

# Singapore Cancer Network (SCAN) Guidelines for Adjuvant Trastuzumab Use in Early Stage HER2 Positive Breast Cancer

The Singapore Cancer Network (SCAN) Breast Cancer Workgroup

## Abstract

**Introduction:** The SCAN breast cancer workgroup aimed to develop Singapore Cancer Network (SCAN) clinical practice guidelines for adjuvant trastuzumab use in early stage HER2 positive breast cancer. **Materials and Methods:** The workgroup utilised a modified ADAPTE process to calibrate high quality international evidence-based clinical practice guidelines to our local setting. **Results:** Five international guidelines were evaluated—those developed by the National Comprehensive Cancer Network (2015), the National Institute of Health and Clinical Excellence (2006, 2009), the European Society of Medical Oncology (2013), the Breast Cancer Disease Site Group in conjunction with the Program in Evidence-Based Care and Cancer Care Ontario (2011) and the Scottish Intercollegiate Guidelines Network (2013). Recommendations on suitable candidacy for adjuvant trastuzumab, whether adjuvant trastuzumab should be given concurrently with a taxane or sequentially after completion of adjuvant chemotherapy, the optimal frequency of cardiac monitoring during adjuvant trastuzumab and the optimal duration of adjuvant trastuzumab were developed. **Conclusion:** These adapted guidelines form the SCAN Guidelines 2015 for adjuvant trastuzumab use in early stage HER2 positive breast cancer.

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**Key words:** Guideline adaptation, Anti-HER2 targeted therapy

## Introduction

Breast cancer is the most common malignancy among Singaporean females, with approximately 1700 new cases and 400 deaths per year in the period between 2008 and 2012.<sup>1</sup>

Approximately 20% to 25% of invasive breast cancers in Singapore are HER2 positive as defined by either immunohistochemistry (IHC) or fluorescence in-situ hybridisation (FISH).<sup>2,3</sup> HER2 positivity is an independent prognostic marker of increased risk of disease recurrence and mortality.<sup>2,4</sup> Older studies have reported that even for small node negative HER2 positive breast cancers measuring 1 to 10 mm in size, distant recurrence risk can be as high as 15% to 30%,<sup>5-8</sup> although these studies did not distinguish outcomes between T1a (1 to 5 mm) and T1b (>5 to 10 mm) tumours. More recently, a cohort study reported similar

distant recurrence risks for node negative estrogen receptor negative HER2 positive T1a tumours (n=49, 5-year distant relapse-free survival 93%, 95% CI, 0.80 to 0.98) and T1b tumours (n=17, 5-year distant recurrence-free survival 94%, 95% CI, 0.63 to 0.99) treated by surgery alone, although confidence intervals were wide due to the small patient numbers.<sup>9</sup> In contrast, a separate cohort study using the National Comprehensive Cancer Network Database found a very low risk of distant recurrence for untreated T1a and T1b tumours but not in T1b tumours measuring exactly 1 cm where the 5-year distant recurrence risk-free survival was 93% (95% CI, 76% to 98%).<sup>10</sup>

The advent of anti-HER2 directed therapy has dramatically improved outcomes for HER2 positive breast cancer in the adjuvant<sup>11</sup> and advanced disease settings.<sup>11,12</sup> One such drug is trastuzumab, a fully humanised monoclonal antibody

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which targets the extracellular domain of HER2.

Individual trials<sup>13-17</sup> and meta-analyses<sup>18,19</sup> have demonstrated that the addition of adjuvant trastuzumab to a variety of chemotherapy regimens reduces the risk of disease recurrence by 40% and the risk of mortality by one-third. A single outlier is a relatively small study involving sequential rather than concurrent trastuzumab which demonstrated a 14% reduction in the risk of disease recurrence that did not reach statistical significance.<sup>20</sup>

Although trastuzumab has such strong efficacy data, trastuzumab is associated with an increased risk of asymptomatic decline in cardiac ejection fraction as well as overt congestive cardiac failure.<sup>13,21,22</sup> In particular, concurrent trastuzumab with a taxane immediately following adjuvant anthracycline-based regimens is associated with a 3% to 4% risk of congestive cardiac failure.<sup>14, 21,22</sup> Hence, risks may outweigh benefits in a subset of patients with low risk node negative HER2 positive breast cancers. This has led to significant practice variation in the threshold for inclusion of patients for adjuvant trastuzumab.

Data from a single randomised trial comparing 4 cycles of doxorubicin cyclophosphamide followed by 3 months of paclitaxel with concurrent trastuzumab against a sequential approach in which trastuzumab is administered after completion of the same adjuvant chemotherapy suggests superiority for the concurrent approach.<sup>23</sup> However, a number of international guidelines have advocated the use of sequential trastuzumab after completion of all adjuvant chemotherapy rather than concurrent trastuzumab with a taxane as described above.

