Pertuzumab in combination with trastuzumab and docetaxel for the treatment of HER2-positive metastatic or locally recurrent unresectable breast cancer

A NICE Single Technology Appraisal

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Key Points for Decision Makers

- The clinical and cost effectiveness evidence presented was based on a well-designed randomized controlled trial (RCT). The clinical data for the effectiveness of pertuzumab + trastuzumab + docetaxel appeared to be promising for the treatment of women with human epidermal growth factor receptor 2-positive (HER2+) metastatic breast cancer (MBC). However, the overall survival data were immature. This poses problems for the assessment of longer-term clinical and cost effectiveness
- The majority of patients treated in the RCT were trastuzumab naïve as, at the time patients were recruited, this was the norm. However, today in clinical practice, the majority of patients with HER2+ MBC receive trastuzumab for the treatment of early breast cancer. This may pose problems in the assessment of the relevance of the trial data to current clinical practice
- The cost effectiveness evidence based on economic modelling of the RCT data suggests that it would be impossible to set a price at which pertuzumab + trastuzumab + docetaxel could ever meet acceptability criteria for cost effectiveness typically applied by the National Institute for Health and Care Excellence (NICE). This is an issue that needs further exploration. As a result, the NICE Decision Support Unit are undertaking a discussion paper for assessing technologies that are not cost effective at a zero price.

Abstract

The National Institute for Health and Care Excellence (NICE) invited the manufacturer of pertuzumab [Roche] to submit evidence for the clinical and cost effectiveness of pertuzumab + trastuzumab + docetaxel for the treatment of human epidermal growth factor receptor 2-positive (HER2+) metastatic or locally recurrent unresectable breast cancer in accordance with the Institute's Single Technology Appraisal (STA) process. The Liverpool Reviews and Implementation Group (LRiG) at the University of Liverpool was commissioned to act as the Evidence Review Group (ERG). This article summarizes the ERG's review of the evidence submitted by the manufacturer and provides a summary of the Appraisal Committee's (AC) initial decision. At the time of writing, final guidance had not been published by NICE.

The clinical evidence was mainly derived from an ongoing phase III randomized double-blind placebo-controlled international multicentre clinical trial (CLEOPATRA), designed to evaluate efficacy and safety in 808 patients, which compared pertuzumab + trastuzumab + docetaxel (pertuzumab arm) with placebo + trastuzumab + docetaxel (control arm). Both progression-free survival (PFS) and overall survival (OS) were analysed at two data cut-off points – May 2011 (median follow-up of 18 months) and May 2012 (median follow-up of 30 months). At both time points PFS was significantly longer in the pertuzumab arm (18.5 months compared with 12.4 months in the control arm at the first data cut-off point and 18.7 months vs 12.4 months at the second data cut-off point). Assessment of OS benefit suggested an improvement for patients in the pertuzumab arm with a strong trend towards an OS benefit at the second data cut-off point; however, due to the immaturity of the OS data, the magnitude of the OS benefit was uncertain. Importantly, cardiotoxicity was not increased in patients treated with a combination of pertuzumab + trastuzumab + docetaxel. The ERG's main concern with the clinical effectiveness data was the lack of mature OS data. An additional concern of the AC was that the majority of patients in the RCT were trastuzumab naïve, which does not reflect current clinical practice.

The incremental cost effectiveness ratios (ICERs) generated by the manufacturer's model is considered to be commercial in confidence data and therefore cannot be published. Nevertheless, the results of the manufacturer's probabilistic sensitivity analyses suggest that pertuzumab + trastuzumab + docetaxel has a 0% probability of being cost effective at a willingness-to-pay of £30,000 per quality adjusted life year (QALY) gained when compared with trastuzumab + docetaxel. The ERG believes that more realistic estimates of the ICERs are considerably higher, almost double, those presented by the manufacturer. This is because the

ERG believes that due to the manner in which the economic model is constructed, the additional survival benefit following disease progression that is generated for patients treated with pemetrexed + trastuzumab + docetaxel are unrealistic. At the time of writing NICE had not made final decision regarding this technology but had instead referred the issue of the assessment of technologies that are not effective at a zero price to their Decision Support Unit for advice.

1 Introduction

The National Institute for Health and Care Excellence (NICE) is an independent organization responsible for providing national guidance to the NHS in England and Wales on a range of clinical and public health issues, as well as the appraisal of new health technologies. The NICE Single Technology Appraisal (STA) process is specifically designed for the appraisal of a single health technology for a single indication, where most of the relevant evidence lies with one manufacturer or sponsor.[1] Typically, the process is used for new pharmaceutical products close to launch. The evidence for a STA is principally derived from a submission by the manufacturer/sponsor of the technology, which should be based on a specification developed by NICE. The manufacturer's submission is critiqued by members of the independent Evidence Review Group (ERG) who produce a report to be considered by a NICE Appraisal Committee (AC).

