REVIEW ARTICLE

Biologic Drug Quality Assurance to Optimize HER2 + Breast Cancer Treatment: Insights from Development of the Trastuzumab Biosimilar SB3

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Abstract

SB3 is a biosimilar of trastuzumab that has been approved for use in the treatment of human epidermal growth factor 2-positive breast cancer and human epidermal growth factor 2-positive gastric cancer. Antibody-dependent cellular cytotoxicity is one of several critical quality attributes of trastuzumab. Data from the development of SB3 support the hypothesis of a relationship between antibody-dependent cellular cytotoxicity activity and clinical outcomes in terms of the response rate and long-term survival. Current analytic methods utilizing advanced technology allow the detection of small changes in other quality attributes that influence antibody-dependent cellular cytotoxicity, such as glycosylation and FcγRIIIa binding. Use of such methods to monitor batch-to-batch consistency enables production of trastuzumab biosimilars with consistent quality. Trastuzumab biosimilars such as SB3 therefore have the potential to increase accessibility to trastuzumab-based therapy without compromising efficacy or safety.

Key Points

Patterns of change were detected in certain quality attributes of the trastuzumab reference product that may affect clinical outcomes.

In a clinical study of SB3 vs the trastuzumab reference product in patients with human epidermal growth factor 2-positive breast cancer, relatively high rates of breast pathologic complete response rates and long-term patient survival after SB3 treatment lend support to the hypothesis that critical quality attributes can influence clinical outcomes in terms of response rate and long-term survival.

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1 Introduction

Biologic drugs targeting human epidermal growth factor 2 (HER2), such as the anti-HER2 monoclonal antibody trastuzumab, have revolutionized the treatment of HER2-positive (HER2 +) breast cancer [1]. Trastuzumab-containing regimens are the standard of care for patients with early or metastatic HER2 + breast cancer and have considerably improved outcomes in these indications [2–6]. However, biologic drugs like trastuzumab are also expensive and account for much of the rising cost of cancer care [7, 8], placing enormous financial pressure on healthcare budgets and patients. Moreover, cost alone may prohibit access to biologic therapy, meaning that not all patients with HER2 + breast cancer receive trastuzumab as indicated with devastating consequences [9–11].

Patents for the trastuzumab reference product recently expired in the European Union (EU) and USA (2014 and 2019, respectively) [12], and several trastuzumab biosimilars have been approved for use in the treatment of HER2 + breast cancer, including SB3 (Ontruzant; Samsung Bioepis), PF-05280014 (Trazimera; Pfizer), MYL-1401O (Ogivri; Mylan), CT-P6 (Herzuma; Celltrion), and ABP 980 (Kanjinti; Amgen) [13–15]. These lower cost trastuzumab biosimilars, which are now being integrated into the latest European and North American breast cancer clinical practice guidelines [3, 6], have the potential to help contain

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rising healthcare expenditure and provide sustainable access to trastuzumab-based therapies in breast cancer care [10, 13, 16–19]. However, this may be undermined if oncologists are unsure of the quality of trastuzumab biosimilars and are reluctant to use them [7, 16]. Unlike chemically synthesized small-molecule medicines, which can be easily characterized and identically copied as generic drugs, biologic drugs are structurally complex, intrinsically variable molecules produced in living systems using complex manufacturing processes, and cannot be identically replicated [20–22]. A biosimilar is a biologic drug containing a similar version of the active substance of an already approved reference product with no clinically meaningful differences in quality, safety, or efficacy relative to the reference biologic drug [23–25]. The quality profiles of biosimilar and reference biologic drugs depend on physicochemical and functional critical quality attributes (CQAs).

In contrast to generic medications, for which European Medicines Agency and US Food and Drug Administration (FDA) approval is mainly based on the demonstration of bioequivalence with the original product in pharmacokinetic studies, the approval of biosimilars is a highly regulated and a uniquely detailed process [13, 20, 21, 26]. Biosimilars undergo a rigorous comprehensive comparability exercise that involves a step-wise approach to building a body of evidence (the totality of evidence) demonstrating biosimilarity with the reference product. Compared with the development process for reference products, there is more emphasis on the characterization of biosimilars in relation to quality, and less emphasis on clinical testing [21, 23, 25]. As is the case for all biologic drugs, once a biosimilar is approved, collection of post-marketing data and a risk management plan are required for pharmacovigilance purposes [16, 17, 21, 25]. Quality data that may affect the clinical safety and efficacy of trastuzumab (reference product and biosimilars) in patients with HER2 + breast cancer are reviewed in this article. In relation to this, we discuss the first published clinical results to support the hypothesis of a relationship between quality drifts in the trastuzumab reference product and long-term outcomes in patients with HER2 + breast cancer [27]. These results were observed during the development of the first European Medicines Agency-approved trastuzumab biosimilar, SB3.

2 Importance of Biologics Quality in Clinical Practice

The quality profiles of biosimilar and reference biologic drugs depend on quality attributes (QAs), which are the physicochemical and functional characteristics of a biologic drug that might affect its clinical profile [26]. Critical quality attributes are the foundation of the quality-by-design approach to drug development, which is dependent on a thorough understanding of the relationship between CQAs and the immunogenicity, safety, pharmacokinetics, and efficacy of the product [28, 29].

To guarantee consistent clinical performance, the quality profiles of approved biologic products must be consistently maintained, but biologics are inherently variable and all will demonstrate some degree of variability [28, 30]. Biologic drugs are also highly sensitive to changes in manufacturing conditions, thus even minor modifications to the manufacturing process can lead to drifts in QAs and add to variability [30–32]. Variations in QAs among different batches of the marketed biologic drugs etanercept and rituximab have been historically reported, including changes in the glycosylation profile of both products and the antibody-dependent cellular cytotoxicity (ADCC) activity of rituximab [33]. The size and abrupt nature of these changes suggest that they were a result of changes in manufacturing processes such as the production cell line, growth conditions and/or purification sequence, all of which influence the glycosylation profile [33].

Changes in biologic drug manufacturing processes are a common occurrence [34]. For example, the trastuzumab reference product has had more than 25 changes in manufacturing since its approval in the EU in 2000 [34]. In accordance with good pharmacovigilance practice, comparability exercises for pre- and post-change products must be performed to provide analytical evidence that differences in QAs introduced by manufacturing changes will not adversely impact the drug's clinical profile [31, 34].

2.1 Trastuzumab Quality Attributes

At the time of development of SB3, product-specific QAs were organized into three tiers for statistical testing purposes as outlined by the FDA [23, 26]; this FDA guideline was withdrawn in 2018 [35]. Critical quality attributes were divided into tiers based on a criticality risk assessment of their impact on immunogenicity, safety, pharmacokinetics, and efficacy [26, 36]. High- and moderate-impact CQAs assessed using analytical methods amenable to statistical testing were assigned to tier 1 analysis (equivalence testing) and tier 2 analysis (quality range analysis), respectively [26, 36]. Low-impact QAs or QAs assessed using analytical methods not considered amenable to statistical analysis were assigned to a tier 3 analysis (comparison of raw data or graphical presentation of results) [26, 36]. Inhibition of cell proliferation and ADCC represent the major mechanisms of action of trastuzumab, with anti-proliferation activity mediated by binding of the trastuzumab Fab region to HER2, and ADCC activity mediated by the binding of the Fc region to Fcγ receptors (FcγRs) on immune effector cells [30, 37–39].

Anti-proliferation and ADCC activities were classified as tier 1 QAs for SB3 [36, 38]. Tier 2 QAs included HER2 binding, FcγRIIIa binding, and the sum level of afucose plus high mannose, which are glycoforms that have an influence on FcγRIIIa binding and ADCC activity [30, 36, 38]. Tier 3 QAs included FcγRIa, FcγRIIa, FcγRIIb, and FcγRIIb binding, in vitro angiogenesis, and surface HER2 expression [36].

To ensure that there are no clinically meaningful differences between the biosimilar and the reference product, CQAs must be within a pre-specified target range that accounts for expected batch-to-batch variability and is representative of the reference product [26, 28, 40]. For example, the equivalence margin for equivalence testing of SB3 tier 1 QAs was based on 1.5 times the variability of trastuzumab reference product lots [36]. Once approved, it is particularly important that the QAs related to the mechanism of action are consistently maintained over time. Therefore, CQAs such as the HER2-binding assay, anti-proliferation assay, and FcγRIIIa binding assay were included as part of the release specification throughout the product life cycle of SB3 in the USA [36].

2.2 Trastuzumab Reference Product Quality Drifts

As part of the biosimilar development process, the physicochemical and functional properties of different batches of the reference product should be monitored frequently over a long-term period so that unintended patterns of change in CQAs can be detected and an accurate quality target range based on non-drifted batches can be established [30, 38, 40]. SB3 was developed based on an in-depth understanding of trastuzumab QAs obtained by analyzing up to 154 lots of EU- and US-sourced trastuzumab reference products for up to 8 years using standard and the latest state-of-the-art analytic techniques, including fluorescence resonance energy transfer to assess HER2 binding, Alphascreen™ technology to assess Fc-related biologic activity, and a hydrophilic interaction liquid chromatography-ultra-performance liquid chromatography system for analysis of glycosylation [30, 38]. In relation to glycosylation (determined by hydrophilic interaction liquid chromatography-ultra-performance liquid chromatography), FcγRIIIa binding (assessed using Alphascreen™), and ADCC activity (assessed in the HER2-overexpressing human breast cancer cell line SKBR3 using a CytoTox-Glo® kit), two periods of drift were observed for batches of trastuzumab reference product with expiry dates ranging from mid-2018 to December 2019, as reported by Kim et al. and Lee et al. (Fig. 1) [30, 38]. A marked downward drift in %afucose plus %high mannose, FcγRIIIa binding activity, and ADCC activity during the first drift period was followed by an upward drift in the second drift period [30], with these CQAs returning to pre-change levels in the more recently monitored lots [30, 38]. There was no change in the antiproliferative activity of the trastuzumab reference product, which was assessed using CellTiter-Blue® or BrdU proliferation assay to indicate cell viability in the HER2-overexpressing human breast cancer cell line BT474 [30, 38]. Overall, relative ADCC activity was correlated with the sum of %afucose plus %high-mannose [38]. Drifted lots of the trastuzumab reference product were not included in the CQA target ranges for SB3, and the SB3 used in clinical trials was similar to the pre-drift trastuzumab reference product [38, 41].

Considering that ADCC is one of the main mechanisms of action of trastuzumab, the drift in ADCC activity observed with the trastuzumab reference product may potentially have an impact on clinical efficacy [30, 38, 42]. This was suggested in phase III equivalence studies of SB3 and ABP 980, which were conducted by Pivot et al. and von Minckwitz
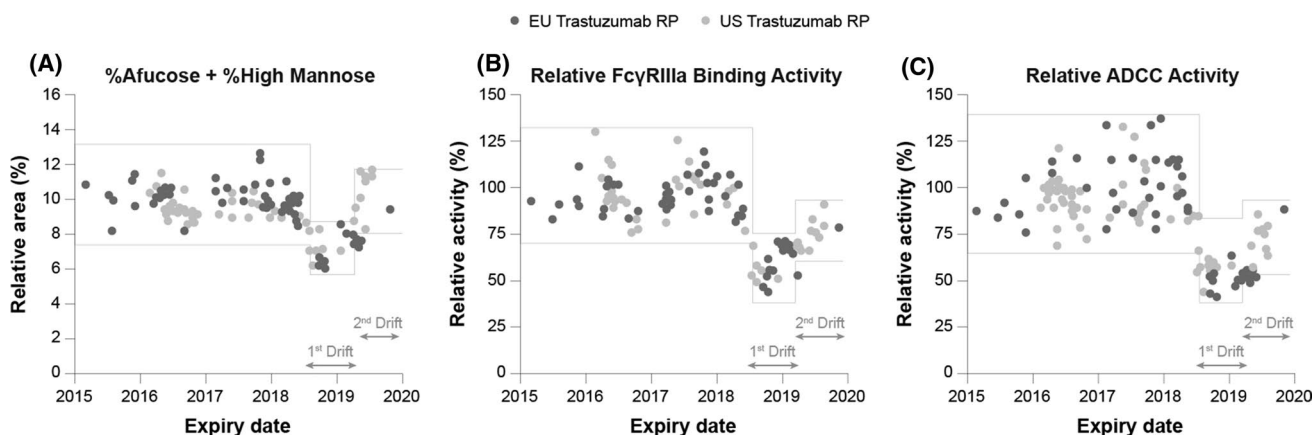
Fig. 1 Changes in **a** %Afucose plus %high mannose, **b** FcγRIIIa binding, and **c** antibody-dependent cell-mediated cytotoxicity (ADCC) activity for multiple lots of European Union (EU)- and US-sourced trastuzumab reference product expiring between March 2015 and December 2019 [30]. Adapted from Kim et al. (2017) (Fig. 1c) and 711 (Fig. 5a, b). *RP* reference product

et al., respectively, in patients with HER2 + early breast cancer using the trastuzumab reference product sourced from a combination of batches with expiry dates within and outside the drift period [41–44]. In these studies, the upper limits of the confidence intervals (CIs) for pathological complete response (pCR) primary endpoints for neoadjuvant SB3 and ABP 980 vs the trastuzumab reference product exceeded predefined equivalence margins, meaning that potential superiority could not be ruled out [41, 44].

In the SB3 and the ABP 980 equivalence studies, equivalence was assessed on the basis of the risk ratio and risk difference of pCR [41, 44]. The primary pCR endpoint was defined as the absence of histologic evidence of residual invasive tumor cells in the breast (bpCR) in the SB3 study [41], and as the total pCR (tpCR) in the breast tissue and axillary lymph nodes in the ABP 980 study [44]. Total pCR was included as a secondary endpoint in the SB3 study, and bpCR was included as a secondary endpoint in the ABP 980 study. In both studies, the primary pCR analysis was based on local laboratory findings, but the ABP 980 study was the first large, international, multicenter neoadjuvant breast cancer study to conduct a sensitivity analysis based on a central independent laboratory review of tumor samples, which has the potential to reduce inter-pathologist variability [41, 44–46]. In the SB3 study, the risk difference was 10.70% (95% CI 4.13–17.26), with a lower upper boundary of the 95% CI within the predefined equivalence margin of ± 13%, and the upper boundary exceeding it, demonstrating non-inferiority but not non-superiority [41]. The bpCR ratio of 1.259 (90% CI 1.112–1.426) was, however, within the predefined 90% CI equivalence margin (0.785–1.546), demonstrating equivalent efficacy [47]. Based on a local laboratory review of tumor samples in the ABP 980 study, the upper bounds of the 90% CI for the tpCR risk difference (7.3%; 90% CI 1.2–13.4) and risk ratio (1.88; 90% CI 1.033–1.366) exceeded the predefined 90% CI equivalence margins of ± 13% and 0.759–1.318, respectively [44]. However, the tpCR risk difference (5.8; 90% CI 0.5 to 12.0) and risk ratio (1.142; 90% CI 0.993–1.312) obtained after central review of tumor samples were contained within the predefined equivalence margins, indicating similar efficacy [44].

A proposed biosimilar cannot be superior to its reference product [23, 40, 46], but in the ABP 980 and SB3 phase III equivalence studies, it was observed that pCR rates were lower in patients treated with drifted batches of the trastuzumab reference product than those treated with the pre-drifted trastuzumab reference product or biosimilar trastuzumab [42, 43]. As described in European Public Assessment Reports for SB3 and ABP 980 [42, 43], it has been acknowledged that the downward drifts in ADCC activity in some of the trastuzumab reference product batches used in these studies could have at least partially confounded the results by contributing to the observed differences in pCR

rates between treatment arms and their relatively high upper CI limits [13, 15]. Taking totality of evidence into account, SB3 and ABP 980 were therefore considered comparable, rather than superior, to the reference product, and approved as biosimilars of trastuzumab [15, 42, 43, 45].

3 Confirming Biosimilarity of SB3 Based on Clinical Evidence

There are generally two clinical steps involved in the development of biosimilars: a phase I pharmacokinetic equivalence study in healthy volunteers followed by a pivotal phase III clinical equivalence study in an appropriate patient population [13, 23, 25]. Clinical studies of potential biosimilars are designed to detect clinically meaningful differences between the biosimilar and the reference product [21, 23, 25]. As well as being assessed during the pivotal clinical efficacy study, clinical safety and immunogenicity are initially assessed during clinical pharmacokinetic studies [23, 25].

3.1 Phase I Studies

The primary aim of the phase I study is to demonstrate pharmacokinetic equivalence of a biosimilar candidate and its reference product, usually in healthy volunteers [13, 25]. Compared with patients who may have disease-related factors and take concomitant medications that influence pharmacokinetic profiles, healthy volunteers represent a relatively homogenous group in which to detect clinically meaningful drug-related pharmacokinetic differences between the biosimilar and reference products [13, 25]. Although a single-dose crossover study design can reduce pharmacokinetic variability, a parallel study design is most appropriate for monoclonal antibodies with long half-lives because of the risk of immune response after repeated exposures. [13, 25].

Pharmacokinetic equivalence was observed for SB3 and US- and EU-sourced trastuzumab reference products in a randomized, parallel, single-dose pharmacokinetic study in 108 healthy male volunteers, with 90% CIs for the primary area under the curve and maximum concentration pharmacokinetic parameters falling within the pre-specified 0.8–1.25 equivalence margin [48]. In addition, a pharmacokinetic analysis was performed as a secondary endpoint in a subset of patients with HER2 + breast cancer in the phase III clinical study comparing SB3 and the trastuzumab reference product. Mean trough concentration profiles were similar and within predefined equivalence margins in cycles 3–8 for SB3 and for the trastuzumab reference product [41].

3.2 Phase III Studies

The aim of phase III biosimilarity clinical trials is not to independently establish safety and efficacy of the biosimilar, which has already been established in clinical trials conducted with the reference product, but to demonstrate comparable clinical performance of the biosimilar in relation to the reference product and to resolve residual uncertainty [21, 25, 26]. The statistical design, patient population, and primary endpoints of the study are therefore selected to facilitate the detection of differences between the two products [21, 23, 25]. In general, a phase III equivalence design with a pre-specified equivalence margin is recommended to rule out inferiority or superiority of the biosimilar candidate to its reference product in the most sensitive and homogenous patient population possible using practical and sensitive endpoints [23, 25, 49]. A recommended approach for deriving equivalence margins relies on preserving 50−60% of the reference treatment effect based on major historic studies [50, 51].

Phase III studies of trastuzumab biosimilar candidates are often conducted in patients with early breast cancer, which, compared with metastatic disease, represents a relatively homogenous population with fewer confounding factors, such as metastatic burden and previous therapies, to influence efficacy and safety evaluations [13, 22, 49]. Long-term survival endpoints, which are the preferred primary efficacy endpoints in cancer indications, may not be feasible or sufficiently sensitive to demonstrate comparability, thus shorter term surrogate endpoints can be used, including pCR, which is correlated with long-term survival in the neoadjuvant breast cancer setting [13, 22, 47, 49, 52, 53]. Pathological complete response may be assessed as bpCR or tpCR. Although tpCR has a stronger correlation with long-term survival, bpCR avoids confounding factors related to axillary lymph node status and assessment [41, 50]. Initial use of a surrogate endpoint like pCR does not obviate the need to assess survival during a longer term follow-up [13, 22].

As previously mentioned in this review, a large randomized double-blind study of SB3 vs the trastuzumab reference product was conducted in women with early or locally advanced HER2 + breast cancer ($n = 875$) using bpCR assessed after neoadjuvant treatment as the primary endpoint [41]. In relation to predefined equivalence margins, the 10.7% risk difference in bpCR rates observed in this equivalence study (51.7% with SB3 and 42.0% with the trastuzumab reference product) ruled out inferiority but not superiority of SB3, whereas the risk ratio of bpCR rates demonstrated equivalence. After surgery, patients received adjuvant treatment with SB3 or the trastuzumab reference product to complete 1 year of treatment [41]. Event-free survival (EFS) was included as a secondary endpoint [41]. After completion of neoadjuvant and adjuvant therapy, Pivot et al. reported that there was no difference in EFS between SB3 and the trastuzumab reference product and bpCR and tpCR were shown to be significantly related to EFS, supporting their validity as surrogate markers for survival [47]. Safety profiles of SB3 and the trastuzumab reference product were similar throughout the study, with no unexpected safety issues, and the overall incidence of anti-drug antibody was low (0.7%) [41, 47].

3.3 SB3 Extension Study

A 5-year treatment-free extension of the phase III study is ongoing to assess the cardiac safety of SB3 (ClinicalTrials.gov identifier: NCT02771795) [27], reflecting a cautious pharmacovigilance approach. In addition to cardiac and other safety outcomes, EFS and overall survival (OS) are being assessed. Demographic and baseline disease characteristics of patients participating in the extension study ($n = 367$) reflect the composition of the main study, with no apparent differences between the SB3 and trastuzumab reference product treatment arms [27, 41]. Patients in the extension study had no symptomatic cardiac events during the main study and had no early breast cancer recurrence during adjuvant therapy [27]. Pivot et al. have reported 3-year follow-up data from the extension study [27]. During the 3-year follow-up after the completion of adjuvant treatment, cardiac events were very rare [27]. Asymptomatic significant decreases in left ventricular ejection fraction were reported in one (0.5%) patient treated with SB3 and two (1.1%) patients treated with the trastuzumab reference product [27]. No other cardiac-related events were reported [27]. Unlike the comparable EFS rates obtained in the two treatment arms at the end of the main study [44], the 3-year EFS rate was higher with SB3 (91.9%) than with the trastuzumab reference product (85.2%), with events occurring in 17 (9.1%) and 31 (17.1%) patients, respectively, resulting in a hazard ratio of 0.47 (95% CI 0.26−0.87) [27]. The 3-year OS rate was 97.0% with SB3 and 92.9% with the trastuzumab reference product [27].

Pivot et al. performed a post hoc analysis of the 3-year follow-up data from the extension study to identify factors contributing to the surprising difference in EFS observed between the SB3 and trastuzumab reference product treatment arms [27]. Among the covariates analyzed, ADCC activity and bpCR (or tpCR) were the only factors associated with EFS (Fig. 2) [27]. Antibody-dependent cellular cytotoxicity activity was designated according to whether patients treated with the trastuzumab reference product were exposed to a trastuzumab lot with drifted ADCC activity during neoadjuvant treatment ($n = 126$ and 55, respectively) [27]. Among the 25 lots of trastuzumab reference product used during the neoadjuvant period in the main study, the ADCC activities of 12 lots were analyzed directly [27].
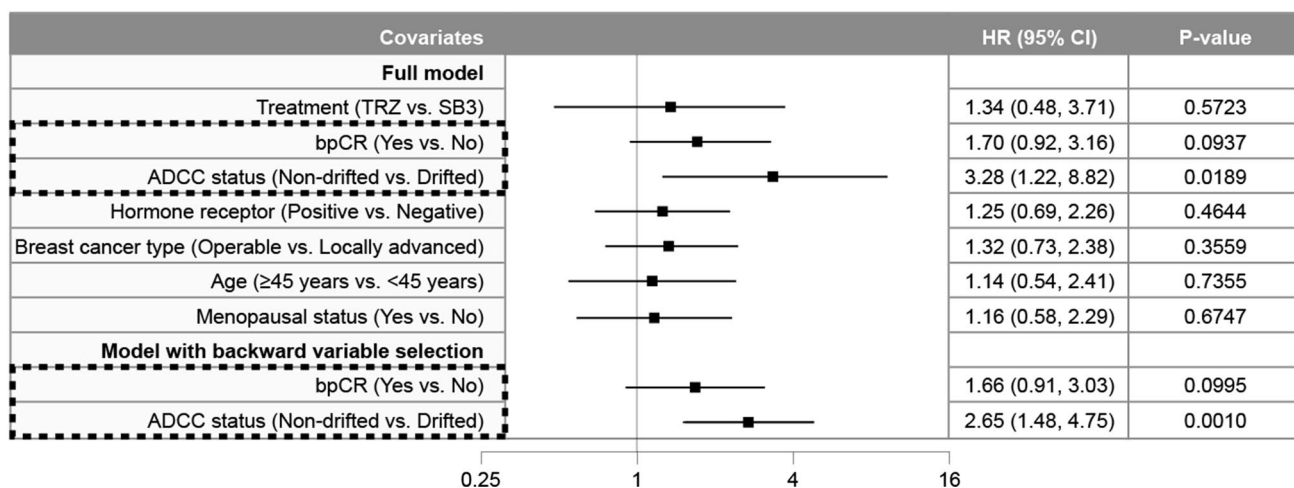
Antibody-dependent cellular cytotoxicity activity for the remaining 13 lots was assumed based on their expiry dates and drifts in ADCC activity previously reported by Kim et al. [30], thus lots with expiry dates from August 2018 to December 2019 were assumed to have drifted ADCC activity [27]. Overall, 13 trastuzumab reference product lots were classified as having a drift in ADCC activity (eight based on available analyses and five based on expiry dates), and the remainder 12 lots were considered to have non-drifted ADCC activity (four based on available analysis and eight based on expiry dates) [27]. There was insufficient power to test the hypothesis of a relationship between ADCC activity and EFS, but the 3-year EFS rate was higher in patients not exposed to the drifted trastuzumab reference product (92.7%) than in those exposed to the drifted product (81.7%), whereas, as a result of comparable events rates (hazard ratio 0.93; 95% CI, 0.31−2.85), EFS curves for SB3 and the non-drifted trastuzumab reference product appeared superimposable (Fig. 3) [27]. Similar trends were observed for OS, but a longer follow-up is required to analyze the effect of ADCC status on OS [27].

4 Conclusions

Technology has advanced enormously since the first approval of the original trastuzumab product over 20 years ago, with current analytic methods allowing the detection of small changes in QAs such as FcγRIIIa binding and glycosylation and enabling sensitive monitoring of batch-to-batch consistency [30, 38, 54]. This is very important as small changes in FcγRIIIa binding and the level of fucose and mannose affect trastuzumab ADCC activity and potentially impact clinical outcomes, including long-term survival. Biosimilar companies are at the forefront of technology and are therefore able to produce trastuzumab biosimilars at the most technologically advanced capacity, with CQAs that are consistently within target range. Going forward, all drug companies manufacturing biosimilar or reference biologic drugs should release frequent quality data to assure that efficacy and safety demonstrated in clinical trials will be maintained in clinical practice.

Based on the totality of the evidence, which includes sophisticated analytic and clinical assessments, approved biosimilars of trastuzumab, such as SB3, have the potential to increase accessibility to trastuzumab-based therapy without compromising efficacy or safety [13, 15, 27, 30, 38, 41, 44]. Furthermore, although the phase III study of SB3 in patients with early HER2 + breast cancer was not designed to detect a relationship between ADCC and clinical outcomes, and survival results by exposure to ADCC drift were derived from a post hoc analysis, the SB3 development process has provided some evidence to support the hypothesis of a relationship between ADCC activity and long-term survival [27]. At the very least, it highlights an underlying need to consistently provide patients with the best quality trastuzumab. Well characterized European Medicines Agency- and/or FDA-approved trastuzumab biosimilars have fulfilled this need.

Covariates	HR (95% CI)	P-value
Full model		
Treatment (TRZ vs. SB3)	1.34 (0.48, 3.71)	0.5723
bpCR (Yes vs. No)	1.70 (0.92, 3.16)	0.0937
ADCC status (Non-drifted vs. Drifted)	3.28 (1.22, 8.82)	0.0189
Hormone receptor (Positive vs. Negative)	1.25 (0.69, 2.26)	0.4644
Breast cancer type (Operable vs. Locally advanced)	1.32 (0.73, 2.38)	0.3559
Age (≥45 years vs. <45 years)	1.14 (0.54, 2.41)	0.7355
Menopausal status (Yes vs. No)	1.16 (0.58, 2.29)	0.6747
Model with backward variable selection		
bpCR (Yes vs. No)	1.66 (0.91, 3.03)	0.0995
ADCC status (Non-drifted vs. Drifted)	2.65 (1.48, 4.75)	0.0010

(axis: 0.25 1 4 16)

Fig. 2 Factors influencing event-free survival (using breast pathologic complete response [bpCR] status as a covariate) in patients with human epidermal growth factor 2-positive breast cancer randomized to neoadjuvant plus the adjuvant trastuzumab reference product (TRZ)- or SB3-based therapy during a phase III study and followed for 3 years thereafter during an extension study [27]. Adapted from Pivot et al. (2019) (Fig. 4a). 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 = estrogen receptor and/or progesterone receptor positive. Negative = estrogen receptor and progesterone receptor negative. *ADCC* antibody-dependent cell-mediated cytotoxicity, *CI* confidence interval, *HR* hazard ratio
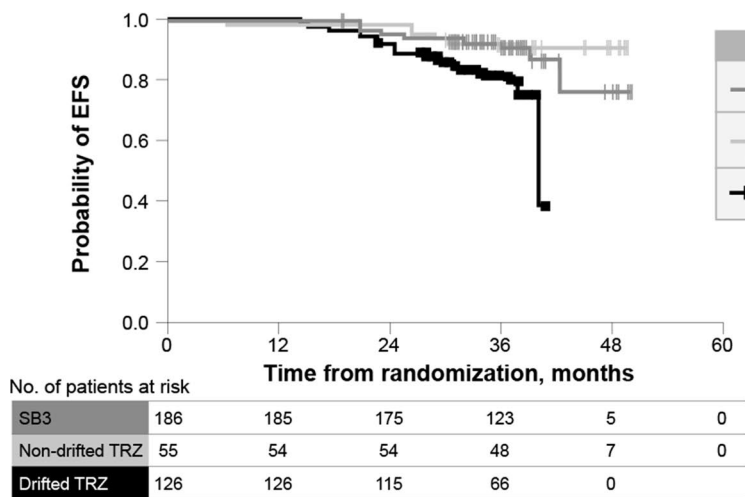
Fig. 3 Kaplan–Meier curve for event-free survival for SB3, non-drifted trastuzumab reference product (TRZ), and drifted TRZ in patients with human epidermal growth factor 2-positive breast cancer randomized to neoadjuvant plus adjuvant TRZ- or SB3-based therapy during a phase III study and followed for 3 years thereafter during an extension study [27]. Adapted from Pivot et al. (2019) (Fig. 3a). 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, *HR* hazard ratio

Declarations

Author contributions Not applicable

Availability of data and material Not applicable

Consent to participate Not applicable

Consent for publication Not applicable

Code availability Not applicable

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