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Original Research

Three-year follow-up from a phase 3 study of SB3 (a trastuzumab biosimilar) versus reference trastuzumab in the neoadjuvant setting for human epidermal growth factor receptor 2–positive breast cancer

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Long-term extension study

Abstract ***Background:*** We assessed long-term cardiac safety and efficacy in patients with human epidermal growth factor receptor 2–positive early breast cancer treated with a trastuzumab biosimilar (SB3) or its reference product, trastuzumab (TRZ), in a phase 3 study.
Methods: Patients who completed the phase 3 study could be enrolled in this extension study. The outcomes included the incidence of symptomatic congestive heart failure (CHF), asymptomatic significant left ventricular ejection fraction (LVEF) decrease, incidence of other cardiac events, event-free survival (EFS), and overall survival. In post hoc analysis, the Cox proportional hazards regression model was used to assess factors associated with EFS.
Results: A total of 367 patients were enrolled in the study (SB3, n = 186; TRZ, n = 181). The median follow-up duration from the main study enrolment was 40.8 and 40.5 months for SB3 and TRZ, respectively. During the two-year follow-up after adjuvant therapy, incidence of asymptomatic significant LVEF decrease was rare (SB3, n = 1; TRZ, n = 2), with all patients

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recovering with LVEF ≥ 50%, and no cases of symptomatic CHF or other cardiac events were reported. At 3 years, the EFS was 91.9% with SB3 and 85.2% with TRZ. The number of patients with events was 17 (9.1%) with SB3 and 31 (17.1%) with TRZ [hazard ratio: 0.47, 95% confidence interval: 0.26–0.87]. Antibody-dependent cell-mediated cytotoxicity (ADCC) activity and the breast pathologic complete response rate were the factors associated with EFS.
Conclusion: Cardiotoxicity was rare in this extension study. EFS was higher with SB3 versus TRZ, with post hoc analysis suggesting that a downward drift in ADCC activity was a contributing factor.
Clinical trial registration numbers: NCT02771795 (EudraCT 2015-005663-17).

1. Introduction

SB3 (Ontruzant® [Samfenet® in Korea]; Samsung Bioepis Co., Ltd., Incheon, the Republic of Korea), an approved biosimilar of the trastuzumab reference product (hereafter referred to as TRZ), is registered in Europe, the United States, the Republic of Korea and Australia [1–3]. A phase 3 randomised controlled study (NCT02149524, EudraCT 2013-004172-35; hereafter referred to as the main study) was conducted on 875 women with human epidermal growth factor receptor 2 (HER2)–positive early or locally advanced breast cancer treated in the neoadjuvant setting [4]. The breast pathologic complete response (bpCR) rates in the per-protocol set were 51.7% and 42.0% with SB3 and TRZ, respectively. The adjusted ratio of bpCR was 1.259 (90% confidence interval [CI], 1.112–1.426), which was within the predefined equivalence margins of 0.785 and 1.546. However, the adjusted difference in the per-protocol set was 10.70% (95% CI, 4.13–17.26), with the upper limit of the 95% CI outside the equivalence margin of ±13.0%. A similar trend was observed in total pathologic complete response (tpCR) rates. No difference was observed between SB3 and TRZ in event-free survival (EFS) and overall survival (OS) at 1-year follow-up [5].

On monitoring physicochemical and biological properties of TRZ for the development of SB3, a downward drift in the level of glycosylation, FcγRIIIa binding activity, and antibody-dependent cell-mediated cytotoxicity (ADCC) activity was observed in TRZ lots with expiry dates from August 2018 to December 2019, as previously reported by Kim *et al.* [6]. Some of the drifted TRZ lots were used in the phase 3 study and may have contributed to the observed difference between arms in terms of bpCR and tpCR rates in the main study [4].

The objective of this long-term extension of the main study was to investigate cardiac safety, EFS and OS in patients who received SB3 or TRZ. A post hoc analysis aimed to assess the factors contributing to the observed difference in EFS.

2. Methods

The extension study (NCT02771795, EudraCT 2015-005663-17) was conducted in accordance with the ethical principles of the Declaration of Helsinki and consistent with Good Clinical Practice guidelines. The extension study and protocol were approved by independent ethics committees or institutional review boards.

2.1. Study design and participants

The extension study was an observational cohort study from the main study; inclusion and exclusion criteria for the main study were previously reported [4]. After regulatory recommendation, patients from prespecified countries (Bosnia and Herzegovina, Bulgaria, the Czech Republic, France, Poland, Romania, the Russian Federation and Ukraine) who completed the neoadjuvant treatment, surgery and adjuvant treatment and provided written informed consent were eligible to participate in the treatment-free extension study. The participants in the extension study had not experienced symptomatic cardiac events during the main study and had not experienced early recurrence while they received adjuvant therapy.

2.2. Assessments

The patients will be followed up for 5 years after the end of the main study. Follow-up visits were recommended every 6 months for 2 years and then yearly for an additional 3 years. During follow-up visits, physical examination including clinical breast examination, mammography, left ventricular ejection fraction (LVEF) measurement (2D echocardiography or the Multigated acquisition (MUGA) scan) and monitoring of cardiac events was performed in the routine care setting. The primary outcome of this extension study was the incidence of symptomatic congestive heart failure (New York Heart Association class II–IV confirmed by a cardiologist and accompanied by a significant LVEF decrease) and the incidence of an

asymptomatic significant LVEF decrease, defined as a decrease of ≥10% from the baseline with a resulting value of <50%. The incidences of cardiac death and other significant cardiac conditions (e.g., acute myocardial infarction, severe arrhythmia, ischaemic heart disease and valvular dysfunction) were secondary safety outcomes. Secondary efficacy outcomes were EFS (time from the date of randomisation to the date of disease recurrence, progression [local, regional, distant or contralateral] or death) and OS (time from the date of randomisation to the date of death, regardless of cause).

2.3. Statistical analysis

Demographics and baseline disease characteristics are summarised using descriptive statistics for patients who were enrolled in this extension study from the main study. Including efficacy data from the main and extension studies, Kaplan-Meier curves for EFS and OS were generated by treatment arms (SB3 and TRZ), which were assigned in the main study. Hazard ratios (HRs) with 95% CI were determined for SB3 over TRZ based on a stratified Cox proportional hazards regression model adjusted for stratification factors (hormone receptor status, breast cancer type and region).

Among the 25 TRZ lots that were used in the main study, 12 TRZ lots were obtained, and their ADCC activities were analysed (Supplementary Figure 1A). The ADCC activity for the remaining 13 TRZ lots was assumed based on their expiry dates: TRZ lots with expiry dates from August 2018 to December 2019 were assumed to have a drift in ADCC activity based on the analysis results from the study by Kim *et al.* [6].

Of the 25 TRZ lots, 13 were classified as having a drift in ADCC activity (eight based on the available analysis results and five based on expiry dates). The ADCC activity of the remaining 12 lots was considered to be in the normal range (four based on the available analysis results and eight based on expiry dates). Distribution of TRZ vials used in the phase 3 study by site and visit date can be found in Supplementary Figure 1B.

Among patients who were treated with TRZ, those exposed to at least one vial from a drifted TRZ lot during the neoadjuvant period were designated as the 'Drifted TRZ' group, and those who were never exposed to any vials from a drifted TRZ lot during the neoadjuvant period were designated as the 'non-drifted TRZ' group. Results based on exposure during the neoadjuvant period are mainly presented in this study; however, the same analysis was performed by exposure to at least one vial of the drifted TRZ lot during the adjuvant period or the entire treatment period.

As for post hoc analysis, the Cox proportional hazards regression model was used to find the factors that are associated with EFS. The backward variable selection method was used to select statistically significant factors. The HR with its respective p value for each covariate was presented. The significance level for eliminating a factor from the model in the backward selection method was 0.10. Treatment arm (SB3/TRZ), bpCR (no/yes), tpCR (no/yes), ADCC activity (drifted/non-drifted), hormone receptor status (oestrogen receptor− and progesterone receptor−negative/positive), breast cancer type (locally advanced/operable), age (<45 years/> = 45 years) and menopausal status (no/yes) were considered as factors. Because bpCR and tpCR were highly correlated to each other, they were analysed in separate models.

Kaplan-Meier curves for EFS and OS were generated by the treatment group and ADCC activity (SB3, non-drifted TRZ and drifted TRZ). The stratified Cox proportional hazards regression model with ADCC activity (or treatment arm) and bpCR as covariates were used to estimate HRs and the corresponding 95% CI of the treatment arm (SB3/non-drifted TRZ) and ADCC activity (non-drifted TRZ/drifted TRZ), respectively.

