



Original article

Neoadjuvant chemotherapy and HER2 dual blockade including biosimilar trastuzumab (SB3) for HER2-positive early breast cancer: Population based real world data from the Danish Breast Cancer Group (DBCG)



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ARTICLE INFO

Article history:

Received 28 September 2020

Received in revised form

28 October 2020

Accepted 29 October 2020

Available online 3 November 2020

Keywords:

Real-world
Ontruzant
SB3
Trastuzumab
Pertuzumab
NACT
Neoadjuvant
Breast cancer

ABSTRACT

Background: Dual blockade with trastuzumab and pertuzumab combined with neoadjuvant chemotherapy (NACT) has been increasingly used for HER2-positive tumours >2 cm and/or with positive axillary lymph nodes in order to evaluate pathologic response and obtain better surgical management. SB3 is a registered biosimilar trastuzumab approved following a phase III trial demonstrating similar efficacy in the neoadjuvant setting as trastuzumab. However, the study was done without pertuzumab. **Method:** The database of the Danish Breast Cancer Group was used to extract data on all patients who started NACT with SB3 and pertuzumab between September 1, 2018 and August 31, 2019. The primary endpoint was pathological complete response (pCR) rate.

Results: In total 215 patients received NACT and dual blockade. The median age was 55 (24–81). NACT used was cyclophosphamide and epirubicin followed by weekly paclitaxel (62% on six cycles, 35% on eight cycles) or other chemotherapy followed by weekly paclitaxel (3%). Overall, 56% of patients achieved pCR. 60 of 88 node-positive patients pre-NACT achieved ypN0(i-) after neoadjuvant treatment. pCR rate was significantly associated with estrogen receptor status and malignancy grade. An association with CEP17/HER2-ratio was assessed.

Conclusion: Real world data on dual blockade with SB3 and pertuzumab in combination with NACT in a nationwide population-based study show a pCR rate comparable to that seen in previous clinical studies.

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Introduction

The humane epidermal growth factor receptor, HER2, was first described in 1984 in rat neuro/glioblastomas [1]. It was followed by an investigation of human breast tumours, where an over-expression was shown to correlate to worse overall survival (OS) and progression free survival (PFS) [2]. Overexpression is seen in around 13% of early breast cancer tumours [3].

Monoclonal antibodies fused with human IgG, targeting the extracellular domain of HER2 was developed in 1992, and led to the development of trastuzumab (Herceptin, Genentech) [4,5]. Trastuzumab for HER2-positive metastatic breast cancer was approved in 1998 based on a phase II trial showing improved OS and PFS and approved in 2005 for HER2-positive early breast cancer (EBC) after showing a significant improvement of disease-free survival and OS [6,7].

Neoadjuvant treatment of EBC has been used to gain insight in the anti-tumoural processes of new therapies. Furthermore, neoadjuvant treatment has been used in order to turn in-operable breast cancer to operable, facilitate breast conserving surgery, avoid axillary lymph node dissection by node-conversion from

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cN + to ypN0, and to improve post-surgical cosmesis. A further advantage of the neoadjuvant approach is that it allows to evaluate response to the treatment. Pathological complete response (pCR, absence of residual invasive tumour in the breast and axillary lymph nodes, ypT0/Tis, ypN0) has been shown to be related to improved long-term outcome in breast cancer patients with HER2-positive tumours [8,9]. The KATHRINE study demonstrated that intensified HER2-targeted therapy with trastuzumab emtansine (T-DM1) for patients who did not obtain pCR after surgery significantly improved disease-free survival (hazard ratio for invasive disease or death, 0.50, 95% CI 0.39–0.64) [10]. Adjuvant T-DM1 is now by many considered standard of care for patients who do not obtain pCR [11].

Clinical testing of pertuzumab (Perjeta, Genentech) a humanized antibody targeting the dimerisation domain of HER2 with synergistic effect with trastuzumab was done in a neoadjuvant setting where dual blockade was shown to improve pCR [12–16]. Before this, pertuzumab had shown a significant effect on overall survival in metastatic breast cancer [17].

Newer studies evaluating the ratio between HER2 and CEP17 indicate a direct relationship between HER2/CEP17 ratio and pCR-rate [18,19].

The patent on trastuzumab (Herceptin) expired in the EU in 2014 leading to several new biosimilars being approved in 2017 and 2018 [20]. Biosimilars are not identical to their reference product due to intrinsic heterogeneity in these large complexes and can therefore not be equated to generic products [21]. Approval of a biosimilar drug requires that the manufacturer proves structural and physicochemical similarities to the reference product as well as clinical equivalence using sensitive endpoints [22]. Approval of the biosimilar drug is thus given not only in the setting in which it was tested but for all approved uses of the reference product. The structural differences between biosimilars and the reference product can theoretically raise questions regarding efficiency and safety.

SB3 (Ontruzant, Samsung Bioepis Co., Ltd., Incheon, Republic of Korea) is biosimilar trastuzumab approved by EMA in 2017 based on the totality of evidence including comparable efficacy, safety and immunogenicity in a randomised clinical trial in neoadjuvant/adjuvant treatment of HER2-positive EBC in which it was tested against Herceptin [23]. However, no data exist on the efficacy of the combination of neoadjuvant chemotherapy (NACT) with pertuzumab and SB3 instead of Herceptin.

This investigator-initiated study was conducted to assess real world efficacy of SB3 in combination with pertuzumab and NACT based on data from the Danish Breast Cancer Group (DBCG). For reimbursement reasons all treatment in Denmark with trastuzumab was switched from Herceptin to SB3 from September 1, 2018.

Material and methods

This is a retrospective observational population-based study involving all Danish departments of oncology (12 sites, see supplementary data). All breast cancer patients in Denmark are discussed at multidisciplinary conferences with attendance of pathologists, oncologists, breast surgeons and radiologists. This study included all women aged 18+ who started treatment with SB3, pertuzumab and NACT for unilateral HER2-positive EBC between September 1, 2018 and August 31, 2019. There were no exclusion criteria.

Data sources

The DBCG was established in 1977 and has since then provided guidelines for treatment of breast cancer patients, conducted nationwide clinical trials of adjuvant breast cancer therapy and collected data into the database. From the DBCG data on demographics, pre-NACT clinical stage, pre-NACT pathology, type of NACT and post-NACT pathology was obtained. The Danish departments involved in breast cancer treatment are all obligated by law to add surgical, pathological and oncological data to the DBCG database [24,25].

Measures

The primary outcome was to describe real-world efficacy for patients with a HER2-positive EBC who underwent NACT with dual blockade. Efficacy was defined as treatment outcomes at surgery, pCR rate and number of patients with breast conserving surgery. pCR was defined as absence of residual invasive tumour in the breast and axillary lymph nodes (ypT0/Tis, ypN0(i-)). A grade 1 response is pCR, grade 2 is > 90% tumour response, grade 3 is 30–90% response and grade 4 is < 30% response [26].

HER2 testing is done on all breast tumours in Denmark in accordance to international standards. All tumours are tested with immunohistochemistry. A score of IHC-3+ is regarded as HER2 positive. IHC-2+ qualifies for further evaluation with fluorescent in-situ hybridisation [27,28]. The centromere enumeration probe for chromosome 17 (CEP17) is used for evaluating HER2 gene copy numbers and amplification [28]. ER positivity was set to 10% [29]. PgR is not measured routinely in Danish patients.

Ethical approval

The study is register-based and does not involve contact to patients. By Danish law, no ethical board approval or patient consent is required for this type of study.

Statistics

Association between demographic and pre-NACT pathoanatomical factors, and pCR was evaluated by χ^2 -test, excluding unknowns. For histological type, ductal and lobular were included, and Fishers exact test used. For HER2/CEN17 ratio test for trend was applied. All p-values are two-sided, and level of significance set to 5%. Statistical analysis was done using the SAS 9.4 software program package (SAS Institute, Cary, NC).

Results

During the study period, 215 women with HER2-positive EBC received NACT combined with dual blockade including SB3.

The mean age was 55 years (range 24–81). The study included 44% premenopausal women. Twenty-three percent had a tumour of 5 cm or more. Biopsy-verified axillary node-positivity was found in 41% of participating women pre-NACT. Ki67 analysis was done on 120 tumours with a mean of 47 (range 4–90).

NACT

Cyclophosphamide and epirubicin (CE) followed by weekly paclitaxel combined with SB3 and pertuzumab three-weekly was

Table 1

Top: Post NACT treatment outcome in tumour and axilla. Bottom: Pre and post NACT nodal status. Highlighted patients who obtained pCR and node-conversion. NE: Not examined, ITC: isolated tumour cells.

