First-Line Treatment of HER2-Positive Metastatic Breast Cancer With Dual Blockade Including Biosimilar Trastuzumab (SB3): Population-Based Real-World Data From the DBCG

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ABSTRACT

PURPOSE: Dual blockade with trastuzumab and pertuzumab in combination with chemotherapy is the recommended first-line therapy for human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer (mBC). The purpose of this retrospective study is to examine the clinical outcomes of the trastuzumab biosimilar SB3 in first-line dual blockade treatment using real-world data of patients with HER-positive mBC.

METHODS: In Denmark, all women with breast cancer are registered in the database of the Danish Breast Cancer Group (DBCG). From this prospective observational registry, we extracted information on primary diagnosis and treatment of all women with HER2-positive mBC who received first-line treatment with SB3 and pertuzumab from September 1, 2018, to February 29, 2020. Retrospectively collected data from the DBCG database included information concerning treatment start, end, and reason for discontinuation. The primary endpoints for the study were overall survival (OS) and progression-free survival (PFS).

RESULTS: The study included 117 women who received first-line treatment with SB3 and pertuzumab for their HER2-positive mBC. The study population had a mean age of 60 years. A total of 71 patients (61%) had recurrent disease and 46 patients (39%) presented with de novo mBC. The median follow-up was 11.1 and 15.4 months for PFS and OS, respectively. At 12 months, OS was 84% (95% confidence interval [CI], 78-91), whereas the median OS was not reached. The median PFS was 12.7 months (95% CI, 11.1-16.2). Median time on treatment was 8.7 months (95% CI, 7.6-11.4); 36 patients (31%) were still on treatment at end of study.

CONCLUSIONS: This retrospective real-world, nationwide study demonstrated comparable median PFS to the historical data of using reference trastuzumab and pertuzumab as first-line dual blockade.

KEYWORDS: Trastuzumab, biosimilar pharmaceuticals, breast

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Introduction

Some patients with breast cancer experience a distant recurrence after a disease-free period of variable time. This group of patients, as well as the group of patients diagnosed with stage IV disease are said to have metastatic breast cancer (mBC). Metastatic breast cancer is characterized as being incurable with a poor disease prognosis with a 20% to 30% 5-year survival.[1,2] Human epidermal growth factor receptor 2 positivity (HER2-positivity) is seen in 15% to 20% of cases of mBC and is associated with an aggressive disease course.[3,4] HER2-targeting therapy with trastuzumab (Herceptin, F. Hoffmann-La Roche Ltd) and pertuzumab (Perjeta, F. Hoffmann-La Roche Ltd) in combination with chemotherapy improves progression-free survival (PFS) and overall survival (OS) in individuals with HER2-positive mBC and is the recommended first-line treatment of patients with HER2-positive mBC.[5-7]

SB3 (Ontruzant, Samsung Bioepis), a biosimilar trastuzumab, was approved by the European Medicines Agency (EMA) in 2017 and has since September 2018 replaced trastuzumab for treatment of HER2-positive breast cancer in Denmark due to reimbursement reasons.[8] A biosimilar drug is a biological drug highly similar to its reference drug. Because biosimilars are made in living organisms, minor differences from the reference medicine can occur. Minor differences are an inherent characteristic of therapeutic antibodies and appear in both reference medicine and biosimilar products. To make sure that these differences are not clinically meaningful, regulatory agencies recommend a comparative

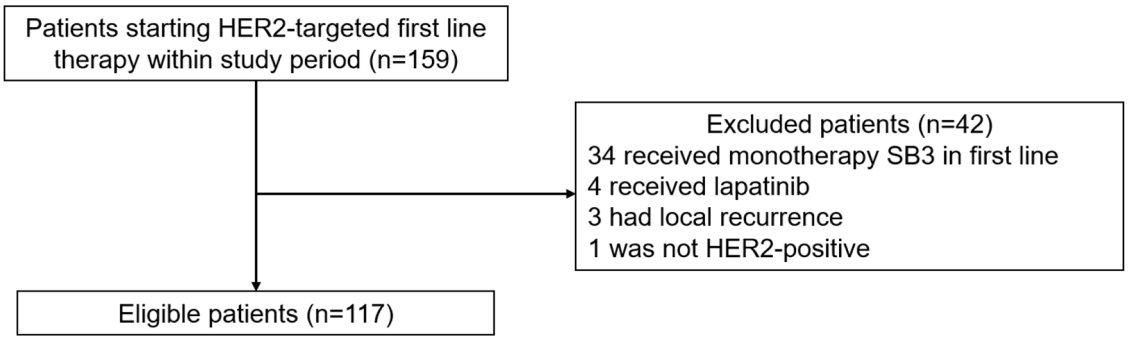

Figure 1. Flow diagram describing the excluded and eligible patient population. HER2 indicates human epidermal growth factor receptor 2.

exercise of analytical (physicochemical and biological) and clinical studies. Based on this totality-of-evidence, regulatory agencies may decide to approve a biosimilar, which can then be used in place of a reference medicine.[9,10] The switch from a reference to a biosimilar drug is usually financially motivated. SB3 has been compared with trastuzumab in neoadjuvant treatment of early HER2-positive breast cancer, but the effect of SB3 in combination with pertuzumab in a metastatic, real-world setting has not yet been assessed.[11]

This investigator-initiated study was conducted to examine SB3 and pertuzumab as first-line treatment for patients with HER2-positive mBC in a real-world setting, using data from the Danish Breast Cancer Group (DBCG).

Methods

Study design

This is a population-based observational study involving all departments of oncology in Denmark using the DBCG database.

Patient selection criteria

The study included all known women in Denmark diagnosed with HER2-postive mBC who initiated first-line treatment with SB3 and pertuzumab from September 1, 2018, to February 29, 2020.

Data sources

The nationwide, population-based clinical DBCG database includes data on demographic, diagnosis, treatment, pathology, and follow-up. From the DBCG database, prospectively collected data concerning primary diagnosis and treatment were extracted. Retrospectively collected data from the DBCG database concerning metastatic disease included date of disease progression, location of metastasis, treatment modalities with start and end date as well as reason for discontinuation.

Approvals

This is a retrospective register-based study and thereby exempted from approval from the Danish National Committee on Health Research Ethics (NVK). The study was approved in the DBCG's scientific committee for medical oncology. Approval was also obtained from the Danish Data Protection Agency (P-2020-788).

Measures

The primary endpoints were OS and PFS. The date of relapse or date of stage IV diagnosis was defined as the index date. Overall survival was calculated as the time from index date until death of any cause, while PFS was calculated as the time from index date to progression or death of any cause. The date November 15, 2020, was used for censoring in patients without an event in PFS analysis, and November 30, 2020, was used for censoring patients without an event in OS analysis. Time on treatment was calculated as time from treatment start until end of treatment with dual blockade. The institutions in Denmark switched treatment from SB3 to another biosimilar trastuzumab in March 2020 due to reimbursement reasons. Therefore, time on dual blockade with the other biosimilar trastuzumab and pertuzumab following February 29, 2020, was added to the patient's total time on treatment with dual blockade.

Statistical analysis

Categorical variables were analyzed by descriptive statistics and survival data by Kaplan-Meier estimates including 95% confidence intervals (CIs). The statistical analyses were made using R-software, version 4.0.2.

Results

Study population

From September 1, 2018, to February 29, 2020, 159 women were registered with initiation of first-line HER2-targeted treatment from 12 oncology departments in Denmark. Of these, 117 patients diagnosed with HER2-postive mBC started treatment with SB3 and pertuzumab (Figure 1). All patients received chemotherapy in combination with dual blockade, except 2 patients who did not receive any chemotherapy in combination with the HER2 dual blockade. Patient characteristics and demographics are given in Table 1.

Table 1. Characteristics of patient population.

Women	117 (100%)
Age (years)	
Mean age (range)	60 (31-84)
<65	70 (60%)
65-75	28 (24%)
75+	19 (16%)
Site of cancer	
Visceral	88 (75%)
Nonvisceral	29 (25%)
Brain metastases	
Yes	12 (10%)
No	105 (90%)
ER status	
Positive	74 (63%)
Negative	43 (37%)
HER2 status	
Immunohistochemistry	
0/1	0 (0%)
2+	25 (21%)
3+	92 (79%)
FISH	
Positive	35 (30%)
Negative	0 (0%)
Not performed	82 (70%)
Prior (neo)adjuvant therapy	
Yes	64 (55%)
No	53 (45%)
(Neo)adjuvant therapy (n=64)	
Anthracycline	50 (78%)
Taxane	48 (75%)
Hormone	48 (75%)
Trastuzumab	37 (58%)

Abbreviations: ER, estrogen receptor; FISH, fluorescence in situ hybridization; HER2, human epidermal growth factor receptor 2.

The median age at diagnosis of metastatic disease was 61 years for the patient population. The study population consisted of 46 (39%) de novo patients and 71 (61%) patients with recurrent breast cancer. Forty-three percent of the patients with recurrent disease had previously received adjuvant trastuzumab.

Visceral metastases were present in 88 patients (75%). The most common sites of metastasis were bone (62%), liver (43%), and lung/pleura (38%). Brain metastases were present in 12 patients (10%).

Treatment

SB3 and pertuzumab was combined with vinorelbine in 99 patients (85%), with taxane in 11 patients (9%), and with other chemotherapy in 5 patients (4%). Maintenance endocrine therapy was given to 24 patients (21%) following initial chemotherapy.

All patients received an initial loading dose of SB3 given intravenously as 8 mg/kg followed by a maintenance dose of 6 mg/kg every 3 weeks. SB3 was given in combination with intravenous pertuzumab with a loading dose of 840 mg followed by a maintenance dose of 420 mg every 3 weeks.

The median time on treatment was 8.7 months (95% CI, 7.6-11.4). In total, 81 patients (69%) discontinued first-line treatment with dual blockade, 45 (38%) because of progressive disease, 10 (9%) due to side effect, 10 (9%) due to switch from dual blockade to monotherapy with SB3 alone, 10 (9%) due to switch to other treatment, and 6 patients (5%) due to death. Thirty-six patients (31%) were still on treatment.

Of 64 patients who received (neo)adjuvant therapy, 50 (78%) received an anthracycline, 48 (75%) received a taxane, 48 (75%) received hormone therapy, and 37 (58%) had been given trastuzumab. Of the 37 patients who received trastuzumab, 6 patients were diagnosed with mBC within 12 months of ended adjuvant therapy.

Outcomes

In total, 70 patients (60%) experienced an event in form of disease progression (n=58) or death (n=12). The median follow-up was 11.1 and 15.4 months for PFS and OS, respectively. The median PFS (mPFS) was 12.7 months (95% CI, 11.1-16.2) (Figure 2A). After 6 and 12 months, the PFS was 78% (95% CI, 71-86) and 53% (95% CI, 45-64), respectively. Further PFS analysis was done for patients with de novo stage IV disease (n=46), for patients with recurrent breast cancer who did not receive adjuvant trastuzumab (n=34), and for patients with recurrent breast cancer who did receive adjuvant trastuzumab (n=37) (Figure 2B). The mPFS for the de novo group was 14.6 months (95% CI, 9.1-NE). The mPFS for the patient group that did not receive adjuvant trastuzumab was 11.1 months (95% CI, 8.8-NE). For the patient group that did receive adjuvant trastuzumab, the mPFS was 12.4 months (95% CI, 11.4-16.8).

The median OS (mOS) for the study population was not reached. At 12 months, the OS estimate was 84% (95% CI, 78-91). Twenty-four patients (21%) had died at the end of follow-up.

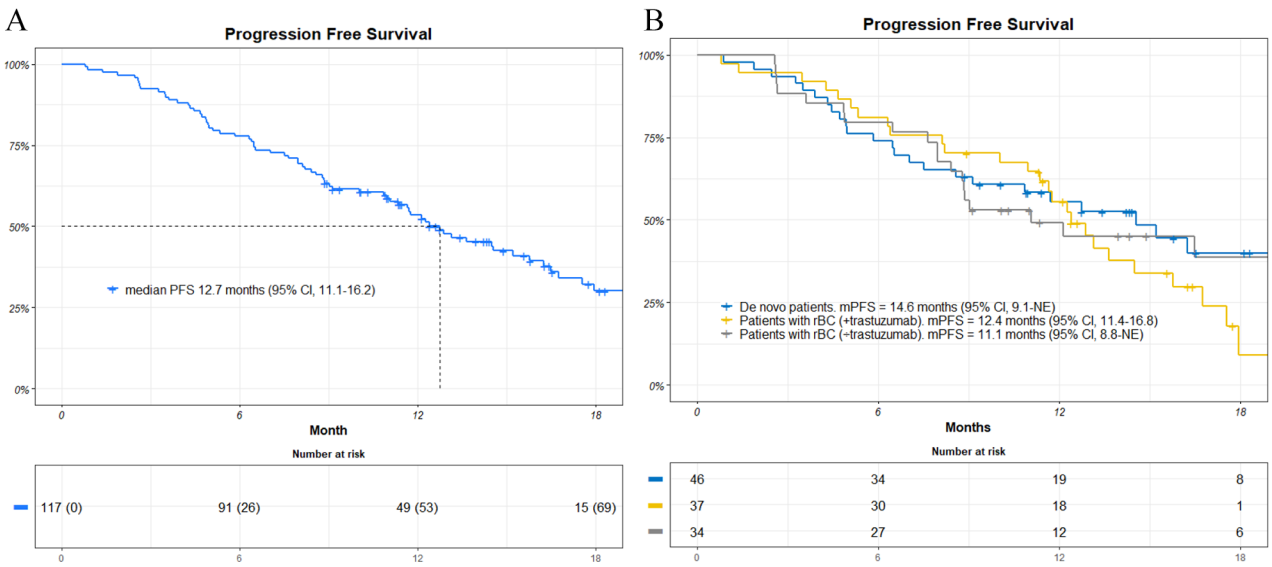

Figure 2. (A) Kaplan-Meier estimate of PFS among total patient population. In parentheses is the number of patients who had experienced an event at given time. (B) Kaplan-Meier estimate of PFS among 3 subgroups of patients. CI indicates confidence interval; mPFS, median progression-free survival, progression-free survival.
Abbreviation: rBC, recurrent breast cancer.

Comparative analysis

Supplemental statistical comparison was done between our cohort (A) and another cohort (B) from a previous DBCG real-world study examining originator trastuzumab and pertuzumab in first-line therapy for HER2-positve mBC.[12] The other real-world study included 291 patients. Hazard ratio (HR) for PFS (A vs B) between the two cohorts was 1.31 (95% CI, 0.98-1.75). Hazard ratio for OS between the two cohorts was 0.99 (95% CI, 0.62-1.57).

Discussion

In this observational, retrospective, nationwide, population-based study, we included all patients who initiated SB3 and pertuzumab as first-line treatment for HER2-positive mBC in Denmark during September 1, 2018, to February 29, 2020. Median PFS was 12.7 months (95% CI, 11.1-16.2) and 12 months OS 84% (95% CI, 78-91).

A population-based observational study from the DBCG published in 2020 examined the efficacy of trastuzumab and pertuzumab in first-line treatment of HER2-positive mBC using real-world data from the DBCG database.[12] The study included 291 patients from all departments of oncology in Denmark and had a follow-up period from April 2013 until August 2017. The study showed an mPFS of 15.8 months (95% CI, 14.0-19.9) and mOS of 41.8 months (95% CI, 37.7-NE). The mPFS in this study is numerically shorter, but the 95% CIs are overlapping. With an HR of 1.31 (95% CI, 0.98-1.75), we cannot reject that the 2 study cohorts' PFS are alike. Although a comparability cannot be declined, there is evidence of a trend favoring the first DBCG study. In this study, 24 patients experienced an event in form of death within follow-up. In the other real-world DBCG study, 107 of 291 patients died before the end of follow-up. Hazard ratio was 0.99 (95% CI, 0.62-1.57) for OS and shows great comparability between the 2 cohorts. The 2 studies differed regarding patient populations as more patients in this study had visceral metastasis (75% vs 69%), metastases in liver and lung/pleura (43% vs 18% and 38% vs 16%). Furthermore, 12 patients (10%) who received SB3 had brain metastases at baseline vs only one in the real-world study examining reference trastuzumab and pertuzumab. Liver, lung, and especially brain metastasis are associated with worse disease prognosis with shorter PFS and OS.[13-15] The database used in the 2 studies was the same, and such a considerable difference in frequencies of metastasis is notable. Furthermore, the age distribution among the two studies also differed. In our study population, only 60% of patients were under 65 years of age vs 67% for the patient population in the other real-world study. In addition, 16% of patients in this study were of the age 75 years or above vs 10% in the other study.

The real-world PERUSE study included 1436 patients who received at least 1 treatment dose of dual blockade with reference trastuzumab and pertuzumab.[16] The study found an mPFS of 20.6 months (95% CI, 18.9-22.7). The mPFS was longer than the one found in this study. Median age for patients included in the PERUSE study was 54 years. Patients with brain metastases would only be eligible if they were stable for ⩾3 months preceding screening after receiving local therapy without anti HER2 therapy. Patients were also required to have an Eastern Cooperative Oncology Group (ECOG) performance status ⩽2 and a life expectancy ⩾12 weeks. Furthermore, the PERUSE study included patients if they presented with local recurrence. In our study, the median age was higher (60 years), all patients with brain metastasis were eligible, and ECOG performance status and life expectancy

were not considered. Finally, patients with local recurrence were not included in our study.

Another US-based, observational real-world study describes the efficacy of first-line HER2-targeted therapies in patients with de novo metastatic (n = 487) vs recurrent HER2-positive mBC (n = 490).[17] Of all the eligible patients, 712 (73%) had received dual blockade with reference trastuzumab and pertuzumab in first line. Median PFS for the de novo group was 17.7 months (95% CI, 16.0-19.7), and for the recurrent group, mPFS was 11.9 months (95% CI, 11.0-13.2). The mPFS for the de novo group is higher than the one found in this study, but again, the estimate in our study is with wide confidence limits. The mPFS for the recurrent group in the US study was not stratified based on prior trastuzumab treatment but results are similar to our recurrent patients.

A taxane was mainly used in combination with the dual blockade in the PERUSE and the US-based study. This is partly due to the CLEOPATRA trial where dual blockade was administered with docetaxel.[6] Most patients in this study as well as the other Danish real-world study were treated with vinorelbine as the chemotherapy backbone supplementing the dual blockade. The HERNATA study compared docetaxel with vinorelbine both combined with trastuzumab and found similar efficacy but considerably less toxicity with vinorelbine.[18] This led to the implementation of vinorelbine as the preferred chemotherapy backbone to the HER2-targeting therapies used in first-line treatment of HER2-positive mBC in Denmark.

The phase III randomized clinical trial (RCT), CLEOPATRA, examined the efficacy and safety of first-line treatment with dual blockade (trastuzumab and pertuzumab) in combination with a taxane for patients with HER2-positive mBC.[6] The CLEOPATRA study lead to the implementation of dual blockade in combination with taxane chemotherapy backbone as the recommended choice as first-line treatment for HER2-positive mBC. Comparison to RCTs, such as the CLEOPATRA study, should be done with caution. Only 10% of patients in the CLEOPATRA study had received (neo) adjuvant trastuzumab. Knowing the potential mechanisms of resistance, this could have resulted in better mPFS among patients naïve to HER2-targerting therapies.[19] In this study population, 26% of patients were previously treated with trastuzumab. Furthermore, 10% of the patients included in this study would not have been judged eligible for the CLEOPATRA study, as they presented brain metastases at baseline. This would again support the incomparability between study populations found in real-world studies such as ours and in RCTs such as CLEOPATRA.

An Italian real-world study also examined the efficacy of dual blockade with a taxane as first-line treatment of HER2-positve mBC.[20] The study included 155 patients who had an mPFS of 27.8 months. This point estimate is over double the length of the mPFS found in our study. Furthermore, the mPFS of the Italian real-world study surpassed the CLEOPATRA study's mPFS with almost 10 months. The study included relatively young mBC patients with a median age of 52 years (29-79). The study had a lower number of patients with visceral metastases as well compared with our study. Other than age and visceral metastases, the patient population did not differ considerably from ours. Although not comparable, this study confirms the efficacy of dual blockade in a real-life setting, supporting the findings in RCTs such as CLEOPATRA.

Supplemental Table 2 compares baseline characteristics between studies cited in the discussion.

This study contains certain strengths and limitations. A strong point is that due to reimbursement reasons, every patient in Denmark who initiated treatment for their metastatic HER2-positive disease had to receive SB3 in first line. Furthermore, this study used the DBCG national database, which meant that all known patients who initiated dual blockade with SB3 and pertuzumab as first-line treatment for their metastatic disease were included, making the study nationwide and population based. A small patient population was eligible for this study, which was a great limitation in terms of efficacy examination. Only 117 patients were known to have received dual blockade with SB3, which is considerably lower compared with the other Danish real-world study (n = 291). SB3 was only administered for 1.5 years (September 2018 through February 2020), after being replaced by the other trastuzumab biosimilar which is the main explanation for the low patient count seen in this study. Due to reimbursement reasons, biosimilars are more frequently switched as preferred drug of use. This makes utilization of real-world data difficult, as short study periods result in smaller study populations. Therefore, the applicability of real-world data in studies concerning specific biosimilars in Denmark will be limited due to short follow-up and possible changes in biosimilars. In addition, mOS was not reached in this study due to short follow-up, which made comparison with related studies tougher. Finally, no data was available concerning toxicity, why safety of the treatment in a real-world setting could not be assessed.

Conclusions

This real-world, retrospective, Danish national, population-based study included 117 patients who initiated SB3 and pertuzumab as first-line treatment for HER2-positive mBC. SB3 as substitute for reference trastuzumab in dual blockade showed comparable mPFS and OS when compared with a similar Danish real-world study with originator trastuzumab.

Author Contributions

AS contributed to the conception, design, and writing of the article. NMA contributed to the analysis, design, and reviewing

of the article. AEA and DRI contributed to the coding and analysis of the article.

AC contributed to the data curation, formal analysis, investigation, writing – original draft, visualization. TB contributed to the conceptualization, investigation, methodology, resources, supervision, writing – review & editing. LB contributed to the formal analysis. MBJ contributed to the conceptualization, data curation, formal analysis, investigation, methodology, software, supervision, writing – review & editing. BE contributed to the methodology, supervision, writing – review & editing. AK contributed to the methodology, supervision, writing – review & editing. MA contributed to the conceptualization, funding acquisition, methodology, project management, supervision, writing – review & editing.

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Supplemental Material

Supplemental material for this article is available online.

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