3. Results

3.1. Patients

The extension study was initiated in April 2016 and is ongoing. Patient disposition is shown in Fig. 1. Of 875 patients randomised in the main study (SB3, $n = 437$; TRZ, $n = 438$), a total of 367 patients (SB3, $n = 186$; TRZ, $n = 181$) were enrolled in the extension study. As of the cut-off date (12th September 2018), the study was ongoing for 339 patients (SB3, $n = 175$; TRZ, $n = 164$). The median (range) follow-up duration from enrolment for the main study was 40.8 (18.4−52.3) and 40.5 (23.4−51.8) months for SB3 and TRZ, respectively. The most common reason for early termination was death in both arms (SB3, $n = 5$; TRZ, $n = 13$). Demographics and baseline disease characteristics were well balanced, with no apparent differences between the SB3 and TRZ arms (Table 1).

3.2. Cardiac safety

Symptomatic congestive heart failure was not reported in either the SB3 or TRZ arm. There were three asymptomatic significant LVEF decreases reported during the extension study (SB3, $n = 1$; TRZ, $n = 2$). No other cardiac-related events, including cardiac death, occurred. Changes in LVEF over time were similar between the SB3 and TRZ arms (Fig. 2).

3.3. Efficacy

EFS in the SB3 and TRZ arms is shown in Fig. 3A. The number of patients with events was 17 (9.1%) in the SB3 arm and 31 (17.1%) in the TRZ arm, with a HR (SB3/

