

# Practical consensus recommendations regarding the management of HER2 neu positive early breast cancer

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## Abstract

Over-expression of HER2 is generally considered to be a negative prognostic feature because it accompanies an increase in breast cancer mortality. However, the development of agents that specifically target HER2 has improved the management of patients with these tumours. This expert group used data from published literature, practical experience and opinion of a large group of academic oncologists to arrive at these practical consensus recommendations with regards to the use of these agents and the management of HER2 neu early breast cancer for the benefit of community oncologists.

**Key words:** Adjuvant trastuzumab, double agent, TCH regimen, tumor size

## Introduction

The incidence of Her2 positivity in Indian population is between 26% and 50%.<sup>[1-3]</sup> A number of studies have established that HER2 over-expression is a poor prognostic factor in patients with early breast cancer.<sup>[4-9]</sup> The development of trastuzumab, a humanized monoclonal antibody against the extracellular domain of HER2 and other targeted therapies has led to a marked improvement in the outcome of patients with early breast cancer whose tumours over-express the HER2 receptor.<sup>[10-13]</sup> However, trastuzumab is an expensive treatment that is beyond the reach of the majority of patients in developing countries.<sup>[14,15]</sup> This manuscript was prepared to help community oncologists better manage HER2 neu positive early breast cancer and provide guidelines regarding the use of trastuzumab and other agents.

Expert oncologists from all over India met to discuss and reach a consensus statement to provide community oncologists practical guidelines on the management of HER2 neu early breast cancer. The discussion was based on published evidence and practical experience in real life management of such patients. The expert group discussions were moderated by Dr Ankur Bahl and Dr Randeep Singh. The core expert group consisted of Dr Jyoti Wadhwa, Dr Ashutosh Gupta and Dr Mushtaq Ahmed. Members of the panel were also allowed to share their personal experiences and make comments. This manuscript is the outcome of the expert group discussion and consensus arrived at in 2017.

## Defining Clinical Cohort and Practice of Expert Group Panel Members

The primary objective was to provide a consensus statement for community oncologists that could be applicable as ready-to-use practical recommendations. Hence, the applicable setting was outlined by defining the clinical cohort and current practice of the participating delegates and expert group panel members – on the basis of which this document was prepared. The experts discussed a case of a 40 year old premenopausal lady diagnosed with infiltrating duct carcinoma in left breast. She

underwent modified radical mastectomy. Histopathology results were - T1N0M0, ER-80%, PR-80% and HER2 neu-3+. Based on this case, a series of questions were put up for poll upon which the expert group discussed and aimed to reach a consensus. Each question had multiple choice options from which participants were to select the one most appropriate for their clinical practice setting. The expert group then formed the practical consensus recommendations for the community oncologists.

## Trastuzumab Treatment and the Size of Tumour

Trastuzumab is not used routinely for early-stage, HER2-positive breast cancers that are 0.5 cm or smaller. The polled oncologists concurred with this notion as 65.5% were not in support of recommending trastuzumab treatment to patients with tumour size of 0.5 cm [Table 1]. This is because the risk of recurrence of these types of breast cancers is relatively low. A study at Kaiser Permanente Northern California between 2000 and 2006 was carried out to observe the recurrence rate in mostly untreated patients with T1a and T1b tumours.<sup>[16]</sup> After a median 6 years of follow up, out of 237 HER2-positive cases, 15 invasive recurrences were observed. Out of these invasive recurrences, only 4 were in patients with T1a tumour. Out of the 7 distant recurrences that were observed, only 1 was in a patient with T1a tumour. The 5-year distant relapse-free rate was 89.5% for T1b and 99.1% for T1a tumours. Only 1 patient out of 101 with a T1a tumour not treated with chemotherapy experienced a distant recurrence. The experts discussed whether a risk for distant recurrence approaching 1% is worth a year of treatment for the patients with a 0.5 cm tumour. The expert consensus was that adjuvant Trastuzumab is not recommended in patients with tumour size less than or equal to 0.5 cm.

As to the question whether they would recommend trastuzumab treatment in patients with a tumour size between 0.5 cm and 1 cm, majority of the polled oncologists gave an affirmative response as indicated in Table 2. The experts were divided in their opinion regarding this matter. For node-positive disease and node-negative cancers greater in size than 1 cm, chemotherapy and trastuzumab is generally recommended, but oncologists today vary in their practice for treating tumours

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with size between 0.5 cm and 1 cm.<sup>[17]</sup> Still, there is evidence that sub-centimetre HER2-positive tumours carry a higher risk of recurrence than their HER2-negative counterparts.<sup>[18,19]</sup> Also, as stated by Fehrenbacher *et al.*,<sup>[16]</sup> T1b tumours have a higher risk of recurrence than their T1a counterparts. A meta-analysis by Zhou *et al.*<sup>[20]</sup> concluded that adjuvant trastuzumab might bring significant survival benefit to HER2-positive patients with pT1a-bN0M0 breast cancer. Some other studies have also suggested that adjuvant trastuzumab-based therapy may improve outcomes for T1 tumours that are HER2-positive.<sup>[21-23]</sup> The expert panel discussed about a Cochrane meta-analysis<sup>[24]</sup> which suggests that trastuzumab significantly improves OS and DFS in HER2-positive women with early and locally advanced breast cancer, although it also significantly increases the risk of congestive heart failure. The experts opined that the risk to benefit ratio in patients at lower risk (small tumour) must be carefully evaluated. The panel concluded that for node-negative tumours with size between 0.5 and 1.0 cm, adjuvant trastuzumab treatment can be considered based on age and co-morbidities.

### Treatment for Patients with T1c Tumours

According to the NCCN guidelines, all HER2 positive patients with tumour size more than 1 cm should be offered chemotherapy with trastuzumab.<sup>[25]</sup> The question arises as to what treatment should be accompanied with trastuzumab. When posed with this question, 41.7% of the polled oncologists were in support of recommending a treatment plan of weekly taxol for 12 weeks and trastuzumab. Another 41.7% of the polled oncologists voted in support of TCH treatment and the remaining 16.6% voted for 4ACTH treatment [Table 3]. The BCIRG 006 trial<sup>[26]</sup> has indicated that the addition of 1 year of adjuvant trastuzumab to chemotherapy significantly improves disease-free and overall survival among women with HER2-positive breast cancer. The risk-benefit ratio favoured the non-anthracycline TCH regimen over AC-TH, given its similar efficacy, fewer acute toxic effects, and lower risks of cardio-toxicity and leukemia. The expert panel was also of the opinion that it is best to avoid anthracycline based treatment regimens citing their cardiotoxicity.<sup>[27-29]</sup> Now, the recently concluded Adjuvant Paclitaxel and Trastuzumab (APT) study of 406 women with HER2-positive, node-negative tumours lesser than 3 cm in size demonstrated that lower-intensity chemotherapy and trastuzumab is associated with fewer side effects.<sup>[30]</sup> Patients received postoperative weekly treatment with paclitaxel and trastuzumab for 12 weeks, followed by 9 months of treatment with trastuzumab alone. At a median follow-up of 4 years, the 3-year rate of survival free from invasive disease was 98.7%. Twelve patients relapsed, 2 due to distant metastatic breast cancer. Two patients had symptomatic congestive heart failure. Another study by Hayes *et al.*<sup>[31]</sup> has also indicated paclitaxel to be beneficial to HER2-positive patients with node positive tumours. The expert panel consensus was that in patients with tumour size between 1 cm and 2 cm, weekly paclitaxel along with trastuzumab should be offered whereas in patients with tumour size more than 2 cm, either paclitaxel with trastuzumab or TCH should be offered based on individual preference.

### Combination of Trastuzumab with other Anti-Her2 Agents

Trastuzumab was the first anti-HER2 agent that was developed. Since then, some other anti-HER2 drugs like pertuzumab and South Asian Journal of Cancer ♦ Volume 7 ♦ Issue 2 ♦ April-June 2018

lapatinib have also been developed. All these anti-HER2 agents target HER2 in a different way. So, the question regarding the use of these agents in a combination is a valid one, but when asked, the majority of the polled oncologists were not in support of adding any other anti-HER2 agent to trastuzumab [Table 4]. The experts discussed about some ongoing trials on the matter. The main highlight of the discussion was the ALTO trial<sup>[32]</sup> which compared the effect of trastuzumab plus lapatinib with only trastuzumab treatment in adjuvant setting for HER2-positive patients. A total of 8,381 patients were enrolled in the study between 2007 and 2011. The study concluded that adjuvant treatment that includes lapatinib with trastuzumab did not significantly improve disease free survival compared with trastuzumab alone. Along with this, it was also seen that the lapatinib containing arm suffered from higher toxicity. The benefit of adding lapatinib is not yet clear as there have been conflicting results from different studies.<sup>[33,34]</sup> Regarding pertuzumab data, the experts were of the opinion that it is not yet mature enough for reaching a consensus over its use in combination with trastuzumab. The expert panel recommended that it is best to wait for further data before the financial burden of the patients is increased. The panel concluded that as of now, there is no recommendation for adding another anti-HER2 agent to trastuzumab in the adjuvant setting.

### Need for Anthracyclines in Node Positive HER2 Disease

To the question that if they choose to give trastuzumab to patients with HER2 and node positive tumour, would they always combine it with anthracycline, the polled oncologists

**Table 1: Question 1 - Would you recommend trastuzumab for patients with 0.5 cm tumour?**

Options	Yes	No
Percentage of polled oncologists	65.5	34.5

Expert group consensus: Adjuvant trastuzumab is not recommended in patients with tumour size  $\leq 0.5$  cm, unless there are other high risk factors

**Table 2: Question 2 - Would you recommend trastuzumab for patients with tumour size between 0.5 and 1 cm?**

Options	Yes	No
Percentage of polled oncologists	70	30

Expert group consensus: For patients with tumour size between 0.5 and 1.0 cm, adjuvant trastuzumab treatment can be recommended based on other risk benefit factors

**Table 3: Question 3 - What protocol would you recommend if the tumour size is 2 cm?**

Options	Weekly taxol $\times 12$ and TCH	TCH	4AC $\rightarrow$ TH
Percentage of polled oncologists	41.7	41.7	16.6

Expert group consensus: Weekly paclitaxel along with trastuzumab should be offered to patients with tumour size between 1 and 2 cm. Either paclitaxel with trastuzumab or TCH should be considered for patients with tumour size  $> 2$  cm

**Table 4: Question 4 - Would you add another anti-human epidermal growth factor receptor 2 agent to trastuzumab?**

Options	Yes	No
Percentage of polled oncologists	23.1	76.9

Expert group consensus: There is no recommendation for adding another anti-HER2 agent to trastuzumab in the adjuvant setting. HER2=Human epidermal growth factor receptor 2

**Table 5: Question 5 - Would you always combine trastuzumab with anthracycline for the treatment of node positive patients?**

Options	Yes	No
Percentage of polled oncologists	0.0	100

Expert group consensus: In HER 2 positive patients with positive lymph nodes, TCH regimen should be first chemotherapy option. Anthracyclines may be considered in higher risk patients. HER2=Human epidermal growth factor receptor 2

unanimously gave negative answer as indicated in Table 5. The anthracyclines are among the most effective anticancer treatments ever developed.<sup>[35-37]</sup> Their main adverse effect is cardiotoxicity, which considerably limits their usefulness.<sup>[27-29]</sup> Use of anthracyclines has also been shown to be significantly associated with cycle 1 severe or febrile neutropenia.<sup>[38]</sup> The BCIRG 006 trial<sup>[26]</sup> has already shown that non-anthracycline regimens have similar efficacy and lower risks of toxic adverse effects in node positive as well as high risk node negative early breast cancer patients. A study has also shown a non-anthracycline regimen to provide better DFS and OS than the anthracycline regimen.<sup>[39,40]</sup> TCH regimen has now been backed up by the BETH trial<sup>[41]</sup> which showed that TCH has a much better safety profile than anthracycline/trastuzumab combinations and also equally effective in HER2 positive, node positive patients. Even as new non-anthracycline treatment regimens are being developed to replace those with anthracyclines, the efficacy and benefits of anthracyclines cannot be overlooked.<sup>[42]</sup> Anthracyclines have been extensively tested in clinical trials spanning several decades<sup>[43-46]</sup> and have been shown to be one of the most effective group of agents for the treatment of breast cancer. Considering all the evidence at hand, the expert panel concluded that in HER2 positive patients with positive lymph nodes, TCH regimen should be offered over anthracyclines. The panel added that anthracyclines may be used in higher risk patients in whom the tumour has spread to numerous regional lymph nodes (N3).

### Take Home Message

1. Adjuvant trastuzumab is not recommended in patients with tumour size less than or equal to 0.5 cm, unless there are other high risk factors
2. For patients with tumour size between 0.5 and 1.0 cm, adjuvant trastuzumab treatment can be recommended based on other risk benefit factors
3. Weekly paclitaxel along with trastuzumab should be offered to patients with tumour size between 1 cm and 2 cm. Either paclitaxel with trastuzumab or TCH for patients with tumour size more than 2 cm
4. There is no recommendation for adding another anti-HER2 agent to trastuzumab in the adjuvant setting
5. In Her 2 positive patients with positive lymph nodes, TCH regimen should be first chemotherapy option. Anthracyclines may be considered in higher risk patients

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### Conflicts of interest

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