The association between location of BRCA mutation and efficacy of PARP inhibitor as a frontline maintenance therapy in advanced epithelial ovarian cancer: a multicenter real-world study in South Korea

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ABSTRACT

The association between location of BRCA mutation and efficacy of PARP inhibitor as a frontline maintenance therapy in advanced epithelial ovarian cancer: a multicenter real-world study in South Korea

The location of BRCA mutations may influence sensitivity to PARP inhibitors. This study evaluated progression-free survival (PFS) benefit from PARP inhibitors in newly diagnosed ovarian cancer based on BRCA1/2 mutation location. Among 380 patients with BRCA1 (63.7%) or BRCA2 (36.1%) mutations, those with DNA binding domain (DBD) mutations showed significant PFS benefit (BRCA1: HR, 0.34; BRCA2: HR, 0.25; p=0.01). In contrast, BRCA1 BRCT domain mutations showed no significant benefit (HR, 0.76; p=0.44). PFS benefit was observed in both OCCR (HR, 0.49) and non-OCCR (HR, 0.51) groups (p<0.01). These findings suggest that frontline PARP inhibitors provide significant PFS benefit, particularly for patients with DBD mutations, while BRCT domain mutations show limited benefit.

Key words: Ovarian cancer, PARP inhibitor, BRCA

1. Introduction

1.1. Research background

The Ovarian cancer is the leading cause of death among gynecologic cancers, with approximately 324,400 new cases and 207,000 deaths reported in 2022[1; 2]. At the time of diagnosis, the majority of ovarian cancer patients present with advanced-stage disease characterized by peritoneal carcinomatosis. Although up to 80% of patients respond to frontline chemotherapy, approximately 75% experience relapse within a median of 18 to 24 months in the absence of maintenance therapy.

The introduction of Poly (ADP-ribose) polymerase (PARP) inhibitor as a maintenance therapy has led to major change in the approaches to manage patients with BRCA-mutated newly diagnosed epithelial ovarian cancer[3-5]. In the pivotal SOLO1 trial, olaparib demonstrated a durable progression-free survival (PFS) benefit beyond the end of treatment in patients with advanced ovarian cancer and *BRCA1/2* mutations[3]. Similarly, in the PRIMA trial, niraparib significantly improved survival outcomes in patients with homologous recombination deficiency (HRD), including those with *BRCA1* or *BRCA2* mutations, in newly diagnosed advanced ovarian cancer at high risk of recurrence[4; 6]. Both olaparib and niraparib have been approved for first-line maintenance treatment, with no significant difference in PFS or overall survival (OS) observed between the two agents[7].

BRCA1 and *BRCA2* are two large genes, with exon 11 comprising a substantial portion of both[8; 9]. These genes harbor distinct functional domains, which are specific regions within the proteins that facilitate DNA repair and maintain genome stability. *BRCA1* is characterized by three key functional domains: the N-terminal RING domain, a DNA-binding domain (DBD) essential for DNA repair; and the C-terminal BRCT domain, which binds phosphorylated proteins involved in the DNA damage response[10; 11]. BRCA2 has two key functional domains, which plays a crucial role in homologous recombination by recruiting RAD51 recombinase to double-strand breaks: a RAD51-binding domain (RAD51-BD), and a highly conserved C-terminal DBD[11].

Several studies have indicated that the location of BRCA mutations within functional domains may affect sensitivity to PARP inhibitors and platinum-based chemotherapy. For instance, a post-hoc analysis of the PAOLA trial demonstrated that the PFS benefit of maintenance therapy with

olaparib and bevacizumab was particularly notable in patients with mutations located in the DBD of *BRCA1*[12]. Building upon these findings, this study aimed to evaluate the impact of *BRCA1/2* mutation location on the PFS benefit conferred by maintenance therapy with PARP inhibitors.

2. Methods

2.1. Patients and Study Design

From July 2019 to December 2022, we enrolled patients who were newly diagnosed with epithelial ovarian cancer, fallopian tube carcinoma, or primary peritoneal carcinoma from four hospitals in Korea. This study was a multicenter retrospective analysis conducted in compliance with the Declaration of Helsinki, Good Clinical Practice guidelines, and all applicable local laws and regulations. Ethical approval was granted by the institutional review boards of the four participating centers in Korea: National Cancer Center (NCC2023-0024), Seoul National University Hospital (H-2108-169-1248), Severance Hospital (4-2024-0835), and Kosin University Hospital (KUGH 2023-03-008). The requirement for obtaining informed consent was waived.

Patients meeting the following criteria were included in this study: (1) diagnosed with International Federation of Gynecology and Obstetrics (FIGO) stage III and IV disease; (2) completed at least four cycles of frontline platinum-based chemotherapy and achieved either a complete or partial response, as determined by investigators; and (3) carried deleterious germline or somatic mutations in *BRCA1* and/or *BRCA2* genes. BRCA testing was primarily performed using tumor specimens obtained during diagnostic surgery, ensuring molecular profiling from the primary tumor site. Exclusion criteria included patients with BRCA wild-type tumors or variants of unknown significance (VUS), used bevacizumab as a frontline maintenance treatment, insufficient clinical data, or those lost to follow-up during frontline treatment. Patients who received both bevacizumab and olaparib as a maintenance was excluded in this study.

2.2. Study outcomes

The main objective of this study was to assess PFS between patients who received PARP inhibitors (niraparib or olaparib) as a frontline maintenance treatment, and those who did not. PFS was defined as the time from the completion of platinum-based chemotherapy to disease progression or death from any cause, whichever occurred first. Disease assessment was conducted by the investigators, using computed tomography or positron emission tomography-computed tomography

scan every 3 to 6 months in accordance with Response Evaluation Criteria in Solid Tumors, version 1.1[13].

PFS was assessed according to location of *BRCA1/2* mutation. The description of mutations was given at genomic level on transcripts NM_007294.3 (*BRCA1*) and NM_000059.3 (*BRCA2*) on Human Genome hg19. Location of *BRCA1/2* variants are grouped into functional domain and ovarian cancer cluster region. For *BRCA1*, the functional domains were defined as follows: (i) RING domain: amino acids (AA) 8-96; DBD: AA 452-1092; BRCT: AA 1646-1736 and 1760-1855[14]. For *BRCA2*, functional domains were defined as follows: (i) RAD51-BD: AA 900-2000; (ii) DBD: AA 2459-3190[15].

Ovarian cancer cluster region (OCCR) was associated with a relative increase of ovarian cancer risk to breast cancer, compared to other regions. For *BRCA1*, OCCR is located from c.1380 to c.4062. For *BRCA2*, there are multiple OCCR; c.3249 to c.5681, and c.6645 to c.7471.[16]

2.3. Statistical Analysis

Baseline characteristics including age, histology, FIGO stage, timing of surgery, postoperative residual disease, CA-125, and response to platinum-based chemotherapy is compared between patients who received PARP inhibitors and those who did not. For categorical variables, comparisons between patients treated with PARP inhibitors and those without were conducted using the chi-square test, Z-test or Fisher′s exact test, where appropriate. Continuous paired data were analyzed using Wilcoxon rank sum test. PFS was estimated using the Kaplan-Meier method, and survival differences between the groups were compared using log-rank test.

All statistical analyses were conducted using R (version 4.2.1, R Foundation for Statistical Computing, Vienna, Austria) and SAS software (version 9.4 or later, SAS Institute Inc., Cary, NC, USA). A two-tailed p-value of less than 0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics

A total of 380 patients who harbored *BRCA1/2* mutations were included in the analysis. Of these, 209 (55.0%) patients received PARP inhibitor as a frontline maintenance therapy. 168 patients (80.4%) received olaparib, and 41 patients (19.6%) received niraparib.

The clinical characteristics according to two groups are summarized in **Table 1**. Overall, median age at diagnosis was 57 years (interquartile range [IQR]; 49–64). 94.2% (358/380) of patients were high-grade serous carcinoma, and 44.5% (169/380) of patients were diagnosed at stage IV. Neoadjuvant chemotherapy followed by interval cytoreductive surgery was performed in 47.4% (180/380), and 64.3% (243/380) of patients achieved no gross residual disease after surgery. Median CA-125 levels at initial diagnosis was 1080 (IQR; 381–3160). 341 (89.7%) patients achieved clinically complete response which was defined to no evidence disease or complete response. All variables fount no significant difference between patients who received frontline PARP inhibitor maintenance therapy than in those who did not.

