Progression Patterns as Determinants of Post-Progression Survival in Hormone Receptor-Positive/Human Epidermal Growth Factor Receptor 2-Negative Metastatic Breast Cancer Treated with Cyclin-Dependent Kinase 4/6 Inhibitors

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What is already known on this topic?

- *Cyclin-dependent kinase 4/6 (CDK4/6) inhibitors have changed the first-line management of hormone receptor–positive/human epidermal growth factor receptor 2–negative metastatic breast cancer, yet most patients eventually require treatment change because of progression.*
- *Survival after progression varies widely between patients.*
- *Most prognostic assessments in this setting still rely on baseline disease features, although the pattern seen at progression may also be informative.*

What this study adds to this topic?

- *This study evaluates the anatomical pattern of first progression after CDK4/6 inhibitor therapy.*
- *New visceral involvement, particularly new liver metastasis, was associated with shorter post-progression survival.*
- *Progression pattern may be a simple imaging-based marker to consider after CDK4/6 inhibitor failure.*

Abstract

Objective: Cyclin-dependent kinase 4/6 (CDK4/6) inhibitors have improved outcomes in hormone receptor–positive (HR+), human epidermal growth factor receptor 2–negative (HER2−) metastatic breast cancer; however, most patients eventually develop disease progression. The clinical significance of progression patterns in this setting remains poorly defined.

Methods: This retrospective single-center study included patients with HR+/HER2− metastatic breast cancer who developed progression during first-line CDK4/6 inhibitor therapy. Progression patterns were categorized according to newly developed metastatic sites, including visceral, liver-specific, bone-only, and multisite progression. Post-progression survival (PPS) was evaluated using Kaplan–Meier analysis and Cox regression models.

Results: A total of 87 patients were included. At progression, 86.2% developed new metastatic lesions, with new visceral progression observed in 56.3% and new liver metastases in 35.6%. In multivariable analysis, new visceral progression was independently associated with worse PPS (hazard ratio [HR], 2.93; 95% CI, 1.48-5.82; $P = .002$), as was new liver metastasis (HR, 3.41; 95% CI, 1.79-6.50; $P < .001$). Patients with new visceral progression had significantly shorter median PPS compared to those without (8.4 vs. 16.5 months), and similar findings were observed for liver involvement (8.0 vs. 15.8 months). Multisite progression showed a trend toward inferior survival, whereas bone-only progression was not associated with worse outcomes.

Conclusion: In patients with HR+/HER2− metastatic breast cancer, the site of first progression after CDK4/6 inhibitor therapy may help estimate subsequent prognosis. New visceral disease, especially liver involvement, was linked to shorter PPS, whereas bone-only progression followed a less aggressive course. These routinely available imaging findings may add practical value when assessing risk after CDK4/6 inhibitor failure.

Keywords: CDK4/6 inhibitors, liver metastasis, metastatic breast cancer, post-progression survival, progression patterns, visceral metastasis

Introduction

[Hormone receptor–positive (HR+), HER2-negative metastatic breast cancer represents the most common subtype of advanced breast cancer and is characterized by a relatively indolent yet ultimately progressive disease course. Although its clinical course may be slower than that of other subtypes, metastatic disease remains incurable for most patients. The addition of cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors to endocrine therapy has become a major first-line treatment approach in this setting.[1-4] Despite these advances, nearly all patients eventually develop disease progression under CDK4/6 inhibitor therapy. Resistance to CDK4/6 inhibition is biologically heterogeneous and may arise through multiple mechanisms, including alterations in cell cycle

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regulation, activation of bypass signaling pathways, and endocrine resistance.[5-7] Following progression, treatment selection remains challenging, as no universally accepted standard approach exists and clinical outcomes vary considerably across patients.[8] In addition, post-CDK4/6 inhibitor treatment selection is increasingly influenced by molecular alterations such as phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA), estrogen receptor 1 (ESR1), and BRCA1/2 DNA repair-associated genes, which may guide the use of biomarker-directed therapeutic strategies.

This variability suggests that factors beyond baseline tumor characteristics may play a role in determining prognosis after treatment failure.

The site and extent of metastatic involvement have long been recognized as key determinants of survival in metastatic breast cancer. Several studies have demonstrated that patients with visceral metastases, particularly liver involvement, experience significantly worse outcomes compared to those with non-visceral or bone-only disease.[9-11] In addition to baseline disease distribution, increasing evidence indicates that patterns of disease dissemination may also have prognostic significance. Specifically, the emergence of metastases in new organ systems and the presence of multisite involvement have been associated with more aggressive tumor biology and inferior survival outcomes.[12,13]

However, most available data have focused on baseline metastatic characteristics, and the clinical relevance of progression patterns during or after systemic therapy remains insufficiently defined. In the era of CDK4/6 inhibitors, where patients often achieve prolonged disease control before progression, the pattern of disease progression may provide important insights into tumor behavior and subsequent prognosis. In particular, it remains unclear whether the development of new visceral or liver metastases represents merely disease progression or reflects a transition to a more aggressive disease phenotype with distinct prognostic implications.[14,15]

In this context, the present study aimed to evaluate the distribution of progression patterns in patients with HR+/HER2– metastatic breast cancer who developed disease progression under first-line CDK4/6 inhibitor therapy and to investigate the association between these patterns and post-progression survival (PPS).

Methods

Study Design and Patient Population

This study retrospectively screened patients treated at the institution between January 2018 and June 2025. The study population consisted of patients with HR+, HER2– metastatic breast cancer who had received a CDK4/6 inhibitor together with endocrine therapy as first-line treatment for metastatic disease. Patients were included only if disease progression was documented during this treatment. Cases with missing essential clinical information or inadequate follow-up for survival analysis were excluded.

Data Collection

Patient-level data were obtained from institutional electronic records. The collected variables included age, Eastern Cooperative Oncology Group (ECOG) performance status, menopausal status, histological subtype, tumor grade, estrogen receptor and progesterone receptor expression, Ki-67 index, metastatic sites at baseline, the CDK4/6 inhibitor used, and the accompanying endocrine therapy. This study also recorded best treatment response, features of progression, newly involved metastatic sites, survival status, and the first systemic treatment given after CDK4/6 inhibitor discontinuation when this information was available.

Treatment Response and Progression Assessment

Radiological response during CDK4/6 inhibitor therapy was assessed using the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.[16] According to the best response achieved during treatment, patients were grouped as responders if they had complete response, partial response, or stable disease, and as non-responders if progressive disease was recorded. Progression during CDK4/6 inhibitor therapy was primarily defined according to RECIST 1.1, including at least a 20% increase in the sum of target lesion diameters or the detection of new metastatic lesions. When formal RECIST-based reassessment was not available, progression was accepted if there was clear clinical worsening or physician-documented progression that resulted in a change of systemic treatment, consistent with real-world practice.

Definition of Progression Patterns

Progression pattern was determined by reviewing the organs or anatomical sites that were newly involved at the time progression was documented. Any newly detected metastatic lesion was recorded as a new metastasis. New visceral progression was assigned when progression included visceral organs or spaces, such as the liver, lung, peritoneum, pleura, adrenal gland, brain, or malignant effusion. Because liver involvement has a recognized adverse prognostic role in metastatic breast cancer, newly detected hepatic disease was also analyzed as a separate category.[10,17] Bone-only progression was defined as progression restricted to the skeleton without simultaneous visceral involvement. Multisite progression was recorded when 2 or more new organ systems were involved at the same progression assessment.[13]

Outcome Measures

The primary endpoint was PPS. Post-progression survival was calculated from the date of documented progression during CDK4/6 inhibitor therapy until death from any cause. Patients who were alive at the final follow-up were censored on the date of their last known assessment.

Statistical Analysis

Continuous data were described using medians and ranges, while categorical data were summarized as counts and percentages. Categorical comparisons were made with the chi-square test or Fisher's exact test, depending on the distribution of the data. The Mann–Whitney *U*-test was used for comparisons of continuous variables. Post-progression survival was estimated with the Kaplan–Meier method, and differences between survival curves were assessed by the log-rank test. Cox proportional hazards regression analyses were performed to examine the relationship between progression patterns and PPS. Clinically relevant variables were entered into the multivariable models. Effect estimates were presented as hazard ratios (HRs) with 95% CIs. Statistical significance was set at a 2-sided P value of <.05. Analyses were conducted using IBM Statistical Package for the Social Sciences Statistics, version 27.0 (IBM SPSS Corp., Armonk, NY, USA).

Ethics Approval

The study protocol complied with the Declaration of Helsinki and received approval from Clinical Research Ethics Committee of İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine (Approval No.: 2025/503; Document No.:

E-74555795-050.04-1419635; Date: September 17, 2025). Given the retrospective design, informed consent was waived by the ethics committee.

Results

A total of 87 patients who developed disease progression during first-line CDK4/6 inhibitor therapy were included in the analysis. The median follow-up from CDK4/6 initiation was 29.4 months, while the median post-progression follow-up was 11.5 months.

At the time of progression, 75 patients (86.2%) developed at least 1 new metastatic lesion. New visceral progression was observed in 49 patients (56.3%), while new liver metastases were detected in 31 patients (35.6%). Bone-only progression was identified in 16 patients (18.4%), and 34 patients (39.1%) exhibited multisite progression involving 2 or more newly affected organs. The overall distribution of progression patterns is presented in Supplementary Table 1. First post-CDK4/6 inhibitor treatment modalities are summarized in Supplementary Table 2. Chemotherapy was the most frequent subsequent treatment modality, administered to 70 patients (80.5%), while everolimus-based therapy and PI3K/AKT pathway inhibitor-based therapy were used in 5 (5.7%) and 3 (3.4%) patients, respectively.

Table 1. Baseline Characteristics According to New Visceral Progression

Variable	Total (n = 87)	No New Visceral (n = 38)	New Visceral (n = 49)	*P*
Age, years	56 (27-85)	54 (27-77)	56 (32-85)	.283
Age ≥ 65, n (%)	22 (25.3)	8 (21.1)	14 (28.6)	.466
ECOG , n (%)				
0	50 (57.5)	19 (50.0)	31 (63.3)	
≥1	37 (42.5)	19 (50.0)	18 (36.7)	.275
Menopausal status, n (%)				
Premenopausal	26 (29.9)	12 (31.6)	14 (28.6)	
Postmenopausal	61 (70.1)	26 (68.4)	35 (71.4)	.816
Histology, n (%)				
IDC	72 (82.8)	32 (84.2)	40 (81.6)	
ILC	9 (10.3)	3 (7.9)	6 (12.2)	
Other	6 (6.9)	3 (7.9)	3 (6.1)	.787
ER, median (range)	95 (30-100)	90 (30-100)	95 (30-100)	.266
PR, median (range)	30 (0-100)	20 (0-100)	50 (0-100)	.122
Ki-67, median (range)	30 (8-80)	25 (10-70)	30 (8-80)	.904
Ki-67 ≥ 20, n (%)	61 (70.1)	27 (71.1)	34 (69.4)	1.000
Tumor grade, n (%)				
Grades 1 and 2	50 (57.5)	26 (68.4)	24 (49.0)	
Grade 3	37 (42.5)	12 (31.6)	25 (51.0)	.083
De novo metastatic, n (%)	44 (50.6)	18 (47.4)	26 (53.1)	.668
Baseline visceral metastasis, n (%)	46 (52.9)	17 (44.7)	29 (59.2)	.201
Baseline liver metastasis, n (%)	24 (27.6)	9 (23.7)	15 (30.6)	.629
Type of CDK4/6 inhibitor, n (%)				
Palbociclib	24 (27.6)	13 (34.2)	11 (22.4)	
Ribociclib	63 (72.4)	25 (65.8)	38 (77.6)	.238
Endocrine partner, n (%)				
Aromatase inhibitor	65 (74.7)	29 (76.3)	36 (73.5)	
Fulvestrant	22 (25.3)	9 (23.7)	13 (26.5)	.808

CDK4/6, cyclin-dependent kinase 4/6; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; PR, progesterone receptor.

Baseline clinicopathological characteristics according to the presence of new visceral progression are summarized in Table 1. The 2 groups were generally comparable, with no statistically significant differences observed in age, ECOG performance status, menopausal status, histological subtype, hormone receptor expression, Ki-67 index, de novo metastatic presentation, baseline visceral involvement, type of CDK4/6 inhibitor, or endocrine partner. A numerically higher proportion of grade 3 tumors was observed in patients with new visceral progression compared to those without (51.0% vs. 31.6%), although this difference did not reach statistical significance ($P = .083$).

When progression patterns were examined according to survival status (Table 2), new liver metastasis was significantly more frequent among patients who died compared to those alive at last follow-up (48.9% vs. 21.4%, $P = .014$). New visceral progression was also more common in the deceased group (66.7% vs. 45.2%), although this difference did not reach statistical significance ($P = .072$). Other progression patterns, including new lung metastasis, bone-only progression, and multisite progression, were not significantly different between groups.

In univariable Cox regression analysis, new visceral progression was significantly associated with worse PPS (HR, 3.01; 95% CI, 1.57-5.78; $P = .001$). This association remained significant after adjustment for age, ECOG performance status, and baseline visceral metastasis (adjusted HR, 2.93; 95% CI, 1.48-5.82; $P = .002$). Similarly, new liver metastasis was strongly associated with inferior PPS in both univariable (HR, 3.74; 95% CI, 2.02-6.93; $P < .001$) and multivariable analyses adjusted for age, ECOG performance status, and baseline liver metastasis (adjusted HR, 3.41; 95% CI, 1.79-6.50; $P < .001$). The full Cox regression results are summarized in Table 3.

Kaplan–Meier survival analyses confirmed these findings. Patients with new visceral progression had a markedly shorter median PPS compared to those without (8.4 vs. 16.5 months; HR, 3.01; $P = .001$) (Figure 1). Likewise, the development of new liver metastasis was associated with substantially inferior survival (8.0 vs. 15.8 months; HR, 3.74; $P < .001$) (Figure 2). The Cox regression findings are further illustrated in Figure 3.

Multisite progression was associated with shorter PPS compared to single-site progression (7.4 vs. 14.4 months), although this difference did not reach statistical significance (HR, 1.76; $P = .067$). In contrast, bone-only progression was not associated with worse survival outcomes (HR, 0.62; $P = .249$).

Table 2. Distribution of Progression Patterns According to Survival Status

Variable	Alive (n = 42), n (%)	Dead (n = 45), n (%)	*P*
Any new metastasis	35 (83.3)	40 (88.9)	.66
New visceral progression	19 (45.2)	30 (66.7)	.072
New liver metastasis	9 (21.4)	22 (48.9)	.014
New lung metastasis	7 (16.7)	5 (11.1)	.66
Bone-only progression	8 (19.0)	7 (15.6)	.88
Multisite progression (≥2 organs)	13 (31.0)	18 (40.0)	.51

Data are presented as n (%). *P* values were calculated using the chi-square test or Fisher's exact test, as appropriate.

The relationships between different progression patterns are further detailed in Supplementary Tables 3 and 4. Notably, a substantial proportion of patients with new visceral progression also had concomitant liver metastases, and the majority of patients with new liver metastases exhibited multisite disease involvement, suggesting a more aggressive dissemination pattern.

Kaplan–Meier analyses stratified by baseline visceral status are presented in Supplementary Figure 1. Kaplan–Meier curves illustrating PPS according to multisite and bone-only progression patterns are presented in Supplementary Figures 2 and 3, respectively.

Finally, the distribution of progression patterns according to initial response to CDK4/6 inhibitors is shown in Supplementary Table 5.

Discussion

In this retrospective cohort of patients with HR+/HER2– metastatic breast cancer who developed disease progression under first-line CDK4/6 inhibitor therapy, it was observed that progression patterns were not uniformly distributed and were strongly associated with post-progression outcomes. In particular, the development of new visceral and liver metastases, as well as multisite progression, identified a subgroup of patients with markedly poorer survival, whereas bone-only progression was associated with relatively more favorable outcomes.

