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Real-World Outcomes of CDK4/6 Inhibitors in Germline BRCA-Mutated Hormone Receptor-Positive, HER2-Negative Metastatic Breast Cancer: Turkish Oncology Group (TOG) Study

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Research Article

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Abstract

Background

Germline BRCA1/2-mutated (gBRCAm) hormone receptor-positive/HER2-negative (HR+/HER2−) metastatic breast cancer (MBC) represents a biologically distinct subset in which the efficacy of cyclin-dependent kinase 4/6 (CDK4/6) inhibitors remains incompletely characterized. Given the interplay between DNA damage repair deficiency and cell-cycle regulation, BRCA-associated tumors may demonstrate differential therapeutic sensitivity. We evaluated real-world outcomes, safety, and prognostic factors in a multicenter cohort.

Methods

This multicenter retrospective cohort study included patients with pathogenic germline BRCA1 and/or BRCA2 mutations treated with a CDK4/6 inhibitor plus endocrine therapy for HR+/HER2 − MBC (June 2020–September 2025) at participating centers in Turkey. Progression-free survival (PFS) and overall survival (OS) were estimated using Kaplan–Meier methods and compared by log-rank testing. Cox proportional hazards models were used for univariable and multivariable analyses.

Results

Among 121 patients, 30 (24.8%) had BRCA1, 88 (72.7%) BRCA2, and 3 (2.5%) dual BRCA1 + BRCA2 mutations; 66.9% received CDK4/6 inhibitors as first-line therapy. Ribociclib was used in 69.4% and palbociclib in 29.8%. Objective response rate was 69.4% and clinical benefit rate 82.6%. Median PFS was 17.0 months and median OS was 47.0 months. PFS differed significantly by BRCA subtype (25.0 months for BRCA1, 14.0 months for BRCA2, and 6.0 months for BRCA1 + 2; log-rank p = 0.013). Median OS also differed (57.0, 49.0, and 11.0 months, respectively; log-rank p = 0.016). PFS did not differ between ribociclib and palbociclib (p = 0.192); OS favored ribociclib at a borderline level (p = 0.050), not confirmed in Cox regression. In multivariable analysis, ECOG ≥ 1 (HR 1.846; p = 0.010) and fulvestrant-based therapy (HR 1.735; p = 0.041) predicted shorter PFS; fulvestrant predicted worse OS (HR 2.389; p = 0.008). Dose reductions occurred in 16.5% and discontinuation in 2.5%.

Conclusions

CDK4/6 inhibitor–based therapy demonstrates clinically meaningful activity in gBRCAm HR+/HER2 − MBC; however, survival outcomes differ by BRCA subtype, suggesting underlying biological heterogeneity. These findings support further investigation of BRCA subtype–specific tumor biology and its implications for therapeutic sequencing in this molecularly defined population.

1. Introduction

Breast cancer remains the most frequently diagnosed malignancy and the leading cause of cancer-related mortality among women worldwide, with an estimated 2.3 million new cases and 685,000 deaths in 2020 [1]. Hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) breast cancer represents approximately 70% of all breast cancer cases and is characterized by expression of estrogen receptor (ER) and/or progesterone receptor (PR) in the absence of HER2 amplification or overexpression.

The introduction of cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors has fundamentally changed the treatment paradigm for HR+/HER2- metastatic breast cancer (MBC). Palbociclib, ribociclib, and abemaciclib have demonstrated significant improvements in progression-free survival (PFS) and overall survival (OS) when combined with endocrine therapy in both first-line and later-line settings [2–4]. In pivotal first-line trials, median PFS ranged from 24.8 to 28.2 months, establishing CDK4/6 inhibitor-based combinations as the standard of care. These agents inhibit CDK4 and CDK6, preventing phosphorylation of the retinoblastoma (Rb) protein and blocking cell cycle progression from G1 to S phase [5].

Germline mutations in BRCA1 and BRCA2 (gBRCAm) occur in approximately 5–10% of breast cancer patients [6]. BRCA proteins play essential roles in homologous recombination repair of DNA double-strand breaks, and their loss leads to genomic instability and increased sensitivity to DNA-damaging agents and poly(ADP-ribose) polymerase (PARP) inhibitors [7]. Although BRCA1-mutated tumors are commonly associated with triple-negative phenotypes, approximately 20–30% of BRCA1- and 70–80% of BRCA2-mutated breast cancers are HR-positive [8, 9]. Consequently, a substantial proportion of gBRCAm carriers present with HR+/HER2- disease and require optimized endocrine-based strategies.

PARP inhibitors have demonstrated efficacy in BRCA-mutated HER2-negative MBC. In the OlympiAD and EMBRACA trials, olaparib and talazoparib significantly improved PFS compared with chemotherapy (median PFS 7.0 vs 4.2 months and 8.6 vs 5.6 months, respectively) [10, 11]. However, the optimal sequencing of PARP inhibitors and CDK4/6 inhibitors remains uncertain. Importantly, most pivotal CDK4/6 inhibitor trials either excluded or underrepresented patients with germline BRCA mutations, limiting subgroup-specific conclusions [12].

Biological interactions between DNA damage repair pathways and cell cycle regulation may influence treatment response [13]. Preclinical studies suggest that CDK4/6 inhibition can affect homologous recombination repair capacity, raising questions regarding potential synergy or resistance mechanisms in BRCA-mutated tumors [14]. Furthermore, BRCA-mutated cancers may demonstrate distinct biological characteristics, including higher proliferative activity and differential endocrine sensitivity, which could modify CDK4/6 inhibitor benefit [15].

Several mechanisms have been proposed to explain potentially reduced CDK4/6 inhibitor efficacy in this subgroup. Safonov et al. reported enrichment of RB1 alterations among HR+/HER2- tumors in gBRCA2 carriers, suggesting that co-loss of BRCA2 and RB1 (both located on chromosome 13q) may predispose

to resistance under CDK4/6 inhibitor selective pressure [16]. Frenel et al. described higher cumulative incidence of ESR1 mutation emergence during first-line aromatase inhibitor plus palbociclib therapy in BRCA1/2-PALB2 mutation carriers [17]. In addition, Rodriguez et al. observed a high prevalence of non-luminal intrinsic subtypes in gBRCA2-associated HR+/HER2- tumors, which have been associated with inferior CDK4/6 inhibitor outcomes [18, 19].

Despite these biological considerations and the widespread use of CDK4/6 inhibitors in clinical practice, real-world evidence specifically evaluating their effectiveness in BRCA-mutated HR+/HER2- MBC remains limited and heterogeneous [20]. Many published studies include small numbers of gBRCAm patients, and methodological issues such as immortal time bias and inconsistent control group definitions have been highlighted [21, 22]. Current NCCN and ESMO guidelines recommend CDK4/6 inhibitors as preferred first-line therapy for HR+/HER2- MBC irrespective of BRCA mutation status, largely extrapolated from trials not specifically designed to evaluate this molecular subgroup.

This study aimed to evaluate real-world clinical outcomes of CDK4/6 inhibitor-based therapy in patients with germline BRCA1/2 mutations and HR+/HER2- metastatic breast cancer, including progression-free survival, overall survival, response rates, safety profile, and independent prognostic factors, with particular attention to differences between BRCA1 and BRCA2 mutation carriers.

