Original Article | Clinical Studies

Survival outcomes of Zo-NAnTAx: a five-year analysis of zoledronic acid added to a neoadjuvant regimen for HER2-positive breast cancer

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Background: Zoledronic acid (ZA) improved outcomes in breast cancer. In pre-clinical studies, ZA increased tumour regression in combination chemotherapy and anti-human epidermal growth factor receptor 2 (HER2) target therapy. The Zo-NAnTax study, a clinical trial combining ZA with neoadjuvant therapy for HER2-positive tumours met the primary endpoint, showing a higher pathological complete response (pCR) rate than predicted in patients receiving surgery. Here, we report the exploratory relapse-free survival (RFS) and overall survival (OS) analysis after five years of follow-up.

Methods: Adult women with HER2-positive breast cancer amendable to curative surgery who consented to the study received four cycles of ZA at 4 mg + doxorubicin 60 mg/m^2 + cyclophosphamide 600 mg/m^2 followed by four cycles of ZA at 4 mg + docetaxel 100 mg/m^2 + trastuzumab 6 mg/kg (8 mg/kg as a loading dose), all in a 21 days-cycle, totalizing 8 cycles before surgery. To achieve the primary endpoint of pCR rate between 22% and 35%, 56 patients were needed. The secondary endpoints included safety, gene expression according to treatment response, prediction of pCR rate by an interim breast magnetic resonance imaging (bMRI).

Results: Beyond the overall pCR rate of 42%, alongside a good safety profile, we showed similar pCR rates in both hormonal receptor (HR) positive (40%) and HR-negative (44%). RFS and OS at five years were evaluated in 58 subjects, and the overall rate was 79.3% and 86.2%, respectively. Numerically higher values of both RFS and OS were observed in patients achieving pCR *vs*. non-achieving, respectively 83.3% *vs*. non-pCR 76.5% (P=0.57) and 95.8% *vs*. non-pCR 79.4% (P=0.08). Although not statistically significant, OS was numerically equivalent according to HR status, respectively 85.7% *vs*. 87.5% for HR-positive and HR-negative (P=0.91), which contrasted with RFS, HR-positive 81% *vs*. HR-negative 75% (P=0.58). None of the assessed clinicopathological biomarkers significantly correlated with survival.

Conclusions: ZA plus neoadjuvant therapy in HER2-positive breast cancer shows provoking survival outcomes. Clinical and pre-clinical investigation with dual anti-HER2 blockage is warranted.

Keywords: Human epidermal growth factor receptor 2 positive (HER2-positive); breast cancer; neoadjuvant

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Introduction

Chemotherapy associated with blockage of the human epidermal growth factor receptor 2 (HER2) is the standard of care for high-risk patients with HER2-positive breast cancer in the curative setting (1). The increase in the pathological complete response (pCR) rate, with regimens containing trastuzumab alone or in combinations, was further validated as a surrogate outcome of relapse-free survival (RFS) and overall survival (OS) (2,3). Therefore, increasing the pCR rate has been the primary goal of the neoadjuvant approach.

Despite significant improvement in patient outcomes, unmet needs remain in the HER2-positive disease. Although evidence from trials evaluating surrogate endpoints to tailoring neoadjuvant treatment is emerging, it remains a challenge to precisely define at a patient level which ones deserve escalated versus de-escalated intervention (4,5). The majority of regimens are limited in inducing comparable pCR rates in hormonal receptor (HR)-positive as in HR-negative, as summarized in *Table 1* (6-14). Beyond that, the financial toxicity of dual blockage remains substantial, especially in developing countries, and more importantly, the recurrences are markedly frequent in patients not achieving pCR, highlighting the need for treatment optimization (3).

Zoledronic acid (ZA) is a bisphosphonate improved outcomes in breast cancer and it should be discussed as an adjuvant treatment (15). The mevalonate pathway (MVP), is a secondary pathway with a relevant interplay in the estrogen receptor (ER)-HER2 crosstalk, which is blocked by ZA (16). Pre-clinical evidence suggests that ZA synergizes with anthracycline and paclitaxel (17,18). Moreover, by blocking the MVP, it can inhibit this pathway of resistance to anti-HER2 therapy (19). To test the hypothesis that patients could benefit from an increase in the pCR rate by adding ZA to a trastuzumab containing neoadjuvant regimen, we designed and conducted the ZonAnTax trial. This phase 2, single-arm, clinical study recruited patients with HER2-positive locally advanced breast cancer. We previously reported that the study met its primary endpoint; a pCR rate of 42% was observed in the population evaluable for efficacy analysis. The unplanned analysis showed that the rate of pCR for HR+ was 40% (17/42), comparable to pivotal trials using dual blockage, and similar rates to HR– 44% (7/16). Moreover, we demonstrated the favourable safety profile of this combination, once the adverse events did not differ from clinical trials using similar regimens not containing ZA with minimum added cost. Here, we expand the discussion of the mature 5-year survival analysis (20). We present this article in accordance with the TREND reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-23-1880/rc).

Highlight box

Key findings

- The 5-year survival analysis of Zo-NanTAx shows provoking results of recurrence-free and overall survival rates in human epidermal growth factor receptor 2 (HER2)-positive breast cancer patients, respectively 79.3% and 86.2%, of zoledronic-acid combined with neoadjuvant chemotherapy and trastuzumab.

What is known and what is new?

- Anti-HER2 target therapy increases pathological complete response rate, when combined with neoadjuvant chemotherapy, a surrogate for long-term benefit outcomes. Although the dual anti-HER2 blockage offers an incremental benefit, there is a substantial increase in therapy cost.
- Zo-NanTAx demonstrated that a much more affordable regimen can deliver provoking long term survival benefits and potentially relevant to developing countries.

What is the implication, and what should change now?

- Clinical and pre-clinical investigation with the dual blockage is warranted.

Methods

Study design

ZoNanTax (NCT01472146) was a single-arm, open-label, phase 2 study carried out at the Instituto Nacional de Câncer in Brazil according to the Declaration of Helsinki (as revised in 2013), and obtained ethical approval from the Instituto Nacional de Câncer Ethics Committee (Approval No. 154/10), and the detailed design as well as statistical analysis for the primary and secondary endpoints can be found in the first publication (6). Informed consent was signed by all patients before enrolment in this study.

Table 1 Examples of clinical trials using HER2-blockage in the neoadjuvant setting

Trial	Intervention	Median FU (months)	pCR rate (%)			RFS/PFS (%)			RFS pCR (%)			RFS no pCR (%)			OS (%)			OS pCR (%)			mOS no pCR (%)		
			All	HR+	HR–	All	HR+	HR –	All	HR+	HR–	All	HR+	HR–	All	HR+	HR–	All	HR+	HR–	All	HR+	HR–
Zo-NAnTAx (6)	ACx4 + ZAx4 > DTx4 + ZAx4	60	42	40	44	79.3	–	–	83.3[£]	88.2[£]	71.4[£]	76.5[£]	76[£]	71.8	86.2	–	–	95.8[£]	94.1[£]	100[£]	79.4	80	77.8
NEOSPhere (7)	DH > FEC	60	21.5	20.0	36.8	81	–	–	85	90	84	76	80	72		–			–			–	
	DHP > FEC	61.2	39.3	26.0	63.2	84	–	–															
	HP > FEC	60.5	11.2	5.9	27.3	80	–	–															
	DP > FEC	62.3	17.7	17.4	30.0	75	–	–															
Technos (8)	ECTH	–	38.7	35.4	42.3		–			–			–			–			96.3*			85.0*	
CALGB 40601 (9)	THL	83	52.0	41.0	68.0	93	–	–	89	–	–		76%		96	–	–		95			86	
	TH		44.0	39.0	50.0	79	–	–							88	–	–						
	TL		27.0	26.0	30.0	69	–	–							84	–	–						
Cher-Lob (10)	CT + H	60	25	–	–	77.8	–	–	97.3[£]	–	–		72.7[£]			–			97.2[£]			89.5[£]	
	CT + L		25.7	–	–	77.1	–	–															
	CT + H + L		44.2	–	–	85.8	–	–															
NeoALTTO (11)	TL	~68	20.0	16.1	33.7	67[&]	73[&]	61[&]	77[&]	–	–		65[&]		82[&]	85[&]	79[&]		89[&]			77[&]	
	TH		27.6	22.7	36.5	67[&]	71[&]	63[&]		–			–		79[&]	82[&]	75[&]		–			–	
	THL		46.8	41.6	61.3	74[&]	72[&]	74[&]		–			–		85[&]	88[&]	81[&]		–			–	
neoCARH (12)	EC-TH	–	37.3	26	48		–			–			–			–			–			–	
	TCH		55.9	47	65																		
Tryphaena (13)	FECHP > DHP	61.1	61.6	41.1	73.5	87	–	–		–			–			94			–			–	
	FEC > DHP	61.8	57.3	45.7	62.5	88	–	–								94							
	TCaHP	60.9	66.2	47.5	81.1	90	–	–								93							
TRAIN 2 (14)	TCaHP	48.8	67	44	84	93.6*	–	–		92.9			84.7			98.2*			–			–	
	FEC > THP		68	51	89	92.7*	–	–								97.7*							

