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Real-world effectiveness of PARP inhibitors after CDK4/6 inhibitor therapy in BRCA-mutated HR-positive/HER2-negative advanced breast cancer

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Poly(ADP-ribose) polymerase inhibitors (PARPi) are established as standard-of-care therapy for patients with hormone receptor-positive/HER2-negative advanced breast cancer (HR+/HER2− aBC) who harbor germline *BRCA1/2* likely pathogenic or pathogenic variants (LP/PV). However, the real-world efficacy of PARPi following tumor progression on first-line (1 L) cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) in combination with endocrine therapy (ET) remains inadequately explored. In this cohort of 81 patients with HR+/HER2− aBC harboring germline *BRCA* LP/PV, 64 (79%) received 1 L treatment with CDK4/6i plus ET. Considering the subsequent therapy administered after tumor progression on 1 L CDK4/6i, patients treated with PARPi showed a significantly longer median real-world PFS (11.8 months) compared to those receiving ET, monochemotherapy, or polychemotherapy. This benefit was confirmed in a multivariable analysis, supporting PARPi as the preferred option in eligible patients. Our findings suggest that PARPi should be prioritized in the post-CDK4/6i treatment sequence for *BRCA* LP/PV carriers with HR+/HER2 aBC and highlight the critical role of germline *BRCA* testing.

Approximately 7% of hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2−) breast cancers arise in patients harboring germline *BRCA1* or *BRCA2* likely pathogenic or pathogenic variants (LP/PV)[1,2]. In the advanced setting, the standard-of-care frontline treatment for HR+/HER2− breast cancer, regardless of the presence of a germline *BRCA* LP/PV, is represented by the combination of cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) and endocrine therapy (ET)[3–8]. However, several studies have suggested that clinical outcomes in patients carrying *BRCA* LP/PVs who receive ET plus CDK4/6i may be poorer, compared with patients with wild-type *BRCA*[9–17].

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Poly (ADP-ribose) polymerase inhibitors (PARPi), which represent a milestone in genomically-directed therapies, are available for *BRCA* LP/PV carriers. In the phase III OlympiAD and EMBRACA trials, the PARPi olaparib and talazoparib demonstrated a statistically significant and clinically meaningful improvement in progression-free survival (PFS), when compared to chemotherapy, in advanced breast cancer patients carrying germline *BRCA1* or *BRCA2* LP/PVs[18,19]. International guidelines recommend PARPi monotherapy in the second-line setting for patients with HR+/HER2− advanced breast cancer and germline *BRCA* LP/PVs, upon tumor progression to first-line CDK4/6i plus ET[20,21]. However, both the OlympiAD and EMBRACA trials were conducted in a treatment landscape that preceded the approval and widespread use of CDK4/6i in the management of HR+/HER2− advanced breast cancer. As a result, patients enrolled in these studies had not received prior treatment with CDK4/6i[18,19]. Consequently, there is a significant lack of clinical data evaluating the effectiveness of PARPi in patients who have previously been treated with CDK4/6i plus ET. In particular, it is not known whether PARPi are associated with greater effectiveness compared to other therapeutic classes, such as ET or chemotherapy.

In this observational, multicenter, real-world study, we investigated post-CDK4/6i treatments in a cohort of patients with HR+/HER2− advanced breast cancer harboring germline *BRCA1* or *BRCA2* LP/PVs.

Results

Study cohort

At the data cut-off of April 15, 2025, we included 81 HR+/HER2− advanced breast cancer patients harboring *BRCA* LP/PVs, and who started CDK4/6i in combination with ET between May 1, 2017 and November 15, 2024 (Table 1). Median follow-up was of 45.8 months [95% confidence interval (CI) 35.9-58.0].

Eleven patients (13.6%) carried a LP/PV in *BRCA1* and 70 (86.4%) in *BRCA2*.

Median patient age at CDK4/6i initiation was 48 years (range, 28–81). The cohort was predominantly female (98.8%). Eastern Cooperative Oncology Group performance status (ECOG PS) was 0 in the majority of patients (82.8%); 16% of patients were diagnosed with de novo metastatic disease. Around 88% of patients had 1–3 metastatic sites, while 12% had metastatic involvement of more than three sites. The most frequent metastatic locations included bone (59.3%), lymph nodes (49.4%) and liver (39.5%).

The combination of CDK4/6i and ET was administered as first-line therapy in 64 (79.0%) patients, as second-line therapy in 10 (12.4%), and as third-line or subsequent line of therapy in 7 (8.6%) of enrolled patients. Palbociclib was the most frequently prescribed CDK4/6i (35.8%), followed by ribociclib (33.3%) and abemaciclib (30.9%). Regarding the type of ET, 35.8% of patients received an aromatase inhibitor (AI) and 64.2% fulvestrant. Luteinizing hormone-releasing hormone (LHRH) analog was used in 34.6% of cases. 40 (49.4%) patients had received risk-reducing bilateral salpingo-oophorectomy.

Real-world PFS during CDK4/6i plus ET

Among 64 patients who received CDK4/6i plus ET as first-line treatment, median rw progression-free survival (rwPFS) was 14.1 months (95% CI 11.8–18.5). Patients with endocrine-sensitive disease had a rwPFS of 18.4 months (95% CI 14.2–22.8), whereas median rwPFS was 11.9 months (95% CI 9.1–18.7) in patients with endocrine-resistant disease.

No significant rwPFS difference was found when comparing *BRCA1* and *BRCA2* LP/PV carriers (median rwPFS 11.9 months, 95% CI 7.4-NA, and median rwPFS 14.8 months, 95% CI 11.8–18.7, respectively, $p = 0.77$, Supplementary Fig. 1).

Among 10 patients who received CDK4/6i as second-line treatment for advanced disease, median rwPFS was 12.4 months (95% CI 4.6-NA), whereas it was 6.8 months (95% CI 2.6-NA) for third-line and beyond (7 patients).

