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Research Article

Clinicopathological Characteristics of Patients with HR-Positive/HER2-Negative Metastatic Breast Cancer Experiencing Early Progression Within 6 Months of CDK4/6 Inhibitor Therapy

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Abstract

Objectives: To investigate the clinicopathological characteristics of patients with hormone receptor (HR)-positive/human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer who experienced early progression during first-line CDK4/6 inhibitor therapy and to identify factors associated with ultra-early progression.

Methods: This retrospective, single-center study included patients with radiologically confirmed disease progression within 6 months of first-line CDK4/6 inhibitor-based therapy between 2020 and 2025. Patients progressing within 3 months were classified as ultra-early progressors, whereas those progressing between 3 and 6 months served as the reference group. Clinicopathological features, treatment characteristics, and survival outcomes were analyzed. Logistic regression was performed to identify factors associated with ultra-early progression.

Results: Among 418 treated patients, 55 (13.2%) developed early progression; 26 (47.3%) progressed within 3 months and 29 (52.7%) between 3 and 6 months. Liver metastasis was significantly more common in ultra-early progressors (57.7% vs. 31.0%, p=0.047) and showed a trend toward an independent association with ultra-early progression (OR 3.05, 95% CI 0.99–9.44, p=0.053). No significant association was observed between MCV changes or progression timing and overall survival.

Conclusion: Liver metastasis may identify patients at increased risk of ultra-early progression during first-line CDK4/6 inhibitor therapy and may facilitate early risk stratification.

Keywords: CDK4/6 inhibitors, Early progression, Metastatic breast cancer

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Within the spectrum of breast cancer molecular subtypes, the HR-positive/HER2-negative form is overwhelmingly the most frequent, representing 60–70% of diagnoses and the dominant phenotype encountered in the metastatic context.[1] Over the past decade, the therapeutic landscape has shifted markedly with the advent of cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors.[2] Pivotal trials conducted under the PALOMA, MONALEESA, and MONARCH umbrellas demonstrated conclusively that combining Palbociclib, Ribociclib, or Abemaciclib with endocrine agents significantly prolongs both progression-free and overall survival, thereby positioning CDK4/6 inhibitor-based regimens as the established first-line standard for HR-positive/HER2-negative metastatic breast cancer.[3-5]

Despite these gains, a considerable proportion of patients will eventually develop resistance, resulting in disease progression.[6] While many individuals achieve sustained disease control, a subset manifests primary resistance almost from the outset, with progression occurring early in the treatment course. Disease progression within the first 6 months of CDK4/6 inhibitor initiation is widely considered an indicator of poor prognosis and limited endocrine treatment benefit. Evidence from real-world clinical cohorts suggests that early progressors carry a more aggressive tumour phenotype and experience worse survival outcomes than patients achieving prolonged responses.[7-9]

Resistance to CDK4/6 inhibition arises from a complex, incompletely understood interplay of mechanisms. Among the molecular drivers identified are disruption of retinoblastoma protein (Rb) tumour suppressor activity, cyclin E1 amplification, constitutive activation of the PI3K/AKT/mTOR signalling axis, genomic alterations involving the fibroblast growth factor receptor (FGFR), and TP53 loss-of-function mutations.[10] In particular, loss of RB1 function and CCNE1 amplification have been implicated in primary resistance to CDK4/6 inhibition by facilitating cell-cycle progression despite CDK4/6 blockade. Alterations in the PI3K/AKT/mTOR pathway, including PIK3CA mutations, have also been associated with reduced sensitivity to CDK4/6 inhibitor-based therapy and may contribute to early treatment failure.[11,12]

In addition to molecular determinants, tumour-related clinical features play a role in shaping treatment outcomes. Extensive visceral involvement, elevated disease burden, high Ki-67 expression, and reduced functional status have each been reported to diminish the degree of benefit derived from CDK4/6 inhibitor-based therapy.[13-15] The ability to identify patients at heightened risk for early therapeutic failure would therefore allow for more individualised clinical decision-making and improved selection of alternative strategies.

Although CDK4/6 inhibitor efficacy and resistance mechanisms have attracted extensive research attention, studies focused specifically on patients who fail treatment within the opening months of first-line therapy are limited. Accordingly, the clinicopathological profile of this subgroup has not been well-defined in everyday clinical practice. This study was therefore conceived to characterise patients with HR-positive/HER2-negative metastatic breast cancer who progressed within 6 months of CDK4/6 inhibitor therapy and to identify factors potentially implicated in early therapeutic resistance.

