STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Pertuzumab in combination with trastuzumab and docetaxel for the treatment of HER2 positive metastatic or locally recurrent unresectable breast cancer: A Single Technology Appraisal

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Title: Pertuzumab in combination with trastuzumab and docetaxel for the treatment of HER2 positive metastatic or locally recurrent unresectable breast cancer: A Single Technology Appraisal

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1 SUMMARY

1.1 Scope of the submission

The remit of the Evidence Review Group (ERG) is to comment on the clinical and cost-effectiveness evidence submitted to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Clinical and economic evidence have been submitted to NICE from Roche in support of the use of pertuzumab (Perjeta®) for the treatment of human epidermal growth factor 2 positive (HER2+) metastatic or locally recurrent unresectable breast cancer that has previously received chemotherapy or HER2 directed treatment for metastatic disease or in patients whose disease has recurred after adjuvant therapy.

The manufacturer's submission outlines the use of pertuzumab when added to a regimen of trastuzumab and docetaxel in this patient population.

Pertuzumab has been approved 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".

1.2 Critique of the decision problem in the manufacturer's submission

The patient population and intervention addressed by the manufacturer's submission (MS) accurately reflects this licence. The combination of pertuzumab with trastuzumab and docetaxel is compared with trastuzumab and docetaxel, a relevant comparator in clinical practice and specified in the NICE scope. Outcomes addressed in the decision problem include overall survival (OS), progression-free survival (PFS), response rates, adverse events (AEs) and health-related quality of life (HRQoL). These outcomes are standard in this disease area and are appropriate.

1.3 Summary of clinical effectiveness evidence submitted by the manufacturer

Only one trial (CLEOPATRA) was identified for inclusion in the systematic review which compared pertuzumab + trastuzumab + docetaxel (pertuzumab arm) to a control arm who received placebo + trastuzumab + docetaxel (control arm). This is an on-going phase III, randomised, double-blind, placebo-controlled, international, multicentre clinical trial, designed to evaluate efficacy and safety in 808 patients with previously untreated HER2+ metastatic breast cancer (MBC).

Progression-free survival (PFS) was measured both centrally by an independent review facility (IRF) and by local investigators. For the primary outcome, IRF assessed PFS after a median follow-up of 19 months (first data-cut, May 2011), an improvement of 6.1 months was measured in patients in the pertuzumab arm compared with the control arm (18.5 months vs 12.4 months, hazard ratio [HR] 0.62, 95% CI: 0.51 to 0.75). A similar finding was reported for local investigator assessed PFS at both the

first data-cut (18.5 months vs 12.4 months, HR 0.65, 95% CI: 0.54 to 0.78) and the second data-cut (May 2012) after a median follow up of 30 months (18.7 months vs 12.4 months, HR 0.69, 95% CI: 0.58 to 0.81). A significant improvement in OS (HR 0.66, 95% CI: 0.52 to 0.84) was reported at the second data-cut although the data are not fully mature (the median OS has not yet been reached in the pertuzumab arm).

Improvements in objective response rate (ORR) and duration of response were also reported (ORR: 80.2% vs 69.3%, according to IRF assessment; 77.4% vs 68.2% according to local assessment; duration of response: 87.6 weeks vs 54.1 weeks and 73.7 weeks vs 54.0 weeks according to IRF and local investigator assessment, respectively). No differences between treatment arms in terms of health-related quality of life were reported (HRQoL).

No new safety concerns were identified. The most common AEs in both arms were alopecia, diarrhoea, neutropenia, nausea and fatigue. A slightly higher incidence of cardiac events were reported in the control group. Other AEs reported (in particular diarrhoea, neutropenia, and mucositis) appear to be exacerbated by treatment with docetaxel and when this drug is stopped, there is little difference in terms of the incidence of AEs between patients treated with pertuzumab + trastuzumab and those treated with trastuzumab alone.

Evidence for trastuzumab + paclitaxel as a comparator was provided through a descriptive indirect comparison of two trials. These trials employed trastuzumab in combination with a taxane (docetaxel or with paclitaxel) vs a taxane alone. Data on PFS, OS and ORR from each of the trial arms are compared. This indirect comparison suggests that regimens containing trastuzumab and a taxane are superior to those of a taxane alone and of the four regimens, trastuzumab + docetaxel may be the most efficacious. Evidence comparing taxane monotherapies is presented from a trial in the adjuvant setting. This reports a similar effect for disease-free survival for 3-weekly docetaxel (HR 1.23, 95% CI: 1.00 to 1.52) and weekly paclitaxel (HR 1.27, 95% CI: 1.03 to 1.57).

1.4 Summary of the ERG's critique of clinical effectiveness evidence submitted

The CLEOPATRA trial is of good methodological quality with minimum risk of bias. The population in the study reflects people who would normally be eligible for trastuzumab-based treatment outside of the clinical trial setting, although it is noted that a greater proportion of patients are trastuzumab naïve than would now be expected in clinical practice.

Indirect evidence from two trials comparing trastuzumab + taxane regimens could be described as a 'naïve indirect comparison'. These comparisons have been criticised for discarding the within trial comparison, increasing the risk of bias and presenting estimates without a degree of uncertainty (e.g.

confidence intervals) Differences also exist in terms of the patient populations of the two trials. A head-to-head comparison is presented only for taxane monotherapy, from a study conducted in the adjuvant setting. In addition, it used taxane monotherapies so it is unclear how the addition of trastuzumab would affect the results. No safety data are presented by the manufacturer for these trials.

1.5 Summary of cost-effectiveness submitted evidence by the manufacturer

The manufacturer developed a *de novo* economic model. The model is constructed in Microsoft Excel and structured using three patient health states (PFS (stable disease), progressed disease and death). Variants of this model structure have been used in the modelling of metastatic oncology for a number of NICE STAs. The model population is based on the participants enrolled in the CLEOPATRA trial. In the base case, exponential survival models have been appended to Kaplan-Meier data to allow PFS and OS to be forecast for a period of 25 years and the perspective is that of the UK NHS. Resource use, costs and utilities are estimated based on information from trial data and published sources.

The base-case incremental cost-effectiveness ratio (ICER) results generated by the manufacturer's model show the ICERs for the target population are [redacted] per quality adjusted life year (QALY) gained and [redacted] per life-year gained. The manufacturer carried out a wide range of deterministic sensitivity analyses. These generated ICERs that ranged from [redacted] to [redacted] per QALY gained. The manufacturer's probabilistic sensitivity analyses (PSA) suggests 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.

1.6 Summary of the ERG's critique of cost-effectiveness evidence submitted

The economic model is logically structured and implemented competently with adequate annotation provided to allow most features to be readily understood. The manufacturer chose not to provide selected data requested as part of the clarification process implying that the ERG were exceeding their brief. This report provides the ERG's response to this with an explanation of why the data were requested and needed to complete their critique of the submitted evidence. In the absence of the requested information the ERG has been unable to offer alternative projections of the PFS, OS, time to off treatment (TTOT) and post progression survival (PPS) trial results as the currently available data suffer from systematic bias. The manufacturer did provide additional detail on conversations held between themselves and the regulator in relation to subgroups, and the additional time-to-event information requested for subgroups, albeit not using the method specified. This report is therefore able to discuss issues relating to the projection of PFS, OS and TTOT in broad terms, but is unable to provide the Appraisal Committee with fully detailed economic sensitivity analyses in relation to these central questions.

The ERG has proposed a number of model amendments. The three cost and utility changes have only a minor impact. However, changing the method of projecting OS [redacted] has a sizeable impact. It has not been possible to implement accurate survival estimates due to the limitation of the trial data available to the ERG. However, the use of long-term mortality trends from the Munich Registry data provides a realistic scenario [redacted]

Overall, the ERG considers that a revised ICER of £[redacted] per QALY gained best reflects the cost-effectiveness of pertuzumab use in this population.

1.6.1 Strengths

The clinical evidence is derived from a well conducted randomised controlled trial (RCT) (CLEOPATRA) that compares the intervention of interest (pertuzumab in combination with trastuzumab and docetaxel) to a relevant comparator of interest (placebo with trastuzumab and docetaxel). The population of patients included in CLEOPATRA is the same group of patients who are specified in the decision problem and for which pertuzumab has received a marketing licence from the European Commission.

1.6.2 Weaknesses and areas of uncertainty

The majority of patients included in CLEOPATRA were trastuzumab naïve whereas, in clinical practice today, the majority of patients are likely to have received trastuzumab therapy in the early breast cancer setting. It is therefore unclear if the findings of CLEOPATRA would be replicated in current practice. A subgroup analysis of a small group of patients (n=88) who had previously received trastuzumab was carried out at the first data-cut. This analysis reported that, for these patients, the HRs for PFS and OS are similar to those for the whole trial population.

Paclitaxel is used as an alternative to docetaxel in clinical practice. There is no direct evidence of the efficacy of pertuzumab in combination with trastuzumab and paclitaxel. The manufacturer provided indirect evidence in an attempt to demonstrate that docetaxel is at least as efficacious as paclitaxel when used in combination with trastuzumab.

Given the current available data it is not possible to estimate the absolute difference in median OS between patients treated in the pertuzumab arm and those in the control arm because the data are too immature (the median OS has not yet been reached in the pertuzumab arm).

1.6.3 Overall conclusions

The currently available clinical data indicates that the addition of pertuzumab to the treatment regimen of trastuzumab and docetaxel in this patient population provides improved PFS. Overall survival data are not mature and modelling of the currently available data is limited.

The manufacturer presents a base–case ICER of [redacted] per QALY gained. The evidence presented in the MS includes a PSA that demonstrates that pertuzumab compared with control has a 0% probability of being cost-effective at a willingness-to-pay of £30,000 per QALY gained.

Analysis of the trial data show that [redacted], unlike the estimates given in the manufacturer's base case. When this anomaly is corrected, the estimated ICER increases substantially. Model amendments made by the ERG (predominately related to OS) provide a revised ICER of £[redacted] per QALY gained, which best reflects the cost-effectiveness of pertuzumab use in this population.

2 BACKGROUND

2.1 Critique of manufacturer's description of underlying health problem

The context section of the MS[1] (Section 2), appropriately presents the key issues relating to human epidermal growth factor receptor 2-positive (HER2+) metastatic breast cancer (MBC). Highlighting that breast cancer is the most common malignancy affecting women in the UK,[2] key issues in relation to epidemiology and prognosis taken from the MS[1] (p17-19) are summarised in Box 1.

Box 1 Epidemiology and prognosis of patients with MBC

Epidemiology

- Approximately 50,000 people were diagnosed with breast cancer in the UK in 2010, of which 99% were women[2]
- Around 25% of patients with breast cancer have MBC[3]
- HER2+ disease is present in approximately 23% of people with MBC[4]
- People with HER2+ breast cancer are approximately five years younger than the general breast cancer population[5,6]

Prognosis:

- MBC remains largely incurable, with the majority of people dying due to their disease. Without targeted therapy, HER2+ disease is associated with poor survival[7]
- HER2+ MBC is associated with aggressive disease, higher rates of recurrence, shorter disease-free survival and shorter overall survival compared with tumours that do not overexpress HER2[8-14]

2.2 Critique of manufacturer's overview of current service provision

The manufacturer states that there is minimal variation or uncertainty about best practice in the treatment of patients with HER2+ MBC. The ERG agrees that based on NICE guidance,[15,16] trastuzumab in combination with chemotherapy (docetaxel or paclitaxel) is the standard first line treatment of patients with HER2+ MBC. According to clinical advice received by the ERG, the choice of chemotherapy to some extent depends on the patient's health status. Three-weekly docetaxel is generally preferred since fewer hospital visits are necessary. However, a weekly paclitaxel regimen may be more suitable for patients who are unable to tolerate the AEs associated with the docetaxel regimen.

The manufacturer argues that despite recent advances in the treatment of HER2+ MBC, including the proven efficacy of trastuzumab and chemotherapy,[17] there still exists a significant need for new treatments that can increase response rates. Pertuzumab is stated to constitute a step-change in treatment since by targeting HER2 differently to trastuzumab, the combination of the two drugs offers a comprehensive HER2 blockade. The manufacturer estimates that if approved, just over 2,000 patients in England and Wales would be eligible each year to receive pertuzumab in combination with

trastuzumab and docetaxel for first line treatment of HER2+ MBC, i.e. around 20% of all patients with breast cancer and approximately 90% of all patients with HER2+ MBC.

The ERG notes that pertuzumab has no other licensed indications. Therefore, if approved, these would be the only patients in the UK (outside of any clinical trials) receiving pertuzumab.

3 CRITIQUE OF MANUFACTURER'S DEFINITION OF DECISION PROBLEM

Table 1 displays the decision problem presented in the MS.[1] (Section 5, Table 5, p27) Each parameter is discussed in more detail in the text following the table.

Table 1 Decision problem specified by NICE and addressed in the manufacturer's submission[1]

Parameter	Final scope issued by NICE	Decision problem addressed in the manufacturer's submission
Intervention	Pertuzumab (in combination with trastuzumab and docetaxel)	As per NICE scope
Population	Adults with HER2+ metastatic or locally recurrent, unresectable breast cancer who have not previously received chemotherapy or HER2 directed treatment for metastatic disease or whose disease has recurred after adjuvant therapy	As per NICE scope
Comparator(s)	Trastuzumab in combination with a taxane (docetaxel or paclitaxel)	As per NICE scope
Outcomes	Progression free survival Overall survival Response rate Adverse effects of treatment Health-related quality of life	As per NICE scope
Economic analysis	The cost-effectiveness of treatments should be expressed in incremental cost per QALY The time horizon should be sufficiently long to reflect differences in costs or outcomes between the technologies. Costs will be considered from an NHS and PSS perspective.	As per NICE scope
Subgroups to be considered	No subgroups identified	As per NICE scope
Special considerations including equity or equality issues	No potential equity or equality issues identified	As per NICE scope

QALY, Quality adjusted life year; PSS, Personal Social Services

3.1 Population

The patient population addressed by the MS[1] accurately reflects that of the NICE scope and the EMA marketing authorisation for pertuzumab, namely 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" (section 1.3, p13 of MS[1]). While patients should not have received previous anti-HER2 therapy or chemotherapy for their metastatic disease, the NICE scope stipulates that disease could have recurred after adjuvant therapy. In clinical practice, the majority of patients today are likely to have received anti-HER2 therapy and chemotherapy in the adjuvant setting for the treatment of early breast cancer.

Patients pre-treated in this way were enrolled into the CLEOPATRA[18] trial from which the majority of the evidence in the MS[1] is derived. However, at the time the trial was conducted, patients pre-treated with trastuzumab constituted only a minority of patients (10.9%). Today, in clinical practice in the UK, the proportion of patients pre-treated with trastuzumab would be expected to be much greater since trastuzumab is now the standard of care for patients with HER2+ early breast cancer, as recommended by NICE.[19]

3.2 Intervention

Pertuzumab has received marketing authorisation for the patient population addressed in this submission in combination with trastuzumab and docetaxel (hereafter referred to as pertuzumab). The intervention specified in the NICE scope is the same as the intervention provided in the CLEOPATRA[18] trial from which the majority of the evidence was derived.[18] However, the ERG notes that in this trial, the median number of cycles of docetaxel (either as part of the intervention or control) was eight. According to advice received by the ERG, docetaxel is rarely given to patients for more than six cycles in clinical practice in the UK. The manufacturer also notes that protocols in many tertiary centres in the UK recommend a maximum of six cycles, with eight only being recommended in exceptional cases (MS,[1] p101).

3.3 Comparators

Trastuzumab in combination with a taxane (docetaxel or paclitaxel) was the comparator specified in the NICE scope. Trastuzumab in combination with docetaxel plus a placebo (hereafter referred to as control) was the comparator in the CLEOPATRA[18] trial from which the majority of the evidence in the MS[1] is derived. Trastuzumab in combination with paclitaxel was also used as a comparator in the economic model. The ERG agrees that trastuzumab in combination with any taxane is the appropriate comparator as used in clinical practice. The ERG has received clinical advice that indicates that trastuzumab in combination with docetaxel is likely to be the preferred regimen. The exception to this could be in cases where it is felt that weekly paclitaxel would be better tolerated than three-weekly docetaxel.

3.4 Outcomes

The outcomes listed in the final scope are OS, PFS, response rates, AEs and health-related quality of life (HRQoL) and all are included in the MS.[1] These outcomes are standard in this disease area and are therefore appropriate. The ERG notes that although OS is considered to be the most robust outcome in trials of cancer treatments, very few trials of treatments for patients with MBC employ OS as the primary endpoint. The CLEOPATRA[18] trial from which the majority of the evidence is derived, specified PFS as its primary outcome. However, it is also powered to detect differences in OS between trial arms after 385 events.[1]

3.5 Economic analysis

As specified in the final NICE scope, the cost-effectiveness of treatments was expressed 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 (PSS) perspective.

3.6 Subgroups

A number of subgroup analyses were conducted in the CLEOPATRA[18] trial. No subgroups are modelled for the cost-effectiveness analyses.

4 CLINICAL EFFECTIVENESS

Table 2 provides an outline of the manufacturer's approach in terms of deriving evidence for the clinical effectiveness of adding pertuzumab to combination treatment with trastuzumab and docetaxel and its location within the MS.[1] The purpose of the table is to signpost the reader to the areas of clinical information within the MS.[1]

Table 2 Location of clinical information in the manufacturer's submission[1]

Key information	Page number	Key tables/figures
Description of the technology	12 to 17	
Context	17 to 23	
Innovation	24 to 25	
Statement of decision problem	27	Table 5
Literature search	29, 178 to 181	
Study selection	29 to 30, 181 to 185	Figure 2
Quality assessment of key trial	57 to 58	Table 14
Study characteristics of key trial	31, 35 to 37	Table 7
Participant characteristics of key trial	37 to 41	Table 10
Outcomes measured in key trial	42 to 45	
Statistical analysis and definition of study groups	45 to 54	Figure 4
Clinical efficacy from key trial	59 to 75	Table 15
Safety	54 to 55, 80 to 90	Table 17 and Table 18
Indirect clinical effectiveness evidence	76 to 78	
Interpretation of all above clinical evidence	90 to 102	

4.1 Critique of the methods of review(s)

A systematic review was undertaken in order to identify all direct evidence relevant to the decision problem. It was not possible to conduct a meta-analysis because only one trial was identified.[18] It is not clear if the approach taken to derive the indirect evidence for the relative efficacy of docetaxel and paclitaxel in combination with trastuzumab was conducted systematically.

4.1.1 Searches

Direct evidence

The MS[1] describes the search strategies for the systematic review. Electronic databases were searched on 13 or 14 February 2013 using terms which included (but were not limited to) 'pertuzumab', 'trastuzumab' and 'metastatic breast cancer'. Databases included: MEDLINE, EMBASE, EMBASE Alert, BIOSIS Previews and the Cochrane Library. In addition, the manufacturer searched conference

abstracts from the annual meetings of the American Society of Clinical Oncology 2007 to 2012 and the 2012 San Antonio Breast Cancer Symposium. The ERG believes the search strategy employed was sufficient to identify relevant studies. To confirm this, the ERG also conducted its own searches and did not identify any additional studies although two additional publications of the included trial were identified, published after the original search conducted by the manufacturer.[20,21]

In addition to the main publication which presented trial results,[18] the manufacturer states its search identified a further five full-text publications of the same trial. The full citations for these publications are not provided. However, the manufacturer does present a further nine citations for the same trial, only one[22] of which is a full published paper, the others all being conference presentations.[23-30]

Indirect evidence

It is not clear how the manufacturer identified the studies cited for the indirect evidence. For this reason, the ERG conducted its own searches of Ovid MEDLINE and Ovid OLDMEDLINE 1946 to present with Daily Update (conducted on 21 May 2013) and EMBASE (conducted on 29 May 2013). No additional relevant trials were identified by the searches.

4.1.2 Eligibility criteria

Direct clinical evidence

The inclusion and exclusion criteria are presented in section 10.2.6 of the MS[1] and reproduced below in Table 3. The criteria appear to be appropriate to the decision problem.

Table 3 Eligibility criteria used in manufacturer's search strategy

	Clinical effectiveness
Inclusion criteria	Published papers or abstracts which evaluated the following were included: • Pertuzumab had to be the major focus of the study, in order to eliminate references which merely mentioned pertuzumab as part of a discussion of treatments for MBC or other cancers • Metastatic breast cancer had to be the major focus of the study, in order to eliminate papers addressing the use of pertuzumab in other breast cancers e.g. Inflammatory breast cancer, or in other settings e.g. early breast cancer • Studies in which patients receiving pertuzumab therapy in combination with trastuzumab and docetaxel, to be consistent with the anticipated pertuzumab licence. Data addressing the efficacy of pertuzumab in combination with agents other than trastuzumab and docetaxel are not in line with this submission • Studies in which patients received study therapy for the first-line treatment of MBC, to be consistent with the anticipated pertuzumab licence • Efficacy endpoints associated with the treatment of MBC were the focus for the data ie. Progression-free survival, overall survival and response rates • Clinical trial data, not case reports, retrospective reviews, etc. • Documents relating to humans – since work in animal models is not relevant to this submission
Exclusion criteria	• References which were not randomised, controlled trials • Studies where pertuzumab was not included • Studies which were in non-relevant populations i.e. Early breast cancer, other cancers. • Studies which included other agents in combination with pertuzumab which are not relevant to this submission.

MBC=metastatic breast cancer

Indirect evidence

No eligibility criteria are specified for the indirect evidence.

4.1.3 Data extraction

Direct evidence

Only one trial (CLEOPATRA[18]) was included in the systematic review and the majority of relevant data appear to be presented for this trial with the exception of protocol violations, statistical tests for interaction for subgroup analyses, and additional data on AEs and health related quality of life (HRQoL) outcomes subsequently requested by the ERG in its clarification letter. Information on therapy received following disease progression was also omitted from the MS[1] but was subsequently published by Swain et al 2013.[20]

Indirect evidence

Relevant efficacy data were presented for the trials providing indirect evidence comparing docetaxel and paclitaxel and included information on treatment setting (early, advanced or MBC) was also provided.

4.1.4 Risk of bias

Direct evidence

The manufacturer conducted an assessment of risk of bias for the CLEOPATRA[18] trial. It was conducted using a checklist recommended by the Cochrane Collaboration.[31] The ERG agrees this is an appropriate tool for assessing risk of bias and with the conclusions regarding the high quality of the trial.

Indirect evidence

The trials included in the indirect evidence synthesis were not assessed for their risk of bias by the manufacturer. While this may have been informative, the ERG does not believe this was necessary given the supportive role of this evidence.

4.1.5 Evidence synthesis

Direct evidence

Because only one trial (CLEOPATRA[18]) was identified by the systematic review, only data relating to one trial was presented in the MS.[1]

Indirect evidence

Two trials[17,32] comparing trastuzumab + a taxane in the metastatic setting were compared with each other. It was not possible to compare these using a standard statistical method and so this descriptive (or naïve) indirect comparison should only be considered exploratory. A further trial[33] comparing different regimens of docetaxel and paclitaxel in the adjuvant setting was also included and evidence from this trial was presented separately.

4.2 Critique of trials of the technology of interest

4.2.1 Identified studies

One RCT[18] was included in the systematic review. This trial, known as CLEOPATRA,[18] is still on-going and OS data are not mature. Efficacy and AE data from the first data-cut (May 2011) were presented in a published paper in 2012[18] with updated OS data from the second data-cut (May 2012) published on 18 April 2013.[20] Final OS data will be presented after approximately 385 deaths (expected to be mid to late 2014).

In addition to the main published paper for CLEOPATRA,[18] the manufacturer cited eight conference citations [23-30] presenting trial evidence. Data are also available from two additional publications of focusing on OS[20] and cardiotoxicity[21] and from the EPAR,[34] The majority of the evidence from these sources was presented in the MS.[1] Additional data considered relevant by the ERG were requested from the manufacturer, and were provided in the 2011 and 2012 Clinical Study Reports (CSRs)[35,36] and in the manufacturer's response to the clarification letter. Unless explicitly specified, reference to the CSR in this report refers to the 2012 CSR.[36]

As only one appropriate RCT was identified, the manufacturer states that it was not possible to perform a meta-analysis. The ERG agrees that this is appropriate.

4.2.2 Trial characteristics

CLEOPATRA[18] is a phase III, randomised, double-blind, placebo-controlled, international, multicentre clinical trial, designed to evaluate the efficacy and safety of pertuzumab + trastuzumab + docetaxel (pertuzumab arm) compared with placebo + trastuzumab + docetaxel (control arm) in people with previously untreated HER2+ MBC. The key trial characteristics are summarised in Table 4.

A number of endpoints were specified in the protocol and reported in the MS.[1] The pre-specified primary endpoint of the study was PFS based on tumour assessments by an IRF. Local investigator assessed PFS was also measured. Both outcomes were reported after a median follow-up of 19 months (first data-cut, May 2011) and 30 months (second data-cut, May 2012). A number of other pre-specified secondary outcomes including OS, objective response rate (ORR), duration of objective response, HRQoL (reported as time to symptom progression as measured using the Functional Assessment of Cancer Therapy-Breast [FACT-B] Version 4 questionnaire) and safety data, were also reported at both these time points.

Table 4 CLEOPATRA[18] trial characteristics

Characteristic	Description
Size	808 patients were enrolled
Location	International (204 centres in 25 countries)
Design	Randomised, double-blind, placebo-controlled, phase III trial
Intervention	Pertuzumab + trastuzumab + docetaxel (n=402) • Pertuzumab: loading dose of 840mg/kg IV infusion, followed by 420mg/kg IV every 3 weeks (q3w) • Trastuzumab: loading dose of 8mg/kg IV infusion, followed by 6mg/kg IV q3w • Docetaxel dose of 75mg/m^2 IV infusion q3w for at least six cycles[a]
Comparator	Placebo + trastuzumab + docetaxel (n=406) • Pertuzumab placebo: IV infusion (q3w) • Trastuzumab: loading dose of 8mg/kg IV infusion, followed by 6mg/kg IV infusion q3w • Docetaxel dose of 75mg/m^2 IV infusion q3w for at least six cycles[a]
Duration	Treatment was given until investigator assessed radiographic or clinical progressive disease (or unacceptable toxicity or withdrawal of patient consent) Participants were withdrawn from the study if pertuzumab or placebo and/or trastuzumab were permanently discontinued or withheld for more than two cycles of treatment. If docetaxel was permanently discontinued for unacceptable toxicity, withdrawal from the study was not required. Dose reductions were not permitted for placebo, pertuzumab, or trastuzumab
Method of randomisation	Randomisation in a 1:1 ratio and stratified with the following baseline factors: • Geographic region (Asia, Europe, North America, or South America) • Prior treatment status (prior adjuvant or neoadjuvant chemotherapy vs none)
Method of blinding (care provider, patient and outcome assessor)	Investigators, site staff, and monitors remain blinded until the end of the study, except in cases of suspected, unexpected, serious adverse events considered related to study medication
Method of allocation	Patient identification numbers were allocated sequentially in the order in which the participants were enrolled using an Interactive Voice Response System
Primary endpoint	Progression-free survival (IRF, first data-cut)[b]
Secondary endpoints	Progression-free survival (local investigator- assessed, first data-cut and second data-cut)[b] Overall survival (first data-cut, second data-cut) Objective response rate (first data-cut)[b] Duration of objective response (first data-cut) Health related quality of life – time to symptom progression (first data-cut and second data-cut) Safety parameters (first data-cut and second data-cut): • Incidence of CHF and asymptomatic LVEF events • LVEF measurements over the course of the study • Incidence and severity of AEs and serious adverse events (SAEs) • Laboratory test abnormalities
Duration of follow-up	First data-cut (May 2011) – median follow-up of 19 months Second data-cut (May 2012) – median follow-up of 30 months

CHF-Congestive Heart Failure; IRF=independent review facility; LVEF-Left ventricular ejection fraction
[a] may be increased to 100mg/m^2 at the investigators discretion
[b] Using RECIST criteria

Detailed inclusion and exclusion criteria are presented in the MS[1] (Table 8 [p37] and Table 9 [p38]) and are not presented here. Briefly, patients with HER2+ locally advanced or MBC and aged 18 years or older, who had not received prior chemotherapy and/or biologic therapy for their metastatic disease, were eligible whether they had measurable or non-measurable disease. However, participants were allowed prior adjuvant therapy (including chemotherapy) and/or one line of hormonal therapy for MBC. Patients with stage IV disease at initial presentation or at disease progression occurring at least 12 months after neoadjuvant or adjuvant therapy were included. Trastuzumab and/or taxanes were acceptable neoadjuvant or adjuvant treatments. The manufacturer argues that: "The population for the study reflects people who would normally be eligible for trastuzumab-based treatment outside of the clinical trial setting." (p37 of the MS[1]) The ERG notes that patients must also have a left ventricular ejection fraction (LVEF) of 50% or more at baseline (determined by echocardiography [ECHO] or multiplegated acquisition scanning [MUGA], ECHO being the preferred method), thus excluding patients with greatest risk of cardiotoxicity. The ERG agrees that the patient population broadly reflects patients currently considered for trastuzumab in routine clinical practice. Patients were also required to have Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1. Again this broadly reflects clinical practice as patients with worse ECOG PS are unlikely to be considered for treatment with docetaxel.

4.2.3 Participant characteristics

Table 5 presents data from the MS[1] related to patient baseline characteristics by treatment group. Characteristics were well balanced across groups. The only baseline characteristic for which the treatment arms were imbalanced was baseline ECOG PS with fewer participants in the control arm with an ECOG PS of 0 (248 people [61.1%] compared with 274 people [68.2%] in the pertuzumab arm).

The population of the study reflects people who would normally be eligible for trastuzumab-based treatment outside of the clinical trial setting, although it is noted that a greater proportion of patients are trastuzumab naïve than would now be expected in clinical practice and a relatively large proportion of patients were from Asia (32.3%) who on average are smaller and lighter than patients from Europe and the UK (which is relevant in relation to doses of docetaxel which are based on body surface area [BSA]; this is discussed in section 5.2.3). Just over a third of patients were enrolled in Europe (37.9%) which included patients from the UK (but it is not stated in the MS[1] how many). Only two men were enrolled in the trial, both in the control arm. Patients had a median age of 54 years, with over 80% of people in both arms aged less than 65 years (342 people [85.1%] in the pertuzumab arm and 339 people [83.5%] in the control arm). The majority of women were post-menopausal (63.5%). The manufacturer notes that the age of this recruited population is comparable to the ages of participants recruited in previous trastuzumab studies[17,32] and younger than the general breast cancer

population.[5,6] The ERG further notes that as the choice to administer docetaxel to some extent dependent on a patient's health status (a lower ECOG PS being common), then so it is likely that patients who would be considered for pertuzumab would also be younger than the general breast cancer population, as was the case in CLEOPATRA.[18]

Table 5 Baseline characteristics in CLEOPATRA[18] reported in the manufacturer's submission[1]

Baseline characteristic	Pertuzumab[a] (n=402)[a]	Control[b] (n=406)
Median (range) age (years)	54.0 (22-82)	54.0 (27-89)
Female	402 (100.0%)	404 (99.5%)
Race or ethnic group		
Asian	128 (31.8%)	133 (32.8%)
Black	10 (2.5%)	20 (4.9%)
White	345 (60.9%)	235 (57.9%)
Other	19 (4.7%)	18 (4.4%)
Region		
Asia	125 (31.1%)	128 (31.5%)
Europe	154 (38.3%)	152 (37.4%)
North America	67 (16.7%)	68 (16.7%)
South America	56 (13.9%)	58 (14.3%)
ECOG performance status		
0	274 (68.2%)	248 (61.1%)
1	125 (31.1%)	157 (38.7%)
≥2	3 (0.7%)	1 (0.2%)
Disease type at screening		
Non-visceral	88 (21.9%)	90 (22.2%)
Visceral	314 (78.1%)	316 (77.8%)
Hormone receptor status		
ER-positive, PgR-positive or both	189 (47.0%)	199 (49.0%)
ER-negative, PgR-negative	212 (52.7%)	196 (48.3%)
Unknown	1 (0.2%)	11 (2.7%)
HER2 status, as assessed by IHC		
0 or 1+	4 (1.0%)	2 (0.5%)
2+	47 (11.7%)	32 (7.9%)
3+	350 (87.1%)	371 (91.4%)
Data not available	1 (0.2%)	1 (0.2%)
HER2 status, assessed by FISH		
Positive	384 (95.5%)	383 (94.3%)
Negative	1 (0.2%)	4 (1.0%)
Data not available	17 (4.2%)	19 (4.7%)
Prior adjuvant or neoadjuvant chemotherapy		
No	218 (54.2%)	214 (52.7%)
Yes	184 (45.8%)	192 (47.3%)
Anthracycline	150 (37.3%)	164 (40.4%)
Hormone	106 (26.4%)	97 (23.9%)
Taxane	91 (22.6%)	94 (23.2%)
Trastuzumab	47 (11.7%)	41 (10.1%)

ECOG= ECOG=Eastern Cooperative Oncology Group; ER=oestrogen receptor; FISH=fluorescence in situ hybridization; HER2= human epidermal growth factor 2; IHC=immunohistochemistry; PgR=progesterone receptor
[a] Pertuzumab=pertuzumab + trastuzumab + docetaxel
[b] Control=placebo + trastuzumab + docetaxel

4.2.4 Statistical approach

Sample size calculation

The trial protocol states that the sample size calculation was based on OS, a secondary outcome. However, in the MS[1] and published paper for CLEOPATRA[18] it states that the sample size was based on PFS. The ERG did not ask for clarification on this point.

The median OS in the control arm was assumed to be 36 months and OS was assumed to be exponentially distributed. It was hypothesised that pertuzumab would provide a clinically meaningful 33% improvement in OS. In order to detect a HR of 0.75 with 80% power, using a log rank test and a Lan-Demets alpha-spending function with an O'Brien-Fleming type boundary at two-sided 5% level of significance, 385 OS events were required. In order to observe these events it was estimated that 800 patients were needed over an enrolment period of 26.5 months.

Assuming that PFS is exponentially distributed with a median of 10.5 months in the control arm, it was estimated that 381 IRF assessed PFS events, corresponding to approximately 448 local investigator assessed events, will have occurred when 50% of the required deaths (193 deaths) were reached. It was hypothesised that pertuzumab would provide a clinically meaningful 33% improvement in PFS with 80% power (or 40% improvement with 90% power), using a log rank test at two-sided 5% level of significance.

The ERG is unclear as to why the sample size appears to be based on OS, a secondary outcome, rather than PFS which is the primary outcome. However, the protocol states that since both PFS and OS analyses are event-driven, and to avoid a prolonged waiting period after final PFS analysis for OS data to reach the required number of events, the trial is designed to enrol a sufficient number of patients such that approximately 50% of the required deaths will have been observed at the time of final PFS analysis. The ERG considers it an advantage of the trial that it is powered for OS given the importance of this outcome.

