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ORIGINAL RESEARCH ARTICLE

Anthracyclines versus No Anthracyclines in the Neoadjuvant Strategy for HER2+ Breast Cancer: Real-World Evidence

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Abstract

Background and Objectives Deescalation strategies omitting anthracyclines (AC) have been explored in early human epidermal growth factor receptor 2-positive breast cancer (HER2+ EBC), showing similar efficacy regarding pathological complete response (pCR) and long-term outcomes as AC-containing regimens. The standard treatment for this tumor subtype is based on chemotherapy and dual HER2 blockade with trastuzumab and pertuzumab, with AC-containing regimens remaining a frequent option for these patients, even in non-high-risk cases. The primary aim of this study was to assess and compare the effectiveness of neoadjuvant regimens with and without AC used in the treatment of HER2+ EBC in the clinical practice according to the pCR achieved with each.

Methods This retrospective multicentric study included patients with HER2+ EBC from Portuguese, Spanish, and Chilean hospitals (January 2018–December 2021). Patients receiving neoadjuvant therapy (NAT) with dual HER2 blockade (trastuzumab and pertuzumab), followed by surgery, were included. Statistical analysis used chi-squared/Fisher's exact test for associations, multivariate logistic regression for pCR, and Kaplan–Meier method for event-free survival (EFS). IBM SPSS Statistics 29.0 analyzed the data.

Results The study included 371 patients from eight hospitals. Among them, 237 received sequential AC and taxane-based chemotherapy with 4 cycles of trastuzumab and pertuzumab, while 134 received 6 cycles of TCHP (docetaxel, carboplatinum, trastuzumab, and pertuzumab). The average age of the patients was 52.8 years and 52.7 years, respectively. Omitting AC from the neoadjuvant approach did not preclude achieving pCR [$p = 0.246$, 95% confidence interval (CI) 0.235–0.257] and was safe regardless of patient characteristics. Relapse rates were 6.8% (16 patients) in the AC group and 4.5% (6 patients) in the TCHP group. Over a median follow-up of 2.9 years, the estimated 3-year EFS was 92.5% in the AC group and 95.4% in the TCHP group (hazard ratio 0.602, 95% CI 0.234–1.547, $p = 0.292$, favoring TCHP).

Conclusion This study reports real-world evidence showing similar pCR and EFS outcomes with treatment regimens with and without AC and raises awareness of possible overtreatment and long-term toxicity in some patients with HER2+ EBC with the use of AC.

Key Points

Retrospective data from 371 patients with HER2+ breast cancer showed similar pCR and event-free survival outcomes with treatment regimens, with and without anthracyclines.

Real-world data supports the use of TCHP as an effective neoadjuvant treatment regimen for patients with early HER2+ BC.

1 Introduction

The neoadjuvant setting represents the ideal setting for translational, drug, and biomarker research in early human epidermal growth factor receptor 2-positive breast cancer (HER2+ EBC), given the possibility of using pathological complete response (pCR) as a surrogate for long-term outcomes [1, 2]. Achieving pCR after neoadjuvant therapy (NAT) is generally associated with favorable prognosis and longer disease-free survival in these patients [3, 4]. The current standard treatment for HER2+ EBC with ≥ 2 cm or nodal involvement is NAT with dual HER2 blockade with trastuzumab and pertuzumab. This strategy should also be

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considered for tumors measuring 1−2 cm with high-risk features, and also to cover patients who would be candidates for mastectomy into eligible candidates for breast-conserving surgery [5, 6]. With this therapy, the disease-free survival (DFS) at 5 years is approximately 85% in patients who achieve pCR and 75% in patients who do not [3, 4].

Several strategies have been explored to optimize the systemic therapy for patients with HER2+ EBC and thereby improve their quality of life, reduce short- and long-term side effects, and avoid unnecessary costs, while optimizing patient outcomes. Some of these strategies include decreasing the duration of trastuzumab therapy, using adjuvant trastuzumab emtansine (T-DM1) in patients who do not achieve pCR following NAT, and omitting anthracyclines (AC) from the neoadjuvant treatment regimen.