The AC considers the submissions from the manufacturer and the ERG alongside testimony from experts, patients and other stakeholders to formulate preliminary guidance. All stakeholders have an opportunity to comment on this preliminary guidance, after which the AC meets again to produce the final guidance (final appraisal determination [FAD]). This article presents a summary of the ERG report for the STA of pertuzumab + trastuzumab + docetaxel for the treatment of human epidermal growth factor receptor 2-positive (HER2+) metastatic or locally recurrent unresectable breast cancer.

Full details of all relevant appraisal documents (including the appraisal scope, ERG report, manufacturer and consultee submissions, Appraisal Consultation Document [ACD], FAD and comments on each of these) can be found on the NICE website.[2]

2 The Decision Problem

Breast cancer is the most common malignancy in women in the UK. Approximately 50,000 people were diagnosed with breast cancer in the UK in 2010, of whom 99% were women.[3] Approximately 25% of patients with breast cancer develop metastatic breast cancer (MBC).[4]

Typically, patients who present with locally advanced or metastatic disease have been previously treated in the adjuvant setting for early breast cancer; between 5% and 10% of women initially present with *de novo* metastatic disease.[5-7] Patients with *de novo* disease are reported to have a better prognosis than those who have been previously treated for breast

cancer. A population study of *de novo* vs relapsed disease conducted in Texas, USA, reported a median overall survival (OS) of 39.2 months vs 27.2 months ($p < 0.0001$).[7] UK survival rates are reported to be lower than rates in much of the rest of Europe and North America, but do appear to be improving.[8, 9] Based on 34,598 cases from six UK-based cancer registries, a recent study estimated that the 5-year survival rate for patients with MBC is 79% and the 10-year survival rate is 71%.[10]

It has been estimated that 23% of patients who present with MBC have tumours that overexpress HER2.[4] HER2+ MBC is considered to be an aggressive form of disease and is associated with higher rates of recurrence, shorter progression-free survival (PFS) and shorter OS than for patients with tumours that do not overexpress HER2.[11-17]

There is minimal variation or uncertainty about best practice in the treatment of patients with HER2+ MBC. In the UK, based on NICE guidance,[18, 19] trastuzumab + taxane-based chemotherapy (docetaxel or paclitaxel) is the standard first-line treatment for patients with HER2+ MBC. Despite recent advances in the treatment of HER2+ MBC, including the proven efficacy of trastuzumab + docetaxel,[20] it is argued that a significant need still exists for new treatments with improved response rates.[4]

Pertuzumab (Roche) is a monoclonal antibody that binds to HER2 receptors on the surface of tumours and prevents HER2 dimerizing with other members of the HER family (HER1, HER3 and HER4).[4] This results in inhibition of the signalling inside the cell that leads to tumour growth and hence pertuzumab is considered to be the first in a new class of targeted cancer treatments called 'HER2 dimerization inhibitors'.[4] Pertuzumab is considered to be particularly effective in combination with trastuzumab, another type of monoclonal antibody directed against HER2, as the combination leads to an improved block of the signalling pathway.[4] Pertuzumab has recently been approved by the European Medicines Agency (EMA) for use "in combination with trastuzumab and docetaxel in adults with HER2-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease".[21]

NICE developed a scope for the assessment of pertuzumab which specified that the clinical and cost effectiveness of this drug should be established within its licensed indication. The population and intervention specified in the NICE scope and addressed by the manufacturer were the same as those approved by the EMA.[21] Trastuzumab in combination with a taxane

(docetaxel or paclitaxel) was the comparator specified in the NICE scope and addressed by the manufacturer. Outcomes specified in the NICE scope and addressed by the manufacturer included (but were not limited to) OS, PFS, response rates, adverse events (AEs) and health-related quality of life. As specified in the final NICE scope, the cost effectiveness of treatments were expressed by the manufacturer in terms of the incremental cost per quality-adjusted life year (QALY) gained. The time horizon was lifetime (maximum 25 years), which is sufficiently long to reflect differences in costs or outcomes between the technologies. Costs were considered from an NHS and Personal Social Services perspective. No specific subgroups were identified in the decision problem. In addition, no potential equity or equality issues were identified.

3 Independent Evidence Review Group Report

The evidence provided by the manufacturer comprises an initial submission and the manufacturer's response to the ERG's request for clarification on a number of issues.[4] The ERG report[22] is a critical review of the evidence for the clinical and cost effectiveness of the technology. It has the following three aims:

- To assess whether the manufacturer's submitted evidence conforms to the methodological guidelines issued by NICE
- To assess whether the manufacturer's interpretation and analysis of the evidence are appropriate
- To indicate the presence of other sources of evidence or alternative interpretations of the evidence that could help inform the development of NICE guidance

In addition to providing this detailed critique, the ERG modified a number of key assumptions and parameters within the manufacturer's economic model to examine the impact of such changes on cost effectiveness results.

The majority of the clinical effectiveness evidence was derived from a single randomized controlled trial (RCT) known as CLEOPATRA, which at the time of the manufacturer's literature search had been described in one full peer-reviewed publication.[23] Additional sources of data used by the ERG included a subsequently published paper on the CLEOPATRA trial,[24] the Clinical Study Report (CSR)[25] and the updated CSR.[26)] The latter two documents were both provided by the manufacturer at the ERG's request.

3.1 Clinical Evidence

CLEOPATRA[24] is an ongoing phase III randomized double-blind placebo-controlled international multicentre clinical trial involving 808 patients with previously untreated HER2+ MBC. The trial was designed to evaluate the efficacy and safety of pertuzumab + trastuzumab + docetaxel (pertuzumab arm) compared with placebo + trastuzumab + docetaxel (control arm). Both OS and PFS were analysed at two data cut-off points – May 2011 (median follow-up of 18 months) and May 2012 (median follow-up of 30 months). The primary outcome was PFS assessed by an independent review facility (IRF) at the first data cut-off point. To date, OS analyses are only interim as the data are still not mature. Final OS data are planned to be presented after approximately 385 deaths (expected mid to late 2014). Interim rates of OS are summarized alongside the rates for PFS in Table 1. A significant improvement in both IRF- and local investigator-assessed PFS of 6.1 months was reported at the first data cut-off point and a similar finding (6.3 months) was reported for local investigator-assessed PFS at the second data cut-off point. A significant improvement in OS was only reported at the second data cut-off point; whilst $P<0.05$ at the first time point, the estimated hazard ratio did not meet the O'Brien-Fleming stopping boundary of the Lan-DeMets α-spending function so the finding was not considered to be significant.

Results from planned subgroup analyses were generally consistent with the results from the overall study population. However, it appeared that OS was higher in patients in the control arm in the subgroup with non-visceral disease, although the subgroup was small (*n* = 178) and there were few events. The difference therefore was not statistically significant and the confidence intervals (CI) around the hazard ratio (HR) were wide (HR 1.42, 95% CI: 0.71 to 2.84). In addition to the planned subgroup analyses, and at the behest of the EMA,[27] an exploratory subgroup analysis of patients who had previously received trastuzumab was also conducted at the first data cut-off point (May 2011). This analysis was requested because, in current clinical practice, the majority of patients are likely to have received prior trastuzumab for the treatment of early breast cancer. Again, patient numbers were small (*n* = 88), but, findings were consistent with those for the overall population (subgroup findings: PFS, HR 0.62, 95% CI: 0.35 to 1.07; OS, HR 0.68, 95% CI: 0.30 to 1.55).

A summary of key AEs reported from the second data cut-off point is presented in Table 2. The main difference between the two treatment arms were a higher incidence of serious adverse events (SAEs) and AEs leading to dose interruption or modification in the pertuzumab arm than in the control arm. Since trastuzumab is thought to increase the risk of cardiotoxicity, particular

emphasis was placed on collecting data on cardiac disorders. Relatively few cardiac events were reported in either arm (Table 2). The most common AEs in both arms (pertuzumab vs control) were alopecia (60.8% vs 60.6%), diarrhoea (68.1% vs 48.2%), neutropenia (52.9% vs 49.7%), nausea (43.9% vs 42.4%) and fatigue (38.0% vs 37.4%). Some AEs appeared to be exacerbated by treatment with docetaxel (in particular diarrhoea, neutropenia, and mucositis) and once this drug was stopped, there was little difference in terms of the incidence of AEs between patients treated with pertuzumab + trastuzumab and those treated with trastuzumab alone.

Because the evidence from CLEOPATRA[24] included docetaxel as the taxane regimen, additional evidence for the relative effectiveness of paclitaxel + trastuzumab was derived from a descriptive indirect comparison of two studies[20, 28] conducted in the metastatic setting. These compared docetaxel or paclitaxel + trastuzumab with taxane monotherapy; in both trials, taxanes were administered every 3 weeks. The results implied that regimens containing trastuzumab and a taxane are superior to those of a taxane alone (Table 3) and that trastuzumab + docetaxel may be the most efficacious. Evidence was also presented from a large RCT of 4950 patients in the adjuvant setting comparing four different taxane regimens, albeit all delivered as monotherapies: once weekly or 3-weekly docetaxel or paclitaxel.[29] The factorial design of the trial enabled 3-weekly paclitaxel to be compared to three experimental regimens: once-weekly paclitaxel, 3-weekly docetaxel and once-weekly docetaxel regimens. Compared to 3-weekly paclitaxel, the authors of the RCT[29] reported significant improvements in disease-free survival (DFS) (HR 1.27, 95% HR: 1.03 to 1.57) and OS (HR 1.32; 95% HR: 1.02 to 1.72) for once-weekly paclitaxel. Significant differences were also observed in DFS for 3-weekly docetaxel (HR 1.23, 95% HR: 1.00 to 1.52) but not OS (HR 1.13, 95% HR: 0.88 to 1.46). Once-weekly docetaxel yielded neither significant gains in DFS (HR 1.09, 95% HR: 0.89 to 1.34) or OS (HR 1.02, 95% HR: 0.80 to 1.32). In their submission,[4] the manufacturer notes that weekly paclitaxel and 3-weekly docetaxel regimens were associated with comparable 5-year DFS (81.5% and 81.2% respectively) and OS (89.7% and 87.3% respectively).

