

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal document

Pertuzumab for adjuvant treatment of HER2- positive early stage breast cancer

1 Recommendations

1.1 Pertuzumab, with intravenous trastuzumab and chemotherapy, is recommended for the adjuvant treatment of human epidermal growth factor receptor 2 (HER2)-positive early stage breast cancer in adults, only if:

- they have lymph-node-positive disease
- the company provides it according to the commercial arrangement (see [section 2](#)).

1.2 This guidance is not intended to affect adjuvant 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 the size of the clinical benefit for pertuzumab in the adjuvant treatment of HER2-positive early stage breast cancer at high risk of recurrence. Clinical trial evidence measuring invasive disease-free survival suggests that 1.7% fewer people with this type of cancer have invasive disease at 4 years with adjuvant pertuzumab. Evidence from people with lymph-node-positive disease (that is, disease that has spread to lymph nodes in the armpit) suggests more benefit in

this population, with 3.2% fewer people having invasive disease at 4 years. However, it is not known whether this means that adjuvant pertuzumab increases the overall length of time people live.

Because of the uncertainty in the clinical-effectiveness evidence, the cost-effectiveness estimates are very uncertain. Given this uncertainty, an estimate above £20,000 per quality-adjusted life year (QALY) gained is not considered a cost-effective use of NHS resources. The company's final model, includes only people with lymph node-positive disease, and incorporates the committee's preferred conservative estimates of how long treatment benefit with pertuzumab lasts after treatment is stopped. If the commercial discount to the price of pertuzumab, together with a weighted discount for biosimilar intravenous trastuzumab are taken into consideration, the cost-effectiveness estimate is comfortably below £20,000 per QALY gained. Therefore adjuvant pertuzumab is recommended for HER2-positive early stage breast cancer in people with lymph-node-positive disease.

2 Information about pertuzumab

Marketing authorisation	Pertuzumab (Perjeta, Roche) is indicated as '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 and chemotherapy for 1 year (maximum 18 cycles) for patients with high-risk disease, 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 online, accessed May 2018). The company has a commercial arrangement (simple discount patient access scheme). 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 6](#)) 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 HER2-positive early stage 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 HER2-positive early stage breast cancer affects daily living (including restricting employment and social activities) and puts a 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 now mostly delivered subcutaneously. This means that most people having pertuzumab would need to spend more time in hospital than they do currently. It would also mean that trastuzumab would need to be administered intravenously, in line with the clinical trial protocol. The patient experts noted that not all people would consider the additional treatment benefit of pertuzumab (at the level seen in the APHINITY trial, see section 3.3) 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 although the absolute benefit of pertuzumab over trastuzumab and chemotherapy in the APHINITY trial is low, patients and their families would welcome any new treatment options that could 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 HER2-positive early stage 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 with disease 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 patients in APHINITY (the main trial in the adjuvant setting) had not had neoadjuvant therapy. However, it also heard that, if pertuzumab were to be 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 to be available in the adjuvant setting for patients with nodal disease, clinicians might decide to start treatment after surgery. The committee accepted that the treatment benefit of adjuvant pertuzumab may well 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 primary outcome of APHINITY is acceptable but there is an absence of mature overall-survival data

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

disease and to allow for an additional 1,000 patients with lymph node-positive disease 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. The overall-survival data are immature and, at the time of the primary analysis, there was no apparent difference in overall survival between the treatment groups. 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 usually includes second primary non-breast cancer events. A clinical expert noted that although disease-free survival is a widely accepted surrogate for overall survival, recent studies have used invasive disease-free survival as a compound surrogate outcome for overall survival. This incorporates both distant and loco-regional recurrence, which are both relevant to overall survival and important to patients. This outcome definition had been identified as meeting US Food and Drug Administration criteria and the European Medicines Agency requirements for a relevant surrogate endpoint. The clinical expert commented that there is about a 10% difference between disease-free survival and invasive disease-free survival events, the latter excluding events such as new local cancers that are of little or no prognostic significance. 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 the only available data for decision making. However, it recognised that the extent to which invasive disease-free survival translates into long-term overall-survival benefit is not known.

Clinical evidence

Trial results suggest that pertuzumab offers only a small incremental treatment benefit compared with placebo in the whole trial population

3.4 In the intention-to-treat population, the absolute difference in invasive disease-free survival event rates between the 2 treatment arms was very small. When pertuzumab was added to trastuzumab and chemotherapy 1.7% fewer people had invasive disease at 4 years. From this, the committee concluded that the incremental treatment benefit of pertuzumab for the whole population is likely to be small.

