Prognostic and Predictive Factors in Metastatic Breast Cancer Patients Treated with CDK4/6 Inhibitors

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ABSTRACT

Objective: To evaluate the safety and efficacy of CDK4/6 inhibitors in combination with hormone therapy, and to investigate potential predictive markers of treatment in metastatic breast cancer (MBC).

Study Design: An observational study.

Place and Duration of the Study: Department of Medical Oncology, Faculty of Medicine, Eskisehir Osmangazi University, Eskisehir, Turkiye, from January 2019 to December 2023.

Methodology: Eighty patients with HR+ HER2- MBC treated with CDK4/6 inhibitors were inducted. Mean overall survival (OS) and progression-free survival (PFS) were compared using t-tests or ANOVA, while Pearson's correlation was used to assess relationships between continuous variables and survival. Kaplan-Meier and Cox regression analyses were performed to analyse variables affecting PFS and OS and to determine treatment response to risk factors.

Results: Ribociclib was used in 70 patients, and palbociclib in 10 patients. A significant difference in PFS was observed between the CDK4/6 inhibitor agents ($p = 0.034$), with a longer mean PFS in the palbociclib group. A weak negative correlation was found between NLR and PFS ($r = -0.289$, $p = 0.010$). The number of involved lymph nodes showed a weak positive correlation with OS ($r = 0.327$, $p = 0.040$). Time to metastasis and treatment duration contributed significantly to OS as an independent variable ($p = 0.001$ and $p = 0.003$), and the CDK4/6 agent contributed significantly to PFS as an independent variable ($p = 0.008$). There was no statistically significant change in OS with the preferred CDK4/6 agent.

Conclusion: There is a significant difference in the use of CDK4/6, which may supplement standard hormone therapy in the treatment of HR+ HER2- MBC patients.

Key Words: *CDK4/6 inhibitors, Breast cancer, Neutrophil-to-lymphocyte ratio*.

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INTRODUCTION

Breast cancer is the most common malignancy in women and has the 2nd highest mortality rate after lung cancer.[1,2] Metastatic breast cancer (MBC) is a disease that cannot be cured, with an average survival of 25% in 3-5 years.[3] The HR+ HER2- subgroup constitutes 70% of MBC cases, which are histologically divided into four main groups. The basis of HR+ MBC treatment is endocrine therapy. However, endocrine resistance develops in patients after a certain period, leading to disease progression. With new studies, endocrine therapies combined with CDK4/6 inhibitors, which overcome this resistance and provide significant survival benefits, are being used in the agenda.[4]

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CDK4/6 promotes replication of genes during DNA synthesis by forming a complex with cyclin D and is involved in the G1-S phase of the cell cycle.[5] CDK4/6 inhibitors (Abemaciclib, palbociclib, and ribociclib) are FDA-approved agents that stop the cycle at the transition from G1 to S.[6] CDK4/6 phosphorylates the Retinoblastoma (Rb) gene, which stops the progression of the cell cycle and releases E2F. Thus, the progression of the mitosis process is ensured.[6] Estrogen receptors also contribute to the progression of the cell cycle by increasing CD1 production in this process. CDK4/6 inhibitors selectively inhibit CDK4/6-dependent Rb phosphorylation and stop the cell cycle at this point.[6,7] As a result of this mechanism, treatment with CDK4/6 inhibitors combined with hormonotherapy constitutes the most powerful step in MMC treatment.

In previous studies, CDK4/6 inhibitors have been used in combination with a non-steroidal aromatase inhibitor (AI) or selective oestrogen receptor (ER) degrader fluvestrant in the first- and second-line treatment of MBC. In phase III trials of CDK4/6 inhibitors in combination with first-line AI (PALAMO-2, MONELEESA-2, MONARCH-3), although a difference in progression-free survival (PFS) was observed, only ribociclib and abemasiclib showed a significant overall survival (OS) benefit.[8-10]

In addition, in a phase III study, ribociclib and ovarian suppression were combined in pre-perimenopausal patients, and a PFS benefit was also observed.[11] A significant difference in PFS was also observed in phase III studies (PALAMO-3, MONELEESA-3, MONARCH-2), in which all three agents were combined with fluvestrant in the second-line.[12-14]

This study was conducted to investigate the efficacy of CDK4/6 inhibitors and to identify potential predictive and prognostic factors associated with these agents in HR+ HER2-negative MBC patients.

METHODOLOGY

Eighty patients diagnosed with HR+ HER2- ABC who were followed up in the Department of Medical Oncology, Faculty of Medicine, Eskisehir Osmangazi University, Eskisehir, Turkiye, from January 2019 to December 2023, were retrospectively evaluated. HR+ HER2- MBC patients were included, and HER2+ patients were excluded.

Demographic information, menopausal status, disease stage, and metastasis status of the patients were analysed. Histopathological features, hormone receptor positivity, and Ki-67 level were evaluated. Hormonotherapy combined with CDK4/6 inhibitor drugs, treatment-related side effects, OS, and PFS times were calculated. OS was defined as the time from diagnosis to death, while PFS was measured from the diagnosis of advanced disease to progression.

Descriptive statistics for continuous variables were presented as mean ± standard deviation or median (IQR), as appropriate. The degree of hormone receptor positivity, Ki-67, lactate dehydrogenase (LDH), tumour marker levels, and neutrophil-to-lymphocyte ratio (NLR) are measured as specific variables. The normality of the distribution for continuous variables, including OS and PF, was assessed using both graphical methods (histograms and Q-Q plots) and by examining skewness and kurtosis values.[15] The independent samples t-test was used to compare mean survival times (OS and PFS) between two groups for normally distributed data, and an Analysis of Variance (ANOVA) was applied for comparisons across more than two groups. A Pearson's correlation analysis was performed to evaluate the linear relationships between continuous clinic-opathological variables and survival outcomes. Kaplan-Meier and Cox regression analyses were performed to analyse variables affecting PFS and OS and to determine treatment response to risk factors. Results from the Cox models were reported as hazard ratios (HR) with 95% confidence intervals (CI). IBM SPSS Statistics version 23 software was used for statistical analysis. A p-value of <0.05 was considered statistically significant.

RESULTS

The mean age of the patients was 56.29 ± 14.30 (31-84) years. The mean PFS and OS times were 14.03 ± 9.38 and 60.21 ± 47.75, respectively. There were 31 (38.8%) premenopausal patients and 49 (61.3%) postmenopausal patients. Of the patients, 38 (47.5%) were *de nova*, and 42 (52.5%) were metastatic cases at follow-up. When the metastasis sites were analysed, 58.7% were visceral, and 41.3% were nonvisceral metastatic disease. Ribociclib was used in 70 (87.5%) patients, and palbociclib in 10 (12.5%) of the 80 patients included in the study. While 60.0% of CDK4/6 agents were combined with a nonsteroidal aromatase inhibitor, 40.0% were combined with fluvestrant. Of these patients, 40% received CDK4/6 inhibitors as first-line treatment, while 60% received them as the second-line. While 23.75% patients had no side effects associated with the CDK4/6 inhibitor, 76.25% had side effects of varying degrees (grade 3-4 in 47.5%). No mortality was detected. Dose reduction was performed in 22.5% patients due to side effects (Table I). The comparison of PFS and OS according to baseline demographic and treatment-related variables is presented in Table II.

An independent t-test showed that menopausal status, dose change, choice of CDK4/6 inhibitor in first- and second-line settings, hormone agent in combination with CDK4/6, ER positivity rate, and exitus status did not have a significant impact on changes in PFS and OS (p >0.05).

The analysis of the CDK4/6 inhibitor agents revealed a statistically significant difference in PFS between the two treatment groups (p = 0.034). Patients administered palbociclib demonstrated a markedly longer mean PFS (24.11 ± 13.28 months), compared with those treated with ribociclib (12.71 ± 7.98 months). While a notable numerical difference was observed—with the palbociclib group showing a higher mean OS (86.11 ± 42.64 months) *versus* the ribociclib group (56.83 ± 47.62 months)—this association did not reach statistical significance (p = 0.084).

Table I: Patient demographic data.

Patient characteristics	Number (%)	
Age	56.29 ± 14.30 (31-84)†	
PFS	14.03 ± 9.38 (2-37)	
OS	60.21 ± 47.75 (4-192)	
State of menopause		
Premenapause	31	38.8%
Postmenapause	49	61.3%
Time of metastasis		
De nova metastatic	38	47.5%
Matastatic in follow-up	42	52.5%
Metastasis focus		
Visceral	47	58.7%
Nonvisceral	33	41.3%
CDK4/6 agent		
Ribociclib	70	87.5%
Palbociclib	10	12.5%
Time of treatment		
Step 1	32	40%
Step 2 and beyond	48	60%
Combined hormone agent		
Aromatase inhibitor	48	60.0%
Fluvestrant	32	40.0%
Side effects	61	76.25%
Grade 3 and above side effects	38	47.5%
Toxicity-related dose reduction	18	22.5%

† Mean ± SD (minimum-maximum).

Table II: Comparison of PFS and OS according to baseline demographics and treatment-related variables.

Study variables		PFS		OS	
		Mean ± SD	p-values	Mean ± SD	p-values
Menopausal status	Premenapause	14.45 ± 10.27	0.608*	59.39 ± 49.41	0.846*
	Postmenapause	13.31 ± 7.77		61.59 ± 45.63	
Human epidermal growth factor receptor	Positive	7.50 ± 6.36	0.347*	69.50 ± 20.51	0.754*
	Negative	14.06 ± 9.70		58.67 ± 48.26	
Time to metastasis	Denova	14.18 ± 9.37	0.885*	31.39 ± 23.64	**<0.001***
	On follow-up	13.88 ± 9.50		87.58 ± 48.93	
Foci of metastasis	Lean (body mass)	14.85 ± 9.70	0.418**	54.70 ± 43.67	0.167**
	Visceral (fat)	15.00 ± 10.22		75.96 ± 46.77	
	Both lean and visceral	11.77 ± 7.90		52.00 ± 52.64	
Dose change	Performed	16.44 ± 10.21	0.231*	62.22 ± 47.08	0.780*
	Not performed	13.39 ± 9.13		58.61 ± 48.12	
Side effects	No side effects	12.05 ± 8.49	0.550**	77.68 ± 48.47	**0.043****
	Clinical side effects present	14.00 ± 10.58		93.50 ± 71.64	
	Hematological side effects present	14.82 ± 9.73		51.75 ± 43.82	
CDK4/6 agent	Ribociclib	12.71 ± 7.98	**0.034***	56.83 ± 47.62	0.084*
	Palbociclib	24.11 ± 13.28		86.11 ± 42.64	
Time of treatment	Step 1	15.23 ± 9.66	0.362*	49.52 ± 51.17	0.109*
	Step 2 and beyond	13.23 ± 9.21		67.26 ± 44.51	
Hormone agent in combination with CDK4/6	Aromatase Inhibitor	13.55 ± 9.23	0.587*	53.83 ± 50.50	0.148*
	Fluvestrant	14.74 ± 9.71		69.87 ± 42.20	
ER positivity rate	1-10%	12.17 ± 6.31	0.459*	76.00 ± 47.28	0.215*
	>10%	14.36 ± 9.84		57.33 ± 47.62	
Outcomes	Death	10.74 ± 9.77	0.079*	66.63 ± 49.76	0.504*
	Live	15.08 ± 9.08		58.14 ± 47.33	

** Independent samples t-test and **ANOVA.*

Table III: Pearson's correlation analysis of PFS and OS with continuous study variables and prognostic factors evaluated by univariate and multivariate regression analyses for OS and PFS.

Study variables	PFS		OS	
	r	p-values	r	p-values
Progesterone receptor status	0.135	0.281	0.024	0.849
ER	-0.077	0.530	-0.010	0.933
Ki-67 proliferation index	-0.111	0.410	-0.006	0.966
Tumour grade	-0.060	0.674	0.050	0.729
Tumour size	-0.016	0.919	-0.224	0.155
Lymph node	-0.122	0.453	**0.327**	**0.040**
NLR	**-0.289**	**0.010**	0.156	0.173
	Univariate analysis (p*)	**Multivariate analysis p* (HR 95% CI)**	**Univariate analysis (p*)**	**Multivariate analysis p* (HR 95% CI)**
Menopausal status	0.482		0.740	
Time to metastasis	0.900		**0.001**	**0.001** (0.666; 0.510-0.869)
Human epidermal growth factor receptor	0.138		0.879	
Foci of metastasis	0.549		0.627	
Dose change	0.263		0.500	
Progesterone receptor status	0.813		0.654	
Ki-67	0.761		0.838	
Tumour grade	0.680		0.363	
Tumour size	0.119		0.915	
Lymph node	0.747		0.932	
NLR	0.128		0.937	
Side effects	0.200		0.237	
CDK4/6 agent	**0.008**		0.340	
Time of treatment	0.563		**0.003**	**0.003** (0.209; 0.112-0.390)
Hormone agent in combination with CDK4/6	0.452		0.185	
ER positivity rate	0.271		0.387	

**All statistical analyses were conducted using the Cox regression analyses. ER: Oestrogen receptor; NLR: Neutrophil-to-lymphocyte ratio.*

Therefore, the specific choice of CDK4/6 agent was significantly associated with PFS but not with OS in this cohort. This might be due to a disparity in the number of patients treated with either agent.

ANOVA showed that the foci of metastasis had no effect on changes in PFS and OS ($p > 0.05$). Similarly, no effect of side effects on changes in PFS was observed ($p > 0.05$). However, a significant effect of the foci of metastasis on OS was found ($p < 0.05$).

An independent t-test showed that the time to metastasis did not have a significant impact on PFS changes ($p > 0.05$). Results indicated a significant impact of the time to metastasis on OS changes ($p < 0.05$).

As shown in Table III, a Pearson's correlation analysis was performed to assess the relationship between continuous clinicopathological variables and survival outcomes. The results indicated a statistically significant weak negative correlation between the NLR and PFS ($r = -0.289$, $p = 0.010$), whereas its correlation with OS was not significant ($r = 0.156$, $p = 0.173$).

Conversely, the number of involved lymph nodes showed a significant weak positive correlation with OS (r = 0.327, p = 0.040); however, its correlation with PFS was not significant (r = -0.122, p = 0.453). No other significant correlations were observed; specifically, progesterone receptor status, ER status, Ki-67 proliferation index, tumour grade, and tumour size showed no significant linear relationship with either PFS or OS (all p >0.05).

Univariate analysis revealed that the CDK4/6 agent was a significant factor for PFS (p = 0.008, HR:0.290; CI: 0.116-0.721). There was no significant correlation between PFS and menopausal status, time to metastasis, human epidermal growth factor receptor, foci of metastasis, dose change, progesterone receptor status, Ki-67, tumour grade, tumour size, lymph node, side effect, CDK4/6 sequence, hormone agent in combination with CDK4/6, and ER positivity rate (p >0.05).

Univariate analysis indicated that the time to metastasis (p = 0.001, HR: 0.217; CI: 0.119-0.395) and choice of CDK4/6 inhibitor in first-line and later-line settings (p = 0.003, HR: 0.684; CI: 0.534-0.875) were significant factors for OS.

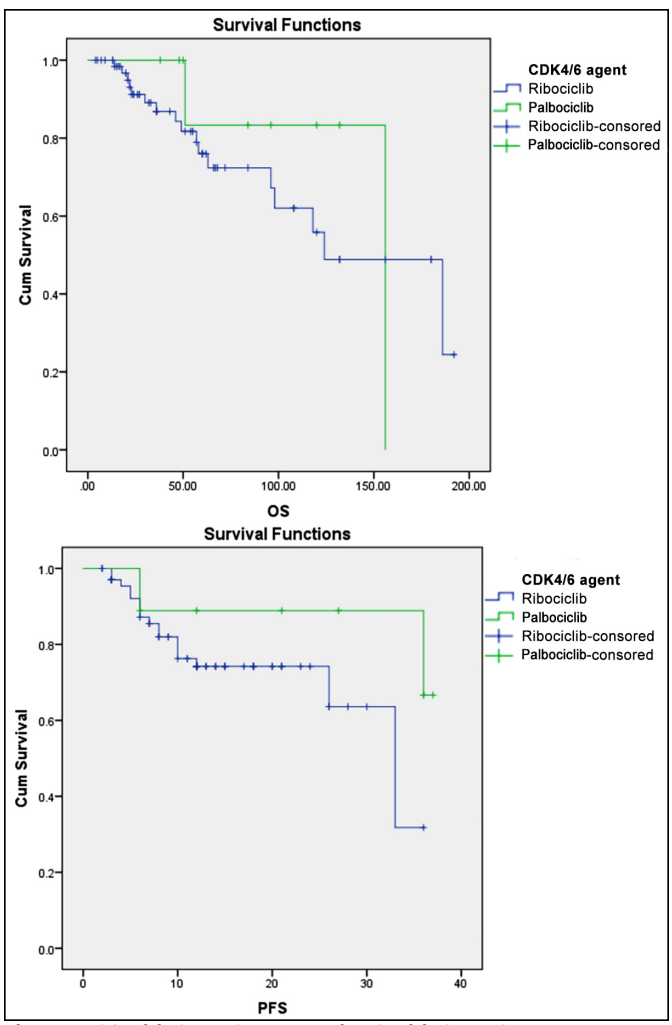


Figure 1: OS with CDK4/6 agent and PFS with CDK4/6 agent.

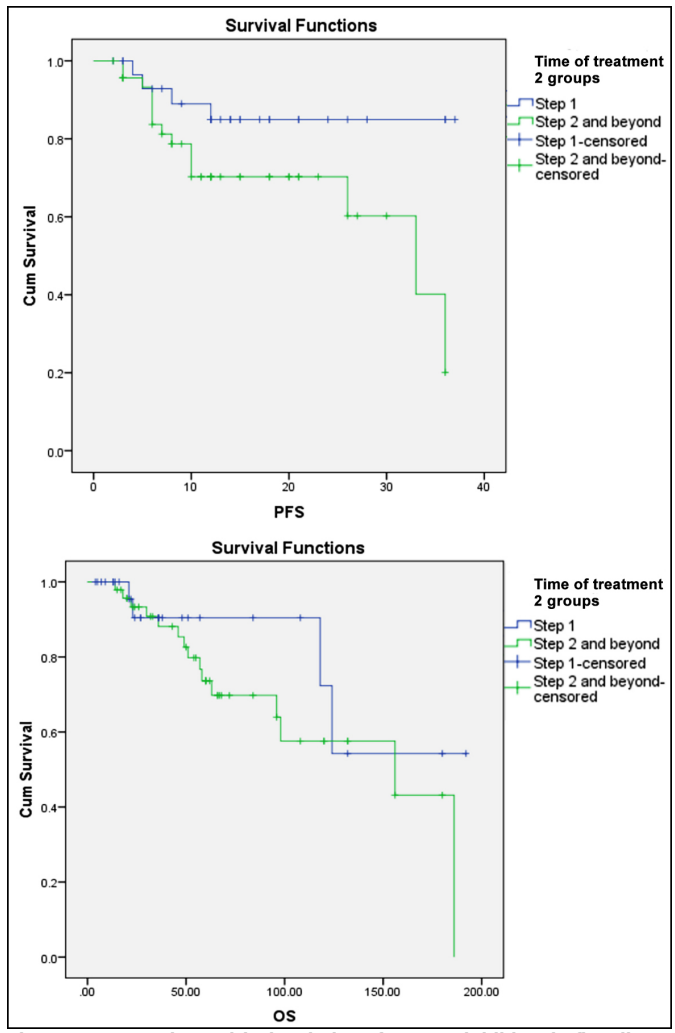


Figure 2: PFS and OS with the choice of CDK4/6 inhibitor in first-line and later-line settings.

There was no significant correlation between OS and menopausal status, human epidermal growth factor receptor, foci of metastasis, dose change, progesterone receptor status, Ki-67, tumour grade, tumour size, lymph node, side effect, CDK4/6 agent, hormone agent in combination with CDK4/6, and ER positivity rate (p >0.05).

Multivariate analysis was performed to identify independent prognostic factors for survival. It demonstrated that no variable was a significant independent prognostic factor for PFS. On the other hand, time to metastasis and choice of CDK4/6 inhibitor in first-line and later-line settings were independent prognostic factors for OS (p = 0.001, HR: 0.666; CI: 0.510-0.869; p = 0.003, HR: 0.209; CI: 0.112-0.390, respectively).

No statistically significant difference in PFS was observed between the two CDK4/6 inhibitor groups (Log-rank p = 0.194). The median PFS was 33.0 months (95% CI: 23.0-43.0) for the ribociclib group, while it was not reached in the palbociclib group, whose mean PFS was 33.3 months. Although a numerical trend favoured palbociclib, a high censoring rate (75.4% for ribociclib and 77.8% for palbociclib) indicates the data were immature, and the difference was not statistically significant.

The analysis of OS revealed no statistically significant difference between the treatment groups (Log-rank p = 0.495). The median OS was 124.0 months (95% CI: 77.3-170.7) for ribociclib and 156.0 months for palbociclib, with a higher mean OS also observed in the palbociclib group (138.5 *vs*. 129.5 months). Despite these numerical differences favouring palbociclib, the survival distributions were not statistically distinct. No survival difference was detected with CDK4/6 inhibitors (Figure 1).

A statistically significant difference in PFS was observed based on the line of treatment (Log-rank p = 0.047). Patients who received CDK4/6 inhibitors as first-line therapy had a notably longer mean PFS (32.5 months, 95% CI: 28.5-36.6) compared to those treated in the second line or beyond (mean PFS: 25.7 months, 95% CI: 21.3-30.1). The median PFS was not reached in the first-line group, whereas it was 33.0 months (95% CI: 20.7-45.3) in the later-line group. The higher censoring rate in the first-line cohort (87.1% *vs*. 68.1%) further supports a more favourable PFS profile with earlier intervention (Figure 2).

In contrast to PFS, the OS analysis did not reveal a statistically significant difference between the treatment lines (Log-rank p = 0.315). Although a numerical advantage was observed—with a mean OS of 150.1 months (95% CI: 117.2-183.0) in the first-line group compared to 127.5 months (95% CI: 103.2-151.9) in the later-line group—this difference did not reach statistical significance. The median OS was not reached in the first-line group, while it was 156.0 months (95% CI: 40.5-271.5) for patients receiving CDK4/6 inhibitors in later lines (Figure 2).

DISCUSSION

According to current international guidelines, CDK4/6 inhibitors in combination with hormonotherapy are the first-line treatment of choice for patients without contraindications. If not used in the first-line setting, these agents may also be used in later lines of treatment. However, no studies have directly compared these three agents with one another.

In this study, 80 patients with HR+ HER2- MBC treated with CDK4/6 were examined. Since there was no experience with abemaciclib at this centre, the data of 80 patients treated with ribocyclic or palbociclib were retrospectively analysed with regard to treatment responses, side effects, and predictive and prognostic factors. Although the phase III study of all three agents showed a significant PFS contribution compared with the arm using hormonotherapy alone, ribocycline has been shown to provide a higher OS contribution compared with the other two agents.

OS did not differ between patients receiving ribociclib and palbociclib in both univariate and multivariate analyses. Although the fact that the number of patients receiving ribociclib was much higher than the number of patients receiving palbociclib was a limitation in this study. It is known that *de novo* metastatic disease is a high-risk factor in many solid cancer types; in this study, time to metastasis as an independent variable was found to be a significant factor in survival. Similarly, tumour-related inflammation has been investigated in many studies, and its significance has been shown. For this purpose, NLR is frequently evaluated as a parameter.[16,17] In this study, NLR values were investigated in univariate and multivariate analyses and showed no significant effects on survival and disease prognosis.

In this study, the relationship between ER positivity and the CDK4/6 response was evaluated, considering OS and PFS durations. ER positivity can be evaluated using several methods in the literature, and the Allred scoring system is a frequently preferred method for this purpose. According to this scoring system, ER staining rate and staining intensity are evaluated with numbers, and patients are categorised by summing the results.[18] In this study, the pathology reports of the patients were retrospectively examined, and the ER levels were categorised according to the staining rate. Although there was no statistically significant difference in the analysis, the mean survival was 60 months in the weakly ER-positive (<10%) group, whereas it was up to 120 months in the ER-positive (>10%) group. In addition, the fact that statistically significant survival was achieved in patients with luminal A histology was considered a variable that strengthens the idea that endocrine therapy combined with CDK4/6 inhibitors is a predictive parameter, showing that endocrine therapy is effective as ER positivity increases. Based on this, the fact that statistical significance was found in OS in luminal A tumours characterised by high ER positivity can be considered as a marker that can be evaluated to predict that increased ER positivity in tumours can achieve better responses in treatment with CDK4/6 inhibitors.[19,20]

This study has several limitations, including its single-centre, retrospective design and small sample size. Furthermore, the disparity in the size of the comparator groups, with the number of patients receiving ribociclib being much higher than those receiving palbociclib, limits the robustness of the comparative analysis. Additionally, the retrospective nature of the investigation may have led to incomplete data on potential confounding factors, such as comorbidities and medication use, which could influence blood values and affect the results.

CONCLUSION

This study showed that the use of CDK4/6 in the first-line settings contributed significantly to survival. Studies, including real-world data, conducted and to be conducted in this way, provide valuable insights that help inform and shape clinical practice.

ETHICAL APPROVAL:

This study was approved by the Local Ethics Committee of Eskisehir Osmangazi University, Eskisehir, Turkiye (Project No. E-25403353-050.04-2400013654; date: 16/01/2024).

COMPETING INTEREST:
The authors declared no conflict of interest.

PATIENTS' CONSENT:
Informed consent was obtained from all patients.

AUTHORS' CONTRIBUTION:
ND: Conception and design of the study, data analysis, interpretation of data, drafting, and revision of the manuscript for important intellectual content.
BY: Conception and drafting of the manuscript.
MD: Study design and revision of the manuscript.
All authors approved the final version of the manuscript to be published.

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