HER2-low expression is associated with inferior progression-free survival in HR-positive metastatic breast cancer treated with CDK4/6 inhibitors

F. Kemik[1], B. Koylu[1], C. I. Kikili[1], N. Demir[1], B. Guney[2], A. K. Guren[3], E. Karanci[4], D. Tunali[1], S. Lacin[1], D. Tural[1], R. U. Gursu[2], O. Kostek[3], D. Kivrak Salim[4], F. Selcukbiricik[1], **S. Gunduz**[1];

[1] Department of Medical Oncology, Koç University School of Medicine, Istanbul, TURKEY,
[2] Medical Oncology, Istanbul Training and Research Hospital, Istanbul, TURKEY,
[3] Department of Medical Oncology, Marmara University School of Medicine, Istanbul, TURKEY,
[4] Department of Medical Oncology, Antalya Training and Research Hospital, Antalya, TURKEY.

Abstract Control Number: 2025-A-1263

BACKGROUND

- CDK4/6 inhibitors combined with endocrine therapy are the current standard of care for HR-positive/HER2-negative metastatic breast cancer (mBC).
- However, the prognostic role of HER2-low expression (IHC 1+ or 2+/ISH–) under CDK4/6 inhibition remains uncertain.
- Given the emerging biological distinctiveness of HER2-low tumors, we aimed to assess whether HER2 expression level influences progression-free survival (PFS) outcomes under first-line CDK4/6-based therapy in a multicenter real-world setting.

METHODS

Study Design and Setting
A multicenter retrospective cohort study was conducted across four academic oncology centers in Türkiye between January 2018 and April 2025.
The study population included consecutive patients diagnosed with hormone receptor–positive (HR+)/HER2-negative mBC who received first-line endocrine therapy combined with a CDK4/6 inhibitor in routine clinical practice.

Patient Selection
Eligible patients were ≥18 years old, had histologically confirmed HR+/HER2– mBC, and available HER2 immunohistochemistry (IHC) results.
Patients receiving concurrent HER2-targeted therapy, those with incomplete follow-up data, or missing survival outcomes were excluded.

HER2 Classification
HER2 expression was evaluated on primary or metastatic tumor samples using ASCO/CAP guidelines. HER2-negative: IHC 0, HER2-low: IHC 1+ or 2+/ISH–

Endpoints

The primary endpoint was PFS, defined as the time from CDK4/6 inhibitor initiation to radiologic or clinical progression or death from any cause.

Disease progression was assessed approximately every 12 weeks using RECIST v1.1 criteria.

RESULTS

Baseline Characteristics

- A total of 344 patients with HR+/HER2– metastatic breast cancer were included, with a median age of 58 years (range, 27–87).
- Most patients were postmenopausal (70.8%), had ECOG 0–1 (97.7%), and received ribociclib (78.8%) or palbociclib (21.2%) in combination with endocrine therapy. Baseline demographic and clinical characteristics of the patients are summarized in Table 1.
- Overall, 29.7% of patients were classified as HER2-low (IHC 1+ or 2+/ISH–) and 70.3% as HER2-0.
- Patient characteristics were generally well balanced between HER2 subgroups.

Table 1. Baseline Demographic and Clinical Features of the Patients

Variables	Category	n (%)
Age Group	<65 / ≥65	231 (67.2) / 113 (32.8)
Menopausal Status	Premenopausal / Postmenopausal	99 (29.2) / 240 (70.8)
ECOG Performance Status	0 / 1 / ≥2	261 (75.9) / 75 (21.8) / 8 (2.3)
Histological Subtype	IDC / ILC / Other and missing	263 (76.4) / 47 (13.7) / 34 (9.9)
Histologic Grade	Grade 2 / Grade 3/ missing	208 (60.5) / 110 (32) / 26 (7.6)
ER Expression	≥90% / <90%	262 (76.2) / 82 (23.8)
PR Status	Positive / Negative	292 (84.9) / 52 (15.1)
HER2 IHC Score	0 / 1+ / 2+	242 (70.3) / 56 (16.3) / 46 (13.4)
Ki-67 Proliferation Index	<20% / ≥20% / missing	136 (39.5) / 191 (55.5) / 17 (4.9)
Number of Metastatic Sites	1 / ≥2	239 (69.5) / 105 (30.5)
Visceral Metastasis	Yes / No	207 (60.2) / 137 (39.8)
Type of Metastasis	De novo / Recurrent	209 (60.8) / 135 (39.2)
CDK 4/6 Agent	Ribociclib / Palbociclib	271 (78.8) / 73 (21.2)

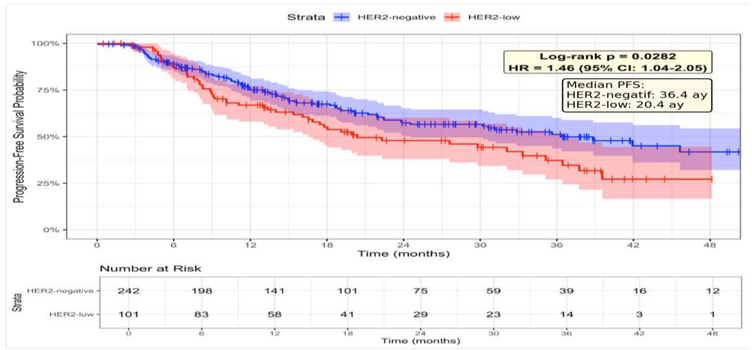
Progression-Free Survival (Primary Endpoint)

- ❖ Median follow-up was 20.0 months (IQR, 11.4–34.4).
- ❖ Median PFS:
  - ✓ HER2-negative: 36.4 months (95% CI, 27.1–45.7)
  - ✓ HER2-low: 20.4 months (95% CI, 8.5–32.2)
  - ✓ Log-rank p = 0.028
- ❖ Risk of progression: HER2-low tumors showed a 75% higher risk of progression (HR 1.75; 95% CI 1.23–2.49; p = 0.002) compared with HER2-negative disease.
- ❖ Progression-free survival according to HER2 expression is illustrated in Figure 1.

Subgroup Analysis (HER2-low stratification)

- ❖ Within the HER2-low group:
  - ✓ IHC 1+: median PFS 22.3 months
  - ✓ IHC 2+/ISH–: median PFS 19.9 months
- ❖ No significant difference was observed between these two subcategories (p = 0.75).

Figure 1. Kaplan–Meier Curves for Progression-Free Survival According to HER2 Expression (HER2-Negative vs HER2-Low)



Multivariable Cox Regression

Independent predictors of PFS:

HER2-low status: HR 1.75 (95% CI, 1.23–2.49), p = 0.002

PR positivity: HR 0.46 (95% CI, 0.31–0.70), p < 0.001

Histologic grade 3: HR 1.68 (95% CI, 1.18–2.39), p = 0.004

≥2 metastatic sites: HR 1.72 (95% CI, 1.14–2.60), p = 0.009

- ❖ Factors associated with progression-free survival in the univariate and multivariable Cox regression analyses are summarized in Table 2.

Table 2. Cox Regression Analysis of Factors Associated with Progression-Free Survival

Variable	Univariate HR (95% CI)	Univariate p-value	Multivariate HR (95% CI)	Multivariate p-value
Age (<65 vs. ≥65)	0.92 (0.65–1.31)	0.650	—	—
ER ≥90%	0.70 (0.48–1.01)	0.056	—	—
PR status	0.44 (0.29–0.65)	<0.001	0.46 (0.31–0.70)	<0.001
HER2 status (low vs. 0)	1.46 (1.04–2.05)	0.029	1.75 (1.23–2.49)	0.002
Grade (2 vs. 3)	1.88 (1.33–2.65)	<0.001	1.68 (1.18–2.39)	0.004
Histological subtype	0.86 (0.66–1.11)	0.247	—	—
Ki-67 (<20% vs. ≥20%)	1.11 (0.79–1.56)	0.546	—	—
Comorbidity (yes vs. no)	0.86 (0.55–1.35)	0.516	—	—
Menopausal status	0.82 (0.57–1.18)	0.283	—	—
Metastasis type (de novo vs recurrent)	1.00 (0.72–1.40)	0.995	—	—
Metastatic site count	1.80 (1.22–2.65)	0.003	1.72 (1.14–2.60)	0.009
Visceral metastasis	1.77 (1.24–2.52)	0.002	—	—

CONCLUSION

- ✓ HER2-low expression was independently associated with shorter progression-free survival in patients with HR+/HER2– metastatic breast cancer treated with first-line endocrine therapy plus CDK4/6 inhibitors.
- ✓ PR positivity was an independent favorable prognostic factor, suggesting the importance of hormone signaling integrity.
- ✓ These findings highlight that HER2-low disease represents a biologically distinct subgroup within HR+/HER2– breast cancer, with potential implications for future therapeutic sequencing.
- ✓ Integrating HER2 and PR status into clinical decision-making may help refine prognostic assessment and identify patients who could benefit from novel HER2-directed strategies after CDK4/6 inhibitor progression.

For further information please contact Seyda Gunduz: segunduz@ku.edu.tr