Breast Cancer Research and Treatment
https://doi.org/10.1007/s10549-023-07171-z

EPIDEMIOLOGY

Impact of HER2-low status for patients with early-stage breast cancer and non-pCR after neoadjuvant chemotherapy: a National Cancer Database Analysis

Huiyue Li[1] · Jennifer K. Plichta[2,3,4] · Kan Li[5] · Yizi Jin[6,7] · Samantha M. Thomas[1,2] · Fei Ma[8] · Li Tang[9] · Qingyi Wei[2,3,10] · You-Wen He[11] · Qichen Chen[12] · Yuanyuan Guo[1] · Yueping Liu[13] · Jian Zhang[6,7] · Sheng Luo[1]

Received: 19 September 2023 / Accepted: 2 November 2023

Abstract

Purpose To investigate potential differences in pathological complete response (pCR) rates and overall survival (OS) between HER2-low and HER2-zero patients with early-stage hormone receptor (HR)-positive and triple-negative breast cancer (TNBC), in the neoadjuvant chemotherapy setting.

Methods We identified early-stage invasive HER2-negative BC patients who received neoadjuvant chemotherapy diagnosed between 2010 and 2018 in the National Cancer Database. HER2-low was defined by immunohistochemistry (IHC) 1+ or 2+ with negative in situ hybridization, and HER2-zero by IHC0. All the methods were applied separately in the HR-positive and TNBC cohorts. Logistic regression was used to estimate the association of HER2 status with pCR (i.e. ypT0/Tis and ypN0). Kaplan–Meier method and Cox proportional hazards model were applied to estimate the association of HER2 status with OS. Inverse probability weighting and/or multivariable regression were applied to all analyses.

Results For HR-positive patients, 70.9% ($n = 17{,}934$) were HER2-low, whereas 51.1% ($n = 10{,}238$) of TNBC patients were HER2-low. For both HR-positive and TNBC cohorts, HER2-low status was significantly associated with lower pCR rates [HR-positive: 5.0% vs. 6.7%; weighted odds ratio (OR) = 0.81 (95% CI: 0.72–0.91), $p < 0.001$; TNBC: 21.6% vs. 24.4%; weighted OR = 0.91 (95% CI: 0.85–0.98), $p = 0.007$] and improved OS [HR-positive: weighted hazard ratio = 0.85 (95% CI: 0.79–0.91), $p < 0.001$; TNBC: weighted hazard ratio = 0.91 (95% CI: 0.86–0.96), $p < 0.001$]. HER2-low status was associated with favorable OS among patients not achieving pCR [HR-positive: adjusted hazard ratio = 0.83 (95% CI: 0.77–0.89), $p < 0.001$; TNBC: adjusted hazard ratio = 0.88 (95% CI 0.83–0.94), $p < 0.001$], while no significant difference in OS was observed in patients who achieved pCR [HR-positive: adjusted hazard ratio = 1.00 (95% CI: 0.61–1.63), $p > 0.99$; TNBC: adjusted hazard ratio = 1.11 (95% CI: 0.85–1.45), $p = 0.44$].

Conclusion In both early-stage HR-positive and TNBC patients, HER2-low status was associated with lower pCR rates. HER2-zero status might be considered an adverse prognostic factor for OS in patients not achieving pCR.

Keywords HER2-low · HER2-zero · Triple-negative breast cancer · Hormone receptor-positive breast cancer · Pathological complete response · Overall survival

Introduction

Breast cancer (BC) is the most common cancer among women in the US with high heterogeneity at both the biological and clinical levels [1, 2]. This heterogenous disease can be divided into four subgroups, based on the immunohistochemistry (IHC) and/or in situ hybridization (ISH) status of the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2), which often have different responses to treatment [3]. Accounting for 15–20% of BC cases, patients with HER2-positive disease (IHC 3+, or IHC 2+ and ISH-positive) typically benefit from anti-HER2 targeted therapy; however, those with HER2-negative disease (IHC 0, IHC 1+, or IHC 2+ and ISH-negative) demonstrate minimal benefit from traditional anti-HER2 targeted therapy [4–7].

Within HER2-negative tumors, those with low to moderate expression of HER2 without amplification are defined as HER2-low (IHC 1+, or IHC 2+ and ISH-negative),

Extended author information available on the last page of the article

Published online: 08 December 2023

comprising 45–55% of all BC tumors [8–10]. Recently, novel antibody drug conjugates (ADCs) trials, including trastuzumab deruxtecan (T-DXd, DS-8201a) and trastuzumab duocarmazine (SYD985), have demonstrated clinical benefits in both HER2-positive and HER2-low BC patients [11–14], suggesting that HER2-low tumors may be a distinct entity largely overlooked in the existing literature.

As novel ADCs emerge, exploring HER2-low early-stage BC in the setting of neoadjuvant chemotherapy (NACT) gains importance for guiding future treatment regimens. However, studies related to HER2-low early-stage BC in response to NACT are limited. A pooled-multicenter clinical trial on early-stage BC patients treated with NACT supported the notion that HER2-low BC tumors could be identified as a distinct biologic subtype [15]. Whether HER2-low could be characterized as a distinct subgroup of early-stage BC from HER2-zero, potentially impacting treatment decisions and prognosis, remains controversial, although detailed reporting of HER2 IHC and ISH status is recommended by national organizations [8, 16–21]. Therefore, further exploratory studies with larger sample sizes and prolonged follow-up are warranted. Furthermore, the impact of HER2-low status on early-stage BC should be stratified by hormone receptor (HR) status since triple-negative breast cancer (TNBC; ER and PR negative) is notably distinct from HR-positive BC (ER and/or PR positive). For example, TNBC has different molecular features associated with more aggressive biological behaviors, such as higher proliferation rates and increased genetic instability, while HR-positive BC is typically associated with lower proliferation index and more indolent clinical course, which leads to different treatment response and prognosis [22–24].

In this retrospective cohort study, we aimed to assess the impact of HER2-low status (vs. HER2-zero) on pCR rates and overall survival (OS) in early-stage HR-positive or TNBC patients.

Methods

Database and patient cohort

Established in 1989, the National Cancer Database (NCDB) is a nationwide hospital-based clinical cancer registry sponsored by the American College of Surgeons and American Cancer Society, capturing approximately 80% of all newly diagnosed breast cancers across the United States. [25] The present study was granted Duke University Institutional Review Board exemption and waiver of informed consent due to the use of de-identified patient data.

Adult female patients (18–80 years old) diagnosed with HER2-negative invasive early-stage BC between 2010 and 2018, who received NACT, were identified from the NCDB (2019 release). Exclusion criteria were summarized in Fig. 1. Eligible patients were then divided into two study cohorts based on HR status (i.e. HR-positive vs HR-negative, where those with HR-negative disease were classified as having TNBC). Next, patients within the HR-positive and the TNBC cohorts were further subdivided into HER2-low and HER2-zero subgroups based on the HER2 IHC score and/or ISH status. Namely, patients with IHC 1+, or IHC 2+ and ISH-negative were defined as HER2-low, whereas patients with IHC 0 were defined as HER2-zero. The study was reported in accordance with the REMARK criteria. [26]

Study variables

Baseline clinicopathological variables of interest included age at diagnosis, race/ethnicity (Hispanic, non-Hispanic White, non-Hispanic Black, non-Hispanic Asian, and other), clinical T and N category (cT and cN), tumor grade, tumor histological type, Charlson-Deyo comorbidity score (0, 1, or > = 2), surgery type, facility type, and diagnosis year (2010–2012, 2013–2015, and 2016–2018). Furthermore, administration of adjuvant therapy including endocrine therapy (ET), immunotherapy (IT) and/or radiotherapy (RT) were included in the OS analyses. Of note, anti-HER2 directed therapy is included as IT in the NCDB.

Statistical analysis

All the below methods were applied separately in the HR-positive and TNBC cohorts. Based on the assumption of missing at random (MAR) and prior research demonstrating that excluding patients with missing data may skew the results [27], we performed multiple imputations by the chained equations to impute missing values for race and tumor grade (2.5% and 5.6% missingness for HR-positive cohort; 2.2% and 4.4% missingness for TNBC cohort). We hypothesized that the MAR assumption was plausible, because a wide range of variables which applied in the substantive analyses, were added into the imputation models, per suggestion by Sterne et al. [28] According to the guidelines, the number of imputations should be similar to the percentage of missing cases; therefore, we generated eight and seven complete datasets for subsequent analyses in the HR-positive and TNBC cohorts, respectively [29].

We compared baseline characteristics between HER2-low and HER2-zero patients separately for the HR-positive and TNBC cohorts. The balance in baseline characteristics was assessed by the standardized mean difference (SMD), and an SMD < 0.1 suggested an acceptable balance of the factors between the HER2-low and HER2-zero subgroups.