A third area in need of consensus is the frequency of cardiac monitoring during trastuzumab therapy, for which local institutional guidelines are lacking.

### **The SCAN Guidelines for Adjuvant Trastuzumab Use in Early Stage HER2 Positive Breast Cancer**

The SCAN Guidelines are clinical practice guidelines for adjuvant trastuzumab use in early stage HER2 positive breast cancer.

These first edition guidelines are intended to serve as treatment recommendations by members of this working group reflecting their views on current existing international guidelines for the management of early stage HER2 positive breast cancer. While it hopes to harmonise the management of this disease, it is not intended to serve as the standard of care or to replace good clinical judgment and the individualisation of treatments.

### **Target Users of the Guidelines**

The guidelines will be of interest to oncologists, oncology

nurse specialists, pharmacists, allied health workers and general practitioners involved in the management of women with breast cancer.

### **Guideline Recommendations/Development**

The SCAN breast cancer workgroup comprises a panel of 11 medical oncologists and 1 oncology pharmacist, all of whom have subspecialty interest in breast cancer management. Membership of the workgroup was by invitation. The workgroup elected its own chairperson and decided on its own scope. Guideline selection was conducted through workgroup consensus. Potential conflicts of interest were declared by the International Committee of Medical Journal Editors (ICJME) guidelines. Secretarial support for the overall guideline development effort was provided by Annals, Academy of Medicine Singapore. No other financial support was obtained. Guideline searching was conducted by the authors. Guideline searching was conducted by a Pubmed search using the following keywords: breast cancer, adjuvant therapy, trastuzumab, pertuzumab, management guidelines. The group met once in person, and completed guideline development through email communication.

The ADAPTE framework<sup>24</sup> was used as a pragmatic structure and guidance for calibration of international high quality guidelines to the Singapore context. The framework involves 3 phases: set-up, adaptation and finalisation. During the set-up phase, available resources were considered. During the adaptation phase, high quality guidelines were selected for evaluation and structured approaches developed for guideline evaluation and selection. This involved the extraction of data on source guideline development, the setting up of mechanisms for selecting recommendations and also recognising possible dissent amongst panel members. Calibration of guidelines to the local context based on available Singapore data was encouraged. The finalisation phase involved writing, external review, stakeholder feedback, and the setting up of a mechanism for regular updating. For each individual recommendation, agreement was established by a simple majority for established international recommendations and by a two-third majority for independent local recommendations. Dissenting workgroup members were invited to include comments for each recommendation. International measures of cost-effectiveness for each recommendation were obtained where available but not used to inform the recommendations.

These guidelines set out to answer the following questions pertaining to adjuvant trastuzumab use in early stage HER2 positive breast cancer (Table 1):

1. Which HER2 positive early breast cancer patients are candidates for adjuvant trastuzumab?
2. Should adjuvant trastuzumab be given concurrently

with a taxane or sequentially after completion of adjuvant chemotherapy?

3. What is the frequency of cardiac monitoring during adjuvant trastuzumab?
4. What is the optimal duration of adjuvant trastuzumab?

Five international guidelines were selected for review (Supplementary Table 1):

- “NCCN Clinical Practice Guidelines in Oncology Breast Cancer” (version 2.2015) by the National Comprehensive Cancer Network (NCCN, USA)<sup>25</sup>
- “Early and Locally Advanced Breast Cancer: Diagnosis and Treatment (CG80)”, 2009 and “Trastuzumab as Adjuvant Treatment for Early Stage HER2 Positive Breast Cancer” (NICE Technology Appraisal Guidance 107), 2006 by the National Institute of Health and Clinical Excellence (NICE)<sup>26,27</sup>
- “Breast Cancer: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up” by the European Society for Medical Oncology (ESMO), 2013<sup>28</sup>
- “The Role of Trastuzumab in Adjuvant and Neoadjuvant Therapy in Women with HER2 Overexpressing Breast Cancer Evidence Based Series 1-24 Version 2” by the Breast Cancer Disease Site Group (DSG), Program in Evidence-Based Care (PEBC) and Cancer Care Ontario (CCO), 2011. In Review<sup>29</sup>
- “Treatment of Primary Breast Cancer (SIGN134)” by the Scottish Intercollegiate Guidelines Network (SIGN), 2013<sup>30</sup>

These guidelines will be reviewed or updated every 2 years. If there are significant new developments that impact the management of early stage HER2 positive breast cancer, it will be reviewed earlier.

