Bevacizumab in Advanced High Grade Serous Ovarian Cancer: The Impact of BRCA Mutation Status

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Abstract: *Introduction*: BRCA mutation status plays a pivotal role in determining sensitivity to PARP inhibitors. however, its influence on the clinical benefit derived from Bevacizumab remains less clearly established. This study aims to assess survival outcomes of Bevacizumab in advanced high-grade serous ovarian cancer (HGSOC) based on BRCA mutation status.

Methods: The study included 101 patients with advanced HGSOC who were diagnosed and treated at Tanta University Hospital. All patients were tested for BRCA1/2 mutations. Patients received six cycles of weekly carboplatin and paclitaxel, with or without Bevacizumab, followed by maintenance Bevacizumab. Patients were categorized into two groups based on whether they received Bevacizumab or not, and were further stratified according to BRCA mutation status.

Results: Bevacizumab significantly improved progression-free survival (PFS) among patients with BRCA wild-type tumors (median PFS was 24.0 months versus 18.0 months, HR (95% CI: 0.1764 (0.07581 to 0.4103), P = 0.012). BRCA-mutated patients did not show a significant PFS advantage (median PFS 23 vs. 20 months, P = 0.111). OS did not differ significantly with the use of Bevacizumab, either in the BRCA wild-type or mutated group. Univariate analysis identified FIGO stage and residual tumor (RT) as significant predictors of PFS. In the multivariate model, only the residual tumor remained significant. For OS, the FIGO stage was the sole significant factor.

Conclusion: Bevacizumab added a significant PFS advantage in BRCA wild-type patients, while patients with BRCA mutations did not achieve the same benefit, suggesting that Bevacizumab may be prioritized for BRCA wild-type patients.

Keywords: Bevacizumab, Advanced, High Grade, Serous Ovarian Cancer, BRCA, Mutation.

INTRODUCTION

Epithelial ovarian cancer (EOC) represents the vast majority of ovarian cancer cases (85%–90%), with 70%–80% of the patients having high-grade serous carcinoma (HGSC) [1]. Germline BRCA1/2 mutations and TP53 mutations are considered the primary molecular changes in HGSOC [2].

About 70% of EOC relapses within 5 years of diagnosis, despite the surgical and medical efforts during initial treatment [3]. Platinum-paclitaxel systemic chemotherapy is administered after primary debulking surgery as a part of routine treatment [4]. Over the past decade, the maintenance treatments utilizing antiangiogenic therapy or PARP inhibitors (PARPi) have been implemented in advanced OC [5-8].

Bevacizumab, a monoclonal antibody that targets VEGF signaling, encounters challenges originating from the tumour microenvironment's (TME) heterogeneity [9]. Two previous large clinical trials, ICON 7 and GOG 218, evaluated the role of Bevacizumab as a first-line treatment. A prolonged median (PFS) was achieved by introducing Beva concurrently with standard chemotherapy and continuing as a maintenance [5-8]. Further subgroup analyses that identified patients who can benefit from the addition of Bevacizumab reported that PFS and OS improved specifically in females with ascites [10], stage IV disease [9, 11] and patients with stage III with >1.0 cm residual disease postoperatively [9, 11]. However, no predictive biomarkers were identified to guide the utilization of Bevacizumab.

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BRCA mutation status has been identified as an independent prognostic factor associated with prolonged PFS [12]. Moreover, BRCA mutation and homologous recombination deficiency (HRD) have become well-defined predictors for PARP inhibitors; however, there are no reliable predictive biomarkers for the efficacy of Bevacizumab.

In women with advanced HGOC, the PAOLA trial investigated the addition of maintenance Olaparib with Bevacizumab following chemotherapy plus Bevacizumab versus Bevacizumab alone. The combination was significantly associated with longer PFS [13]. However, the trial did not evaluate the impact of Bevacizumab maintenance among patients harboring BRCA mutations.

Thus, BRCA mutation status plays a pivotal role in determining sensitivity to PARP inhibitors; however, its influence on the clinical benefit derived from Bevacizumab remains less clearly established. Although some previous studies have investigated the possible role of BRCA and Bevacizumab efficacy [14, 15], the data are limited and inconclusive. Furthermore, the recent 2022 FDA withdrawal of PARP inhibitors as monotherapy for recurrent OC [16, 17] underscores the importance of re-evaluating the positioning of Bevacizumab in the treatment algorithm of BRCA-mutant patients.

