



2020 exceptional surveillance of early and locally advanced breast cancer: diagnosis and management (NICE guideline NG101)

Surveillance report

Published: 9 June 2020

www.nice.org.uk

Contents

Surveillance decision	3
Reasons for the decision	3
Development of NICE's current guideline	4
Views of topic experts	5
Impact.....	6
How we made the decision	8
Evidence.....	8
Views of topic experts	9
Views of stakeholders	9
Equalities	9

Surveillance decision

We will not update the [NICE guideline on early and locally advanced breast cancer](#).

Reasons for the decision

New published evidence

The purpose of this exceptional review was to examine any impact on NICE's guideline on early and locally advanced breast cancer following completion of the [PERSEPHONE trial](#), a National Institute for Health Research (NIHR) funded study (HTA 06/303/98) which published findings in [The Lancet](#). The full Health Technology Assessment report and economic analysis is awaiting publication (see the [NIHR webpage](#) for updates).

The PERSEPHONE trial (n=4,089) compared 12 months (standard treatment length) with 6 months of adjuvant trastuzumab in early breast cancer. The Lancet publication referenced several other studies comparing shorter and longer treatment durations, therefore we performed a search for randomised controlled trials (RCTs) and systematic reviews to examine this area in detail.

We found 2 systematic reviews, and 12 publications originating from 9 individual RCTs, of longer compared to shorter durations of adjuvant trastuzumab in people with HER2-positive early breast cancer. Among the 9 RCTs, the standard duration of 12 months trastuzumab was compared with: 6 months trastuzumab in 3 trials, 9 weeks trastuzumab in 3 trials, 12 weeks trastuzumab in 2 trials, and 2 years trastuzumab in 1 trial.

Survival outcomes

Among 6 RCTs investigating non-inferiority of various short trastuzumab regimens, only 1 (the PERSEPHONE trial) concluded that a short duration (6 months) was non-inferior to 12 months. A second RCT (the PHARE trial) with a very similar size and design to PERSEPHONE found an almost identical hazard ratio and confidence interval when comparing disease-free survival with 6 months and 12 months trastuzumab. However, it used a different definition of non-inferiority, and concluded that 6 months treatment was not non-inferior to 12 months. The other 4 non-inferiority studies used a variety of

approaches to analyse non-inferiority and were also unable to claim non-inferiority across a range of short-duration treatments (9 weeks up to 6 months) compared to 12 months treatment.

However, a subgroup analysis of the PHARE trial did find that in people at very low risk of metastasis, 6 months of trastuzumab appeared to be similarly effective as 12 months.

Two separate meta-analyses of the same set of 6 RCTs (including the PERSEPHONE and PHARE trials) found that disease-free survival was significantly worse with a short duration of trastuzumab (9 weeks up to 6 months) than with 12 months trastuzumab.

Cardiotoxicity outcomes

Cardiotoxicity data were reported in 9 individual RCTs, and in the 5 trials that reported statistical analysis in the abstract (or full text if freely available), 4 trials found that a shorter duration of trastuzumab (9 weeks or 6 months) was significantly less cardiotoxic than 12 months of treatment. Two separate meta-analyses of the same set of 6 RCTs found that compared with the standard 12 months of trastuzumab, shorter trastuzumab treatment (ranging from 9 weeks to 6 months) was associated with significantly less cardiotoxicity.

Development of NICE's current guideline

NICE's first recommendation on adjuvant trastuzumab in early breast cancer was made in NICE's technology appraisal guidance on trastuzumab for the adjuvant treatment of early-stage HER2-positive breast cancer. This published in 2006 and recommended adjuvant trastuzumab for 1 year in women with early-stage human epidermal growth receptor 2 (HER2)-positive breast cancer. It also recommended assessing cardiac function before starting trastuzumab, and not offering it to women with particular cardiac diseases or poorly controlled hypertension. The technology appraisal decision was based primarily on the HERA trial of 3,387 patients with HER2-positive and either node-negative (with tumour size larger than 1 cm) or node-positive (any size tumour) breast cancer. It found that 1 year of trastuzumab significantly improved disease-free survival compared to observation.

