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ORIGINAL ARTICLE

Benefit from maintenance with PARP inhibitor in newly diagnosed ovarian cancer according to *BRCA1/2* mutation type and site: a multicenter real-world study

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Background: Knowledge about the association between the *BRCA1/2* mutation type and location and response to poly (ADP-ribose) polymerase inhibitors (PARPis) as single agent in ovarian cancer is limited. This study aimed to investigate the effectiveness of PARPi based on functional domains (FD) [RING, BRCT, DNA-binding (BD), RAD51-BD] and types (frameshift, missense, nonsense, splicing) of *BRCA1/2* gene mutations in ovarian cancer.

Materials and methods: This multicenter real-world study retrospectively enrolled *BRCA1/2*-mutated ovarian cancer patients receiving olaparib maintenance between January 2010 and December 2022. Data were compared with historical series of patients who did not receive olaparib and analyzed based on the FD involved in *BRCA1/2* mutations. Progression-free survival was calculated from the date of the last platinum-based treatment until recurrence or last follow-up.

Results: After a median follow-up of 46 months (range 32-60 months), 140 patients who underwent olaparib maintenance were compared with 128 who did not. PARPi showed efficacy in the overall population. The no-exon 11 patients benefitted more from olaparib than exon 11 patients [hazard ratio (HR) 0.48, 95% confidence interval (CI) 0.25-0.93]. In the *BRCA1* group, patients with mutations in RING and BRCT domains had significant benefits from PARPi (HR 0.08, 95% CI 0.01-0.75; HR 0.10, 95% CI 0.02-0.38, respectively). Among *BRCA2*-mutated patients, RAD51-BD mutations were associated with higher response to olaparib (HR 0.23, 95% CI 0.10-0.52). According to the mutation type, the major effect of PARPi was in the missense group (HR 0.04, 95% CI 0.01-0.31). No patients with p.(Ala1708Glu) in the BRCT domain (*BRCA1*) receiving PARPi experienced recurring disease in the study period.

Conclusions: *BRCA1/2*-mutated patients benefit from olaparib, but with variations according to the mutation type and FDs. *BRCA1*-mutated patients in the RING or BRCT and *BRCA2*-mutated in the RAD51-BD have the greatest benefit. Patients with missense mutations, especially those with p.(Ala1708Glu), have the most significant advantage from maintenance with PARPi.

Key words: ovarian cancer, *BRCA* mutation, PARP inhibitors, mutation type, mutation site

INTRODUCTION

Ovarian cancer is the second most common cause of gynecologic cancer death in women worldwide.[1] Over 50%-60% of ovarian malignancies are categorized as high-grade serous ovarian cancer (HGSOC).[2,3] About 50% of cases have a genetic mutation in DNA repair proteins. In particular, the most common mutations were detected in BReast CAncer genes (*BRCA*) 1 and 2, covering ∼20%-25% of all HGSOC.[4-6] These two genes play a fundamental role in the repair processes of double-stranded DNA damage by homologous

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recombination. The mutations in these genes can affect different sites, impacting their functions differently.[7,8] Notably, *BRCA1* contains several important functional domains (FDs) that interact with various proteins. The Really Interesting Gene RING-finger domain (RING) binds to *BRCA1* Associated RING Domain 1 (*BARD1*). The DNA-binding domain (DNA-BD) contributes to the DNA-repair-related functions mediated through the *BRCA1*-associated surveillance complex (BASC). The *BRCA1* C-Terminal (BRCT) domains bind to many proteins, including RNA polymerase II.[9]

The central region of *BRCA2* contains a RAD51-binding domain (RAD51-BD). At the C terminus of *BRCA2*, a prominent DNA-binding domain (DNA-BD) is present.[10] Because of the interaction of *BRCA1*, *BRCA2,* and all these proteins, the reparation of DNA damage is possible. Furthermore, in the *BRCA1* and *BRCA2* genes, a large central area called exon 11 is recognized. Data showed inconsistencies regarding the impact of exon 11 involvement on prognosis and response to treatments.[11-13]

The most commonly used databases (Breast Cancer Information Core BIC nomenclature, *BRCA* Exchange, and ClinVar)[14-16] consider several types of mutation, including missense, nonsense, frameshift, and splicing, that alter the protein with different effects on structure and functions.[17-20] Currently, we have limited knowledge about the association between the type and location of *BRCA1/2* mutations, the prognosis, and the response to treatment, particularly to poly (ADP-ribose) polymerase inhibitors (PARPi) when used as a single agent in HGSOC. Clinical data from the PAOLA-1 study indicate that patients with mutations in the DNA-BD of *BRCA1* are more responsive to the combination of olaparib and bevacizumab, while those with mutations in the DNA-BD of *BRCA2* have better outcomes, regardless of the administered maintenance.[13]

The aim of this study was to investigate the effectiveness of the PARPi olaparib and survival outcomes based on the FDs of *BRCA1/2* gene mutation. The impact of different mutation types (frameshift, nonsense, missense, and splicing) on survival and the involvement of exon 11 was also evaluated.

