Safety and Clinical Evaluation of Dual Inhibition with Pertuzumab and Trastuzumab Biosimilar SB3 in HER2-Positive Breast Cancer Patients

Christoph Suppan^a Daniel Steiner^a Eva Valentina Klocker^a Florian Posch^a
Elisabeth Henzinger^b Hannah Deborah Müller^a Herbert Stöger^a
Nadia Dandachi^a Marija Balic^a

^aDepartment of Internal Medicine, Division of Oncology, Medical University of Graz, Graz, Austria;

^bPharmacy University Clinical Center Graz, Graz, Austria

Keywords

HER2 positive · Dual inhibition · Breast cancer

Abstract

Background: The addition of trastuzumab to standard chemotherapy has improved survival in patients with HER2-positive breast cancer in neoadjuvant, adjuvant, and metastatic settings. In higher tumor stages, the addition of pertuzumab is now a standard of care and associated with a favorable toxicity profile. We evaluated the safety and efficacy of the trastuzumab biosimilar SB3 in combination with pertuzumab in HER2-positive breast cancer patients. **Methods:** Seventy-eight patients with HER2-positive breast cancer treated at the Division of Oncology at the Medical University of Graz were included. Summary measures are reported as medians (25th to 75th percentile) for continuous variables and as absolute frequencies (%) for count data. **Results:** Thirty-five patients received a median of 4 (3–7) cycles of trastuzumab biosimilar SB3 plus pertuzumab. All patients had a normal baseline left ventricular ejection fraction (LVEF; >50%) prior to the initiation of SB3 plus pertuzumab treatment with a median LVEF of 60% (60–65). Twenty-one patients had a median absolute LVEF decline of 1% (–5 to 0). Two patients (5.7%) had a LVEF reduction ≤50%, but none ≥10%. There were no unexpected adverse events. Twenty-two of 35 patients (63%) were treated with trastuzumab biosimilar SB3

and pertuzumab in the neoadjuvant setting and 11 patients (50%) achieved a pathological complete response. The safety and the efficacy in this setting was comparable to the trastuzumab plus pertuzumab combination in neoadjuvantly treated matched samples. **Conclusion:** In this series of HER2-positive breast cancer patients, the combination of SB3 plus pertuzumab was consistent with the known safety and efficacy profile of trastuzumab and pertuzumab combination.

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Introduction

The overexpression or amplification of the HER2 (human epidermal growth factor receptor 2) in breast cancer patients was associated with worse clinical outcomes before HER2-directed therapies were implemented [1]. Trastuzumab, a monoclonal antibody targeting the extracellular domain of the HER2 protein, changed the course of the disease. First approved in the metastatic setting, trastuzumab showed efficacy as a monotherapy and particularly in combination with chemotherapy [2, 3]. As an addition to first-line chemotherapy, trastuzumab achieved slower progression and prolonged survival [4]. Consequently, its efficacy was also investigated in the adjuvant setting, showing an increase in disease-free sur-

vival and overall survival when trastuzumab was added to chemotherapy and continued for 12 months after adjuvant chemotherapy. Since then, this therapy has remained the standard of care for HER2-positive early breast cancer patients, thereby providing a favorable toxicity profile [5–7]. However, in the first phase III trial, there was a significant increase in the rate of cardiac dysfunction (CD), including congestive heart failure, which led to a retrospective investigation of all clinical trials on trastuzumab by an independent Cardiac Review and Evaluation Committee [4, 8]. The highest incidence rates of CD were seen in patients receiving anthracyclines and trastuzumab concomitantly [9]. Consequently, upcoming clinical trials excluded patients fulfilling the criteria of CD and anthracyclines and trastuzumab were given sequentially. Moreover, this newly acquired knowledge resulted in improved cardiac monitoring as well as prospectively defined cardiac-related events [10].

Due to the resistance of cancer cells and disease progression, other HER2-signaling blocking agents such as lapatinib and pertuzumab have been developed. Pertuzumab is a humanized monoclonal antibody that binds HER2 to a different epitope of the HER2 extracellular domain than trastuzumab does, preventing HER2 from dimerizing with other ligand-activated HER2 receptors [11]. In the phase III CLEOPATRA trial, the combination of pertuzumab with trastuzumab and docetaxel improved progression-free survival and overall survival when compared to trastuzumab and docetaxel alone [12, 13]. The efficacy and safety of both HER2-directed agents in combination with chemotherapy was also confirmed in the neoadjuvant setting, demonstrating low rates of CD when pertuzumab and trastuzumab were given in combination with anthracycline-free chemotherapy, but also with anthracycline-containing regimens [14–17]. Cardiac safety was confirmed in a 5-year follow-up [18].