Efficacy analyses

As stated in the trial protocol, analysis of PFS, OS and time to symptom progression was performed on the full analysis set, consisting of all randomised patients. Analyses followed the intention-to-treat principle, analysing patients according to the treatment and stratum they were allocated to at randomisation. For objective response, only patients with measurable disease at baseline were included in the analysis and for duration of response, only responders were included in the analysis. The statistical methods that were used to analyse the pre-specified efficacy outcomes in the trial and which are reported in the MS[1] are presented in Table 6. The ERG is generally satisfied that these methods of analysis are appropriate.

Table 6 Efficacy analyses reported in the manufacturer's submission[1a]

Outcome	Definition	Method of analysis
Progression-free survival (PFS)	Time from randomisation to the date of the first documented radiographic disease progression or death due to any cause	The distribution of PFS was compared between two treatment groups using a stratified log-rank test (by prior treatment status and region). The Kaplan-Meier approach was used to estimate median PFS for each treatment arm. The stratified Cox regression model was used to estimate the HR of PFS along with the 95% CI PFS was censored at the last IRF reviewed evaluable tumour assessment (or, if no tumour assessments are performed after the baseline visit, at the time of randomisation plus 1 day) For investigator assessed PFS, analysis was the same as above but PFS was censored at the time of the last investigator tumour assessment (or, if no tumour assessments are performed after the baseline visit, at the time of randomisation plus 1 day)
Overall survival (OS)	Time from the date of randomisation to the date of death due to any cause	The distribution of OS was compared between two treatment groups using a stratified log-rank test (by prior treatment status and region). The Kaplan-Meier approach was used to estimate median OS for each treatment arm. The stratified Cox regression model was used to estimate to estimate the HR of OS along with the 95% CI OS was censored at the last known alive date. Patients with no post-baseline information will be censored at the time of randomisation plus 1 day
Objective response rate (ORR)	Proportion of patients with complete response (CR) or partial response (PR) on two consecutive occasions >=4 weeks apart and determined by the IRF	Proportions of subjects with ORR were presented by treatment group along with 95% CIs. The difference in objective response rate was also provided with 95% CIs. The Cochran-Mantel Haenszel chi-square test (strata based on the randomisation stratification factors) was used to compare the two treatment groups. An unadjusted Fisher's exact test result will also be provided as a sensitivity analysis. Analysis of ORR was based on IRF assessments
Duration of response (DoR)	Period from the date of initial confirmed PR or CR until the date of progressive disease or death from any cause, was also measured at the first data-cut	DoR was summarised by treatment group. Distribution of DoR was estimated using the Kaplan-Meier method and the median response duration was presented along with 95% CI. Comparisons between treatment arms using the unstratified log-rank test and estimation of HR using Cox regression was also made The method for handling censoring is the same as that described for the primary endpoint. Analysis of duration of objective response was based on IRF assessments
Time to symptom progression	Time from randomisation to the first symptom progression in the TOI-PFB[b]	The distribution of time to symptom progression was compared between two treatment groups using a stratified log-rank test (by prior treatment status and region). The Kaplan-Meier approach was used to estimate median time to symptom progression for each treatment arm. The stratified Cox regression model was used to estimate to estimate the HR of time to symptom progression along with the 95% CI Data for patients who do not have an observed symptom progression was censored at the last observed TOI-PFB assessment date. If baseline TOI-PFB assessment was unavailable, or if there was no post-baseline TOI-PFB assessment performed, data was censored at the time of randomisation plus 1 day

CI=confidence interval; CR=complete response; DoR=duration of response; FACT-B= Functional Assessment of Cancer Therapy-Breast; IRF= independent review facility; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PR=partial response; TOI-PFB= Trial Outcomes Index-Physical/Functional/Breast

[a] As described in the trial protocol[37]

[b] The TOI-PFB is a 24-item subscale generated using three subsections from the FACT-B questionnaire: Physical Well-being, Functional Well-being and Additional Concerns. A decrease of five points is considered clinically significant, and thus symptom progression. Analysis of time to symptom progression was deemed to be exploratory

As stated in the trial protocol, the fixed-sequence testing procedure of Westfall and Krishen[38] was used to adjust for multiple statistical testing of IRF assessed PFS, OS, ORR, and duration of response. The four variables were tested at an overall two-sided 5% significance level in the order specified. Overall survival was hierarchically tested in the following way: if the test for PFS was significant, OS would be tested for significance. If the test for OS yielded a significant result, the ORR endpoint would be tested. If the test for PFS was not found to be significant then the remaining endpoints would still be tested for significance, but the results would be deemed to be exploratory.

In addition to analyses conducted in Table 6, pre-specified biomarker analysis and post-hoc exploratory analyses of time to response and clinical benefit response (CBR) were conducted. The results of these analyses are not reported in the MS[1] but were reported in the 2011 CSR[35] and elsewhere.[23]

Sensitivity analyses

Sensitivity analyses of PFS were performed to address the impact of possible differences between investigator and IRF tumour assessment; censoring at the time of Next Anti-Cancer Therapy (NACT); IRF assessed PFS on treatment; potential bias introduced by varied tumour assessment intervals as a result of missing visit(s); timing of death – including all deaths as an event and patients stopping early due to toxicity. A sensitivity analysis to assess the impact of stratification on PFS was also performed where treatment groups were compared using an unstratified log-rank test and a HR (with associated 95% CI) was obtained using an unstratified Cox regression model. A number of further supportive analyses were also implemented.

Subgroup analyses

The following nine pre-specified subgroup analyses for PFS were described in the protocol:

- Prior treatment status (stratification factor)
- Region (stratification factor)
- Age (< 65 years and ≥ 65 years)
- Age (< 75 years and ≥ 75 years)
- Race (white, black, Asian and other)
- Disease type (visceral disease vs non-visceral disease)
- Immunohistochemistry (IHC) HER2 Status (3+)
- Fluorescence in situ hybridization (FISH) (positive)
- oestrogen receptor (ER)/ progesterone receptor (PgR) Status (ER- and PgR- vs ER+ and/or PgR+)

A further four exploratory subgroup analyses were described in the MS:[1]

- HER2 IHC 2+
- Baseline ECOG PS (0 vs 1+)

- People with prior neoadjuvant treatment, split into people who had received prior trastuzumab and people who had not received prior trastuzumab
- Docetaxel dose escalation to 100mg/m^2 (Yes vs No)

The ERG recognises that there are a large number of subgroups and this approach to analysis is not generally recommended as it increases the possibility of chance findings.

Safety population

The safety population consisted of all patients who received any amount of the study treatment and had at least one post-baseline safety assessment. Patients were analysed according to the treatment they actually received.

4.2.5 Risk of bias

The manufacturer conducted an assessment of the risk of bias using the universally accepted tool recommended by the Cochrane Collaboration.[31] The ERG conducted its own assessment of the risk of bias using the same tool (see Appendix 1) and reached the same conclusions as the manufacturer. However, one point to consider is that if a trial is designed to be double-blind, the presence of AEs related to a particular study drug always risks compromising the blinding. According to the manufacturer, blinding "was rigorously maintained even after the results of the primary efficacy analysis (May 2011) were known" (MS,[1], p96). Furthermore, it is argued that because AEs from both arms of the trial were similar, it is unlikely that investigators could have deduced to which arm a patient belonged. As reported in section 4.2.6, the estimates of PFS were remarkably similar, both in terms of relative and absolute effects, indicating that there is a low likelihood of bias.

4.2.6 Efficacy

Most of the efficacy outcomes are presented in the MS[1] (Table 15, page 62). Additional outcomes (including the same endpoint measured by IRF and local investigator assessment and at the first data-cut and second data-cut) were also presented in the MS.[1] However survival probabilities and their respective 95% CIs were not reported in the MS.[1]

Progression-free survival data are presented in Table 7. The primary analysis was based on IRF assessment; local investigator assessments were analysed to provide support. The ERG notes that both IRF assessed and local investigator analyses at the first data-cut achieved statistically significant results, strongly in favour of pertuzumab compared to control. At the second data-cut, only investigator assessed PFS was available since this was additional analysis after the final reporting of the primary endpoint of IRF assessed PFS at the first data-cut. The finding was almost identical to that reported at the first data-cut.

Overall survival data are also presented in Table 7. A trend towards improved survival was noted at the first data-cut. At the second data-cut, a statistically significant result for OS in favour of pertuzumab was reported although it should be stressed that the data are not yet mature. The MS[1] states that the majority of deaths in both arms were due to disease progression.

Table 7 Progression-free and overall survival reported in CLEOPATRA,[18] first data-cut, May 2011 and second data-cut, May 2012

Outcome	Pertuzumab[a]	Control[b]	Result between arms
PFS (IRF assessment, first data-cut)			
n	402	406	
No (%) people with event	191 (47.5)	242 (59.6)	HR 0.62 (95% CI: 0.51 to 0.75)
Median time to event (months)	18.5	12.4	p <0.0001
PFS (local assessment, first data-cut)[c]			
n	402	406	
No (%) people with event	[redacted]18.5	[redacted]12.4	HR 0.65 (95% CI: 0.54 to 0.78)
Median time to event (months)			
PFS (local assessment, second data-cut)			
n	402	406	
No (%) people with event	257 (63.9)	296 (72.9)	HR 0.69 (95% CI: 0.58 to 0.81)
Median time to event (months)	18.7	12.4	p <0.0001
OS (first data-cut)[d]			
n	402	406	
No (%) people who died	[redacted]not reached	[redacted]not reached	HR 0.64 (95% CI: 0.47 to 0.88)
Median time to event (months)			p=0.0053
OS (second data-cut)			
n	402	406	
No (%) people who died	113 (28.1)	154 (37.9)	HR 0.66 (95% CI: 0.52 to 0.84)
Median time to event (months)	not reached	37.6	p=0.0008

CI=confidence interval; HR=hazard ratio; IRF=independent review facility; OS=overall survival PFS=progression-free survival
[a] Pertuzumab=pertuzumab + trastuzumab + docetaxel
[b] Control=placebo + trastuzumab + docetaxel
[c] Data taken from Table 22 of 2011 Clinical Study Report [35]
[d] Data taken from p119 of 2011 Clinical Study Report [35]

It may be hypothesised that apparent improvements in OS arise from subsequent lines of treatment rather than from the intervention itself. However, the ERG notes that in the paper on OS published by Swain et al,[20] cytotoxic agents provided to patients who discontinued study treatment were similar in both treatment arms and that pertuzumab was not allowed in subsequent cancer treatment thus minimising the risk of any bias.

The ERG notes that the sensitivity analyses for PFS that are pre-specified in the protocol are reported in the CSR.[36] The results presented in the CSR[36] from the sensitivity analyses [redacted]

Exploratory univariate and multivariate Cox regression analyses were performed on the updated OS. It is reported that overall, the treatment effect remained consistent when adjusted for covariates in both the univariate and multivariate models, with the HR for the treatment effect ranging from 0.62 to 0.67. The exploratory Cox regression analyses reinforce the significant treatment effect observed in the updated OS analysis. In addition, the key covariates identified as potential prognostic factors remained consistent, compared to the analyses reported in the first data data-cut.

Objective response and duration of response, estimated using Kaplan-Meier methods, were only measured at the first data-cut where the ORR was considerably higher in the pertuzumab arm than the control arm. Duration of response was also considerably greater in the pertuzumab arm than the control arm. The findings from IRF and local investigator assessment were similar for both ORR and duration of response.

Table 8 Objective response and duration of response reported in CLEOPATRA,[18] first data-cut, May 2011

Outcome	Pertuzumab[a]	Control[b]	Result between arms
Objective response (IRF assessment)			
n	343	336	
Responders	275	233	
ORR (%)	80.2	69.3	10.8
95% CI for ORR (%)	(75.6 to 84.3)	(64.1 to 74.2)	(4.2 to 17.5) p=0.001
No (%) people with complete response	19 (5.5)	14 (4.2)	
No (%) people with partial response	256 (74.6)	219 (65.2)	
No (%) people with stable disease	50 (14.6)	70 (20.8)	
No (%) people with progressive disease	13 (3.8)	28 (8.3)	
Objective response (local assessment)[a]			
n	367	371	
Responders	284	253	p=0.0049, stratified analysis
ORR (%)	77.4	68.2	
95% CI for ORR (%)	Not reported	Not reported	
Duration of response (IRF assessment)			
n			
Median duration of response (weeks)	275	233	HR 0.66 (0.51 to 0.85)
95% CI for median	87.6	54.1	
	(71 to106)	(46 to 64)	
Duration of response (local assessment)[c]			
n	367	371	
Median duration of response (weeks)	73.7	54.0	HR 0.67 (0.52 to 0.85)
95% CI for median	Not reported	Not reported	

CI=confidence interval; HR=hazard ratio; IRF=independent review facility; ORR=objective response rate
[a] Pertuzumab=pertuzumab + trastuzumab + docetaxel
[b] Control=placebo + trastuzumab + docetaxel
[c] described as sensitivity analyses in the MS[1]

Regarding HRQoL, only females (n=806) were required to complete the FACT-B questionnaire after every three cycles of treatment. This resulted in 806 of the 808 ITT population included in the FACT-B analyses. It is reported that the compliance rate with completion of the FACT-B questionnaire was high, with at least 75% compliance observed beyond the first year within both treatment groups. No differences between treatment arms were reported in terms of time to symptom progression as measured by the 24-item FACT-B Trial Outcomes Index-Physical/Functional/Breast (TOI-PFB) subscale. Descriptive statistics of the individual item or other scored sub-scale scores of FACT-B data were not provided in the MS.[1] Descriptive statistics of the individual items of the FACT-B questionnaire were sent to the ERG in response to the clarification letter and are consistent with the findings reported for time to symptom progression.

Table 9 Health-related quality of life reported in CLEOPATRA,[18] first data-cut, May 2011

Outcome	Pertuzumab[a]	Control[b]	Result between arms
Symptom progression (TOI-PFB)			
n	402	404	HR 0.97 (95% CI: 0.81 to 1.16)
No (%) people reporting	239 (59.5)	229 (56.7)	
Median time to symptom progression (weeks)	18.4	18.3	

TOI-PFB=Trial Outcomes Index-Physical/Functional/Breast subscale
[a] Pertuzumab=pertuzumab + trastuzumab + docetaxel
[b] Control=placebo + trastuzumab + docetaxel

A summary of the mean change from baseline in TOI-PFB taken from the MS[1] is presented in Figure 1.

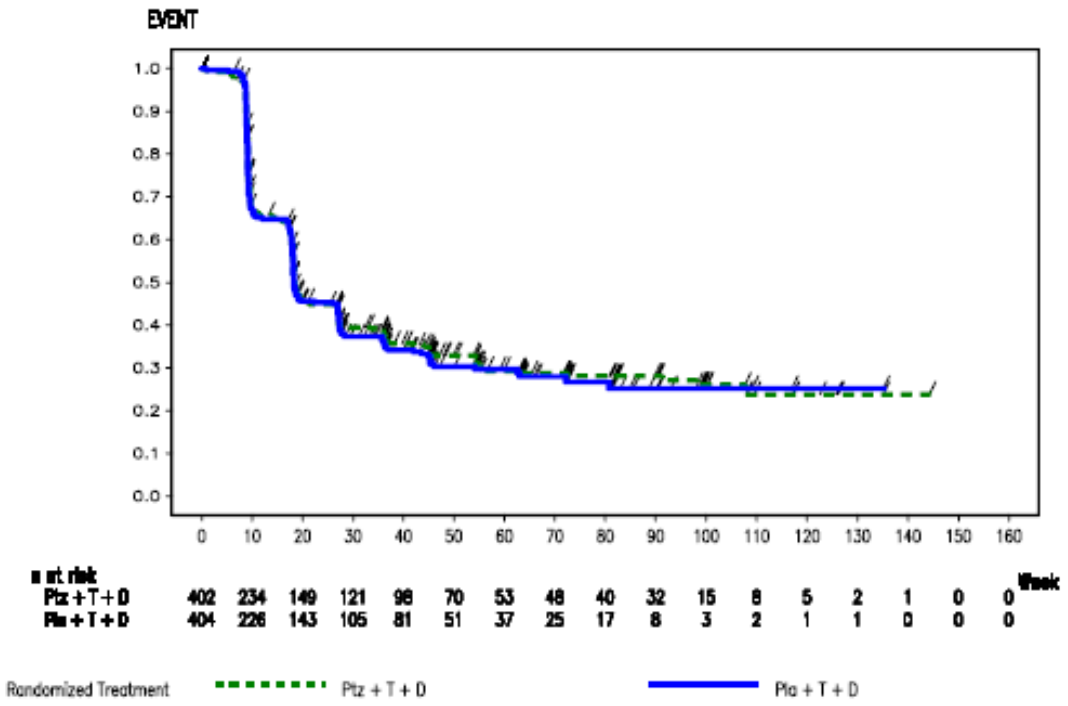


Figure 1 mean change from baseline in FACT-B Trial Outcomes Index-Physical/Functional/Breast (time to symptom progression) reported in the manufacturer's submission[1]

Subgroup analyses

Subgroup analyses were also presented for IRF assessed (Figure 2) and investigator assessed PFS (Figure 3). For OS, the protocol stated that subgroup analyses would be undertaken at the time of the final OS. However, exploratory subgroup analyses for OS were also reported at the time of the second data-cut (Figure 4). Tests for interaction were not provided in the MS[1] but were provided in the manufacturer's clarification response. The results from the subgroup analyses are consistent with the results in the overall study population. The tests for interaction indicate a statistically significant difference for visceral disease status and FISH status.

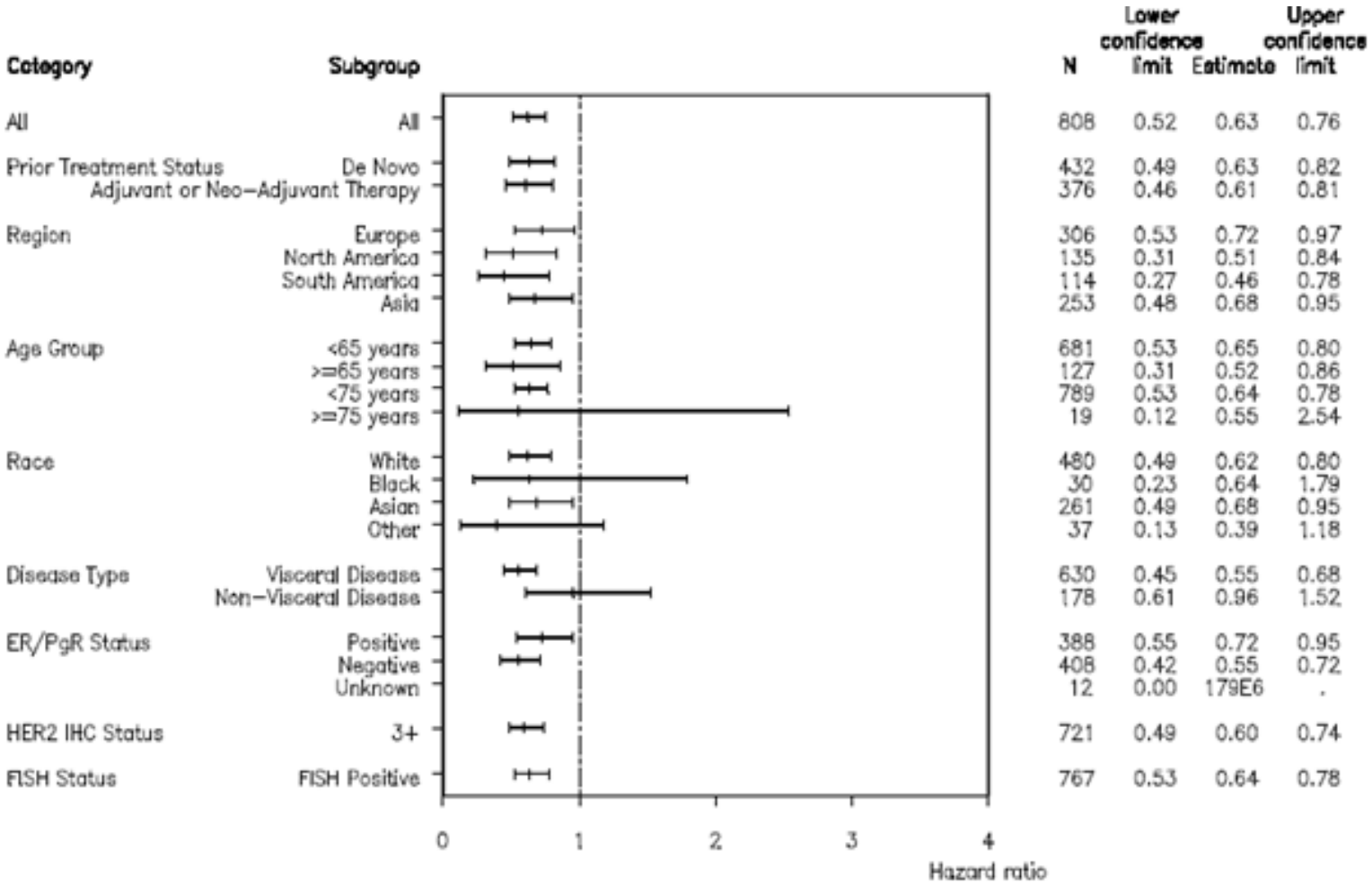
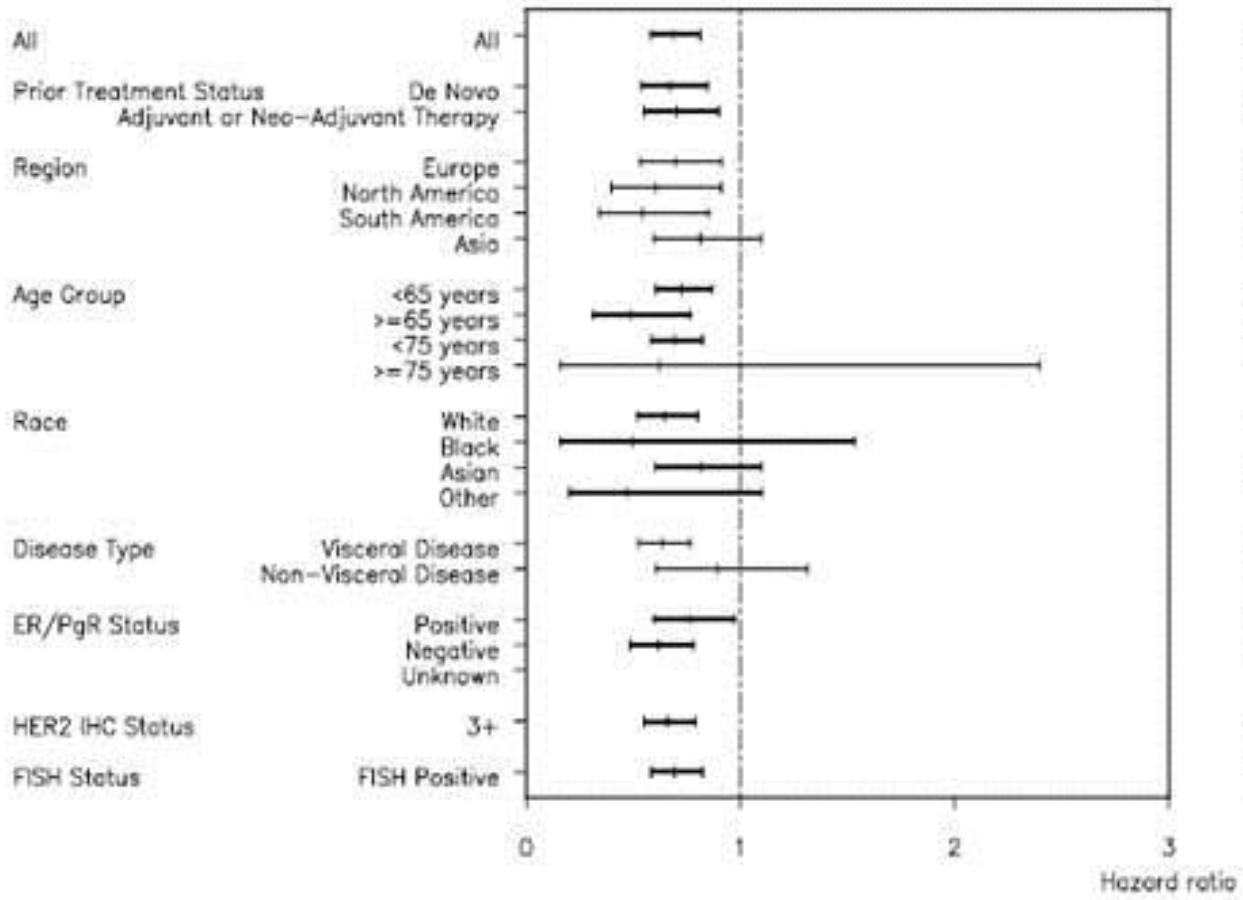


Figure 2 Progression-free survival for subgroups in CLEOPATRA,[18] reported in the manufacturer's submission,[1] first data-cut, May 2011, independent review facility assessed



Category	Subgroup	N	Lower confidence limit	Estimate	Upper confidence limit
All	All	808	0.58	0.69	0.81
Prior Treatment Status	De Novo	432	0.54	0.67	0.85
	Adjuvant or Neo-Adjuvant Therapy	376	0.55	0.70	0.90
Region	Europe	306	0.53	0.70	0.91
	North America	135	0.40	0.60	0.91
	South America	114	0.34	0.54	0.85
	Asia	253	0.60	0.81	1.10
Age Group	<65 years	681	0.60	0.72	0.87
	>=65 years	127	0.31	0.49	0.76
	<75 years	789	0.59	0.69	0.82
	>=75 years	19	0.16	0.62	2.40
Race	White	480	0.52	0.65	0.80
	Black	30	0.16	0.50	1.54
	Asian	261	0.60	0.81	1.10
	Other	37	0.20	0.47	1.10
Disease Type	Visceral Disease	630	0.53	0.63	0.76
	Non-Visceral Disease	178	0.61	0.89	1.31
ER/PgR Status	Positive	388	0.60	0.76	0.97
	Negative	408	0.49	0.62	0.78
	Unknown	12	0.00	179E6	.
HER2 IHC Status	3+	721	0.55	0.66	0.79
FISH Status	FISH Positive	767	0.59	0.70	0.83

Figure 3 Progression-free survival for subgroups in CLEOPATRA,[18] reported in the manufacturer's submission,[1] second data-cut, May 2012, local investigator assessed

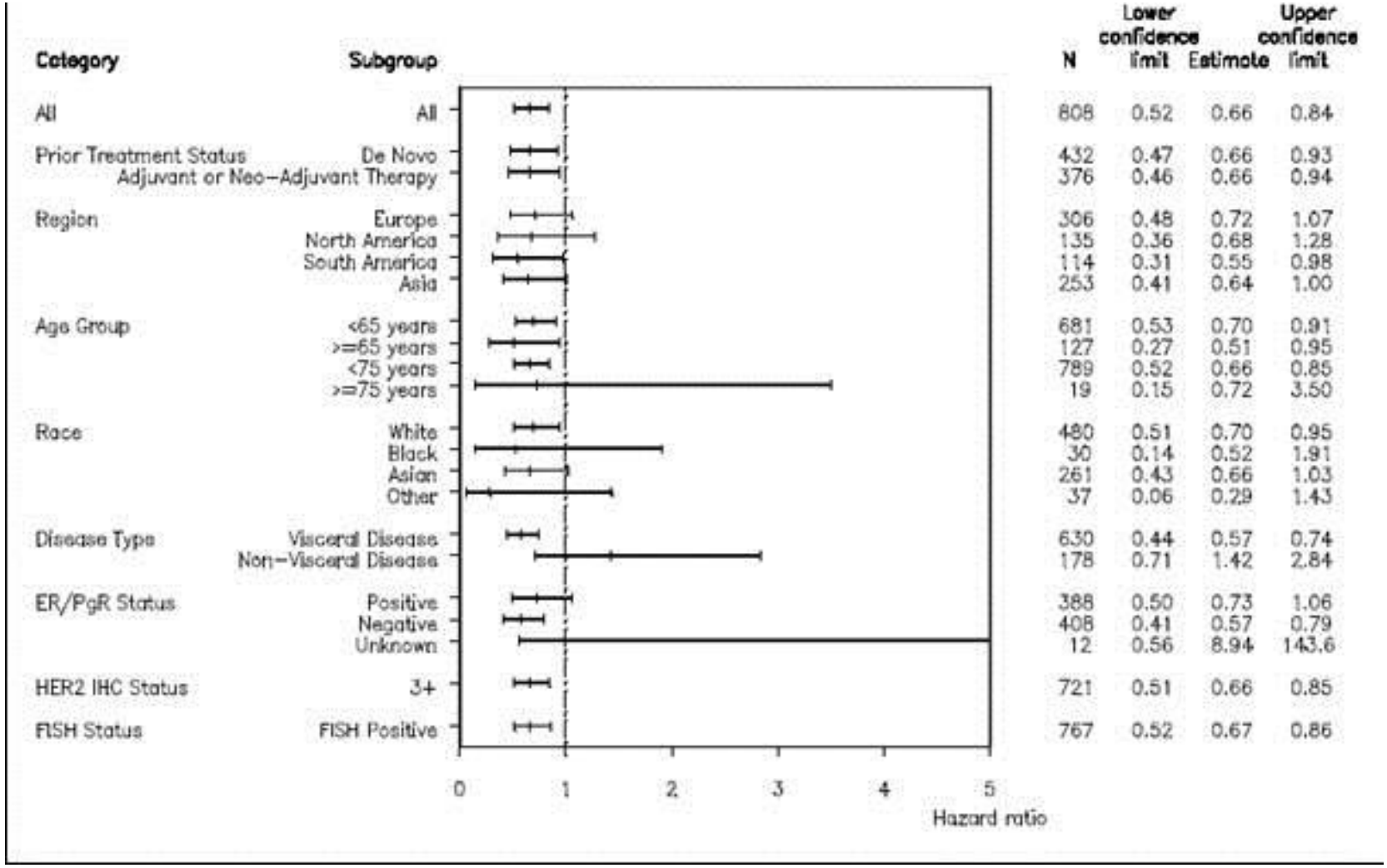


Figure 4 Overall survival for subgroups in CLEOPATRA,[18] reported in the manufacturer's submission,[1] second data-cut, May 2012

Table 10 Results of statistical tests for progression-free survival forest plot hazard, first data-cut, May 2011, independent review facility assessed

Interaction of treatment effect	p-value
Prior treatment status	0.8960
Prior trastuzumab therapy	0.9263
Docetaxel dose escalation to 100mg	0.8543
Region	0.3381
Age group (>=65 vs <65)	0.4180
Age group (>=75 vs <75)	0.3104
Race	0.8037
Visceral disease status	0.0332
HER2 IHC status	0.1252
FISH status	0.0254
ER/PgR status	0.1277
ECOG PS	0.2132
Previous taxane use	0.7970

ECOG=Eastern Cooperative Oncology Group; ER=estrogen receptors; ; FISH=fluorescence in situ hybridization; HER2=human epidermal growth factor 2; IHC=Immunohistochemistry; FISH=fluorescence in situ hybridization; PgR=progesterone receptors; PS=performance status

Table 11 Results of statistical tests for progression-free survival forest plot, second data-cut, May 2012, local investigator assessed

Interaction of treatment effect	p-value
Prior treatment status	0.7888
Prior trastuzumab therapy	0.586
Docetaxel dose escalation to 100mg	0.6007
Region	0.4171
Age group (>=65 vs <65)	0.1388
Age group (>=75 vs <75)	0.7296
Race	0.4196
Visceral disease status	0.1064
HER2 IHC status	0.1931
FISH status	0.0241
ER/PgR status	0.1646
ECOG PS	0.6586
Previous taxane use	0.5485

ECOG=Eastern Cooperative Oncology Group; ER=estrogen receptors; ; FISH=fluorescence in situ hybridization; HER2=human epidermal growth factor 2; IHC=Immunohistochemistry; FISH=fluorescence in situ hybridization; PgR=progesterone receptors; PS=performance status

Table 12 Results of statistical tests for overall survival forest plot, second data-cut, May 2012

Interaction of treatment effect	p-value
Prior treatment status	0.9892
Prior trastuzumab therapy	0.9207
Docetaxel dose escalation to 100mg	0.8124
Region	0.8575
Age group (>=65 vs <65)	0.3190
Age group (>=75 vs <75)	0.6862
Race	0.6425
Visceral disease status	0.0138
HER2 IHC status	0.6987
FISH status	0.1900
ER/PgR status	0.3272
ECOG PS	0.5854
Previous taxane use	0.7076

ECOG=Eastern Cooperative Oncology Group; ER=estrogen receptors; ; FISH=fluorescence in situ hybridization; HER2=human epidermal growth factor 2; IHC=Immunohistochemistry; FISH=fluorescence in situ hybridization; PgR=progesterone receptors; PS=performance status

The difference in IRF assessed PFS related to visceral disease was considered particularly interesting given patients with visceral disease tend to have worse outcomes than those with non-visceral disease. However, in CLEOPATRA,[18] patients with non-visceral disease (n=178) appeared to get the smallest benefit from the addition of pertuzumab based on this subgroup analysis (from IRF assessed PFS at first data-cut, HR 0.96, 95% CI: 0.61 to 1.52, from local investigator assessed at second data-cut, HR 0.89, 95% CI: 0.61 to 1.31). As highlighted in the MS,[1] the EMA sought clarification from the manufacturer on this subgroup finding before licensing pertuzumab. The manufacturer's response to the EMA was also provided to the ERG in their clarification letter response. This contained additional analyses, including baseline characteristics. In summary, the manufacturer noted differences in key baseline characteristics that could have explained this finding. Furthermore, the relatively lower event rate of PFS in this subgroup and the wide confidence interval around the HR for patients with non-visceral disease means a benefit for pertuzumab could not be excluded. Therefore it was concluded that there were unlikely to be any real differences in PFS by subgroups.

In addition to pre-planned subgroup analyses, an exploratory subgroup analysis of patients who had previously received trastuzumab was also conducted at the behest of the EMA since in current clinical practice, the majority of patients are likely to have received prior trastuzumab. This was a small subgroup (n=88) in which findings at the first data-cut for PFS (HR 0.62, 95% CI: 0.35 to 1.07) and OS (HR 0.68, 95% CI: 0.30 to 1.55) were similar to those for the whole patient population (HR 0.65, 95% CI: 0.54 to 0.78 and HR 0.64, 95% CI: 0.47 to 0.88, respectively). Hence the EMA CHMP[34] concluded these data (alongside those from the phase II BO17929 study which demonstrated activity

of the pertuzumab-trastuzumab combination in 66 people previously treated with trastuzumab in the metastatic setting[39]) support the efficacy of pertuzumab in people pre-treated with trastuzumab.

The ERG also notes that it is reported in the EPAR [34] that: "Relatively few patients had the docetaxel dose uptitrated to 100mg/m^2 (n= 109). The data indicate that the higher docetaxel dose did not have a major impact on the efficacy results as HR for PFS = 0.62 (0.50; 0.76) in patients who were not dose escalated compared to HR= 0.65 (0.37, 1.13) in patients who received the highest docetaxel dose." (p108)

4.2.7 Safety

An overview of the cumulative safety data reported at the time of both data-cuts was provided in the MS[1] in Table 17 (p80). It is noted by the manufacturer that the results were similar between the two data-cuts in terms of incidence, severity and specificity of AEs. The ERG agrees with this statement and hence this section only presents a summary of the AEs from the second data-cut. A summary of the types of AEs reported are presented in Table 13 where it can be seen pertuzumab was broadly comparable with that of control in terms of the incidence and severity of AEs, discontinuations due to AEs, and AEs leading to death. However, there were a greater proportion of serious adverse events (SAEs) in the pertuzumab arm and a greater proportion of AEs leading to dose interruption or modification were reported in the control arm. The majority of AEs leading to discontinuation of any study medication in either arm largely resulted in the discontinuation of [redacted]

Table 13 Summary of adverse events reported in CLEOPATRA,[18] second data-cut, May 2012

Adverse events	Pertuzumab[a] (%) (n=408)	Control[b] (%) (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
AE leading to discontinuation of any study medication	30.6	29.2
AE leading to discontinuation of pertuzumab or trastuzumab[c]	[redacted]	[redacted]
AE leading to dose interruption or modification	54.3	61.8
AE leading to death	2.0	3.0

AE=adverse event; SAE=serious adverse event
[a] Pertuzumab=pertuzumab + trastuzumab + docetaxel
[b] Control=placebo + trastuzumab + docetaxel
[c] Data provided in Clinical Study Report,[36] section 5.11and p1422

The most common AEs are summarised in Table 14. Adverse events experienced by at least around half of all patients in both arms were alopecia, diarrhoea and neutropenia. Diarrhoea was particularly

prevalent in the pertuzumab arm, being experienced by around 20% more patients than in the control arm. Other common AEs where the incidence was higher by ≥ 5% in one arm over another were rash and mucosal inflammation (higher in pertuzumab arm) and peripheral oedema and constipation (higher in control arm). In addition, the incidence of the following less common AEs was higher (≥ 5% difference) in the pertuzumab arm compared with the control arm: febrile neutropenia (13.7% vs 7.6%), dry skin (10.8% vs 5.8%) and pruritus (16.7% vs 10.1%).

Table 14 Summary of most common adverse events (>20% in one or both arms) reported in CLEOPATRA,[18] second data-cut, May 2012

Adverse events	Pertuzumab[a] (%) (n=408)	Control[b] (%) (n=396)
Alopecia	60.8	60.6
Diarrhoea	68.1	48.2
Neutropenia	52.9	49.7
Nausea	43.9	42.4
Fatigue	38.0	37.4
Rash	36.5	24.0
Asthenia	27.0	30.6
Decreased appetite	29.7	26.5
Oedema peripheral	24.8	30.8
Vomiting	25.5	24.5
Myalgia	23.8	24.5
Nail disorder	23.0	23.2
Anaemia	23.5	19.4
Cough	23.0	19.7
Headache	23.8	18.9
Peripheral neuropathy	21.6	19.9
Constipation	15.4	25.5
Leukopenia	18.4	20.7

[a] Pertuzumab=pertuzumab + trastuzumab + docetaxel
[b] Control=placebo + trastuzumab + docetaxel

The majority of episodes of diarrhoea experienced in both arms were reported to be mild to moderate in severity (Grade 3 ≥ 9.1% in the pertuzumab arm vs 5.1% in the control). It was reported that most episodes occurred in the first three cycles of treatment and < 10% of people overall experienced diarrhoea after Cycle 6. Overall, although diarrhoea was more frequent (68.1% vs 48.2%) and prolonged (median duration of longest episode, 17 days vs 8 days according to the EPAR[34]) in the pertuzumab arm than the control arm, the manufacturer stated that it was generally manageable and had no major impact on participants' ability to continue study treatment. In response to a clarification question from the ERG, the manufacturer also noted that 41.5% in the pertuzumab arm compared to 20.0% of patients in the control arm received antidiarrheal medication during the study. The majority

of participants in both arms were treated with loperamide: 39.8% vs 19.2%, respectively. According to the EPAR,[34] the relatively high incidence of diarrhoea is to be expected as diarrhoea is thought to be an off-target intestinal effect caused by the inhibition of HER1/HER2 and HER2/HER heterodimers. The EPAR[34] also noted that few patients actually discontinued study medication due to diarrhoea and risk factors were Asian race, patients with a history of bowel disease and patients receiving concomitant chemotherapy.

The MS[1] states that the majority of rashes were mild to moderate in severity: 11 people (2.7%) in the pertuzumab arm and five people (1.3%) in the control arm experienced severe events. In the EPAR[34] it is reported that rash mostly occurred during the first two cycles and decreased in frequency with subsequent cycles. By Cycle 10, less than 2% of people in either treatment arm experienced a rash. Rashes led to dose interruption or modification of study treatment in 3.7% of people in the pertuzumab arm and 1.6% of people in the control arm, and to discontinuation of study medication in 2.5% and 0.3% of participants, respectively.

From the CSR,[36] the ERG notes that [redacted] The most common SAEs are presented in Table 15. Although the incidence of gastrointestinal SAEs were similar in the two treatment arms,[1] diarrhoea was observed in 3.2% of pertuzumab arm and 1.3% of people in control arm. Blood and lymphatic system disorders were more common in the pertuzumab arm than the control. As reported in Table 13, a greater proportion of SAEs were reported in the pertuzumab arm than the control arm. Differences in SAE incidence between treatment arms were attributed by the manufacturer as mainly due to febrile neutropenia (11.3% vs 5.1%). Febrile neutropenia was reported to be most common in participants from Asia (25.6% compared with 8.5% of people from the rest of the world). Consequently, the manufacturer argues that the overall rates of febrile neutropenia seen in CLEOPATRA[18] are likely to be greater than the expected incidence in the UK population.

Table 15 Summary of most common serious adverse events ≥1% in one or both arms) reported in CLEOPATRA,[18] second data-cut, May 2012[a]

Adverse events	Pertuzumab[b] (%) (n=408)	Control[c] (%) (n=396)
Blood and lymphatic system disorders	[redacted]	[redacted]
Infections and infestations (including febrile neutropenia)	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]
Immune system disorders	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]
Neoplasms benign, malignant and unspecified (including cysts and polyps)	[redacted]	[redacted]
Renal and urinary disorders	[redacted]	[redacted]

[a] Data taken from Table 34 (p94) of Clinical Study Report[36]
[b] Pertuzumab=pertuzumab + trastuzumab + docetaxel
[c] Control=placebo + trastuzumab + docetaxel

Details of treatment-related SAEs were requested from the manufacturer who in response directed the ERG to p469 in the CSR.[36] This contained data on treatment-related AEs rather than SAEs. It is evident from this table that the most common treatment-related AEs were: [redacted] No other treatment related AE was reported at an incidence >2%.

Given pertuzumab's mechanism of action and given it was administered in tandem with trastuzumab in CLEOPATRA,[18] particular emphasis was placed on collecting data on cardiotoxicity. As summarised in Table 16, there was no increase in cardiotoxicity in patients treated with pertuzumab arm. Indeed, for a number of cardiac disorders, including SAEs, incidence was higher in in the control arm. Nevertheless, although not reported in the MS,[1] it was evident from the CSR[36] (p1422) that [redacted]

Table 16 Summary of cardiac safety reported in CLEOPATRA,[18] second data-cut, May 2012

Cardiac disorders	Pertuzumab[a] (%) (n=408)	Control[b] (%) (n=396)
All cardiac disorders	15.4	17.4
Cardiac SAE	1.7	3.5
SAE suggestive of CHF / any Grade	1.5	2.0
SAE suggestive of CHF / Grade 3+	1.2	1.8
Symptomatic LVSD adjudicated by IRF / any Grade	1.0	1.0
Symptomatic LVSD adjudicated by IRF / Grade 3+	0.7	0
Symptomatic LVSD adjudicated by local investigator / any Grade	1.2	1.8
Symptomatic LVSD adjudicated by local investigator / Grade 3+	0.7	1.0
Left ventricular dysfunction	5.4	8.6
Left ventricular dysfunction / Grade 3+	1.2	3.3
QT prolongation / any Grade	2.2	1.3
QT prolongation / Grade 3+	1.0	0.3

CHF=congestive heart failure; IRF=independent review facility; LVSD=left ventricular systolic dysfunction; SAE=serious adverse event
[a] Pertuzumab=pertuzumab + trastuzumab + docetaxel
[b] Control=placebo + trastuzumab + docetaxel

Finally, the manufacturer notes that AEs were reported less frequently after discontinuation of docetaxel treatment. The data presented indicate that of all cases of mucositis, only 16.7% and 8.2% occurred after doxetaxel was withdrawn. Similarly, no febrile neutropenia events occurred after docetaxel discontinuation. The ERG notes from p140 of the EPAR[34] that exacerbation of chemotherapy/docetaxel-associated neutropenia has been identified as an important risk to be monitored in the post marketing surveillance. The exposure to docetaxel was very similar between the study arms with an identical median number of docetaxel cycles (8 cycles), very similar median dose per cycle (125mg in the control arm compared with 123mg in the pertuzumab arm) and a very similar median dose intensity per week (24.8mg/m^2 per week in the control arm compared with 24.6mg/m^2 per week in the pertuzumab based arm)

4.3 Critique of the indirect evidence

It is argued in the MS[1] (p77) that: "Docetaxel has been shown to have comparable efficacy and safety profiles when compared with paclitaxel, when used alone in treating people with HER2-negative disease or when used in combination with trastuzumab for the treatment of HER2-positive disease." However, no formal statistical analyses were conducted to support this statement. Rather the manufacturer reported efficacy findings from a descriptive indirect comparison of two trials[17,32] conducted in the metastatic setting and a head-to-head comparison of 3-weekly docetaxel and weekly paclitaxel regimens in the adjuvant setting[33] to support claims of clinical efficacy.

Table 17, summarises the findings of the descriptive indirect comparison from the metastatic setting presented by the manufacturer. The implication from the evidence presented appears to be that regimens containing trastuzumab and a taxane are superior to those of a taxane alone and of the four regimens, trastuzumab + docetaxel appears to be the most efficacious. However, extreme caution should be taken when making such comparisons, particularly when it is considered that some differences also exist in terms of the patient populations in each trial. For example, 98% of patients treated with trastuzumab + paclitaxel or paclitaxel alone had received prior adjuvant chemotherapy and 92% prior hormonal therapy,[32] compared with 69% and 45% respectively of patients who received trastuzumab + docetaxel or docetaxel alone.[17] In CLEOPATRA,[18] from which the direct evidence presented in the MS[1] is derived, the proportions of patients pre-treated with chemotherapy or hormonal therapy were lower again (47% and 25% respectively).

Table 17 Comparison of trastuzumab + docetaxel/paclitaxel vs docetaxel/paclitaxel alone in the metastatic setting

Key endpoints	Trastuzumab + docetaxel vs docetaxel[17]		Trastuzumab + paclitaxel vs paclitaxel[32]	
	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
Median TTP (months)	11.7	6.1	6.9	3.0
ORR (%)	61	34	38	16

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

The head-to-head comparison in the adjuvant setting of 3-weekly docetaxel vs once weekly paclitaxel reported by Sparano et al[33] reports a similar effect for disease-free survival for 3-weekly docetaxel (HR=1.23, 5 CI: 1.00 to 1.52) and weekly paclitaxel (HR=1.27, 95% CI: 1.03 to 1.57). However, the main weakness of this evidence aside from the fact that patients did not receive concomitant trastuzumab is that it is derived from the adjuvant rather than the metastatic setting and fewer than 20% of patients were HER2+. Furthermore, it should also be noted that all of the patients enrolled into this trial also received four cycles of intravenous doxorubicin and cyclophosphamide at 3-week intervals before receiving either docetaxel or paclitaxel whereas as noted above, fewer than half (47%) of patients in CLEOPATRA[18] had received prior chemotherapy.

In terms of safety, no safety data for docetaxel vs paclitaxel were presented by the manufacturer. However, safety data presented in Sparano et al[33] and summarised here in Table 18 supports the assumption that, in general, paclitaxel has a more favourable safety profile than docetaxel, at least for patients with early breast cancer treated in the adjuvant setting.

Table 18 Most common (≥5%) adverse events from docetaxel and paclitaxel resulting from the taxane component of therapy reported in the adjuvant setting by Sparano et al[33] 2008

Adverse events	3-weekly docetaxel (%)	Weekly paclitaxel (%)
Grade 4		
Neutropenia	46	2
Febrile neutropenia	16	1
Grade 3 or 4		
Infection	13	3
Stomatitis	5	0
Fatigue	9	3
Myalgia	6	2
Arthralgia	6	2
Lacrimation	<1	0
Neuropathy	4	8
Grade 2, 3, or 4		
Neuropathy	16	27

Taken together, none of the indirect evidence presents convincing evidence to support, or refute, the hypothesis that 3-weekly docetaxel and weekly paclitaxel are equivalent in terms of efficacy and safety, certainly not in the group of patients specified in the decision problem. A major uncertainty surrounds the additional impact on efficacy and safety from adding trastuzumab to these regimens. The comparison presented in Table 17 is only descriptive and cannot be considered robust or reliable, not least because of differences in key participant characteristics across the trials. Such a simple comparison has been termed a 'naïve indirect comparison' which has been criticised for discarding the within trial comparison, increasing the risk of bias and presenting estimates without a degree of uncertainty (e.g. confidence intervals).[40]

4.4 Conclusions of the clinical effectiveness section

CLEOPATRA,[18] the identified trial from which the majority of evidence is derived, is a relatively large trial of good methodological quality. Local investigator and central IRF assessed reviews of PFS are remarkably similar. These both suggest pertuzumab increases PFS by 6.1 months after 19 months of follow-up (first data-cut, May 2011). Additional PFS data based on local assessment only from 30 months of follow-up (second data-cut, May 2012) reports an improvement in PFS of 6.3 months (HR 0.69, 95% CI: 0.58 to 0.81, p <0.0001). A significant improvement in OS (HR 0.66, 95% CI: 0.52 to 0.84, p=0.0008) is reported at 30 months (second data-cut, May 2012) although the data are not fully mature. No new safety concerns have as yet been identified. The most common AEs (all grades of severity, regardless of causality) in both arms were alopecia, diarrhoea, neutropenia, nausea and fatigue. Importantly, the study suggests that cardiotoxicity was not increased in patients treated with a combination of pertuzumab + trastuzumab. Other AEs identified (in particular diarrhoea, neutropenia,

and mucositis) appear to be exacerbated by treatment with docetaxel and once this drug is stopped, there is little difference in terms of the incidence of AEs between patients treated with pertuzumab + trastuzumab and those treated with trastuzumab alone.

In summary, the clinical evidence addresses all relevant parameters (intervention, population, comparators and outcomes) specified in the decision problem. The main uncertainty from the clinical evidence base is that it is not possible to estimate the absolute difference in OS between patients treated in the pertuzumab arm and the control arm because median OS has not yet been reached in the pertuzumab arm It is also unclear if the findings would be replicated in patients who have previously received trastuzumab, as would be the norm in current clinical practice in the UK, since in CLEOPATRA[18] the majority of patients were trastuzumab naïve. However, a post-hoc subgroup analysis of 88 patients who had received prior trastuzumab suggests this may be the case. There is also no direct evidence to compare the efficacy or safety of pertuzumab with trastuzumab + paclitaxel (which it has been assumed by the manufacturer to have equal efficacy to trastuzumab + docetaxel).

5 COST-EFFECTIVENESS

This section provides a structured critique of the economic evidence submitted by Roche in support of pertuzumab for the treatment of HER2+ MBC. The two key components of the economic evidence presented in the MS[1] are (i) a systematic review of the relevant literature and (ii) a report of the manufacturer's *de novo* economic evaluation. Table 19 contains details of the location of key information within the MS.[1] The manufacturer has also provided an electronic version of their economic model which was developed in Microsoft Excel.

Table 19 Location of key cost-effectiveness information in the manufacturer's submission[1]

Key information	Page number	Tables/figures
Details of the systematic review of the economic literature	103 to105, 189 to191	Table 19, Figure 12
De novo analysis	106 to110	Table 20, Figure 13,
Clinical evidence used in economic evaluation	110 to128	Table 21, Figures 14 to 26
Measurement and valuation of health effects	128 to138	Tables 22 to 26, Figure 27
Resource identification, measurement and valuation	138 to152	Tables 27 to 31, Figure 28
Methods of sensitivity analysis	152 to155	Tables 32 to 34
Results - base-case analysis	155 to158	Tables 35 to 40
Results - sensitivity analysis	158 to163	Tables 41 to 43, Figures 29 to 30
Validation	163	
Sub-group analysis	163 to164	
Interpretation of economic evidence	164 to165	
Assessment of factor relevant to the NHS and other parties	166 to168	Tables 44 to 46

5.1 ERG comment on manufacturer's review of cost-effectiveness evidence

5.1.1 Objective of the manufacturer's cost-effectiveness literature review

To determine whether *de novo* modelling was necessary to answer the decision problem the manufacturer carried out a search to identify studies assessing the cost-effectiveness of pertuzumab. The EMBASE, EMBASE Alert, Medline and the NHS Economic Evaluation Database (NHS EED) were searched using the Centre for Reviews and Dissemination (CRD) website. All searches were carried out on 25 October 2012. It is reported that key word strategies were developed using key references retrieved through initial scoping searches. However, the search strategy was not provided in the MS.[1] The search spanned 1993 to 25 October 2012. The title and abstract of each search result were assessed for relevance according to pre-defined inclusion and exclusion criteria (see Table 20).

Table 20 Economic evaluation search inclusion and exclusion criteria

Parameter	Inclusion criteria	Exclusion criteria
Population	Female, HER2+ advanced or MBC patients	Non breast cancer patients, non HER2+ patients non Female
Intervention	Pertuzumab + trastuzumab + docetaxel	
Comparator	Trastuzumab + docetaxel Trastuzumab + paclitaxel	
Outcome	Cost per QALY gained, Cost per LY gained	
Study design	Economic evaluations (cost-effectiveness analyses, cost utility analyses, cost minimisation analyses)	RCTs, observational data, budget impact assessments

HER2=human epidermal growth factor 2; LY=life year; MBC=metastatic breast cancer; QALY=quality adjusted life year; RCT=randomised controlled trial

No studies assessing the cost-effectiveness of pertuzumab were identified.

5.1.2 Conclusions of the cost-effectiveness literature review

The manufacturer's search to identify studies reporting the cost-effectiveness of pertuzumab did not identify any relevant publications. As a marketing authorisation for pertuzumab was only granted by the European Commission in March 2013[34] the ERG is reasonably confident that no studies assessing the cost-effectiveness of pertuzumab have been published to date.

5.2 Summary and critique of manufacturer's submitted economic evaluation

5.2.1 Checklists

Table 21compares how closely the manufacturer's submitted economic evaluation accords with the requirements for a base-case analysis as set out in the NICE reference case checklist[41] and Table 22 summarises the ERG's appraisal of the economic evaluation conducted by the manufacturer using the Drummond checklist.[42]

Table 21 NICE reference case checklist

Attribute	Reference case	Does the *de novo* economic evaluation match the reference case?
Decision problem	The scope developed by the Institute	Yes
Comparator(s)	Alternative therapies routinely used in the NHS	Yes
Perspective costs	NHS and Personal Social Services	Yes
Perspective benefits	All health effects on individuals	Yes
Form of economic evaluation	Cost-effectiveness analysis	Yes
Time horizon	Sufficient to capture differences in costs and outcomes	Yes (25 years)
Synthesis of evidence on outcomes	Systematic review	There are no relevant studies
Outcome measure	Quality adjusted life years	Yes
Health states for QALY	Described using a standardised and validated instrument	Published mixed methods model used for defined health states
Benefit valuation	Time-trade off or standard gamble	Standard gamble
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	Sample of 100 members of UK population
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Sensitivity analysis	Probabilistic sensitivity analysis	Yes

HRQoL= health related quality of life; QALY= quality adjusted life year

Table 22 Critical appraisal checklist for the economic analysis

Question	Critical appraisal	ERG comment
Was a well-defined question posed in answerable form?	Yes	-
Was a comprehensive description of the competing alternatives given?	Yes	-
Was the effectiveness of the programme or services established?	Partially	Gain in Progression-free survival demonstrated, but magnitude of OS gain subjected to large uncertainty
Were all the important and relevant costs and consequences for each alternative identified?	Yes	-
Were costs and consequences measured accurately in appropriate physical units?	Partially	Incidence of febrile neutropenia not consistent with CSR[36] reported values
Were the cost and consequences valued credibly?	Partially	Drug acquisition and administration costs inaccurate. Inappropriate NHS Reference Cost used for febrile neutropenia.
Were costs and consequences adjusted for differential timing?	Yes	-
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	-
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	-
Did the presentation and discussion of study results include all issues of concern to users?	No	No exploration of identified subgroups

CSR=Clinical Study Report; ICER=Incremental cost-effectiveness ratio; OS=overall survival

5.2.2 Model structure

A schematic of the model structure is shown in Figure 5. Variants of this structure have been used in the modelling of metastatic oncology for numerous NICE STAs (for example, eribulin [TA 250][43] and bevacizumab in combination with capecitabine [TA 263][44]).

The model uses a partitioned survival approach. Three health states are used to model disease progression. All patients enter the model in the PFS health state. At the end of each cycle a person can either progress to a 'worse state' (i.e. from PFS to progressed disease or from progressed disease to death) or remain in the same health state.

The model has been developed in Microsoft Excel and has a one week cycle length. It uses data from the May 2012 cut of the CLEOPATRA[18] data. The base case time horizon is 25 years. A discount rate of 3.5% is used for both costs and outcomes. The perspective is that of the NHS and health effects are measured in quality-adjusted life years (QALYs).

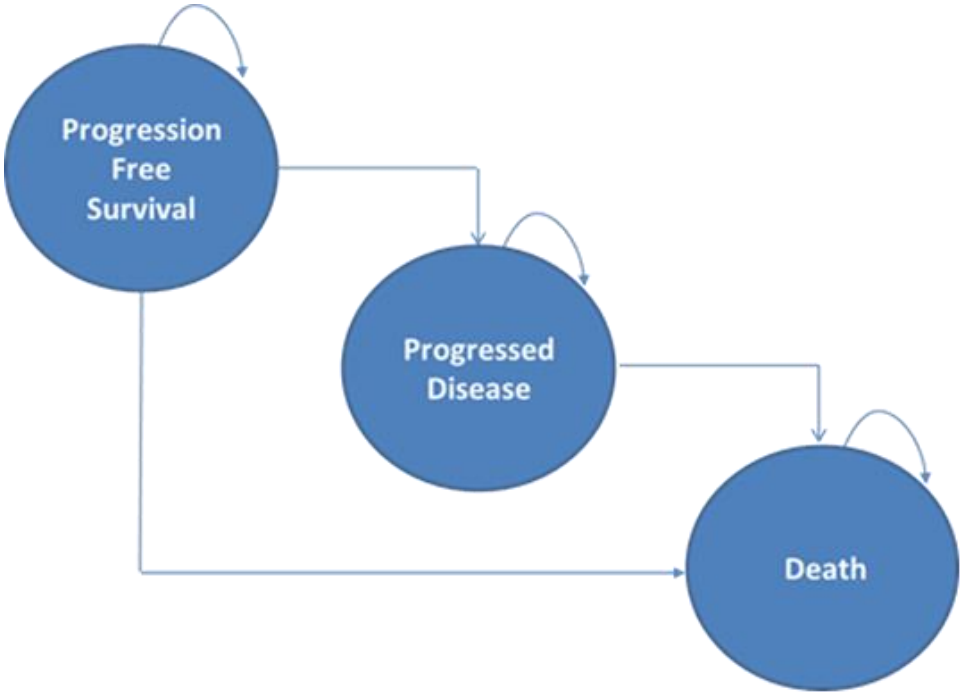


Figure 5 Schema of manufacturer's model

5.2.3 Population

The patient group considered in the base case is patients with HER2+ MBC. Patients in the model have a mean age of 53.5 years, mean body weight of 66.6kg, mean height of 158.8cm and mean BSA of 1.686m^2 (calculated using the Dubois formula).[45] These mean values are identical to the baseline characteristics of patients in the CLEOPATRA[18] trial. Just over 30% of the trial population are from Asia, a population that is likely to be smaller and lighter than the average UK population.

5.2.4 Interventions and comparators

The technology considered in this analysis is pertuzumab + trastuzumab + docetaxel (pertuzumab). The main comparator is trastuzumab + docetaxel (control). Trastuzumab + paclitaxel is also considered but only in terms of costs, i.e. trastuzumab + paclitaxel is assumed to have the same efficacy profile as trastuzumab + docetaxel although the only evidence provided to support this assumption is from a 'naïve indirect comparison' (see section 4.3).

The treatments have been implemented as set out in their marketing authorisations (see Table 23). However, it is standard practice in the UK to administer capecitabine at a dose of 1000mg/m^2 rather than 1250mg/m^2.

Table 23 Drug administration

Drug	Dose
First line treatments	
Pertuzumab	Intravenous infusion once every 3 weeks at an initial dose of 840mg, followed by a maintenance dose of 420mg
Trastuzumab	Intravenous infusion once every 3 weeks at a dose of 8mg/kg for initial dose, followed by a 3 weekly maintenance dose of 6mg/kg.
Docetaxel	Intravenous infusion every 3 weeks at a dose of 75mg/m^2 body surface area (using the Du Bois formula) which could be increased to 100mg/m^2 at investigator's discretion
Paclitaxel	Intravenous infusion applied for 18 cycles at a weekly dose of 90mg/m^2 BSA
Second line treatments	
Vinorelbine	Initial dose of 25mg/m^2 BSA every three weeks, followed by weekly maintenance dose of 30mg/m^2 weekly
Capecitabine	1250mg/m^2 given twice daily for 14 days followed by a 7 day treatment gap

BSA=body surface area

5.2.5 Perspective, time horizon and discounting

The economic appraisal is undertaken from the perspective of the NHS. Outcomes are expressed in terms of gains in life years and quality adjusted life years (QALYs). The time horizon in the base case is set at 25 years and, in line with the NICE Methods Guide to Technology Appraisal,[41] both costs and benefits are discounted at 3.5%.

5.2.6 Treatment effectiveness and extrapolation

Treatment effectiveness and extrapolation are implemented using the same approach for both arms of the base-case comparison.

Progression-free survival

The model uses investigator assessed progression data from the second data-cut (May 2012) of the CLEOPATRA[18] trial [18] until week 117 in the pertuzumab arm and until week 152 in the control arm. In the pertuzumab arm a weekly transition probability of 0.00906 is used until week 139. After week 139 in the pertuzumab arm and after week 152 in the control arm a common weekly transition probability of 0.0077 is used.

Overall survival

In the model, data from the second data-cut of the CLEOPATRA[18] trial are used directly up until month 35, with constant hazards thereafter (0.0152 in the pertuzumab arm and 0.0222 in the control arm).

External validity

The external validity of this model was compared with survival of patients included in a registry of 523 people diagnosed with HER2+ MBC between 2002 and 2009 in Munich, Germany

(Tumorregister-Muenchen, 2012[46]). The manufacturer reports that their model shows strong face validity when compared with these data.

A summary of the transition probabilities applied in the economic model are presented in Table 24. The ERG notes that confidence intervals were not provided in the MS.[1]

Table 24 Transition probabilities used in the model

Phase	Time span	Value	
		Pertuzumab	Control
Progression-free survival weekly hazard	Week 0 to 116	Kaplan-Meier estimates	
	Week 0 to151		Kaplan-Meier estimates
	Week 117 to 139	0.00906	
	Week 139 onwards	0.00770	
	Week 152 onwards		0.00770
Overall survival weekly hazard	Month 0 to 32	Kaplan-Meier estimates	Kaplan-Meier estimates
	Month 32 onwards	0.01520	0.00220

5.2.7 Health related quality of life

The manufacturer carried out a search of the literature to identify all potentially relevant utility scores that had been used in MBC health technology evaluations. This search was an update of a previous search which had been carried out for the NICE Technology Appraisal of bevacizumab in combination with capecitabine (TA263).[44]

The updated search identified no new relevant studies. The manufacturer concluded that the most appropriate approach was to use the model outlined by Lloyd et al[47] to estimate QALYs. This approach was used in TA263[44] and has also been used in a number of other NICE Technology Appraisals for MBC.

Using the Lloyd et al[47] model a common health state utility value of 0.5 was obtained for the progressed health state for patients in both treatment arms.[1] To estimate utility values for patients in the PFS state the manufacturer calculated a treatment-specific weighted average of the Lloyd et al[47] model values for stable disease and treatment response based on the reported objective response rate (79.6% for pertuzumab, 69.4% for control) observed in the CLEOPATRA[18] trial. These response rates, which are used in the manufacturer's model, do not correspond to figures shown on pages 61(IRF assessed ORR) and 73 (local investigator assessed ORR) of the MS or in the 2011 and 2012 CSRs,[35,36] but appear to derive from a separate analysis of trial data. However the differences in these

values to the IRF and local investigator assessed ORRs appear to be minor (80.2% vs 69.3% and 77.4% vs 68.2%, respectively).

The manufacturer has restricted use of a utility decrement for febrile neutropenia to the period during which patients receive docetaxel or paclitaxel. This approach is based on their observation that patients in the CLEOPATRA[18] trial only experienced febrile neutropenia during the period that they receive docetaxel.

Disutilities associated with anaemia and peripheral neuropathy are not included in the Lloyd et al[47] model. Instead, the manufacturer uses the mean of the disutilities reported in Lloyd et al[47] for all individual AEs, excluding febrile neutropenia. A similar approach to estimating unknown disutilities was used by the ERG in TA 250.[48]

A summary of the utility values used in the manufacturer's model is presented in Table 25.

Table 25 Utility values

Description	State	Utility value	Source
Treatment			
Pertuzumab arm	PFS – during docetaxel treatment	0.772	Lloyd et al[47]
	PFS – after docetaxel treatment	0.785	Lloyd et al[47]
Control arm	PFS – during docetaxel treatment	0.769	Lloyd et al[47]
	PFS – after docetaxel treatment	0.777	Lloyd et al[47]
All treatments	Progressed disease	0.496[a]	Lloyd et al[47]
Additional adverse events			
Anaemia	-	-0.120	Lloyd et al[47]
Peripheral neuropathy	-	-0.120	Lloyd et al[47]

PFS=progression-free survival
[a] Number used in the model, not that reported in the MS[1]

5.2.8 Resources and costs

First line drug related treatment costs

It is reported that drug costs are taken from the Joint National Formulary 2012,[49] administration costs from NHS Reference costs 2011/12[50] and pharmacy costs from Millar et al[51] and PSSRU 2012.[52] Intervention and comparator costs for initial and subsequent treatment cycles are summarised in Table 26.

Second line drug related treatment costs

The second line treatments applied in the model are capecitabine and vinorelbine. Costs associated with these two drugs are displayed in Table 27. The model calculates costs by taking an average of the total cost of both treatments multiplied by the proportion of people transitioning to the progressed

disease health state each week. Second line costs are applied for 4.3 months (the period during which Cameron et al [53] reports that patients with metastatic cancer whose disease had progressed following treatment with trastuzumab were treated with capecitabine). The ERG notes that the manufacturer states that deaths which may occur during this period are not accounted for in the analysis and that this is likely to lead to the over-estimation of the cost of second line treatment.

Table 26 Intervention and comparator drug costs in the cost-effectiveness analysis

Item cost	Pertuzumab	Source
Pertuzumab		
Drug cost	420mg vial @ £2,395	Roche[1]
Dose cost	Initial cycle: £4790 Subsequent cycles: £2,395	
Trastuzumab		
Drug cost	150mg vial @ £407.40[†]	BNF[49]
Dose cost	Initial cycle: £1,629.60 Maintenance: £1,222.20	
Docetaxel		
Drug cost	80mg vial @ £20.00 20mg vial @ £5.00	eMIT[54]
Dose cost	All cycles: £35	
Paclitaxel		
Drug cost	100mg vial @ £7.00 30mg vial @ £6.30	BNF[49]
Dose cost	All cycles: £19.50	
Administration and pharmacy costs – all treatments		
First administration	£248	NHS reference costs 2011/12 SB13Z: Deliver more complex parenteral chemotherapy at first attendance (Chemotherapy delivery: Day case and regular day/night)
All subsequent administrations	£197	NHS reference costs 2011/12 SB12Z: Deliver simple parenteral chemotherapy at first attendance (Chemotherapy delivery: Outpatient)
Pharmacy	£9.40	Millar et al 2008[51]; PSSRU 2012[52]

BNF=British National Formulary; eMIT=Electronic Market Information Tool; PSSRU=Personal Social Services Research Unit

Table 27 Second line treatment costs

Drug	Cost	Administration and Pharmacy costs
Vinorelbine (IV)		
Drug cost (eMIT[54])	£0.42/mg	As for first line treatments (see Table 26)
Dose cost	Initial three weeks: £17.71/week Subsequent weeks: £21.25/week	
Capecitabine		
Drug cost (BNF[49])	150mg (60 tab pack) = £40.02 (£0.66/tab) 500mg (120 tab pack) = £265.55 (£2.21/tab)	None applied as capecitabine is an oral therapy
Dose cost	£134.98 (during treatment weeks)	

BNF=British National Formulary; eMIT=Electronic Market Information Tool

Health care costs

Monthly supportive care costs during PFS and post progression are as described in NICE clinical guideline for advanced breast cancer,[16] excluding three one-off costs occurring whilst patients are in the PFS state (namely the costs of a social worker visit, a consultant outpatient appointment and a CT scan). End of life costs have been estimated by inflating figures calculated by Guest et al 2006[55] to current prices using inflation indices for Hospital and Community Health Services (PSSRU).[52] In addition, cardiac monitoring is also carried out during the PFS state. Details of these costs are displayed in Table 28.

Table 28 Costs associated with different health states

Health state	Value	Source
Progression-free survival	BSC: £157.66 per month	NICE CG81[16] NHS Reference Costs 2011/12[50] PSSRU 2012[52]
	Cardiac assessment: £130.20[a]	NHS Reference Costs 2011/12[50]
Post-progression	BSC: £157.66 per month	NICE CG81[16] NHS Reference Costs 201/12[50] PSSRU 2012[52]
End of life	£3,608 (one off cost applied at death)	Guest et al (2006) [55] PSSRU 2012[52]

BSC=best supportive care; ECHO=echocardiography; MUGA=multiplegated acquisition scanning; PSSRU=Personal Social Services Research Unit

[a] Received every 9 months for pertuzumab arm patients and every 12 months for control arm patients. The cost is a weighted average: 30% MUGA scan and 70% ECHO scan

Adverse event costs

Only AEs occurring in 2% or more people in either arm of the CLEOPATRA[18] trial at grade 3, 4 or 5 severity are incorporated into the model. They are applied in week one in the model and are therefore not discounted. It is assumed that treatment regimens of trastuzumab and docetaxel and trastuzumab and paclitaxel have the same toxicity profile. Table 29 reproduces the AEs costs that are presented in the MS.[1]

Table 29 Key model parameters: adverse events

Adverse events	Pertuzumab arm (%)	Control arm (%)	Cost per episode	Source (NHS reference cost 2011/12)[50]
Anaemia (Grade 3)	1.99	2.22	£331	Iron Deficiency Anaemia with CC (Regular Day / night admissions) SA04D
Diarrhoea (Grade 3)	6.72	3.45	£391	Malignant Breast Disorders with Major CC (regular day/night admission) JA12A
Fatigue (Grade 3)	1.49	2.71	£391	Malignant Breast Disorders with Major CC (regular day/night admission) JA12A
Febrile Neutropenia (Grade 3 and 4)	13.43	7.14	£10,799	Febrile Neutropenia with Malignancy - Elective Inpatient HRG Data: PA45Z
Neutropenia (Grade 3 and 4)	62.19	58.13	£215	High Cost Drugs: Outpatient - Neutropenia Drugs, Band 1 XD25Z
Peripheral Neuropathy (Grade 3)	2.49	1.72	£391	Malignant Breast Disorders with Major CC (regular day/night admission) JA12A
Leukopenia (Grade 3)	10.20	12.56	£215	High Cost Drugs: Outpatient - Neutropenia Drugs, Band 1 XD25Z

CC=complicating conditions

5.2.9 Cost-effectiveness results

The base-case incremental results generated by the manufacturer's model are presented in Table 30. Compared with trastuzumab and docetaxel therapy, treatment with trastuzumab and paclitaxel [redacted] and the ICER for pertuzumab, trastuzumab and docetaxel is [redacted] per QALY gained and [redacted] per life-year gained. A summary of predicted resource use by category of cost is presented in Table 31.

Table 30 Base-case results

Technologies	Total costs	Total LYG	Total QALYs	Inc costs	Inc LYG	Inc QALYs	ICER (Cost/ life-year)	ICER (Cost/ QALY)
Trastuzumab and docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-		
Trastuzumab and paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0	[redacted]	[redacted]
Pertuzumab, trastuzumab and docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.833	[redacted]	[redacted]

ICER=incremental cost-effectiveness ratio; Inc=incremental; LYG=life years gained; QALYs=quality-adjusted life years [redacted]

Table 31 Summary of predicted resource use by category of cost for the base case[a]

	Pertuzumab[b]	Control[c]	Increment
PFS			
Pertuzumab + trastuzumab + docetaxel	[redacted]		[redacted]
Trastuzumab + docetaxel		[redacted]	[redacted]
Drug administration	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]
Supportive care	[redacted]	[redacted]	[redacted]
Mean cost of PFS	[redacted]	[redacted]	[redacted]
Mean cost of progression	[redacted]	[redacted]	[redacted]
End of life	[redacted]	[redacted]	[redacted]
Mean total cost (GBP)	[redacted]	[redacted]	[redacted]

PFS=Progression-free survival
[a] The values presented in this table have been generated by the ERG running the manufacturer's model and are not presented in the MS[1]
[b] Pertuzumab=pertuzumab + trastuzumab + docetaxel
[c] Control=placebo + trastuzumab + docetaxel

5.2.10 Sensitivity analyses

Sensitivity analyses

The manufacturer undertook a wide range of deterministic sensitivity analyses. Results from the most influential parameters are shown in Table 32 and full details may be found in the MS[1] (Tables 40 and 41, p159 to 161).

Table 32 Deterministic univariate sensitivity analysis results

	Base case value	High value	Low value
Outcomes			
Progression-free survival utility (after docetaxel)	Different utility values in treatment arms	Use utility values for pertuzumab in both arms	Use utility values for control in both arms
	[redacted]	[redacted]	[redacted]
Progression-free survival utility (after docetaxel)		BCV +0.2 for both arms	BCV -0.2 for both arms
	[redacted]	[redacted]	[redacted]
Progressed utility		BCV +0.2 for both arms	BCV -0.2 for both arms
	[redacted]	[redacted]	[redacted]
Parametric functions			
Parametric fit	Kaplan-Meier data with piecewise exponential tail	Kaplan-Meier with (non-piecewise) tail and treatment duration set to exponential	
		Weibull	[redacted]
		Exponential	[redacted]
		Log-logistic	[redacted]
		Log normal	[redacted]
		Gamma	[redacted]
Overall survival	Kaplan-Meier data with piecewise exponential tail	Kaplan-Meier with (non-piecewise) tail	
		Weibull	[redacted]
		Exponential	[redacted]
		Log-logistic	[redacted]
		Log normal	[redacted]
		Gamma	[redacted]
Other			
Cost discount rate	3.5%	6%	0
	[redacted]	[redacted]	[redacted]
Health outcomes discount rate	3.5%	6%	0
	[redacted]	[redacted]	[redacted]
Health and cost discount rates	3.5% both arms	6% both arms	0% both arms
	[redacted]	[redacted]	[redacted]

BCV=Base case value[redacted]

Probabilistic sensitivity analysis

The manufacturer's PSA results suggest that pertuzumab, trastuzumab and docetaxel has a 0% probability of being cost-effective at a willingness-to-pay threshold of £30,000 per QALY gained (see Table 33 for details).

Table 33 Probabilistic sensitivity analysis results

Technology (and comparators)	Total cost £	Total QALY	Inc. cost £	Inc. QALY	ICERs vs baseline (A) £	Inc. analysis £
Trastuzumab and docetaxel (A)	[redacted]	[redacted]	[redacted]	-		
Trastuzumab and paclitaxel	[redacted]	[redacted]	[redacted]	0	[redacted]	[redacted]
Pertuzumab, trastuzumab and docetaxel	[redacted]	[redacted]	[redacted]	0.834	[redacted]	[redacted]

ICER=incremental cost-effectiveness ratio; Inc=incremental; QALYs=quality-adjusted life years

[redacted]

A cost-effectiveness acceptability curve for pertuzumab, trastuzumab and docetaxel vs trastuzumab and docetaxel is included in the MS[1] and reproduced in

Figure 6. A scatter plot was not included in the MS.1[redacted]

Figure 6 Cost-effectiveness acceptability curve for the comparison of pertuzumab, trastuzumab and docetaxel vs trastuzumab and docetaxel.[redacted]

5.2.11 Model validation and face validity check

The manufacturer reports that the model was validated at two advisory board meetings and by a health economics consultancy. Additionally, the model functionality was checked and the clinical inputs and assumptions were validated. Furthermore, the extrapolation conducted was discussed with an academic health economist and two panels of clinicians who noted that whilst subject to uncertainty the extrapolation approach employed appeared reasonable given the evidence currently available.

5.3 Critique of manufacturer's decision model

The submitted economic model has been developed as a Microsoft Excel application. It is logically structured and implemented competently. There is adequate annotation provided to allow most features to be readily understood, with key variables, range names and data sources identified throughout. Standard principles of cost-effectiveness modelling (such as correct use of discounting and mid-interval correction) have been followed throughout. In this section we comment only on areas of concern, grouped into major issues, and minor issues.

5.3.1 Major issues

Response to clarification questions

The manufacturer did not provide the information requested by the ERG in their priority questions B1 and B2, which concern alternative survival analyses from the CLEOPATRA[18] trial data (see Appendix 2). In addition, the manufacturer stated that these are not clarification questions, implying that the ERG was thereby exceeding their brief. The manufacturer claims that the method of analysis (alternative censoring definition) is 'significantly flawed', and also that any consideration by the ERG of subgroups is 'not legitimate'.

It is important to respond to these statements to demonstrate:

- that these matters fall within the scope of the ERG's role in the STA process
- that the analyses requested are relevant to the Appraisal Committee's consideration of the available evidence for this STA
- that failure to provide the requested analyses has seriously impeded the ERG's assessment of the accuracy and robustness of the cost-effectiveness results presented by the manufacturer.

ERG's role

Unlike the NICE Multiple Technology Appraisal (MTA) process, the STA process does not involve the independent academic group (ERG) in developing their own decision model. However, it does require the ERG to comment on the robustness and accuracy of the submitted model and the data used to populate the model, and where possible to carry out sensitivity analyses using the manufacturer's submitted model to indicate what they consider to be the most reliable estimate of cost-effectiveness. Both survival and patient subgroups are explicitly included in the STA evidence submission template, and the ERG is required to consider these matters alongside all other issues on which the manufacturer is asked to submit evidence.

Relevance of requested information

The sensitivity of time-to-event analyses to alternative assumptions, where these analyses provide key data driving the decision model, is clearly within the remit of the ERG, and fully employed (where available) in framing the ERG's comments and conclusions.

Although the manufacturer commented in their submission on the issue of differential response to treatment among subgroups arising from discussions with the EMA, they chose not to include any facility in their model to permit exploration of this potentially important question in terms of relative cost-effectiveness, and made no reference to subgroups in the cost-effectiveness section of their submission. It is important for the ERG to consider and comment on this question, and a request for information directly relevant to this matter is therefore wholly appropriate. Since subgroup differences were sufficient to require careful consideration in terms of efficacy and safety by the EMA,[34] it is no less important that they should also be considered in relation to cost-effectiveness.

Impact of non-provision of requested analyses

In the absence of the information requested in clarification questions B1 and B2, the ERG has been unable to offer alternative interpretations of the PFS, OS, time to off treatment (TTOT) and post-progression survival (PPS) trial results in relation to long-term projection of survival trends, as the current data provided appear to suffer from systematic bias. The ERG is grateful for the additional detail provided on the conversations held between the manufacturer and the regulator in relation to subgroups, and the additional time-to-event information provided for subgroups, albeit not using the method requested. As a consequence, the following sections of this report are able to discuss these matters in broad terms,[1] but not to provide the Appraisal Committee with fully detailed economic sensitivity analyses in relation to these central questions.

5.3.2 Robustness of time-to-event analyses

An important problem arises in analysis of time-to-event data from clinical trials because of the common practice of censoring patient records when the trial is terminated before all patients have experienced the target event (e.g. death). This censoring is usually based on the 'last observation data' rule, so that for a patient who is routinely seen every 6 months (say) and is not known to have died when the trial is terminated (say 5 months after their last contact) will be counted as leaving the trial 5 months before the trial end. This has the effect of underestimating the time many patients were at risk in the latter stages of the trial while still counting deaths right up to the termination date, so that the mortality rate (deaths / time at risk) is artificially exaggerated.

Figure 7 uses a simple simulation to illustrate the consequences of using a 'last observation date' rule for censoring patients still at risk when a trial closes. The simulation assumes that 1000 patients are

recruited steadily into the study over a 9 month period, and then followed up for minimum of 9 months, being seen for assessment every 3 months. Eighteen months after the first enrolment the trial was stopped and the data analysed according to two censoring rules. When all in-period events (e.g. deaths) are reported, but at-risk periods are truncated at the end of the study, the hazard rate is overstated in the latter part of the trial so that the Kaplan-Meier estimates become seriously biased in the final part of the survival curve. This is because the 'last observation' rule is not uninformative, and so violates a fundamental assumption of Kaplan-Meier estimation. A typical pattern of bias is seen when the survival plot begins to drift lower than expected, and then suffers a sudden shift in trend at the end of the observation period (downward 'kink'). This is often more clearly seen as a strong upward change in the slope of the hazard trend line in the cumulative hazard plot.

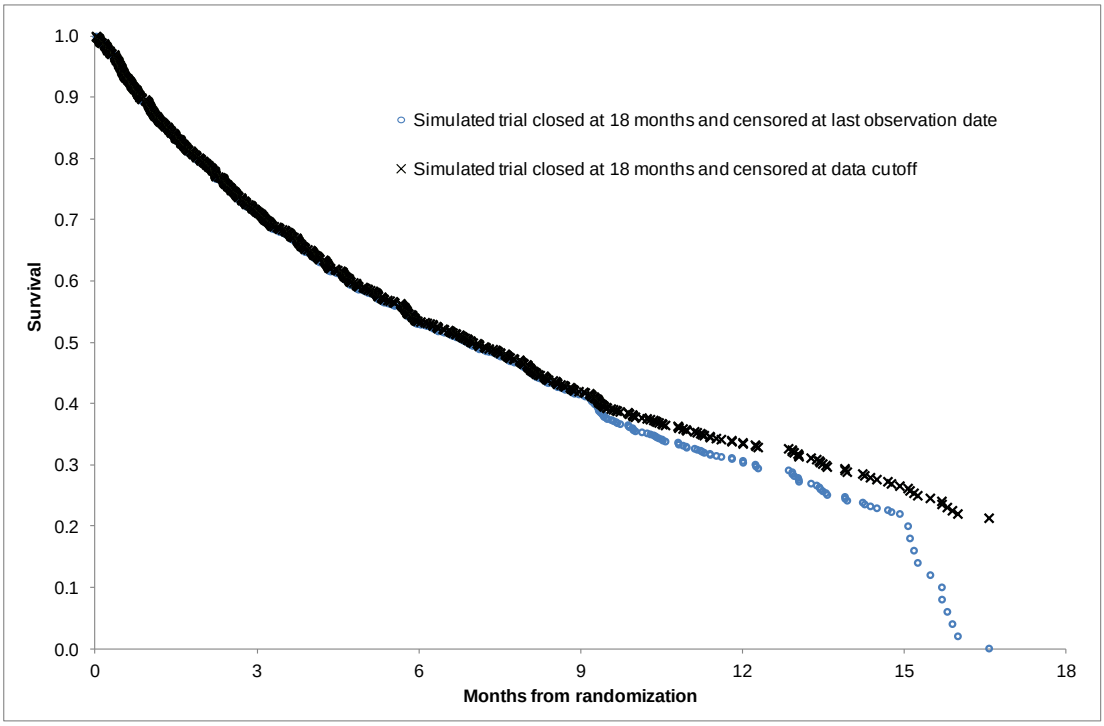


Figure 7 Simulated trial results comparing censoring at study cut-off date (18 months from first recruitment) and censoring by last observation date.

For this reason the ERG requested re-analysis of all time-to-event CLEOPATRA[18] trial data used in the manufacturer's model, so that projective modelling could be carried out free from this important source of bias, which can easily lead to misspecification of parametric survival models (such as assuming non-linear trends are present when in fact the underlying trend is linear). Unfortunately the manufacturer chose not to respond to this request.

Figure 8 compares the conventionally censored CLEOPATRA[18] OS trial results with the long-term survival analysis from the Munich Registry.[46] After the initial trial period (about 300 days) the two

arms of the trial follow separate long-term trends which are approximately linear. However from about 1000 days onwards both trial cohorts show the same sudden increase in hazard (upward 'kink') so that the placebo arm crosses the stable trend line of the Munich Registry data.[46] This provides a strong indication that the informative censoring has caused bias in the final section of the analysis of CLEOPATRA[18] data,[18] and should not be used as the basis for projective modelling of survival. Similar anomalies were detected in the PFS and TTOT Kaplan-Meier analyses. These problems can only be resolved by rerunning the Kaplan-Meier analyses using the alternate censoring method requested by the ERG.

