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ORIGINAL ARTICLE

# Assessment of Survival and Cardiotoxicity of Adjuvant Trastuzumab among HER2 Breast Cancer Patients in an Oncology Centre in Malaysia

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## ABSTRACT

**Introduction:** Adjuvant trastuzumab has been used in human epidermal growth factor-2 (HER2) breast cancer to improve survival but with concern of cardiotoxicity. Our study is the first to review efficacy and toxicity of adjuvant trastuzumab in Malaysia. **Methods:** This is a retrospective cohort study on HER2 non metastatic breast cancer patients in University Malaya Medical Centre diagnosed between October 2006 and May 2011. Two cohorts were created based on whether or not they received adjuvant trastuzumab. Disease free survival (DFS) and overall survival (OS) for both groups were estimated using Kaplan Meier method and compared using Log rank test. Cox proportional hazards regression models analysed for potential covariates of age, tumour size and grade, node and estrogen receptor (ER) status. Trastuzumab cardiotoxicity was defined as left ventricular systolic dysfunction or heart failure with or without symptoms and graded using Common Terminology Criteria for Adverse Events (CTCAE 4.0). **Results:** 170 HER2 non metastatic breast cancer patients were identified. Thirty-three received trastuzumab and 136 did not. Median age was 53.4 ± 10.3 years old. Significantly more ER negative patients received trastuzumab. Four years DFS in 'trastuzumab' versus 'no trastuzumab' cohort was 90.9% vs 74.5% (p = 0.027). Four years OS was 91% vs 84.7% (p = 0.30) respectively. Majority tolerated trastuzumab with no toxicity. Five patients (15.2%) experienced cardiotoxicity (all grade I).**Conclusions:** Adjuvant trastuzumab significantly improved DFS in HER2 breast cancer. Treatment was well tolerated. With this we propose the justification for adjuvant trastuzumab in HER2 breast cancer in our population.

**KEYWORDS: breast cancer, trastuzumab, survival, cardiotoxicity**

## INTRODUCTION

Breast cancer is the most common cause of cancer death in Malaysia [1]. About 20 to 30% of breast cancer patients have amplification of HER2 gene which confer them with more aggressive and poorer prognosis disease even when they received similar adjuvant treatment as their counterparts [2, 3].

Trastuzumab is a monoclonal antibody that blocks activation of HER2 receptors. There are seven major randomised trials on adjuvant trastuzumab in early HER2 breast cancer [4-9]. Three meta-analyses on these trials by different groups concur that adjuvant trastuzumab would be able to reduce recurrences and improve survival of HER2 breast cancer patients [10-12]. However, two of the meta-analyses also found that trastuzumab increases risk for decline in heart function which could be as high as 2.45 folds [10, 11].

This observation of improving survival but increase in cardiotoxicity with the use of adjuvant trastuzumab has also been reported in several retrospective studies worldwide [13-19]. To date, no study of such has been done in Malaysia where trastuzumab has been used in adjuvant setting since 2006.

Therefore, the objective of this study is to analyse efficacy and toxicity of adjuvant trastuzumab in Malaysia by conducting the study in one of the main oncology tertiary centre in Malaysia.

## METHODS

This is a two arm retrospective cohort study. The study cohort consisted of all non-metastatic HER2 positive breast cancer patients treated at University Malaya Medical Centre (UMMC) from October 2006 until May 2011. This starting date of our cohort was chosen

as October 2006 as this is when trastuzumab was first approved to be used for adjuvant breast cancer. Meanwhile the end date of our study cohort was May 2011 to give at least 2 years of follow up data because the cut-off date for data analysis was May 2013.

Our patients' HER2 status was determined using immunohistochemistry (IHC) as in-situ hybridization testing was only available in UMMC in September 2012. HER2 positivity was defined as tumour IHC staining score of 3+ as per ASCO/CAP guidelines [20].

Two sources were used to identify patients for the study to ensure all eligible patients were captured. The first source was a prospectively maintained breast cancer database which was managed by UMMC surgical team. The second source was the oncology chemotherapy daycare appointment diaries to ensure that all patients who received adjuvant trastuzumab within the study timeframe were not missed out from the study. The two lists were compared and any overlap was noted.

After excluding those who were lost to follow up, a total of 170 patients fulfilled the inclusion criteria for the study (Table 1) and were included for the final analysis. Of these, 33 patients received adjuvant trastuzumab and the remaining 137 patients did not. Based on whether patients received adjuvant trastuzumab or not, we divided them into two cohort: 'trastuzumab' and 'no trastuzumab' cohort. As this is a retrospective study there was no control over the baseline characteristics or number of patients included in each arm and some imbalances were expected. These imbalances will be addressed statistically and will be discussed in subsequent part of the paper.

A data collection sheet was used to capture demographic, histopathological data, treatment received, site of first relapse, and date of relapse or death. Disease free survival (DFS) is defined as time from diagnosis to recurrence of the cancer either locally, regionally or distantly. We defined overall survival (OS) as time from diagnosis to death from any cause.

For our first study objective of survival analysis, we identified two cohorts as explained above: 'trastuzumab' and 'no trastuzumab' cohort. Baseline characteristic between the two groups were compared using chi-squared test for categorical variables and independent t-test or Mann-Whitney test for continuous variables. DFS and OS were estimated for both groups using Kaplan-Meier method. Comparison of these outcomes between the two groups was based on a log rank test. Cox proportional hazards regression models was used to analyse for potential covariates of age at diagnosis (39 years or younger, 40 to 49 years, 50 to 59 years, or 60 years of age or older), nodal status (0, 1 to 3, 4 to 9, or 10 or more positive nodes), tumour stage as per standard international AJCC staging (T1, T2, T3 and T4), receptor status (ER positive vs ER negative) and grade of tumour (grade I vs grade II vs grade III). All statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) version 21.0. Significance of all tests was taken as $p < 0.05$.

**Table 1** Inclusion and exclusion criteria

| Inclusion Criteria | Exclusion Criteria |
|---|---|
| Non metastatic breast cancer | Metastatic disease |
| HER2 positive | HER2 negative |
| | Recurrent breast cancer |
| | Ductal carcinoma in situ |
| | Trastuzumab used in neoadjuvant setting |
| | Refuse clinically indicated other standard adjuvant treatment |
| | Did not complete other standard adjuvant treatment |
| | Lost to follow up |

For the second study objective of trastuzumab toxicity, we divided the toxicity as either cardiac related or non-cardiac related. The toxicities were graded using the internationally accepted Common Terminology Criteria for Adverse Event (CTCAE) version 4.0.

Trastuzumab induced cardiotoxicity (TIC) was defined as either asymptomatic drop in left ventricular ejection function (LVEF), or symptomatic heart failure [21-27]. Asymptomatic drop in LVEF was defined as a decline in LVEF of at least 10% to below 55% without accompanying signs or symptoms [28].

Patients' LVEF were measured using echocardiography at baseline and at 3, 6, 9 and 12 months whilst on treatment as a standard protocol at UMMC. Therefore to analyse for trastuzumab induced cardiotoxicity (TIC), we recorded the measured LVEF

as well as development of any clinical signs and symptoms of heart failure during the course of treatment.

We also recorded additional information to investigate potential risk factors for trastuzumab cardiotoxicity base on previous studies [21, 22, 25, 27, 29, 30, 31,] which are age, low baseline LVEF, previous anthracycline exposure, hypertension, diabetes, hyperthyroidism, previous history of ischaemic heart disease and left sided radiotherapy.

Ethics committee of University Malaya approved the study on 28 March 2013 in accordance with good clinical practice guidelines.

## RESULTS

### Overall

The study cohort consisted of 170 newly diagnosed non metastatic HER2 positive breast cancer patients. Median age was 53.4 ± 10.3 (range 31 - 81) years old. Of 170 patients in this study, 33 (19.4%) received adjuvant trastuzumab while 137 did not. Despite this being a retrospective study with no control over who gets into one group over the other, surprisingly the demographic and clinicopathological features between the two groups were statistically balanced except for ER negativity which was higher in the trastuzumab group.

