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The effect of switching from ribociclib to palbociclib due to toxicity in hormone receptor-positive, HER2-negative metastatic breast cancer: a real-world, multicenter, retrospective study

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Abstract

Purpose: The standards of care for hormone receptor (HR)-positive, HER2-negative metastatic breast cancer are CDK 4/6 (cyclin-dependent kinase) inhibitors. Treatment-related toxicity may develop, leading to a switch between CDK 4/6 inhibitors. This study aimed to investigate the effect of switching from ribociclib to palbociclib on prognosis.

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Materials and methods: Forty-four patients were included in the retrospective, multicenter study. Toxicity causes, Drug-Drug Interactions (DDI), Objective Response Rates (ORR), and Discontinuation Free Survival (DFS) were examined.

Results: All patients were female, with a median age of 57 (50.25-67.5). De novo metastatic disease was present in 30 (68.2%) patients, and 33 (75%) patients were postmenopausal.

The most common reason for the switch was an increase in alanine aminotransferase in 16 patients (36.3%). The median (m) time to switching was 4.3 months, and the median follow-up period was 23.9 months. There was no statistically significant difference between DDI and switch time, p=0.118. The ORR was 70.9% in those treated with ribociclib before toxicity and 73.1% after switching. In patients treated with ribociclib in the first line, mDFS1+ DFS2 was 31.6 (23.6-39.6) months in those who switched <4.3 months (n:18), while in those who switched ≥ 4.3 months (n:16), mDFS1+ DFS2 was 25.5 (20.1-31) months, p=0.618. Time-dependent Cox regression analysis revealed that the timing of the switch did not affect the prognosis.

Conclusion: In HR-positive HER2-negative metastatic breast cancer, no statistically significant negative association was observed in terms of survival and prognosis when switching from ribociclib to palbociclib after toxicity. Switching may be considered in selected patients during the treatment.

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Introduction

Breast cancer is the most common cancer worldwide, accounting for around 30% of all cancers in women and resulting in a mortality rate of 15-20% (1). Breast cancer, a heterogeneous disease, is clinically divided into three main subtypes. This is based on the presence or absence of molecular markers for estrogen or progesterone receptors and human epidermal growth factor receptor 2 (HER2). The three subtypes are hormone receptor (HR) positive/HER2 negative (70% of patients) breast cancer, HER2 positive (15-20%) breast cancer, and HR negative- HER2 negative breast cancer (15%) (2).

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The standard treatment for HR-positive, HER2-negative metastatic breast cancer is a combination of aromatase inhibitors (AIs) or fulvestrant combined with cyclin-dependent kinase 4/6 (CDK 4/6) inhibitors. While ribociclib has been shown to improve overall survival (3), abemaciclib (4) and palbociclib (5) met the primary endpoint of progression-free survival (PFS) but did not prolong overall survival. However, the risk of side effects is not negligible with any of the three CDK 4/6 inhibitors. Ribociclib is particularly associated with more frequent QTc prolongation and liver toxicity, while cytopenias are more prominent with palbociclib. Abemaciclib, on the other hand, is associated with a higher incidence of diarrhea (6). It has been shown that drug interactions are another cause of these side effects (7).

Dose reduction due to side effects has been evaluated in different studies; although the results are conflicting, it can be done for treatment continuity (8, 9). Switching between CDK 4/6 inhibitors due to toxicity is an option, not just dose reduction. However, there is insufficient real-world data on this topic. Nevertheless, it has been noted that this could be a treatment option for oncologists, allowing different side effects to be managed in this way (10).

In this study, we aimed to investigate the clinical effect of switching from ribociclib to palbociclib in patients who developed toxicity, whether there was a difference in terms of survival, and whether toxicity persisted or new side effects developed after the switch.

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Results

The study included 44 patients (3.1%). All patients were female, with a median age of 57 (50.25-67.5), and 33 (75%) were postmenopausal. Thirty-four (77.3%) patients used ribociclib as first-line therapy, while 30 (68.2%) patients had de novo metastatic disease. Other clinical and pathological characteristics are shown in Table 1.

