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Pertuzumab for the neoadjuvant treatment of early stage HER2-positive breast cancer: An Evidence Review Group Perspective of a NICE Single Technology Appraisal

Running title: Neoadjuvant pertuzumab treatment for HER2-positive breast cancer: Evidence Review Group Perspective

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Abstract

As part of its Single Technology Appraisal process, the National Institute for Health and Care Excellence (NICE) invited the manufacturer of pertuzumab (Perjeta®; Roche Products Limited) to submit evidence of its clinical and cost-effectiveness for the neoadjuvant treatment of women with high risk early stage, HER2-positive breast cancer when used in combination with trastuzumab and chemotherapy. High risk women included those with locally advanced (including inflammatory) breast cancer and women with high risk early breast cancer (classified as T2/3 or N1). The School of Health and Related Research Technology Appraisal Group at the University of Sheffield was commissioned to act as the independent Evidence Review Group (ERG). This article presents the critical review of the company's submission by the ERG and the outcome of the NICE guidance. The clinical data were mainly taken from a Phase II, randomised, open-label, active controlled study (NeoSphere), which reported a significant advantage in terms of pathological complete response (pCR) rates of pertuzumab in combination with trastuzumab and chemotherapy, compared with trastuzumab alone with chemotherapy (45.8% versus 29.0%, p=0.0141). The company did not make any indirect comparisons. A meta-analysis of 12 neoadjuvant studies investigating the relationship between pCR and event-free survival (EFS) was used to extrapolate the outcomes reported in the NeoSphere study. A cardiac safety study (TRYPHAENA) demonstrated the safety of pertuzumab. The company undertook a model-based economic evaluation of neoadjuvant pertuzumab plus trastuzumab and docetaxel compared with neoadjuvant trastuzumab and docetaxel over a lifetime horizon from the National Health Service (NHS) and Personal Social Services (PSS) perspective. The probabilistic incremental cost-effectiveness ratio (ICER) was estimated to be £20,104 per quality-adjusted life-year (QALY) gained for pertuzumab alongside trastuzumab and docetaxel compared with trastuzumab and docetaxel, which was revised to £21,869 per QALY gained following the clarification process. The ERG corrected an error in the digitisation of the survivor functions and modified the clinically inappropriate assumption that recurrence is zero after 7 years. The ERG's probabilistic base case was £23,962 per QALY gained. During the appraisal, to mitigate the uncertainties associated with the evidence, the company offered a patient access scheme (PAS), which led to the NICE Appraisal Committee recommending pertuzumab in this patient group, subject to the company providing the agreed discount in the PAS.

Key points for decision makers

- Neoadjuvant pertuzumab in combination with trastuzumab and chemotherapy provides a statistically significant advantage in terms of pathological complete response rates compared with trastuzumab and chemotherapy for treating HER2-positive breast cancer which is either locally advanced, inflammatory, or early stage (at a high-risk of recurrence).
- The safety of pertuzumab has been demonstrated.
- Given the patient access scheme proposed by the company, neoadjuvant pertuzumab is considered to be a cost-effective use of NHS resources.

1. Introduction

The National Institute for Health and Care Excellence (NICE) is an independent organisation whose responsibilities include providing national guidance to the National Health Service (NHS) in England on health technologies. The NICE Single Technology Appraisal (STA) process usually covers new health technologies

within a single indication, soon after UK market authorisation national [1]. The company submits evidence on the clinical and cost-effectiveness of the technology, including a *de novo* economic model, and an independent Evidence Review Group (ERG) reviews the submission. The NICE Appraisal Committee (AC) considers the evidence submitted by the company and the ERG, alongside testimony from experts and other stakeholders, in order to develop national recommendations for England. These findings are reported within a Final Appraisal Determination (FAD). An Appraisal Consultation Document (ACD) is initially produced if the recommendations from the AC are restrictive or additional clarification is required from the company about their submission. All stakeholders have an opportunity to comment on the ACD before the AC meets again to produce the FAD.

The School of Health and Related Research Technology Assessment Group (ScHARR-TAG) at the University of Sheffield were the independent Evidence Review Group (ERG) who produced a critical review of the company's submission. This article presents a summary of the ERG report at the time of the assessment and the outcome of the NICE guidance for the STA of neoadjuvant pertuzumab for treating patients with HER2-positive breast cancer who are at high risk of recurrence, when used in combination with trastuzumab and chemotherapy. This is one of a series of STA summaries being published in PharmacoEconomics. Full details of all relevant appraisal documents can be found on the NICE website [2].

2. The Decision Problem

Pertuzumab is licensed for use in patients with early stage HER-2 positive breast cancer at high risk of recurrence (locally advanced, inflammatory or early stage breast cancer), before the patient undergoes surgery, to be used in combination with trastuzumab and chemotherapy [3]. Pertuzumab is also licensed for metastatic breast cancer treatment; however, its use for this indication was not considered within this appraisal.

HER2-positive breast cancer is associated with a significantly worse prognosis and higher recurrence rate than other breast cancers [4]. It accounts for around 15% of all breast cancers [4]. Neoadjuvant therapy is sometimes indicated for locally advanced or inflammatory cancer to facilitate or permit surgery in previously inoperable disease. It may be indicated in early breast cancer to facilitate breast conservation surgery or ensure early systemic treatment if surgery may be complicated, such as when reconstruction is planned or to enable gene test results to become available, which may impact on treatment planning. In most cases, neoadjuvant therapy is only advised in women who are at sufficiently high risk of recurrence that they would need adjuvant systemic therapy post operatively [5].

Based on published evidence, the company (Roche Products Limited) estimates that each year there are 5,113 patients with newly diagnosed HER2-positive breast cancer in England. Of these, 27% of patients (based on the company's market research data) would receive neoadjuvant therapy, resulting in 1,380 newly eligible patients per annum for treatment with pertuzumab.

Pertuzumab is given by intravenous infusion. The recommended first dose is 840mg, followed by a dose of 420mg every three weeks until the patient undergoes surgery [3], which will usually be between 3 and 6 doses.

The comparator described within the company's statement of the decision problem is 'neoadjuvant trastuzumab in combination with chemotherapy', whilst the comparator within the final NICE scope was more broadly described as 'standard neoadjuvant therapy without pertuzumab for HER-2 positive breast cancer'. NICE guidance does not currently recommend which treatments to provide within the neoadjuvant setting for these patients. Whilst the company's market research and the ERG's clinical experts suggest that most patients in England would be given the combination regimen of 5-fluorouracil, epirubicin and cyclophosphamide (FEC) followed by a taxane alongside trastuzumab, some patients may receive alternative therapies. Given that no evidence about clinical and cost-effectiveness was provided by the company for patients who would not receive trastuzumab, this assessment was limited to those patients who will receive trastuzumab as neoadjuvant therapy, which the company state is the relevant patient population. It should be noted that whilst the comparator has not been evaluated in terms of cost-effectiveness in the neoadjuvant setting, clinical advisors to the ERG suggest that trastuzumab as adjuvant therapy (which has been assessed and recommended by NICE [6]) has simply been moved to an earlier stage in the patient pathway.

The primary outcome considered was pathological complete response (pCR). Whilst evidence relating to overall survival (OS) and disease-free survival (DFS) was included within the company submission, the key clinical studies were not powered to assess these. Adverse events were reported. The health economic outcome employed within the company's health economic model was the incremental cost per quality-adjusted life year gained, as set out within the NICE Reference Case [1].

3. The Independent ERG Review

The company provided a submission to NICE on the clinical and cost-effectiveness of pertuzumab for treating HER2-positive breast cancer at high risk of recurrence (locally advanced, inflammatory or early stage breast cancer, T2/3 or N1), before the patient undergoes surgery, to be used in combination with trastuzumab and chemotherapy [2]. This submission was critically appraised by the ERG. In addition, the ERG identified areas requiring clarification, for which the company provided additional evidence prior to completion of the ERG report [2]. The ERG also modified the company's decision analytic model to produce an ERG base case assessment of cost-effectiveness and to assess the impact of alternative parameter values and assumptions on the model results. This section summarises the evidence presented in the company's submission and the ERG's review of that evidence.

3.1 Clinical Evidence provided by the Company

The company submission included a systematic review of the clinical evidence of neoadjuvant pertuzumab. The main supporting evidence was derived from two company-sponsored, multi-country, multi-centre, randomised, open-label, active controlled studies (NeoSphere and TRYPHAENA) [7, 8] assessing the efficacy and safety of neoadjuvant pertuzumab in combination with trastuzumab and chemotherapy for the treatment of HER2-positive early breast cancer.

3.1.1 Clinical study design

The NeoSphere study (a proof of concept study) was a four arm, Phase II trial that randomised 417 treatment-naïve women, (aged over 18 years) with operable, locally advanced or inflammatory centrally confirmed HER2-positive breast cancer (primary tumours >2 cm in diameter) to receive four neoadjuvant cycles of trastuzumab plus docetaxel (Arm A, n=107); pertuzumab plus trastuzumab plus docetaxel (Arm B, n=107); pertuzumab plus trastuzumab (Arm C, n=107) or pertuzumab plus docetaxel (Arm D, n=96) [7]. Pertuzumab was administered at a loading dose of 840mg, followed by a 420mg dose every 3 weeks. Trastuzumab was administered at a loading dose of 8mg/kg, followed by a 6mg/kg dose every 3 weeks. Docetaxel was administered at a dose of 75mg/m^2 (with escalation to 100mg/m^2, if tolerated) every 3 weeks. Following surgery, all patients received three cycles of adjuvant chemotherapy with the FEC regimen (5-fluorouracil, 600mg/m^2; epirubicin, 90mg/m^2; and cyclophosphamide, 600mg/m^2 administered intravenously every 3 weeks) and trastuzumab every 3 weeks to complete 1 year of therapy. Postoperative loco-regional radiotherapy and endocrine treatments for oestrogen receptor positive tumours were given according to local and national guidelines. The primary endpoint was pathological complete response (pCR) in the breast (bpCR), defined in the study as absence of invasive tumour in the breast irrespective of ductal carcinoma in-situ or nodal involvement, ypT0/Tis. Total pathological complete response (tpCR) was also reported, defined in the study as absence of invasive tumour in breast and lymph nodes irrespective of ductal carcinoma in-situ, ypT0/is ypN0. The marketing authorisation for pertuzumab in the neoadjuvant setting is restricted to use in combination with trastuzumab and chemotherapy only; hence, Arm C and Arm D of the NeoSphere study were not considered relevant to the appraisal by the ERG.

The TRYPHAENA study (a cardiac safety study) was a Phase II study that randomised 225 treatment naïve women, (aged over 18 years) with operable, locally advanced or inflammatory centrally confirmed HER2-positive breast cancer (primary tumours > 2cm in diameter) to receive one of three neoadjuvant treatments: Arm A (n=73) included pertuzumab and trastuzumab in cycles 1 to 6 plus FEC (5-fluorouracil, 500mg/m^2; epirubicin, 100mg/m^2 and cyclophosphamide 500mg/m^2) in cycles 1 to 3 and docetaxel (75mg/m^2 increased to 100mg/m^2 if tolerated) in cycles 4 to 6; Arm B (n=75) included FEC alone in cycles 1 to 3 followed by pertuzumab, trastuzumab and docetaxel (75mg/m^2 increased to 100mg/m^2 if tolerated) in cycles 4 to 6; Arm C (n=77) included pertuzumab, trastuzumab, docetaxel (75mg/m^2 with no dose escalation) and carboplatin in cycles 1 to 6 [8]. Pertuzumab was given at an initial dose of 840mg, with subsequent doses of 420mg. Trastuzumab was given at an initial loading dose of 8mg/kg, followed by 6mg/kg. All regimens were given intravenously every 3 weeks for a total of six neoadjuvant cycles. Following surgery, all patients received trastuzumab every 3 weeks to complete 1 year of therapy. Postoperative loco-regional radiotherapy and endocrine treatments for oestrogen receptor positive tumours were given according to local and national guidelines. The primary endpoint of the study was cardiac safety. The statistical analysis plan did not include any pre-planned hypothesis testing and the submission did not include any statistical comparisons between the treatment arms for any outcome. In addition, because all groups in this study received pertuzumab, comparative efficacy of pertuzumab in combination with trastuzumab and chemotherapy versus trastuzumab and chemotherapy without pertuzumab cannot be estimated using this study.

3.1.2 Clinical study results

Clinical effectiveness

In general, the bpCR rate (trial definition of pCR) in the NeoSphere study was significantly higher in Arm B (combination of pertuzumab, trastuzumab and docetaxel, 45.8%) compared with Arm A (combination of trastuzumab plus docetaxel, 29.0%), with a difference of 16.8% (p=0.0141) [7]. The rates of tpCR (EMA and FDA preferred definition of pCR) was broadly similar to that of bpCR (Arm B, 39.3% versus Arm A, 21.5%; difference of 17.8%, p=0.0063). In the TRYPHAENA study, bpCR and tpCR were consistently high and similar across all treatment groups (approximately 60%) [8].

Although the NeoSphere study was not powered to assess long-term outcomes or subgroups, 5-year progression-free survival (PFS) was 86% for Arm B (95% CI: 77% to 91%) compared with 81% (95% CI: 71% to 87%) for Arm A [7]. The hazard ratio for PFS for Arm B versus Arm A was 0.69 (95% CI: 0.34 to 1.40). The 5-year disease-free survival (DFS) data were 81% and 84% in Arms A and B respectively. The DFS hazard ratio for Arm B versus Arm A was 0.60 (95% CI: 0.28 to 1.27) [7]. In the TRYPHAENA study, DFS data was not yet available at the time of company submission. Data relating to health related quality-of-life (HRQoL) were not collected in either study [8]. Table 1 shows the summary outcomes from the relevant arms of the NeoSphere trial.

Safety

During the neoadjuvant period of the NeoSphere (<3% across all arms) and TRYPHAENA studies (<8% across all arms), adverse events leading to treatment discontinuation were low [7]. In the neoadjuvant phase of the NeoSphere study, grade ≥3 neutropenia was numerically higher in patients who received docetaxel (Arm A, 57.0%; Arm B, 44.9%; Arm D, 55.3%) than in patients who did not receive docetaxel (Arm C, 1%). The other most common grade ≥3 adverse events were febrile neutropenia (range 7.4% to 8.4% in docetaxel arms and none in the arm without docetaxel) and leucopenia (range 5% to 12% in the docetaxel arms and none in the arm without docetaxel) [7]. There was 1 death possibly related to treatment, in the dual treatment arm (B) in the NEOSPHERE study from fulminant hepatitis. In the TRYPHAENA study, similar incidences of grade ≥3 adverse events were observed (neutropenia, range 46.1% to 47.2%; febrile neutropenia, range 9.3% to 18.1%; leucopenia, range 11.8% to 19.4%) [8]. In the NEOSPHERE study, the number of patients with cardiac dysfunction adverse events was low in all trial arms; this was highest in Arm B (3% to 6% across the treatment periods). Similarly, in the TRYPHAENA study, incidence of symptomatic left ventricular systolic dysfunction (LVSD) and significant declines in left ventricular ejection fraction (LVEF) (≥10% points from baseline to <50%) were low across all arms but highest in Arm B (1.3% to 12.3% across the treatment periods) [8].

3.2 Critique of the Clinical Evidence and Interpretation

3.2.1 Critique of systematic review

The systematic review process followed by the company was reasonably comprehensive. Despite minor limitations in the company's search strategy, the ERG is confident that all relevant controlled studies of pertuzumab in combination with trastuzumab and chemotherapy for the treatment of HER2-positive early breast cancer were included in the company submission, including data from ongoing or planned studies. However, the ERG is not confident that all relevant non-randomised and non-controlled studies have been identified and

included in the company submission, as details of the systematic review process (e.g. identification, selection, data extraction, quality assessment and analysis and interpretation) were lacking. The specified inclusion and exclusion criteria were mostly appropriate and generally reflect the decision problem set out in the final NICE scope. The validity assessment tool used to appraise the included studies (NeoSphere and TRYPHAENA [7, 8]) was considered appropriate by the ERG.

3.2.2 Critique of clinical evidence

Although the efficacy (measured in terms of pCR response) and safety of pertuzumab in combination with trastuzumab and chemotherapy compared with trastuzumab and chemotherapy was positively demonstrated in the key included studies, there are a number of limitations and uncertainties in the evidence base which warrant caution in its interpretation.

Limitations of the RCTs

The main evidence for clinical efficacy and safety of pertuzumab in the company submission was derived from two, Phase II, randomised, open-label, active controlled studies [7, 8]. There was no evidence from a RCT powered adequately for DFS and OS endpoints. As with many cytotoxic cancer drugs, the nature of the interventions precludes blinding and is almost universally absent from oncology trials; however, blinded outcome assessment can enhance bias reduction. The TRYPHAENA study, which was a cardiac safety study, included pertuzumab in all arms and did not provide evidence of comparative efficacy with treatments without pertuzumab [8]. In addition, because of current practice varying between countries, the generalisability of the results from the RCTs to England is unclear.

pCR as a surrogate endpoint

The FDA and EMA both granted approval of neoadjuvant pertuzumab on acceptance of pCR as a surrogate endpoint in neoadjuvant treatment for high risk early stage breast cancer based upon work by Cortazar *et al*.,[9] subject to the need to collect long-term clinical outcomes data [10]. Cortazar *et al*. performed a patient-level responder analysis and a study-level analysis to investigate the relationship between pCR and both EFS and OS [9]. The authors identified 12 neoadjuvant studies, including 11,955 patients in the responder analysis and 9,440 patients in the study-level analysis. In all patients, this analysis suggested that patients who achieved pCR defined as absence of invasive cancer in the breast and axillary nodes had an improved EFS (Hazard Ratio (HR) 0.48 95% CI: 0.43, 0.54) and OS (HR 0.36 95% CI: 0.31, 0.42) compared to those who did not have a pCR. The greatest association was in patients with HER2-positive, hormone receptor-negative tumours who received trastuzumab (EFS: HR 0.15 95% CI: 0.09, 0.27; OS: HR 0.08 95% CI: 0.03, 0·22) and those in the triple-negative subgroup. However, the analysis was unable to demonstrate a relationship between the effect of treatment on pCR (estimated using an odds ratio) and the effect of treatment on EFS and OS (estimated using a hazard ratio) at the study level. These findings are generally consistent with other similar studies [11, 12]. The ERG accepts that there is evidence at the patient-level that a pCR responder is associated with a lower risk of EFS and OS. However, the evidence that a positive treatment effect on pCR translates into a positive effect on OS is not convincing. Therefore, the predictive value of pCR for estimating the long-term survival benefit in the target patient population is highly uncertain.

3.3 Cost-Effectiveness Evidence submitted by the Company

The company identified one existing economic evaluation of pertuzumab for early stage breast cancer in their economic review. This was developed by the company and is similar to the model within the company submission. The company undertook model-based economic evaluation of neoadjuvant pertuzumab plus trastuzumab and docetaxel compared with neoadjuvant trastuzumab and docetaxel over a lifetime horizon from the NHS and PSS perspective. The company's *de novo* model adopts a cohort level state transition approach based on six health states: event-free, locoregional recurrence, remission, metastatic not-progressed, metastatic progressed and death, as shown in Figure 1. Costs and outcomes are evaluated using a monthly cycle length. Patients in the event-free state can transit to locoregional recurrence, the metastatic not-progressed state or death. Patients spend 12 months in locoregional recurrence (which is modelled as a tunnel state without the possibility of transitioning to death), after which they transition to the remission state. Patients in the remission state can transition to the metastatic not-progressed state or death. Patients in the metastatic not-progressed state can transition to the metastatic progressed state or death. Patients in the metastatic progressed state can transition only to death.

Although the company used the term DFS within the clinical section of the company submission, they used event-free survival (EFS) within the cost-effectiveness section. The ERG believes that the company's intention was that these terms be considered synonymous. Given the limited number of EFS events within the key clinical studies, the company used results from a meta-analysis of 12 neoadjuvant studies investigating the relationship between pCR and EFS by the Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC) group [9] to extrapolate the pCR outcomes reported in the NeoSphere trial. The company digitised the EFS Kaplan-Meier survivor functions from the CTNeoBC meta-analysis and used it to reconstruct the data for patients achieving pCR or not achieving pCR, using the algorithm reported by Guyot et al [13]. The company fitted a number of parametric survivor functions (exponential, Weibull, log logistic, log normal, Gompertz and Generalised gamma) to the reconstructed data, and assessed the best fit using visual inspection and Akaike information criterion (AIC)/ Bayesian information criterion (BIC) statistics. In the base case analysis, the company used gamma distributions for patients achieving pCR and for patients not achieving pCR. The EFS for each treatment arm in the model was then estimated by multiplying the survivor functions of pCR and no pCR by the proportions of patients achieving pCR and no pCR in the respective arms in the NeoSphere trial.

Within the model it was assumed that the treatment effect persists for seven years. The company also assumed that seven years after treatment initiation, patients who have not experienced locoregional or metastatic recurrence are assumed to be cured, with only the risk of general population mortality. A utility was assigned to the 'event-free', 'locoregional', and 'metastatic non-progressed' health states based on a study of 361 consecutive breast cancer patients attending an outpatient clinic in Stockholm between April and May 2005 by Lidgren *et al.*[14] The utility value for the metastatic progressed health state was informed by a mixed model analysis by Lloyd *et al.*[15] Dis-utilities for adverse events were not applied. The model includes costs associated with drug acquisition based on the British National Formulary[16] for pertuzumab and trastuzumab and the Commercial Medicines Unit 2014 electronic Market Information Tool[17] for generic drugs. It also

includes costs associated with drug administration, the treatment of adverse events occurring in more than 5% of patients in either arm of the NeoSphere trial at grade 3, 4 or 5 severity and supportive care (all based on Personal Social Services Research Unit (PSSRU) 2014 costs[18] and NHS Reference Costs 2013/14[19]). Costs and health outcomes were discounted at 3.5% per annum.

The company reported a probabilistic ICER within their original submission of £20,104 per QALY gained for pertuzumab alongside trastuzumab and docetaxel compared with trastuzumab and docetaxel. The company amended their base case during the clarification process to £21,869 per QALY gained, by costing trastuzumab using the split in usage of infusional and subcutaneous formulations of trastuzumab based on their market research data. After the clarification process, the ERG highlighted an error around the digitised survivor functions which resulted in a new substantially reduced company probabilistic ICER of £9,047 per QALY gained for pertuzumab alongside trastuzumab and docetaxel compared with trastuzumab and docetaxel. The one-way sensitivity analysis performed by the company suggests that the key driver of the model results is the pCR rates.

3.3.1 Critique of the Cost-Effectiveness Evidence and Interpretation

The *de novo* model developed is generally appropriate for the decision problem defined in the final scope, although not all possible comparators have been included. The perspective, outcomes, discount rate, and measurement and valuation of costs and outcomes adhere to the NICE Reference Case. The model was generally well described within the company submission.

The key area of uncertainty concerned the validity of pCR as a surrogate endpoint for EFS and the approach for extrapolation. Although pCR has been used as a surrogate outcome for regulatory approval [10], the ERG has concerns about the use of pCR as a predictor of EFS. The CTNeoBC analyses found a correlation between pCR and EFS at the individual level, but could not validate pCR as a surrogate endpoint for improved EFS at the study-level [9]. The choice of parametric distribution used for extrapolation is shown within sensitivity analysis to impact upon the model results substantially and there is limited longer term data within this patient population to be able to satisfactorily validate this choice. The use of pCR as a surrogate outcome to predict EFS within the health economic model is a poor predictor of the EFS within the NeoSpere trial, irrespective of which parametric distribution is chosen. However, the company did also undertake an analysis using the EFS data directly from the NeoSphere trial which suggested that pertuzumab dominates (i.e. is more effective and less costly than the comparator).

The ERG also identified an error in the digitisation of the survivor function from the CTNeoBC meta-analysis. In the model, the company appeared to have used the data from all breast cancer patients up until around nine years (the length of follow up available for the HER2-positive subgroup, rather than the 18 year follow up available for all breast cancer patients), alongside the numbers at risk from the HER2-positive subgroup. The company and the ERG corrected this error by using only the data from the HER2-positive subgroup.

The justification for the assumption that after seven years from treatment initiation, patients who have not experienced locoregional or metastatic recurrence are assumed to be cured was unclear. Clinical advisors to the ERG suggested that whilst this may be reasonable for the hormone receptor (HR)-negative group, HR-positive patients are likely to continue to experience events and have greater mortality beyond seven years following treatment initiation compared with the general population [20]. Since the clinical advisors to the ERG suggested that cure of all HR-positive patients after 7 years is not clinically plausible, this assumption was amended in the ERG's base case analysis (see Section 3.4).

In addition, the uncertainty around the model parameters for the PSA was inadequately characterised. Within the company submission, the distributions and parameters used in the PSA were neither presented nor justified. Some uncertain model parameters were not characterised by probability distributions, and where included, the characterisation of uncertainty surrounding some model parameters appeared arbitrary. For example, the parameterisation of uncertainty in adverse event cost, administration cost, pharmacy time required for intravenous preparation and supportive care cost was assumed to be a proportion (typically 10-25%) of the mean. In addition, tabled results of the PSA were not presented by the company. Therefore, a clear analysis of uncertainty was not presented.

3.4 Additional Work Undertaken by the ERG

The ERG produced a revised base case which was similar to the company's base case following the clarification process. The ERG corrected the error in the digitisation of the survivor functions and modified the clinically inappropriate assumption that the probability of recurrence is zero after seven years. Whilst these changes individually impacted upon the ICER substantially, they acted in different directions and, when incorporated together, did not have a substantial impact on the company's results. The ERG-preferred probabilistic ICER for pertuzumab in combination with trastuzumab plus docetaxel compared with trastuzumab plus docetaxel is estimated to be £23,962 per QALY gained. Similarly, the ERG's deterministic base case ICER is estimated to be £23,467 per QALY gained. Whilst the ERG did not have sufficient time to improve the PSA, the more extensive univariate sensitivity analysis undertaken by the ERG suggested that the key drivers of the model results are: the relative pCR rates associated with the interventions; the parametric distribution employed for extrapolation of EFS; the number of cycles of pertuzumab administered; the costs of second line metastatic treatment; whether the treatment effect is assumed to continue beyond the trial follow-up duration; and health utility values.

3.5 Conclusions of the ERG Report

The ERG considered the efficacy (in terms of pCR response [using various definitions]) and safety evidence of pertuzumab in combination with trastuzumab and chemotherapy to be positively demonstrated (compared with trastuzumab and chemotherapy) in the key included studies. However, there are a number of limitations and uncertainties in the evidence base for cost-effectiveness that warrant caution in its interpretation. Treatment effects may be confounded because of the open-label design of the phase II studies. The key uncertainties in the evidence base relate to the use of pCR as a surrogate endpoint for survival outcomes (including magnitude of

benefit), the lack of results from high quality phase III RCTs, and the generalisability of the study results to England and the NHS.

The *de novo* model developed was generally appropriate for the decision problem defined in the final NICE scope, though it should be noted that the only comparator tested within the economic evaluation was trastuzumab alongside docetaxel. The model structure was considered by the ERG to be reasonable; however, there are uncertainties associated with the use of pCR as a surrogate measure for EFS and it does not appear to be a good predictor of the EFS data from the NeoSphere trial. The company's probabilistic ICER using this surrogate outcome was £20,104 per QALY gained for pertuzumab alongside trastuzumab and docetaxel compared with trastuzumab and docetaxel. The company amended their base case during the clarification process to £21,869 per QALY gained, by costing trastuzumab using the split in usage of infusional and subcutaneous formulations of trastuzumab based on their market research data. In addition to this change, the ERG have corrected an error in the digitisation of the survivor functions and modified the clinically inappropriate assumption that recurrence is zero after 7 years, resulting in a probabilistic ICER of £23,962 per QALY gained for pertuzumab alongside trastuzumab and docetaxel compared with trastuzumab and docetaxel. An alternative analysis was undertaken by the company using the EFS data from the NeoSphere study directly within the analysis, which suggested that pertuzumab, trastuzumab and docetaxel dominates (i.e. is more effective and less costly) compared with trastuzumab and docetaxel alone. The univariate sensitivity analysis undertaken by the ERG suggested that the key drivers of the model results are: the relative pCR rates associated with the interventions; the parametric distribution employed for extrapolation of EFS; the number of cycles of pertuzumab administered; the costs of second line metastatic treatment; whether the treatment effect is assumed to continue beyond the trial follow-up duration; and health utility values.

4. Key Methodological Issues

4.1 Short term data and the use of surrogate outcomes

NeoSphere was designed to demonstrate efficacy using pCR rates to enable accelerated use. Several studies have attempted to assess the relationship between pCR and event-free and overall survival. pCR was accepted for accelerated approval by both the European and US licensing authorities as a valid and meaningful clinical endpoint for regulatory approval of neoadjuvant breast cancer studies, subject to the need to collect long-term clinical outcomes data [10]. However, there remains uncertainty around whether an effect on pCR translates into effects on survival outcomes. There may be a difference between the evidence requirements for regulatory approval of a health technology and those for making funding decisions in England.

4.2 The impact of metastatic treatment costs and the Cancer Drugs Fund upon the model results

A key driver of the health economic model results was the assumption about which treatments for metastatic disease would be provided to patients. Costs of metastatic treatment would be incurred in both the intervention and comparator groups; however, a higher cost of metastatic treatment is favourable for the intervention (pertuzumab). This is because fewer patients would receive metastatic treatment in the intervention group since patients are not progressing so quickly and hence are more likely to die before metastatic progression. In

addition, discounting leads to reduced metastatic costs when incurred later. Thus, costs of subsequent treatment can substantially impact upon the cost-effectiveness of the intervention being assessed.

Due to the Cancer Drugs Fund (CDF), more expensive health technologies have been routinely available to patients than NICE have considered as a cost-effective use of NHS resources. At the time of this appraisal, the use of the CDF was being modified and NICE were in the process of reviewing the cost-effectiveness of all treatments available to patients using the fund. The timing of these reviews meant that it was unknown which metastatic treatments would become standard practice in England during the appraisal. Moreover, if the treatments currently available on the CDF were recommended they would likely be subject to a PAS and hence this would result in a less favourable ICER for pertuzumab. The cost of the metastatic treatments was shown, within sensitivity analysis, to impact substantially upon the model results. To mitigate the uncertainty associated with this, the company proposed a PAS for pertuzumab based upon a pessimistic scenario that neither of the health technologies for metastatic breast cancer which were available on the CDF would be funded following the review by NICE.

4.3 Sensitivity analyses

Given the substantial uncertainties associated with the evidence and current metastatic practice, it is important for the appraisal committee to have a clear understanding of the uncertainty which has and has not been incorporated into the model and its impact upon the model results. As described previously, the uncertainty was inadequately characterised within the PSA and insufficient information was provided within the company submission about both the PSA inputs and outputs. In addition, a univariate sensitivity analysis can help the committee to understand the impact of key parameters within the model, and the company did not assess many of the key drivers of the model results such as the number of cycles of pertuzumab and the cost of treating metastatic disease within their submission.

5. NICE Guidance

A PAS to discount the price of pertuzumab was proposed by the company following a decision not to recommend neoadjuvant pertuzumab resulting from the first appraisal committee meeting and reported within the ACD. The negative recommendation was because of the substantial uncertainty around the ICER, mainly associated with the use of pCR as a surrogate marker for long term outcomes and whether CDF-funded treatments for metastatic disease which are or will be under review should be included within the analysis. The company therefore proposed a PAS to mitigate the risk associated with recommending pertuzumab, the level of discount being designated as commercial in confidence. When the company used the ERG's assumptions and made the conservative assumption that treatment of metastatic disease did not include CDF-funded treatments, with the incorporation of the PAS, the ICER fell within the range normally considered to be a cost-effective use of NHS resources. The ERG was not asked to undertake any additional analysis around the PAS. In November 2016, NICE published its Final Appraisal Determination (FAD), which states that pertuzumab, in combination with trastuzumab and chemotherapy, is recommended as an option for the neoadjuvant treatment of HER2-positive breast cancer at high risk of recurrence, only if the company provides pertuzumab with the discount agreed in the PAS. Patients should normally have no more than four cycles.

6. Conclusions

The evidence suggests that pertuzumab is an effective and safe option for the neoadjuvant treatment of patients with early stage HER2-positive breast cancer at high risk of recurrence, to be used together with trastuzumab and chemotherapy. However, uncertainty remains around the extent to which short term improvements in pCR translate to long term gains in survival. The estimated base case ICER reported by both the company and the ERG fell below £30,000 per QALY gained compared with trastuzumab and docetaxel; although there was substantial uncertainty around this estimate. To mitigate this uncertainty, a PAS was proposed by the company, which allowed NICE to recommend pertuzumab for this indication as an expected cost-effective use of NHS resources.

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HS drafted the manuscript and takes responsibility as guarantor of the content. AP, PT, JS, EK, MC, RC and LW revised the manuscript for important intellectual content. All authors have given their approval for the final version to be published. This summary has not been externally reviewed by PharmacoEconomics.

Compliance with Ethical Standards

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Conflicts of interest

HS, AP, PT, JS, EK, MC, RC and LW have no potential conflicts of interest.

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