

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

Appraisal consultation document

**Neratinib for extended adjuvant treatment of
hormone receptor-positive, HER2-positive
early stage breast cancer after adjuvant
trastuzumab**

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using neratinib in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees.

It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the [committee papers](#)).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal document.
- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using neratinib in the NHS in England.

For further details, see NICE's [guide to the processes of technology appraisal](#).

The key dates for this appraisal are:

Closing date for comments: 28 August 2019

Second appraisal committee meeting: 11 September 2019

Details of membership of the appraisal committee are given in section 6.

1 Recommendations

1.1 Neratinib is recommended as an option for the extended adjuvant treatment of hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-positive early stage breast cancer in adults who completed adjuvant trastuzumab-based therapy less than 1 year ago only if:

- trastuzumab is the only HER2-directed treatment in the adjuvant setting they have had, and
- if they had neoadjuvant treatment, they still had residual invasive disease in the breast or axilla following the neoadjuvant treatment, and
- the company provides neratinib according to the commercial arrangement (see section 2).

1.2 This recommendation is not intended to affect treatment with neratinib that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Trastuzumab is a HER2-directed treatment. It can also be given in combination with another HER2-directed treatment, pertuzumab, to reduce the risk of cancer returning after surgery in early stage cancer (adjuvant treatment). Neratinib is an option for extended adjuvant treatment in people who completed a standard course of HER2-directed adjuvant treatment.

Clinical trial evidence shows that women who have treatment with neratinib have less risk of disease recurrence than women who have treatment with a placebo. We do not know if neratinib increases the length of time people live because the final trial results are not yet available.

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The cost-effectiveness estimates are uncertain, but within the range that NICE normally considers an acceptable use of NHS resources. Therefore, neratinib is recommended for people if trastuzumab is the only HER2-directed treatment in the adjuvant setting they have had, and if they still have signs of cancer in tissue samples (residual invasive disease in the breast or armpit, known medically as the axilla) if they had treatment before surgery to reduce tumour size (neoadjuvant treatment).

The neratinib trial did not include people who received adjuvant pertuzumab. Also, the trial did not include people who had a pathological complete response (no sign of residual invasive disease in the breast or axilla) after neoadjuvant treatment, therefore these groups were not included in the recommendations.

2 Information about neratinib

Marketing authorisation indication	Neratinib (Nerlynx, Pierre Fabre) is indicated for the extended adjuvant treatment of adults with early stage hormone receptor-positive, HER2-overexpressed/amplified breast cancer and who are less than 1 year from the completion of prior adjuvant trastuzumab-based therapy.
Dosage in the marketing authorisation	Neratinib is administered orally. The recommended dose is 240 mg neratinib, administered as 6 × 40 mg tablets taken once daily and continually for 1 year.
Price	£4,500 per box of 180 tablets (30 days treatment) (excluding VAT; company's submission). The company has a commercial arrangement (simple discount patient access scheme). This makes neratinib 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 6) considered evidence submitted by Pierre Fabre, a review of this submission by the evidence review group (ERG), and the technical report developed through engagement with 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 that:

- In the absence of overall survival data, the invasive disease-free survival definition used in the ExteNET trial is suitable for decision making (issue 2, see technical report page 10–11).
- The mean neratinib treatment duration and the mean neratinib dose based on ExteNET is suitable for decision making (issue 5, see technical report page 17–19).
- Age-adjusted utilities, the ExteNET value for disease-free state, and Lindgren et al. 2007 value for distant recurrence are suitable for decision making (issue 6, see technical report page 20–23).

The committee recognised that there were remaining areas of uncertainty associated with the analyses presented (see technical report, table 2, page 26), and took these into account in its decision making. It discussed the following issues (issues 1, 3 and 4), which were outstanding after the technical engagement stage.

Treatment pathway

Neratinib is an oral treatment in a new place in the pathway

- 3.1 [NICE's guidance on early breast cancer](#) recommends offering adjuvant trastuzumab for 1 year in combination with surgery, chemotherapy and radiotherapy as appropriate. In March 2019, NICE recommended [pertuzumab, with trastuzumab and chemotherapy, for the adjuvant treatment of human epidermal growth factor receptor 2 \(HER2\)-positive early stage breast cancer](#) in adults who have lymph node positive disease. Neoadjuvant treatment is also an option, to reduce tumour size before surgery. NICE recommends [pertuzumab with trastuzumab and chemotherapy as a neoadjuvant treatment](#) for HER2-positive, locally advanced, inflammatory or early breast cancer at high risk of recurrence. Neratinib is an oral treatment with a marketing authorisation for the extended adjuvant treatment of adults with hormone receptor-positive,

HER2-positive early breast cancer who are less than 1 year from the completion of previous adjuvant trastuzumab-based treatment.

It is unclear who would receive neratinib in clinical practice

3.2 Since the clinical study for neratinib was conducted, the treatment pathway has changed. People can now receive pertuzumab alongside trastuzumab for adjuvant treatment in HER2-positive early stage breast cancer if they have lymph node positive disease. There are no data for neratinib after combination treatment with pertuzumab for early breast cancer. The clinical experts noted that adjuvant pertuzumab treatment is not available for people with node-negative disease and that neratinib could be considered in this population. The clinical experts stated that the decision about the most suitable treatment for patients with node positive disease would be based on the patient's preferences. The clinical experts explained that some people may prefer neratinib because it's an oral treatment. They may prefer to have treatment with just trastuzumab as the HER2-directed treatment in the adjuvant setting administered subcutaneously, followed by extended adjuvant treatment with neratinib, as both treatments can be given at home, rather than intravenous adjuvant combination treatment with pertuzumab. However, it was noted that neratinib's high level of toxicity (see section 3.7) may mean some people have to go to hospital for diarrhoea treatment. The committee recognised that some people who did not receive adjuvant pertuzumab would benefit from extended adjuvant treatment with neratinib. However, it is unclear which people would receive neratinib in clinical practice.

Clinical evidence

ExteNET is the key trial relevant to this appraisal

3.3 ExteNET (n=2,840) is a phase 3 randomised controlled trial that compared neratinib treatment with placebo in women with HER2-positive breast cancer who had completed adjuvant trastuzumab treatment within 2 years. The company based its submission on a subgroup of women with

early hormone receptor-positive cancer who were less than 1 year from completing adjuvant trastuzumab-based treatment (n=1,334). This subgroup, referred to as the 'label' population, is in line with the neratinib marketing authorisation. It showed better clinical effectiveness and less side effects than the whole trial. The ERG noted that ExteNET was not designed to have statistical power to detect differences between treatments within subgroups. In addition, it noted that only 80 patients were recruited in the UK and that differences in clinical effectiveness by geographical region were reported. The clinical experts suggested that the trial is generalisable to the UK population. However, they noted that clinical trials tend to recruit fitter participants, and that there may be some limitation to the trial generalisability. The committee concluded that ExteNET is the key trial relevant to this appraisal and suitable for estimating the clinical effectiveness of neratinib.

There is no evidence for neratinib in people with a pathological complete response after neoadjuvant treatment

3.4 ExteNET did not include people who had a pathological complete response after neoadjuvant treatment. A pathological complete response means that there was no residual invasive cancer in the breast or axilla after completing neoadjuvant treatment. The committee concluded that there are no data on the clinical effectiveness of neratinib in people who had a pathological complete response after neoadjuvant treatment.

There is no evidence for neratinib in people who have had pertuzumab treatment

3.5 ExteNET did not include people who received pertuzumab alongside trastuzumab in the adjuvant setting. The committee concluded that there are no data on the clinical effectiveness of extended adjuvant neratinib after adjuvant pertuzumab treatment.

Neratinib improves invasive disease-free survival compared with placebo

3.6 Invasive disease-free survival was the primary outcome in ExteNET. The 5-year hazard ratio for invasive disease-free survival for the whole trial was 0.73 (95% confidence interval [CI] 0.57 to 0.92). The 5-year hazard ratio for invasive disease-free survival for the label population was 0.58 (95% CI 0.41 to 0.82). This suggests a statistically significant improvement in invasive disease-free survival for neratinib compared with placebo. Overall survival data were collected in the trial, but had not yet been fully analysed at the time of this appraisal. Only 121 deaths were recorded in the whole trial and the final analysis is expected after 248 deaths. Overall survival results for the label population were not available at the time of this appraisal. The committee concluded that neratinib improves invasive disease-free survival compared with placebo in the label population. However, it is not known whether neratinib increases the length of time people live because the final trial results are not available.

Adverse events

Diarrhoea is severe in some people but could be managed with prophylaxis

3.7 Neratinib is associated with high rates of diarrhoea, nausea and fatigue and may require hospital visits to treat diarrhoea. In ExteNET, diarrhoea prophylaxis was not used, although people were treated for diarrhoea as needed. The company explained that if diarrhoea prophylaxis is used, diarrhoea lasts approximately 5 days. Clinical experts confirmed that diarrhoea is not an issue for all people and that it can usually be managed with prophylaxis. One clinical expert reported feedback from 2 people who were given neratinib. One person did not have any diarrhoea, and the other had severe symptoms. It took some time to adjust the diarrhoeal treatment for this person before the symptoms diminished, but the person wanted to continue taking neratinib. The committee agreed that diarrhoea toxicity is high in some people but could be managed with prophylaxis and diarrhoeal treatments.

Invasive disease-free survival modelling

The company's use of general population mortality in the model is appropriate

3.8 The company developed a 5-state Markov model to evaluate the cost effectiveness of neratinib (the states were: invasive disease-free, local recurrence, remission, distant recurrence and dead). In the absence of overall survival data, invasive disease-free survival in the label population of the ExteNET trial and a general population mortality rate was used to estimate overall survival. The ERG noted that death from breast cancer is only possible from the distant recurrence health state. Mortality risk for all other health states (invasive disease-free, local recurrence and remission) is based on general population mortality. The ERG said that this assumption could underestimate the cost-effectiveness results. The company explained that patients are most likely to move into the distant recurrence health state first and that no patients in ExteNET died from breast cancer without first experiencing a distant recurrence. The clinical experts and the ERG agreed that this was a reasonable assumption. The committee was satisfied that the use of the general mortality in the model was appropriate.

It is unclear which approach to invasive disease-free survival modelling is the most appropriate

3.9 The company investigated whether neratinib's treatment effect could be modelled assuming proportional hazards between the neratinib and placebo arms of the trial. It concluded that it could, and invasive disease-free survival data in the label population were pooled and modelled together with a treatment effect as a covariate. The company chose a flexible-spline Weibull with 1 knot to model invasive disease-free survival. The ERG explained that the assumption of proportional hazards is uncertain because some of the analyses provided by the company suggested that it is not valid. The ERG assessed an overall-goodness-of-fit of the models considered by the company, and stratified models for which the proportional hazard assumption is not needed. It found that the

stratified generalised gamma model provided the best overall fit for the invasive disease-free survival data and included this model in its preferred base case. In response to technical engagement the company considered the ERG's model to be a conservative approach resulting in cost-effectiveness results that are at the high end of the most plausible range. The clinical experts considered both extrapolations plausible, however they noted that the extrapolations are difficult to judge because 5-year follow-up data from ExteNET is extrapolated for the next 50 years. The committee agreed that the proportional hazards assumption was met for the duration of the trial but not for the extrapolation put forward by the company. The committee concluded that it is unclear which approach to invasive disease-free survival modelling is the most appropriate and that both approaches could be plausible.

Duration and type of treatment effect

The ERG's approach is appropriate

3.10 The company assumed that the treatment effect observed in ExteNET would last beyond the trial time horizon until patients had a risk of invasive disease-free survival equal to the mortality rate in the general population. The duration of the treatment effect depends on the curve used to model invasive disease-free survival and general population mortality. The company assumed a continued effect and applied the invasive disease-free survival 5-year hazard ratio from the ExteNET label population of 0.58 (95% CI 0.41 to 0.82) from month 62.98 (as observed 4 years after 1 year of treatment with neratinib) to month 129 (when neratinib and general population mortality hazards are the same). This continued effect is followed with an implicit taper period until month 176 (when placebo and general population mortality hazards are the same). Using the ERG's preferred method to extrapolate invasive disease-free survival, the treatment effect stops at month 140. However, the ERG assumed that the tapering starts at the end of the trial and lasts until month 140. In response to the technical engagement, the company considered the

ERG's approach to modelling neratinib treatment effect and duration to be plausible, although conservative. The clinical experts considered the ERG's approach to be appropriate. The committee concluded that the ERG's approach to modelling neratinib treatment effect and duration is appropriate for decision making.

Cost-effectiveness estimates

The cost-effectiveness estimates are uncertain, but within the range NICE normally considers an acceptable use of NHS resources

3.11 Both the company's and ERG's preferred incremental cost-effectiveness ratios (ICERs) for people for whom trastuzumab is the only HER2-directed treatment in the adjuvant setting, and who did not have a pathological complete response to neoadjuvant treatment (see section 3.4–5) were within the range NICE normally considers an acceptable use of NHS resources. ICERs were presented as commercial in confidence to maintain the confidentiality of the proposed commercial agreement for neratinib, and therefore cannot be reported here. The committee was aware of the uncertainty associated with some of the inputs and assumptions in the model (for example invasive disease-free survival modelling as discussed in section 3.8–9), and the impact of the additional uncertainties as summarised in the technical report (table 2 on page 26–29, and table 3 on page 30–31). It considered that the most plausible ICER is unknown and could be higher or lower than the company's and ERG's preferred ICERs. However, it agreed the most plausible ICER is unlikely to exceed the range NICE normally considers an acceptable use of NHS resources. It therefore recommended neratinib for hormone receptor-positive, HER2-positive early breast cancer in adults who completed adjuvant trastuzumab-based treatment less than 1 year ago, only if trastuzumab was the only HER2-directed treatment in the adjuvant setting, and if their cancer did not have a pathological complete response in the neoadjuvant setting (if they had neoadjuvant treatment).

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 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.
- 4.3 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 hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-positive early breast cancer and the doctor responsible for their care thinks that neratinib is the right treatment, it should be available for use, in line with NICE’s recommendations.

5 Proposed date for review of guidance

- 5.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Brian Shine

Chair, appraisal committee

August 2019

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6 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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