

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Pertuzumab for adjuvant treatment of early HER2-positive breast cancer

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using pertuzumab for adjuvant treatment of HER2-positive early-stage breast cancer 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 pertuzumab for adjuvant treatment of HER2-positive early stage breast cancer 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: 7 September 2018

Third appraisal committee meeting: 16 October 2018

Details of membership of the appraisal committee are given in section 5.

1 Recommendations

- 1.1 Pertuzumab is not recommended, within its marketing authorisation, for the adjuvant treatment of early-stage human epidermal growth factor receptor 2 (HER2)-positive breast cancer in adults with high risk of disease recurrence.
- 1.2 This guidance is not intended to affect treatment with pertuzumab 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

There is uncertainty about how clinically effective pertuzumab is when used as adjuvant treatment for HER2-positive breast cancer in people at high risk of recurrence. The cost-effectiveness estimates are implausible because overall survival is very likely to be overestimated. The most plausible cost-effectiveness estimate is likely to be much higher than those presented by the company. Because of this, pertuzumab cannot be recommended for early-stage HER2-positive breast cancer.

2 Information about pertuzumab

Marketing authorisation	On 26 April 2018, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending a variation to the terms of the marketing authorisation for the medicinal product pertuzumab (Perjeta, Roche). The CHMP adopted a new indication as follows: 'the adjuvant treatment of adult patients with HER2-positive early stage breast cancer at high risk of recurrence'.
Dosage in the marketing authorisation	Intravenous 840 mg loading dose, then 420 mg every 3 weeks. Pertuzumab should be given with trastuzumab for 1 year (maximum 18 cycles) for high-risk patients, regardless of the timing of surgery.
Price	Pertuzumab costs £2,395 per 420-mg vial; trastuzumab costs £407.4 per 150-mg vial (excluding VAT; British national formulary [BNF] online [accessed May 2018]). The company has a commercial arrangement (simple discount) which would apply if the technology had been recommended. This makes pertuzumab 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 and a review of this submission by the evidence review group (ERG). See the [committee papers](#) for full details of the evidence.

New treatment option

Patients and their families would welcome new effective treatments that reduce the risk of recurrence

- 3.1 The patient experts explained that early-stage HER2-positive breast cancer has a considerable effect on patients and their families: diagnosis can be distressing and treatment is associated with negative side effects. The patient experts emphasised that living with early-stage HER2-positive breast cancer affects daily living (including restricting employment and

social activities) and puts strain on relationships. They identified disease recurrence as a common cause of stress and anxiety, both in terms of the possibility of progression to non-curable metastatic disease, and because of the need to have further treatment. The patient experts also noted that all treatments have side effects but targeted therapies, such as pertuzumab, tend to be well tolerated by patients. The patient experts recognised that a potential disadvantage of pertuzumab is that it is administered intravenously, whereas the standard of care (trastuzumab) is mostly delivered subcutaneously. This means that, for most people, having pertuzumab would require them to spend more time in hospital than they do currently. The patient expert noted that not all people would consider the additional treatment benefit of pertuzumab in the APHINITY trial to be worthwhile. However, they noted that most patients would consider a reduced risk of recurrence worth the potential inconvenience of spending longer in hospital. The committee concluded that patients and their families would welcome any new treatment options that effectively reduce the risk of recurrence.

Clinical management

Pertuzumab is already used as neoadjuvant therapy

3.2 A clinical expert explained that since the publication of NICE technology appraisal guidance on [pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer](#), many patients with early-stage HER2-positive breast cancer who are at high risk of recurrence have 4 to 6 cycles of neoadjuvant pertuzumab with trastuzumab and chemotherapy, followed by surgery and adjuvant trastuzumab (and endocrine and radiotherapy if appropriate). The company noted that the marketing authorisation for pertuzumab specifies that it should be given with trastuzumab for 1 year (maximum 18 cycles) for patients at high risk of recurrence, regardless of the timing of surgery. Opinions expressed by clinical experts varied in terms of how the use of adjuvant pertuzumab