MATERIALS AND METHODS

In this multicenter real-world study, data were collected from a cohort of patients diagnosed with ovarian cancer who were treated between January 2010 and December 2022 in four Italian academic centers: Fondazione Policlinico Agostino Gemelli in Rome, Policlinico San Matteo in Pavia, University of Milan-Bicocca and University of Palermo (ESMO-GROW Flowchart, Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2025.104533).

Patients with newly diagnosed advanced HGSOC and high-grade endometrioid cancer with a definitely pathogenetic germline and/or somatic mutation in *BRCA* genes [class 5 Evidence-based Network for the Interpretation of Germline Mutant Alleles (ENIGMA) and the International Agency for Cancer Research (IARC)[21]] were enrolled, irrespective of surgical treatment (primary debulking surgery and interval cytoreductive surgery). Other histotypes, *BRCA* status unknown (neither germline nor somatic), or a variant of uncertain significance (VUS) in the *BRCA1/2* gene (class 3) excluded patients from the analysis. Data of follow-up should be available.

According to maintenance treatment received after standard carboplatin—paclitaxel, patients were matched 1 : 1 in two cohorts: those who received olaparib maintenance and those who did not (a historical series of patients with similar clinical characteristics who did not undergo maintenance per clinical practice due to comorbidities, lack of indication or drug availability, clinician discretion, or patient preference). Information regarding patients' characteristics, clinical data, disease presentation at diagnosis, medical and surgical treatment received, and survival outcomes was recorded in an anonymous database protected by a password.

The collection of detailed genetic data in the *BRCA* mutation variant was supervised and reviewed by specialized genomic experts (A.M, M.D.B). All patients signed the informed consent for their data to be collected for scientific purposes. The study was approved by the ethics committee. Mutations were reported on LRG_292t1 and LRG_293t1 on Human Genome hg19. For *BRCA1,* the following FDs were considered: RING domain involving amino acids (aa) 8-96; DNA-BD aa 452-1092; and BRCT aa 1646-1736 and 1760-1855.[22,23] The following functional domains of *BRCA2* were considered: RAD51-BD covering aa 900-2000 and DNA-BD aa 2459-3190.[10] Exon 11 encompasses aa 225-1366 and aa 638-2281 in *BRCA1* and *BRCA2* genes, respectively.[24] Regardless of the FD, analysis according to the type of *BRCA1/2* gene mutation (frameshift, missense, nonsense, and splicing) was carried out.

The primary endpoint was to assess the extent of the benefit from olaparib maintenance in terms of progression-free survival (PFS), based on the functional domain involved in mutations in the *BRCA1* and *BRCA2* genes. Secondary endpoint was the assessment of the PFS according to the type of *BRCA1/2* mutation and the involvement of exon 11.

Statistical analysis

The data were summarized using descriptive statistical measures. In-depth, qualitative data were expressed as absolute and percentage frequency. Quantitative data distribution was assessed by the Shapiro—Wilk test, and then variables were described either as mean and standard deviation or median and interquartile range, as appropriate. Between-group differences were evaluated, as for qualitative data, by the chi-square test. For quantitative variables, either one-way ANOVA or Student's *t*-test and the Mann—Whitney *U* test or Kruskal—Wallis test were applied, as appropriate. PFS was defined as the time interval between the last administration of platinum (first chemotherapy line) and the date of subsequent progression or last follow-up.

To evaluate the correlation between the *BRCA* mutation site, the type of mutation, and PFS, Kaplan—Meier survival

Table 1. Characteristics and treatment of patients in the overall population, and according to PARPi maintenance