Methods

We retrospectively reviewed the medical records of patients with hormone receptor-positive/human epidermal growth factor receptor 2-negative metastatic breast cancer at a single tertiary oncology centre. The study population comprised patients who initiated first-line CDK4/6 inhibitor plus endocrine therapy between 2020 and 2025. Among 418 patients who received such therapy, 55 developed disease progression within the first 6 months and constituted the analytical sample. Clinicopathological data, metastatic disease sites, receptor profiles, treatment-related parameters, haematological indices, and imaging response information were extracted retrospectively for each patient.

In this study, early progression was operationally defined as imaging-confirmed disease progression within 6 months of starting CDK4/6 inhibitor treatment. Participants were stratified by timing into two pre-specified groups: those progressing during the first 3 months (ultra-early progressors) and those progressing during months 3–6 (early progressors). Key baseline clinicopathological characteristics and treatment-related variables were then compared across these two groups.

The principal research objective was to delineate the clinicopathological characteristics of patients whose disease progressed within 6 months of initiating first-line CDK4/6 inhibitor therapy. Exploratory secondary aims included comparing clinical features between ultra-early and early progressors and determining variables associated with ultra-early progression.

Patient data were retrieved through systematic review of institutional electronic records. The following variables were captured for analysis: age, menopausal status, comorbidities, de novo versus relapsed metastatic presentation, histopathological subtype, surgical history, prior neoadjuvant and adjuvant treatments, oestrogen receptor (ER) and progesterone receptor (PR) expression, HER2 status, Ki-67

proliferation index, metastatic sites, CDK4/6 inhibitor type, endocrine backbone agent, treatment-related toxicities, dose adjustments, therapy interruptions, and routine laboratory findings. Imaging assessments performed roughly 3 months after treatment initiation were also reviewed. For MCV analysis, the absolute change in mean corpuscular volume (MCV) from baseline to the 3-month assessment was calculated in femtolitres (fL) and categorised as <10 fL or ≥10 fL. MCV changes were also compared according to the CDK4/6 inhibitor used (palbociclib vs. ribociclib).

Statistical computations were performed with IBM SPSS Statistics for Windows (Version 26.0; IBM Corp., Armonk, NY, USA). Descriptive statistics for continuous data are presented as mean±standard deviation or median with range; categorical data are summarised as frequencies and percentages. The chi-square or Fisher's exact test was used for group comparisons of categorical variables, and the Student's t-test or Mann–Whitney U test was used for continuous variables, selected according to data distribution. To examine predictors of ultra-early progression, univariable logistic regression was first applied, with associations quantified as odds ratios (ORs) and 95% confidence intervals (CIs). Clinically plausible variables and those showing a trend in univariable analyses were advanced to a multivariable model. In view of the modest sample size and limited event count, this model was intentionally kept simple to preclude overfitting. Kaplan–Meier analysis was used to generate survival estimates for overall survival (OS) and post-progression survival (PPS), with the log-rank test used to compare groups. A p-value below 0.05 on two-sided testing was considered statistically significant.

The study was approved by the Ethics Committee of the University of Health Sciences, Prof. Dr. Cemil Taşcıoğlu City Hospital (Approval No: 2026/78; Approval Date: 25 February 2026). All procedures were performed in accordance with the ethical principles of the Declaration of Helsinki. Owing to the retrospective design of the study, the requirement for written informed consent was waived by the Ethics Committee.

Results

A total of 418 patients with HR-positive/HER2-negative metastatic breast cancer were treated with first-line CDK4/6 inhibitor-based therapy at our institution between 2020 and 2025. Of these, 55 (13.2%) progressed within 6 months and were included in the study cohort; 26 (47.3%) had ultra-early progression, and 29 (52.7%) progressed between months 3 and 6. The median duration of follow-up was 27.3 months, and patients had a mean age of 52.8 years. Baseline clinicopathological features of the cohort are displayed in Table 1.