These therapies are associated with high costs of treatment, which led to the development of biosimilars for trastuzumab and other drugs [19]. Lower treatment costs associated with biosimilars are expected to result in increased patient access and wider clinical use [20]. In a phase III trial, the trastuzumab biosimilar SB3 showed equivalent efficacy and highly similar safety and immunogenicity results compared to trastuzumab in neoadjuvant and adjuvant early breast cancer patients and is now approved as a biosimilar [21, 22]. However, none of the biosimilars, including SB3, were tested in combination with the pertuzumab originator, and no data have been made available so far regarding the safety of this combination. The purpose of our study was to evaluate the cardiac safety and efficacy of trastuzumab biosimilar SB3 in combination with pertuzumab in HER2-positive breast cancer patients.

Table 1. Baseline characteristics of the study population ($n = 78$)

	SB3/pertuzumab	Trastuzumab/pertuzumab
Total patients, n	35	43
Age at treatment start, years	57 (50–70)	54 (47–62)
Treatment setting		
Neoadjuvant ¹	24 (68.6)	43 (100)
Adjuvant	2 (5.7)	0
Palliative	9 (25.7)	0
Hormone receptor status		
ER and PR negative	7 (20)	18 (42)
ER and/or PR positive	28 (80)	25 (58)
HER2 positive	35 (100)	43 (100)
LVEF, %	60.0 (60–65)	64 (60–66)

Data are presented as the median (25th–75th percentile) for continuous variables, and n (%) for categorical data.

¹ Includes 2 patients treated for local relapse.

Materials and Methods

Study Design and Population

This study was a non-interventional phase IV single-center ambispective study of the tolerability of trastuzumab biosimilar SB3 with pertuzumab. Seventy-eight breast cancer patients were included in this study, receiving either concurrent trastuzumab biosimilar SB3 and pertuzumab or reference trastuzumab and pertuzumab at the Division of Oncology, Medical University of Graz. The baseline characteristics are presented in Table 1. In the trastuzumab biosimilar SB3 and pertuzumab cohort, 35 female HER2-positive breast cancer patients were scheduled for the combination of SB3 with pertuzumab either in the (neo)adjuvant or in the palliative setting between September 2018 and August 2019. In the reference trastuzumab and pertuzumab cohort, 43 female HER2-positive breast cancer patients were included who received the combination of trastuzumab with pertuzumab in the neoadjuvant setting between January 2014 and December 2016.

The primary objective of our study was cardiac safety of the biosimilar SB3 and pertuzumab combination, and the secondary objectives included overall safety and response rates in the neoadjuvant setting. The median administered dose and the median number of cycles of administered trastuzumab SB3 and pertuzumab were calculated, left ventricular ejection fraction (LVEF) levels were measured by echocardiography at baseline and at the end of treatment (or in the case of ongoing treatment, the last available assessment was used), and toxicities and treatment modifications were monitored. In the neoadjuvant setting, the efficacy of the combination was assessed in terms of the proportion of patients with a pathological complete response (pCR) at surgery, defined as ypT0/is ypN0. Progression-free survival was not calculated due to the low number of patients and events.

Statistical Methods

All statistical analyses were performed with Stata 16.1 (Stata Corp., Houston, TX, USA). Continuous variables were reported as medians (25th to 75th percentile), and count data as absolute frequencies (%). The distribution of continuous variables between 2 groups was compared with rank-sum tests, whereas the association between 2 categorical variables was investigated with Pearson χ^2 and Fisher exact tests.

Fig. 1. Consort flow diagram of the total study population. * Two patients were treated for local relapse and were excluded for efficacy assessment.

Fig. 2. LVEF changes during treatment with SB3/pertuzumab. Absolute change of LVEF (left panel) and percent change of LVEF (right panel). * In the case of ongoing treatment, the last EF assessment was used.

Results

Altogether, 78 patients were included in the study, where 35 patients received the combination of trastuzumab biosimilar SB3 plus pertuzumab in the neoadjuvant or palliative setting and 43 patients received pertuzumab and trastuzumab in the neoadjuvant setting. The whole cohort is depicted in Figure 1. In the cohort of patients treated with the combination of trastuzumab biosimilar SB3 plus pertuzumab, a median of 4 (3–7) cycles were administered. The median cumulative trastuzumab biosimilar SB3 dose was 1,904 mg (1,560–2,640) and the median cumulative pertuzumab dose was 2,100 mg (1,680–3,360). Eight of 35 patients (23%) switched from trastuzumab to trastuzumab SB3 during treatment, and no issues have been identified thus far from this switch.

All patients had a normal baseline LVEF (>50%) prior to the initiation of trastuzumab SB3 plus pertuzumab

treatment with a median LVEF of 60% (60–65). At completion of trastuzumab SB3 plus pertuzumab treatment (or, in the case of ongoing therapy, the last EF assessment), the median LVEF was 60.0% (58–62). Twenty-one patients had a median absolute LVEF decline of 1% (–5 to 0), corresponding to a median percent change of 1.7% points (–7.7 to 0). Two patients (5.7%) had an LVEF reduction to $\leq 50\%$ after treatment. None of the patients had a decline in LVEF of $\geq 10\%$ (Fig. 2). In the cohort of patients treated with pertuzumab and trastuzumab, 1 patient (2.3%) had a decline in LVEF $\geq 10\%$.

Dose reduction or discontinuation due to other toxicities occurred in 15/35 (43%) patients. As described below, the reduction was mostly related to concomitant chemotherapy. Adverse events are summarized in Table 2. The main toxicity in patients treated with trastuzumab biosimilar SB3 and pertuzumab in combination with chemotherapy was polyneuropathy, which occurred in 5 patients (14.3%) and was clearly associated with the use of

Fig. 3. pCR in patients treated with trastuzumab biosimilar SB3 and pertuzumab in combination with chemotherapy (11/22, 50%), and trastuzumab and pertuzumab in combination with chemotherapy (25/43, 58%). Error bars represent 95% CIs. * p value for difference of pCR rates is from Pearson χ^2 test.

Table 2. Summary of observed toxicity events (any grade) of patients receiving SB3/pertuzumab and trastuzumab/pertuzumab

	SB3/pertuzumab (<i>n</i> = 35)	Trastuzumab/ pertuzumab (<i>n</i> = 43)	<i>p</i> value
Polyneuropathy	5 (14.3)	3 (7.0)	0.456
Diarrhea	4 (11.4)	7 (16.3)	0.540
Infect	0 (0)	3 (7.0)	0.248
Neutropenia	0 (0)	1 (2.3)	1
Cardiotoxicity	0 (0)	1 (2.3)	1
Hair loss	0 (0)	0 (0)	1
Allergic reaction	1 (2.9)	3 (7.0)	0.623
Other	9 (25.7)	20 (46.5)	–

Data are presented as *n* (%). p values for difference between SB3/pertuzumab vs. trastuzumab/pertuzumab are from Pearson χ^2 tests (categorical variables with expected cell counts ≥ 5) and Fisher exact tests (categorical variables with expected cell counts < 5).

taxanes. Diarrhea occurred in 4 patients (11.4%) treated with trastuzumab SB3 plus pertuzumab. There was 1 case of an allergic event which was associated with paclitaxel. In this case, the antibody combination could be continued. None of the observed toxicities were grade 3 or 4. The toxicities that occurred were comparable to those in the cohort of patients neoadjuvantly treated with pertuzumab and trastuzumab – there were no significant differences (summarized in Table 2).

In terms of efficacy, the analysis for pCR was performed in 24 of 35 patients (69%) who were treated with trastuzumab SB3 plus pertuzumab in the neoadjuvant

Fig. 4. Neoadjuvantly administered cumulative doses of SB3 or trastuzumab and pertuzumab in the SB3/pertuzumab cohort ($n = 22$) and in the trastuzumab/pertuzumab cohort ($n = 43$). Error bars represent 95% CIs. p values for difference of cumulative doses are from rank-sum tests.

setting. Two of these patients were treated for local relapse and were excluded for the efficacy assessment. Of the remaining 22 patients, 11 achieved a pCR (ypT0/ypTis and ypN0; pCR = 50%). In 43 patients treated neoadjuvantly with the pertuzumab and trastuzumab combination, the pCR rate was achieved in 25 out of 43 patients (58%). There was no significant difference in the pCR rates between the 2 cohorts, as shown in Figure 3 ($p = 0.532$). In Table 3, clinical pathological patients' characteristics are summarized for the cohort of patients treated with the trastuzumab biosimilar and pertuzumab combination and the trastuzumab and pertuzumab combination. These cohorts were comparable. In addition, patients' characteristics from the NeoSphere group B are shown in the last row as well, allowing for interpretation of our presented data.

In the neoadjuvant setting, 22 patients received a median of 4 (3–4) cycles of trastuzumab SB3 plus pertuzumab with a median cumulative trastuzumab biosimilar SB3 dose of 1,790 mg (1,300–2,002) and a median cumulative pertuzumab dose of 2,100 mg (1,680–2,100). In addition, 20 patients received an anthracycline (epirubicin) + taxane-based chemotherapy (91%) and 2 patients (9%) received a taxane-based chemotherapy. The administration of trastuzumab SB3 and pertuzumab was initiated

Table 3. Comparison of clinicopathological characteristics of breast cancer patients in the neoadjuvant setting

	SB3/ pertuzumab	Trastuzumab/ pertuzumab	<i>p</i> value	NeoSphere B
Total patients, <i>n</i>	22	43		107
Age, years	56 (32–72)	54 (28–75)	0.703	50 (32–74)
HR status				
ER and/or PR positive	17 (77)	25 (58)	0.127	50 (47)
ER and PR negative	5 (23)	18 (42)		57 (53)
Lymph node status				
N0	18 (82)	35 (83) ¹	0.307	31 (29) ¹
N1	4 (18)	4 (10) ¹		53 (50) ¹
N2	0	3 (7) ¹		22 (21) ¹
Clinical tumor size				
cT1	8 (36)	13 (31) ¹	1.000	NA
cT2	11 (50)	21 (50) ¹		NA
cT3	1 (5)	3 (7) ¹		NA
cT4	2 (9)	5 (12) ¹		NA
Clinical tumor size, mm	NA	NA	NA	55 (20–150)
Pathological complete response	11 (50)	25 (58)	0.532	49 (46)

Data are presented as *n* (%) or the median (range). *p* values for difference between SB3/pertuzumab vs. trastuzumab/pertuzumab are from Pearson χ^2 tests (categorical variables with expected cell counts ≥ 5), Fisher exact tests (categorical variables with expected cell counts < 5), or Wilcoxon rank-sum test (continuous variables). NA, not available.

¹ Data missing for 1 patient.

after the completion of anthracyclines and not concomitantly.

Nine patients (26%) received the combination of trastuzumab SB3 and pertuzumab in the palliative setting. Two of these patients (22%) have progressed and 7 still have ongoing palliative treatment. These 9 patients received a median of 9 (7–11) cycles of trastuzumab SB3 plus pertuzumab with a median cumulative trastuzumab SB3 dose of 2,860 mg (2,292–3,672) and a median cumulative pertuzumab dose of 3,780 mg (3,360–4,620).

In the reference trastuzumab and pertuzumab cohort, the median cumulative trastuzumab dose was 1,800 mg (1,430–2,094) and the median cumulative dose for pertuzumab was 2,100 mg (2,100–2,100). In this setting, the administration of trastuzumab and pertuzumab was also initiated after the completion of anthracyclines and not concomitantly. Patients received similar cumulative doses of trastuzumab or pertuzumab in the 2 cohorts (rank-sum $p = 0.533$ and $p = 0.238$; Fig. 4).

Discussion

In recent years, there has been an increase in the number of developed biosimilars and their clinical implementation. Biosimilars were immediately applied in the tested indications, but the use was also translated in combinations of antibodies not previously tested in clinical trials

(“off-label” use). A biosimilar is defined as a biological medication that is highly similar to a reference product, with only minor differences in clinically inactive components and no meaningful differences in regard to potency, safety, and purity [20]. The approval process of these medications is based on the totality of evidence including evaluation of functional and structural characteristics, assessment of pharmacokinetics and pharmacodynamics, and evidence of comparable clinical studies with the originator. One major aim of implementing biosimilars into clinical routine is achieving long-term cost savings as well as initiating market competition, which led to the availability of at least 5 FDA-approved trastuzumab biosimilar medications.