Table 1. Clinic and pathologic characteristics

	n: 44

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Age, median (IQR)	57 (50.25-67.5)
Comorbidity, yes/no, n (%)	30 (68.2) / 14 (31.8)
Pre-post menopausal patients, n (%)	11 (25) /33 (75)
De-novo metastatic disease, n (%)	30 (68.2)
First-line treatment, n (%)	34 (77.3)
Invasive ductal carcinoma, n (%)	35 (79.5)
Invasive lobular carcinoma, n (%)	7 (15.9)
Other pathologies, n (%)	2 (4.6)
ER, median (IQR)	90 (80-95)
PR positive patients, n (%)	38 (86.4)
HER2 null, n (%)	25 (56.8)
HER2 +1, n (%)	13 (29.5)
HER2 +2, n (%)	6 (13.7)
Grade 1-2, n (%)	29 (65.9)
Grade 3, n (%)	15 (34.1)
Ki-67, median (IQR)	25 (10-40)
ECOG PS 0, n (%)	32 (72.7)
ECOG PS 1-2, n (%)	12 (27.3)
Endocrine partner (AI/ F), n (%)	31 (70.5) / 13 (29.5)
Bone metastasis, yes/no, n (%)	33 (75) / 11 (25)
Lung metastasis, yes/no, n (%)	16 (36.4) / 28 (63.6)
Liver metastasis, yes/no, n (%)	5 (11.4) / 39 (88.6)

IQR: interquartile range, ER: Estrogen receptor, PR: Progesterone receptor, ECOG PS: Eastern Cooperative Oncology Group Performance Status, AI: Aromatase inhibitor, F: Fulvestrant

The most common toxicity leading to switching from ribociclib to palbociclib was grade 3 alanine aminotransferase increase, observed in 16 (36.3%) patients. Grade 3 aspartate aminotransferase increase was observed in 2 (4.5%) patients. Prolonged corrected QT interval was observed in 9

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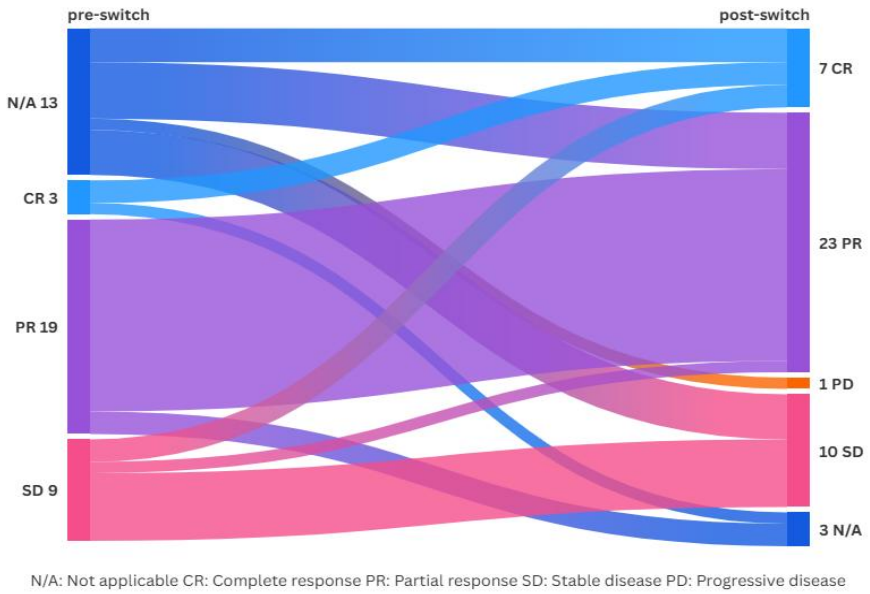
patients (20.4%), and complete atrioventricular block in 3 patients (6.8%). In 6 patients (13.6%), pruritus accompanied by skin rash, in 4 patients (9%), vitiligo-like lesions, in 1 patient (2.2%), alopecia, in 1 patient (2.2%), photosensitivity, and in 1 patient (2.2%), bullous dermatitis were the causes of toxicity. Refractory grade 3 neutropenia in 2 patients (4.5%), grade 3 creatinine increased in 3 patients (6.8%), and grade 3 anemia in 1 patient (2.2%). Dose reduction was performed in 30 (68.2%) patients before the switch. One step of permanent dose reduction was performed in 22 (50%) patients, and two steps were performed in 8 (18.2%) patients. Toxicity did not persist after the switch. Grade 2 neutropenia was observed in 9 (20.4%) patients and grade 1 neutropenia in 6 (13.6%) patients. Fatigue developed in 5 (11.4%) patients.