Whether pertuzumab's relative treatment effect is greater for lymph-node-positive than lymph-node-negative disease is unclear but absolute benefit seems to be greater

3.5 The company's initial submission focused on patients with either lymph-node-positive disease or hormone receptor-negative disease because these 2 subgroups are considered to be at higher risk of disease recurrence and are covered by the marketing authorisation. The clinical experts stated 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 higher risk of recurrence if there were lymph node involvement (which is an indicator of disease spread and metastatic potential) 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 numerically lower hazard ratios for these populations (lymph-node positive: hazard ratio [HR] 0.77, 95% confidence interval [CI] 0.62 to 0.96; hormone receptor negative: HR 0.76, 95% CI 0.56 to 1.04) compared with the

intention-to-treat population (HR 0.81, 95% CI 0.66 to 1.00). However the absolute difference in event rates across the treatment arms of all hormone receptor and lymph node-status subgroups was small (range 0.5% to 3.2%). The committee also noted that statistical tests for interaction did not indicate evidence of heterogeneity in the magnitude of treatment effect defined by lymph node status ($p=0.17$) or hormone receptor status ($p=0.54$). However, it also noted that a very small overall number of events occurred in the lymph 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 lymph-node-positive subgroup). The committee heard from the clinical experts, and accepted the biological plausibility, that people with lymph-node-positive disease would have more recurrences, so that even with the same relative effectiveness the numerical reduction in recurrences and absolute benefit would therefore be greater. It also noted that the hazard ratio for this subgroup in the trial reached statistical significance (HR 0.77, 95% CI 0.62 to 0.96). The committee accepted that the subgroup with lymph-node-positive disease represents a population at increased risk of recurrence, and that the company's decision to focus on people with lymph-node-positive disease is reasonable.

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 1 of the serious cardiac events measured in the trial (New York Heart Association class III or 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 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 they 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 acceptable to patients.

Cost-effectiveness model

The model structure is appropriate but results in an unusual treatment-effect profile

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 on 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 lymph 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 (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 1 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, noting that it is impossible to predict the treatment-effect duration, or its decline, in the absence of more mature data. It accepted the ERG's conclusion that the choice of parametric curves and the rationale for the adjustments seems reasonable. The committee concluded that although the overall design and structure of the model appears acceptable, there is inherent uncertainty in the extrapolation of treatment benefit.

Cost-effectiveness estimates

There is substantial uncertainty in the predicted benefit of adjuvant pertuzumab over a long time horizon

3.8 The company revised their cost-effectiveness analysis during the consultation on the appraisal consultation document. This was to make it better aligned to the ERG's preferred assumptions (cure adjustment introduced at year 3, and a maximum cure proportion of 95% at 10 years), and the duration of treatment benefit (waning of treatment effect beginning at year 4 and ending at year 7). 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 were based on more recent trial data. The committee accepted that although both the company's and the ERG's revised base-case analyses were informed by data from relevant sources, many assumptions had to be made because of the immaturity of the available trial data. 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 noted that many of the ERG's preferred assumptions were used in the company's revised model. However, despite this, there was still uncertainty in projecting a 3% benefit in disease-free survival in the lymph node-positive group to a 0.4 quality-adjusted life year (QALY) gain. It also noted that any assessment of the acceptability of the estimated incremental cost-effectiveness ratio (ICER) should take this uncertain long-term benefit into account. The committee concluded that the long-term QALY gain is highly uncertain.

Pertuzumab can be recommended for adjuvant treatment of HER2-positive early stage breast cancer in people with lymph node-positive disease

3.9 The updated model included assumptions preferred by the committee for the duration of treatment benefit, which had a large impact on the ICER, and a new commercial discount to the price of pertuzumab. The committee noted that biosimilars for intravenous trastuzumab are now available in England, which will reduce the overall cost of pertuzumab combination therapy. It 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 biosimilar trastuzumab market share to be most appropriate for decision making because this is in line with what has been considered in other NICE appraisals. It considered that a weighted-average biosimilar trastuzumab discount gave the best estimate of current price for the purposes of estimating the ICER. The Cancer Drugs Fund clinical lead also confirmed that the effect of introducing biosimilar intravenous trastuzumab only needed to be considered in the intervention arm of the model because, if trastuzumab is delivered without pertuzumab, the current practice of providing adjuvant subcutaneous trastuzumab is unlikely to change. When the weighted-average biosimilar

discount and market share estimates were taken into account in the updated model the company's base-case ICER was comfortably lower than £20,000 per QALY gained. The committee was aware that this ICER incorporated considerable uncertainty in: the size of the effect of pertuzumab on overall survival based on the APHINITY trial (see section 3.4), the specific benefit of pertuzumab in the lymph-node-positive group (see section 3.5), a modelled QALY gain of 0.4 (see section 3.8), and the estimate weighted-average discount applicable to biosimilar intravenous trastuzumab. While the committee still had concerns that the 0.4 QALY gain could be an overestimate, it acknowledged that pertuzumab had been shown to be an effective treatment in both the neoadjuvant and metastatic setting. It considered that, because the updated ICER is comfortably below £20,000 per QALY gained using the committee's preferred assumptions, the new commercial offer is sufficient to offset the uncertainty about the estimated QALY gain. The committee therefore concluded that pertuzumab can be recommended in the NHS as a cost-effective treatment option for the adjuvant treatment HER-2 positive early stage breast cancer in people with lymph-node-positive disease.

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 human epidermal growth factor receptor 2-positive early stage breast cancer and the doctor responsible for their care thinks that pertuzumab is the right treatment, it should be available for use, in line with NICE's recommendations.

5 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 Jane Adam
Chair, appraisal committee
January 2019

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.

Juliet Kenny

Technical Lead

Eleanor Donegan

Technical Adviser

Thomas Feist

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ISBN: