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The impact of HER2-low status on pathological complete response and disease-free survival in early-stage breast cancer

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Abstract

Background The HER-2 status of breast cancer (BC) has been classified as negative or positive for a long time. Given the efficacy of novel anti-HER2-targeted antibody drug conjugates (ADCs) in HER2-low BC, a distinct subgroup of HER2-low tumors has emerged within BC. The biology and prognostic impact of HER2-low expression are not yet well defined, and inconsistent results were reported. This study aims to evaluate the impact of low HER-2 status on the response to neoadjuvant chemotherapy (NACT) and disease- free survival (DFS) rates.

Methods We retrospectively analyzed BC patients treated with NACT from 2017 to 2023 in two cancer centers. HER2-negative patients were included. HER-2 low status was defined by IHC + 1 or + 2/ISH non-amplified, and HER2-zero was defined by IHC 0. Pathological complete response (pCR) rates and DFS between HER2-low and HER2-zero populations were compared.

Results 170 patients were identified. 122 (72%) of these patients were HER2- zero BC, whereas 48 (28%) were HER2-low BC. Overall, pCR was achieved in 35 (20.5%) patients. Of these, pCR was observed in 30 patients (44.6%) from the HER2- zero group, compared to 5 patients (10.4%) from the HER2-low group ($p = 0.046$), but significance was lost in multivariate analysis. Among the hormone receptor (HR) positive subtype, pCR was achieved 19.8% of HER2-zero tumors and 7.5% of HER2-low tumors ($p = 0.08$). For HR-negative subtype 34.1% HER2-zero tumors had pCR and 25% of the HER2-low tumors had pCR ($p = 0.614$). There was no association between DFS and HER2-low status.

Conclusions Our study indicates that HER2-low status had no impact on pCR or DFS.

Keywords Breast cancer, HER2-low expression, Pathological complete response

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Introduction

Breast cancer (BC) is a heterogeneous disease with different molecular subtypes and biological characteristics. HER2-positive BC, which is one of these subtypes, is observed in 20–25% of BC patients and is associated with a poor prognosis [1]. Since the introduction of anti-HER-2 treatments, the course of HER2-positive breast cancer has changed both in the early and metastatic stages [2, 3].Within the HER2-negative subtype, HER2-low BC which is characterized by immunohistochemistry (IHC)+1 or +2 and lack of in situ hybridization (ISH) amplification is a new entity [4]. In a study, low HER2 expression was detected in 60% of HER2-negative tumors [5]. However, HER2- low BC does not benefit from traditional anti-HER2 treatments such as trastuzumab and pertuzumab [6, 7].

Trastuzumab deruxtecan (T-DXd) and trastuzumab duocarmazine, two novel anti-HER2 targeted antibody drug conjugates (ADCs), have recently demonstrated favorable outcomes in clinical trials involving advanced HER2-low BC patients [8, 9]. Since these studies demonstrated that HER2-low status could be predictive, interest in this subtype has increased progressively. There are currently inconsistent results regarding the clinical and pathological characteristics of HER2-low BC, as well as its effects on prognosis [10–12]. In addition, the efficacy of novel ADCs in treating advanced BC has generated interest in their potential as neoadjuvant or adjuvant treatments for early BC. Hence, for the development of novel therapeutic strategies, it is critical to clarify the biological characteristics of the HER2-low subtype, including its potential differential response to conventional chemotherapy and its impact on survival rates.

In this multicenter study, we aimed to compare the clinicopathological features of HER2- zero and HER2-low subtypes, investigate the pathological complete response (pCR) rates after neoadjuvant chemotherapy (NACT), and determine the disease-free survival (DFS) of these two groups.

Materials and methods

Patients

We retrospectively analyzed BC patients treated with NACT from 2017 to 2023 in two cancer centers. The inclusion criteria for this study comprised the following: female gender, age≥18, diagnosis of invasive BC cancer, and completion of a curative surgery subsequent to NACT.

HER2-positive tumors, patients without adequate data, and bilateral BC patients were excluded. Age, menopausal status, histological subtype and grade, hormone receptor (HR) and HER2 status, Ki67 expression, T stage, N stage, NACT regimen, type of surgery, pathological results after surgery, and disease recurrence were obtained from medical records.