		Post-NACT axillary lymph nodes						
		Macro metastases	Micro metastases	ITC	No tumour cells	Unknown	Total	%
Response grade	NE	0	0	0	3	0	3	1
	1 (No invasive tumour cells)	2	2	3	115	2	124	58
	2 (>90% loss)	4	3	4	31	0	42	20
	3 (30–90% loss)	9	5	0	14	0	28	13
	4 (<30% loss)	9	0	0	2	1	12	6
	Unknown	0	0	0	1	5	6	3
Total		24	10	7	166	8	215	100
%		11	5	3	77	4		
		Post-NACT axillary lymph nodes						
Pre-NACT	Negative	6	3	5	106	7	127	59
	Positive	18	7	2	60	1	88	41
Total		24	10	7	166	8	215	100

Table 2

Type of surgery in relation to pre-NACT clinical tumour size. ALND: Axillary lymph node dissection. NOS: Not otherwise specified.

		Surgery			
		Mastectomy ± ALND	Lumpectomy ± ALND	Surgery NOS	Total
Pre-NACT clinical tumour size	<5 cm	42	112	10	164
	≥5 cm	35	12	2	49
	Unknown	0	2	0	2
Total		77	126	12	215
%		36	59	6	

administered to 209 patients. 104 patients received three cycles of CE and three cycles of paclitaxel and 75 patients received four cycles of each. Thirty patients received 1–2 cycles of CE and 4–5 cycles of paclitaxel.

The remaining six patients received another chemotherapy followed by weekly paclitaxel combined with pertuzumab and SB3 three-weekly.

The mean interval from start of NACT to last pertuzumab and SB3 infusion was 110 days (range⁰–429). The mean interval from start of NACT to date of surgery was 156 (range 52–218, n = 203).

Treatment outcomes

Of 215 patients 115 (56%) obtained pCR. 42 (20%) had grade 2 response (>90% tumour loss) [26]. 12 patients (6%) had a grade 4 response (<30% loss). Of 88 women with pre-NACT positive axillary lymph nodes, 60 (68%) were lymph node negative post-NACT (Table 1). Of 127 women with pre-NACT negative axillary lymph nodes, 13 (10%) patients had 1 or more lymph nodes without metastasis but with treatment response (see appendix table 1 for more).

Lumpectomy with or without ALND (axillary lymph node dissection) was the preferred surgical option (59%). However, as expected most women with cT3 tumour underwent mastectomy (Table 2).

pCR-rate was significantly related to low pre-NACT estrogen receptor content and high pre-NACT malignancy grade (Table 3) but

¹ Three patients began their treatment course with paclitaxel and only received one dose of dual blockade. All three patients continued their treatment course with SB3.

not to pre-NACT tumour size or pre-NACT nodal status. The relationship for HER2/CEP17 ratio was not statistically significant (trend-test, p = 0.10), although a higher pCR rate was seen with increasing ratio (Table 3).

Discussion

This is the first study that to our knowledge examines the efficacy of SB3 in combination with pertuzumab and NACT for EBC in a real-world setting. We have shown a pCR rate of 56% (95% CI 0.49; 0.63) which is higher than the original phase III trial of SB3 with neoadjuvant docetaxel followed by flurouracil, epirubicin and cyclophosphamide (tpCR 45,8%) [23]. A recently published systematic review and meta-analysis found that 56% obtained a pCR (95% CI, 0,45–0,63) in four single-arm studies (two phase II trials and two retrospective trials) [30]. The study populations were comparable to ours regarding stage but only one study included patients treated with an anthracycline.

Real-world evidence provides a useful piece of evidence by confirming the results from controlled clinical trials. Other groups have examined dual blockade in a real-world setting. A 2018 study among 78 women with HER2-positive EBC found an overall pCR rate of 47% and a 2019 study among 166 patients found a pCR rate of 55% [31,32]. Neither studies used biosimilar trastuzumab.

The future of oncology is most likely full of biosimilars due to outdating patents. As previously stated, approvals of biosimilars are – among other – based on clinical trials with sensitive endpoints leading to approval of the biosimilar for all the reference product’s indications. SB3 was initially not tested with pertuzumab but has been used as a biosimilar for all trastuzumab’s indications in Denmark since September 1, 2018.

The present study shows that patients with an ER-positive

Table 3
pCR in relation to demographic and pre-NACT pathoanatomical factors. pCR (yes: response grade 1 and no axillary macro-and/or micrometastases and/or isolated tumour cells, no otherwise).

	PCR					Total	p
	Yes		No		Unknown		
Age	n	%	N	%			0.86
<55	58	56	46	44	8	112	
≥55	57	57	43	43	3	103	
Menopausal status							0.79
Pre	50	57	37	43	8	95	
Post	65	56	52	44	3	120	
Clinical tumour size							0.14
<5 cm	92	59	64	41	8	164	
≥5 cm	22	47	25	53	2	49	
Unknown	1		0		1	2	
Pre-NACT nodal status							0.67
Negative	68	58	50	42	9	127	
Positive	47	55	39	45	2	88	
Histological type							0.74
Ductal	90	52	84	48	9	183	
Lobular	4	44	5	56	0	9	
Apocrine	0		0		1	1	
Carcinoma, not specified	21	100	0	0	1	22	
Malignancy grade							0.03
I	2	20	8	80	0	10	
II	73	61	46	39	6	125	
III	34	52	31	48	2	67	
Unknown	6		4		3	13	
Estrogen receptor							0.0006
0%	49	72	19	18	4	72	
1–9%	10	77	3	23	1	14	
10–100%	56	46	67	54	6	129	
HER2/CEP17 ratio, quartiles#							0.10
≤2.31	2	20	8	80		10	
2.31-≤3.33	3	33	6	67		9	
3.33-≤4.76	4	44	5	56		9	
>4.76	5	56	4	44		9	

#N = 167 patients with IHC-HER2-3+ had no ISH analysis for HER2/CEN17 ratio.

disease (10–100%) were significantly less likely to obtain pCR. This might be explained by crosstalk between ER and HER2 signalling pathways leading to an up-regulation of ER in absence of ER-targeted therapy during neoadjuvant treatment [33]. A similar trend has been observed in other studies such as the BERENICE trial with pCR rate of 51.6% and 81.5% in HR-positive and HR-negative patients, respectively [16].

An analysis of the National Cancer Database (NCDB) showed a linear relationship between HER2/CEP17 ratio and pCR in HER2-positive EBC treated with neoadjuvant therapy. We did not find a significant relationship in our study and only 37 patients had an ISH-analysis. We did however see that higher ratios were associated with higher pCR (20% pCR in the lowest quartile vs 56% in the highest quartile) [18].

Our study has several strengths and limitations. One strength is the non-selected population based on all breast cancer patients in Denmark who initiated neoadjuvant therapy with SB3 in the specified time period. Another strength is that due to reimbursement rules all newly diagnosed patients had to initiate SB3 after the September 1, 2018. A limitation is the fact that we could not present toxicity data and thus not be able to report safety in a real-world setting. Furthermore, our short follow-up did not allow for evaluation of long-term outcome. Another limitation is the use of the Miller-Payne response grading instead of the RCB score that have

not been implemented by the Danish pathologist before 2020 [34].

Conclusion

Dual blockade with SB3 and pertuzumab combined with NACT shows efficacy in a real-world population with pCR rates comparable to randomised trials and meta-analysis.

Funding

The DBCG received an institutional grant from Samsung Bioepis CO., LTD.

Declaration of competing interest

MBJ: Institutional grants from Nanostring Technologies and Oncology Venture, EHJ: Advisory board for Pfizer, Roche, Astra Zeneca and Novartis.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.breast.2020.10.014>.

Appendix table 1

Lymph node (LN) treatment response (reported as number of LNs with “With metastasis and treatment response” and “Without metastasis but with treatment response”) and presence of metastases after NACT.

		Post-NACT axillary lymph nodes				
		Macro metastases	Micro metastases	ITC	No tumour cells ^a	Unknown ^b
Pre-NACT						
Negative	0 LN with metastasis and treatment response	1	1	4	101	1
	≥1 LN with metastasis and treatment response	5	2	1	0	0
	0 LN without metastasis but with treatment response	4	3	4	88	0
	≥1 LN without metastasis but with treatment response	2	0	1	13	0
	Positive	0 LN with metastasis and treatment response	7	0	0	59
Positive	≥1 LN with metastasis and treatment response	11	7	2	0	0
	0 LN without metastasis but with treatment response	13	2	0	12	0
	≥1 LN without metastasis but with treatment response	5	5	2	47	0
	Total	24	10	7	166	8

^a 5 pre-NACT negative patients with unknown in either category. 1 pre-NACT positive patient with unknown in either category.

^b 6 pre-NACT negative patients with unknown in “With metastasis and treatment response” and 7 patients with unknown in “Without metastasis but with treatment response”. 1 pre-NACT positive patient with unknown in either category.

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