Original Article

Association between human epidermal growth factor receptor 2 status, namely low and zero expression, and prognosis in hormone receptor-positive breast cancer: a single-center retrospective study

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Background: The recently developed anti-human epidermal growth factor receptor 2 (HER2) therapy has substantially improved the prognosis of HER2-positive breast cancer. The DESTINY-Breast04 trial results showed that trastuzumab deruxtecan (T-DXd) significantly prolonged the survival of patients with HER2-low breast cancer, thus presenting a paradigm shift in anti-HER2 therapy. This may facilitate a change in the treatment strategy for HER2-low breast cancer. However, the implication of HER2-low in hormone receptor (HR)-positive breast cancer is unclear. In this retrospective study, we aimed to reveal the association between HER2 status, namely HER2-low and HER2-zero, and prognosis in HR-positive breast cancer.

Methods: We collected the data of 247 patients with estrogen receptor (ER)-positive/HER2-negative breast cancer (159 with HER2-low and 88 with HER2-zero breast cancer) who underwent surgery. Patients were divided into HER2-low and HER2-zero groups. Univariate analysis was performed to evaluate the baseline characteristics using the Wilcoxon rank sum test and Fisher's exact test. Survival analysis of the HER2-low and HER2-zero groups was performed using the Kaplan-Meier method.

Results: The median observation period was 2,706 days, and the median period until recurrence was 1,380 days; 25 patients (10%) had recurrences. Age (P=0.004) and menopausal status (P=0.04) were significant variables in the univariate analysis of baseline characteristics. In the subgroup analysis of luminal A- and B-like breast cancers, there was a significant difference in overall survival (OS) only in patients with luminal A-like breast cancer, but relapse-free survival (RFS) of the HER2-low luminal B-like cancer subgroups tended to be relatively short.

Conclusions: We inferred that the HER2-low and HER2-zero statuses do not affect the RFS and OS of patients with ER-positive breast cancer. The prognostic significance of HER2-low or HER2-zero status in luminal A- and B-like breast cancers might differ, and a new treatment strategy is required for the HER2-low subgroup.

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Introduction

Background

Human epidermal growth factor receptor 2 (HER2)-positive breast cancer is defined as cancer with an immunohistochemistry (IHC) score of 3+ or with an IHC score of 2+ along with gene amplification as assessed using in situ hybridization (ISH) (1). It is more aggressive and has a poorer prognosis than hormone receptor (HR)-positive/HER2-negative breast cancer. The frequency of HER2-positive breast cancer is 15–20% among all breast cancer subtypes (2), and the incidence of HR-positive/HER2-positive and HR-negative/HER2-positive breast cancer is 16–21 and 7–10 per 100,000 individuals, respectively (3). In addition to being an influencing factor of poor prognosis, HER2 is a predictor of the efficacy of anti-HER2 therapy. The prognosis for HER2-positive breast cancer has considerably improved following the development of anti-HER2 therapy, and the 5-year survival rate of patients with HER2-positive breast cancer ranges from 77% to 92% (3). However, only patients with HER2-positive breast cancer, not HER2-negative breast cancer, are eligible for anti-HER2 therapy.

Trastuzumab deruxtecan (T-DXd), a new anti-HER2 drug, is an antibody-drug conjugate, consisting of a humanized monoclonal antibody against HER2 linked with a camptothecin derivative with topoisomerase I inhibitor activity. It is effective for HER2-positive breast cancer with resistance to conventional anti-HER2 therapy (4,5). Moreover, the DESTINY-Breast04 trial results showed that T-DXd significantly prolonged progression-free survival and overall survival (OS) when compared with the physician's choice of chemotherapy for HER2-low breast cancer, with an IHC score of 2+ without gene amplification as assessed using ISH or an IHC score of 1+ (6). These results present a paradigm shift in anti-HER2 therapy and may lead to a change in the treatment strategy for HER2-low breast cancer.

Highlight box

Key findings

- The human epidermal growth factor receptor 2 (HER2)-zero luminal A-like and HER2-low luminal B-like breast cancer subgroups exhibited poor overall survival (OS) and a trend towards a relatively short relapse-free survival (RFS), respectively.

What is known and what is new?

- HER2 is a prognostic factor and predictor of the efficacy of anti-HER2 therapy. The prognosis for HER2-positive breast cancer has improved considerably following the development of anti-HER2 therapy; however, HER2-negative breast cancer prognosis remains the same. Recently, trastuzumab deruxtecan (T-DXd) significantly prolonged progression-free survival and OS for HER2-positive and HER2-low breast cancer. The implications of HER2-low in hormone receptor-positive breast cancer are unclear.
- We found that the 5-year RFS rate of patients with luminal A-like breast cancer was 98.6% [95% confidential interval (CI): 95.8–100%] in the HER2-low group and 97.6% (95% CI: 93.0–100%) in the HER2-zero group. The 5-year RFS rate of patients with luminal B-like breast cancer was 93.5% (95% CI: 88.2–99.2%) in the HER2-low group and 100% (95% CI: 100–100%) in the HER2-zero group.