The evaluation of HER2 and HR status was performed on pre-treatment biopsy specimens by independently by each center's own pathologist. Tumors with estrogen (ER) and/or progesterone receptor (PR) levels≥1% were considered HR positive, while tumors with ER<1% and PR<1% were defined as triple negative breast cancer (TNBC). HER2 status was assessed in accordance with American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines [13]. HER-2 low status was defined by IHC+1 or +2/ISH non-amplified, and HER2-zero was defined by IHC 0. The study's primary objective was to compare the pCR rates between the HER2-zero and HER2-low patient groups. pCR was defined as ypT0/N0 or Tis/N0 based on the postoperative pathology. In addition, the study also evaluated the DFS between these two groups.

The study was approved by the Ethics Committee of Istanbul University-Cerrahpasa (date: September 19,2023, number: 786180) and this study was performed in line with the principles of the Declaration of Helsinki. The need for informed consent was waived because of the retrospective nature of this study.

Statistical analysis

Fisher's exact test and Chi-square test were utilized to compare categorical variables among patients with HER2-zero and HER-2 low. Using the Mann-Whitney U test, continuous variables were compared between the two groups. Follow-up period was calculated using the inverse Kaplan-Meier method. The survival endpoint was DFS, defined as the time from surgery to local or distant invasive BC relapse or death from any cause. No-event patients were censored at the end of the last follow-up. The Kaplan-Meier method was used to estimate the DFS and compared with the log-rank test. Using a binary logistic regression model, univariable and multivariable analyses of clinicopathological factors associated with pCR were performed. Odds ratios (ORs) and 95% confidence intervals (CIs) were given. Statistical tests were two-sided, and a p-value less than 0.05 was considered statistically significant. The statistical analyses were conducted using SPSS version 23.

Results

Characteristics of patients

Overall, 170 patients were evaluated. Median follow-up was 23.0 months (95 CI 19.8–26.2). 121 (71%) patients had HR positive subtype and 49 (29%) patients had TNBC. 122 (72%) of all patients had HER2- zero BC, whereas 48 (28%) had HER2-low BC. The baseline characteristics of the patients are described in Table 1. Median age was 50.5 (range 24–83). There was no

Table 1 Baseline characteristics of patients according to HER2-expression

	HER2-zero	HER2-low	*P* -value
	(*n* = 122) No. (%)	(*n* = 48) No. (%)	
Age			
Range	24–83	31–72	
Median	50	52	0.841
Histological type			
Invasive ductal carcinoma	99 (81.1)	44 (91.7)	
Invasive lobular carcinoma	7 (5.7)	1 (2.1)	
Others	16 (13.1)	3 (6.3)	0.237
Hormone receptor status			
Positive	81 (66.4)	40 (83.3)	
Negative	41 (33.6)	8 (16.7)	**0.028**
Menopausal status			
Premenopausal	54 (44.3)	20 (41.7)	
Perimenopausal	6 (4.9)	4 (8.3)	
Postmenopausal	62 (50.8)	24 (50)	0.690
Histologic grade			
Grade 1–2	67 (54.9)	32 (66.7)	
Grade 3	55 (45.1)	16 (33.3)	0.162
T stage			
cT1	19 (15.6)	4 (8.3)	
cT2	69 (56.6)	31(64.6)	
cT3	9 (7.4)	3 (6.3)	
cT4	25 (20.5)	10 (20.8)	0.620
N stage			
cN0	5 (4.1)	3 (6.3)	
cN1	67 (54.9)	22 (45.8)	
cN2	35 (28.7)	12 (25)	
cN3	15 (12.3)	11(22.9)	0.309
Ki-67 expression			
≤ 15.0%	31(25.4)	17 (35.4)	
15.1–35.0%	43 (35.2)	18 (37.5)	
> 35.0	48 (39.3)	13 (27.1)	0.257
Neoadjuvant chemotherapy regimen			
AC based	90 (73.8)	36 (75)	
AC-T	59 (48.4)	33 (69)	
ddAC-T	20 (16.4)	1 (2)	
ddAC-TK	3 (2.4)	1 (2)	
AC-TK	6 (5)	1 (2)	
AC-TK-P	2 (1.6)	-	
Non-AC based	32 (26.2)	12 (25)	
FEC	4 (3.3)	1 (2)	
FEC-T	25 (20.5)	10 (21)	
EC-T	-	1(2)	
Paclitaxel	2 (1.6)	-	
TK	1 (0.8)	-	0.869
Surgery			
BCS + SLNB	18 (14.8)	3 (6.3)	
BCS + ALND	19 (15.6)	7 (14.6)	
Mastectomy + SLNB	17 (13.9)	3 (6.3)	
Mastectomy + ALND	68 (55.7)	35 (72.9)	0.142

