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Original Research

Pathological complete response, long-term outcomes, and recurrence patterns in HER2-low versus HER2-zero breast cancer after neoadjuvant chemotherapy

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Abstract ***Background:*** The interest in HER2-low breast cancer (BC) has increased in recent years with the development of novel anti-HER2 antibody–drug conjugates. Here, we investigated the clinical outcomes and relapse patterns of patients with HER2-low or -zero BCs in an Asian population.

Methods: We retrospectively identified HER2-low or -zero BC patients with stage I–III tumours who were treated with neoadjuvant chemotherapy and underwent curative surgery, between 2014 and 2018 at Asan Medical Center, Seoul, Korea.

Results: A total of 818 and 754 HER2-zero and HER2-low BC patients, respectively, were consecutively included in this analysis. The HER2-low group had more hormone receptor [HR]-positive patients (81% versus 56%, $P < 0.001$). The HER2-zero group had a higher proportion of patients who achieved pathological complete response (pCR) (14.7% versus 9.8%, $P = 0.003$); however, no significant differences of pCR rate by HER2 status were identified in

Abbreviations: BC, Breast Cancer; HER2, Human Epidermal Growth Factor Receptor 2; ASCO/CAP, American Society of Clinical Oncology/College of American Pathologist; IHC, Immunohistochemistry; ISH, In situ hybridisation; ADCs, Antibody drug conjugates; T-DXd, Trastuzumab deruxtecan; pCR, Pathological complete response.

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the HR-positive (P = 0.4) and HR-negative groups (P = 0.3) when analysed separately. The HER2-low BC cases had higher 5-year overall survival (OS) and disease-free survival (DFS) rates (P < 0.001 for OS; P = 0.002 for DFS); however, no differences were observed in terms of OS and DFS by HER2 status in the HR-positive group (P = 0.21 for OS and P = 0.66 for DFS).

Conclusions: Our current findings do not support that HER2-low BC had different biology and clinical features compared to HER2-zero BC in patients who treated with neoadjuvant chemotherapy. However, the prognostic impact of HER2-low status in BC remains controversial; thus warranting further research.

1. Introduction

Breast cancer (BC) is defined as a heterogeneous group of tumours with distinct biology and prognosis. Treatment decisions among patients with BC are primarily based on the hormone receptor status and human epidermal growth factor receptor 2 (HER2) status of their tumours. HER2 is a well-known oncogene, and its overexpression is an important prognostic and predictive marker in BC [1,2]. The HER2 status of a BC lesion is defined in accordance with the 2018 American Society of Clinical Oncology/College of American Pathologist (ASCO/CAP) guidelines using immunohistochemistry (IHC) and/or in situ hybridisation (ISH) assays [3]. Currently, the HER2-positive subtype (IHC3+ or IHC2+ with ISH positivity) accounts for approximately 20–25% of all BCs and is a therapeutic target of anti-HER2 targeted therapy, whereas HER2-negative BC is not.

Recent clinical trials using novel anti-HER2 targeted antibody drug conjugates (ADCs) such as trastuzumab deruxtecan (T-DXd) [4,5] and trastuzumab duocarmazine [6] have demonstrated potential clinical benefits of these therapies in BC subgroups with HER2-low (IHC1+) or -moderate (IHC2+ with ISH negativity), which have traditionally been classified as HER2-negative tumours. These findings suggest a predictive role of a low HER2 expression level in the BC response to ADCs and that the development of novel anti-HER2 agents may enable the anti-HER2 targeted treatment of not only HER2-positive BCs but also HER2-low or -moderate subtypes.

Based on these findings, 'HER2-low' is now considered a new BC entity, defined as tumours that are IHC1+ or IHC2+ with ISH negativity. The biology and predictive prognostic implications of a HER2-low BC are not yet well-elucidated and previous reported results are inconsistent [7,8]. A better understanding of the characteristics of HER2-low BCs will be essential for developing future BC therapies.

Here, we have comprehensively investigated differences in the biology and patient-level clinical outcomes such as the pathological complete response (pCR) rate after neoadjuvant chemotherapy, relapse pattern, disease-free survival (DFS), and overall survival (OS), between HER2-low and HER2-zero (IHC 0) tumours.

2. Methods

2.1. Participants

This was a retrospective study conducted at Asan Medical Center, a tertiary hospital in Seoul, Republic of Korea. Fig. 1 shows the consort diagram of patient selection. We identified patients diagnosed with stage I–III BCs between 2014 and 2018 who were treated with neoadjuvant chemotherapy at our hospital (n = 2513). Among this initial population, we excluded all patients with a HER2-positive tumour (IHC3+ or IHC2+ with ISH positivity, n = 833) or with unknown HER2 status (n = 10). Other exclusion criteria were: disease progression during neoadjuvant chemotherapy (n = 7), unknown neoadjuvant chemotherapy regimen (n = 4), recipient of neo-adjuvant endocrine therapy (n = 39), participation in a clinical trial (n = 41), the presence of bilateral BC (n = 5), and patient refused surgery after neoadjuvant chemotherapy (n = 2). Finally, 754 patients with HER2-low BCs (IHC1+ or 2+ with negative ISH) and 818 patients with HER2-zero (IHC0) were included in the analysis. We retrospectively reviewed the patient data from their medical records including age, sex, and tumour characteristics (e.g. hormone receptor status, Ki-67 expression, tumour-infiltrating lymphocyte [TIL], T stage, N stage, histologic type, and tumour grade), post-operative pathology report, neoadjuvant treatment regimen, and survival outcomes.

Oestrogen receptor (ER) and progesterone receptor (PgR) status were assessed by IHC using the Allred scoring system. Hormone receptor status was defined as positive if tumour cells showed ER and/or PgR expression (cut-off defined as Allred score $\geq$3). HER2 status was assessed in accordance with 2018 ASCO/CAP guidelines [3]. Hormone receptor status and HER2 status were determined in each case using pre-treatment core-biopsy tissue.

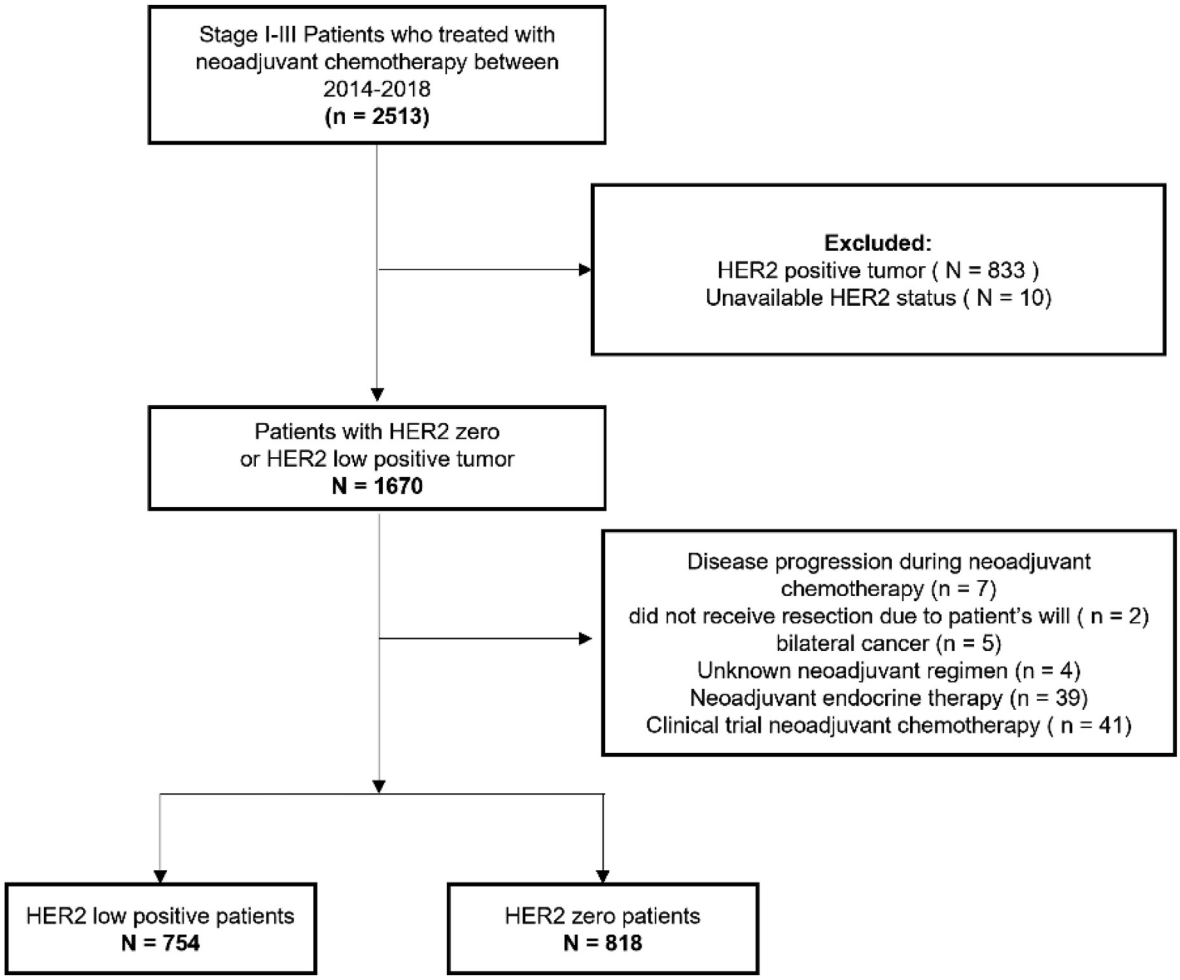

Fig. 1. Flow diagram of study patient inclusion.

2.2. Outcomes

The primary study outcome was the pCR rate, defined as ypT0/N0 or ypTis/N0, based on the pathologic reporting after surgery. The secondary outcomes included the OS, DFS, recurrence patterns after surgery depending on the hormone receptor and HER2 status, and the hazard ratio (HR) for the OS and DFS depending on the HER2 status. The recurrence pattern was estimated based on the relapse rate by every three months (the number of patients who developed recurrence at three months divided by the total number of patients experiencing relapse during the entire follow-up period). The DFS was estimated from the date of surgery to the date when a recurrence or secondary malignancy was confirmed, or the date of death from any cause, whichever occurred first. The OS was estimated from the date of surgery to the date of death from any cause. The date of death was obtained from the national healthcare data linked to our institution.

2.3. Statistical analysis

Pearson's chi-square test and Fisher's exact test were used to analyse the association between HER2 status and categorical variables among our BC cohorts. The Mann–Whitney test was employed to analyse the association between any continuous variables and HER2 status. The Kaplan–Meier method was used to estimate the DFS and OS rates and the log-rank test was used to compare tumour groups depending on their HER2 status. Bivariable and multivariable logistic regression analyses were used to estimate the relationship between HER2 status and other variables, which showed significant differences between HER2-low BC and HER2-zero BC. Furthermore, logistic regression analysis was used to evaluate the association between pCR rate and other variables including the HER2 status (HER2-zero versus HER2-low), age ($\leq$40 years versus >40 years), T-stage (cT1-2 versus cT3-4), N stage (cN0 versus cN+), tumour grade (I–II versus III), and hormone receptor status (negative versus positive). Univariate analysis

Table 1
Baseline characteristics of the included study patients.

	HER2-low (n = 754)	HER2-zero (n = 818)	P-value
Age (years)			0.9
<30	28 (3.7%)	26 (3.2%)	
30 to <40	180 (24%)	186 (23%)	
40 to <50	292 (39%)	333 (41%)	
50 to <60	183 (24%)	207 (25%)	
60 to <70	61 (8.1%)	57 (7.0%)	
≥70	10 (1.3%)	9 (1.1%)	
Median (range)	46 (22–78)	46 (23–79)	>0.9
Histological type			0.5
Invasive ductal carcinoma	707 (94%)	757 (93%)	
Invasive lobular carcinoma	23 (3.1%)	25 (3.1%)	
Others	24 (3.2%)	36 (4.4%)	
ER status			**<0.001**
Negative	146 (19%)	358 (44%)	
Positive	608 (81%)	460 (56%)	
ER Allred score	N = 608	N = 460	**0.021**
3–4	10 (6.5%)	15 (18%)	
5–6	11 (7.2%)	7 (8.3%)	
7–8	132 (86%)	62 (74%)	
Unknown	455	377	
PgR status			**<0.001**
Negative	266 (35%)	466 (57%)	
Positive	488 (65%)	352 (43%)	
PgR Allred score	N = 488	N = 352	**0.7**
3–4	24 (21%)	8 (15%)	
5–6	34 (29%)	17 (32%)	
7–8	59 (50%)	29 (53%)	
Unknown	371	298	
Nuclear grade			<0.001
1	8 (1.1%)	8 (1.0%)	
2	588 (78%)	557 (68%)	
3	154 (20%)	250 (31%)	
Missing	4 (0.5%)	3 (0.4%)	
Histologic grade			<0.001
1	9 (1.2%)	11 (1.3%)	
2	586 (78%)	553 (68%)	
3	155 (21%)	251 (31%)	
Missing	4 (0.5%)	3 (0.4%)	
T stage			0.6
cT0	7 (0.9%)	3 (0.4%)	
cTis	0 (0%)	1 (0.1%)	
cT1	74 (9.8%)	81 (9.9%)	
cT2	469 (62%)	517 (63%)	
cT3	158 (21%)	167 (20%)	
cT4	46 (6.1%)	47 (5.7%)	
Missing	0 (0%)	2 (0.2%)	
N stage			0.7
cN0	209 (28%)	241 (29%)	
cN1	356 (47%)	376 (46%)	
cN2	56 (7.4%)	53 (6.5%)	
cN3	133 (18%)	146 (18%)	
Missing	0 (0%)	2 (0.2%)	
Ki-67 expression			<0.001
≤15.0%	158 (21%)	122 (15%)	
15.1–35.0%	249 (33%)	168 (21%)	
>35.0%	346 (46%)	528 (65%)	
Missing	1	0	
Tumour-infiltrating lymphocytes			<0.001
≤10.0%	577 (77%)	549 (67%)	
10.0–59.0%	108 (14%)	153 (19%)	
>59.0%	13 (1.7%)	25 (3.1%)	
Missing	56 (7.4%)	91 (11%)	
Neoadjuvant chemotherapy regimen			0.2
AC based	**712 (94%)**	**760 (93%)**	
AC 4	204 (27%)	199 (24%)	
AC 4 → Docetaxel 4	495 (66%)	526 (64%)	
AC 4 → Weekly Paclitaxel 12	4 (0.5%)	18 (2.2%)	
AC 4 → Docetaxel, Carboplatin 4	9 (1.2%)	17 (2.1%)	
Non-AC based	**42 (5.6%)**	**58 (7.1%)**	
DA 4	4 (0.5%)	7 (0.9%)	
FAC 6	0 (0%)	2 (0.2%)	
FEC 3 → Docetaxel 3	38 (5.0%)	49 (6.0%)	
pCR status			0.003
Not achieved pCR	680 (90%)	697 (85%)	
Achieved pCR	74 (9.8%)	121 (14.7%)	
ypT0N0	61 (8.1%)	108 (13%)	
ypTisN0	13 (1.7%)	13 (1.6%)	

Abbreviations: ER, oestrogen receptor; PgR, progresterone receptor; pCR, pathological complete response; AC, adriamycin plus cyclophosphamide; DA, docetaxel plus Adriamycin; FAC, 5-fluorouracil, adriamycin, cyclophosphamide; FEC, 5-fluorouracil, epirubicin, cyclophosphamide.

using a Cox proportional hazards model was performed to evaluate the prognostic implications of the HER2 status, Ki-67 expression level, TILs, and the same variables that had been included in the logistic regression model. In the multivariate analysis, variables that exhibited a potential association with survival ($P < 0.2$) were included in the univariate analysis. P-values <0.05 were considered as statistically significant. All statistical analyses were performed using software R, version 4.0.5 (R core Development Team, Vienna, Austria).

2.4. Ethical approval and consent to participate

This study was reviewed and approved by the institutional review board of Asan Medical Center (number 2022-0541; approved on April 27, 2022), which waived the requirement for written informed consent due to the analysis' retrospective nature.

3. Results

3.1. Study patients' baseline characteristics

Table 1 lists the patients' baseline characteristics. In both tumour groups, the median patient age was 46 years and the most common histologic type was invasive ductal carcinoma. An anthracycline/cyclophosphamide (AC)-based neoadjuvant chemotherapy regimen was the most commonly used in both groups (94% in the HER2-low

and 93% in the HER2-zero BCs). The number of hormone receptor-positive patients was significantly higher among the HER2-low cases (81% versus 56%, P < 0.001). Among the ER-positive patients, the ER Allred score could be assessed in 153 (25.1% of 608) and 84 (18.2% of 460) patients in the HER2-low and HER2-zero groups, respectively. The number of ER-low (Allred score 3–4) patients was significantly higher among the HER2-zero cases (6.5% versus 18%, P = 0.021).

Regarding the histologic and nuclear grade, the proportion of grade 2 tumours was higher among the HER2-low patients (78% versus 68%), whereas that of grade 3 was higher in the HER2-zero group (21% versus 31% in the histologic grade and 20% versus 31% in the nuclear grade; P < 0.001 for both the histologic and nuclear grades). Additionally, HER2-low BCs showed a lower Ki-67 expression level (P < 0.001) and lower percentage of TILs (P = 0.013) compared to the HER2-zero tumours.

3.2. Association between HER2 status and hormone receptor status

In the bivariable logistic regression analysis to investigate the relationship between hormone receptor status and HER2 status, hormone receptor positivity had a positive association with HER2-low status (Odds ratio [OR] 3.31 [95% confidence interval (CI) 2.64–4.17], P < 0.001). In the multivariate logistic regression analysis including the variables that showed a significantly uneven distribution in baseline characteristics between HER2-low and HER2-zero BC (histologic grade, Ki-67 expression, and TIL), similar results were observed (OR 3.1 [95% CI 2.35–4.11], P < 0.001) (Supplementary Table 1).

3.3. Pathological complete response rates according to the HER2 status

The patients with a HER2-zero BC showed a higher pCR rate (14.79% versus 9.81%, P = 0003; Fig. 2A), which is consistent with the results of bivariable logistic regression ([OR] 0.62, 95% CI 0.46–0.85; Fig. 2B). However, multivariate logistic regression analysis revealed no significant differences in the pCR rate by HER2 status (OR 0.91, 95% CI 0.64–1.28; Fig. 2B). In addition, no significant differences in the pCR rate by HER2 status were identified in the hormone receptor-positive (5.4% versus 6.7%, P = 0.4) or negative (26.8% versus 22.6%, P = 0.3; Fig. 2A) groups.

3.4. Clinical outcomes and factors associated with the BC prognosis

Fig. 3 presents Kaplan–Meier curves of the OS and DFS outcomes between the two BC tumour groups. The HER2-low BC patients showed significantly better OS and DFS (Fig. 3A and B). The 5-year OS was 92.4% (95% CI 90.3–94.4) and 84.1% (81.5–86.7) and the 5-year DFS was 77.8% (74.6–81.2) and 71.6% (68.3–75.1), for patients with HER2-low and HER2-zero tumours, respectively (P < 0.001 for OS; P = 0.002 for DFS). In the subset of patients with a hormone receptor-positive BC, no differences were identified in terms of the OS and DFS by HER2 status (Fig. 3C, D; P = 0.21 for OS, P = 0.66 for DFS). In the patients with a hormone receptor-negative BC, there were no significant differences in terms of the OS (Fig. 3E; 5-year OS 83.8% [77.7–90.3] versus 75.4% [70.9–80.2], P = 0.052), whereas a significantly improved DFS was evident in patients with HER2-low BC (Fig. 3F; 5-year DFS 76.4% [69.5–83.8] versus 65.6% [60.5–70.9]; P = 0.02).

In the multivariate analysis of all patients included in this present study, a HER2-zero tumour subtype was significantly associated with a worse OS (HR 1.41 [95% CI 1.04–1.90], P = 0.026), but there was no difference in the DFS (HR 1.21 [0.98–1.50], P = 0.076; Table 2). Other factors that were significantly related to the shorter OS outcome included a T3–4 (versus T1–2, HR 1.73), lymph node positivity (versus node negative, HR 2.54), hormone receptor-negative status (versus positive, HR 1.94), and a Ki-67 expression level >35% (versus ≤15%, HR 3.37). In terms of the DFS outcome, age below 40 years (versus ≥40 years, HR 1.37), a T3–4 grade (HR 1.47), lymph node positivity (HR 2.03), hormone receptor negativity (HR 1.51), and a Ki-67 expression >35% (HR 1.50) showed a significant association with a worse DFS.

In the multivariate analysis of our subsets of hormone receptor-positive and hormone receptor-negative patients, the results (Fig. 4) were consistent with the findings from the bivariable analysis shown in Fig. 3. No interaction between the hormone receptor status and HER2 status was observed (P = 0.6 for OS, P = 0.078 for DFS; Fig. 4).

3.5. Relapse patterns depending on HER2 status

Fig. 5 presents the relapse patterns after curative resection in accordance with the HER2 status and hormone receptor status. In the HER2-zero BC cohort (dotted red line (in the web version), Fig. 5A), the relapse rate surged at 12 months after surgery and then declined steadily. This pattern of relapse was similar to that found in a subset of hormone receptor-negative, HER2-zero BC patients (pink line (in the web version), Fig. 5A). There was a relapse peak in the hormone receptor-negative patients (pink line); however, this was much higher than that for the whole HER2-zero tumour group (dotted red line). In the hormone receptor-positive and HER2-zero tumour subgroup, a major relapse peak occurred at 24 months after surgery with additional small peaks arising at 54 and 84 months (red line (in the web version), Fig. 5A).

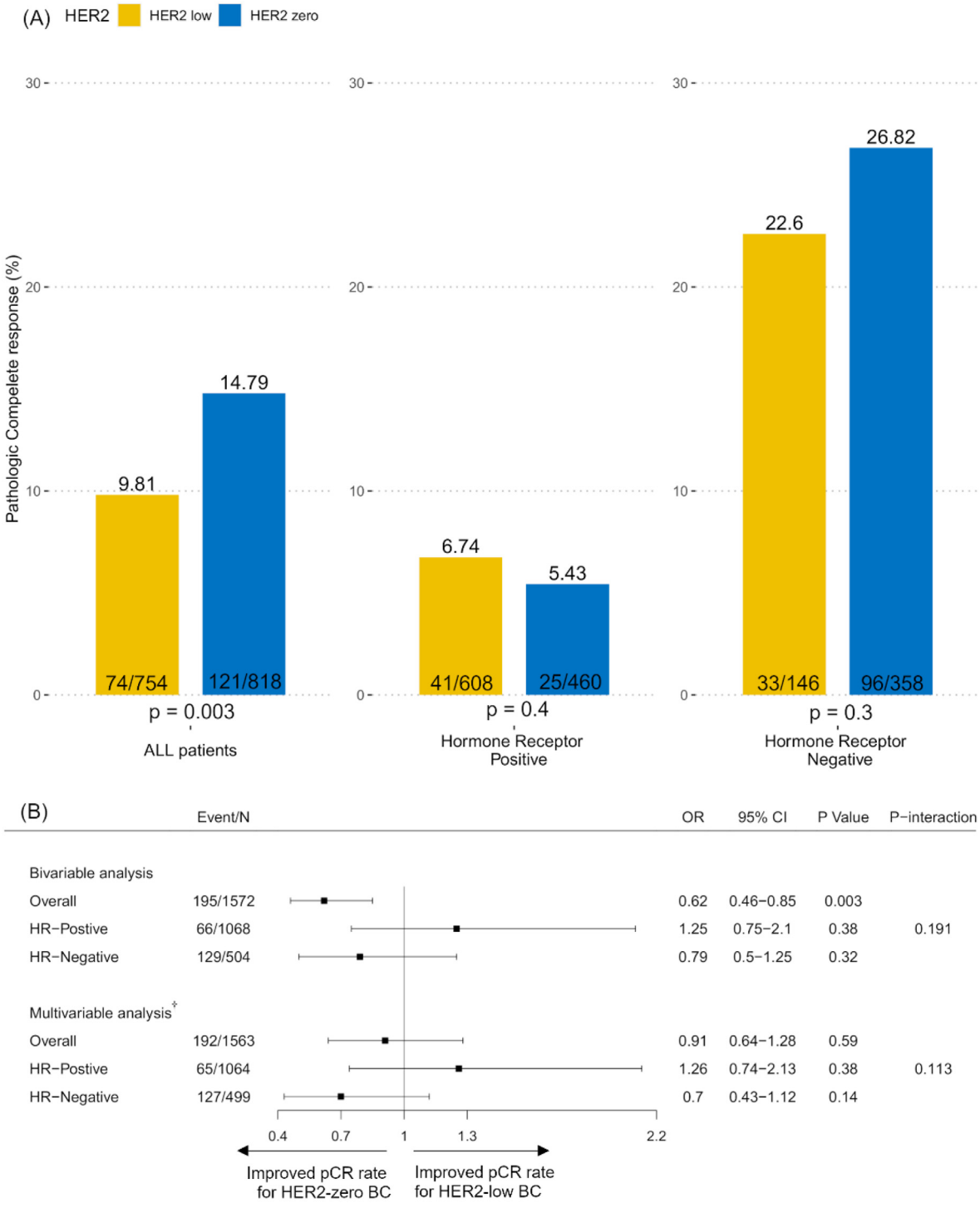

Fig. 2. (A) Comparison of pathological complete response rates (ypT0N0/ypTisN0) depending on the HER2 status. (B) Forest plots from the bivariable and multivariable logistic analyses of the pathological complete response rates for HER2-low compared to HER2-zero breast cancer patients.

In the whole HER2-low tumour population (dotted blue line) and hormone receptor-positive (dark blue line) subgroup (Fig. 5B), the relapse rate showed a steady increase after surgery and a peak at 30 months. In contrast, the relapse rate of the hormone receptor-negative subgroup (sky blue line (in the web version), Fig. 5B) in the HER2-low group peaked at 12 months after surgery, similar to the HER2- zero/hormone receptor-negative

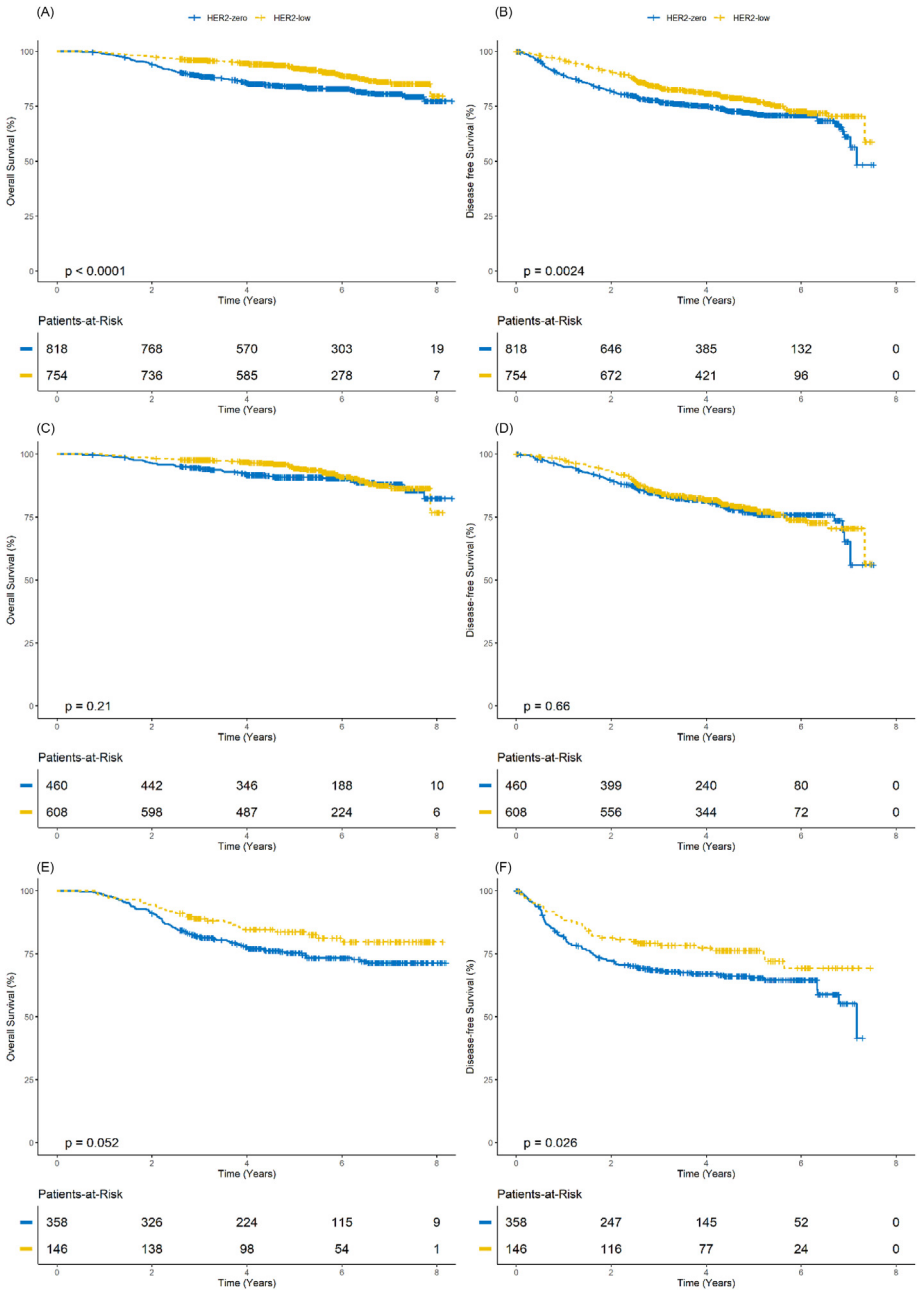

Fig. 3. Overall and disease-free survival curves for the HER2-low and HER2-zero breast cancer groups for the entire cohort (A and B), and for the hormone receptor-positive (C and D) and -negative (E and F) subgroups.

tumours (pink line (in the web version) in Fig. 5A). Fig. 5C and D shows the relapse patterns in the hormone receptor-positive and -negative groups by HER2 status, respectively. In the hormone receptor-positive patients group, the peaks of the relapses were at 24 and 30 months after surgery for the HER2-zero (red line) and HER2-low cases (blue line), respectively (Fig. 5C). In the hormone receptor-negative group, the relapse peak occurred at 12 months after surgery in both groups but was much higher among the HER2-zero patients (Fig. 5D).

4. Discussion

Interest in HER2-low BCs has been increasing in recent years with the development of novel anti-HER2 targeting agents. Here, we conducted a retrospective analysis to compare the clinical characteristics and outcomes between HER2-low and HER2-zero BC lesions. We observed that patients with a HER2-low BC had more favourable prognostic factors such as a lower nuclear and histologic grade, lower percentage of TILs,

Table 2
Factors associated with disease-free and overall survival outcomes (multivariate analysis).

	Disease-free survival						Overall survival					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
Age <40 (versus ≥40)	1.45	1.16–1.81	0.001	1.37	1.10–1.72	0.006	1.44	1.07–1.94	0.015	1.33	0.98–1.79	0.063
cT3 or cT4 (versus cT1, cT2)	1.51	1.22–1.87	<0.001	1.47	1.19–1.83	<0.001	1.80	1.36–2.38	<0.001	1.73	1.31–2.30	<0.001
cN+ (versus cN0)	1.97	1.52–2.55	<0.001	2.03	1.56–2.65	<0.001	2.45	1.67–3.58	<0.001	2.54	1.72–3.74	<0.001
Histologic grade 3 (versus 1, 2)	1.55	1.25–1.92	<0.001	1.20	0.93–1.54	0.2	2.05	1.56–2.71	<0.001	1.21	0.89–1.65	0.2
Invasive lobular carcinoma (versus IDC)	0.66	0.33–1.33	0.2				0.64	0.24–1.74	0.4			
Other histology (versus IDC)	1.19	0.73–1.94	0.5				1.46	0.81–2.61	0.2			
Hormone receptor -negative (versus positive)	1.76	1.44–2.16	<0.001	1.51	1.18–1.92	<0.001	2.86	2.18–3.76	<0.001	1.94	1.41–2.67	<0.001
HER2-zero (versus low)	1.37	1.12–1.68	0.002	1.21	0.98–1.50	0.076	1.83	1.38–2.44	<0.001	1.41	1.04–1.90	0.026
Ki-67 expression 15.1–35.0% (versus ≤15.0)	1.46	1.01–2.11	0.044	1.29	0.89–1.87	0.2	2.43	1.20–4.91	0.014	2.12	1.05–4.30	0.037
Ki-67 expression >35.0% (versus ≤ 15.0%)	2.15	1.55–2.98	<0.001	1.50	1.05–2.15	0.026	5.74	3.03–10.9	<0.001	3.37	1.72–6.59	<0.001
TIL 10.0–59.0% (versus ≤ 10.0%)	1.02	0.77–1.35	0.9			1.31	0.92–1.86	0.14				
TIL >59.0% (versus ≤ 10.0%)	1.04	0.53–2.02	>0.9			1.13	0.46–2.77	0.8				

Abbreviation: HR, hazard ratio; CI, confidence interval; IDC, invasive ductal carcinoma; TIL, tumour-infiltrating lymphocyte.

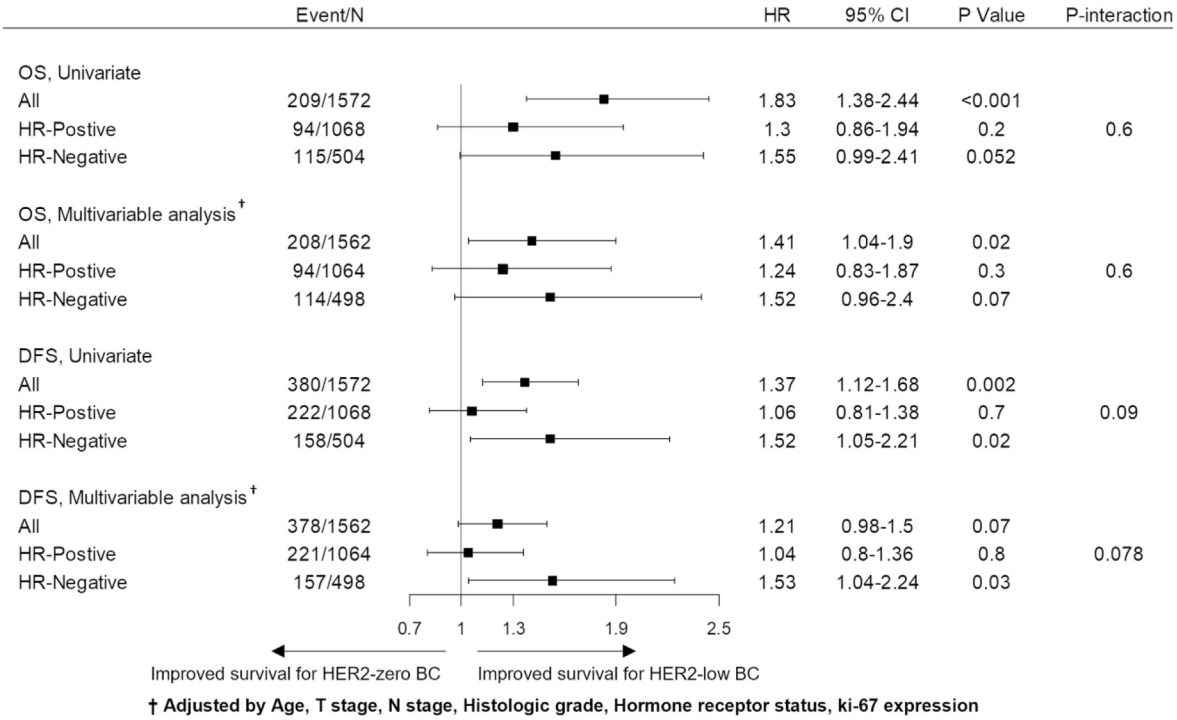

Fig. 4. Bivariable and multivariable Cox regression analysis of overall and disease-free survival.

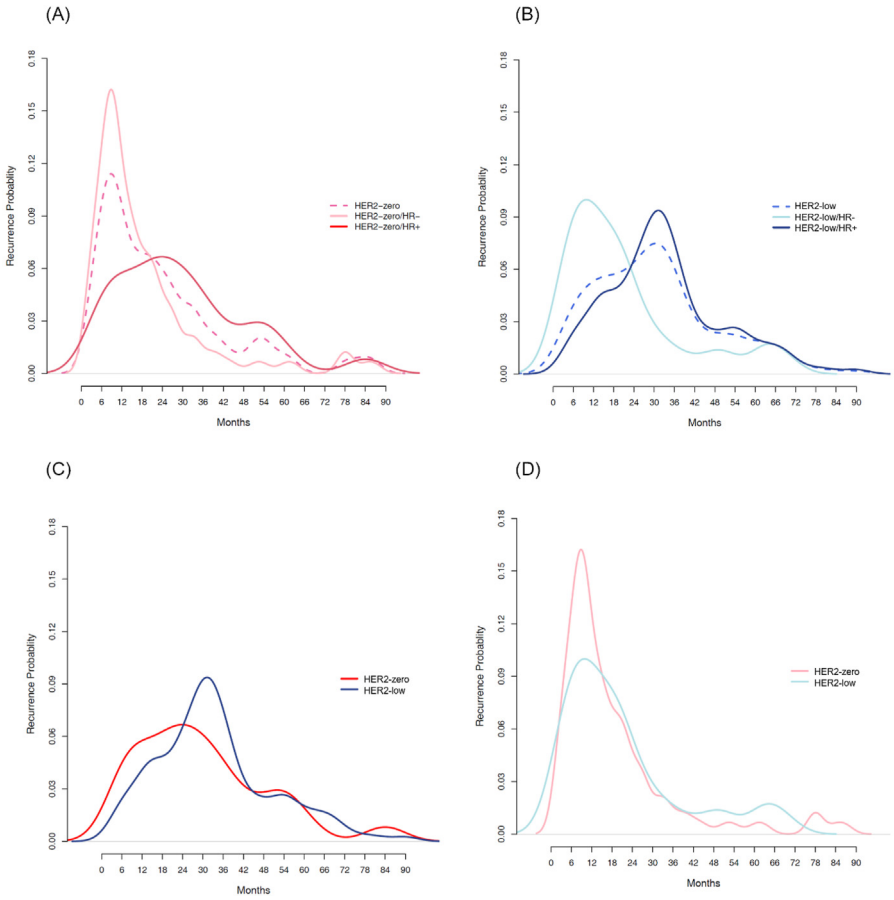

Fig. 5. Relapse rates following curative surgery in the HER2-zero and HER2-low patients. (A) HER2-zero patients. (B) HER2-low patients. (C) Hormone receptor-positive patients. (D) Hormone receptor-negative patients.

lower Ki-67 expression, and higher prevalence of hormone receptor positivity.

Although HER2-zero BC showed a higher pCR rate, no significant differences in pCR rate were observed among hormone receptor-positive (P = 0.38) and hormone receptor-negative subsets (P = 0.32) and in the multivariate analysis after adjusting for other factors, including hormone receptor status (0.59). In terms of clinical outcomes, HER2-low BC showed better OS (P = 0.02) in multivariate analysis (Fig. 4); however, no differences in OS were identified when separately analysing by hormone receptor status. Additionally, no differences in DFS rate were identified between HER2-low and HER2-zero BC in multivariate analysis for the overall population (P = 0.07, Fig. 4) or hormone receptor-positive population (P = 0.7, Fig. 4). Taken together, our current findings did not demonstrate meaningful differences in pCR rate or clinical outcomes between HER2-low and HER2-zero in multivariate analysis, which is consistent with recently published reports, see Tarantino et al. [8] and other previous studies [9–12].