Aim

To assess the survival outcomes of Bevacizumab in advanced HGSOC based on BRCA mutation status.

MATERIALS AND METHODS

The study included 101 patients with advanced high-grade serous ovarian cancer who were diagnosed between January/2019 and December/2023 and treated at Tanta University Hospital with the approval of the Research Ethics Committee (36264PR912/10/24). All patients underwent BRCA mutation testing on germline DNA using a Next-Generation Sequencing panel covering the BRCA1 and BRCA2 genes. Patients received six cycles of weekly carboplatin ([AUC] 2) plus weekly paclitaxel (80mg/m²); with or without Bevacizumab (7.5 mg/kg IV on Day 1 and every 21 days for 5–6 cycles and maintenance Bevacizumab for an additional 12 cycles or till recurrence/progression). Patients who received Bevacizumab in conjunction with neoadjuvant chemotherapy and subsequent maintenance therapy were also included. Patients with BRCA wild-type-HRD positive status were excluded, or those who received PARP inhibitors. The PFS was defined as the time elapsed between diagnosis and progression, last follow-up, or death as a result of the disease. The OS was defined as the time elapsed between diagnosis and death or the last follow-up. Patients were categorized into 2 groups based on whether they received Bevacizumab or not. The two groups were compared in terms of Clinicopathological characteristics, surgical outcomes, chemotherapy treatment, BRCA mutational status, PFS, and OS, with further stratification according to BRCA mutation status.

Statistical Analysis

The statistical analysis was conducted using SPSS v28 (IBM Inc., Armonk, NY, USA). The normality of the data distribution was assessed using histograms and the Shapiro-Wilks test. An unpaired Student's t-test was used to analyze quantitative parametric data, which were displayed as mean and standard deviation (SD). The Mann-Whitney test was used to analyze quantitative non-parametric data, which were shown as the median and interquartile range (IQR). The chi-square test or Fisher's exact test was used to analyze the qualitative variables, which were displayed as frequency and percentage (%). The PFS and OS were presented using the Kaplan-Meier curve. The impacts of several independent factors on a time-to-event outcome were ascertained using Cox Regression. Statistical significance was defined as a two-tailed P value of less than 0.05 was considered statistically significant. The Median follow-up was calculated using the reverse Kaplan–Meier method.

RESULTS

Figure **1** shows the distribution of the studied patients in the study.

Patients and Tumor Characteristics

The current study included 101 patients with a mean age of 52.70±12.3 years. Positive family history was reported in 62 patients (61.38%). Sixty-nine patients (68.32%) were stage III, and 32 (31.68%) patients were stage IV according to FIGO stage. Thirty-one (30.69%) patients were BRCA positive (twenty-six (25.74%) patients were BRCA1, and 5 (4.95%) patients were BRCA2), while 70 (69.31%) patients were BRCA negative. The median CA125 level at diagnosis was 976 UI/mL. Forty-six (45.54%) patients received ADJ therapy, while 55 (54.46%) patients underwent NACT. Seventy-five patients (74.26%) had no residual tumor

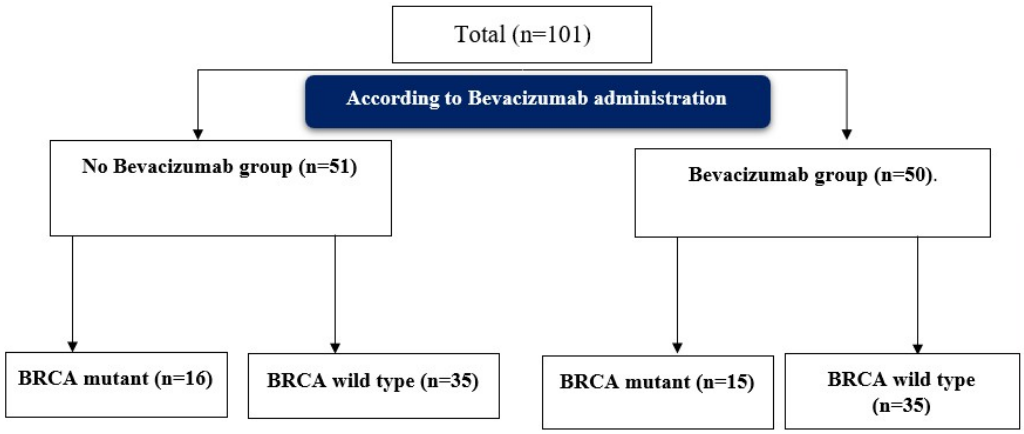


Figure 1: CONSORT flowchart of the enrolled patients.

after surgery. Forty-eight (47.52%) patients presented with as cites.

