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ORIGINAL ARTICLE

Clinical Differences in Triple-Positive Operable Breast Cancer Subtypes in Korean Patients: An Analysis of Korean Breast Cancer Registry Data

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Purpose: Triple-positive breast cancer is defined by estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 (HER2) positivity. Several systemic breast cancer therapies target hormonal and HER2 responsiveness. We compared clinical outcomes of triple-positive disease with those of HER2-enriched and luminal HER2-negative disease and investigated the clinical efficacy of anti-HER2 therapy for triple-positive disease. **Methods:** We retrospectively compared overall and recurrence-free survival among cases included in the Korean Breast Cancer Society (KBCS) and Seoul St. Mary's Hospital breast cancer registries and the therapeutic efficacy of trastuzumab for triple-positive and HER2-enriched cases. **Results:** KBCS registry data (2006–2010; median follow-up, 76 months) indicated that patients with triple-positive breast cancer had intermediate survival between those with luminal A and HER2-enriched subtypes ($p<0.001$). Trastuzumab did not improve overall survival among patients with triple-positive breast cancer ($p=0.899$) in contrast to the HER2-enriched subtype ($p=0.018$). Seoul St. Mary's Hospital registry data indicated similar recurrence-free survival outcomes ($p<0.001$) and a lack of improvement with trastuzumab among patients with triple-positive breast cancer (median follow-up, 33 months; $p=0.800$). Multivariate analysis revealed that patients with triple-positive breast cancer had better overall survival than those with HER2-enriched disease and similar survival as those with the luminal A subtype (triple-positive: hazard ratio, 1.258, $p=0.118$; HER2-enriched: hazard ratio, 2.377, $p<0.001$). **Conclusion:** Our findings showed that anti-HER2 therapy was less beneficial for treatment of triple-positive breast cancer than for HER2-enriched subtypes of breast cancer, and the triple-positive subtype had a distinct prognosis.

Key Words: *Breast neoplasms, ErbB-2 receptor, Estrogen receptors, Hormones, Trastuzumab*

INTRODUCTION

Breast cancer is a heterogeneous disease of multiple subtypes with distinct morphologies and clinical implications. In clinical practice, these breast cancer subtypes can be distinguished using immunohistochemistry (IHC) to detect expression of the estrogen receptor (ER), progesterone receptor (PR), and c-erbB-2 receptor, and fluorescence or silver *in situ* hybridization (FISH or SISH, respectively), which is used to identify the human epidermal growth factor receptor 2 (HER2) gene locus. The resulting breast cancer classification system has led to the application of multiple systemic therapeutic strategies.

The term "triple-positive" breast cancer was first introduced by Vici et al. [1] to describe a distinctive subtype. It is defined as a luminal HER2 tumor that expresses both the ER and PR. This type of tumor also expresses high HER2 levels and exhibits a biologically distinct phenotype and specific clinical behavior. In current clinical settings, systemic therapeutic approaches for triple-positive breast cancer comprise hormone receptor (HR)-specific hormonal therapies, HER2-directed therapy, and systemic chemotherapy; these may include other therapeutic approaches and may be applied in all cases, except in patients with early stage breast cancer who have good prognostic factors [2]. Previous clinical data of patients with HER2-positive breast cancer have demonstrated better prognostic outcomes with HR-positive than HR-negative disease [3]. Additionally, previous clinical and experimental data have revealed that HER2-directed therapy is less effective for HR-

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positive/HER2-positive breast cancer but may prolong survival. This outcome may be supported by the finding that crosstalk between the ER and HER2 pathways plays a role in resistance to endocrine therapy [4-11].

Despite these earlier findings, previous clinical data obtained from patients with HER2-positive breast cancer have been limited owing to their focus on HR positivity. Previous results suggest that only a subset of HR-positive/HER2-positive breast cancers do not undergo significant reduction due to HER2-directed therapy. Therefore, a more detailed analysis is needed to identify the distinct characteristics of triple-positive breast cancer. Here, we investigated the clinical outcomes of triple-positive breast cancer relative to HER2-enriched/HR-negative and HR-positive/HER2-negative breast cancer, as well as the therapeutic efficacy of anti-HER2 therapy (trastuzumab) for triple-positive breast cancer, using patient data from two South Korean breast cancer data registries.

METHODS

Patients and data selection

In this retrospective study, we analyzed data from two different clinical breast cancer data registries in South Korea. The Korean Breast Cancer Society (KBCS) breast cancer registry is a nationwide multicenter registry of data collected from South Korean hospitals between 2006 and 2010. The KBCS approved our research objective and request for data in October 2016. From this registry, we included patients who received an initial diagnosis of breast cancer and underwent breast cancer treatment surgery during the registry period. Patients with ductal carcinoma *in situ* were excluded. Our study included 31,266 patients, of which 1,740 patients had triple-positive breast cancer (Figure 1). Overall survival (OS) data were collected from the Korean National Statistical Information Service, which records the dates of death and other clinical and demographic data of patients.

We also obtained data collected from April 2009 through March 2016 by Seoul St. Mary's Hospital of the Catholic Medical Center (CMC data). From this registry, we included patients who received a new diagnosis of breast cancer and underwent primary breast cancer surgery at Seoul St. Mary's Hospital and for whom clinicopathologic data were available. Patients with inoperable stage IV breast cancer and ductal carcinoma *in situ* were excluded. The analysis finally included 2,216 patients from this registry. Recurrence-free survival (RFS) was defined as the time from the initial diagnosis of breast cancer to the first recurrence (including locoregional and distant recurrences) or the last follow-up. This study was approved by the Institutional Review Board of Seoul St. Mary's Hospital (KC 17RED10533). Informed consent from the patients was not required.

Classification of intrinsic molecular subtypes

In this study, the breast cancer molecular subtypes were identified using IHC for ER, PR, HER2, and Ki-67 proliferative index. In the CMC dataset, an Allred score of > 3 indicat-

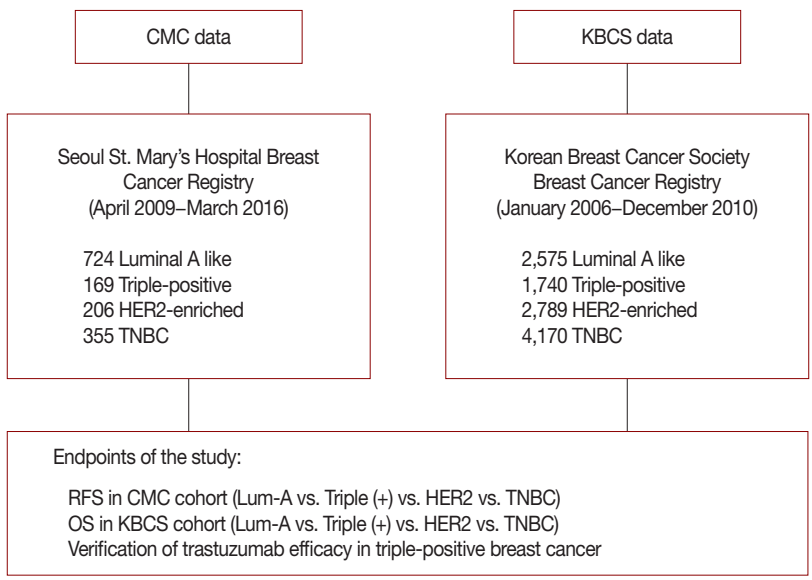

Figure 1. Schematic diagram of the study cohorts, intrinsic subtype distributions, and list of study endpoints.
CMC = Seoul St. Mary's Hospital of the Catholic Medical Center; KBCS = Korean Breast Cancer Society; TNBC = triple-negative breast cancer; RFS = recurrence-free survival; Lum-A = luminal A subtype; HER2 = human epidermal growth factor receptor 2; OS = overall survival.

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ed ER and PR positivity; all Allred scores in this dataset ranged from 3 to 8. IHC or FISH was used to evaluate HER2 status. HER2 positivity was defined as an IHC score of 3+. For cases with equivocal IHC CMC (2+), the samples were retested via single-probe SISH (CMC and KBCS data) or FISH (KBCS data only). For Ki-67 expression, a level of < 14% was considered low.

Breast cancer molecular subtypes were classified according to the 14th St. Gallen International Expert Consensus [12] as follows: (1) luminal A: ER and/or PR positive, HER2 negative, and low Ki-67 (< 14%); (2) HER2 enriched: HER2 positive, and ER and PR negative; (3) triple-negative breast cancer (TNBC): ER, PR, and HER2 negative; (4) triple-positive: ER, PR, and HER2 positive; and (5) luminal B: ER and/or PR positive, HER2 negative or positive, and high Ki-67 (≥ 14%). All cancers were staged according to the seventh edition of the American Joint Committee on Cancer (AJCC) staging manual.

Clinical endpoints and statistical analysis

The primary endpoint was a comparison of prognostic outcomes between patients with triple-positive breast cancer and those with other molecular subtypes. For this endpoint, we obtained RFS outcomes from CMC data and OS outcomes from KBCS data. The secondary endpoint was the efficacy of anti-HER2 therapy (i.e., trastuzumab) for triple-positive breast cancer.

Clinicopathologic features were assessed using the Student t-test, chi-square test, and Fisher exact test. Differences in follow-up times among the intrinsic subtypes were calculated using one-way analysis of variance. Cumulative survival probabilities were estimated using Kaplan-Meier analysis, and differences in survival rates were compared using the log-rank and generalized Wilcoxon tests. Additionally, multivariate analysis was performed using the Cox proportional hazards model. All variables are described as hazard ratios and 95% confidence intervals (CIs). A two-sided *p*-value of < 0.05 was considered significant. All statistical analyses were performed using IBM SPSS software version 22.0 for Windows (IBM Corp., Armonk, USA).

RESULTS

During a mean follow-up period of 35.49 ± 21.72 months, 169 of 2,216 patients in the CMC registry were identified as having triple-positive breast cancer, whereas 206 and 724 patients were identified as having HER2-enriched and luminal A disease, respectively (Supplementary Table 1, available online). The various clinicopathologic characteristics and an analysis of these three subtypes are described in Supplementary Table 1. During the study period, recurrences were reported in 11 of 169 patients (6.5%) with triple-positive breast cancer, 29 of 724 patients (4.0%) with the luminal A subtype, and 22 of 206 patients (10.7%) with the HER2-enriched subtype.

As mentioned earlier, the KBCS data included 31,266 cases, among which 1,740 were identified as triple-positive breast cancer, 2,789 as the HER2-enriched subtype, and 2,575 as the luminal A subtype (Figure 1). During a mean follow-up period of 73.58 months, 120 (6.9%), 344 (12.3%), and 109 patients (4.2%) with triple-positive, HER2-enriched, and luminal A breast cancer, respectively, died (Table 1). The various clinicopathologic characteristics are described in Table 1.

Table 1. Clinical and pathologic characteristics of patients of the Korean Breast Cancer Society cohort

Characteristic	Subtype			*p*-value
	Triple-positive (n = 1,740) No. (%)	Luminal A (n = 2,575) No. (%)	HER2-enriched (n = 2,789) No. (%)	
Age at diagnosis (yr)				< 0.001
< 40	215 (12.4)	222 (8.6)	298 (10.7)	
40–49	854 (49.1)	1,135 (44.0)	793 (28.4)	
50–59	442 (25.4)	673 (26.1)	1,117 (40.1)	
≥ 60	229 (13.2)	545 (21.2)	581 (20.8)	
pT stage				< 0.001
T1	957 (55.0)	1,710 (66.4)	1,531 (54.9)	
T2	680 (39.1)	744 (28.9)	1,070 (38.4)	
T3	75 (4.3)	86 (3.3)	126 (4.5)	
T4	28 (1.6)	35 (1.4)	62 (2.2)	
pN stage				< 0.001
N0	958 (56.0)	1,627 (64.8)	1,671 (61.1)	
N1	471 (27.5)	628 (25.0)	599 (21.9)	
N2	186 (10.9)	183 (7.3)	241 (8.8)	
N3	96 (5.6)	73 (2.9)	224 (8.2)	
M stage				0.078
M0	1,691 (98.4)	2,533 (98.9)	2,719 (98.2)	
M1	27 (1.6)	27 (1.1)	49 (1.8)	
TNM stage				< 0.001
I	495 (31.7)	917 (41.7)	876 (34.9)	
II	727 (46.5)	929 (42.3)	1,068 (42.5)	
III	313 (20.0)	325 (14.8)	626 (24.9)	
IV	27 (1.7)	27 (1.2)	49 (2.0)	
Ki-67 (%)	25.93 ± 19.98	6.21 ± 3.77	32.07 ± 21.91	< 0.001
Histologic grade				< 0.001
G1	180 (11.2)	855 (36.5)	77 (3.1)	
G2	806 (50.3)	1,293 (55.2)	902 (36.7)	
G3	615 (38.4)	194 (8.3)	1,480 (60.2)	
Trastuzumab treatment	162 (9.3)	3 (0.1)	262 (9.4)	< 0.001
Death	120 (6.9)	109 (4.2)	344 (12.3)	< 0.001
Follow-up duration (mo)*	75.82 ± 19.50	75.77 ± 18.64	72.62 ± 21.42	< 0.001†

HER2 = human epidermal growth factor receptor 2.
*Mean ± SD; †Dunnett T3 method and one-way analysis of variance; luminal A vs. triple-positive, $p = 1.000$; others, $p < 0.001$.

Survival outcomes of patients with triple-positive, luminal A, and HER2-enriched breast cancer

The results of univariate analysis of RFS and OS are listed in Table 2. The RFS of patients with triple-positive, luminal A, and HER2-enriched breast cancer was calculated using CMC data. During a mean follow-up period of 35.88 ± 21.90 months, patients with the triple-positive subtype showed intermediate RFS between those of patients with luminal A and HER2-enriched subtypes (Figure 2A). Although patients with triple-positive breast cancer had significantly better RFS outcomes than those with the HER2-enriched subtype (generalized Wilcoxon test, $p = 0.025$), we observed no significant difference between patients with the triple-positive and luminal A subtypes (generalized Wilcoxon test, $p = 0.315$).

We then used KCBS data to calculate OS among patients with triple-positive, luminal A, and HER2-enriched breast cancer. Similarly, during a median follow-up period of 76 months, patients with triple-positive breast cancer showed an intermediate OS between those of patients with the luminal A and HER2-enriched subtypes (log-rank test; triple-positive vs. luminal A, $p < 0.001$; triple-positive vs. HER2-enriched, $p < 0.001$) (Figure 2B). Considering the natural disease course without anti-HER2 therapy among patients with triple-positive and HER2-enriched subtypes in the KBCS registry, better survival outcomes were observed in patients with the triple-positive subtype than in those with HER2-enriched breast cancer (log-rank test; triple-positive vs. HER2-enriched, $p < 0.001$) (Figure 2C). These survival outcomes demonstrate that triple-positive breast cancer has a better prognosis than HER2-enriched breast cancer, regardless of OS and RFS.

Multivariate analysis

After identifying significant differences in RFS and OS between the triple-positive and HER2-enriched subtypes, we performed multivariate analyses to adjust for interactions between other factors. Details of the multivariate analysis of KBCS data are shown in Table 3. In this group, we observed no significant difference in OS between patients with triple-positive and luminal A subtypes ($p = 0.118$; hazard ratio, 1.258; 95% CI, 0.944–1.677). In contrast, we observed significantly worse OS among patients with HER2-enriched and ER-positive/PR-negative/HER2-positive subtypes than OS in patients with the luminal A subtype (hazard ratio, 2.377, $p < 0.001$; and hazard ratio, 1.978, $p < 0.001$, respectively). As such, the prog-

Table 2. Univariate analysis of overall survival and recurrence-free survival among the triple-positive, luminal A, and HER2-enriched breast cancer subtypes

Variable		Subtype	Overall survival (KBCS data)			Recurrence-free survival (CMC data)		
			No. of events	Mean (95% CI) (mo)	*p*-value*	No. of events	Mean (95% CI) (mo)	*p*-value†
Total		Triple- positive	120/1,740	120.223 (118.943–121.503)	Reference	11/169	83.189 (78.838–87.540)	Reference
		Luminal A	109/2,575	134.960 (133.923–135.997)	<0.001	29/724	84.149 (78.838–87.540)	0.315
		HER2-enriched	344/2,789	121.215 (119.938–122.491)	<0.001	22/206	74.938 (71.393–78.482)	0.025
Stage	I	Triple-positive	13/495	124.165 (122.372–125.957)	Reference	1/64	85.750 (83.628–87.872)	Reference
		Luminal A	16/917	133.850 (132.508–135.193)	0.290	6/418	83.700 (82.666–84.733)	0.413
		HER2-enriched	35/876	130.093 (128.802–131.938)	0.144	2/75	81.692 (78.543–84.842)	0.186
	II	Triple-positive	41/727	114.963 (113.340–116.585)	Reference	4/76	85.182 (79.807–90.557)	Reference
		Luminal A	41/929	135.093 (133.605–136.580)	0.257	10/229	83.649 (80.944–86.354)	0.971
		HER2-enriched	120/1,896	101.084 (99.733–102.436)	<0.001	10/95	67.417 (63.040–71.795)	0.095
	III	Triple-positive	45/313	99.433 (96.801–102.064)	Reference	6/29	59.699 (48.804–70.593)	Reference
		Luminal A	37/325	105.404 (102.772–108.035)	0.293	13/73	67.353 (61.320–73.385)	0.505
		HER2-enriched	146/519	88.016 (85.068–90.965)	<0.001	10/36	57.791 (47.300–68.281)	0.202
	IV	Triple-positive	26/18	56.840 (45.351–68.329)	Reference	N/A	N/A	N/A
		Luminal A	9/27	102.031 (87.081–116.982)	0.001	N/A	N/A	N/A
		HER2-enriched	34/49	48.806 (37.827–59.785)	0.355	N/A	N/A	N/A
Trastuzumab	(–)	Triple-positive	112/1,578	120.197 (118.879–121.515)	0.899	6/64	82.942 (77.057–88.827)	0.927
	(+)		8/162	94.200 (92.287–96.113)	Reference	5/99‡	77.560 (72.925–82.196)	Reference
	(–)	HER2-enriched	329/2,527	120.751 (119.403–122.099)	0.018	9/71	73.802 (67.642–79.962)	0.497
	(+)		15/262	91.847 (89.708–93.985)	Reference	12/128§	70.939 (67.162–74.715)	Reference

HER2 = human epidermal growth factor receptor 2; KBCS = Korean Breast Cancer Society; CMC = Seoul St. Mary's Hospital of the Catholic Medical Center; CI = confidence interval; N/A = not assessed.

*p-values were estimated using the log-rank test; †p-values were estimated using the generalized Wilcoxon test; ‡6 Cases of trastuzumab data were missed in triple-positive group; §7 Cases of trastuzumab data were missed in HER2-enriched group.

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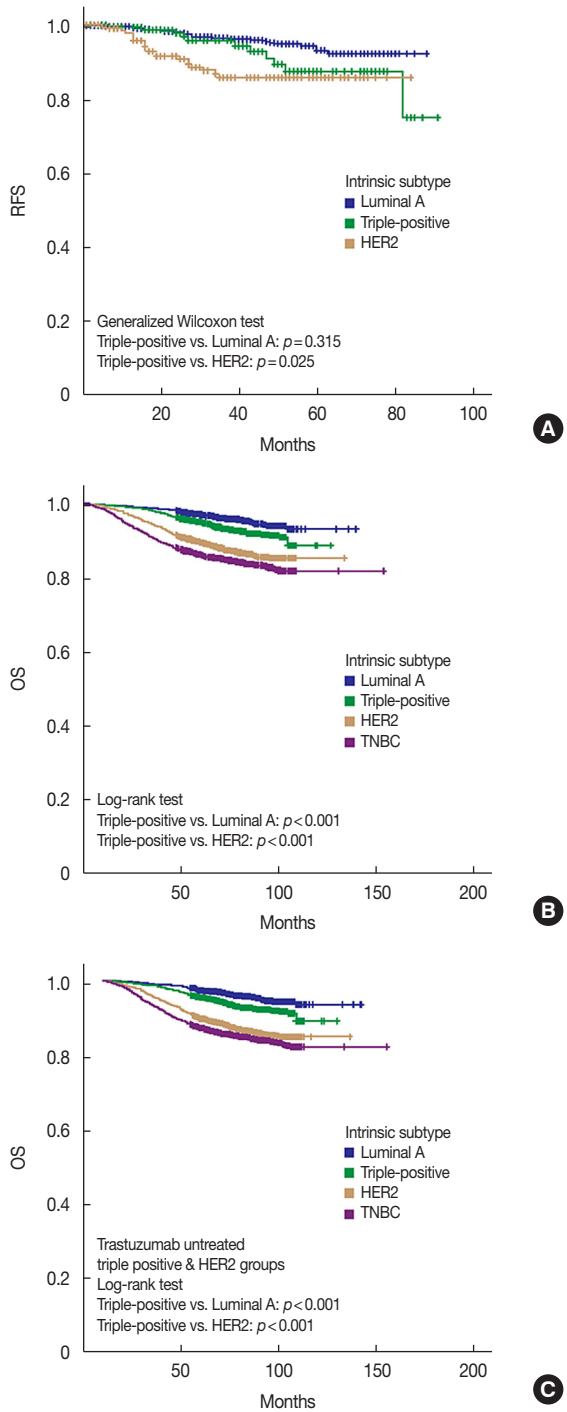

Figure 2. Survival outcomes of patients with triple-positive, luminal A, and human epidermal growth factor receptor 2 (HER2)-enriched breast cancer. (A) Recurrence-free survival (RFS) among the intrinsic subtypes. Data were obtained from the cohort of Seoul St. Mary's Hospital of the Catholic Medical Center. (B) Overall survival (OS) among intrinsic subtypes in the Korean Breast Cancer Society cohort (2006–2010). (C) OS among intrinsic subtypes in the Korean Breast Cancer Society cohort (2006–2010). Patients not treated with anti-HER2 therapy in the triple-positive and HER2-enriched groups.
TNBC = triple-negative breast cancer.

Table 3. Multivariate analysis of data from the Korean Breast Cancer Society registry

Characteristic	Hazard ratio	95% CI	*p*-value*
Age (yr)			
<40	1.000	Reference	-
≥40	0.935	0.796–1.099	0.416
T stage			
T1	1.000	Reference	-
T2	1.167	0.975–1.398	0.092
T3	1.652	1.285–2.124	<0.001
T4	3.080	2.345–4.045	<0.001
N stage			
N0	1.000	Reference	-
N1	1.648	1.367–1.988	<0.001
N2	1.530	1.121–2.088	0.007
N3	2.251	1.667–3.038	<0.001
TNM stage†			
I	1.000	Reference	-
II	1.433	1.092–1.881	0.009
III	2.670	1.821–3.913	<0.001
IV	10.348	6.880–15.563	<0.001
Histological grade			
1	1.000	Reference	-
2	1.130	0.822–1.552	0.452
3	1.399	1.016–1.928	0.040
Subtype			
Luminal A	1.000	Reference	-
Triple-positive	1.258	0.944–1.677	0.118
HER2-enriched	2.377	1.853–3.048	<0.001
TNBC	3.352	2.637–4.260	<0.001
ER(+)/PR(–)/HER2(+)	1.978	1.425–2.744	<0.001
Trastuzumab therapy			
Triple-positive	0.856	0.369–1.988	0.718
HER2-enriched	0.441	0.252–0.773	0.004

CI = confidence interval; HER2 = human epidermal growth factor receptor 2; TNBC = triple-negative breast cancer; ER = estrogen receptor; PR = progesterone receptor.
**p*-values were determined using a Cox regression forward conditional stepwise model; †TNM stages were determined according to the 7th edition of the American Joint Committee on Cancer staging system.

nosis of triple-positive breast cancer more closely resembled that of the luminal A subtype. Moreover, trastuzumab therapy did not prolong the OS in patients with triple-positive breast cancer ($p = 0.718$; hazard ratio, 0.856; 95% CI, 0.369–1.988) but did significantly prolong OS in patients with the HER2-enriched subtype ($p = 0.004$; hazard ratio, 0.441; 95% CI, 0.252–0.773). However, multivariate analysis of CMC data did not confirm significant differences in RFS among the triple-positive, luminal A, and HER2-enriched subtypes.

Survival differences among patients with triple-positive, luminal A, and HER2-enriched breast cancer in the same stage

The 8th edition of the AJCC staging system was recently in-

troduced. This newer version combines the conventional anatomic stage and the newly developed "prognostic stage" to more precisely determine prognosis. The prognostic stage incorporates various biologic factors such as ER, PR, HER2 expression, and histological grade and reflects the differences in disease prognosis according to the expression statuses of these markers. Applying the newer prognostic staging system might advance the cancer stage from a conventional anatomic stage, according to the HR and HER2 status. Therefore, we compared OS among triple-positive, luminal A, and HER2-enriched breast cancer at each conventional anatomic stage (i.e., AJCC staging system, 7th edition) using the KBCS dataset.

At stage I, we observed no differences in OS among the triple-positive, luminal A, and HER2-enriched subtypes ($p=0.290$), and only TNBC was associated with a poor prognosis ($p<0.001$). However, at stages II and III (AJCC staging system, 7th edition), the OS curves differed according to ER, PR, and HER2 statuses (Table 3). Here, the OS curve of triple-positive breast cancer resembled that of the luminal A subtype (stage II, $p=0.257$; stage III, $p=0.293$); the HER2-enriched and TNBC subtypes had worse OS than triple-positive breast cancer at both stages (stage II, $p<0.001$; stage III, $p<0.001$).

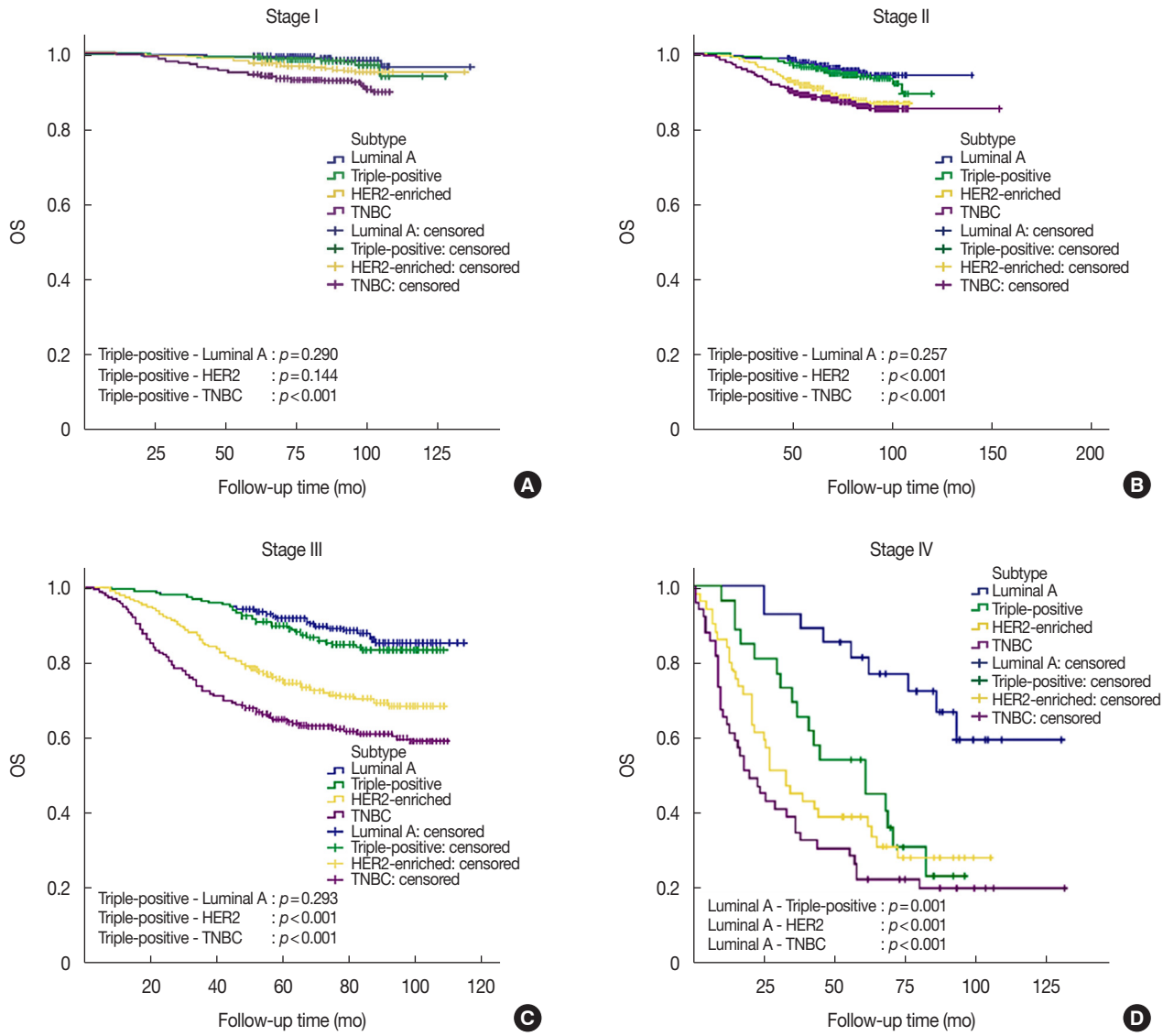

Figure 3. Overall survival (OS) among luminal A, triple-positive, human epidermal growth factor receptor 2 (HER2)-enriched and triple-negative breast cancer (TNBC) subtypes in the Korean Breast Cancer Society cohort (2006–2010), according to the 7th edition of the American Joint Committee on Cancer staging system for breast cancer. OS was estimated using Kaplan-Meier survival analysis. (A) Stage I, (B) stage II, (C) stage III, and (D) stage IV.

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At stage IV (i.e., patients who underwent surgery for local control of the primary tumor), only those with the luminal A subtype had good OS (luminal A vs. triple-positive subtypes, $p=0.001$; luminal A vs. HER2-enriched subtypes, $p<0.001$; luminal A vs. TNBC subtypes, $p<0.001$) (Table 2 and Figure 3). According to our results, the prognosis varies according to the intrinsic subtype, even in the same anatomic stage, and triple-positive breast cancer has greater likelihood of being downstaged, when the newer prognostic staging system (8th edition of the AJCC staging system) is adopted, if it is accompanied by the luminal A subtype.

Efficacy of trastuzumab therapy for triple-positive breast cancer

To address the mechanism of crosstalk between the HER2 and ER signaling pathways, we evaluated the efficacy of trastuzumab for triple-positive breast cancer relative to HER2-enriched breast cancer. Using KBCS data, trastuzumab therapy did not significantly improve OS among patients with triple-positive breast cancer (Kaplan-Meier analysis, $p=0.899$) (Table 2), regardless of tumor stage (Kaplan-Meier analysis, stage I, $p=0.727$; stage II, $p=0.969$; stage III, $p=0.512$) (Figure 4). In contrast to the results obtained for patients with triple-

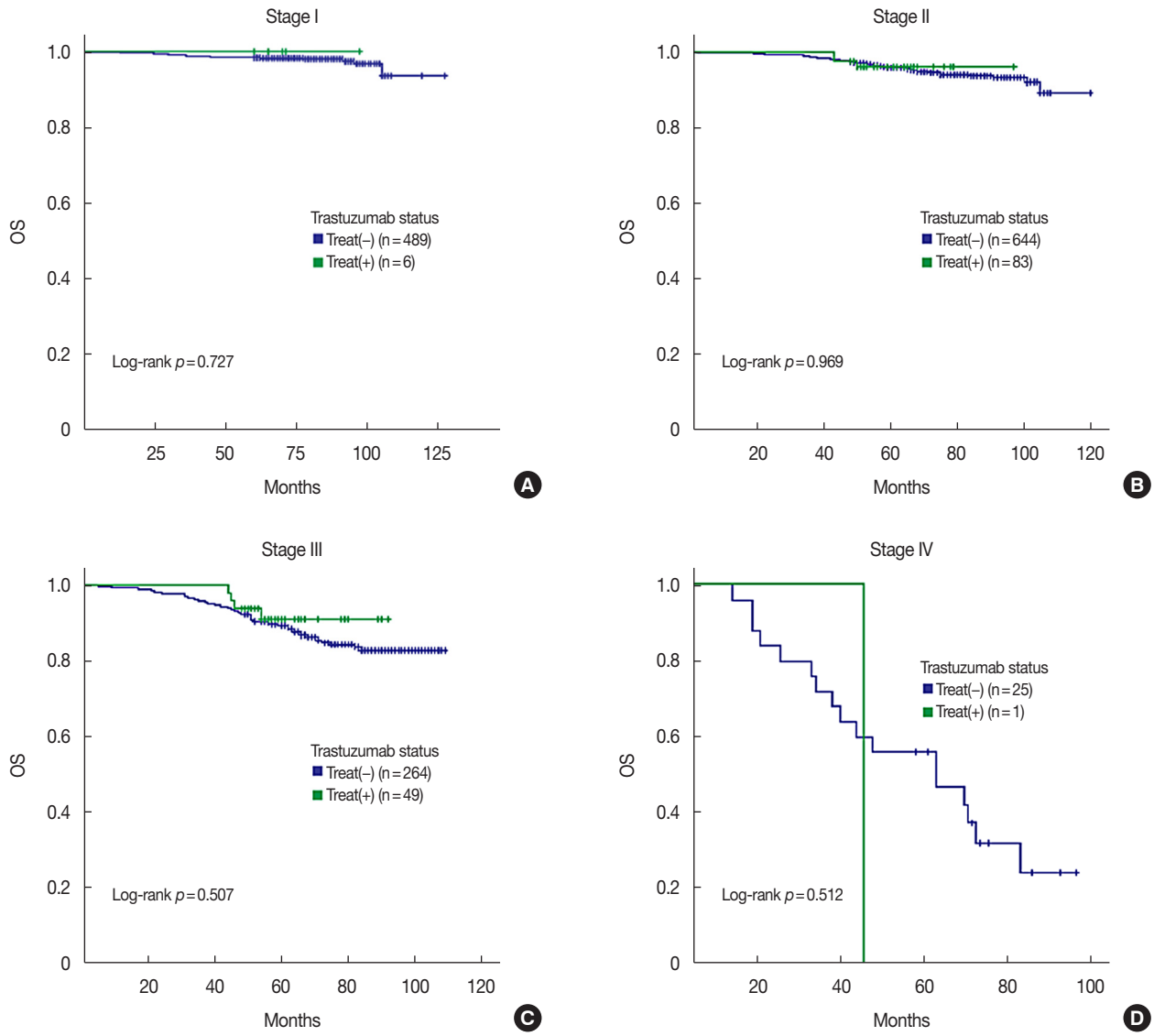

Figure 4. Efficacy of trastuzumab for triple-positive breast cancer in the Korean Breast Cancer Society cohort (2006–2010). Cases were staged according to the 7th edition of the American Joint Committee on Cancer staging system for breast cancer. Overall survival (OS) was estimated using Kaplan-Meier survival analysis. (A) Stage I, (B) stage II, (C) stage III, and (D) stage IV.

positive breast cancer, those with the HER2-enriched subtype experienced significant improvement in OS with trastuzumab therapy ($p = 0.018$) (Table 2), particularly patients with stage III breast cancer ($p = 0.018$) (Supplementary Figure 1, available online). However, only a small number of patients received trastuzumab therapy in stages I and IV for both triple-positive and HER2-enriched breast cancer subtypes (Figure 4 and Supplementary Figure 1). Therefore, interpretation of the above results requires caution.

We also investigated the effect of trastuzumab therapy on RFS using CMC data. However, during a median follow-up period of 32 months, trastuzumab treatment did not improve breast cancer recurrence among patients with triple-positive breast cancer ($p = 0.562$) (Table 2), regardless of the breast cancer stage (stage I, not assessed; stage II, $p = 0.738$; stage III, $p = 0.356$) (Supplementary Table 2, available online).

DISCUSSION

In this study, we identified the prognostic characteristics and responses to trastuzumab in two cohorts of South Korean patients with triple-positive breast cancer from a large multicenter breast cancer registry and a single-center data registry. With respect to RFS and OS, triple-positive breast cancer exhibited prognostic features comparable to those of the luminal A subtype and more favorable than those of the HER2-enriched subtype. However, although multivariate analysis of KBCS data confirmed the OS findings, a similar analysis of CMC data failed to uphold the statistical differences in RFS among the different breast cancer subtype. This discrepancy might be attributable to the lack of follow-up data in the CMC registry (median follow-up, 35 months). Notably, the KBCS data were derived from a multicenter cohort registry and represented the characteristics of breast cancer in South Korea. The KBCS data demonstrated that triple-positive breast cancer has distinct characteristics and a prognosis more similar to that of the luminal A subtype than that of the HER2-enriched subtype.

In the 8th edition of the AJCC staging system, ER, PR, and HER2 statuses are reflected in the prognostic stage. Using the Surveillance, Epidemiology, and End Results 18 database, Wang et al. [13] found that restaging based on this most-recent system led to downstaging of the anatomic stage in 81.3% of triple-positive breast cancers, with no upstaging for cases of anatomic stage III (i.e., locally advanced) breast cancer. Similarly, our data suggest the importance of the ER/PR/HER2 status and indicate that this newly developed prognostic stage-based system provides accurate prognostic information, especially regarding triple-positive breast cancer. These results suggest that an unconventional therapeutic approach may be useful.

Triple-positive breast cancer is considered a subset of the HER2-enriched subtype, characterized by coexpression of the ER and PR. As noted earlier, Vici et al. [1] provided the first definition and description of this subtype in 2015 in a review addressing ER and PR status-based differences in tumor biology and clinical outcomes of HER2-positive breast cancer. They concluded that triple-positive breast cancer might be driven primarily by the HR status and thus would biologically behave like HER2-negative/HR-positive breast cancer. However, previous studies have mainly focused on the biomolecular status of HER2-positive/HR-positive (i.e., ER- or PR-positive) breast cancer rather than triple-positive tumors. For example, Untch et al. [3] demonstrated trastuzumab efficacy in the HR-negative and HR-positive cohorts in the HERA trial, and Perez et al. [14] reported the effects of trastuzumab in a comparison of HR-negative and HR-positive groups from the NSABP B-31 and NCCTG N9831 trials (4-year disease-free survival rates, HR-negative vs. HR-positive, 81.6% vs. 89.4%). Both studies demonstrated that patients with HER2-positive/HR-positive disease had more favorable prognoses than those with the HER2-enriched subtype and revealed the poor efficacy of trastuzumab therapy in the former group.

The current consensus is that adjuvant and neoadjuvant anti-HER2 therapies are effective for patients with HER2-positive breast cancer, irrespective of the HR status [10,15-18]. Therefore, the National Comprehensive Cancer Network Guidelines, Version 1.2017 [2], state that endocrine therapy is recommended as an initial treatment for patients with HR-positive/HER2-positive breast cancer whereas adjuvant chemotherapy with trastuzumab is strongly recommended for patients with tumors of >1 cm in size or node-positive disease. Additionally, the European School of Oncology-the European Society for Medical Oncology second international consensus guidelines [19] suggest that for patients with ER-positive/HER2-positive advanced breast cancer for whom endocrine therapy is selected over chemotherapy, the addition of anti-HER2 therapy should be considered when initiating endocrine therapy [10]. Nonetheless, the paradigm of chemotherapy plus anti-HER2 therapy remains the mainstay of treatment for advanced HER2-positive breast cancer, regardless of the HR status. Recent evidence, however, suggests an inverse correlation between the HER2 positive status and HR-positive status, which consequently reduces the efficacies of both hormonal and anti-HER2 therapies [4,6,20,21]. These results demonstrate the low efficacy of anti-HER2 therapy for HR-positive/HER2-enriched breast cancer.

Several mechanisms distinguish triple-positive breast can-

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cer from other subtypes. One such mechanism involves crosstalk between the ER and HER2 pathways, both of which have been shown to play roles in not only acquired resistance to endocrine therapy but also resistance to anti-HER2 therapy [5,22,23]. Previously, Shou et al. [24] described the mechanism underlying tamoxifen resistance associated with increased ER/HER2 crosstalk in ER-positive/HER2-positive breast cancer. Furthermore, increased bidirectional ER/HER2 crosstalk converts tamoxifen into an agonist by which ER activates growth factor signaling only in ER-positive/HER2-positive breast cancer [25]. Another mechanism involves the ability of breast tumors to alternate between ER and HER2 as the dominant signaling pathway. Additionally, triple-positive breast cancer predominantly utilizes the ER pathway and consequently behaves like the HR-positive/HER2-negative subtype [20,23,26-29]. In triple-positive breast cancer, this ER dominance is enhanced by PR positivity, as the PR pathway has a key role in the distinctive characteristics of triple-positive breast cancer. Notably, in a previous adjuvant/neoadjuvant endocrine trial, the PR exhibited a significant prognostic value, as breast cancers expressing both HRs were found to have a more favorable prognosis [30].

This study has several limitations. First, the follow-up duration in the CMC dataset was rather short. Second, the KBCS data registry contains missing data regarding HER2 positivity (particularly FISH/SISH) and Ki-67 expression. Third, the proportion of patients who received trastuzumab therapy in the KBCS dataset was < 10% of patients with HER2-positive breast cancer, therefore, our results did not reflect the recent trend associated with anti-HER2 therapy for HER2-positive breast cancer. Most patients in the KBCS dataset who received trastuzumab therapy had stage II or III lymph node-positive breast cancer. However, to our knowledge, our study is the first to evaluate trastuzumab efficacy and prognostic characteristics in a cohort of patients with triple-positive breast cancer from a multicenter breast cancer data registry.

In conclusion, triple-positive breast cancer possesses distinct clinical and biological characteristics and should be considered separately from other HER2-positive breast cancers when considering therapeutic approaches. In this study, we identified the following points. First, triple-positive breast cancer behaves more like luminal subtypes than HER2-enriched subtypes, indicating that anti-hormonal therapy should be primarily considered over other therapeutic agents. Second, anti-HER2 therapy (trastuzumab) appears to be less beneficial for triple-positive breast cancer, especially in stages II and III, than for HER2-enriched subtypes. Hence, anti-HER2 therapy might be considered an overtreatment in patients with triple-positive breast cancer. Overall, our results suggest that despite several previous and ongoing studies concerning HER2-positive breast cancer, the triple-positive subtype requires additional attention and consideration as a distinct intrinsic subtype.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

REFERENCES

1. Vici P, Pizzuti L, Natoli C, Gamucci T, Di Lauro L, Barba M, et al. Triple positive breast cancer: a distinct subtype? Cancer Treat Rev 2015;41:69-76.
2. Gradishar WJ, Anderson BO, Balassanian R, Blair SL, Burstein HJ, Cyr A, et al. NCCN guidelines insights: breast cancer, version 1.2017. J Natl Compr Canc Netw 2017;15:433-51.
3. Untch M, Gelber RD, Jackisch C, Procter M, Baselga J, Bell R, et al. Estimating the magnitude of trastuzumab effects within patient subgroups in the HERA trial. Ann Oncol 2008;19:1090-6.
4. De Laurentiis M, Arpino G, Massarelli E, Ruggiero A, Carlomagno C, Ciardiello F, et al. A meta-analysis on the interaction between HER-2 expression and response to endocrine treatment in advanced breast cancer. Clin Cancer Res 2005;11:4741-8.
5. Thery JC, Spano JP, Azria D, Raymond E, Penault Llorca F. Resistance to human epidermal growth factor receptor type 2-targeted therapies. Eur J Cancer 2014;50:892-901.
6. Nahta R, O'Regan RM. Therapeutic implications of estrogen receptor signaling in HER2-positive breast cancers. Breast Cancer Res Treat 2012;135:39-48.
7. Benz CC, Scott GK, Sarup JC, Johnson RM, Tripathy D, Coronado E, et al. Estrogen-dependent, tamoxifen-resistant tumorigenic growth of MCF-7 cells transfected with HER2/neu. Breast Cancer Res Treat 1992;24:85-95.
8. Pietras RJ, Arboleda J, Reese DM, Wongvipat N, Pegram MD, Ramos L, et al. HER-2 tyrosine kinase pathway targets estrogen receptor and promotes hormone-independent growth in human breast cancer cells. Oncogene 1995;10:2435-46.
9. Johnston S, Pippen J Jr, Pivot X, Lichinitser M, Sadeghi S, Dieras V, et al. Lapatinib combined with letrozole versus letrozole and placebo as first-line therapy for postmenopausal hormone receptor-positive metastatic breast cancer. J Clin Oncol 2009;27:5538-46.
10. Kaufman B, Mackey JR, Clemens MR, Bapsy PP, Vaid A, Wardley A, et al. Trastuzumab plus anastrozole versus anastrozole alone for the treatment of postmenopausal women with human epidermal growth factor receptor 2-positive, hormone receptor-positive metastatic breast cancer: results from the randomized phase III TAnDEM study. J Clin Oncol 2009;27:5529-37.
11. Rimawi MF, Mayer IA, Forero A, Nanda R, Goetz MP, Rodriguez AA, et al. Multicenter phase II study of neoadjuvant lapatinib and trastuzumab with hormonal therapy and without chemotherapy in patients with human epidermal growth factor receptor 2-overexpressing breast cancer: TBCRC 006. J Clin Oncol 2013;31:1726-31.
12. Coates AS, Winer EP, Goldhirsch A, Gelber RD, Gnant M, Piccart-

Gebhart M, et al. Tailoring therapies: improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. Ann Oncol 2015;26:1533-46.
13. Wang M, Chen H, Wu K, Ding A, Zhang M, Zhang P. Evaluation of the prognostic stage in the 8th edition of the American Joint Committee on Cancer in locally advanced breast cancer: an analysis based on SEER 18 database. Breast 2018;37:56-63.
14. Perez EA, Romond EH, Suman VJ, Jeong JH, Davidson NE, Geyer CE Jr, et al. Four-year follow-up of trastuzumab plus adjuvant chemotherapy for operable human epidermal growth factor receptor 2-positive breast cancer: joint analysis of data from NCCTG N9831 and NSABP B-31. J Clin Oncol 2011;29:3366-73.
15. Smith I, Procter M, Gelber RD, Guillaume S, Feyereislova A, Dowsett M, et al. 2-Year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. Lancet 2007;369:29-36.
16. Perez EA, Romond EH, Suman VJ, Jeong JH, Sledge G, Geyer CE Jr, et al. 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 2014;32:3744-52.
17. Slamon D, Eiermann W, Robert N, Pienkowski T, Martin M, Press M, et al. Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med 2011;365:1273-83.
18. Gianni L, Pienkowski T, Im YH, Roman L, Tseng LM, Liu MC, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. Lancet Oncol 2012;13:25-32.
19. Cardoso F, Costa A, Norton L, Senkus E, Aapro M, André F, et al. ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2). Breast 2014;23:489-502.
20. Lipton A, Ali SM, Leitzel K, Demers L, Chinchilli V, Engle L, et al. Elevated serum Her-2/neu level predicts decreased response to hormone therapy in metastatic breast cancer. J Clin Oncol 2002;20:1467-72.
21. Llombart-Cussac A, Cortés J, Paré L, Galván P, Bermejo B, Martínez N, et al. HER2-enriched subtype as a predictor of pathological complete response following trastuzumab and lapatinib without chemotherapy in early-stage HER2-positive breast cancer (PAMELA): an open-label, single-group, multicentre, phase 2 trial. Lancet Oncol 2017;18:545-54.
22. Osborne CK, Schiff R. Mechanisms of endocrine resistance in breast cancer. Annu Rev Med 2011;62:233-47.
23. Gutierrez MC, Detre S, Johnston S, Mohsin SK, Shou J, Allred DC, et al. Molecular changes in tamoxifen-resistant breast cancer: relationship between estrogen receptor, HER-2, and p38 mitogen-activated protein kinase. J Clin Oncol 2005;23:2469-76.
24. Shou J, Massarweh S, Osborne CK, Wakeling AE, Ali S, Weiss H, et al. Mechanisms of tamoxifen resistance: increased estrogen receptor-HER2/neu cross-talk in ER/HER2-positive breast cancer. J Natl Cancer Inst 2004;96:926-35.
25. Knowlden JM, Hutcheson IR, Jones HE, Madden T, Gee JM, Harper ME, et al. Elevated levels of epidermal growth factor receptor/c-erbB2 heterodimers mediate an autocrine growth regulatory pathway in tamoxifen-resistant MCF-7 cells. Endocrinology 2003;144:1032-44.
26. Massarweh S, Osborne CK, Creighton CJ, Qin L, Tsimelzon A, Huang S, et al. Tamoxifen resistance in breast tumors is driven by growth factor receptor signaling with repression of classic estrogen receptor genomic function. Cancer Res 2008;68:826-33.
27. Lopez-Tarruella S, Schiff R. The dynamics of estrogen receptor status in breast cancer: re-shaping the paradigm. Clin Cancer Res 2007;13:6921-5.
28. Creighton CJ, Massarweh S, Huang S, Tsimelzon A, Hilsenbeck SG, Osborne CK, et al. Development of resistance to targeted therapies transforms the clinically associated molecular profile subtype of breast tumor xenografts. Cancer Res 2008;68:7493-501.
29. Munzone E, Curigliano G, Rocca A, Bonizzi G, Renne G, Goldhirsch A, et al. Reverting estrogen-receptor-negative phenotype in HER-2-over-expressing advanced breast cancer patients exposed to trastuzumab plus chemotherapy. Breast Cancer Res 2006;8:R4.
30. Stendahl M, Rydén L, Nordenskjöld B, Jönsson PE, Landberg G, Jirström K. High progesterone receptor expression correlates to the effect of adjuvant tamoxifen in premenopausal breast cancer patients. Clin Cancer Res 2006;12:4614-8.

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Supplementary Table 1. Baseline characteristics of patients included in the data registry of the Seoul St. Mary's Hospital of the Catholic Medical Center

Characteristic	Subtype				*p*-value
	Triple-positive (n=169) No. (%)	Luminal A (n=724) No. (%)	HER2-enriched (n=206) No. (%)	Luminal B with HER2(–) (n=668) No. (%)	
Age at diagnosis (yr)					<0.001
<40	26 (15.4)	64 (8.8)	19 (9.2)	81 (12.1)	
40–49	66 (39.1)	252 (34.8)	42 (20.4)	241 (36.1)	
50–59	44 (26.0)	232 (32.0)	102 (49.5)	200 (29.9)	
≥60	33 (19.5)	176 (24.2)	43 (20.9)	146 (21.9)	
BMI (kg/m^2)					0.389
<18.5	8 (4.7)	29 (4.0)	5 (2.4)	24 (3.6)	
18.5–22.9	83 (49.1)	326 (45.0)	81 (39.3)	274 (41.0)	
23–24.9	37 (21.9)	166 (22.9)	50 (24.3)	155 (23.2)	
≥25	41 (24.3)	203 (28.0)	70 (34.0)	215 (32.2)	
pT stage					<0.001
T1	91 (53.8)	528 (72.9)	104 (50.5)	390 (58.4)	
T2	67 (39.6)	165 (22.8)	82 (39.8)	248 (37.1)	
T3	8 (4.7)	25 (3.5)	16 (7.8)	25 (3.7)	
T4	3 (1.8)	3 (0.4)	2 (1.0)	2 (0.3)	
Tis	0	3 (0.4)	2 (1.0)	1 (0.1)	
pN stage					0.002
N0	97 (57.4)	512 (70.7)	117 (56.8)	445 (66.6)	
N1	45 (26.6)	151 (20.9)	58 (28.2)	162 (24.3)	
N2	15 (8.9)	43 (5.9)	18 (8.7)	35 (5.2)	
N3	12 (7.1)	18 (2.5)	13 (6.3)	26 (3.9)	
TNM stage					<0.001
I	64 (37.9)	418 (57.7)	75 (36.4)	307 (46.0)	
II	76 (45.0)	232 (32.0)	95 (46.1)	293 (43.9)	
III	29 (17.2)	74 (10.2)	36 (17.5)	68 (10.2)	
EGFR					<0.001
Negative	135 (86.0)	638 (90.0)	102 (51.5)	553 (83.8)	
Positive	22 (14.0)	71 (10.0)	96 (48.5)	107 (16.2)	
Recurrence	11 (6.5)	29 (4.0)	22 (10.7)	42 (6.3)	0.001
Follow-up duration (mo)*	36.79±23.97	39.49±21.57	35.95±20.33	31.18±20.66	0.001†

HER2=human epidermal growth factor receptor 2; BMI=body mass index; EGFR=epidermal growth factor receptor.
*Mean±SD; †One way ANOVA.

Supplementary Table 2. Trastuzumab efficacy for triple-positive breast cancer in CMC data according to the stage

Stage	RFS*	*p*-value
I	Log-rank (Mantel-Cox)	Not assessed
II	Log-rank (Mantel-Cox)	0.738
III	Log-rank (Mantel-Cox)	0.356

CMC = Seoul St. Mary's Hospital of the Catholic Medical Center; RFS = recurrence-free survival.
*Kaplan-Meier survival analysis of RFS.

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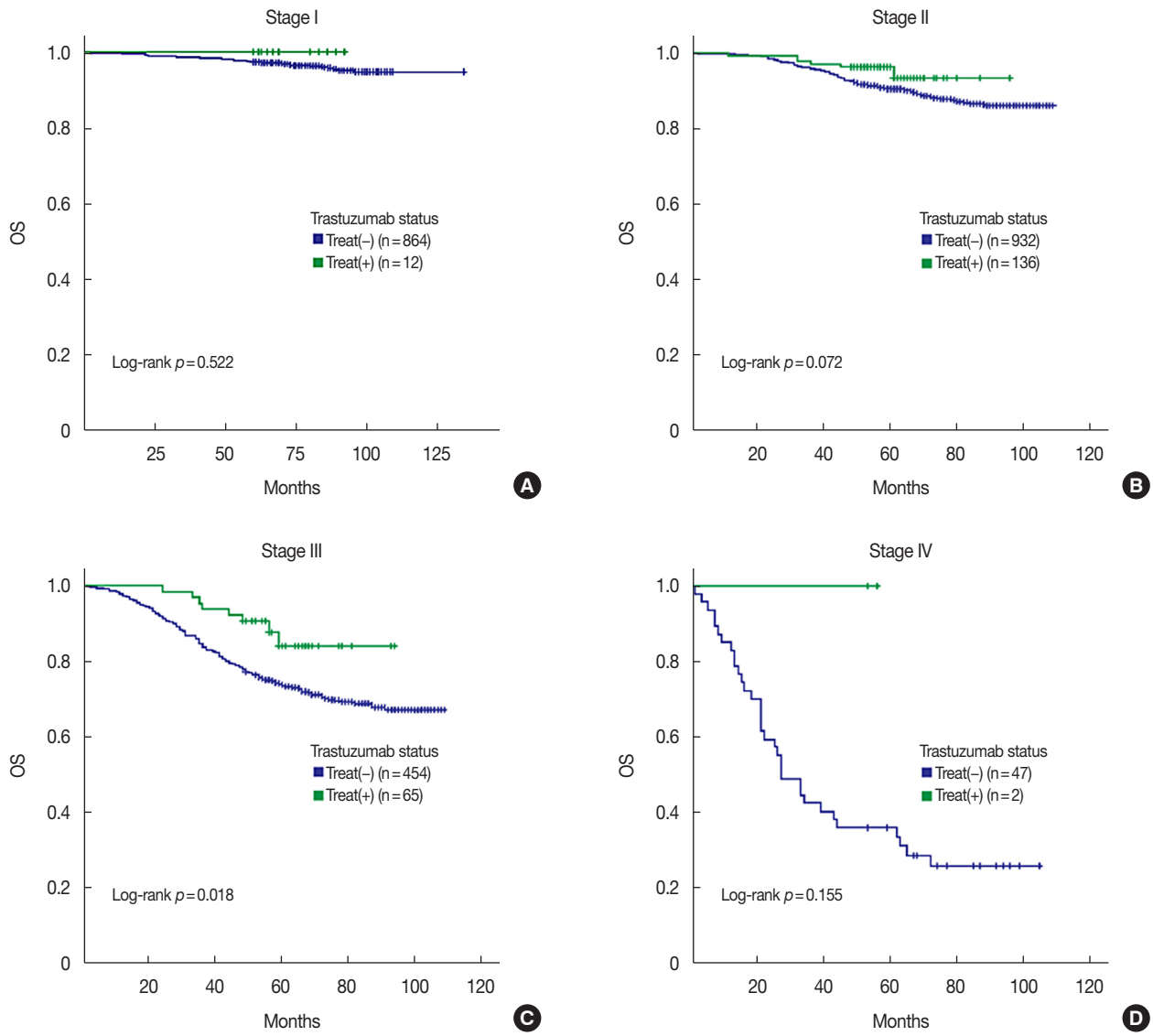

Supplementary Figure 1. Efficacy of trastuzumab for human epidermal growth factor receptor 2 (HER2)-enriched breast cancer in the Korean Breast Cancer Society cohort (2006–2010). Cases were staged according to the 7th edition of the American Joint Committee on Cancer staging system for breast cancer. Overall survival (OS) was estimated using Kaplan-Meier survival analysis. (A) Stage I, (B) stage II, (C) stage III, and (D) stage IV.