

# HER<sub>2</sub> positive breast cancer and its treatment with trastuzumab, where are we now?

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Published by

ARDA.

## Abstract

HER<sub>2</sub>-positive breast cancer is one of the most common types of female breast cancer around the world. This review summarizes information and results of HER<sub>2</sub>-positive breast cancer trials and compares their results with the standards in Bosnia and Herzegovina. It is done based on a literature search on PubMed and Google Scholar. This review analyzed trastuzumab as a golden treatment standard for HER<sub>2</sub>-positive cancer treatments. Trastuzumab is a monoclonal anti-human epidermal growth factor receptor antibody and besides its effect in the treatment of breast cancer, suggests the treatment with trastuzumab within 1 year. Bosnia and Herzegovina have also accepted standards and guidelines for the treatment of HER<sub>2</sub>-positive breast cancer and they are in step with the latest achievements worldwide.

**Keywords:** HER<sub>2</sub> positive breast cancer; trastuzumab; neoadjuvant therapy; adjuvant therapy; HER therapy

## 1. Introduction

Breast cancer (BC) is one of the most frequent cancers that occurs in female population around the whole world, and it is the leading cause of the premature deaths in this population [1, 2]. The number of BC diagnosis is followed by the diagnosis of colorectal, lung and cervical cancer [1, 3]. There are many risk factors that can contribute to the development of BC such as old age, family history, eating habits, exposure to female reproductive hormones, benign breast disease and environmental factors. Although we know all this information, the exact causes of BC are still unknown and not well studied [2]. According to the International Agency for Research on Cancer and data that are updated until 2020 (Figure 1), there are more than 2.2 millions of BC cases in the world [1]. During the 2020, estimated number of BC patients in Bosnia and Herzegovina was 1554 representing 23.3% of all BC cases diagnosed in women [1].

If we take into consideration terms such as histologic types, natural history, clinical behavior, and response to the treatment, we can say that BC is a diverse disease. As time passed and with the development of effective treatment for different types of the disease that expressed hormone receptors such as estrogen receptor (ER), progesterone receptor (PR) as well as anti-human epidermal growth factor receptor 2 (HER<sub>2</sub>), BC has been classified according to its expression of ER, PR and HER<sub>2</sub>. Beside this classification, one additional type, triple-negative BC (TNBC) is used to describe BC lacking ER, PR, and HER<sub>2</sub> [4].

HER<sub>2</sub> is overexpressed in 15-20% of all BC cases [5]. Overexpression of HER<sub>2</sub> contributes to HER<sub>2</sub> positive BC which is associated with aggressive form of the disease, high recurrence probability and worse prognosis if it is not treated adequately and on time [2, 5]. Since it is a very complex disease, adequately treatment is the most important part towards the outcome. It is necessary to determine stage of the disease, biological characteristics of the tumor and the initial treatment protocol [2]. According to the World Health Organization (WHO), cancer is the 2<sup>nd</sup> leading cause of death worldwide (9.6 million deaths) [6].

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The development of HER<sub>2</sub>-tageted therapies have shown increased curing rate for early diagnosed disease as well as for metastatic breast cancer. After the involvement of trastuzumab, many HER<sub>2</sub> targeted agents have been developed and thanks to them different treatment possibilities were available. In both, neoadjuvant and adjuvant (post-operative) therapy trastuzumab should be used in combination with other drugs that are used for anti-HER<sub>2</sub> therapy [2]. Survival is closely related to BC sub-type and according to the studies that are performed until now, the most successful progress has been observed in HER<sub>2</sub> positive BC patients [7]. Increased number of cancer patients is directly connected with the physical, emotional, and financial status and health system. Some health systems in poor countries are less prepared to give diagnosis and treatment on time. On the other hand, developed countries have higher survival rate since their health system is strong and patients get early detection, quality treatment and survivorship care [3,6]. Early stage of HER<sub>2</sub> positive BC is described as the disease that is detected in the breast and nearby lymph nodes with the confirmation that disease has not spread to other areas of the body [8].

## 2. Material and methods

This study is based on literature research for HER<sub>2</sub> positive BC and its treatment with trastuzumab. Aim of this study was to compare treatment of this type of BC in Bosnia and Herzegovina and worldwide. It relies on PubMed (<https://pubmed.ncbi.nlm.nih.gov/>) and Google Scholar (<https://scholar.google.com/>) search. Articles that are published in the last 10 years are taken into the consideration, together with the most impactful trials done in this field.

