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Benefits of neoadjuvant therapy compared with adjuvant chemotherapy for the survival of patients with HER2-positive breast cancer: A retrospective cohort study at FUSCC

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ABSTRACT

Purpose: Neoadjuvant therapy (NAT) is considered the standard of care for patients with HER2-positive breast cancer (BC). However, there is no proven survival benefit of NAT compared to adjuvant therapy for the survival of patients with early-stage HER2-positive BC. This study aimed to compare the prognosis of HER2-positive BC patients treated with NAT to that of patients treated with adjuvant therapy.

Methods: This was a single-center real-world retrospective study. This study analyzed the disease-free survival (DFS) and overall survival (OS) of 538 HER2-positive BC patients treated with neoadjuvant therapy and 2684 patients treated with adjuvant therapy at Fudan University Shanghai Cancer Center (FUSCC) between 2012 and 2016. Patients with a clinical tumor size (cT) ≤5 cm or >5 cm were matched using the propensity score matching (PSM) method to prevent selection bias.

Results: After PSM, among patients with cT ≤ 5 cm, there was no significant difference in DFS ($P = 0.08$) or OS ($P = 0.11$) between the two groups. The analysis of survival outcomes of patients treated with neoadjuvant and adjuvant therapy in the different chemotherapy subgroups yielded consistent results. According to multivariate analysis, lymph node status and response to NAT showed independent prognostic value for OS and DFS. Among patients with cT > 5 cm, the DFS ($P = 0.25$) and OS ($P = 0.57$) of patients treated with NAT were similar to those of patients treated with adjuvant therapy after PSM.

Conclusion: We confirmed the equivalent effects of adjuvant therapy and NAT in HER2-positive BC patients. Neoadjuvant therapy should be used for patients with HER2-positive BC.

1. Introduction

Neoadjuvant therapy (NAT) has gradually become the standard treatment for patients with inoperable locally advanced breast cancer and inflammatory breast cancer [1,2]. NAT can decrease tumor sizes and allow more patients to undergo breast-conserving surgery. NAT can also facilitate the monitoring of treatment responses in vivo via observations of pathological findings that indicate residual disease in the breast and axilla [3,4].

Human epidermal growth factor receptor (HER2)-positive breast cancer is a unique type of breast cancer in which the oncogene ERBB2 is overexpressed [5]; HER2-positive breast cancer that is not treated with HER2-targeted therapies is associated with a worse prognosis. Previous trials have shown that HER2-positive breast cancer is more chemosensitive than other subtypes of breast cancer [6,7]. Pathological complete response (pCR) is commonly defined by the absence of invasive cancer in both the breast and/or lymph nodes after NAT. pCR can also provide information regarding the responsiveness of a tumor to NAT. A meta-analysis by Rouzier R et al. showed that the pCR rates among patients with HER2-positive breast cancer who receive HER2-targeted therapies and neoadjuvant therapies can reach 60% or higher [5].

Previous clinical trials have shown that NAT is equally as effective as

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adjuvant therapy in terms of overall survival (OS) and disease-free survival (DFS) [2,8]. A meta-analysis of the long-term outcomes of patients with early breast cancer who were treated with neoadjuvant chemotherapy versus adjuvant chemotherapy was conducted by Early Breast Cancer Trialists' Collaborative Group (EBCTCG) [9], and the analysis showed that the distant recurrence rate and OS were similar in patients who received NAT and patients who received adjuvant therapy. However, the studies that addressed the equal efficacy of these two therapies did not routinely evaluate HER2 status. According to the St. Gallen international expert consensus conference in 2017, the panel favored the preference for neoadjuvant therapy in HER2 positive breast cancer [10]. A recent study indicated that NAT is more beneficial than adjuvant therapy, particularly in cN-positive and postmenopausal patients with HER2-positive breast cancer [11]. However, these studies ignored the important prognostic factor pCR. Although the meta-analysis by EBCTCG showed that responders to NAT had lower distant recurrence rates and breast cancer-related mortality than non-responders, the authors did not compare the distant recurrence rate and breast cancer-related mortality between responders to NAT and responders to adjuvant therapy. We conducted this retrospective study to confirm the equal efficacy of NAT and adjuvant therapy in patients with HER2-positive breast cancer in the real world and to further compare the outcomes of patients who respond to NAT and patients who are treated with adjuvant therapy.

The primary aim of our study was to determine the OS and DFS of HER2-positive breast cancer patients treated with NAT versus patients treated with adjuvant therapy in a single-center cohort of Chinese breast cancer patients. In addition, we aimed to identify the population of patients with HER2-positive breast cancer who are most likely to benefit from treatment with neoadjuvant therapy. The secondary aim was to evaluate the current regimens for the treatment of patients with HER2-positive breast cancer with NAT or adjuvant therapy.

2. Methods

2.1. Study design and eligibility

This was a single-center, retrospective study. Patients with primary invasive HER2-positive breast cancer and who were treated with neoadjuvant or adjuvant therapy at Fudan University Shanghai Cancer Center (FUSCC) between 2012 and 2016 were analyzed. This study was approved by the Ethics Committee of Fudan University Shanghai Cancer Center (1905202-7) and conducted in accordance with the Declaration of Helsinki. This was a retrospective cohort study, so informed consent of the patients was not required.

Consecutive female patients aged 18–85 years with invasive HER2-positive breast cancer diagnosed by core-needle aspiration were analyzed in the study. Pathological HER2 status was defined according to the ASCO/CAP 2007 guidelines [12]. A HER2 expression score of 3+ by immunohistochemical staining was considered positive; a score of 2+ required verification by fluorescence in situ hybridization (FISH), and FISH positivity was considered to indicate HER2 amplification. Patients with other cancers or recurrent breast cancer when they were first diagnosed in our center were not eligible for this study. Other exclusion criteria included metastatic disease before surgery and male breast cancer. Targeted therapy refers to the completion of one year of trastuzumab treatment, and the patients did not receive other targeted therapies, such as pertuzumab and lapatinib, during this retrospective study.