The strategy of omitting AC in neoadjuvant setting is based on the acknowledgment that these agents are associated with long-term toxicity, namely heart dysfunction and congestive heart failure in 9%−26% of patients, and myelodysplastic syndrome and acute myeloid leukemia in 0.4%, with increased risk with cumulative doses [7, 8]. This strategy was explored in two studies specifically investigating the omission of AC from the backbone of a neoadjuvant regimen with dual HER2 blockade—the phase 3 TRAIN-2 and the phase 2 TRYPHAENA trials—and was shown to have an impact on patients' clinical outcomes [9, 10]. It has been suggested that the use of the AC-sparing regimen TCHP (carboplatin, docetaxel, and dual blockade) could be at least equivalent in terms of pCR and DFS to AC-containing regimens and have decreased cardiotoxicity [9, 10]. However, there are few prospective data comparing both regimens and real-world evidence (RWE) is scarce. In addition, some clinical trials in this setting have used non-standard therapies, such as carboplatin plus paclitaxel, or have not included patients treated with adjuvant T-DM1 [9, 10], which reinforces the importance of collecting more data about this subject.

The primary aim of this study was to assess and compare the effectiveness of neoadjuvant regimens with and without AC used in the treatment of HER2+ EBC in the clinical practice according to the pCR achieved with each regimen. The secondary aim was to assess patients' clinicodemographic profile and event-free survival (EFS).

2 Methods

2.1 Patient Selection

This was a retrospective multicentric study of patients with HER2+ EBC diagnosed and treated in Portuguese, Spanish, and Chilean hospitals between January 2018 and December 2021. The study included patients who received NAT with dual HER2 blockade with trastuzumab and pertuzumab, followed by surgery. Patients with disease progressing during NAT were excluded. The following data were retrieved from patients' electronic clinical records: initial disease stage, chemotherapy regimen, expression of hormone receptors (HR), Ki-67, type of surgery, type of adjuvant therapy, distant recurrence, and pCR (defined as ypT0/is and ypN0/is or ypT0/is if the patient did not undergo axillary surgery).

2.2 Statistical Analysis

Associations between categorical outcome measures, such as stage and pCR, were assessed by chi-squared or Fisher's exact test. Multivariate logistic regression was used to investigate the association between parameters retrieved from patients' clinical records and pCR. Survival analyses were performed for EFS according to the Kaplan–Meyer method. EFS was calculated from the beginning of NAT until local or distant relapse, second primary, death by cancer, or last patient contact, whichever occurred first. IBM SPSS Statistics 29.0 was used for statistical analysis.

3 Results

3.1 Patient Characteristics

A total of 371 patients from eight hospitals were included in the study, of whom 237 had been treated with sequential AC and taxane-based chemotherapy (12 cycles of paclitaxel), with 4 cycles of trastuzumab and pertuzumab, and 134 had been treated with 6 cycles of TCHP. Patients had a mean age of 52.8 and 52.7 years, respectively. The baseline characteristics of the two study groups are presented in Table 1. T2-3/N0-1 clinical stages were the most prevalent in both groups, and HR positivity was present in 72.6% of the AC group and 57.5% of the TCHP group. All patients received adjuvant radiotherapy.

3.2 pCR According to NAT

In the AC group, 136 of 237 (57.4%) patients achieved pCR compared with 85 of 134 (63.4%) patients in the TCHP group [p value = 0.246, 95% confidence interval (CI) 0.235–0.257; Fig. 1] . The pCR for both groups was not related to HR expression ($p = 0.82$; Fig. 2).

No significant differences were found in pCR rates according to HR status, age, tumor size, or nodal

involvement after multiple logistic regression analysis (Fig. 3). A trend was observed toward better performance of TCHP in patients with ≥ 50 years, larger tumor size, and nodal disease, although it was only statistically significant for nodal involvement ($p = 0.007$; Fig. 3).

3.3 Surgical Procedure According to NAT

Breast-conserving surgery (BCS) was performed in 120 of 237 (50.6%) patients in the AC group and in 76 of 134 (56.7%) patients in the TCHP group. In the AC group, sentinel lymph node biopsy (SLNB) was performed in 113 patients (47.7%), and axillary lymph node dissection (ALND) in 118 (49.8%). In the TCHP group, 86 patients (64.2%) underwent SLNB, and 48 (35.8%) ALND (Table 1).

3.4 Adjuvant Treatment

Regarding anti-HER2 therapy, trastuzumab was the most commonly prescribed drug for patients who received AC or TCHP, with prescription rates of 86.1% and 77.6%, respectively. Among patients with HR+ tumors, aromatase inhibitors were the most frequently prescribed, 47.7% and 53.2%, followed by tamoxifen, 23.8% and 27.8%, respectively.