## 3. Results

### 3.1. Trastuzumab

During the 1998, United States Food and Drug Administration (FDA) accepted and approved trastuzumab (Herceptin®) as the first (antibody-targeted) therapy for BC [9]. Soon after that, Canada also approved trastuzumab for the treatment of metastatic BC. Trastuzumab binds to the extracellular domain IV of HER<sub>2</sub> and in that way it inhibits downstream cell signaling implicated in cell proliferation, motility, adhesion, and survival [8]. A series of recent studies has indicated that treatment with trastuzumab in combination with chemotherapy increases the chance to disease progression as compared to chemotherapy alone [9]. When it comes to the prognosis of HER<sub>2</sub> positive BC patients, this type is associated with poor prognosis in BC patients. Authors state that HER<sub>2</sub> overexpression is closely related to tumor grade, positive lymph node metastases and mitotic count. This type of disease has shown increased resistance to endocrine therapy and patients involved in therapy do not responds to non-anthracycline, non-taxane-containing chemotherapy. On the other side, HER<sub>2</sub> positive BC patients has shown good response to anthracycline and paclitaxel therapy [8].

### 3.2. Immunohistochemistry (IHC)

IHC staining is the technique that is using for initial testing of HER<sub>2</sub> status in early diagnosed BC patients. It is quantitative evaluation since HER<sub>2</sub> is expressed in epithelial cells of breast. IHC staining technique is performed to state availability of certain patient to start with anti-HER<sub>2</sub> therapy. Around 80% of newly diagnosed BC patients in US goes through IHC assays and it is considered as the primary determining test for HER<sub>2</sub> status [10]. Advantages of this technique are common pathologic routine, wide availability, low cost while some of the limitations are duration, fixation, and subjective slide scoring system. When it comes to this subjective slide scoring system, United Kingdom have some recommendation such that this analysis should be performed only in laboratories which performs annual minimum of 250 IHC. [10]

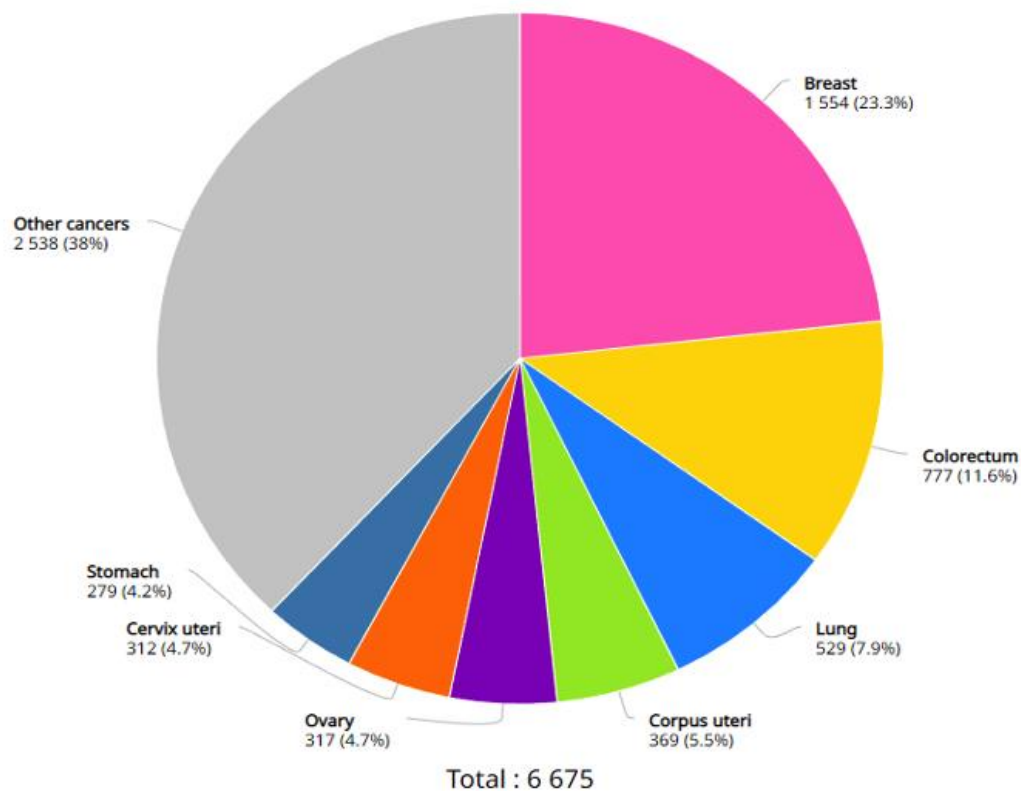
### 3.3. Fluorescence in situ hybridization (FISH)

Fluorescence in situ hybridization (FISH) is used for the detection of HER<sub>2</sub> gene amplification, and it is done by using fluorescent-labeled probes is a morphology-driven slide-based DNA hybridization assay. By performing this technique, chromosome-17 probe (CEP17) is used as an internal control). It is objective scoring method from the societal perspective with the advantages of 2 HER<sub>2</sub> signals [10].

### 3.4. Neoadjuvant anti HER therapy treatment of HER<sub>2</sub> positive BC in Bosnia and Herzegovina

Neoadjuvant anti HER<sub>2</sub> therapy is a standard in Bosnia and Herzegovina for the treatment of early HER<sub>2</sub> positive and locally advanced BC [2]. Neoadjuvant systemic therapy is performed to put tumor from inoperable to operable stage. In that way, chance of breast-conserving surgery will be increased, less radical axillary dissection will be done, morbidity associated with breast surgery will be reduced and disease prognosis will be

better. Neoadjuvant therapy will increase survival rate [2, 11]. It will also downstages axillary lymph node involvement in a case when therapy includes an anthracycline and taxane [11]. Anti HER<sub>2</sub> therapy should only be given in a combination with chemotherapy. Efficiency of the therapy is measured in two ways: good and poor. Good response is in a case that the tumor gets smaller by 50% compared to the initial measurement and poor response in case that the tumor diameter is larger than 50% compared to the initial measurement. “Stable disease” is a case when there is no therapeutic response. This stage will lead to the disease progression (tumor diameter >20% or more than the initial measurement). Histopathological evaluation of the breast tissue will be a key component for evaluating the effect of the neo-adjuvant therapy. If neo-adjuvant therapy results are not good, the next step is neoadjuvant radiotherapy together with trastuzumab [2]. Neoadjuvant therapy is followed by surgery, and it is the key step in the treatment of early HER<sub>2</sub> positive BC. Survival rate after BC surgery and radiotherapy is equal to the survival rate after radical mastectomy. Axillary surgery will be performed after cytological aspiration or biopsy of the node [27].



**Figure 1.** Data representation of women diagnosed with BC in Bosnia and Herzegovina in 2020 [1]

### 3.5. Adjuvant HER<sub>2</sub> positive BC therapy in Bosnia and Herzegovina

Further chemotherapy in adjuvant treatment is not recommended in a case if a patient received 4-8 cycles of anthracyclines and taxanes. It is recommended to start with only anti-HER<sub>2</sub> therapy that will be performed for up to 1 year. Adjuvant administration is recommended only in patients with tumors >1 cm, 0.6 cm - 1 cm with negative lymph nodes as well as in tumors <0.6 cm with micro metastases in axillary lymph nodes [2]. Big improvement is done since after introduction of trastuzumab for 1 year in combination with chemotherapy, 1 out of 4 patients will experience recurrence within 10-11 years of diagnosis [12]. In a case of HER<sub>2</sub> positive metastatic BC, 50% of the patients that are treated with a combination of pertuzumab and trastuzumab with taxane in first-line treatment will die within 5 years. The highest risk of recurrence of disease is observed in patients that have positive lymph nodes and hormone receptor negative disease [13]. There are patients that will experience residual disease present in breast and/or tissue after the systemic neoadjuvant treatment of BC. This group of patients have high risk for disease recurrence. Their treatment should be escalated and 14 cycles of trastuzumab emtansine should be performed [2]. Bosnian and Herzegovinian oncologists are following the mentioned treatment based on the results of the KATHERINE trial. Authors working on the KATHERINE trial

concluded that adjuvant therapy with trastuzumab emtansine (T-DM1) should lower the risk of recurrence of invasive BC (or death by 50%). Results of this study are discussed after comparison with treatment with trastuzumab alone (88.3% patients treated with T-DM1 live without disease recurrence for 3 years compared to 77% patients treated with trastuzumab only) [2, 14].

### 3.6. Adjuvant BC radiation therapy

The main goal of the adjuvant radiotherapy is to improve local disease control and reduce relapse rates [2]. In case that radiotherapy is performed after neoadjuvant therapy, following tumor characteristics should be considered:

- presence of residual tumor after neoadjuvant therapy- number of lymph nodes involved.
- relation of lymph node metastasis to node capsule
- infiltration of perinodal tissue and
- presence of any high-risk factor for disease recurrence (high histological grade (G3), negative ER status, central tumor localization, positive resection margins, lymphovascular and/or perineural invasion and younger age (<50) [2].

### 3.7. Metastatic HER<sub>2</sub> positive BC

The golden standard for first line treatment of metastatic HER<sub>2</sub> positive BC is dual blockade (trastuzumab + pertuzumab) + chemotherapy. This treatment is supported by all worldwide treatment guidelines (AGO, ESMO, NCCN and St. Gallen) [15, 16, 17, 18]. It is also confirmed based on the results of Cleopatra clinical trial. Results of Cleopatra clinical trials have shown statistically significant survival rate by performing dual blockade instead of using only trastuzumab with chemotherapy. Also, risk of death was reduced by 34% [2, 19]. Second line therapy for metastatic HER<sub>2</sub> positive BC should be T-DM1 and it is proven in EMILIA trial that patients which received this therapy lived on average 5.8 month longer than patients which received lapatinib and capecitabine [20].

## 4. Discussion

Trastuzumab therapy improves survival rate and quality of life in patients with advanced HER<sub>2</sub> positive BC. This statement is confirmed in Cochrane meta-analysis which includes 6 adjuvant and 2 neoadjuvant studies [21]. It is important to mention that the benefits of trastuzumab can have some disadvantages for the heart (cardiac toxicity). Heart complications could be at higher risk in a BC patient with previous significant heart diseases. The optimal therapy with trastuzumab is still unknown. HERA trial did not show any differences between 2 years treatment with trastuzumab compared to the 1-year treatment. HERA trial was the only trial that have studied 1 vs 2 years efficiency of treatment with trastuzumab. Also, the PHARE trial compared achievements of 6 months vs 12 months therapy with trastuzumab, and they failed to show non-inferiority of the shorter treatment administration. For now, 1 year of adjuvant trastuzumab therapy remains the golden standard until some other results negate these findings [26]. Patients that experienced trastuzumab therapy longer than 1 year developed mildly symptomatic cardiac events but without developing some severe cardiac toxicity. HERA and PHARE trial were performed in France, and it involves more than 3380 women. Some of them continue with trastuzumab after 6 months until they reach 1 year treatment and some of them just stop after the completion of 6 months of therapy. Results just confirm that gold standard of the treatment with trastuzumab is 1 year. Authors state that this drug is relatively safe for heart and that most cardiac events take place during the drug administration [21, 25, 26].

The literature review shows that pertuzumab to the neoadjuvant therapy treatment (trastuzumab + chemotherapy) could increase life years and quality of life [22, 23, 24, 29]. This study was performed on women in Canada with locally advanced, inflammatory, or early HER<sub>2</sub> positive BC with tumor diameter bigger than 2 cm and compared with NeoSphere and Tryphaena trial. First group of patients (NeoSphere trial) includes early BC patients that received 4 cycles of neoadjuvant therapy (performed intravenously every 21 days). After surgery this group of patients were treated with additional three cycles of anthracycline chemotherapy. Differences between Canadian practice and NeoSphere trial is that patients in Canada are treated with 6-8 cycles of chemotherapy + HER<sub>2</sub> targeted therapies. Mentioned treatment needs to be performed until the surgery. On the other side, Tryphaena trial was performed on the patients that are receiving neoadjuvant therapy that includes docetaxel, carboplatin and trastuzumab. This regimen is also one of the approved ways for the treatment HER<sub>2</sub>

positive BC in Canada. Results from both studies confirmed that addition of pertuzumab to the neoadjuvant therapy will increase life years and quality of life [10, 22, 26].

As has been previously reported in the literature, prognosis of HER<sub>2</sub> positive BC has changed incredibly since the introduction of trastuzumab. Another study was performed on 4.481 female patients with diagnosis of BC. Study was done in Dresden, Germany. Data were collected and documented in the population-based Regional Clinical Cancer Registry Dresden. 465/4.481 patients were diagnosed with HER<sub>2</sub> positive BC. The aim of the study was to evaluate effect of trastuzumab in selected patients. Adjuvant chemotherapy included anthracyclines and cyclophosphamide. Also, patients with positive node received taxane additionally. This drug showed good effectiveness in patients that were under the study. Adjuvant treatment with trastuzumab has shown improved recurrence-free survival among patients with HER<sub>2</sub> positive BC compared to those patients with the same cancer type but not treated with trastuzumab. Patients with the poorest life prognosis were those with HER<sub>2</sub> positive BC but without receiving trastuzumab. Similar results were observed in metastatic patients. Prognosis of HER<sub>2</sub> positive BC patients was better than for HER<sub>2</sub> negative breast cancer [23].

For instance, another study conducted on 112 patients with HER<sub>2</sub> positive metastatic breast cancer, treated patients with trastuzumab-based chemotherapy. Here, 99/112 patients were treated with Trastuzumab (first line treatment) and 107/112 patients received trastuzumab + chemotherapy which includes taxane as the most frequently used drug. Therapy was completed in 91/112 patients and 8 of them showed progression of the disease. This therapy has shown clinical benefit and good response rate. Only patients with fewer than 80% of tumor cells with a HER<sub>2</sub>/CEP<sub>17</sub> ratio which is more than 2.2 and with IHC score of 3+ have significantly lower response to trastuzumab-based chemotherapy [24].

Over time, another study was performed on 406 patients with tumors up to 3 cm in dimension. Those patients received therapy that includes paclitaxel and trastuzumab for 12 weeks (followed by 9 months of therapy which includes only trastuzumab). 207/406 patients were diagnosed with hormone receptor positive disease with median age of 55 years. Results from these studies has shown a low risk of cancer recurrence (less than 2% at 3 years). Important to say is that these results are analyzed in a cohort in which the rate of serious toxic effect was low (incidence of heart failure was 0.5%). At the end, authors conclude that therapy design which include trastuzumab + chemotherapy will lead to the effective treatment [25].

A study that proposed major findings in the treatment of BC is the KATHERINE trial, a study that included 1486 patients with HER<sub>2</sub> positive, treated with neoadjuvant chemotherapy that included a taxane and trastuzumab, followed by surgery. Some of them have residual invasive disease in the breast or axilla after receiving neoadjuvant therapy. Patients were selected randomly. Some of them received T-DM1 and another one received trastuzumab for 14 cycles. As a result, invasive disease survival rate was higher in T-DM1 group compared to the trastuzumab patients. This study proposed the intake of taxane in adjuvant therapy since it has less adverse events [14]. On the other side, CLEOPATRA trial which include 808 metastatic HER<sub>2</sub> BC patients has shown that addition of pertuzumab increased survival rate by addition of pertuzumab compared to trastuzumab and chemotherapy alone [10].

Further, a meta-analysis of 13.864 women with HER<sub>2</sub> positive BC (node negative or node positive, operable BC, chemotherapy (adjuvant or neoadjuvant), trastuzumab or chemotherapy alone was conducted in 2021. The aim of this study was to compare efficiency of treatment in two groups of patients. First group were treated only with trastuzumab, and second group of patients were treated with trastuzumab + chemotherapy. This meta-analysis state that there were some studies which are indicating that patients treated with chemotherapy + trastuzumab has shown substantial benefits despite increased cardiac toxicity. It is proved (compared with the results of treatment with chemotherapy alone) that therapy with trastuzumab effectively reduced the rate of BC recurrence by 34% as well as the rate of BC mortality by 33%. Important to mention is that adding of trastuzumab to chemotherapy for the patients with early stage of HER<sub>2</sub> positive BC could reduce disease recurrence and mortality by a third [26]. Important to mention is that taxol has shown big efficacy combined with trastuzumab. This type of chemotherapy is performed in BC patients that do not have cardiac risk. Combination of mentioned two drugs impacts that benefits emerge earlier. The biggest impact was noticed on recurrence of the disease in the first 2 years together with no increase in toxicity. Authors state that there are some limitations of this study, and they recommend longer follow-up of these trials to evaluate safety more than 10 years after treatment. Also, individual data for patients' cardiac morbidity were not able, and they used data from individual trial reports which are stating that the serious toxicity is rare. As we already mention, golden standard for trastuzumab treatment is 1 year.

There is no study which confirm that some changes happen even if therapy with trastuzumab is more than 1 year. Despite, HER2 directed therapy with neratinib immediately after the treatment with trastuzumab is more effective than continuous trastuzumab [21, 26, 28, 29].

Recent studies suggest that there is no significant difference between therapy with trastuzumab that will be longer than 1 year. Results are the same, only cardiac toxicity will be higher. Lymph node treatment with taxane also provides great results. Surgery is recommended after neoadjuvant therapy which is in most cases followed by radiation therapy. After the radiation therapy is completed, anti-HER<sub>2</sub> therapy will be performed for up to 1 year. On the other side, the golden standard for metastatic HER<sub>2</sub> positive BC is dual blockade (trastuzumab + pertuzumab) + chemotherapy. Results from studies performed on patients that received dual blockade have shown that risk of death was reduced by 34%. Although a lot of studies are done, authors always state that improvements in any part of BC treatment are always more than welcome [21-29]. Comparison of the most impactful studies discussed in this article has shown in Table 1.

Table 1. Comparison of the most impactful studies that are done on HER2 positive BC patients and trastuzumab effectiveness.

Study	Comparable Trial		Conclusion	Reference
Standard in Bosnia and Herzegovina	-		Neoadjuvant therapy: anti HER2 therapy (trastuzumab and/or pertuzumab) + chemotherapy	[2]
	Katherine trial		Adjuvant therapy: Further chemotherapy is not recommended in a case if a patient received 4-8 cycles of anthracyclines and taxanes. It is recommended to start with only anti-HER2 therapy that will be performed for up to 1 year.	
Cochrane meta-analysis	HERA trial	Differences between 2 years treatment with trastuzumab compared to the 1-year treatment	Golden standard: 1 year treatment with trastuzumab	[21]
	PHARE trial	Failed to show non-inferiority of the shorter treatment administration (6 months vs 1 year treatment)		
HER2 positive BC diagnosed in Canadian women with locally advanced, inflammatory, or early HER2 positive BC with tumor diameter bigger than 2 cm	Neosphere trial	6-8 cycles of chemotherapy + HER2 targeted therapies with following surgery	Addition of pertuzumab to the neoadjuvant therapy will increase life years and quality of life	[22]
	Tryphaene trial	Neoadjuvant therapy that includes docetaxel, carboplatin and trastuzumab		
Dresden, Germany	-	-	Adjuvant treatment with trastuzumab has shown improved recurrence-free survival among patients with HER2 positive BC compared to those patients with the	[23]

			same cancer type but not treated with trastuzumab	
Seoul National University Bundang Hospital	-	-	Trastuzumab + chemotherapy which includes taxane as the most frequently used drug has shown clinical benefit and good response rate	[24]
Katherine	-	-	Neoadjuvant therapy was performed with taxane and trastuzumab. As a result, invasive disease survival rate was higher	[10]
Cleopatra	-	-	Addition of pertuzumab increased survival rate by addition of pertuzumab compared to trastuzumab and chemotherapy alone	
Meta-analysis	-	-	Therapy with trastuzumab (compared with the results of treatment with chemotherapy alone) effectively reduce the rate of BC recurrence by 34% as well as the rate of BC mortality by 33%.	[26]

## 5. Conclusion

To the best of our knowledge, this review paper shows how HER<sub>2</sub> positive BC is diagnosed and how it is treated in Bosnia and Herzegovina and worldwide. Since BC is the most frequent cancer in the female population, an incredible number of studies are done in this field to perform better treatment and easier diagnosis. Many studies are done, and a lot of information is presented with the only one reason: to have a golden standard in the treatment of this disease. HER<sub>2</sub> positive BC is associated with aggressive form of the disease, high recurrence probability and worse prognosis if it is not treated adequately and on time. Golden standard therapy for the treatment of HER<sub>2</sub> positive BC is trastuzumab. It is used in combination with other drugs that are used for anti-HER<sub>2</sub> therapy. Survival prognosis is closely related to the early diagnosis of the disease. Developed countries have a higher survival rate since their health system is strong and patients get early detection, quality treatment and survivorship care. Safety consideration and treatment potential should always be a priority. Effective and proven therapy needs to be given to the patients worldwide despite its cost.

## Declaration of competing interest

"The authors declare that they have no known financial or non-financial competing interests in any material discussed in this paper."

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