What is the implication, and what should change now?

- The prognostic significance of HER2 status in luminal A- and B-like breast cancers may differ. Treatment strategies for HER2-low breast cancer should be considered in future research, as they could facilitate the identification of such subgroups and improve prognosis following treatment with T-DXd and newly developed drugs.

Rationale and knowledge gap

HER2-low breast cancer accounts for 45–55% of all breast cancers (7). The HER2 status indicates dynamic changes as the amount of estrogen receptor (ER) expression increases (8) and advances breast cancer progression (9). Considering these reports, if patients with metastatic HER2-zero breast cancer undergo re-biopsy at the metastatic site, they may be eligible for the administration of T-DXd to prolong their survival.

Reviews on HER2-low breast cancer have been published recently, but the implications and prognostic effects of HER2-low in HR-positive early breast cancer are

controversial (10-12).

Objective

In this retrospective study, we aimed to reveal the association between HER2 status, namely HER2-low and HER2-zero, and the prognosis of HR-positive breast cancer. Additionally, we examined the interpretation of HER2 status for luminal A- and B-like breast cancer subgroups in a real-world clinical setting and further tried to explore treatment possibilities in these populations. We present this article in accordance with the REMARK reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-2216/rc).

Methods

Patients

We retrospectively reviewed the charts of 247 patients with ER-positive/HER2-negative breast cancer who underwent surgery at Sasebo City General Hospital, Japan, between January 2011 and December 2018, and collected their data. The data of male patients with breast cancer and patients with pathological stage 0 or IV cancer according to the tumor-node-metastasis (TNM) classification system (8th edition) (13) and inflammatory breast cancer were excluded. Patients were divided into two groups—those with HER2-low cancer, defined as having an IHC score of 2+ without gene amplification as assessed using ISH or an IHC score of 1+, and those with HER2-zero cancer, defined as having an IHC score of 0 using the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines (1). This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Sasebo City General Hospital, Nagasaki, Japan (No. 2021-A018). Individual consent for this retrospective analysis was waived and an opt-out approach was used.

Clinicopathological assessments and molecular subtypes

Clinical variables included age, body mass index (BMI), and menopausal status. Histopathological variables were pathological TNM staging, excluding that of patients on neoadjuvant chemotherapy (NAC), progesterone receptor (PR) staining, HER2 expression, Ki-67 staining, histological grade (HG), and diagnosis of histological classification. The luminal A-like subtype was ER-positive/PR-positive/HER2-negative/Ki-67 low, and the luminal B-like subtype was ER-positive/PR-negative or low/HER2-negative/Ki-67 high (14,15). In this study, we considered Ki-67 low as <20%, Ki-67 high as ≥20%, PR-negative as 0%, and PR-low as 1–9%. We used the Nottingham Histologic Scoring system (16,17) to determine the HG.

Treatment

Treatment-related variables included NAC, various methods of breast and axillary surgery, and adjuvant therapy, including endocrine therapy (ET), chemotherapy, and radiation therapy. Most patients with large tumors or metastatic axillary lymph nodes received NAC, whereas others did not receive chemotherapy. Breast surgeries, including partial mastectomy (Bp) and total mastectomy (Bt), were selected based on the degree of tumor progression, the patient's wish, and the physician's recommendations. Patients with clinical axillary lymph node metastasis or sentinel lymph node metastasis upon sentinel lymph node biopsy (SLNB) underwent axillary lymph node dissection (ALND). Patients with ER-positive breast cancer received ET. According to ET, premenopausal patients were treated with tamoxifen (TAM) for 10 years, and those with high-risk recurrence were treated with ovarian suppression therapy using a luteinizing hormone-releasing hormone agonist for 2 years. Postmenopausal patients were treated with aromatase inhibitors (AIs) for 5 years. If the patients were postmenopausal at the end of 5 years of TAM treatment, they were treated with additional AI for 2 to 3 years. Adjuvant chemotherapy was administered to patients with lymph node metastasis, pathological grade T3 or T4, high Ki-67 or HG3. Residual breast irradiation was administered to patients who underwent Bp, and those with four or more lymph node metastases received irradiation to the regional lymph node area. Patients with four or more lymph node metastases who underwent Bt received irradiation to the chest wall and regional lymph node area.