Abbreviations TNBC, triple negative breast cancer; ER, oestrogen receptor; pCR, pathological complete response; AC, adriamycin plus cyclophosphamide; T, taxane; dd, dose dense; FEC, 5-fluorouracil, epirubicin, cyclophosphamide; TK, paclitaxel and carboplatine; P, pembrolizumab. Bold factors reflect statistical significance; p<0.05.

difference in the median age of the two groups (50 versus 52, $p=0.841$). The predominant histological subtype in both groups was invasive ductal carcinoma. Patients were most commonly postmenopausal in both groups.

The only statistically significant difference between the two groups was HR positivity. HR positivity was significantly higher in the HER2-low group ($p=0.028$). In the HER2-zero group, the median ER (%) level was 87.5 (IQR 0–95), whereas in the HER2-low subtype, it was 90 (IQR 90–95) ($p=0.005$). Additionally, there was also statistically significant differentiation between the median ER (%) levels of the HER2-low and HER2-zero groups in the HR-positive subgroup. The median ER (%) level in the HR-positive/HER2-low group was 92.5 (IQR 90-97.2), while it was 90 (IQR 82.5–95) in the HR-positive/HER2-zero groups ($p=0.048$). There was no statistically significant difference observed between the groups in terms of histologic type and grade, Ki67 index, clinical T stage, and clinical N stage.

Adriamycin plus cyclophosphamide (AC) based regimen was the mostly preferred regimen in both groups. In TNBC, dose-dense (dd) regimens were used more frequently, and carboplatin and pembrolizumab were used as neoadjuvant therapy. Mastectomy plus axillary dissection was performed in 55.7% of the HER2- zero patients and in 72.9% of the HER2- low patients ($p=0.142$).

Efficacy and survival outcomes

Overall, pCR was achieved in 35 (20.5%) patients. Among HER2-zero patients 30 (24.6%) had pCR while 5 (10.4%) patients had pCR in the HER2-low group ($p=0.046$) (Fig. 1). In univariate analysis factors could be associated with pCR including age, menopausal status, T stage, N stage, grade, Ki67 index, HR status and HER2 -low status were tested. In addition to HER2-zero status, higher grade, Ki67 index>35, and HR negativity were found to be significantly associated with pCR. The association between HER2 status and pCR was no longer seen in multivariate analysis (OR 2.17 (95 CI 0.73–6.42); $p=0.161$). Additionally, HR status and higher-grade lost significance in multivariance analysis. The only variable that remained significant in relation to pCR was Ki67

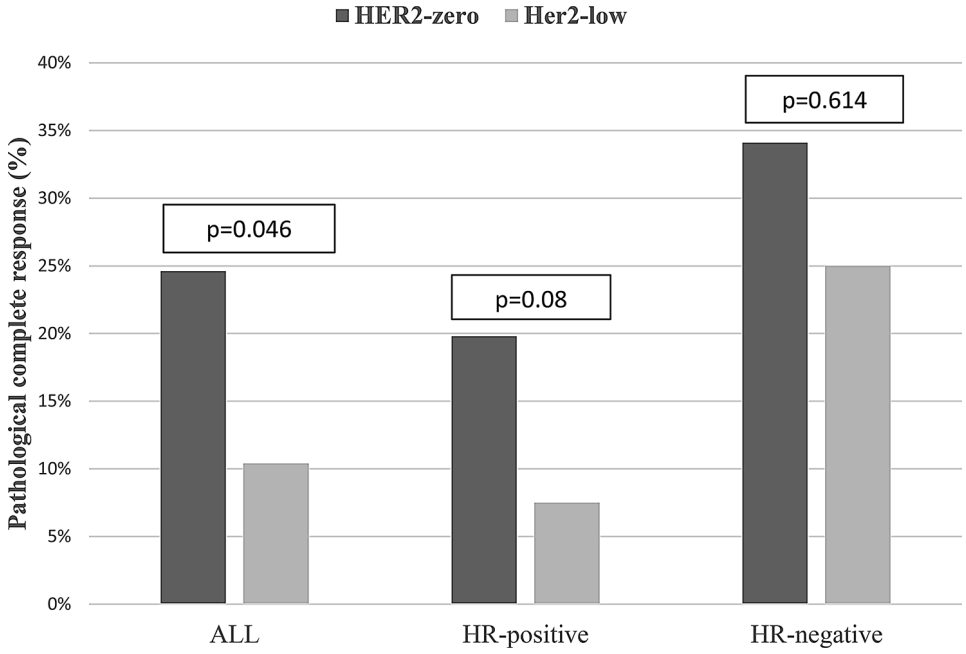

Fig. 1 Pathological complete response rates for all, HR-positive and HR-negative patients

index > 35 in multivariate analysis (OR 8.47 (95 CI 1.63–43.89); $p=0.011$) (Table 2).

Bold factors reflect statistical significance; p<0.05.

Of the 121 h positive tumors, 81 (67%) were in the HER2-zero subtype and 40 (33%) were in the HER2- low subtype. pCR was observed in 16 (19.7%) patients of the HR positive/HER2-zero subtype and 3 (7.5%) patients of the HR positive/HER2-low subtype ($p=0.08$). Of the 49 TNBC patients 41(84%) had HER2-zero subtype while 8 (16%) of had HER2-low subtype. pCR was observed in 14 (34.1%) patients of the TNBC/HER2-zero subtype and 2 (25%) patients of the TNBC/HER2-low subtype ($p=0.614$). (Fig. 1).

Due to the absence of follow-up data for six patients' post-surgery, these individuals were excluded from the DFS analysis. Patients with HER2-zero tumors had a 2-year DFS of 91.5%, compared to 84.8% with HER2-low tumors ($p=0.218$). There was no significant difference in 2-year DFS between HER2-zero and HER2-low subtypes among HR-positive patients (93.6% vs. 87.2% respectively, $p=0.312$). Additionally, among TNBC groups, there was also no statistically significant difference in DFS. Patients with TNBC/HER2-zero had a 2-year DFS of 87.5%, compared to 71.4% for patients with TNBC/HER2-low ($p=0.144$). (Fig. 2).

Discussion

According to the latest ASCO/CAP guidelines, HER2 status has long been classified as binary; HER2-negative or HER2-positive [13]. The DESTINY-Breast 04, a phase 3 clinical trial that introduced T-DXd, a novel anti-HER2 target drug that significantly improved the survival for metastatic HER2-low-positive BC, shifted the paradigm regarding this issue [8]. Based on this finding, there has been a growing interest in the biological and genetic characteristics as well as the prognosis of HER2-low BC. However, researches on this topic have resulted in inconsistent results [14]. In this retrospective dual-center trial, we aimed to investigate the clinicopathological features, NACT responses, and prognosis of the HER2-low BC subtype. Concordant with recent researches, we found that HR positivity was associated with HER2-low status [5, 10, 15, 16]. This was verified by PAM50 analyses: while HER2-low tumors were frequently of the luminal type, HER2-zero tumors were of the basal-like intrinsic subtype [5]. We found no significant differences in baseline clinical and pathological characteristics between HER2-zero and HER2- low tumor types, with the exception of HR positivity. However, several studies comparing the clinicopathological characteristics of HER2-low and HER2-zero tumors resulted in contradictory findings. A research conducted by the Korean Breast Cancer Society comprising 30,491 patients revealed that HER2-low BC was correlated with fewer T4 tumors, higher histological grade and negative lymphatic invasion [11] while another study by Schettini et al., showed that HER2-low tumors had larger primary tumor size and more frequent nodal involvement [5]