Among the 101 patients, 51 did not receive bevacizumab, while 50 were treated with bevacizumab. In the non-bevacizumab group, 16 patients (31.3%) carried BRCA mutations, compared with 15 patients (30%) in the bevacizumab group. There was no significant difference between the two groups in terms of age, family history, FIGO stage, BRCA status, CA125 level at diagnosis, chemotherapy strategy, and the incidence of as cites (Table **1**).

Table **2** indicates that BRCA-mut women had a significantly higher family history than BRCA-wt patients (P = 0.008). The two groups did not differ

Table 1: Patients' Characteristics, Clinicopathological Data, and Outcome according to Bevacizumab Administration

		Total (n=101)	No Bevacizumab group (n=51)	Bevacizumab group (n=50)	P value
Age (years)	**Mean± SD**	52.70± 12.3	53.52± 9.72	51.81± 14.65	0.491
Family history, n (%)					
Yes		62 (61.38%)	30 (58.82%)	32(64%)	0.593
No		39 (38.61%)	21 (41.18%)	18 (36%)	
FIGO staging, n (%)					
Stage III		69 (68.32%)	39 (76.47%)	30 (60%)	0.075
Stage IV		32 (31.68%)	12 (23.53%)	20 (40%)	
BRCA mutations, n (%)					
BRCA mutant		31 (30.69%)	16 (31.37%)	15 (30%)	0.881
BRCA wild type		70 (69.31%)	35 (68.63%)	35 (70%)	
BRCA 1		26 (25.74%)	13 (25.49%)	13 (26%)	0.909
BRCA2		5 (4.95%)	3 (5.88%)	2 (4%)	
CA125 at diagnosis (UI/mL)	**Median (IQR)**	976 (422.7- 2916.7)	962 (366 – 1540)	1352 (645 – 4257)	0.196
Chemotherapy, n (%)					
ADJ		46 (45.54%)	19 (37.25%)	27 (54%)	0.091
NACT		55 (54.46%)	32 (62.75%)	23 (46%)	
Surgery, n (%)					
RT		26 (33.66%)	17(33.33%)	9(18%)	0.101
No RT		75 (66.34%)	34(66.67%)	41(82%)	
Ascites, n (%)		48 (47.52%)	28 (54.90%)	20 (40%)	0.134

Data presented as mean ± SD, median (IQR) or frequency (%), FIGO: International Federation of Gynecology and Obstetrics, ADJ: Adjuvant, NACT: Neoadjuvant chemotherapy, RT: residual tumor, *: statistically significant as p value <0.05.

Table 2: Patients' Characteristics and Clinicopathological Data according to BRCA Status

Category		BRCA mutant (n=31)	BRCA wild type (n=70)	P value
Age (years)	**Mean± SD**	**47.6 ± 3.31**	**51.14 ±15.12**	**0.201**
Family history, n (%)				
Yes		25(80.65%)	37(52.86%)	0.008*
No		6 (19.35%)	33 (47.14%)	
FIGO stage, n (%)				
Stage III		22 (70.97%)	47 (67.14%)	0.703
Stage IV		9 (29.03%)	23 (32.86%)	
CA125 (UI/mL) at diagnosis	**Median (IQR)**	645 (140-5510)	990 (362-3878)	0.927
Chemotherapy, n (%)				
ADJ		13 (41.94%)	36 (51.43%)	0.378
NACT		18 (58.06%)	34 (48.57%)	
Surgery, n (%)				
RT		12 (38.71%)	17(24.28%)	0.139
No RT		19 (61.29%)	53 (75.71%)	
Ascites, n (%)		11 (35.48%)	37 (52.86%)	0.107

Data presented as mean ± SD, median (IQR) or frequency (%), FIGO: International Federation of Gynecology and Obstetrics, ADJ: Adjuvant, NACT: Neoadjuvant chemotherapy, *: statistically significant as p value <0.05.

significantly in terms of age, FIGO stage, initial CA125 level, NACT chemotherapy, or as cites.

