L. Physicians recruited the next sequential patient who met these inclusion criteria, to ensure as broad a cohort of patients as possible whilst minimizing selection bias, with data recorded at the point of consultation to minimize recall bias. The survey was designed to facilitate understanding of real-world clinical practice, and thus physicians could only report on data they had to hand at the time of the consultation. Therefore, this represents the evidence they had when making any clinical treatment and other management decisions at that consultation. No additional tests, treatments, or investigations were performed as part of this survey.

2.2 Study variables

Physicians completed record forms for each patient, which captured a wide range of both subjective (opinion-based) and objective variables, clinical information about individual patients, their disease and treatment. This included details on demographics, clinical characteristics, BReast CAncer (*BRCA*) gene testing details, current treatment for OC and OC treatment history (including duration of treatment and response to 1L treatment). Completion of the physician-reported questionnaire was undertaken through consultation of existing patient clinical records, as well as the judgement and diagnostic skills of the respondent physician, which is entirely consistent with decisions made in routine clinical practice. Due to the inclusion criteria, the DSP did not capture survival data, as this was a point-in-time survey of currently consulting patients in real-word clinical practice.

Patients were classified based on response to 1L treatment as *platinum sensitive* if progression was noted >6 months after 1L platinum therapy, *platinum resistant* if progression was noted within 0–6 months after 1L platinum therapy or *platinum refractory* if progression occurred during 1L platinum therapy.

2.3 Analysis

This study focused on real-world bevacizumab usage and outcomes at 1L and beyond in patients with advanced OC. Patients were included in the analysis if their 1L treatment consisted of chemotherapy only with no maintenance (chemotherapy only) or chemotherapy plus bevacizumab followed by bevacizumab maintenance treatment (chemotherapy + bevacizumab).

All analyses were descriptive, with values calculated for patient demographics, clinical characteristics and treatment patterns. Treatment duration and outcomes were summarized for 1L treatment. 2L treatment with platinum or non-platinum chemotherapy was summarized. Missing data were

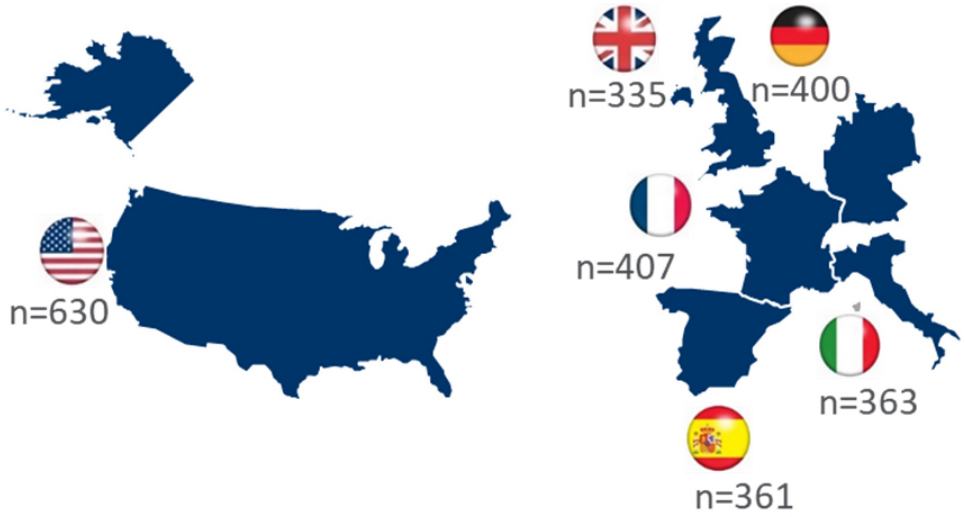

Fig. 1. Patients recruited by country.

not imputed; therefore, the base of patients for analysis could vary from variable to variable and is reported separately for each analysis.

Mean, standard deviation and range were calculated for continuous variables, and frequency counts and percentages for categorical variables. All analyses were conducted in Stata v16.0 (StataCorp LLC, Texas City, TX, USA) [28].