	Overall population	PARPi	No PARPi	*P* value[a]
Total *n* (%)	268 (100)	140 (100)	128 (100)	
Age at diagnosis				
Mean (SD)	54.26 (10.06)	54.69 (9.7)	53.79 (10.4)	0.46
Median (IQR)	53.5 (47-61)	54 (48-61)	52.5 (47-61)	0.90
***BRCA* gene** *n* (%)				
BRCA1	167 (62.3)	86 (61.4)	81 (63.3)	0.75
BRCA2	101 (37.7)	54 (38.6)	47 (36.7)	
Functional domain *n* (%)				
BRCA1 RING	13 (4.9)	8 (5.7)	5 (3.9)	0.24
BRCA1 DNA-BD	25 (9.3)	8 (5.7)	17 (13.3)	
BRCA1 BRCT	29 (10.8)	19 (13.6)	10 (7.8)	
BRCA1 other	100 (37.3)	51 (36.4)	49 (38.3)	
BRCA2 RAD51-BD	51 (19)	28 (20)	23 (18)	
BRCA2 DNA-BD	16 (6)	10 (7.1)	6 (4.7)	
BRCA2 other	34 (12.7)	16 (11.4)	18 (14.1)	
Mutation type *n* (%)				
Frameshift	151 (56.3)	72 (51.4)	79 (61.7)	0.38
Missense	32 (11.9)	18 (12.9)	14 (10.9)	
Nonsense	74 (27.6)	43 (30.7)	31 (24.2)	
Splicing	11 (4.1)	7 (5)	4 (3.1)	
EXON 11 *n* (%)				
No	125 (46.6)	68 (48.6)	57 (44.5)	0.50
Yes	143 (53.4)	72 (51.4)	71 (55.5)	
FIGO stage *n* (%)				
III	227 (84.7)	116 (82.9)	111 (86.7)	0.38
IV	41 (15.3)	24 (17.1)	17 (13.3)	
Histology *n* (%)				
Serous	265 (98.9)	138 (98.6)	127 (99.2)	0.53
Endometrioid	3 (1.1)	2 (1.4)	1 (0.8)	
Family history *n* (%)				
No	89 (33.2)	34 (24.3)	55 (43)	<0.001
Yes	167 (62.3)	102 (72.9)	65 (50.8)	
Missing	12 (4.5)	4 (2.8)	8 (6.2)	
Performance status *n* (%)				
0	230 (85.8)	119 (85)	111 (86.7)	0.65
1	34 (12.7)	19 (13.6)	15 (11.7)	
Missing	4 (1.5)	2 (1.4)	2 (1.6)	
Surgery *n* (%)				
PCS	175 (65.3)	89 (63.6)	86 (67.2)	0.44
NACT + ICS	92 (34.3)	51 (36.4)	41 (32)	
No surgery	1 (0.4)	0	1 (0.8)	
Residual tumor at surgery *n* (%)				
No RT	216 (80.6)	122 (87.1)	94 (73.4)	0.13
RT present	39 (14.6)	17 (12.1)	22 (17.2)	
Missing	12 (4.5)	1 (0.7)	11 (8.6)	
No surgery	1 (0.4)	0	1 (0.8)	
Type of chemotherapy *n* (%)				
Platinum + paclitaxel	261 (97.4)	138 (98.6)	123 (96.1)	0.48
Platinum alone	1 (0.4)	0	1 (0.8)	
Other platinum doublet	5 (1.9)	2 (1.4)	3 (2.3)	
Missing	1 (0.4)	0	1 (0.8)	
Best response *n* (%)				
CR	218 (81.3)	111 (79.3)	107 (83.6)	0.20
PR	44 (16.4)	27 (19.3)	17 (13.3)	
Missing	6 (2.2)	2 (1.4)	4 (3.1)	
Recurrence *n* (%)				
No	120 (44.8)	100 (71.4)	20 (15.6)	<0.001
Yes	148 (55.2)	40 (28.6)	108 (84.4)	

CR, complete response; DNA-BD DNA-binding; FIGO, International Federation of Gynecology and Obstetrics; ICS, interval cytoreductive surgery; IQR, interquartile range; NACT, neoadjuvant chemotherapy; PARPi, poly (ADP-ribose) polymerase inhibitors; PCS, primary cytoreductive surgery; PR, partial response; RAD51-BD, RAD51-binding; RT, residual tumor, SD, standard deviation.

[a]Only in patients with available data.

analysis was computed. Notably, the log-rank test was used to assess the prognostic value of the *BRCA* mutation site and type on clinical outcomes. To reduce bias in survival estimation due to different follow-up durations in the two groups, PFS data were recorded up to a maximum of 60 months.

Estimated hazard ratios (HRs) and their two-sided 95% confidence intervals (CIs) were calculated using the Cox

Table 2. PARPi benefit in the overall population, according to the gene involved, the site, and the type of mutation (hazard ratio)

	Hazard ratio (95% CI)	*P* value
Overall population	0.25 (0.17-0.36)	<0.001
***BRCA* gene**		
BRCA1	0.29 (0.18-0.45)	<0.001
BRCA2	0.20 (0.10-0.38)	<0.001
Mutation site		
BRCA1 RING	0.08 (0.01-0.75)	0.02
BRCA1 DNA-BD	0.75 (0.23-2.43)	0.64
BRCA1 BRCT	0.10 (0.02-0.38)	0.001
BRCA1 other	0.35 (0.20-0.61)	<0.001
BRCA2 RAD51-BD	0.23 (0.10-0.52)	<0.001
BRCA2 DNA-BD	0.24 (0.04-1.34)	0.10
BRCA2 other	0.15 (0.04-0.54)	0.003
Mutation type		
Frameshift	0.21 (0.13-0.35)	<0.001
Missense	0.04 (0.01-0.31)	0.002
Nonsense	0.43 (0.22-0.82)	0.01
Splicing	1.03 (0.18-5.69)	0.96

CI, confidence interval; DNA-BD, DNA-binding; PARPi, poly (ADP-ribose) polymerase inhibitors; RAD51-BD, RAD51-binding.

proportional hazards model. According to the results obtained in the PAOLA-1 study,[13] a sample size of at least 200 patients would allow the detection of an HR of ≥0.50 with a power of 80% at a significance level of 1%, taking into account multiple testing. A *P* value <0.05 was considered statistically significant. All analyses were carried out using Statistical Package for Social Science (version 17.0, SPSS Inc., Chicago, I).

RESULTS

A total of 140 *BRCA*-mutated patients who underwent olaparib as first-line maintenance were compared with 128 *BRCA*-mutated patients who did not receive PARPi in the same setting. The clinical and demographic characteristics according to the maintenance arm are summarized in Table 1. With the only exception of family history of cancer, the two groups were homogeneous regarding clinical characteristics, up-front treatment, and the response to platinum-based chemotherapy.