3.1.1 Critique of Clinical Evidence and Interpretation

The CLEOPATRA trial[23] is of good methodological quality with minimum risk of bias. The population in the study largely reflects people who would normally be eligible for trastuzumab- and docetaxel-based treatment outside of the clinical trial setting (i.e. with a 12-month disease-free interval following previous treatment with chemotherapy, which is likely to have included docetaxel). However, only a minority of patients (10.9%) in the trial had previously been treated with trastuzumab for early breast cancer. In current clinical practice, a much greater proportion

of patients would be pre-treated with trastuzumab. This concern was also raised by the EMA.[27] The results of the exploratory subgroup analysis including the small number of patients who had previously received trastuzumab were noted, as were the conclusions of the EMA,[27] i.e. that these data, alongside those from the phase II BO17929 study[30] (which demonstrated activity of the pertuzumab + trastuzumab combination in 66 people previously treated with trastuzumab in the metastatic setting) support the efficacy of pertuzumab in people pre-treated with trastuzumab.

Another potentially important subgroup difference noted by the ERG (and also by the EMA [27]) involved patients with and without visceral disease. Patients with non-visceral disease appeared to gain the smallest benefit from the addition of pertuzumab. The ERG noted that the manufacturer suggested that the discrepancy may be attributable to the small number of patients with non-visceral disease in the trial and some differences between treatment arms in baseline characteristics.

A final uncertainty identified by the ERG in relation to the efficacy evidence from CLEOPATRA[23] concerned the OS data. It was not possible to estimate the absolute difference in median OS between patients treated in the pertuzumab arm and those in the control arm because of immature data. This has important implications when trying to model OS for assessing cost effectiveness.

Regarding the additional supporting evidence for different types of trastuzumab + taxane regimens, the ERG noted that the indirect evidence from the two trials[20, 28] could be described as a naïve indirect comparison. Such a comparison has been criticized in the literature for discarding the within-trial comparison, increasing the risk of bias and presenting estimates without a measure of uncertainty (e.g. 95% CIs).[31] The merit of using the trials in any type of comparison with each other may also be questioned, as apparent differences between the trials exist in terms of the patient populations. For example, of patients treated with a paclitaxel regimen, 98% had received prior adjuvant chemotherapy and 92% prior hormonal therapy,(28) compared with 69% and 45%, respectively, of patients who received trastuzumab + docetaxel or docetaxel alone.[20] Furthermore, it is noted by the ERG that in CLEOPATRA,[23] the proportions of patients pre-treated with chemotherapy (47%) or hormonal therapy (25%) were even lower. A number of issues were also highlighted by the ERG regarding the data from the head-to-head comparisons of taxane regimens.[29] First, and most obviously, the taxane regimens under investigation were monotherapies and not offered in combination with

trastuzumab (or pertuzumab). Second, the setting for the interventions was the adjuvant setting and so none of the patients had metastatic disease. Third, fewer than 20% of the patients enrolled into the trial had HER2+ disease. Finally it is noted that all patients had received prior chemotherapy.

The ERG noted that no safety data were presented by the manufacturer from the three trials offering supportive evidence.[20, 28, 29] While safety data were presented in the published paper of the trial in the adjuvant setting,[29] the applicability of these data to the current decision problem could be questioned given this was a population of patients treated with a taxane monotherapy in the adjuvant setting of whom only a minority had HER2+ disease.

3.1.2 Evidence Review Group Conclusions on the Submitted Clinical Evidence

CLEOPATRA[23] is a relatively large trial of good methodological quality. Local investigator and central IRF-assessed reviews of PFS both suggest that patients in the pertuzumab arm experience an increase in PFS of approximately six months. A significant improvement in OS was reported at a median of 30 months follow-up (second data cut-off point, May 2012) although the data are not fully mature and so the difference in median OS cannot be estimated. No new safety concerns were identified. Importantly, cardiotoxicity was not increased in patients treated with a combination of pertuzumab + trastuzumab.

3.2 Cost effectiveness Evidence

The manufacturer's submission[4] included a literature review of cost effectiveness evidence. It was reported that there were no relevant published economic evaluations available for consideration.