Table 1 | Patient baseline characteristics at the initiation of CDK4/6i and ET

Characteristics	Total *N* = 81
Age, years (range)	48 (28–81)
gBRCA LP/PV, *n* (%)	
gBRCA1 LP/PV	11 (13.6)
gBRCA2 LP/PV	70 (86.4)
Gender, *n (%)*	
Female	80 (98.8)
Male	1 (1.2)
ECOG PS, *n* (%)	
0	53 (82.8)
1	7 (10.9)
2	4 (6.3)
NA	17
Endocrine sensitivity, *n* (%)	
Primary ER	10 (13.0)
Secondary ER	39 (50.6)
ES	28 (36.4)
NA	4
Line of CDK4/6i+ET, *n* (%)	
1	64 (79.0)
2	10 (12.4)
≥3	7 (8.6)
Type of CDK4/6i, *n* (%)	
Palbociclib	29 (35.8)
Ribociclib	27 (33.3)
Abemaciclib	25 (30.9)
Type of ET, *n* (%)	
AI	29 (35.8)
Fulvestrant	52 (64.2)
Risk-reducing bilateral salpingo-oophorectomy	
Yes	40 (49.4)
Use of LHRH analogs, *n* (%)	
Yes	28 (34.6)
De novo metastatic disease, *n* (%)	
Yes	13 (16.0)
Number of metastatic sites, *n* (%)	
≤3	71 (87.7)
>3	10 (12.3)
Visceral disease, *n* (%)	
Yes	45 (55.6)
Bone metastases, *n* (%)	
Yes	48 (59.3)
Liver metastases, *n* (%)	
Yes	32 (39.5)
Lung metastases, *n* (%)	
Yes	21 (25.9)
Brain metastases, *n* (%)	
Yes	6 (7.4)
Skin/soft tissue metastases, *n* (%)	
Yes	13 (16.0)
Lymph node metastases, *n* (%)	
Yes	40 (49.4)

AI aromatase inhibitor, *gBRCA* germline *BRCA*, *gBRCA1* germline *BRCA1*, *gBRCA2* germline *BRCA2, CDK4/6i* cyclin-dependent kinase 4/6 inhibitor, *ECOG PS* Eastern Cooperative Oncology Group performance status, *ER* endocrine resistance, *ES* endocrine sensitivity, *ET* endocrine therapy, *LHRH* luteinizing hormone-releasing hormone, *LP/PV* likely pathogenic/pathogenic variant, *NA* not available.
Significant *p*-values in bold.

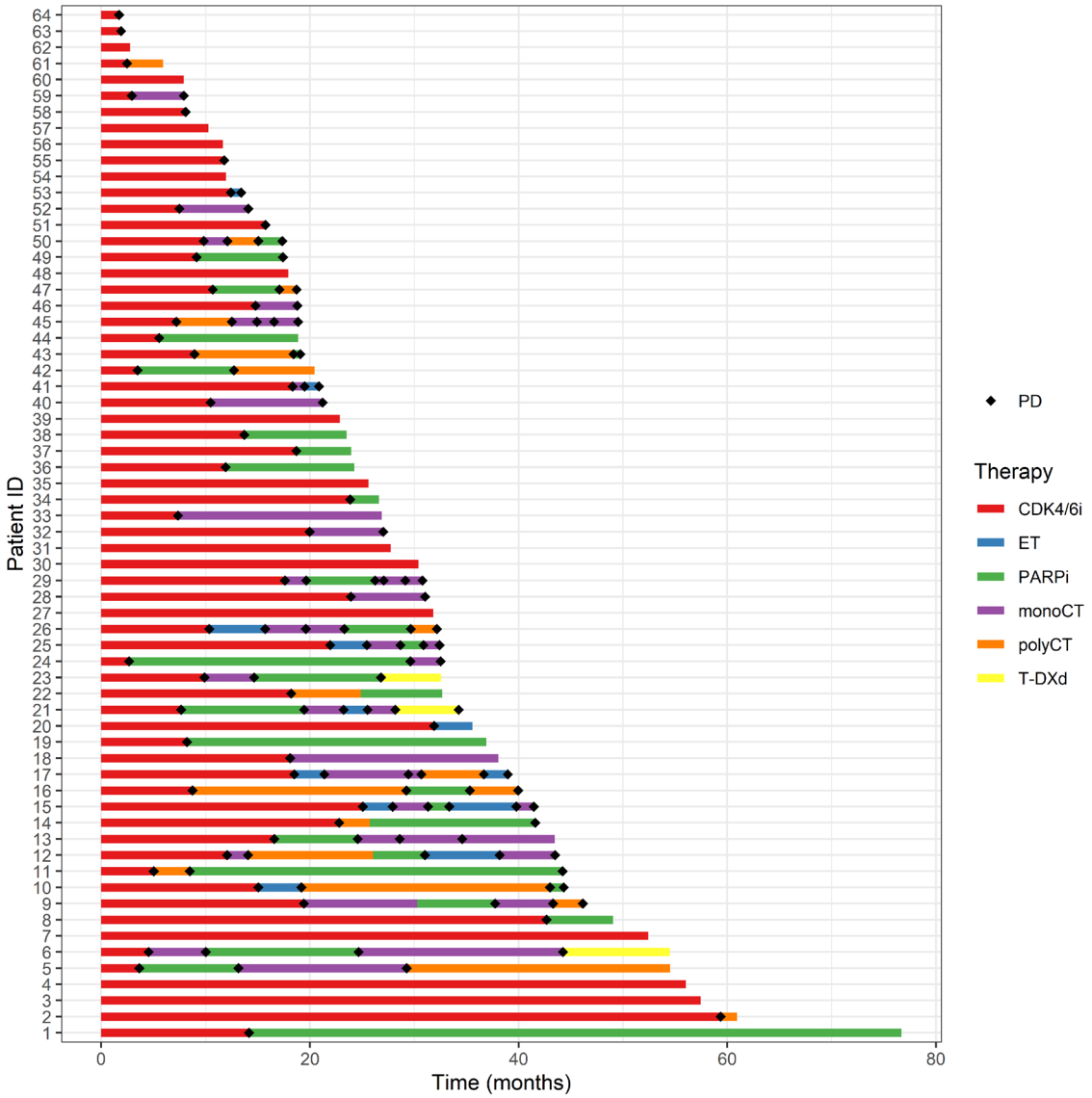

Fig. 1 | Swimmer plot depicting outcomes of patients receiving first-line CDK4/6i and ET (red bar), followed by ET (blue bar), PARPi (green bar), monoCT (violet bar), polyCT (orange bar) or T-DXd (yellow bar) after tumor progression. No patient received T-DXd as the first subsequent therapy following tumor progression on a CDK4/6i. Black diamonds indicate tumor progression. CDK4/6i, cyclin-dependent kinase 4/6 inhibitors; ET, endocrine therapy; monoCT: mono-chemotherapy; PARPi, poly (adp-ribose) polymerase inhibitor; PD, progressive disease; polyCT, polychemotherapy; T-DXd, trastuzumab deruxtecan.

Real-world PFS during first subsequent line of therapy upon tumor progression to first-line CDK4/6i plus ET

The analysis of post-CDK4/6i outcomes was limited to patients with HR + /HER2− advanced breast cancer who had received CDK4/6i in the first-line setting (64/81). Figure 1 provides a swimmer plot illustrating individual treatment sequencing of systemic therapies in this cohort of 64 patients.

Among these 64 patients, 14 (21.9%) were still on treatment at the time of data cut-off and were therefore excluded from the post-progression analysis. Of the remaining 50 patients who experienced disease progression on CDK4/6i, 4 (8%) died before receiving any subsequent line of therapy.

Among 46 patients eligible for second-line treatment, 15 (32.6%) received a PARPi, 7 (15.2%) received ET with or without a biological agent, 15 (32.6%) received monochemotherapy (monoCT), and 9 (19.6%) received polychemotherapy (polyCT). Detailed regimens for each of the four treatment groups are reported in Supplementary Table 1.

Baseline clinical and pathological characteristics of patients stratified by treatment group are presented in Table 2 and Supplementary Table 2. No statistically significant differences were observed among the groups in terms of age, *BRCA* LP/PV distribution, ECOG PS, menopausal status. Most patients in each group had bone and/or lymph node metastases. Patients treated with chemotherapy (either monoCT or polyCT) had more frequently liver metastases ($p = 0.025$) compared with those in the ET and PARPi groups, and tended to have higher metastatic burden (more than 30% with >3 metastatic sites, compared to no and 6.7% of patients with >3 metastatic sites for ET and PARPi group, respectively, $p = 0.100$). No patients with brain metastases received ET or PARPi as subsequent line after first-line CDK4/6i progression ($p = 0.055$).

Treatment with PARPi was associated with significantly longer median rwPFS compared to other treatment groups (PARPi: 11.8 months, 95% CI 9.2–NA; ET: 3.5 months, 95% CI 2.9–NA; monoCT: 5.2 months, 95% CI 4.0–NA; polyCT: 9.5 months, 95% CI 3.5–NA; log-rank $p < 0.001$) (Fig. 2).

In the univariate analysis, none of the patient or disease characteristics were significantly associated with the risk of tumor progression (Table 3).

In the multivariable analysis, the type of therapy administered after progression on CDK4/6i was strongly associated with rwPFS. Compared to PARPi, patients treated with ET had higher risk of disease progression [adjusted HR (aHR: 13.57, 95% CI 3.24–56.80, $p < 0.001$), as did those receiving monoCT (aHR 5.62, 95% CI 1.85–17.09, $p = 0.002$). PolyCT was

Table 2 | Patient characteristics according to the four post-CDK4/6i groups

	ET group *n* = 7	monoCT group *n* = 15	PARPi group *n* = 15	polyCT group *n* = 9	*P* value
Age, years (range)	44 (30–60)	49 (40–76)	44 (35–78)	47 (35–76)	0.506
g*BRCA* LP/PV, *n* (%)					
gBRCA1	2 (28.6)	2 (13.3)	0	3 (33.3)	0.052
gBRCA2	5 (71.4)	13 (86.7)	15 (100)	6 (66.7)	
Menopausal status					
Premenopausal	4 (57.1)	11 (73.3)	11 (73.3)	5 (55.6)	0.698
Postmenopausal	3 (42.9)	4 (26.7)	4 (26.7)	4 (44.4)	
Timing of the g*BRCA* test, *n* (%)					
Before[a]	2 (40.0)	12 (85.7)	11 (100.0)	7 (100.0)	**0.037**
After[a]	3 (60.0)	2 (14.3)	0	0	
NA[b]	2	1	4	2	
Endocrine sensitivity[c], *n* (%)					
Primary ER	2 (33.3)	2 (13.3)	1 (6.7)	0	0.346
Secondary ER	2 (33.3)	6 (40.0)	9 (60.0)	6 (75.0)	
ES	2 (33.3)	7 (46.7)	5 (33.3)	2 (25.0)	
NA	1	0	0	1	
ECOG PS, *n* (%)					
0	6 (100.0)	9 (75.0)	13 (100.0)	5 (62.5)	0.334
1	0	3 (25.0)	0	2 (25.0)	
2	0	0	0	1 (12.5)	
NA	1	3	2	1	
De novo metastatic disease, *n* (%)					
Yes	2 (28.6)	3 (20.0)	1 (6.7)	3 (33.3)	0.364
Number of metastatic sites, *n* (%)					
≤3 >3	7 (100.0) 0	10 (66.7) 5 (33.3)	14 (93.3) 1 (6.7)	6 (66.7) 3 (33.3)	0.100
Visceral disease, *n* (%)					
Yes	3 (42.9)	12 (80.0)	10 (66.7)	6 (66.7)	0.403
Bone metastases, *n* (%)					
Yes	6 (85.7)	13 (86.7)	11 (73.3)	7 (77.8)	0.846
Liver metastases, *n* (%)					
Yes	3 (42.9)	11 (73.3)	5 (33.3)	8 (88.9)	**0.025**
Lung metastases, *n* (%)					
Yes	1 (14.3)	4 (26.7)	3 (20.0)	3 (33.3)	0.894
Brain metastases, *n* (%)					
Yes	0	2 (13.3)	0	3 (33.3)	0.055
Lymph node metastases, *n* (%)					
Yes	4 (57.1)	8 (53.3)	9 (60.0)	5 (55.6)	0.987

ER endocrine resistance, *ES* endocrine sensitivity, *ET* endocrine therapy, *monoCT* monochemotherapy, *PARPi* poly (ADP-ribose) polymerase inhibitor, *polyCT* polychemotherapy.
[a]it refers to the starting of the present line, i.e., the second-line of treatment for advanced disease.
[b]Missing date of gBRCA test.
[c]at CDK4/6i initiation.
Significant *p*-values in bold.

not independently associated with higher risk of progression (aHR 1.90, 95% CI 0.37–9.71, $p = 0.440$) when compared with PARPi.

Both postmenopausal status (aHR 3.00, 95% CI 1.28–7.02, $p = 0.012$) and the presence of brain metastases (aHR 5.26, 95% CI 1.05–26.33, $p = 0.043$) were independently associated with shorter rwPFS.

Line of therapy–dependent efficacy of systemic treatments following CDK4/6i progression

In the previous analysis, we examined the first line after CDK4/6i progression, only considering patients who received CDK4/6i as first-line treatment. However, in the whole cohort of 81 patients, 40 (49.4%) patients received PARPi as any-line post-CDK4/6i.

When used as first-line therapy after CDK4/6i, PARPi were associated with a 93% reduction in the risk of progression compared to ET (HR 0.07, 95% CI 0.01–0.36, $p = 0.001$) (Supplementary Table 3). In contrast, a marked decline in efficacy was observed when PARPi were administered in later lines, with more than a twofold increased risk of progression (interaction HR 2.35, 95% CI 1.18–4.72, $p = 0.016$). As shown in Fig. 3, the impact of line of administration on rwPFS was more pronounced for PARPi than for other post-CDK4/6i treatments: both ET and monoCT showed a relatively stable rwPFS across treatment lines (HR 0.91, 95% CI 0.58–1.43,

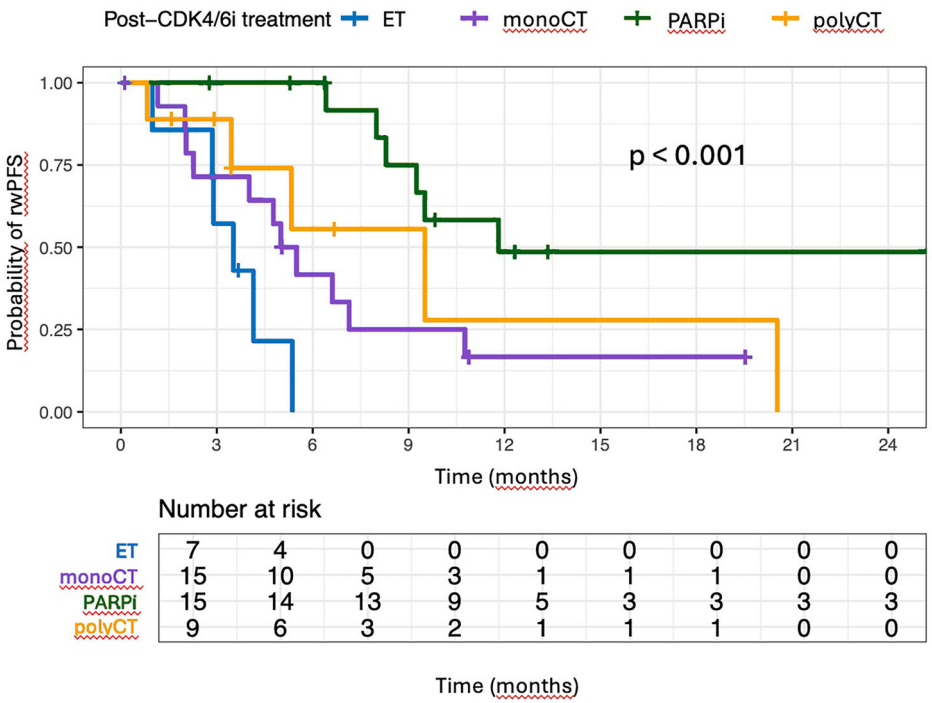

Fig. 2 | Kaplan–Meier rwPFS curves for the first-line post-CDK4/6i treatment groups. ET, endocrine therapy; monoCT, monochemotherapy; PARPi, poly (ADP-ribose) polymerase inhibitor; polyCT, polychemotherapy; rwPFS, real-world progression-free survival.

$p = 0.697$ and HR 1.15, 95% CI 0.69–1.90, $p = 0.593$, respectively), while for polyCT, although a decrease in rwPFS was observed with later-line use, the difference did not reach statistical significance (HR 1.85, 95% CI 0.95–3.59, $p = 0.069$).

Real-world PFS according to specific *BRCA2* LP/PV types or locations

An exploratory analysis investigating the association between germline *BRCA* LP/PV types or locations within *BRCA* genes and rwPFS with CDK4/6i plus ET or PARPi was conducted. For this specific analysis, *BRCA1* carriers were excluded due to limited sample size. Detailed mutation type and location information was available for 57/70 *BRCA2* cases (81.4%). Regarding *BRCA2* LP/PV types, 37 (64.9%) INDELs and 20 (35.1%) SNVs were identified. The coding consequences included 33 (57.9%) frameshift, and 24 other coding consequences [16 (28.1%) nonsense, 5 (8.8%) splicing and 3 (5.2%) missense LP/PVs]. Protein impact analysis showed that the vast majority were truncating LP/PVs (49, 85.9%), while only 3 (5.3%) were non-truncating, and 5 (8.8%) were unclassifiable. Due to the limited number of non-truncating LP/PV, the association between protein impact and rwPFS was not explored. Regarding *BRCA2* LP/PV location, 32 (56.1%) LP/PV were located in exon 11, while 25 (43.9%) in other exons. Among the 40 cases for which LP/PV domain location was available, 19 (47.5%) were located in the BRC domain of the BRCA2 protein, 14 (35.0%) in the OB domain and 7 (17.5%) in other domains.

As shown in Supplementary Fig. 2 and Supplementary Table 4, no association was found between *BRCA2* LP/PV type or location and the risk of disease progression during CDK4/6i plus ET, even after adjusting for the line of treatment with CDK4/6i plus ET, except for LP/PVs located in domains other than the BRC and OB domains (aHR 0.21, 95%CI 0.06–0.77, $p = 0.018$). However, due to the limited sample size, this finding should be interpreted with caution. No *BRCA2* LP/PV type or location was significantly associated with differences in rwPFS during treatment with PARPi, even after adjusting for the line of treatment with PARPi (Supplementary Fig. 3 and Supplementary Table 4).

Discussion

In this real-world, multicenter cohort of patients with HR+/HER2− advanced breast cancer harboring germline *BRCA1* or *BRCA2* LP/PVs, PARPi appeared to be associated with greater effectiveness compared with other treatment options, when used as subsequent treatment line after disease progression to first-line CDK4/6i and ET. To our knowledge, this is the first study specifically assessing treatment sequences in germline *BRCA*-mutated HR+/HER2− advanced breast cancer patients, a population for whom clinical trials often fail to provide specific evidence.

In our study, 64 patients received CDK4/6i plus ET as first-line therapy for advanced disease. Median rwPFS in the first-line setting was 14.1 months in the overall cohort of germline BRCA1 or BRCA2 LP/PV carriers, 18.4 months (95% CI, 14.2–22.8) for endocrine-sensitive disease, and 11.9 months (95% CI, 9.1–18.7) for endocrine-resistant tumors. No significant difference in rwPFS was observed between germline *BRCA1* and *BRCA2* LP/PV carriers, although the small number of *BRCA1*-mutated patients may limit the validity of this comparison.

The observed rwPFS with CDK4/6i plus ET in patients harboring germline *BRCA1* or *BRCA2* LP/PVs is consistent with prior studies, which suggested a potentially reduced benefit from such therapy in this population, compared with non-carriers[9–17]. One possible explanation is the loss of *RB1* observed in patients with germline *BRCA*2 LP/PVs[12]. RB1 inactivation is an established resistance mechanism to CDK4/6i[22]. Because *RB1* and *BRCA2* genes are syntenic on chromosome 13q, heterozygous RB1 deletion frequently co-occurs with *BRCA2* loss of heterozygosity, even before exposure to CDK4/6i plus ET. Under the selective pressure of CDK4/6i, biallelic inactivation of *RB1* might promote early emergence of resistance[12].

When evaluating the first line of therapy following tumor progression to CDK4/6i plus ET, subsequent therapies appeared to have limited effectiveness, particularly for ET (median rwPFS of 3.5 months, 95%CI 2.9-NA). The majority of patients in this cohort received exemestane plus everolimus or fulvestrant as ET regimens following CDK4/6i progression. The observed median rwPFS aligns with prior evidence on the limited effectiveness of everolimus plus exemestane[23,24] or fulvestrant[25,26] in this setting. To the best of our knowledge, these studies enrolled patients regardless of *BRCA* mutation status; consequently, the comparison is made with a *BRCA*-unselected population.

Importantly, data on *ESR1, AKT, PIK3CA* or *PTEN* tumor status in our cohort were not available and no patient received elacestrant or capivasertib plus fulvestrant after CDK4/6i plus ET progression. Therefore, this cohort reflects a treatment landscape preceding the recent therapeutic

Table 3 | Univariate and multivariable models for the first-line post-CDK4/6i

Variable	Category	Univariate analysis				Multivariable analysis			
		HR	95% CI		*P* value	aHR	95% CI		*P* value
Age		1.00	1.00	1.00	0.620				
BMI		0.90	0.79	1.02	0.103				
Menopause	Premenopausal	Ref.				Ref.			
	Postmenopausal	2.06	0.95	4.48	0.068	3.00	1.28	7.02	**0.012**
g*BRCA* LP/P	*gBRCA1*	Ref.							
	gBRCA2	0.87	0.33	2.29	0.771				
De novo metastatic disease	No	Ref							
	Yes	1.66	0.67	4.11	0.278				
ECOG PS	0–1	Ref							
	2	1.48	0.50	4.41	0.483				
Visceral metastases	No	Ref.							
	Yes	0.87	0.41	1.88	0.730				
Number of metastatic sites	≤3	Ref.							
	>3	1.38	0.52	3.66	0.519				
Liver metastases	No	Ref.				Ref.			
	Yes	1.16	0.56	2.42	0.693	0.88	0.37	2.06	0.762
Lung metastases	No	Ref							
	Yes	0.91	0.34	2.41	0.845				
Brain metastases	No	Ref.				Ref			
	Yes	2.66	0.90	7.88	0.077	5.26	1.05	26.33	**0.043**
Bone metastases	No	Ref.							
	Yes	1.03	0.41	2.54	0.957				
Lymph node metastases	No	Ref.							
	Yes	1.02	0.49	2.10	0.963				
Endocrine sensitivity	Primary ER	Ref.							
	Secondary ER	1.01	0.29	3.47	0.993				
	ES	0.80	0.22	3.00	0.745				
First post-CDK4/6i line of therapy	PARPi	Ref.				Ref.			
	ET	13.48	3.67	49.58	**<0.001**	13.57	3.24	56.80	**<0.001**
	monoCT	4.25	1.53	11.82	**0.006**	5.62	1.85	17.09	**0.002**
	polyCT	3.07	0.93	10.13	**0.066**	1.90	0.37	9.71	0.440

aHR adjusted hazard ratio, *BMI* body mass index, *CDK4/6i* cyclin-dependent kinase 4/6 inhibitor, *CI* confidence interval, *ECOG PS* Eastern Cooperative Oncology Group performance status, *ER* endocrine resistance, *ES* endocrine sensitivity, *ET* endocrine therapy, *gBRCA LP/PV* germline BRCA1 or BRCA2 likely pathogenic/pathogenic variant, *HR* hazard ratio, *monoCT* monochemotherapy, *PARPi* poly(ADP-ribose) polymerase inhibitor, *polyCT* polychemotherapy, *Ref.* reference category. Significant *p*-values in bold.

advancements and shifts in the management paradigm of HR+/HER2– advanced breast[27,28]. The therapeutic potential of targeting *ESR1* mutations or the *AKT/PIK3CA* pathway in individuals carrying germline *BRCA* LP/PVs remains under investigation and further studies are warranted.

In our cohort, none of the patients received trastuzumab deruxtecan (T-DXd) as a first-line therapy following progression on CDK4/6i. Following the results of the phase III DESTINY-Breast06 trial, T-DXd has also emerged as a potential therapeutic option after CDK4/6i progression, in patients with HER2-low or ultra-low tumors[29]. Furthermore, subgroup analyses from trials involving T-DXd suggest that *BRCA*-mutated patients may derive differential benefit from this therapy, although findings remain conflicting[30,31]. Real-world data on the efficacy of T-DXd in *BRCA*-mutated patients progressing on CDK4/6i are therefore highly awaited.

More than 50% of patients in our cohort received chemotherapy (15 to monoCT, 9 to polyCT) after progression on CDK4/6i plus ET, despite the fact that information on germline *BRCA* LP/PV was already available at the time of treatment selection (see Table 2). It is not certain whether a PARPi was available at the treating institution at that time. However, patients who were candidates for chemotherapy in this study had more frequently liver and/or brain metastatic involvement and tended to have higher metastatic burden. Therefore, the choice of chemotherapy may reflect the selection of treatment regimens based on tumor characteristics rather than on the presence of a germline *BRCA* LP/PV.

Median rwPFS was significantly longer for patients receiving PARPi as the first treatment following CDK4/6i progression (11.8 months), compared to monoCT (5.2 months), or polyCT (9.5 months). These results persisted after adjustment for potential confounders (including the presence of liver or brain metastases) in multivariable analysis, with ET and monoCT associated with an independently higher risk of progression. This suggests that PARPi may be associated with superior disease control in this setting, regardless of metastatic disease burden. This finding corroborates the recommendations by international guidelines to use PARPi as the preferred treatment option upon progression on CDK4/6i and ET in patients with a germline *BRCA* LP/PV[20,21].

As previously mentioned, the OlympiAD and EMBRACA trials were conducted in the pre-CDK4/6i era. Moreover, patients enrolled in these studies were generally more heavily pretreated than those in our cohort: in fact, in addition to ET, over 60% had received at least one prior line of

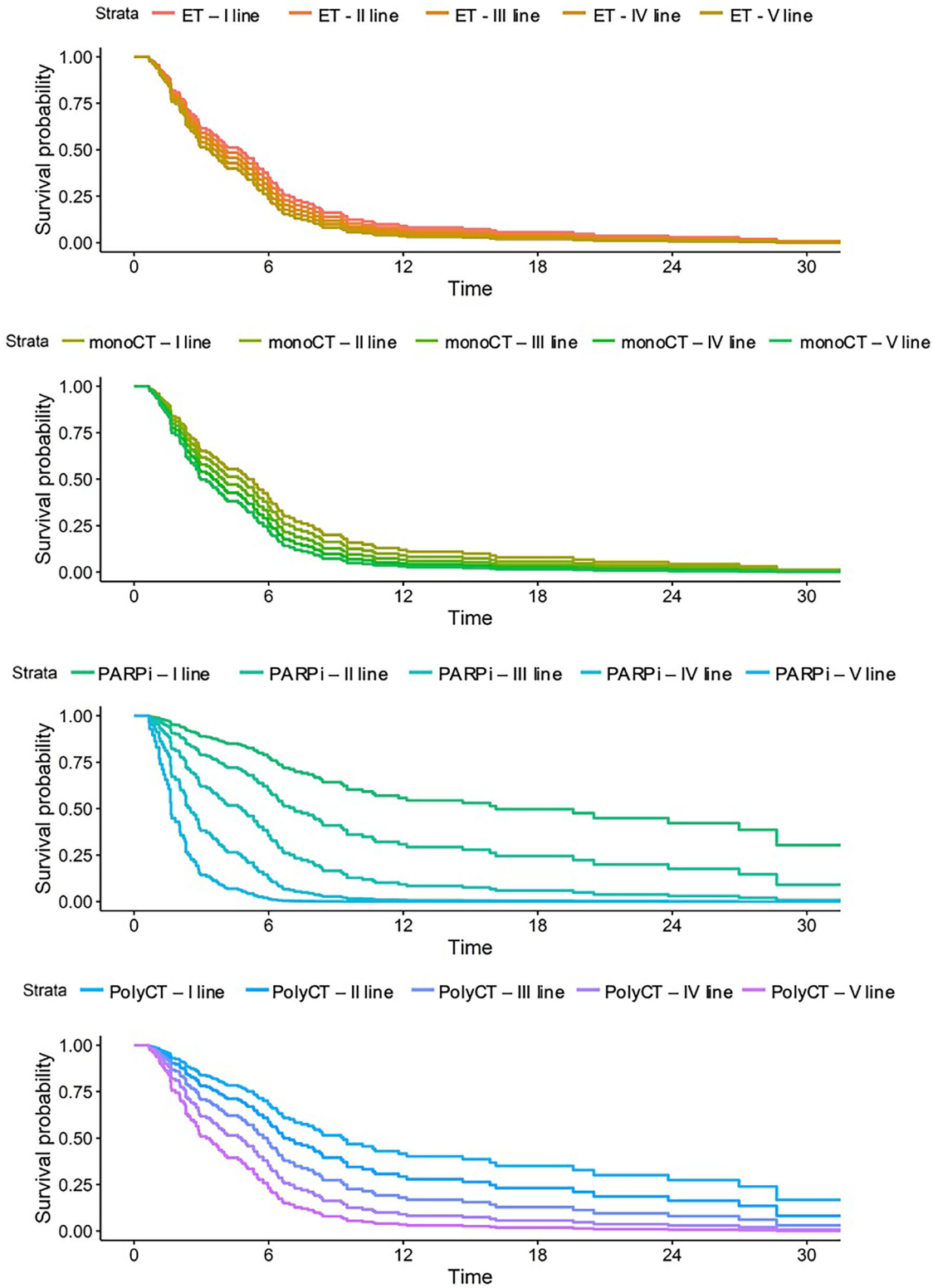

Fig. 3 | Kaplan–Meier curves illustrating rwPFS for the four treatment groups, stratified by the line of therapy following CDK4/6i progression. ET, endocrine therapy; monoCT, monochemotherapy; PARPi, poly (ADP-ribose) polymerase inhibitor; polyCT, polychemotherapy; rwPFS, real-world progression-free survival.

chemotherapy for advanced disease[18,19]. This could partly explain the improved rwPFS observed in the PAMBRACA study compared to the two pivotal trials. In fact, among patients who received PARPi as second-line treatment for advanced disease in the PAMBRACA cohort, the rwPFS was 11.8 months, thus longer than that reported in OlympiAD (7.0 months) and EMBRACA (8.6 months)[18,19].

More speculatively, some preclinical studies showed that, in certain cases, tumor cells that had developed resistance to CDK4/6i exhibited a reduced capacity for double-strand break (DSB) repair. Tumor cells with impaired DSB repair were shown to be highly sensitive to olaparib[32]. Therefore, CDK4/6i might sensitize tumor cells to subsequent treatment with PARPi[33].

Another interesting finding of our study is that earlier use of PARPi is associated with greater benefit. We specifically evaluated whether there was an interaction between the type of therapy (ET, monoCT, PARPi, polyCT) and the line of treatment in which it was administered, and this interaction was found to be significant only for PARPi ($p = 0.016$). The finding of a greater magnitude of benefit for PARPi used in earlier lines is consistent with the results of the two phase III trials[18,19]. In the OlympiAD trial, the greatest overall survival (OS) benefit was achieved by patients who received olaparib as first-line therapy for advanced disease[34].

Aligned with the strategy of anticipating the use of PARPi to maximize their efficacy, the ongoing phase III EvoPAR-Breast01 trial (NCT06380751) is evaluating the PARPi saruparib in the first-line setting for patients with HR+/HER2− advanced breast cancer harboring *BRCA1*, *BRCA2*, or *PALB2* LP/PVs. This study is assessing the efficacy of saruparib combined with the oral selective estrogen receptor degrader camizestrant versus a CDK4/6i plus ET or CDK4/6i plus camizestrant as first-line treatment[35].

Lastly, to the best of our knowledge, this is the first study exploring the association between specific *BRCA2* LP/PV types or locations and rwPFS with CDK4/6i plus ET or PARPi. The analysis for *BRCA1* carriers was not performed due to the limited sample size. In a recent international study of young breast cancer patients with *BRCA1* or *BRCA2* LP/PVs, truncating variants were linked to worse overall survival, whereas missense variants were associated with better outcomes in both *BRCA1* and *BRCA2* carriers[36]. We found no significant association between specific *BRCA2* LP/PV types or locations and benefit from CDK4/6i plus ET or PARPi. However, the small sample size limits the strength of these findings, and larger studies are warranted to confirm or challenge these observations.

Our study has several limitations. First, the retrospective, observational design and limited sample size (particularly in subgroup analyses) reduce the robustness and generalizability of our findings. Second, treatment allocation was not randomized, and residual confounding cannot be excluded. As observed in other real-world studies, the choice of a treatment regimen following CDK4/6i plus ET progression may have been influenced by several factors, including: (i) the timing of approval and market availability of PARPi; (ii) individual physician preferences; (iii) patient comorbidities; and (iv) concomitant medications, which may interact differently with the treatment regimens. Another limitation is that this analysis did not adjust for potential immortal time bias introduced by the timing of *BRCA* testing (i.e., germline testing can only be performed if patients survive long enough)[37], due to the limited sample size and missing test dates in a subset of patients. However, this bias may have led to an overestimation of rwPFS in the ET and monoCT groups, whereas treatment with PARPi requires a prior positive germline result, potentially mitigating the impact of this bias on the rwPFS observed with PARPi. Furthermore, although rwPFS is a clinically relevant endpoint in real-world settings, it may be subject to assessment biases. Nevertheless, the median follow-up of nearly four years, along with detailed data on treatment sequencing and clinical outcomes and the multicenter nature of the study, lends strength to our analysis.

In conclusion, following tumor progression on CDK4/6i plus ET, PARPi appears to be associated with meaningful clinical benefit compared to alternative strategies and may be considered for these patients. Furthermore, earlier use of PARPi seems to correlate with enhanced efficacy. These findings underscore the importance of prompt germline *BRCA* testing to inform post-CDK4/6i treatment decisions and suggest that PARPi should be prioritized in the treatment sequence for germline *BRCA* LP/PV carriers with HR+/HER2− advanced breast cancer. Larger, prospective studies are needed to validate these observations and establish the optimal sequencing of CDK4/6i and PARPi in this biologically distinct patient population.