*, 3 years rate; [£], 5 years rate; [&], 6 years rate. HER2, human epidermal growth factor receptor 2; FU, follow-up; pCR, pathological complete response; HR, hormonal receptor; RFS, relapse-free survival; PFS, progression-free survival; OS, overall survival; mOS, median OS; ZA, zoledronic acid; D, docetaxel; H, trastuzumab; T, taxane; C, cyclophosphamide; Ca, carboplatin; E, epirubicin; F, 5-fluorouracil; P, pertuzumab; L, lapatinib.

To summarize, breast cancer patients with stage IIA to IIIB HER2-positive breast cancer were recruited to receive 4 cycles of doxorubicin + cyclophosphamide (AC) + ZA followed by 4 cycles of docetaxel + trastuzumab (DT) + ZA, before surgery. After curative surgery, patients received adjuvant trastuzumab for one year, and HR-positive hormonal therapy was given according to the institutional guidelines (Figure S1).

Statistical analysis of survival

RFS and OS were exploratory endpoints of this study. RFS accounted time was defined as the time between the surgery date until disease relapse, death, or censure, and the OS was defined as the time between the date from study entry until death or censure.

Kaplan-Meier survival curves were estimated, and the Log-rank statistical test was performed to evaluate the hypothesis of survival differences between groups in OS and RFS according to a set of explanatory variables, such as the pCR status, HR, cancer stage, among others, considering 5% as the level of significance. The analysis used R statistical software, packages survival, survMisc, and survminer.

Results

Of the 71 HER2+ BC patients with stage who signed consent, 11 screen failed due to metastatic disease found at screening, and two refused surgery. The primary, secondary, and main early clinical endpoints of the 60 patients eligible for safety and 58 for efficacy analysis were previously reported (6). The relevant findings include a median age of 54 [26–74] years, 63% were post-menopausal, 73% were HR-positive, median tumor size 61 [15–120] cm, 52% had clinically positive lymph node, clinical stage II was 55% and IIIA 45%. Safety was evaluated in 60 patients, showing similar results from previous studies using regimens without ZA, and encouragingly, no adverse events related to the drug were reported (8,12). Of the 58 patients eligible for efficacy, 24 (42%) achieved pCR, and according to HR status, 17 (40%) of HR-positive patients achieved pCR and 7 (44%) of HR-negative.

RFS at five years was evaluated in 58 subjects, and the overall rate was 79.3%, and the preliminary results were presented at the ESMO-Breast conference in 2023 (20). Numerically higher RFS rates were observed in patients achieving pCR 83.3% *vs.* non-pCR 76.5% (P=0.57) (*Figure 1A*) This observation was also confirmed in stratification by HR status, where RFS in HR-negative pCR was 71.4% *vs.* non-pCR 71.8% (P=0.72), and for HR-positive pCR was 88.2% *vs.* non-pCR 76% (P=0.32) (*Figure 1B*). RFS was also numerically higher for HR-positive 81% *vs.* HR-negative 75% (P=0.58) (*Figure 1C,1D*). It is important to highlight that in our opinion, the numerically higher but not statistically significant RFS for HR-negative patients non achieving pCR than achieving pCR are likely to be attributed to the small number of subjects (*Figure 1D*).

Overall, 58 patients were eligible for OS evaluation, and the five years was 86.2%, and presented alongside the RFS as above (20). As RFS, pCR was associated with numerically higher OS rates 95.8% *vs.* non-pCR 79.4% (P=0.08) (*Figure 1E*). OS according to pCR status stratified by HR for HR-negative pCR was 100% *vs.* non-pCR 77.8% (P=0.23) and for HR-positive pCR was 94.1% *vs.* non-pCR 80% (P=0.20) (*Figure 1F*). Contrastingly to RFS, OS was equivalent according to HR, respectively 85.7% *vs.* 87.5% for HR-positive and HR-negative (P=0.91) (*Figure 1G,1H*).

None of the assessed biomarkers with potential association with RFS or OS, including Ki67, p53, staging, angiolymphatic invasion, and lymphocyte infiltration, demonstrated a statistically significant difference (Tables S1,S2).

Discussion

This is the first clinical trial to show 5-year survival outcomes of ZA incorporated into the neoadjuvant regimen for HER2 positive breast cancer. The findings in our population, where 52% were lymph-node positive and the median tumour size of 61 millimetres [15–120] clinically, are consistent with prior studies without ZA and escalated neoadjuvant treatment by associating a second anti-HER2 blockage to trastuzumab-containing regimens, as summarized in *Table 1*, whilst Zo-NanTax is a more affordable regimen with similar efficacy.

In the Zo-NanTAx trial, 42% of all patients and 40% of HR+ achieved pCR when exposed to a regimen containing ZA, having taxane, trastuzumab, and anthracycline as a backbone. Higher pCR rates were achieved with regimens including dual anti-HER2 blockage and anthracycline before surgery, such as in the TRYPHAENA trial (13), but similar when anthracycline was given after surgery, such as in the NEOSPHERE trial (7), as summarized on *Table 1*. Anthracyclines have been the standard of care in the adjuvant setting for high-risk HER2-positive tumors and safely allow the reduced duration of HER2 blockage (21,22). However, given the potentially fatal or life-treating

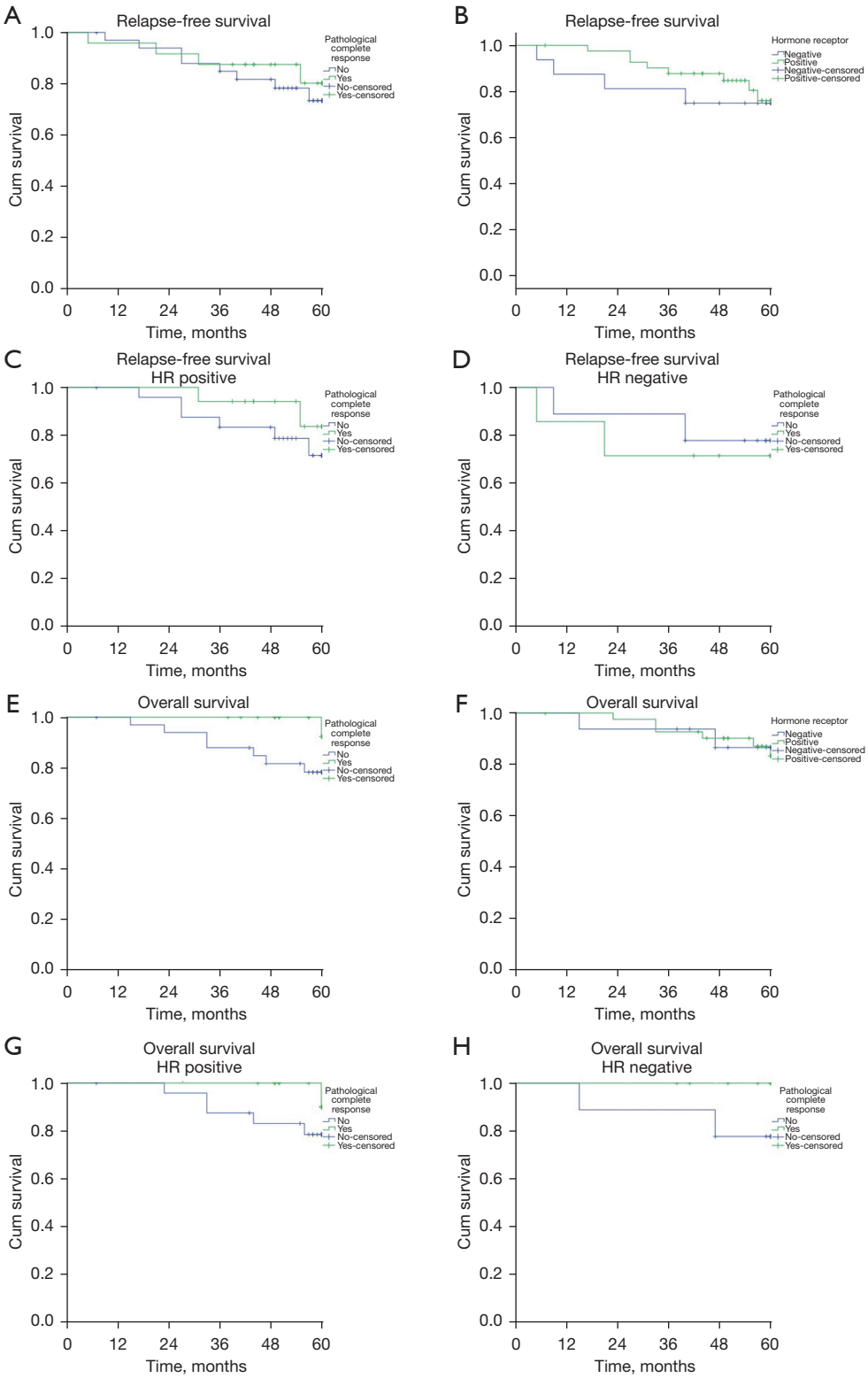

Figure 1 Kaplan-Meier curves of survival at five years. RFS according to pCR status (A) and HR status (B). RFS controlled by pCR in HR+ (C) and HR– (D). OS according to pCR status (E) and HR status (F). OS controlled by pCR in HR+ (G) and HR– (H). pCR, pathological complete response; HR, hormonal receptor; RFS, relapse-free survival; OS, overall survival.

toxicities associated, several studies investigated the use of neoadjuvant regimens anthracycline-free. Robust evidence supports that a regimen containing trastuzumab or dual HER2 blockage plus a taxane alongside a platinum agent can induce pCR rates higher than anthracycline-containing regimens (14). The survival analysis of this study was exploratory, as most pivotal trials demonstrated in the *Table 1*. However, the 5-year RFS rate of 79.3% and OS rate of 86.2% in the Zo-NAnTAx study are encouragingly similar to what was found in the aforementioned trials. Beyond that, achieving pCR was associated with a numerically higher DFS and OS than non-pCR. The heterogeneous long-term follow-up in larger trials demonstrated that achieving pCR provides statistically significant RFS and OS benefits in the overall population and HR+ (*Table 1*). Therefore, given the favourable toxicity profile of the bisphosphonate in the Zo-NAnTAx trial, adding ZA is warranted and safer whilst studies combined with the dual-blockage and/or with an anthracycline-free regimen are awaited.

Somewhat limited to the sample but still intriguing, we observed that the 5-year RFS rates were practically the same for HR– (71.4% *vs.* 71.8%) but were numerically different for HR+ (88.2% *vs.* 76%), for patients achieving pCR *vs.* non-pCR. On the other hand, the 5-year OS rates were numerically better in patients achieving pCR *vs.* non-pCR for both HR+ (94.1% *vs.* 80%) and HR– (100% *vs.* 77.8%). Historically, there has always been a challenge to increase the pCR rate in HR+ tumors, even questionable if this would be the best surrogate outcome for survival, especially since the dual blockage is responsible for an absolute uplift of approximately 10% from trastuzumab-containing regimens (5,23). However, a recent meta-analysis cleared the controversy that HR+ outcomes will be solely influenced by adjuvant hormonal therapy and demonstrated marked survival benefit when HR+HER2+ patients achieve pCR (24). Although currently, patients not achieving pCR could receive an antibody-drug conjugate (23), the evidence discussed above, taken together with our study, which previously reported the relationship between MVP blockade and differentially expressed genes in these subtype of tumors according to pCR, suggests that pursuing neoadjuvant regimens able to improve pCR in all HER2 populations should be the goal of the next-generation therapeutic agents (16).

Limitations

Although this survival analysis data of the Zo-NanTAx trial is encouraging, the results should be interpreted in light of the design limitations. Our small single arm study limits the comparison with studies. At the time of this study's approval, Pertuzumab was not available for standard practice in Brazil. Therefore, it was not possible to evaluate the performance of ZA + the dual-blockage. Moreover, the long-term evidence demonstrating that regimens not containing anthracycline are equally effective and potentially safer from both a cardiac and bone marrow perspective was not robust when this study was conducted as of today. Along the same line, a paucity of evidence was available to suggest that extending ZA to the adjuvant setting would benefit HER2-positive patients and, therefore, was not offered to any patients enrolled in the study. As the pivotal trials, we did not include power in the design to test differences in RFS and OS for patients achieving pCR, nor a stratification of this analysis by HR, and equally to our design, led to limitations in assess survival benefit. Finally, dual blockage is the current standard of care for HER2+ tumors in the neoadjuvant setting. Although we favour physicians considering personalizing treatment by adding ZA to the dual blockage, the combination has yet to be tested and is under consideration by the group.

Conclusions

This follow-up analysis of the Zo-NAnTAx trial shows encouraging 5-year DFS and OS rates comparable to pivotal trials. Adding ZA to the neoadjuvant treatment should be considered. Investigation of partnering with dual-blockage and/or anthracycline-free regimens is warranted.

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Footnote

Reporting Checklist: The authors have completed the TREND reporting checklist. Available at https://atm.

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Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-23-1880/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-23-1880/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was carried out according to the Declaration of Helsinki (as revised in 2013) and obtained ethical approval from the Instituto Nacional de Câncer Ethics committee (Approval No. 154/10). Informed consent was signed by all patients before enrolment in this study.

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Supplementary

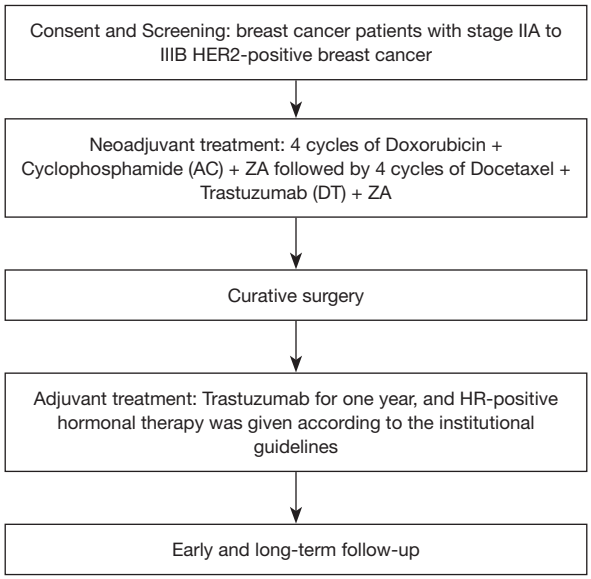

Figure S1 Patients flow.

Table S1 Relapse-free survival evaluation in pathological variables

Variable	Total number	Events	Percentage	P value
Pathological response				0.574
No	34	8	76.5%	
Yes	24	4	83.3%	
Overall	58	12	79.3%	
HR				0.586
Negative	16	4	75.0%	
Positive	42	8	81.0%	
Overall	58	12	79.3%	
Pathological response in HR-positive				0.723
No	25	6	76.0%	
Yes	17	2	88.2%	
Overall	42	8	81.0%	
Pathological response in HR-negative				0.327
No	9	2	77.8%	
Yes	7	2	71.4%	
Overall	16	4	75.0%	
Ki 67				0.897
<20%	8	2	75.0%	
≥20%	50	10	80.0%	
Overall	58	12	79.3%	

Table S1 *(continued)*

Variable	Total number	Events	Percentage	P value
p53				0.566
<10%	25	6	76.0%	
≥10%	33	6	81.8%	
Overall	58	12	79.3%	
Cancer stage				0.456
IIA	11	1	90.9%	
IIB + III	47	11	76.6%	
Overall	58	12	79.3%	
Inflammatory infiltrate				0.195
No	24	3	87.5%	
Yes	34	9	73.5%	
Overall	58	12	79.3%	
Angiolymphatic invasion				0.391
No	55	12	78.2%	
Yes	3	0	100%	
Overall	58	12	79.3%	

HR, hormonal receptor.

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Table S2 Overall survival evaluation in pathological variables

Variable	Total number	Events	Percentage	P value
Pathological response				0.085
No	34	7	79.4%	
Yes	24	1	95.8%	
Overall	58	8	86.2%	
HR				0.911
Negative	16	2	87.5%	
Positive	42	6	85.7%	
Overall	58	8	86.2%	
Pathological response in HR-positive				0.201
No	9	2	80.0%	
Yes	7	2	94.1%	
Overall	16	4	85.7%	
Pathological response in HR-negative				0.237
No	9	2	77.8%	
Yes	7	0	100%	
Overall	16	2	87.5%	
Ki 67				0.813
<20%	8	1	87.5%	
≥20%	50	7	86.0%	
Overall	58	8	79.3%	
p53				0.229
<10%	25	5	80.0%	
≥10%	33	3	90.9%	
Overall	58	8	86.2%	
Cancer Stage				0.192
IIA	11	0	100%	
IIB + III	47	8	83.0%	
Overall	58	8	86.2%	
Inflammatory infiltrate				0.306
No	24	2	82.4%	
Yes	34	6	91.7%	
Overall	58	8	86.2%	
Angiolymphatic invasion				0.391
No	55	8	85.5%	
Yes	3	0	100%	
Overall	58	8	86.2%	

HR, hormonal receptor.

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