3.5 Relapse Rate According to NAT

Regarding adjuvant treatment, majority of patients in both groups had received single-agent trastuzumab [$n = 204$ (86.1%) in the AC group and $n = 104$ (77.6%) in the TCHP]. Other adjuvant treatment options included TDM-1 and HP (Table 1).

Relapse occurred in 16 patients (6.8%) in the AC group and in 6 (4.5%) patients in the TCHP group. With a median follow-up of 2.9 years, the estimated 3-year EFS in the AC group was 92.5%, and in the TCHP group was 95.4% [hazard ratio 0.602, 95% confidence interval (CI) 0.234–1.547, $p = 0.292$, favoring TCHP]. Based on these data, the estimated 5-year EFS according to NAT is depicted in Fig. 4.

4 Discussion

Several NAT deescalation strategies have been pursued in HER2+ EBC, aiming to reduce the use of chemotherapy, in particular AC. Most studies investigating these strategies used pCR as surrogate marker for survival [1, 2]. However, due to the limited availability of survival data, the optimal use of NAT in this setting remains unclear.

In the adjuvant setting, two studies by Tolaney et al. indicated that patients with HER2+ EBC may waive AC from their treatment regimens and still achieve very favorable long-term outcomes with trastuzumab and paclitaxel in small node-negative tumors [11, 12]. This was also demonstrated in the 10-year

Table 1 Patient characteristics

Characteristics	AC-based chemotherapy group	TCHP group
Number of patients	237	134
Age, years (mean)	52.8	52.7
Clinicopathological characteristics		
cT1	24 (10.1)	17 (12.7)
cT2	129 (54.4)	73 (54.5)
cT3	55 (23.2)	31 (23.1)
cT4	29 (12.2)	13 (9.7)
cN0	111 (46.8)	63 (47.0)
cN1	112 (47.3)	54 (40.3)
cN2	8 (3.4)	13 (9.7)
cN3	6 (2.5)	4 (3.0)
G1	4 (1.8)	1 (2.5)
G2	115 (52.8)	17 (42.5)
G3	99 (45.4)	22 (55.0)
HR negative	65 (27.4)	57 (42.5)
HR positive	172 (72.6)	77 (57.5)
BCS	120 (50.6)	76 (56.7)
Mastectomy	117 (49.4)	58 (43.3)
No axillary surgery	6 (2.5)	0 (0)
SLNB	113 (47.7)	86 (64.2)
ALND	118 (49.8)	48 (35.8)
pCR	136 (57.4)	85 (63.4)
Adjuvant HER2 treatment		
None	4 (1.7)	3 (2.2)
Trastuzumab	204 (86.1)	104 (77.6)
TDM-1	17 (7.2)	27 (20.1)
HP	12 (5.1)	0 (0)
Adjuvant endocrine therapy		
Tamoxifen	41 (23.8)	21 (27.3)
Aromatase inhibitors	82 (47.7)	41 (53.2)
Tamoxifen + ovarian suppression	16 (9.3)	5 (6.5)
Aromatase inhibitors + ovarian suppression	18 (10.5)	4 (5.2)
None	15 (8.7)	6 (7.8)
Relapse	16 (6.8)	6 (4.5)

Values are expressed as *n* (%), unless specified otherwise

AC anthracycline, *ALND* axillary lymph node dissection, *BCS* breast-conserving surgery, *G* grade, *HER2* human epidermal growth factor receptor 2, *HP* trastuzumab plus pertuzumab, *HR* hormone receptor, *N* lymph nodes on TNM classification of malignant tumors, *pCR* pathological complete response, *SLNB* sentinel lymph node biopsy, *T* tumor on TNM classification of malignant tumors, *TCHP* carboplatin, docetaxel, and dual blockade, *TDM-1* trastuzumab emtansine

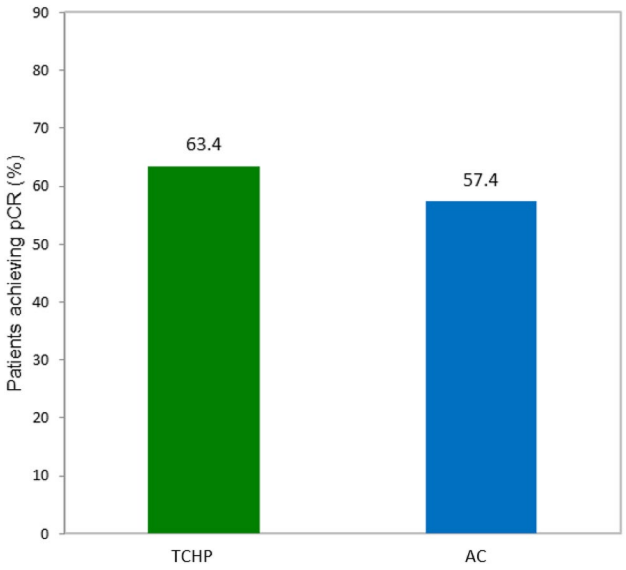

Fig. 1 Pathological complete response (pCR) according to neoadjuvant therapy. *AC* anthracycline, *TCHP* carboplatin, docetaxel, trastuzumab and pertuzumab