Methods

Patient population and inclusion criteria

This was an observational, retrospective, multicenter study conducted in six Italian Cancer Centers [Department of Oncology and Hematology, Azienda Ospedaliero-Universitaria of Modena (coordinating center); Division of New Drugs and Early Drug Development for Innovative Therapies, European Institute of Oncology IRCCS of Milan; Comprehensive Cancer Center, Agostino Gemelli University Polyclinic (IRCCS) of Rome; Division of Oncology 2, Veneto Institute of Oncology IOV IRCCS of Padova; Department of Medical Oncology, IRCCS Ospedale Policlinico San Martino of Genoa; Medical Oncology Department, Fondazione IRCCS Istituto Nazionale dei Tumori of Milan].

Data were collected through an electronic database. Main inclusion criteria were: (i) age ⩾18 years; (ii) presence of a documented germline *BRCA1* or *BRCA2* LP/PV; (iii) histologically confirmed diagnosis of HR+/HER2− advanced breast cancer; (iv) treatment with palbociclib, ribociclib or abemaciclib in combination with ET (AI or fulvestrant) as any line of therapy for advanced disease; (v) pre-, peri- or postmenopausal women [pre- and peri-menopausal patients also received concomitant treatment with a LHRH analog (i.e., goserelin, triptorelin or leuprolide)]. Main exclusion criteria were: (i) presence of a germline *BRCA1* or *BRCA2* variant of unknown significance (VUS); (ii) patients who received CDK4/6i in the adjuvant setting. All patients were followed up until death, loss of contact, or the data cut-off date (15 April 2025).

Approval for data sharing and analysis was obtained from the local ethics committees of all six participating institutions: Department of Oncology and Hematology, Azienda Ospedaliero-Universitaria of Modena; Division of New Drugs and Early Drug Development for Innovative Therapies, European Institute of Oncology IRCCS of Milan; Comprehensive Cancer Center, Agostino Gemelli University Polyclinic (IRCCS) of Rome; Division of Oncology 2, Veneto Institute of Oncology IOV IRCCS of Padova; Department of Medical Oncology, IRCCS Ospedale Policlinico San Martino of Genoa; Medical Oncology Department, Fondazione IRCCS Istituto Nazionale dei Tumori of Milan. Written informed consent was obtained from all patients who were alive at the time of study conduction. The study was carried out in accordance with the Good Clinical Practice guidelines and the Declaration of Helsinki.

Study objectives and endpoints

The main objective of this analysis was to compare the real-world effectiveness of the first treatment line administered upon first-line CDK4/6i treatment plus ET tumor progression in HR+/HER2− advanced breast cancer patients harboring *BRCA* LP/PVs. Due to the observational nature of the study, the specific drugs were prescribed according to the choice of the treating physician. Radiological tumor assessments were carried out according to local practice.

The primary endpoint of this analysis was rwPFS, defined as the time between the initiation of the first systemic treatment after tumor progression to CDK4/6i plus ET treatment and the detection of disease progression or patient death from any cause, whichever occurred first[38]. Patients without a rwPFS event were censored at the time of data cut-off or last follow-up, if the latter occurred before data cut-off. Secondary objectives of this analysis were: to evaluate rwPFS with CDK4/6i combined with ET in HR+/HER2− advanced breast cancer patients harboring *BRCA* LP/PVs, in the whole cohort and according to endocrine sensitivity, as defined by the ESO-ESMO ABC 5 Clinical Practice Guideline[39]; to evaluate the benefit from the different treatment regimens according to their line of therapy following tumor progression to CDK4/6i plus ET.

Statistical methods and analyses

Standard descriptive statistics were used to report clinical and biological patients' characteristics. Categorical variables were described using absolute frequencies and percentages, whereas numerical variables were reported as median and interquartile range. Median patient follow-up was calculated with the reverse Kaplan–Meier estimator[40]. Survival curves for PFS were obtained with the Kaplan–Meier method.

Univariable multinomial logistic regression models were applied to investigate factors associated with the selection of post-CDK4/6i therapy. The dependent variable was the treatment of choice. Independent variables included patient demographics and clinical parameters.

Univariable and multivariable Cox regression modeling was used to investigate survival outcomes, with the proportional hazard assumption checked by testing and plotting Schoenfeld residuals. Means of restricted cubic splines were used to handle nonlinear effects for all continuous variables. Results of Cox models were summarized using HR, along with the corresponding 95% CI and Wald p values. In Cox models, the HR for continuous variables was reported per inter-quartile range (interval between the 25th and 75th quantiles).

The selection of relevant covariates to be included in the multivariable model was performed based on two criteria: I. covariates which were not balanced among the post-CDK4/6i treatment groups; II. covariates which were significantly associated with rwPFS at univariate analysis. Variance Inflation Factor (VIF) was used to test multicollinearity among the covariates included in the model. Variables whose inclusion caused the occurrence of values of VIF greater than 5 were excluded from the model.

To explore the impact of the line of therapy on treatment efficacy, a mixed effect Cox proportional hazard regression model was used. The model included a random intercept term to deal with repeated measures on the same individuals. The model analysed PFS and included as covariates: post-CDK4/6i therapy, line of therapy, and post-CDK4/6i therapy x therapy line interaction term. The results were reported as HR with 95% CI and p-values.

Statistical analyses were performed with R software (version 4.3.2, R Foundation for Statistical Computing). The conventional 5% two-sided threshold was set for statistical significance. Missing data were not imputed.

Data availability

The data supporting the findings of this study are available from corresponding author, upon reasonable request.

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Author contributions

Study design: A.T., E.Z., O.P.; Data collection: E.Z., O.P., A.T., A.M., A.P., G.G., C.V., J.E., L.P., A.D., M.D.M., O.P., L.C., M.L., M.M., F.C.; Data analysis: R.C.C., E.Z.; Data interpretation: E.Z., A.T., R.C.C., A.M., A.P., A.M., G.G., C.V.; Manuscript Writing and editing: All authors. Final approval of manuscript: All authors.

Competing interests

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Additional information

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