Survival Outcomes

After a median follow-up of 45.53 months, the 2-year PFS rate was 45.54% and the 5-year OS rate was 34.65%. In the overall population, the mPFS was 21.7 ms. Although Beva was associated with a longer PFS, the observed difference did not reach statistical significance. The mPFS was 23.7 ms in the Beva group compared to 20.0 ms in the non-Beva group (*P* = 0.202). Similarly, no statistically significant difference in mOS was observed between the two groups (42.7 vs. 41.0 ms, respectively; *P* = 0.826) (Figure **2A**, **B**).

In women with BRCA mutations, the use of Beva did not result in a statistically significant improvement in survival outcomes. The mPFS was 23.0 ms in the Beva group and 20.0 ms in the non-Beva group (P = 0.111). Similarly, the mOS was 43.0 ms for patients who received Beva compared with 41.53 ms for those who did not (P = 0.792) (Figure **3A**, **B**).

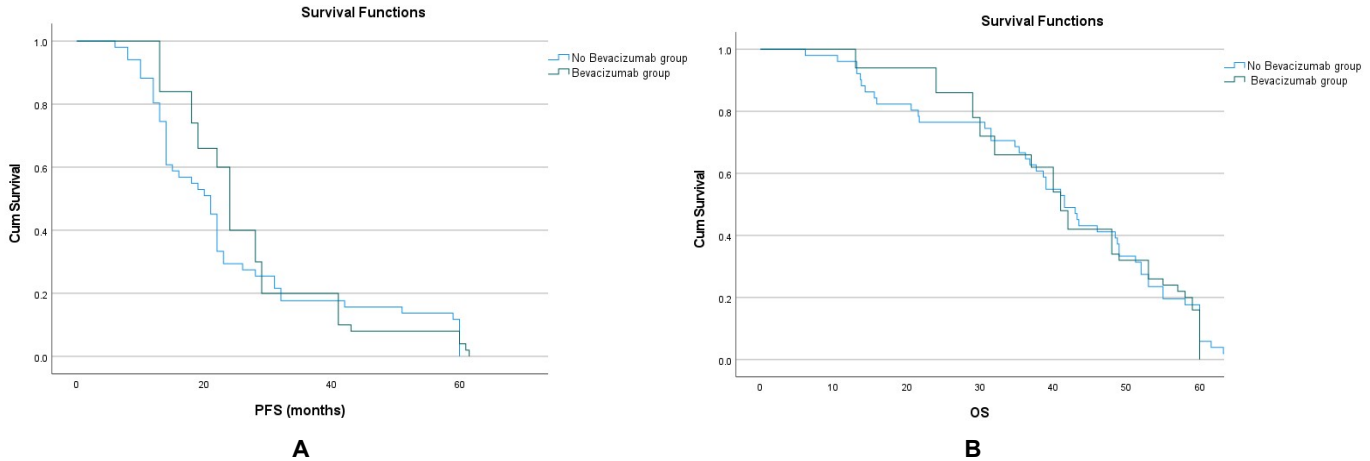
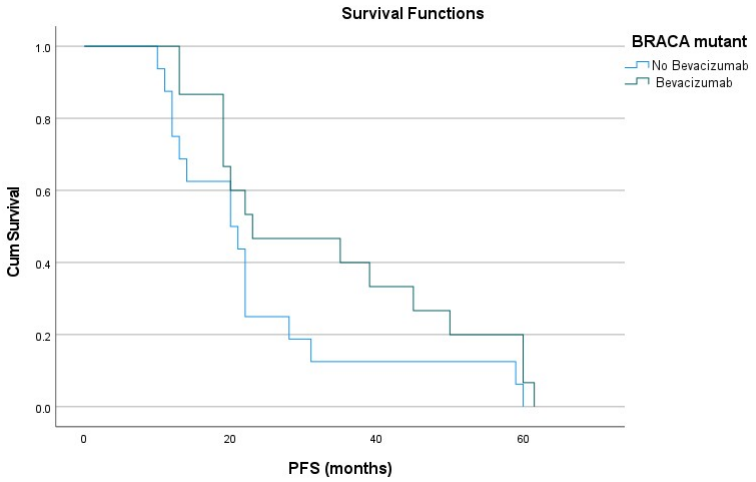


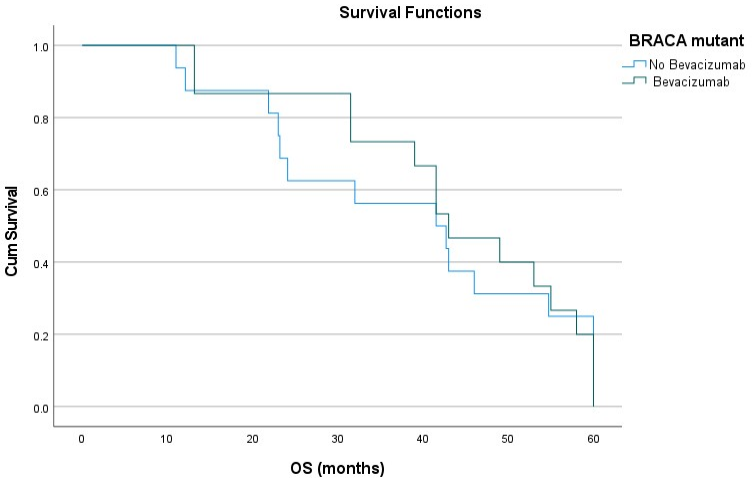
Figure 2: Kaplan Mayer for Survival analysis **A**) PFS according to Beva administration (Beva versus No Beva group mPFS: 23.7 versus 20 ms, P = 0.202). **B**) OS according to Beva administration, Beva versus No Beva group (mOS: 42.7 ms versus 41 ms, P=0.826).



Number at risk (PFS) (BRCA mutant)

Groups	Time (months)							
	0	**10**	**20**	**30**	**40**	**50**	**60**	**70**
Group: No Beva	16	15	10	4	3	3	0	0
Group: Beva	15	15	6	3	3	3	1	0

A



Number at risk (OS) (BRCA mutant)

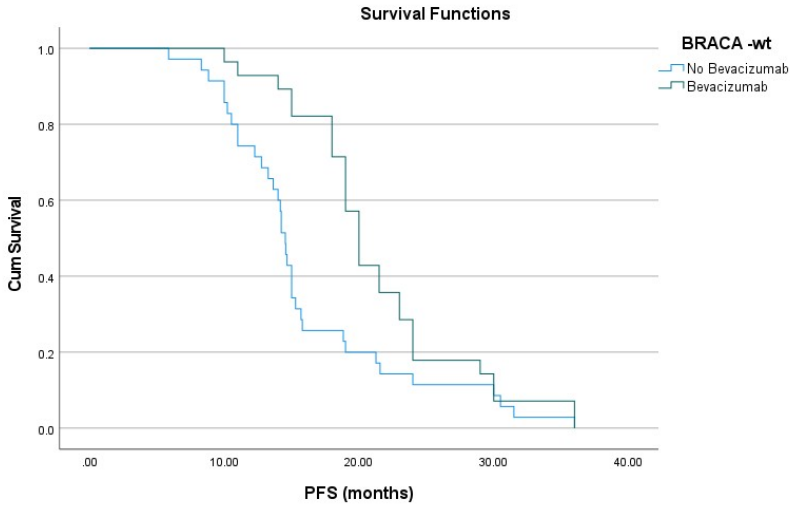
Groups	Time (months)							
	0	**10**	**20**	**30**	**40**	**50**	**60**	**70**
Group: No Beva	16	16	13	9	8	6	3	0
Group: Beva	15	15	11	11	6	3	0	0

B

Figure 3: Kaplan Mayer for Survival analysis **A**) PFS in the BRCA-mut group according to BEVA administration (BRCA-mut/ Beva versus BRCA-mut/ no Beva group mPFS: 23.0 versus 20.0 ms, P = 0.111). **B**) OS in BRCA-mut group according to BEVA administration (BRCA-mut/ Beva versus BRCA-mut/ no Beva group mOS: 43.00 ms versus 41.53 ms, P=0.792).

In BRCA-wt women, Beva treatment resulted in a statistically significant improvement in PFS. The mPFS was 24.0 ms in the Beva group compared with 18.0 ms in the non-Beva group (HR (95% CI): HR (95% CI: 0.1764 (0.07581 to 0.4103), *P* = 0.012). However, OS did not significantly differ between the BRCA-wt Beva and non-Beva groups (41.4 vs. 39.0 ms, respectively; *P* = 0.524) (Figure **4A**, **B**).

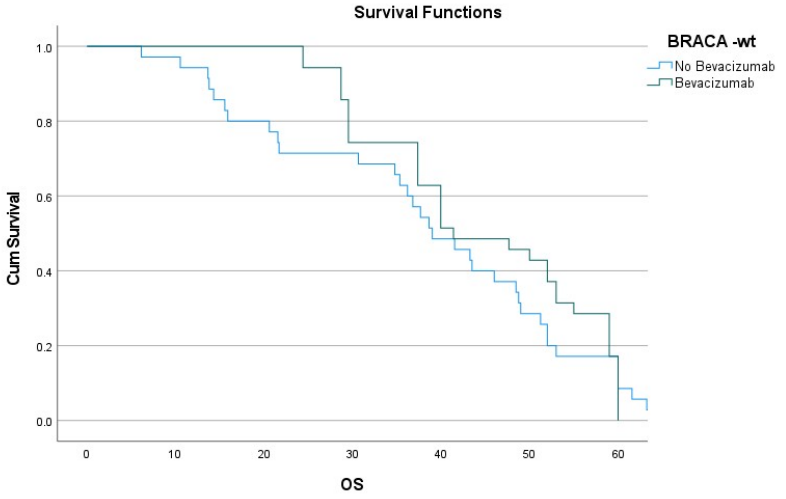
The univariate COX regression analysis indicated that FIGO staging (HR (95% CI): 0.2775 (0.0819 to 0.9401), P=0.039) and RT after surgery (HR (95% CI):



Number at risk (PFS) (BRCA -wt)

Groups	Time (months)							
	0	10	20	30	40	50	60	70
Group: No Beva	35	30	15	8	5	2	0	0
Group: Beva	35	35	25	5	5	0	0	0

A



Number at risk (OS) (BRCA -wt)

Groups	Time (months)							
	0	10	20	30	40	50	60	70
Group: No Beva	35	33	26	22	13	6	4	0
Group: Beva	35	35	35	20	11	1	0	0

B

Figure 4: Kaplan Mayer for Survival analysis **A**) PFS in BRCA-wt group according to BEVA administration (BRCA-wt/Beva versus BRCA-wt/no Beva group mPFS: 24 versus 18 ms, P = 0.012). **B**) OS in the BRCA-wt group according to BEVA administration (BRCA-wt/Beva versus BRCA-wt/no Beva group mOS: 41.40 ms versus 39 ms, P=0.524).

0.3295 (0.1114 to 0.9749), P=0.040) were significant predictors for the PFS. The multivariate COX regression analysis showed that RT after surgery (HR (95% CI): 0.2673 (0.0784 to 0.9117), P=0.045) remained a significant predictor of PFS (Table **3**).

The univariate COX regression analysis showed that only FIGO staging (HR (95% CI): 0.4009 (0.1705 to 0.9427), P=0.036) was a significant predictor for the OS (Table **4**).

Table 3: COX Regression Analysis for PFS

	Univariate			Multivariate		
	HR	95% CI	P value	HR	95% CI	P value
Age (years)	0.9870	0.9529 to 1.0225	0.468	--	--	--
FIGO staging	0.2775	0.0819 to 0.9401	0.039*	0.4794	0.1285 to 1.7885	0.274
BRCA	0.6640	0.2573 to 1.7136	0.397	--	--	--
CA125 (UI/mL)	0.9998	0.9996 to 1.0001	0.151	--	--	--
Chemotherapy (ADJ/NACT)	1.0001	0.4272 to 2.3410	0.998	--	--	--
RT after surgery	0.3295	0.1114 to 0.9749	0.040*	0.2673	0.0784 to 0.9117	0.045*
Bevacizumab	0.5693	0.1984 to 1.6333	0.064	--	--	--
Ascites	0.6766	0.3152 to 1.4524	0.316	--	--	--

FIGO: International Federation of Gynecology and Obstetrics, RT: Residual Tumor after Surgery: HR: hazard ratio, CI: confidence interval, *: statistically significant as p value <0.05.

Table 4: COX Regression Analysis for OS

	Univariate			Multivariate		
	HR	95% CI	P value	HR	95% CI	P value
Age (years)	0.9942	0.9606 to 1.0291	0.742	--	--	--
FIGO staging	0.4009	0.1705 to 0.9427	0.036*	--	--	--
BRCA	1.1564	0.5606 to 2.3855	0.694	--	--	--
CA125 (UI/mL)	1.0000	0.9999 to 1.0001	0.368	--	--	--
Chemotherapy (ADJ/NACT)	0.9979	0.4940 to 2.0159	0.995	--	--	--
RT after surgery	1.2663	0.5993 to 2.6758	0.536	--	--	--
Bevacizumab	0.5285	0.2336 to 1.1958	0.126	--	--	--
Ascites	0.9980	0.8259 to 1.2060	0.984	--	--	--

FIGO: International Federation of Gynecology and Obstetrics, RT: Residual Tumor after Surgery: HR: hazard ratio, CI: confidence interval, *: statistically significant as p value <0.05.

DISCUSSION

Our study has shown that Bevacizumab improved PFS in patients with advanced HGSOC. The significant benefit was observed only among women with BRCA-wt tumors (mPFS 24 vs 18 ms, P = 0.012), whereas those with BRCA mutations did not experience a significant advantage (mPFS 23 vs 20 ms, P = 0.111). There was no significant benefit in OS with the administration of Bevacizumab (mOS in BRCA-wt group 41.4 vs 39 ms, P=0.524, and in BRCA-mut group (43 vs 41.53 ms, P=0.792). These results support a more personalized approach in which bevacizumab may be preferentially considered for BRCA wild-type disease.

The GOG 218 and ICON7 trials assessed the role of bevacizumab as a first-line treatment. In the GOG 218 trial, the incorporation of Bevacizumab along with standard chemotherapy and continuation as maintenance resulted in a prolonged mPFS (14 versus 11 ms), at a median follow-up of 17 months [5]. Nevertheless, there was no improvement in OS; the mOS for all arms was close to 41 ms [11]. In the ICON7 trial, at the 42-month follow-up, the inclusion of Bevacizumab (7.5mg/kg) led to a higher mPFS (24 versus 22 ms) and more severe adverse events (grade 3/4) (66 vs 56%) [6], with no difference in OS or QOL [6, 18].

To identify women who could benefit from using Bevacizumab, additional subgroup analyses were carried out that showed improved PFS and OS in females with ascites [10], stage III with >1.0 cm residual disease postoperatively [9, 11], and stage IV disease [11]. Nevertheless, no predictive biomarkers were found to direct the administration of Bevacizumab.

Olaparib maintenance therapy combined with Bevacizumab was assessed in the phase III PAOLA-1/ENGOT-ov25 trial for patients with advanced OC who

responded to first-line platinum-based chemotherapy plus Bevacizumab. The combination significantly improved PFS, particularly in women with BRCA1/2 mutations and HRD-positive tumors [19]. Notably, the trial did not evaluate the impact of Bevacizumab maintenance among patients harboring BRCA mutations.

To overcome this limitation, a population-adjusted indirect comparison of SOLO1 and PAOLA-1/ENGOT-ov25 trials was carried out to evaluate the relative effectiveness of maintenance treatment with Olaparib with or without Bevacizumab, versus Bevacizumab, versus placebo for recently diagnosed BRCA-mut advanced OC. PFS at 2 years was 76% for Olaparib plus Bevacizumab,73% for Olaparib, 44% for Bevacizumab, and 36% for placebo. In addition, (20%) in the PAOLA1 study discontinued treatment because of toxicity, versus 10% of women in the SOLO1 trial. Therefore, adding Bevacizumab to Olaparib did not result in a meaningful survival advantage [20]. Thus, the benefit should be weighed against toxicity in BRCA-mutated patients.

Our findings are in line with the Italian study, which demonstrated that BRCA wild-type patients with advanced OC experienced prolonged PFS with front-line Bevacizumab maintenance (20 vs 15 ms, p = .019). In contrast, BRCA-mutated cases did not derive the same oncological benefit (24 vs. 22 ms, p = .3) [14].

Additionally, in a report on maintenance therapy with Bevacizumab in women with OC, it was noted that maintenance Bevacizumab resulted in a mPFS improvement only in BRCA-wt patients (15.7 vs 10.6 ms; P=.0001), not in those with mutations. The authors concluded that “patients may start Bevacizumab treatment while waiting for BRCA mutation testing results. Patients harboring BRCA1/2 mutations can be transitioned to maintenance therapy with Olaparib” [21].

Furthermore, the mPFS was significantly prolonged with niraparib plus Bevacizumab compared to niraparib monotherapy (11.9 vs 5.5 ms, P=0.0001) as demonstrated in the phase II randomized trial involving platinum-sensitive relapsed OC. Significantly longer PFS was observed among BRCA wild-type women (11.3 vs 4.2 months, P=0.0001), but not in BRCA mutant (14.4 vs 9.0 months, P=0.095). This suggests that the combination with Bevacizumab may not be necessary for BRCA-mutated tumors [22].

The tumor microenvironment could biologically explain these findings. Four molecular subgroups of HGSOC-differentiated, immunoreactive, mesenchymal, and proliferative-were identified by the Cancer Genome Atlas research network [2]. Tumours with BRCA mutations are more commonly recognized as an immunoreactive subtype, which is defined by an increased number of tumor-infiltrating lymphocytes. Conversely, the mesenchymal subtype expresses more genes associated with angiogenesis and fewer genes linked to immune cells [23]. Consequently, it is hypothesized that Bevacizumab is less active in BRCA-mutated tumors.

Furthermore, the systemic inflammatory marker, neutrophil-to-lymphocyte ratio (NLR), is commonly used to assess the equilibrium between neutrophil-dependent protumor inflammation and lymphocyte-associated antitumor immune response. An elevated NLR prolonged the PFS and OS in patients with OC receiving Bevacizumab, according to a real-world retrospective study, and in a sub-analysis, high NLR was associated with BRCA wild-type tumors [24].

Thus, the combined maintenance treatment with Olaparib and Bevacizumab would prevent the administration of Bevacizumab upon recurrence and limit subsequent treatment options. This concern has become even more relevant in the light of recent FDA regulatory changes: Between June and September 2022, all three indications for PARPi as monotherapy in recurrent OC were withdrawn, based on the results of phase 3 clinical trials [16]. Results from the phase III ARIEL4 trial that evaluated rucaparib versus standard chemotherapy in BRCA-mut recurrent OC, revealed that mOS was 19.4 ms vs. 25.4 ms, with the chemotherapy group having a longer OS [25, 26].

Final OS results from SOLO3 suggest that patients receiving Olaparib might have had a lower OS than those receiving chemotherapy, particularly in patients who had received three or more lines of chemotherapy. However, the difference was not statistically significant. The mOS was 39.4 ms with chemotherapy and 29.9 ms with Olaparib [26]. The decision to withdraw niraparib was based on "the totality of information" from PARPi therapy in recurrent situations and the observed lower OS with other PARPi in BRCAmut and heavily pretreated advanced OC [27]. Currently, there are no remaining FDA approvals for PARP inhibitor monotherapy in recurrent OC [17].

In this context, our findings support sparing BRCA-mutant women from Bevacizumab at first-line treatment, therefore maintaining its use at recurrence. This approach is particularly relevant after the FDA

withdrawal of PARP inhibitors as monotherapy in recurrent settings and considering that Bevacizumab can generally be administered only once during the disease course, and extending treatment beyond progression is not a standard practice.

Moreover, both Bevacizumab and PARPi are associated with substantial toxicity profiles and high economic burden. Although GOG 218 did not assess the actual cost data. A subsequent cost-effectiveness analysis using available PFS and OS data revealed that the addition of Bevacizumab to chemotherapy resulted in an adverse cost-effectiveness ratio [28]. In addition, cost-effectiveness analyses have questioned the value of Bevacizumab and PARPi combination outside biomarker-selected populations, suggesting that careful patient stratification is essential to balance clinical benefit against toxicity risks and financial sustainability [29, 30].

Our findings support that the biomarker-based selection may improve balancing clinical benefit against financial burden, particularly in low- and middle-income countries.

The current study has certain limitations, such as a small sample size and the retrospective design, which may result in selection bias or unmeasured confounding factors.

CONCLUSION

Bevacizumab added a significant PFS advantage in BRCA wild-type patients, while patients with BRCA mutations did not achieve the same benefit. These findings underscore the significance of optimizing treatment sequencing, re-examining the positioning of Bevacizumab in the treatment algorithm, and tailoring future therapeutic combinations with PARPi for BRCA-mutant women.

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Not applicable.

DECLARATION OF CONFLICTING INTEREST

The Author(s) declare(s) that there are no relevant financial or non-financial competing interests to report.

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AUTHOR'S CONTRIBUTION

Conceptualization: M.A., methodology: M.A., Z.F.A. & E.E.F., Formal analysis and investigation: M.A., A.M.E.& R.A.M, Writing—original draft preparation: M.A., Writing—review and editing: M.A., A.M.E., E.E.F., supervision, validation and final editing: R.A.M., & Z.F.A, all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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