Most patients were diagnosed with International Federation of Gynecology and Obstetrics (FIGO) stage III ovarian cancer with serous histotype. More than 60% of patients underwent primary cytoreductive surgery without residual tumor. Almost all patients received neoadjuvant and/or adjuvant therapy with carboplatin and paclitaxel with complete/partial response after treatment.

Among the enrolled population, 62.3% harbored mutation in *BRCA1* ($n = 167$) and 37.7% in *BRCA2* ($n = 101$). Without statistical difference according to olaparib administration, BRCT was the most frequently mutated FD in the *BRCA1* gene (17.4%, $n = 29/167$), followed by DNA-BD (15%, $n = 25/167$) and RING domain (7.8%, $n = 13/167$). For *BRCA2*, more than half of the mutations were located in the RAD51-BD (50.5%, $n = 51/101$), followed by DNA-BD (15.8%, n 16/101). A significant portion of the mutations were detected outside these FDs of *BRCA1* and *BRCA2,* comprising 59.9% ($n = 100/167$) and 33.7% ($n = 34/101$) of the mutations, respectively. The most frequent type of mutation was frameshift (56.3%), followed by nonsense (27.6%), without statistical difference between patients who received PARPi and patients who did not. Slightly more than 50% of the mutations occurred in exon 11.

After a median follow-up of 46 months (range 32-60 months), better survival was observed in patients who received olaparib after first-line treatment. Relapse was observed in 84.4% of patients without olaparib maintenance ($n = 108$) compared with 28.6% in the PARPi group ($n = 40$). The benefit from maintenance with PARPi was observed in the overall population (HR 0.25, 95% CI 0.17-0.36) and in both the genes (*BRCA1*, HR 0.29, 95% CI 0.18-0.45; *BRCA2*, HR 0.20, 95% CI 0.10-0.38; Table 2).

Patients with or without mutations located in exon 11 of both genes derived benefit from PARPi (exon 11, HR 0.38, 95% CI 0.24-0.61; no-exon 11, HR 0.14, 95% CI 0.08-0.26; Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.104533). The no-exon 11 patients tended to benefit more from receiving olaparib than exon 11 patients (HR 0.48, 95% CI 0.25-0.93). The magnitude of the benefit was particularly evident in *BRCA2* no-exon 11

Table 3. PARPi benefit in the overall population, according to the gene involved, the site, and the type of mutation (24-month PFS and median PFS)

	PARPi 24-month PFS (%)	No PARPi 24-month PFS (%)	PARPi median PFS, months (95% CI)	No PARPi median PFS, months (95% CI)	*P* value
Overall population	81.8	42.1	NR	19.0 (14.6-23.4)	<0.001
Mutation site					
BRCA1 RING	65.6	0	NR	11.0 (8.8-13.1)	0.006
BRCA1 DNA-BD	100	58.8	31.0 (29.9-32.1)	33.0 (7.4-58.5)	0.63
BRCA1 BRCT	94.4	30	NR	13.0 (9.9-16.1)	0.001
BRCA1 other	75	44.8	NR	20.0 (13.2-26.8)	<0.001
BRCA2 RAD51-BD	81	43.5	NR	20.0 (7.5-32.5)	<0.001
BRCA2 DNA-BD	77.8	66.7	NR	28.0 (0.56-55.4)	0.08
BRCA2 other	87.5	27.8	NR	16.0 (11.8-20.2)	<0.001
Mutation type					
Frameshift	85.8	36.6	NR	17.0 (12.9-21.0)	<0.001
Missense	92.3	35.7	NR	17.0 (11.5-22.5)	<0.001
Nonsense	74.5	58.1	NR	29.0 (17.0-41.0)	0.007
Splicing	57.1	50	30.0 (6.9-53.1)	14.0 (0-48.6)	0.96

CI, confidence interval; DNA-BD, DNA-binding; NR, not reached; PARPi, poly (ADP-ribose) polymerase inhibitors; PFS, progression-free survival; RAD51-BD, RAD51-binding.

