Turkish Journal of Clinics and Laboratory

TTo cite this article: Bayram S, Ozdogan M. Real-world outcomes of CDK4/6 inhibitors in HR-positive/HER2-negative metastatic breast cancer: a single-center cohort from Turkey. Turk J Clin Lab 2026; 1: 1838613.

Research Article

Real-world outcomes of CDK4/6 inhibitors in HR-positive/HER2-negative metastatic breast cancer: a single-center cohort from Turkey

HR pozitif/HER2 negatif metastatik meme kanserinde CDK4/6 inhibitörlerinin gerçek yaşam sonuçları: Türkiye'den tek merkezli bir kohort

Selami Bayram[1*], Mustafa Ozdogan[2]

[1]Department of Medical Oncology, Memorial Antalya Hospital, Antalya, Türkiye
[2]Department of Medical Oncology, Memorial Goztepe Hospital, İstanbul, Türkiye

Abstract

Aim: Endocrine therapy (ET) plus a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) is the standard first-line treatment for hormone receptor–positive/human epidermal growth factor receptor 2–negative (HR+/HER2–) metastatic breast cancer (MBC); however, real-world data from routine practice in Türkiye remain limited. We evaluated the effectiveness and safety of CDK4/6i-ET across treatment lines and explored first-line outcomes with palbociclib–letrozole versus ribociclib–letrozole.

Material and Methods: This single-center, retrospective cohort study included consecutive adults with HR+/HER2– MBC treated with palbociclib or ribociclib plus ET (letrozole or fulvestrant) in routine practice. The primary endpoint was progression-free survival (PFS), the and secondary endpoints were overall survival (OS), objective response rate (ORR), clinical benefit rate (CBR: CR+PR+SD ≥24 weeks), and safety. Survival was estimated using Kaplan–Meier methods and compared with log-rank tests and univariable Cox models. Exploratory analyses examined outcomes by treatment line (first, second, and ≥third) and compared first-line palbociclib–letrozole with ribociclib–letrozole.

Results: A total of 124 patients were included; CDK4/6i-ET was administered as first-, second-, and ≥ third-line therapyin 65.3%, 19.4%, and 15.3% of patients, respectively. Overall, 51 patients (41.1%) experienced disease progression, and 19 (15.3%) died. Twelve-month PFS rates were 82.7%, 69.9%, and 42.1% in the first-, second-, and ≥third-line groups, respectively; the risk of progression or death was higher in the second line (HR 2.20, 95% CI 1.09–4.46) and ≥third line (HR 4.71, 95% CI 2.45–9.05) than in the first line. Twelve-month OS rates were 93.4%, 86.5%, and 83.6%, with a significantly higher hazard of death in the ≥third line (HR 3.88, 95% CI 1.41–10.71) compared with the first line. The ORR was 37.9%, and the CBR was 87.9%. In the first-line aromatase inhibitor subset, no statistically significant differences were observed between palbociclib–letrozole and ribociclib–letrozole for PFS (HR 0.77, 95% CI 0.43–1.39; p=0.392) or OS (HR 0.83, 95% CI 0.20–3.47; p=0.797). At least one adverse event occurred in 85·4% of patients; grade ≥3 neutropenia occurred in 42.7% of patients, while permanent discontinuation due to toxicity was infrequent (2.4%).

Conclusion: In this real-world cohort, CDK4/6i-ET achieved clinically meaningful disease control with a safety profile consistent with pivotal trials. The earlier introduction of CDK4/6 inhibition was associated with longer PFS and OS, whereas exploratory first-line comparisons did not demonstrate a significant difference between palbociclib and letrozole and ribociclib–letrozole. These findings support the early incorporation of CDK4/6i-ET in HR+/HER2– MBC and the individualized choice of regimen based on comorbidities, monitoring requirements, and patient preference.

Keywords: metastatic breast cancer, HR-positive/HER2-negative, CDK4/6 inhibitor, palbociclib, ribociclib, real-world data, progression-free survival, overall survival

Corresponding Author*: Selami Bayram, MD. Department of Medical Oncology, Memorial Antalya Hospital, 07040, Antalya, Turkey.
E-mail: drselamibayram@gmail.com Phone: +90 5302945006
Orcid: 0000-0002-0930-5025
Doi: 10.18663/tjcl.1838613
Received: 08.12.2025 accepted: 21.01.2025 publication date: 01.03.2026

Öz

Amaç: Hormon reseptör pozitif/human epidermal growth factor reseptör 2 negatif (HR+/HER2-) metastatik meme kanserinde (MMK) endokrin tedavi (ET) ile kombinasyon halinde siklin bağımlı kinaz 4/6 inhibitörleri (CDK4/6i) birinci basamak standart tedavidir; ancak Türkiye'den gerçek yaşam verileri sınırlıdır. Bu çalışmada CDK4/6i-ET'nin farklı tedavi basamaklarındaki etkinlik ve güvenlilik sonuçları ile birinci basamakta palbosiklib-letrozol ve ribosiklib-letrozol rejimlerinin sonuçları araştırıldı.

