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 stagebreast 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: 6 July 2018

Second appraisal committee meeting: 19 July 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

The cost-effectiveness estimates are implausible, because the model appears to overestimate overall survival and there is uncertainty about the effectiveness of pertuzumab as adjuvant treatment. 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 £2,395 per 420 mg vial; trastuzumab £407.4 per 150 mg vial (excluding VAT; British national formulary [BNF] online [accessed May 2018]). Costs may vary in different settings because of negotiated procurement discounts. 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 clinical and patient expert were in agreement that not all people would consider the additional treatment benefit of pertuzumab in the APHINITY trial to be worthwhile. However, they noted that some patients may 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. The clinical expert explained 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 patients would most likely 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. The committee also heard that there is some ongoing debate about whether the benefits of trastuzumab therapy currently delivered over 12 months may be derived over a shorter treatment duration than is currently recommended. The committee accepted that the treatment benefit of adjuvant pertuzumab may be the same whether or not the 18 cycles of treatment are started in the neoadjuvant setting. It therefore concluded that people who had 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 versus 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 was 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. A clinical expert noted that invasive disease-free survival is a compound surrogate outcome for overall survival, which incorporates both distant and loco-regional recurrence: these are both important to patients. The committee concluded that in the absence of mature overall survival data, the primary outcome used in the trial was acceptable for decision-making.

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.

Subgroups

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

3.5 The company 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. The

company argued that these patients would be more likely to benefit from pertuzumab. The committee noted that these subgroups are in line with the marketing authorisation for pertuzumab, and 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, but noted that the absolute difference in event rates across the treatment arms of all the node-status and hormone receptor status groups was small (range 0.5% to 3.2%). They also noted that a very small number of events occurred in the node-negative subgroups overall (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 felt that there was considerable uncertainty in the findings for the node-negative subgroup and it was not reasonable to conclude that pertuzumab did not benefit these patients. Finally the committee noted that statistical tests for interaction resulted in p values for invasive disease-free survival of less than 0.05 (p=0.17 for interaction between nodal status and invasive disease-free survival; p=0.54 for interaction between hormone receptor status) suggesting that neither nodal nor hormone receptor status were associated with a statistically significant difference in treatment effect.

Furthermore company's submission did not fully investigate all potentially important subgroups

3.6 The company's submission focused on subgroups based on nodal and hormone receptor status, but it did not evaluate other important baseline characteristics: in particular, tumour size and menopausal status. The

committee considered that tumour size is potentially of similar prognostic importance to nodal or hormone receptor status. It did not accept the company's assertion that tumour size was less relevant based on a non-statistically significant p value for interaction, because the interactions between nodal status and hormone receptor status had also been non-significant. Moreover, menopausal status had the lowest p value for interaction (p=0.07) but had not been prioritised either. A clinical expert explained that menopausal status is not an objectively measurable risk factor, and that it can be particularly difficult to determine in people with chemotherapy-induced amenorrhea, or in people who are perimenopausal. The clinical expert also noted that menopausal status can overlap with other known risk factors for recurrence such as hormone receptor status, and that there was no obvious clinical rationale for why menopausal status alone might determine treatment effect. The committee noted these points and accepted the uncertainty of menopausal status as a risk factor. However, it considered that patients with larger tumours were potentially at higher risk of recurrence and therefore a clinical relevant subgroup within the 'high risk' definition of the marketing authorisation. The committee was of the view that the effect of these baseline characteristics had not been subject to the same level of scrutiny in the company's submission as other characteristics, and the rationale underpinning this decision was not convincing. It concluded that, although patients at high-risk of recurrence would benefit most from pertuzumab as adjuvant therapy in absolute terms, there is little evidence of heterogeneity between subgroups in the relative treatment effect.

Adverse events

Pertuzumab is generally well tolerated

3.7 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 worse 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 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 the APHINTY study 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 model

The model structure is appropriate and suitable for decision-making

3.8 The company's cost model was applied separately for patients with node-positive disease and patients with hormone receptor-negative disease. Inputs were based on data for the relevant subgroups from APHINITY, as well as information from other relevant sources. The long-term treatment effect was modelled in the same way for both groups. 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. A

log-logistic curve was used for the node-positive population and an exponential curve was used for the hormone receptor-negative 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 considered that the overall design and structure of the model, including the choice of parametric curves and the rationale for the adjustments, was acceptable for decision-making.

