NICE National Institute for Health and Care Excellence

NICE guidance

Pertuzumab with trastuzumab and docetaxel for treating HER2-positive breast cancer

Technology appraisal guidance
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Your responsibility

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

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

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

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

Contents

1 Recommendations

1.1 Pertuzumab, in combination with trastuzumab and docetaxel, is recommended, within its marketing authorisation, for treating HER2-positive metastatic or locally recurrent unresectable breast cancer, in adults who have not had previous anti-HER2 therapy or chemotherapy for their metastatic disease, only if the company provides pertuzumab within the agreed commercial access arrangement.

Why the committee made these recommendations

This recommendation is for a drug that has been available on the Cancer Drugs Fund for several years and the committee recognised this as an exceptional circumstance. In this context, the committee considered it reasonable to apply flexibility in its interpretation of the criteria for special consideration as a life-extending treatment for people with a short life expectancy, but noted that the weight applied to the quality-adjusted life years gained would not be at the maximum allocated in other, more regular, circumstances where the end of life criteria have been applied. With this in mind, the committee accepted that the incremental cost-effectiveness ratio, taking into account the commercial access arrangement, provides for an acceptable use of NHS resources.

2 The technology

Information about pertuzumab

Description of the technology	Pertuzumab (Perjeta, Roche Products) is a monoclonal antibody targeting human epidermal growth factor receptor 2 (HER2). Pertuzumab binds to the HER2 receptor and inhibits intracellular signalling. It is administered by intravenous infusion.
Marketing authorisation	Pertuzumab has a UK marketing authorisation for use 'in combination with trastuzumab and docetaxel in adult patients with HER2 positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti HER2 therapy or chemotherapy for their metastatic disease'.
Adverse reactions	The summary of product characteristics lists the following adverse reactions for pertuzumab in combination with trastuzumab and docetaxel: left ventricular dysfunction (including congestive heart failure), infusion reactions, hypersensitivity reactions (including anaphylaxis), neutropenia, febrile neutropenia, leukopenia, diarrhoea, alopecia and rash. For full details of adverse reactions and contraindications, see the summary of product characteristics.
Recommended dose and schedule	The recommended dose of pertuzumab is an initial loading dose of 840 mg followed every 3 weeks by a maintenance dose of 420 mg in combination with trastuzumab and docetaxel. Treatment with pertuzumab should be continued until disease progression or unmanageable toxicity.
Price	Pertuzumab is £2,395 per 420-mg vial (BNF 17). Therefore the cost of pertuzumab (excluding VAT) is estimated to be £4,790 for the initial dose and £2,395 for subsequent doses. The company has agreed a commercial access arrangement for pertuzumab with NHS England. The commercial access arrangement replaces the patient access scheme agreed with the Department of Health for pertuzumab. The details of this commercial access arrangement are commercial in confidence.

3 Evidence

3.1 The appraisal committee (section 6) considered evidence submitted by Roche and a review of this submission by the evidence review group. The appraisal was paused in 2014 to allow NICE's decision support unit to provide a discussion paper and then later reconsidered as part of the transition to the new Cancer Drugs Fund system. The reconsideration focussed on the final analysis of the CLEOPATRA trial and an updated economic model that incorporated a confidential commercial access arrangement. See the committee papers for full details of the evidence.

3.2 The company included 1 randomised controlled trial in its original submission (CLEOPATRA). This was a double-blind, randomised, placebo-controlled trial assessing the efficacy and safety of pertuzumab plus trastuzumab and docetaxel in 808 adults with human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer in 25 countries including the UK. Randomisation was stratified by geographic region (Asia, Europe, North America and South America) and prior treatment status (de novo and prior adjuvant or neoadjuvant chemotherapy). Investigators randomised patients in a 1:1 ratio to either pertuzumab plus trastuzumab and docetaxel (n=402), or placebo plus trastuzumab and docetaxel (n=406). Patients had either pertuzumab at a loading dose of 840 mg followed by 420 mg every 3 weeks or by placebo every 3 weeks, until disease progression or unacceptable toxicity occurred. All patients had trastuzumab at a loading dose of 8 mg/kg body weight followed by 6 mg/kg body weight every 3 weeks, and docetaxel 75 to 100 mg/m^2 (at investigator discretion) every 3 weeks for at least 6 cycles.

4 Committee discussion

4.1 The appraisal committee reviewed the data available on the clinical and cost effectiveness of pertuzumab plus trastuzumab and docetaxel, having considered evidence on the nature of human epidermal growth factor receptor 2 (HER2)-positive metastatic or locally recurrent unresectable breast cancer and the value placed on the benefits of pertuzumab plus trastuzumab and docetaxel by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

4.2 The committee discussed the management of HER2-positive metastatic or locally recurrent unresectable breast cancer. It noted comments received from professional groups that over 90% of people in the UK with HER2-positive breast cancer have trastuzumab, usually in combination with docetaxel, in the neoadjuvant or adjuvant setting. The committee noted a comment received in consultation suggesting that 90% could be an overestimate because some people would have metastatic disease at first diagnosis and would not have adjuvant therapy, or they would have had treatment for primary breast cancer before adjuvant therapy with trastuzumab became standard practice. The clinical expert highlighted that the introduction of neoadjuvant or adjuvant trastuzumab for early breast cancer had dramatically changed the disease course and prognosis of people with HER2-positive breast cancer. The committee concluded that in clinical practice pertuzumab would be used in combination with trastuzumab and docetaxel or paclitaxel for treating HER2-positive metastatic or locally recurrent unresectable breast cancer in people who have not had previous anti-HER2 therapy or chemotherapy for their metastatic disease, and that the majority of people would have had trastuzumab before this as adjuvant or neoadjuvant therapy.

4.3 The committee was aware that people with metastatic breast cancer understand that they have a life-limiting incurable disease that will eventually progress. It heard from the patient experts that although extension to life is important to patients, the benefits of progression-free survival should not be underestimated because it allows them to maintain a good quality of life during this period. The patient experts also

stated that treatments that extend life, even for a few weeks or months, are important to people, and that they may be willing to accept the side effects associated with such treatments. The committee also heard from the patient experts that they consider pertuzumab to be an innovative technology because of the benefits shown in terms of progression-free survival and overall survival. The committee concluded that the availability of new treatments such as pertuzumab is important to people with HER2-positive metastatic or locally recurrent unresectable breast cancer.

4.4 When it reconsidered the evidence after pertuzumab had been available on the Cancer Drugs Fund for nearly 4 years, the committee heard from the clinical and patient experts that pertuzumab was now considered standard of care for all patients with metastatic or locally recurrent unresectable breast cancer who meet the criteria. The committee heard from the NHS England representative that although pertuzumab may be perceived by patients and clinicians to be standard of care, the Cancer Drugs Fund was always intended to be a temporary mechanism for access to treatments that have not been recommended by NICE. For this reason, pertuzumab with trastuzumab and docetaxel cannot be strictly considered as standard of care, because it has a different status to treatments that are recommended for baseline commissioning.

4.5 The committee heard from the clinical experts that pertuzumab with trastuzumab and docetaxel is a very effective treatment, and has been shown to improve overall survival by approximately 16 months compared with trastuzumab plus docetaxel. The patient expert noted that pertuzumab represents one of the most important advances in the treatment of HER2-positive metastatic breast cancer in recent years. It is generally well tolerated, giving patients good quality of life while they are taking it. This enables many patients to return to normal activities including work and family life, which is highly valued by patients and their families. Furthermore, in a disease with no cure, the availability of such an effective treatment gives patients hope and a more positive outlook on their treatment regimen and course of disease. The committee also heard that because pertuzumab with trastuzumab and docetaxel had become standard of care through its availability in the Cancer Drugs Fund, patients have an expectation that this treatment will continue to be

available as a treatment option. If it were no longer available that would be a devastating blow. The committee appreciated the importance placed on the availability of effective treatments for breast cancer.

Clinical effectiveness

4.6 The committee noted that the main source of evidence for the clinical effectiveness of pertuzumab plus trastuzumab and docetaxel was the CLEOPATRA trial. It agreed with the evidence review group (ERG's) comments that overall this was a well-designed double-blind randomised, placebo-controlled trial and that the prevention of crossover between arms before the May 2012 data cut-off minimised the risk of bias. However, the committee heard from the clinical expert that the CLEOPATRA protocol and inclusion criteria do not reflect current clinical practice in the UK. The clinical expert highlighted that only 11% of the randomised population in CLEOPATRA had previously had trastuzumab in the adjuvant setting. This is a different population compared with patients in clinical practice in the UK, where trastuzumab is standard treatment in the neoadjuvant or adjuvant setting. The committee heard from the company that although trastuzumab was available in the UK from 2006, it was not a standard adjuvant therapy in all 25 different countries where the CLEOPATRA trial was conducted. The committee was aware that the results of the additional subgroup analysis on the clinical effectiveness of pertuzumab in patients who had received previous treatment with trastuzumab in the adjuvant setting (requested by the Committee for Medicinal Products for Human Use) were consistent with the results found for the whole trial population. It noted, however, the clinical expert's comment about the small number of patients in this subgroup. The committee also considered comments received from professional groups that the inclusion criteria of the CLEOPATRA trial specified disease progression occurring at least 12 months after neoadjuvant or adjuvant therapy. It heard from the clinical expert that people who had experienced a 12-month disease-free interval might be expected to have a better prognosis than the whole population with HER2-positive metastatic breast cancer. The committee considered that there were differences between the population in the CLEOPATRA trial and people currently having treatment for HER2-positive metastatic breast cancer in the NHS, and expressed some

reservations about the applicability and generalisability of the CLEOPATRA trial to UK clinical practice. However, there was no way for the committee to resolve this issue. It concluded that there remained uncertainty as to whether the clinical effectiveness of pertuzumab in clinical practice in the UK would be the same as demonstrated in the CLEOPATRA trial because of the inclusion of patients who might have a better prognosis, and the inclusion of only small numbers of people previously treated with HER2-targeted therapies, which might affect their subsequent response.

4.7 The committee discussed the end points in the CLEOPATRA trial. It noted that pertuzumab plus trastuzumab and docetaxel was associated with a statistically significant gain in median progression-free survival of 6.1 months at the first data cut-off. In the final analysis of the CLEOPATRA data (February 2014) in which patients had been followed up for a median of 49.5 months in the pertuzumab group and 50.6 months in the control group, pertuzumab was associated with an additional 6.3 months progression-free survival compared with the control group. The committee noted that the final analysis of overall survival (which was not adjusted for crossover from the control to the pertuzumab arm) showed a 15.7 month median overall survival benefit with the addition of pertuzumab, compared with trastuzumab and docetaxel. The committee heard from clinical experts that this magnitude of overall survival benefit is unprecedented in the treatment and palliation of advanced breast cancer and represents a step change in the treatment of patients with HER2-positive advanced breast cancer. The committee concluded that the addition of pertuzumab to trastuzumab and docetaxel results in substantial benefits for patients in improved progression-free and overall survival.

Cost effectiveness

4.8 The committee considered the structure, assumptions and results of the company's economic model, which was based on data from CLEOPATRA. It noted that the ERG considered the company's model structure to be appropriate to describe the decision problem, easy to understand and correctly implemented. The committee was aware that the model structure had been used in other appraisals of metastatic breast cancer.

It concluded that the model adhered to the NICE reference case for economic analysis and was acceptable for assessing the cost effectiveness of pertuzumab plus trastuzumab and docetaxel for treating HER2-positive metastatic breast cancer.

4.9 The committee considered the way in which progression-free survival and overall survival data had been extrapolated in the company's model. It noted that the company's base-case cost-effectiveness estimate for pertuzumab in combination with trastuzumab and docetaxel is associated with a 0% probability of being cost effective at £30,000 per quality-adjusted life year (QALY) gained. The committee further considered the deterministic sensitivity analysis and the ERG's exploratory analysis, which demonstrated that the model was sensitive to the long-term projection of overall survival.