**Table 2** Clinical and pathological characteristic of patients according to subgroups

| Characteristics | Trastuzumab [n (%)] | No trastuzumab [n (%)] | P-value |
|---|---|---|---|
| **Age at diagnosis (years)** | | | |
| Median (SD) | 51.4 (SD±10.5) | 53.8 (SD±10.1) | 0.226(a) |
| **Age range** | 33-68 years old | 31 – 81 years old | |
| **Age group** | | | |
| **≤ 39** | 5 (15.1) | 14 (10.2) | 0.884 |
| **40 – 49** | 6 (18.2) | 26 (19.0) | |
| **50 – 59** | 13 (39.4) | 57 (41.6) | |
| **≥ 60** | 9 (27.3) | 40 (29.2) | |
| **Race** | | | |
| Malay | 9 (27.3) | 37 (27.0) | 0.909 |
| Chinese | 19 (57.6) | 73 (53.3) | |
| Indian | 5 (15.1) | 26 (19.0) | |
| Others | 0 (0) | 1 (0.7) | |
| **Tumour size (T stage)** | | | |
| T1 (< 2cm) | 8 (24.2) | 43 (31.4) | 0.706 |
| T2 (2cm – 5cm) | 22 (66.7) | 78 (56.9) | |
| T3 (> 5cm) | 3 (9.1) | 14 (10.2) | |
| T4 (locally advanced) | 0 (0) | 2 (1.5) | |
| **Tumour size** | | | |
| Mean (cm) ±SD | 3.5 ± 2.6 | 3.8 ± 3.1 | 0.542 (a) |
| **Tumour grade** | | | |
| 1 | 0 (0) | 5 (3.6) | 0.418 |
| 2 | 16 (48.5) | 61 (44.5) | |
| 3 | 17 (51.5) | 65 (47.4) | |
| Unknown | 0 (0) | 6 (4.4) | |
| **Lymph node status** | | | |
| 0 | 13 (39.3) | 78 (56.9) | 0.052 |
| 1-3 | 14 (42.4) | 27 (19.7) | |
| 4-9 | 4 (12.1) | 18 (13.1) | |
| >9 | 2 (6.1) | 14 (10.2) | |
| **Estrogen receptor (ER)** | | | |
| Positive | 8 (24.2) | 64 (46.7) | **0.019** |
| Negative | 25 (75.8) | 73 (53.3) | |

(a) Independent t-test; All other variables were analysed using chi-squared or fisher-exact test; SD = standard deviation

### Disease Free Survival (DFS)

At time of analysis in May 2013, 44 out of 170 patients in the cohort (25.9%) developed recurrences.

Of the 44 patients who recurred at time of analysis, 41 occurred in patients who did not receive adjuvant trastuzumab. Meanwhile only three patients who did receive adjuvant trastuzumab, developed breast cancer recurrence. This resulted in a significant different of DFS between the two groups [(90.9% in trastuzumab group vs 74.5% in 'no trastuzumab' group ($p = 0.027$)] (Figure 1).

Univariate and multivariate analysis showed that DFS of our patients are affected by tumour size, number of nodal involvement and whether or not they received adjuvant trastuzumab.

The number of event in trastuzumab cohort is too small for robust statistical analysis but it can be seen that all patients regardless of age at diagnosis, tumour size, estrogen receptor status and tumour grade would significantly benefit from adjuvant trastuzumab in improving their DFS (Table 3). The magnitude of difference in DFS from adjuvant trastuzumab is largest

in those younger than 39 years old whereby all five patients who received adjuvant trastuzumab were free of disease (100%) compared to only 50% of those in the same age group who did not get adjuvant trastuzumab (Table 3 and Figure 2).

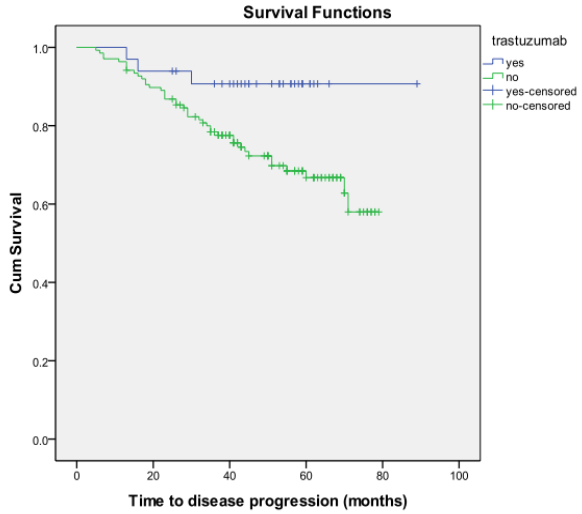


**Figure 1** Kaplan Meier curve: Disease free survival (DFS) between trastuzumab and 'no trastuzumab' group

**Table 3** Analysis of DFS between trastuzumab and non trastuzumab group

| | Number of Events (%) | | |
|---|---|---|---|
| **Factor** | **Trastuzumab (n = 33)** | **No trastuzumab (n = 137)** | **P-value (Stratified Logrank)** |
| **Age group** | | | |
| <39 years old | 0/5 (0) | 7/14 (50.0) | **0.025** |
| 40 – 49 | 1/6 (16.7) | 7/26 (26.9) | |
| 50 – 59 | 2/13 (15.4) | 18/57 (31.6) | |
| >60 years old | 0/9 (0) | 9/49 (18.4) | |
| **Tumour stage** | | | |
| T1 | | | |
| T2 | 1/8 (12.5) | 7/43 (16.3) | **0.022** |
| T3 | 1/22 (4.5) | 28/78 (35.9) | |
| *T4 | 1/3 (33.3) | 4/14 (28.5) | |
| | - | 2/2 (100) | |
| **N stage** | | | |
| N0 | 0/14 (0) | 18/81 (22.2) | 0.066 |
| N1 | 0/13 (0) | 7/24 (29.2) | |
| N2 | 1/4 (25.0) | 7/18 (38.9) | |
| N3 | 2/2 (100) | 9/14 (64.3) | |
| **Estrogen receptor (ER)** | | | |
| ER positive | | | |
| ER negative | 1/8 (12.5) | 18/64 (28.1) | **0.021** |
| | 2/25 (8.0) | 23/73 (31.5) | |
| **Grade** | | | |
| *I | - | 3/5 (60.0) | **0.033** |
| II | 2/16 (12.50 | 14/59 (23.7) | |
| III | 1/17 (5.9) | 20/63 (31.7) | |

*There were no grade I and T4 patient in trastuzumab group

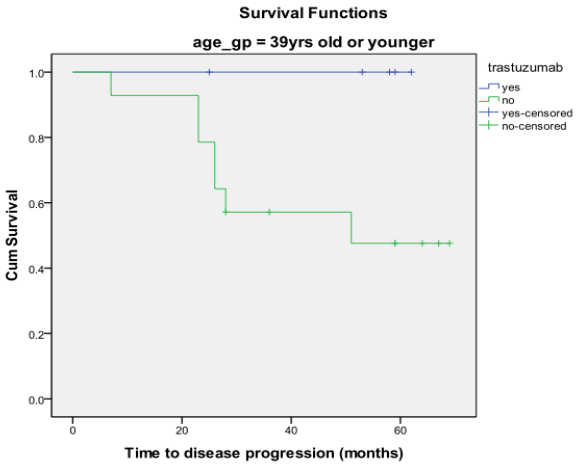


**Figure 2** Kaplan Meier curve of DFS difference between trastuzumab and non trastuzumab cohort in those aged 39 years old or younger

## Overall Survival

Four-years OS in trastuzumab group was 91% compared to 84.7% in non-trastuzumab group and was non-statistically significant (p=0.30) although the two graphs are separating widely at the end of the analysis (Figure 3).

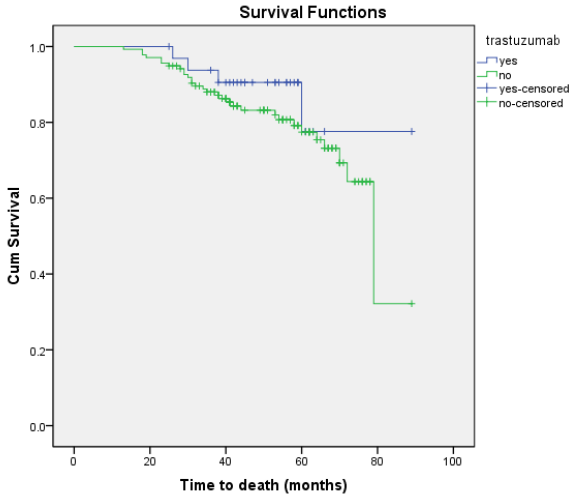


**Figure 3** Kaplan Meier curve of overall survival between trastuzumab and non-trastuzumab cohort

## Trastuzumab Treatment Experienced

At the time that this study was carried out, there was no accepted guideline on how trastuzumab should ideally be given. Therefore, among our study cohort, out of 33 patients who received adjuvant trastuzumab, 24 patients (72.7%) received trastuzumab following the last cycle of chemotherapy, every three weeks for 17 times as per HERA trial protocol [5]. Four patients (12.1%) while also receiving 17 times of three weekly

trastuzumab, started having the treatment concurrently with adjuvant chemotherapy. Another four patients (12.1%) received adjuvant trastuzumab weekly for nine times concurrently with either vinorelbine or docetaxel as per FinHER protocol [7]. Meanwhile one patient received adjuvant trastuzumab together with docetaxel and carboplatin (TCH regime) as per BCIRG trial protocol [6]. After an update of the FinHER protocol in 2009 showing no significant benefit of both DFS and OS [25], no more patients at the centre received trastuzumab following the FinHER protocol.

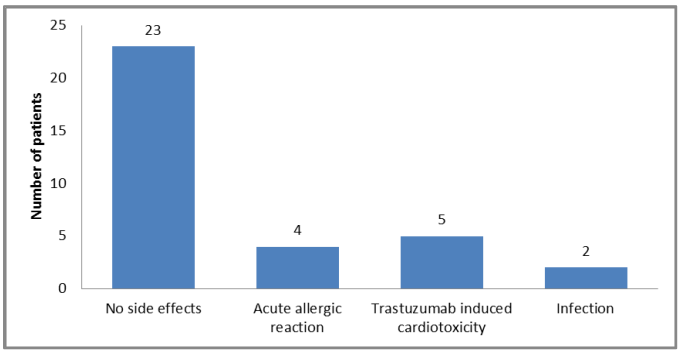


**Figure 4** Trastuzumab side effects

Most patients (69.7%) tolerated trastuzumab with no side effects (Figure 4). Five patients (15.2%) had trastuzumab induced cardiotoxicity and they are all of grade I toxicity. No patients suffer higher grade II, III or IV cardiotoxicity. Of the five patients who experienced cardiotoxicity, only one patient had a drop of LVEF to less than 50% resulting in permanent discontinuation of trastuzumab. The other four patients had recovery of their LVEF after momentarily withholding treatment and subsequently were able to complete the planned course of adjuvant trastuzumab. No obvious risk factor for developing trastuzumab associated cardiotoxicity could be identified (Table 4).

## DISCUSSION

The DFS rate at four year of 90.9% in this study is similar to that reported in adjuvant trials [5, 26, 32]. Adjuvant trastuzumab benefited our patients regardless of age group, tumour size, tumour stage, ER status and tumour grade.

Interestingly we found that oncologists at our centre tend to offer adjuvant trastuzumab to ER negative patients rather than those with ER positive disease. This may be because it is known that ER negativity equates to poorer prognosis [33, 34] compared to ER positive disease whereby prolong hormonal therapy can be offered.

**Table 4** Risk factors for cardiotoxicity

| | **Cardiac toxicity (n = 5)** | **No cardiac toxicity (n = 28)** | **P value** |
|---|---|---|---|
| **Age (mean)** | 57.6 +-8.4 years old | 50.3 +-10.6 years old | 0.158 (a) |
| **Baseline LVEF Mean ± SD** | 67.8% ±7.9 | 69.4% ± 6.2 | 0.612 (a) |
| **Anthracycline exposure** | | | |
| Yes | 5 (100%) | 25 (75.8%) | 1.00 |
| No | 0 (0%) | 3 (9.1%) | |
| **Hypertension** | | | |
| Yes | 1 (20%) | 4 (12.1%) | 1.00 |
| No | 4 (80%) | 24 (72.7%) | |
| **Diabetes** | | | |
| Yes | 0 (0%) | 1 (3.0%) | 1.00 |
| No | 5 (100%) | 27 (81.8%) | |
| **Hyperthyroidism** | | | |
| Yes | 0 (0%) | 1 (3.0%) | 1.00 |
| No | 5 (100%) | 27 (81.8%) | |
| **IHD** | | | |
| Yes | 0 (0%) | 1 (3.0%) | 1.00 |
| No | 5 (100%) | 27 (81.8%) | |
| **Left sided radiotherapy** | | | |
| Yes | 4 (80%) | 9 (27.3%) | 0.06 |
| No | 1 (20%) | 19 (57.6%) | |

(a) Independent t-test; other categorical variables were analysed using Fisher-Exact test as does not fulfill requirement for Chi-squared test

### Overall Survival

Adjuvant trastuzumab does not seem to have significant impact on overall survival of our patients although it was seen that the Kaplan-Meir curves for OS between the two groups were starting to separate at the end of the study period. It could be hypothesized that with larger sample size and longer follow up, the difference could become significant.

### Trastuzumab Induced Cardiotoxicity (TIC)

When compared to major landmark trials, the incidence of trastuzumab induced asymptomatic drop in LVEF in our study of 15.2% is comparable to

18.9% reported in BCIRG trial [6] but higher compared to 7% reported in HERA trial [26].

What appear to be almost double increase in cardiotoxicity in our study population compared to HERA trial may well be related to the difference in the definition of trastuzumab induced cardiotoxicity (TIC) used. In fact, if the definition used in HERA trial is adapted to our study, only one of our patients has a drop of LVEF to less than 50% resulting in 3% trastuzumab related cardiac event, which would be comparable to that of 7% in HERA trial [26].

As for grade III/IV trastuzumab related cardiotoxicity, it is reassuring that none of our patients develop grade III/ IV cardiotoxicity compared to 4.5% incidence across the five major RCTs [10].

Meanwhile, comparing our result with other retrospective studies, our cardiotoxicity rate of 15.2% was much lower compared to most studies found. For example the rate of cardiotoxicity was 28.2% among Japanese patients [19] and 38% among Moroccan patients [29]. The Japanese study had more elderly patients which may explain the higher incidence of cardiotoxicity as age itself increases cardiac risk [19]. On the other hand the Moroccan study did not specify why their cardiotoxicity rate was higher than that of RCTs [29].

Analyzing potential risk factors for trastuzumab induced cardiotoxicity (TIC), those having left sided breast/chest wall radiotherapy tend to show a higher risk of getting TIC. Interestingly having previous history of ischaemic heart disease does not predispose one to TIC. However this results need to be interpreted with caution due to small number of event observed in trastuzumab group of our study (five events).

Even though several meta-analysis of major adjuvant trials have shown highly significant benefit of adjuvant trastuzumab in HER2 overexpressed breast cancer, trials were done under controlled environment on selected patients' population which can be quite different to what actually happen in real practice especially in countries with limited resources and different culture and belief, like Malaysia, whereby clinical practice sometimes cannot follow international guidelines or that as outlined in trials' protocol. Furthermore even though more than 13000 patients were included in all five major randomised trials, only HERA trial included Asian patients [5].

Therefore, our observational retrospective study provides results that directly reflect practice at our centre and are directly applicable to our study population. Furthermore while there may be many retrospective studies already done on the issue of safety and efficacy of adjuvant trastuzumab in breast cancer, most of them were of single arm study. Our study on the other hand has patients from the same population as the comparison arm. Not only do our patients have similar demographic features, but as they come from the same cancer centre, they would tend to have less different variation in other aspects of breast cancer treatment thus producing a more equal group for results comparison.

As with other retrospective studies, missing data was a limitation. The missing data were from missing folders and untraceable patients despite attempts to trace them. These patients were excluded from final analysis although none were from the trastuzumab group.

The low rate of prescription for adjuvant trastuzumab at our centre resulted in a small sample size for the trastuzumab group despite the cohort spanning over five years. This small sample size was a major limitation for more robust statistical analysis.

It is suggested that the study be repeated in the future as it is expected that the number of patients receiving adjuvant trastuzumab will be increased at our centre. Collaboration with other major oncology tertiary centres also would lead to bigger sample size and a more representative study population.

## CONCLUSION

Our study is the first in Malaysia to document a significant effect of adjuvant trastuzumab in improving DFS. Our results also show a trend towards better OS in our HER2 amplified breast cancer patients who were treated with adjuvant trastuzumab compared to those who did not receive the drug.

We also found that treatment was well tolerated. The only one case of permanent discontinuation of trastuzumab due to treatment related cardiotoxicity highlighted the importance of

appropriate patient selection for treatment and careful cardiac monitoring of patients who were on treatment.

Therefore, our study concluded that adjuvant trastuzumab should be considered in HER2 amplified breast cancer patients as the risk of trastuzumab induced cardiotoxicity can be justified, given the significant absolute improvement in DFS by 16%.

## Conflict of Interest

Authors declare none.

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