NICE National Institute for Health and Care Excellence

NICE guidance

Trastuzumab emtansine for adjuvant treatment of HER2-positive early breast cancer

Technology appraisal guidance

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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance are at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Trastuzumab emtansine is recommended, within its marketing authorisation, as an option for the adjuvant treatment of human epidermal growth factor receptor 2 (HER2)-positive early breast cancer in adults who have residual invasive disease in the breast or lymph nodes after neoadjuvant taxane-based and HER2-targeted therapy. It is recommended only if the company provides trastuzumab emtansine according to the commercial arrangement.

Why the committee made these recommendations

Neoadjuvant therapy aims to reduce the size of the tumour before surgery. It sometimes shrinks completely, but people may still have cancer remaining when they have their surgery (residual invasive disease). The cancer may have spread to lymph nodes in the armpit (node-positive disease).

Adjuvant treatment aims to reduce the risk of cancer returning after surgery. Trastuzumab is an adjuvant treatment for people with node-negative or node-positive disease. Pertuzumab plus trastuzumab with chemotherapy is an adjuvant treatment for node-positive disease but not for node-negative disease. Trastuzumab emtansine would be an alternative adjuvant treatment for people with node-negative or node-positive disease.

Clinical trial evidence shows that in people with residual invasive disease after neoadjuvant therapy and surgery, trastuzumab emtansine increases the time people remain free of disease compared with trastuzumab alone. We do not know if trastuzumab emtansine increases the length of time people live because the final trial results are not yet available. An indirect comparison in people with node-positive disease suggests that trastuzumab emtansine increases the time until cancer progresses compared with pertuzumab plus trastuzumab with chemotherapy, but this is uncertain because there are differences between people in the 2 trials.

The cost-effectiveness estimates are within what NICE considers an acceptable use of NHS resources. Therefore, trastuzumab emtansine is recommended.

2 Information about trastuzumab emtansine

Marketing authorisation indication

2.1 Trastuzumab emtansine (Kadcyla, Roche), as a single agent, is indicated for 'the adjuvant treatment of adult patients with HER2-positive early breast cancer who have residual invasive disease, in the breast and/or lymph nodes, after neoadjuvant taxane-based and HER2-targeted therapy'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics.

Price

2.3 Trastuzumab emtansine costs £1,641.01 per 100-mg vial and £2,625.62 per 160-mg vial (powder for solution for infusion; excluding VAT; British national formulary online, accessed March 2020). The company has a commercial arrangement. This makes trastuzumab emtansine available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The appraisal committee (section 5) considered evidence submitted by Roche, a review of this submission by the evidence review group (ERG), the technical report, and responses from stakeholders. See the committee papers for full details of the evidence.

The appraisal committee was aware that several issues were resolved during the technical engagement stage, and agreed:

- Invasive disease-free survival extrapolation: The company's original approach overestimated invasive disease-free survival for trastuzumab during the observed period of the KATHERINE trial. The ERG suggested that using the Kaplan–Meier data plus extrapolation is more appropriate. The company adopted the ERG's approach after technical engagement in its base case (issue 3, see technical report pages 18 to 25).
- Drug costs and modelling assumptions: The company's assumptions in its original submission followed those used in NICE's guidance on adjuvant treatment with pertuzumab. These were validated during technical engagement. No changes were made after technical engagement (issue 6, see technical report pages 31 to 33).
- Modelling the intention-to-treat (ITT) population: The company updated the ITT population model after technical engagement and provided supportive results for a comparison of trastuzumab emtansine against pertuzumab plus trastuzumab with chemotherapy, and against trastuzumab-based therapy using the ITT population (issue 7, see technical report page 34).
- Modelling the lymph node positive population: The company updated the lymph node positive population model with population-specific data after technical engagement (issue 8, see technical report pages 34 to 37).

  The committee recognised that there were remaining areas of uncertainty associated with the analyses presented (see technical report, table 2, page 42), and took these into account in its decision making. It discussed the following issues (issues 1, 2, 4 and 5), which were outstanding after the technical engagement stage.

Treatment pathway

Trastuzumab emtansine is a new adjuvant treatment for people

with residual invasive disease after neoadjuvant therapy

3.1 Human epidermal growth factor receptor 2 (HER2)-positive breast cancer has a considerable effect on patients and their families. In early HER2-positive breast cancer, neoadjuvant treatment may be used to eradicate or reduce tumour size before surgery. NICE recommends pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer, with trastuzumab and chemotherapy, for locally advanced, inflammatory or early breast cancer at high risk of recurrence. The patient expert explained that when residual disease is found during surgery this is a disappointing outcome, and preventing the cancer returning is very important to patients. After surgery, adjuvant treatment is used to reduce the risk of recurrence. NICE recommends pertuzumab for adjuvant treatment of HER2-positive early stage breast cancer, with trastuzumab and chemotherapy, in adults who have lymph node positive disease. People with lymph node negative disease are offered adjuvant trastuzumab, in line with NICE's guideline on early breast cancer. Trastuzumab emtansine is a new adjuvant treatment for HER2-positive early breast cancer for people who have residual invasive disease after neoadjuvant therapy. It can be offered to people with node-positive or node-negative disease.

There is a clinical need for an additional treatment for people who have residual disease after neoadjuvant therapy

3.2 The clinical experts explained that people who have residual invasive disease after neoadjuvant therapy are considered to be at higher risk of disease recurrence than those who have a pathological complete response (that is, no residual invasive disease was found during surgery). Most people with HER2-positive early breast cancer have pertuzumab with trastuzumab and chemotherapy as neoadjuvant treatment. The clinical experts explained that a complete pathological response after neoadjuvant pertuzumab and trastuzumab is considered to show that the disease is sensitive to this combination, and the patient would benefit from having it again in the adjuvant setting. However, residual invasive disease after neoadjuvant treatment with pertuzumab and trastuzumab is considered to show that the disease is resistant to this treatment, and the patient would benefit from an alternative treatment such as trastuzumab emtansine. The committee concluded that there is an unmet clinical need for an additional adjuvant therapy for people who have residual disease after neoadjuvant therapy.

Clinical evidence

Trastuzumab emtansine improves invasive disease-free survival compared with trastuzumab

3.3 KATHERINE (n=1,486) is an open-label, randomised, multicentre trial of adjuvant trastuzumab emtansine compared with adjuvant trastuzumab, in people with HER2-positive early breast cancer who had residual invasive disease after trastuzumab-based neoadjuvant therapy with chemotherapy. Invasive disease-free survival was the primary outcome. In the trial, about 20% of people had neoadjuvant pertuzumab plus trastuzumab and 80% had neoadjuvant trastuzumab. The clinical experts considered that the trial results are generalisable to clinical practice, although in clinical practice most people would have pertuzumab plus trastuzumab as neoadjuvant therapy. They also noted that the hazard ratios for invasive disease-free survival were very similar for people who had had trastuzumab previously and those who had pertuzumab plus trastuzumab. The hazard ratio for invasive disease-free survival for the ITT population was 0.50 (95% confidence interval [CI] 0.39 to 0.62). The hazard ratio for invasive disease-free survival for the lymph node negative population (n=689), who would have trastuzumab in clinical practice, was 0.44 (95% CI 0.28 to 0.68). For node-positive disease (n=797), the hazard ratio was 0.52 (95% CI 0.38 to 0.71). Interim overall-survival results are available, however the data are immature. The committee concluded that trastuzumab emtansine improves invasive disease-free survival compared with trastuzumab. However, it is not known whether trastuzumab emtansine increases the length of time people live because the data are immature.

Indirect comparison of trastuzumab emtansine against pertuzumab plus trastuzumab and chemotherapy

The estimates are uncertain but appropriate for decision making

3.4 No study directly compared trastuzumab emtansine with pertuzumab plus trastuzumab with chemotherapy. The company therefore did an indirect comparison using data from KATHERINE and the APHINITY trial. APHINITY (n=4,804) is a double-blind, randomised, multicentre trial of adjuvant pertuzumab plus trastuzumab and chemotherapy compared with adjuvant placebo with trastuzumab and chemotherapy, in people with HER2-positive

early breast cancer who had not had neoadjuvant therapy. Because adjuvant treatment with pertuzumab plus trastuzumab and chemotherapy is only recommended for people who have lymph node positive disease, a subgroup of people with lymph node positive disease from KATHERINE (n=689) and APHINITY (n=3,006) was used for the comparison. The indirect comparison hazard ratio for invasive disease-free survival in the node-positive subgroup was 0.722 (95% CI 0.50 to 1.04). Both the company and the ERG considered the results uncertain because all patients in KATHERINE had residual invasive disease after neoadjuvant therapy, whereas patients in APHINITY had not had neoadjuvant therapy before surgery. However, they agreed that the results represented the best available evidence for trastuzumab emtansine compared with pertuzumab plus trastuzumab and chemotherapy. The clinical experts considered that the indirect comparison results may be a conservative estimate because in KATHERINE people had already had a suboptimal response to neoadjuvant therapy and were therefore preselected to be at higher risk. The committee concluded that the results of the indirect comparison for trastuzumab emtansine compared with pertuzumab plus trastuzumab and chemotherapy are uncertain, but they are suitable for decision making.

Treatment-waning effect of trastuzumab emtansine

The ERG's approach is uncertain but appropriate for decision making

3.5 Before technical engagement the company assumed that trastuzumab emtansine's treatment effect is maintained for 7 years, then gradually decreases to no treatment effect at 10 years. The ERG agreed with the company that the treatment effect lasts beyond the KATHERINE follow-up time. However, it used annualised hazard ratios from KATHERINE to estimate the start and end of treatment waning. In the ERG's approach, the trastuzumab emtansine treatment effect is maintained for 3 years, then gradually decreases to no treatment effect at 8 years. The company considered the ERG's approach to be conservative because updated data from APHINITY suggest that benefit from adjuvant pertuzumab is still present at 6 years. However, it adopted the ERG's approach after technical engagement. The company noted that all its exploratory analyses, with varied assumptions about the duration of treatment effect, resulted in cost-effectiveness estimates within the acceptable range. The committee accepted the ERG's approach of using KATHERINE data and was

reassured by the company's exploratory analyses. It concluded that although the duration of the treatment effect is currently unknown, the ERG's approach is suitable for decision making.

Utilities

The utilities are appropriate for decision making

3.6 The company used utility values from KATHERINE for invasive disease-free survival. No significant difference was found between the results for trastuzumab emtansine and for trastuzumab, therefore the values were pooled. This assumes that people having either treatment have the same health-related quality of life. KATHERINE did not collect utilities for people who had metastatic recurrence, so the company used Lloyd et al. (2006) utilities for progressed disease because this study has been used in previous appraisals. The ERG noted that the model did not include any disutilities for adverse effects. It preferred to use individual treatment utilities for invasive disease-free survival to capture any differences between the 2 treatments. Also, it preferred to use Lidgren et al. (2007) for metastatic states, because these correspond more closely to the NICE reference case than Lloyd et al. After technical engagement, the company adopted the ERG's approach. The committee noted that both Lloyd et al. and Lidgren et al. have been used in previous NICE appraisals. However, it favoured the ERG's approach. It concluded that the utilities from KATHERINE, calculated per treatment for invasive disease-free survival, and the Lidgren et al. utilities for metastatic states were suitable for decision making.

Cost-effectiveness estimates

The ICERs for trastuzumab emtansine compared with trastuzumab are within what NICE considers acceptable

3.7 After technical engagement, the company's preferred incremental cost-effectiveness ratio (ICER) for trastuzumab emtansine compared with trastuzumab in the node-negative population was £8,829 per quality-adjusted life year (QALY) gained. The ERG agreed with the company's revised base case in this population. The company provided supportive data from the ITT population of KATHERINE. The ICER in the ITT population was £5,985 per QALY gained.

The ERG preferred extrapolating invasive disease-free survival using Kaplan–Meier data and a generalised gamma curve, instead of the company's preference of Kaplan–Meier data and an exponential curve. The ERG's preferred ICER for the ITT population was £7,213 per QALY gained. These estimates include commercial arrangements for trastuzumab emtansine, trastuzumab and an assumed discount for trastuzumab biosimilars of 70%. Estimates that include all commercial arrangements remained within the range NICE normally considers an acceptable use of NHS resources.

The ICERs for trastuzumab emtansine compared with pertuzumab plus trastuzumab with chemotherapy are within what NICE considers acceptable

3.8 After technical engagement, the company's preferred ICER for trastuzumab emtansine compared with pertuzumab plus trastuzumab and chemotherapy in the node-positive population was £4,955 per QALY gained. The model assumed that chemotherapy would have been given in the neoadjuvant setting and therefore no chemotherapy cost was included as part of the adjuvant pertuzumab plus trastuzumab treatment. The ERG agreed with the company's revised base case in this population. The company provided supportive data from the KATHERINE and APHINITY ITT populations, and it used the hazard ratio from the indirect comparison using the node-positive populations (see section 3.4). The company's ICER in the ITT population was £8,203 per QALY gained. The ERG preferred to extrapolate invasive disease-free survival using Kaplan–Meier data and a generalised gamma curve, rather than the company's method of Kaplan–Meier data and an exponential curve. The ERG's preferred ICER for the ITT population was £6,388 per QALY gained. These estimates include commercial arrangements for trastuzumab emtansine, pertuzumab, trastuzumab and an assumed discount for trastuzumab biosimilars of 70%. Estimates that include all commercial arrangements remained within the range NICE normally considers an acceptable use of NHS resources.

The cost-effectiveness estimates are uncertain but trastuzumab emtansine is recommended

3.9 Both the company's and the ERG's preferred ICERs were within the range NICE normally considers an acceptable use of NHS resources (see section 3.7 and section 3.8). The committee was aware of the uncertainty associated with the

indirect comparison estimate (see section 3.4) and treatment effect (see section 3.5), and the effect of the additional uncertainties as summarised in the technical report (see table 2 on pages 41 to 42, and table 3 on pages 43 to 44). It considered that the most plausible ICER was unknown and could be higher or lower than the company's and the ERG's preferred ICERs. However, it agreed that the most plausible ICER was unlikely to be above what NICE normally considers an acceptable use of NHS resources. It therefore recommended trastuzumab emtansine as an option for the adjuvant treatment of HER2-positive early breast cancer in adults who have residual invasive disease after neoadjuvant therapy.

4 Implementation

4.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

4.2 Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or fast track appraisal), at which point funding will switch to routine commissioning budgets. The NHS England and NHS Improvement Cancer Drugs Fund list provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.

4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

4.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has HER2-positive early breast cancer with residual invasive disease after neoadjuvant therapy and the doctor responsible for their care thinks that trastuzumab emtansine is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee A.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Marcela Haasova
Technical lead

Joanna Richardson
Technical adviser

Thomas Feist
Project manager

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Accreditation