In our study, although pCR rates in the HER2-low group were lower than those in the HER2-zero group, this difference was lost in multivariate analysis. In both HR-positive and TNBC patients, there were no significant

Table 2 Associations between clinicopathological factors and pCR in univariate and multivariate analyses

	Univariable analysis		Multivariable analysis	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
Age				
<40	Ref			
≥40	1.67 (0.54–5.19)	0.371		
Menopausal status				
Premenopausal	Ref			
Perimenopausal	1.20 (0.55–2.62)	0.635		
Postmenopausal	1.87 (0.43–8.05)	0.398		
cT				
1	Ref			
2	0.70 (0.24–2.02)	0.520		
3	1.41 (0.31–6.47)	0.653		
4	0.47 (0.12–1.78)	0.268		
cN				
0	Ref			
1	0.87 (0.16–4.64)	0.870		
2	0.52 (0.08–3.14)	0.481		
3	0.90 (0.14–5.67)	0.911		
Grade				
1 or 2	Ref			
3	2.97 (1.37–6.41)	**0.006**	1.12 (0.35–3.53)	0.840
Ki-67 (%)				
≤15	Ref			
15.1–35	2.94 (0.76–11.3)	0.118	2.41 (0.58–10.09)	0.225
>35	8.46 (2.35–30.44)	**0.001**	8.47 (1.63–43.89)	**0.011**
Subtype				
HR-positive	Ref			
HR-negative	2.60 (1.20–5.63)	**0.015**	0.85 (0.28–2.56)	0.786
HER2 status				
HER2-low	Ref			
HER2-zero	2.80 (1.01–7.72)	**0.046**	2.17 (0.73–6.42)	0.161

differences between HER2-zero and HER2-low pCR rates. Similar to our findings, in the study conducted by Nonneville et al., although pCR rates were lower in HER2-low tumors in univariate analysis, this relationship was not detected in multivariate analysis [15]. In the pooled analysis of four prospective neoadjuvant clinical studies conducted by Denkert et al., although the pCR rate in HER2-low tumors was significantly lower than HER2-zero tumors, this significance was lost in the multivariate analysis [12]. However, in the previous research, in contrast to ours, univariate analysis revealed that the pCR rate was also higher in HR-positive/HER2-zero tumors than HR-positive/HER2-low tumors. But, in that study, HER2-zero tumors had higher grade and higher Ki67 scores and lower HR-positivity than HER2-low tumors. Since there were more HER-2-low subset in HR positive tumors, less aggressive tumor characteristics in the HR-positive/ HER2-low group may have led to this result. With the exception of HR positivity, our study did not identify any clinicopathological distinctions between HER2-low and HER2-zero tumors; therefore, it was expected that there were no statistically significant differences in pCR rates among the HR positive/HER2-zero and HR-positive/HER2 low groups. The study conducted by Kang et al. also revealed similar results to our own. Although HER2- zero BC showed a higher pCR rate, no relationship was found between pCR and HER2-status in multivariate analysis. There was also no relationship with pCR and HER2 status in the HR-positive and negative groups [17]

In our study, there was no significant association between the HER2 status and the 2-year DFS in all patients, as well as in the subgroups of patients with HR-positive or TNBC. Multiple studies have assessed the impact of HER2-low status on survival in early-stage BC, but conflicting results have been observed. In the study of Kang et al., HER2-low BC patients had higher 5-year overall survival (OS) and DFS; however, no differences were observed in the HR-positive subgroup in both OS and DFS. In HR-negative patients, while there was no difference in OS, DFS was significantly improved in HER2-low tumors. However, in this study, the relationship