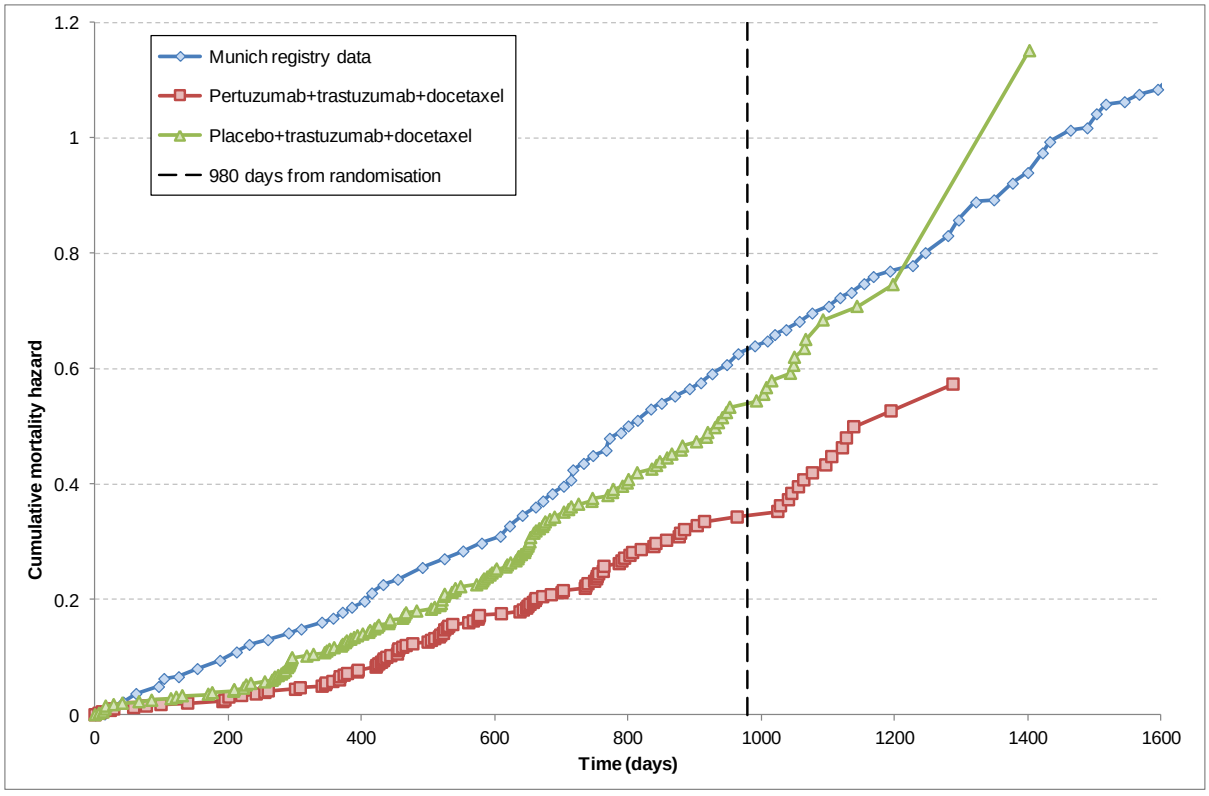


Figure 8 Comparison of CLEOPATRA[18] overall survival cumulative hazard data (censoring at last observation date) with Munich registry data[46]

5.3.3 Exploration of subgroups

The EMA[34] observed that patients with only non-visceral disease in the CLEOPATRA[18] trial (n=178) appeared to gain much less benefit from use of pertuzumab, than did the larger visceral disease group (n=630). Despite additional multivariate Cox regression analyses this difference persisted, and no potential explanations have been offered. The manufacturer has suggested that the discrepancy may be attributable to the smaller number of non-visceral patients and some differences between treatment arms in baseline characteristics.

Examination of the results of Kaplan-Meier analysis is instructive in considering this issue. The cumulative hazard plot for PFS (Figure 9) indicates [redacted] Taken together, these findings suggest that [redacted] Figure 9 Progression-free survival cumulative hazard plots for four patient subgroups in the CLEOPATRA[18] trial

If in future it is possible to identify patients belonging to [redacted]

5.3.4 Modelling and projection of progression-free survival data

In the manufacturer's base-case decision analysis, Kaplan-Meier analysis results are used directly up to 35 months post-randomisation, and thereafter an exponential projection is applied to each trial arm. The exponential parameters are calibrated by least squares minimisation against the Kaplan-Meier results beyond 36 weeks for each arm. This approach leads to mean undiscounted PFS estimates of [redacted] months (pertuzumab) vs [redacted] months (control), a gain of [redacted] months favouring pertuzumab.

Although the ERG considers that the Kaplan-Meier data available are subject to serious bias, an exploratory projective modelling exercise was undertaken to assess the sensitivity of the manufacturer's method of curve-fitting to alternative assumptions. In the light of [redacted], the ERG considered that long-term hazard trends should only be estimated based on the segment of the trial data after 600 days. Moreover, it was observed that if the final data points showing evidence of serious bias (sudden upward rise) are ignored, then the long-term trends appeared to follow simple near-linear trajectories. On this basis the ERG fitted linear trend lines to estimate long-term linear hazard trends to each trial arm and applied these to project PFS from day 600 onwards.

This approach yielded ERG exploratory PFS mean undiscounted estimates of [redacted] months (pertuzumab) and [redacted] months (control), indicating a PFS gain of [redacted] months favouring pertuzumab.

Thus the ERG confirms that addition of pertuzumab to trastuzumab and docetaxel results in a clear improvement in PFS, though the size of that improvement is subject to considerable uncertainty.

5.3.5 Modelling and projection of overall survival data

In the manufacturer's base-case decision analysis [redacted] of the estimated life extension occurs in the post-progression health state, and [redacted] of the discounted QALY gain occurs after disease progression. However, it is clear from the Kaplan-Meier analysis of post-progression survival data from CLEOPATRA[18] (Figure 10)
[redacted]

Figure 10 Kaplan-Meier post-progression survival in the CLEOPATRA[18] trial

This finding casts serious doubt over the eleven different parametric model formulations for projecting long-term survival for both treatment arms included in the manufacturer's decision model. All these options involve long-term hazard trends which diverge so that the risk of death is greater in the comparator arm. The finding that [redacted]This can only be implemented in the manufacturer's model by overriding the parametric projections with an option to apply the long-term mortality trend from the Munich registry study equally in both arms of the decision model. The effect of this approach is to preserve the PFS gains from use of pertuzumab while reducing the PPS gains from [redacted] months to less than [redacted]. As a result, the estimated ICER is increased from [redacted] per QALY gained to [redacted] per QALY gained.

It is not possible to substitute a reliable alternative OS projective formulation directly into the model, because the manufacturer did not provide the revised Kaplan-Meier analyses requested by the ERG. The use of the biased data in the later stages on the trial period (as discussed above), would seriously impact on attempts to fit reliable long-term projective trends.

Probably the best method for arriving at a reliable estimate of OS benefits accruing from use of pertuzumab is to use the most robust estimate of PFS and add to it a small adjustment arising from any difference in the proportion of patients dying before disease progression ([redacted]). Applying this approach to the manufacturer's base-case results, reduces OS gain from more than [redacted] months to [redacted] months, reduces discounted QALY gain from [redacted]to [redacted] and consequently increases the estimated ICER from [redacted]per QALY gained to about £[redacted] per QALY gained.

5.3.6 Minor issues

Estimation of utility values

The manufacturer has employed the Lloyd[47] mixed methods utility model in a similar manner to its use in the NICE appraisal of eribulin (TA250).[43] However, there are some errors in the method of calculation which tend to bias the estimation of utility values in favour of pertuzumab:

- a formula error results in a slight over-estimate of the utility value for the progressive disease state (0.5 instead of the standard value of 0.4964)
- patient frequencies (proportions) for AEs have been used in the calculation of utility values instead of binary figures (0 or 1). This is inaccurate in a logistic model where estimates should be obtained separately for the states with and without each AE, and the results subjected to weighted averaging outside of the mixed model
- in the estimation of utilities for PFS, utilities for the progressive disease state have been erroneously included in the weighted average calculation

Table 34 Health state utility values using Lloyd[47] mixed methods model and CLEOPATRA[18] trial data

Health state	Manufacturer's utility value	ERG's utility value
Progression-free survival control arm (during docetaxel or paclitaxel)	0.7694	0.7864
Progression-free survival pertuzumab arm (during docetaxel or paclitaxel)	0.7719	0.7827
Progression-free survival control arm (after docetaxel or paclitaxel)	0.7767	0.7952
Progression-free survival pertuzumab arm (after docetaxel or paclitaxel)	0.7854	0.7989
Progressed	0.5000	0.4964

The differences in estimated utility values are shown in Table 34. Applying the ERG estimates increases the base case ICER by [redacted] per QALY gained.

Chemotherapy acquisition costs

Treatments with doses calculated according to individual body weight (trastuzumab) or according to BSA (docetaxel and paclitaxel) were calculated using the body measurements of all patients in the CLEOPATRA[18] trial, and an average cost calculated for each drug. However, CLEOPATRA[18] is a multi-national clinical trial with patients entered from centres in four continents. An analysis of patient characteristics by region indicates wide differences in body weight and size, ranging from Asians with an average weight of 57.0 kg and BSA of 1.55 m^2 to North Americans with mean weight of 74.0 kg and BSA of 1.77m^2. The ERG considers that using the average characteristics of the whole CLEOPATRA[18] trial is likely to underestimate the doses that would be required for UK patients. The

ERG has re-estimated chemotherapy acquisition costs using published survey estimates for England and Wales.[56] In addition, the ERG has employed two methods based on using either the latest BNF unit costs of generic medications, or the latest surveyed average NHS contract prices for November 2102 (eMIT[54]).

Table 35 indicates that the manufacturer's estimates for trastuzumab are 5% to 6% lower than those of the ERG. The manufacturer does not offer estimates based on the BNF list prices for generic products, and uses eMIT[54] prices which differ somewhat from the latest NHS negotiated prices.

The impact of these alterations on the cost-effectiveness of pertuzumab are quite small, only increasing the ICER by [redacted] (BNF prices) or [redacted](eMIT[54] prices) per incremental QALY gained.

Table 35 Chemotherapy acquisition cost per dose

Drug	Roche Base Case	ERG BNF prices	ERG eMIT[54] prices
Pertuzumab (loading)	£4790		
Pertuzumab (maintenance)	£2395		
Trastuzumab (loading)	£1638.17[a]	£1744.93	
Trastuzumab (maintenance)	£1284.72[a]	£1359.55	
Docetaxel	£33.81[a]	£760.49	£39.37
Paclitaxel	£20.58 [a]	£346.42	£12.58

BNF=British National Formulary; eMIT=Electronic Market Information Tool
[a] Values presented in the table are derived from the model, these differ slightly to those reported in the MS[1]

Chemotherapy administration costs

The ERG has reviewed the figures for the costs of chemotherapy administration in the manufacturer's model, and concluded that these have been overestimated. Revised estimates have been calculated using the most recent NHS Reference Costs for 2011/12.[50] Weighted average costs are used across the different modes of administration (day case / out-patient / other), and classifying a single infusion as 'simple parenteral chemotherapy', and multiple infusions at a single session as 'more complex'. In addition, the ERG has identified that pharmacy costs should apply to each infusion in a single session.

The effect of these changes is to reduce the costs of administration and to reduce the base-case ICER by [redacted]/QALY.

Duration of chemotherapy

The manufacturer's decision model offers two options for estimating the duration of treatment (and therefore the cost of treatment): the time from the beginning of the trial until disease progression

(PFS), or until the date of last treatment (TTOT). The former does not allow for patients and clinicians to decide to discontinue treatment for other reasons prior to disease progression. The ERG agrees with the manufacturer that the use of TTOT is fully justified in the base-case scenario, and more accurately reflects normal clinical practice.

Dosing variations for docetaxel

The CLEOPATRA[18] trial protocol allows the dose of docetaxel to be varied by investigators from the standard dose of 75mg/m^2 upwards to 100mg/m^2 or downwards to 55mg/m^2. The decision model estimates the cost of docetaxel according to the standard level (75mg/m^2). The ERG asked for further information on doses received by cycle, and this indicates that the overall average of doses received is only slightly different from the standard level (77.1mg/m^2 in pertuzumab patients and 74.3mm/m^2 in placebo patients). In view of the low price of generic docetaxel, the ERG considers these differences to be insignificant.

Adverse events and related costs

The proportion of patients experiencing AEs in the CLEOPATRA[18] trial CSR[36] do not appear to correspond to those shown in the MS[1] and submitted model. For example, Table 30 of the MS[1] shows Grade 3/4 febrile neutropenia in 7.14% of patients in control arm and in 13.43% in the pertuzumab arm (corresponding to 28 and 56 patients respectively). However, Table 66 of the 2011 CSR[35] shows only [redacted] patients with Grade 3/4 febrile neutropenia (the 2012 CSR[36] did not contain the corresponding table of febrile neutropenic infection events).

The selected NHS reference cost[50] for febrile neutropenia is for elective admissions costing on average £10,799 for a mean stay of 8.17 days. A more realistic option would be to use the non-elective unit cost of £4,384 (mean stay 5.55 days). The ERG also has concerns over the appropriateness of other unit costs for AEs in the manufacturer's model. However, in the base-case analysis AEs contribute less that [redacted] of the overall incremental cost, so that if it were possible to obtain more reliable information on the cost of AEs this is not likely to alter the size of the estimated ICER noticeably.

Probability sensitivity analysis coding error

A coding error has been detected in the manufacturer's model which affects the calculation of PSA results when exponential survival functions are used to project trial PFS and OS data. The single parameter governing the exponential function refers to an empty spreadsheet cell resulting in all PSA iterations taking the same erroneous parameter value of one. As a consequence PSA results reported by the manufacturer for exponential projection scenarios are unreliable.

5.3.7 Impact on the ICER of analysis by ERG

Table 36 shows the effect on the estimated ICER for use of pertuzumab of each of the model amendments considered appropriate by the ERG. The three cost and utility changes have only a minor impact, whereas changing the method of projecting OS to more closely reflect the finding that [redacted] has more than a minor impact. It has not been possible to implement accurate survival estimates due to the limitation of the trial data available to the ERG. However, the use of long-term mortality trends from the Munich Registry data[46] provide a very good approximation and provide a realistic scenario [redacted]. Overall, the ERG considers that a revised ICER of £[redacted] per QALY gain best reflects the cost-effectiveness of pertuzumab use in this population.

Table 36 Revised cost and outcome effects of ERG model amendments relative to the manufacturer's original base case analysis

Adjustment	Trastuzumab + docetaxel				Pertuzumab + trastuzumab + docetaxel				Incremental				
	Therapy cost	Other costs	Survival (months)[a]	QALYs	Therapy cost	Other costs	Survival (months)[a]	QALYs	Survival (months)[a]	Cost	QALYs	ICER (£/QALY)	ICER change
Original Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**0.833**	[redacted]	[redacted]
ERG utility values	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.828	[redacted]	[redacted]
ERG drug prices	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.833	[redacted]	[redacted]
ERG chemo admin costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.833	[redacted]	[redacted]
Munich survival estimates	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.432	[redacted]	[redacted]
Revised base case including all amendments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**0.430**	[redacted]	[redacted]

ICER=incremental cost-effectiveness ratio; QALY=quality adjusted life year
[a] survival is undiscounted, all other figures are discounted

6 END OF LIFE

There is no case put forward in the MS[1] to consider this treatment within the NICE End of Life criteria

7 OVERALL CONCLUSIONS

The currently available clinical data indicates that the addition of pertuzumab to the treatment regimen of trastuzumab and docetaxel in this patient population provides improved PFS. Overall survival data are not mature and modelling of the currently available data is limited.

The manufacturer presents a base–case ICER of [redacted] per QALY gained. The evidence presented in the MS[1] includes a PSA that demonstrates that pertuzumab compared with control has a 0% probability of being cost-effective at a willingness-to-pay of £30,000 per QALY gained.

Analysis of the trial data show that [redacted] unlike the estimates given in the manufacturer's base case. When this anomaly is corrected, the estimated ICER increases substantially. Model amendments made by the ERG (predominately related to OS) provide a revised ICER of [redacted] per QALY gained, which best reflects the cost-effectiveness of pertuzumab use in this population.

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9 APPENDICES

Appendix 1: Assessment of the risk of bias

Study question	Manufacturer response with reasoning	ERG comment
Was randomisation carried out appropriately?	Yes. After written consent was obtained and eligibility established, the study site obtained the patient's identification number and randomisation to treatment arm from the interactive voice response system. A complete block randomisation scheme was applied to achieve balance in treatment assignment within each of the eight strata, as defined by prior treatment status (*de novo* vs prior adjuvant or neoadjuvant therapy) and region (Europe, North America, South America and Asia)	Agree
Was the concealment of treatment allocation adequate?	Yes. A double-blind placebo control was used to minimise any bias.	The ERG agrees with the response but not the reasoning. The manufacturer's response to the ERG's clarification letter specified patients were allocated via an interactive voice response system, hence adequate treatment allocation
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes. The patient demographics and characteristics were generally well balanced in both arms of the study. However there were slightly fewer people in the placebo arm with an ECOG performance status of 0 indicating a slightly worse performance status in the placebo arm	Agree
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Yes. The study was designed as 'double-blind'. A placebo control was used to minimise bias in the assessment of disease response and adverse event reporting. Additionally the use of an Independent Review Facility to assess the primary endpoint of the study further minimised the risk of bias	Agree
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No. There were no unexpected imbalances in drop outs	Agree
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No. There is no evidence to suggest this	Agree [a]
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes. Efficacy analyses were conducted on the intention to treat population. Safety analyses were conducted on people who received at least one dose of study medication	Agree

[a] It is evident the manufacturer has been required to conduct a number of exploratory analyses which were not pre-specified, whether all were presented is not known with certainty

Appendix 2, clarification questions B1 and B2

The following two questions were included in the clarification letter sent to the manufacturer:

B1. **Priority Question:** Please provide full Kaplan-Meier analysis results (see SAS output table for example below) showing Kaplan-Meier survival estimates at each event time, for each treatment arm in the CLEOPATRA[18] trial for Overall Survival (OS), Progression-Free Survival (PFS), Time to Off Treatment (TTOT) and Post-Progression Survival (PPS). These analyses should use the May 2012 data-cut-off, be based on investigator assessments of disease progression, and any patient still at risk at the date of data-cut should be censored at the date of data-cut-off, *not* the date of last contact/assessment.

B2. **Priority Question:** Please provide full Kaplan-Meier analysis results (see SAS output table for example below) showing Kaplan-Meier survival estimates at each event time, for each treatment arm in the CLEOPATRA[18] trial, by the following sub-groups:

a) Patients with visceral disease
b) Patients with non-visceral disease

The same analyses for OS, PFS, TTOT and PPS should be carried out as for Question B1 (i.e. using same definition of disease progression, same data-cut-off and censoring rule).