Gereç ve Yöntemler: Bu tek merkezli, retrospektif kohort çalışmasına, rutin pratikte palbosiklib veya ribosiklib ile ET (letrozol veya fulvestrant) kombine edilerek tedavi edilen ardışık HR+/HER2– MMK'li erişkin hastalar dahil edildi. Birincil sonlanım noktası progresyonsuz sağkalım (PFS) idi. İkincil sonlanım noktaları genel sağkalım (OS), objektif yanıt oranı (OYO), klinik yarar oranı (KYO; KR+KY+SD ≥24 hafta) ve güvenlilikti. Sağkalım Kaplan–Meier yöntemi ile hesaplandı, log-rank testi ve tek değişkenli Cox modelleri ile karşılaştırıldı. Keşifsel analizlerde tedavi basamağına (1., 2., ≥3. basamak) göre sonuçlar ve birinci basamakta palbosiklib-letrozol ile ribosiklib-letrozol karşılaştırıldı.

Bulgular: Toplam 124 hasta dahil edildi; CDK4/6i-ET birinci, ikinci ve ≥üçüncü basamakta sırasıyla %65,3, %19,4 ve %15,3 oranında kullanıldı. Toplam 51 hastada (%41,1) progresyon ve 19 hastada (%15,3) ölüm izlendi. Birinci, ikinci ve ≥üçüncü basamakta 12 aylık PFS oranları sırasıyla %82,7, %69,9 ve %42,1 idi; birinci basamağa kıyasla progresyon veya ölüm riski ikinci basamakta daha yüksek bulundu (HR 2,20; %95 GA 1,09–4,46) ve ≥üçüncü basamakta daha da belirgindi (HR 4,71; %95 GA 2,45–9,05). 12 aylık OS oranları sırasıyla %93,4, %86,5 ve %83,6 olup, ≥üçüncü basamakta ölüm riski anlamlı derecede artmıştı (HR 3,88; %95 GA 1,41–10,71). OYO %37,9, KYO %87,9 idi. Birinci basamak aromataz inhibitörü alt grubunda, palbosiklib-letrozol ile ribosiklib-letrozol arasında PFS (HR 0,77; %95 GA 0,43–1,39; p=0,392) ve OS (HR 0,83; %95 GA 0,20–3,47; p=0,797) açısından istatistiksel olarak anlamlı fark saptanmadı. En az bir advers olay hastaların %85,4'ünde görüldü; derece ≥3 nötropeni oranı %42,7 iken toksisiteye bağlı kalıcı tedavi kesilmesi nadirdi (%2,4).

Sonuç: Bu gerçek yaşam kohortunda CDK4/6i-ET, faz III çalışmalara uyumlu bir güvenlilik profili ile klinik olarak anlamlı hastalık kontrolü sağlamıştır. CDK4/6 inhibitörlerinin daha erken basamakta kullanılması daha uzun PFS ve OS ile ilişkili bulunurken, birinci basamaktaki rejim-düzeyindeki karşılaştırmalar palbosiklib-letrozol ile ribosiklib-letrozol arasında anlamlı fark göstermemiş ve keşifsel olarak yorumlanmalıdır. Bulgularımız, HR+/HER2– MMK'de CDK4/6i-ET'nin erken dönemde tedaviye entegre edilmesini ve rejim seçiminin komorbiditeler, izlem gereksinimleri ve hasta tercihine göre bireyselleştirilmesini desteklemektedir.

Anahtar Kelimeler: metastatik meme kanseri, hormon reseptör pozitif/HER2 negatif, CDK4/6 inhibitörü, palbosiklib, ribosiklib, gerçek yaşam verisi, progresyonsuz sağkalım, genel sağkalım

Introduction

Hormone receptor positive/human epidermal growth factor receptor 2 negative (HR+/HER2–) metastatic breast cancer (MBC) is the most common biological subtype of advanced breast cancer and remains a major global health burden [1]. Endocrine therapy [ET] is the therapeutic backbone, and the integration of cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) into ET-based regimens has transformed management across treatment lines by improving disease control and, in several phase III trials, overall survival (OS) [2-6]. Contemporary international guidelines therefore recommend ET plus a CDK4/6 inhibitor for most patients with HR+/HER2– MBC, with regimen selection and sequencing tailored to clinical context (e.g., de novo vs relapse on/after adjuvant ET, visceral crisis, prior ET exposure, and comorbidities) [7,8].

In routine practice, effectiveness and tolerability may differ from trial settings due to broader eligibility (age, comorbidity burden, performance status), variations in monitoring/assessment schedules, and pragmatic sequencing [9-11]. Safety profiles also influence regimen choice and persistence: hematologic toxicity (particularly neutropenia) is common with CDK4/6 inhibitors, while QTc prolongation and other cardiovascular signals have been highlighted most prominently for ribociclib in pharmacovigilance and meta-analytic evidence [12-15]. These real-world considerations may modulate treatment delivery (dose interruption/reduction) and, consequently, clinical outcomes.

Despite mature randomized evidence, key gaps remain regarding outcomes by line of therapy and comparative effectiveness of commonly used first-line regimens (notably

palbociclib–letrozole vs ribociclib–letrozole) in unselected populations [9-11]. Therefore, we conducted a single-center retrospective cohort of consecutive HR+/HER2– MBC patients treated with ET plus palbociclib or ribociclib. The primary objective was progression-free survival (PFS); secondary objectives included OS, objective response and clinical benefit, and safety based on routine clinical documentation.

Material and Methods

We performed a single-center, observational, retrospective cohort study at the Department of Medical Oncology, Memorial Antalya Hospital (Antalya, Türkiye). The index date was the start of cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) therapy in the metastatic setting. All consecutive eligible patients who initiated endocrine therapy (ET) plus a CDK4/6 inhibitor during the study period were screened, and follow-up was administratively censored at the data lock (cut-off date: 01.01.2024).

The eligibility criteria were as follows: age ≥ 18 years, pathologically confirmed HR-positive/HER2-negative advanced/metastatic breast cancer, receipt of palbociclib or ribociclib combined with ET (letrozole or fulvestrant) for metastatic disease, and availability of key baseline and outcome data. We excluded patients with HER2-positive or triple-negative disease, those enrolled in interventional trials likely to confound outcomes, and those with insufficient follow-up for endpoint assessment. Inclusion was consecutive to limit selection bias. (Abemaciclib was not used in this cohort.)

The selection of CDK4/6i (palbociclib or ribociclib) and ET partner (letrozole or fulvestrant) was guided by national and international guidelines, physician expertise, patient comorbidities, prior treatment history, and preferences. For instance, ribociclib's specific monitoring requirements (ECG/electrolytes) or a patient's cardiac history may influence treatmentchoice. Dosing, dose modifications, and monitoring schedules strictly adhered to the prescribing information for each agent and local institutional guidelines, which are regularly updated based on emerging evidence and regulatory approval. Imaging frequency for disease assessment was typically performed every 3-6 months, consistent with the standard clinical follow-up for MBC.

Data were abstracted from electronic medical records, radiology information systems, and pharmacy/infusion charts into a pre-specified case report form. Baseline covariates included age, menopausal status, ECOG performance status, metastatic pattern (visceral vs. non-visceral; bone-only), number of metastatic sites, de novo metastatic presentation vs. late relapse, and prior therapies. The treatment variables included the CDK4/6i agent, ET partner, starting dose, and subsequent dose modifications/interruptions. Laboratory parameters were obtained during routine examinations.

The primary endpoint was progression-free survival (PFS), defined as the time from the index to the first documented disease progression or death from any cause, whichever occurred first. The secondary endpoints were overall survival (OS) (time from index to death from any cause), objective response rate (ORR), clinical benefit rate (CBR) defined as CR+PR+SD ≥ 24 weeks, and safety. Tumor response was assessed according to RECIST v1.1 or the closest routine radiologic assessment with adjudication. Adverse events (AEs) were graded using the CTCAE v5.0, and the worst on-treatment grade per patient was analyzed.

For PFS, patients without an event were censored at the most recent tumor assessment or clinic visit documenting non-progression, whichever occurred later. For OS, patients alive at the data lock were censored at the last known date. Patients who were lost to follow-up were censored at their last contact.

Selection bias was reduced through consecutive inclusion and standardized eligibility. Information/measurement bias was limited by predefined operational definitions and dual data checking with third-party adjudication of discrepancies. Potential confounders (age, ECOG, de novo metastasis, metastatic pattern/extent, chosen CDK4/6i and ET partner, and prior therapies/disease-free interval) were considered.

The study was approved by the Memorial Antalya Hospital Clinical Research Ethics Committee (Approval no:848/2025, Date: 20.10.2025). Given the retrospective, non-interventional design and de-identified data, the requirement for informed consent was waived. This study complied with the Declaration of Helsinki and local regulations.

Statistical Analysis

Continuous variables are summarized as mean ± standard deviation (SD) and median (range), and categorical variables are summarized as counts and percentages. Progression-free survival (PFS) and overall survival (OS) were estimated using the Kaplan–Meier method with two-sided 95% confidence intervals (CIs). Between-group differences in survival were compared using the log-rank test. When estimable, we reported the median PFS and OS with 95% CIs; when medians were not reached at the time of data lock, we presented landmark survival probabilities at pre-specified time points (12, 36, and 60 months). To quantify the associations between baseline or treatment variables and time-to-event outcomes, we fitted univariable Cox proportional

hazards models and reported hazard ratios (HRs) with 95% CIs, using first-line CDK4/6 inhibitor use as the reference, where applicable. Given the limited number of OS events, survival analyses—particularly regimen-level comparisons in the first-line subset—should be considered exploratory and were not adjusted for multivariable models. Missing data were generally low; analyses were performed on available cases (complete case analysis), and no multiple imputations were applied. All tests were two-sided with α = 0.05. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 23 (IBM Corp., Armonk, NY, USA).

Results

A total of 124 consecutive patients were enrolled in this study. The median follow-up time, estimated using the reverse Kaplan–Meier method, was 19.0 months (95% CI, 17.7–20.3). At data lock, 105 (84.7%) were alive, 19 (15.3%) had died, and 51 (41.1%) had experienced disease progression. Event counts for time-to-event analyses were as follows: OS events 8/81 (first line), 4/24 (second line), and 7/19 (≥3rd line), and PFS events 23/81, 12/24, and 16/19, respectively (see Table 4 for OS and Table 5 for PFS). Missingness was limited: histological grade was available in 96/124 (77.4%) and Ki-67 in 114/124 (91.9%) patients; the presence/absence of any adverse event (AE) was recorded in 123/124 (99.2%) patients. The denominators for the analyses varied and are specified in the footnotes of Tables 1 and 8.

The mean age was 55.6 ± 12.1 years (median, 55.5; range, 25–88 years); 99.2% were women, and 65.3% were postmenopausal. All patients were diagnosed with stage IV disease. Visceral metastases were present in 63/124 (50.8%) patients, and bone metastases were present at baseline in 108/124 (87.1%) patients. The ECOG performance status was 0, 1, and 2 in 20.2%, 70.2%, and 2 in 9.7% of patients, respectively. By tumor biology, HER2 IHC was 0 in 62.9%, 1+ in 26.6%, and 2+/FISH– in 10.5%; ER averaged 89.4 ± 15.7% (median 95), PR 50.4 ± 33.0% (median 50), and Ki-67 31.9 ± 21.6% (median 26.5; n = 114) (Table 1).