Statistical analysis

All statistical analyses were performed using R 4.2.2 software (R Foundation for Statistical Computing, Vienna, Austria). Continuous and categorical data are expressed as median [interquartile range (IQR)] and number (%), respectively. Univariate analysis was performed to evaluate the baseline characteristics using the Wilcoxon rank sum

test and Fisher's exact test. Survival analysis was performed using the Kaplan-Meier method, and the survival of patients with HER2-low was compared with that of patients with HER2-zero using the log-rank test. We defined relapse-free survival (RFS) as the period ranging from the day of operation to the day of recurrence or death from any cause and OS as the period ranging from the day of operation to the day of death from any cause. When a proportional hazard was established from the results of survival analyses, the variables which might affect the results were calculated as the hazard ratio and 95% confidential interval (CI) using Cox regression analysis. Statistical significance was set at $P \leq 0.05$ for the univariate analysis, log-rank test, and Cox regression analysis.

Results

Patient characteristics

In total, 247 patients (159 with HER2-low and 88 with HER2-zero status) were included in this study. *Table 1* presents the characteristics of ER-positive breast cancer with HER2-low or HER2-zero status. In patients with HER2-low status, 26 (16.4%) were premenopausal, and 133 (83.6%) were postmenopausal, with median age of 67 (IQR, 59–76) years and BMI of 23.0 (IQR 20.9–25.4) kg/m^2. With respect to surgery, 74 (46.5%), 85 (53.5%), 131 (82.4%), and 28 (17.6%) patients underwent Bp, Bt, SLNB, and ALND, respectively. In TNM staging, the number of patients with pathological grades T1, T2, T3, and T4 was 117 (75.5%), 35 (22.6%), 2 (1.3%), and 1 (0.6%), respectively, and that of patients with pathological grades N0, N1, N2, and N3 was 122 (78.7%), 23 (14.8%), 7 (4.5%), and 3 (1.9%), respectively. Thirty-nine (24.5%) patients had PR-negative or PR-low cancer cells, and 120 (75.5%) patients had PR-positive cancer cells. Ki-67 expression was observed in 15 (IQR, 9–25) patients; regarding HG, 62 (41.3%) patients had HG1, 66 (44.0%) had HG2, and 22 (14.7%) patients had HG3. Luminal A-like breast cancer was observed in 79 (49.7%) patients, and luminal B-like breast cancer was observed in 80 (50.3%) patients. Diagnosis with invasive ductal carcinoma (IDC), invasive lobular carcinoma (ILC), and other invasive carcinomas occurred in 128 (80.5%), 11 (6.9%), and 20 (12.6%) patients, respectively. Four (2.5%) and 29 (18.2%) patients received NAC and adjuvant chemotherapy, respectively. ET was administered to 156 (98.1%) patients, and 74 (46.5%) patients received radiotherapy: 64 (40.3%) patients received radiotherapy after breast-conserving surgery and 10 (6.3%) received regional lymph node irradiation. Three (1.9%) patients had local recurrences and 14 (8.8%) had distant recurrences. The observation period was 2,679 (IQR 2,008–3,681) days, and 7 (4.4%) patients died of varying causes.

For patients with HER2-zero, the median age was 62 (IQR, 52–71) years, BMI was 22.8 (IQR, 20.8–25.1) kg/m^2, number of premenopausal patients was 24 (27.3%), and number of postmenopausal patients was 64 (72.7%). Regarding surgery, the number of patients who underwent Bp, Bt, SLNB, and ALND was 43 (48.9%), 45 (51.1%), 74 (84.1%), and 14 (15.9%), respectively. Regarding TNM staging, the number of patients with pathological grades T1, T2, T3, and T4 was 67 (80.7%), 15 (18.1%), 0, and 1 (1.2%), respectively, and that of patients with pathological grades N0, N1, N2, and N3 was 66 (79.5%), 14 (16.9%), 2 (2.4%), and 1 (1.2%), respectively. Twenty-two (25.0%) patients had PR-negative or low cancer, and 66 (75.0%) patients had PR-positive cancer. The expression of Ki-67 was observed in 16 (IQR, 4–33) patients; regarding HG, 28 (33.3%) patients had HG1, 47 (56.0%) patients had HG2, and 9 (10.7%) patients had HG3. Luminal A-like breast cancer was observed in 47 (53.4%) patients, and luminal B-like breast cancer was observed in 41 (46.6%) patients. Diagnosis with IDC, ILC, and other invasive carcinomas occurred in 71 (80.7%), 5 (5.7%), and 12 (13.6%) patients, respectively. Five (5.7%) and 25 (28.4%) patients received NAC and adjuvant chemotherapy, respectively. ET was administered to 87 (98.9%) patients, and 46 (52.3%) patients received radiotherapy: 42 (47.7%) patients received radiotherapy after breast-conserving surgery and 4 (4.5%) received regional lymph node irradiation. Three (3.4%) patients had local recurrences and 5 (5.7%) had distant recurrences. The observation period was 2,773 (IQR, 2,066–3,202) days, and 6 (6.8%) patients died of varying causes.

Significant variables identified using the univariate analysis included age (P=0.004) and menopausal status (P=0.04): the patients with HER2-zero were younger and premenopausal when compared to the patients with HER2-low in this study (*Table 1*).