These findings are clinically relevant in the current therapeutic landscape, where CDK4/6 inhibitors have significantly prolonged disease control but have not eliminated the challenge of treatment resistance. Importantly, accumulating evidence suggests that outcomes following progression are highly heterogeneous and influenced not only by baseline characteristics but also by the biological behavior of the disease at the time of progression. In this context, recent real-world data have demonstrated that patients with aggressive disease features, particularly those with liver involvement and endocrine-resistant profiles, exhibit inferior survival outcomes and may derive differential benefit from subsequent treatment strategies.[18] The present findings align with this concept and further extend it by showing that the pattern of progression itself provides meaningful prognostic stratification.

Several prior studies have demonstrated that metastatic site is a key determinant of survival in advanced breast cancer. Visceral involvement, especially liver metastasis, has consistently been associated with worse outcomes compared to non-visceral disease.[10,19,20] Liver metastases are widely considered a surrogate for biologically aggressive disease, characterized by higher proliferative activity and reduced endocrine sensitivity.[9,21] In this cohort, newly developed liver metastases were strongly associated with inferior PPS, reinforcing the notion that disease biology may shift toward a more aggressive phenotype at the time of progression under CDK4/6 inhibitor therapy.

Beyond organ-specific involvement, the extent of disease dissemination also emerged as a critical factor. Multisite progression, reflecting the involvement of multiple newly affected organ systems, was associated with poorer outcomes and likely represents a higher tumor burden and systemic disease escape. This observation is consistent with previous reports indicating that widespread metastatic dissemination correlates with inferior survival and treatment resistance.[22,23] In contrast, bone-only progression was associated with a relatively more indolent clinical course, in line with prior studies suggesting that skeletal-dominant disease is linked to more favorable outcomes.[20,24]

Taken together, these findings support the concept that disease progression under CDK4/6 inhibition is not a uniform event but rather reflects an evolving biological process. Tumor evolution

Table 3. Cox Regression Analysis for Post-Progression Survival

Variable	Univariable HR (95% CI)	*P*	Multivariable Model 1 (Visceral) HR (95% CI)	*P*	Multivariable Model 2 (Liver) HR (95% CI)	*P*
Age ≥ 65	1.46 (0.83-2.57)	.19	1.77 (0.87-3.61)	.119	1.64 (0.81-3.32)	.176
ECOG ≥ 1	1.52 (0.86-2.70)	.15	1.24 (0.62-2.49)	.539	1.25 (0.63-2.48)	.516
De novo metastatic	1.18 (0.67-2.08)	.56	—	—	—	—
Grade 3	1.41 (0.81-2.45)	.22	—	—	—	—
Baseline visceral metastasis	1.29 (0.74-2.26)	.36	1.29 (0.68-2.45)	.442	—	—
Baseline liver metastasis	1.34 (0.73-2.46)	.34	—	—	1.43 (0.75-2.71)	.274
New visceral progression	3.01 (1.57-5.78)	.001	2.93 (1.48-5.82)	.002	—	—
New liver metastasis	3.74 (2.02-6.93)	<.001	—	—	3.41 (1.79-6.50)	<.001
Bone-only progression	0.62 (0.28-1.40)	.249	—	—	—	—
Multisite progression	1.76 (0.96-3.22)	.067	—	—	—	—

Variables included in multivariable models were selected based on clinical relevance. Model 1 includes age, ECOG performance status, baseline visceral metastasis, and new visceral progression; Model 2 includes age, ECOG performance status, baseline liver metastasis, and new liver metastasis.
ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio.

under therapeutic pressure may lead to the emergence of resistant clones with distinct metastatic patterns and clinical behavior.[25,26] The preferential development of new visceral or liver metastases may therefore indicate a shift toward a more aggressive and treatment-refractory disease state. Post-CDK4/6 inhibitor treatment strategies are increasingly influenced by biomarker status and include options such as PI3K/AKT pathway inhibitors, oral selective estrogen receptor degraders (SERDs), and antibody–drug conjugates, which may also affect PPS in addition to anatomical progression patterns.[27]

From a clinical standpoint, the present results highlight the potential value of progression patterns as a simple and readily applicable tool for post-progression risk stratification. In routine practice, treatment decisions following CDK4/6 inhibitor progression remain heterogeneous, and there is a lack of robust markers to guide therapy selection. Patients exhibiting new visceral or multisite progression may warrant closer monitoring and consideration of more aggressive treatment strategies, whereas those with limited or bone-only progression may be managed with more conservative approaches.