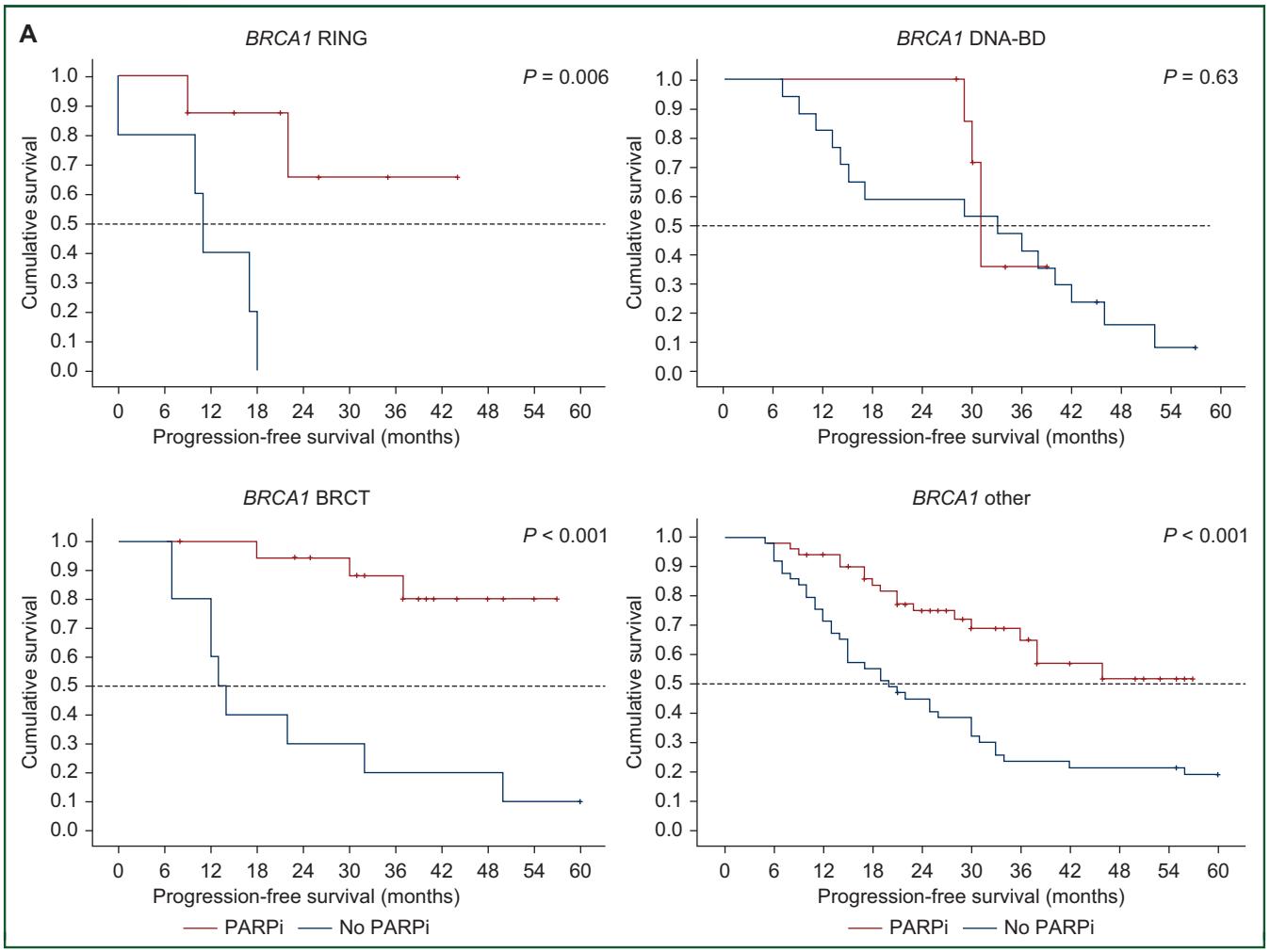

Figure 1. Progression-free survival according to functional domain in the *BRCA1*-mutated population (A) and in the *BRCA2*-mutated population (B).
DNA-BD, DNA-binding; PARPi, poly (ADP-ribose) polymerase inhibitors; RAD51-BD, RAD51-binding.

patients (HR 0.10, 95% CI 0.02-0.47); Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.104533).

Differences in outcomes were found when comparing groups according to the involved FD and the type of mutations. Notably, among patients with *BRCA1* involvement, those with mutation located in the RING and BRCT domains showed a significant benefit from olaparib maintenance [RING 24-month PFS: 65.6% versus 0%, median PFS (mPFS): not reached (NR) versus 11 months, HR 0.08, 95% CI 0.01-0.75 and BRCT 24-month PFS: 94.4% versus 30%, mPFS: NR versus 13 months, HR 0.10, 95% CI 0.02-0.38, respectively] (Tables 2 and 3, Figure 1A). For *BRCA2*-mutated patients, among cases with mutation in FDs, those with mutations in the RAD51-BD had the most relevant advantage from PARPi (24-month PFS: 81% versus 43.5%, mPFS: NR versus 20 months, HR 0.23, 95% CI 0.10-0.52; Tables 2 and 3, Figure 1B).

Regarding the type of mutation, the major effect of olaparib was obtained in missense mutation (24-month PFS: 92.3% versus 35.7%, mPFS: NR versus 17 months, HR 0.04, 95% CI 0.01-0.31; Tables 2 and 3, Figure 2). No significant benefit from PARPi was observed in patients with splicing mutation or in the *BRCA1/2* DNA-BD groups (Tables 2 and 3, Figures 1 and 2).

Among the patients with missense mutations in our population, 28% ($n = 9/32$) presented with the mutation p.(Ala1708Glu), located in the BRCT domain (*BRCA1*). Eight received PARPi after first-line chemotherapy. None of these eight patients experienced recurrence during the study period (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2025.104533).