RFS and OS

Figure 1 shows the RFS and OS of all patients. The 5-year RFS rate of all patients with ER-positive breast cancer was 96.0% (95% CI: 92.8–99.2%) in the HER2-low group and 98.7% (95% CI: 96.3–100%) in the HER2-zero group. In addition, the 5-year OS rate of all patients with ER-positive

Table 1 Characteristics of ER-positive breast cancer with HER2-low (n=159) or HER2-zero status (n=88)

Variables	HER2-low (n=159)	HER2-zero (n=88)	P value
Age (years)	67 [59, 76]	62 [52, 71]	0.004
BMI (kg/m^2)	23.0 [20.9, 25.4]	22.8 [20.8, 25.1]	0.90
Menopausal status			0.04
Premenopausal	26 (16.4)	24 (27.3)	
Postmenopausal	133 (83.6)	64 (72.7)	
Breast surgery			0.70
Bp	74 (46.5)	43 (48.9)	
Bt	85 (53.5)	45 (51.1)	
Axillary surgery			0.70
SLNB	131 (82.4)	74 (84.1)	
ALND	28 (17.6)	14 (15.9)	
Pathological grade T	N=155	N=83	0.60
T1	117 (75.5)	67 (80.7)	
T2	35 (22.6)	15 (18.1)	
T3	2 (1.3)	0	
T4	1 (0.6)	1 (1.2)	
Pathological grade N	N=155	N=83	0.90
N0	122 (78.7)	66 (79.5)	
N1	23 (14.8)	14 (16.9)	
N2	7 (4.5)	2 (2.4)	
N3	3 (1.9)	1 (1.2)	
PR			0.90
Negative/low	39 (24.5)	22 (25.0)	
Positive	120 (75.5)	66 (75.0)	
Ki-67	15 [9, 25]	16 [4, 33]	0.70
HG	N=150	N=84	0.20
Grade I	62 (41.3)	28 (33.3)	
Grade II	66 (44.0)	47 (56.0)	
Grade III	22 (14.7)	9 (10.7)	
Luminal type			0.60
Luminal A-like	79 (49.7)	47 (53.4)	
Luminal B-like	80 (50.3)	41 (46.6)	
Diagnosis			0.90
IDC	128 (80.5)	71 (80.7)	
ILC	11 (6.9)	5 (5.7)	
Others	20 (12.6)	12 (13.6)	

Table 1 (*continued*)

Table 1 (*continued*)

Variables	HER2-low (n=159)	HER2-zero (n=88)	P value
ET	156 (98.1)	87 (98.9)	0.90
Chemotherapy			0.07
NAC	4 (2.5)	5 (5.7)	
AC	29 (18.2)	25 (28.4)	
Radiotherapy			0.50
Residual breast	64 (40.3)	42 (47.7)	
Regional lymph nodes	10 (6.3)	4 (4.5)	
Recurrence			0.50
Local	3 (1.9)	3 (3.4)	
Distant	14 (8.8)	5 (5.7)	
Cause of death			0.11
Cancer	5 (3.1)	1 (1.1)	
Others	2 (1.3)	5 (5.7)	
Observation period (days)	2,679 [2,008, 3,681]	2,773 [2,066, 3,202]	0.20

Continuous data are expressed as median [IQR]; categorical data are expressed as n (%). ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; BMI, body mass index; Bp, partial mastectomy; Bt, total mastectomy; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection; PR, progesterone receptor; HG, histological grade; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; ET, endocrine therapy; NAC, neoadjuvant chemotherapy; AC, adjuvant chemotherapy; IQR, interquartile range.

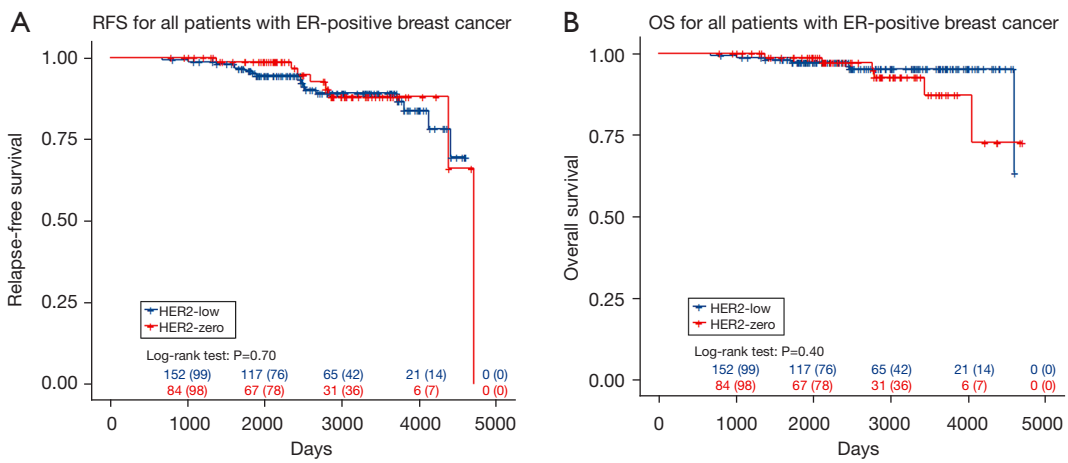

Figure 1 Survival analysis using Kaplan-Meier curves for ER-positive breast cancer in the HER2-low and HER2-zero groups. (A) RFS and (B) OS. P values were analyzed using the log-rank test. RFS, relapse-free survival; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; OS, overall survival.

breast cancer was 97.3% (95% CI: 94.8–100%) in the HER2-low group and 98.7% (95% CI: 96.3–100%) in the HER2-zero group. No significant difference was observed in the RFS and OS rates among all patients with HER2-low and HER2-zero ER-positive breast cancer.

Subgroup analysis

Of the 126 patients with luminal A-like breast cancer, 79 had HER2-low and 47 had HER2-zero cancer. Of the 121 patients with luminal B-like breast cancer, 80 had

HER2-low and 41 had HER2-zero cancer (*Table 2*). In the univariate analysis according to luminal type, the significant variables were BMI (P=0.02) and cause of death (P=0.03) for luminal A-like breast cancer, and age (P=0.02), BMI (P=0.02), chemotherapy administered (P=0.009), and recurrence (P=0.02) for luminal B-like breast cancer. The HER2-zero group had a lower BMI and more deaths due to causes unrelated to cancer than the HER2-low group of luminal A-like breast cancer. Moreover, the HER2-zero group was younger, received chemotherapy, and had a higher BMI than the HER2-low group, while the HER2-low group relapsed distant metastasis when compared to the HER2-zero group of luminal B-like breast cancer.

Figure 2 shows the RFS and OS of patients with luminal A- or B-like breast cancer by HER2-low and HER2-zero status. The 5-year RFS rate of patients with luminal A-like breast cancer was 98.6% (95% CI: 95.8–100%) in the HER2-low group and 97.6% (95% CI: 93.0–100%) in the HER2-zero group (*Figure 2A*). In addition, the 5-year OS rate of patients with luminal A-like breast cancer was 98.5% (95% CI: 95.7–100%) in the HER2-low group and 97.6% (95% CI: 93.0–100%) in the HER2-zero group (*Figure 2B*). However, the 5-year RFS rate of patients with luminal B-like breast cancer was 93.5% (95% CI: 88.2–99.2%) in the HER2-low group and 100% (95% CI: 100–100%) in the HER2-zero group (*Figure 2C*). Moreover, the 5-year OS rate for patients with luminal B-like breast cancer was 96.2% (95% CI: 92.0–100%) in the HER2-low group and 100% (95% CI: 100–100%) in the HER2-zero group (*Figure 2D*). A significant difference was observed in the OS based on only luminal A-like breast cancer (P=0.01). However, there may have been a trend towards a shorter RFS in the HER2-low luminal B-like breast cancer subgroup. No significant difference was observed in Cox regression analysis of OS for luminal A-like and RFS for luminal B-like breast cancer in subgroups (*Table 3*).

Discussion

Key findings

The patients with HER2-low ER-positive breast cancer were older and postmenopausal when compared to those with HER2-zero in this study. In subgroup analyses, the HER2-zero group had a lower BMI and more deaths due to causes unrelated to cancer, than the HER2-low group of luminal A-like breast cancer. Moreover, the HER2-zero group was younger, received chemotherapy, and had a higher BMI than the HER2-low group, while the HER2-low group relapsed distant metastasis than the HER2-zero group of luminal B-like breast cancer. No significant difference was observed between the RFS and OS for all patients with HER2-low and HER2-zero ER-positive breast cancer. However, subgroup analysis of luminal A- and B-like breast cancer showed a significant difference in OS only in patients with luminal A-like breast cancer, and there might have been a trend towards a relatively poor RFS in patients with HER2-low luminal B-like breast cancers.

Strengths and limitations

The main strength of this study was that it examined the significance of HER2 status for luminal A- and B-like breast cancer subgroups in a real-world clinical setting. This study had three main limitations. First, this was a single-center, retrospective study with a small number of patients, and we were unable to eliminate selection bias and collect data. Second, ER-positive breast cancer exhibited a tendency for late recurrence. Finally, this study is limited by the short observation period.

Comparison with similar studies and explanation of findings

The association between HER2 status, namely HER2-low and HER2-zero, and the prognosis of ER-positive breast cancer is controversial. Previous studies suggest that HER2-low breast cancer has a poorer prognosis than HER2-negative breast cancer (18,19). Eggemann *et al.* (20) reported that HER2-low status is associated with poor prognosis for ER-positive breast cancer, but not for ER-negative breast cancer. However, the HER2-low status in the aforementioned study was defined by an IHC score of 2+ without gene amplification as assessed using ISH, and HER2-zero status by an IHC score of 1+ or 0.

Recent studies have shown that HER2-low (IHC score 1+ or IHC score of 2+ with negative ISH) breast cancer has a more optimized prognosis than HER2-zero (IHC score 0) breast cancer and there is no difference between their prognoses. Denkert *et al.* (21) and Zhou *et al.* (22) reported that the OS of patients with HER2-low breast cancer was prolonged when compared to that of patients with HER2-zero breast cancer. The ER status may affect the OS of patients with HER2-low and HER2-zero ER-negative breast cancer, but not that of patients with ER-positive breast cancer. Mutai *et al.* (23) reported that HER2-low

Table 2 Characteristics of subgroups by luminal type divided by HER2-low and HER2-zero status

Variables	Luminal A-like			Luminal B-like		
	HER2-low (n=79)	HER2-zero (n=47)	P value	HER2-low (n=80)	HER2-zero (n=41)	P value
Age (years)	69 [60, 77]	65 [52, 73]	0.07	66 [59, 74]	60 [51, 70]	0.02
BMI (kg/m^2)	24.3 [21.3, 26.8]	22.4 [20.6, 24.6]	0.02	22.3 [20.3, 24.1]	23.4 [21.6, 26.8]	0.02
Menopausal status			0.30			0.06
Premenopausal	14 (17.7)	12 (25.5)		12 (15.0)	12 (29.3)	
Postmenopausal	65 (82.3)	35 (74.5)		68 (85.0)	29 (70.7)	
Breast surgery			0.90			0.50
Bp	36 (45.6)	21 (44.7)		38 (47.5)	22 (53.7)	
Bt	43 (54.4)	26 (55.3)		42 (52.5)	19 (46.3)	
Axillary surgery			0.90			0.60
SLNB	66 (83.5)	39 (83.0)		65 (81.3)	35 (85.4)	
ALND	13 (16.5)	8 (17.0)		15 (18.8)	6 (14.6)	
Pathological grade T	N=76	N=45	0.90	N=79	N=38	0.60
T1	57 (75.0)	37 (82.2)		60 (75.9)	30 (78.9)	
T2	17 (22.4)	8 (17.8)		18 (22.8)	7 (18.4)	
T3	1 (1.3)	0		1 (1.3)	0	
T4	1 (1.3)	0		0	1 (2.6)	
Pathological grade N	N=76	N=45	0.90	N=79	N=38	0.50
N0	61 (80.3)	37 (82.2)		61 (77.2)	29 (76.3)	
N1	10 (13.2)	6 (13.3)		13 (16.5)	8 (21.1)	
N2	3 (3.9)	2 (4.4)		4 (5.1)	0	
N3	2 (2.6)	0		1 (1.3)	1 (2.6)	
PR						0.60
Negative/low	0	0		39 (48.8)	22 (53.7)	
Positive	79 (100.0)	47 (100.0)		41 (51.3)	19 (46.3)	
Ki-67	11 [5.4, 14.7]	8.2 [2.8, 15.6]	0.40	24 [15, 29]	31 [7, 44]	0.30
HG	N=75	N=46	0.08	N=75	N=38	0.90
Grade I	40 (53.3)	17 (37.0)		22 (29.3)	11 (28.9)	
Grade II	28 (37.3)	27 (58.7)		38 (50.7)	20 (52.6)	
Grade III	7 (9.3)	2 (4.3)		15 (20.0)	7 (18.4)	
Diagnosis			0.70			0.40
IDC	63 (79.7)	36 (76.6)		65 (81.3)	35 (85.4)	
ILC	4 (5.1)	4 (8.5)		7 (8.8)	1 (2.4)	
Others	12 (15.2)	7 (14.9)		8 (10.0)	5 (12.2)	
ET	78 (98.7)	47 (100.0)	0.90	78 (97.5)	40 (97.6)	0.90

Table 2 (*continued*)

Table 2 (*continued*)

Variables	Luminal A-like			Luminal B-like		
	HER2-low (n=79)	HER2-zero (n=47)	P value	HER2-low (n=80)	HER2-zero (n=41)	P value
Chemotherapy			0.80			0.009
NAC	3 (3.8)	2 (4.3)		1 (1.3)	3 (7.3)	
AC	6 (7.6)	5 (10.6)		23 (28.8)	20 (48.8)	
Radiotherapy			0.40			0.50
Residual breast	30 (38.0)	21 (44.7)		34 (42.5)	21 (51.2)	
Regional lymph nodes	6 (7.6)	1 (2.1)		4 (5.0)	3 (7.3)	
Recurrence			0.50			0.02
Local	1 (1.3)	0		2 (2.5)	3 (7.3)	
Distant	4 (5.1)	5 (10.6)		10 (12.5)	0	
Cause of death			0.03			0.30
Cancer	0	1 (2.1)		5 (6.3)	0	
Others	1 (1.3)	4 (8.5)		1 (1.3)	1 (2.4)	
Observation period (days)	2,661 [1,999, 3,750]	2,547 [2,028, 3,340]	0.40	2,694 [2,047, 3,534]	2,827 [2,083, 3,132]	0.50

Continuous data are expressed as median [IQR]; categorical data are expressed as n (%). HER2, human epidermal growth factor receptor 2; BMI, body mass index; Bp, partial mastectomy; Bt, total mastectomy; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection; PR, progesterone receptor; HG, histological grade; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; ET, endocrine therapy; NAC, neoadjuvant chemotherapy; AC, adjuvant chemotherapy; IQR, interquartile range.

status is associated with a more optimized prognosis than that of HER2-zero status in ER-positive breast cancer with a high recurrence score (RS), whereas no difference was observed between the OS for patients with HER2-low and HER2-zero breast cancer characterized by a low RS. These results suggest that HER2 status, namely HER2-low and HER2-zero, may affect prognosis in certain populations with ER-positive breast cancer.

Among studies reporting no difference between the OS of patients with HER2-low and HER2-zero patients with breast cancer, Qi *et al.* (24) showed that the OS of patients with HER2-low was longer than that of patients with HER2-zero breast cancer with a high Ki-67 index. Moreover, Horisawa *et al.* (25) suggested that HER2-low breast cancer tended to have a more optimized prognosis than that of HER2-zero breast cancer regardless of HR status. With respect to the intrinsic subtypes classified by Predictor Analysis of Microarray (PAM)50, HER2-enrichment and ERBB2 overexpression were more common in HER2-low than in HER2-zero breast cancer (26). Moreover, Schettini *et al.* (27) reported that basal-like breast cancer accounted for 43.7%, and luminal A- and B-like breast cancer accounted for 47.6% of HER2-zero breast cancer; however, basal-like breast cancer accounted for 9.8–15.2% and luminal A- and B-like breast cancer accounted for 77.0–84.4% of HER2-low breast cancer.

Two reasons may underlie our findings of poor OS for patients with HER2-zero status with luminal A-like breast cancer. First, this result was from a subgroup analysis of a small number of patients with luminal A-like breast cancer (28). Second, more patients with HER2-zero luminal A-like breast cancer died due to varying causes when compared to those with HER2-low. The relatively poor RFS of HER2-low patients with luminal B-like cancer may be due to the fact that patients with HER2-zero status received more NAC or adjuvant chemotherapy than those with HER2-low status.

Implications and actions needed

The significance of HER2 status, namely HER2-low and HER2-zero, in ER-positive breast cancer may vary in subgroups classified according to luminal A- or B-like and genetic testing. Clinical trials have shown that trastuzumab, pertuzumab, and T-DM1 were ineffective in the treatment

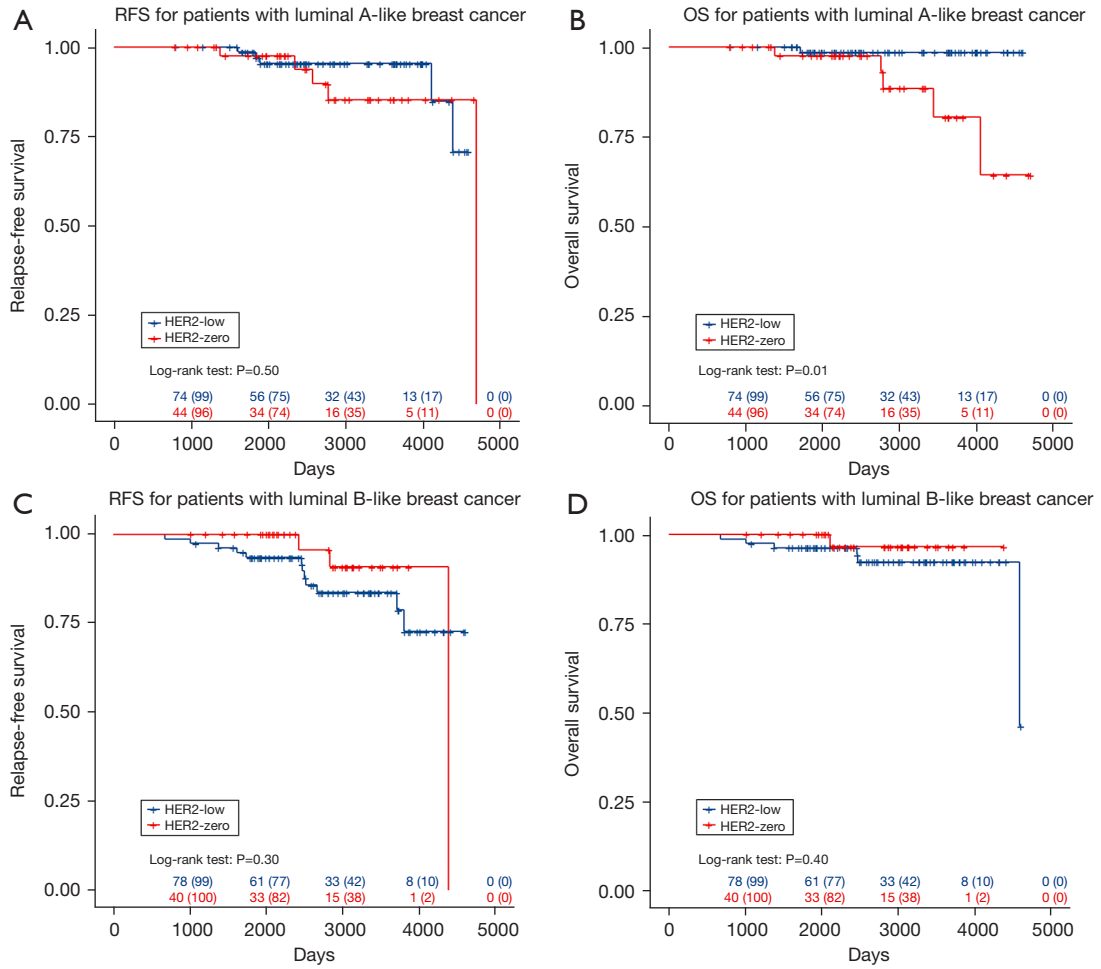

Figure 2 Survival analysis using Kaplan-Meier curves for patients with luminal A-like or B-like breast cancer by HER2-low and HER2-zero status. (A) RFS and (B) OS of patients with luminal A-like breast cancer. (C) RFS and (D) OS of patients with luminal B-like breast cancer. P values were analyzed using the log-rank test. RFS, relapse-free survival; HER2, human epidermal growth factor receptor 2; OS, overall survival.

Table 3 Cox regression analysis of OS for luminal A-like and RFS for luminal B-like breast cancer in subgroups

Variables	HR	P value (95% CI)
A: luminal A-like		
Age	1.04	0.30 (0.97 to 1.11)
BMI	0.88	0.30 (0.68 to 1.14)
HG	0.70	0.60 (0.20 to 2.46)
B: luminal B-like		
Age	1.04	0.10 (0.99 to 1.09)
BMI	0.93	0.30 (0.79 to 1.09)
Menopausal status	1.46	0.60 (0.41 to 5.21)
Chemotherapy	0.38	0.13 (0.11 to 1.34)

OS, overall survival; RFS, relapse-free survival; HR, hazard ratio; CI, confidence interval; BMI, body mass index; HG, histological grade.

of HER2-low breast cancer (29-32). The DESTINY-Breast01 (4) and 04 (6) trials showed that T-DXd is effective in treating HER2-low breast cancer. This efficacy for HER2-low breast cancer is explained bystander effects wherein T-DXd is taken up by HER2-expressed tumor cells and a camptothecin derivative with topoisomerase I inhibitor activity is released, whereby it exerts a cytotoxic effect on the surrounding HER2-negative tumor cells (4). However, the results should be interpreted with caution as the DESTINY-Breast04 trial excluded patients with HER2-zero (0 IHC) breast cancer. Moreover, Mosele *et al.* (33) suggested that certain patients with HER2-zero breast cancer responded to T-DXd. Whether T-DXd is effective in the treatment of HER2-zero breast cancer remains unclear; however, it is effective in the treatment of HER2-low and HER2-positive breast cancer. Based on the results of our study, especially in HER2-low luminal B-like breast cancer, survival for certain populations of these subgroups may be improved by T-DXd treatment. Treatment strategies for HER2-low breast cancer should be considered in future research, which could facilitate identification of such subgroups and improving prognosis following treatment with T-DXd and newly developed drugs.

Conclusions

This study indicates that the HER2 expression status, namely HER2-low and HER2-zero, does not affect the RFS and OS of patients with ER-positive breast cancer. However, it suggested that the poor OS only in patients with HER2-zero luminal A-like breast cancer, and there may have been a trend towards a relatively poor RFS in patients with HER2-low luminal B-like breast cancers. The prognostic significance of HER2 status in luminal A- and B-like breast cancers may differ; there is a need to identify the population with these cancer subtypes and develop a new treatment strategy for the HER2-low subgroup.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Sasebo City General Hospital, Nagasaki, Japan (No. 2021-A018). Individual consent for this retrospective analysis was waived and an opt-out approach was used.

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