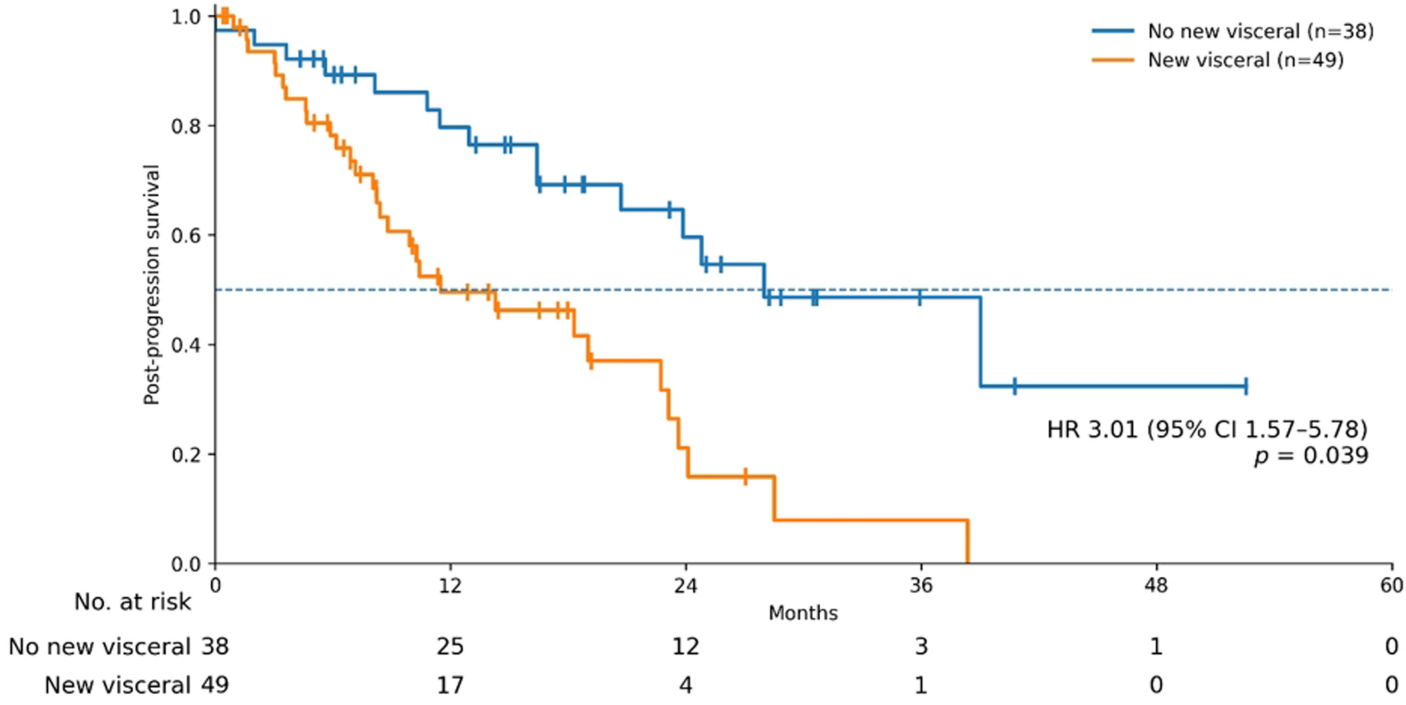

Figure 1. Kaplan–Meier Curve for post-progression survival (PPS) according to new visceral progression. Kaplan–Meier estimates of PPS according to the presence of new visceral progression. *P*-value derived from the log-rank test.

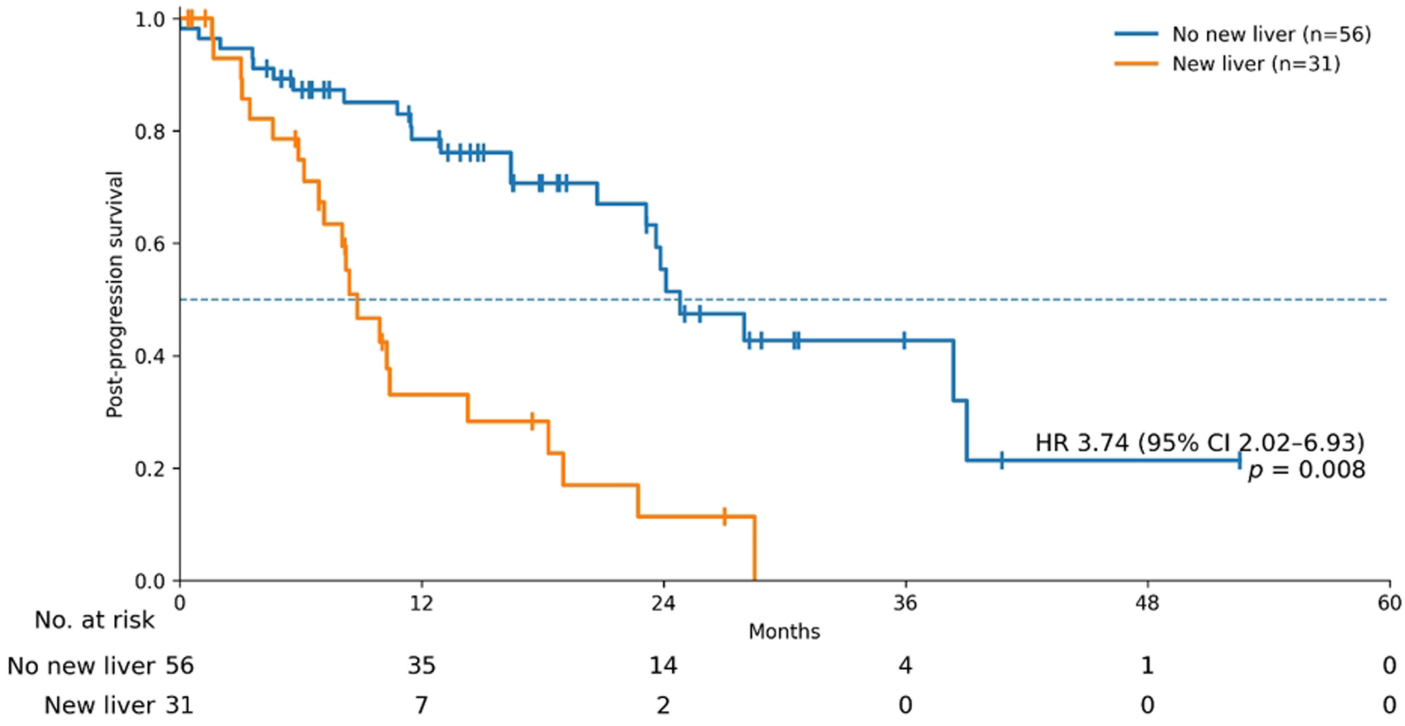

Figure 2. Kaplan–Meier Curve for post-progression survival (PPS) according to new liver metastasis. Kaplan–Meier estimates of PPS according to the presence of new liver metastases. *P*-value derived from the log-rank test.

This study has several limitations. Its retrospective design introduces potential selection bias and limits causal interpretation. The relatively small sample size may have reduced the statistical power of subgroup analyses. Progression assessment was based on routine clinical practice rather than centralized radiological review, which may have introduced variability in the classification of progression patterns. In addition, PIK3CA, ESR1, and BRCA1/2 mutation analyses were not systematically available in

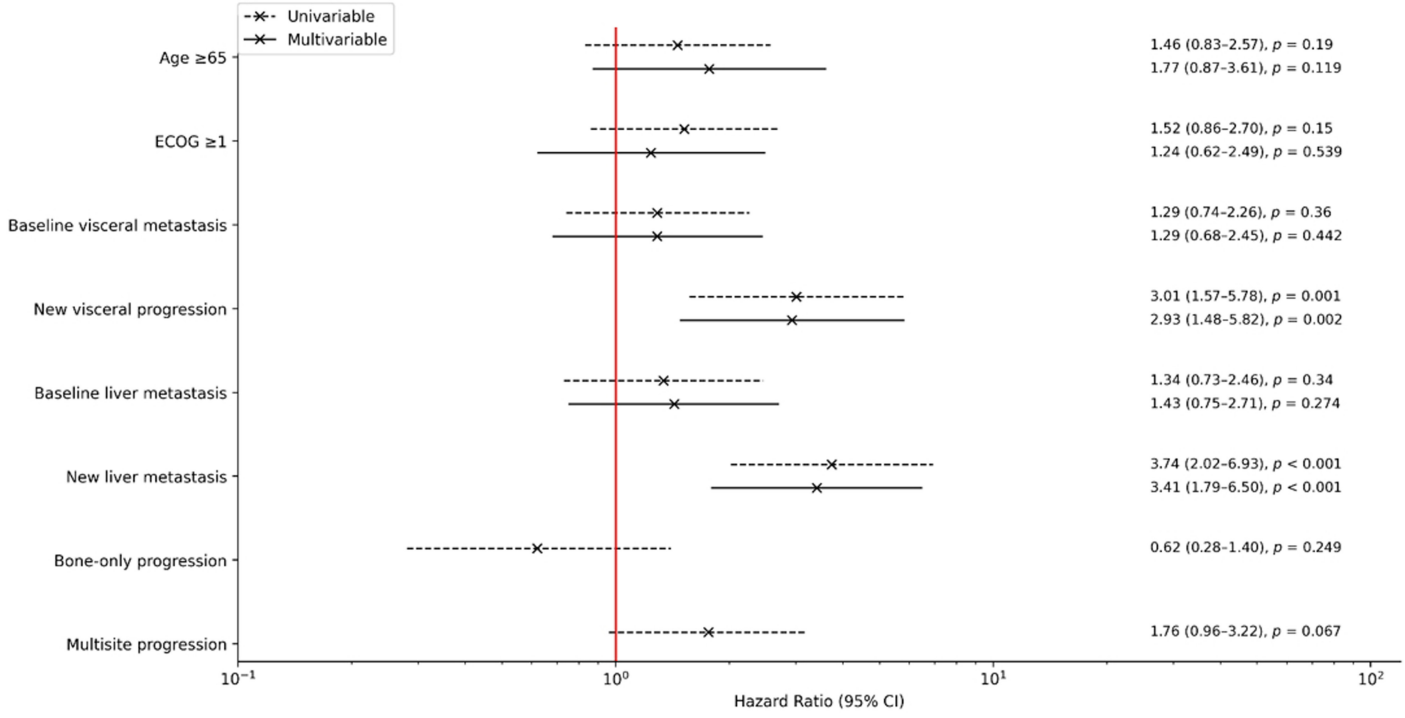

Figure 3. Factors associated with post-progression survival (PPS). Hazard ratios for PPS survival are shown for univariable and multivariable Cox regression analyses. Dashed lines represent univariable estimates and solid lines represent multivariable estimates. Model adjustment includes age, Eastern Cooperative Oncology Group performance status, and baseline metastatic involvement. Horizontal lines indicate 95% CIs, and the vertical line denotes a hazard ratio of 1.

this cohort, limiting the ability to evaluate biomarker-directed post-CDK4/6 inhibitor treatment decisions and their association with PPS.

Post-progression treatments were not standardized and may have influenced survival outcomes. Because post-CDK4/6 inhibitor treatment groups were highly unbalanced and non-randomized, these variables were not incorporated into the primary multivariable Cox models to avoid unstable estimates and treatment-selection bias. In addition, detailed information regarding local therapies after progression, including transarterial radioembolization (TARE) or transarterial chemoembolization (TACE) for newly developed liver lesions and radiotherapy to metastatic sites, was not consistently available; therefore, the potential impact of these interventions on PPS could not be evaluated. Finally, the single-center nature of the study may limit the generalizability of the findings.

In patients with HR+/HER2− metastatic breast cancer progressing under first-line CDK4/6 inhibitor therapy, patterns of disease progression appear to carry meaningful prognostic information beyond baseline characteristics. The emergence of new visceral, particularly liver, metastases identifies a subgroup with markedly worse PPS, whereas bone-only progression is associated with a more favorable clinical course. These findings suggest that progression patterns may serve as a practical and readily accessible tool for post-progression risk stratification in routine clinical practice. Incorporating such dynamic disease features into clinical decision-making may help refine treatment strategies following CDK4/6 inhibitor failure. Prospective studies are warranted to validate these observations and to determine whether progression patterns can guide personalized therapeutic approaches in this setting.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Artificial Intelligence Usage Statement: OpenAI's ChatGPT was used solely for language editing and proofreading during the preparation of the manuscript. It was not used for data analysis, interpretation of results, or generation of scientific content.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of İstanbul University–Cerrahpaşa, Cerrahpaşa Faculty of Medicine (Approval No.: 2025/503; Date: September 17, 2025).

Informed Consent: The requirement for informed consent was waived by the Ethics Committee due to the retrospective design of the study and the use of de-identified data.

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Supplementary Material

This section provides additional analyses and detailed data supporting the main findings of the study. Supplementary tables and figures present the distribution of progression patterns, their overlap, and subgroup analyses of post-progression survival.

Supplementary Table 1. Overall distribution of progression patterns following CDK4/6 inhibitor therapy

Variable	Total (n=87)
Any new metastasis, n (%)	75 (86.2)
New visceral progression, n (%)	49 (56.3)
New liver metastasis, n (%)	31 (35.6)
New lung metastasis, n (%)	12 (13.8)
Bone-only progression, n (%)	15 (17.2)
Multisite progression (≥2 organs), n (%)	31 (35.6)

This table summarizes the distribution of progression patterns observed after CDK4/6 inhibitor treatment. Patients may have experienced multiple sites of progression; therefore, percentages do not sum to 100%. Visceral progression was defined as the development of metastases in organs including liver, lung, adrenal glands, peritoneum, pleura, brain, or effusion.

Supplementary Table 2. First Post-CDK4/6 Inhibitor Treatment Modality

First post-CDK4/6 inhibitor treatment modality	n (%)
Chemotherapy	70 (80.5)
Everolimus-based therapy	5 (5.7)
PI3K/AKT pathway inhibitor-based therapy	3 (3.4)
Best supportive care / no further systemic therapy	3 (3.4)
Unknown / unavailable	6 (6.9)

Data are presented as n (%). CDK4/6, cyclin-dependent kinase 4 and 6.

Supplementary Table 3. Detailed Distribution of Progression Sites and Number of Newly Involved Organs

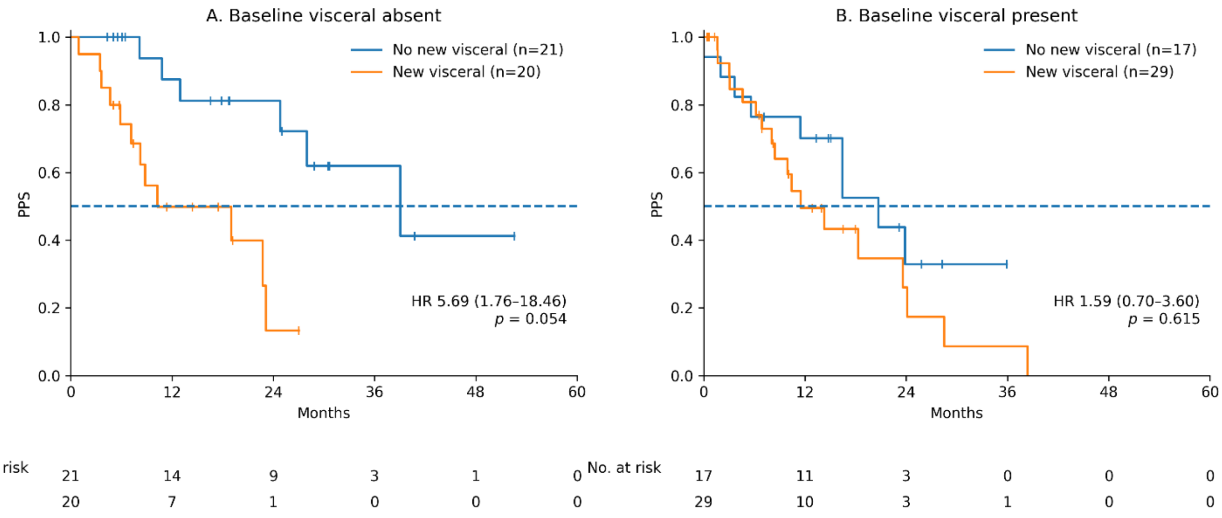
Organ site	n (%)
Bone	41 (47.1)
Liver	31 (35.6)
Non-regional lymph nodes	26 (29.9)
Lung	12 (13.8)
Peritoneum	5 (5.7)
Adrenal gland	3 (3.4)
Effusion	3 (3.4)
Pleura	2 (2.3)
Brain	1 (1.1)
Variable	
Single-organ progression	53 (60.9)
Two-organ progression	22 (25.3)
≥3 organs	12 (13.8)

This table provides a detailed breakdown of newly developed metastatic sites at progression. Patients with multiple metastatic sites were counted in each relevant category. Non-regional lymph nodes refer to distant nodal involvement beyond regional drainage areas. The lower section summarizes the number of newly involved organ systems per patient.

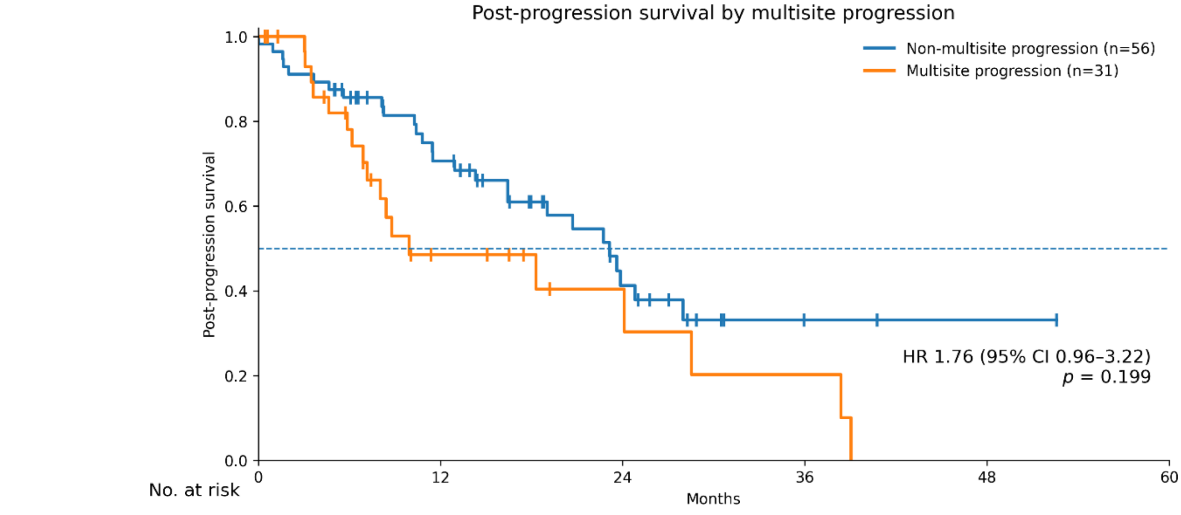
Supplementary Table 4. Overlap Between Progression Patterns at the Time of Disease Progression

Variable	n (%)
New visceral progression (n=49)	
With liver metastasis	31 (63.3)
Without liver metastasis	18 (36.7)
Multisite progression	21 (42.9)
New liver metastasis (n=31)	
Multisite progression	21 (67.7)
Bone-only progression	—
Without visceral involvement	—

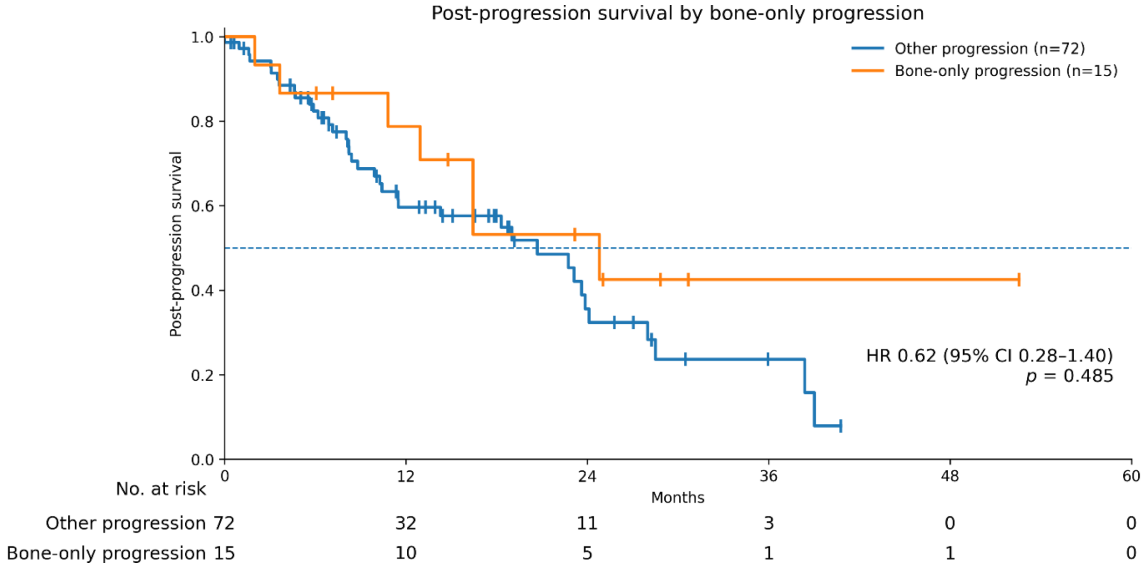
This table illustrates the overlap between different progression patterns at the time of disease progression. A substantial proportion of patients with new visceral progression also developed liver metastases. In addition, the majority of patients with new liver metastases had multisite disease involvement, indicating a more aggressive dissemination pattern.



Supplementary Figure 1. Subgroup analysis of the prognostic impact of new visceral progression according to baseline visceral status. Kaplan–Meier curves for post-progression survival stratified by the presence or absence of newly developed visceral metastases.



Supplementary Figure 2. Post-progression survival according to multisite versus non-multisite progression. Kaplan–Meier curves for post-progression survival stratified by single-site versus multisite progression.



Supplementary Figure 3. Post-progression survival according to bone-only versus non–bone-only progression. Kaplan–Meier curves comparing patients with bone-only progression versus all other progression patterns.

Supplementary Table 5. Distribution of Progression Patterns According to Initial Response to CDK4/6 Inhibitors

Variable	Non-responder (n=25)	Responder (n=62)
New visceral progression	40.0%	62.9%
New liver metastasis	32.0%	37.1%
Multisite progression	36.0%	35.5%

This table presents the distribution of progression patterns according to initial response to CDK4/6 inhibitor therapy. Responders were defined as patients achieving complete response, partial response, or stable disease, whereas non-responders included patients with primary progressive disease.