3. Results

3.1 Participants

A total of 340 physicians participated (France: 50, Germany: 50, Italy: 46, Spain: 46, UK: 36, US: 112). Data were collected for 2496 patients (Fig. 1), with 998 patients excluded due to initiation of alternative treatment regimens at 1L. In total, 1498 patients (60%) were eligible for analysis (EU5: 1, 101 [73%], US: 397 [27%]); of which 1232 (82%) initiated chemotherapy only at 1L (EU5: 879 [80%], US: 353 [89%]) and 266 (18%) initiated chemotherapy + bevacizumab at 1L (EU5: 222 [20%], US: 44 [11%]) (Fig. 2). In the analysed population, 945 patients (63%) had completed 1L therapy. Of these, 522 (55%) were tested for *BRCA*1/2 mutations (either germline or somatic). 360 (69%) of those tested were confirmed to be *BRCA* wildtype and 139 (27%) had a *BRCA* mutation (unknown: 23 [4%] patients) (Fig. 2).

When we compared patients who had chemotherapy only at 1L with those who received initiated chemotherapy + bevacizumab at 1L, patients in both 1L treatment groups were of similar age, with comparable family history of OC, histological findings and impact of OC on activities of daily living (ADL), In both groups, more patients had stage IV disease than stage III disease (Table 1). However, compared with patients prescribed chemotherapy only, patients prescribed chemotherapy + bevacizumab at 1L were more likely to have undergone suboptimal debulking surgery, have good performance status at initial diagnosis and at the time of data collection, and be tested for *BRCA* (Table 1).

3.2 Treatment and 2L BRCA screening

When we compared 1L bevacizumab use across different regions, just under half of EU5 patients who had completed 1L therapy received a bevacizumab-based regimen at 1L, compared to one-third of US patients (Table 2). The highest levels of use in the EU5 were seen in France and Germany (both 56%), with the lowest seen in Spain (37%). The highest proportion of patients showing a complete or partial response to 1L treatment was in the UK (85%), with the lowest in Italy (64%). 1L maintenance treatment was received by 40–50% of patients; 40% of patients in the US, Spain and the UK, and 50% in Germany (Table 2).

When we investigated *BRCA*1/2 screening patterns, of patients who initiated 2L treatment, a higher proportion of patients in the EU5 than in the US had been screened for *BRCA*1/2 (57% vs 45%, respectively). Within the EU5, screening rates were the lowest in Italy (43%) and highest in Germany and Spain (66%).

Overall, the majority of patients were prescribed a platinum-based regimen at 2L, with $\geq$70% of patients in France, Spain and the UK receiving this form of treatment (Table 2). In total, 60% of patients who had either completed 1L treatment or initiated 2L treatment received bevacizumab at, with the rate higher in the EU5 compared with the US (62% vs 55%, respectively). Across the EU5, the highest rate of bevacizumab usage in patients who had either completed 1L or initiated 2L treatment was seen in France (70%) and Germany (68%), with the lowest in the UK (45%).

A small proportion of patients initiated 2L maintenance treatment (17%), with a higher proportion in the US (25%) compared to the EU5 (15%). In total, 44% of patients that initiated 2L maintenance treatment received a PARPi-based regimen (25% received a bevacizumab-based regimen and 31% received other treatment), with more patients in the EU5 (47%) undergoing 2L maintenance PARPi treatment than in the US (39%).

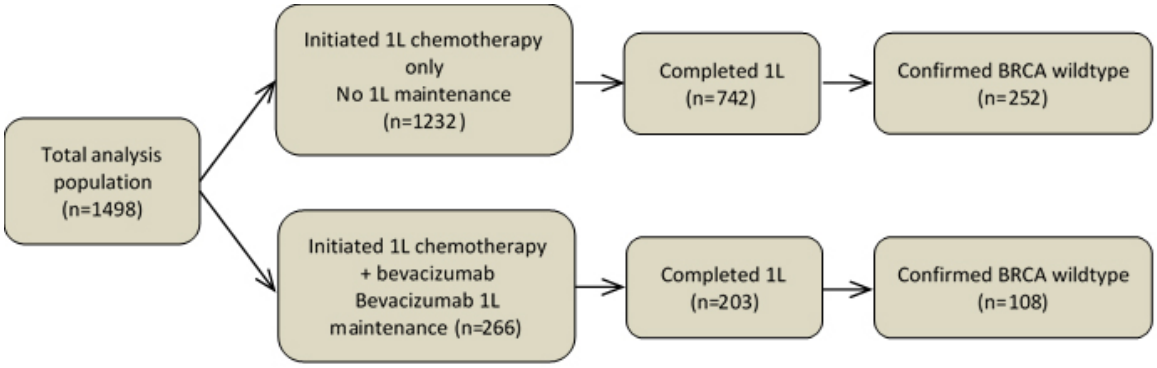

Fig. 2. Patients included in analysis. 1L, first-line treatment; *BRCA*, BReast CAncer gene.