4.10 At its first committee meeting, the committee considered the most plausible incremental cost-effectiveness ratio (ICER) for pertuzumab plus trastuzumab and docetaxel compared with trastuzumab and docetaxel presented by the company and by the ERG in its exploratory analyses. These were based on list prices for the technologies concerned. The committee noted that the company's base-case ICER was well outside the range normally considered to be a cost-effective use of NHS resources. It noted that the ERG's preferred ICER was based on an assumption of no benefit from pertuzumab in the post-progression state and this reflected the worst case scenario. At that stage, the committee noted the considerable uncertainty around the presence or magnitude of benefit from pertuzumab in the post-progression state when treatment has been stopped. However, even if the company's base-case ICER was accepted as plausible, there was a 0% probability that pertuzumab plus trastuzumab and docetaxel could be considered cost effective at a maximum acceptable ICER of £30,000 per QALY gained. The committee concluded that pertuzumab plus trastuzumab and docetaxel would not be a cost-effective use of NHS resources for treating HER2-positive metastatic or locally recurrent unresectable breast cancer compared with trastuzumab and docetaxel alone.

4.11 In its revised submission for the Cancer Drugs Fund reconsideration, the company included:

- an additional 2 years follow-up data from CLEOPATRA, used to model progression-free and overall survival
- a commercial access arrangement between Roche and NHS England
- an updated model incorporating new data and using some of the ERG's preferred assumptions:
  - including subcutaneous trastuzumab in the comparator arm only
  - using the commercial medicines unit price for docetaxel
  - updating the pharmacy, administration and health-state costs
  - correcting the utility values for progression-free and progression health states in response to errors identified by the ERG
- evidence on the uptake of pertuzumab with trastuzumab and docetaxel through the Cancer Drugs Fund since April 2013
- a request for flexibility in the application of the life expectancy criteria in this appraisal.

4.12 The committee considered the company's updated economic model and the ERG's critique and exploratory analyses. The committee considered several amendments made by the ERG to the updated company model to explore the impact on the company ICER. The ERG used digitalised values for the Swain et al. paper (based on the final analysis of the CLEOPATRA data) to validate the company's long-term extrapolation of progression-free and overall survival. The committee noted that although the ERG preferred an exponential projection of the Kaplan–Meier data (compared with a log-logistic extrapolation in the updated company model) and an exponential extrapolation of the overall survival data (compared with gamma function in the updated company model) the method of extrapolation had little effect on the ICER. The ERG also corrected an error in the mean age of participants who estimated utility, which should have been 47 years for consistency with the participants in the original EQ-5D calibration panel (but was 38.2 years in the company model). This also had little effect on the ICER. The committee was reassured that although the combined effect of the ERG's changes slightly increased the ICER it remained similar to the company's base-

case ICER. The ICER is commercial in confidence to protect the confidentiality of the commercial access agreement. The committee accepted that the commercial access arrangement reduced the ICER from the original submission, but that it still remained in excess of what is considered to be a cost-effective use of NHS resources for technologies that are not given special consideration as life-extending treatments for people with a short life expectancy.

Innovation

4.13 The committee discussed whether pertuzumab should be considered an innovative treatment. It noted that the clinical expert emphasised the benefits of HER2 therapies in changing the prognosis of people with this disease and the significant progression-free survival benefit observed with this new HER2-targeted therapy. Patient experts regard it as an innovative treatment because it significantly increases the duration of progression-free survival, thereby maintaining a good quality of life for patients. The committee considered that the innovative nature of pertuzumab had been demonstrated in the statistically significant progression-free survival gain in CLEOPATRA and had been incorporated in the economic model. The committee concluded that all relevant health-related benefits of pertuzumab had been captured in the QALY calculation.

End-of-life considerations

4.14 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's final Cancer Drugs Fund technology appraisal process and methods. The committee also noted the request from the company that the committee exercise 'flexibility' around the interpretation of the extension-to-life criteria (which specifies that life expectancy of patients would be normally less than 24 months) because of the substantial extension in overall survival of adding pertuzumab to trastuzumab and docetaxel. The committee acknowledged that the wording referring to the end-of-life criteria is deliberately expressed to provide committees with discretion required when they consider it reasonable to apply a weight to the QALYs gained

in circumstances where one of the criteria does meet the exact level described in the policy.

4.15 The committee noted that the survival benefit with pertuzumab met, and far exceeded the 3 month extension to life criteria, and it had heard from the clinical experts that a 15.7 month median survival gain was unprecedented in the treatment of metastatic HER2-positive breast cancer and represented a step-change in the treatment of this condition. The committee noted that the life expectancy of patients on chemotherapy alone based on the unadjusted median overall survival in the control arm of CLEOPATRA was 40.8 months, which exceeds the 24 months stated in the end-of-life criteria. However, people in the CLEOPATRA trial may have a better prognosis than people in UK clinical practice (see section 4.6). The committee also noted the company's estimates for overall survival with a trastuzumab and chemotherapy containing regimen, which were between approximately 2 and 3 years. The committee agreed that although life expectancy in the trial was greater than 24 months, the exceptional proportional gain in survival with pertuzumab in people with a relatively modest life expectancy should be taken into account. The committee concluded that it was fair and reasonable to accept that pertuzumab fulfilled the criteria for special consideration on this basis.

4.16 The committee recognised the exceptional nature of this decision, which it found reasonable in the context of ensuring continued access to a highly effective treatment option for people with advanced breast cancer. In this context, the committee considered it reasonable to expect that the weight that needs to be applied to the QALYs gained in order to allow continued access would not have to be at the very maximum allocated in other, more regular, circumstances where the end of life criteria have been applied. With this in mind, the committee accepted that the ICER, taking into account the commercial access arrangement, provides for an acceptable use of NHS resources.

Conclusions

4.17 The committee considered that the updated clinical-effectiveness evidence clearly demonstrates that the addition of pertuzumab to

trastuzumab leads to a substantial improvement in progression-free and overall survival, which is unprecedented in the treatment of advanced breast cancer. When considering the clinical and cost effectiveness of pertuzumab the committee thought it relevant that pertuzumab in combination with trastuzumab and docetaxel for metastatic HER2-positive breast cancer is currently a Cancer Drugs Fund transition topic and will remain on the Cancer Drugs Fund until guidance is issued by NICE. It considered the appraisal of pertuzumab to be a special case because it has been available for this indication for 4 years in the NHS. When considering the evidence it was mindful that it was deliberating whether pertuzumab should continue to be funded by the NHS or removing funding for an effective treatment which has become, in the minds of patients and clinicians, standard of care for treating metastatic breast cancer. The committee appreciated the different impact of disinvestment compared with investment decisions on opportunity cost. The committee noted that there is no specific guidance in the methods for technology appraisal for disinvestment decisions.

4.18 The committee acknowledged the flexibilities in the application of the end-of-life criteria. The committee considered that the unprecedented survival benefit with the addition of pertuzumab should be considered in the light of modest life expectancy of these patients and concluded that it was fair and reasonable to accept that pertuzumab fulfils the end-of-life criteria. The committee further accepted that in the context of the exceptional circumstance this case presents, it would be reasonable not to be asked to have to apply the maximum weight to the QALYs gained by pertuzumab. The committee accepted that the ICER, taking into account the commercial access arrangement, provides for an acceptable use of NHS resources.

5 Implementation

5.1 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.

5.2 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 determination.

5.3 NHS England and Roche have a commercial access agreement that makes pertuzumab available to the NHS at a reduced cost. The financial terms of the agreement are commercial in confidence. Any enquiries from NHS organisations about the commercial access agreement should be directed to global.pas@roche.com.

6 Appraisal committee members and NICE project team

Appraisal committee members

The technology appraisal committees are standing advisory committees of NICE. This topic was considered by members of the existing standing committees who have met to reconsider drugs funded by the Cancer Drugs Fund. The names of the members who attended are in the minutes of the appraisal committee meeting, which are posted on the NICE website.

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.

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.

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