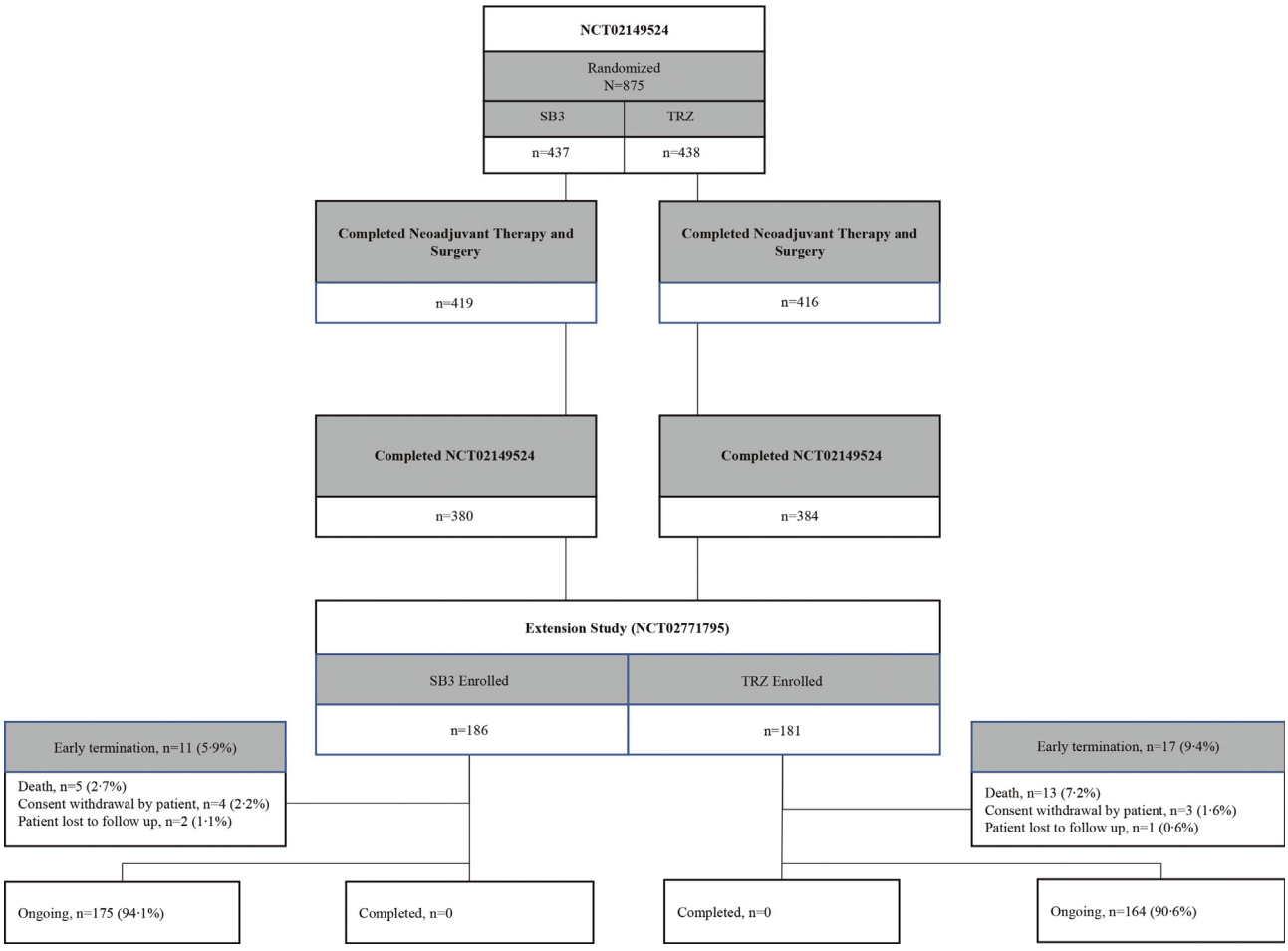

Fig. 1. **Patient disposition**. TRZ, trastuzumab reference product.

TRZ) of 0.47 (95% CI, 0.26–0.87). The 3-year EFS rate was 91.9% in the SB3 arm and 85.2% in the TRZ arm.

OS in the SB3 and TRZ arms is shown in Fig. 3B. The number of deaths was 5 (2.7%) in the SB3 arm and 13 (7.2%) in the TRZ arm, with a HR (SB3/TRZ) of 0.37 (95% CI, 0.13–1.04). The 3-year OS rate was 97.0% in the SB3 arm and 92.9% in the TRZ arm.

3.4. Post hoc analysis results

The results of the Cox proportional hazards regression models with backward elimination showed that, among the covariates analysed, ADCC activity and bpCR (or tpCR) were the factors that were associated with EFS at the 0.1 significance level (Fig. 4).

3.4.1. Efficacy by exposure to drifted TRZ during the neoadjuvant period

The number of patients in the non-drifted and drifted TRZ groups was 55 and 126, respectively. Demographics and baseline disease characteristics were well balanced between both groups (Table 1).

EFS is shown by exposure to drifted TRZ during the neoadjuvant period in Fig. 3C. The percentage of patients with events was significantly higher in the drifted TRZ group (n = 26, 20.6%) than in the non-drifted TRZ group (n = 5, 9.1%), with a HR (drifted TRZ/non-drifted TRZ) of 5.31 (95% CI, 1.74–16.25). The 3-year EFS rate was 81.7% in the drifted TRZ group and 92.7% in the non-drifted TRZ group. No significant difference in EFS was observed between the SB3 and non-drifted TRZ group (HR, 0.93 [95% CI, 0.31–2.85]; Fig. 3C).

OS is shown by exposure to drifted TRZ during the neoadjuvant period in Fig. 3D. A higher percentage of deaths was observed in the drifted TRZ group (n = 12, 9.5%) than in the non-drifted TRZ group (n = 1, 1.8%), with a HR (drifted TRZ/non-drifted TRZ) of 7.96 (95% CI, 0.95–67.00). The 3-year OS rate was 89.4% in the drifted TRZ group and 100% in the non-drifted TRZ group. OS was comparable between the SB3 and non-drifted TRZ groups (HR, 0.53 [95% CI, 0.05, 5.51]; Fig. 3D).

3.4.2. Efficacy by exposure to drifted TRZ during the adjuvant or the entire treatment period

The results analysed by exposure to drifted TRZ during the adjuvant treatment period (Supplementary Table

Table 1
Patient demographics and baseline disease characteristics.