3.3 Outcomes of bevacizumab treatment

When treatment duration was investigated, patients who received 1L chemotherapy + bevacizumab followed by bevacizumab maintenance spent more time on 1L therapy overall (12.7 months vs 5.1 months, respectively) and less time off therapy during the first two years following diagnosis (2.7 months vs 8.4 months, respectively) compared to patients receiving 1L chemotherapy only. This increased treatment duration reflects the additive benefit of bevacizumab; outcomes of 1L treatment using chemotherapy + bevacizumab are improved compared to those treated with chemotherapy only (Table 3).

Patients who received 1L chemotherapy + bevacizumab were more likely to initiate platinum chemotherapy at 2L (72% vs 58%, respectively) compared with patients who received chemotherapy only; however, both 1L treatment groups responded to therapy (96% vs 79%, respectively). When outcomes were analysed by current OC stage, more patients at stage III showed a response to 1L treatment than patients at stage IV, regardless of whether they received chemotherapy only or chemotherapy + bevacizumab (87% vs 81%, respectively). Patients at stage IV who received 1L chemotherapy only were less likely to be classified as platinum sensitive compared with patients who received chemotherapy + bevacizumab (33% vs 61%, respectively), while for patients at stage III there was little difference between patients who received 1L chemotherapy only and those who received chemotherapy + bevacizumab (42% vs 47%, respectively).

When treatment outcomes were considered by patient *BRCA* status, patients with a *BRCA* mutation had a higher rate of response at 1L (91% vs 85%) than *BRCA* wildtype patients. Although rates of platinum sensitivity were similar between groups (50% vs 51%, respectively), more patients with a *BRCA* mutation were initiated on platinum chemotherapy at 2L compared to those with *BRCA* wildtype (76% vs 67%, respectively).

When treatment outcomes were considered only for patients with tumours known to be *BRCA* wildtype (n = 360), the proportions of patients responding to treatment (85% vs 83%, respectively), sensitive to platinum (51% vs 40%, respectively) and initiating platinum chemotherapy at 2L following 1L treatment (67% vs 61%, respectively) were similar to those in the total study population (n = 945) (Table 3). This was also observed in *BRCA* wildtype patients who received chemotherapy + bevacizumab (n = 108) compared with *BRCA* wildtype patients who received chemotherapy only (n = 252), with increased proportions of treatment responders (96% vs 80%, respectively), platinum sensitive patients (63% vs 46%, respectively) and those in receipt of 2L platinum chemotherapy (73% vs 65%, respectively) (Table 3).

4. Discussion

This study explored real-world utilization of bevacizumab, 1L treatment response, 2L treatment options and *BRCA* status in patients with advanced OC across Europe and the US.

Although the addition of bevacizumab to 1L chemotherapy plus bevacizumab maintenance therapy in advanced OC has been shown to increase PFS [15, 17] and OS in patients with poor prognosis [16], there is limited evidence for the real-world effectiveness of this treatment approach. A retrospective study of 60 patients with advanced OC assigned 1L treatment of chemotherapy + bevacizumab followed by bevacizumab maintenance reported 52% of patients achieved a complete response, 38% of patients a partial response and 8% of patients had stable disease [29], comparable with the 52%, 33% and 10% of patients, respectively, in our study. Another study reported a complete or partial response rate of 77.5% in 239 patients with advanced OC receiving a 1L regimen of chemotherapy + bevacizumab [30], comparable with 85% of patients in our study.

Most OC patients are clinically eligible for bevacizumab, with use in our study primarily influenced by its reimbursement status across different countries. Overall bevacizumab usage at either completed 1L or initiated 2L varied, with the highest rate of usage seen in France (70%) and Germany (68%) compared to the US (55%) and the UK (45%). Access-related issues (not reimbursed by healthcare system/insurers or high out-of-pocket costs) have been reported as barriers to prescribing bevacizumab at 1L, with 58% and 69% of on-

Table 1. Patient demographics, clinical characteristics and *BRCA* screening.

		1L therapy	
	Total	Chemotherapy only, no maintenance	Chemotherapy + bevacizumab with bevacizumab maintenance
	(n = 1498)	(n = 1232)	(n = 266)
Age, years[a]			
N	1487	1222	265
Mean (SD)	63.5 (9.7)	63.9 (9.9)	61.4 (8.6)
Min, max	25, 89	25, 89	30, 82
OC stage at data collection, n (%)			
Stage II	43 (3)	43 (3)	0
Stage III	473 (32)	409 (33)	64 (24)
Stage IVa[b]	243 (16)	215 (17)	28 (11)
Stage IVb[b]	738 (49)	564 (46)	174 (65)
Unknown/Not assessed	1 (<1)	1 (<1)	0
Family history of OC, n (%)			
Yes	139 (9)	98 (8)	41 (15)
No	1217 (81)	1007 (82)	210 (79)
Unknown	142 (9)	127 (10)	15 (6)
Histology, n (%)			
Serous epithelial OC	975 (65)	791 (64)	184 (69)
Mucinous epithelial OC	162 (11)	141 (11)	21 (8)
Endometrial epithelial OC	107 (7)	97 (8)	10 (4)
Clear cell epithelial OC	118 (8)	92 (7)	26 (10)
Undifferentiated epithelial OC	69 (5)	61 (5)	8 (3)
Fallopian tube cancer	23 (2)	18 (1)	5 (2)
Peritoneal cancer	38 (3)	28 (2)	10 (4)
Other	6 (<1)	4 (<1)	2 (1)
ECOG performance status at initial OC diagnosis, n (%)			
0–1	1213 (81)	969 (79)	244 (92)
≥2	250 (17)	234 (19)	16 (6)
Unknown/Not assessed	35 (2)	29 (2)	6 (2)
ECOG performance status at data collection, n (%)			
0–1	1119 (75)	905 (73)	214 (80)
≥2	356 (24)	307 (25)	49 (18)
Unknown/Not assessed	23 (2)	20 (2)	3 (1)
BRCA tested, n (%)	773 (52)	584 (47)	189 (71)
Positive for *BRCA*, n (%)[c]	187 (24)	145 (25)	42 (22)
Impact of OC on ADL at data collection, n (%)			
No decrease	406 (27)	328 (27)	78 (29)
Mild decrease	776 (52)	648 (53)	128 (48)
Moderate decrease	292 (19)	235 (19)	57 (21)
Extreme decrease	24 (2)	21 (2)	3 (1)
Outcome of most recent debulking surgery, n (%)[d]			
N[d]	354	295	59
R0 resection (0 cm)	116 (33)	101 (34)	15 (25)
Optimally debulked (>1 mm–1 cm)	155 (44)	131 (44)	24 (41)
Suboptimally debulked/ Incomplete resection (>1 cm)	74 (21)	56 (19)	18 (30)
Unknown	9 (3)	7 (2)	2 (3)

Total patient base: n = 1498 (patients who initiated 1L and received chemotherapy only with no maintenance or chemotherapy + bevacizumab with bevacizumab maintenance; sample includes patients who had not completed 1L).

[a] Patients <90 years old. [b] Stage IVa = pleural effusion only; Stage IVb = any metastasis other than pleural effusion. [c] %s calculated based on number of patients tested. [d] Includes all patients who had received cytoreductive or debulking surgery.

1L, first-line treatment; ADL, Activities of Daily Living; *BRCA*, BReast CAncer gene; ECOG, Eastern Cooperative Oncology Group; OC, ovarian cancer; R0 resection, complete margin negative resection; SD, standard deviation.

Table 2. Treatment regimens by country*.

	Total	France	Germany	Italy	Spain	UK	EU5	US
Ongoing 1L, n (%)	n = 1004	n = 154	n = 150	n = 135	n = 136	n = 143	n = 718	n = 286
Receiving bevacizumab-based regimen within current 1L (treatment or maintenance)	423 (42)	76 (49)	69 (46)	90 (67)	52 (38)	54 (38)	341 (47)	82 (29)
Receiving bevacizumab-based regimen within current 1L maintenance	198 (18)	32 (21)	33 (22)	36 (22)	29 (21)	24 (17)	154 (21)	44 (15)
Completed 1L, n (%)	n = 1492	n = 253	n = 250	n = 228	n = 225	n = 192	n = 1148	n = 344
Responded to 1L regimen (complete or partial response)	1132 (76)	208 (82)	208 (83)	147 (64)	154 (68)	163 (85)	880 (77)	252 (73)
Received bevacizumab-based regimen within completed 1L	679 (46)	142 (56)	140 (56)	115 (51)	84 (37)	84 (44)	566 (49)	113 (33)
Received and completed 1L maintenance treatment	648 (43)	118 (47)	126 (50)	99 (43)	90 (40)	77 (40)	510 (44)	138 (40)
Initiated 2L, n (%)	n = 1492	n = 253	n = 250	n = 228	n = 225	n = 192	n = 1148	n = 344
2L + *BRCA* screening rate	811 (54)	159 (63)	165 (66)	97 (43)	148 (66)	86 (45)	655 (57)	156 (45)
Initiated 2L platinum-based regimen	931 (62)	181 (72)	145 (58)	123 (54)	157 (70)	140 (73)	746 (65)	185 (54)
Initiated 2L bevacizumab-based regimen	292 (20)	56 (22)	34 (14)	36 (16)	72 (32)	3 (2)	201 (18)	91 (26)
Received bevacizumab-based regimen within completed 1L OR Initiated 2L bevacizumab-based regimen	897 (60)	176 (70)	170 (68)	142 (62)	134 (60)	86 (45)	708 (62)	189 (55)
Initiated 2L PARPi-based regimen	178 (12)	41 (16)	29 (12)	14 (6)	23 (10)	6 (3)	113 (10)	65 (19)
Initiated 2L maintenance	259 (17)	54 (21)	39 (16)	47 (21)	27 (12)	7 (4)	174 (15)	85 (25)
Of those initiating 2L maintenance, received PARPi	115 (44)	32 (59)	16 (41)	12 (26)	17 (63)	5 (71)	82 (47)	33 (39)

*When reporting treatment regimens/treatment responses this includes both treatment and maintenance combined.

Total patient base: n = 1492 (all patients who had completed 1L treatment). 1L, first-line treatment; 2L, second-line treatment; EU5, France, Germany, Italy, Spain and the UK; *BRCA*, BReast CAncer gene; PARPi, poly ADP-ribose polymerase inhibitor.

cologists from the US and Europe, respectively, reporting they prescribed bevacizumab "always" or "frequently" at 1L in metastatic OC [31].

In this study, around 80% of patients received platinum-based chemotherapy only at 1L, with no maintenance phase. Around 20% of patients received bevacizumab, initially in combination with chemotherapy, or as maintenance treatment. Maintenance treatment prevents and/or delays relapse, ultimately leading to improved PFS and OS, and has a greater chance of success when starting treatment earlier. A higher proportion of patients from the EU5 received chemotherapy + bevacizumab at 1L compared with the US (20% vs 11%, respectively). Bevacizumab was approved by the European Medicines Agency in December 2011 [32], and by the US Food and Drug Administration in June 2018 [33]; therefore, differences in utility could be driven by the later approval of bevacizumab in the US market [18]. An analysis of national US database showed use of bevacizumab at 1L in OC more than doubled between 2008 and 2014, with a sharp increase in 2012, following addition of bevacizumab to the National Comprehensive Cancer Network clinical practice guidelines [34].

A cross-sectional survey across Europe and the US demonstrated that *BRCA* wildtype patients were most commonly prescribed bevacizumab in the 1L maintenance setting [35]. In patients with a *BRCA* mutation, bevacizumab monotherapy was commonly used, though olaparib monotherapy also represented a large proportion of prescriptions. Frequent use of bevacizumab in the 1L setting highlights the potential size of the population eligible for maintenance therapy, in which patients could further benefit from addition of a PARPi such as olaparib [36].

In our analysis, while the duration of treatment was longer in patients receiving chemotherapy + bevacizumab, we observed a higher proportion of patients who received 1L chemotherapy + bevacizumab responding to therapy, being classified as platinum sensitive, and initiating platinum chemotherapy at 2L, compared with patients receiving chemotherapy only, regardless of *BRCA* status. Bevacizumab is an effective treatment in this setting and should be considered in the treatment paradigm.

Our study had a number of limitations. The study was descriptive and not designed to formally compare 1L treatment options or assess causal relationships. The sample was a convenience sample from physicians likely to practice in specialized centers. While minimal inclusion criteria governed physician selection, participation was influenced by willingness to complete the survey. Physicians provided data for a consecutive series of patients to avoid selection bias, with data collected at time of consultation to limit recall bias. Patients who consulted more frequently may be over-represented, and patients with very severe disease being treated as hospital inpatients not represented. As this study only included patients receiving active treatment, platinum sensitivity classifications did not account for patients who were unable to receive 2L therapy subsequent to 1L; therefore, patients with worse 1L outcomes may be underrepresented. Data were not collected on whether this treatment

Table 3. Treatment outcomes following 1L therapy.

	Total	Chemotherapy only, no maintenance treatment	Chemotherapy + bevacizumab with bevacizumab maintenance treatment	Patients with confirmed *BRCA* mutation	Patients with confirmed *BRCA* wildtypec	Chemotherapy only, no maintenance treatment (*BRCA* wildtype)	Chemotherapy + bevacizumab with bevacizumab maintenance treatment (*BRCA* wildtype)
	(n = 945)	(n = 742)	(n = 203)	(n = 139)	(n = 360)	(n = 252)	(n = 108)
All patients[a]							
Response on completion of 1L treatment, n (%)[b]							
Complete response	488 (52)	383 (52)	105 (52)	82 (59)	202 (56)	147 (58)	55 (51)
Partial response	230 (24)	162 (22)	68 (33)	40 (29)	80 (22)	45 (18)	35 (32)
Stable disease	65 (7)	44 (6)	21 (10)	4 (3)	23 (6)	9 (4)	14 (13)
Complete/Partial response or stable disease	783 (83)	589 (79)	194 (96)	126 (91)	305 (85)	201 (80)	104 (96)
Platinum status, n (%)							
Platinum sensitive	377 (40)	259 (35)	118 (58)	70 (50)	185 (51)	117 (46)	68 (63)
Platinum resistant	130 (14)	100 (13)	30 (15)	17 (12)	42 (12)	25 (10)	17 (16)
Platinum refractory	134 (14)	126 (17)	8 (4)	9 (6)	52 (14)	49 (19)	3 (3)
Unknown	304 (32)	257 (35)	47 (23)	43 (31)	81 (23)	61 (24)	20 (19)
2L treatment, n (%)							
Initiated platinum chemotherapy	575 (61)	428 (58)	147 (72)	105 (76)	242 (67)	163 (65)	79 (73)
Did not initiate platinum chemotherapy	370 (39)	314 (42)	56 (28)	34 (24)	118 (33)	89 (35)	29 (27)
Patients currently at Stage III[a]							
N	240	202	38	35	84	62	22
Response on completion of 1L treatment, n (%)[b]							
Complete response	164 (68)	138 (68)	26 (68)	25 (71)	58 (69)	47 (76)	11 (50)
Partial response	37 (15)	27 (13)	10 (26)	5 (14)	13 (15)	4 (6)	9 (41)
Stable disease	8 (3)	8 (4)	0	0	2 (2)	2 (3)	0
Complete/Partial response or stable disease	209 (87)	173 (86)	36 (95)	30 (86)	73 (87)	53 (85)	20 (91)
Platinum status, n (%)							
Platinum sensitive	103 (43)	85 (42)	18 (47)	20 (57)	40 (48)	28 (45)	12 (55)
Platinum resistant	28 (12)	25 (12)	3 (8)	3 (9)	13 (15)	10 (16)	3 (14)
Platinum refractory	20 (8)	18 (9)	2 (5)	3 (9)	9 (11)	7 (11)	2 (9)
Unknown	89 (37)	74 (37)	15 (39)	9 (26)	22 (26)	17 (27)	5 (23)

Table 3. Continued.