Table 1. Baseline characteristics

	Overall N= 380	PARP inhibitor (-) N= 171	PARP inhibitor (+) N=209	p-value
Age at diagnosis, years				0.34*
Median (IQR)	57 (49-64)	57 (49-64)	56 (49-63)	
Histologic type				0.01†
High grade serous	358 (94.2%)	155 (90.6%)	203 (97.1%)	
Others	22 (5.8%)	16 (9.4%)	6 (2.9%)	
FIGO stage 2014				0.29†
III	211 (55.5%)	100 (58.5%)	111 (53.1%)	

IV	169 (44.5%)	71 (41.5%)	98 (46.9%)	
Timing of cytoreductive surgery				0.44‡
Upfront	199 (52.4%)	86 (50.3%)	113 (54.1%)	
Interval	180 (47.4%)	84 (49.1%)	96 (45.9%)	
No surgery	1 (0.3%)	1 (0.6%)	0 (0%)	
Residual disease (Missing=2)				0.53†
No gross residual disease	243 (64.3%)	113 (66.9%)	130 (62.2%)	
Macroscopic <1cm	114 (30.2%)	46 (27.2%)	68 (32.5%)	
Macroscopic ≥1cm	21 (5.6%)	10 (5.9%)	11 (5.3%)	
Serum CA-125 levels at initial diagnosis, IU/ml (Missing =5)				0.20*
Median (IQR)	1080 (381-3160)	1287 (432-3620)	972.5 (337-3023.5)	
Response to platinum-based chemotherapy				
Clinical CR	341 (89.7%)	150 (87.7%)	191 (91.4%)	0.24#
PR	35 (9.2%)	17 (9.9%)	18 (8.6%)	0.66#
SD	1 (0.3%)	1 (0.6%)	0 (0%)	>0.99#
Maintenance use				-
Olaparib	-	-	168 (80.4%)	
Niraparib	-	-	41 (19.6%)	

IQR, Interquartile range; HRD, Homologous recombination deficiency; CR, Complete response; PR, Partial response; SD, Stable disease

*: Wilcoxon rank sum test, †: Chi-squared test, ‡: Fisher's exact test, #: Z-test

3.2. Location and type of mutations in *BRCA1* and *BRCA2*

Of the 380 patients, 242 (63.7%) harbored *BRCA1* pathologic or likely pathologic variants (PV/LPV), 137 (36.1%) harbored *BRCA2*, and one (0.3%) harbored both *BRCA1* and *BRCA2*. Mutational type and location of mutation is summarized on **Table 2**. Frameshift mutations were the most common in mutational type, observed in 46.4% (175/377) of cases, followed by missense mutations (34.0%, 128/377), nonsense mutations (9.3%, 35/377), splice-site mutations (6.6%, 25/377), and large rearrangements (3.7%, 14/377). No significant difference in mutational types was observed between two groups. Regarding the cluster region, 49.1% (185/377) of mutations were located within the OCCR, while 50.9% (192/377) were located outside the OCCR.

For BRCA1 variants (N=240), most mutations were located in BRCT domain (21.3%, 51/240), followed by DNA binding domain (15.4%, 37/240), and RING domain (3.8%, 9/240). For *BRCA2* variants (N=137), 30.7% (42/137) occurred in the DBD, and 34.3% (47/137) in the RAD51-binding domain. The distribution of specific binding domain mutations did not differ significantly between the two groups for either *BRCA1* (p=0.22) or *BRCA2* (p=0.25).

Table 2. Mutational type and location of mutation

	Overall N= 380	PARP inhibitor (-) N= 171	PARP inhibitor (+) N=209	p-value
BRCA mutation				0.52‡
BRCA1	242 (63.7%)	111 (64.9%)	131 (62.7%)	
BRCA2	137 (36.1%)	59 (34.5%)	78 (37.3%)	
BRCA1 and BRCA2	1 (0.3%)	1 (0.6%)	0 (0%)	
Mutational type (Missing =3)				0.16‡
Frameshift	175 (46.4%)	82 (48.5%)	93 (44.7%)	
Nonsense	35 (9.3%)	11 (6.5%)	24 (11.5%)	
Missense	128 (34%)	62 (36.7%)	66 (31.7%)	
Splice-site	25 (6.6%)	11 (6.5%)	14 (6.7%)	
Large rearrangement	14 (3.7%)	3 (1.8%)	11 (5.3%)	

Cluster region (Missing=3)				0.32†
OCCR	185 (49.1%)	87 (51.5%)	98 (47.1%)	
Non-OCCR	192 (50.9%)	82 (48.5%)	110 (52.9%)	
Specific binding domain				
BRCA1 (N=240)				0.22‡
DNA binding	37 (15.4%)	13 (11.8%)	24 (18.5%)	
DNA binding/RING	1 (0.4%)	0 (0%)	1 (0.8%)	
RING	9 (3.8%)	2 (1.8%)	7 (5.4%)	
BRCT	51 (21.3%)	26 (23.6%)	25 (19.2%)	
Others	142 (59.2%)	69 (62.7%)	73 (56.2%)	
BRCA2 (N=137)				0.25†
DNA binding	42 (30.7%)	22 (37.3%)	20 (25.6%)	
RAD51-Binding	47 (34.3%)	20 (33.9%)	27 (34.6%)	
Others	48 (35%)	17 (28.8%)	31 (39.7%)	

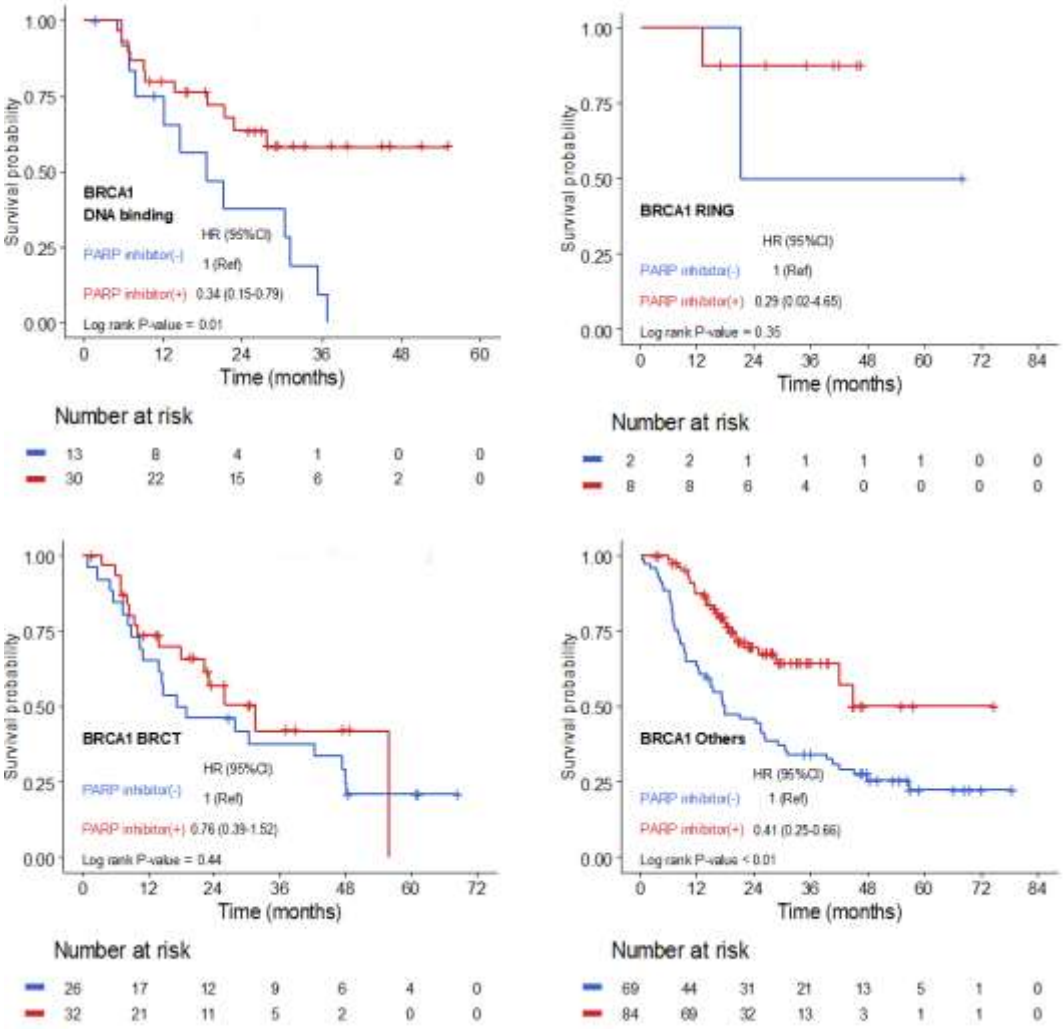
OCCR, Ovarian cancer cluster region; RING, really interesting gene; BRCT, C-terminal domain of BRCA1; †: Chi-squared test, ‡: Fisher's exact test

3.3. Survival outcome according to location of mutated gene

With a median follow-up of 35.8 months (IQR, 31.8–39.6), PFS outcomes varied among subgroups defined by mutation locations within *BRCA1/2* domains (**Figures 1, 2**). For *BRCA1*, patients with mutations in the DBD exhibited a significantly improved response to PARP inhibitor therapy, with a hazard ratio of 0.34 (95% CI, 0.15–0.79) compared to those not receiving PARP inhibitors (p=0.01; Figure 2A). In contrast, patients with *BRCA1* mutations in the BRCT domain showed a less pronounced benefit from PARP inhibitor therapy, with a hazard ratio of 0.76 (95% CI, 0.39–1.52; p=0.44; Figure 1B). For patients with *BRCA1* mutations located outside functional

domains, PARP inhibitor therapy resulted in a significant improvement in PFS compared to no PARP inhibitor use, with a hazard ratio of 0.41 (95% CI, 0.25–0.66; log-rank p<0.01; Figure 1D).

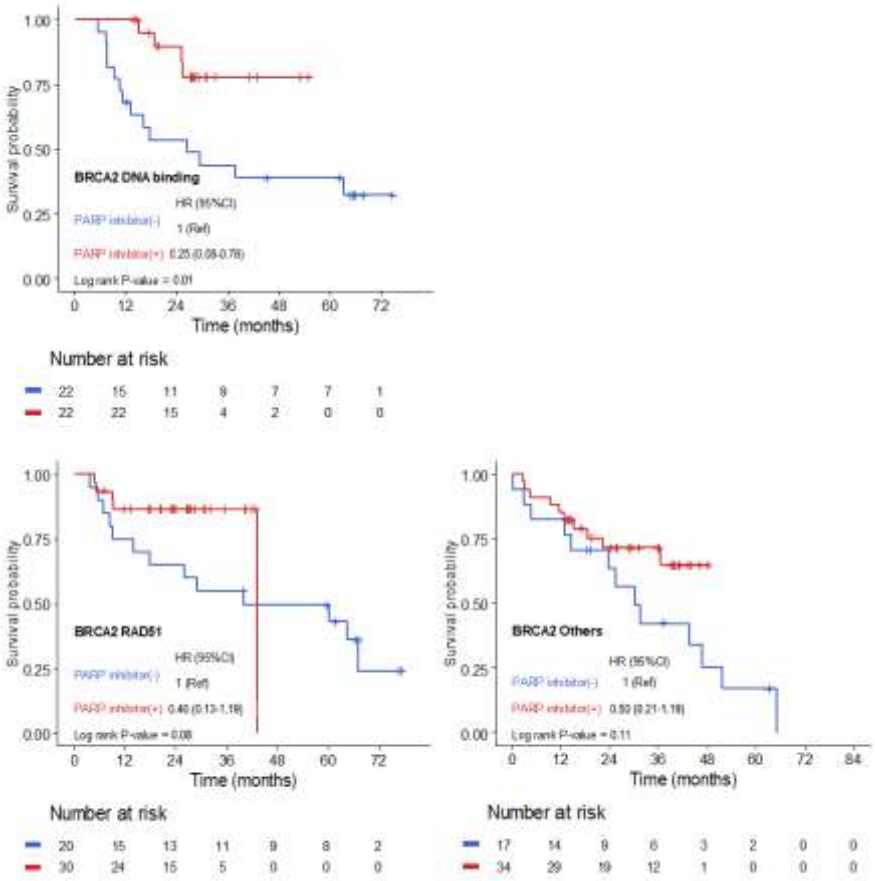
<Fig 1> The Kaplan–Meier Curve for progression-free survival by mutation locations within the BRCA1 domain



For *BRCA2*, patients with mutations in the DBD demonstrated a significantly enhanced response

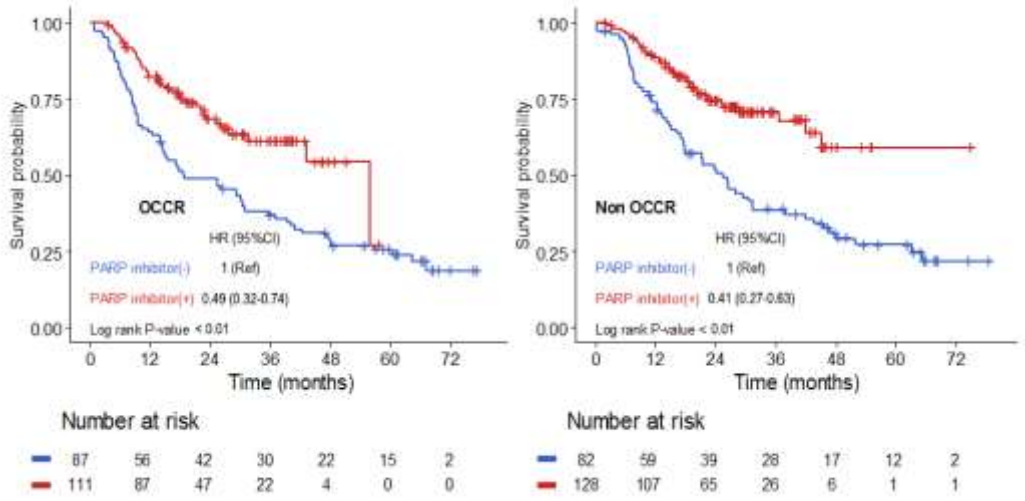
to PARP inhibitor therapy, with a hazard ratio of 0.25 (95% CI, 0.08−0.78, p=0.01; Figure 2A). Similarly, patients with mutations in the RAD51-binding domain also demonstrated a substantial benefit from PARP inhibitors, with a hazard ratio of 0.40 (95% CI, 0.13−1.19; p=0.08; Figure 2B). In contrast, patients with *BRCA2* mutations located outside functional domains showed a less pronounced, statistically non-significant improvement in PFS, with a hazard ratio of 0.50 (95% CI, 0.21−1.19; p=0.11; Figure 2C).

<Fig 2> Kaplan−Meier Curve for progression-free survival by mutation locations within the BRCA2 domain



PFS outcomes were analyzed based on the presence or absence of *BRCA1/2* mutations in the OCCR (**Figure 3**). Patients with mutations located within the OCCR demonstrated a significant benefit from PARP inhibitor therapy, with a hazard ratio of 0.49 (95% CI, 0.32–0.74, p<0.01; **Figure 3A**). Similarly, patients with BRCA mutations outside the OCCR (non-OCCR) also experienced a substantial improvement in PFS with PARP inhibitors, with a hazard ratio of 0.41 (95% CI, 0.27–0.63; p<0.01; **Figure 3B**). These findings indicate that PARP inhibitors provide significant PFS benefit regardless of whether BRCA mutations are located within or outside the OCCR.

<Fig 3> Kaplan–Meier Curve for progression-free survival by mutation locations within the ovarian cancer cluster region



4. DISCUSSION

The present study investigated the PFS benefit of frontline PARP inhibitor therapy based on *BRCA1/2* mutation locations. Mutations within functional domains, particularly the DBD of *BRCA1* and *BRCA2*, demonstrated the most pronounced benefit, with hazard ratios of 0.34 and 0.25, respectively. In contrast, *BRCA1* mutations within the BRCT domain showed no statistically significant PFS benefit, highlighting variability in therapeutic response by mutation location.

The study is aligned with the results from the post-hoc analysis of PAOLA-1/ENGOT-ov25 trial[5; 12], which explored the PFS benefits of addition of olaparib to bevacizumab as a maintenance therapy especially focusing on the functional domains of BRCA mutations. A key similarity between the two studies lies in the pronounced benefit of PARP inhibitors for patients with DBD mutations in *BRCA1*. The post-hoc analysis of PAOLA-1 trial demonstrated that *BRCA1* DBD mutations yielded the highest PFS benefit, with an impressive HR of 0.08 (95% CI, 0.02-0.28; p=0.03), indicating exceptional sensitivity to the olaparib-bevacizumab combination. Our findings similarly indicate that patients with *BRCA1* or *BRCA2* DBD mutations significantly benefit from frontline PARP inhibitor maintenance therapy.

Compared to the PAOLA-1 post-hoc analysis, which focused predominantly on the efficacy of the olaparib-bevacizumab combination in patients with BRCA1/2 mutations, this study exclusively evaluated the frontline use of PARP inhibitors (olaparib or niraparib) without bevacizumab. Furthermore, the current analysis provides a more detailed investigation into mutation-specific outcomes within an Asian cohort, highlighting demographic and geographic variability in mutation distributions and responses.

Differences in the efficacy of PARP inhibitors across functional domains may be attributed to the presence of reversion mutation hotspots that vary by domain, potentially influencing PARP inhibitor resistance. Previous studies have proposed that, unlike other functional domains, *BRCA1 and BRCA2* DBD may be less prone to reversion mutations, potentially preserving HRD and thereby extending efficacy to PARP inhibitors[17-19]. Furthermore, functional domains differ in their capacity to disrupt DNA repair pathways, which directly influences synthetic lethality. *BRCA2* DBD plays a critical role in homologous recombination repair by facilitating RAD51 recombinase activity[20].