## 1. Which HER2 Positive Early Breast Cancer Patients are Candidates for Adjuvant Trastuzumab?

### Systematic Recommendations

The SCAN workgroup voted 9 to 3 in support of the adoption of the ESMO guidelines (Supplementary Table 1) for the inclusion of patients for adjuvant trastuzumab.

Under these guidelines, adjuvant trastuzumab can be considered for node negative HER2 positive breast cancers under 1 cm, especially if the patient is unresponsive to hormonal therapy as defined by lack of expression of oestrogen and progesterone receptors. For HER2 positive tumours larger than 1 cm or with lymph node involvement, adjuvant trastuzumab is recommended.

While distant recurrence risk is significant for patients with small node negative HER2 positive early breast cancers, there is little or conflicting data<sup>9,10</sup> to suggest a clear demarcation of risk between tumours which are T1a (1 to 5 mm) versus T1b (>5 and up to 10 mm). As such, the workgroup members who are in favour of the ESMO guidelines indicate that ESMO guidelines offer higher flexibility in daily practice compared to the NCCN guidelines in this regard.

Support for the ESMO guidelines was not unanimous. One workgroup member expressed that although several retrospective studies have suggested a higher risk of relapse when HER2 is overexpressed, there is no Level I evidence supporting the administration of trastuzumab-based postoperative chemotherapy in small under 1 cm HER2 positive tumours, and preferred the more conservative NICE guidelines<sup>26,27</sup> with regards to recommending trastuzumab and chemotherapy to this group of patients. A separate workgroup member supported the NCCN guidelines as it is more specific in its recommendation for T1a versus T1b node negative tumours.

Table 1. Singapore Cancer Network (SCAN) Guidelines for Adjuvant Trastuzumab Use in Early Stage HER2 Positive Breast Cancer

Guideline Recommendations	
Which HER2 positive early breast cancer patients are candidates for adjuvant trastuzumab?	ESMO Guidelines: Can be considered for node negative tumours less than 1 cm especially if ER and PR negative; recommended for tumours larger than 1 cm or node positive tumours.
Should adjuvant trastuzumab be given concurrently with a taxane or sequentially after completion of adjuvant chemotherapy?	Adjuvant trastuzumab should be given concurrently.
What is the frequency of cardiac monitoring during adjuvant trastuzumab?	ESMO Guidelines: Frequency of cardiac monitoring should be 3-monthly.
What is the optimal duration of adjuvant trastuzumab?	Until data from other studies comparing a shorter duration versus 1 year of adjuvant trastuzumab become available, the standard duration for adjuvant trastuzumab is 1 year.

ESMO: European Society for Medical Oncology

The workgroup notes that under the latest NCCN Clinical Practice Guidelines in Oncology Breast Cancer version 2.2015, adjuvant chemotherapy and trastuzumab can be considered for patients with T1a tumours, and as such, there is now less distinction between the ESMO and NCCN recommendations with regard to T1a and T1b HER2 positive breast cancers.

The SCAN breast cancer workgroup acknowledges that there is no local efficacy data on adjuvant trastuzumab in early breast cancer.

In reviewing the risk benefits, the workgroup considered the pooled analysis of adjuvant trastuzumab which shows a relative reduction in the risk of distant disease recurrence by 40% and a relative reduction in the risk of death by 30%.<sup>13-19</sup>

The main toxicity of concern associated with adjuvant trastuzumab is New York Heart Association (NYHA) class III or IV congestive cardiac failure, the incidence of which varies according to the choice of chemotherapy backbone used. With a non-anthracycline containing adjuvant regimen, this risk is approximately 0.5%<sup>15,31</sup> but increases to 3% to 4% with a regimen comprising an anthracycline followed by concurrent trastuzumab and taxane.<sup>21,22</sup>

Local data for trastuzumab-induced cardiotoxicity has been presented in which the overall rate of symptomatic decline in left ventricular ejection fraction is 9%. However, the rate of NYHA class III or IV congestive cardiac failure attributable to trastuzumab, independent of cardiac events caused by anthracyclines prior to the use of trastuzumab is not described and the paper has only been presented in abstract form.<sup>32</sup>

## **2. Should Adjuvant Trastuzumab be Given Concurrently with a Taxane or Sequentially after Completion of Adjuvant Chemotherapy?**

### *Systematic Recommendations*

The workgroup was also unanimous in its recommendation to use trastuzumab in a concurrent fashion during taxane-based chemotherapy rather than sequentially only after completion of all adjuvant chemotherapy, based on direct randomised evidence from one trial<sup>23</sup> and indirect evidence from 2 studies.<sup>13,20</sup>

## **3. What is the Frequency of Cardiac Monitoring during Adjuvant Trastuzumab?**

### *Systematic Recommendations*

There is no data comparing various intervals for cardiac monitoring and the workgroup members unanimously

adopted the 3 monthly interval recommended by ESMO for simplicity.

## **4. What is the Optimal Duration of Adjuvant Trastuzumab?**

Two years versus 1 year of adjuvant trastuzumab does not confer any advantage,<sup>33</sup> while 6 months of adjuvant trastuzumab failed to show non-inferiority compared to 1 year.<sup>34</sup> Until data from other studies comparing a shorter duration versus 1 year of adjuvant trastuzumab become available, the standard duration for adjuvant trastuzumab is 1 year.

### **Cost-Effectiveness Analyses**

The cost-effectiveness of adjuvant trastuzumab is approximately USD \$27,790 per additional quality adjusted life years (QALY) gained for the 3-weekly regimen based on estimates from the NICE evidence review group.<sup>27</sup> Other scenarios modelled on this estimate by the same group gave incremental costs per QALY gained ranging from USD \$24,700 to USD \$50,950.

A study based on local societal costs and benefits found that average cost per QALY was USD \$19,175 (median: USD \$18,994) in 2005.<sup>35</sup>

### **Unsystematic Recommendations**

There are no unsystematic recommendations.

Pertuzumab is a monoclonal antibody which binds to the dimerisation domain of HER2. When combined with trastuzumab and a taxane-based chemotherapy, the addition of pertuzumab has been shown to increase pathological complete response rate in the neoadjuvant setting<sup>36</sup> and improve overall survival in the metastatic setting<sup>37</sup> for HER2 positive breast cancer.

Given the above data, the latest NCCN Clinical Practice Guidelines in Oncology Breast Cancer version 2.2015 considers it reasonable to incorporate pertuzumab concurrently with trastuzumab and a taxane into the adjuvant therapy for patients with  $\geq T2$  or  $\geq N1$  HER2 positive breast cancer who did not receive prior neoadjuvant pertuzumab.<sup>25</sup> Given the absence of direct evidence of benefit from adjuvant pertuzumab, the overwhelming majority of the SCAN breast cancer workgroup members do not endorse this recommendation.

The workgroup notes the ongoing APHINITY trial which is assessing the addition of a pertuzumab to chemotherapy and trastuzumab in the adjuvant setting.<sup>38</sup> If the results are positive and the use of pertuzumab is incorporated in other international guidelines, the SCAN guidelines will be amended accordingly in the future.

Lastly, subcutaneous trastuzumab has been found to be non-inferior to intravenous trastuzumab in terms of efficacy, pharmacokinetic profile and safety.<sup>39</sup> The workgroup will await incorporation of this product in international guidelines before further assessment of its applicability in the local context.

#### Conflicts of Interest

*Dr Ang reports receiving advisory board fees from Roche; Dr Dent, receiving advisory board fees from Roche; Dr Khoo, receiving conference support and advisory board fees from Roche; Dr Lee, receiving conference support and lecture fees from Roche and receiving advisory board fees from Roche, Pfizer, Astra Zeneca and Novartis; Dr Shang, receiving advisory board fees from Roche; Dr Wong, receiving conference support from Roche; Dr Wong, receiving travel grants and advisory board fees from Roche; Dr Yap, receiving conference support and advisory board fees from Roche; Dr Lim, Dr Ng, Dr Shih and Dr Tan have nothing to disclose.*

#### Workgroup Members

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#### Reviewers

*Invited reviewers were Ian F Tammoek, MD, PhD, DSc, Princess Margaret Cancer Centre, University of Toronto, Canada; Gilberto Lopes, MD, MBA, Oncoclinicas Group, Brazil; Fatima Cardoso, MD, Breast Unit, Champalimaud Clinical Center, Portugal.*

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Supplementary Table 1. International Guidelines for Adjuvant Trastuzumab Use in Early Stage HER2 Positive Breast Cancer

Guideline Title	NCCN Clinical Practice Guidelines in Oncology Breast Cancer Version 2.2015	NICE Early and Locally Advanced Breast Cancer: Diagnosis and Treatment (CG80) and NICE Trastuzumab as Adjuvant Treatment for Early Stage HER2 Positive Breast Cancer (NICE Technology Appraisal Guidance 107)	Breast Cancer: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up	The Role of Trastuzumab in Adjuvant and Neoadjuvant Therapy in Women with HER2 Overexpressing Breast Cancer Evidence-Based Series 1 – 24 Version 2 In Review	Treatment of Primary Breast Cancer SIGN134	SCAN Systematic Recommendations	SCAN Unsystematic Recommendations
Date Released	6 March 2014	February 2009, June 2007	22 August 2013	15 September 2011	1 September 2013	March 2014	March 2014
Guideline Developer	National Cancer Comprehensive Network (NCCN), United States	National Institute of Health and Clinical Excellence (NICE), United Kingdom	European Society for Medical Oncology (ESMO)	Breast Cancer Disease Site Group (DSG), Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)	Scottish Intercollegiate Guidelines Network (SIGN)	SCAN Breast Cancer Workgroup	SCAN Breast Cancer Workgroup
Description of Method of Guideline Validation	Statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Validation method not specified.	Guideline development group made up of health professionals, patient and carer groups and technical experts assesses the available evidence and makes recommendations. After the guideline development group finalises the recommendations, the collaborating centre produces the final guideline. NICE formally approves the final guideline and issues its guidance to the NHS.	Recommendations developed from discussion at consensus conferences (CCs). Group decision-making that seeks the consensus of experts and the fulfillment of objectives. Guidelines are endorsed by the Japanese Society of Medical Oncology (JSMO)	Based on comprehensive systematic review of the clinical evidence, an interpretation of and consensus agreement on that evidence by the Breast Cancer DSG and Guideline Development Group, PEBC, CCO, the resulting clinical recommendations, and an external review by Ontario clinicians in the province for whom the topic is relevant.	Guidelines are developed by multidisciplinary groups of practising clinicians using a standard methodology based on a systemic review of the evidence. The guideline is reviewed in draft form by independent expert referees and the guideline group addresses every comment made by the external reviewers and must justify any disagreement with the reviewers' comments.	Systematic recommendations are derived from existing guidelines with support of at least 50% of voting workgroup members (excluding abstaining individuals). Recommended changes in dosing of established standard drugs may be included under systematic recommendations. Abstaining is not recommended unless the member belongs to a different speciality or has a significant conflict of interest.	Unsystematic recommendations are not derived from existing guidelines, but represent best practice recommendations in Singapore supported by at least two-thirds of voting workgroup members, excluding abstaining individuals. Abstaining is not recommended unless the member belongs to a different speciality or has a significant conflict of interest.
Target Population	HER2 positive early breast cancer	HER2 positive early breast cancer	HER2 positive early breast cancer	HER2 positive early breast cancer	HER2 positive early breast cancer	HER2 positive early breast cancer	HER2 positive early breast cancer
Candidates for Adjuvant Trastuzumab	≤0.5 cm: consider; ≤0.5 cm and N1mic or 0.6 – 1 cm N0: consider; >1 cm: recommended	Early HER2 positive breast cancer; EF >55%	<1 cm: consider especially if ER and PR negative; >1 cm or node positive: recommended	>1 cm or node positive; patients who have received adjuvant chemotherapy	All patients who have received adjuvant chemotherapy	ESMO Guidelines	NA

NA: Not applicable; NHS: National Health Service

Supplementary Table 1. International Guidelines for Adjuvant Trastuzumab Use in Early Stage HER2-Positive Breast Cancer (Cont'd)

Guideline Title	NCCN Clinical Practice Guidelines in Oncology Breast Cancer Version 2.2015	NICE Early and Locally Advanced Breast Cancer: Diagnosis and Treatment (CG80) and NICE Trastuzumab as Adjuvant Treatment for Early Stage HER2 Positive Breast Cancer (NICE Technology Appraisal Guidance 107)	Breast Cancer: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up	The Role of Trastuzumab in Neoadjuvant Therapy in Women with HER2 Overexpressing Breast Cancer Evidence-Based Series 1-24 Version 2 In Review	Treatment of Primary Breast Cancer SIGN134	SCAN Systematic Recommendations	SCAN Unsystematic Recommendations
Member Votes			9 out of 3 votes			NA	NA
Frequency of Cardiac Monitoring	Baseline, 3, 6 and 9 months	Every 3 months	Periodic monitoring	Not discussed	Regular monitoring required	ESMO Guidelines	NA
Member Votes			12 of 12 votes			NA	NA
Duration of Adjuvant Trastuzumab	1 year	1 year	1 year	1 year	1 year	1 year	NA
Member Votes						12 of 12 votes	NA
Sequential or Concurrent Trastuzumab (With Taxane But Not Anthracycline)	Concurrent preferred	Sequential after chemotherapy	Concurrent preferred	Sequential	Concurrent or sequential	Concurrent	NA
Member Votes						12 of 12 votes	NA

NA: Not applicable; NHS: National Health Service