2. Materials and Methods

2.1. Study Design and Patient Selection

This retrospective, multi-center cohort study included patients with pathogenic germline BRCA1 or BRCA2 mutations who received CDK4/6 inhibitor-based therapy for HR+/HER2- metastatic breast cancer between June 2020 and September 2025 at participating centers in Turkey. This research obtained ethical approval from the Gaziantep City Hospital Ethics Committee (Project code: 244/2025). The study was approved by the institutional review boards of all participating centers and conducted in accordance with the Declaration of Helsinki.

Inclusion criteria comprised: (1) confirmed pathogenic germline BRCA1 or BRCA2 mutation by validated genetic testing; (2) histologically confirmed breast carcinoma; (3) HR-positive (ER ≥ 10% by immunohistochemistry) and HER2-negative disease (according to ASCO/CAP guidelines); (4) metastatic disease (Stage IV) at the time of CDK4/6 inhibitor initiation; (5) treatment with at least one dose of a CDK4/6 inhibitor (palbociclib, ribociclib, or abemaciclib) in combination with endocrine therapy; (6) age ≥ 18 years at treatment initiation; and (7) adequate baseline clinical and radiological data available for assessment. Exclusion criteria included: (1) presence of other concurrent malignancies; (2) insufficient follow-up data (< 1 imaging assessment); and (3) use of CDK4/6 inhibitors outside of standard-of-care indications.

2.2. Data Collection

Clinical and demographic data were extracted from electronic medical records, including demographic characteristics (age, menopausal status, ECOG performance status), tumor characteristics (histological subtype, tumor grade, ER/PR expression, Ki-67 proliferation index, sites of metastatic disease), genetic characteristics (BRCA mutation type), treatment details (CDK4/6 inhibitor agent, endocrine therapy partner, line of therapy, treatment duration, dose modifications), outcomes (best response, progression dates, survival status), and adverse events (type, grade per CTCAE v5.0). Tumor responses were assessed according to the treating physician's documentation and radiologic evaluations, in line with routine clinical practice, and categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). Objective response rate (ORR) was defined as CR + PR, and clinical benefit rate (CBR) as CR + PR+SD.

2.3. Study Endpoints

Primary endpoints were: (1) PFS—time from CDK4/6 inhibitor initiation to radiological/clinical disease progression or death from any cause; and (2) OS—time from CDK4/6 inhibitor initiation to death from any cause. Secondary endpoints included: (1) ORR; (2) CBR; (3) 24-month survival rates; and (4) Safety profile—treatment-related dose modifications and discontinuations.

2.4. Statistical Analysis

Descriptive statistics were used to summarize patient characteristics. Categorical variables were expressed as frequencies and percentages, continuous variables as medians with interquartile ranges. Survival analyses were performed using the Kaplan-Meier method. PFS and OS were estimated with 95% confidence intervals (CIs). Comparisons between subgroups were performed using the log-rank test for survival outcomes and Fisher's exact test or chi-square test for categorical variables. Univariable Cox proportional hazards regression analyses were conducted to assess the association between baseline variables and PFS or OS. Variables with a p value < 0.10 in univariable analysis and/or with established clinical relevance were included in multivariable Cox regression models. Results are presented as hazard ratios (HRs) with 95% CIs. All statistical tests were two-sided, and p-values < 0.05 were considered statistically significant. Statistical analyses were performed using SPSS version 28.0 (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Patient Characteristics

A total of 121 patients with HER2-negative metastatic breast cancer harboring pathogenic BRCA mutations were included. Of these, 30 (24.8%) had BRCA1 mutations, 88 (72.7%) had BRCA2 mutations, and 3 (2.5%) carried concurrent BRCA1 and BRCA2 mutations.

Baseline clinicopathologic characteristics are summarized in Table 1. The majority of patients were female (94.2%), premenopausal (57.0%), and had ECOG performance status 0 (58.7%). Most tumors were ductal histology (93.4%) and grade 2 (65.3%). Visceral metastases were present in 43.8% of

patients, with liver involvement in 20.7%. CDK4/6 inhibitors were administered in the first-line setting in 66.9% of cases. Ribociclib was used in 69.4% and palbociclib in 29.8% of patients. There were no statistically significant baseline differences between BRCA1 and BRCA2 groups.

Table 1
Baseline Characteristics

Characteristic	All	BRCA1	BRCA2	BRCA1 + 2	p
Age (median)	44	45	44	37	0.186
Sex					
Female	114 (94.2%)	28 (93.3%)	83 (94.3%)	3 (100.0%)	1.000
Male	7 (5.8%)	2 (6.7%)	5 (5.7%)	0 (0.0%)	
Menopausal status					
Premenopausal	69 (57.0%)	16 (53.3%)	51 (58.0%)	2 (66.7%)	0.905
Postmenopausal	45 (37.2%)	12 (40.0%)	32 (36.4%)	1 (33.3%)	
Male	7 (5.8%)	2 (6.7%)	5 (5.7%)	0 (0.0%)	
ECOG					
0	71 (58.7%)	18 (60.0%)	50 (56.8%)	3 (100.0%)	0.816
≥ 1	50 (41.3%)	12 (40.0%)	38 (43.2%)	0 (0.0%)	
Disease presentation					
De novo metastatic	54 (44.6%)	13 (43.3%)	40 (45.5%)	1 (33.3%)	1.000
Recurrent	67 (55.4%)	17 (56.7%)	48 (54.5%)	2 (66.7%)	
Histology					
Ductal	113 (93.4%)	29 (96.7%)	82 (93.2%)	2 (66.7%)	0.678
Lobular	8 (6.6%)	1 (3.3%)	6 (6.8%)	1 (33.3%)	
ER, % (median)	90	90	90	80	0.414
PR, % (median)	40	45	40	80	0.860
Ki-67, % (median)	30	30	30	40	0.876
Grade					
1	4 (3.3%)	0 (0.0%)	3 (3.4%)	1 (33.3%)	0.248
2	79 (65.3%)	20 (66.7%)	58 (65.9%)	1 (33.3%)	
3	38 (31.4%)	10 (33.3%)	27 (30.7%)	1 (33.3%)	

Footnote: Values are n (%) unless otherwise indicated. Continuous variables are presented as median (IQR). P-values compare BRCA1 vs BRCA2 groups only; patients with dual BRCA1 + BRCA2 variants are shown descriptively. Abbreviations: ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; PR, progesterone receptor; CNS, central nervous system.

Characteristic	All	BRCA1	BRCA2	BRCA1 + 2	p
Visceral metastasis	53 (43.8%)	13 (43.3%)	40 (45.5%)	0 (0.0%)	1.000
Bone metastasis	87 (71.9%)	21 (70.0%)	64 (72.7%)	2 (66.7%)	0.820
Liver metastasis	25 (20.7%)	7 (23.3%)	18 (20.5%)	0 (0.0%)	0.794
Lung metastasis	30 (24.8%)	7 (23.3%)	23 (26.1%)	0 (0.0%)	0.808
CNS metastasis	7 (5.8%)	2 (6.7%)	5 (5.7%)	0 (0.0%)	1.000
CDK4/6 inh. line					
1st line	81 (66.9%)	17 (56.7%)	62 (70.5%)	2 (66.7%)	0.212
≥ 2nd line	40 (33.1%)	13 (43.3%)	26 (29.5%)	1 (33.3%)	
CDK4/6 inh.					
Ribociclib	84 (69.4%)	17 (56.7%)	65 (73.9%)	2 (66.7%)	0.098
Palbociclib	36 (29.8%)	13 (43.3%)	22 (25.0%)	1 (33.3%)	
Abemaciclib	1 (0.8%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	
Endocrine partner					
Letrozole	84 (69.4%)	17 (56.7%)	65 (73.9%)	2 (66.7%)	0.098
Fulvestrant	37 (30.6%)	13 (43.3%)	23 (26.1%)	1 (33.3%)	

Footnote: Values are n (%) unless otherwise indicated. Continuous variables are presented as median (IQR). P-values compare BRCA1 vs BRCA2 groups only; patients with dual BRCA1 + BRCA2 variants are shown descriptively. Abbreviations: ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; PR, progesterone receptor; CNS, central nervous system.

3.2. Efficacy, Survival and Safety Outcomes

Overall response rate was 69.4% and clinical benefit rate was 82.6%. Median PFS for the entire cohort was 17.0 months and median OS was 47.0 months. Dose reduction occurred in 16.5% and treatment discontinuation in 2.5% of patients. The efficacy, survival and safety outcomes stratified by BRCA mutation type are summarized in Table 2.

Table 2
Efficacy, survival and safety outcomes according to BRCA status

Best response	All (N = 121)	BRCA1 (n = 30)	BRCA2 (n = 88)	BRCA1 + 2 (n = 3)	p*
CR	15 (12.4%)	6 (20.0%)	9 (10.2%)	0 (0%)	0.37
PR	69 (57.0%)	17 (56.7%)	50 (56.8%)	2 (66.7%)	
SD	16 (13.2%)	4 (13.3%)	11 (12.5%)	1 (33.3%)	
PD	21 (17.4%)	3 (10.0%)	18 (20.5%)	0 (0%)	
ORR (CR + PR)	84 (69.4%)	23 (76.7%)	59 (67.0%)	2 (66.7%)	0.34
CBR (CR + PR+SD)	100 (82.6%)	27 (90.0%)	70 (79.5%)	3 (100%)	0.18
Progression, n (%)	86 (71.1%)	17 (56.7%)	66 (75.0%)	3 (100%)	—
Median PFS, months (95% CI)	17.0 (14.1–19.9)	25.0 (15.9–34.1)	14.0 (10.3–17.7)	6.0 (NA)	**0.013‡**
24-month PFS rate, %	33%	45%	29%	0%	—
Death, n (%)	42 (34.7%)	11 (36.7%)	28 (31.8%)	3 (100%)	—
Median OS, months (95% CI)	47.0 (38.2–55.8)	57.0 (23.1–90.9)	49.0 (NA)	11.0 (3.0–19.0)	**0.016‡**
24-month OS rate, %	78%	72%	82%	0%	—
Dose reduction due to toxicity, n (%)	20 (16.5%)	3 (10.0%)	17 (19.3%)	0 (0%)	0.23
Discontinuation due to toxicity, n (%)	3 (2.5%)	0 (0%)	3 (3.4%)	0 (0%)	0.55

Footnote: * p-values for categorical variables were calculated using χ^2 or Fisher's exact test as appropriate. ‡ p-values for PFS and OS were calculated using log-rank test. Abbreviations: CBR, clinical benefit rate; CI, confidence interval; CR, complete response; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

When stratified by BRCA mutation type, significant differences in PFS were observed across the three groups (log-rank p = 0.013; Fig. 1). BRCA2 mutations were associated with shorter PFS compared with BRCA1 in Cox regression analysis. Patients harboring concurrent BRCA1 and BRCA2 mutations demonstrated markedly inferior outcomes; however, due to the very small sample size (n = 3), these

results should be interpreted cautiously. Safety outcomes were comparable between BRCA1 and BRCA2 groups. For OS, median survival differed numerically between groups, but overall survival curves did not significantly differ (log-rank p = 0.09; Fig. 2). Patients with dual BRCA1 + 2 mutations showed the poorest survival.

When stratified by CDK4/6 inhibitor, median PFS was numerically longer with ribociclib than with palbociclib; however, this difference was not statistically significant (log-rank p = 0.192; Fig. 3). For OS, Kaplan–Meier curves demonstrated separation favoring ribociclib (log-rank p = 0.050; Fig. 4). In univariable Cox analysis, ribociclib was associated with numerically lower risk of death, though not statistically significant.

Survival outcomes were compared according to the treatment line in which CDK4/6 inhibitors were administered (Fig. 5). In the first-line setting, no significant differences were observed in PFS or OS between ribociclib and palbociclib. In the ≥ 2nd-line setting, ribociclib showed numerically longer PFS and OS; however, differences did not reach statistical significance.

3.3. Univariable and Multivariable Analysis: Independent Predictors of PFS and OS

Univariable and multivariable Cox regression analyses for PFS and OS are summarized in Tables 3 and 4. For PFS, ECOG performance status ≥ 1 and fulvestrant-based endocrine therapy were independently associated with shorter progression-free survival in multivariable analysis. For OS, endocrine partner remained the only independent prognostic factor. Fulvestrant-based therapy was associated with inferior overall survival compared with letrozole-based therapy. ECOG performance status and CDK4/6 inhibitor type were not independently associated with OS.

Table 3
Univariable and Multivariable Cox Regression Analysis for PFS

Variable	Univariable HR (95% CI)	p	Multivariable HR (95% CI)	p
Age (per year)	0.995 (0.977–1.013)	0.560	0.987 (0.968–1.007)	0.206
ECOG ≥ 1 vs 0	**1.789 (1.169–2.736)**	**0.007**	**1.846 (1.159–2.940)**	**0.010**
BRCA2 vs BRCA1	1.492 (0.875–2.546)	0.142	1.246 (0.714–2.176)	0.439
Liver metastasis	1.748 (1.057–2.891)	0.029	1.366 (0.798–2.340)	0.255
De novo metastatic disease	0.646 (0.416–1.003)	0.051	0.817 (0.503–1.327)	0.415
Fulvestrant vs letrozole	**2.031 (1.285–3.211)**	**0.002**	**1.735 (1.024–2.941)**	**0.041**
Bone metastasis	1.206 (0.734–1.983)	0.459	—	—
Lung metastasis	0.925 (0.564–1.518)	0.758	—	—
Brain metastasis	1.623 (0.705–3.736)	0.255	—	—
Visceral metastasis	1.291 (0.836–1.992)	0.249	—	—
CDK4/6 inh.	0.776 (0.485–1.241)	0.290	—	—
Line of CDK4/6 inh. use	1.302 (0.824–2.058)	0.258	—	—
Prior CT before CDK4/6 inh.	1.288 (0.804–2.064)	0.292	—	—
Grade ≥ 3 toxicity	0.747 (0.426–1.308)	0.307	—	—
Dose reduction	0.827 (0.465–1.471)	0.517	—	—

Footnote: Variables with $p < 0.10$ in univariable analysis and/or considered clinically relevant a priori (age, BRCA type) were included in the multivariable Cox proportional hazards model. The multivariable model was adjusted for age, ECOG performance status (0 vs ≥ 1), BRCA mutation type (BRCA1 vs BRCA2), presence of liver metastasis, de novo metastatic disease, and endocrine partner (letrozole vs fulvestrant). Abbreviations: PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group, CT, Chemotherapy