	Total	Chemotherapy only, no maintenance treatment	Chemotherapy + bevacizumab with bevacizumab maintenance treatment	Patients with confirmed *BRCA* mutation	Patients with confirmed *BRCA* wildtypec	Chemotherapy only, no maintenance treatment (*BRCA* wildtype)	Chemotherapy + bevacizumab with bevacizumab maintenance treatment (*BRCA* wildtype)
	(n = 945)	(n = 742)	(n = 203)	(n = 139)	(n = 360)	(n = 252)	(n = 108)
Patients currently at Stage IV[a]							
N	697	532	165	104	275	189	86
Response on completion of 1L treatment, n (%)[b]							
Complete response	319 (46)	240 (45)	79 (48)	57 (55)	144 (52)	100 (53)	44 (51)
Partial response	191 (27)	133 (25)	58 (35)	35 (34)	66 (24)	40 (21)	26 (30)
Stable disease	56 (8)	35 (7)	21 (13)	4 (4)	21 (8)	7 (4)	14 (16)
Complete/Partial response or stable disease	566 (81)	408 (77)	158 (96)	96 (92)	231 (84)	147 (78)	84 (98)
Platinum status, n (%)							
Platinum sensitive	273 (39)	173 (33)	100 (61)	50 (48)	145 (53)	89 (47)	56 (65)
Platinum resistant	102 (15)	75 (14)	27 (16)	14 (13)	29 (11)	15 (8)	14 (16)
Platinum refractory	114 (16)	108 (20)	6 (4)	6 (6)	43 (16)	42 (22)	1 (1)
Unknown	208 (30)	176 (33)	32 (19)	34 (33)	58 (21)	43 (23)	15 (17)

[a] Total patient base: n = 945, includes patients who had completed the full regimen (chemotherapy only with no maintenance or chemotherapy + bevacizumab with bevacizumab maintenance) of 1L therapy, or who terminated 1L treatment early, but excludes patients still receiving 1L therapy at the time of data collection. [b] Not all possible responses are reported, and more than one response could be selected; %s may therefore not total 100%. [c] Includes *BRCA* wildtype patients who had completed the full regimen of 1L therapy, or who terminated 1L treatment early, but excludes patients still receiving 1L therapy at the time of data collection.
1L, first-line treatment; 2L, second-line treatment; *BRCA*, BReast CAncer gene.

was neoadjuvant or adjuvant therapy, or whether the delivery method was intravenous or intraperitoneal. Despite such limitations, real-world studies provide insights into current clinical practice.

5. Conclusions

This study highlights differences in outcomes between patients with advanced OC who were receiving, or who had received, 1L chemotherapy only and those who were receiving, or who had received, chemotherapy + bevacizumab at 1L. Regardless of *BRCA* status, patients who received 1L chemotherapy + bevacizumab were more likely to respond, be considered platinum sensitive and receive platinum chemotherapy at the time of recurrence than those receiving chemotherapy alone. Given the relatively low proportion of patients receiving 1L chemotherapy + bevacizumab and the benefits observed, it could be concluded that some patients with advanced OC do not receive optimal 1L treatment, with differences in reimbursement rates and timing of approval between countries potentially driving this under-utility.

Abbreviations

1L, first-line treatment; 2L, second-line treatment; ADL, Activities of Daily Living; *BRCA*, BReast CAncer gene; DSP, Disease Specific Programme; ECOG, Eastern Cooperative Oncology Group; EU5, France, Germany, Italy, Spain and the UK; OC, ovarian cancer; OS, overall survival; R0 resection, complete margin negative resection; SD, standard deviation; PARPi, poly ADP-ribose polymerase inhibitor; PFS, progression-free survival; PRF, patient record form; UK, United Kingdom; US, United States.

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; (4) contributed to editorial changes in the manuscript; and (5) read and approved the final 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. 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, patients provided informed consent for use of their anonymized and aggregated data for research and publication in scientific journals. 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 [1] 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 [2], and Health Information Technology for Economic and Clinical Health Act legislation [3]. Using a check box, physicians and patients provided informed consent for use of their anonymized and aggregated data for research and publication in scientific journals. 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.

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[2] US Department of Health and Human Services. Summary of the HIPAA Privacy Rule. 2003.

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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. JPH is employed by Adelphi Real World and declare 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.

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