In our observation of relapse patterns, HER2-zero and HER2-low BC showed different peaks, at 12 and 30 months after surgery, respectively (dotted line in Fig. 5A and B). However, considering that this peak occurred later in the hormone receptor-positive patients than in the hormone receptor-negative group for both HER2-low and HER2-zero BCs, the differences in the relapse peaks among the entire cohort may have been due to a higher proportion of hormone receptor-positive patients among the HER2-low BC cases, and the effect of endocrine treatment for those patients.

Considering the positive association between HER2-low and hormone receptor positivity (OR 3.1), and the lack of difference in pCR rate and DFS after adjustment with hormone receptor status (P = 0.07 in multivariate analysis), favourable outcomes of HER2-low BC may be affected by hormone receptor positivity. A previous study suggested that hormone receptor status is an important determinant of the underlying biology among HER2-low BCs [8].

Additionally, although the number of patients with available ER Allred score was limited, the proportion of ER-low (ER Allred score 3–4) was higher in HER2-zero BC (18% versus 6.5%, P = 0.021). We think that this finding is in line with Tarantino et al., which showed that higher-ER expression is related to

higher ERBB2 expression [8]. Considering that ER-low BC is now considered as having similar biology to TNBC [13,14], worse outcomes of HER2-zero BC in our study might be related to the higher proportion of ER-low BC, not HER2 status. However, the number of patients with ER-low was too small in our study (n = 10 in HER2-low BC, n = 15 in HER2-zero BC); thus, further investigation is warranted to confirm this hypothesis.

However, we observed that HER2-low BC had significantly better DFS in the hormone-negative subset in multivariate analysis (Fig. 4, P = 0.03), contrary to Tarantino et al. [8], which did not identify any significant differences in OS or DFS by HER2 status in the TNBC subset. Indeed, the P-interaction between HER2 status and hormone receptor status was not significant in the multivariate analysis of DFS (P = 0.078, Fig. 4), which implies that the effect of HER2 status was not different in the hormone−receptor-positive and -negative group subsets in our multivariate analysis. Therefore, we assume that it is difficult to interpret this as HER2-low BCs having significantly better DFS in TNBC subsets based on our findings.

Currently, the evidence for the prognostic implications of HER2-low remains inconclusive. One explanation for these conflicting results is the difficulty of distinguishing HER2-low from HER2-zero when using the conventional HER2 scoring system. Fernandez et al. recently reported only a 26% concordance rate among 18 experienced pathologists when discriminating HER2-IHC0 from HER2-IHC1+, contrary to the 58% concordance rate between HER2-IHC2+ and HER2 IHC3+ [15]. A wide discordance rate for HER2-IHC0 versus HER2-IHC1+ has also been observed in other studies [9,16]. Indeed, the current HER2 assay was developed to identify patients with a HER2 overexpression tumour who benefited from trastuzumab, and it has a limitation when evaluating the lower ranges of HER2 expression [17]. This might be the reason for the wide variability of incidence of HER2-low in retrospective studies, from 16.2% [18] to 64.4% [19]. These findings suggested that more precise diagnostic methods are necessary to distinguish HER2-low BC from HER2-zero BC.

A randomised phase III DESTINY-Breast 04 study (NCT03734029) was recently published [5] in which T-DXd therapies were associated with a significantly better PFS and OS compared to the physician's treatment of choice for patients with HER2-low unresectable/metastatic BC. Moreover, the DAISY trial demonstrated that T-DXd showed promising anti-tumour effect not only in HER2 overexpression BC but also in HER2-low and HER2-zero BC in patients with advanced BC [20]. Definitely, with this practice changing results, further investigation is warranted to identify the optimal candidates for T-DXd to further expand to a neoadjuvant setting.

There were several limitations of note in our study. It was conducted at a single center and was retrospective, which creates a susceptibility to selection bias. Nevertheless, the number of patients in our study was relatively large and chemotherapy regimens were chosen with the same principle. Hence, there was a homogeneity of treatment over the study period. Additionally, the pathologic findings such as the presence of TILs and Ki-67 expression were interpreted by the same experienced pathologists, thus adding to the data's concordance and reliability. Another limitation is that substantial numbers of Allred scores for ER and/or PgR were unavailable.

In conclusion, our current findings did not support the theory that HER2-low BCs have a different biology and clinical features to HER2-zero lesions treated with neoadjuvant chemotherapy. However, the prognostic impact of HER2-low status in BC remains somewhat controversial and requires further research to better elucidate the biology of HER2 and its therapeutic implications in real-world BC settings. Our current findings will be useful when designing further clinical studies.

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Author contributions

Sora Kang: data curation, formal analysis, writing, review and editing of the manuscript, So Heun Lee: data curation, writing, review and editing of the manuscript, Hee Jin Lee: review and editing of the manuscript, Hyehyun Jeong: data curation, review and editing of the manuscript, Jae Ho Jeong: data curation, review and editing of the manuscript, Jeong Eun Kim: data curation, review and editing of the manuscript, Jin-Hee Ahn: data curation, review and editing of the manuscript, Kyung Hae Jung: data curation, review and editing of the manuscript, Gyungyub Gong: review and editing of the manuscript, Hak Hee Kim: review and editing of the manuscript, Saebyeol Lee: review and editing of the manuscript, Jongwon Lee: review and editing of the manuscript, Sung-Bae Kim: conceptualisation, methodology, project administration, supervision, writing, review and editing of the manuscript.

Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Kyung Hae Jung has advisory roles at Astra-Zeneca, BIXINK, MSD, Novartis, Pfizer, Roche, Takeda and Everest Medicine.

Sung-Bae Kim is a consultant on the advisory boards of Novartis, AstraZeneca, Lilly, Dae Hwa Pharmaceutical Co. Ltd, ISU Abxis, and Daiichi-Sankyo, and has received research funding from Novartis, Sanofi-Aventis, and DongKook Pharm Co., and owns stock in Genopeaks and NeogeneTC. None of the other authors has any conflicts of interest to declare in relation to this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2022.08.031.

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