

Impact of HER2-low status on survival outcomes in patients with metastatic breast cancer treated with CDK4/6 inhibitors: A single-center experience

CDK4/6 inhibitörleriyle tedavi edilen metastazlı meme kanseri hastalarında HER2-low durumunun sağkalım sonuçları üzerindeki etkisi: Tek merkez deneyimi

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ABSTRACT

Aim: Cyclin-dependent kinase (CDK) 4/6 inhibitors combined with endocrine therapy are recommended as the first-line treatment for hormone receptor-positive, HER2-negative metastatic breast cancer without visceral crisis. However, CDK4/6 inhibitor efficacy has been reported to differ between HER2-low and HER2-zero tumors; emerging data suggest that the therapeutic efficacy of CDK4/6 inhibitors may be reduced in HER2-low breast cancer. Therefore, we aimed to evaluate this association in a cohort of patients treated with CDK4/6 inhibitors.

Material and Methods: In this single-center retrospective study, 121 patients with hormone receptor-positive, HER2-negative metastatic breast cancer treated with CDK4/6 inhibitors between January 2019 and March 2025 were evaluated. Cases were classified as HER2-low or HER2-zero. Progression-free survival (PFS) and overall survival (OS) were assessed using the Kaplan-Meier method.

Results: Among 121 hormone receptor-positive, HER2-negative metastatic breast cancer patients treated with CDK4/6 inhibitors, 53.7% were in the HER2-zero group and 46.3% in the HER2-low group. The median follow-up duration was 28.6 months (range: 5.1-56.4 months) and the median age was 62 years (range: 33-89 years). Ribociclib was used in 68.6% and palbociclib in 31.4% of these cases. The incidence of grade 3-4 toxicities was comparable between the groups ($p=0.948$). There

ÖZ

Amaç: Siklin bağımlı kinaz (CDK) 4/6 inhibitörleri, endokrin terapi ile birlikte, viseral kriz olmayan hormon reseptörü pozitif, HER2 negatif metastatik meme kanserinde birinci basamak tedavi olarak önerilmektedir. Bununla birlikte, CDK4/6 inhibitörlerinin etkinliğinin HER2-low ve HER2-zero tümörler arasında farklılık gösterdiği bildirilmiştir; ortaya çıkan veriler, CDK4/6 inhibitörlerinin terapötik etkinliğinin HER2-low meme kanserinde azalabileceğini düşündürmektedir. Bu nedenle, CDK4/6 inhibitörleri ile tedavi edilen bir hasta kohortunda bu ilişkiyi değerlendirmeyi amaçladık.

Gereç ve Yöntemler: Bu tek merkezli retrospektif çalışmada, Ocak 2019 ile Mart 2025 tarihleri arasında CDK4/6 inhibitörleri ile tedavi edilen hormon reseptörü pozitif, HER2-negatif metastatik meme kanseri olan 121 hasta değerlendirildi. Hastalar HER2-low veya HER2-zero olarak sınıflandırıldı. Hastalık ilerlemesiz sağkalım (PFS) ve genel sağkalım (OS) Kaplan-Meier yöntemi kullanılarak değerlendirildi.

Bulgular: CDK4/6 inhibitörleri ile tedavi edilen 121 hormon reseptörü pozitif, HER2 negatif metastatik meme kanseri hastasının %53,7'si HER2-zero grubunda ve %46,3'ü HER2-low grubundaydı. Medyan takip süresi 28,6 ay (aralık: 5,1-56,4 ay) ve medyan yaş 62 yıl (aralık: 33-89 yıl) idi. Ribosiklib %68,6'unda ve palbosiklib %31,4'ünde kullanıldı. 3-4. derece toksisite insidansı gruplar arasında karşılaştırılabilir düzey-

was no statistically significant difference in median PFS (31.1 vs 34.8 months, $p=0.314$) or OS (42.3 vs 39.9 months, $p=0.946$) between the HER2-zero and HER2-low groups. Ribociclib and palbociclib demonstrated similar survival outcomes across HER2 subgroups.

Conclusion: The clinical significance of HER2 status in patients treated with CDK4/6 inhibitors remains unclear. In our cohort, we were unable to demonstrate an association between HER2 status and PFS or OS among patients receiving CDK4/6 inhibitor therapy.

Keywords: HR+/HER2- advanced breast cancer, CDK4/6 inhibitor, progression-free survival, overall survival

deydi ($p=0.948$). HER2-zero ve HER2-low grupları arasında medyan PFS (31.1'e karşı 34.8 ay, $p=0.314$) veya OS (42,3'e karşı 39,9 ay, $p=0.946$) açısından istatistiksel olarak anlamlı bir fark bulunmamıştır. Ribosiklib ve palbosiklib, HER2 alt gruplarında benzer sağkalım sonuçları göstermiştir.

Sonuç: CDK4/6 inhibitörleri ile tedavi edilen hastalarda HER2 durumunun klinik önemi belirsizliğini korumaktadır. Kohortumuzda, CDK4/6 inhibitör tedavisi alan hastalarda HER2 durumu ile progresyonsuz sağkalım veya genel sağkalım arasında bir ilişki gösterilemedi.

Anahtar Kelimeler: HR+/HER2- ileri evre meme kanseri, CDK4/6 inhibitörü, progresyonsuz sağkalım, genel sağkalım

Highlights

- The clinical significance of HER2-low status was investigated in metastatic breast cancer patients treated with CDK4/6 inhibitors.
- Overall survival and progression-free survival were analyzed according to HER2 expression status. No significant differences in survival outcomes were observed between HER2-low and HER2-zero subgroups.
- These findings suggest that HER2-low status may not have a prognostic impact in this treatment setting.

INTRODUCTION

Global cancer statistics from 2020 indicate that female breast cancer is the leading cancer worldwide, accounting for over 2 million diagnoses each year (1). Breast cancer is a significant cause of cancer-related mortality worldwide. Although metastatic breast cancer remains incurable, recent therapeutic developments have significantly improved survival outcomes. Metastatic breast cancer exhibits profound biological heterogeneity, comprising several molecular subtypes with distinct therapeutic strategies and clinical outcomes; specifically, gene expression profiling identifies five primary subtypes: luminal A, luminal B, basal-like, normal-like, and HER2-enriched (2). Luminal A and luminal B tumors are characterized by estrogen receptor-related gene expression, while the HER2-enriched subtype shows activation and amplification of the HER2 signaling pathway. Basal-like tumors typically lack both hormone receptor (HR) and HER2 expression and are associated with a more aggressive clinical course.

The therapeutic approach in metastatic breast cancer is primarily determined by estrogen receptor (ER), progesterone receptor (PR), and HER2 expression profiles. In HR-positive, HER2-negative metastatic breast cancer, treatment is generally initiated with endocrine therapy, except in cases of visceral crisis. HER2-positive breast cancer is defined by an immunohistochemistry (IHC) score of 3+, or a 2+ score with concurrent HER2 gene amplification confirmed via in situ hybridization (ISH). Approximately 20% of HR-positive breast cancers exhibit HER2 overexpression or amplification. These tumors require treatment with HER2-directed therapies. The HER2-low phenotype is defined by a score of IHC 1+, or a score of IHC 2+ with negative ISH, indi-

cating low but detectable HER2 expression without gene amplification (3). Findings from the DESTINY-Breast04 trial demonstrated that trastuzumab deruxtecan (T-DXd) provides a significant clinical benefit for this patient population. Consequently, these data indicate that HER2-low tumors constitute a distinct clinical subgroup rather than merely a subset of HER2-negative disease (4).

For patients diagnosed with HR-positive, HER2-negative disease, combining endocrine therapy with cyclin-dependent kinase (CDK) 4/6 inhibitors represents the preferred frontline standard treatment. These combined agents have significantly prolonged progression-free survival (PFS) compared to endocrine monotherapy alone (5). Additionally, ribociclib has shown an overall survival benefit when combined with endocrine therapy (6). Due to interactions between HER2 and HR signaling pathways, HER2-low expression may be associated with endocrine resistance (7). However, the prognostic impact of low-level HER2 expression on survival outcomes remains uncertain and has not been clearly defined (8). The objective of the present study was to assess the impact of HER2 status on both overall survival (OS) and PFS outcomes in patients with HR-positive, HER2-negative advanced breast cancer receiving CDK4/6 inhibitors.

MATERIAL and METHODS

This study included 121 patients with metastatic breast cancer who received first-line CDK4/6 inhibitors plus endocrine therapy (aromatase inhibitor or fulvestrant) at our institution between January 2019 and March 2025. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institu-

tional and national) and with the Declaration of Helsinki of 1975, as revised in 2008. The relevant institution granted ethics committee approval (No: 2023/154) and informed consent was obtained from all patients. The approval was updated in 2026 to include additional patients treated between 2023 and 2025.

Patient data were collected from the medical charts of the patients, including comorbid conditions, age, Eastern Cooperative Oncology Group (ECOG) performance status, HR and HER2 status, Ki-67 index and tumor grade, stage at diagnosis, prior surgery, chemotherapy and radiotherapy, menopausal status, de novo metastatic or recurrent presentation, site of metastasis, type of CDK4/6 inhibitor (*ribociclib* or *palbociclib*) and endocrine therapy (*aromatase inhibitor* or *fulvestrant*), and treatment response. PFS was defined as the time from treatment initiation to disease progression and OS was defined as the time from treatment initiation to death or the date of the last visit. ER, PR, and HER2 statuses were assessed using the most recent pathology specimens in our department, in accordance with the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines.

A threshold of $\geq 10\%$ IHC nuclear staining was used to define ER or PR positivity. Tumors were classified as HER2-zero when no membranous HER2 staining was observed on IHC and as HER2-low when IHC 1+ or IHC 2+ staining was observed with negative ISH results. Baseline patient characteristics, treatment response to CDK4/6 inhibitors plus endocrine therapy (*aromatase inhibitor* or *fulvestrant*) according to the Response Evaluation Criteria in Solid Tumors (RECIST v1.1), PFS, and OS were evaluated in patients with HER2-low and HER2-zero tumors.

Inclusion Criteria

Patients aged 18 years or older with HR-positive, HER2-negative metastatic breast cancer and first-line treatment with CDK4/6 inhibitors plus endocrine therapy were included in the analysis.

Exclusion Criteria

Patients with a follow-up duration of less than 3 months, inability to assess treatment response, or failure to attend scheduled clinical visits were excluded.

Statistical Analysis

Patient data collected within the scope of the study were analyzed with IBM SPSS Statistics 26.0 for Windows (IBM Corp., Armonk, NY, USA). Descriptive statistics included mean, standard deviation, median, minimum, maximum, frequency, and percentage values. The distributions of the variables were assessed using the *Kolmogorov-Smirnov* and *Shapiro-Wilk* tests. For quantitative independent variables that did not demonstrate normal distribution, the

Mann-Whitney U test was used. For qualitative independent variables, the *chi-square* test was applied, and the *Fisher Exact* test was used when the assumptions of the *chi-square* test were not met. Survival analyses were performed using Cox regression (*univariate* and *multivariate*) and the *Kaplan-Meier* method. Results were considered statistically significant at a $p < 0.05$.

RESULTS

A total of 121 female patients were included in this study, 65 (53.7%) of whom were in the HER2-zero group while 56 (46.3%) were in the Her2-low group. The median follow-up duration was 28.6 months (*range: 5.1-56.4 months*). The median age was 62 years (*range: 33-89 years*). There was no statistically significant difference in median age between the HER2-low and HER2-zero groups (62 vs. 60 years, $p = 0.539$). The prevalence of comorbid conditions such as hypertension, diabetes, ischemic heart disease, and stroke was similar between the two groups.

In both the HER2-low and HER2-zero groups, nearly 61% of patients had de novo metastatic disease and 39% had recurrent disease ($p = 0.931$). The most common histopathological subtype among these patients was invasive ductal carcinoma (81.8%), followed by invasive lobular carcinoma (13.2%). Ribociclib was used for 68.6% of the patients, while palbociclib was used for 31.4%.

There was no significant difference between the HER2-low and HER2-zero groups in terms of treatment with palbociclib and ribociclib ($p = 0.590$). In combination therapy with CDK4/6 inhibitors, 73.5% of patients received an aromatase inhibitor and 26.4% received fulvestrant.

Postmenopausal status was reported by 76% of the patients. Comorbidities including diabetes mellitus, hypertension, or ischemic heart disease were present in approximately half of the patients. Most patients (92.6%) had an ECOG performance status of 0-1. There were no significant differences in median ER %, PR %, Ki-67 proliferation index, or tumor grade between the HER2-low and HER2-zero groups. The baseline characteristics of the patients are displayed in Table 1.

Bone and lymph node-only metastases were present in 57% of patients, whereas visceral metastases were observed in 43%. Metastatic sites were similar between the HER2-zero and HER2-low groups. Forty-six patients developed metastasis as a recurrence of early-stage breast cancer. Biopsy was feasible in 30 of 46 cases. Central nervous system metastasis was observed in 7% of patients, liver metastasis in 13%, and lung metastasis in 22%.