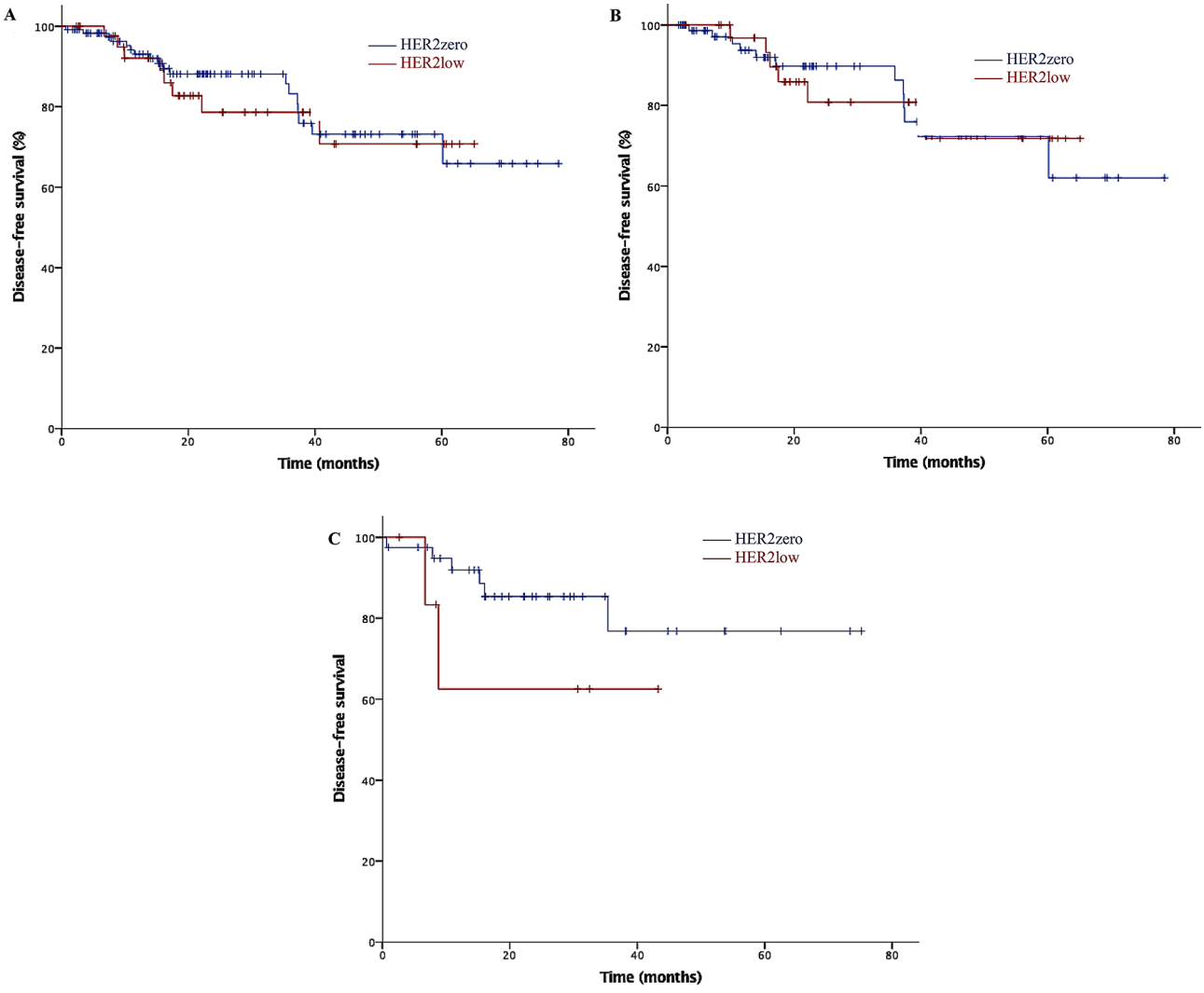

Fig. 2 Kaplan-Meier survival curves for DFS in all, HR-positive and HR-negative patients

between DFS and HER2-low status lost significance in multivariate analysis [17]. In Denker et al.'s study, it was found that HER2-low-positive tumors had significantly longer 3-year OS and DFS; these differences were also observed in the HR-negative group. However, the impact of HER2 status on OS and DFS was not observed in the HR-positive group [12]. In several trials, including our own, no effect of HER2-low status on OS or DFS was observed [10, 15, 16, 18–20]

Because of the cross-talk between HR signaling and HER2 signaling, it is unclear whether the HER2-low subtype is characterized by a distinct biological mechanism or simply the features associated with HR positivity. In our study, the median ER (%) level was statistically higher in HER2-low tumors than HER2-zero tumors even in HR-positive subtypes, which supports this. HR positivity appears to be the defining characteristic of HER2-low tumors, according to genomic analysis [5]. In genetic sequencing performed in patients with metastatic breast cancer, when adjusting for the confounding factor ER expression, no difference in gene mutation, copy number variations of oncogenic genes, or tumor mutational burden was detected between HER2-zero and HER2-low tumors, except for the ERBB2 copy count, which was higher in HER2-low tumors [21]. These results were consistent with those of other genomic landscape studies; they indicated that HER2-low BC did not appear to be a distinct subtype of the disease and that it shared genomic characteristics with its more classically defined subset of HR-positive or HR-negative disease [22, 23]. The findings in our study that a HER2-low status was correlated with HR-positivity but unrelated to pCR rates or DFS is consistent with these molecular findings as well. The comparable molecular and clinical properties of both groups raise the question of whether T-DXd is effective in the HER2-zero group also. The final results of the DESTINY-Breast 06 (NCT04494425) phase 3 study, which assessed the T-DXd response in the HER2-low and HER2-ultralow

(i.e. score 0 with incomplete and faint staining in ≤10% of tumor cells) [24] groups, will provide an answer to this issue

The rate of HER2-2low breast cancer varies between studies, ranging from 31.2% [11] to 64.4% [25]. In our study the rate of HER2-low was 28%, which was quite low compared to other studies. The discrepancy among pathologists, particularly regarding the definitions of HER2-zero and HER2+1 tumors, is a significant factor in this fact. In the study conducted by Lambein et al., it was shown that 76% of tumors defined as HER2-0 by the local pathologist were reclassified as HER2 1+in the central laboratory [26]. The research conducted by Fernandez et al. revealed that among breast cancer specimens assessed by 18 experienced pathologists, the concordance between HER2-0 and HER2+1 was an only 26%, whereas the concordance between HER2+2 and HER2+3 was 58% [27]. In the phase 2 DAISY trial, it has been observed that T-Dxd had a moderate antitumor effect in HER2-zero patients. Therefore, it has been suggested that HER2-zero tumors consist of a heterogeneous group that also contains tumors with some level of HER2 expression and that a subset of these patients is sensitive to T-DXd [28]. Considering both the variability among pathologists and the fact that those with some level of HER2 expression among HER2-zero patients may respond to T-Dxd, IHC does not seem to be an optimal method for HER2 expression definition. As these results indicate, the definition of HER2 expression requires the development of more precise and sensitive diagnostic methods

Our study has several limitations, including its retrospective nature, relatively small sample size and the short follow-up time for an optimal evaluation of survival outcomes. Another limitation of our study is that the differences in pathologist evaluations in both institutions and the lack of a central pathological examination may have affected our HER2-low rate and results. Despite these limitations, the fact that the patients included in our study were diagnosed in the last 6 years and that the techniques and guidelines for HER2-testing did not change much during this period were an advantage for our study

In conclusion, according to our findings, HER2-low BC did not have a different biology, different NACT responses, or prognosis. However, it is obvious that there is a need for consensual evaluation methods that will reduce the discrepancy rate in the pathological assessment of HER2-low status. In addition, further prospective studies are needed on how to incorporate new HER2-targeted ADCs into neoadjuvant therapy in HER2-low BC

Abbreviations

BC	Breast cancer
ADCs	Antibody drug conjugates
NACT	Neoadjuvant chemotherapy
DFS	Disease- free survival
pCR	Pathological complete response
IHC	Immunohistochemistry
T-DXd	Trastuzumab deruxtecan
TNBC	Triple negative breast cancer
ASCO/CAP	American Society of Clinical Oncology/College of American Pathologists
ORs	Odds ratios
CIs	Confidence intervals
AC	Adriamycin plus cyclophosphamide
dd	Dose dense

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Author contributions
GAŞ: Conceptualization, data curation, writing-original draft preparation. NŞÖ, EA: Visualization, investigation. ED Writing, data curation. GAŞ, MG: Methodology, software. ZHT, NSD: Supervision, editing. FHD: Reviewing and editing.

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Data availability
The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical approval
This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of İstanbul University Cerrahpaşa (date: September 19, 2023, number: 786180). The need for informed consent was waived because of the retrospective nature of this study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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