Although the use of biosimilars should not be associated with increased or unexpected toxicity, we do believe that evaluating these combinations and demonstrating their safety in clinical trials is of importance and value for the treated patients and their treating clinicians, particularly in “off-label” indications.

Our study demonstrates for the first time that safety and efficacy of the combination of trastuzumab biosimilar SB3 and pertuzumab is consistent with the known safety profile of trastuzumab in this combination. Therefore, trastuzumab biosimilar SB3 may replace trastuzumab in this combination, thereby being an efficient option when given alone or in combination with pertuzumab both in neoadjuvant/adjuvant and in metastatic settings.

The limitations of our study are the retrospective nature of the evaluation, a small patient cohort, and their different stages of disease. However, it is important to note that due to the small patient number, the aim of our study was not to demonstrate a non-inferiority of the trastuzumab biosimilar SB3 in this combination, but to evaluate the consistency with the previous reports of clinical trials and results achieved in our patients in terms of preliminary safety and efficacy.

Pivot et al. [21, 22] presented the largest neoadjuvant trial with 800 HER2-positive breast cancer patients randomized, comparing both trastuzumab SB3 and the originator trastuzumab in combination with standard chemotherapy. They demonstrated similarity in pCR rates and efficacy, as well as comparable survival data [20]. When taking into account that breast cancer is the most common cancer in women worldwide and that approximately 20% of these women suffer from HER2-positive disease, the implementation of trastuzumab biosimilars may not only reduce costs and improve access to these agents worldwide, but with this also have an impact on disease outcome.

The approval of the combination of pertuzumab and trastuzumab is based on the metastatic trial CLEOPATRA for the metastatic setting [12, 23] and neoadjuvant trials NeoSphere and Tryphaena in the neoadjuvant setting [14, 15]. The latter was a conditional approval which had to be confirmed in the positive adjuvant Aphinity trial [16]. All these trials led to wide implementation of the combination in HER2-positive patients [17]. Thus, it can be expected that trastuzumab biosimilars will be widely implemented in this combination to lower the total costs of the treatment. It surely cannot be expected that all biosimilars demonstrate the safety and efficacy of the combination in large clinical trials. This enhances the importance of the real-life data.

Due to retrospective analysis, the measurement of CD was not predefined and as such is not a precise parameter. It does not take into account the interobserver variability or the method of measurement of LVEF. However, what is of great importance is that patients did not develop symptoms of CD, and the LVEF values were stable over time. Here, we demonstrate the consistency in cardiac safety with patients treated previously with trastuzumab and pertuzumab at our department.

The cohorts of neoadjuvantly treated patients are small. Demonstrated efficacy is summarized in Table 3, also including cohort B of the NeoSphere trial. It is of note that greater-risk patients with higher stages were included in the NeoSphere trial and only the taxane combination with trastuzumab and pertuzumab was given neoadjuvantly, and the remaining chemotherapy after surgery. In our patients and retrospective comparison, the pCR rates were comparable.

Conclusion

Our study represents a first report demonstrating that the safety and efficacy of SB3 plus pertuzumab was consistent with the known safety and efficacy profile of the trastuzumab and pertuzumab combination. Larger cohorts of breast cancer patients and longer follow-up should stay in focus of further clinical evaluations.

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Statement of Ethics

This ambispective study was approved by the local Ethics Committee of the Medical University of Graz, Austria (No. 31-212 ex. 18/19). For this study no written informed consent from the subjects was required.

Conflict of Interest Statement

C.S., F.P., H.S., and M.B. have received personal fees and consulting fees from Amgen, AstraZeneca, Eli Lilly, Novartis, Pfizer, Roche, and Samsung.

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Author Contributions

C.S. designed the work, interpreted the data, and wrote the manuscript. M.B. and H.S. designed the work, interpreted the data, drafted the work, and gave final approval of the version to be published. F.P. and N.D. did the statistical analysis, interpreted the data, revised it critically, and gave final approval of the version to be published. D.S., H.D.M., and E.V.K. interpreted the data, revised it critically, and gave final approval of the version to be published. E.H. provided the pharmaceutical doses, interpreted the data, revised it critically, and gave final approval of the version to be published. All authors agree to ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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