follow-up of the BCIRG-006 study [13]. This study showed worse toxic effects of adjuvant AC-based regimen and similar DFS compared with non-AC-based chemotherapy. Preliminary results of the DAPHNE trial, a single-arm feasibility study of adjuvant trastuzumab/pertuzumab deescalation in patients with pCR following neoadjuvant THP (paclitaxel, trastuzumab, and pertuzumab) showed a promising overall pCR rate of 55% ($n = 51$ of 93 patients) [14].

Regarding the use of AC in the neoadjuvant setting of HER2+ EBC, the TRAIN-2 and TRYPHAENA trials demonstrated non-inferiority in terms of pCR and EFS and lower toxicity with TCHP compared to AC-containing regimens [9, 10]. The results of the present study agree with those results by showing that a deescalation strategy without AC may be effective regardless of patients' characteristics. The omission of AC did not preclude achieving pCR in subgroup analyses. In fact, contrary to what could be expected, the odds of achieving pCR were 2.3-fold higher in the TCHP group for patients with nodal disease (95% CI 1.25–4.215, $p \leq 0.05$). Although there was a favorable trend toward improved survival outcomes in the TCHP group, differences in EFS between AC and non-AC groups were not statistically different. Longer follow-up will predictably help to understand the relevance of the trend observed here and help clarify this issue.

RWE about deescalation strategies in this setting of HER2+ EBC treatment is scarce, and no real-world large-scale studies have been conducted to date. Two retrospective studies in India [15] and South Korea [16] evaluated the use of TCHP in NAT setting. Both reported high pCR rates (64% and 55.6%, respectively) and an acceptable toxicity profile with this regimen. In addition, the Korean study documented a three-year EFS of 90%, while the Indian study, which included stage IV oligometastatic patients, reported a BCS conversion rate from planned mastectomy of 26.6% and a clinical overall response rate of 100%.