Mutations in this domain disrupt RAD51 loading at double-strand break sites, compromising the DNA repair process. This disruption renders tumor cells highly dependent on PARP-mediated repair pathways, making them more vulnerable to synthetic lethality induced by PARP inhibitors.

Moreover, both studies consistently demonstrated that the PFS benefit for patients with mutations in the BRCT domain of *BRCA1* is relatively modest (post-hoc analysis of PAOLA-1, HR, 0.55; 95% CI, 0.2-1.56; present study, HR, 0.764, HR; 0.385-1.516). The lack of benefit may be attributed to the mechanisms underlying PARP inhibitor resistance, particularly in the BRCA1 BRCT domain mutations. Johnson et al. demonstrated that BRCT domain mutations often lead to protein instability due to misfolding and protease-mediated degradation. However, under PARP inhibitor selection pressure, heat shock protein 90 (HSP90)-mediated stabilization of the truncated mutant protein can enable partial functionality, allowing interactions with PALB2-BRCA2-RAD51 complexes and facilitating RAD51 loading. This stabilization may contribute to a reduced dependency on PARP-mediated repair pathways, thereby diminishing the efficacy of PARP inhibitors[21]. In addition, Bouwman et al. highlighted that allow DNA repair activity to persist through alternative pathways. This partial restoration of homologous recombination, facilitated by factors like TP53BP1 loss, reduces tumor dependency on PARP-mediated repair, contributing to PARP inhibitor resistance[22]. Although the smaller sample size for BRCT mutations in both studies necessitates cautious interpretation, this finding raises important questions regarding the functional implications of BRCT mutations in PARP inhibitor response.

In addition to domain specific functions, the relative position of mutations within the BRCA1 and BRCA2 genes, whether located toward the N-terminal or C-terminal regions, may also affect treatment outcomes. Several studies have suggested that mutations located in the N-terminal regions, such as the RING domain in *BRCA1* or the RAD51-binding domain in *BRCA2*, are more frequently associated with reversion mutations and the formation of hypomorphic proteins that retain partial homologous recombination activity[17; 23; 24]. These alterations can promote early PARP inhibitor resistance, even in the absence of full homologous recombination restoration. In contrast, C-terminal mutations, particularly those involving the DNA-binding domains of *BRCA1* and *BRCA2*, are located in structurally and functionally conserved regions and are less prone to reversion mutations[25]. As a result, tumors harboring these mutations often remain in an HR-deficient state and are more likely to exhibit sustained sensitivity to PARP inhibition. These findings underscore the complexity

of BRCA-associated PARP inhibitor response and resistance and highlight the need for future studies that incorporate both domain-specific and positional (N- vs. C-terminal) mutation analyses.

In the current study, we further investigated the relationship between *BRCA1/2* mutation location and PARP inhibitor efficacy, focusing on the OCCR. The OCCR refers to regions within BRCA1/2 associated with a higher risk of ovarian cancer compared to breast cancer[16]. While the OCCR classification has proven valuable for cancer risk stratification, its utility in assessing clinical outcomes and prognosis remains limited. Regarding the survival outcomes, Ha et al. reported with 162 *BRCA1* mutated patients that patients with *BRCA1* mutation in the OCCR had shorter PFS compared to non-OCCR in univariable analysis[26]. However, location of *BRCA1* mutation in OCCR was not a significant prognostic factor for PFS, after adjusting clinical variables including platinum sensitivity and clinical stage[26]. Our findings indicate that PARP inhibitor efficacy appears independent of OCCR status. OCCR is not strictly aligned with functional domains, requiring caution in interpreting results, as mutation effects vary based on their impact on homologous recombination and other cellular processes.

The mutation profiles in BRCA1 and BRCA2 exhibit notable differences between our Asian cohort and the predominantly European cohort of the PAOLA-1 trial, underscoring potential demographic and geographic variability. Notably, the PAOLA-1 trial included only 24 Japanese patients. In this study, 63.7% of patients carried BRCA1 mutations, and 36.1% carried BRCA2 mutations, compared to 68.2% and 31.8%, respectively, in the PAOLA-1 trial. Regarding the distribution of mutation in functional domains, BRCA1 mutations in the DBD accounted for 15.4% in our cohort versus 25.2% in PAOLA-1, whereas BRCT domain mutations comprised 21.3% and 20.8%, respectively. Similarly, BRCA2 RAD51-BD mutations represented 34.3% in our cohort, compared to 48.6% in PAOLA-1. These findings underscore the need to consider population-specific mutation distributions when evaluating PARP inhibitor efficacy.