2.2. Follow-up

All the patients were followed up through outpatient interviews or telephone calls. Local relapse was defined as relapse at the breast, chest wall, pectoral muscles, ipsilateral supraclavicular nodes, and internal mammary nodes. Distant metastasis was considered if it was observed in clinical and imaging studies. OS was calculated from the date of diagnosis to the date of death or last follow-up. DFS was calculated from the first date of no disease, i.e., date of surgery, to the date of disease relapse (local relapse, metastasis, or death from any cause). pCR was defined by the absence of invasive cancer in both the breast and lymph nodes after NAT.

2.3. Statistics

The clinical and pathological stages of the patients included in the analysis were classified according to the AJCC 8th edition guidelines. Because there were only 68 patients with a clinical tumor size (cT) larger than 5 cm in the adjuvant therapy group, the patients were divided into two groups: those with a clinical tumor size smaller than 5 cm and those with a clinical tumor size larger than 5 cm. The propensity score matching (PSM) methodology was used to reduce the treatment selection bias in the nonrandom assignment. Matching was performed with the use of a 1:3 or 3:1 matching protocol with a caliper width equal to 0.2 of the standard deviation of the logit of the propensity score for patients with clinical tumor size $\leq$5 cm or >5 cm who received NAT and adjuvant therapy, respectively. Patients were stratified according to age ($\leq$35 years, 35–65 years, or $\geq$65 years), clinical tumor size ($\leq$2.0 cm, 2.1–5.0 cm, or >5.0 cm), clinical lymph nodal status (negative or positive), estrogen receptor (ER) status, progesterone receptor (PR) status, and Ki-67 status (0–20% or $\geq$20%). Positive clinical lymph nodal status was identified by axillary lymph node aspiration cytology. For ER and PR status, samples with $\geq$1% of cells with strongly stained tumor nuclei were considered positive, and samples with <1% of cells with strongly stained tumor nuclei were considered negative [13].

Continuous variables are expressed as the mean values or median values, while categorical variables are expressed as frequencies. We conducted a survival analysis of patients who received and did not receive neoadjuvant therapy. Patients without adverse events or who did not die were censored at the last follow-up. Comparability of the NAT and adjuvant therapy groups at baseline was assessed using t tests and chi-square tests. Univariate and multivariate survival analyses were performed using the Cox regression model. Survival curves were estimated using the Kaplan–Meier method, and the log-rank test was used to analyze differences between groups. All the P values reported were two-sided and were calculated at a significance level of 0.05. All the statistical procedures were carried out using SPSS and R software.

3. Results

3.1. Patient characteristics

A total of 3222 consecutive patients were analyzed in our study, including 538 (16.7%) patients treated with NAT and 2684 (83.3%) patients treated with adjuvant therapy. The median age of these patients was 50 years (range 21–78 years, interquartile range, IQR 43–57 years). The patient characteristics are listed in Table 1. Patients received trastuzumab at FUSCC or their local hospital. The patients who received NAT and those who received adjuvant therapy differed in terms of clinical tumor stage (cT, $P < 0.0001$), pretreatment clinical nodal status (cN, $P < 0.0001$), estrogen receptor status (ER, $P < 0.0001$) and progesterone receptor (PR) status ($P = 0.008$). The patients who received NAT were characterized by higher clinical-stage distributions and lower HR-positive rates. The proportion of patients with clinical tumors larger than 5 cm in the NAT group was higher than that in the adjuvant treatment group (34.9% vs. 2.5%). For clinical nodal status, 73.8% of patients in the NAT group had lymph node metastasis at baseline, and only 42.8% of patients in the adjuvant therapy group had lymph node metastasis at baseline. In the NAT group, the overall pCR rate was 40.1% (216/538). Compared with the patients who did not achieve pCR, the patients who achieved pCR had a higher rate of HR-negative status ($P <$ 0.0001). More patients received endocrine therapy in the adjuvant

Table 1
Patient characteristics according to treatment group.

	Number of patients(%)		χ2	P-value
	NAT N = 538	Adjuvant N = 2684		
Age			3.87	0.15
≤35	54 (10.0%)	229 (8.5%)		
36–64	460 (85.5)	2284 (85.1%)		
≥65	24 (4.5%)	171 (6.4%)		
Tumor stage			812.65	<0.0001
T1	42 (7.8%)	1433 (53.4%)		
T2	308 (57.2%)	1183 (44.1%)		
T3/4	188 (34.9%)	68 (2.5%)		
Nodal status			173.02	<0.0001
N0	141 (26.2%)	1536 (57.2%)		
N+	397 (73.8%)	1148 (42.8%)		
ER positive	226 (42.0%)	1388(51.8%)	16.83	<0.0001
PR positive	176 (32.7%)	1042(38.8%)	7.06	0.008
Ki-67			4.07	0.13
<20%	48(8.9%)	215(8%)		
≥20%	490(91.1%)	2451(91.3%)		
Unknown	0	18(0.7%)		
Chemotherapy			552.29	<0.0001
Taxane	407(75.7%)	640(23.8%)		
Anthracycline	16(3.0%)	320(11.9%)		
Taxane and anthracycline	115(21.4%)	1607(59.9%)		
Others	/	117(4.4%)		
Radiotherapy			207.01	<0.0001
Yes	379 (70.4%)	1001 (37.3%)		
No	128 (23.8%)	1499 (55.8%)		
Unknown	31 (5.8%)	184 (6.9%)		
Trastuzumab			21.36	<0.0001
yes	424 (78.8%)	1870 (69.7%)		
No	79 (14.7%)	633 (23.6%)		
Unknown	35 (6.5%)	181 (6.7%)		
Endocrine treatment			17.44	<0.0001
Yes	191(35%)	1214(45.2)		
No	316(58.7%)	1328(49.5%)		
Unknown	31(5,8%)	142(5.3%)		

therapy group than in the NAT group due to the hormone receptor status ($P < 0.0001$).

Comparing the systemic treatment of patients who received neoadjuvant therapy with patients who received adjuvant therapy, the results showed that the regimen including anthracycline was mostly used for adjuvant chemotherapy (71.8%), and the regimen without anthracycline was mainly used for NAT (75.7%). The primary regimen for NAT was paclitaxel, carboplatin and trastuzumab (PCbH) therapy. More patients received trastuzumab in the NAT group (78.8%) than in the adjuvant therapy group (69.7%), $P < 0.0001$.

3.2. Survival analysis for all patients

The median follow-up time was 54.1 months (IQR 40.8–68.9 months). The 5-year OS rate was lower in patients treated with NAT than in those treated with adjuvant therapy (86.5% vs. 95.6%, $P < 0.0001$, Fig. 1 A). The multivariate Cox regression analysis suggested that patient age, cT, cN, and PR status were independent predictors of OS (Table 2). A lower tumor burden and positive PR status (HR = 1.75, 95% CI 1.24–2.48, $P < 0.0001$) were related to improved OS. The 5-year DFS rate was inferior in patients treated with NAT than in those treated with adjuvant therapy (80.7% vs. 91.4%, $P < 0.0001$, Fig. 1C). According to the multivariate Cox regression analysis, patient age, cT, and cN were independent prognostic factors for DFS (Table 2). Patients with younger age, smaller tumor size, and negative clinical nodal status had a more favorable DFS. There were no significant differences between the different chemotherapy regimen groups among the patients with HER2-positive breast cancer($P = 0.81$). For patients treated with taxanes without anthracyclines and those treated with taxanes combined with anthracyclines, the OS and DFS of patients treated with adjuvant therapy were higher than those of patients treated with NAT ($P < 0.0001$, Supplement Fig 1).

Forest plots of the hazard ratios (HRs) for OS and DFS were generated to describe the prognostic value of NAT in the HER2-positive breast cancer subgroups (Supplement Fig 2). The results showed that the HRs for OS and DFS observed with NAT versus adjuvant therapy were significant in most subgroups. Compared with patients treated with adjuvant therapy, patients treated with NAT presented higher HRs for OS and DFS (Supplement Fig 2.3).

Response to treatment was an independent predictor of prognosis among patients with HER2-positive breast cancer (Fig. 1 B, D). Achieving pCR after NAT was associated with significantly improved OS compared to not achieving pCR (5-year OS rate 98.5% vs. 78.6%, $P < 0.0001$). After adjusting for the patient's age, cN, and PR status, multivariate analysis showed that patients who achieved pCR had the best OS, resulting in an 83% reduction in the relative risk of death, and the relative risk of death for patients who did not achieve pCR after NAT was increased 2.57-fold. Similar results were observed for DFS (Table 2).

3.3. Survival analysis of patients with cT1/T2 stage disease

As noted in the preceding text, patients who received NAT were characterized by higher clinical-stage distributions and a lower HR-positive rate. To avoid the effect of baseline characteristics on survival outcome, we analyzed the patients with propensity score matching. Before PSM, there were 2616 patients who received adjuvant therapy and 350 patients who received NAT. The patient characteristics differed in terms of cT ($P < 0.0001$), cN ($P < 0.0001$) and ER status ($P = 0.04$). After PSM, there were 346 patients who received NAT and 952 patients who received adjuvant therapy. The baseline levels of patients treated with NAT and adjuvant therapy were not significantly different (Table 3).

For these patients, 70.8% of the patients who were treated with adjuvant therapy received taxane combined with anthracycline. A total of 74.9% of patients who were treated with NAT received taxane and carboplatin without anthracycline. There was no significant difference between patients treated with NAT and those treated with adjuvant therapy in terms of the proportion of patients who received trastuzumab-based targeted therapy. For the patients with cT1 or cT2 at baseline, the proportion of patients treated with NAT who received adjuvant radiotherapy was 68.8%, which is higher than the proportion of patients treated with adjuvant therapy who received adjuvant radiotherapy (50.5%, $P < 0.0001$).

Separate survival curves for HER2-positive patients treated with or without NAT are shown in Fig. 2A (OS) and Fig. 2C (DFS). There was no significant difference between the groups in terms of DFS ($P = 0.08$) or OS ($P = 0.11$). Data about the pathological response to NAT was available for 135 patients out of 346 patients, and the pCR rate was equal to 39%. Achieving pCR after NAT was significantly related to improved OS (HR 0.13, 95% CI 0.02–0.92; $P = 0.04$) and DFS (HR 0.37, 95% CI 0.16–0.85, $P = 0.02$) compared with receiving adjuvant therapy. Patients who did not achieve pCR after NAT had the worst survival outcomes, with a 5-year OS of 83% and a 5-year DFS of 76.7% (Fig. 2B.; Table 4). Among patients who were treated with trastuzumab, there were no significant differences between the NAT group and the adjuvant therapy group in terms of patients who were treated with taxanes without anthracycline or patients who were treated with taxanes combined with anthracyclines (Supplement Fig 4). Multivariate analysis

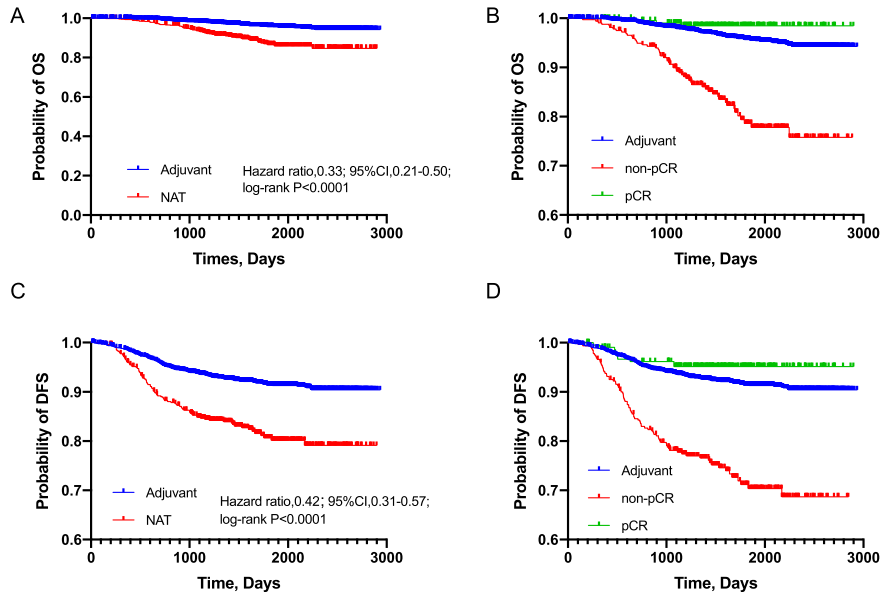

Fig. 1. Kaplan-Meier survival curves for OS (A) and DFS (C), in patients treated with adjuvant therapy (blue) and those treated with NAT(red). Kaplan-Meier survival curves for OS (B) and DFS (D), in patients treated with adjuvant therapy (blue), populations achieving pathologic complete response (pCR) at surgery (green) and those with residual disease at time of surgery (red). NAT= Neoadjuvant therapy.

Table 2
Cox regression analysis of OS, and DFS in all patients.

Variable	OS						DFS					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Age												
≤35	1	Ref		1	Ref		1	Ref		1	Ref	
36–64	1.03	0.58–1.82	0.93	1.00	0.56–1.78	1.00	0.92	0.62–1.36	0.67	0.93	0.63–1.37	0.70
≥65	2.62	1.31–5.23	0.01	2.52	1.25–5.08	0.01	1.76	1.05–2.93	0.03	1.78	1.07–2.97	0.03
Tumor stage												
T1	1	Ref		1	Ref		1	Ref		1	Ref	
T2	2.45	1.66–3.61	<0.0001	1.71	1.14–2.56	0.01	2.10	1.61–2.73	<0.0001	1.56	1.18–2.06	0.002
T3/T4	6.43	4.04–10.22	<0.0001	3.26	1.87–5.67	<0.0001	4.42	3.14–6.20	<0.0001	2.70	1.79–4.05	<0.0001
Nodal status												
N0	1	Ref		1	Ref		1	Ref		1	Ref	
N+	4.20	2.88–6.13	<0.0001	3.15	2.12–4.68	<0.0001	3.22	2.50–4.15	<0.0001	2.56	1.97–3.34	<0.0001
ER Status												
+	1	Ref		–	–	–	1	Ref		–	–	–
-	1.18	0.86–1.60	0.31	–	–	–	1.08	0.87–1.36	0.48	–	–	–
PR positive												
+	1	Ref		1	Ref		1	Ref		–	–	–
-	1.58	1.124–2.23	0.01	1.75	1.24–2.48	0.001	1.20	0.95–1.52	0.12	–	–	–
Ki-67 ≥ 20%												
≥20%	1	Ref		–	–	–	1	Ref		–	–	–
<20%	1.05	0.59–1.85	0.87	–	–	–	0.78	0.49–1.24	0.29	–	–	–
Timing of chemotherapy												
Adjuvant therapy	1	Ref		–	–	–	1	Ref		–	–	–
NAT	3.08	2.23–4.25	<0.0001	–	–	–	2.34	1.84–2.98	<0.0001	–	–	–
Response to treatment												
Adjuvant therapy	1	Ref		1	Ref		1	Ref		1	Ref	
pCR	0.38	0.12–1.20	0.10	0.17	0.05–0.54	0.003	0.58	0.31–1.10	0.10	0.31	0.16–0.60	0.001
non-pCR	5.01	3.6–6.95	<0.0001	2.57	1.73–3.81	<0.0001	3.64	2.83–4.69	<0.0001	1.99	1.47–2.69	<0.0001

Abbreviations: HR: Hazard ratio; NAT: neoadjuvant chemotherapy; AC: adjuvant chemotherapy; pCR: pCR, pathologic complete response.

showed that cN and response to treatment were independent predictors of OS and DFS. Patients who were younger and had negative clinical nodal status showed improved OS and DFS.

Stratified survival analysis according to the patient's clinical nodal status at baseline showed that achieving pCR after NAT was not a significant independent predictor of OS ($P = 0.96$) or DFS ($P = 0.42$) in patients with no lymph node metastasis (Table 5). However, patients who did not achieve pCR after NAT had the worst prognosis, with a 2.21-fold relative risk of death and a 1.87-fold relative risk of disease progression. Among patients with positive nodal status, achieving pCR after NAT was associated with improved survival outcomes compared to receiving adjuvant therapy, which reduced the relative risk of death by 88%. Patients who did not achieve pCR had the worst OS and DFS (Fig. 3).

Table 3
Clinical characteristic of patients with cT1 and cT2 before or after being matched.

	Before matched			Matched		
	Number of patients(%)		P-value	Number of patients(%)		P-value
	NAT N = 350	Adjuvant N = 2616		NAT N = 346	Adjuvant N = 952	
Age			0.15			0.48
≤35	35(10.0%)	223(8.5%)		35 (10.1%)	76 (8.0%)	
36-64	301(86.0%)	2225(85.1%)		297 (85.8%)	838 (88.0%)	
≥65	14(4.0%)	168(6.4%)		14 (4.0%)	38 (4.0%)	
Tumor stage			<0.0001			0.60
T1	42(12%)	1433(54.8%)		42(12.1%)	126 (13.2%)	
T2	308(88%)	1183(45.2%)		826(86.8%)	304 (87.9%)	
Nodal status			<0.0001			0.62
N0	94(26.9%)	1512(57.8%)		94 (27.2%)	272 (28.6%)	
N+	256(73.1%)	1104(42.2%)		252 (72.8%)	680 (71.4%)	
ER positive	161(46.0%)	1359(51.9%)	0.04	161(46.5%)	450(47.3%)	0.81
PR positive	123(35.1%)	1024(39.1%)	0.15	119(34.4%)	339(35.6%)	0.69
Ki-67			0.14			0.08
<20%	35(10.0%)	210(8.0%)		35(10.1%)	66(6.9%)	
≥20%	315(90.0%)	2388(91.3%)		311(89.9%)	882(92.6%)	
Unknown	0	18(0.7%)			4(0.4%)	
Chemotherapy			<0.0001			<0.0001
Taxane	262(74.9%)	626(23.9%)		259(74.9%)	135(14.2%)	
Anthracycline	14(4.0%)	319(12.2%)		14(4.0%)	109(11.4%)	
Taxane and anthracycline	74(21.1%)	1558(59.6%)		73(21.1%)	674(70.8%)	
Others	0	113(4.3%)		0	34(3.6%)	
Radiotherapy			<0.0001			<0.0001
Yes	242(69.1%)	959(36.7%)		238(68.8%)	481(50.5%)	
No	82(23.4%)	1482(56.7%)		82(23.7%)	384(40.3%)	
Unknown	26(7.4%)	175(6.7%)		26(7.5%)	87(9.1%)	
Trastuzumab			0.005			0.13
yes	266(76.0%)	1819(69.5%)		262(75.7%)	680(71.4%)	
No	56(16.0%)	620(23.7%)		56(16.2%)	202(21.2%)	
Unknown	28(8.0%)	177(6.8%)		28(8.1%)	70(7.4%)	
Endocrine treatment			0.005			0.301
Yes	129(36.9%)	1189(45.5%)		128(37%)	386(40.5%)	
No	194(55.4%)	1289(49.3%)		191(55.2%)	510(53.6%)	
Unknown	27(7.7%)	138(5.3%)		27(7.8%)	56(5.9%)	

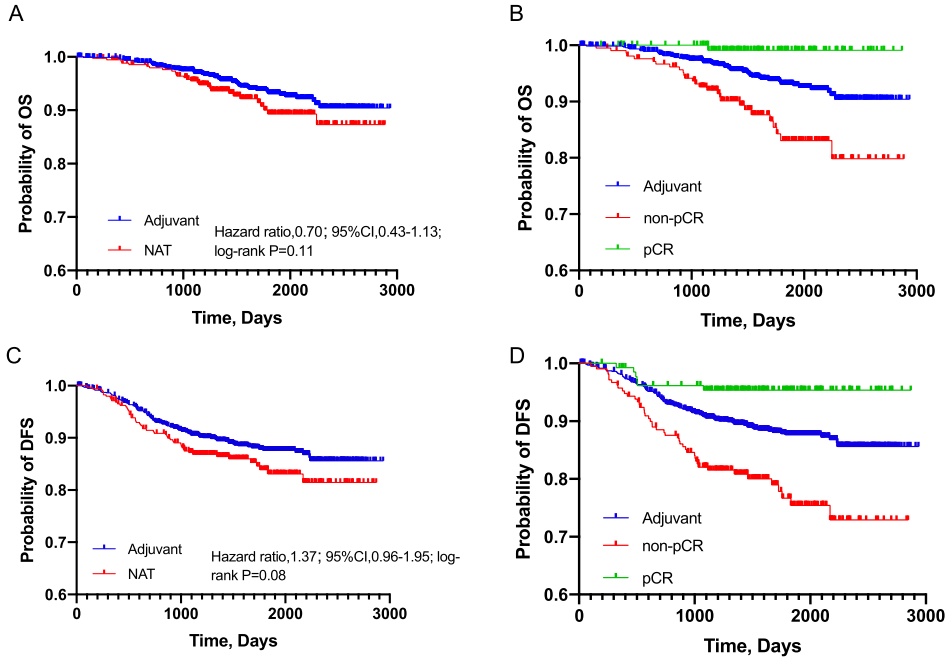

Fig. 2. Among propensity score matched patients with clinical tumor size smaller than 5 cm at baseline. Kaplan-Meier survival curves for OS (A) and DFS (C) in patients treated with adjuvant therapy (blue) and those treated with NAT(red). Kaplan-Meier survival curves for OS (B) and DFS (D), in patients treated with adjuvant therapy(blue), populations achieving pathologic complete response (pCR) at surgery (green) and those with residual disease at time of surgery (red). NAT= Neoadjuvant therapy.

3.4. Survival analysis of patients with cT3/4 stage disease

There were 256 patients with clinical tumor sizes ≥5 cm, 26.6% of whom received adjuvant therapy, and 188 patients received chemotherapy before surgery. There were no statistically significant differences in the baseline characteristics of both groups. After PSM, 145

Table 4
Cox regression analysis of OS, and DFS in patients with cT1-cT2.

Variable	OS						DFS					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Age												
≤35	1	Ref		1	Ref		1	Ref		1	Ref	
36–64	1.37	0.55–3.40	0.49	1.34	0.54–3.35	0.52	0.76	0.45–1.28	0.30	0.75	0.45–1.26	0.28
≥65	5.80	2.02–16.72	0.001	4.05	1.39–11.84	0.01	2.14	1.05–4.39	0.04	1.87	0.91–3.84	0.09
Tumor stage												
T1	1	Ref		–	–	–	1	Ref		–	–	–
T2	0.85	0.46–1.57	0.61	–	–	–	1.08	0.67–1.74	0.75	–	–	–
Nodal status												
N0	1	Ref		1	Ref		1	Ref		1	Ref	
N+	3.96	1.91–8.20	<0.0001	3.61	1.73–7.50	0.001	2.32	1.50–3.58	<0.0001	2.27	1.47–3.50	<0.0001
ER Status												
+	1	Ref		–	–	–	1	Ref		–	–	–
-	1.16	0.76–1.78	0.50	–	–	–	0.98	0.72–1.34	0.92	–	–	–
PR positive												
+	1	Ref		1	Ref		1	Ref		–	–	–
-	1.80	1.1–2.95	0.02	1.82	1.10–3.00	0.02	1.18	0.85–1.65	0.32	–	–	–
Ki-67												
≥20%	1	Ref		–	–	–	1	Ref		–	–	–
<20%	1.03	0.48–2.24	0.94	–	–	–	0.90	0.49–1.67	0.75	–	–	–
Response to treatment												
Adjuvant therapy	1	Ref		1	Ref		1	Ref		1	Ref	
pCR	0.13	0.02–0.92	0.04	0.12	0.02–0.84	0.03	0.39	0.17–0.88	0.02	0.37	0.16–0.85	0.02
non-pCR	2.33	1.48–3.69	<0.0001	2.44	1.54–3.87	<0.0001	2.00	1.41–2.83	<0.0001	1.96	1.38–2.77	<0.0001

Table 5
Stratified survival analysis according to the patient's clinical nodal status of patients being matched in cT1-cT2.

	Variable	OS						DFS					
		Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
		HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
cT1-cT2 & cN0	Timing of chemotherapy												
	Adjuvant therapy	1	Ref		–	–	–	1	Ref		–	–	–
	NAT	3.44	0.85–13.95	0.08	–	–	–	2.24	0.99–5.06	0.05	–	–	–
	Response to treatment												
	Adjuvant therapy	1	Ref		1	Ref		1	Ref		1	Ref	
	pCR	1	–	0.99	1	–	0.96	1.78	0.51–6.20	0.37	1.68	0.48–5.90	0.42
	non-pCR	5.4	1.34–21.89	0.02	5.65	1.38–23.09	0.02	2.5	1.01–6.21	0.048	2.60	1.05–6.50	0.04
cT1-cT2 & cN+	Timing of chemotherapy												
	Adjuvant therapy	1	Ref		–	–	–	1	Ref		–	–	–
	NAT	1.28	0.79–2.07	0.32	–	–	–	1.20	0.83–1.73	0.34	–	–	–
	Response to treatment												
	Adjuvant therapy	1	Ref		1	Ref		1	Ref		1	Ref	
	pCR	0.13	0.02–0.92	0.04	0.12	0.02–0.88	0.04	0.21	0.07–0.66	0.01	0.21	0.07–0.66	0.01
	non-pCR	2.10	1.29–3.43	0.003	2.21	1.35–3.62	0.002	1.91	1.31–2.79	0.001	1.87	1.28–2.73	0.001

patients who received NAT were matched with 62 patients who received adjuvant therapy. There were no significant differences between the groups in terms of clinical nodal status, age, ER, PR, and Ki-67 status (Table 6). The pCR rate of these patients after NAT was 42.1% in patients with cT3/4 after PSM. In addition, 74.5% of NAT patients received adjuvant radiotherapy, and the proportion of patients treated with adjuvant therapy was 64.5% ($P = 0.016$).

After PSM, the DFS and OS of patients treated with NAT were similar to those of patients treated with adjuvant therapy (Fig. 4). The 5-year OS was 83.2% in patients treated with NAT and 91.2% in patients treated with adjuvant therapy ($P = 0.25$). Patients who did not achieve pCR had the worst prognosis, with a 5-year OS of 73.8%. There were no significant differences between the OS of the patients who achieved pCR and those treated with adjuvant therapy ($P = 0.26$). After adjusting for the patient's age, cN, ER, PR, and Ki-67 status, multivariate analysis showed that the DFS of patients who achieved pCR was better than that of patients treated with adjuvant therapy (HR 0.29, 95% CI 0.09–0.92, $P = 0.04$) (Table 7). There were no significant differences among patients with cT3/4 who were treated with different chemotherapy regimens in terms of OS and DFS. For patients treated with taxanes without anthracycline and patients treated with taxanes combined with anthracyclines, there were no significant differences in OS and DFS between the NAT group and the adjuvant therapy group (Supplement Fig 5).

4. Discussion

The study retrospectively evaluated the survival outcomes of Chinese patients with HER2-positive breast cancer who were treated with NAT or adjuvant therapy. Based on the large sample size and long follow-up time, the results had high credibility. The reproducibility of trial data in real-world populations is an increasing concern as we investigate new therapies for breast cancer. According to the real-world cohort analysis, we proved that there was no difference in survival outcomes among breast cancer patients who were treated with NAT and those who were treated with adjuvant therapy, and patients who achieved pCR after receiving NAT had superior outcomes compared with patients who were treated with adjuvant therapy. We identified the population of patients

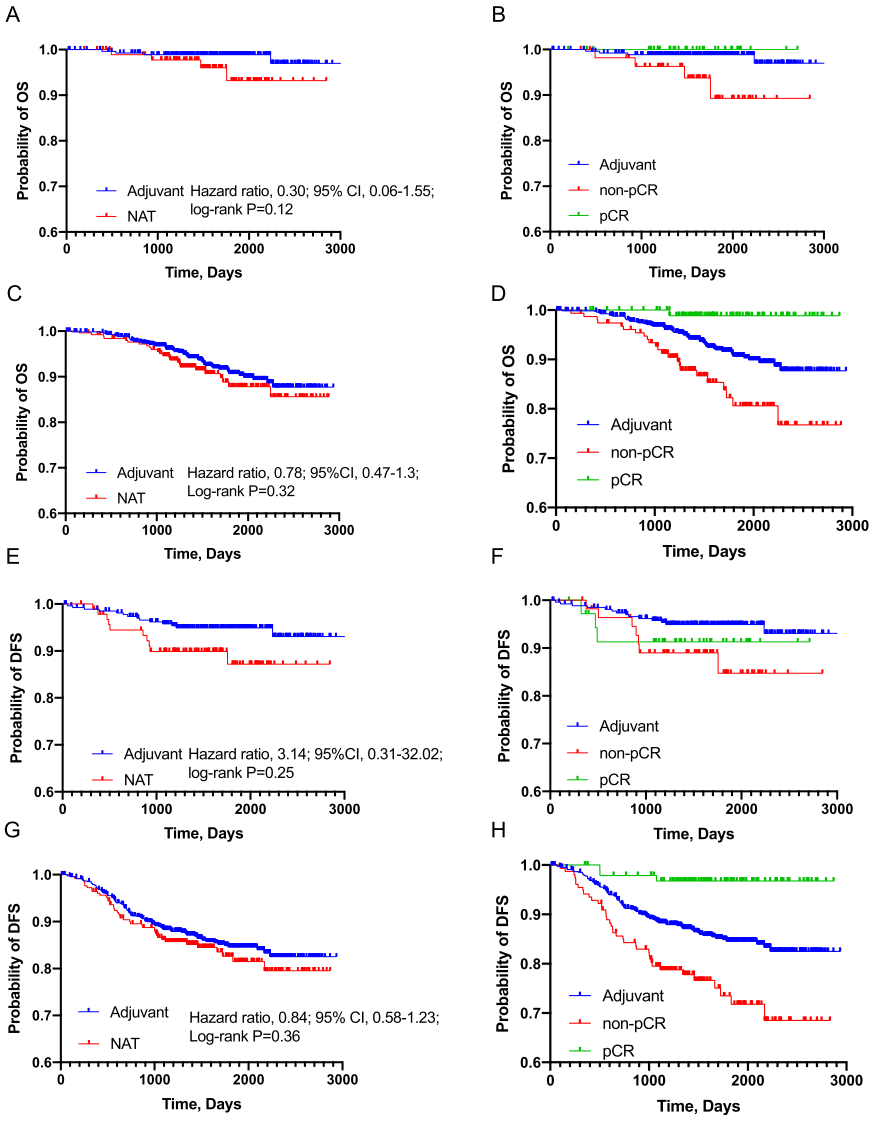

Fig. 3. Kaplan-Meier survival curves for OS and DFS among patients with cT1 and cT2 being matched. A-B.E-F. For patient with negative nodal status. C-D.G-H For patients with positive nodal status.

with HER2-positive breast cancer who were most likely to benefit from neoadjuvant treatment. Patients with cT3/4 or those with positive clinical nodal status were more likely to benefit from NAT. The authors of the Adjuvant Paclitaxel and Trastuzumab (APT) Trial suggested that administering adjuvant paclitaxel and trastuzumab to patients with stage I Her2-positive breast cancer represented a de-escalating therapy that preserved quality of life and achieved excellent outcomes for these patients [14,15]. Adjuvant Trastuzumab Emtansine Versus Paclitaxel in Combination with Trastuzumab for Stage I HER2-Positive Breast Cancer (ATEMPT) showed that among patients with stage I HER2-positive breast cancer, one year of adjuvant T-DM1 was associated with excellent 3-year invasive disease-free survival (iDFS) compared with paclitaxel plus trastuzumab [16,17].

The study demonstrates that HER2-positive breast cancer patients had worse survival after treatment with NAT than after treatment with adjuvant therapy. However, these *P* values failed to be significant after adjusting for the baseline characteristics of the patients. These findings were basically consistent with NSABP B-18, EORTC 10902, and the IBBGS, three large randomized trials that evaluated NAT vs. adjuvant therapy [9,18,19]. The results of these trials showed that there was no difference in survival outcomes among breast cancer patients treated with NAT and those treated with adjuvant therapy. Our study proved this finding among HER2-positive breast cancer patients in China.

Knowledge of the pathological response to NAT also presents an opportunity for adjuvant therapy and helps to identify high-risk patients for enrollment in novel clinical trials. The study showed that patients who have residual invasive carcinoma after the treatment of HER2-positive breast cancer with NAT have poor prognoses. These patients may benefit from sequential intensive adjuvant chemotherapy. Katherine clinical trials suggested that among patients with HER2-positive early breast cancer who had residual invasive disease after the completion of neoadjuvant therapy, the risk of invasive breast cancer recurrence or death was 50% lower after treatment with adjuvant T-DM1 than after treatment with trastuzumab alone [20]. For patients with cT1-cT2, or cN0not achieving pCR after NAT was an independent predictor of poor prognosis, and sequential intensive adjuvant chemotherapy was necessary for these patients. This may be the potential value of NAT for patients with a low tumor burden.

There are also limitations in our retrospective study of this real-world cohort. We only enrolled patients from a single center, and only 68 patients with a tumor size >5 cm were included, so the population may be slightly underrepresented. Considering that there were fewer

Table 6
Clinical characteristic of patients with cT3/4 before or after being matched.

	Unpaired			Paired		
	Number of patients(%)		P-value	Number of patients(%)		P-value
	NAT N = 188	Adjuvant N = 68		NAT N = 145	Adjuvant N = 62	
Age			0.91			0.81
≤35	19(10.1%)	6(8.8%)		8 (5.5%)	3 (4.8%)	
36-64	159(84.6%)	59(86.8%)		136 (93.8%)	58 (93.5%)	
≥65	10(5.3%)	3(4.4%)		1 (0.7%)	1 (1.6%)	
Nodal status			0.12			0.32
N0	47(25%)	24(35.3%)		39 (26.9%)	21 (33.9%)	
N+	141(75%)	44(64.7%)		106 (73.1%)	41 (66.1%)	
ER positive	65(34.6%)	29(42.6%)	0.24	54(37.2%)	25 (40.3%)	0.76
PR positive	53(28.2%)	18(26.5%)	0.88	40(27.6%)	18(29.0%)	0.87
Ki-67			1.00			0.74
<20%	13(6.9%)	5(7.4%)		7(4.8%)	4(6.5%)	
≥20%	175(92.6%)	63(92.6%)		138(95.2%)	58(93.5%)	
Unknown	0	18(0.7%)			4(0.4%)	
Chemotherapy			<0.0001			<0.0001
Taxane	145(77.1%)	14(20.6%)		110(75.9%)	12(19.4%)	
Anthracycline	2(1.1%)	1(1.5%)		1(0.7%)	1(1.6%)	
Taxane and anthracycline	41(21.8%)	49(72.1%)		34(23.4%)	46(74.2%)	
Others	0	4(5.9%)		0	3(4.8%)	
Radiotherapy			0.004			0.02
Yes	137(72.9%)	42(61.8%)		108(74.5%)	40(64.5%)	
No	46(24.5%)	17(25%)		33(22.8%)	14(22.6%)	
Unknown	5(2.7%)	9(13.2%)		4(2.8%)	8(12.9%)	
Targeted therapy			0.26			0.19
yes	158(84%)	51(75%)		123 (84.8%)	46(74.2%)	
No	23(12.2%)	13(19.1%)		17(11.7%)	13(21%)	
Unknown	7(3.7%)	4(5.9%)		5(3.4%)	3(4.8%)	
Endocrine treatment			0.23			0.39
Yes	62(33%)	25(36.8%)		48(33.1%)	22(35.5%)	
No	122(64.9%)	39(57.4%)		93(64.1%)	36(58.1%)	
Unknown	4(2.1%)	4(5.9%)		4(2.8%)	4(2.8%)	

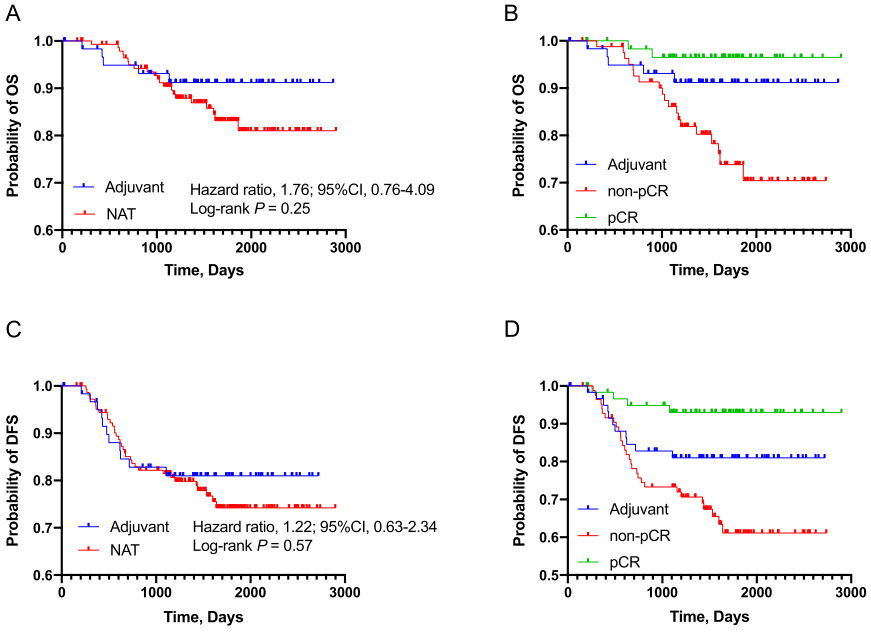

Fig. 4. Kaplan-Meier survival curves for OS(A.B) and DFS(C.D) among patients with cT3/4 matched.

patients with cN2 and cN3 in this study, this study only evaluated patients with clinical nodal negative or positive status, except those who were classified by stage of clinical nodal status. Over 20% of these patients did not receive an anti-HER2 agent as part of NAT. Based on real-world research, some patients failed to receive targeted therapy during 2012–2016 due to economic or other reasons. However, after PSM, there were no significant differences between the NAT group and the adjuvant therapy group in terms of treatment with targeted therapy. Therefore, this limitation did not affect the accuracy of the conclusion. Due to the limitations of retrospective studies, the types of chemotherapy administered to patients who received NAT and those who received adjuvant therapy are different. However, under actual conditions, the

Table 7
Cox regression analysis of OS, and DFS in patients with cT3/4 after being matched.

Variable	OS						DFS					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Age												
≤35	1	Ref		–	–	–	1	Ref		–	–	–
36–64	1.62	0.22–11.97	0.636	–	–	–	2.79	0.38–20.23	0.31	–	–	–
≥65	0	0	0.985	–	–	–	0	0	0.98	–	–	–
Nodal status												
N0	1	Ref		1	Ref		1	Ref		1	Ref	
N+	5.02	1.19–21.22	0.028	4.19	0.98–17.89	0.05	4.36	1.56–12.20	0.005	3.92	1.39–11.01	0.01
ER Status												
+	1	Ref		–	–	–	1	Ref		–	–	–
-	1.52	0.70–3.28	0.29	–	–	–	1.01	0.55–1.84	0.99	–	–	–
PR positive												
+	1	Ref		–	–	–	1	Ref		–	–	–
-	1.03	0.45–2.38	0.94	–	–	–	0.80	0.51–1.58	0.52	–	–	–
Ki-67												
≥20%	1	Ref		–	–	–	1	Ref		–	–	–
<20%	0.58	0.14–2.46	0.46	–	–	–	1.19	0.29–4.93	0.81	–	–	–
Timing of chemotherapy												
Adjuvant therapy	1	Ref		–	–	–	1	Ref		–	–	–
NAT	1.76	0.66–4.67	0.26	–	–	–	1.22	0.62–2.42	0.57	–	–	–
Response to treatment												
Adjuvant therapy	1	Ref		1	Ref		1	Ref		1	Ref	
pCR	0.39	0.08–1.99	0.26	0.37	0.07–1.91	0.23	0.33	0.11–1.04	0.06	0.29	0.09–0.92	0.04
non-pCR	2.81	1.05–7.52	0.04	2.66	0.98–7.17	0.05	1.94	0.98–3.88	0.06	1.76	0.88–3.56	0.11

chemotherapy regimens selected for these patients were determined by multidisciplinary experts and complied with international department standards. For patients treated with neoadjuvant therapy, cytotoxic and targeted drugs are usually administered at the same time at the beginning of treatment to achieve a better tumor-killing effect. For patients treated with adjuvant therapy, considering the substantial cardiac side effects of combination therapy, targeted therapy is often used after anthracycline therapy. This may be one of the possible factors that contributes to the better prognosis of patients who receive neoadjuvant therapy than patients who receive adjuvant therapy. To further confirm these results, multicenter prospective studies are needed.

5. Conclusion

Systemic treatment is essential for patients with HER2-positive breast cancer. In this single-center real-world retrospective study, it was found that neoadjuvant therapy was primarily administered to patients with higher clinical stages. The regimen including anthracycline was mostly used for adjuvant chemotherapy, and the regimen without anthracycline was mainly used for patients treated with NAT. According to a retrospective real-world study, we confirmed the equivalent efficacy of adjuvant therapy and NAT in HER2-positive BC patients.

Ethics approval

This study was approved by the Ethics Committee Review Board of the Fudan University Shanghai Cancer Center (approval number: 1905202-7).

Consent for publication

Not applicable.

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Author contributions

Shuyue Zheng: Conceptualization, investigation, writing–original draft and writing–review, and editing. Lun Li: Help analysis data and draft–review. Ming Chen, Benlong Yang, Jiajian Chen, Guangyu Liu: Help to collect the data. Jiong Wu: Supervise the planning and design of the study; data collection; statistical analysis and data interpretation; have full access to all the data in the study and be responsible for the integrity of the data and the accuracy of the data analysis; and manuscript review, revision, and reporting.

Declaration of competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2022.03.015.

Abbreviations

NAT	Neoadjuvant Therapy
pCR	Pathological Complete Response
OS	Overall Survival
DFS	Disease-Free Survival
ER	Estrogen Receptor
PR	Progesterone Receptor
HER2	Human Epidermal Growth Factor Receptor
IQR	Interquartile Range

PSM	Propensity Score Matching
FISH	Fluorescence in Situ Hybridization
FUSCC	Fudan University Shanghai Cancer Center
EFS	Event-Free Survival
CSCO	Chinese Society of Clinical Oncology
AJCC	American Joint Committee on Cancer
HR	Hazard Ratio

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