The best response to treatment was partial response in 67.7% of the patients, stable disease in 19%, and progressive disease in 13.2%, with no significant difference between

Table 1: Baseline characteristics of patients

Variable	Total (n=121)	HER2-zero (n=65)	HER2-low (n=56)	p
Age, years, median (range)	62 (33-89)	60 (33-86)	62 (37-89)	0.539
Comorbidities, n (%)				
Yes	61 (50.4)	33 (50.7)	28 (50)	1.000
No	60 (49.5)	32 (49.3)	28 (50)	
Histology, n (%)				
IDC	99 (81.8)	52 (80)	47 (83.9)	0.899
ILC	16 (13.2)	10 (15.4)	6 (10.7)	
IDC + ILC	2 (1.6)	1 (1.6)	1 (1.7)	
Other	4 (3.4)	2 (3)	2 (3.5)	
ECOG performance status				
0-1	112 (92.6)	61 (93.8)	51 (91)	0.816
2-3	9 (7.4)	4 (6.1)	5 (8.9)	
Metastatic disease status, n (%)				
Recurrent disease	46 (38)	25 (38.4)	21 (37.5)	0.931
De novo	75 (61.9)	40 (61.5)	35 (62.5)	
CDK4/6 inhibitors, n (%)				
Ribociclib	83 (68.6)	43 (66.1)	40 (71.4)	0.590
Palbociclib	38 (31.4)	22 (33.8)	16 (28.5)	
Menopausal status, n (%)				
Premenopausal	29 (23.9)	19 (29.2)	10 (17.8)	0.176
Postmenopausal	92 (76)	46 (70.7)	46 (82.1)	
ER %, median (range)	90 (15-100)	90 (20-100)	90 (15-100)	0.658
PR %, median (range)	50 (0-100)	50 (0-100)	55 (0-100)	0.471
Ki-67 index %, median (range)	20 (2-60)	20 (2-60)	20 (3-60)	0.606
Tumor grade, n (%)				
Grade I	8 (6.6)	5 (7.6)	3 (5.3)	0.634
Grade II	95 (78.5)	52 (80)	43 (76.7)	
Grade III	18 (14.8)	8 (12.3)	10 (17.8)	
Site of metastasis, n (%)				
Bone/soft tissue	69 (57)	40 (61.5)	29 (46.4)	0.197
Visceral	8 (6.6)	2 (3)	6 (10.7)	
Bone + visceral	44 (36.3)	23 (35.3)	21 (37.5)	
Endocrine therapy, n (%)				
AI	89 (73.5)	49 (75.3)	40 (71.4)	0.701
Fulvestrant	32 (26.4)	16 (24.6)	16 (28.5)	
Best response, n (%)				
Partial response	82 (67.7)	43 (66.1)	39 (69.6)	0.834
Stable disease	23 (19)	14 (21.5)	9 (16)	
Progressive disease	16 (13.2)	8 (12.3)	8 (14.2)	
Grade 3-4 toxicity, n (%)	35 (28.9)	19 (29.2)	16 (28.5)	0.948
Dose reduction, n (%)	29 (23.9)	16 (24.6)	13 (23.2)	0.968

HER2: Human epidermal growth factor receptor, **IDC:** Invasive ductal carcinoma, **ILC:** Invasive lobular carcinoma, **ECOG:** Eastern Cooperative Oncology Group, **CDK:** Cyclin-dependent kinase, **ER:** Estrogen receptor, **PR:** Progesterone receptor, **AI:** Aromatase inhibitor

the HER2-zero and HER2-low groups. Disease progression occurred in 64.6% of patients in the HER2-zero group and in 51.9% of those in the HER2-low group, with no significant difference between the groups ($p=0.165$). At the last follow-up, 65 patients (53.7%) were alive and 56 patients (46%) had died. There was no statistically significant difference in median PFS (34.8 vs. 31.1 months, $p=0.314$) or OS (median OS: 39.9 vs. 42.3 months, $p=0.946$) between the

HER2-low and HER2-zero groups. When evaluated individually, ribociclib and palbociclib had similar PFS and OS in the HER2-low and HER2-zero subgroups. Survival analyses are illustrated in Figures 1-3.

In univariate Cox regression analysis, tumor grade (hazard ratio [HR]: 2.185, 95% confidence interval [CI]: 1.154-4.137, $p=0.016$), central nervous system metastasis (HR: 2.658, 95% CI: 1.261-5.605, $p=0.010$), and liver metastasis

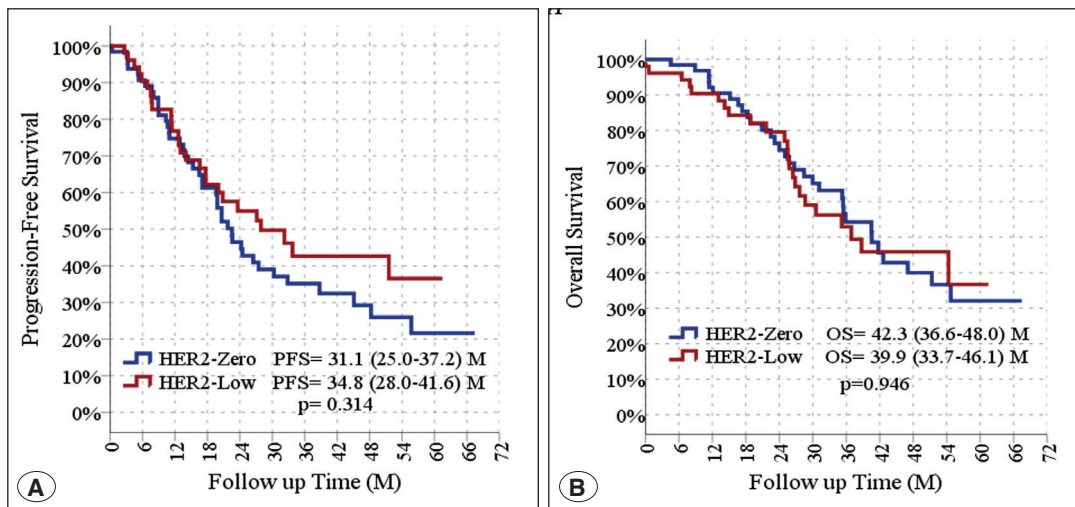


Figure 1: Progression-free survival (PFS) (A) and overall survival (OS) (B) in patients with HER2-low and HER2-zero disease.

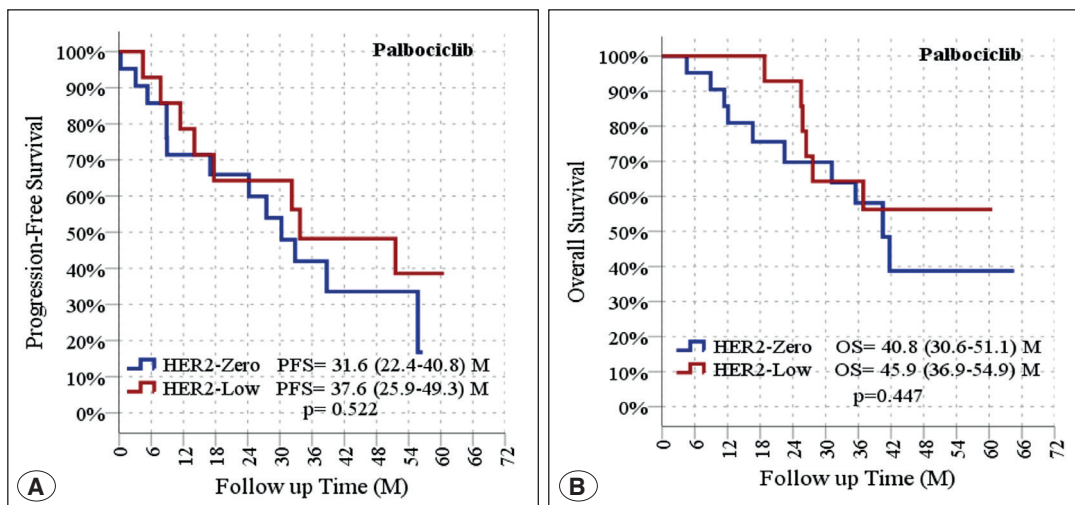


Figure 2: Progression-free survival (PFS) (A) and overall survival (OS) (B) in patients treated with palbociclib stratified by HER2 status.

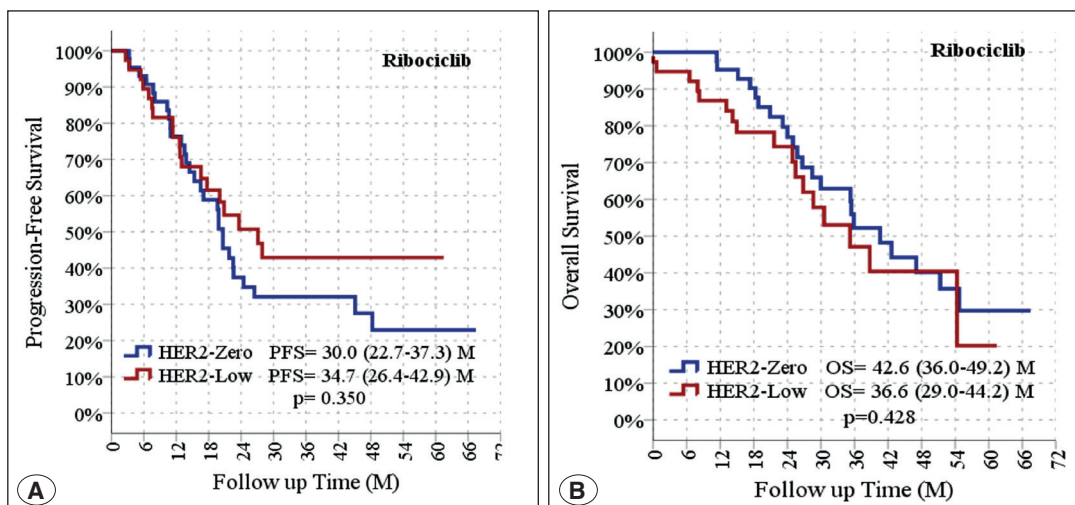


Figure 3: Progression-free survival (PFS) (A) and overall survival (OS) (B) in patients treated with ribociclib stratified by HER2 status.

(HR: 2.445, 95% CI: 1.253-4.418, $p=0.003$) were associated with inferior PFS. In multivariate analysis, tumor grade (HR: 2.389, 95% CI: 1.196-4.771, $p=0.014$), central nervous system metastasis (HR: 2.517, 95% CI: 1.106-5.726, $p=0.028$), and liver metastasis (HR: 2.356, 95% CI: 1.228-4.517, $p=0.010$) remained independent predictors of progression-free survival. These results are shown in Table 2.

Univariate Cox regression analysis for OS showed that ECOG performance status ($p=0.003$), central nervous system metastasis ($p=0.009$), and liver metastasis ($p=0.002$) were significantly associated with worse survival outcomes. In multivariate analysis, ECOG performance status remained an independent prognostic factor for OS (HR: 1.579, 95% CI: 1.015-2.456, $p=0.043$). Other clinicopathological variables were not significantly related to OS (Table 3).

DISCUSSION

Breast cancer outcomes have improved over time with the introduction of modern systemic therapies and a better understanding of tumor biology. HER2 status is a well-established

biomarker in breast cancer with clear implications for prognosis and treatment. However, it is still uncertain whether HER2-low tumors behave differently, particularly in the setting of CDK4/6 inhibitor therapy.

Our study cohort had a median age of 62 years. Baseline clinicopathological characteristics were similar among patients with HER2-low and HER2-zero disease. Age, performance status, comorbidities, HR expression, tumor grade, Ki-67 index value, metastatic pattern, type of CDK4/6 inhibitor, and rate of use of endocrine therapy were comparable between the two groups. In addition, treatment response, toxicity, and dose reduction rates did not differ significantly. In multivariate analysis performed for PFS, tumor grade, central nervous system metastasis, and liver metastasis were independent predictors of poorer outcomes. In multivariate analysis for OS, ECOG performance status remained an independent predictor.

In a large multicenter analysis including 428 patients treated with endocrine therapy plus CDK4/6 inhibitors, individuals with HER2-low tumors appeared to experience shorter

Table 2: Cox regression analysis for progression-free survival

	Univariate model			Multivariate model		
	HR	95% CI	p	HR	95% CI	p
Age	0.986	0.971-1.001	0.076			
Comorbidity	0.785	0.490-1.257	0.314			
ECOG performance status	1.222	0.841-1.776	0.294			
Histology						
IDC	1.205	0.659-2.206	0.545			
ILC	0.753	0.411-1.378	0.357			
Other	1.852	0.257-13.368	0.541			
Menopausal status	1.175	0.733-1.884	0.503			
CDK4/6 inhibitors						
Ribociclib	0.778	0.466-1.300	0.338			
Palbociclib	1.394	0.903-2.153	0.134			
Endocrine therapy						
AI	0.781	0.510-1.224	0.284			
Fulvestrant	1.280	0.840-1.960	0.210			
Maximum ER (%)	1.001	0.989-1.013	0.837			
Maximum PR (%)	0.989	0.982-0.997	0.005			
Ki-67 index (%)	1.018	0.997-1.039	0.089			
HER2 status						
HER2-zero	0.925	0.661-1.294	0.649			
HER2-low	0.781	0.481-1.267	0.316			
Tumor grade	2.185	1.154-4.137	0.016	2.389	1.196-4.771	0.014
Sites of metastasis						
CNS	2.658	1.261-5.605	0.010	2.517	1.106-5.726	0.028
Liver	2.445	1.353-4.418	0.003	2.356	1.228-4.517	0.010
Lung	1.275	0.736-2.208	0.386			

HR: Hazard ratio, **CI:** Confidence interval, **ECOG:** Eastern Cooperative Oncology Group, **IDC:** Invasive ductal carcinoma, **ILC:** Invasive lobular carcinoma, **CDK4-6:** Cyclin-dependent kinase 4 and 6, **AI:** Aromatase inhibitor, **ER:** Estrogen receptor, **PR:** Progesterone receptor, **HER2:** Human epidermal growth factor receptor 2, **CNS:** Central nervous system

Table 3: Cox regression analysis for overall survival

	Univariate model			Multivariate model		
	HR	95% CI	p	HR	95% CI	p
Age	1.009	0.991-1.028	0.318			
Comorbidity	0.813	0.480-1.376	0.441			
ECOG performance status	1.901	1.248-2.897	0.003	1.579	1.015-2.456	0.043
Histology						
IDC	1.560	0.823-2.958	0.173			
ILC	0.586	0.309-1.110	0.101			
Other	1.445	0.199-10.476	0.715			
Menopausal status	0.595	0.337-1.050	0.073			
CDK4/6 inhibitors						
Ribociclib	0.705	0.395-1.258	0.236			
Palbociclib	0.842	0.486-1.459	0.541			
Endocrine therapy						
AI	1.106	0.650-1.882	0.711			
Fulvestrant	1.248	0.742-2.097	0.405			
Maximum ER (%)	1.010	0.993-1.028	0.233			
Maximum PR (%)	0.995	0.987-1.004	0.282			
Ki-67 index (%)	1.011	0.990-1.032	0.325			
HER2 status						
HER2-zero	0.978	0.669-1.429	0.908			
HER2-low	1.019	0.595-1.742	0.946			
Tumor grade	1.330	0.680-2.604	0.405			
Sites of metastasis						
CNS	2.904	1.303-6.473	0.009			
Liver	2.761	1.444-5.281	0.002			
Lung	1.803	0.992-3.279	0.053			

HR: Hazard ratio, **CI:** Confidence interval, **ECOG:** Eastern Cooperative Oncology Group, **IDC:** Invasive ductal carcinoma, **ILC:** Invasive lobular carcinoma, **CDK4-6:** Cyclin-dependent kinase 4 and 6, **AI:** Aromatase inhibitor, **ER:** Estrogen receptor, **PR:** Progesterone receptor, **HER2:** Human epidermal growth factor receptor 2, **CNS:** Central nervous system

PFS and OS independently of other risk factors compared to those in the HER2-zero group (9). In a small retrospective study investigating endocrine therapy combined with palbociclib in the HR-positive, HER2-negative metastatic breast cancer setting, objective response rates and PFS were found to be similar between HER2-zero and HER2-low patients (10). A meta-analysis synthesizing data from nine studies and more than 2700 patients evaluated the prognostic value of HER2-low status. The pooled results demonstrated that HER2-low tumors are associated with an increased risk of disease progression or mortality during CDK4/6 inhibitor therapy compared to HER2-zero tumors (11). In a study from Greece, no significant difference in PFS was documented between the HER2-low and HER2-zero cohorts among patients receiving first-line CDK4/6 inhibitors (12). Önder *et al.* demonstrated that within the cohort of HR-positive, HER2-negative metastatic breast cancer patients undergoing ribociclib plus endocrine treatment, those with HER2-low tumors exhibited significantly lower PFS than the HER2-zero group (13). However, this pattern

was not observed in the palbociclib cohort, where PFS outcomes were similar across HER2 subgroups. In the study by Bao *et al.*, among patients with HR-positive, HER2-negative metastatic breast cancer receiving CDK4/6 inhibitors, those with HER2-low tumors had a poorer PFS relative to the HER2-zero group (14). A multicenter analysis from Türkiye also examined whether HER2-low expression affected treatment outcomes in HR-positive/HER2-negative metastatic breast cancer; however, no statistically significant difference in PFS was observed between the HER2-low and HER2-zero cohorts undergoing CDK4/6 inhibitor plus endocrine therapy (15). A large French cohort including more than 15,000 patients with metastatic breast cancer demonstrated a slightly superior OS in HER2-low metastatic breast cancer relative to HER2-zero disease (16). A study assessing 257 patients with HR-positive, HER2-negative metastatic breast cancer receiving ribociclib combined with endocrine therapy, HER2-zero cases demonstrated higher response rates and longer PFS compared to HER2-low disease (17). In a prospective cohort evaluating endocrine

therapy with or without CDK4/6 inhibitors, HER2-low and HER2-zero patients receiving CDK4/6-based treatment showed similar PFS rates (18). In a study by *Guliyev et al.*, no statistically significant difference in PFS or OS was observed between HER2-low and HER2-zero cohorts with HR-positive, HER2-negative metastatic breast cancer receiving CDK4/6 inhibitors plus endocrine therapy (19). In our study, ribociclib and palbociclib yielded similar PFS and OS rates in both the HER2-low and HER2-zero subgroups. This finding remained consistent in subgroup analyses according to the type of CDK4/6 inhibitor. Patients treated with palbociclib and those treated with ribociclib had comparable PFS and OS outcomes regardless of HER2-low or HER2-zero status.

Clinical outcomes from the recent PALOMA, MONARCH, and MONALEESA studies have established CDK4/6 inhibitors plus endocrine therapy as the preferred frontline therapeutic standard for most patients with HR-positive, HER2-negative breast cancer (20–28). Molecular crosstalk between HR and HER2 pathways allows for HER2 expression modulation independent of gene amplification (29,30). One explanation for resistance to endocrine therapy is bidirectional crosstalk between HR and HER2. In multiple neoadjuvant chemotherapy trials for breast cancer, patients with HER2-zero tumors demonstrated superior pathological complete response rates compared to those with HER2-low status (31). Nevertheless, the specific impact of low HER2 expression on CDK4/6 inhibitor efficacy in HR-positive, HER2-negative metastatic breast cancer patients has yet to be determined.

Numerous studies have examined the prognostic implications of HER2-low status since the phase 3 clinical study *DESTINY-Breast 04* showed that T-DXd is effective in treating metastatic HER2-low breast cancer (32–34). In cases of high-risk cancers, such as HR-negative tumors that do not exhibit a histological complete response following neoadjuvant therapy or those treated without adjuvant treatment, HER2-low tumors are potentially associated with superior clinical outcomes compared to HER2-negative disease (35). *Schettini et al.* demonstrated that in HER2-low breast cancer, genes linked to proliferation were markedly down-regulated (36). In contrast, genes related to luminal traits were upregulated. *Park et al.* found that among patients with HR-positive, HER2-low disease, oncological outcomes varied according to menopausal state (37). In our study, the best response to treatment was partial response in 67.7% of cases, followed statistically by stable disease in 19% and progressive disease in 13.2%, with no significant difference between the HER2-zero and HER2-low groups. Disease progression occurred in 64.6% of patients in the HER2-zero group and in 51.9% of those in the HER2-low group, with no significant difference between the groups.

This study has several limitations, including its retrospective design and relatively limited number of patients. However, the analysis is strengthened by the use of real-world data from a single center and a relatively homogeneous patient population that allows for a more uniform assessment of outcomes according to HER2 status.

Conclusion

The clinical significance of HER2 status in patients treated with CDK4/6 inhibitors remains unclear. In our cohort, we were unable to demonstrate an association between HER2 status and PFS or OS among patients receiving CDK4/6 inhibitor therapy.

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Author Contributions

Study conception and design: **Esra Aydın**; data collection: **Esra Aydın**, **Çiğdem Öztürk**, **Oğuzhan Okçu**; analysis and interpretation of results: **Esra Aydın**, **Ahmet Emin Öztürk**, **Anıl Yıldız**, **Muhammed Aydın**, **Bayram Şen**; draft manuscript preparation: **Esra Aydın**, **Oğuzhan Kesen**, **Muhammed Aydın**, **Eyyüp Ayas**, **Neşe Alyıldız**, **Recep Ak**, **Sema Yılmaz Rakıcı**. The author(s) reviewed the results and approved the final version of the article.

Conflicts of Interest

The authors declare no conflict of interest.

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Ethical Approval

This study was approved by Recep Tayyip Erdoğan University Faculty of Medicine Ethics Committee (approval number:2023/154, date: 17 July 2023). The approval was updated in 2026 to include additional patients treated between 2023 and 2025. Written informed consent was obtained from all participants.

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