CDK4/6 inhibitor therapy was administered as first-line therapy in 81/124 (65.3%) patients, second-line therapy in 24/124 (19.4%) patients, and in the ≥3rd line to 19/124 (15.3%) patients. The regimens were ribociclib + letrozole in 60 (48.4%), palbociclib + letrozole in 34 (27.4%), palbociclib + fulvestrant in 20 (16.1%), and ribociclib + fulvestrant in 10 (8.1%). Overall, ribociclib was used in 70 (56.5%) and palbociclib in 54 (43.5%) patients; the endocrine partner was letrozole in 94 (75.8%) and fulvestrant in 30 (24.2%) patients. Bone-modifying agents were frequently co-administered (zoledronic acid 41.1%; denosumab 41.9%) (Table 2).

Table 1. Patient demographics and disease characteristics (n = 124).

	n	%
Gender		
Female	123	99.2
Male	1	0.8
Age, years		
Mean±SD	55.59 ± 12.05	
Median (Min–Max)	55.5 (25–88)	
Menopausal status		
Premenopausal	43	34.7
Postmenopausal	81	65.3
Stage at diagnosis		
IV	124	100
Site of metastasis		
Non-Visceral	61	49.2
Visceral	63	50.8
Denovo bone metastasis		
Yes	108	87.1
No	16	12.9
HER-2		
0	78	62.9
1+	33	26.6
2+ (FISH–)	13	10.5
Histological grade*		
Grade 1	4	4.2
Grade 2	63	65.6
Grade 3	29	30.2
ECOG		
0	25	20.2
1	87	70.2
2	12	9.7
ER (%)		
Mean±SD	89.37 ± 15.66	
Median (Range)	95 (17–100)	
PR (%)		
Mean±SD	50.41 ± 33.04	
Median (Range)	50 (0–100)	
Ki-67 (%) †		
Mean±SD	31.92 ± 21.56	
Median (Range)	26.5 (4–90)	

** Grade available for n = 96; percentages within the available data. † Ki-67 was available for n = 114.*

PFS differed significantly according to the treatment line (log-rank $\chi^2[2] = 25.16$; $p < 0.001$; Table 5, Figure 2B). In first-line therapy (n = 81; 23 events), 12-, 36-, and 60-month PFS rates were 82.7% (95% CI, 74.6–91.8), 66.8% (95% CI, 55.9–79.8), and 44.5% (95% CI, 19.6–100.0), respectively. In the second-line therapy group (n = 24; 12 events), the 12-month PFS rate was 69.9% (95% CI, 53.4–91.4). In the ≥3rd line (n = 19; 16

events), the 12-month PFS rate was 42.1% (95% CI, 24.9–71.3). In univariable Cox models (reference: first line), the risk of progression or death was higher in the second line (HR 2.20, 95% CI, 1.09–4.46; p = 0.028) and in the ≥3rd line (HR 4.71, 95% CI, 2.45–9.05; p <0.001), indicating progressively shorter disease control with later-line initiation of CDK4/6 inhibition.

Table 2. Treatment characteristics.

	n	%
CDK4/6 treatment line		
1st line	81	65.3
2nd line	24	19.4
≥3rd line	19	15.3
Combination regimen		
Palbociclib + Letrozole	34	27.4
Palbociclib + Fulvestrant	20	16.1
Ribociclib + Letrozole	60	48.4
Ribociclib + Fulvestrant	10	8.1
CDK4/6 inh		
Palbociclib	54	43.5
Ribociclib	70	56.5
Endocrine treatment		
Letrozole	94	75.8
Fulvestrant	30	24.2
Bone-modifying agent		
None	21	16.9
Zoledronic acid	51	41.1
Denosumab	52	41.9

Overall survival (OS) also varied according to the treatment line (log-rank $\chi^2[2] = 7.89$; p = 0.001; Table 4, Figure 2A). At data lock, eight of 81 patients (9.9%) treated in the first line, four of 24 (16.7%) in the second line, and seven of 19 (36.8%) in the ≥3rd line had died. In the first-line group, 12- and 36/60-month OS rates were 93.4% (95% CI, 88.0–99.2) and 87.8% (95% CI, 80.0–96.5), respectively. In the second line, 12- and 36/60-month OS rates were 86.5% (95% CI, 73.3–100.0) and 81.1% (95% CI, 65.8–99.8), whereas in the ≥3rd line they were 83.6% (95% CI, 68.2–100.0) and 57.8% (95% CI, 37.9–88.0). The median OS was not reached for any treatment line at the time of data lock. Compared with first-line use, the hazard of death was numerically higher with second-line initiation (HR 1.70, 95% CI, 0.51–5.66; p = 0.384) and significantly higher with ≥3rd-line use (HR 3.88, 95% CI, 1.41–10.71; p = 0.009), although OS estimates remained immature (Table 4).

Among patients who received an aromatase inhibitor plus a CDK4/6 inhibitor as first-line therapy, survival did not differ significantly between those who received palbociclib + letrozole (n = 25) and those who received ribociclib + letrozole (n = 55) (Figure 1). For OS, the log-rank test yielded $\chi^2(1) = 0.066$ (p = 0.797) with an HR of 0.83 (95% CI, 0.20–3.47), based on three versus five deaths (Table 6). Twelve-month OS exceeded 90% in both groups [95.8% (95% CI, 88.2–100.0) vs 92.3% (95% CI, 85.3–99.9)], and 36-month OS remained above 80% [83.0% (95% CI, 66.2–100.0) vs 89.9% (95% CI, 81.8–98.8)]. For PFS, there was no statistically significant difference (log-rank χ^2 [1] = 0.256; p = 0.613; HR 0.77, 95% CI, 0.43–1.39) (Table 7). Twelve-month PFS rates were 85.7% (95% CI, 72.0–100.0) with palbociclib + letrozole and 80.4% (95% CI, 70.2–92.1) with ribociclib + letrozole. The median PFS and OS were not reached in either first-line group at the time of data lock. Given the small number of OS events and the absence of multivariable adjustment, these regimen-level comparisons are underpowered and should be interpreted as exploratory analyses.

The best overall response comprised partial response in 47/124 (37.9%), stable disease in 62/124 (50.0%), and progressive disease in 15/124 (12.1%); no complete responses were observed. The objective response rate was 37.9%, and the clinical benefit rate was 87.9% (Table 3).

Table 3. Best tumor response and status at last follow-up (n=124).

	n	%
Response		
CR	0	0
PR	47	37.9
SD	62	50
PD	15	12.1
Objective response rate	47	37.9
Clinical benefit rate	109	87.9
Progression occurred		
Yes	51	41.1
No	73	58,9
Vital status		
Alive	105	84.7
Death	19	15.3

At least one AE was documented in 105/123 (85.4%) patients with available AE-presence data. Hematologic toxicity was dominated by neutropenia: grade 3 in 51/124 (41.1%) and grade 4 in 2/124 (1.6%) (grade ≥3, 42.7%). Grade ≥3 anemia and thrombocytopenia occurred in 4/124 (3.2%) patients. Grade ≥3 liver function test elevations occurred in 3/124 (2.4%) patients, and grade 1 QTc prolongation occurred in 1/124 (0.8%) patients. Dose reductions were implemented in 34/124 (27.4%) patients, and permanent discontinuation due to toxicity occurred in 3/124 (2.4%) patients. Unless otherwise specified, the denominators for the safety endpoints were n = 124 (Table 8).

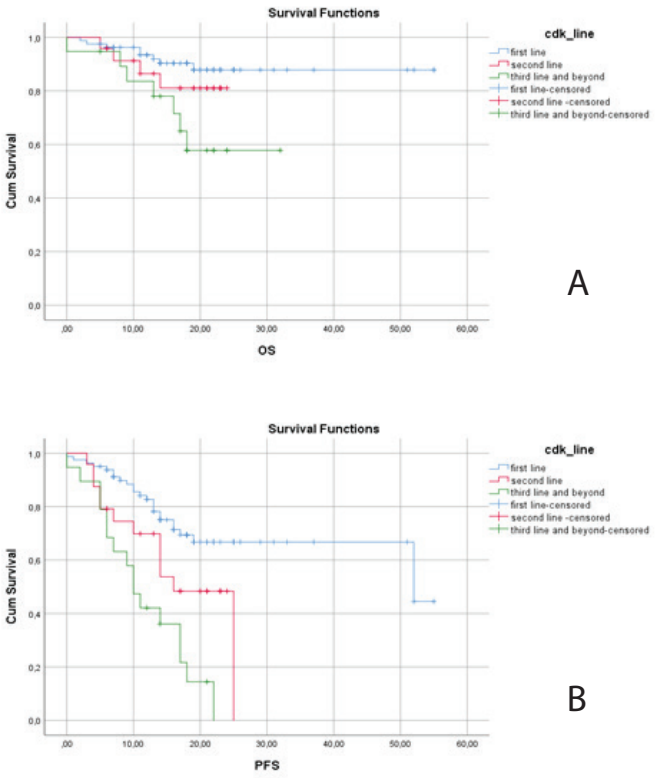

Figure 1. First-line palbociclib–letrozole vs ribociclib–letrozole. Overall survival (OS) and (B) progression-free survival (PFS) in patients treated in the first line with palbociclib–letrozole vs ribociclib–letrozole. Censoring is indicated by tick marks. Numbers at risk at prespecified time points are shown below the curves. No statistically significant difference was observed (OS: log-rank χ^2=0.066, p=0.797; HR 0.83, 95% CI 0.20–3.47. PFS: log-rank χ^2=0.256, p=0.613; HR 0.77, 95% CI 0.43–1.39).

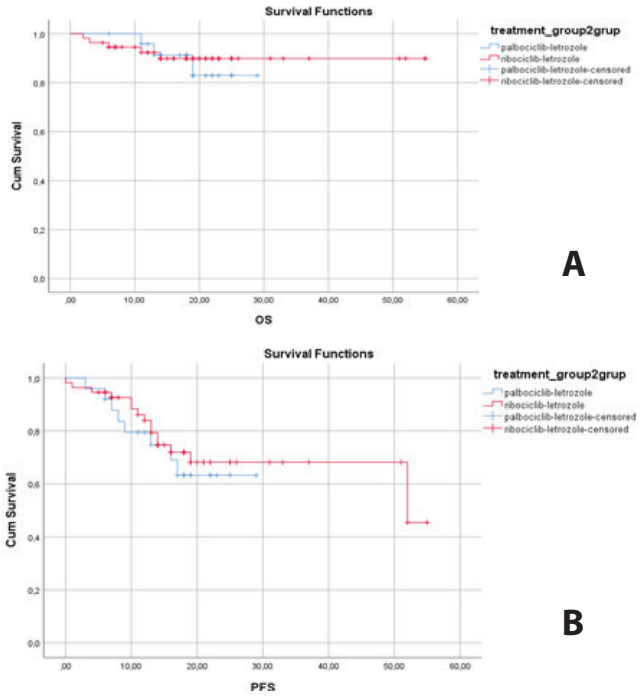

Figure 2. Outcomes by treatment line. (A) OS and (B) PFS by treatment line (1L, 2L, ≥3L). Censoring is indicated by tick marks. Numbers at risk are shown below. Survival differed across lines (OS: log-rank χ^2=7.89, p<0.001; PFS: log-rank χ^2=25.16, p<0.001).

Table 4. Progression-free survival and Overall survival by CDK4/6 treatment line.

	Line	Events / n	KM mean OS-mo (95% CI)	12-mo	36-mo	60-mo	HR/p value
OS	1st line	8 / 81	49.65 (46.11–53.18)	93.4% (88.0–99.2)	87.8% (80.0–96.5)	87.8% (80.0–96.5)	Ref
	2nd line	4 / 24	21.27 (18.81–23.73)	86.5% (73.3–100.0)	81.1% (65.8–99.8)	81.1% (65.8–99.8)	1.70 (0.51–5.66) p = 0.384
	≥3rd line	7 / 19	23.61 (18.62–28.60)	83.6% (68.2–100.0)	57.8% (37.9–88.0)	57.8% (37.9–88.0)	3.88 (1.41–10.71) p= 0.009
PFS	1st line	23 / 81	39.71 (34.58–44.84)	82.7% (74.6–91.8)	66.8% (55.9–79.8)	44.5% (19.6–100.0)	Ref
	2nd line	12 / 24	16.87 (13.13–20.61)	69.9% (53.4–91.4)	0.0% (CI NE)	0.0% (CI NE)	2.20 (1.09–4.46) p = 0.028
	≥3rd line	16 / 19	11.51 (8.37–14.65)	42.1% (24.9–71.3)	0.0% (CI NE)	0.0% (CI NE)	4.71 (2.45–9.05) p < 0.001

Abbrev.: PFS, progression-free survival; OS, overall survival; KM, Kaplan–Meier; CI, confidence interval; HR, hazard ratio; NE, not estimable; Ref, reference group

Table 5. First-line subset: PFS and OS — Palbociclib + Letrozole vs Ribociclib + Letrozole.							
	Regimen	Events / N	KM mean OS-mo (95% CI)	12-mo	36-mo	60-mo	HR/p value
OS	PAL+LET	3 / 25	26.69 (24.27–29.11)	95.8%(88.2–100.0)	83.0% (66.2–100.0)	83.0% (66.2–100.0)	Ref
	RIB+LET	5 / 55	50.22 (46.23–54.21)	92.3% (85.3–99.9)	89.9% (81.8–98.8)	89.9% (81.8–98.8)	0.83 (0.20–3.47) p= 0.797
PFS	PAL+LET	8 / 25	22.22 (18.35–26.09)	85.7% (72.0–100.0)	0.0% (CI NE)	0.0% (CI NE)	Ref
	RIB+LET	15 / 55	40.37 (34.22–46.52)	80.4% (70.2–92.1)	13.7% (6.1–30.6)	0.0% (CI NE)	0.77 (0.43–1.39) p= 0.392
Abbrev.: PFS, progression-free survival; OS, overall survival; KM, Kaplan–Meier; CI, confidence interval; HR, hazard ratio; NE, not estimable; Ref, reference group							

Table 6. Safety and dose modifications (CTCAE).		
	n	%
Any adverse event‡	105	85.4
Neutropenia		
Grade 1	12	9.7
Grade 2	37	29.8
Grade 3	51	41.1
Grade 4	2	1.6
Anemia		
Grade 1	28	22.6
Grade 2	14	11.3
Grade 3	4	3.2
Thrombocytopenia		
Grade 1	2	1.6
Grade 2	1	0.8
Grade 3	3	2.4
Grade 4	1	0.8
LFT elevation		
Grade 1	8	6.5
Grade 2	3	2.4
Grade 3	3	2.4
QTc prolongation		
Grade 1	1	0.8
Dose reduction		
Yes	34	27.4
Permanent discontinuation (toxicity)		
Yes	3	2.4
‡ Adverse-event presence available for n = 123		

Discussion

Randomized phase III trials established endocrine therapy (ET) plus a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) as standard of care in HR+/HER2– metastatic breast cancer (MBC), delivering consistent, clinically meaningful improvements in progression-free survival (PFS) and, for several regimens, overall survival (OS) [2-6]. In first-line disease, adding ribociclib to letrozole significantly prolonged OS in MONALEESA-2 (median 63.9 vs. 51.4 months; HR 0.76) [2]; OS benefits were also shown with ribociclib plus fulvestrant in MONALEESA-3 [3] and in pre/perimenopausal patients in MONALEESA-7 [4]. In contrast, PALOMA-2 (palbociclib + letrozole, first-line) confirmed robust PFS but did not improve OS in the final analysis, with interpretability affected by missing survival status in the control arm [5]. Separately, MONARCH-2 showed that abemaciclib plus fulvestrant improved OS after ET progression, underscoring that the survival benefit within the class is regimen- and context-dependent [6]. Collectively, phase III evidence supports durable disease control with CDK4/6i-ET while highlighting the heterogeneity of OS signals across regimens.

Our cohort mirrored these themes of regimen-level heterogeneity and the importance of real-world context. First, outcomes differed by treatment line: patients who initiated CDK4/6i-ET in the first line experienced longer time-to-event outcomes than those treated later (see Table 4–5, Figure 2). This gradient aligns with trials showing larger absolute gains when CDK4/6 inhibition is introduced early, and it echoes multi-country real-world series in routine practice [9,10,16].

Second, within the first-line subset, survival did not differ significantly between palbociclib + letrozole and ribociclib + letrozole (see Table 6–7, Figure 1). This "no difference detected" result should be interpreted cautiously, given the low OS event count and unadjusted analyses (limited precision/power). Notably, contemporary real-world comparisons are heterogeneous: some large analyses report no OS differences among first-line CDK4/6i regimens, whereas others find longer rwPFS with abemaciclib or ribociclib versus palbociclib in adjusted models [9-11,17]. Thus, our findings are compatible with current RWE and do not contradict phase III data, where cross-trial OS comparisons are inherently limited.

Third, the safety profile predominantly hematologic toxicity led by neutropenia, manageable with dose modification and with low permanent discontinuation was class-consistent (Table 8). Palbociclib and ribociclib commonly cause hematologic

AEs, whereas abemaciclib is associated with higher rates of gastrointestinal AEs [12]. Ribociclib-specific considerations include QT interval monitoring and potential transaminase elevations; adherence to ECG/electrolyte and liver function monitoring in routine care is essential [14, 15]. Our observed grade ≥3 neutropenia rates and overall manageability parallel those of registrational trials and systematic reviews, supporting the feasibility of maintaining dose intensity through protocolized dose adjustments [12].

These findings have the following clinical implications: first, prioritize exposure to CDK4/6 inhibition early in the metastatic trajectory; second, when choosing between PAL+LET vs. RIB+LET for first-line therapy, incorporating monitoring logistics (ribociclib-specific ECG/LFT checks), comorbidities, drug–drug interactions, and patient preference, given mixed comparative-effectiveness signals and the limited power of our head-to-head subset; and Third, high rates of bone metastasis and frequent use of bone-modifying agents in our practice (see Tables 1 and 2) likely contributed to disease control across lines, aligning with supportive-care principles applied in trials. As new targeted combinations emerge (e.g., PI3K/AKT-pathway inhibitors or triplets), sequencing around a CDK4/6 backbone will continue to evolve; for now, CDK4/6i-ET remains the anchor of first-line therapy for most patients with HR+/HER2– MBC [2-6,18].

Limitations of the study

This study had some limitations. First, its retrospective, single-center design is susceptible to selection and information biases, despite consecutive inclusion and standardized data abstraction. Second, residual confounding cannot be excludedfrom this study. Treatment selection (e.g., choice of regimen in the first line, timing of CDK4/6 inhibitor introduction in later lines) may reflect physician judgement and patient factors (confounding by indication) that we could not fully adjust for, and the primary comparative analyses were unadjusted (univariate). Third, the number of OS events was low, particularly within the first-line subset, resulting in limited statistical power and wide confidence intervals for the regimen-level contrasts. Consequently, head-to-head comparisons between palbociclib-LET and ribociclib-LET should be interpreted cautiously. Fourth, real-world assessment schedules (imaging and clinic visit intervals) were not fully standardized, which may have introduced measurement interval bias in PFS estimates and influenced censoring patterns. Fifth, although missing data were generally modest, and we reported denominators transparently, we relied on complete-case analysis without multiple imputation; bias cannot be excluded if data were not missing completely at random. Sixth, OS data remain immature, with medians not reached in several subgroups at the time of data lock, and longer follow-up is required to refine the survival estimates. Finally, safety findings are constrained by routine documentation practices and potential heterogeneity in on-label monitoring (e.g., ECG/electrolyte and liver function testing with ribociclib), which may vary between clinicians and times.

In conclusion, in this real-world cohort of HR+/HER2– metastatic breast cancer, CDK4/6 inhibitor plus endocrine therapy achieved clinically meaningful disease control with a safety profile consistent with the drug class. Outcomes varied by treatment line, with the longest PFS/OS observed when therapy was initiated in the first line, mirroring phase III trends. Within the first-line subset, we observed no statistically significant survival difference between palbociclib and letrozole and ribociclib–letrozole; however, this comparison was underpowered and unadjusted and should be interpreted as hypothesis-generating. Hematologic toxicity, predominantly neutropenia, was common but generally manageable with dose modification, and permanent discontinuation due to toxicity was infrequent. Clinical implications: For most patients, early incorporation of a CDK4/6 inhibitor remains a rational standard, whereasthe choice between common first-line combinations can be individualized based on monitoring logistics (e.g., ECG/LFTs with ribociclib), comorbidities, drug–drug interactions, and patient preference. Research implications: Multicenter, adequately powered analyses using adjusted models and harmonized assessment schedules are needed to clarify the comparative effectiveness between first-line CDK4/6 regimens and to define optimal sequencing as new targeted combinations (e.g., PI3K/AKT pathway inhibitors or triplets) enter routine practice.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

Ethics Approval:

Approved by the Memorial Antalya Hospital Clinical Research Ethics Committee (Approval No. 848/2025, Date: 20.10.2025).

Author Contributions

Conceptualization: S.B.; Methodology: S.B., M.O.; Data curation: S.B., M.O.; Formal analysis: S.B., M.O.; Investigation: S.B., M.O.; Visualization: S.B., M.O.; Writing-original draft: S.B., M.O.; Writing-review & editing: all authors; Supervision: S.B.

Acknowledgments

We thank the nursing staff and data management team of the Memorial Antalya Hospital Oncology Unit for their support in data collection and patient care.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71:209–49.
2. Hortobagyi GN, Stemmer SM, Burris HA, Yap YS, Sonke GS, Hart L, et al. Overall Survival with Ribociclib plus Letrozole in Advanced Breast Cancer. N Engl J Med. 2022;386:942–50.
3. Slamon DJ, Neven P, Chia S, Fasching PA, De Laurentiis M, Im SA, et al. Overall Survival with Ribociclib plus Fulvestrant in Advanced Breast Cancer. N Engl J Med. 2020;382:514–24.
4. Lu YS, Im SA, Colleoni M, Franke F, Bardia A, Cardoso F, et al. Updated Overall Survival of Ribociclib plus Endocrine Therapy versus Endocrine Therapy Alone in Pre- and Perimenopausal Patients with HR+/HER2- Advanced Breast Cancer in MONALEESA-7: A Phase III Randomized Clinical Trial. Clin Cancer Res. 2022;28:851–9.
5. Slamon DJ, Diéras V, Rugo HS, Harbeck N, Im SA, Gelmon KA, et al. Overall Survival With Palbociclib Plus Letrozole in Advanced Breast Cancer. J Clin Oncol. 2024;42:994–1000.
6. Sledge GW, Jr., Toi M, Neven P, Sohn J, Inoue K, Pivot X, et al. The Effect of Abemaciclib Plus Fulvestrant on Overall Survival in Hormone Receptor-Positive, ERBB2-Negative Breast Cancer That Progressed on Endocrine Therapy-MONARCH 2: A Randomized Clinical Trial. JAMA Oncol. 2020;6:116–24.
7. Gennari A, André F, Barrios CH, Cortés J, de Azambuja E, DeMichele A, et al. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. Ann Oncol. 2021;32:1475–95.
8. Burstein HJ, Somerfield MR, Barton DL, Dorris A, Fallowfield LJ, Jain D, et al. Endocrine Treatment and Targeted Therapy for Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Metastatic Breast Cancer: ASCO Guideline Update. J Clin Oncol. 2021;39:3959–77.
9. Harbeck N, Brufsky A, Rose CG, Korytowsky B, Chen C, Tantakoun K, et al. Real-world effectiveness of CDK4/6i in first-line treatment of HR+/HER2- advanced/metastatic breast cancer: updated systematic review. Front Oncol. 2025;15:1530391.
10. Gehrchen ML, Berg T, Garly R, Jensen MB, Eßer-Naumann S, Rønlev JD, et al. Real-world effectiveness of CDK 4/6 inhibitors in estrogen-positive metastatic breast cancer. BJC Rep. 2024;2:44.
11. Rugo HS, Layman RM, Lynce F, Liu X, Li B, McRoy L, et al. Comparative overall survival of CDK4/6 inhibitors plus an aromatase inhibitor in HR+/HER2- metastatic breast cancer in the US real-world setting. ESMO Open. 2025;10:104103.
12. Stanciu IM, Parosanu AI, Nitipir C. An Overview of the Safety Profile and Clinical Impact of CDK4/6 Inhibitors in Breast Cancer-A Systematic Review of Randomized Phase II and III Clinical Trials. Biomolecules. 2023;13: 1422.
13. Murad B, Reis PCA, Deberaldini Marinho A, Marin Comini AC, Pinheiro Xavier D, Mella Soares Pessoa B, et al. QTc prolongation across CDK4/6 inhibitors: a systematic review and meta-analysis of randomized controlled trials. JNCI Cancer Spectr. 2024;8: pkae078.
14. Kim JH. Profiling the Cardiovascular Toxicities of CDK4/6 Inhibitors: A Real-World Pharmacovigilance Study. Cancers (Basel). 2024;16: 2869.
15. Lin W, Zeng Y, Weng L, Yang J, Zhuang W. Comparative analysis of adverse events associated with CDK4/6 inhibitors based on FDA's adverse event reporting system: a case control pharmacovigilance study. BMC Pharmacol Toxicol. 2024;25:47.
16. Demir A, Mandel NM, Paydas S, Demir G, Er Ö, Turhal NS, et al. Efficacy of Palbociclib and Endocrine Treatment in Heavily Pretreated Hormone Receptor-positive/HER2-negative Advanced Breast Cancer: Retrospective Multicenter Trial. Balkan Med J. 2020;37:104–7.
17. Yildirim HC, Kapar C, Koksal B, Seyyar M, Sanci PC, Guliyev M, et al. Efficacy of first-line CDK 4-6 inhibitors in premenopausal patients with metastatic breast cancer and the effect of dose reduction due to treatment-related neutropenia on efficacy: a Turkish Oncology Group (TOG) study. J Chemother. 2025;37:69–75.
18. Beypınar İ, Demir H, Yaslıkaya Ş, Köşeci T, Demir B, Çolak G, et al. Efficacy of everolimus plus hormonal treatment after cyclin-dependent kinase inhibitor; real-life experience, A TOG study. Breast Cancer Res Treat. 2024;208:597–604.