DISCUSSION

In our multicenter retrospective study, we confirmed with compelling evidence that patients carrying *BRCA1/2* mutations derive substantial benefit from olaparib maintenance. Nevertheless, differences in the magnitude of benefit were reported when analyzed according to the specific location and type of mutation. We observed that patients with *BRCA1* mutations in the RING domain and *BRCA2* mutations in the RAD51-BD had the greatest benefit from PARPi administration. No significant benefits were found in *BRCA1/2* DNA-BD mutation groups. Additionally, it appears

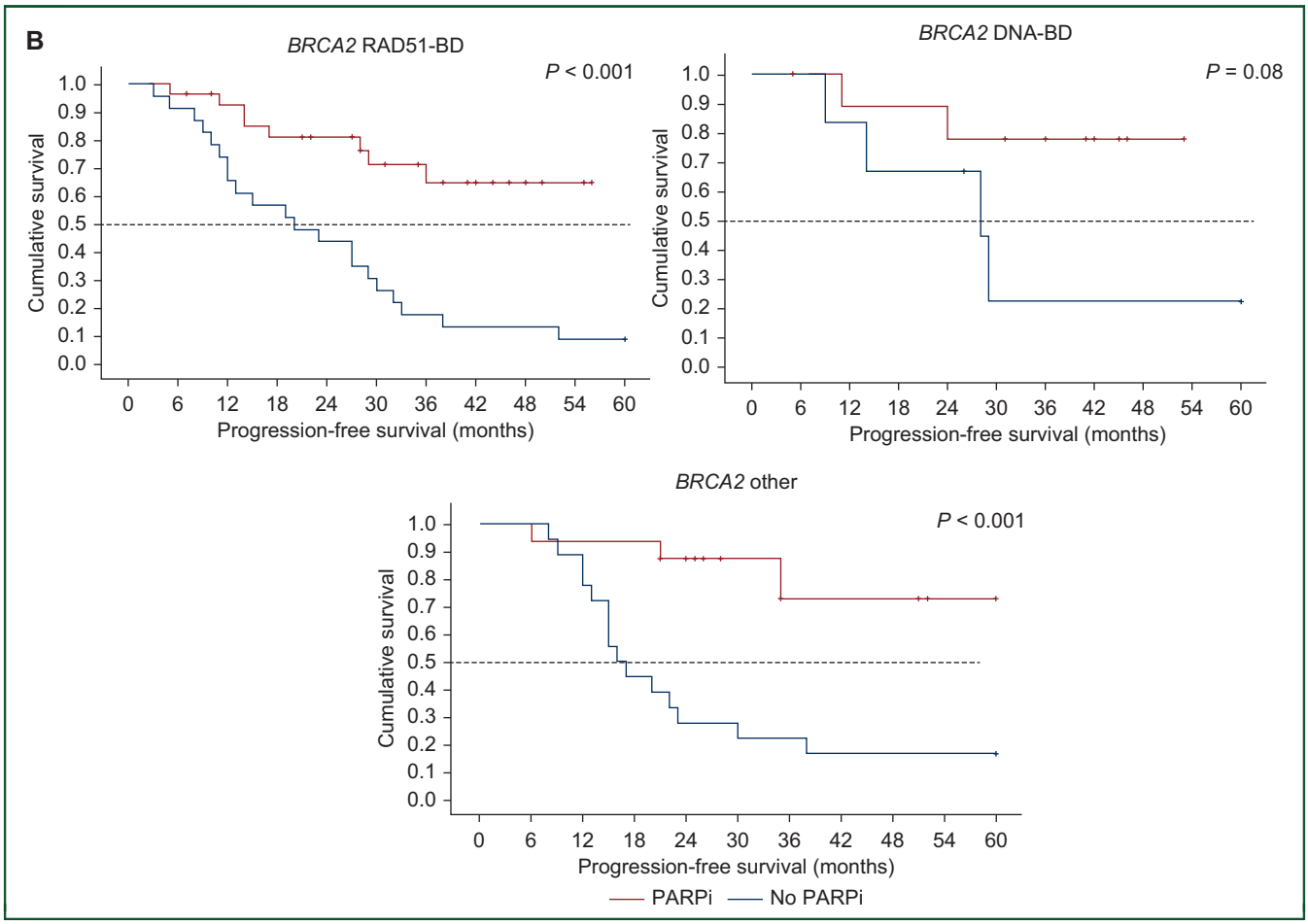

Figure 1. **Continued.**

that patients with missense mutations, especially those with p.(Ala1708Glu), experience the most relevant benefits.

The introduction of PARPi marks a revolutionary advancement in the treatment of *BRCA1/2*-mutated HGSOC. Nevertheless, it has become increasingly evident that the efficacy of PARPi varies among patients according to several variables, including their genomic instability score.[25] Thus, a pathogenic *BRCA* mutation does not always ensure a favorable response to PARPi and resistance can develop over time. Among several mechanisms of primary resistance to PARPi that have been proposed, some suggest that the different *BRCA1/2* mutation types and locations may be associated with platinum and PARPi sensitivity, potentially influencing secondary reversion mutation occurrence.[26-30] *BRCA1* and *BRCA2* are two large genes characterized by large central exon 11 and different FDs. In particular, *BRCA1* includes three different FDs: the RING, the DNA-BD and the BRCT domain, all involved in DNA repair and the latter domain also in cell cycle control (through G2/M and S-phase checkpoints). The two FDs of *BRCA2* are RAD51-BD and DNA-BD and are implicated in homologous recombination pathways. Based on these distinct but complementary functions, some authors have focused on the survival outcomes according to the gene involved and showed different chemotherapy and PARPi sensitivity in *BRCA1* versus *BRCA2*-mutated patients.[26,31,32]