To control for confounding and selection bias, we applied inverse probability weighting (IPW) to adjust for the observed differences in baseline characteristics. Using

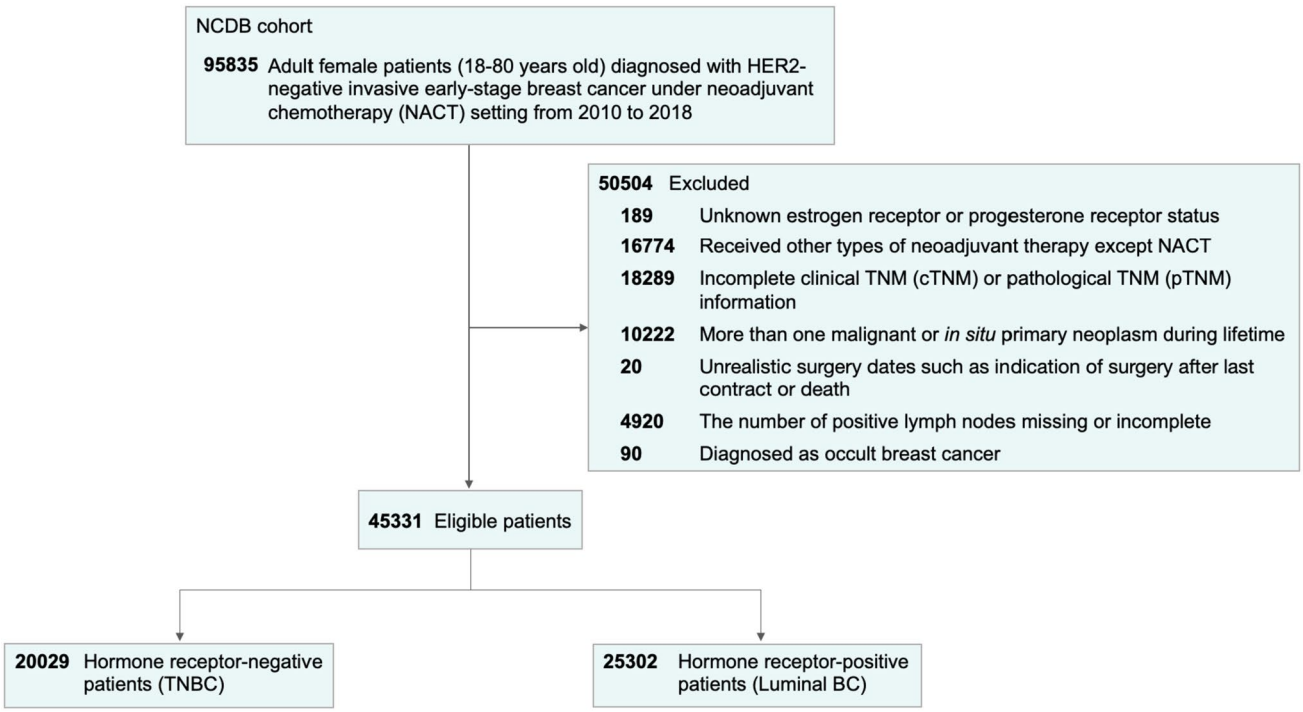

Fig. 1 Consolidated standards of reporting trials (CONSORT) diagram. Exclusion criteria included (1) patients whose estrogen receptor or progesterone receptor status were unknown or borderline; (2) patients who received other types of neoadjuvant therapy including neoadjuvant endocrine therapy, radiotherapy, immunotherapy and other treatments; (3) patients with incomplete clinical and pathological TNM information; (4) patients who had more than one malignant or in situ primary neoplasm during their lifetime; (5) patients with unrealistic surgery date, such as those indicated as having received lumpectomy or mastectomy after last contact or death; (6) patients with missing or incomplete data on the number of positive lymph nodes; and (7) patients diagnosed with occult breast cancer. *NCDB* National Cancer Database, *BC* Breast cancer, *TNBC* Triple-negative breast cancer

a multivariable logistic regression, we first estimated the propensity score (PS) in each imputed dataset, yielding the conditional probability of having HER2-low disease. This multivariable logistic model encompassed various clinicopathological risk factors, including the ten baseline characteristics (i.e. age at diagnosis, race/ethnicity, cT and cN category, tumor grade, histological type, Charlson-Deyo score, surgery type, facility type, and diagnosis year). The estimated PSs from all the imputed datasets were then combined by averaging individual estimates in each dataset according to Rubin's rules [30]. We applied the IPW method based on the estimated PS to weight each patient for balancing baseline characteristics between HER2-low and HER2-zero subgroups.

The outcomes of interest included pCR rate and OS. We compared pCR, defined as ypT0/Tis and ypN0, between the HER2-low and HER2-zero subgroups by performing IPW-adjusted logistic regression. Odds ratios (OR) and 95% confidence intervals (CI) were reported. OS, defined as the time from the date of diagnosis to the date of last contact or death, was analyzed by IPW-adjusted Kaplan–Meier (KM) curves and log-rank test, as well as IPW-adjusted Cox proportional hazards models with additional adjustment for the administration of adjuvant ET, IT, and RT. Hazard ratios with 95% CI of HER2-low versus HER2-zero were reported. Furthermore, we performed IPW-based subgroup analyses to investigate the differences in pCR and OS between the HER2-low and HER2-zero subgroups according to race/ethnicity (non-Hispanic White and non-Hispanic Black), cT category (cT1-2 and cT3-4), cN category (cN0 and cN1-3), histological type (ductal and non-ductal), and tumor grade (grade I-II and grade III). If post-weighting balance could not be reached in a certain subgroup, multivariable regression models were subsequently utilized for additional covariate adjustments. We also conducted interaction tests between HER2 status and baseline characteristics (i.e. race/ethnicity, cT category, cN category, histological type, and tumor grade) to evaluate the heterogeneity of the predictive and prognostic impact of HER2 status across the subgroups.

To assess the impact of pCR on OS, we performed additional analyses by presenting the unweighted KM curves with log-rank tests for patients who achieved pCR versus those who did not achieve pCR (non-pCR) in the HR-positive and TNBC cohorts. Additional multivariable analyses (MVA) using Cox regression with the aforementioned thirteen risk factors (i.e. ten baseline characteristics and

administration of adjuvant ET, IT and RT) were also used to compare OS differences between HER2-low and HER2-zero in the HR-positive and TNBC cohorts according to pCR outcome (i.e. pCR versus non-pCR). In this study, robust sandwich covariance estimators were used in all models to account for the correlation of patients treated at the same facility.

Additionally, we conducted sensitivity analyses using multivariable logistic and Cox regressions on the complete dataset (excluding patients with missing data) with the aforementioned risk factors (i.e. adjustment for ten baseline characteristics for pCR, and additional adjustment for administration of adjuvant ET, IT and RT for OS) to validate our findings. The E-values, defined as "the minimum strength of association of an unmeasured confounder with both exposure and the outcome, conditional on measured covariates, to fully explain away exposure-outcome association", were calculated to evaluate possible effects of the unmeasured confounders on study findings under no assumptions. [31, 32] A large E-value implies that considerable unmeasured confounding would be needed to explain away the exposure-outcome association [31].

All the analyses were performed by R version 4.2.3. And two-sided $p < 0.05$ was considered statistically significant. No adjustments were made for multiple comparisons.

Results

Clinicopathological characteristics

We identified 45,331 early-stage invasive BC patients who met eligibility criteria, of whom 55.8% ($n = 25,302$) were HR-positive and 44.2% ($n = 20,029$) had TNBC (Fig. 1). Among HR-positive patients, 70.9% ($n = 17,934$) were HER2-low, whereas 51.1% ($n = 10,238$) were HER2-low among TNBC patients, indicating that HER2-low was more common among HR-positive patients compared with TNBC patients (Chi-squared test $p < 0.001$; **Supplemental** Figure S1).

Among HR-positive patients, compared with HER2-zero patients, HER2-low patients were more likely to be diagnosed as cN1-3 (64.1% vs. 62.4%), grade I-II (57.5% vs. 53.3%), have histological subtype as ductal (78.4% vs. 75.5%), and receive adjuvant ET (90.8% vs. 88.9%) (Table 1). Additionally, compared with Hispanic patients, of whom 68.6% were HER2-low, Non-Hispanic White (71.0%) and Non-Hispanic Black (70.9%) patients had higher proportions of HER2-low status.

Among TNBC patients, compared with HER2-zero patients, HER2-low patients were more likely to be diagnosed as cN1-3 (45.3% vs. 42.9%), grade I-II (15.7% vs. 13.1%), and receive adjuvant RT (70.6% vs. 68.5%) (Table 2). Additionally, compared with Hispanic patients, of whom 45.5% were HER2-low, Non-Hispanic White (51.9%) and Non-Hispanic Black (50.6%) patients had higher proportions of HER2-low status.

After IPW adjustment, SMDs were smaller than 0.1 for all baseline characteristics between the HER2-low and HER2-zero subgroups (Tables 1, 2, and **Supplemental Figure** S2) indicating that the weighted population in the two subgroups was generally comparable in both the HR-positive and TNBC cohorts.

Outcomes analyses

In the HR-positive cohort, the median follow-up was 65.2 months [interquartile range (IQR), 46.4–89.5]. In the TNBC cohort, the median follow-up was 59.5 months (IQR, 43.5–81.5).

Hormone receptor-positive cohort

Among HER2-low patients, 5.0% ($n = 905$) achieved pCR, compared with 6.7% ($n = 493$) of HER2-zero patients (Fig. 2 and **Supplemental Figure** S3). The pCR rate increased as the diagnosis year increased from 2010 to 2018 (Fig. 3a). In the IPW-adjusted logistic model, HER2-low status was associated with a significantly lower pCR rate [IPW-adjusted odds ratio (OR) = 0.81, 95% CI: 0.72–0.91; $p < 0.001$; Fig. 2].

In subgroup analyses, differences in pCR rates between HER2-low and HER2-zero patients were significantly correlated with race/ethnicity (Non-Hispanic White: IPW-adjusted OR = 0.74, 95% CI: 0.64–0.85 vs. Non-Hispanic Black: IPW-adjusted OR = 1.03, 95% CI: 0.78–1.35; p-interaction = 0.03; Fig. 2) and tumor grade (grade I-II: IPW-adjusted OR = 0.64, 95% CI: 0.49–0.84 vs. grade III: IPW-adjusted OR = 0.83, 95% CI: 0.73–0.95; p-interaction = 0.03; Fig. 2).

Compared with HER2-zero, HER2-low patients consistently had a favorable OS before and after IPW adjustment (unweighted 5-year OS rate: 86.2% vs. 83.5%; weighted 5-year OS rate: 86.1% vs. 83.6%; both log-rank $p < 0.001$; Fig. 4a, **Supplement Figure** S4A and Table S1). Moreover, the analysis using the IPW-adjusted Cox model indicated that patients with HER2-low tumors had improved OS compared to those with HER2-zero tumors (hazard ratio = 0.85, 95% CI: 0.79–0.91; $p < 0.001$; Fig. 5). Particularly, HER2-low patients with IHC 2+ and ISH-negative status had a favorable OS than those with IHC 1+ status, or HER2-zero status (unweighted log-rank $p < 0.001$; **Supplement Figure** S4B).

