

Prognostic Factors and Survival Outcomes of Patients With Early HER2+ Breast Cancer Treated With Trastuzumab in a Brazilian Public Reference Center: A Real-World Study

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Abstract

The survival outcomes of early HER2+ breast cancer patients treated with (neo)adjuvant targeted therapy were evaluated using real-world data from a reference cancer center in Brazil. Patients treated with neoadjuvant trastuzumab presented poor survival outcomes, with different risk factors associated with worse survival. This indicates the importance of early diagnosis and optimized treatment.

Purpose: Trastuzumab was introduced into the Brazilian public health care service for early breast cancer (BC) in 2012. This study describes the survival outcomes and prognostic factors related to early HER2+ BC treatment in a Brazilian reference cancer center. **Patients and Methods:** This was a retrospective, single-center, observational study of early HER2+ BC patients treated with trastuzumab in the (neo)adjuvant setting between 2012 and 2018 at Hospital Pérola Byington. Demographic, clinical, disease-free survival (DFS) and overall survival (OS) data were evaluated. Multivariate analysis was performed to assess independent prognostic factors. **Results:** One hundred seventy-six and 353 patients treated in the neoadjuvant and adjuvant setting were included, respectively. The 3- and 5-year OS rates were 79% and 56% for the neoadjuvant group and 97% and 92% for the adjuvant group, respectively. Node positivity at diagnosis predicted poor OS for both groups. In the neoadjuvant group, stage III disease at diagnosis, delayed surgery, and lack of pathological complete response (pCR) predicted poor prognosis. The 3- and 5-year DFS rates were 67% and 46% in the neoadjuvant group and 91% and 86% in the adjuvant group, respectively. Histological grade 2, stage III disease at diagnosis, and lack of pCR predicted poor DFS for the neoadjuvant group. For the adjuvant group, node positivity at diagnosis predicted poor DFS. **Conclusion:** Our results reveal multiple clinical parameters affecting survival outcomes according to the treatment setting. Patients treated with neoadjuvant therapy have a poor prognosis since they present with more advanced disease, indicating the importance of early diagnosis and optimized treatment.

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Introduction

Breast cancer (BC) is one of the most commonly diagnosed types of cancer worldwide, representing 11.7% of new cancer cases, and is the leading cause of cancer death among women.¹ In Brazil, BC

is the most frequent type of cancer in women, with an estimated incidence of 61 new cases per 100,000 inhabitants.² The overexpression of human epithelial growth factor receptor 2 (HER2+) occurs in approximately 15% to 20% of BC cases, and it is considered an aggressive subtype with a high cancer-specific mortality.^{3,4} In the AMAZONA III study, the largest Brazilian BC cohort, almost a quarter of the patients were diagnosed with HER2+ BC.⁵

In recent decades, the development of new treatments and strategies for disease management has improved the prognosis of HER2+ BC patients.^{4,6} The introduction of anti-HER2 therapies in (neo)adjuvant settings have improved patient clinical outcomes in early stages and is helpful in reducing relapses and preventing the onset of metastatic disease. Trastuzumab was the first targeted therapy introduced and it became the standard of care

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in the management of patients with HER2+ BC.⁷⁻⁹ However, despite improved disease-free survival (DFS) and overall survival (OS) in patients with early disease, the combination of trastuzumab and chemotherapy is still associated with a high recurrence rate.⁷ Thus, several other anti-HER2 agents, including lapatinib and pertuzumab, have been developed and are associated to HER2-directed therapies to improve survival outcomes.¹⁰

Given the biologic heterogeneity within HER2-positive tumors, different responses to the established treatments are observed,⁶ suggesting an influence of factors other than HER2 expression on survival outcomes.¹¹ Axillary lymph node (ALN) involvement is known to be a major risk factor for tumor recurrence, as are histopathological tumor characteristics.¹² A study from Coccione and colleagues showed that the 10-year OS rates for early hormone receptor (HR)-negative/HER2+ BC patients were 83% and 57% for N0 and N+ cases, respectively.¹¹ Moreover, disease stage may also influence the clinical response to treatment in patients with early HER2+ BC as well as pathological complete response (pCR).^{6,13,14} Two meta-analyses, one with almost 12,000 BC patients¹⁵ and another more recent with more than 27,000 patients,¹⁶ showed that among HER2+ subtypes, pCR was associated with improved event-free survival (EFS) and OS, further suggesting pCR as a strong surrogate endpoint in HER2+ BC. In addition, there are different factors related to diagnosis and treatment access that also influence survival outcomes: early diagnosis, time until treatment initiation, and time to systemic treatment initiation after surgery.¹⁷⁻¹⁹

In Brazil, 75% of the population depends on public health care services, which are highly associated with a lengthy patient journey.^{5,20,21} In this scenario, trastuzumab was introduced for locally advanced and early BC in the Brazilian public health system on July 25, 2012.²¹ However, it was effectively made available to the public hospitals only in January 2013 to treat early HER2 positive patients with confirmation by molecular testing (FISH or CISH). Since 2018, a positive HER2 confirmation by immunohistochemistry is now sufficient to qualify patients for treatment with trastuzumab, thus increasing the number of women who benefit from this targeted therapy. The dual HER2-blockade, however, became available in the public setting only in 2021, with the approval of pertuzumab for the treatment of metastatic HER2+ patients.

The impact of trastuzumab on survival outcomes and prognostic factors for early HER2+ BC patients in clinical practice is not well established in the Brazilian population. Therefore, the present study aimed to evaluate real-world data on DFS and OS and the respective influence of prognostic factors in early HER2+ BC patients treated with trastuzumab at a nationally recognized women's health reference public center in Brazil.

Patient and Methods

This hospital-based retrospective database study assessed women ≥ 18 years old who were diagnosed with early HER2+ BC between July 25th, 2012, and January 1st, 2018, and treated with anti-HER2 target therapy in either the neoadjuvant or adjuvant setting at Hospital Pérola Byington. BC was considered "early" when the patient was diagnosed at stages I to III based on the AJCC-TNM

pathological cancer classification.²² The HER2 status was considered positive when the immunohistochemistry score was 2+ or 3+ in 10% or more of the specimens with an in situ hybridization analysis (CISH/FISH) confirming the HER2 amplification (ratio ≥ 2.0). In addition, BC was classified as positive for HRs if the immunohistochemistry showed $\geq 1\%$ of tumor cells with nuclear staining for estrogen and/or progesterone receptors. Assessments were made by the local pathology laboratory following ASCO/CAP recommendations.²³ During the period of analysis, trastuzumab was the only targeted therapy available in the public setting for HER2+ patients (with either early or metastatic disease). Data were obtained from the hospital BC database containing anonymized information on diagnosis, treatment pattern, and clinical outcomes. The study was approved by the institutional ethics committee of the Women's Health Reference Center (Hospital Pérola Byington) under CAAE number 72387317.6.0000.0069.

Early HER2+ BC patients treated with trastuzumab included in the data analysis were separated into 2 cohorts: those who started targeted therapy treatment in the neoadjuvant setting (NAT group) and those who underwent upfront surgery followed by adjuvant trastuzumab treatment (AT group). The demographic and clinical characteristics and treatment patterns were assessed for both cohorts. The primary outcomes were the OS and DFS rates. OS was defined as the time from diagnosis until death by any cause. DFS was defined as death from any cause or the return of the BC after complete response to initial treatment, which included local, regional, or distant recurrence. In addition, the following factors associated with the survival outcomes were evaluated for both cohorts: age, stage, histological grade, lymph node status, Ki67 expression, HR status, time until treatment initiation (any pharmacological or surgical treatment for BC), and type of surgery (breast-conserving surgery or mastectomy). In the NAT group, the pCR status was also evaluated, with pCR defined as the absence of residual invasive cancer cells in the breast and axillary lymph nodes (ypT0/Tis ypN0); for the AT group, the time from surgery until AT initiation was also evaluated.

The following treatment protocol for early HER2+ BC patients was in place at Hospital Pérola Byington: patients with tumors over 2.0 cm or with ALN involvement were treated primarily with AC (doxorubicin plus cyclophosphamide) followed by 4 cycles of docetaxel plus trastuzumab (alternatively, for patients with cardiac risk, 6 cycles of a docetaxel, carboplatin and trastuzumab scheme was indicated) in either the neoadjuvant or adjuvant setting. For patients with tumors over 0.5 cm and up to 2.0 cm with no ALN involvement, adjuvant paclitaxel plus trastuzumab was the preferred regimen.