In preclinical studies, mutations of *BRCA1* involving the exon 11 appear to be associated with less sensitivity to PARPi than those outside the exon 11.[11] Additionally, it was observed that deletion in the DNA-BD of *BRCA2* seemed to increase sensitivity to olaparib and cisplatin in engineered cell lines.[33] In a recent analysis of the PAOLA-1 phase III clinical trial, researchers looked at the impact of the location of *BRCA1/2* mutations on the sensitivity to PARPi and bevacizumab.[13] A total of 233 of 806 randomly assigned patients were analyzed and it was found that those with *BRCA1/2* mutations involving exon 11 derived greater benefit from olaparib plus bevacizumab compared with patients with mutations outside exon 11. Patients with mutations in the DNA-BD of *BRCA1* also showed significant benefit from olaparib plus bevacizumab.[13] Interestingly, in our analysis assessing patients treated with PARPi, we found that among *BRCA1* patients, those with the greatest benefit had mutations in the RING domain (located outside the exon 11), and no-exon 11 patients had a reduced risk of recurrence.

Regarding *BRCA2* mutation carriers in FDs, we found that individuals with mutations in RAD51-BD had significantly

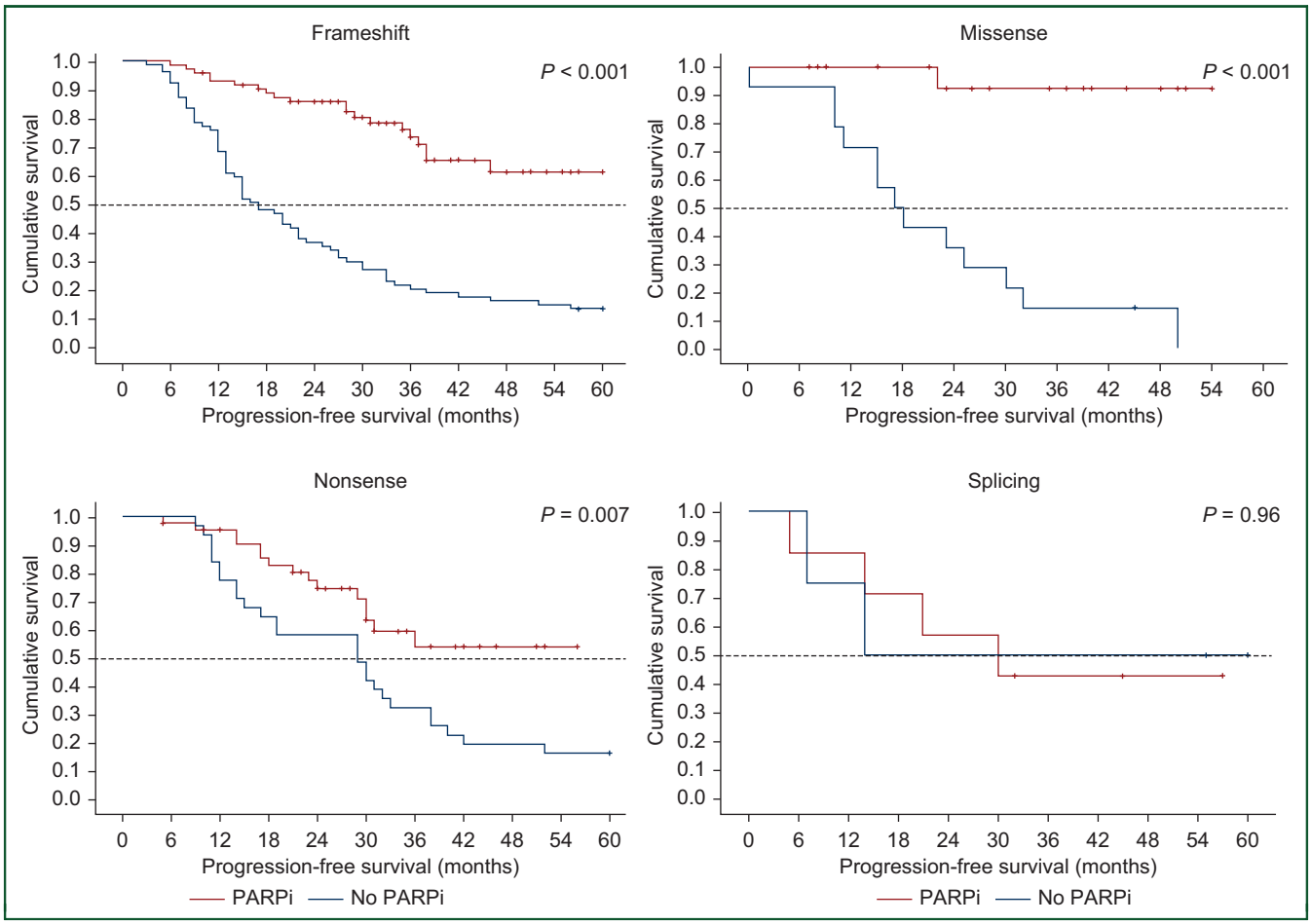

Figure 2. Progression-free survival in the overall population according to the type of mutation.
PARPi, poly (ADP-ribose) polymerase inhibitors.