might affect current practice. The committee heard that that although patients in APHINITY (the main trial in the adjuvant setting) had not had neoadjuvant therapy, if pertuzumab were recommended in the adjuvant setting, many patients would continue to have 4 to 6 cycles before surgery and then the balance of up to the maximum licenced dose (that is, 18 cycles) after surgery. However, it is also possible that if pertuzumab were available in the adjuvant setting, clinicians might decide to start treatment after surgery. The committee also heard that there is ongoing debate about whether the benefits of trastuzumab therapy would be achieved over a shorter treatment duration than is currently recommended (it is currently delivered over 12 months). The committee accepted that the treatment benefit of adjuvant pertuzumab may be similar whether or not the 18 cycles of treatment are started in the neoadjuvant setting. It therefore concluded that people having neoadjuvant pertuzumab should be considered as part of this appraisal (even though they were excluded from the pivotal clinical trial), because this is consistent with how pertuzumab is used in clinical practice.

APHINITY trial

The committee accepted the primary outcome of APHINITY in the absence of mature overall-survival data

3.3 The evidence for pertuzumab came from the APHINITY study, an ongoing randomised controlled trial comparing pertuzumab plus trastuzumab and chemotherapy with placebo plus trastuzumab and chemotherapy in 4,805 patients with early-stage HER2-positive breast cancer who had had surgery. The initial APHINITY study protocol (protocol A) included patients with either node-positive or node-negative disease. Patients with node-negative tumours were only included if the tumour was bigger than 1 cm in diameter, or between 0.5 cm and 1 cm in diameter with at least 1 high-risk feature (high grade histology, oestrogen and progesterone receptor-negative, or aged under 35 years). However, after 3,655 patients had

been randomised, the protocol was amended (protocol amendment B) to stop recruiting patients with node-negative disease and to allow for an additional 1,000 node-positive patients to be recruited. Patients entering the trial were stratified at randomisation according to nodal status, type of adjuvant chemotherapy regimen (anthracycline-based compared with non-anthracycline-based), hormone receptor status and geographical region and protocol version. The overall-survival data are immature, and at the time of the primary analysis there was no apparent difference between the treatment arms in terms of this outcome. The primary outcome for the trial was invasive disease-free survival excluding second primary non-breast cancer events. The committee noted that this is not the standard definition for invasive disease-free survival, which includes second primary non-breast cancer events. The company explained that this outcome definition had been chosen to meet US Food and Drug Administration criteria. The clinical experts expressed different opinions about the usefulness of invasive disease-free survival as a surrogate for longer-term outcomes. One expert noted that invasive disease-free survival is a compound surrogate outcome for overall survival, which incorporates both distant and loco-regional recurrence that are both important to patients. Another expert highlighted that early surrogate markers should be interpreted with caution as they do not always reliably predict metastatic recurrence or overall survival. In the Neosphere trial, for example, higher pathological complete response with neoadjuvant pertuzumab was not associated with improved overall survival in the long term, in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer at high risk of recurrence. The committee acknowledged the difficulty of obtaining mature overall-survival data for adjuvant treatments. It concluded that in the absence of mature overall-survival data, invasive disease-free survival is acceptable for decision-making. However it recognised that the reliability of using the surrogate

measure to inform estimates of overall survival is an important consideration and may influence the cost-effectiveness evidence.

Clinical evidence

Trial results suggest that pertuzumab offers only a small incremental treatment benefit compared with placebo

3.4 At 3 years, in the intention-to-treat population, the difference in invasive disease-free survival event rates between the 2 treatment arms was very small (0.9% at year 3 and 1.7% at year 4). From this, the committee concluded that any incremental treatment benefit of pertuzumab is likely to be small.

