NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using pertuzumab 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 base (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 determination (FAD).
- Subject to any appeal by consultees, the FAD may be used as the basis for NICE's guidance on using pertuzumab 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: 13 June 2016

Second appraisal committee meeting: 21 June 2016

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

1 Recommendations

1.1 Pertuzumab, in combination with trastuzumab and chemotherapy, is not recommended within its marketing authorisation for the neoadjuvant treatment of human epidermal growth factor receptor 2 (HER2)-positive breast cancer; that is, in patients with HER2-positive, locally advanced, inflammatory or early-stage breast cancer at high risk of recurrence.

1.2 This guidance is not intended to affect the position of patients whose treatment with pertuzumab was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop.

2 The technology

2.1 Pertuzumab (Perjeta, Roche) is a recombinant monoclonal antibody which targets human epidermal growth factor receptor 2 (HER2)-positive breast tumours. It interrupts the activation of the HER2 intracellular signalling pathway, leading to cell growth arrest and apoptosis. It is administered by intravenous infusion. Pertuzumab has a marketing authorisation in the UK 'in combination with trastuzumab and chemotherapy for the neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early-stage breast cancer at high risk of recurrence'. The recommended dosage of pertuzumab is an initial loading dose of 840 mg, followed by a maintenance dose of 420 mg every 3 weeks for 3 to 6 cycles.

2.2 The summary of product characteristics includes the following adverse reactions for pertuzumab: decreased appetite, headache, cough, diarrhoea, vomiting, nausea, constipation, rash, pain, oedema, fatigue, asthenia and left ventricular dysfunction. For full details of adverse

reactions and contraindications, see the summary of product characteristics.

2.3 Pertuzumab costs £2,395 per 420 mg vial (excluding VAT). Costs may vary in different settings because of negotiated procurement discounts.

3 Evidence

The appraisal committee (section X) 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.

4 Committee discussion

The appraisal committee reviewed the data available on the clinical and cost effectiveness of pertuzumab, having considered evidence on the nature of HER2-positive breast cancer and the value placed on the benefits of pertuzumab by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

4.1 The committee considered the experience of people with HER2-positive breast cancer. It heard from the patient expert that after having pertuzumab, she had experienced a complete response that her clinician described as 'spectacular'. She felt that taking pertuzumab not only had the benefit of removing the physical signs of cancer, but also had a major effect on her psychological wellbeing. When a person's tumour responds to treatment it can improve quality of life, and reassure them that the treatment is working. The clinical experts agreed that outcomes such as pathological complete response can have a strong psychological benefit for patients. They explained that pathological complete response is an indication that not only are tumour cells in the breast responding to treatment (and, in the case of total pathological response, that tumour cells in the lymph nodes are responding to treatment), but that that any

tumour cells which may have already spread beyond the breast and nodes but that are undetectable (micro-metastases) would also have been treated. In addition, a reduction in size or the disappearance of tumour in the breast potentially allows for less radical surgery in patients who would otherwise be advised to have mastectomy. The committee agreed that neoadjuvant treatment outcomes such as pathological complete response seemed beneficial from a clinical perspective, and could provide important psychological benefits for patients. However, given the limitations of the evidence, it considered that there was uncertainty about whether a pathological complete response after neoadjuvant therapy was the sole and most reliable indicator of, or translated directly into, treatment-related long-term event-free and overall survival benefit (section 4.5). The committee also noted comments from Breast Cancer Now which indicated that although it considered pertuzumab to be a potentially promising treatment, the charity strongly supported the collection of more evidence because many of the cited benefits are hypothetical. The committee concluded that HER2-positive breast cancer can have a substantial negative effect on quality of life, and that patients and clinicians place a strong value on effective early treatments that would be of particular value if they were proven to improve long-term outcomes.

4.2 The committee considered the current treatment pathway for people with HER2-positive breast cancer. It heard from the clinical experts that there is variation across the NHS in the use of neoadjuvant therapy (primary systemic therapy) before surgery in HER2-positive breast cancer, which was demonstrated in an informal survey presented by one of the clinical experts. They stated that this may relate to service configuration issues, such as staffing levels and access to HER2 testing, and that this restricted access to neoadjuvant treatment in some parts of the UK. The clinical experts indicated that neoadjuvant therapy in very extensive or inoperable disease may shrink the tumour and make it operable. In other cases it may allow for breast-conserving surgery, thereby reducing the need for

more complicated procedures (such as mastectomy and breast reconstruction) and their associated risks, lessening the treatment burden for both patients and the NHS. The clinical experts stated that another advantage of neoadjuvant treatment is that outcomes can be more directly linked to treatment (because there is less chance of confounding from other treatments), and that this was useful to inform future treatment decisions. The committee heard from the company and the evidence review group (ERG) that around 75% of neoadjuvant treatment regimens for patients with HER2-positive cancers contain trastuzumab. The clinical experts stated there is variation in the chemotherapy given in combination with trastuzumab. The committee was interested in any disadvantages of neoadjuvant therapy, for example the potential for tumour growth before surgery. It heard that patients are typically closely monitored, including with MRI scans, so that any disease progression is quickly identified. The committee noted the current NICE clinical guidance on the general use of primary systemic therapy (see section 4.6), but understood from the clinical experts that there is a trend towards offering more neoadjuvant therapy in HER2-positive breast cancer.

Clinical effectiveness

4.3 The committee noted that the company had submitted 2 phase II randomised controlled trials relevant to the population in the scope, NeoSphere and TRYPHAENA. However, it considered both of these to have substantial limitations for the purposes of providing comparative effectiveness data for pertuzumab. Both trials were at an early stage of research (phase II) and lacked longer-term efficacy data, had small patient numbers, were open-label and so more susceptible to bias than blinded trials, and were not powered for key outcomes of interest including progression-free survival and overall survival. TRYPHAENA was a cardiac safety trial and so was not primarily designed to test efficacy. It did include pathological complete response as a secondary outcome but all 3 arms of the trial included pertuzumab, so there was no control group. In

NeoSphere, patient numbers were further limited because only 2 of the 4 arms included licensed treatment combinations, arm A (n=107, trastuzumab and docetaxel) and arm B (n=107, pertuzumab, trastuzumab and docetaxel). Furthermore, the committee was aware that the comparators specified in the scope of this appraisal included more than just trastuzumab and docetaxel, which was the comparator in NeoSphere. For example, according to the company data, 25% of neoadjuvant regiments do not contain trastuzumab, and not all patients who have trastuzumab have it in combination with docetaxel. In summary, the clinical trial evidence did not include all relevant comparisons, and the only comparative effectiveness evidence relevant to comparators in the scope comprised data from only 214 patients from one phase II randomised controlled trial. The committee concluded that the relevant comparative clinical trial evidence for pertuzumab in the neoadjuvant setting was severely limited.

4.4 The committee discussed the results of NeoSphere. It noted that the addition of pertuzumab to trastuzumab plus docetaxel was associated with larger increases in all 3 definitions of pathological complete response (see clinical slide 10) than trastuzumab plus docetaxel alone. However, it was aware that the European Assessment Report (EPAR) for pertuzumab in this indication stated that the treatment effect in NeoSphere may have been overestimated, because not all major treatments were given in the neoadjuvant setting (for example anthracyclines). The committee also noted that higher rates of pathological complete response in the breast with pertuzumab were shown in the operable subgroup, but the difference between pertuzumab and trastuzumab was negligible in locally advanced disease, with a small number of patients in each arm (n=32 and 36 in the pertuzumab and trastuzumab arms respectively) and wide, overlapping 95% confidence intervals. In addition, the committee expressed concerns about the reliability of pathological complete response as a surrogate for longer-term survival outcomes for patients (section 4.5). It heard from the

clinical experts that if a patient had a pathological complete response, they considered this to be a good indicator of long-term benefit, particularly in oestrogen receptor negative tumours. The committee noted that of the 3 available definitions of pathological complete response, the primary outcome in NeoSphere, pathological complete response in the breast, was the least stringent measure; it classified patients as responders even if there was residual disease in lymph nodes or ductal carcinoma in situ. Total pathological complete response is the preferred definition for regulatory purposes, which requires the disappearance of invasive cancer in the breast and lymph nodes (although in situ cancer in the breast may still be present). In the NeoSphere trial, total pathological complete response was only collected retrospectively, although it was subsequently used in the cost-effectiveness analysis. The committee concluded that there was some evidence that pertuzumab could improve rates of pathological complete response when added to trastuzumab and docetaxel. However, the evidence was severely limited, and may not be replicable in current NHS practice where patient selection and neoadjuvant therapy may differ from that in the trial. Furthermore, there was no reliable trial evidence of event-free or overall survival benefit.

4.5 The committee discussed the value of pathological complete response as a clinically meaningful indicator of longer-term event-free and overall survival outcomes. It was aware that a number of studies have been done in this area, including the CTNeoBC meta-analysis, which the company had described in its submission and included in its modelling. CTNeoBC evaluated the prognostic value of pathological complete response, and found that at patient-level there was a correlation between pathological complete response and survival outcomes. However, at trial-level, CTNeoBC concluded that the evidence that a treatment-related improvement in pathological complete response translated into a treatment-related improvement in survival outcomes was very weak (correlation coefficients of 0.03 and 0.24 for event-free survival and overall

survival respectively). The committee understood that correlation between two variables at an individual level does not necessarily imply that one variable can be used as a surrogate for the other when estimating the effect of a specific treatment. The committee was also aware that the ERG had reviewed the wider evidence in this area, and had stated that the evidence of a positive treatment effect translating into a positive effect on survival was not convincing. The committee concluded that there was considerable uncertainty about whether pathological complete response was a meaningful indicator of long-term survival outcomes, such that it could be viewed as a surrogate marker of long-term benefit.

4.6 The committee discussed the generalisability of NeoSphere to clinical practice in England. It was not clear if the patient population in the trial represented the patient population in clinical practice in England. The committee noted that most patients in the NeoSphere trial were described as having 'operable' disease (defined as tumours over 2 cm in diameter [T 2-3] with no clinically involved lymph nodes (N0) or involved mobile ipsilateral axillary nodes [N1]), and that people in this category would have the best prognosis. In addition, the low patient numbers in the trial resulted in one of the rare subtypes, inflammatory breast cancer, having only 7 patients in the comparator arm and 10 patients in the intervention arm. The committee also noted that around 25% of patients in England (based on the company evidence) would have non-trastuzumab based neoadjuvant therapy, and the accompanying chemotherapy and adjuvant therapy which followed may also differ from that in the control arm of the NeoSphere trial. The committee considered that there were likely to have been very few UK patients in the trial; there were only 214 patients who received either the intervention or comparator as stated in the scope, across 59 centres, and of these only 2 centres were in the UK. The committee concluded there was uncertainty about the generalisability of the NeoSphere trial to current NHS practice.

4.7 The committee considered the secondary outcome of NeoSphere of breast-conserving surgery, and noted that around 23% of patients originally advised to have mastectomy subsequently had breast-conserving surgery. The committee understood that although this may be an important beneficial outcome for some people, NICE's guideline on early and locally advanced breast cancer states that the increased risk of local recurrence with breast-conserving surgery and radiotherapy compared with mastectomy after systemic therapy should be discussed with the patient.

4.8 The committee discussed the adverse events associated with pertuzumab for people with HER2-positive locally advanced, inflammatory or early-stage breast cancer. It noted that TRYPHAENA was specifically designed to assess the cardiac safety of pertuzumab. However, the committee considered 1 of the 2 primary outcomes used to measure cardiac safety, left ventricular systolic dysfunction, to be a poor indicator of cardiac safety. The committee noted that adverse events in NeoSphere were similar in both the intervention and comparator arms. The committee also heard from the patient expert who found the effects of pertuzumab to be very manageable, with the only notable lasting effects being diarrhoea and a slower than expected return to normal hair growth. The committee concluded that based on the evidence pertuzumab had an acceptable adverse event profile.

Cost effectiveness

4.9 The committee discussed the structure and parameter assumptions of the company model. Although it noted that the locoregional recurrence health state omitted surgery, which would be the best option for patients at this stage of the treatment pathway, the committee considered the general structure of the model and sequencing of health states to be plausible. However, it was concerned that in September 2015 the company had submitted to the Scottish Medicines Consortium (SMC) for consideration

of pertuzumab for the same indication. The committee noted that the incremental costs and cost-effectiveness ratios in the submission to the SMC were double those submitted to NICE. Although the SMC submission was briefly mentioned in the NICE company submission, the company did not disclose any details of the cost-effectiveness analysis. The committee noted that the STA evidence submission template clearly indicates the requirement for the company to disclose any strategies used to inform cost effectiveness, including unpublished data held by the company (5.1.1). The committee expressed disappointment at this omission, and was further disappointed that, upon being made aware of the omission in writing, the company had provided a limited descriptive text that compared the SMC submission with only the second of 3 base cases submitted by the company (and not compared with the original base case submitted to NICE). This prevented a full comparison of the original base cases submitted to NICE and the SMC, although the committee was aware there were several inconsistencies between the 2 submissions (sections 4.11 and 4.12). In addition, the committee identified concerns with the parameter assumptions in the model submitted to NICE, including those for clinical effectiveness (section 4.10), utility values (section 4.11) and costs (sections 4.12 to 4.14). The committee agreed that although the structure of the model was generally appropriate for its decision-making, there were high levels of uncertainty because of some parameter assumptions and the company's unsatisfactory explanation of the variance in results for the models submitted to NICE and the SMC.

4.10 The committee discussed the clinical effectiveness assumptions used in the model. It noted that the clinical effectiveness of pertuzumab was based on event-free survival, but that the data in the NeoSphere trial were not robust enough to be used in the model. The company had instead modelled event-free survival by re-constructing individual level data from the published event-free survival curves from the CTNeoBC meta-analysis, fitting a parametric model (based on a gamma distribution) to

these re-constructed data in each treatment arm, and then multiplying the predicted event-free survival probabilities from this model by the observed rates of total pathological complete response and no total pathological complete response in 214 patients (107 per treatment group) in NeoSphere. However, the committee considered this approach to be problematic for several reasons:

- This approach assumes that there is a direct proportional relationship between pathological complete response and survival. However, the CTNeoBC meta-analysis could not confirm pathological complete response as a validated surrogate outcome for survival outcomes (section 4.5). The committee was prepared to accept that some relationship existed, but did not consider it proven, and had reservations about its use as the sole indicator to model overall survival. This led to considerable uncertainty about the resulting calculations of clinical and cost effectiveness.
- The company had very limited NeoSphere trial data with which to adjust the event-free survival data from the CTNeoBC meta-analysis (n=107 both arms), so the rates of total pathological complete response (a retrospectively collected secondary outcome) in the two treatment groups were estimated with considerable uncertainty, reflected by wide 95% confidence intervals.
- When re-constructing individual level data from the CTNeoBC meta-analysis, the company could have used either the whole population (providing the most data but based on a less directly relevant population) or the HER2-positive subpopulation (providing 90% less patient data but based on a more focused population). The ERG identified that the company had used mixed data sources (event-free survival curves from the whole population but numbers at risk from the HER2-positive subgroup) in its initial submission, which was not reasonable. The company stated that it had intended to extrapolate data from only the HER2-positive subpopulation. As far as the

committee could ascertain, the company had also used mixed data in its submission to the SMC. The clinical experts stated that using the HER2-positive subgroup was the correct approach, because the subtypes of breast cancer are biologically distinct. However, the committee considered that an alternative view would be that the CTNeoBC meta-analysis was a proof-of-concept study designed to establish whether a relationship existed between pathological complete response and overall survival, and that it was not powered to show differences between subgroups. Using a subgroup would imply that pathological complete response is more advantageous in terms of overall survival in some breast cancer subtypes than others. Although there were some indications that this might be the case, using only the HER2-positive subgroup limited the available data in CTNeoBC to just 2 trials. This may be less robust than using the whole 12,000 population in the meta-analysis. The committee would therefore have preferred to see the results using both the HER2-positive subgroup and the whole meta-analysis population.

- The committee was concerned about the generalisability of the CTNeoBC meta-analysis to the population in the scope. The clinical experts indicated that patients included in the meta-analysis were those for whom breast-conserving surgery was unsuitable, and had more advanced disease in terms of stage. The committee considered that this may not reflect the wider population of people who may be considered for this treatment in England. It also noted that the type of surgery and follow-on treatments were also unstated, so the meta-analysis may not reflect the clinical profile or treatments currently being used in the population in the scope.

The committee concluded that the company's approach to model clinical effectiveness as described above meant that the modelled clinical effectiveness results were subject to high levels of uncertainty.

4.11 The committee discussed differences in the quality-adjusted life year (QALY) gains in the SMC and NICE company submissions (0.31 in the SMC submission, 0.261 in the NICE submission). It also discussed the differences in the utility value for the progressed state used in the model (0.5 in the SMC submission, 0.452 in the NICE submission). The committee heard from the company that the difference in QALY gains may be because it had added an extra assumption to the model submitted to NICE, specifically that the utility value could not be higher than the age-matched population without disease. The company also explained that it used a lower utility value in the NICE submission because it considered a study by Lloyd et al. (2006) to provide a more appropriate utility measure. The company did not explain why it considered a different utility value, from that used in the SMC submission, to be appropriate. Although the committee could not be sure of the effect of these differences, it was aware that it was likely to lead to lower QALYs in the comparator arm relative to the intervention arm in the NICE submission, because people in the comparator arm transitioned more quickly to the metastatic health state (because treatment was assumed to be less effective). This would have a favourable effect on the ICER overall. The committee concluded that it was unclear what the justification was for using different utility values for such similar populations as those in England and Scotland. It was also uncertain if the company had disclosed all the different assumptions used in its 2 submissions, how varying the individual assumptions affected the overall cost-effectiveness results, and what precise factors caused different incremental QALYs in the 2 submissions. All of this added further uncertainty to the results.

4.12 The committee discussed the cost assumptions in the company's model. It noted that the incremental costs in the SMC submission were more than double those in the NICE submission (£10,370 compared with £4,557). It heard from the company that this was mainly because of the wider availability of treatments for metastatic disease in England because of the

Cancer Drugs Fund (CDF), which is not available in Scotland. The committee could only assume that patients in the comparator arm were modelled to progress to metastatic disease earlier, and to receive more CDF-funded treatments than those in the pertuzumab arm. The company stated there were several other small adjustments to the SMC submission which might explain the variation in costs. The committee concluded that the large discrepancy in incremental costs between the SMC and NICE submissions was likely to be explained to some extent by drugs funded through the CDF, but without access to the data the committee could not be sure by how much.

4.13 The committee discussed whether the inclusion of drugs funded by the CDF in the metastatic heath state was a fair reflection of the future costs of treatment for HER2-positive breast cancer in England. The committee noted that by including these drugs, the additional costs of neoadjuvant pertuzumab were being offset in the model by increased costs of additional drugs for metastatic disease in the comparator arm funded by the CDF (including pertuzumab and trastuzumab emtansine, both of which are also Roche products). The committee was aware that the CDF is now a temporary funding model for cancer drugs that cannot yet demonstrate cost-effectiveness, and is currently in a transitional period to determine which drugs should be funded. For patients starting neoadjuvant treatment today, the costs of treatment for metastatic disease (if needed) are likely to be incurred several years in the future, by which time there is no guarantee that the CDF will still exist (and if it does exist, what the funding arrangements will be). The committee was aware that when modelling the future costs and benefits of treatments, there is always an element of uncertainty. However, given the temporary and transitional nature of the CDF, the committee questioned the validity of the large cost offsets assumed by the company. The committee also noted the ERG's comment that the company had incorporated pertuzumab as a second-line metastatic treatment in the model although its licence is for

use in combination with trastuzumab and docetaxel in patients with who have not had previous anti-HER2 therapy or chemotherapy for their metastatic disease. The committee also raised concerns about the company's precise drug costs. The company used list prices for the CDF funded treatments in the metastatic setting, but the NHS may be paying lower prices for these drugs which would increase the incremental cost-effectiveness ratio (ICER). Overall the committee concluded that there were high levels of uncertainty, both in the modelled costs of treatments for metastatic disease and in whether the included drugs accurately reflected the treatment pathway for patients with metastatic disease. The committee considered that it would have liked to have seen an analysis from the company which included a scenario in which CDF-funded drugs were excluded.

4.14 The committee discussed the number of cycles of pertuzumab that would be used in clinical practice. It was aware that the model used 4 cycles, but that the licence allowed for 3 to 6 cycles, which was a large variation (effectively meaning that for some patients dosage and costs could be double that of others). It heard from the clinical experts that they would use pertuzumab for 3 to 6 cycles but that this would vary. The committee noted that the ERG had conducted a sensitivity analysis varying the number of cycles of pertuzumab, which caused an increase in the ICER from £23,467 per QALY gained (ERG base case) to up to £42,955 per QALY gained (using 6 cycles of pertuzumab instead of 4 cycles and amending the costs but not the effectiveness of treatment), suggesting the results were sensitive to this assumption. The committee concluded this added further uncertainty to the model.

4.15 The committee considered the cost-effectiveness results presented by the company and the ERG, and considered whether it could determine a most plausible ICER. It noted that there were a number of different base-case scenarios provided by the company (3 base cases ranging from £8,215 to £19,939 per QALY gained) and the ERG (£23,467 per QALY gained), but

that all models were subject to the same levels of uncertainty. In exploratory analyses, both the company and ERG models were most sensitive to assumptions about clinical effectiveness. Altering pathological complete response rates for pertuzumab led to ICERs ranging from £841 to £67,157 per QALY gained in the company model (compared with £17,297 per QALY gained in the company's original base case) and from £5,959 to £76,515 per QALY gained in the ERG model. The committee agreed that the model's sensitivity to this assumption was particularly concerning because of the uncertainty about the use of pathological complete response as a surrogate for survival outcomes (section 4.5). Furthermore, the committee was concerned that the uncertainty it had identified in the cost and utility assumptions were likely to increase the ICER. For costs, the company model included a possible overestimation of treatment costs for metastatic disease (because of the inclusion of CDF funded treatments at list price); for utility values, the company had used a lower utility value for the metastatic health state than that used in the SMC submission, but without providing an adequate rationale. Although the sensitivity of the model to these cost and utility assumptions had not been fully explored, the committee noted that in the ERG's model, changing the costs of treatment for metastatic disease to the cheapest treatment (rather than using a weighted average) substantially increased the ERG's base-case ICER by around £10,000 per QALY gained. Overall the committee agreed that there was too much uncertainty to determine a most plausible ICER, but it had identified uncertainties in the cost and utility assumptions that would be likely to increase all base-case ICERs (sections 4.11 to 4.13). On the basis of the evidence presented, the committee remained very unsure about the long-term benefits of the addition of pertuzumab to trastuzumab and chemotherapy compared with trastuzumab and chemotherapy alone and the cost effectiveness remained highly uncertain. Taking all of these uncertainties into account, the committee concluded that it could not recommend pertuzumab for the neoadjuvant

treatment of HER2-positive breast cancer as a cost-effective use of NHS resources.

4.16 The committee was aware of NICE's position statement on the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS payment mechanism. It accepted the conclusion 'that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The committee heard nothing to suggest that there is any basis for taking a different view about the relevance of the PPRS to this appraisal. It therefore concluded that the PPRS payment mechanism was not relevant in considering the cost effectiveness of the technology in this appraisal.

Summary of appraisal committee's key conclusions

TAXXX	**Appraisal title:**	**Section**
Key conclusion		
Pertuzumab, in combination with trastuzumab and chemotherapy, is not recommended within its marketing authorisation for the neoadjuvant treatment of human epidermal growth factor receptor 2 (HER2)-positive breast cancer; that is, in patients with HER2-positive, locally advanced, inflammatory or early-stage breast cancer at high risk of recurrence. A number of different base-case scenarios were provided by the company and the ERG. In exploratory analyses, both the company and ERG models were most sensitive to assumptions about clinical effectiveness. The committee agreed that the sensitivity of the model to these assumptions was particularly concerning because of the uncertainty about the use of pathological complete response as a surrogate for survival outcomes. The committee also identified		1.1 4.15

uncertainties in the cost and utility assumptions that would be likely to increase all base-case ICERs. Taking all of these uncertainties into account, the committee concluded that it could not recommend pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer as a cost-effective use of NHS resources.		
Current practice		
Clinical need of patients, including the availability of alternative treatments	The committee heard from the patient expert that that taking pertuzumab not only had the benefit of removing the physical signs of cancer, but also had a major effect on her psychological wellbeing. The committee concluded that HER2-positive breast cancer can have a substantial negative effect on quality of life, and that patients and clinicians place a strong value on effective early treatments.	4.1
The technology		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	After having pertuzumab, the patient expert had a complete response that her clinician described as 'spectacular'. The patient expert felt that taking pertuzumab not only had the benefit of removing the physical signs of cancer, but also had a major effect on her psychological wellbeing. The clinical experts agreed response can have an important psychological benefit. In addition a pathological complete response is an indication that not only are tumour cells responding to treatment, but that any micro-	4.1 4.4

	metastases are likely to have also been treated. A reduction or disappearance of tumour in the breast also potentially allows for less radical surgery in patients who would otherwise be advised to have mastectomy. Overall the committee concluded that there was some evidence that pertuzumab could improve rates of pathological complete response when added to trastuzumab and docetaxel. The committee agreed that neoadjuvant treatment outcomes such as pathological complete response seemed beneficial from a clinical perspective, and could provide important psychological benefits for patients. However, it was aware that there was uncertainty about whether a pathological complete response after neoadjuvant therapy was the most reliable indicator of, or translated directly into, a treatment-related long-term outcome and survival benefit	
What is the position of the treatment in the pathway of care for the condition?	The committee heard from the clinical experts that there is variation across the NHS in the use of neoadjuvant therapy before surgery in HER2-positive breast cancer. They stated that this may relate to service configuration issues, such as staffing levels and access to HER2 testing, and that this restricted access to neoadjuvant treatment in some parts of the UK. The committee understood from the clinical	4.2

	experts that there is a trend to offer neoadjuvant treatment to patients with early-stage, inflammatory and locally advanced HER2-positive breast cancer, and that this most commonly includes trastuzumab. A reduction in the size of the tumour may make the disease operable when initially it is very extensive, and in other cases allow breast-conserving surgery, thereby reducing the need for more complicated procedures (such as mastectomy and breast reconstruction) and their associated risks.	
Adverse reactions	The committee noted that adverse events in NeoSphere were similar in both the intervention and comparator arms. The committee also heard from the patient expert who found the effects of pertuzumab to be very manageable. The committee concluded that pertuzumab had an acceptable adverse event profile.	4.8
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The comparative clinical trial evidence did not include all relevant comparisons, and the only comparative effectiveness evidence relevant to comparators in the scope comprised data from only 214 patients from one phase II randomised controlled trial. The committee concluded that the relevant comparative clinical trial evidence for pertuzumab was	4.3

	severely limited.	
Relevance to general clinical practice in the NHS	The committee noted that patients in the NeoSphere trial were described as having 'operable' disease (defined as tumours over 2 cm in diameter with no lymph nodes or only 1 lymph node involved), and people in this category would have the best prognosis. The committee also noted that around 25% (based on the company evidence) of patients in England would have non-trastuzumab neoadjuvant therapy, and the accompanying chemotherapy and adjuvant therapy which followed may also differ from that in the control arm of the NeoSphere trial. The committee considered that there were likely to have been very few UK patients in the trial; there were only 214 patients who received either the intervention or comparator as stated in the scope, across 59 centres, and of these only 2 centres were in the UK. The committee concluded there was uncertainty about the generalisability of the NeoSphere trial to current NHS practice.	4.6
Uncertainties generated by the evidence	The committee noted that the addition of pertuzumab to trastuzumab plus docetaxel was associated with larger increases in all 3 definitions of pathological complete response than trastuzumab plus docetaxel alone. However, it was aware that the European	4.4 4.5

	Assessment Report for pertuzumab in this indication stated that the treatment effect in NeoSphere may have been overestimated, because not all major treatments were given in the neoadjuvant setting (for example anthracyclines). The committee discussed the value of pathological complete response as a clinically meaningful indicator of longer-term survival outcomes. It was aware that a number of studies have been done in this area, including the CTNeoBC meta-analysis. At trial-level, CTNeoBC concluded that the evidence that a treatment-related improvement in pathological complete response translated into a treatment-related improvement in survival outcomes was very weak. The committee was also aware that the ERG had reviewed the wider evidence in this area, and had stated that the evidence of a positive treatment effect translating into a positive effect on survival was not convincing. The committee concluded that there was considerable uncertainty about whether pathological complete response was a meaningful indicator of long-term survival outcomes, such that it could be viewed as a surrogate marker of long-term benefit.	

Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	No specific committee consideration.	
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The company had submitted 2 phase II randomised controlled trials, but both had limitations and only 1 trial was designed to test efficacy. Both trials were at an early stage of research (phase II) and lacked longer-term efficacy data, had small patient numbers, were open label and so more susceptible to bias than blinded trials, and were not powered for key outcomes of interest including progression-free survival and overall survival. Overall the committee concluded that there was some evidence that pertuzumab could improve rates of pathological complete response when added to trastuzumab and docetaxel. However, the evidence was limited, and may not be replicable in current NHS practice where patient selection and neoadjuvant therapy differ from the trial. And there was considerable uncertainty about whether pathological complete response was a meaningful indicator of long-term survival outcomes, such that it could be viewed as a surrogate marker of long-term benefit.	4.3 4.4 4.5

Evidence for cost effectiveness		
Availability and nature of evidence	The company derived a new economic model.	4.9
Uncertainties around and plausibility of assumptions and inputs in the economic model	The committee agreed that although the structure of the model was generally appropriate for its decision-making, there were high levels of uncertainty because of some parameter assumptions (including clinical effectiveness, costs and utility values) and the company's unsatisfactory explanation of the variance in results for the models submitted to NICE and the Scottish Medicines Consortium (SMC).	4.9

Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	The committee noted there were differences in the quality-adjusted life year (QALY) gains for pertuzumab in the SMC and NICE company submissions, and in the utility value for the progressed state used in the model. It heard from the company that the difference in QALY gains may be because it had added an extra assumption to the model submitted to NICE. The company also explained that it used a lower utility value in the NICE submission because it considered a study by Lloyd et al. (2006) to provide a more appropriate utility measure. The company did not explain why it considered a different utility value to be appropriate. The committee concluded that it was unclear what the justification was for using different utility values for such similar populations as those in England and Scotland. It was also uncertain if the company had disclosed all the different assumptions used in its 2 submissions, how varying the individual assumptions affected the overall cost-effectiveness results, and what precise factors caused different incremental QALYs in the 2 submissions. All of this added further uncertainty to the results.	4.11

Are there specific groups of people for whom the technology is particularly cost effective?	No specific committee consideration.	
What are the key drivers of cost effectiveness?	In exploratory analyses, both the company and ERG models were most sensitive to assumptions about clinical effectiveness. The committee agreed that the sensitivity of the model to this assumption was particularly concerning because of the uncertainty about the use of pathological complete response as a surrogate for survival outcomes. Furthermore, the committee was concerned that the uncertainty it had identified in the cost and utility assumptions were likely to increase the ICER.	4.15

Most likely cost-effectiveness estimate (given as an ICER)	The committee noted that there were a number of different base-case scenarios provided by the company (3 base cases ranging from £8,215 to £19,939 per QALY gained) and the ERG (£23,467 per QALY gained), but that all models were subject to the same levels of uncertainty. Overall the committee agreed that there was too much uncertainty to determine a most plausible ICER. On the basis of the evidence presented, the committee remained very unsure about the long-term benefits of the addition of pertuzumab to trastuzumab and chemotherapy compared with trastuzumab and chemotherapy alone and the cost effectiveness remained highly uncertain. Taking all of these uncertainties into account, the committee concluded that it could not recommend pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer as a cost-effective use of NHS resources.	4.15
Additional factors taken into account		
Patient access schemes (PPRS)	N/A	
End-of-life considerations	N/A	

Equalities considerations and social value judgements	N/A	

5 Proposed date for review of guidance

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

Jane Adam
Chair, appraisal committee
May 2016

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.

Carl Prescott
Technical Lead

Joanna Richardson
Technical Adviser

Bijal Joshi/Marcia Miller
Project Managers

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