longer PFS when treated with olaparib, in accordance with previous data.[13] In the PAOLA-1 analysis, it was found that the *BRCA2* DNA-BD group had the better survival outcomes, regardless of whether they had received olaparib—bevacizumab or not.[13] In the setting of recurrence, patients harboring mutations involving *BRCA1* DNA-BD and BRCT domains showed longer PFS during PARPi maintenance in comparison with those with RING domain alterations.[34]

In our *BRCA1/2* DNA-BD-mutated population, a significant improvement with olaparib was not observed. However, the mutation of DNA-BD appeared to be associated with better survival, regardless of the administration of olaparib, in comparison with other FDs. Therefore, it is challenging to determine whether the good prognosis is intrinsically due to the DNA-BD *BRCA1/2* mutation or attributable to the effect of PARPi therapy. Moreover, in our study, patients were treated with PARPi alone (compared with no maintenance) and did not receive bevacizumab. We cannot rule out the possibility that in the PAOLA-1 analysis, bevacizumab's antiangiogenic effect may have interfered with the sensitivity of olaparib.[13] Additionally, both in the PAOLA-1 analysis and in our study, the sample sizes were small and, although a power calculation was carried out in the PAOLA-1 study, the authors themselves suggest that a larger sample size is necessary for a comprehensive analysis with sufficient statistical power.[13]

In the PAOLA-1 study, none of the mutation types were found to affect the benefits of olaparib plus bevacizumab (interaction $P > 0.01$).[13] Excluding data obtained from patients with splicing mutations due to the small numbers, we observed an advantage in PFS across the different mutation types. However, we did find that missense ones, regardless of the genes involved, had a very positive outcome. This was surprising because in the PAOLA-1 study, patients with missense mutations did not seem to benefit from the addition of olaparib to bevacizumab. As a result, we revisited the missense mutations and discovered that our population was enriched with the specific missense mutation p.(Ala1708Glu). This is noteworthy because this specific mutation, in addition to p.(Gly1706Glu), has already been proven to be particularly sensitive to olaparib,[35] due to its specific effect on the DNA repair pathway.

Recently, biphasic recruitment of the *BRCA1* tumor suppressor into DNA damage sites was described.[36] The early recruitment requires PAR recognition by the BRCA1—BARD1 protein complex, while the late phase depends on several specific functions, firstly on the functional *BRCA1*—BRCT domain.

Olaparib was shown to block the early recruitment phase of DNA repair by inhibiting PAR synthesis and late recruitment by decreasing the interaction between the BRCA1-A complex and BRCT. These mechanisms make the cell more dependent on the other functions of the late recruitment stages. In cells with *BRCA1* missense mutations, both defective and normal BRCA proteins are produced[37]: the altered ones could compete with the wild type, hindering the late recruitment path to repair DNA. Conversely, heterozygous truncating mutations lead to degradation of the mutated mRNA and the mutated protein frequently is not produced.[37] Thus, the remaining wild-type proteins maintain their function in the DNA repair through the late recruitment phase and the effect of PARPi is less pronounced.

Coherently, in an *in vitro* study, the recruitment of the BRCA1 protein toward cH2AX (indispensable for the initial recognition of DNA breaks[38]) was proved to be lower in cells with missense mutations p.(Ala1708Glu) and p.(Gly1706Glu) than in wild-type cells and those with truncating mutations.[35] Notably, while these mutations accounted for 28% of all missense mutations in our study, the population in the PAOLA-1 study only had 15% of these specific mutations.[13] Besides, in PAOLA-1, one case (5%) of p.(Gly1706Glu) mutation was reported,[13] and none in our series, suggesting that the mutation distribution might differ across different populations. This emphasizes the importance of considering the type and site of genetic mutations when investigating these issues, especially in *BRCA* mutation carriers. We did not correlate *BRCA* mutation site and type to overall survival since overall survival data are still immature in our population and will require longer follow-up.

We acknowledge some limitations to our study, including its retrospective nature and the relatively small number of patients in each mutation category. However, to our knowledge, our study is the only real-life study comparing PARPi alone with no maintenance, providing a direct analysis of olaparib efficacy independent of platinum sensitivity.

CONCLUSIONS

In conclusion, we have provided additional evidence that the effectiveness of olaparib varies across different types and sites of *BRCA* mutation. We observed that specific missense mutations in the BRCT region of the *BRCA1* gene are particularly sensitive to olaparib treatment, potentially opening up to a new possible research on PARPi sensitivity. Integrating knowledge about the type and the site of mutation may identify patients for whom PARPi are essential and sufficient and others for whom PARPi may not be entirely effective, who may require combination with anti-angiogenic agents. Furthermore, for a more personalized approach, this varying benefit from PARPi based on *BRCA1/2* mutation could justify a possible de-escalation of duration, identifying patients for whom maintenance of even <2 or 3 years might be enough.

If further studies support our findings, we could develop a more effective algorithm for managing *BRCA*-mutated ovarian cancer, selecting patients who will most benefit from PARPi and personalizing their care based on a 'detailed genetic profile'.

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