The technology appraisal guidance was subsequently updated and replaced by NICE's guideline on early and locally advanced breast cancer: diagnosis and treatment, which published in 2009. The guideline considered 8 clinical studies, 1 systematic review and 10 economic evaluations of trastuzumab. Two of these studies examined trastuzumab

treatment durations of less than 1 year, but the overall conclusion of the guideline committee was that 12 months trastuzumab can generally be considered cost effective in the adjuvant setting. The recommendations on trastuzumab, and contraindication in cardiovascular disease, were unchanged from those made in the previous technology appraisal guidance.

NICE's 2009 guideline was then updated and replaced by the current [NICE guideline on early and locally advanced breast cancer](#). This published in 2018 and the review question on trastuzumab from the 2009 guideline was updated and aimed to determine which people with T1 node-negative HER2-positive breast cancer benefit from adjuvant trastuzumab. T1 tumours are sub-divided into T1mi, T1a, T1b and T1c (covering a range of tumour sizes from 0.1 cm or less up to 2 cm). The focus on T1 tumours in the current guideline was due to the large trials previously showing that the benefit of trastuzumab only included cancers of at least 1 cm, but more recent data suggested T1 HER2-positive cancers have a much higher risk of recurrence than equivalently sized HER2-negative cancers, so patients with T1 HER2-positive cancers are likely to benefit from trastuzumab. The current guideline included 7 retrospective cohort studies and 1 systematic review. The review protocol only allowed for comparisons of trastuzumab with no trastuzumab, so evidence comparing longer and shorter durations of trastuzumab was not included.

Moderate quality evidence indicated that adjuvant trastuzumab plus chemotherapy in T1 node-negative HER2-positive invasive breast cancer increased overall survival compared to no adjuvant chemotherapy or trastuzumab. An economic analysis indicated that adjuvant trastuzumab was likely to be cost effective compared with no treatment. The guideline committee noted that even without treatment, 80% to 89% of people with T1a/T1b tumours would be alive at 8 years, but an increase in survival is still important, and only 7 to 11 people would need to be treated for 1 additional person to be free from disease or be alive. The guideline committee therefore modified the recommendation from the 2009 guideline, stating that 1 year of trastuzumab should be offered for people with breast cancer stage T1c and above. A new recommendation was made to consider adjuvant trastuzumab for people with stage T1a/T1b breast cancer, though no treatment duration was specified for this group. The recommendation not to offer trastuzumab to people with cardiac disease or poorly controlled hypertension was also modified to state that trastuzumab should be used with caution in this population.

Views of topic experts

In this exceptional review, we engaged with topic experts who were recruited to the NICE

Centre for Guidelines Expert Advisers Panel to represent their specialty. We received feedback from 3 topic experts (all consultant oncologists with specialist interest in breast cancer). Two of the experts suggested that for low-risk patients (for example, those with small, node-negative cancers), the incremental benefits of 12 months trastuzumab appear to be small and may be outweighed by adverse effects such as cardiotoxicity. They noted that it may be possible to define a low-risk group in whom risk of harm from undertreatment is minimal, and therefore shorter durations of treatment may be suitable (though 1 of the 2 experts making this point noted that the evidence is not conclusive).

A third expert acknowledged that although there may be subgroups of patients for whom shorter trastuzumab regimens may be suitable, this is not yet conclusively known and that longer follow up and better meta-analysis is needed. The expert noted that some of the individual RCTs had similar results but made different conclusions. They noted that systematic reviews used publication-based meta-analysis rather than individual patient level meta-analysis, and that the latter is required to help draw clearer conclusions. The expert highlighted that this is being planned by the [Early Breast Cancer Trialists Collaborative Group](#) and will hopefully provide more robust evidence.

Impact

Recommendation 1.8.4 in NICE's current guideline states 1 year of adjuvant trastuzumab should be offered for people with T1c and above HER2-positive invasive breast cancer. Recommendation 1.8.5 states adjuvant trastuzumab should be considered for people with T1a/T1b HER2-positive invasive breast cancer, taking into account any comorbidities, prognostic features and possible toxicity of chemotherapy. Recommendations 1.8.6 and 1.8.7 further note that cardiac function should be assessed before starting treatment with trastuzumab, and trastuzumab should be used with caution in people with specific cardiac diseases or poorly controlled hypertension.

Among the new evidence identified by surveillance, 2 meta-analyses suggest that disease-free survival is improved with the standard 12 months of trastuzumab compared to shorter regimens. New evidence from RCTs for non-inferiority of shorter regimens is mixed, in particular there is disagreement between 2 large similarly designed trials. Most studies were unable to demonstrate non-inferiority. Heterogeneity of individual RCTs (such as varying lengths of the short trastuzumab regimen, various accompanying chemotherapy regimens, and different definitions of non-inferiority) also complicates any conclusions from this evidence base. A subgroup analysis of an RCT did find that in people at very low risk of metastasis, 6 months of trastuzumab appears to be similarly effective

as 12 months. But this analysis was not prospectively planned, which limits any firm conclusions. An expert noted that individual patient level meta-analysis and longer follow up is ideally needed to help draw clearer conclusions, therefore based on the survival data there is currently no impact on the guideline.

Safety data from meta-analyses and RCTs consistently show that shorter trastuzumab regimens are less cardiotoxic, and there is some limited evidence that the lowest risk patients may have similar survival outcomes with shorter regimens. This suggests that there may be subgroups (for example, people with cardiac disease, or at lower risk of recurrence) for whom shorter trastuzumab regimens may be appropriate. Topic experts also raised this point. However, the studies were not set up to prospectively examine these issues, and further research specifically looking at these areas is needed to confirm findings before an impact on the guideline can be considered.

The European Society for Medical Oncology (ESMO) guideline on early breast cancer was updated in 2019. It recommends that 1 year of (neo)adjuvant trastuzumab remains a standard for the vast majority of HER2-positive patients. It further recommends that shortening trastuzumab duration to 6 months may be discussed in highly selected, low-risk patients. However, the guideline goes on to acknowledge that further data and longer follow up are needed and several questions are still open regarding de-escalation of anti-HER2 therapy, chemotherapy or both in HER2-positive early breast cancer. All the evidence considered by the ESMO guideline in making the recommendation on shortening trastuzumab duration is included in this exceptional review.

NICE will log this area as an issue for the guideline on early and locally advanced breast cancer, and will either respond to future evidence that we become aware of if we believe it may impact the guideline, or will re-consider the issue at the next standard surveillance review of the guideline.

How we made the decision

Exceptionally, significant new evidence may mean an update of a guideline is agreed before the next scheduled check of the need for an update. The evidence might be a single piece of evidence, an accumulation of evidence or other published NICE guidance.

For details of the process and update decisions that are available, see [ensuring that published guidelines are current and accurate](#) in developing NICE guidelines: the manual.

Evidence

A focused search was performed for randomised controlled trials (RCTs) and systematic reviews on adjuvant trastuzumab in adults with early or locally advanced HER2-positive breast cancer, comparing trastuzumab treatment over any designated time period with any shorter period of treatment.

The searches for the current NICE guideline ended in February 2017, but the search strategy used for the review question on trastuzumab would not pick up studies comparing different trastuzumab treatment durations. Therefore, searches were performed from the last date of searches for the first NICE guideline. Search dates were 1 July 2008 to 30 November 2019.

RCTs published on any date during this search period were included. However, to ensure only systematic reviews that included the latest RCTs were identified, systematic reviews were limited to those published in 2019.

RCT sifting was assisted by an automated RCT classifier within EPPI-Reviewer 4 (see [user manual](#) for details).

This surveillance report provides an overview of 2 systematic reviews and 12 publications originating from 9 individual RCTs. The results of these studies, alongside topic expert feedback, were considered in detail to determine if there was an impact on the recommendations within the current NICE guideline.

See [appendix A](#) for details of all evidence considered, and references.

Views of topic experts

For this exceptional surveillance review, we engaged with topic experts who were recruited to the NICE Centre for Guidelines Expert Advisers Panel to represent their specialty. We received feedback from 3 topic experts (all consultant oncologists with specialist interest in breast cancer).

Views of stakeholders

Because this was an exceptional surveillance review, we did not consult on the decision.

Equalities

No equalities issues were identified during the surveillance process.

ISBN: 978-1-4731-3676-2