The magnitude of the survival benefit associated with HER2-low status (vs. HER2-zero) was greatest for those with cT3-4 tumors, although patients with cT1-2

Table 1 Distribution of baseline characteristics and adjuvant therapy among HER2-zero versus HER2-low patients with hormone receptor-positive breast cancer

	HER2-zero ($n=7368$)	HER2-low ($n=17,934$)	p value[a]	Standardized mean difference	
	No. (%)			Unweighted	Weighted[b]
Age (y)					
Mean (SD)	51.41 (11.18)	51.72 (11.28)	0.04	0.028	< 0.001
Race/Ethnicity			0.07	0.037	0.004
Non-Hispanic White	4957 (68.9)	12,139 (69.5)			
Non-Hispanic Black	1116 (15.5)	2714 (15.5)			
Hispanic	712 (9.9)	1557 (8.9)			
Other	409 (5.7)	1065 (6.1)			
Clinical N category			0.02	0.043	0.002
cN0	2772 (37.6)	6442 (35.9)			
cN1	3660 (49.7)	9285 (51.8)			
cN2	604 (8.2)	1406 (7.8)			
cN3	332 (4.5)	801 (4.5)			
Clinical T category			0.83	0.013	0.003
cT1	1223 (16.6)	3033 (16.9)			
cT2	3584 (48.6)	8765 (48.9)			
cT3	1706 (23.2)	4069 (22.7)			
cT4	855 (11.6)	2067 (11.5)			
Tumor Grade			< 0.001	0.084	0.005
Grade I	562 (8.1)	1460 (8.6)			
Grade II	3147 (45.3)	8277 (48.9)			
Grade III	3245 (46.7)	7200 (42.5)			
Histological type			< 0.001	0.071	0.003
Ductal	5566 (75.5)	14,060 (78.4)			
Lobular	1504 (20.4)	3294 (18.4)			
Other	298 (4.0)	580 (3.2)			
Charlson-Deyo Score			0.46	0.017	0.003
0	6448 (87.5)	15,787 (88.0)			
1	749 (10.2)	1764 (9.8)			
≥ 2	171 (2.3)	383 (2.1)			
Surgery type; Mastectomy	5016 (68.1)	12,228 (68.2)	0.88	0.002	0.003
Facility type			0.003	0.051	0.001
Academic/Research	2709 (36.8)	6155 (34.3)			
Integrated Network	1576 (21.4)	3964 (22.1)			
Community	409 (5.6)	1024 (5.7)			
Comprehensive Community	2674 (36.3)	6791 (37.9)			
Diagnosis year			< 0.001	0.145	0.001
2010–2012	1694 (23.0)	5072 (28.3)			
2013–2015	2760 (37.5)	6851 (38.2)			
2016–2018	2914 (39.5)	6011 (33.5)			
Adjuvant IT[c]; Yes	40 (0.5)	194 (1.1)	< 0.001	0.060	–
Adjuvant ET[c]; Yes	6552 (88.9)	16,276 (90.8)	< 0.001	0.061	–
Adjuvant RT[c]; Yes	6021 (81.7)	14,784 (82.4)	0.18	0.019	–

IT Immunotheraphy, *ET* Endocrine therapy, *RT* Radiotherapy

[a]T-test and Chi-squared test

[b]The weighted cohort indicated that assigning weights to each patient by inverse probability weighting method

[c]The variables about the receipt of adjuvant therapy were not adjusted using inverse probability weighting method, but were adjusted as separate covariates in survival analysis

Table 2 Distribution of baseline characteristics and adjuvant therapy among HER2-zero versus HER2-low patients with triple-negative breast cancer

	HER2-zero ($n=9791$)	HER2-low ($n=10,238$)	p value[a]	Standardized mean difference	
	No. (%)			Unweighted	Weighted[b]
Age (y)					
Mean (SD)	51.41 (11.78)	52.36 (11.68)	< 0.001	0.081	< 0.001
Race/Ethnicity			< 0.001	0.071	0.002
Non-Hispanic White	5905 (61.7)	6367 (63.7)			
Non-Hispanic Black	2389 (24.9)	2450 (24.5)			
Hispanic	882 (9.2)	737 (7.4)			
Other	401 (4.2)	449 (4.5)			
Clinical N category			0.003	0.053	< 0.001
cN0	5590 (57.1)	5603 (54.7)			
cN1	3085 (31.5)	3447 (33.7)			
cN2	649 (6.6)	660 (6.4)			
cN3	467 (4.8)	528 (5.2)			
Clinical T category			0.32	0.026	< 0.001
cT1	1965 (20.1)	1951 (19.1)			
cT2	5373 (54.9)	5666 (55.3)			
cT3	1598 (16.3)	1697 (16.6)			
cT4	855 (8.7)	924 (9.0)			
Tumor Grade			< 0.001	0.074	0.002
Grade I	69 (0.7)	92 (0.9)			
Grade II	1160 (12.4)	1450 (14.8)			
Grade III	8114 (86.8)	8254 (84.3)			
Histological type			0.001	0.054	< 0.001
Ductal	8737 (89.2)	9254 (90.4)			
Lobular	339 (3.5)	373 (3.6)			
Other	715 (7.3)	611 (6.0)			
Charlson-Deyo Score			0.27	0.023	< 0.001
0	8483 (86.6)	8822 (86.2)			
1	1025 (10.5)	1138 (11.1)			
≥ 2	283 (2.9)	278 (2.7)			
Surgery Type; Mastectomy	5751 (58.7)	6053 (59.1)	0.59	0.008	< 0.001
Facility Type			< 0.001	0.096	< 0.001
Academic/Research	3781 (38.6)	3486 (34.0)			
Integrated Network	2163 (22.1)	2373 (23.2)			
Community	487 (5.0)	536 (5.2)			
Comprehensive Community	3360 (34.3)	3843 (37.5)			
Diagnosis Year			< 0.001	0.179	< 0.001
2010–2012	1899 (19.4)	2466 (24.1)			
2013–2015	3523 (36.0)	4071 (39.8)			
2016–2018	4369 (44.6)	3701 (36.1)			
Adjuvant IT[c]; Yes	62 (0.6)	89 (0.9)	0.06	0.027	–
Adjuvant ET[c]; Yes	171 (1.7)	235 (2.3)	0.007	0.039	–
Adjuvant RT[c]; Yes	6705 (68.5)	7232 (70.6)	0.001	0.047	–

IT Immunotheraphy, *ET* Endocrine therapy, *RT* Radiotherapy

[a]T-test and Chi-squared test

[b]The weighted cohort indicated that assigning weights to each patient by inverse probability weighting method

[c]The variables about the receipt of adjuvant therapy were not adjusted using inverse probability weighting method, but were adjusted as separate covariates in survival analysis

Population	HER2-zero	HER2-low	OR (95% CI)	P-interaction
	no. of events/patients (%)			
HR-positive BC				
Overall	**493/7368 (6.7)**	**905/17934 (5.0)**	**0.81 (0.72, 0.91)**	
Race/Ethnicity				**0.03**
Non-Hispanic White	330/4957 (6.7)	553/12139 (4.6)	0.74 (0.64, 0.85)	
Non-Hispanic Black	80/1116 (7.2)	186/2714 (6.9)	1.03 (0.78, 1.35)	
Clinical N category				**0.62**
cN0	294/2772 (10.6)	511/6442 (7.9)	0.78 (0.67,0.91)	
cN1-3	199/4596 (4.3)	394/11492 (3.4)	0.84 (0.70,1.00)	
Clinical T category				**0.83**
cT1-2	374/4807 (7.8)	687/11798 (5.8)	0.81 (0.71,0.93)	
cT3-4	119/2561 (4.6)	218/6136 (3.6)	0.80 (0.64, 1.01)	
Histological type				**0.64**
Ductal	444/5566 (8.0)	827/14060 (5.9)	0.80 (0.71, 0.91)	
Non-Ductal	49/1802 (2.7)	78/3874 (2.0)	0.85 (0.59, 1.23)	
Tumor grade				**0.03**
Grade I-II	86/3709 (2.3)	145/9737 (1.5)	0.64 (0.49, 0.84)	
Grade III	384/3245 (11.8)	701/7200 (9.7)	0.83 (0.73, 0.95)	
TNBC (HR-negative)				
Overall	**2388/9791 (24.4)**	**2212/10238 (21.6)**	**0.91 (0.85, 0.98)**	
Race/Ethnicity				**0.19**
Non-Hispanic White	1502/5905 (25.4)	1417/6367 (22.3)	0.89 (0.82, 0.97)	
Non-Hispanic Black	506/2389 (21.2)	496/2450 (20.2)	1.00 (0.87, 1.15)	
Clinical N category				**0.30**
cN0	1684/5590 (30.1)	1497/5603 (26.7)	0.89 (0.82, 0.97)	
cN1-3	704/4201 (16.8)	715/4635 (15.4)	0.95 (0.85, 1.06)	
Clinical T category				**0.14**
cT1-2	2002/7338 (27.3)	1816/7617 (23.8)	0.89 (0.83, 0.96)	
cT3-4	386/2453 (15.7)	396/2621 (15.1)	1.00 (0.86, 1.17)	
Histological type				**0.48**
Ductal	2221/8737 (25.4)	2070/9254 (22.4)	0.91 (0.84, 0.97)	
Non-Ductal	167/1054 (15.8)	142/984 (14.4)	0.97 (0.75, 1.26)	
Tumor grade				**0.36**
Grade I-II	180/1229 (14.6)	213/1542 (13.8)	1.02 (0.81, 1.28)	
Grade III	2099/8114 (25.9)	1892/8254 (22.9)	0.90 (0.84, 0.97)	

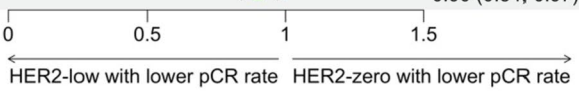

Fig. 2 Pathological complete response rate by HER2 status among the NCDB breast cancer patients diagnosed between 2010 and 2018. Pathological complete response was defined as ypT0/Tis and ypN0. Post-weighting balance was not achieved in non-ductal and grade I-II subgroups among the TNBC cohort; therefore, multivariable logistic regression based on imputed datasets was applied. Other subgroup analyses still applied IPW method. *p*-interaction < 0.05, from multivariable analysis based on imputed datasets, implied significant heterogeneity in the predictive impact of HER2-low status within subgroups of a specific variable. The multivariable logistic models were adjusted for age at diagnosis, race/ethnicity, cT and cN category, tumor grade, histological type, Charlson-Deyo score, surgery type, facility type, and diagnosis year. *OR* odds ratio, *HR* hormone receptor, *TNBC* triple-negative breast cancer

tumors also significantly benefited (cT1-2: IPW-adjusted hazard ratio = 0.89, 95% CI: 0.81–0.98 vs. cT3-4: IPW-adjusted hazard ratio = 0.80, 95% CI: 0.73–0.88; *p*-interaction < 0.05; Fig. 5). However, an OS advantage was only present in ductal patients and not in non-ductal patients (ductal: IPW-adjusted hazard ratio = 0.80, 95% CI: 0.74–0.86 vs. non-ductal: IPW-adjusted hazard ratio = 1.02, 95% CI: 0.89–1.17; *P*-interaction = 0.002; Fig. 5).