Table 4
Univariable and Multivariable Cox Regression Analysis for OS

Variable	Univariable HR (95% CI)	p	Multivariable HR (95% CI)	p
Age (per year)	0.99 (0.96–1.01)	0.341	—	—
ECOG ≥ 1 vs 0	1.85 (0.98–3.49)	0.059	1.705 (0.900–3.233)	0.102
BRCA2 vs BRCA1	0.79 (0.39–1.60)	0.520	—	—
De novo metastatic disease	0.84 (0.44–1.59)	0.584	—	—
Bone metastasis	1.46 (0.66–3.19)	0.350	—	—
Liver metastasis	0.78 (0.34–1.77)	0.556	—	—
Lung metastasis	0.71 (0.33–1.49)	0.358	—	—
Brain metastasis	2.27 (0.69–7.42)	0.177	—	—
CDK4/6 inh.	0.59 (0.31–1.11)	0.104	0.708 (0.371–1.353)	0.296
Fulvestrant vs letrozole	**2.53 (1.35–4.74)**	**0.004**	**2.389 (1.257–4.540)**	**0.008**
Grade ≥ 3 toxicity	1.01 (0.46–2.20)	0.983	—	—
Dose reduction	0.83 (0.47–1.47)	0.517	—	—

Footnote: Variables with $p < 0.10$ in univariate analysis were considered for multivariate modeling. Multivariate model included ECOG, CDK4/6 inhibitor type, and endocrine partner. The final model was statistically significant ($\chi^2 = 12.6$, $p = 0.006$). Abbreviations: HR: hazard ratio; CI: confidence interval; OS: overall survival; ECOG: Eastern Cooperative Oncology Group.

4. Discussion

This multicenter retrospective study represents one of the largest real-world cohorts evaluating CDK4/6 inhibitor–based therapy specifically in patients with germline BRCA1/2-mutated HR+/HER2 − MBC. In the overall population, median PFS was 17.0 months and median OS was 47.0 months. Clinically relevant differences were observed between BRCA subgroups: BRCA1 carriers achieved median PFS of 25.0 months and OS of 57.0 months, whereas BRCA2 carriers demonstrated median PFS of 14.0 months and OS of 49.0 months. Although OS differences were not statistically significant, the PFS separation suggests potential biological and clinical heterogeneity between BRCA1- and BRCA2-associated tumors.

Median PFS in our cohort was numerically shorter than in pivotal trials such as PALOMA-2 and MONALEESA-2 [23, 24]. However, real-world populations differ substantially from trial populations in disease burden, comorbidities, treatment sequencing, and monitoring intervals. Importantly, 33.1% of patients in our study received CDK4/6 inhibitors in second or later lines, which likely contributed to shorter overall PFS. When restricted to first-line treatment, median PFS was 20 months with palbociclib

and 18 months with ribociclib, without significant differences. These results, though somewhat lower than trial outcomes, are consistent with the expected attenuation of benefit in heterogeneous routine-practice cohorts.

In OS analyses across the entire cohort, median OS was 57.0 months with ribociclib and 35.0 months with palbociclib (log-rank p = 0.050). Although ribociclib was associated with a numerically lower risk of death (HR 0.59), this did not reach statistical significance in Cox regression analysis (p = 0.104). In the first-line treatment, median OS was 57.0 months with ribociclib and 47.0 months with palbociclib, without a statistically significant difference (log-rank p = 0.376). Notably, these survival estimates appear shorter than those reported in pivotal randomized trials—63.9 months for ribociclib in MONALEESA-2 and 53.9 months for palbociclib in PALOMA-2. This discrepancy likely reflects real-world case-mix heterogeneity, inclusion of later-line patients, differential treatment sequencing, and the distinct biological features of germline BRCA-mutated tumors rather than intrinsic differences in CDK4/6 inhibitor efficacy.

The interaction between DNA damage response pathways and cell-cycle regulation may further influence CDK4/6 inhibitor efficacy in BRCA-mutated tumors. BRCA deficiency results in impaired homologous recombination repair and increased genomic instability [25]. Preclinical studies have suggested that CDK4/6 inhibition can modulate homologous recombination repair capacity, potentially affecting the response to subsequent DNA-damaging agents or PARP inhibitors [26, 27]. Conversely, some evidence suggests that BRCA mutations might be associated with enhanced sensitivity to CDK4/6 inhibition through mechanisms involving E2F-mediated transcription and replication stress [25, 28].

Our results align closely with the recent systematic review and meta-analysis by Bottosso et al., which demonstrated that gBRCAm patients treated with CDK4/6 inhibitors experienced significantly worse outcomes compared to gBRCA wild-type patients (PFS HR 1.68, OS HR 1.73) [21]. The meta-analysis included 14 studies covering 618 gBRCAm patients, though most were retrospective with moderate-to-high risk of bias. Our study contributes to this growing body of evidence with detailed multivariable analyses identifying independent predictors of survival and comprehensive characterization of the BRCA1 versus BRCA2 subgroups.

A notable observation in our study was the longer PFS and OS among BRCA1 compared with BRCA2 carriers (25.0 vs 14.0 months, p = 0.040; 57.0 vs 49.0 months, p = 0.520 respectively). Although BRCA mutation type was not independently prognostic in multivariable models, biological differences may underlie the observed trend. Safonov et al. identified enrichment for RB1 mutations among gBRCA2 HR+/HER2- breast cancers, hypothesizing that co-loss of heterozygosity of BRCA2 and RB1 (both on chromosome 13) could predispose to biallelic RB1 loss under CDK4/6 inhibitor selective pressure, thereby facilitating resistance [16, 29]. Additionally, Rodriguez et al. reported that 63% of gBRCA2 HR+/HER2- tumors exhibited non-luminal intrinsic subtypes by PAM50, which have been associated with inferior CDK4/6 inhibitor outcomes [18]. These hypotheses require validation through comprehensive

genomic analyses integrating RB1 status, intrinsic subtype, and homologous recombination deficiency signatures.

In multivariable analysis, ECOG performance status and endocrine partner were independent predictors of outcome. ECOG ≥ 1 remained significantly associated with shorter PFS, reinforcing its established prognostic role in metastatic breast cancer. The endocrine backbone also influenced survival endpoints, with fulvestrant-based combinations associated with inferior PFS and OS compared with aromatase inhibitor–based therapy. This likely reflects treatment selection bias rather than intrinsic inferiority of fulvestrant. In routine practice, fulvestrant is frequently administered in later lines or in endocrine-resistant settings, where disease biology is more aggressive and prior endocrine exposure may reduce responsiveness [3, 30]. Nevertheless, randomized trials such as MONALEESA-3 and MONARCH-2 have demonstrated clear benefit of fulvestrant-based CDK4/6 combinations [2, 31].

The shorter outcomes observed with fulvestrant in our cohort may also reflect accumulated endocrine resistance mechanisms, including ESR1 mutations and ligand-independent ER activation [17, 32]. In BRCA-mutated tumors, additional genomic instability and replication stress may accelerate resistance evolution [14]. Frenel et al. reported higher cumulative incidence of ESR1 mutation emergence during first-line palbociclib therapy in BRCA1/2-PALB2 mutation carriers [17], suggesting accelerated acquisition of endocrine resistance mechanisms in this population.

Several biological mechanisms have been proposed to explain reduced CDK4/6 inhibitor benefit in BRCA-mutated tumors beyond RB1 co-deletion. Griguolo et al. reported that higher levels of homologous recombination deficiency signature were associated with reduced sensitivity to endocrine therapy and increased expression of RB-loss signatures in correlative analyses of phase II trials [33]. These findings suggest that BRCA deficiency may confer primary endocrine resistance that is not fully overcome by CDK4/6 inhibition. The absence of comprehensive molecular profiling in our cohort limits mechanistic interpretation, highlighting the need for integrated genomic analyses in future studies.

The optimal sequencing of CDK4/6 inhibitors and PARP inhibitors in gBRCAm HR+/HER2- metastatic breast cancer remains unresolved. PARP inhibitors have demonstrated improved PFS compared with chemotherapy in OlympiAD and EMBRACA [10, 11], though these trials included predominantly pretreated populations. Direct comparison with our cohort is therefore inappropriate. Current clinical guidelines recommend CDK4/6 inhibitors as preferred first-line therapy irrespective of BRCA status. Our data support continued use of CDK4/6 inhibitors in this population, while underscoring the need for prospective studies to define optimal sequencing strategies.

In early-stage disease, adjuvant abemaciclib and ribociclib have demonstrated benefit in high-risk HR+/HER2- populations [34, 35], and adjuvant olaparib improved outcomes in gBRCAm HER2- disease [36]. These overlapping indications may complicate therapeutic prioritization in BRCA-mutated patients. Our metastatic findings do not suggest that CDK4/6 inhibitors should be withheld solely based on BRCA mutation status. Rather, they highlight that BRCA subtype and clinical context should be considered when individualizing therapy.

The safety profile in our cohort was consistent with known CDK4/6 inhibitor toxicities. Dose reductions occurred in 16.5% and discontinuation in 2.5% of patients. As expected, neutropenia was the most common toxicity [23, 38]. No unexpected safety signals were observed, and tolerability did not appear to differ between BRCA1 and BRCA2 carriers. These findings indicate that germline BRCA mutation status does not substantially alter the safety profile of CDK4/6 inhibitors.

This study has several strengths, including a relatively large BRCA-mutated cohort (n = 121), detailed subgroup analyses, and multivariable modeling of prognostic factors. However, limitations must be acknowledged. The retrospective design introduces potential selection bias and limits causal inference. The relatively small number of BRCA1 carriers (n = 30) limits statistical power for subgroup analyses. We lacked comprehensive molecular profiling data beyond BRCA mutation status, including ESR1 mutations, PIK3CA alterations, and tumor mutational signatures that might provide additional insights into treatment resistance.

Clinical Implications and Future Directions

Our findings support CDK4/6 inhibitor-based therapy as an effective treatment option for BRCA-mutated HR+/HER2- metastatic breast cancer, though outcomes appear inferior to unselected populations. The superior PFS observed in BRCA1 versus BRCA2 carriers is hypothesis-generating and warrants validation in larger cohorts. Future research priorities include prospective randomized trials comparing CDK4/6 inhibitors versus PARP inhibitors in first-line therapy, evaluation of optimal treatment sequencing strategies, and identification of predictive biomarkers beyond BRCA mutation status. Integration of comprehensive genomic profiling, including ESR1 mutations, RB1 alterations, and homologous recombination deficiency scores, may enable biomarker-driven treatment selection and elucidate resistance mechanisms in this molecularly distinct population.

5. Conclusion

In this multicenter real-world cohort of patients with germline BRCA-mutated HR+/HER2- metastatic breast cancer, CDK4/6 inhibitor-based therapy demonstrated meaningful clinical efficacy with a median PFS of 17.0 months and median OS of 47.0 months. These outcomes are numerically lower than those observed in unselected HR+/HER2- MBC populations from pivotal trials, consistent with recent meta-analyses. BRCA1 carriers showed significantly superior outcomes compared to BRCA2 carriers, warranting further investigation of underlying biological mechanisms. While CDK4/6 inhibitors provide valuable clinical benefit and should not be withheld from BRCA-mutated patients, prospective comparative trials are needed to optimize treatment sequencing with PARP inhibitors and identify predictive biomarkers in this molecularly distinct population.

Declarations

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Ethics Approval and Consent to Participate

This study was approved by the Gaziantep City Hospital Ethics Committee (Project code: 244/2025) and was conducted in accordance with the Declaration of Helsinki. Due to the retrospective nature of the study, the requirement for individual informed consent was waived by the Ethics Committee.

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Author Contribution

Mustafa Seyyar: Writing – original draft, Writing – review & editing, Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Validation, Project administration. **Ali Kalem:** Data curation. **Mürsel Sali:** Data curation. **Berkan Karabuğa:** Data curation. **Taha Koray Şahin** : Data curation. **Ahmet Kürşad Dişli:** Data curation. **Alper Türkel:** Data curation. **Berkan Karadurmuş:** Data curation. **Ece Şahin Hafızoğlu:** Data curation. **Nilüfer Avcı:** Data curation. **İrem Bilgetekin** : Data curation. **Naziyet Köse Baytemur:** Data curation. **Esma Uğuztemur:** Data curation. **Utku Oflazoğlu:** Data curation. **Hasibe Bilge Gür:** Data curation. **İlhan Hacıbekiroğlu:** Data curation. **Aysun Fatma Akkuş:** Data curation. **Sernaz Topaloğlu:** Data curation. **Ayberk Bayramgil:** Data curation. **Özgecan Dülgar Kaya:** Data curation. **Melike Yazıcı:** Data curation. **Teoman Şakalar:** Data curation. **Seval Akay:** Data curation. **Nargiz Majidova:** Data curation. **Murad Guliyev:** Data curation. **Özkan Alan:** Data curation. **Serkan Gülcü:** Data curation. **Tülay Eren:** Data curation. **Gökşen İnanç İmamoğlu:** Data curation. **Ali Kaan Güren:** Data curation. **Osman Köstek:** Data curation. **Ahmet Ünlü:** Data curation. **Banu Öztürk:** Data curation. **Esra Aydın:** Data curation. **Shamkhal Safarov:** Data curation. **Bekir Doğan:** Data curation. **Mehmet Akif Tükenmez:** Data curation. **Teyfik Demir:** Data curation. **Elif Şahin:** Data curation. **Engin Erdemoğlu:** Data curation. **Fatma Keskin Uzundere:** Data curation. **Osman Bütün:** Data curation. **Bülent Karabulut:** Data curation. **Mehmet Uzun:** Writing – review & editing, Data curation. **Tuba Baydaş:** Formal analysis. **Elanur Karaman:** Data curation. **Hacı Arak:** Writing – review & editing, Data curation. **Ferhat Ekinci:** Data curation. **Musa Barış Aykan:** Data curation. **İsmail Ertürk:** Data curation. **Deniz Can Güven:** Data curation. **Adem Deligönül:** Data curation. **Cengiz Karaçin:** Data curation. **Öztürk Ateş:** Data curation. **Mevlüde İnanç:** Data curation. **Havva Yeşil:** Data curation. **Sercan Aksoy:** Writing – review

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Data Availability

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

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Figures

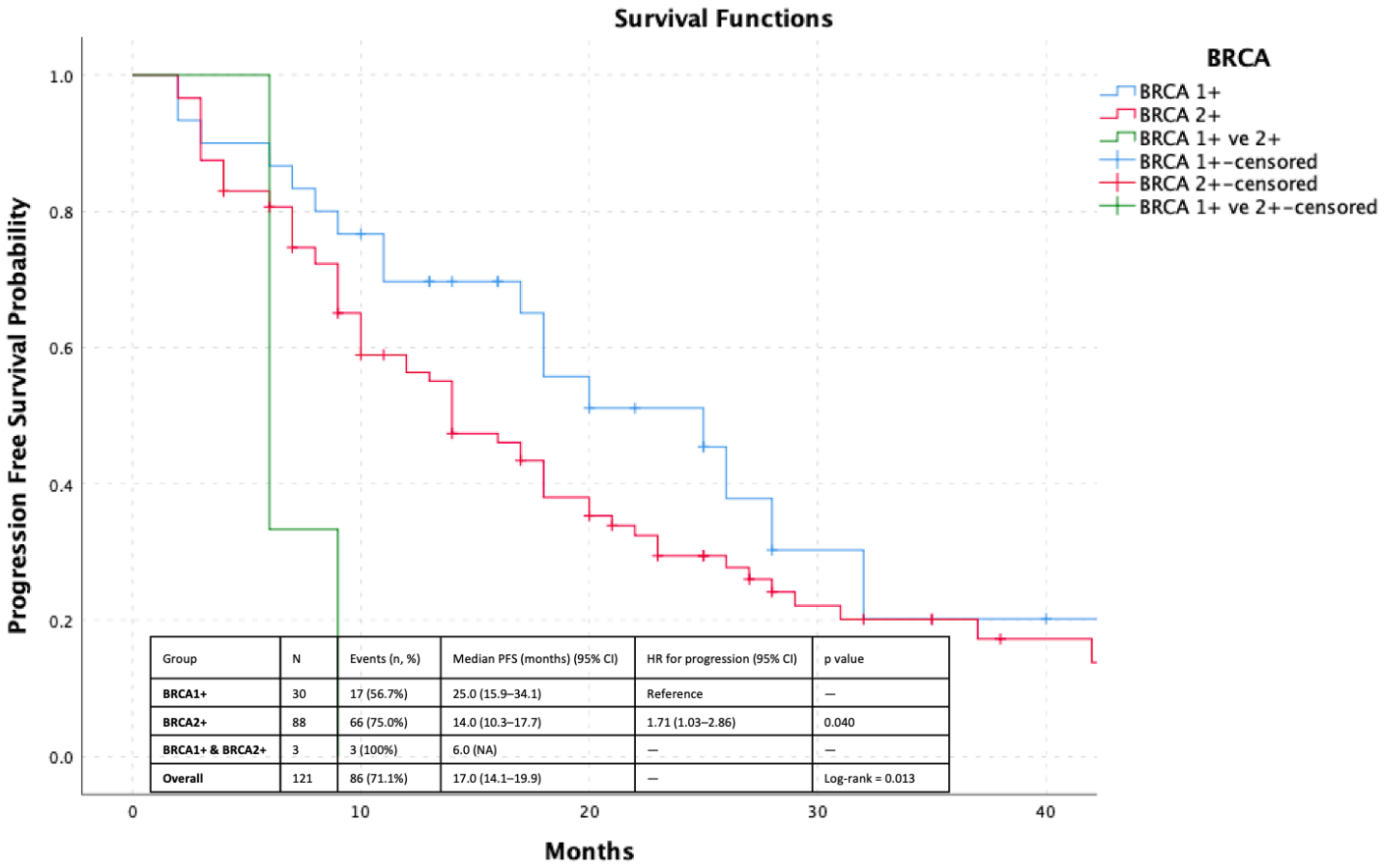
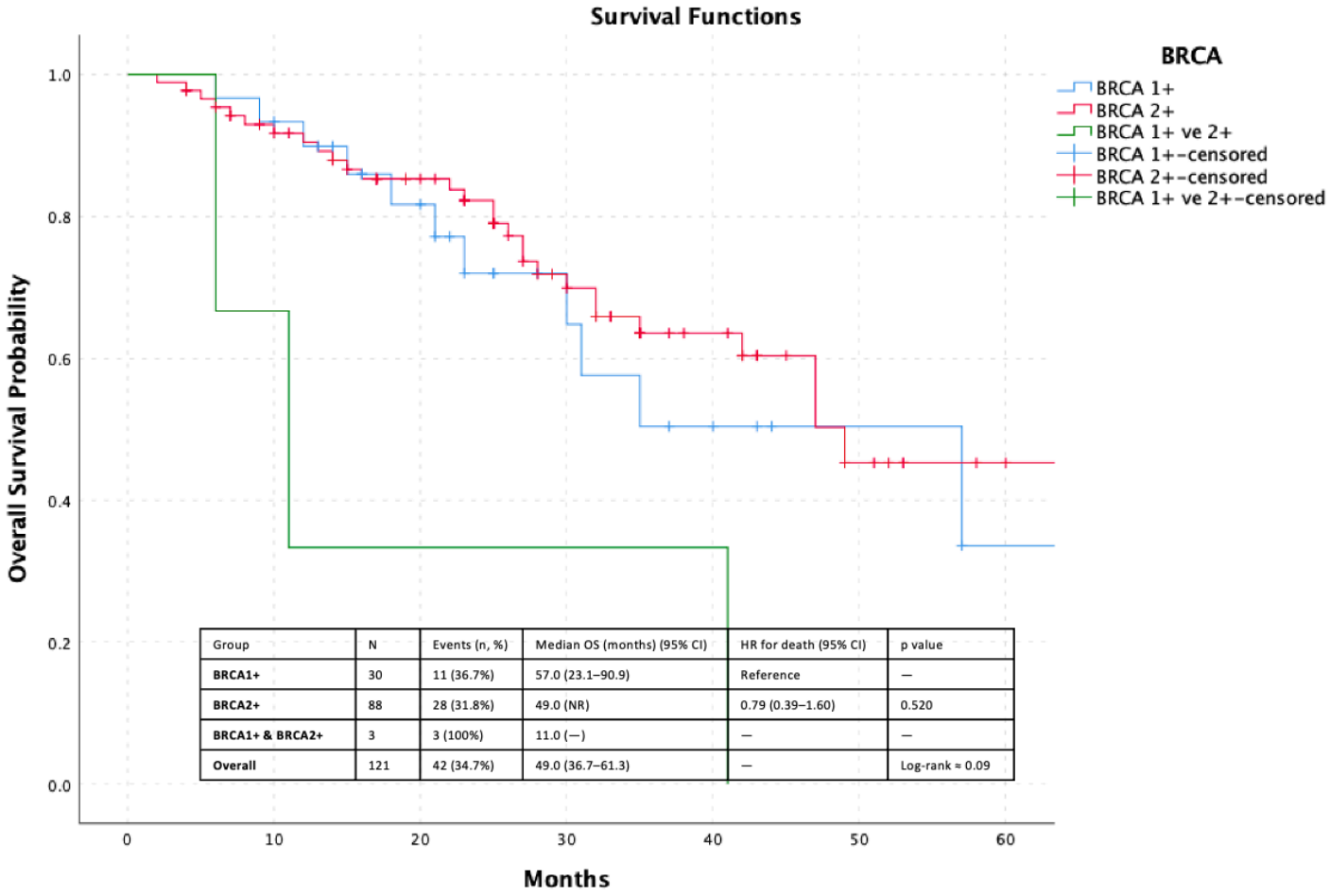


Figure 1

Kaplan-Meier curve for PFS according to BRCA status

Footnote: PFS was estimated using the Kaplan–Meier method and compared across BRCA subgroups using the log-rank test. Hazard ratios and 95% confidence intervals were derived from Cox proportional hazards regression, with BRCA1 as the reference group. The concurrent BRCA1+/BRCA2+ subgroup

included a very small number of patients and is presented descriptively; results for this subgroup should be interpreted with caution.

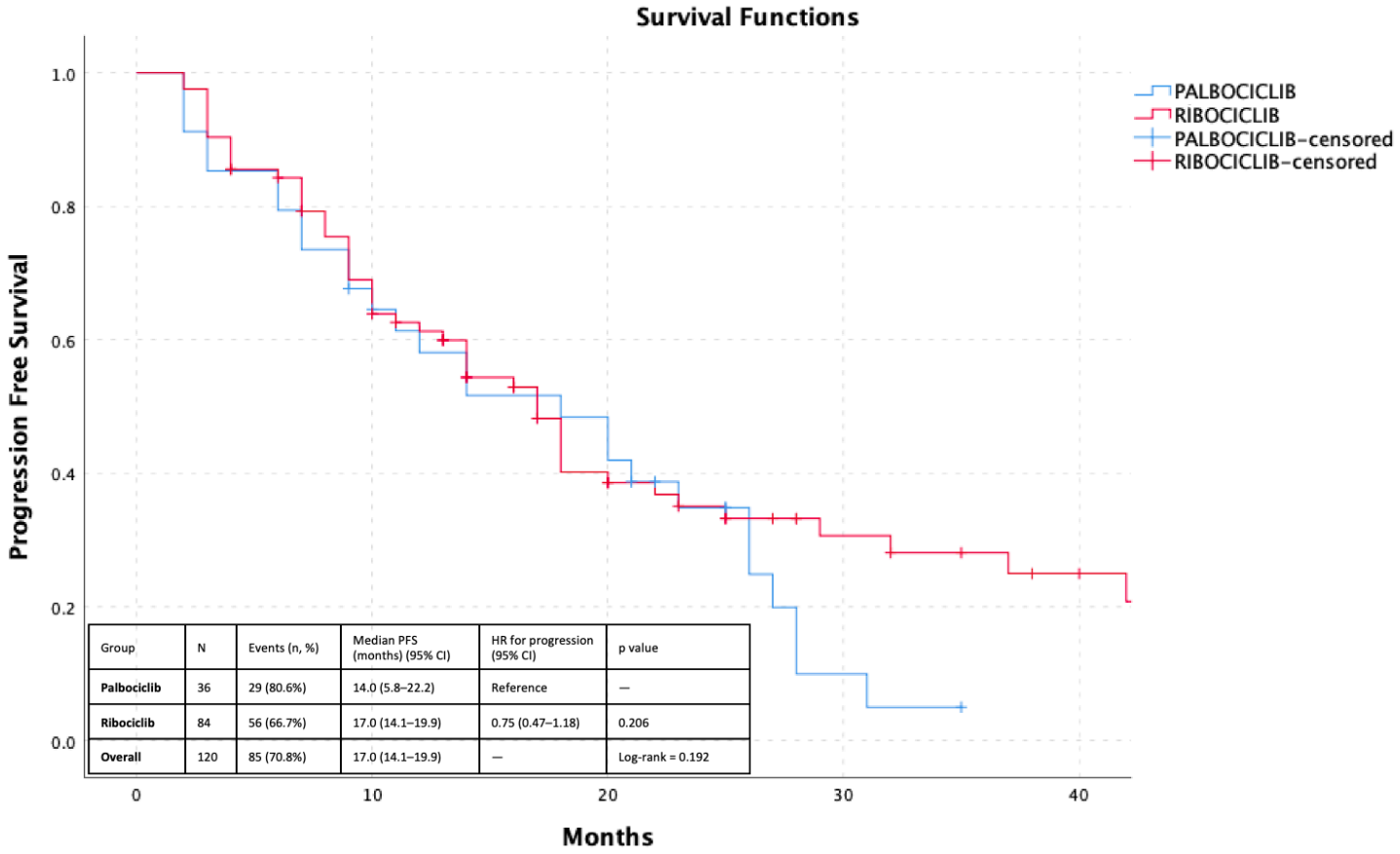


Group	N	Events (n, %)	Median OS (months) (95% CI)	HR for death (95% CI)	p value
BRCA1+	30	11 (36.7%)	57.0 (23.1–90.9)	Reference	—
BRCA2+	88	28 (31.8%)	49.0 (NR)	0.79 (0.39–1.60)	0.520
BRCA1+ & BRCA2+	3	3 (100%)	11.0 (—)	—	—
Overall	121	42 (34.7%)	49.0 (36.7–61.3)	—	Log-rank ≈ 0.09

Figure 2

Kaplan-Meier curve for OS according to BRCA status

Footnote: OS was estimated using the Kaplan–Meier method and compared using the log-rank test. Hazard ratios and 95% confidence intervals were calculated using univariable Cox proportional hazards regression. BRCA1+ was used as the reference category. The BRCA1+/BRCA2+ subgroup included a very small number of patients and should be interpreted with caution.

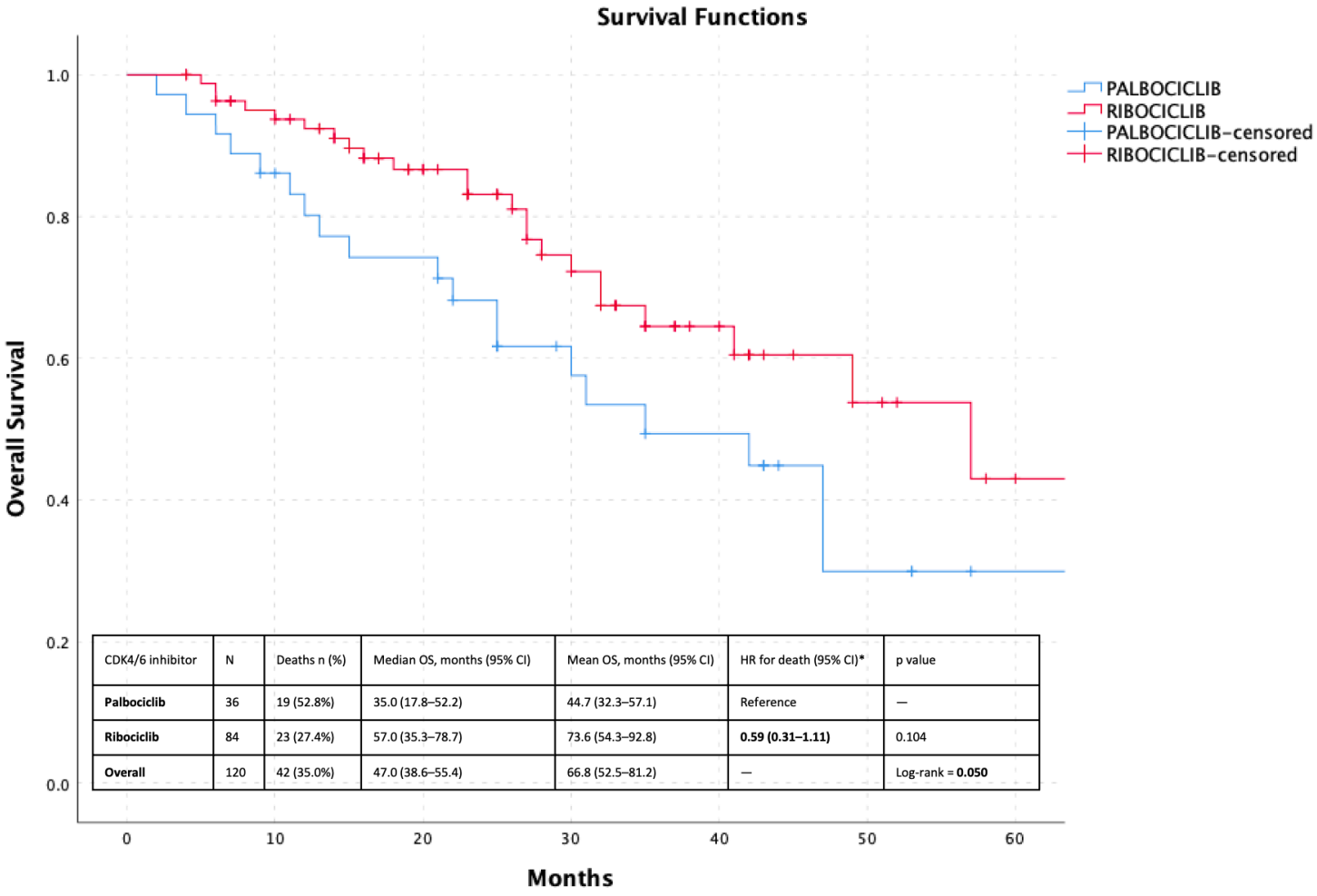


Group	N	Events (n, %)	Median PFS (months) (95% CI)	HR for progression (95% CI)	p value
Palbociclib	36	29 (80.6%)	14.0 (5.8–22.2)	Reference	—
Ribociclib	84	56 (66.7%)	17.0 (14.1–19.9)	0.75 (0.47–1.18)	0.206
Overall	120	85 (70.8%)	17.0 (14.1–19.9)	—	Log-rank = 0.192

Figure 3

Kaplan-Meier curve for PFS according to CDK4/6 inhibitor

Footnote: PFS was estimated using the Kaplan–Meier method and compared using the log-rank test. Hazard ratios and 95% confidence intervals were calculated using univariable Cox proportional hazards regression, with palbociclib as the reference group.



CDK4/6 inhibitor	N	Deaths n (%)	Median OS, months (95% CI)	Mean OS, months (95% CI)	HR for death (95% CI)*	p value
Palbociclib	36	19 (52.8%)	35.0 (17.8–52.2)	44.7 (32.3–57.1)	Reference	—
Ribociclib	84	23 (27.4%)	57.0 (35.3–78.7)	73.6 (54.3–92.8)	**0.59 (0.31–1.11)**	0.104
Overall	120	42 (35.0%)	47.0 (38.6–55.4)	66.8 (52.5–81.2)	—	Log-rank = **0.050**

Figure 4

Kaplan-Meier curve for OS according to CDK4/6 inhibitor

Footnote: Overall survival was estimated using the Kaplan–Meier method and compared using the log-rank test. Hazard ratios and 95% confidence intervals were obtained from univariable Cox proportional hazards regression, with palbociclib as the reference group.

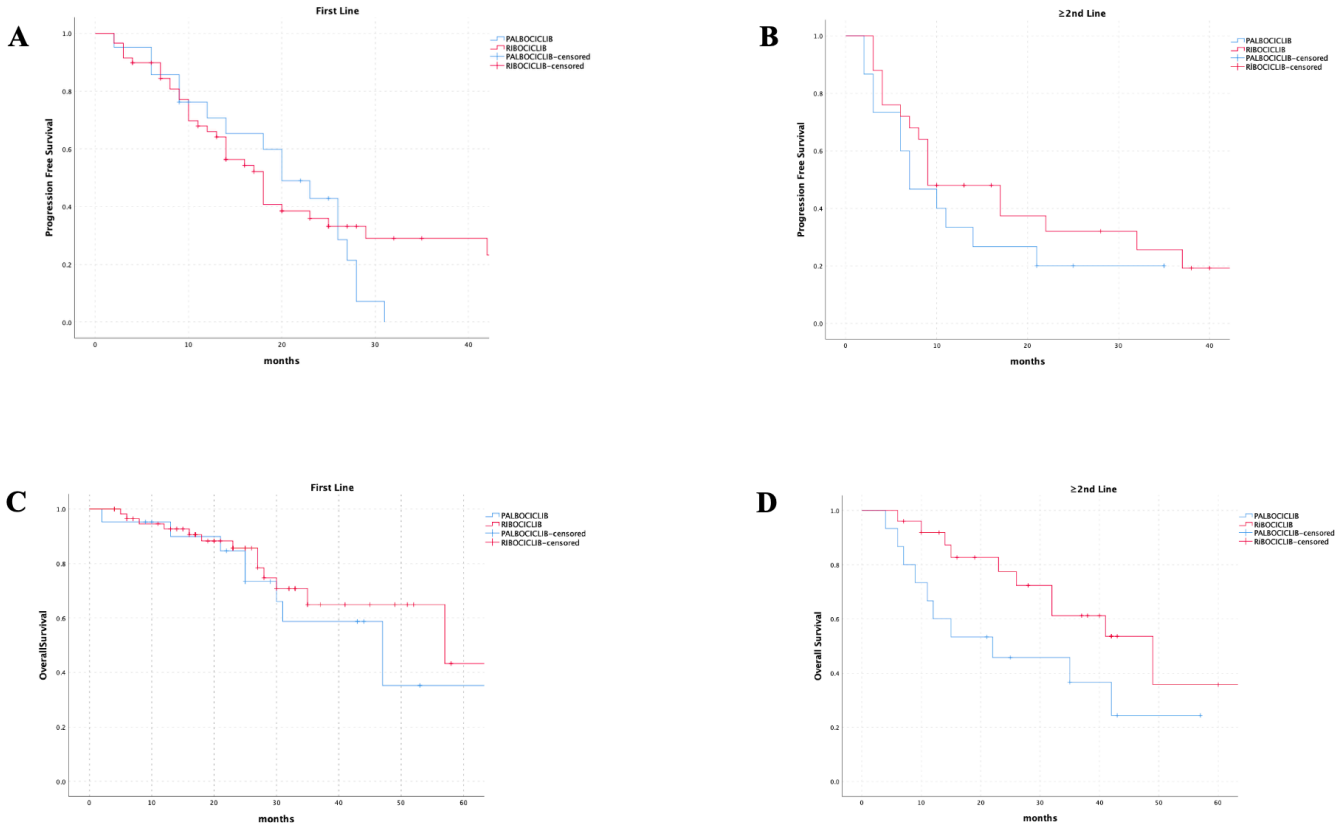


Figure 5

PFS and OS according to CDK4/6 inhibitor type and line of therapy

Footnote: PFS and OS were estimated using the Kaplan–Meier method and compared between treatment groups using the log-rank test. Hazard ratios and 95% confidence intervals were calculated using univariable Cox proportional hazards regression, with palbociclib as the reference group. Analyses were stratified by line of therapy (first line vs. ≥2nd line). (A) PFS in the first-line setting. (B) PFS in patients treated in the ≥ 2nd line setting, (C) OS in the first-line setting. (D) OS in patients treated in the ≥ 2nd line setting.