Cost-effectiveness estimates

Differences between the company's and ERG's ICERs were driven by uncertainty in estimates of treatment benefit

3.9 The company's base-case incremental cost-effectiveness ratios (ICERs) for pertuzumab compared with chemotherapy were:

- £34,087 per quality-adjusted life year (QALY) gained for node-positive disease
- £65,699 per QALY gained for hormone receptor-negative disease.

The ERG did exploratory analyses using their preferred assumptions, which resulted in considerably higher ICERs:

- £60,679 per QALY gained for node-positive disease
- £92,778 per QALY gained for hormone receptor-negative disease.

The differences between the company's and the ERG's ICERs were the result of different assumptions about the model inputs. Specifically, the ERG preferred different values for:

- Length of treatment effect: in the company's model the waning of treatment effect began at year 7 and ended at year 10, whereas the ERG estimated that waning would begin at year 4 and end at year 7.
- Inputs related to the cure adjustment: the company's model introduced the cure adjustment at year 4 reaching a maximum cure proportion of 90% at 10 years, whereas the ERG introduced the cure adjustment at year 3 and reached a maximum cure proportion of 95% at 10 years.
- Proportion of patients with metastatic and non-metastatic recurrent disease:
  - the company's model estimated 81.07% metastatic disease and 18.93% non-metastatic disease in the node-positive population, and 76.87% metastatic disease and 23.13% non-metastatic disease in the hormone receptor-negative population.
  - The ERG estimated 72.40% metastatic disease and 27.60% non-metastatic disease in the node-positive population, and 65.60% metastatic disease and 34.40% non-metastatic disease in the hormone receptor-negative population.

The committee accepted that both the company's base-case and the ERG's exploratory analyses were informed by data from relevant sources but in both analyses, overall, many assumptions had to be made because of the inherently immature nature of the available trial data. The committee did, however, regard the outputs of the company's model to be implausible, specifically the extrapolation of the very marginal benefit in invasive disease-free survival observed in the APHINTY study into a QALY gain of 0.6 for the node-positive population. The committee were of the view that this suggested that overall survival (which was not modelled parametrically from the observed data, but assessed indirectly based on patient progression through the health states) was overestimated in the company's model and did not fit the observed APHINITY data well. The committee recognised that more mature overall survival data would reduce the uncertainty in the inputs used in the model, and provide a

more reliable estimate of cost effectiveness. The company explained that the final overall survival analysis of APHINITY is due in 2023.

Pertuzumab cannot be recommended for adjuvant treatment of early stageHER2-positive breast cancer

3.10 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 was uncertainty in the estimates of effect. It accepted that the subgroups proposed by the company (node-positive and hormone receptor-negative disease) were at high absolute risk of recurrence, but concluded that the evidence for increased relative efficacy in these groups was not convincing (as inferred by the non-significant test for interaction). It noted that the ICERs presented by the company were based on a number of assumptions that cannot be substantiated (including extrapolation of overall survival benefit, which could not be clarified through further analysis of currently available data). It noted that the ERG's analyses did not necessarily provide a more accurate indication of the cost effectiveness of pertuzumab, but demonstrated how the uncertainty in the model affected the ICER. The committee noted that the ICERs for the node-positive population ranged from £34,087 (company estimate) to £60,679 per QALY gained (ERG estimate) and hormone receptor-negative population ICERs ranged from £65,699 (company estimate) to £92,778 per QALY gained (ERG estimate). None of these ICERs fell within the range usually considered to be a cost-effective use of NHS resources. Furthermore, if the observed treatment benefit in the intention-to-treat population of the APHINITY trial were used the ICER could be substantially higher. Therefore, the committee concluded that adjuvant pertuzumab is not cost effective and could not be recommended for routine commissioning in the NHS.

Cancer drugs fund

Pertuzumab is not recommended for inclusion in the Cancer Drugs Fund

3.11 Having concluded that pertuzumab could not be recommended for routine use, the committee considered if it could be recommended for treating early stage HER2-postive 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 related 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 was 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 lowest ICER estimated by the company (£34,087 per QALY gained for the node-positive population) is not within the range normally considered to be a cost effective use of NHS resources, and it was judged to be unrealistically low. The ERG's analyses suggest, despite the uncertainly in the clinical evidence, that the range of possible ICERs in both the node-positive and hormone receptor-

negative subgroups is wide (up to £60,679 and £92,778 respectively). From this, it could be inferred that the range of ICERs for the intention-to-treat population would include estimates that are even higher than those for the subgroups.

- 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 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive when data from the final analysis of the APHINITY trial become available. 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.

Dr Iain Squire
Vice Chair, appraisal committee
June 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

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