The manufacturer developed a *de novo* economic model using a partitioned survival approach structured with three patient health states (PFS [stable disease], progressed disease and death). The patient population included in the model was based on the participants enrolled in the CLEOPATRA trial[23] and the model was populated with data from the second data cut-off point in that trial.[24] Second-line treatments applied in the model were capecitabine and vinorelbine. In the base case, exponential survival models were appended to Kaplan–Meier data to allow PFS and OS to be forecast for a period of 25 years, and the perspective was that of the UK NHS.

The external validity of the model was compared with the survival of patients included in a registry of 523 people diagnosed with HER2+ MBC between 2002 and 2009 in Munich, Germany.[32] It was reported that the model results showed strong face validity when compared with these data.

Drug costs were reported to be taken from the British National Formulary 2012,[33] administration costs from NHS Reference costs for 2011/12[34] and pharmacy costs from Millar et al.[35] and PSSRU 2012.[36] Monthly supportive care costs during PFS and post progression were as described in the NICE clinical guideline for advanced breast cancer,[19] excluding the one-off costs for a social worker visit, a consultant outpatient appointment and a computed tomography scan in the PFS state. Costs for cardiac monitoring were also included during the PFS state. End-of-life costs were estimated by inflating the figures calculated by Guest et al. 2006[37] to current prices using inflation indices for Hospital and Community Health Services (PSSRU).[36] AE costs were only included for AEs reported to occur in 2% or more people in either arm of the CLEOPATRA trial[23] at grade 3, 4 or 5 severity. It was assumed that treatment regimens of trastuzumab + docetaxel and trastuzumab + paclitaxel had the same toxicity profile.

The manufacturer conducted a literature search to identify all potentially relevant utility scores that had been used in health technology evaluations for MBC. This search was an update of a previous search that had been carried out for the NICE Technology Appraisal of bevacizumab in combination with capecitabine (TA263).[38] No new relevant studies were identified and so the manufacturer concluded that the most appropriate approach was to use the model outlined by Lloyd et al.[39] to estimate QALYs. This approach was used in TA263[38] and has also been used in a number of other NICE Technology Appraisals for MBC.

Both costs and benefits were discounted at 3.5%. However, AE costs were only applied in week 1 in the model and are therefore not discounted.

It is reported by the manufacturer that the model was validated at two advisory board meetings and by a health economics consultancy. Model functionality was checked during this process and the clinical inputs and assumptions were validated. Extrapolation of data was discussed with an academic health economist and two panels of clinicians. These advisors noted that although subject to uncertainty, the extrapolation approach employed by the manufacturer appeared reasonable given the evidence currently available.

Deterministic and probabilistic sensitivity analyses were undertaken. Parameters varied in the deterministic analyses included treatment costs, utilities, parametric functions used to extrapolate trial data, discounting rates (for costs and utilities) and the time horizon. Probabilistic sensitivity analyses were undertaken by varying costs for best supportive care and second-line treatment (both using lognormal distributions) and utilities (using beta distributions).

The base-case ICERs generated by the manufacturer's model were all marked as commercial in confidence data as were the ICERs generated from the deterministic and probabilistic sensitivity analyses. The deterministic sensitivity analyses showed the model to be most sensitive to the long term extrapolation of PFS and OS, whilst the probabilistic sensitivity analyses suggested that pertuzumab + trastuzumab + docetaxel had a 0% probability of being cost effective at a willingness-to-pay of £30,000 per QALY gained when compared with trastuzumab + docetaxel.

3.2.1 Critique of Cost effectiveness Evidence and Interpretation

The ERG considered that the manufacturer's economic model was logically structured and competently implemented with adequate annotation to allow most features to be readily understood. In the ERG report,[22] the ERG commented on major and minor issues of concern. The latter related to costs and utilities and only had a minor impact on the size of the final ICER. Hence, only major issues of concern are considered here.

As part of its clarification request to the manufacturer, the ERG requested Kaplan–Meier survival estimates at each event time, for each treatment arm in the CLEOPATRA trial[23] for OS, PFS, time to off treatment (TTOT) and post-progression survival (PPS) censored at the date of data cut-off. These data were requested for the overall trial population as well as for patients with and without visceral disease. The manufacturer responded that by requesting these data, the ERG was exceeding their remit and so these data were not provided. However, the manufacturer did provide information from its communications with the EMA. This included some data describing subgroups and time-to-event information, albeit not censored at the date of data cut-off; therefore the available data appeared to suffer from systematic bias because of inappropriate censoring at the last trial observation date.

The ERG countered that these matters *did* fall within its remit because, as part of the STA process, the ERG is required to comment on the robustness and accuracy of the submitted

models, the data used to populate the models and, where possible, to carry out sensitivity analyses. As alternative assumptions in time-to-event analyses may be critical drivers of any model, and, as subgroup differences were deemed sufficient to require careful consideration in terms of efficacy and safety by the EMA,[27] the data requested by the ERG were clearly relevant to the appraisal. Without these data, the ERG was unable to consider the effect of alternative projections for PFS, OS, TTOT and PPS. Additional information detailing communications between the manufacturer and the regulator did enable the ERG to address the matters in broad terms, but did not enable the ERG to provide the AC with the results of fully detailed economic sensitivity analyses. Although the ERG considered that the Kaplan–Meier data provided were probably subject to serious bias, the ERG did conduct an exploratory projective modelling exercise to assess the sensitivity of the manufacturer's method of curve-fitting to alternative assumptions.

The ERG agreed with the manufacturer that adding pertuzumab to trastuzumab + docetaxel results in an increase in PFS but considered that there was uncertainty about the size of this survival gain. In the model, an exponential projection was applied to each trial arm by the manufacturer in its base case. The ERG considered that long-term hazard trends should only be estimated based on the segment of the trial data after 600 days. Moreover, the ERG observed that, if the final data points showing evidence of serious bias (sudden upward rise) were ignored, then the long-term hazard trends appeared to follow simple near-linear trajectories. On this basis, the ERG fitted linear trend lines to estimate long-term hazard trends for each trial arm and applied these to project PFS from day 600 onwards. As a result, the mean difference in PFS between the two treatment arms estimated by the ERG was substantially smaller than the difference estimated by the manufacturer.

The ERG did not agree with the manufacturer that there was a large difference in OS between treatments. In the manufacturer's base case, the majority of the estimated life extension occurred in the post-progression health state where a higher risk of death in the control arm compared with the pertuzumab arm was assumed. The ERG considered this to be inappropriate and assumed that there was no evidence of any difference in survival between treatment arms after progression. Thus, by applying the mortality trend from the Munich Register[32] to both arms in the model, the PPS gain estimated by the manufacturer was substantially reduced. The ERG also re-estimated OS using the PFS estimates, adjusting them for any difference in the proportion of patients dying before disease progression. Specifically, it used the estimated PFS gain and added to it the additional benefit after progression due to the small difference

between the two treatment arms in the proportion of patients still alive after disease progression, and assumed that the long-term post-progression hazard was the same in both arms. This approach reduced the OS gain to a similar magnitude to that calculated using the Munich register data.[32] Both approaches gave similar ICERs, which were substantially higher than the ICERs estimated in the manufacturer's base case.

3.2.2 Evidence Review Group Conclusions on the Submitted Cost effectiveness Evidence

The ERG considers that the OS data are not mature and that modelling using the currently available data is therefore limited. The ERG agrees with the manufacturer that pertuzumab + trastuzumab + docetaxel compared with trastuzumab + docetaxel has a 0% probability of being cost effective at a willingness-to-pay of £30,000 per QALY gained. However, the ERG believes the true estimate of the ICER to be considerably higher than that presented by the manufacturer. This large discrepancy is attributable to the ERG's belief that analysis of the available trial data shows no additional benefit in survival following disease progression, unlike the estimates given in the manufacturer's base case.

4 National Institute for Health and Care Excellence Guidance

At the first AC meeting the committee did not recommend pertuzumab + trastuzumab + docetaxel within its marketing authorization (i.e. for the treatment of people with HER2+ metastatic or locally recurrent unresectable breast cancer who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease). This decision was contested, and a second AC meeting was held. At the time of writing (May 2014), a final decision from NICE had not been published.

4.1 First Appraisal Committee Meeting

The AC agreed that, compared with trastuzumab + docetaxel, the addition of pertuzumab offered a benefit in PFS and OS but because of the immaturity of the OS data, the magnitude of the OS benefit was uncertain. It was concluded that there was insufficient evidence on which to base specific recommendations for people with visceral and non-visceral disease because of the small number of patients and events in the subgroup with non-visceral disease. The AC noted that the incidence of SAEs in the CLEOPATRA trial[23] was higher in the pertuzumab arm than in the control arm, as were the incidences of AEs leading to dose interruption or modification.

The AC noted the limitations of the naïve indirect comparison of docetaxel and paclitaxel highlighted by the ERG, and agreed that these results should be treated with caution. The clinical specialist told the AC that in clinical practice, 3-weekly docetaxel and weekly paclitaxel regimens are regarded as clinically similar and that the similar clinical effectiveness of these two regimens had been accepted by the AC in a previous technology appraisal (bevacizumab in combination with a taxane for the first-line treatment of metastatic breast cancer).[38] The AC concluded that it was reasonable to assume similar clinical effectiveness between 3-weekly docetaxel and weekly paclitaxel when used in combination with pertuzumab and trastuzumab. However, the AC heard from the clinical specialist that people who had experienced a 12-month disease-free interval following previous treatment with chemotherapy (as in CLEOPATRA[23]) might be expected to have a better prognosis than the whole population with HER2+ MBC. The clinical specialist also highlighted that only a minority (10.9%) of the randomized population in CLEOPATRA[23] had received previous treatment with trastuzumab in the adjuvant setting. This trial population therefore was not representative of a UK population as, in the UK, trastuzumab in the adjuvant or neoadjuvant setting is standard treatment. Hence, the AC questioned whether the trial population of CLEOPATRA[23] was representative of the population who would receive pertuzumab in clinical practice. It also noted comments from the clinical specialist that although pertuzumab is licensed for use in combination with trastuzumab and docetaxel, it may be more likely to be used in combination with trastuzumab and paclitaxel in clinical practice because a large majority of people would have had prior treatment with docetaxel in the adjuvant setting and hence a different taxane might be preferred.

Noting the difference in PPS estimates reported by the manufacturer and the ERG, the AC discussed the relationship between PFS and OS gain in the CLEOPATRA trial.[23] The AC heard from the clinical specialist that the statistically significant benefit of pertuzumab + trastuzumab + docetaxel in terms of PFS could be expected to be translated into a similar, if not greater, gain in OS. However, the AC considered that if OS gain exceeded the PFS gain, this implied a continuing beneficial drug effect in the disease progression phase, after the drug had been stopped. The biological plausibility of pertuzumab having a carry-over effect after treatment has been stopped was therefore discussed. The clinical specialist explained that this carry-over effect had been seen when tamoxifen was used in the adjuvant setting but would not necessarily be seen with HER2-targeted treatments in MBC. The AC heard from the manufacturer that there had been other clinical trials of MBC with trastuzumab that had shown an OS gain exceeding the PFS gain. It was noted that for MBC, these trials compared treatment

with trastuzumab plus a taxane against a taxane alone[20, 28] or trastuzumab and an aromatase inhibitor against an aromatase inhibitor alone.[40] The AC considered that it did not necessarily imply that the same effect would be seen with the addition of pertuzumab to trastuzumab and docetaxel compared with trastuzumab and a taxane alone. The AC concluded that there may, therefore, be various hypothetical explanations for the presence of a carry-over effect with pertuzumab after stopping the drug at disease progression. It considered that although some post-progression benefit might present as a carry-over effect, the manufacturer's calculation that the gain was more than twice as great in the post-progression phase after pertuzumab had been stopped compared to when the patients were receiving the drug in the pre-progression state was likely to be over-optimistic. Given that the immature OS data from the trial did not allow a robust assessment of any PPS benefit, there remained considerable uncertainty around the presence, or magnitude, of any post-progression benefit from the addition of pertuzumab to trastuzumab + docetaxel.

Finally, the AC considered the ICERs per QALY gained for pertuzumab + trastuzumab + docetaxel compared with trastuzumab + docetaxel presented by the manufacturer and by the ERG in its exploratory analyses. It noted that the cost effectiveness estimates from both the manufacturer and the ERG were outside the range normally considered to represent a cost-effective use of NHS resources. It concluded that pertuzumab + trastuzumab + docetaxel would not be a cost-effective use of NHS resources for treating HER2+ MBC compared with trastuzumab + docetaxel alone.

4.2 Second Appraisal Committee Meeting and Final Appraisal Determination

At the time of writing, the decisions reached from the second meeting had not been made public and a final decision from NICE was still outstanding. The NICE website[2] notes "the manufacturer's comment that it is not possible to set a price at which pertuzumab would meet current acceptability criteria for cost effectiveness" and states that the NICE Decision Support Unit (DSU) were undertaking a discussion paper for "assessing technologies that are not cost effective at a zero price." The next steps for reaching a final decision will then be taken by NICE following the outcome of the DSU's explanations.

5 Conclusion

A clinical benefit of pertuzumab + trastuzumab + docetaxel over trastuzumab + docetaxel in terms of PFS is evident from the CLEOPATRA trial.[23] However, because the trial data are immature, uncertainties exist as to whether OS is also improved. Because of the small number of study patients who were pre-treated with trastuzumab in the adjuvant or neo-adjuvant setting, the AC also considered there to be grounds for uncertainty as to the generalizability of the trial results to clinical practice.

Pertuzumab + trastuzumab + docetaxel do not appear to be cost effective compared to trastuzumab + docetaxel when using typically accepted criteria. This is true whether accepting the results from the manufacturer's model in which there is evidence of additional benefit in terms of survival following disease progression, or accepting he ERG's approach that assumed there would be no additional benefit in terms of survival following disease progression. Unfortunately, the AC was limited in its consideration of the evidence by a lack of the requested additional analyses requested from the manufacturer by the ERG. The lack of these analyses prevented the ERG from carrying out robust sensitivity analyses of alternative survival assumptions.