Fifteen (34.1%) patients were not receiving treatment involving drug interactions. Twenty (45.5%) patients were using minor interacting drugs, 2 (4.5%) patients were using moderate interacting drugs, and 7 (15.9%) patients were using major interacting drugs. Median toxicity developed at 4.3 months. Drug interactions were also examined in relation to early toxicity. Toxicity was observed within the first 4.3 months in 10 (66.7%) of the 15 patients without drug interactions, 7 of the 20 patients using minor interacting drugs (35%), and 6 of the 9 patients using moderately to major interacting drugs (66.7%) developed toxicity within the first 4.3 months, p=0.118.

The ORR in 31 patients was 70.9%, as the follow-up period was too short to evaluate response in 13 patients before toxicity. The ORR for these 13 patients is 61.5% after switching to palbociclib. In 3 patients who switched from ribociclib to palbociclib after toxicity, the response could not be evaluated due to the short duration of treatment. The ORR in 41 patients was 73.1% (Figure 1).

Figure 1. Responses before and after the switch in the Sankey Diagram

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N/A: Not applicable CR: Complete response PR: Partial response SD: Stable disease PD: Progressive disease

The median (m) follow-up period was 23.9 months. The OS was not yet mature, as 11 patients (25%) had died. The mDFS1+DFS2 in all patients was 29.9 (24.4-35.5) months. The DFS1+DFS2 rate at month 24 was 65.3%. In patients with a switch in <4.3 months (n:22), mDFS1+DFS2 was 31.4 (24.1-38.8) months, while in patients with a switch in ≥ 4.3 months, mDFS1+DFS2 was 28.4 (22.2-34.6) months, p=0.682 (Figure 2). When patients treated with ribociclib in the first line were evaluated, mPFS was 31.6 (23.6-39.6) months in those with a switch <4.3 months (n:18), while in those with a switch ≥ 4.3 months (n:16) mDFS1+DFS2 was 25.5 (20.1-31) months, p=0.618 (Figure 3). For all patients, the median DFS2 for palbociclib after switching was 24.7 (18.8-30.6) months (Figure 4). In patients with a switch in <4.3 months (n:22), mDFS2 was 25.2 (15.2-35.1) months, while in patients with a switch in ≥ 4.3 months, mDFS2 was 19.6 (14.9-24.3) months, p=0.841 (Figure 5).

Figure 2. DFS1+DFS2 according to the switch time in all patients

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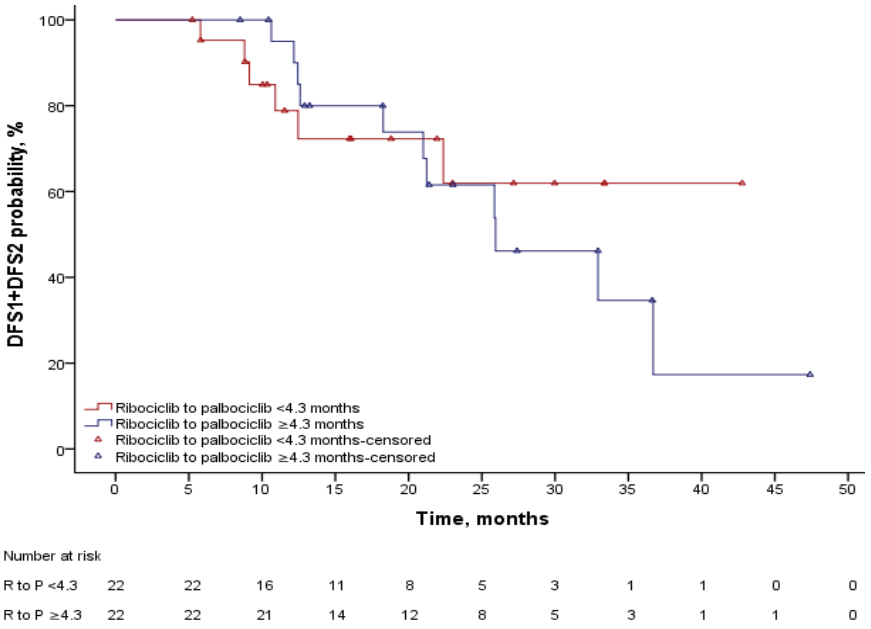


Figure 3. DFS1+DFS2 according to the switch time in first-line treatment

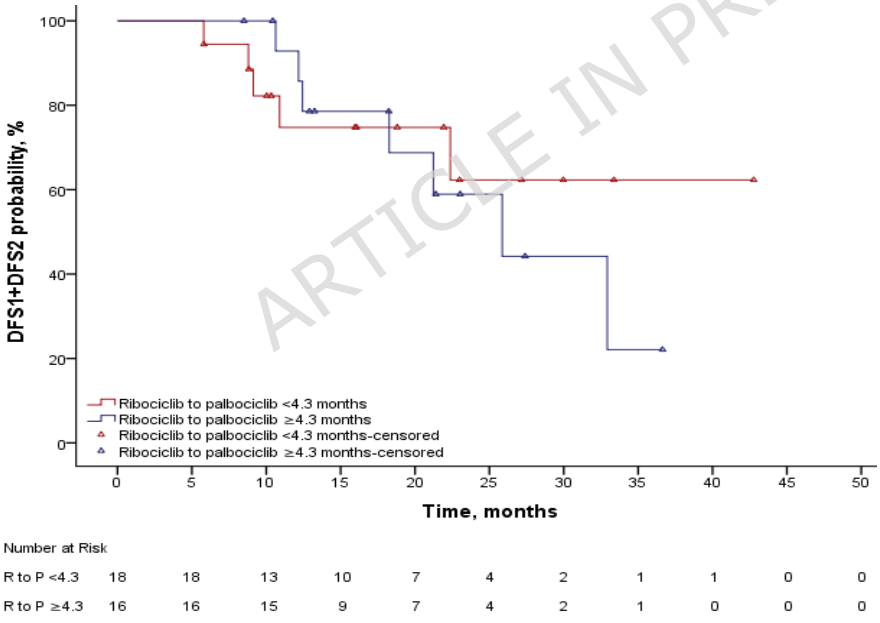
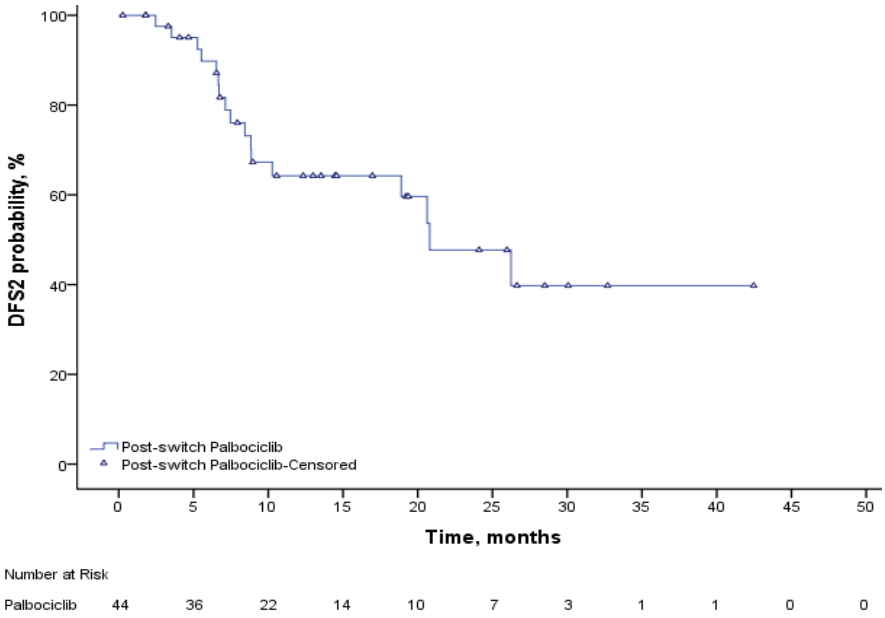


Figure 4. DFS2 in all patients

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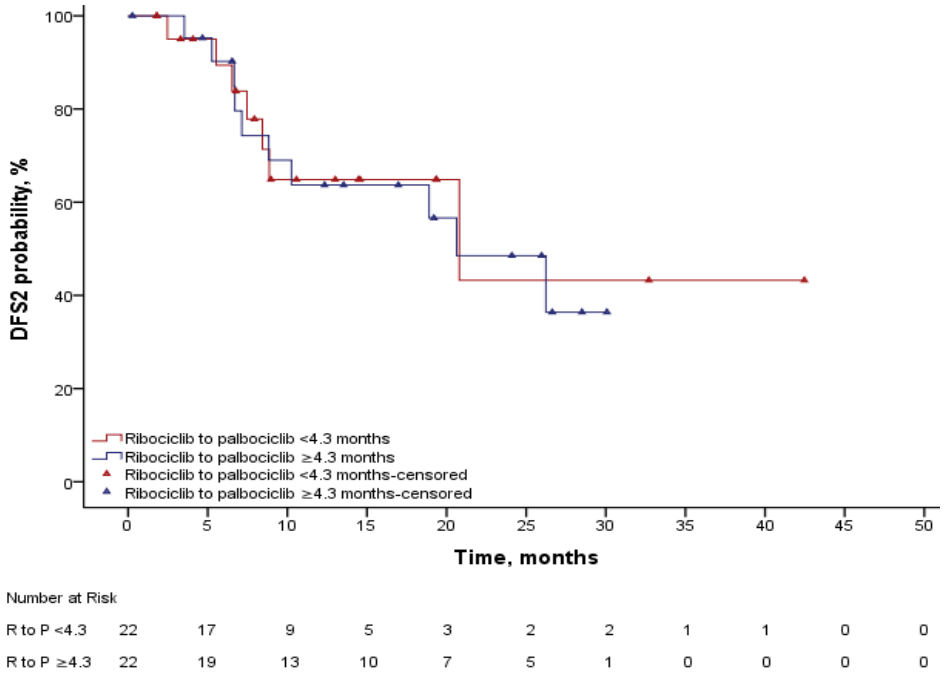
Number at Risk

Palbociclib	44	36	22	14	10	7	3	1	1	0	0

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Figure 5. DFS2 according to the switch time in all patients

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Number at Risk

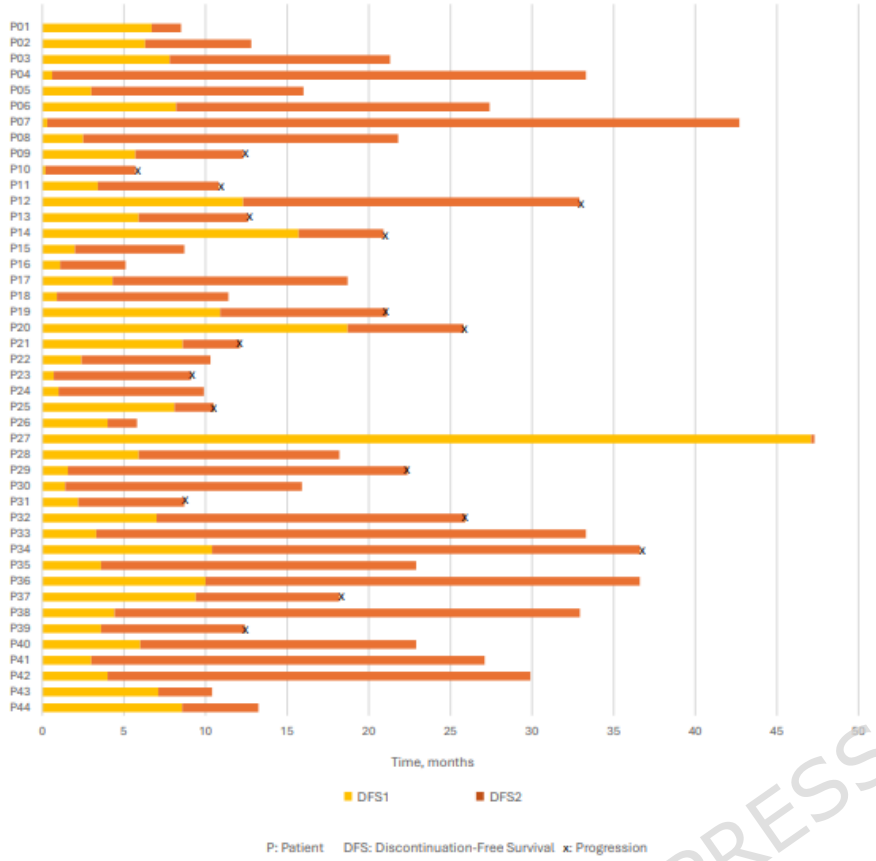
R to P <4.3	22	17	9	5	3	2	2	1	1	0	0
R to P ≥4.3	22	19	13	10	7	5	1	0	0	0	0

Shown in Figure 6 are the switching times, progression status, DFS1, and DFS2 durations for patients who switched from ribociclib to palbociclib.

Figure 6. Switch times, DFS1, and DFS2 for all patients

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As shown in Table 2, the timing of the switch and the variables affecting progression were evaluated in a time-dependent Cox regression analysis. The hazard ratio (95% confidence interval) was determined to be 0.97 (0.26-3.63), p=0.967, indicating that the timing of the switch did not affect DFS1+DFS2.

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Table 2. Time-dependent Cox model for progression

	Hazard Ratio (95% CI)	**p value**
ECOG PS (0 vs. 1-2)	0.86 (0.17-4.37)	0.863
De-novo metastatic disease (+ vs.-)	4.42 (0.94-20.6)	0.059
Menopausal status (post. vs. pre.)	0.84 (0.24-2.96)	0.797
ER % (≥90 vs. <90)	0.27 (0.06-1.15)	0.077
Ki 67 (≥25 vs. <25)	9.00 (1.90-42.4)	0.005

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CDK 4/6 inh. switch time, months (<4.3 vs. ≥4.3)	0.97 (0.26-3.63)	0.967
Bone metastasis (+ vs.-)	0.60 (0.17-2.07)	0.419
Liver metastasis (+ vs.-)	1.78 (0.27-11.5)	0.542

CI: Confidence Interval, ECOG PS: Eastern Cooperative Oncology Group Performance Status, ER: Estrogen receptor, CDK: Cyclin Dependent Kinase

Discussion

In our study, it was determined that switching from ribociclib to palbociclib due to toxicity in HR-positive, HER2-negative metastatic breast cancer did not affect progression-free survival, did not decrease the objective response rate, and did not cause persistent toxicity after switching. The side effects associated with palbociclib started after toxicity could be managed.

In the updated analysis of the MONALEESA-2 study, similar results to our study were obtained at a median follow-up of 25.4 months, with PFS above 60% at 24 months and ORR at 54.5%(11). Although median follow-up periods were shorter in our study, similar DFS1 plus DFS2 was observed in MONALEESA-3 and MONALEESA-7, which had PFS as the primary endpoint according to the investigator (12, 13). Compared to the PALOMA-2 study, our study showed relatively better results for DFS1 and DFS2 and ORR values. It should be noted that this may be due to both the small patient population and the retrospective nature of our study. The fact that treatment could be continued with another CDK 4/6 inhibitor may also have contributed to this result. In the palbociclib-letrozole group, toxicity leading to treatment discontinuation was observed in 43 patients (9.7%) (14). For similar reasons, treatment discontinuation occurred in 27 (8.1%) patients in the MONALEESA-2 study, 41 (8.4%) patients in the MONALEESA-3 study, and 12 (4%) patients in the MONALEESA-7 study (11-13). The median follow-up period of 23.9 months in our study is relatively short. This duration may be insufficient to adequately assess whether changing treatment leads to early resistance, whether the benefit of palbociclib is durable, and whether it is comparable to findings reported in major clinical trials. Furthermore, it should be noted that the studies of the aforementioned CDK 4/6 inhibitors differ

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in terms of study design, patient populations, endpoints, and follow-up duration. Consequently, this patient group continued their treatment by switching to another CDK 4/6 inhibitor. In this respect, our study is important. It should also be noted that the ORR of 13 (29.5%) patients before toxicity and 2 (4.5%) patients after toxicity could not be evaluated due to time constraints.

In our study, the most common toxicity leading to switching was grade 3 alanine aminotransferase increase. Our findings were consistent with a review indicating that ribociclib is the most common cause of hepatobiliary disorders among CDK 4/6 inhibitors (15). Despite dose reduction in 13 (72.2%) of the 18 cases of hepatotoxicity, the toxicity could not be prevented from continuing. Consistent with previous cases, hepatotoxicity did not persist after switching (16, 17). All cases of cardiotoxicity were associated with QTc prolongation, and complete atrioventricular block developed in 2 patients. We believe it is important that these two patients and the other patients did not experience arrhythmia after the switch. Dermatological toxicity is relatively common with CDK 4/6 inhibitors and accounts for 15% of all reported adverse events (18). It is generally mild to moderate in severity and does not typically constitute dose-limiting toxicity (19). However, in the study, 9 (20.9%) patients did not respond to local and systemic treatment. After switching, skin toxicity subsided. It should be remembered that a switch may also be made in cases of persistent creatinine increased despite dose reduction, grade 3 neutropenia, and grade 3 anemia. After switching, as expected, the most common side effects in patients receiving palbociclib were neutropenia and fatigue (20).

Ribociclib and palbociclib are both metabolized by CYP3A4(21, 22). However, the use of drugs that interact with CYP3A4 may reduce the efficacy of CDK 4/6 inhibitors or decrease their metabolism, increasing the risk of toxicity. However, in our study, only 9 (20.4%) patients used additional medications that caused moderate to major drug interactions. The fact that fifteen (34.1%) patients had no additional diseases and did not use any medications, and twenty (45.5%) patients used medications with minor drug interactions, is important in demonstrating that toxicity is not solely due to DDI. However, it should be noted that the low number of patients using drugs with moderate to severe drug interactions may affect the results.

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This study had several limitations. First, the retrospective and observational nature of the study may have led to data loss and bias. However, to minimize bias, all eligible consecutive patients were included in the study. Therefore, considering the small sample size and limited number of events, there is a risk of a Type II error. We acknowledge the potential instability of the model due to the small number of events. Secondly, the fact that abemaciclib is not reimbursed in our country and palbociclib is less preferred due to the inability to demonstrate OS contribution may prevent the generalization of our results to all CDK 4/6 inhibitors. Thirdly, the use of Drugs.com as the sole DDI assessment tool, while common in clinical practice, has limitations in terms of scientific validity. Finally, in such a small cohort, survival curves can become quite unstable, and longer follow-up periods are needed in larger populations. Despite all this, we believe it is important that our study results show that efficacy continues after treatment change and toxicity does not persist.

In conclusion, when toxicity develops with ribociclib in metastatic HR-positive and HER2-negative breast cancer, if dose reduction or drug interruption is not effective, switching to palbociclib may be considered.

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Materials and methods

Study design and patients

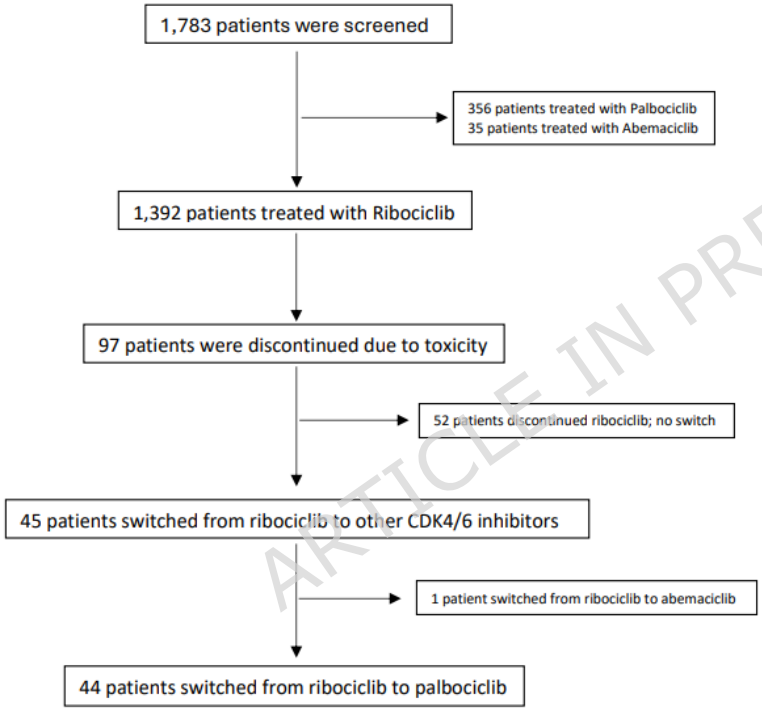
In this retrospective study, HR-positive HER2-negative metastatic breast cancer patients treated with ribociclib between September 2020 and September 2025 were screened. The flow diagram of study population is shown in Figure 5.

The clinical and pathological characteristics of the patients were evaluated. Patients aged 18 years and older with metastatic HR-positive HER2-negative breast cancer and Eastern Cooperative Oncology Group (ECOG) performance status score of 0-2 were included in the study. Patients with a second malignancy that had not undergone curative treatment, or who had cardiac, renal, or hepatic insufficiency that could predispose them to toxicity, were excluded.

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Drug-drug interactions (DDI) causing toxicity with ribociclib were evaluated using the Drugs.com online interaction checker. DDIs are classified into three categories: Major interactions are clinically significant, and these combinations should be avoided if possible due to the higher risk involved. Moderate interactions should not be used without close monitoring. Minor interactions have limited clinical impact; alternative drugs may be considered, preventive measures may be taken, and monitoring protocols may be implemented. This classification prioritizes patient safety and guides clinicians.

Figure 5. Flow diagram of study population



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Statistical analysis and survival

The Kolmogorov–Smirnov test was used to evaluate the normality assumption for continuous variables. Where data did not demonstrate a normal distribution, the Mann–Whitney U test was used to compare groups and the chi-squared test was used for categorical variables. Categorical variables were presented as frequency (n) and percentage (%). A Kaplan–Meier survival curve was used to calculate survival, and the log-rank test was used to compare differences in survival time. All variables

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affecting the prognosis were evaluated using Time-dependent Cox regression analysis. The effects of the variables included in the regression model were expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). All statistical analyses were performed using IBM SPSS Statistics 25.0 (Armonk, New York, USA). Two-sided p-values of less than 0.05 were considered statistically significant.

Discontinuation-Free Survival (DFS)1 was defined as the time from the start of ribociclib treatment to the switch to palbociclib due to toxicity, and DFS2 was defined as the time until progression occurred after palbociclib. For patients without progression, DFS2 was calculated from the switch date. The objective response rate (ORR) was evaluated as the ratio of the total number of complete and partial responses to all responses. ORR was assessed according to RECIST (Response Evaluation Criteria In Solid Tumors) 1.1.

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Author Contribution

We declare that all authors have made significant contributions and that all authors have participated in the content of the article. Study design: AO and MeA, Data collection: AO, İDO, GCU, TKŞ, ST, AAK, EUK, FK, ÖA, Gİİ, SA, BÇ, NÖ, BÖ, FS. Interpretation of results and writing of the article: AO, MZK, MKE, MuA, and MeA.

Conflict of interest

The authors declare that they have no conflict of interest.

Declarations Funding

The authors received no specific funding for this work.

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Data Availability Statement

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

Ethics approval

The principles of the Helsinki Declaration were adhered to during the conduct of this study. Approval for the study was granted by the Ethics Committee of Necmettin Erbakan University on 28 Nov 2025 (No: 2025/6140). Due to the retrospective nature of the study, the Necmettin Erbakan University Ethics Committee waived the need for informed consent (2025/6140).

Informed Consent Statement

The informed consent was waived due to the retrospective nature of the study.

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Trial registration number

Not applicable.

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