

Research Article

Preoperative Neoadjuvant Hormonal Therapy and Neoadjuvant Chemotherapy for Stage 3B and 4 Breast Cancer Patients in Dharmais Hospital-National Cancer Center, Indonesia: A Cohort Study

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ABSTRACT

Background: There are no data of efficacy comparison between primary systemic therapy in stage 3B and 4 breast cancer patients in Indonesia. This study compared long term outcomes of breast cancer patients treated with neoadjuvant hormonal therapy (NAHT) and those treated with neoadjuvant chemotherapy (NACT)

Methods: This was a cohort study conducted from 2011 to 2017. A total of 122 patients with stage 3B and 4 breast cancer received NAHT (n = 62) or NACT (n = 60) within a 6 cycles for NACT and 6 months for NAHT were included. Patients were excluded if they had a mastectomy before treatment, were pregnant, had been given hormonal therapy or chemotherapy before, had a contra-indication of chemotherapy, had a contra-indication of salpingo-oophorectomy bilateral for premenopausal patients, and declined to enter this study. The primary outcome of this study was overall survival. The outcomes were analysed using Kaplan-Meier for survival analysis and cox proportional hazard regression to estimate the hazard ratio.

Results: There was a statistically significant difference in overall survival (p = 0.038). Median overall survival for NAHT patients was 1265 days and for NACT patients was 654 days. The hazard ratio showed NACT patients had a higher risk than NAHT patients (1.7 95% CI 1.03 – 2.9). Pathological complete response rate was higher in the NACT group than in the NAHT group (3.3% vs. 0%).

Conclusions: Neoadjuvant hormonal therapy was superior to neoadjuvant chemotherapy in term of overall survival.

INTRODUCTION

Systemic therapy of breast cancer has been conducted for the last hundred years since Beatson in 1896 first demonstrated that ovarium ablation changes hormonal balancing in woman with breast cancer (1). Today, the choice of chemotherapy or hormonal therapy for breast cancer patients depends on technological advancement such as

immunohistochemistry and biomolecular assay. For early breast cancer, several genomic tests have been developed to more accurately predict clinical outcomes of chemotherapy and hormonal therapy dependent on individual biological characteristics (2-4). One study with gene expression profiling showed that approximately 30% of breast cancer patients who received chemotherapy did not actually require that treatment (2,4,5). However, it is different for advanced breast cancer of which the determination for using systemic

therapy depends on only hormonal receptor status examination (6).

As a care treatment, neoadjuvant systemic therapy is a standard treatment for inoperable patients (7). It offers clinical advantages to reduce tumor size, may increase the proportion of eligible patients for surgical resection or breast-conserving surgery, determine the responses to primary systemic therapy (PST) *in vivo*, and to determine the changes of the cells after drug administration and lead to subsequent treatment decisions (7-10). The administration of neoadjuvant systemic therapy varies from 4 cycles until 6 cycles.

The Indonesian guideline of systemic therapy for breast cancer patients still follows the guideline from Caucasian population. Thus, it may not be suitable for Indonesian population since there are notable differences between the Asian and Caucasian race based on clinical parameters, morphology and genetic factors (11). This study compared the efficacy between two types of primary systemic treatment for advanced breast cancer: neoadjuvant hormonal therapy (NAHT) and those treated with neoadjuvant chemotherapy (NACT).

METHODS

Participants

This was a prospective cohort study conducted from 2011 to 2017 at Dharmais National Cancer Center Hospital, Indonesia. Patients with stage 3B and 4 breast cancer received NAHT for 6 months or NACT within 6 cycles were included. Criteria for 3B and 4 were based on American Joint Committee on Cancer 7th edition guideline (12). ER and PR status were determined by immunohistochemistry test (13). Her2 status was determined by immunohistochemistry resulting in 4 categories: Her2-negative, positive grade 1, positive grade 3 and positive grade 2 which was reconfirmed by performing FISH. Classification of histopathologic grade was based on the Nottingham Grading System. Patients were excluded if they had a mastectomy before treatment, were pregnant, declined to enter this study, had been given hormonal therapy or chemotherapy before, had a contra-indication of chemotherapy, and had contra-indication of salpingo-oophorectomy bilateral (SOB) for premenopausal patients. Patient follow up was done continuously to obtain data of death, censored patients, and patients with new symptoms.

Intervention

There were 122 patients included in this study (62 of NAHT patients and 60 of NACT patients). The study was open-label and non-randomized. Patients were assigned to one of two treatments (NAHT or NACT) by choosing the treatment based on their preferences after the advantages and disadvantages between NAHT and NACT had been explained to them. The NAHT group received Aromatase Inhibitor (AI) or Tamoxifen for postmenopausal patients and for premenopausal patients, they received Tamoxifen only or SOB and AI/Tamoxifen, or if patients rejected SOB they would receive GNRH-analogue and AI/Tamoxifen which was given for 6 months. AI consisted of Letrozole, Anastrozole, and Exemestane. The NACT group received FAC (5-Fluorouracil, Adriamycin, and Cyclophosphamide) which was given for 6 cycles. After treatment, the patients were then able to receive a mastectomy when a surgically technique was possible. If not possible the patient was only able to get a second biopsy. The patient criteria for receiving a mastectomy was when the tumor was not sticking to the chest wall, not beyond the bounds of the breast and a Karnofski score higher than 90%. All patients agreed to enter this study by signing the written inform consent. The flow diagram of the participants is shown in **Figure 1**.

This study was approved by Ethical Committee at Dharmais Hospital-National Cancer Center, Indonesia (Number of Ethic Approval: 049/PEP/08/2011) and registered in ClinicalTrials.gov (number NCT02995772).

Outcomes and Statistical Methods

The primary end point of this study was overall survival and the secondary end point was progression free survival (PFS). Overall survival was defined as the length of time from the date of pathological diagnosis until death from any cause. PFS was defined as the length of time from after treatment until tumor progression or death from any cause. Pathological complete response (pCR) was defined as the absence of residual invasive and *in situ* breast cancer following completion of neoadjuvant systemic therapy. In this study, pCR was defined by pathology anatomy result.

Statistical analyses were done with SPSS IBM version 21.0 and data management was done with Microsoft Excel 2010. The study used Kaplan-Meier survival analysis to produce overall survival and progression free survival. Overall survival was an output of NAHT and NACT comparison which was analyzed from survival time and events (deaths). Progressive free survival was an output of time-lapse of tumor progression after neoadjuvant systemic therapy. Hazard ratio (HR) was estimated using Cox proportional hazard regression.

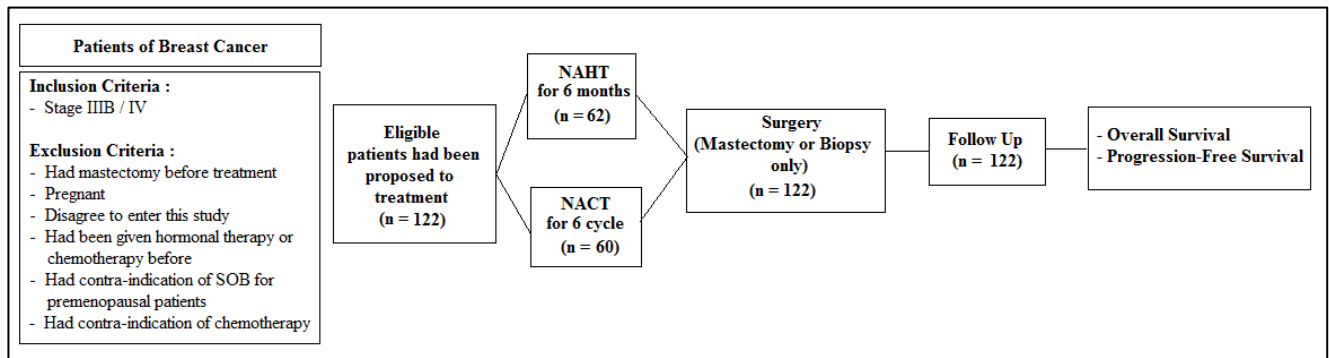


Figure 1. Research workflow

RESULTS

Table 1. Patients' characteristics

Characteristics ^a	NAHT (n = 62)	NACT (n = 60)	P-value ^b
Age (year), mean (SD)	45.7 (9.3)	49.8 (10.5)	0.023 ^c
Range	22 – 68	27 – 75	
Stage			0.011 ^d
Stage 3B	25 (39.7)	38 (60.3)	
Stage 4	37 (62.7)	22 (37.3)	
Grade			0.03 ^d
Low Grade (I and II)	39 (60)	26 (40)	
High Grade (III)	23 (40.4)	34 (59.6)	
Histological Type			0.54 ^d
Ductal	56 (50)	56 (50)	
Lobular	6 (60)	4 (40)	
Hormonal Receptor			< 0.0001 ^d
Positive	59 (64.1)	33 (35.9)	
Negative	3 (10)	27 (90)	
Her2 Status			0.25 ^d
Positive ^e	13 (41.9)	18 (58.1)	
Negative	49 (53.8)	42 (46.2)	
PCR Rate			0.14 ^d
N	0	2	
%	0	3.3	
Mastectomy			0.44 ^d
Yes	43 (48.3)	46 (51.7)	
No	18 (56.3)	14 (43.8)	
Metastase in Stage IV (n = 57)			0.2 ^d
Visceral (lung and liver)	16 (55.2)	13 (44.8)	
Non-visceral (bone)	20 (71.4)	8 (28.6)	
Death/Alive			0.47 ^d
Death	29 (52.5)	32 (47.5)	
Alive	33 (54.1)	28 (45.9)	

NAHT= neoadjuvant hormonal therapy; NACT= neoadjuvant chemotherapy; PCR rate= pathologic complete response rate; SD= standard deviation

^a Values are number percentage

^b Significant value (p-value) set at 0,05 ad two tailed; ^c Independent sample t-test; ^d Pearson's Chi Square

^e Hormonal receptor status positive was from estrogen receptor status positive and/or progesterone receptor status positive.

This research found the mean of patients' age of 45.7 years old \pm 9.3 years (for NAHT group) and 49.8 years old \pm 10.5 years (for NACT group). The youngest patient for NAHT and NACT group were 22 and 27 years old. The oldest patient for NAHT and NACT group were 68 and 75 years old. Pathological complete response (pCR) rate was higher in the NACT group than in the NAHT group (3.3% vs. 0%). The patients characteristics in this study are shown in **Table 1**.

The total number of patients was 122 (62 of NAHT patients and 60 of NACT patients). There were statistical differences in OS ($p = 0.038$). Median of overall survival was 1265 days for NAHT and 654 days for NACT. The hazard ratios of overall survival by Kaplan-Meier curves (**Figure 2**) showed that NACT patients had higher risk of death than NAHT patients (1.7 95% CI 1.03–2.9). But,

there weren't statistical difference in PFS ($p = 0.65$) between NAHT and NACT.

There were statistical differences of overall survival by mastectomy status and hormonal receptor status. Median of overall survival was 1174 days in patients assigned to mastectomy and 587 days in non-mastectomy. The hazard ratios of overall survival by Kaplan-Meier curves (**Figure 3**) showed that patients that were not assigned to mastectomy had higher risk of death than patients assigned to mastectomy, and patients who had negative hormonal receptor had higher risk of death than patients who had positive hormonal receptor. Median of overall survival was 500 days for patients who had negative hormonal receptor and 1265 days for patients who had positive hormonal receptor.

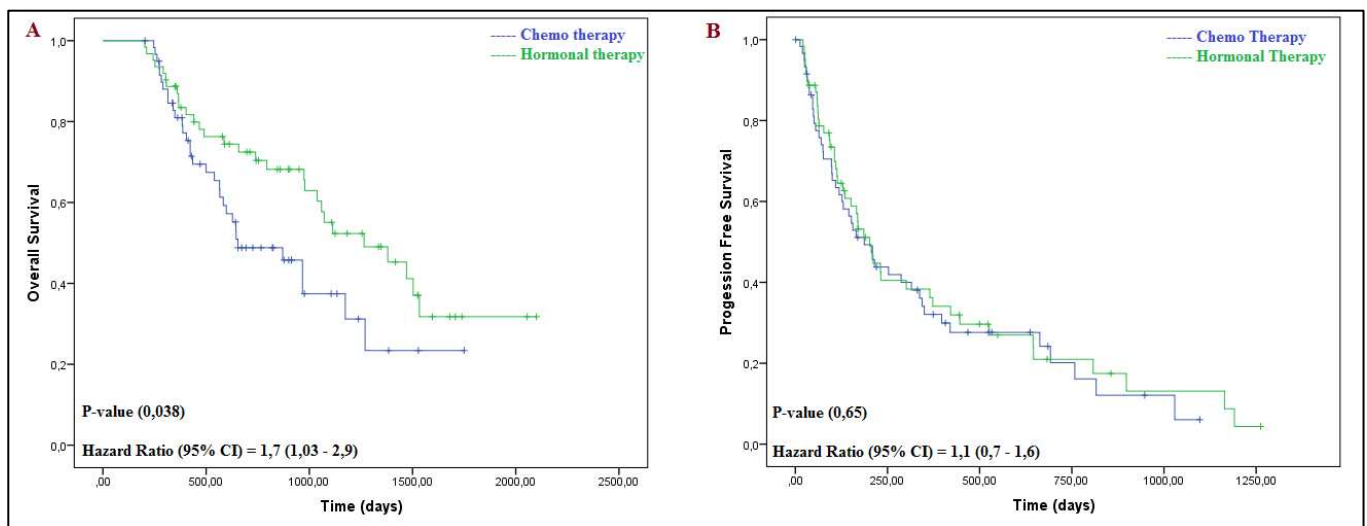


Figure 2. Kaplan-Meier curves for survival by treatment arm (A) overall survival; (B) Progression-free survival

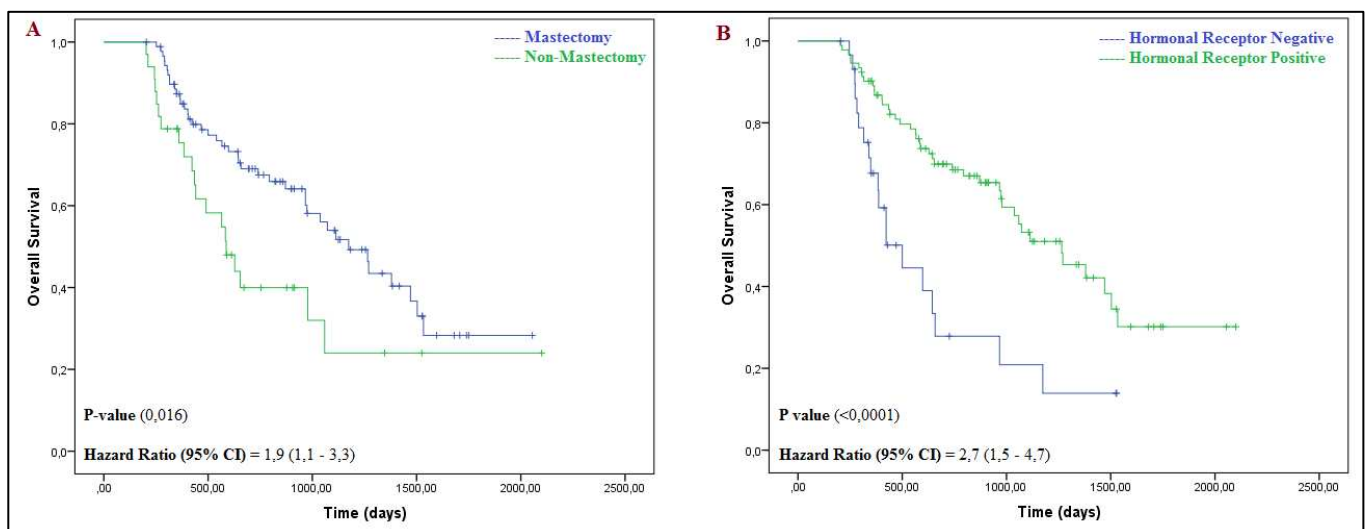


Figure 3. Kaplan-Meier curves for overall survival by (A) mastectomy status; (B) hormonal receptor status

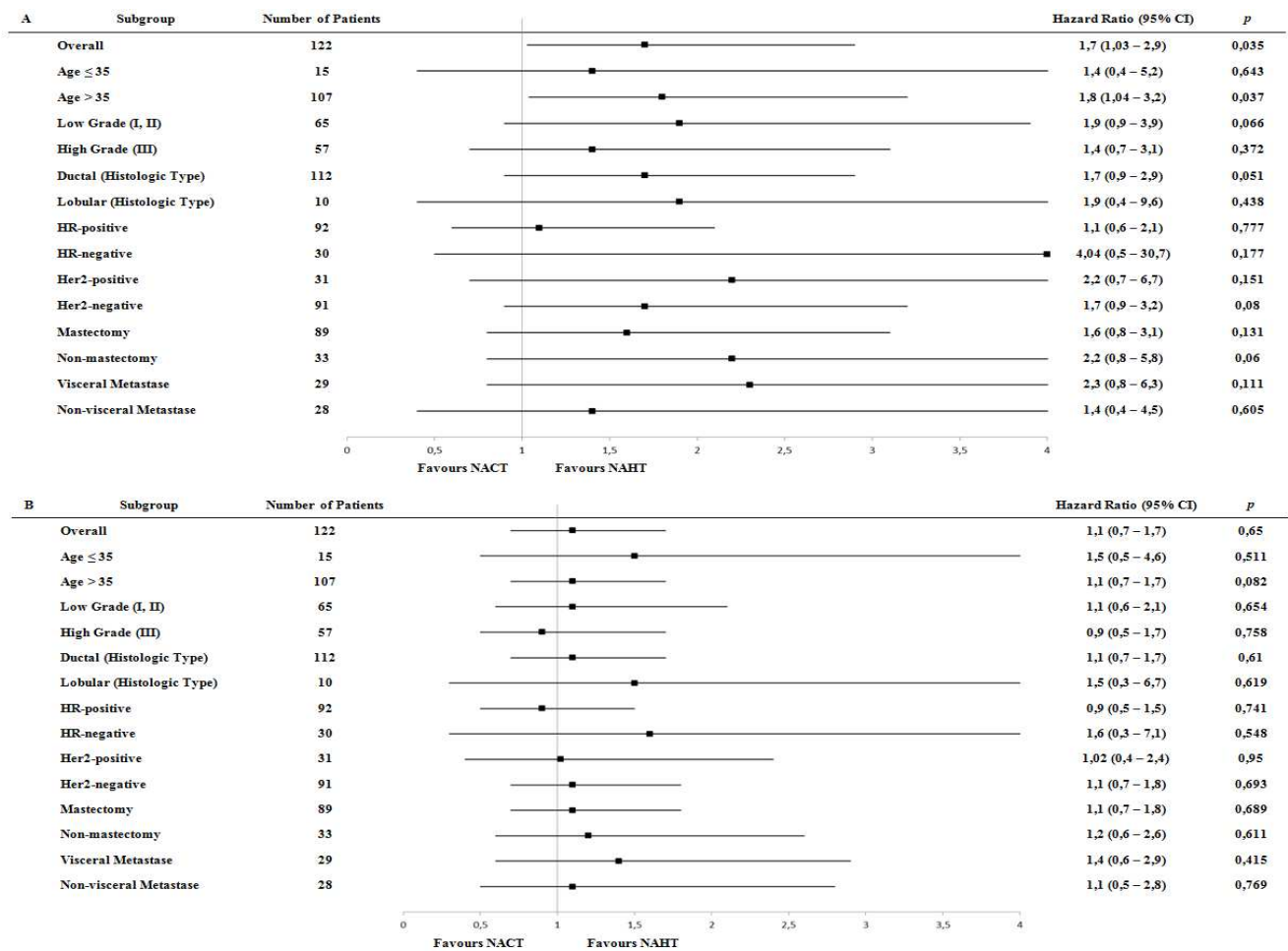


Figure 4. Forest plot of (A) overall survival, and (B) progression free survival in subgroup analysis

DISCUSSION

Findings from our study, there were statistically significant differences between NACT and NAHT in terms of age, stage, grade and hormonal receptor (Table 1). The age of patients that received NAHT is less than NACT. In older patients, there was a statistically significant difference and the Hazard Ratio was 1,8 times higher risk for death for NACT compared to NAHT (Figure 4), which is different with Marcus's study in 2013, where NACT is likely to reduce the risk of future outcomes in younger patients (14). Traditionally, NAHT is given predominantly to fragile postmenopausal patients with poor condition and NACT tends to be given to premenopausal patients to achieve a rapid response prior to surgery if technically possible (14-16).

Numerous study of neoadjuvant systemic therapy had used pCR as their endpoint. However, a common definition of pCR had not been defined until recently (17). Our results showed that NACT has higher pCR rate than NAHT (Table 1). The NSABP B-18 and B-27 study

showed a pCR of NACT patients of 13%. This rate was higher than our result because the study was conducted in early stage breast cancer patients (18). We also found patients with HR-positive, which contrast to some studies which demonstrated HR-negative tumor had higher pCR rate than HR-positive tumor (19,20). Nevertheless, there were studies that concluded pCR rate could not predict survival rate (21,22).

To date, there are still few studies comparing the efficacy of NACT and NAHT in breast cancer patients. Although there are such studies, generally the number of patients is small, overall survival is not frequently obtained and mostly the studies were only done on the positive hormone receptor group. In our study, we obtained statistically significant values in overall survival from comparing NAHT and NACT.

In our case, using various hormonal drugs, the results demonstrated that median survival was longer than NACT patients, median OS and PFS were 1265 days and 202 days for NAHT and 654 days and 187 days for NACT patients, with statistically significant differences

(Figure 2). It is similar with other studies that showed patients who received NAHT alone had a longer median survival than patients who received NACT alone (14,21,23,24).

In this study, 75.4% patients were hormone receptor (HR) positive. HR is a good predictor of outcomes with neoadjuvant hormonal therapy. Earlier, HR was classified with a cut-off point of 10% to be able to response to hormonal therapy. Until now, there is no study comparing NACT and NAHT with an HR cut off point of 1% for advanced breast cancer and we attempted to use a cut-off point of 1% in this study (13). Our result for HR positive in this population was similar with Cochrane meta-analysis study that also found no difference in overall survival between patients receiving hormonal therapy and chemotherapy (25), but NAHT patients tend to have longer median overall survival than NACT patients. This demonstrates that for advanced breast cancer patients, a 1% cut-off for HR-positive patients can still be used as a guide to received NAHT when the aim of treatment is palliation. In this study, we did not use trastuzumab as one of the treatments for patients with Her2 positive advanced breast cancer, because currently trastuzumab is not covered for this indication by the national healthcare insurance.

To our knowledge, there is still no study comparing chemotherapy and hormonal therapy in HR-negative breast cancer patients. Standard treatment for HR-negative advanced breast cancer patients is chemotherapy (6). In this study, there were only 3 patients with HR-negative status who received NAHT because they rejected chemotherapy. Median overall survival time of NAHT HR-negative patients was longer than for NACT HR-negative (658 days and 423 days) but not statistically significant and NACT patients have higher risk of death than NAHT patients although patient number was small (HR 4.1 95% CI 0.5-30.7).

In this study, after receiving 6 cycles of chemotherapy or 6 months of hormonal therapy, patients would undergo a mastectomy if technically possible. The number of mastectomy patients was almost three times of non-mastectomy patients. Patients who underwent mastectomy after treatment had a statistically significant longer median survival than non-mastectomy patients (Figure 3). These results were similar to research conducted by Robertson et al., where the life span of patients undergoing mastectomy is better than with tamoxifen alone. Over a 24 month period only 47% of patients survived when tamoxifen alone was used, versus almost 70% when mastectomy was performed (26). However, there may have been selection bias since only patients in good condition underwent mastectomy. According to systemic therapy, patients showed better OS and PFS with NAHT than NACT for all of the above characteristics (Figure 4),

although some of the results were not statistically meaningful. This suggests that for patients with advanced cancer, chemotherapy has no benefit. It was not similar with Badwe et al. (27), because this study did not only study about advanced breast cancer (4 stage) but also included 3B stage.

The strength of this study is the estimation survival between two arms regardless of HR status. Another strength is related to treatment responses, because there were patients who had HR-negative status but received hormonal therapy. The limitations were the small sample size and the lack of statistical significance in some results. Data distribution was not equal, since this study was not randomized and hence the researcher was less able to control disturbing factors. Another limitation is that we cannot use randomized clinical trial because there was an ethical problem.

CONCLUSIONS

The oncogenesis process in patients with advanced cancer has been completed. Therefore, the treatment should be palliative and should not worsen the quality of life of the patients. In summary, this study has shown that NAHT as initial treatment for stage 3B and 4 breast cancer offers longer OS than NACT regardless of HR status. The efficacy comparison of these two treatment options warrants further investigation with larger sample size and further exploration of the molecular background.

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DECLARATIONS

Competing of Interest

The authors declare that they have no competing interests.

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