Statistical Analysis

The analysis was performed using SAS software (SAS system for Windows; release 9.4; SAS Inst., Cary, NC, 2013). Demographic, clinical characteristic, and treatment pattern data are presented as frequencies. The chi-square and *t* test were used to assess group imbalance (they were not used to perform any group comparisons). Treatment duration and time until treatment are presented as the mean and standard deviation and median. Treatment duration was considered as the time from the first treatment (radiother-

Prognostic Factors and Survival Outcomes of Patients

apy, chemotherapy, hormone therapy, or target therapy) until breast surgery for patients in the NAT group or as the time from the first treatment until the last therapy for patients in the AT group. Time to treatment was defined as the time from therapy end to the start date of the next therapy. Kaplan-Meier analyses were performed to obtain survival estimates, and comparisons of factors between groups were performed with the Wilcoxon test. Univariate and multivariate Cox proportional hazard models were generated to assess the prognostic factors associated with OS and DFS. For the multivariate analysis, all factors associated with the survival outcomes were considered. The tests were considered statistically significant if the *P*-value was $\leq .05$.

Results

A total of 972 patients with HER2+ BC were initially identified in the database. Patients were excluded if they were not treated with trastuzumab (*n* = 280), received trastuzumab only as palliative care (*n* = 25), participated in a clinical trial (*n* = 24), presented with stage IV disease at diagnosis (*n* = 13) and/or had unreliable or missing data (*n* = 102) (the same patient may present more than 1 exclusion criterion). A total of 529 early HER2+ BC patients were included: 176 in NAT group, and 353 in AT group. The sample selection is described in [Figure 1](#).

Demographic and Clinical Characteristics

Demographic and clinical characteristics at diagnosis are shown in [Table 1](#). Patients in NAT group had a median age of 48.5 years, almost half of the patients were HR-, and most of the patients had stage III disease and lymph node positivity at diagnosis. Patients in AT group had a median age of 54 years, were mostly HR+ and had stage II disease and lymph node negativity at diagnosis. Independent of the treatment setting, early HER2+ BC patients were primarily diagnosed with grade 2 invasive carcinoma of no special type (NST), and most patients had a Ki67 level of 15% or higher. Additionally, 31.82% of patients from NAT group achieved pCR.

Treatment Characteristics

As expected, most patients received trastuzumab combined with chemotherapy, independent of the treatment setting ([Appendix Table 1](#)). Women in the NAT group were more likely to undergo mastectomy, and irrespective of the treatment setting, most of the patients did not undergo breast reconstruction ([Appendix Figure A1](#)).

For the patients in the NAT group, the median time from diagnosis until systemic therapy initiation was 2.07 months. The median NAT duration was approximately 15 months, and the period between the end of NAT and breast surgery was 1 month. For patients in the AT group, the median time from diagnosis until breast surgery was 1.97 month, and the time until systemic therapy initiation was 3.2 months. The median AT duration was 18.7 months. Data on treatment duration are shown in [Table 2](#).

Survival Analysis and Prognostic Factors

The 3 and 5-years OS for patients in the NAT group were 79% and 56%, respectively. For patients in the AT group, the 3 and 5-years OS was 97% and 92%, respectively ([Figure 2](#),

[Appendix Table 2](#)). The multivariate subgroup analysis of OS showed that stage III disease at diagnosis, positive lymph nodes at diagnosis, delay from NAT end to initiation of surgery (more than 8 weeks), and lack of pCR were predictors of poor OS for patients in NAT group ([Table 3](#)). Only lymph node positivity at diagnosis was a predictor of poor OS in the AT group ([Appendix Figure A2](#)).

The DFS in the NAT group was 67% and 46% after 3 and 5 years, respectively. For patients in the AT group, the 3- and 5-year DFS rates were 91% and 86%, respectively ([Figure 3](#), [Appendix Table 3](#)). The multivariate subgroup analysis showed that histological grade 2 and stage III disease at diagnosis and lack of pCR were predictors of disease recurrence and progression for patients in the NAT group ([Table 4](#)). Likewise, only lymph node positivity at diagnosis was a predictor of poor DFS in the AT group.

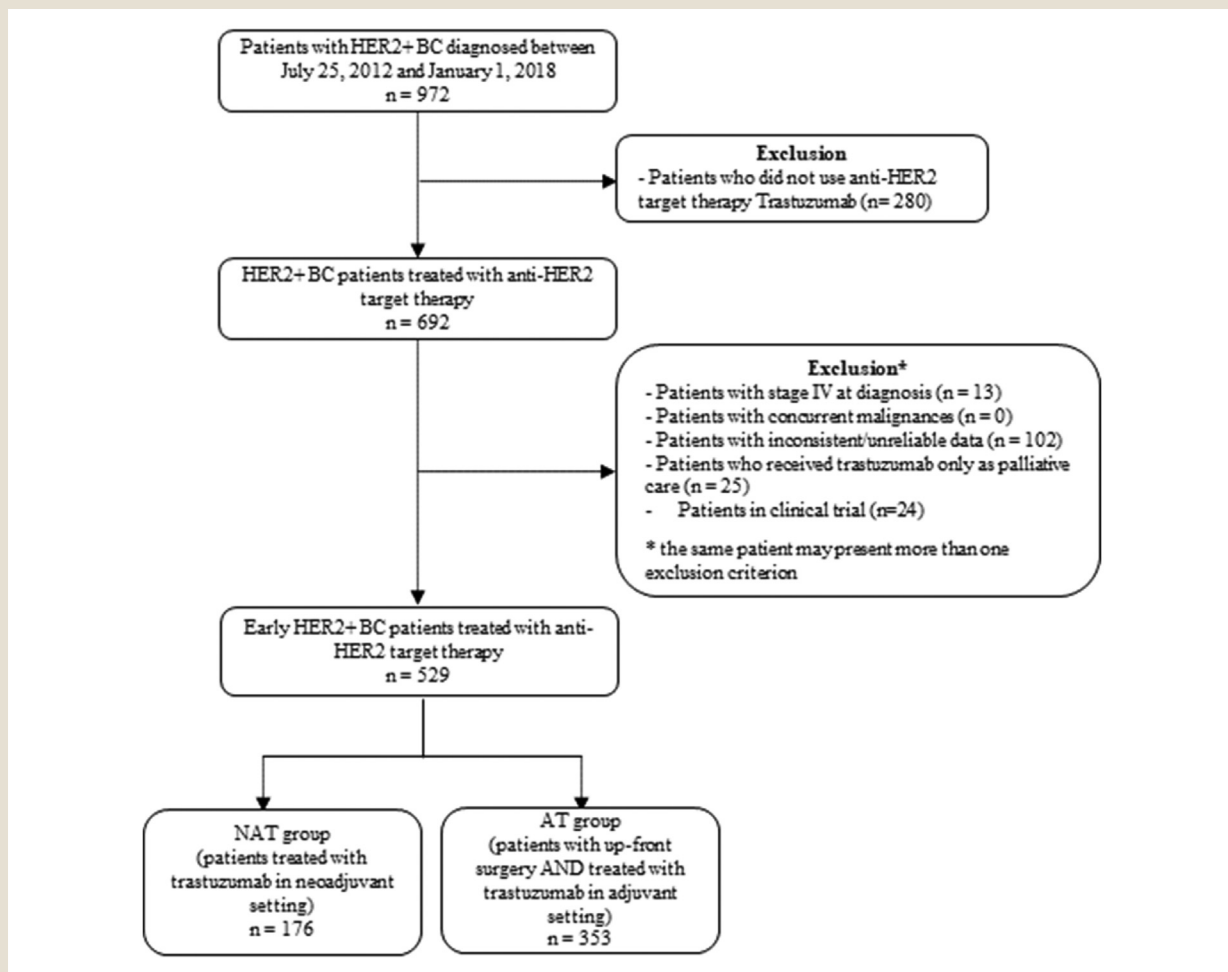
Discussion

In this study, we assessed 2 independent cohorts of HER2+ BC patients: the NAT and AT groups. Given the distinct nature of the cohorts, all the results were described separately, with no intention to perform any outcome comparisons. According to the institution's treatment protocol, NAT is indicated for patients with more advanced disease, as described earlier. Our findings are in accordance with the institution's guidelines, since most patients receiving NAT were diagnosed in a more advanced stage of disease. For stage I T1a/bN0 HER2 + disease, upfront surgery followed by adjuvant therapy is the preferred approach, according to the results of the APT trial.²⁴ However, appropriate management of stage I cT1c cN0 HER2 + BC remains uncertain and most of our patients were submitted to up front surgery. Although some authors discuss neoadjuvant treatment in this scenario, a recent consensus shows that the literature bases are weak for this decision.²⁵ To the best of our knowledge, this is the first study describing survival outcomes for Brazilian early HER2+ BC patients treated with anti-HER targeted therapy in the public setting.

Trastuzumab was approved for early HER2+ patients' treatment in the public health care setting in July 2012, however, its provision was effective only in January 2013. Thus, we observed a proportion of patients who did not receive trastuzumab because of this gap between approval and provision. In addition, between 2012 and 2018, a molecular confirmation of HER2 amplification was mandatory for patients to be considered eligible to receive treatment with trastuzumab. Unfortunately, in some cases, a negative or inconclusive result prevented them to be treated with trastuzumab. Since 2018, however, all immunohistochemically positive HER2 patients who have a tumor larger than 0.5cm are considered eligible for adjuvant treatment with trastuzumab and CISH/FISH exam is no longer required.

Among the early HER2+ patients who received trastuzumab in (neo)adjuvant setting, we observed that most patient were treated with concomitant chemotherapy. According to the clinical protocol and therapeutic guidelines for BC published by the federal government, an anthracycline-based regimen (doxorubicin plus cyclophosphamide followed by docetaxel) is recommended for early HER2+ patients specially for node positive disease.²⁵ Indeed, almost 90% of the patients received anthracycline in association to the trastuzumab. Although previous studies have shown some toxicities that could be

Figure 1 Patient selection. HER2 = human epithelial growth factor receptor 2; BC = breast cancer; TDM1 = trastuzumab emtansine; NAT = neoadjuvant therapy; AT = adjuvant therapy (1 patient was excluded by 2 exclusion criteria).



related to this type of regimen,^{26,27} we could not assess the safety outcomes in our cohort since this information was not available in the database. Nevertheless, the Pérola Byington Hospital follows strict protocols to evaluate the risk associated to the chemotherapy toxicities.

Evaluating one of the largest BC cohorts in Brazil, the AMAZONA project showed that for patients of the HER2+ subtypes, the 5-year OS varies according to the disease stage at diagnosis, ranging from 64.10% for stage III to 82.34% for stage II patients.²⁸ Herein, we also observed that stage III patients presented a lower OS rate than stage I/II patients. In our results, the 3- and 5-year OS rates exceeded 90% for patients in the AT group. Conversely, for NAT group, the 3-year OS was less than 80%. These results suggest that patients who are eligible for NAT present a poor prognosis, which is expected since they usually present a more advanced disease stage. These findings are pivotal since no data on the survival outcomes of Brazilian HER2+ patients treated with trastuzumab in clinical practice are available. It is also interesting to compare the present results with clinical trial findings. After

adjuvant treatment, some trials showed OS around 92% to 96% in the first 5 years,^{7,24,26,29} and DFS varying between 85% and 96% before 10 years of follow-up,^{7,24,29} which resembling our AT group. In neoadjuvant trials, pCR rates after trastuzumab treatment are fairly in agreement with the present study, ranging between 30% and 43%,³⁰⁻³³ while OS is around 85% to 73%,^{31,32} showing higher levels than observed in our analysis. These results suggest that in a real-world scenario, a set of factors beside the targeted therapy has a strong influence on the survival outcomes. Indeed, we observed that the tumor characteristics at diagnosis (staging and lymph node positivity) were the main prognostic factors associated with poor survival outcomes. Considering that we still observe a deficient screening process for BC in Brazil, many women are diagnosed at more advanced stages, which definitely influences survival rates.

There is evidence showing the influence of BC stage at diagnosis on survival outcomes.^{34,35} Ulas et al. showed that for patients with early HER2+ BC treated with adjuvant trastuzumab, stage III disease was an independent prognostic factor for relapse-free survival.¹² Our findings, however, showed node positivity as the

Prognostic Factors and Survival Outcomes of Patients

Table 1 Demographic and Clinical Characteristics at Diagnosis and Clinical Outcomes of Early HER2+ BC Patients Treated With Trastuzumab in the Neoadjuvant or Adjuvant Setting

	Neoadjuvant (n = 176)	Adjuvant (n = 353)	P Value ^a
Patient's age at diagnosis (years)			
Mean, SD	48.9 (11.05)	52.98 (11.12)	<.01
Median, min-max	48.5 (23-84)	54 (23-80)	
Age group, n (%)			
<40	40 (22.73%)	43 (12.18%)	<.01
40-69	131 (74.43%)	289 (81.87%)	
≥70	5 (2.84%)	21 (5.95%)	
Patient distribution, n (%)			
2012	4 (2.27%)	34 (9.63%)	<.01
2013	12 (6.82%)	72 (20.40%)	
2014	38 (21.59%)	62 (17.56%)	
2015	47 (26.70%)	85 (24.08%)	
2016	34 (19.32%)	63 (17.85%)	
2017	41 (23.30%)	37 (10.48%)	
Histologic type, n (%)			
Invasive carcinoma NST	172 (97.73%)	342 (96.88%)	.58
Others	4 (2.27%)	11 (3.12%)	
Hormonal receptor status, n (%)			
Negative	85 (48.3%)	120 (33.99%)	<.01
Positive	91 (51.7%)	233 (66.01%)	
Histological grade, n (%)			
G1	33 (18.75%)	71 (20.11%)	.93
G2	107 (60.8%)	211 (59.77%)	
G3	36 (20.45%)	71 (20.11%)	
Stage at diagnosis, n (%)			
I	2 (1.14%)	75 (21.25%)	<.01
II	49 (27.84%)	201 (56.94%)	
III	125 (71.02%)	77 (21.81%)	
N status, n (%)			
Negative	33 (18.75%)	189 (53.54%)	<.01
Positive	143 (81.25%)	164 (46.46%)	
Ki67			
% or +	5 (2.84%)	3 (0.85%)	.07
<15%	7 (3.98%)	24 (6.8%)	
15%-40%	116 (65.91%)	252 (71.39%)	
> 40%	48 (27.27%)	74 (20.96%)	
pCR status, n (%)			
Achieved	56 (31.82%)	-	
Not achieved	120 (68.18%)	-	

Abbreviations: BC = breast cancer; HER2 = human epithelial growth factor receptor 2; NST = invasive carcinoma no special type; SD = standard deviation.

^a P value was calculated only to assess group imbalance. It was not intended to perform any group comparison.

only independent factor associated with poor DFS and OS in the AT group, which was in accordance with other studies.^{36,37} Fujita et al.³⁸ showed that adjuvant trastuzumab treatment, younger age, positive nodal status at diagnosis, and lack of pCR were significantly associated with poor DFS. The mortality of patients diagnosed with stage III disease is more than 2 times higher than that of patients with stage I and II disease.¹¹ Our results corroborate the literature by showing that stage III disease at diagnosis and lack of pCR are

independent predictors of poor OS in patients eligible for NAT. Our data analysis also showed that lymph node positivity at diagnosis is an independent predictor of poor OS for both groups. Cocciolone et al.¹¹ observed that the number of positive lymph nodes has a strong impact on survival outcomes during the first 5 years, which could explain the impact observed in our study. As these factors are related to higher-risk disease, it is most important to invest in public policies aiming to increase the early diagnosis of HER2+ BC,

Table 2 Treatment Duration and Time Until Each Intervention for Early HER2+ BC Patients Treated With Trastuzumab in the Neoadjuvant or Adjuvant Setting

Characteristic	NAT (n = 176)	AT (n = 353)
Treatment duration, mo		
Mean, SD	15.51 (7.96)	18.25 (6.69)
Median, min-max	14.9 (1.71-64.01)	18.72 (4.77-67.5)
Classification, n (%)		
n valid	115	170
≤8 wk	1 (0.87%)	0 (0%)
>8 wk	114 (99.13%)	170 (100%)
Time from diagnosis to first BC related intervention^a, months		
Mean, SD	2.40 (2.40)	2.24 (2.24)
Median, min-max	2.07 (0.00-13.36)	1.97 (0.00-13.82)
Classification, n (%)		
n valid	176	352
≤ 8 wk	71 (40.34%)	156 (44.32%)
> 8 wk	105 (59.66%)	196 (55.68%)
Time from NAT to surgery^b, months		
Mean, SD	1.23 (0.97)	-
Median, min-max	1.12 (0.00-6.41)	-
Classification, n (%)		
n valid	165	-
≤8 wk	144 (87.27%)	-
>8 wk	21 (12.73%)	-
Time from surgery to AT, months		
Mean, SD	-	3.33 (1.50)
Median, min-max	-	3.22 (0.43-15.20)
Classification, n (%)		
n valid	-	340
≤8 wk	-	46 (13.53%)
>8 wk	-	294 (86.47%)

Abbreviations: AT = adjuvant therapy; BC = breast cancer; HER2 = human epithelial growth factor receptor 2; NAT = neoadjuvant therapy; SD = standard deviation.

^a First BC related intervention is considered as any pharmacological (NAT) or surgical (AT) treatment for breast cancer.

^b Considered as the time elapsed since NAT end until surgery.

validate the benefit of NAT in additional populations, including node-positive patients, and provide better treatment options such as dual HER2 blockade in the neoadjuvant setting for high-risk patients.

Time to treatment is also an important factor for survival outcomes. During clinical practice in the public health care system, the delay before treatment initiation is noticeable due to several factors, including difficulty in receiving proper diagnosis and treatment.^{39,40} In Brazil, as an attempt to overcome this hurdle, local regulation established a maximum of 60 days between diagnosis and treatment initiation. We observed a median time until treatment initiation for NAT of 62 days. Gagliato et al.¹⁸ in a retrospective analysis of stage I to III patients treated with NAT, demonstrated that a delay in initiation of more than 61 days after BC diagnosis was associated with an increased risk of death; thus, the authors suggested that early initiation of treatment should be a priority. In addition, a retrospective study with more than 500 early HER2+ patients receiving neoadjuvant and adjuvant regimens in Ireland showed that initiating trastuzumab more than 12 weeks

after diagnosis had a negative impact on DFS and OS.⁴¹ Herein, the multivariate analysis suggested that time to treatment is an important factor, as a time from NAT end until surgery greater than 8 weeks was identified as an independent prognostic factor for OS. However, time until treatment had no influence on survival outcomes for patients in the AT group, even though the median time from surgery until AT initiation were considerable high (3.2 months). This difference between the 2 cohorts may be related to the more aggressive profile of NAT group patients. Indeed, a study evaluating early-stage disease (stage I-III) showed that delayed treatment resulted in poor outcomes in some subgroups, with a greater impact on stage III BC patients than on patients with other stages of disease.¹⁸ These results suggest that time to treatment is key to improving patient survival outcomes but may be more impactful in the management of higher-risk disease.

Our results also show that pCR is an independent prognostic factor for OS in HER2+ BC. Different studies have shown the impact of achieving pCR on survival outcomes and most of the specialists agree that pCR is an important prognostic factor.²⁵ For

Prognostic Factors and Survival Outcomes of Patients

Table 3 Cox Regression Analysis Estimates of OS for Early HER2+ BC Patients Treated With Trastuzumab in the Neoadjuvant or Adjuvant Setting According to Clinicopathological Variables

Variable	NAT				AT			
	Univariate		Multivariate (n = 160)		Univariate		Multivariate (n = 337)	
	HR (CI 95%)	P-Value	HR (CI 95%)	P-Value	HR (CI 95%)	P-Value	HR (CI 95%)	P-Value
Age at diagnosis, years								
<40	1.00		1.00		1.00		1.00	
40-69	1.13 (0.46-2.82)	.79	1.51 (0.55-4.13)	.42	0.48 (0.13-1.75)	.27	1.02 (0.2-5.19)	.98
>70	0 (inf)	.99	0 (inf)	.99	0.88 (0.09-8.53)	.92	1.56 (0.12-20.79)	.74
HR status								
Positive	1.00		1.00		1.00		1.00	
Negative	0.79 (0.36-1.7)	.54	0.99 (0.42-2.34)	.99	1.72 (0.6-4.99)	.32	1.26 (0.4-4.03)	.69
Ki67								
% or +	0 (inf)	.99	-		0 (inf)	.99	-	
< 15%	1.00		1.00		1.00		1.00	
15%-40%	1.77 (0.24-13.3)	.58	6.6 (0.73-59.71)	.09	1.17 (0.15-9.31)	.88	1.32 (0.15-11.3)	.8
> 40%	0.9 (0.11-7.57)	.93	2.66 (0.26-27.35)	.41	1.5 (0.17-13.46)	.72	1.62 (0.17-15.54)	.68
Stage at diagnosis								
I/II	1.00		1.00		1.00		1.00	
III	2.06 (0.78-5.45)	.15	6.18 (1.47-25.98)	.01	2.15 (0.74-6.21)	.16	0.74 (0.22-2.52)	.63
Histological grade at diagnosis								
G1	1.00		1.00		1.00		1.00	
G2	1.5 (0.51-4.4)	.46	2.47 (0.77-7.94)	.13	0.65 (0.16-2.75)	.56	0.38 (0.07-1.97)	.25
G3	0.61 (0.14-2.73)	.52	0.96 (0.21-4.53)	.96	2.02 (0.5-8.08)	.32	1.14 (0.25-5.31)	.86
Lymph node status at diagnosis								
Negative	1.00		1.00		1.00		1.00	
Positive	0.85 (0.34-2.1)	.72	0.26 (0.07-0.96)	.04	13.62 (1.78-104.2)	.01	12.54 (1.41-111.5)	.02
Time from diagnosis to first BC-related intervention^a								
> 8 wk	1.00		1.00		1.00		1.00	
≤ 8 wk	0.77 (0.33-1.83)	.56	1.04 (0.41-2.66)	.93	1.97 (0.68-5.68)	.21	1.77 (0.56-5.56)	.33
Time from NAT to surgery								
> 8 wk	1.00		1.00		-	-	-	-
≤ 8 wk	0.61 (0.25-1.51)	.29	0.34 (0.12-0.97)	.04	-	-	-	-
Time from surgery to AT								
> 8 wk	-	-	-	-	1.00		1.00	
≤ 8 wk	-	-	-	-	0.9 (0.12-6.96)	.92	0.75 (0.09-6.31)	.79
Type of surgery								
Breast conserving	1.00		1.00		1.00		1.00	
Mastectomy	1.15 (0.35-3.83)	.82	0.71 (0.18-2.76)	.62	4.1 (0.92-18.37)	.06	2.15 (0.43-10.88)	.35
pCR status								
Achieved	1.00		1.00		-	-	-	-
Not achieved	8.92 (2.06-38.58)	<.01	11.05 (2.42-50.37)	<.01	-	-	-	-

Abbreviations: AT = adjuvant therapy; BC = breast cancer; HER2 = human epithelial growth factor receptor 2; NAT = neoadjuvant therapy; pCR = pathological complete response; SD = standard deviation.

^a The first BC-related intervention was defined as any pharmacological (neoadjuvant) or surgical (adjuvant) treatment for BC.

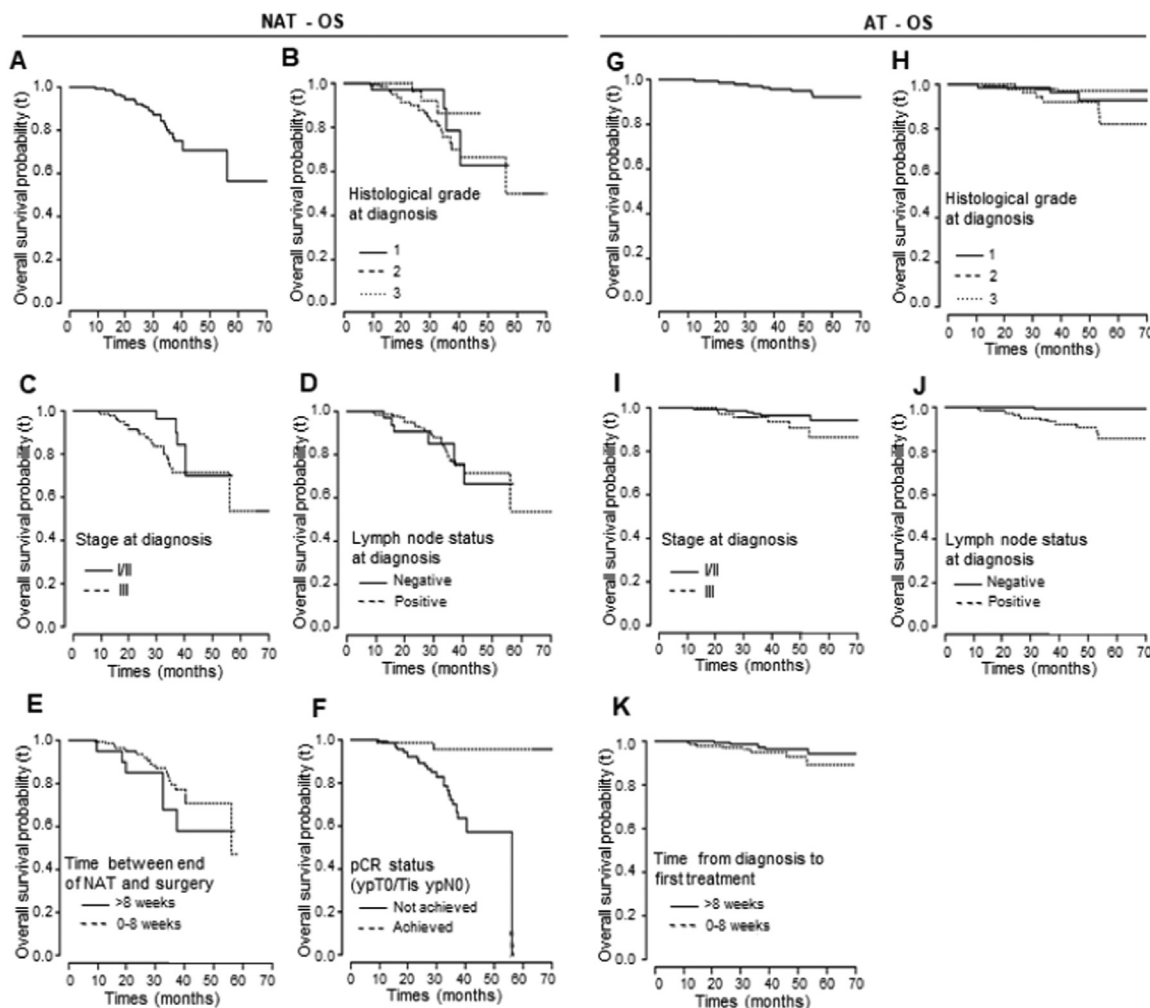
Table 4 Cox Regression Analysis Estimates of DFS for Early HER2+ BC Patients Treated With Trastuzumab in the Neoadjuvant or Adjuvant Setting According to Clinicopathological Variables

Variable	NAT				AT			
	Univariate		Multivariate (n = 160)		Univariate		Multivariate (n = 337)	
	HR (CI 95%)	P-Value	HR (CI 95%)	P-Value	HR (CI 95%)	P-Value	HR (CI 95%)	P-Value
Age at diagnosis, years								
<40	1.00		1.00		1.00		1.00	
40-69	1.09 (0.54-2.21)	0.81	0.95 (0.43-2.09)	0.9	0.63 (0.24-1.68)	0.36	0.77 (0.28-2.12)	0.61
>70	0 (inf)	0.99	0 (inf)	0.99	1.5 (0.36-6.3)	0.58	1.74 (0.38-7.87)	0.47
HR status								
Positive	1.00		1.00		1.00		1.00	
Negative	0.79 (0.43-1.44)	0.44	0.94 (0.49-1.79)	0.84	1.27 (0.6-2.66)	0.54	1.23 (0.57-2.64)	0.6
Ki67								
% or +	0 (inf)	0.99	-		0 (inf)	0.99	-	
< 15%	1.00		1.00		1.00		1.00	
15%-40%	1.27 (0.3-5.38)	0.74	3.2 (0.63-16.13)	0.16	1.16 (0.27-4.99)	0.84	1.13 (0.26-4.98)	0.87
> 40%	1.02 (0.23-4.54)	0.98	1.69 (0.32-9.01)	0.54	1.42 (0.3-6.68)	0.66	1.15 (0.24-5.56)	0.86
Stage at diagnosis								
I/II	1.00		1.00		1.00		1.00	
III	2.07 (0.96-4.45)	0.06	4.55 (1.47-14.09)	<0.01	2.04 (0.98-4.24)	0.06	1.11 (0.44-2.75)	0.83
Histological grade at diagnosis								
G1	1.00		1.00		1.00		1.00	
G2	2.86 (1.01-8.08)	0.04	4.63 (1.57-13.68)	<0.01	0.72 (0.29-1.78)	0.48	0.55 (0.21-1.42)	0.21
G3	1.65 (0.48-5.65)	0.43	2.78 (0.78-9.9)	0.12	1.26 (0.47-3.38)	0.65	0.86 (0.3-2.47)	0.78
Lymph node status at diagnosis								
Negative	1.00		1.00		1.00		1.00	
Positive	1.27 (0.57-2.86)	0.56	0.41 (0.13-1.26)	0.12	2.99 (1.33-6.71)	<0.01	2.74 (1.03-7.28)	0.04
Time from diagnosis to first BC-related intervention^a								
>8 wk	1.00		1.00		1.00		1.00	
≤8 wk	0.6 (0.3-1.22)	0.16	0.67 (0.31-1.44)	0.3	1.44 (0.71-2.96)	0.32	1.61 (0.77-3.35)	0.2
Time from NAT to surgery								
>8 wk	1.00		1.00		-	-	-	-
≤8 wk	0.73 (0.35-1.53)	0.4	0.75 (0.33-1.71)	0.49	-	-	-	-
Time from surgery to AT								
>8 wk	-	-	-	-	1.00		1.00	
≤8 wk	-	-	-	-	2.1 (0.8-5.54)	0.13	2.06 (0.76-5.56)	0.16
Type of surgery								
Breast conserving	1.00		1.00		1.00		1.00	
Radical	1.42 (0.51-3.98)	0.5	0.98 (0.31-3.1)	0.97	1.94 (0.86-4.36)	0.11	1.3 (0.53-3.22)	0.56
pCR status								
Achieved	1.00		1.00		-	-	-	-
Not achieved	5.42 (2.12-13.87)	<0.01	5.73 (2.19-14.96)	<0.01	-	-	-	-

Abbreviations: AT = adjuvant therapy; BC = breast cancer; HER2 = human epithelial growth factor receptor 2; NAT = neoadjuvant therapy; pCR = pathological complete response; SD = standard deviation.

^a The first BC-related intervention was defined as any pharmacological (neoadjuvant) or surgical (adjuvant) treatment for BC.

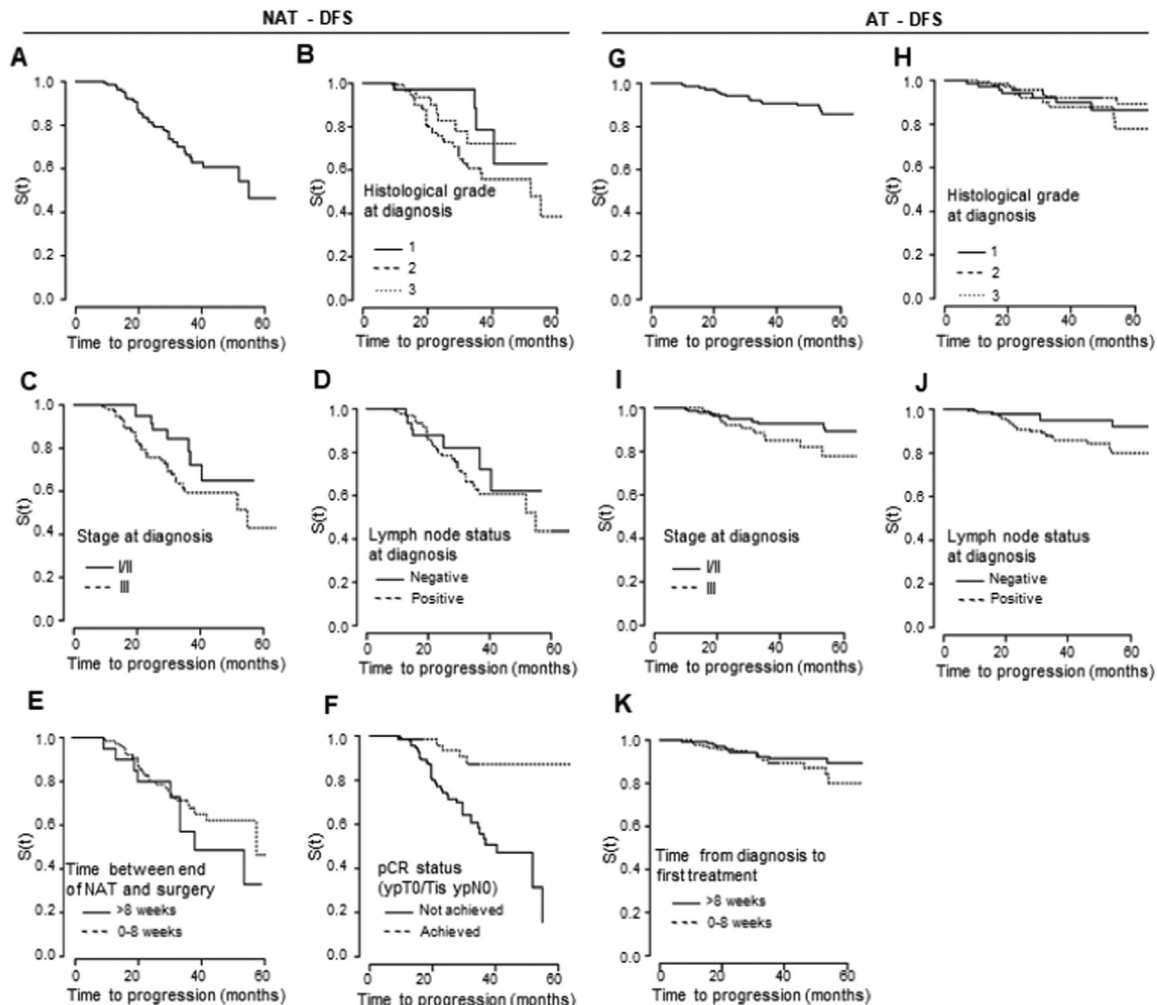
Figure 2 Kaplan-Meier curves of OS for patients treated with trastuzumab in the neoadjuvant or adjuvant setting. For NAT group: (A) Overall survival (OS); (B) OS according to histological grade (1, 2, or 3) at diagnosis; (C) OS according to stage (I/II or III) at diagnosis; (D) OS according to lymph node status (negative or positive); (E) OS according to the period between neoadjuvant therapy end and surgery (0-8 weeks or >8 weeks); (F) OS according to pCR (achieved or not achieved). For AT group: (G) Overall survival; (H) OS according to histological grade (1, 2, or 3) at diagnosis; (I) OS according to stage (I/II or III) at diagnosis; (J) OS according to lymph node status (negative or positive); (K) OS according to the time from diagnosis until first treatment (0-8 weeks or >8 weeks).



instance, a cohort study showed that among HER2+ BC patients who received trastuzumab, those who did not achieve pCR had a 5-year DFS rate of 78%, while patients with obvious pCR had a 95% 5-year DFS rate.⁴² Cortazar et al.¹⁵ showed a strong association between pCR and long-term survival outcomes in HER2+ and HR-negative patients who received trastuzumab. In our study, lack of pCR was a predictor for poor DFS, which is in accordance with the literature.^{33,42,43} Together, these results reinforce the importance of early diagnosis and adequate disease management, such as escalation therapy with dual blockade for higher-risk patients.³³ NAT with pertuzumab significantly increases the rate of pCR and DFS,^{13,14,33} and the use of trastuzumab emtansine (T-DM1) in the adjuvant setting when pCR is not achieved can reduce the risk of recur-

rence of invasive BC or death by 50%.⁴⁴ Currently, the Brazilian public health care system does not provide pertuzumab or T-DM1 for early HER2+ BC treatment.⁴⁵ After a progression the treatment for HER2+ BC in the first line is based on the "Cleopatra trial" that used of dual blockade (pertuzumab and trastuzumab) in addition to a chemotherapy (docetaxel)^{46,47} and also weekly paclitaxel as the backbone chemotherapy.⁴⁸ Only in 2021, the dual blockade with trastuzumab and pertuzumab became available in the public setting for metastatic HER2+ patients. Therefore, during the period of the study assessment, even those patients who later presented a distant recurrence could not be benefit with the dual blockade treatment, which could also have contributed to the lowest OS rate observed in this study. Another treatment options are possible in this scenario,

Figure 3 Kaplan-Meier curves of DFS for patients treated with trastuzumab in the neoadjuvant or adjuvant setting. For NAT group: (A) Overall disease-free survival (DFS); (B) DFS according to histological grade (1, 2, or 3) at diagnosis; (C) DFS according to stage (I/II or III) at diagnosis; (D) DFS according to lymph node status (negative or positive); (E) DFS according to the period between neoadjuvant therapy end and surgery (0-8 weeks or >8 weeks); (F) DFS according to pCR (achieved or not achieved). For AT group: (G) Overall disease-free survival; (H) DFS according to histological grade (1, 2, or 3) at diagnosis; (I) DFS according to stage (I/II or III) at diagnosis; (J) DFS according to lymph node status (negative or positive); (K) DFS according to the time from diagnosis until first treatment (0-8 weeks or >8 weeks).



such as the use of lapatinib associated with trastuzumab, as some studies have shown this option is valid mainly after the use of trastuzumab in neo/adjuvant setting⁴⁹ unfortunately this schema is not available in most public hospitals in Brazil.

Some limitations in this study must be acknowledged. The data used for analyses were derived from patient medical records. This approach presents a risk of bias, like other retrospective studies. The exclusion of part of the original sample (secondary to eligibility criteria) can lead to selection bias and compromise the generalizability of the study. The quality and integrity of the data collected were related to the level of information available in the records. However, as a reference health care center it is expected that the hospital has the resources and standard procedures to ensure proper data recording.

Hospital Pérola Byington is a public setting hospital and the results should not be considered when evaluating the scenario in a private health care perspective. In addition, although the total sample size was large, the number of patients in some subgroups was low, which may have compromised the power of statistical analyses.

Conclusion

In conclusion, our study identified prognostic factors in HER2-positive invasive BC patients receiving NAT or AT and assessed DFS and OS. In the NAT setting, stage III disease, node positivity, lack of pCR and delayed surgical treatment were associated to poor OS. In the AT setting, node positivity was the only independent factor for poor OS. Our findings are aligned with the current literature

Prognostic Factors and Survival Outcomes of Patients

and highlight the importance of escalating anti-HER2 treatment in patients with a higher risk of recurrence.

Clinical Practice Points

- Current, trastuzumab is the only targeted therapy approved to treat early HER2+ BC patients in the Brazilian public health care service, being introduced in 2012.
- Although clinical studies have demonstrated better survival outcomes with the use of trastuzumab for early disease, real world evidence in the Brazilian population is still scarce.
- The survival outcomes of Brazilian HER2+ BC patients treated in adjuvant setting is very similar to what has been observed in clinical trials and in the literature. However, we observed a lower OS for patients treated in neoadjuvant setting than that reported in the clinical trials.
- Patients treated with neoadjuvant trastuzumab presented with a more advanced disease and had several risk factors associated to poor survival outcomes, mainly stage III at diagnosis, negative pCR, and positive lymph node. Conversely, only lymph node positivity was associated to poor survival outcomes for patients treated with adjuvant trastuzumab.

The results show that Brazilian patients are diagnosed at advanced stages, which impacts survival outcomes. Introducing other targeted therapies at the public health care system will positively impact survival outcomes, especially for high risk patients.

Disclosure

The authors have stated that they have no conflicts of interest.

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Appendix Table 1 Management Pattern of Early HER2+ BC Patients Treated With Trastuzumab in the Neoadjuvant or Adjuvant Setting

Intervention	NAT (n = 176)	AT (n = 353)
<i>Hormone therapy, n (%)</i>		
No	174 (98.86%)	173 (49.01%)
Yes	2 (1.14%)	180 (50.99%)
Anastrozole	1 (50%)	79 (43.89%)
Anastrozol + tamoxifen	0 (0%)	3 (1.67%)
Tamoxifen	1 (50%)	95 (52.78%)
Not reported	0 (0%)	3 (1.67%)
<i>Chemotherapy, n (%)</i>		
No	9 (5.11%)	56 (15.86%)
Yes	167 (94.89%)	297 (84.14%)
Doxorubicin + cyclophosphamide/docetaxel	136 (81.44%)	242 (81.48%)
Docetaxel + carboplatin	22 (13.17%)	18 (6.06%)
Other	9 (5.39%)	37 (12.46%)
<i>Type of surgery, n (%)</i>		
Breast conserving	21 (11.93%)	152 (43.06%)
Mastectomy	155 (88.07%)	201 (56.94%)
<i>Reconstruction, n (%)</i>		
Yes	19 (10.8%)	51 (14.45%)
No	157 (89.2%)	302 (85.55%)

Abbreviations: AT = adjuvant therapy; BC = breast cancer; HER2 = human epithelial growth factor receptor 2; NAT = neoadjuvant therapy; SD = standard deviation.

Appendix Table 2 OS Rate of Early HER2+ BC Patients Treated With Trastuzumab in the Neoadjuvant or Adjuvant Setting According to Clinicopathological Variables

Variable	NAT					AT				
	Number of Patients	Number of Events	3-Year OS Probability (IC 95%)	5-Year OS Probability (IC 95%)	P-Value	Number of Patients	Number of Events	3-Year OS Probability (IC 95%)	5-Year OS Probability (IC 95%)	P-Value
Overall	176	27	0.79 (0.7-0.87)	0.56 (0.3-0.82)		353	14	0.97 (0.95-0.99)	0.92 (0.88-0.97)	
Age at diagnosis, years										
<40	40	6	0.78 (0.6-0.95)	-	.55	43	3	0.95 (0.88-1)	0.88 (0.74-1)	.30
40-69	131	21	0.79 (0.69-0.88)	0.53 (0.21-0.84)		289	10	0.97 (0.95-0.99)	0.93 (0.88-0.98)	
70 or more	5	0	1 (1-1)	-		21	1	0.95 (0.85-1)	-	
HR status										
Negative	85	11	0.83 (0.72-0.94)	-	.89	120	6	0.95 (0.91-0.99)	0.93 (0.88-0.99)	.10
Positive	91	16	0.75 (0.62-0.87)	0.64 (0.49-0.8)		233	8	0.98 (0.95-1)	0.92 (0.86-0.98)	
Ki67										
% or +	5	0	1 (1-1)	-	.10	3	0	1 (1-1)	1 (1-1)	.86
<15%	7	1	1 (1-1)	-		24	1	0.95 (0.87-1)	0.95 (0.87-1)	
15%-40%	116	20	0.71 (0.59-0.83)	0.67 (0.54-0.81)		252	9	0.97 (0.95-1)	0.91 (0.84-0.98)	
>40%	48	6	0.88 (0.76-1)	-		74	4	0.95 (0.9-1)	0.92 (0.84-1)	
Stage at diagnosis										
I/II	51	5	0.96 (0.88-1)	-	.02	276	8	0.97 (0.95-0.99)	0.94 (0.9-0.99)	.30
III	125	22	0.71 (0.6-0.83)	0.53 (0.22-0.85)		77	6	0.96 (0.91-1)	0.87 (0.75-0.98)	
Histological grade at diagnosis										
G1	33	4	0.78 (0.55-1)	-	.24	71	3	0.99 (0.96-1)	0.93 (0.85-1)	.50
G2	107	20	0.76 (0.65-0.87)	0.5 (0.2-0.8)		211	5	0.98 (0.96-1)	0.97 (0.94-1)	
G3	36	3	0.86 (0.71-1)	-		71	6	0.92 (0.85-1)	0.82 (0.67-0.97)	
Lymph node status at diagnosis										
Negative	33	6	0.85 (0.7-0.99)	-	.45	189	1	0.99 (0.97-1)	0.99 (0.97-1)	<.01
Positive	143	21	0.77 (0.67-0.87)	0.54 (0.22-0.85)		164	13	0.94 (0.9-0.98)	0.86 (0.78-0.94)	

(continued on next page)

Appendix Table 2 (continued)

Variable	NAT					AT				
	Number of Patients	Number of Events	3-Year OS Probability (IC 95%)	5-Year OS Probability (IC 95%)	P-Value	Number of Patients	Number of Events	3-Year OS Probability (IC 95%)	5-Year OS Probability (IC 95%)	P-Value
Time from diagnosis to first treatment^a										
≤8 wk	71	7	0.86 (0.73-0.98)	0.79 (0.62-0.96)	.80	156	8	0.95 (0.91-0.99)	0.89 (0.81-0.98)	.19
>8 wk	105	20	0.77 (0.66-0.87)	-		196	6	0.98 (0.96-1)	0.94 (0.89-0.99)	
Time from NAT to surgery										
≤8 wk	144	21	0.79 (0.70-0.89)	-	.17	-	-	-	-	-
>8 wk	21	6	0.68 (0.43-0.92)	-		-	-	-	-	-
Time from surgery to AT										
≤8 wk	-	-	-	-	-	46	1	0.97 (0.92-1)	0.97 (0.92-1)	.71
>8 wk	-	-	-	-	-	294	12	0.97 (0.95-0.99)	0.92 (0.86-0.97)	
Type of surgery										
Breast conserving	21	3	0.89 (0.68-1)	0.59 (0.23-0.95)	.38	152	2	0.99 (0.97-1)	0.98 (0.94-1)	.04
Radical	155	24	0.77 (0.68-0.86)	-		201	12	0.95 (0.92-0.98)	0.89 (0.82-0.96)	
pCR status (ypT0/Tis ypN0)										
Achieved	56	2	0.95 (0.89-1)	0.95 (0.89-1)	.01	-	-	-	-	-
Not achieved	120	25	0.7 (0.57-0.82)	-		-	-	-	-	

Abbreviations: AT = adjuvant therapy; BC = breast cancer; HER2 = human epithelial growth factor receptor 2; NAT = neoadjuvant therapy; pCR = pathological complete response.

^a The first treatment was defined as any pharmacological (neoadjuvant) or surgical (adjuvant) treatment for BC.

Appendix Table 3 DFS Rate of Early HER2+ BC Patients Treated With Trastuzumab in the Neoadjuvant or Adjuvant Setting According to Clinicopathological Variables

Variable	NAT					AT				
	Number of Patients	Number of Events	3-Year DFS Probability (IC 95%)	5-Year DFS Probability (IC 95%)	P-Value	Number of Patients	Number of Events	3-Year DFS Probability (IC 95%)	5-Year DFS Probability (IC 95%)	P-Value
Overall	176	44	0.67 (0.56-0.75)	0.46 (0.27-0.64)		353	30	0.91 (0.86-0.94)	0.86 (0.79-0.91)	
Age at diagnosis, years										
<40	40	10	0.65 (0.41-0.81)	-	.53	43	5	0.89 (0.73-0.96)	0.82 (0.59-0.93)	.26
40-69	131	34	0.66 (0.54-.76)	0.45 (0.23-0.64)		289	22	0.92 (0.87-0.95)	0.87 (0.79-0.92)	
70 or more	5	0	1 (1-1)	-		21	3	0.8 (0.49-0.93)	-	
Histologic type										
Invasive carcinoma NST	172	41	0.68 (0.58-0.77)	0.48 (0.27-0.65)	<.01	342	28	0.91 (0.87-0.94)	0.86 (0.79-0.91)	.16
Others	4	3	0 (0-0)	0 (0-0)		11	2	0.76 (0.33-0.94)	0.76 (0.33-0.94)	
HR status										
Negative	85	19	0.71 (0.56-0.81)	-	.71	120	11	0.88 (0.8-0.94)	0.88 (0.8-0.94)	.31
Positive	91	25	0.63 (0.48-0.74)	0.45 (0.22-0.65)		233	19	0.92 (0.87-0.95)	0.85 (0.76-0.91)	
Ki67										
% or +	5	0	1 (1-1)	-	.29	3	0	1 (1-1)	1 (1-1)	.94
<15%	7	2	1 (1-1)	0 (0-0)		24	2	0.91 (0.69-0.98)	0.91 (0.69-0.98)	
15%-40%	116	29	0.61 (0.47-0.72)	0.61 (0.47-0.72)		252	20	0.91 (0.85-0.94)	0.86 (0.77-0.92)	
>40%	48	13	0.71 (0.52-0.84)	-		74	8	0.9 (0.79-0.95)	0.81 (0.63-0.91)	
Stage at diagnosis										
I/II	51	8	0.84 (0.66-0.93)	-	.02	276	18	0.93 (0.88-0.96)	0.89 (0.81-0.94)	.13
III	125	36	0.59 (0.47-0.7)	0.42 (0.21-0.62)		77	12	0.85 (0.74-0.92)	0.78 (0.62-0.88)	
Histological grade at diagnosis										
G1	33	4	0.78 (0.43-0.93)	-	.05	71	7	0.9 (0.78-0.95)	0.86 (0.72-0.94)	.58
G2	107	33	0.61 (0.48-0.71)	0.38 (0.17-0.59)		211	14	0.92 (0.86-0.95)	0.89 (0.8-0.94)	
G3	36	7	0.72 (0.49-0.86)	-		71	9	0.88 (0.76-0.94)	0.78 (0.59-0.89)	

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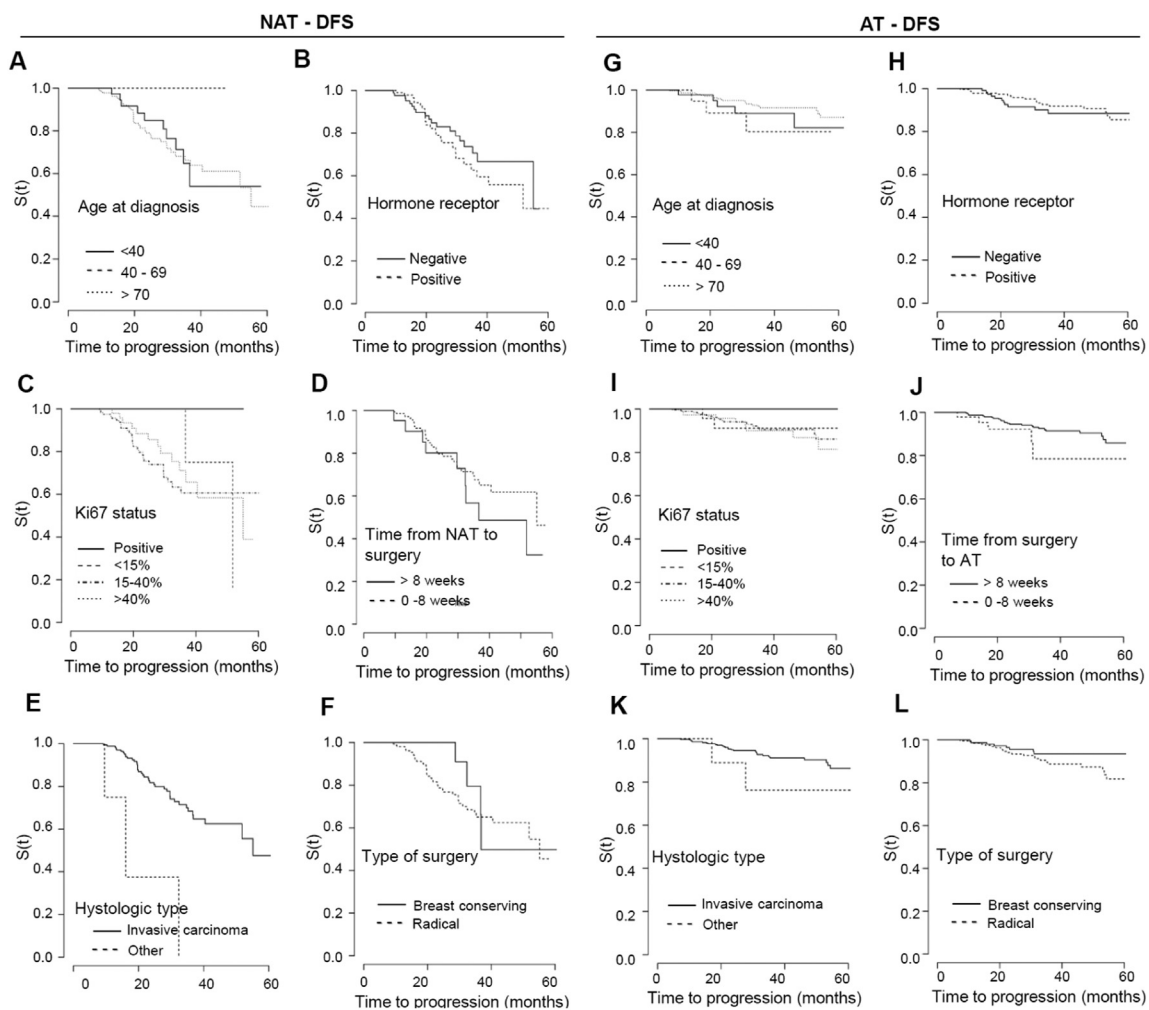
Appendix Table 3 (continued)

Variable	NAT					AT				
	Number of Patients	Number of Events	3-Year DFS Probability (IC 95%)	5-Year DFS Probability (IC 95%)	P-Value	Number of Patients	Number of Events	3-Year DFS Probability (IC 95%)	5-Year DFS Probability (IC 95%)	P-Value
Lymph node status at diagnosis										
Negative	33	7	0.82 (0.62-0.92)	-	.85	189	8	0.95 (0.9-0.98)	0.92 (0.82-0.97)	<.01
Positive	143	37	0.63 (0.51-0.73)	0.43 (0.22-0.63)		164	22	0.86 (0.78-0.91)	0.8 (0.69-0.87)	
Time from diagnosis to first BC-related intervention^a										
≤8 wk	71	10	0.75 (0.55-0.88)	0.69 (0.45-0.84)	.2	156	15	0.89 (0.82-0.94)	0.8 (0.65-0.89)	.59
>8 wk	105	34	0.63 (0.51-0.73)	-		196	15	0.91 (0.86-0.95)	0.89 (0.82-0.94)	
Time from NAT to surgery										
≤8 wk	144	34	0.68 (0.56-0.77)	-	.55	-	-	-	-	-
>8 wk	21	9	0.57 (0.28-0.77)	-		-	-	-	-	
Time from surgery to AT										
≤8 wk	-	-	-	-	-	46	5	0.78 (0.52-0.91)	0.78 (0.52-0.91)	.09
>8 wk	-	-	-	-	-	294	25	0.91 (0.87-0.94)	0.86 (0.78-0.91)	
Type of surgery										
Breast conserving	21	4	0.8 (0.39-0.95)	0.5 (0.13-0.79)	.16	152	8	0.93 (0.87-0.97)	0.93 (0.87-0.97)	.22
Radical	155	40	0.65 (0.54-0.74)	-		201	22	0.89 (0.82-0.93)	0.82 (0.7-0.88)	
pCR status (ypT0/Tis ypN0)										
Achieved	56	5	0.87 (0.71-0.95)	0.87 (0.71-0.95)	<.01	-	-	-	-	-
Not achieved	120	39	0.56 (0.43-0.67)	-		-	-	-	-	

Abbreviations: AT = adjuvant therapy; BC = breast cancer; HER2 = human epithelial growth factor receptor 2; NAT = neoadjuvant therapy.

^a The first BC-related intervention was defined as any pharmacological (neoadjuvant) or surgical (adjuvant) treatment for BC.

Appendix Figure 1 Kaplan-Meier curves of DFS for patients treated with trastuzumab in the neoadjuvant or adjuvant setting according to prognostic factors. For NAT group: (A) Age at diagnosis; (B) hormone receptor; (C) Ki67 status at diagnosis; (D) time from NAT to surgery; (E) histologic type; (F) type of surgery. For AT group: (G) Age at diagnosis; (H) hormone receptor; (I) Ki67 status at diagnosis; (J) time from surgery to AT; (K) Histologic type; (L) type of surgery.



Appendix Figure 2 Kaplan-Meier curves of OS for patients treated with trastuzumab in the neoadjuvant or adjuvant setting according to prognostic factors. For NAT group: (A) Age at diagnosis; (B) hormone receptor; (C) Ki67 status at diagnosis; (D) time from NAT to surgery; (E) histologic type; (F) type of surgery. For AT group: (G) Age at diagnosis; (H) hormone receptor; (I) Ki67 status at diagnosis; (J) time from surgery to AT; (K) Histologic type; (L) type of surgery.