Characteristic	SB3 (N = 186)	TRZ (N = 181)		
		All	Non-drifted[a] (n = 55)	Drifted[b] (n = 126)
Age, median (minimum, maximum), y	52 (27, 65)	53 (22, 65)	52 (22, 63)	53 (22, 65)
Race, *n* (%)				
White	176 (94.6)	171 (94.5)	50 (90.9)	121 (96.0)
Asian	3 (1.6)	2 (1.1)	0 (0)	2 (1.6)
Other	7 (3.8)	8 (4.4)	5 (9.1)	3 (2.4)
Menopause, *n* (%)	92 (49.5)	98 (54.1)	31 (56.4)	67 (53.2)
ECOG performance status, *n* (%)				
0	162 (87.1)	150 (82.9)	45 (81.8)	105 (83.3)
1	24 (12.9)	31 (17.1)	10 (18.2)	21 (16.7)
LVEF, mean (SD), %	65.5 (4.8)	64.8 (5.3)	65.1 (5.7)	64.7 (5.2)
Breast cancer type, *n* (%)				
Operable	124 (66.7)	120 (66.3)	37 (67.3)	83 (65.9)
Locally advanced	56 (30.1)	55 (30.4)	15 (27.3)	40 (31.7)
Inflammatory	6 (3.2)	6 (3.3)	3 (5.5)	3 (2.4)
Histopathologic tumour type, *n* (%)				
Invasive ductal carcinoma	179 (96.2)	176 (97.2)	53 (96.4)	123 (97.6)
Invasive lobular carcinoma	4 (2.2)	1 (0.6)	0 (0)	1 (0.8)
Other	3 (1.6)	4 (2.2)	2 (3.6)	2 (1.6)
Hormone receptor status, *n* (%)				
ER+/PR+	90 (48.4)	67 (37.0)	17 (30.9)	50 (39.7)
ER+/PR−	31 (16.7)	32 (17.7)	11 (20.0)	21 (16.7)
ER−/PR+	4 (2.2)	6 (3.3)	1 (1.8)	5 (4.0)
ER−/PR−	61 (32.8)	76 (42.0)	26 (47.3)	50 (39.7)
Clinical T stage, *n* (%)				
cT1	1 (0.5)	2 (1.1)	1 (1.8)	1 (0.8)
cT2	124 (66.7)	109 (60.2)	31 (56.4)	78 (61.9)
cT3	22 (11.8)	32 (17.7)	11 (20.0)	21 (16.7)
cT4	39 (21.0)	38 (21.0)	12 (21.8)	26 (20.6)
Clinical N stage, *n* (%)				
cN0	45 (24.2)	40 (22.1)	9 (16.4)	31 (24.6)
cN1	104 (55.9)	104 (57.5)	36 (65.5)	68 (54.0)
cN2	30 (16.1)	24 (13.3)	8 (14.5)	16 (12.7)
cN3	7 (3.8)	13 (7.2)	2 (3.6)	11 (8.7)
Clinical TNM staging, *n* (%)				
Stage IIA	38 (20.4)	33 (18.2)	9 (16.4)	24 (19.0)
Stage IIB	76 (40.9)	70 (38.7)	23 (41.8)	47 (37.3)
Stage IIIA	28 (15.1)	34 (18.8)	10 (18.2)	24 (19.0)
Stage IIIB	37 (19.9)	31 (17.1)	11 (20.0)	20 (15.9)
Stage IIIC	7 (3.8)	13 (7.2)	2 (3.6)	11 (8.7)
bpCR in the main study, *n*/*N* (%)	208/402 (51.7)	167/398 (42.0)		
tpCR in the main study, *n*/*N* (%)	175/382 (45.8)	136/380 (35.8)		

bpCR, breast pathologic complete response; ECOG, Eastern Cooperative Oncology Group; ER, oestrogen receptor; LVEF, left ventricular ejection fraction; N, the number of subjects in the per-protocol set in the main study; PR, progesterone receptor; tpCR, total pathologic complete response; TRZ, trastuzumab reference product; SD, standard deviation.

[a] Patients never exposed to any vials from a drifted TRZ lot during the neoadjuvant period.

[b] Patients exposed to at least one vial from a drifted TRZ lot during the neoadjuvant.

2A) and the results analysed by exposure to drifted TRZ during the entire treatment period (Supplementary Table 2B) showed similar trends with those of the neoadjuvant setting.

4. Discussion

Cardiovascular safety profiles were comparable between SB3 and TRZ during this extension study, with no symptomatic congestive heart failure, cardiac deaths or other significant cardiac conditions. The findings in this extension study are consistent with those of other studies that suggest low risk of developing cardiotoxicity after completion of neoadjuvant and adjuvant trastuzumab [7–9], despite its use in combination with anthracyclines [10–13].

In this 3-year follow-up, the SB3 arm was associated with a significantly lower number of events counting for EFS than that of the TRZ arm (HR, 0.47 [95% CI, 0.26–0.87]). The post hoc analysis suggests that the observed difference in EFS between SB3 and TRZ may have been contributed by the subgroup of patients

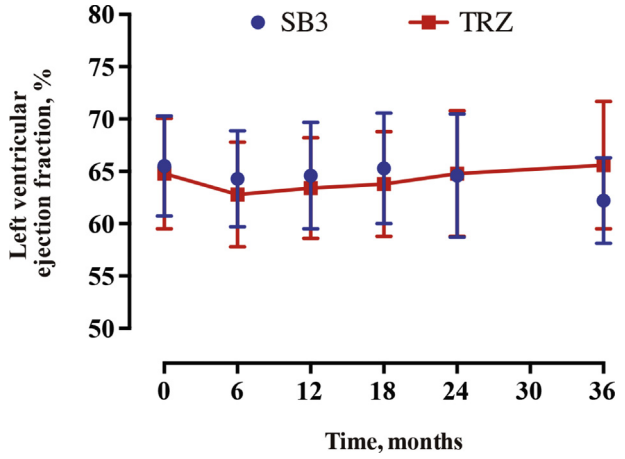

Fig. 2. **Mean left ventricular ejection fraction over time. Error bars represent standard deviations**. TRZ, trastuzumab reference product.

exposed to drifted TRZ in the control arm. In the Cox proportional hazards regression model, ADCC activity and bpCR (or tpCR) were the factors associated with EFS. The percentage of patients with events was 20.6% and 9.1% in the drifted TRZ versus non-drifted TRZ groups, respectively (HR, 5.31 [95% CI, 1.74–16.25]); no significant difference was observed between SB3 and the non-drifted TRZ group (HR, 0.93 [95% CI, 0.31–2.85]). Similar trends were observed for OS; however, extended follow-up is needed to confirm the finding.

pCR has been used as a surrogate end-point of survival in numerous clinical trials of neoadjuvant therapy for breast cancer [12,14–17] and is considered a surrogate marker of survival in this population [18]. Our results are consistent with historical results showing that pCR achievement is associated with improved long-term survival in HER2-positive breast cancer (Fig. 4). Based on the results from the Cox proportional hazards

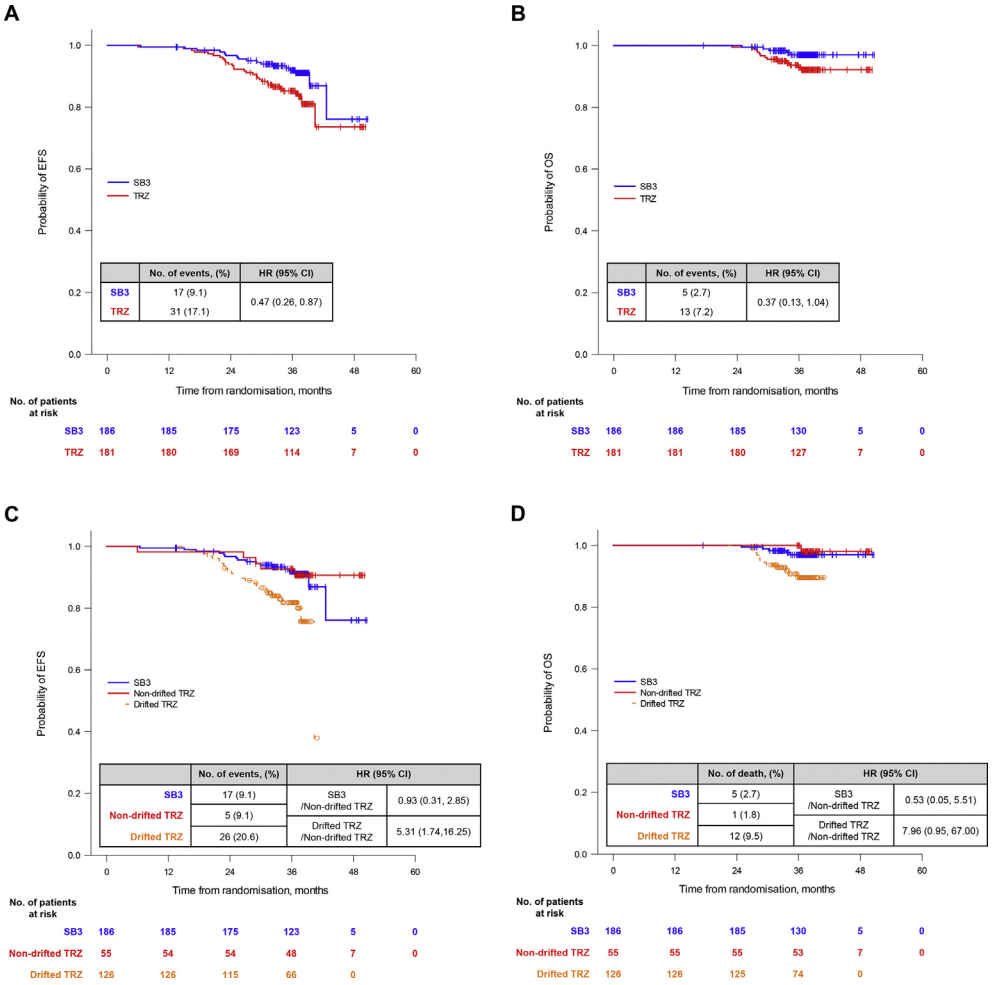

Fig. 3. **Kaplan–Meier curves for (A) EFS for SB3 and TRZ; (B) OS for SB3 and TRZ; (C) EFS for SB3, non-drifted TRZ and drifted TRZ; and (D) OS for SB3, non-drifted TRZ and drifted TRZ**. Non-drifted TRZ = patients who were never exposed to any vials from a drifted TRZ lot during the neoadjuvant period. Drifted TRZ = patients who were exposed to at least one vial from a drifted TRZ lot during the neoadjuvant period. CI, confidence interval; EFS, event-free survival; HR, hazard ratio; OS, overall survival; TRZ, trastuzumab reference product.

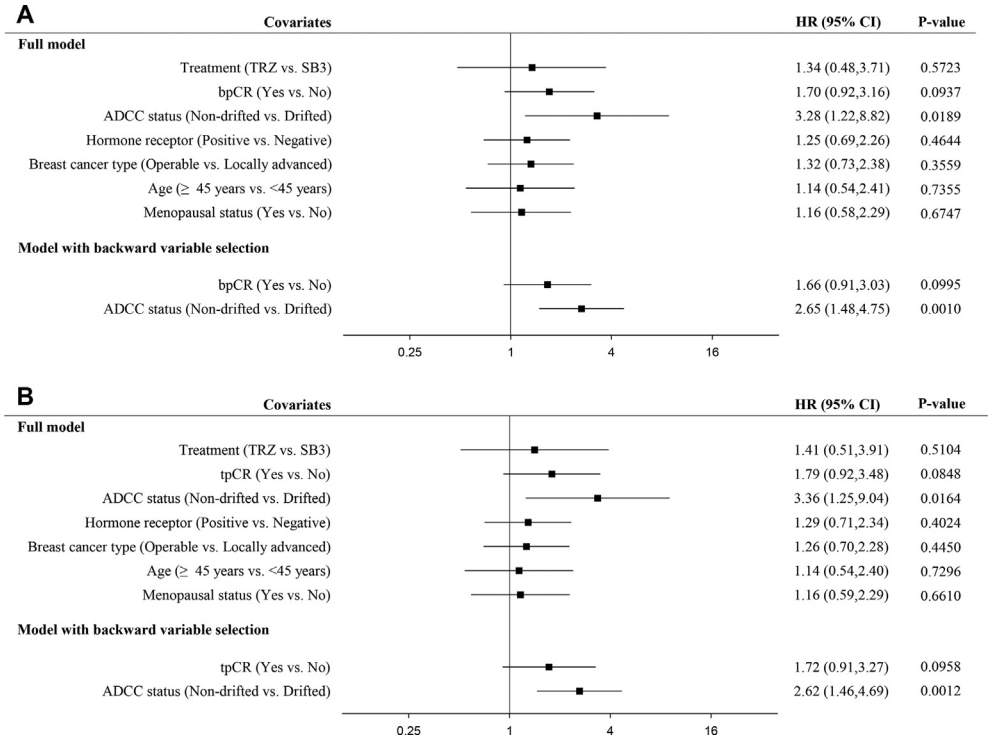

Fig. 4. **Influential factors on EFS (A) with bpCR as a covariate and (B) with tpCR as a covariate**. Drifted = patients who were exposed to at least one vial from a drifted TRZ lot during the neoadjuvant period. Non-drifted = patients who were never exposed to any vials from a drifted TRZ lot during the neoadjuvant period. Positive = ER and/or PR positive. Negative = ER and PR negative. Patients whose bpCR or tpCR is missing are excluded from the model. ADCC, antibody-dependent cell-mediated cytotoxicity; bpCR, breast pathologic complete response; CI, confidence interval; EFS, event-free survival; ER, oestrogen receptor; HR, hazard ratio; PR, progesterone receptor; tpCR, total pathologic complete response; TRZ, trastuzumab reference product.

regression model, ADCC activity was also associated with EFS in both models (Fig. 4). This finding suggests ADCC might be another factor influencing survival. Drifted TRZ has previously been shown to be less able to induce an ADCC response [6], and thus one of the main reasons for the between-arm difference in EFS rates could be a drifted ADCC response induced by drifted TRZ.

ADCC is thought to be an important contributor to the efficacy of trastuzumab [19–21], and amplification of ADCC activity could be a promising area of research [22]. Trastuzumab has been shown to induce ADCC in peripheral blood mononuclear cells in HER2-amplified and non-amplified breast cancer cell lines as well as in trastuzumab-resistant breast cancer cell lines [19,20]. The ADCC response is triggered when the Fab and Fc fragments of trastuzumab engage the tumour cell antigen and Fc gamma receptor (FcγR) of the effector cell, respectively [23]. In preclinical models, trastuzumab did not arrest tumour cell growth in mice deficient in activating FcγR or in the presence of antibodies that disrupted Fc binding [24]. Afucosylated trastuzumab was demonstrated to have increased Fc binding, enhanced ADCC and more than double the median progression-free survival in mice, when compared with conventional trastuzumab [25]. To our knowledge, our findings are the first clinical results to support the hypothesis of a relationship between ADCC activity and long-term survival.

This report is limited in that it does not have sufficient power to test the hypothesis of a relationship between ADCC activity and EFS, and the results are based on a subset of patients from the main study population. And the survival results by exposure to ADCC drift were derived from a post hoc analysis and a disproportionate number of patients in each group within the TRZ arm, with ADCC activity data of only 12 TRZ lots available.

In conclusion, in this extension study, the incidence of cardiotoxicity was rare in both the SB3 and TRZ arms. The EFS rate was higher in the SB3 versus TRZ arm, and the differences could be attributed to a drift in ADCC activity in some of the TRZ lots that were used during the study. Our data support the hypothesis of a relationship between ADCC activity and clinical outcomes in terms of the response rate and long-term survival.

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Conflict of interest statement

X.P. declares no conflict of interest; M.P. reports personal fees from Roche/Genentech, Puma, Novartis, MacroGenics, Samsung Bioepis, Amgen and Pfizer outside the submitted work; J.C. is a consultant/advisor of Roche, Celgene, Cellestia, AstraZeneca, Biothera Pharmaceuticals, Merus, Seattle Genetics, Daiichi Sankyo, Erytech and Athenex, received honoraria from Roche, Novartis, Celgene, Eisai, Pfizer and Samsung, received research funding to the institution from Roche, Ariad Pharmaceuticals, AstraZeneca, Baxalta GmbH/Servier Affaires, Bayer Healthcare, Eisai, F.Hoffman-La Roche, Guardant health, Merck Sharp & Dohme, Pfizer, Piqur Therapeutics, Puma C and Queen Mary University of London and hold stock, patents and intellectual property of MedSIR; D.L. reports personal fees from Amgen, Eli Lilly, Loreal, Teva, Tesaro, Pfizer, Samsung/MSD, Celgene and AstraZeneca and grants and personal fees from Novartis, outside the submitted work; G.H.L. reports personal fees from Samsung Bioepis, Pfizer and Mylan, outside the submitted work; G.C. reports personal fees from Pfizer, Roche-Genentech, Novartis, Samsung, Lilly and Seattle Genetics, and other from Ellipsis outside the submitted work; I.B. declares no conflict of interest; Y.C.Y., Y.K. and C.K. are employees of Samsung Bioepis Co., Ltd.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.07.015.

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