There is little evidence that pertuzumab is more effective for node-positive or hormone receptor-negative disease

3.5 The company's initial submission focused on patients with either node-positive disease or hormone receptor-negative disease, because these 2 subgroups are considered to be at high risk of disease recurrence and are covered by the marketing authorisation. The clinical experts stated that the APHINITY trial does not support the use of adjuvant pertuzumab in both groups; they considered that pertuzumab is likely to be most beneficial in people with lymph-node positive disease. The committee agreed that it is biologically plausible that patients would be at high risk of recurrence if there were lymph node involvement (which is an indicator of disease spread) or if the tumour were hormone receptor-negative (because these patients cannot have endocrine treatment). The committee was concerned that APHINITY was not powered to determine treatment effects within the subgroups of interest. It recognised that the separation of the curves for each treatment arm shown in the Kaplan–Meier plots appeared greater in these subgroups compared with the intention-to-treat population, and this was reflected in the improved hazard ratios for these populations (lymph-node positive 0.77, 95% confidence

interval [CI] 0.62 to 0.96; hormone-receptor negative 0.76, 95% CI 0.56 to 1.04) compared with the intention-to-treat population. However the absolute difference in event rates across the treatment arms of all the node-status and hormone-receptor status subgroups is small (range 0.5% to 3.2%). The committee also noted that even though the trial was not powered to detect interactions, statistical tests for interaction had been performed. These resulted in p values of 0.17 (nodal status and randomised group interaction) and 0.54 (hormone-receptor status and randomised group interaction), implying that there is no evidence that the hazard ratio comparing pertuzumab with placebo differed between subgroups defined by these characteristics. It also noted that a very small overall number of events occurred in the node-negative subgroup (n=32 in the pertuzumab arm and n=29 in the placebo arm, compared with n=139 and n=181 events in the equivalent arms of the node-positive subgroup). The committee therefore considered that there is considerable uncertainty in the results for the node-negative subgroup, and it is not reasonable to conclude that pertuzumab did not provide clinical benefit these patients. The committee therefore concluded that, although patients with lymph-node positive or hormone receptor-negative disease would benefit most from pertuzumab as adjuvant therapy in absolute terms, there is no evidence that the relative treatment effect differs between these subgroups. It therefore considered that the hazard ratio for the intention-to-treat population is the most valid measure of clinical effectiveness.

Adverse events

Pertuzumab is generally well tolerated

3.6 The committee heard that grade 3 or higher adverse events were statistically significantly more common with pertuzumab than with placebo in APHINITY (risk ratio 1.12, 95% CI 1.07 to 1.17; $p < 0.0001$). Rates of diarrhoea, anaemia and one of the serious cardiac events measured in the trial (New York Heart Association class III/IV heart failure and

substantial decrease in left ventricular ejection fraction) were also statistically significantly more common in the pertuzumab arm. The committee noted that although a very low proportion of patients had a primary cardiac event (0.7% with pertuzumab and 0.3% with placebo), there were 17 in the pertuzumab arm compared with only 8 in the placebo arm. Health-related quality of life was measured using a number of validated outcome measures (the EuroQol 5-Dimension, the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 and the EORTC QLQ-BR23). However, the ERG noted that the company's submission stated that the assessment schedule was not designed to detect quality-of-life differences between the treatment arms. The ERG considered that it was also unlikely to have captured the true effect of adverse events, because of infrequent data collection. The committee acknowledged this but heard from the clinical and patient experts that pertuzumab is generally well tolerated. The committee also acknowledged that some of the adverse events experienced by patients in APHINITY occurred when patients were also having chemotherapy treatment, which may have contributed to some of the adverse events. The committee concluded on the basis of the patient and clinical expert testimony that pertuzumab is generally a well-tolerated treatment.

Cost-effectiveness model

The model structure is appropriate and suitable for decision-making

- 3.7 The company's updated cost-effectiveness model focused on the lymph node-positive population. Inputs were based on data for the relevant subgroups from APHINITY, as well as information from other relevant sources. Rates of invasive disease-free survival were projected over the lifetime time horizon (52 years) by fitting parametric curves to the data observed in APHINITY. The choice of curve was based on statistical measures of goodness-of-fit with a log-logistic curve used for the node-

positive population. To account for non-proportional hazards, the curves were fitted independently to each treatment arm. The time period was split into 3 phases to reflect the anticipated periods of time during which the treatments received (intervention or comparator) were expected to be fully effective (phase 1), waning (phase 2) and background mortality rates after treatment effect had ceased (phase 3). The committee noted that this resulted in an unusual treatment-effect profile with increasing benefit of treatment with time over one period (during which the curves separated) and then at a specific time-point a sudden sharp decline and convergence of the curves. The committee found this difficult to explain. However the committee accepted the ERG's conclusion that the choice of parametric curves and the rationale for the adjustments are appropriate, and concluded that the overall design and structure of the model appears acceptable for decision-making.