Additional analyses examining the impact of pCR on OS revealed a notably favorable OS among patients achieving pCR compared to those not achieving pCR (log-rank $p < 0.001$; Fig. 6a). When stratifying the HR-positive cohort by pCR outcome, we found no significant

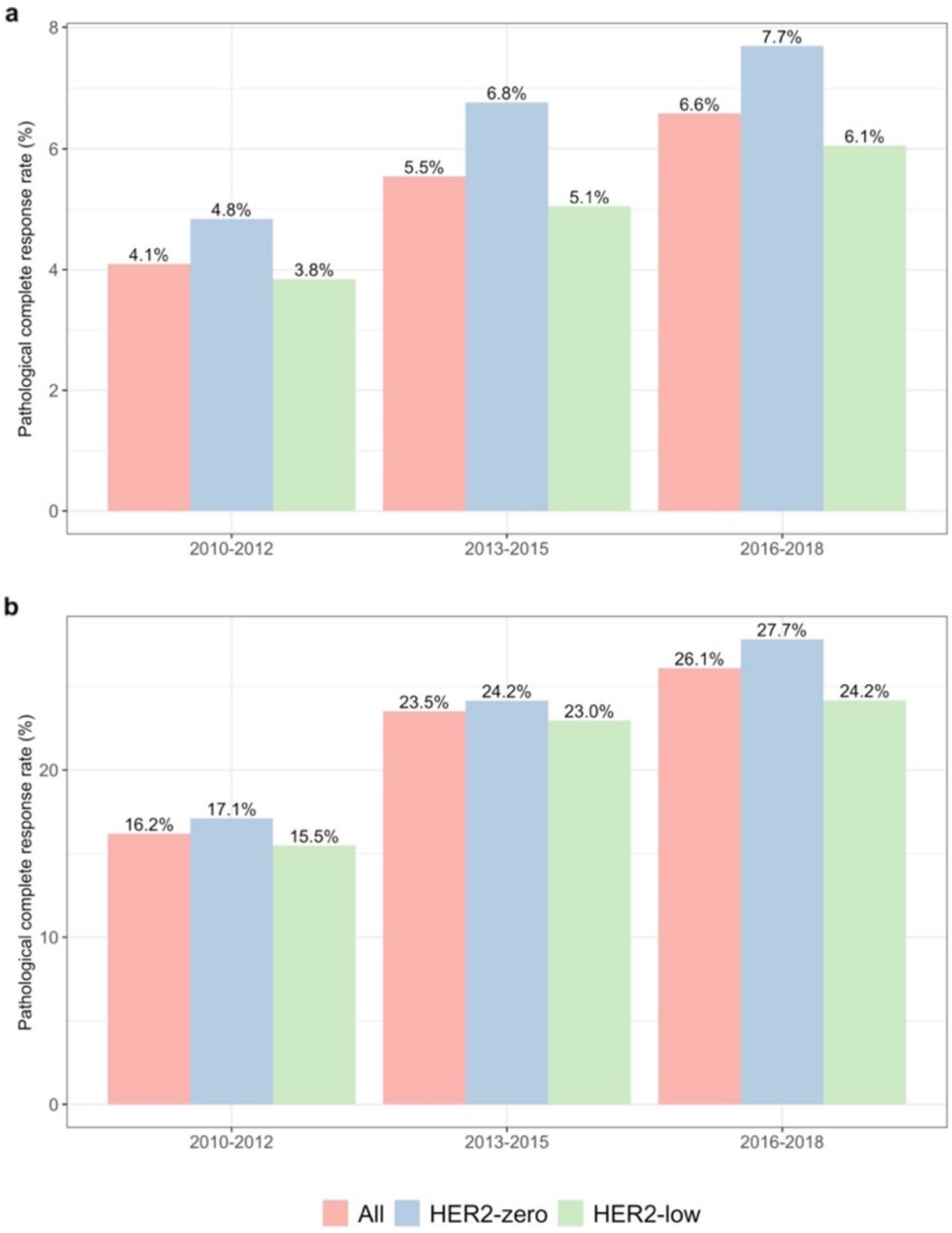

Fig. 3 The change of pathological complete response rate according to the year of diagnosis. Panel **a** shows change of pathological complete response (pCR) rate according to the year of diagnosis among hormone receptor-positive cohort; Panel **b** shows change of pathological complete response rate according to the year of diagnosis among triple-negative breast cancer cohort

difference in OS between HER2-low and HER2-zero for patients achieving pCR (unweighted log-rank $p = 0.66$; MVA-adjusted hazard ratio = 1.00, 95% CI: 0.61–1.63, $p > 0.99$; Fig. 7a). However, HER2-low status was associated with an OS benefit for patients not achieving pCR (unweighted log-rank $p < 0.001$; MVA-adjusted hazard ratio = 0.83, 95% CI: 0.77–0.89, $p < 0.001$; Fig. 7b). In addition to HER2 status, the MVA also revealed that age at diagnosis, race/ethnicity, cT and cN category, tumor grade, Charlson-Deyo score, surgery type, facility type, and adjuvant ET were significant prognostic factors for OS among non-pCR patients (all $p < 0.001$; Table 3).

Triple-Negative Breast Cancer Cohort

Among HER2-low patients, 21.6% ($n = 2212$) achieved pCR, compared with 24.4% ($n = 2388$) of HER2-zero patients (Fig. 2 and **Supplemental Figure** S3). The pCR rate exhibited an upward trend as the diagnosis year increased from 2010 to 2018 (Fig. 3b). In the IPW-adjusted logistic model, a small but significant reduction in pCR rate associated with HER2-low status was observed [IPW-adjusted OR = 0.91, 95% CI: 0.85–0.98; $p = 0.007$; Fig. 2]. Subgroup analyses demonstrated no significant heterogeneity for the differences in pCR rates

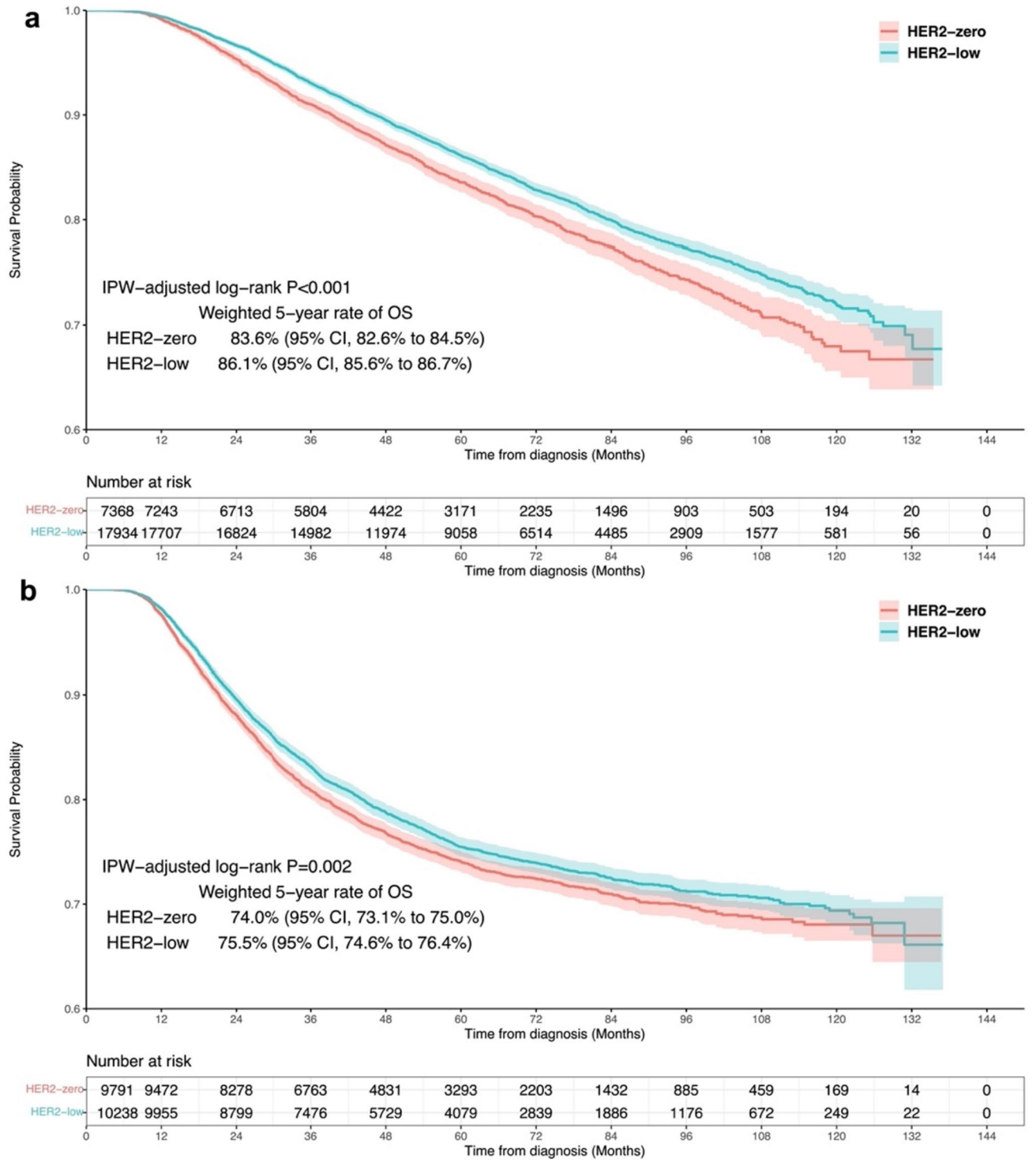

Fig. 4 Kaplan–Meier curves of HER2-low versus HER2-zero after IPW adjustment among the NCDB breast cancer patients diagnosed between 2010 and 2018. Panel **a** shows OS in HER2-zero and HER2-low patients from the HR-positive cohort; Panel **b** shows OS in HER2-zero and HER2-low patients from the TNBC cohort. *IPW* inverse probability weighting, *OS* overall survival, *HR* hormone receptor, *TNBC* triple-negative breast cancer

Population	HER2-zero	HER2-low	Hazard ratio (95% CI)	P-interaction
	no. of events/patients (%)			
HR-positive BC				
Overall	**1284/7368 (17.4)**	**2854/17934 (15.9)**	**0.85 (0.79, 0.91)**	
Race/Ethnicity				**0.33**
Non-Hispanic White	850/4957 (17.1)	1925/12139 (15.9)	0.87 (0.80, 0.94)	
Non-Hispanic Black	248/1116 (22.2)	553/2714 (20.4)	0.83 (0.71, 0.97)	
Clinical N category				**0.18**
cN0	312/2772 (11.3)	692/6442 (10.7)	0.87 (0.76, 1.00)	
cN1-3	972/4596 (21.1)	2162/11492 (18.8)	0.84 (0.78, 0.91)	
Clinical T category				**<0.05**
cT1-2	641/4807 (13.3)	1514/11798 (12.8)	0.89 (0.81, 0.98)	
cT3-4	643/2561 (25.1)	1340/6136 (21.8)	0.80 (0.73, 0.88)	
Histological type				**0.002**
Ductal	988/5566 (17.8)	2173/14060 (15.5)	0.80 (0.74, 0.86)	
Non-Ductal	296/1802 (16.4)	681/3874 (17.6)	1.02 (0.89, 1.17)	
Tumor grade				**0.16**
Grade I-II	492/3709 (13.3)	1232/9737 (12.7)	0.86 (0.78, 0.96)	
Grade III	702/3245 (21.6)	1459/7200 (20.3)	0.85 (0.78, 0.93)	
TNBC (HR-negative)				
Overall	**2312/9791 (23.6)**	**2435/10238 (23.8)**	**0.91 (0.86, 0.96)**	
Race/Ethnicity				**0.80**
Non-Hispanic White	1383/5905 (23.4)	1488/6367 (23.4)	0.90 (0.84, 0.97)	
Non-Hispanic Black	630/2389 (26.4)	660/2450 (26.9)	0.91 (0.82, 1.02)	
Clinical N category				**0.54**
cN0	770/5590 (13.8)	767/5603 (13.7)	0.90 (0.82, 1.00)	
cN1-3	1542/4201 (36.7)	1668/4635 (36.0)	0.91 (0.85, 0.98)	
Clinical T category				**0.60**
cT1-2	1337/7338 (18.2)	1400/7617 (18.4)	0.90 (0.83, 0.97)	
cT3-4	975/2453 (39.7)	1035/2621 (39.5)	0.92 (0.84, 1.01)	
Histological type				**0.24**
Ductal	1987/8737 (22.7)	2153/9254 (23.3)	0.92 (0.86, 0.98)	
Non-Ductal	325/1054 (30.8)	282/984 (28.7)	0.87 (0.74, 1.03)	
Tumor grade				**<0.001**
Grade I-II	305/1229 (24.8)	310/1542 (20.1)	0.69 (0.59, 0.82)	
Grade III	1884/8114 (23.2)	2004/8254 (24.3)	0.94 (0.89, 1.01)	

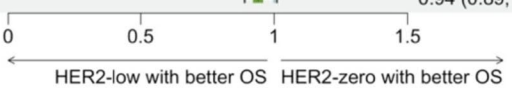

Fig. 5 Overall survival analyses by HER2 status among the NCDB breast cancer patients diagnosed between 2010 and 2018. Overall survival was defined as the time from the date of diagnosis to the date of last contact or death. Post-weighting balance was not achieved in the non-ductal and grade I-II subgroups among the TNBC cohort; therefore, multivariable Cox regression based on imputed datasets was instead applied. Other subgroup analyses still applied IPW method. *p*-interaction < 0.05, from multivariable analysis based on imputed datasets, implied significant heterogeneity in the survival impact of HER2-low status within subgroups of a specific variable. The multivariable Cox models were adjusted for age at diagnosis, race/ethnicity, cT and cN category, tumor grade, histological type, Charlson-Deyo score, surgery type, facility type, diagnosis year, and receipt of adjuvant endocrine therapy, immunotherapy, and radiotherapy. *HR* hormone receptor, *TNBC* triple-negative breast cancer

between HER2 status based on race, cT and cN category, histological type, and tumor grade (all *p*-interaction > 0.05; Fig. 2).

Compared with HER2-zero, HER2-low patients demonstrated a significantly improved OS only after IPW adjustment (weighted 5-year OS rate: 75.5% vs. 74.0%, log-rank $p = 0.002$; unweighted 5-year OS rate: 75.1% vs. 74.7%, log-rank $p = 0.15$; Fig. 4b, **Supplement Figure** S4C and Table S1). Furthermore, the IPW-adjusted Cox model revealed HER2-low tumors had a small but significant OS advantage compared to those with HER2-zero tumors (hazard ratio = 0.91, 95% CI: 0.86–0.96; $p < 0.001$; Fig. 5). More specifically, only patients with HER2 IHC 2+ and ISH-negative status had a more favorable OS than those with HER2-zero status (unweighted log-rank $p = 0.08$ for HER2-low, IHC 2+ and ISH-negative vs. HER2-low, IHC

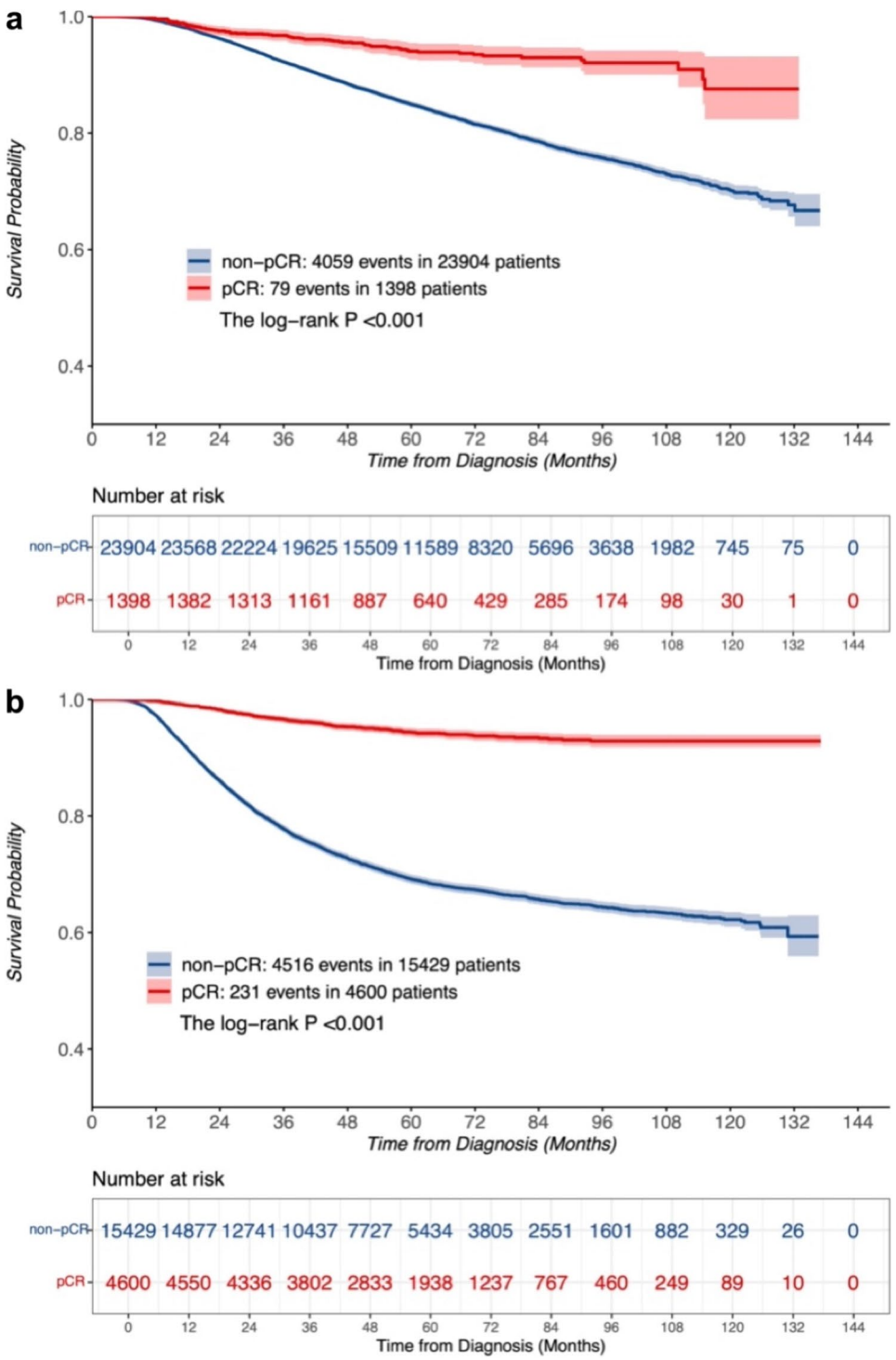

Fig. 6 Kaplan–Meier curves of patients with versus without pathological complete response. Panel **a** shows the Kaplan–Meier (KM) curves according to pathological complete response (pCR) with unweighted log-rank test result for hormone receptor-positive cohort; Panel **b** shows the KM curves according to pCR with unweighted log-rank test result for triple-negative breast cancer cohort

1+ vs. HER2-zero; unweighted log-rank $p = 0.03$ for HER2-low, IHC 2+ and ISH-negative vs. HER2-zero; unweighted log-rank $p = 0.08$ for HER2-low, IHC 2+ and ISH-negative vs. HER2-low, IHC 1+ ; unweighted log-rank $p = 0.51$ for HER2-low, IHC 1+ vs. HER2-zero; **Supplement Figure** S4D). Except for the tumor grade subgroup, the OS benefit observed with the HER2-low tumors was not associated with other subgroup factors (all p-interaction > 0.05; Fig. 5). The OS advantage was only observed in the grade I-II patients and not in the grade III patients (grade I-II: IPW-adjusted hazard ratio = 0.69, 95% CI: 0.59–0.82 vs. grade III: IPW-adjusted hazard ratio = 0.94, 95% CI: 0.89–1.01; p-interaction < 0.001; Fig. 5).

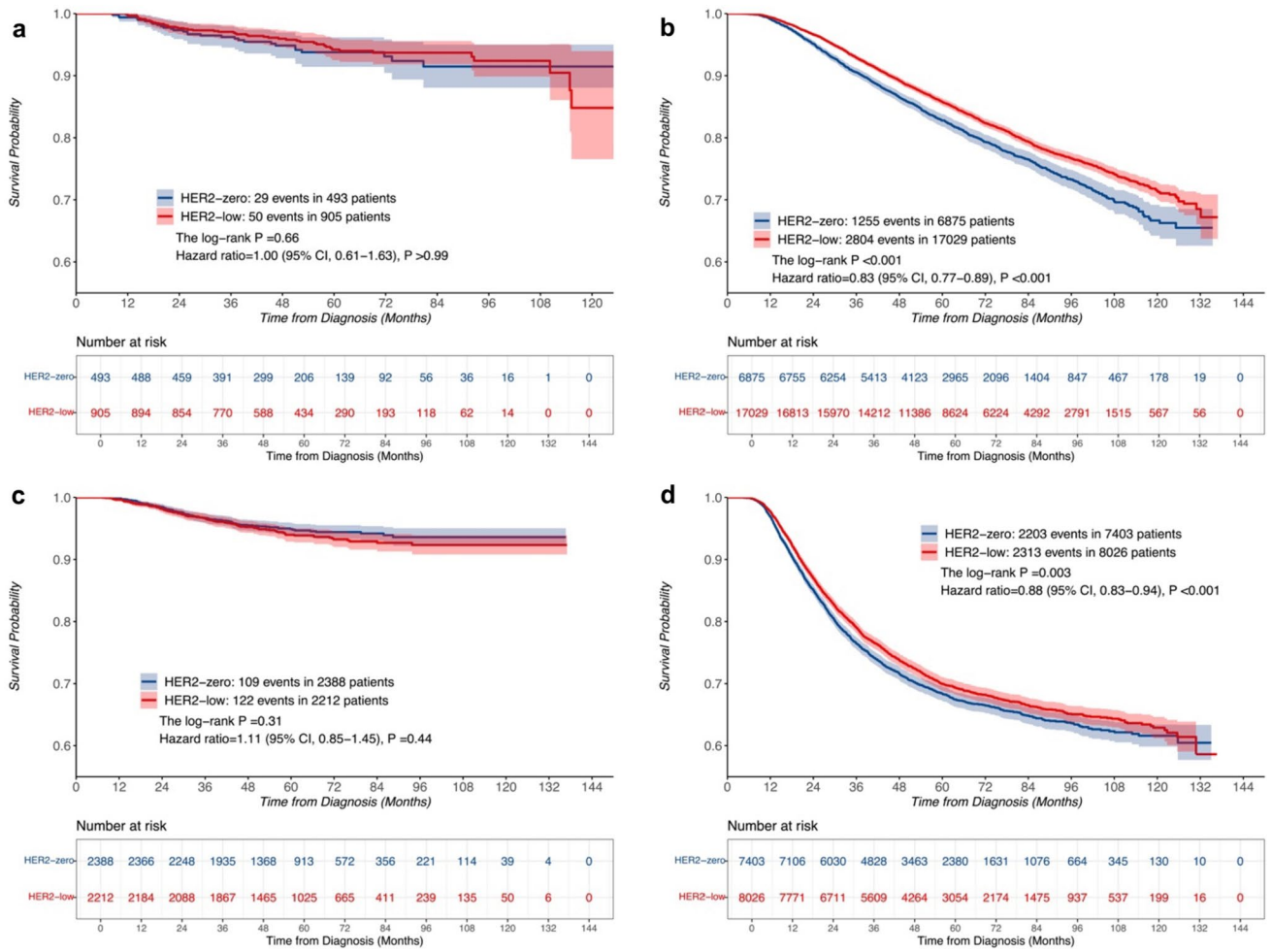

Fig. 7 Kaplan–Meier curves of HER2-low versus HER2-zero stratified by pCR outcome among the NCDB breast cancer patients diagnosed between 2010 and 2018. Panel **a** shows overall survival (OS) in HER2-zero and HER2-low patients who achieved pathological complete response (pCR) among the hormone receptor (HR)-positive cohort; Panel **b** shows OS in HER2-zero and HER2-low patients who did not achieve pCR from the HR-positive cohort; Panel **c** shows OS in HER2-zero and HER2-low patients who achieved pCR from the triple-negative breast cancer (TNBC) cohort; Panel **d** shows OS in HER2-zero and HER2-low patients who did not achieve pCR from the TNBC cohort

Further analyses in the TNBC cohort also showed a significantly improved OS among patients achieving pCR compared to those not achieving pCR (log-rank $p < 0.001$; Fig. 6b). When dividing the TNBC cohort into two subgroups by pCR outcome, no significant difference in OS was observed between HER2-low and HER2-zero patients who achieved pCR (unweighted log-rank $p = 0.31$; MVA-adjusted hazard ratio = 1.11, 95% CI: 0.85–1.45, $p = 0.44$; Fig. 7c). Conversely, among patients not achieving pCR, HER2-low tumors were associated with a survival benefit (unweighted log-rank $p = 0.003$; MVA-adjusted hazard ratio = 0.88, 95% CI: 0.83–0.94, $p < 0.001$; Fig. 7d). In addition to HER2 status, the MVA also identified other factors as significant prognostic indicators of OS among TNBC patients not achieving pCR, including age at diagnosis, race/ethnicity, cT and cN category, tumor grade, Charlson-Deyo score, surgery type, and diagnosis year (all $p < 0.001$ except $p = 0.007$ for diagnosis year; Table 3).

Sensitivity analyses

In the complete case analyses, the results were all consistent with the above IPW-based results (**Supplement Table** S2). We applied the E-value method to assess the possible effect of unmeasured confounding on our study findings, and found that the E-values were relatively small, ranging from 1.0 to 1.8 (**Supplement Table** S3).

Table 3 Multivariable analysis for overall survival among the non-pCR patients diagnosed between 2010 and 2018 in the NCDB

	HR-positive Cohort		HR-negative (TNBC) Cohort	
	Hazard ratio (95% CI)	*p* value [a]	Hazard ratio (95% CI)	*p* value [a]
HER2 status		< 0.001		< 0.001
HER2-zero	1 [Reference]		1 [Reference]	
HER2-low	0.83 (0.77, 0.89)		0.88 (0.83, 0.94)	
Age (y)	1.01 (1.01, 1.02)	< 0.001	1.01 (1.01, 1.01)	< 0.001
Race/Ethnicity		< 0.001		< 0.001
Non-Hispanic White	1 [Reference]		1 [Reference]	
Non-Hispanic Black	1.24 (1.14, 1.35)		1.07 (0.99, 1.14)	
Hispanic	0.84 (0.74, 0.96)		0.88 (0.78, 0.99)	
Other	0.78 (0.67, 0.92)		0.70 (0.59, 0.83)	
Clinical N category		< 0.001		< 0.001
cN0	1 [Reference]		1 [Reference]	
cN1	1.62 (1.49, 1.76)		2.02 (1.88, 2.18)	
cN2	2.06 (1.83, 2.32)		2.42 (2.17, 2.69)	
cN3	2.77 (2.42, 3.17)		2.89 (2.56, 3.26)	
Clinical T category		< 0.001		< 0.001
cT1	1 [Reference]		1 [Reference]	
cT2	1.34 (1.21, 1.50)		1.44 (1.31, 1.58)	
cT3	1.71 (1.52, 1.92)		1.90 (1.70, 2.12)	
cT4	2.25 (1.99, 2.55)		2.30 (2.03, 2.60)	
Tumor Grade		< 0.001		< 0.001
Grade I	0.37 (0.32, 0.43)		0.64 (0.43, 0.94)	
Grade II	0.59 (0.55, 0.63)		0.83 (0.75, 0.91)	
Grade III	1 [Reference]		1 [Reference]	
Histological type		0.06		0.12
Ductal	1 [Reference]		1 [Reference]	
Lobular	1.10 (1.01, 1.19)		1.16 (1.01, 1.33)	
Other	1.09 (0.93, 1.28)		1.03 (0.91, 1.15)	
Charlson-Deyo Score		< 0.001		< 0.001
0	1 [Reference]		1 [Reference]	
1	1.36 (1.24, 1.49)		1.24 (1.14, 1.36)	
≥ 2	1.81 (1.51, 2.16)		1.43 (1.22, 1.67)	
Surgery Type		< 0.001		< 0.001
Lumpectomy	1 [Reference]		1 [Reference]	
Mastectomy	1.30 (1.20, 1.41)		1.54 (1.43, 1.67)	
Facility Type		< 0.001		0.05
Academic/Research	1 [Reference]		1 [Reference]	
Integrated Network	1.12 (1.03, 1.22)		1.05 (0.97, 1.14)	
Community	1.49 (1.31, 1.70)		1.07 (0.92, 1.23)	
Comprehensive Community	1.20 (1.11, 1.29)		1.10 (1.03, 1.18)	
Diagnosis Year		0.18		0.007
2010–2012	1 [Reference]		1 [Reference]	
2013–2015	0.95 (0.88, 1.02)		0.99 (0.92, 1.06)	
2016–2018	0.92 (0.84, 1.01)		0.89 (0.82, 0.96)	
Adjuvant endocrine therapy		< 0.001		0.75
Yes	1 [Reference]		1.03 (0.85, 1.25)	
No	2.28 (2.07, 2.52)		1 [Reference]	
Adjuvant radiotherapy		0.92		0.06
Yes	1 [Reference]		1 [Reference]	
No	1.00 (0.90, 1.10)		0.92 (0.84, 1.00)	
Adjuvant immunotherapy		0.69		0.80
Yes	0.93 (0.65, 1.32)		1.04 (0.78, 1.39)	
No	1 [Reference]		1 [Reference]	

Table 3 (continued)

[a] A Wald test was applied to obtain the *p* values. Multivariable Cox regression models on imputed datasets were applied among HR-positive and TNBC patients who did not achieve pathological complete response. *pCR* pathological complete response, *HR* hormone receptor, *TNBC* triple-negative breast cancer

Discussion

To our knowledge, this real-world cohort study is the first to compare the response to NACT and OS between HER2-low and HER2-zero early-stage BC, using a PS-based method, in separate cohorts of HR-positive and TNBC patients. The present study mainly demonstrated that HER2-low tumors were associated with lower pCR rates yet improved OS in both HR-positive and TNBC patients, compared with HER2-zero tumors. This implies that HER2-low early-stage BC could be considered a distinct entity in clinical practice. Another main finding of this study was that, in both HR-positive and TNBC subtypes, HER2 status was identified as a prognostic factor, and HER2-zero was associated with unfavorable OS, especially in patients not achieving pCR, while no significant difference in OS was observed between HER2-low and HER2-zero patients achieving pCR, regardless of HR status. Notably, the differences in pCR rates between HER2-low and HER2-zero patients were significantly correlated with race/ethnicity among the HR-positive cohort, although the significant differences in pCR rates were only observed in the non-Hispanic White subgroup and not in the non-Hispanic Black subgroup, suggesting racial disparities due to factors that could not be evaluated in the current study (either factors known and not measured, or factors unknown at this time). Also, we observed that compared to Hispanic patients, Non-Hispanic White and Non-Hispanic Black patients had higher proportions of HER2-low status irrespective of HR status.

In the present study, we performed separate analyses in HR-positive and TNBC patients, since HR-positive and TNBC are considered two distinct subtypes. Our study reported that HER2-low tumors were associated with lower pCR rates in both HR-positive and TNBC patients. In comparison, Denkert et al. only reported a significantly positive association of HER2-low tumors with pCR rates in HR-positive tumors [15], whereas Li et al. only observed significant differences in pCR rates between HER2-low and HER2-zero in HR-negative tumors [33]. This discrepancy may be due to the different NACT regimens implemented in the different studies or variability in the study cohorts. Furthermore, we observed that the pCR rate gradually increased with diagnosis year from 2010 to 2018, and such a large time duration could partially explain why the pCR rate in the present study was smaller than that in previous studies. [15, 16] In terms of survival, we observed that HER2-low patients had a significantly better OS regardless of the HR status. In previous studies, Denkert et al. observed that patients with HER2-low tumors showed a significantly longer OS than patients with HER2-zero tumors, which was also true in a subset of HR-negative BC patients [15]. Similarly, Almstedt et al. found that HER2-low patients had a significantly favorable OS compared with HER2-zero patients, and the survival differences remained significant in HR-positive tumors [34]. In general, the observed differences in treatment responses to NACT and long-term outcomes indicated that HER2-low and HER2-zero tumors could be meaningfully distinguished in clinical practice.

Intriguingly, in both HR-positive and TNBC patients, the higher pCR rate among those with HER2-zero tumors did not translate to better survival outcomes. We postulated this "paradox" could be related to unmeasured and unbalanced aggressive characteristics, e.g., Ki-67 and *TP53* mutations, which are considered correlates for aggressiveness and might explain the lower pCR rates and better OS in HER2-low tumors [8, 9, 15]. These findings highlight that while pCR is an important outcome, it is not always directly correlated with survival outcomes, which merits consideration when designing clinical trials and selecting the most appropriate study end points.

Another noteworthy finding was that, among patients not achieving pCR, HER2-low status was identified as a prognostic factor and associated with improved OS, while no significant difference in OS was observed between HER2-low and HER2-zero patients who achieved pCR. Hence, HER2-zero should be recognized as an additional adverse prognostic factor, specifically in patients not achieving pCR. This unique subgroup with worse outcomes (HER2-zero patients not achieving pCR) may be a critical cohort to evaluate in future studies.

This large cohort study applied PS-based methods to investigate potential differences in pCR rates and OS between HER2-low and HER2-zero patients with early-stage HR-positive or TNBC, ensuring balanced risk factors between HER2-zero and HER2-low subgroups. However, several limitations should be noted. Registry data in the NCDB may have some systematic errors in registrar coding or reporting, and no central HER2 testing was conducted. Additionally, the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) made significant updates to their guidelines in 2013 and 2018 in regards to HER2 testing in BC, such us reclassifying HER2 ultra-low as HER2-zero in the ASCO/CAP 2013 guideline, and eliminating ISH equivocal status in the ASCO/CAP 2018 guidelines [35–37]. Due to the overlapping time periods with our study, these updates are also reflected in our study, as we observed a higher

rate of HER2-zero BC diagnoses in the late 2010s compared to early 2010s (**Supplemental Table** S4). This could introduce a slight bias that potentially overestimates the survival differences between HER2-low and HER2-zero BC tumors, although detailed reporting of HER2 IHC and ISH status is recommended by ASCO/CAP 2023 guideline. [21] Despite applying PS-based methods to control measurable confounders, we cannot exclude residual bias from unmeasured confounders. Of note, Ki-67 is only available for patients diagnosed after 2018. Therefore, future studies including Ki-67 and other confounders are warranted. Although the E-values are small, achieving associations of unmeasured confounders with HER2 status or outcomes through pathways independent of all risk factors, remains challenging. [31] Finally, the NCDB lacks additional granularity, such as disease-free survival and more detailed systemic therapy regimen information, which could impact findings.

In conclusion, in both early-stage HR-positive TNBC patients, HER2-low status was associated with lower pCR rates compared with HER2-zero status. HER2-zero status might be recognized as a negative prognostic factor for OS in patients not achieving pCR, and better therapeutic strategies are needed to improve the prognosis of this subgroup.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10549-023-07171-z.

Acknowledgements The National Cancer Database (NCDB) is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society. The CoC's NCDB and the hospitals participating in the CoC's NCDB are the source of the de-identified data used herein; they have not verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors.

The authors thank Ms. Li Kong, President of Academy of Clinical Research and Study, for coordinating this research work and communication.

Author contributions Conception and design: Huiyue Li, Qichen Chen, Jennifer K. Plichta, Sheng Luo, Jian Zhang. Material preparation, data collection and analysis: Huiyue Li, Sheng Luo, Samantha M. Thomas, Jennifer K. Plichta. The first draft of the manuscript was written by Huiyue Li and Yizi Jin, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding This work was not funded.

Data availability The data that support the findings of this study are available from the National Cancer Database, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are, however, available from the authors upon reasonable request and with the permission of NCDB.

Declarations

Competing interests The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article. The authors have no relevant financial or non-financial interests to disclose. Dr. J. Plichta was the recipient of research funding by the Color Foundation (PI: Plichta). She serves on the National Comprehensive Cancer Network (NCCN) Breast Cancer Screening Committee. The content of this manuscript is solely the responsibility of the authors and does not necessarily represent the official view of the NIH and other organizations.

Ethical approval The present study was granted Duke University Institutional Review Board exemption and waiver of informed consent due to the use of de-identified patient data.

References

1. Giaquinto AN, Sung H, Miller KD, Kramer JL, Newman LA, Minihan A et al (2022) Breast cancer statistics. CA 72(6):524–541
2. Knape N, Park JH, Agala CB, Spanheimer P, Morrow M, Downs-Canner S et al (2023) Can we forgo sentinel lymph node biopsy in women aged ≥ 50 years with early-stage hormone-receptor-positive HER2-negative special histologic subtype breast cancer? Ann Surg Oncol 30(2):1042–1050. https://doi.org/10.1245/s10434-022-12626-6
3. Burguin A, Diorio C, Durocher F (2021) Breast cancer treatments: updates and new challenges. J Pers Med 11(8):808. https://doi.org/10.3390/jpm11080808
4. von Minckwitz G, Procter M, de Azambuja E, Zardavas D, Benyunes M, Viale G et al (2017) Adjuvant Pertuzumab and Trastuzumab in early HER2-positive breast cancer. N Engl J Med 377(2):122–131. https://doi.org/10.1056/NEJMoa1703643
5. Perez EA, Romond EH, Suman VJ, Jeong JH, Sledge G, Geyer CE Jr et al (2014) Trastuzumab plus adjuvant chemotherapy for human epidermal growth factor receptor 2-positive breast cancer: planned joint analysis of overall survival from NSABP B-31 and NCCTG N9831. J Clin Oncol 32(33):3744–3752. https://doi.org/10.1200/jco.2014.55.5730
6. Fehrenbacher L, Cecchini RS, Geyer CE Jr, Rastogi P, Costantino JP, Atkins JN et al (2020) NSABP B-47/NRG oncology Phase III randomized trial comparing adjuvant chemotherapy with or without Trastuzumab in high-risk invasive breast cancer negative for HER2 by FISH and With IHC 1+ or 2. J Clin Oncol 38(5):444–453. https://doi.org/10.1200/jco.19.01455
7. Gianni L, Lladó A, Bianchi G, Cortes J, Kellokumpu-Lehtinen PL, Cameron DA et al (2010) Open-label, phase II, multicenter, randomized study of the efficacy and safety of two dose levels of Pertuzumab, a human epidermal growth factor receptor 2 dimerization inhibitor, in patients with human epidermal growth factor receptor 2-negative metastatic breast cancer. J Clin Oncol 28(7):1131–1137. https://doi.org/10.1200/jco.2009.24.1661
8. Zhou S, Liu T, Kuang X, Zhen T, Shi H, Lin Y et al (2022) Comparison of clinicopathological characteristics and response to neoadjuvant chemotherapy between HER2-low and HER2-zero breast cancer. Breast 67:1–7. https://doi.org/10.1016/j.breast.2022.12.006
9. Li Y, Abudureheiyimu N, Mo H, Guan X, Lin S, Wang Z et al (2021) In real life, low-level HER2 expression may be associated with better outcome in HER2-negative breast cancer: a study of the national cancer center. China Front Oncol 11:774577. https://doi.org/10.3389/fonc.2021.774577

10. Schettini F, Chic N, Brasó-Maristany F, Paré L, Pascual T, Conte B et al (2021) Clinical, pathological, and PAM50 gene expression features of HER2-low breast cancer. NPJ Breast Cancer 7(1):1. https://doi.org/10.1038/s41523-020-00208-2
11. Modi S, Saura C, Yamashita T, Park YH, Kim SB, Tamura K et al (2020) Trastuzumab Deruxtecan in previously treated HER2-positive breast cancer. N Engl J Med 382(7):610–621. https://doi.org/10.1056/NEJMoa1914510
12. Modi S, Park H, Murthy RK, Iwata H, Tamura K, Tsurutani J et al (2020) Antitumor activity and safety of Trastuzumab Deruxtecan in patients with HER2-low-expressing advanced breast cancer: results from a phase Ib study. J Clin Oncol 38(17):1887–1896. https://doi.org/10.1200/jco.19.02318
13. Modi S, Jacot W, Yamashita T, Sohn J, Vidal M, Tokunaga E et al (2022) Trastuzumab Deruxtecan in previously treated HER2-low advanced breast cancer. N Engl J Med 387(1):9–20. https://doi.org/10.1056/NEJMoa2203690
14. Banerji U, van Herpen CML, Saura C, Thistlethwaite F, Lord S, Moreno V et al (2019) Trastuzumab duocarmazine in locally advanced and metastatic solid tumours and HER2-expressing breast cancer: a phase 1 dose-escalation and dose-expansion study. Lancet Oncol 20(8):1124–1135. https://doi.org/10.1016/s1470-2045(19)30328-6
15. Denkert C, Seither F, Schneeweiss A, Link T, Blohmer JU, Just M et al (2021) Clinical and molecular characteristics of HER2-low-positive breast cancer: pooled analysis of individual patient data from four prospective, neoadjuvant clinical trials. Lancet Oncol 22(8):1151–1161. https://doi.org/10.1016/s1470-2045(21)00301-6
16. Tarantino P, Jin Q, Tayob N, Jeselsohn RM, Schnitt SJ, Vincuilla J et al (2022) Prognostic and biologic significance of ERBB2-low expression in early-stage breast cancer. JAMA Oncol 8(8):1177–1183. https://doi.org/10.1001/jamaoncol.2022.2286
17. Kang S, Lee SH, Lee HJ, Jeong H, Jeong JH, Kim JE et al (2022) Pathological complete response, long-term outcomes, and recurrence patterns in HER2-low versus HER2-zero breast cancer after neoadjuvant chemotherapy. Eur J Cancer 176:30–40. https://doi.org/10.1016/j.ejca.2022.08.031
18. Alves FR, Gil L, Vasconcelos de Matos L, Baleiras A, Vasques C, Neves MT et al (2022) Impact of Human Epidermal Growth Factor Receptor 2 (HER2) low status in response to neoadjuvant chemotherapy in early breast cancer. Cureus 14(2):e22330. https://doi.org/10.7759/cureus.22330
19. de Moura LL, Cesca MG, Tavares MC, Santana DM, Saldanha EF, Guimarães PT et al (2021) HER2-low status and response to neoadjuvant chemotherapy in HER2 negative early breast cancer. Breast Cancer Res Treat 190(1):155–163. https://doi.org/10.1007/s10549-021-06365-7
20. Shao Y, Yu Y, Luo Z, Guan H, Zhu F, He Y et al (2022) Clinical, pathological complete response, and prognosis characteristics of HER2-low breast cancer in the neoadjuvant chemotherapy setting: a retrospective analysis. Ann Surg Oncol 29(13):8026–8034. https://doi.org/10.1245/s10434-022-12369-4
21. Wolff AC, Somerfield MR, Dowsett M, Hammond MEH, Hayes DF, McShane LM et al (2023) Human epidermal growth factor receptor 2 testing in breast cancer: ASCO-College of American Pathologists Guideline Update. J Clin Oncol 41(22):3867–3872. https://doi.org/10.1200/jco.22.02864
22. Perou CM, Sørlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA et al (2000) Molecular portraits of human breast tumours. Nature 406(6797):747–752. https://doi.org/10.1038/35021093
23. Sørlie T, Perou CM, Tibshirani R, Aas T, Geisler S, Johnsen H et al (2001) Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci U S A 98(19):10869–10874. https://doi.org/10.1073/pnas.191367098
24. Kennecke H, Yerushalmi R, Woods R, Cheang MC, Voduc D, Speers CH et al (2010) Metastatic behavior of breast cancer subtypes. J Clin Oncol 28(20):3271–3277. https://doi.org/10.1200/jco.2009.25.9820
25. Mallin K, Browner A, Palis B, Gay G, McCabe R, Nogueira L et al (2019) Incident cases captured in the national cancer database compared with those in U.S. Population Based Central Cancer Registries in 2012–2014. Ann Surg Oncol 26(6):1604–1612. https://doi.org/10.1245/s10434-019-07213-1
26. McShane LM, Altman DG, Sauerbrei W, Taube SE, Gion M, Clark GM (2006) REporting recommendations for tumor MARKer prognostic studies (REMARK). Breast Cancer Res Treat 100(2):229–235. https://doi.org/10.1007/s10549-006-9242-8
27. Plichta JK, Rushing CN, Lewis HC, Rooney MM, Blazer DG, Thomas SM et al (2023) Implications of missing data on reported breast cancer mortality. Breast Cancer Res Treat 197(1):177–187. https://doi.org/10.1007/s10549-022-06764-4
28. Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG et al (2009) Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ 338:b2393. https://doi.org/10.1136/bmj.b2393
29. White IR, Royston P, Wood AM (2011) Multiple imputation using chained equations: Issues and guidance for practice. Stat Med 30(4):377–399. https://doi.org/10.1002/sim.4067
30. Rubin DB (1996) Multiple imputation after 18+ years. J Am Stat Assoc 91(434):473–489
31. VanderWeele TJ, Ding P (2017) Sensitivity analysis in observational research: introducing the E-Value. Ann Intern Med 167(4):268–274. https://doi.org/10.7326/m16-2607
32. Haneuse S, VanderWeele TJ, Arterburn D (2019) Using the E-Value to assess the potential effect of unmeasured confounding in observational studies. JAMA 321(6):602–603. https://doi.org/10.1001/jama.2018.21554
33. Li JJ, Yu Y, Ge J (2023) HER2-low-positive and response to NACT and prognosis in HER2-negative non-metastatic BC. Breast Cancer. https://doi.org/10.1007/s12282-022-01431-4
34. Almstedt K, Heimes AS, Kappenberg F, Battista MJ, Lehr HA, Krajnak S et al (2022) Long-term prognostic significance of HER2-low and HER2-zero in node-negative breast cancer. Eur J Cancer 173:10–19. https://doi.org/10.1016/j.ejca.2022.06.012
35. Ahn S, Woo JW, Lee K, Park SY (2020) HER2 status in breast cancer: changes in guidelines and complicating factors for interpretation. J Pathol Transl Med 54(1):34–44. https://doi.org/10.4132/jptm.2019.11.03
36. Wolff AC, Hammond ME, Hicks DG, Dowsett M, McShane LM, Allison KH et al (2013) Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. J Clin Oncol 31(31):3997–4013. https://doi.org/10.1200/jco.2013.50.9984
37. Wolff AC, Hammond MEH, Allison KH, Harvey BE, Mangu PB, Bartlett JMS et al (2018) Human Epidermal Growth Factor Receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. J Clin Oncol 36(20):2105–2122. https://doi.org/10.1200/jco.2018.77.8738

Authors and Affiliations

Huiyue Li[1] · Jennifer K. Plichta[2,3,4] · Kan Li[5] · Yizi Jin[6,7] · Samantha M. Thomas[1,2] · Fei Ma[8] · Li Tang[9] · Qingyi Wei[2,3,10] · You-Wen He[11] · Qichen Chen[12] · Yuanyuan Guo[1] · Yueping Liu[13] · Jian Zhang[6,7] · Sheng Luo[1]

✉ Jian Zhang
syner2000@163.com

✉ Sheng Luo
sheng.luo@duke.edu

1 Department of Biostatistics and Bioinformatics, Duke University School of Medicine, Durham, NC 27710, USA

2 Duke Cancer Institute, Duke University, Durham, NC 27710, USA

3 Department of Population Health Sciences, Duke University School of Medicine, Durham, NC 27710, USA

4 Department of Surgery, Duke University School of Medicine, Durham, NC 27710, USA

5 Merck & Co., Inc., Rahway, NJ, USA

6 Department of Oncology, Shanghai Medical College, Fudan University, Shanghai 200032, China

7 Department of Phase I Clinical Trial Center, Fudan University Shanghai Cancer Center, No. 270, Dong'an Road, Shanghai 200032, China

8 Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

9 Department of Biostatistics, St. Jude Children's Research Hospital, Memphis, TN, USA

10 Department of Medicine, Duke University School of Medicine, Durham, NC, USA

11 Department of Integrative Immunobiology, Duke University School of Medicine, Durham, NC, USA

12 Department of Hepatobiliary Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

13 Department of Pathology, the Fourth Hospital of Hebei Medical University, Shijiazhuang, Hebei, China