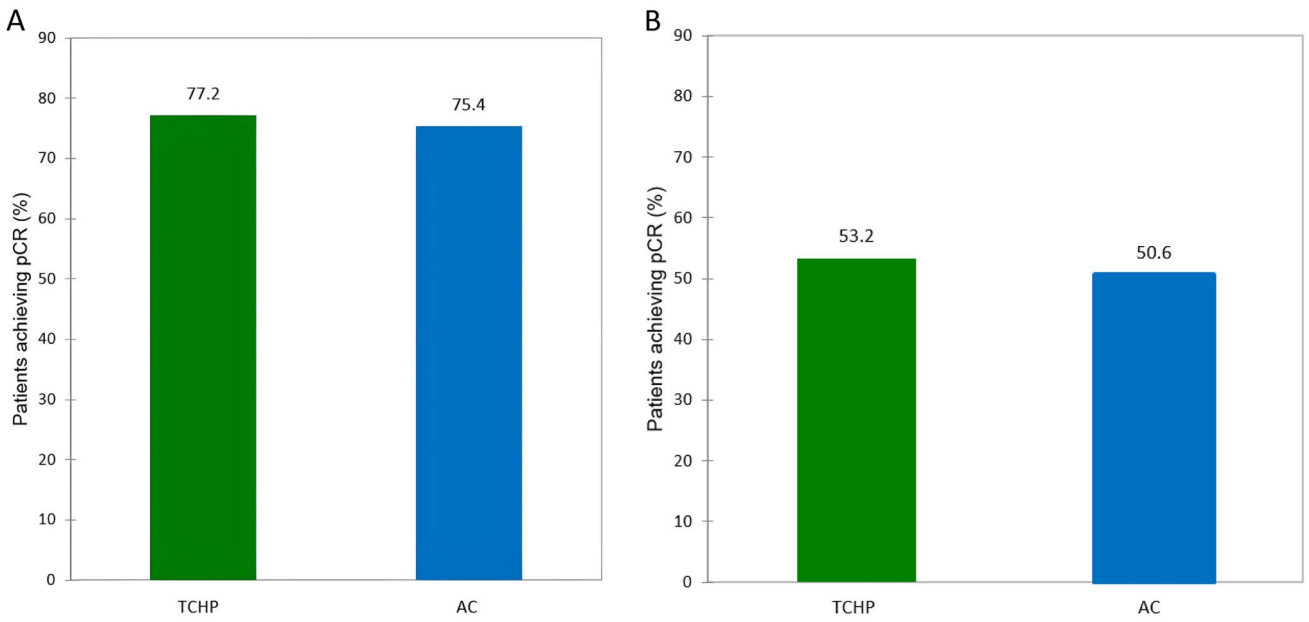

Fig. 2 Pathological complete response (pCR) according to hormone receptor (HR) status and neoadjuvant therapy. **a** HR negative. **b** HR positive. *AC* anthracycline, *HR* hormone receptor, *TCHP* carboplatin, docetaxel, trastuzumab and pertuzumab

	AC based chemotherapy group [a] (n=237)	TCHP group (n=134)	Odds ratio (95% CI)
HR status			
Negative	49/65 (75.4%)	44/57 (77.2%)	1.105 (0.478-2.553)
Positive	87/172 (50.6%)	41/77 (53.2%)	1.113 (0.650-1.906)
Age			
< 50 years	55/95 (57.9%)	38/65 (58.5%)	1.024 (0.540-1.941)
≥ 50 years	81/142 (57.0)	47/69 (68.1%)	1.609 (0.878-2.948)
Tumor Size			
T 1-2	94/153 (61.4%)	55/90 (61.1)	0.986 (0.578-1.683)
T 3-4	42/84 (50.0%)	30/44 (68.2%)	2.143 (0.997-4.605)
Nodal Stage			
N0	76/111 (68.5%)	37/63 (58.7%)	0.655 (0.345-1.245)
N+	60/126 (47.6%)	48/71 (67.6%)	2.296 (1.250-4.215) *
All patients	136/237 (57.4%)	85/134 (63.4%)	1.288 (0.833-1.992)

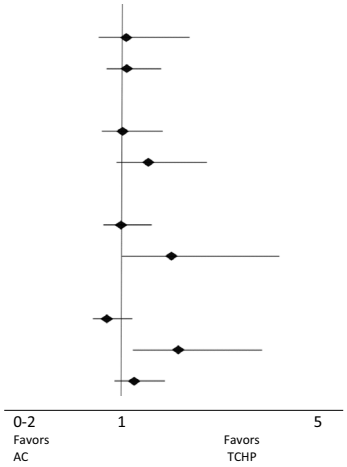

Fig. 3 Forest plot of pathologic complete response (pCR) according to subgroup. [a]Reference group. *Statistically significant ($p < 0.05$). *AC* anthracycline, *CI* confidence interval, *HR* hormone receptor, *N* lymph nodes on TNM classification of malignant tumors, *T* tumor on TNM classification of malignant tumors, *TCHP* carboplatin, docetaxel, trastuzumab and pertuzumab

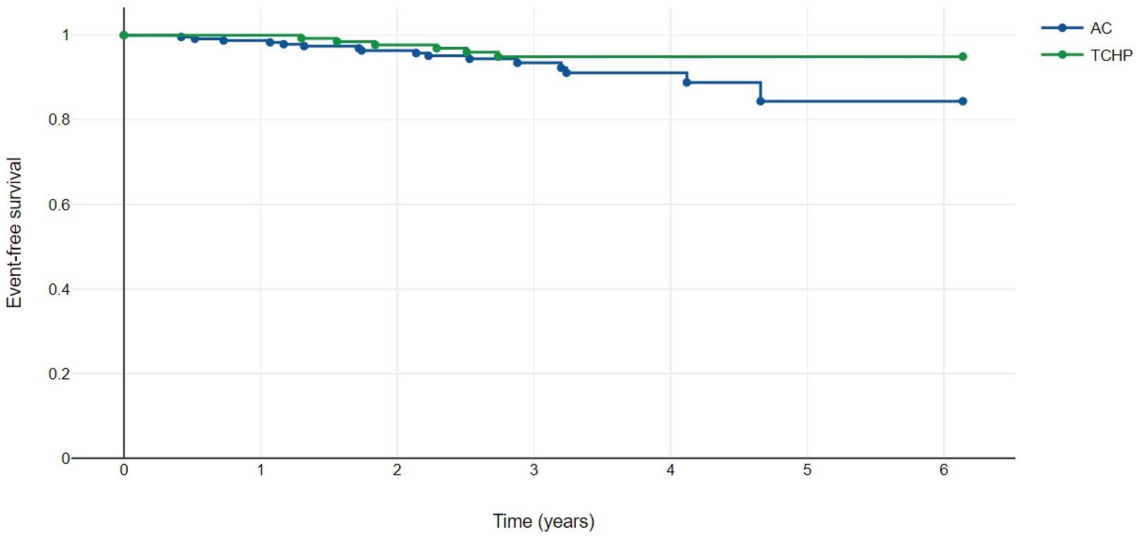

Fig. 4 Event-free survival according to neoadjuvant therapy. *AC* anthracycline, *TCHP* carboplatin, docetaxel, trastuzumab and pertuzumab

Moving forward in the deescalation strategy for HER2+ EBC toward a total chemotherapy-free neoadjuvant approach, the WSG-ADAPT-HER2+/HR− phase 2 trial compared a neoadjuvant strategy with taxanes plus pertuzumab and trastuzumab with another with pertuzumab and trastuzumab without chemotherapy [17]. The trial was stopped early due to superior pCR in the chemotherapy arm (90% versus 30%). However, survival outcomes presented at ASCO 2021, including invasive DFS, distant DFS, and OS, showed no significant differences between 12-week-deescalated trastuzumab plus pertuzumab, with and without weekly paclitaxel [18].

Early-stage tumors with low-risk features (e.g., node-negative and/or well differentiated) are expected to have a smaller absolute benefit from the use of AC compared with node-positive counterparts, while maintaining a low risk of recurrence [19–21]. In the NEOSPHERE trial, 17% of patients treated with four cycles of trastuzumab and pertuzumab achieved pCR, suggesting that chemotherapy could be omitted in some patients [22].

This study adds relevant RWE supporting the use of a deescalation NAT approach in HER2+ EBC. Among a population of 371 patients with various risk factors and disease stages (mostly T2–3/N0–1), the study demonstrated similar pCR and EFS with and without the use of AC in the treatment regimen. Regarding the choice of surgery, the use of AC was generally not associated with an increase in BCS or decreased axillary dissection rate. Overall, these results and the possibility of long-term toxicity with AC should raise awareness to the potential overtreatment of patients.

The present study has certain limitations that need to be acknowledged. Firstly, it is important to note that the study design was retrospective, which means that it relied on past data and may be subject to biases and confounding factors. Additionally, there is a lack of toxicity data, which limits a comprehensive understanding of the treatment's potential side effects and safety profile.

While the international multicenter nature of the study brings valuable diversity and generalizability to the findings, it also introduces a potential challenge. The heterogeneity among different institutions in terms of treatment approaches could have an impact on the results. For example, the availability and reimbursement of adjuvant T-DM1 varied across countries and could have influenced the outcomes. It is crucial to consider these differences when interpreting and applying the study results.

To validate the findings and draw more robust conclusions, long-term follow-up is necessary, particularly for patients with HR+ tumors. This extended observation period will help verify the durability and efficacy of the treatment approach over time.

Furthermore, it is important to highlight that the study was not statistically powered to assess treatment non-inferiority in specific patient subgroups that were predefined. Conducting future studies with adequate statistical power in these subgroups will be essential to clarify the obtained results and potentially establish standardized clinical management for this specific patient population.

5 Conclusion

The findings of this study provide valuable RWE in support of a deescalation NAT approach for HER2+ EBC. The study demonstrated that the omission of AC from the treatment regimen did not significantly impact pCR rates. While these results are promising, longer follow-up periods are needed to determine if this approach translates into improved EFS outcomes. Further investigation and validation of these findings will contribute to the refinement and optimization of treatment strategies for patients with HER2+ EBC, ultimately improving their long-term prognosis and quality of life.

Declarations

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Consent to participate Not applicable as anonymized data were retrospectively collected from electronic clinical records.

Consent for publication Not applicable.

Availability of data and material Not applicable.

Code availability Not applicable.

Author contributions I.P.: investigation, methodology, writing—original draft preparation; P.L.: investigation, methodology, writing—original draft preparation; L.A., R.L.B., V.P., M.E.M., L.G., R.F., D.M., M.R.G., I.F., S.A.C., S.G., and J.B.C.: investigation; I.S.V.: investigation; J.G.C. and A.S.F.: supervision, writing—review and editing; R.T.S. and L.C.: supervision, validation.

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