Table 1. Baseline clinicopathological and treatment-related characteristics according to progression timing

Variable	Category	Total, n=55 (%)	≤3 months, n=26 (%)	3–6 months, n=29 (%)	p
Age category, years	<65 years	45 (81.8)	22 (84.6)	23 (79.3)	0.733
	≥65 years	10 (18.2)	4 (15.4)	6 (20.7)	
Comorbidity	No	25 (45.5)	12 (46.2)	13 (44.8)	0.921
	Yes	30 (54.5)	14 (53.8)	16 (55.2)	
Menopausal status	Premenopausal	26 (47.3)	11 (42.3)	15 (51.7)	0.484
	Postmenopausal	29 (52.7)	15 (57.7)	14 (48.3)	
De novo metastatic disease	Yes	14 (25.5)	7 (26.9)	7 (24.1)	0.812
	No	41 (74.5)	19 (73.1)	22 (75.9)	
Histopathology	IDC	49 (89.1)	24 (92.3)	25 (86.2)	0.589
	Non-IDC	6 (10.9)	2 (7.7)	4 (13.8)	
Prior surgery	No	14 (25.5)	8 (30.8)	6 (20.7)	0.392
	Yes	41 (74.5)	18 (69.2)	23 (79.3)	
Neoadjuvant chemotherapy	No	44 (80.0)	21 (80.8)	23 (79.3)	0.893
	Yes	11 (20.0)	5 (19.2)	6 (20.7)	
Adjuvant chemotherapy	No	26 (47.3)	13 (50.0)	13 (44.8)	0.701
	Yes	29 (52.7)	13 (50.0)	16 (55.2)	
Adjuvant endocrine therapy	None	14 (25.5)	7 (26.9)	7 (24.1)	0.512
	Tamoxifen	23 (41.8)	12 (46.2)	11 (37.9)	
	Letrozole	11 (20.0)	3 (11.5)	8 (27.6)	
	Anastrozole	7 (12.7)	4 (15.4)	3 (10.3)	

Table 1. Continue

Variable	Category	Total, n=55 (%)	≤3 months, n=26 (%)	3–6 months, n=29 (%)	p
Adjuvant radiotherapy	No	16 (29.1)	9 (34.6)	7 (24.1)	0.393
	Yes	39 (70.9)	17 (65.4)	22 (75.9)	
Metastatic ER expression	10–49%	6 (10.9)	3 (11.5)	3 (10.3)	0.887
	50–100%	49 (89.1)	23 (88.5)	26 (89.7)	
Metastatic PR expression	0%	18 (32.7)	9 (34.6)	9 (31.0)	0.935
	1–49%	21 (38.2)	10 (38.5)	11 (37.9)	
	50–100%	16 (29.1)	7 (26.9)	9 (31.0)	
Metastatic HER2 IHC status	0	39 (70.9)	20 (76.9)	19 (65.5)	0.720
	1+	13 (23.6)	5 (19.2)	8 (27.6)	
	2+	3 (5.5)	1 (3.8)	2 (6.9)	
Ki-67 category	<20%	11 (20.0)	5 (19.2)	6 (20.7)	0.893
	≥20%	44 (80.0)	21 (80.8)	23 (79.3)	
CDK4/6 inhibitor	Palbociclib	21 (38.2)	10 (38.5)	11 (37.9)	0.968
	Ribociclib	34 (61.8)	16 (61.5)	18 (62.1)	
Endocrine partner	AI	34 (61.8)	16 (61.5)	18 (62.1)	0.968
	Fulvestrant	21 (38.2)	10 (38.5)	11 (37.9)	
Grade 3–4 toxicity	No	45 (81.8)	22 (84.6)	23 (79.3)	0.733
	Yes	10 (18.2)	4 (15.4)	6 (20.7)	
Dose reduction due to toxicity	No	47 (85.5)	22 (84.6)	25 (86.2)	1.000
	Yes	8 (14.5)	4 (15.4)	4 (13.8)	
Bone metastasis	No	12 (21.8)	5 (19.2)	7 (24.1)	0.660
	Yes	43 (78.2)	21 (80.8)	22 (75.9)	
Lung metastasis	No	29 (52.7)	12 (46.2)	17 (58.6)	0.355
	Yes	26 (47.3)	14 (53.8)	12 (41.4)	
Liver metastasis	No	31 (56.4)	11 (42.3)	20 (69.0)	**0.047**
	Yes	24 (43.6)	15 (57.7)	9 (31.0)	
Brain metastasis	No	52 (94.5)	26 (100.0)	26 (89.7)	0.238
	Yes	3 (5.5)	0 (0.0)	3 (10.3)	

IDC: Invasive ductal carcinoma; ER: Estrogen receptor; PR: Progesterone receptor; HER2: Human epidermal growth factor receptor 2; IHC: Immunohistochemistry; AI: Aromatase inhibitor; CDK4/6: Cyclin-dependent kinase 4 and 6.

Among the 55 early progressors, most patients (81.8%) were below 65 years of age, and 52.7% had reached menopause. Invasive ductal carcinoma was the prevailing histological subtype (89.1%), with de novo metastatic disease present in one in four patients (25.5%). ER expression in the high range (50–100%) was observed in 89.1% of cases, and a Ki-67 index of ≥20% was observed in 80.0%. Skeletal involvement was the most commonly detected metastatic site (78.2%), followed by pulmonary (47.3%) and liver (43.6%) metastases. Ribociclib was selected as the CDK4/6 inhibitor in 61.8% of patients; aromatase inhibitors formed the endocrine backbone in an equal proportion.

Baseline clinicopathological profiles were largely homogeneous between the ultra-early (≤3 months) and early (3–6 months) progression groups. The sole characteristic reaching statistical significance was liver metastasis, which was present at a considerably higher rate among ultra-early progressors than in the comparison group (57.7% vs. 31.0%, p=0.047). No significant intergroup differences were detected for patient age, menopausal status, histological subtype, hormone receptor expression, Ki-67 category, choice of CDK4/6 inhibitor, endocrine partner, or other metastatic sites.

Table 2 summarises the logistic regression outputs for ultra-early progression (≤3 months). Univariable anal-

Table 2. Univariate and multivariate logistic regression analyses for ultra-early progression

Variable	Univariate OR (95% CI)	p	Multivariate OR (95% CI)	p
Age category, years				
<65 (Ref)	0.69 (0.17–2.81)	0.612	1.46 (0.33–6.52)	0.623
Menopausal status				
Premenopausal (Ref)	1.46 (0.50–4.24)	0.486	—	—
De novo metastatic disease				
Yes (Ref)	0.86 (0.26–2.91)	0.813	—	—
ER expression				
10-49% (Ref)	0.88 (0.16–4.82)	0.887	—	—
PR expression				
0% (Ref)				
1-49%	0.91 (0.26–3.20)	0.882	—	—
50-100%	0.78 (0.20–3.01)	0.716	—	—
Ki-67 category				
<20% (Ref)	1.10 (0.29–4.13)	0.893	—	—
CDK4/6 inhibitor				
Palbociclib (Ref)	0.98 (0.33–2.91)	0.968	—	—
Bone metastasis				
No (Ref)	1.34 (0.37–4.87)	0.661	—	—
Lung metastasis				
No (Ref)	1.65 (0.57–4.81)	0.356	0.53 (0.17–1.67)	0.277
Liver metastasis				
No (Ref)	3.03 (1.00–9.16)	0.050	3.05 (0.99–9.44)	0.053
MCV increase				
<10 fL (Ref)	1.91 (0.65–5.59)	0.239	—	—

OR: Odds ratio; CI: Confidence interval; Ref: Reference category; ER: Estrogen receptor; PR: Progesterone receptor; CDK4/6: Cyclin-dependent kinase 4 and 6; MCV: Mean corpuscular volume; fL: Femtolitre.

ysis identified liver metastasis as the variable with the strongest predictive signal for ultra-early progression (p=0.050). Age group, menopausal status, de novo presentation, receptor expression status, Ki-67 category, CDK4/6 inhibitor choice, bone metastasis, and lung metastasis each failed to achieve statistical significance. Additionally, MCV variation between the pre-treatment measurement and the 3-month evaluation point was not linked to ultra-early progression (p=0.239). Following multivariable adjustment incorporating age category and lung metastasis, liver metastasis showed a trend toward an independent association with ultra-early progression (OR 3.05, 95% CI 0.99–9.44, p=0.053), although the association did not reach conventional statistical significance.

Kaplan–Meier survival analysis showed no statistically significant difference in OS between ultra-early progressors and those progressing between months 3 and 6 (Fig. 1). Median OS reached 17.4 months (95% CI, 10.01–24.79) in the ultra-early progression group and 12.9 months (95% CI, 9.44–16.36) in the 3–6-month group (log-rank p=0.351).

Although liver metastasis showed a trend toward predicting ultra-early progression in regression models, this association was not mirrored by a significant OS difference within the early-progressor cohort (Fig. 2). Median OS was 17.4 months in those with liver involvement versus 14.0 months in those without (log-rank p=0.818).

At the time of the analysis, 20 patients were alive, while 35 had died. Of the patients who died during the follow-up period, 14 out of 26 in the ultra-early progression group (≤3 months) and 21 out of 29 in the 3–6-month progression group had died. The median overall survival (OS) for the entire cohort was 14.03 months.

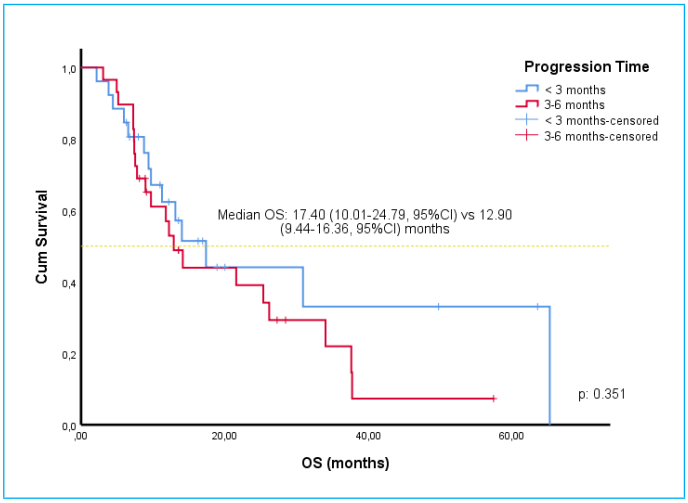

Figure 1. Kaplan–Meier curve of overall survival according to progression time (p=0.351).

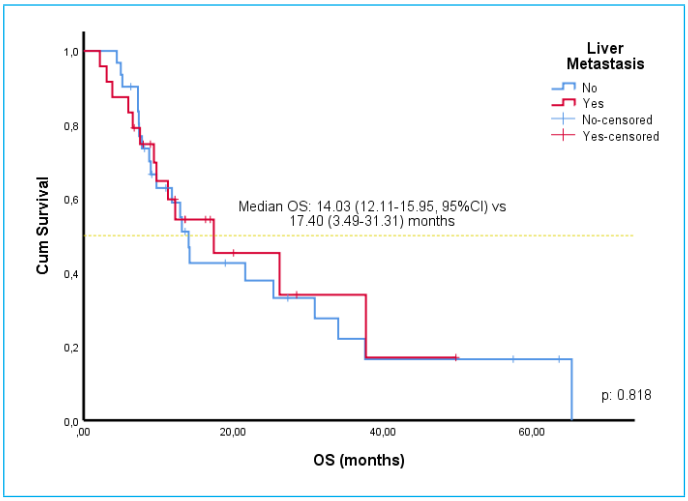

Figure 2. Kaplan–Meier curve of overall survival according to liver metastasis status (p=0.818).

Discussion

The present retrospective investigation examined the clinicopathological characteristics of patients with HR-positive/HER2-negative metastatic breast cancer who failed first-line CDK4/6 inhibitor therapy within 6 months. Early progression occurred in 13.2% (n=55) of the 418 treated patients. The early-progressor population was predominantly characterised by high ER expression, elevated Ki-67, and widespread visceral disease. Liver metastasis was the only variable showing a trend toward an independent association with ultra-early progression (≤3 months), whereas neither overall survival nor MCV dynamics during treatment showed a significant association with progression timing.

Although CDK4/6 inhibitors produce substantial and durable clinical benefit in most patients with HR-positive/HER2-negative metastatic breast cancer, our findings confirm that a clinically relevant minority experiences rapid treatment failure from the outset. This aligns with previously published data documenting early or primary resistance to CDK4/6 inhibitor regimens.[10,16]

The key finding of this analysis was the link between liver metastasis and ultra-early progression. Patients with liver disease were roughly three times as likely to progress within 3 months of CDK4/6 inhibitor initiation. This observation aligns with prior reports associating liver metastasis with more aggressive tumour behaviour, endocrine resistance, and reduced progression-free survival in HR-positive/HER2-negative metastatic breast cancer.[17,18] Our results lend additional credence to the hypothesis that liver involvement may denote a subgroup of patients whose tumours have diminished sensitivity to hormone-based treatments and who are prone to rapid therapeutic failure. It is noteworthy, however, that the association of liver metastasis with ultra-early progression was not accompanied by a significant OS difference in Kaplan–Meier analysis. This discordance may be attributable to the limited cohort size, retrospective design, heterogeneous post-progression treatment regimens, and a low number of survival events.

A median OS of only 14.03 months across the entire cohort underscores the grave prognosis carried by early progression on CDK4/6 inhibitor therapy. By comparison, patients enrolled in the pivotal PALOMA, MONALEESA, and MONARCH randomised trials achieved median OS values that routinely exceeded 50 months.[19,20] The considerably inferior survival seen in our cohort is consistent with the view that early disease progression in this setting reflects a tumour phenotype rooted in intrinsic endocrine resistance, with little sustained benefit from standard hormone-based regimens.

No association was detected between treatment-induced MCV changes and ultra-early progression. Several prior studies have suggested that MCV rises during CDK4/6 inhibitor treatment may reflect on-target drug activity and predict more favourable clinical outcomes.[21,22] However, in the current cohort, the magnitude of MCV shift between pre-treatment baseline and the 3-month assessment did not differentiate ultra-early progressors from those who progressed later. Our results suggest that the magnitude of MCV increase during CDK4/6 inhibitor therapy may not reliably distinguish ultra-early from early progression. When MCV changes were evaluated according to the CDK4/6 inhibitor used, a numerically greater increase was observed with ribociclib than with palbociclib; however, this difference did not reach statistical significance. This lack of association may once again be related to the restricted sample

size, retrospective study design, and the small number of evaluable patients.

The study has certain limitations that must be noted. Being single-centre and retrospective, it is susceptible to selection bias and does not allow adequate adjustment for unmeasured confounders. The small patient sample also constrained statistical power for both subgroup analyses and survival comparisons. In the multivariable logistic regression model, 26 ultra-early progression events were available for three variables, corresponding to approximately 8.7 events per variable. Although the model was intentionally kept parsimonious to minimise the risk of overfitting, the limited number of events warrants cautious interpretation of the regression findings. Moreover, as the study focused on clinicopathological variables, biologically relevant treatment-related parameters could not be examined with the desired depth. Despite these constraints, this work contributes real-world insight into a clinically significant yet insufficiently studied patient population—those experiencing primary failure during CDK4/6 inhibitor therapy.

Taken together, this study delivers real-world evidence on the clinical and pathological profile of HR-positive/HER2-negative metastatic breast cancer patients who fail first-line CDK4/6 inhibitor treatment within 6 months. Baseline high ER expression, elevated Ki-67, and extensive visceral metastatic involvement were the dominant features, suggesting an inherently aggressive tumour phenotype at treatment initiation. Liver metastasis showed a trend toward an independent association with ultra-early progression, suggesting its potential relevance for risk stratification in this patient subset. MCV changes were non-predictive, and no OS gap was identified between the two progression timing groups. Collectively, these results call attention to the importance of pre-treatment risk stratification and the pressing need for innovative therapeutic approaches for patients who fail early.

Conclusion

In this real-world dataset of patients with HR-positive/HER2-negative metastatic breast cancer, about 13% developed disease progression within 6 months of first-line CDK4/6 inhibitor therapy. Among the variables assessed, liver metastasis showed a trend toward an independent association with ultra-early progression, although statistical significance was not reached. These results reinforce the clinical importance of individualised risk assessment at treatment onset and highlight an unmet need for alternative first-line strategies in patients with hepatic disease involvement. Future prospective studies combining molecular profiling, circulating tumour DNA analysis, and evaluation of novel treatment combinations will be necessary to clarify the mechanisms underlying primary resistance and to design optimised management pathways for this therapeutically challenging population.

Abbreviations

AI:	Aromatase inhibitor
CDK4/6:	Cyclin-dependent kinase 4 and 6
CI:	Confidence interval
ER:	Estrogen receptor
fL:	Femtolitre
HER2:	Human epidermal growth factor receptor 2
HR:	Hormone receptor
IDC:	Invasive ductal carcinoma
IHC:	Immunohistochemistry
MCV:	Mean corpuscular volume
OR:	Odds ratio
OS:	Overall survival
PFS:	Progression-free survival
PR:	Progesterone receptor
Ref:	Reference category

Disclosures

Ethics Committee Approval: The study was approved by the Ethics Committee of the University of Health Sciences, Prof. Dr. Cemil Taşcıoğlu City Hospital, İstanbul, Türkiye (Approval No: 2026/78; Approval Date: 25 February 2026).

Informed Consent: Owing to the retrospective design of the study, the requirement for written informed consent was waived by the Ethics Committee.

Conflict of Interest: The authors declare no competing interests.

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