This study has several limitations that should be acknowledged. First, as a retrospective analysis, it is inherently susceptible to selection bias, which may have influenced the study′s findings. Second, the results from subgroup analyses, particularly those based on specific *BRCA1/2* functional domains, are limited by small sample sizes within each subgroup. This necessitates cautious interpretation, as the statistical power to detect subtle differences may be compromised. Lastly, while

the study identifies significant associations between *BRCA1/2* mutation location and PARP inhibitor efficacy, the biological mechanisms underlying such domain-specific sensitivity remain speculative.

Despite these limitations, this study utilizes a multicenter Asian cohort to provide a comprehensive analysis of both functional domains and OCCR. It builds upon the post-hoc analysis of the PAOLA-1 trial by demonstrating differences in PARP inhibitor efficacy based on functional domain mutations. Additionally, the research indicates that these variations might be associated with the ability of certain domains to interfere with DNA repair mechanisms and their role in PARP inhibitor resistance processes, thus affecting treatment outcomes.

5. CONCLUSION

In conclusion, frontline PARP inhibitor maintenance therapy provides a substantial PFS benefit for newly diagnosed epithelial ovarian cancer patients with BRCA pathogenic variants, with the most pronounced efficacy observed in mutations located within the DNA-binding domains of *BRCA1* and *BRCA2*. Conversely, the limited benefit seen in *BRCA1* BRCT domain mutations raises important questions about domain-specific therapeutic vulnerabilities.

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Abstract in Korean

BRCA 변이 위치와 PARP 억제제의 유지 치료 효과 간의 연관성: 한국 다기관 실제 임상 연구

본 논문은 진행성(III–IV기) 상피성 난소암 환자에서 BRCA1/2 변이 위치와 1차 PARP 억제제 유지 치료의 무진행 생존율(progress-free survival, PFS) 혜택 간의 연관성을 분석한 다기관 실제 임상 연구이다. BRCA 변이의 위치는 폴리(ADP-리보스) 중합효소(poly (ADP-ribose) polymerase, PARP) 억제제 및 백금 기반 화학요법의 치료 반응에 영향을 미칠 수 있으며, 이에 본 연구에서는 Olaparib 또는 Niraparib을 1차 유지 치료로 투여한 환자군과 투여하지 않은 환자군 간의 임상 및 분자 데이터를 비교하고, BRCA 변이의 기능적 영역과 난소암 클러스터 영역(ovarian cancer cluster region, OCCR)에 따른 하위 분석을 수행하였다.

총 380명의 환자 중 63.7%가 BRCA1 변이, 36.1%가 BRCA2 변이를 보유하고 있었으며, 0.3%는 두 유전자의 변이를 모두 보유하였다. 중앙 추적 관찰 기간은 35.8개월이었으며, BRCA1과 BRCA2의 DNA 결합 도메인(DNA binding domain, DBD) 변이를 보유한 환자에서 특히 유의미한 PFS 혜택이 관찰되었다(BRCA1: HR 0.34, 95% CI 0.15–0.79, p=0.01; BRCA2: HR 0.25, 95% CI 0.08–0.78, p=0.01). 반면, BRCA1의 C-말단 도메인(BRCT) 변이를 가진 환자에서는 PARP 억제제의 유의한 PFS 혜택이 확인되지 않았다(HR 0.76, 95% CI 0.39–1.52, p=0.44). OCCR(HR 0.49, 95% CI 0.32–0.74, p<0.01) 및 비-OCCR(HR 0.51, 95% CI 0.27–0.63, p<0.01) 환자 모두에서 PARP 억제제의 PFS 혜택이 확인되었다.

본 연구는 실제 임상 데이터를 바탕으로 BRCA 변이의 위치가 PARP 억제제 치료 효과에 미치는 영향을 분석한 최초의 연구 중 하나로, BRCA1/2 변이를 가진 환자에서 1차 PARP 억제제 유지 치료가 유의미한 PFS 혜택을 제공함을 시사한다. 특히 BRCA1 및 BRCA2의 DBD 변이 환자에서 혜택이 두드러지며, BRCA1의 BRCT 도메인 변이 환자에서는 상대적으로 제한적일 가능성이 있다. 본 연구는 BRCA 변이의 위치를 고려한 개인 맞춤형 치료 전략 수립에 중요한 근거를 제공하며, 향후 난소암 치료 최적화를 위한 추가 연구의 필요성을 제시한다.

핵심 되는 말: 난소암, PARP 저해제, BRCA