Of particular note is the observation by the manufacturer that there is no price at which pertuzumab used in combination chemotherapy in this population could be deemed cost effective by NICE. Although this situation is uncommon, it cannot be considered an artefact of the NICE methods of appraisal, but is fully consistent with the principles of economic evaluation. Any intervention which generates sufficient additional patient survival linked to substantial additional treatment costs can lead to such a situation (e.g. in chronic relapsing/remitting conditions which require repeated high-cost in-patient rescue interventions, or where extended survival also involves additional expensive co-medication costs). In such circumstances, it is possible that an incremental cost per patient can be generated, excluding the additional cost of the appraised intervention, which is sufficient to result in an ICER greater than any specific maximum willingness-to-pay of the funder. A treatment may just be too expensive because it is linked to other additional costs which cannot be offset by cost savings.

Finally, reviewers of this paper commented that the transparency of the NICE appraisal process may appear to be undermined when data, in particular estimates of ICERs, are withheld because they are deemed to be commercially or academically in confidence. The ERG is

cognizant of the difficulties that this presents and endeavours whenever possible to present as full a picture of the data as possible.

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Kerry Dwan: Critical appraisal of clinical statistical approach

Rumona Dickson: Summary and critical appraisal of the clinical evidence

Chris Proudlove : Critical appraisal of the manufacturer's submission

Yenal Dundar: Cross checking of manufacturer's search strategies

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Table 1 Main efficacy findings from CLEOPATRA trial

Outcome	Pertuzumab[a]	Control[b]	Result between arms
PFS (IRF assessment, May 2011), n Median time to event (months)	402 18.5	406 12.4	HR 0.62 (95% CI: 0.51 to 0.75) $p < 0.0001$
PFS (local assessment, May 2011), n Median time to event (months)	402 18.5	406 12.4	HR 0.65 (95% CI: 0.54 to 0.78)
PFS (local assessment, May 2012), n Median time to event (months)	402 18.7	406 12.4	HR 0.69 (95% CI: 0.58 to 0.81) $p < 0.0001$
OS (May 2011), n Median time to event (months)	402 not reached	406 not reached	HR 0.64 (95% CI: 0.47 to 0.88) $p = 0.0053$
OS (May 2012), n Median time to event (months)	402 not reached	406 37.6	HR 0.66 (95% CI: 0.52 to 0.84) $p = 0.0008$
Objective response (IRF assessment, May 2011),[c] n Responders ORR (%) 95% CI for ORR (%)	 343 275 80.2 (75.6 to 84.3)	 336 233 69.3 (64.1 to 74.2)	 10.8 (4.2 to 17.5), $p = 0.001$
Objective response (local assessment, May 2011),[c] n Responders ORR (%) 95% CI for ORR (%)	 367 284 77.4 Not reported	 371 253 68.2 Not reported	 $p = 0.0049$, stratified analysis

This table is adapted from data presented in the manufacturer's submission[(4)] and tabulated in Fleeman et al[(22)] (Crown copyright)

CI confidence interval; *HR* hazard ratio; *IRF* independent review facility; *ORR* objective response rate; *OS* overall survival; *PFS* progression-free survival

[a] Pertuzumab = pertuzumab + trastuzumab + docetaxel
[b] Control = placebo + trastuzumab + docetaxel
[c] Objective response was only analysed at the first data cut-off point (May 2011)

Table 2 Summary of adverse events reported in the CLEOPATRA trial (second data cut-off point, May 2012)[a]

Adverse events	**Pertuzumab[b] (%) (*n* = 408)**	**Control[c] (%) (*n* = 396)**
Any AE/ any grade	100.0	98.7
Any AE/ grade 3+	76.2	73.5
Treatment-related AEs	97.3	96.2
SAE	36.3	29.0
All cardiac disorders	15.4	17.4
Cardiac SAE	1.7	3.5
AE leading to discontinuation of any study medication	30.6	29.2
AE leading to dose interruption or modification	61.8	54.3
AE leading to death	2.0	3.0

The table is adapted from data presented in the manufacturer's submission[(4)] and Fleeman et al.[(22)] (Crown copyright)

AE adverse event; *SAE* serious adverse event

[a] No tests for statistical significance between groups were conducted
[b] Pertuzumab=pertuzumab + trastuzumab + docetaxel
[c] Control=placebo + trastuzumab + docetaxel

Table 3 Comparison of efficacy findings for trastuzumab + taxane vs taxane alone in metastatic breast cancer

Key endpoints	**Trastuzumab + docetaxel vs docetaxel[20]**		**Trastuzumab + paclitaxel vs paclitaxel[28]**	
	Trastuzumab + docetaxel (*n* = 92)	**Docetaxel (*n* = 94)**	**Trastuzumab + paclitaxel (*n* = 92)**	**Paclitaxel (*n* = 96)**
Median OS (months)	31.2	22.7	22.1	18.4
	P=0.0325		*P*=0.17	
Median TTP (months)	11.7	6.1	6.9	3.0
	P=0.0001		P<0.001	
ORR (%)	61	34	38	16
	P=0.0002		P<0.001	

This table is adapted from data presented in the manufacturer's submission[4] and Fleeman et al.[22] (Crown copyright)

ORR objective response rate; *OS* overall survival; *TTP* time to progression