Cost-effectiveness estimates

Model inputs

3.8 The company revised their cost-effectiveness analysis during the consultation on the appraisal consultation document, so that it was better aligned to the ERG's preferred assumptions (cure adjustment introduced at year 3, and a maximum cure proportion of 95% at 10 years). It also included an updated commercial access agreement, and updated the proportion of metastatic and non-metastatic recurrence before and after 18 months. The ERG agreed with the revised proportions of metastatic and non-metastatic recurrence because the updated values are based on more recent trial data, rather than the assumptions in the ERG's original base case. Therefore, the company and the ERG agreed on all of the key model assumptions with the exception of the duration of treatment effect. The company accepted that there is uncertainty about the duration of treatment effect but it considered that the ERG's preferred assumptions (waning of treatment effect beginning at year 4 and ending at year 7) are

too conservative. It therefore applied its original assumption (waning of treatment effect begins at year 7 and ends at year 10) in its updated analysis, but also provided some exploratory analysis to show the combined impact on the incremental cost-effectiveness ratios (ICERs) of different assumptions about the duration of treatment effect and the market share and list price discount of biosimilar intravenous trastuzumab. The committee accepted that although both the company's and the ERG's revised base-case analyses are informed by data from relevant sources, many assumptions had to be made because of the immaturity of the available trial data. The committee noted that despite use of many of the ERG's preferred assumptions in the company's revised model the results still seem implausible, based on the extrapolation of the marginal benefit in invasive disease-free survival observed in APHINITY into a discounted QALY gain of 0.56 for the node-positive population. The committee considered the estimate of overall survival, which was not modelled parametrically from the observed data but assessed indirectly based on patient-progression through the health states. It remained of the view that overall survival is likely to be overestimated in the company's model and does not fit the observed APHINITY data well. It recognised that more mature data on invasive disease-free survival or overall survival would reduce the uncertainty in the model, and provide a more reliable estimate of cost effectiveness. However it was aware that the final overall-survival analysis of APHINITY is not due until 2023. It considered the conflicting views expressed by the clinical experts about whether improvements in invasive disease-free survival are likely to lead to long term benefits. It concluded that this lack of consensus adds to the concern about the validity of the model outputs and justifies a conservative approach to decision making, given the difference between the ICERs presented. The committee's preference is to accept the ERG's ICERs, which are based on less optimistic assumptions about the duration of treatment effect.

The most plausible ICERs are likely to be higher than those reported in either the company or the ERG's updated estimates

3.9 The company's updated base-case ICER for pertuzumab compared with chemotherapy for node-positive disease is £30,561. The ERG's updated exploratory analyses using its preferred assumptions in the same population results in a considerably higher ICER of £47,856. The committee noted that both these estimates are based on the results for the lymph-node positive subgroup in APHINITY, and represent optimistic estimates for the relative effectiveness of pertuzumab. The committee also noted that the tariff costs used for administration (by the company and the ERG) are out of date, and the most up-to-date tariff should have been used. This would increase the difference in the chemotherapy administration costs for intravenous pertuzumab and trastuzumab plus chemotherapy, compared with subcutaneous trastuzumab plus chemotherapy, from £40 to £151. The ERG provided updated ICERs using the correct administration costs for the company's and the ERG's revised base-case (£33,700 and £52,136 per QALY gained respectively). These are higher than the range normally considered to be a cost-effective use of NHS resources.

Biosimilar intravenous trastuzumab will lower the cost of adjuvant pertuzumab treatment but it is still unlikely to be cost effective

3.10 The committee noted that biosimilars for trastuzumab are now available in England, which will reduce the overall cost of pertuzumab combination therapy. The committee heard from the Cancer Drugs Fund clinical lead that the initial tendering process for biosimilar trastuzumab has only recently been completed and that prices and market share are likely to change over time. The committee considered the current commercial-in-confidence price and market share to be most appropriate for decision making, because this is in line with what has been considered in other NICE appraisals. The committee considered the exploratory threshold

analysis (with a biosimilar discount of 70% to 90% and a market share of 90% to 100%) provided by the company, but noted that this does not take into account the error in the tariff costs (see section 3.9). The Cancer Drugs Fund clinical lead informed the committee of a weighted-average price and market share estimate for biosimilar trastuzumab products (that took account of the confidential discounts and market shares of each currently available product) that had been used in the NICE Budget Impact Test analysis. The committee considered this weighted average gave the best estimate of current price and market share for the purposes of estimating the ICER. The Cancer Drugs Fund clinical lead also confirmed that the impact of the introduction of biosimilar intravenous trastuzumab only needs to be considered in the intervention arm of the model, because, if it is delivered as a standalone treatment, the current practice of providing adjuvant trastuzumab subcutaneously is unlikely to change. When the weighted average biosimilar discount and market share estimates were taken into account, the company's and the ERG's base-case ICERs were £24,985 and £39,939 per QALY gained respectively. The committee therefore concluded that although the availability of biosimilar trastuzumab will greatly reduce the overall cost of the adjuvant pertuzumab regimen, the ERG's updated base-case ICER still does not fall within the range usually considered to be a cost-effective use of NHS resources.

Pertuzumab cannot be recommended for adjuvant treatment of early-stage HER2-positive breast cancer

- 3.11 The committee noted that an improvement in invasive disease-free survival was observed in the intention-to-treat population of APHINITY, but the improvement was marginal and there is uncertainty in the estimates of effect. It accepted that the subgroups proposed by the company (node-positive and hormone receptor-negative disease) are at high absolute risk of recurrence, but concluded that the evidence for increased relative efficacy in these groups is not convincing (because of

the non-significant test for interaction in each of these subgroups). It noted that the company's ICERs include an optimistic assumption for the duration of treatment benefit, and it considered that the ERG's analyses provide a more plausible estimate of the cost effectiveness of pertuzumab. It also noted the ERG's ICER for node-positive disease that included the correction for the tariff costs and the biosimilar trastuzumab discount and market share, which is £39,939 per QALY gained. The committee concluded that this did not represent a cost-effective use of NHS resources and pertuzumab cannot be recommended for routine commissioning in the NHS.

Cancer drugs fund

Pertuzumab is not recommended for inclusion in the Cancer Drugs Fund

3.12 Having concluded that pertuzumab could not be recommended for routine use, the committee considered if it could be recommended for treating early-stage HER2-positive breast cancer within the Cancer Drugs Fund. The committee discussed the arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting the [addendum to the NICE process and methods guides](#).

- The committee noted the uncertainties in the clinical-effectiveness data for pertuzumab, which relate to the subgroups prioritised by the company (patients with node-positive and hormone-receptor negative disease). It considered that the treatment effect observed in the intention-to-treat population is marginal, and the impact of pertuzumab on overall survival is unknown because data for this outcome are immature.
- It acknowledged that further invasive disease-free survival data or mature overall-survival data from APHINITY may help to resolve some of the uncertainty in the cost-effectiveness estimates. However, having concluded that overall survival had been overestimated in the

company's model and given the low overall event rates in this population, the committee concluded that further data collection through the Cancer Drugs Fund is unlikely to confirm benefits as great as, or greater than, those estimated by the company's model.

- There is no plausible potential to satisfy the criteria for routine use because the most robust ICER for the lymph-node positive population is £39,939 per QALY gained.
- The committee concluded that pertuzumab does not meet the criteria to be considered for inclusion in the Cancer Drugs Fund. It did not recommend pertuzumab for use within the Cancer Drugs Fund as an option for people with early-stage HER2-positive breast cancer.

4 Review of guidance

The guidance on this technology will be considered for review 3 years after publication of the guidance. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Dr Iain Squire

Vice Chair, appraisal committee

July 2018

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.

Juliet Kenny

Technical Lead

Eleanor Donegan

Technical Adviser

Thomas Feist

Project Manager

ISBN: