NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Pertuzumab in combination with trastuzumab and docetaxel for treating HER2 positive metastatic or locally recurrent unresectable breast cancer

This premeeting briefing is a summary of:

- the evidence and views submitted by the manufacturer, the consultees and their nominated clinical specialists and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document is a summary of the information available before the manufacturer has checked the ERG report for factual inaccuracies.

Key issues for consideration

Clinical effectiveness

- The CLEOPATRA trial was conducted in 204 centres in 25 countries including the UK. The Evidence Review Group (ERG) noted that patients in the trial received a median of 8 cycles of treatment with docetaxel whereas standard practice in the UK is to administer up to a maximum of 6 cycles. The ERG further noted that there was a minority of patients in the trial (10.9% of the 808 randomised patients) who had previously received adjuvant or neoadjuvant therapy with trastuzumab, whereas in the UK the majority of patients will have received adjuvant therapy with trastuzumab. However, the ERG also noted that a post-hoc analysis for patients who had previously received trastuzumab requested by the Committee for Medicinal Products for Human Use provided results that were consistent with the results observed for the whole patient population in the CLEOPATRA trial. What is the Committee's view on the generalizability of the CLEOPATRA trial and its results to UK clinical practice?

- Two interim analyses of overall survival were conducted by the manufacturer (May 2011, when 165 patients had died; and May 2012, when 267 patients had died). The ERG agreed with the manufacturer that the overall survival data were immature and noted that no cross-over had occurred. Results for the first interim analysis showed a trend towards an increase in overall survival for the pertuzumab group compared with the placebo group; however this difference did not meet the criteria to be considered statistically significant. Results for the second analysis of overall survival showed that median overall survival was 37.6 months in the placebo arm but median overall survival had not been reached in the pertuzumab arm, this showed a statistically significant overall survival increase for pertuzumab compared with placebo. What is the Committee's view on the overall survival data?
- The manufacturer presented a number of subgroup analyses that were not listed in the scope. The ERG noted that patients with non-visceral disease did not obtain the same results from the addition of pertuzumab compared with patients with visceral disease in terms of progression-free survival (PFS) and overall survival and that the Committee for Medicinal Products for Human Use had requested further clarification on these results. What is the Committee's view on the subgroup analyses presented by the manufacturer?
- The manufacturer assumed similar clinical efficacy and safety of 3-weekly docetaxel and weekly paclitaxel based on its descriptive indirect comparison. The ERG noted that the manufacturer did not conduct any formal statistical analysis and considered that the evidence presented by the manufacturer was subject to a high degree of uncertainty and that no safety data had been presented in the manufacturer's comparison. The ERG considered that the conclusions from the manufacturer's indirect comparison should be taken with extreme caution. What is the Committee's view on the efficacy and safety of the different taxane regimens?
- The manufacturer noted that treatment with pertuzumab can extend survival and grants women more time to contribute to their families (both financially and via informal care of both children and elderly parents). It further noted that these wider societal benefits are not captured in the QALY calculation but highlighted that they should be taken into account because of society's potential preference for QALYs

gained in people with a high burden of illness. The manufacturer noted that this preference is not captured by the use of the end of life criteria. Does the Committee consider that special considerations should be taken into account when appraising pertuzumab for treating HER2-positive metastatic or locally recurrent breast cancer?

Cost effectiveness

- The manufacturer presented a de novo economic model based on the data observed in the CLEOPATRA trial and used these data to extrapolate survival in the model. The ERG requested additional analyses using a different censoring rule (censoring for the time of data cut-off) because of the risk of bias in the manufacturer's data (censoring for the last observation trial date). The manufacturer did not provide the additional analyses requested and the ERG concluded that it has been unable to offer alternative interpretations of the PFS, overall survival, time to off treatment and post-progression survival results in relation to long-term projection of survival gains. What is the Committee's view about the risk of bias in the manufacturer's analyses and the alternative analyses proposed by the ERG?
- The ERG agreed with the manufacturer that there was an increase in PFS for the pertuzumab arm compared with the placebo arm in the model but noted that the estimate of this gain was uncertain. The manufacturer's extrapolation of PFS data (based on Kaplan – Meier analysis up to week 35 followed by an exponential trajectory) estimated a PFS gain of [redacted] months favouring pertuzumab. The alternative ERG extrapolation (assuming linear trends in both arms from day 600 onwards) estimated a PFS gain of [redacted] months. What is the Committee's view on the PFS estimates used in the model?
- The manufacturer did not include any subgroup analyses in the economic model. The ERG noted that because of the differences in PFS found for people with metastatic breast cancer and visceral disease, the subgroup analyses would have helped to identify those patients for whom pertuzumab could potentially be more cost-effective. The ERG concluded that

  [redacted]

[redacted] What is the Committee's view on the potential cost-effectiveness of pertuzumab in this subgroup?

- The manufacturer applied a constant hazard of death post progression in the model that was lower for the pertuzumab arm compared with the placebo arm which resulted in a post progression survival gain of [redacted] months in the pertuzumab compared to the placebo arm. The ERG noted that this resulted in approximately [redacted] of the survival gain in the pertuzumab arm being generated in the post-progression state. The ERG considered that [redacted] and applied similar constant hazards of death post-progression to both treatment arms in the model based on the results observed in the Munich registry data. This resulted in a post-progression survival gain of less than [redacted] in the pertuzumab compared to the placebo arm. The ERG also estimated overall survival using the PFS estimates, adjusting them for the additional benefit post-progression due to the small difference between the 2 treatment arms in the proportion of patients still alive following disease progression and assuming that the long-term post-progression hazard is the same in both arms. This approach reduced the overall survival gain from [redacted] to [redacted] months. Both of the ERG's approaches to estimate overall survival yielded to similar ICERs, and both were higher than the manufacturer's base-case. What is the Committee's view on the post-progression survival estimates used by the manufacturer and the ERG?
- The manufacturer presented incremental results in its base case for the comparisons of pertuzumab plus trastuzumab and docetaxel with; trastuzumab and docetaxel, and with trastuzumab and paclitaxel. The manufacturer assumed, based on its indirect comparison, that docetaxel and paclitaxel were equally clinically effective and concluded that [redacted]. What is the Committee's view on these results in view of the ERG's comments on the manufacturer's indirect comparison?
- The ERG identified and corrected minor errors in the manufacturer's model: errors in the formula for the estimation of utility values; the method for adjusting the dose

of chemotherapy based on body surface area and weight of the patients; the sources for the calculation of chemotherapy acquisition and administration costs; inconsistencies between the incidence of adverse events shown in the CLEOPATRA clinical study report and those shown in the manufacturer's submission and the model; and the source of some adverse events costs. The ERG noted that these corrections had limited impact on the ICER. What is the Committee's view on the ERG's corrections to the manufacturer's model?

1 Background: clinical need and practice

1.1 Breast cancer is the most common malignant cancer affecting women in the UK. A breast lump is often the first symptom of breast cancer. Metastatic breast cancer describes the presence of disease at distant sites such as bone, liver, or lung. The lymph nodes may also be affected. HER2 is a receptor for a growth factor called human epidermal growth factor 2, which occurs naturally in the body. When human epidermal growth factor attaches itself to HER2 receptors on breast cancer cells, it can stimulate the cells to divide and grow. Some breast cancer cells have more HER2 receptors than others and the HER2 level is scored from 0 to 3+. Tumours expressing HER2 scored at levels of 3+ are known as HER2-positive. It is thought that about 1 in 5 women with breast cancer will have HER2-positive tumours. The aggressive nature of HER2-positive breast cancer is partly due to the activation of the receptor binding to other HER receptors, a process known as dimerization. This leads to increased proliferation of tumour cells and disease progression.

1.2 In 2010, there were 44,226 people diagnosed with breast cancer and over 10,000 people died in England and Wales. It has been estimated that 5% of women initially presenting with breast cancer have locally advanced disease or distant metastases. Approximately 20–30% of people with metastatic breast cancer have HER2-positive tumours.

1.3 Breast cancer incidence rates generally increase with age; with over 80% of new diagnoses in women aged over 50 years. It is estimated that 95%

of women are expected to survive their disease for at least 1 year and 85% of women survive 5 years or more.

1.4 The role of current treatments for metastatic breast cancer is to palliate symptoms, prolong survival and maintain a good quality of life with minimal adverse events. Treatment depends on, oestrogen receptor status, HER2 status and the extent of the disease. NICE Clinical Guideline 81 (Advanced breast cancer: diagnosis and treatment) recommends assessment of HER2 status at the time of disease recurrence if receptor status was not assessed at the time of initial diagnosis. NICE technology appraisal guidance 34 (The clinical effectiveness and cost effectiveness of trastuzumab for breast cancer) recommends trastuzumab in combination with paclitaxel as an option for people with tumours expressing HER2 scored at levels of 3+ who have not received chemotherapy for metastatic breast cancer and in whom anthracycline treatment is inappropriate. In clinical practice, trastuzumab in combination with either paclitaxel or docetaxel may be used as first-line therapy for people with HER2-positive metastatic breast cancer.

2 The technology

2.1 Pertuzumab (Perjeta, Roche Products) is a monoclonal antibody targeting HER2. Pertuzumab binds to the HER2 receptor and prevents the dimerization of HER2 with other HER family receptors, inhibiting intracellular signalling. It is administered by intravenous infusion. Pertuzumab has a UK marketing authorisation 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’. The recommended dose of pertuzumab is an initial loading dose of 840 mg followed every 3 weeks thereafter by a maintenance dose of 420 mg in combination with trastuzumab and docetaxel. Treatment with pertuzumab should be continued until disease progression or unmanageable toxicity.

2.2 The summary of product characteristics lists the following adverse reactions for pertuzumab: left ventricular dysfunction (including congestive heart failure), infusion reactions, hypersensitivity reactions (including anaphylaxis), neutropenia, febrile neutropenia, leucopenia, diarrhoea, alopecia and rash. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 The manufacturer's submission states that the list price of pertuzumab is £2395 per 420 mg vial (excluding VAT; Roche Products). Therefore the cost of pertuzumab (excluding VAT) is estimated to be £4790 for the initial dose, followed by £2395 for subsequent doses. Costs may vary in different settings because of negotiated procurement discounts.

3 Remit and decision problem(s)

3.1 The remit from the Department of Health for this appraisal was: To appraise the clinical and cost-effectiveness of pertuzumab in combination with trastuzumab and docetaxel within its licensed indication for the treatment of human epidermal growth factor receptor 2 (HER2) positive metastatic or locally recurrent unresectable breast cancer, which has not been previously treated, or has relapsed after adjuvant therapy.

	Final scope issued by NICE	**Decision problem addressed in the submission**
Population	Adults with HER2-positive 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	

3.2 The ERG noted that the population addressed by the manufacturer in its submission accurately reflects the marketing authorisation of pertuzumab. However, the ERG highlighted that current clinical practice in the UK is to administer trastuzumab plus chemotherapy in the adjuvant setting and that at the time the CLEOPATRA trial was conducted there was only a minority of patients (10.9% of the 808 randomised patients) pre-treated

with trastuzumab. The ERG considered that this proportion would be expected to be much greater in clinical practice.

	Final scope issued by NICE	Decision problem addressed in the submission
Intervention	Pertuzumab (in combination with trastuzumab and docetaxel)	

3.3 The ERG noted that the intervention in the manufacturer's submission is in line with the marketing authorisation of pertuzumab and the scope issued by NICE. The manufacturer and the ERG highlighted that in the CLEOPATRA trial, the median number of cycles of docetaxel was 8 and that in clinical practice in the UK, docetaxel is generally given a maximum of 6 cycles with 8 cycles only recommended in exceptional circumstances.

	Final scope issued by NICE	Decision problem addressed in the submission
Comparators	Trastuzumab in combination with a taxane (docetaxel or paclitaxel)	

3.4 The ERG noted that the comparators addressed by the manufacturer in its submission matched the comparators listed in the scope. The ERG's clinical expert highlighted that the preferred treatment for HER2-postive metastatic breast cancer is likely to be trastuzumab plus docetaxel, with paclitaxel only used in cases where clinicians felt weekly paclitaxel would be better tolerated than 3-weekly docetaxel.

	Final scope issued by NICE	Decision problem addressed in the submission
Outcomes	-progression free survival -overall survival -response rate -adverse effects of treatment -health-related quality of life	

	Final scope issued by NICE	Decision problem addressed in the submission
Economic evaluation	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.	

3.5 The ERG noted that the manufacturer had provided direct evidence on the outcomes listed in the scope and that the cost effectiveness analysis was assessed as recommended in the NICE reference case.

	Final scope issued by NICE	Decision problem addressed in the submission
Subgroups to be considered	None	

3.6 The ERG highlighted that the manufacturer presented the following subgroup analyses in the clinical effectiveness section of the submission based on the CLEOPATRA trial but no subgroups were included in the cost-effectiveness analyses:

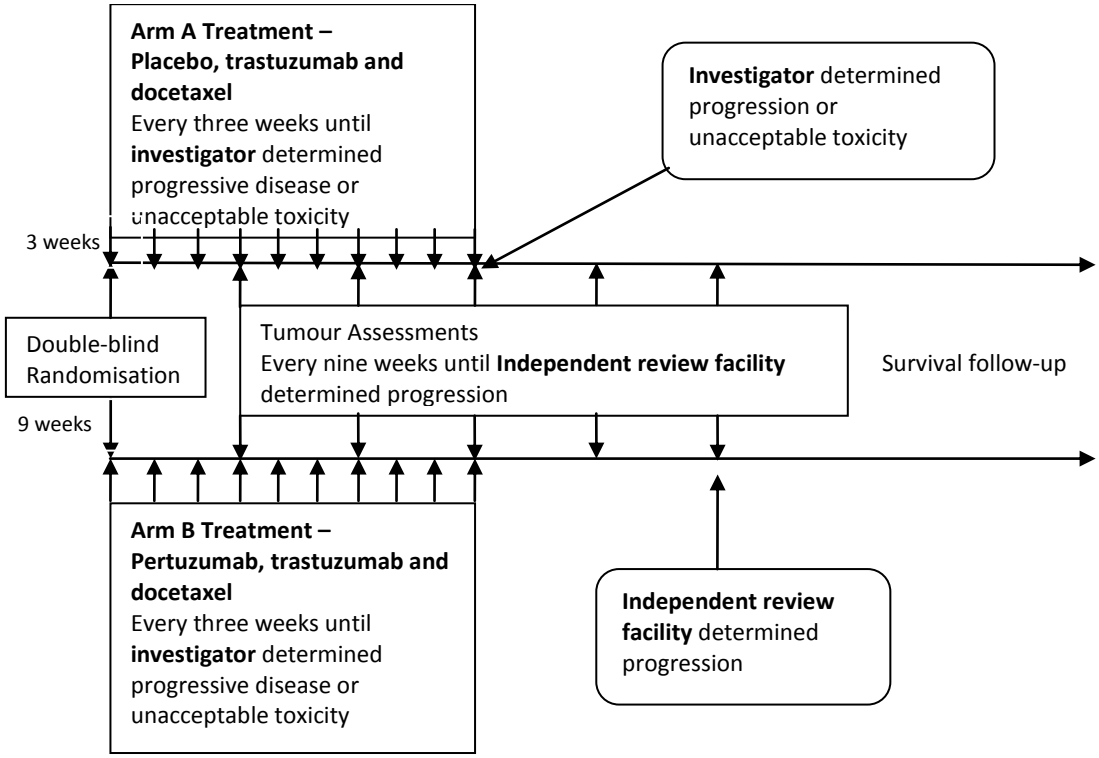
- Prior treatment
- Prior trastuzumab therapy
- Docetaxel dose escalation to 100mg
- Region
- Age group (>=65 vs <65)
- Age group (>=75 vs <75)
- Race
- Visceral disease status
- HER2 IHC status (3+)
- FISH status
- ER/PgR status
- ECOG PS
- HER2 IHC status (2+)

4 Clinical-effectiveness evidence

4.1 The manufacturer conducted a literature review and identified 1 randomised controlled trial, the CLEOPATRA trial, from which it obtained the key clinical evidence. The CLEOPATRA trial was a randomised, double-blind, placebo-controlled trial that assessed the efficacy and safety of pertuzumab plus tratuzumab and docetaxel in 808 adults with HER2-positive metastatic breast cancer in 204 centres in 25 countries including the UK. Investigators randomised patients in a 1:1 ratio to either pertuzumab plus trastuzumab and docetaxel (n=406) or placebo plus trastuzumab and docetaxel (n=404) (see figure 1). Patients received either pertuzumab at a loading dose of 840 mg followed by 420 mg every 3 weeks or placebo every 3 weeks until disease progression or unacceptable toxicity. All patients then received trastuzumab loading dose of 8 mg/kg body weight followed by 6 mg/kg body weight every 3 weeks and docetaxel 75 to100 mg/m^2 (at investigator discretion) every 3 weeks for at least 6 cycles.

Randomisation was stratified by geographic region (Asia, Europe, North America and South America) and prior treatment status (de novo and prior adjuvant or neoadjuvant therapy).

Figure 1 CLEOPATRA study design



Source: Manufacturer's submission, figure 3, page 35

4.2 The manufacturer stated that overall the baseline characteristics of the patients were comparable between treatment arms. The median age in both treatment arms was 54 years with over 80% of people in both treatment arms aged less than 65 years. The manufacturer noted that this age was comparable to the age reported in previous studies with trastuzumab but younger than the general population with breast cancer. The majority of patients were from a White (59.4%) or Asian (32.3%) ethnic group and approximately 50% of patients in each treatment arm had received prior adjuvant or neoadjuvant therapy. Of the 808 randomised patients 11.7% in the pertuzumab arm and 10.2% in the placebo arm had been treated with prior adjuvant or neoadjuvant trastuzumab. The manufacturer noted that the ECOG status was an imbalanced characteristic between treatment arms, with fewer patients in the placebo arm with an ECOG performance status of 0 (248 patients [61.1%] compared with 274 patients [68.2%] in the pertuzumab arm).

4.3 The primary endpoint in the CLEOPATRA trial was progression-free survival (PFS), defined as the time from randomisation to the first documented progressive disease as determined by the independent review facility according to the Response Evaluation Criteria for Solid Tumours (RECIST) criteria, or death from any cause (within 18 weeks of last tumour assessment), whichever occurred first. PFS was also assessed by investigator assessment (defined as the time from randomisation to the first documented radiographic progression based on RECIST criteria or death from any cause). Sensitivity analyses of PFS accounted for: a possible difference between investigator and independent review facility tumour assessments in which the earliest progression date assessed by either the independent review facility or the investigator was used; censoring at the time of next-line anti-cancer therapy; independent review facility assessed PFS on treatment in which events occurring no later than 42 days after the last administration of treatment were included in the analysis; potential bias introduced by varied tumour assessment intervals as a result of missed visits; timing to death including all deaths occurring more than 18 weeks after the last tumour assessment as an event; and controlling for treatment withdrawals due to toxicity. Other secondary endpoints were overall survival (defined as the time from randomisation to death from any cause), overall response rate (defined as a complete response or partial response determined by the independent review facility based on RECIST criteria on 2 consecutive occasions more than 4 weeks apart), duration of objective response (defined as the time from initial confirmed partial or complete response to progression or death from any cause) and health-related quality of life. Exploratory endpoints included time to response, clinical benefit response rate (defined as the percentage with an objective response or stable disease maintained for at least 180 days) and safety parameters.

4.4 Of the 808 randomised patients: 2 patients received no treatment; 1 patient received non-randomised treatment in the pertuzumab arm; and 2

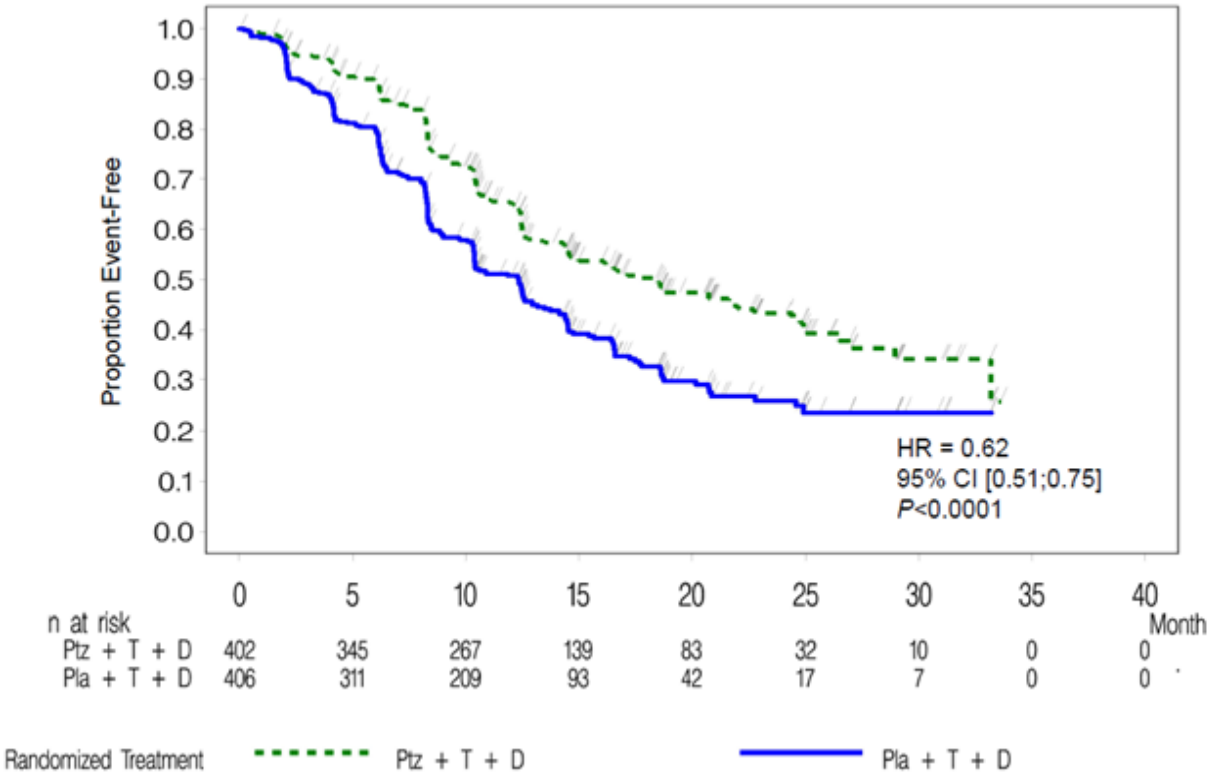
and 8 patients received no treatment and non-randomised treatment respectively in the placebo arm. Of the patients who actually received treatment, 223 (57.2%) and 279 (70.3%) patients stopped treatment in the pertuzumab and placebo arms respectively. The majority of them (87.1% and 88.9% in the pertuzumab and placebo arms respectively) stopped treatment because of a non-safety reason. The manufacturer did not include information on therapy received following disease progression.

4.5 Analysis of the primary endpoint, PFS assessed by the independent review facility in the intention-to-treat population, was based on a cut-off date of May 2011 once 191 (47.5%) patients in the pertuzumab arm and 242 (59.6%) people in the placebo arm had experienced disease progression or death. PFS in the pertuzumab arm was compared with the placebo arm using a stratified log-rank test. Stratification factors were prior treatment status (de novo and prior adjuvant or neoadjuvant therapy) and region (Europe, North America, South America and Asia). Results from an unstratified log-rank test were also presented. The manufacturer used Kaplan-Meier methodology to estimate the median PFS for each treatment arm and the stratified Cox proportional hazard to estimate the hazard ratio (HR) and its 95% confidence interval (CI) between the 2 arms. The manufacturer performed this analysis in pre-defined demographic subgroups, and it also carried out univariate and multivariate Cox regression analyses to investigate the association between the predefined stratification and baseline covariates with PFS.

4.6 At the cut-off date of May 2011 and for a median follow up of 19 months the independent review facility assessment analysis showed a statistically significant difference in median PFS of 6.1 months in favour of the pertuzumab arm (median PFS of 18.5 and 12.4 months in the pertuzumab and placebo arms respectively; HR 0.62, 95% CI 0.51 to 0.75, $p<0.0001$) (see figure 2). Median PFS assessed by the investigator at the cut-off date of May 2011 was also statistically significant different in the pertuzumab arm compared with the placebo arm (HR 0.65, 95% CI 0.54

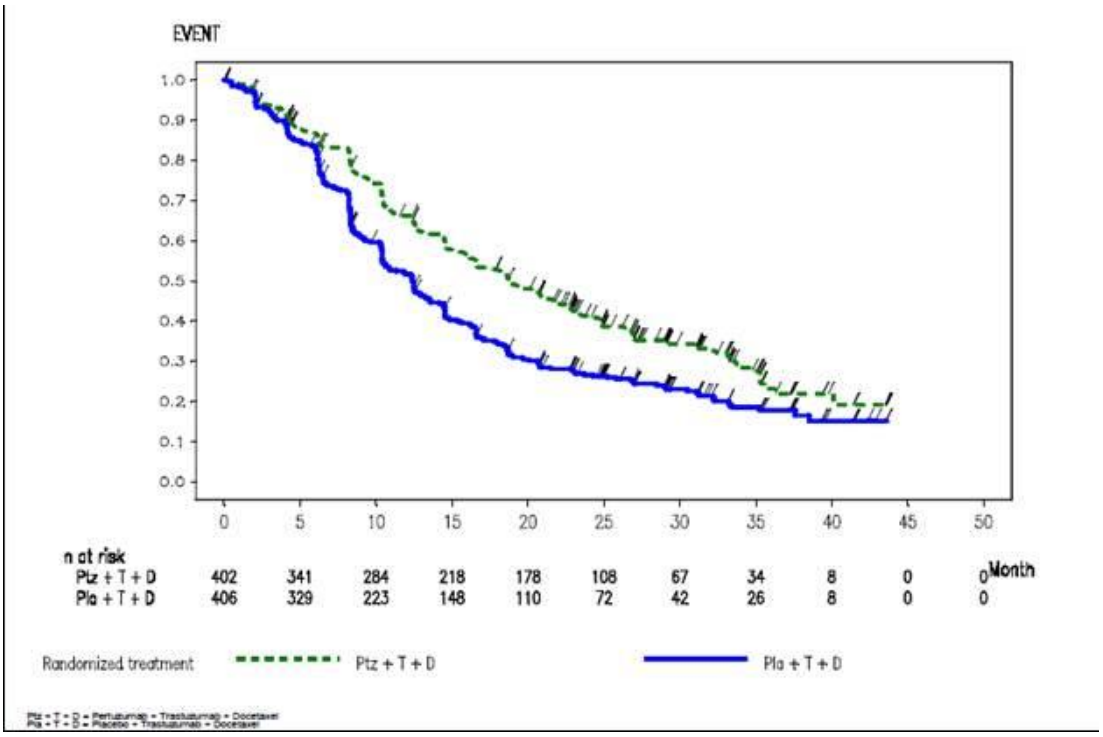
to 0.78, p<0.0001). The manufacturer also carried out an analysis of median PFS assessed by the investigators based on a data cut-off May 2012, when 1553 people (68%) had progressed or died (64% and 73% of the patients in the pertuzumab and in the placebo arm respectively) and for a median follow up of 30 months. Results showed that there was a difference in median PFS of 6.3 months (18.7 months in the pertuzumab arm compared with 12.4 months in the placebo arm; HR 0.69, 95% CI 0.58 to 0.81) (see figure 3). A summary of the results is shown in table 1.

Figure 2 Kaplan-Meier plots for PFS assessed by independent review facility (data cut-off May 2011)



Source: Manufacturer's submission, figure 5, page 63

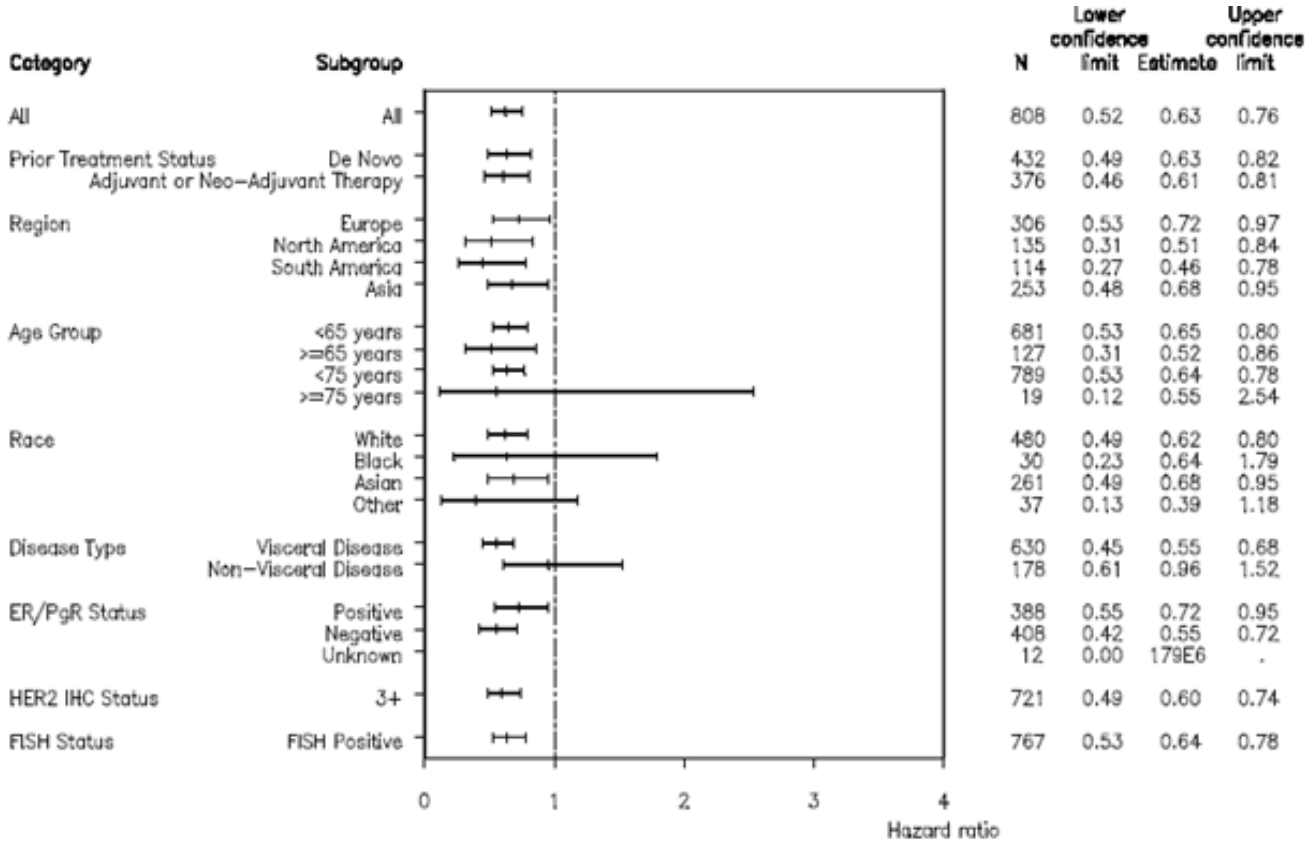
Figure 3 Kaplan-Meier plots PFS assessed by investigators (data cut-off May 2012)



Source: Manufacturer's submission, figure 9, page 71

4.7 The manufacturer also conducted subgroup analyses for PFS based on the predefined stratification and baseline factors (see figure 4). PFS results based on independent review facility assessment (data cut-off May 2011) were generally consistent with the results seen in the study population. For the subgroup based on disease type (visceral and non-visceral disease) the HR for PFS was 0.55 (95% CI 0.45 to 0.68) for people with visceral disease (N=630) and 0.96 (95% CI 0.61 to 1.52) in people with non-visceral disease (statistical test for interaction p=0.0332).

Figure 4 PFS assessed by independent review facility (data cut-off May 2011)

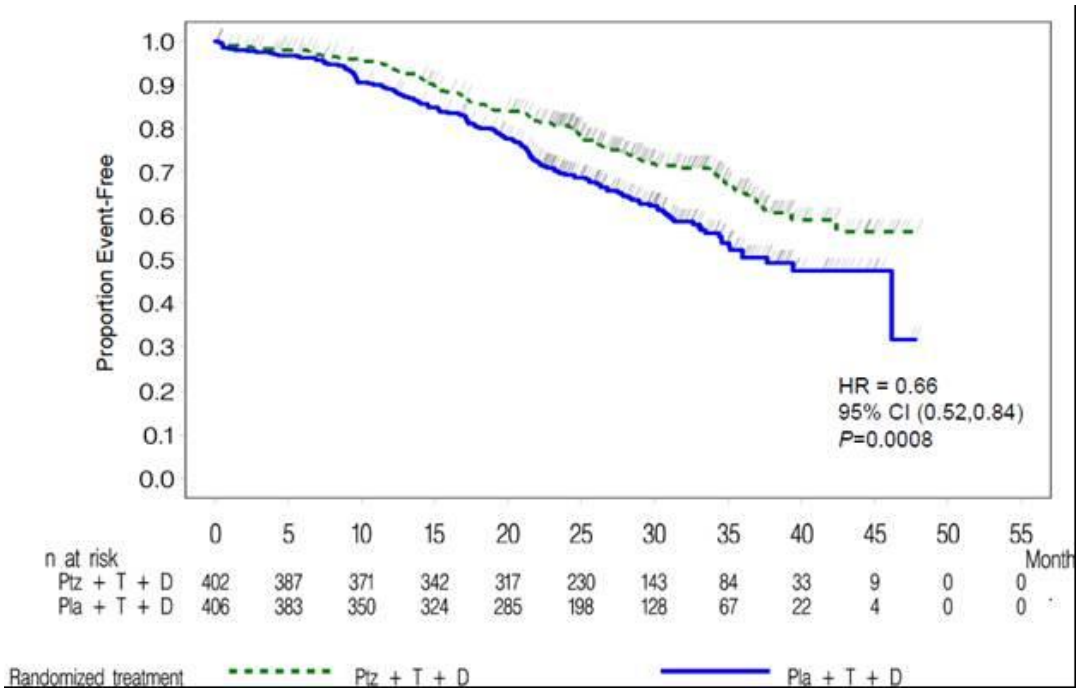


Source: Manufacturer's submission, figure 6, page 65

4.8 Two interim overall survival analyses were conducted by the manufacturer for data cut offs May 2011 and May 2012 respectively. The second overall survival analysis was required by the regulatory authorities at the time the first overall survival analysis was presented. The manufacturer states that the final overall survival data will be presented after approximately 385 deaths. It stated that to account for the first interim analysis a Lan-deMets α-spending function with the O'Brien−Fleming stopping boundary was applied to the overall survival analyses making the alpha level to be 0.0031. Results for the first interim analysis (May 2011) showed a trend towards an increase in overall survival for the pertuzumab group compared with the placebo group, however this difference did not meet the criteria to be considered statistically significant (HR 0.64, 95% CI 0.47 to 0.8, p=0.005). At the time of the second interim analysis (May 2012),

267 deaths had occurred (113 deaths [28.1%] in the pertuzumab arm and 154 deaths [37.9%] in the placebo arm) for a median follow-up of 30 months in both arms. The manufacturer noted that in order to allow formal statistical interpretation of the second interim overall survival analysis without inflating the overall type I error, the Lan − DeMets α-spending function with the O'Brien − Fleming stopping boundary was applied in the same way as for the first overall survival interim analysis making the boundaries to be HR ≤ 0.739, p ≤ 0.0138. Results for the second analysis (May 2012) of overall survival showed that median overall survival was 37.6 months in the placebo arm but the median overall survival had not been reached in the pertuzumab arm, with a statistically significant overall survival increase for pertuzumab compared with placebo (HR 0.66, 95% CI 0.52 to 0.84, p=0.0008) (see table 1 and figure 5). The manufacturer conducted sensitivity analyses on overall survival and concluded that all results supported the overall survival gain with pertuzumab in comparison with placebo in the second overall survival analysis.

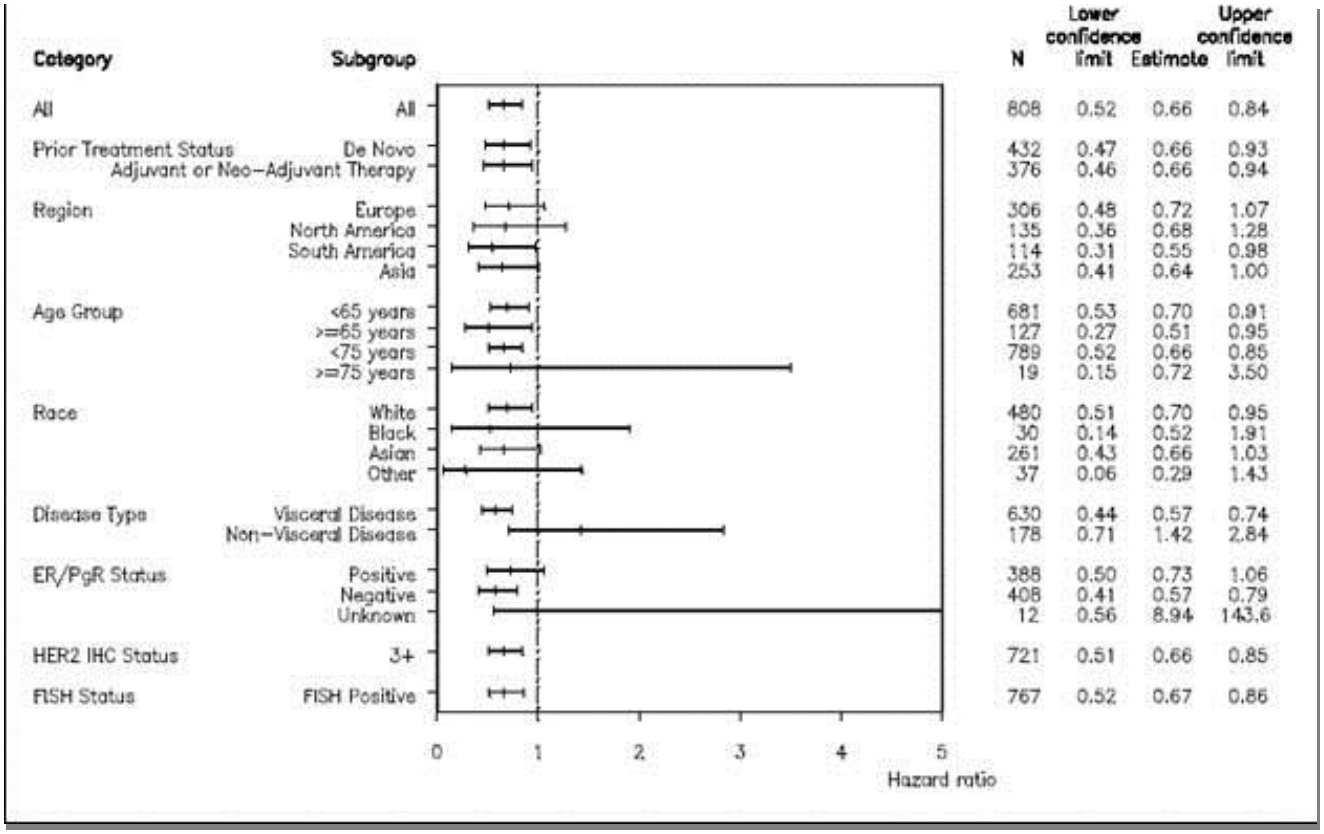
Figure 5 Kaplan-Meier plots for overall survival (data cut-off May 2012)



Source: Manufacturer's submission, figure 7, page 67

4.9 The manufacturer also reported subgroup analyses of overall survival based on the predefined stratification and baseline factors (see figure 6). The majority of these subgroup analyses were consistent with the results seen in the overall survival analysis for the study. For the subgroup of people with non-visceral disease the HR for overall survival was 1.42 (95% CI 0.71 to 2.84). The manufacturer noted that the variability around this estimate in this subgroup was demonstrated in its wide confidence interval, and that the sample size and the number of patients who died in this subgroup were low (33 of 178 patients died [18.5%]). The manufacturer explained that the Committee for Medicinal Products for Human Use concluded that the relatively small sample size of this subgroup and low event rate may have affected the probability to detect a true treatment effect and that the licence of pertuzumab should not be restricted based on visceral disease status. Subgroup analyses for prior treatment status were consistent with the results seen in the study population.

Figure 6 Subgroup analyses for overall survival (data cut-off May 2012)



Source: Manufacturer's submission, figure 8, page 69

Table 1 PFS and overall survival results

Outcome	Pertuzumab[a]	Control[b]	Result between arms
PFS (IRF assessment, first data-cut) n No (%) people with event Median time to event (months)	 402 191 (47.5) 18.5	 406 242 (59.6) 12.4	 HR 0.62 (95% CI: 0.51 to 0.75) p <0.0001
PFS (local assessment, first data-cut)[c] n No (%) people with event Median time to event (months)	 402 [redacted]18.5	 406 [redacted]12.4	 HR 0.65 (95% CI: 0.54 to 0.78)
PFS (local assessment, second data-cut) n No (%) people with event Median time to event (months)	 402 257 (63.9) 18.7	 406 296 (72.9) 12.4	 HR 0.69 (95% CI: 0.58 to 0.81) p <0.0001
OS (first data-cut)[d] n No (%) people who died Median time to event (months)	 402 [redacted]not reached	 406 [redacted]not reached	 HR 0.64 (95% CI: 0.47 to 0.88) p=0.0053
OS (second data-cut) n No (%) people who died Median time to event (months)	 402 113 (28.1) not reached	 406 154 (37.9) 37.6	 HR 0.66 (95% CI: 0.52 to 0.84) 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
[d] Data taken from p119 of 2011 Clinical Study Report

Source: ERG's report, table 7, page 28

4.10 Objective response (data cut-off May 2011) was based on the best overall response (complete response or partial response) recorded from the start of trial treatment until independent review facility assessed progression, death or first administration of next line anti-cancer therapy. A higher percentage of patients achieved objective response in the pertuzumab arm (275 patients [80.2%]) compared with the placebo arm (233 patients [69.3%], p=0.0011). The median duration of objective response was longer in the pertuzumab arm (87.6 weeks) compared with the placebo arm (54.1 weeks) (HR 0.66, 95% CI 0.51 to 0.85). The manufacturer also conducted a sensitivity analysis of objective response based on investigator assessment in the intention-to-treat population with investigator determined measurable disease (n=367 in the pertuzumab arm, n=371 in the placebo arm). These results were in line with the independent review facility analysis (284 patients [77.4%] in the

pertuzumab arm compared with 253 patients [68.2%] in the placebo arm, p=0.0049). Median duration of response assessed by the investigators was also in line with results in the independent review facility analysis (73.7 weeks in the pertuzumab arm compared with 54.0 weeks in the placebo arm, HR 0.67, 95% CI 0.52 to 0.85) (see table 2).

Table 2 Objective response and duration of response

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

Source: ERG's report, table 8, page 29

4.11 Health-related quality of life was measured with the Functional Assessment of Cancer Therapy-Breast (FACT-B) version 4 questionnaire which provides a total quality of life score and information about physical well-being, social/family wellbeing, functional wellbeing, and disease-specific concerns (data cut-off May 2011). This questionnaire was completed at each scheduled visit every 9 weeks only for female patients

(806 people). A decrease of 5 points in a specific composite score (FACT TOI-PFB) from the FACT-B questionnaire derived from the physical wellbeing, functional wellbeing and additional concerns subscales was used to measure time to symptom progression. No differences between treatments arms in terms of health related quality of life were reported. The number of patients experiencing symptom progression was similar in the 2 treatment arms (239 [59.5%] in the pertuzumab arm and 229 [56.7%] in the placebo arm) with a median time to symptom progression of 18.4 weeks in the pertuzumab arm compared with 18.3 weeks in the placebo arm (HR 0.97, 95% CI 0.81 to 1.16).

4.12 The manufacturer in its submission stated that the safety profile for all patients treated with pertuzumab (n=1412) taken from the key CLEOPATRA trial and 16 other phase I and II studies was consistent with the safety profile observed in CLEOPATRA and noted that 57.7% of 1412 patients received concurrent chemotherapy (with or without trastuzumab) and that it was expected that the safety profile of pertuzumab would be dominated by the toxicity of any concurrent chemotherapy. The manufacturer presented adverse event data for both data cut-off dates in CLEOPATRA and mentioned that overall the results were similar between the 2 analyses. The incidence of serious adverse events (data cut-off May 2012) was higher in the pertuzumab arm (36.3%) compared with the placebo arm (29.0%) and the incidence of adverse events leading to dose interruption or modification was higher in the placebo arm (61.8%) compared with the pertuzumab arm (54.3%) (see table 3).

[redacted]. The incidence of diarrhoea, rash, mucosal inflammation, febrile neutropenia, dry skin and pruritus was at least 5% higher in the pertuzumab arm compared with the placebo arm, whereas peripheral oedema and constipation were more common in the placebo arm. The manufacturer noted that the incidence of febrile neutropenia was likely to be associated with docetaxel treatment and that no febrile neutropenia events occurred after docetaxel was stopped in the

trial. The manufacturer also mentioned that people from Asia experienced more febrile neutropenia events. It explained that this could be because docetaxel clearance is reduced in people with low body surface area and concluded that the incidence of febrile neutropenia in CLEOPATRA was likely to be greater than the expected incidence for the UK population. The incidence of left ventricular dysfunction and cardiac heart failure was similar in both treatment arms although more serious cardiac adverse events occurred in the placebo arm (3.5%) compared with the pertuzumab arm (1.7%).

Table 3 Summary of adverse events (data cut-off 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, section 5.11and p1422

Source: ERG's report, table 13, page 37

4.13 The manufacturer noted that there are 2 taxanes (paclitaxel and docetaxel) that are routinely used in clinical practice with trastuzumab for treating HER2-positive metastatic breast cancer but that there is no direct evidence that compares the efficacy of pertuzumab plus trastuzumab and docetaxel compared with trastuzumab plus paclitaxel and therefore an indirect comparison of these 2 regimens was needed. The manufacturer noted that the relative efficacy of docetaxel and paclitaxel (albeit as monotherapies) was discussed in NICE technology appraisal guidance 214 (Bevacizumab in combination with a taxane for the first-line treatment of metastatic breast cancer) where the Appraisal Committee concluded that the evidence available indicated that 3 weekly docetaxel and weekly

paclitaxel were clinically equivalent. The manufacturer referred to the rationale of the discussion in NICE technology appraisal guidance 214 where, based on a naïve indirect comparison of 2 different trials, it was shown that docetaxel had comparable efficacy and safety profiles when compared with paclitaxel when used in combination with trastuzumab for the treatment of HER2-positive disease (Slamon et al. 2011; Marty et al. 2005). The manufacturer also noted that there was a study (Sparano et al. 2008) that provided head to head evidence on the relative efficacy of different taxanes in the adjuvant treatment for HER2-negative early disease that showed that 3 weekly docetaxel and weekly paclitaxel were the most effective regimens with similar 5-year disease free survival and overall survival results. The manufacturer concludes that because of: the lack of direct evidence in the metastatic setting; the data available from naïve indirect comparisons in the metastatic setting and head to head data in the adjuvant setting; the opinion of the manufacturer's clinical experts; and the Appraisal Committee discussion in NICE technology appraisal guidance 214 the outcomes for people treated with trastuzumab in combination with weekly paclitaxel would be similar to the outcomes observed for the placebo arm in the CLEOPATRA trial.

Evidence Review Group comments and exploratory analyses

4.14 The ERG considered that the manufacturer's search strategy in the systematic review of the clinical effectiveness was sufficient. It was satisfied that all relevant evidence was identified for the direct comparison of pertuzumab plus trastuzumab and docetaxel compared with trastuzumab and docetaxel. The ERG identified 2 relevant additional publications published after the original search conducted by the manufacturer. The ERG noted that in addition to the main publication which presented the CLEOPATRA trial results, the manufacturer stated that 5 further full-text publications of the same trial had been identified but no citations for these publications were provided. However, the manufacturer provided in its submission 9 additional citations for the CLEOPATRA trial of which 8 were conference abstracts.

4.15 The ERG considered the CLEOPATRA trial to be of good methodological quality with minimum risk of bias. The ERG highlighted that the manufacturer stated that blinding was maintained during the whole trial duration but noted that the incidence of adverse events associated with a specific drug could have added a risk of bias. As the incidence of adverse events was similar in both treatment arms and the estimates of PFS were similar in relative and absolute terms the ERG concluded that the risk of bias was low. The ERG stated that with the exception of protocol violations, statistical tests for interaction for subgroup analyses, and additional data on adverse events and health related quality of life subsequently requested in the clarification stage, the manufacturer's submission presented the relevant data. The ERG further noted that the manufacturer did not include information on therapy received following disease progression but identified 1 publication (published after the manufacturer's search was carried out) that included these data (Swain et al. 2013). The ERG heard from clinical experts that clinical practice in the UK is to administer a maximum of 6 cycles of docetaxel; whereas the CLEOPATRA trial allowed patients to receive a minimum of 6 cycles of docetaxel therapy, after which continuation was at clinician's discretion. Patients in the CLEOPATRA trial received a median of 8 cycles of docetaxel therapy. The ERG also noted that a minority of patients in the CLEOPATRA trial (n=88) had received prior adjuvant or neoadjuvant treatment with trastuzumab which is standard of care in the UK and stated that it was unclear if the results observed in the CLEOPATRA trial would be observed in clinical practice. However, the ERG noted that a post-hoc analysis for patients who had previously received trastuzumab requested by the Committee for Medicinal Products for Human Use provided results that were consistent with the results observed for the whole patient population in the CLEOPATRA trial.

4.16 The ERG noted that the overall survival data from the CLEOPATRA trial were immature. It considered that the main uncertainty around these results was that it was not possible to estimate the absolute difference in

median overall survival between patients in the pertuzumab arm and in the placebo arm because median overall survival had not been reached in the pertuzumab arm. The ERG noted that the manufacturer stated in its submission that final overall survival data will be presented after approximately 385 deaths (expected to be mid to late 2014). The ERG highlighted that it may be hypothesised that apparent improvements in overall survival observed for the pertuzumab arm may arise from subsequent lines of treatment rather from pertuzumab. However, the ERG noted that Swain et al. (2013) showed that treatments received by patients who discontinued study treatment were similar in both treatment arms and that pertuzumab was not provided as a subsequent line of treatment. The ERG considered that this minimised the risk of bias in the overall survival results.

4.17 The ERG noted that there were a large number of subgroup analyses included in the manufacturer's submission and considered that this is not generally recommended because it increases the probability of chance results. The ERG highlighted the results obtained for the subgroups of patients with visceral and non-visceral disease. It noted that patients with visceral disease tend to have worse outcomes than those with non-visceral disease but that in the CLEOPATRA trial patients with non-visceral disease appear to have smaller benefit from the addition of pertuzumab. The manufacturer noted that the Committee for Medicinal Products for Human Use requested the manufacturer conduct further analyses on this and the manufacturer included these analyses in the clarification response along with the explanation provided to the Committee for Medicinal Products for Human Use. The ERG noted that the manufacturer stated that differences in key baseline characteristics, the relative lower event rate of PFS in this subgroup and the wide confidence intervals around the hazard ratio for patients with non-visceral disease could have affected these results. The ERG also highlighted an issue related to the subgroup analysis for patients who received a higher dose of docetaxel. It noted that in the European public assessment report

it was reported that relatively few patients (n= 109) had received the increased dose (up to 100 mg/m^2) of docetaxel in the trial and that the data indicated that the higher dose did not have a major impact on the efficacy results.

4.18 The ERG noted from the clinical study report of the CLEOPATRA trial that [redacted] patients stopped treatment [redacted] or trastuzumab ([redacted]patients stopped treatment [redacted] [redacted]. The ERG agreed with the manufacturer that the incidence of adverse events was similar in both treatment arms and that the estimates of PFS were similar in relative and absolute terms.

4.19 The ERG discussed the indirect evidence provided by the manufacturer in its submission for the comparison between docetaxel and paclitaxel. The ERG noted that the manufacturer concluded that docetaxel has been shown to have comparable efficacy and safety profile when compared with paclitaxel but noted that the manufacturer did not conduct any formal statistical analyses to support this statement. In contrast, the ERG noted that the manufacturer based its conclusion on a descriptive indirect comparison of 2 trials comparing trastuzumab plus a taxane in the metastatic setting, and a head to head comparison of 3 weekly docetaxel and weekly paclitaxel regimens in the adjuvant setting. The ERG reviewed these studies and considered that extreme caution should be taken because there were differences in terms of the patient populations in the trials and because in the head to head comparison conducted in the adjuvant setting, patients did not receive trastuzumab. It highlighted that in 1 study 98% of patients treated with trastuzumab plus paclitaxel or paclitaxel alone had received prior adjuvant chemotherapy and 92% prior hormonal therapy (Slamon et al. 2001); and in the other study 69% and 45% of patients treated with trastuzumab plus docetaxel or docetaxel alone received prior adjuvant and hormonal therapy respectively (Marty et

al. 2005). It also noted that all patients included in the head to head comparison received prior chemotherapy (Sparano et al. 2008). In contrast, 47% and 25% of patients received prior treatment with chemotherapy and hormonal therapy respectively in the CLEOPATRA trial. The ERG further noted that the manufacturer did not present safety data for the comparison between docetaxel and paclitaxel and highlighted that safety data from Sparano et al. (2008) showed that paclitaxel has generally a more favourable safety profile than docetaxel in patients with early breast cancer who received treatment in the adjuvant setting. The ERG noted that naïve indirect comparisons, such as these, have been criticised for discarding the within trial comparison, increasing the risk of bias and presenting estimates without a degree of uncertainty (such as confidence intervals).

5 Comments from other consultees

5.1 The professional and patient groups agreed that the current management of HER2 positive metastatic breast cancer was treatment with trastuzumab and chemotherapy (often docetaxel). The professional groups noted that in clinical practice the majority of patients would receive neo/adjuvant trastuzumab, whilst in the trial it was only a minority of patients who received trastuzmab in the neo/adjuvant setting.

5.2 The professional groups commented on the outcome measures in the CLEOPATRA trial. They noted that the trial measured progression-free survival and stated that this is an appropriate outcome. They commented that because the trial restricted cross over between treatment arms PFS outcomes should predict overall survival.

5.3 Patient groups highlighted that it was important to patients to have control of disease progression and to have access to treatments that would improve their quality of life allowing them to spend more quality time with their friends and family. They stated further that patients are often willing to experience significant side effects to gain control of the disease and

hope for potential survival benefit, even of a few weeks or months. Furthermore, as progression can be associated with a decrease in quality of life, preventing progression delays the debilitating symptoms and emotional distress and may allow patients to continue some aspects of their normal daily life. The professional groups supported this statement, noting that as there is no cure for the disease, controlling disease progression can give patients a more positive outlook on their treatment regimen and the course of their illness.

5.4 Patient groups highlighted that early clinical data from the CLEOPATRA trial indicated improved PFS and overall survival results with pertuzumab, and that the side effects experienced in the pertuzumab arm of the study would be tolerable. They noted that improvements in overall survival by only a few months or weeks is extremely important to these patients, where life expectancy is significantly reduced due to disease progression.

5.5 Patient and professional groups noted that treatment with pertuzumab is given at the same time as current standard therapy and therefore does not need any additional hospital visits or venous access. The professional groups however noted that pertuzumab delivery time would increase by at least 1 hour. The professional groups commented further that pertuzumab would be prescribed in secondary care, but could be delivered in primary care or at home as is the case for trastruzumab.

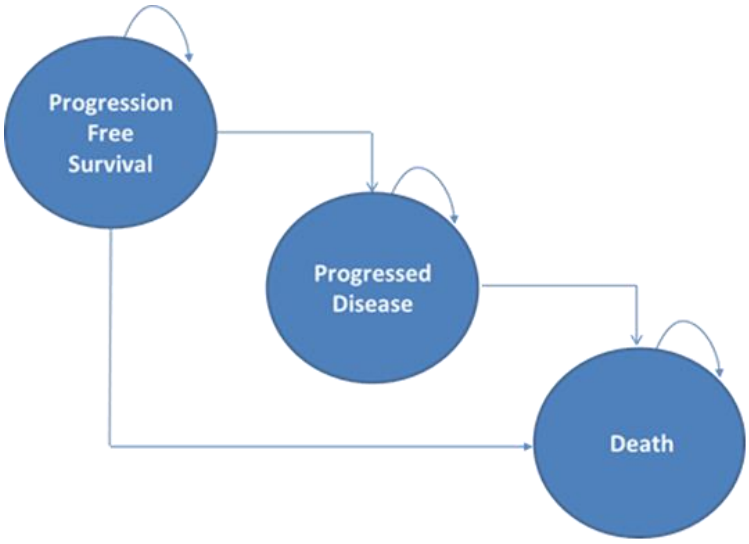
6 Cost-effectiveness evidence

6.1 The manufacturer carried out a systematic review to identify published economic evaluations in the use of pertuzumab plus trastuzumab and docetaxel in comparison with trastuzumab plus docetaxel or paclitaxel for treating HER2-postive metastatic breast cancer. Of the 10 publications identified, none of them were considered relevant by the manufacturer because they were not cost-effectiveness analyses and did not include pertuzumab as an intervention.

Manufacturer's economic model

6.2 The manufacturer submitted a de novo economic analysis that assessed the cost effectiveness of pertuzumab plus trastuzumab and docetaxel compared with: placebo plus trastuzumab and docetaxel; and trastuzumab and paclitaxel for treating people with HER2-positive metastatic breast cancer who have not previously received chemotherapy or HER2 therapy in the metastatic setting. The model was a partitioned survival model with 3 states consisting of progression-free survival (PFS), progressed disease and death (see figure 7). Data from the CLEOPATRA trial were used to guide model inputs. The cost-effectiveness analysis was conducted from an NHS and personal social services perspective, costs and outcomes were discounted at 3.5% per annum and a lifetime time horizon that equates to 25 years was used. The cycle length was 1 week.

Figure 7 Model structure



Source: Manufacturer's submission, figure 13, page 106

6.3 All patients entered the model in the PFS state. Inputs in the model were estimated using parametric survival functions for both PFS and overall survival from the May 2012 analyses of the CLEOPATRA trial. The proportion of patients in the PFS state was derived using the Kaplan-Meier estimates observed in the trial and the proportion of patients in the

progressed disease state was the difference between the proportion of patients that were alive and the proportion of patients that were progression-free. The progressed disease state represented the duration from first treatment relapse until death and included the possible sequence of remission and relapse of second line treatments.

6.4 PFS in the model was derived using the Kaplan-Meier estimates observed in both treatment arms in the CLEOPATRA trial (data cut-off May 2012). The manufacturer presented the Kaplan-Meier plots and cumulative hazard plots to investigate the change in the hazard of progression over time that guides the extrapolation of the observed data in the model. The manufacturer noted that this method could guide both the extrapolation of the baseline risk without the intervention and how the intervention arm may differ from that baseline risk if further follow-up were available. The manufacturer noted that for the placebo arm there were 2 distinct periods of time with different constant linear hazards associated, these being the hazard of progression which was steeper up to week 86 and then flatter from week 87 onwards. The hazard of progression in the pertuzumab arm seemed to be constant and linear over time and lower when compared with the hazard of progression in the placebo arm. The manufacturer investigated different scenarios based on the relatively stable hazard observed in the placebo arm from week 87 onwards and the possibility to use an exponential function when extrapolating these data in the model. The 4 possible explanations investigated by the manufacturer were:

- Scenario 1: the flattening of the curve may be due to small number of people at week 87 in the placebo arm and the steep part of the curve may reflect the true hazard rate of people treated with placebo. This scenario utilised the probability of remaining in PFS observed up to week 86 and used an exponential function to extrapolate these data onwards.

- Scenario 2: the flattening of the curve is actually reflecting the true probability of remaining in PFS for people in the placebo arm. This scenario assumed that PFS in the placebo arm was composed of 2 different curves.

- Scenario 3: if people in the pertuzumab arm were followed up over a longer period of time the curve would experience a flattening similar to that seen in the placebo arm representing a separate clinically distinct cohort of people in both treatment arms that responds better to treatment than those in the steeper part of the curve. This scenario applied the same weekly transition probability used to extrapolate the flattened part of the placebo curve to the pertuzumab curve from week 117 onwards. The manufacturer mentioned that week 117 was considered as a transition point from using Kaplan-Meier data and the exponential tail in the pertuzumab arm because this was the point at which the observed Kaplan-Meier data flattened slightly before rising sharply, that is what would be expected to be seen if there were 2 clinically distinct cohorts of people in the arm.

- Scenario 4: if the flattening of the curve represents a separate clinically distinct cohort of people that respond better to treatment than those in the steeper part of the curve, then the treatment benefit associated with pertuzumab would also be seen if people in the trial were followed for a longer duration. In this scenario the manufacturer multiplies the hazard rate observed on the flat part of the placebo curve by the hazard ratio observed for the steep parts of both arms and used the relative treatment effect associated with pertuzumab observed up to week 139 for the extrapolation onwards.

The manufacturer chose scenario 3 for the base case in its economic model. It noted that based on its clinical experts' advice, there was a group of people that had a long-term response to treatment with trastuzumab in clinical practice, and that it was clinically plausible that the

addition of pertuzumab resulted in a longer duration of response compared with trastuzumab. The manufacturer explored the rest of the scenarios and alternative extrapolation approaches in its sensitivity analyses.

6.5 Overall survival in the model was also derived using the Kaplan-Meier estimates observed in both treatment arms in the CLEOPATRA trial (data cut-off May 2012). The manufacturer also presented the Kaplan-Meier plots and cumulative hazard plots to investigate the change in the hazard of death over time that guides the extrapolation of the observed data in the model. The manufacturer mentioned that the hazard of death in both treatment arms appeared to be low for the first 8 months followed by an increased but constant hazard that may be due to the exclusion criteria preventing people who were at immediate risk of death from being included in the trial. The manufacturer incorporated the hazards of death in both treatment arms in the model using Kaplan-Meier data up to month 35 and used a constant hazard from that point onwards. The manufacturer noted that the last concordance between the trend and the observed data before the cumulative hazard plot became erratic was observed at month 35. The manufacturer assessed the external validity of these curves based on a registry of 523 people with HER2-positive metastatic breast cancer between 2002 and 2009 in Munich (Germany) and noted that the cumulative hazard plots indicated a constant linear hazard that supported the use of the exponential distribution for extrapolating the data. The manufacturer explored alternative extrapolation approaches in sensitivity analyses.

Utility values

6.6 The manufacturer noted that there was no mapping function available to transform the quality of life data collected from the CLEOPATRA trial to utility values to be used in the model. The manufacturer therefore conducted an update of a previous search carried out for NICE technology appraisal guidance 263 (Bevacizumab in combination with capecitabine

for the first-line treatment of metastatic breast cancer) to identify relevant utility values that had been used in economic evaluations of treatments for metastatic breast cancer. The manufacturer's updated search identified no new relevant studies. Utility values applied in the model were obtained from a regression analysis detailed in a study (Lloyd et al. 2006) which had been identified in the previous search and used in NICE technology appraisal guidance 263. This study reported utility values obtained from 100 participants from the general population who were asked to value different health states and adverse events associated with metastatic breast cancer using the standard gamble technique. The manufacturer calculated a treatment-specific weighted average for stable disease and treatment response based on the overall response rate to apply it in the PFS state in the model (see table 4). The manufacturer included disutilities associated with grade 3, 4 and 5 severity of adverse events that affected more than 2% of people in either treatment arm in the CLEOPATRA trial and which were deemed to affect quality of life according to clinical opinion. The utility decrement associated with febrile neutropenia was applied only during treatment with docetaxel or paclitaxel (see section 4.11). The manufacturer mentioned that clinical specialists indicated that the utility values used in the model were conservative and that they would expect to see a higher quality of life in the progressed disease state. The manufacturer investigated the impact of varying utility values in its sensitivity analysis.

Table 4 Summary of utility values used in the economic model

Description	State	Utility value
Treatment		
Pertuzumab arm	PFS – during docetaxel treatment	0.772
	PFS – after docetaxel treatment	0.785
Control arm	PFS – during docetaxel treatment	0.769
	PFS – after docetaxel treatment	0.777
All treatments	Progressed disease	0.496
Additional adverse events		
Anaemia	-	-0.120
Peripheral neuropathy	-	-0.120

Source: Adapted from ERG's report, table 25, page 52

Resource use

6.7 The manufacturer also carried out an update of a previous literature search conducted for NICE technology appraisal guidance 236 to identify published studies of resource use. However, no relevant studies were considered by the manufacturer to meet the inclusion criteria and therefore resource use in the model was based on clinical guidelines, previous NICE technology appraisals and advice from its clinical specialists and health economist. The manufacturer used the distribution of body weight of patients in the CLEOPATRA trial to derive the dosage of trastuzumab, docetaxel and paclitaxel. Drug prices were taken from the 'British National Formulary' (BNF 65th edition) and the Commercial Medicines Unit 2012 electronic Market Information Tool (CMU eMIT). The manufacturer assumed in its base case that any unused drug in a vial was wasted. Administration costs were obtained from NHS Reference costs 2011/12 and the associated pharmacy time was assumed to be 12 minutes (see table 5).

Table 5 Cost of treatments

Items	Pertuzumab	Trastuzumab	Docetaxel	Paclitaxel
Technology costs	£2,395 (420 mg vial)	£407.4 (150 mg vial)	£20 (80 mg vial) £5 (20 mg vial)	£7.00 (100 mg vial) £6.30 (30 mg vial)
Administration cost (first)	£248	£248	£248	£248
Administration cost (subsequent)	£197 for all subsequent administrations			
Pharmacy cost	£9.40	£9.40	£9.40	£9.40

Source: adapted from manufacturer's submission, table 27, page 142

6.8 The weekly costs of second line treatments were applied to the progressed disease state in the model (see table 6). The manufacturer used patient level data from the CLEOPATRA trial to estimate time to off-treatment using Kaplan-Meier curves to determine the proportion of patients receiving pertuzumab plus trastuzumab and docetaxel or trastuzumab plus docetaxel each week of the model. Costs for the second line treatment with vinorelbine and capecitabine were obtained from the CMU eMIT database and the BNF. These costs were applied for 4.3 months based on a study (Cameron et al. 2008) in which people with metastatic breast cancer whose disease had progressed following treatment with trastuzumab were treated with capecitabine. The manufacturer noted that death had not been accounted for in the calculation of these costs and therefore there was likely to be an overestimation of the cost of second line treatment. Costs and assumptions for supportive and palliative care are summarised in table 6. Costs associated with adverse events which occurred at grade 3, 4 or 5 severity in more than 2% of patients from the CLEOPATRA trial were incorporated into the analysis. NHS reference costs were utilised and all adverse events were assumed to occur in week 1 of the model and so were not discounted. The manufacturer assumed that patients receiving trastuzumab plus docetaxel and patients receiving trastuzumab plus

paclitaxel had the same toxicity profile and therefore the same costs associated with adverse events were applied.

Table 6 Costs for supportive and palliative care

Health states	Items	Frequency	Unit cost (£)	Total Cost (£)
Progression-free survival best supportive care	Community Nurse (home visit)	20 mins every 2 weeks	61 (per hour)	40.66
	GP Contact (surgery visit)	1 every month	36 (per patient contact lasting 11.7 mins)	36.00
	Clinical Nurse Specialist	1hr every month	81 (per hour of client contact)	81.00
	Total Monthly Cost	**-**	**-**	**157.66**
	Social worker	1hr once	54 (Client related work)	-
	Cardiac Assessment (MUGA/ECHO)	1 every 3 months	238 / 84 (30%/70%) =130.20	-
	Outpatient CT scan	1 scan once	125	-
	Consultant outpatient visit	1 visit once	113	-
Post progression survival best supportive care	Community Nurse (home visit)	20 mins every 2 weeks	61 (per hour)	40.66
	GP Contact (surgery visit)	1 every month	36 (per patient contact lasting 11.7 mins)	36.00
	Clinical Nurse Specialist	1hr every month	81 (per hour of client contact)	81.00
	Total Monthly Cost	**-**	**-**	**157.66**
	Dose	**Frequency**		**Weekly cost (£)**
Progressed disease: Second line treatment costs	Vinorelbine 25 mg/m² loading dose	Once weekly (first three weeks)		17.71
	Vinorelbine 30 mg/m² maintenance dose	Once weekly (subsequent weeks)		21.25
	Capecitabine 1250 mg/m^2	Twice daily for 14 days followed by a 7-day rest period		134.98 (during treatment weeks)
End of life care cost	3,608.69			

Source: adapted from manufacturer's submission tables 28 and 29, pages 148 and 149

Base-case results

6.9 The manufacturer's base-case results presented an incremental analysis showing that [redacted]. The base-case results estimated that adding pertuzumab to trastuzumab and docetaxel provided an additional [redacted] life years and 0.83 quality-adjusted life years (QALYs). These benefits were achieved with an incremental cost of £[redacted] resulting in an incremental cost-effectiveness ratio (ICER) of £[redacted] per QALY gained for pertuzumab plus trastuzumab and docetaxel compared with trastuzumab and docetaxel alone. The base-case results, as presented in the manufacturer's submission, are summarised in table 7.

Table 7 Manufacturer's base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/(QALY)
Trastuzumab and docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	
Trastuzumab and paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0	[redacted]
Pertuzumab, trastuzumab and docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.833	[redacted]

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; Dominated, was more expensive and less effective than a combination of two other treatments.
Source: Manufacturer's submission, table 39, page 158

Sensitivity analyses

6.10 The manufacturer undertook sensitivity analyses to explore the impact of changes in the base-case assumptions in the ICER. Results showed that the model was most sensitive to assumptions around the extrapolations of PFS and overall survival. When parametric distributions were applied to the Kaplan-Meier curves for the extrapolation of PFS data in the model, the ICERs ranged from £[redacted] to £[redacted] per QALY gained applying a log-normal and a gamma distribution respectively. When parametric

distributions were explored for the overall survival data, the ICERs ranged between £[redacted] to £[redacted] per QALY gained using an exponential and a gamma distribution respectively. The manufacturer investigated which parametric function had the best fit to the Kaplan-Meier data and found that the distributions which provided the best fit were the log-logistic for the PFS data (ICER of £[redacted] per QALY gained) and the gamma for the overall survival data (ICER of £[redacted] per QALY gained). The model was also sensitive to the assumption of first-line treatment duration, the utility values in PFS (after docetaxel treatment) and progressed disease states, and health and costs discount rates. The manufacturer also investigated the different assumptions for extrapolating PFS data in different scenario analyses (see section 6.4). The resulting ICERs were £[redacted], £[redacted] and £[redacted] per QALY gained for scenarios 1, 2 and 4 respectively.

6.11 The manufacturer also undertook probabilistic sensitivity analyses to explore uncertainty around the parameters in the model. The probability of pertuzumab plus trastuzumab and docetaxel being cost effective compared with trastuzumab and docetaxel alone at a threshold of £30,000 per QALY gained was 0.0%. The manufacturer concluded that the key drivers of the cost-effectiveness results were the cost of pertuzumab, the long term projection of PFS and overall survival data and the utility values used.

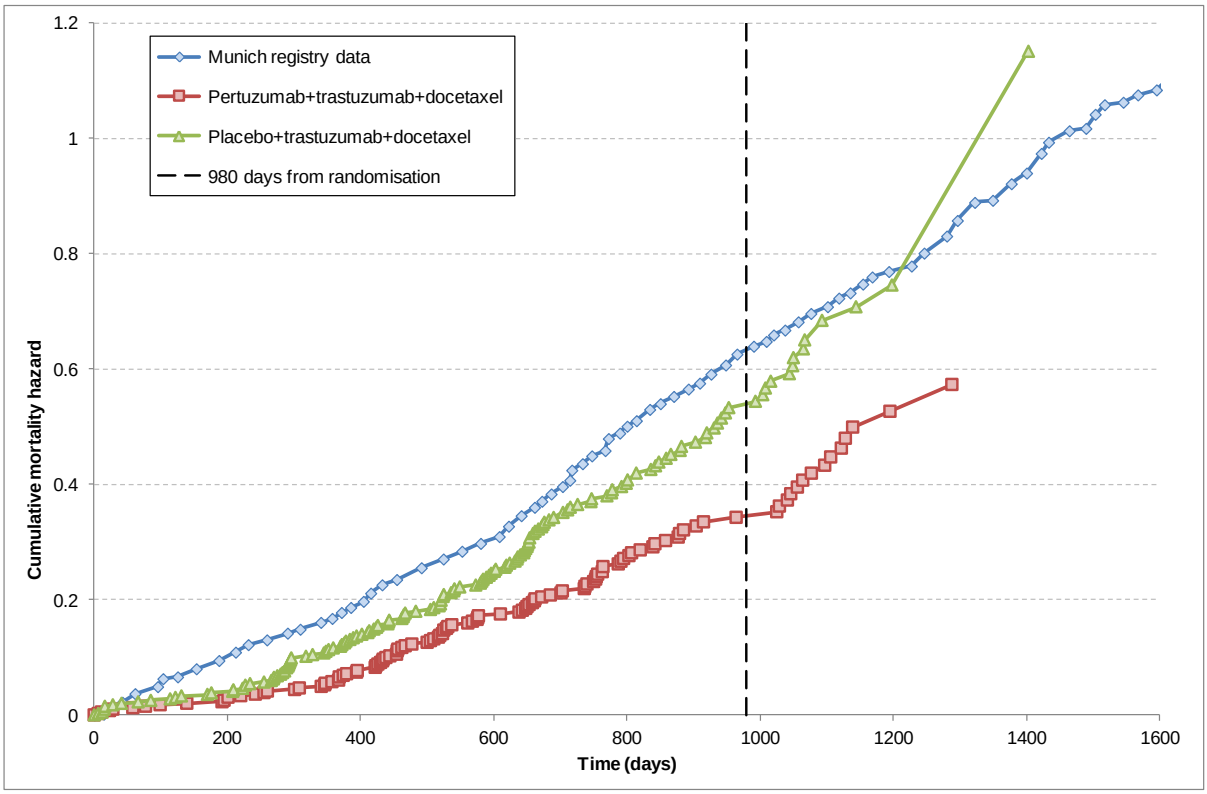
ERG comments and exploratory analysis

6.12 The ERG agreed with the manufacturer that no cost-effectiveness studies of pertuzumab had been published and considered that the manufacturer's model structure was appropriate to describe the decision problem, was easy to understand and correctly implemented. However, the ERG highlighted that during clarification the manufacturer did not provide alternative survival analyses from the CLEOPATRA trial, and that the available data appeared to suffer from systematic bias because of censoring for the last trial observation date. The ERG noted that in the absence of these requested data it has been unable to offer alternative

interpretations of the PFS, overall survival, time to off treatment and post-progression survival results in relation to long-term projection of survival gains.

6.13 The ERG highlighted that the main criticism of the submitted model was the methods for projecting overall survival data in the model and noted that the overall survival data were not mature. The ERG noted that when censoring time-to-event data it is usual to base it on the last trial observation and that 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. The ERG used the overall survival data from the Munich registry to support its assumption that the manufacturer's methods for projecting overall survival in the model are subject to bias as it can be seen that the stable trend of overall survival in the Munich registry data is crossed by the overall survival results of the placebo arm at the end of the CLEOPATRA trial period (see figure 8).

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



Source: ERG's report, figure 8, page 63

6.14 The ERG further noted that in the manufacturer's model [redacted] of the life years gained and [redacted] of the discounted QALY gained occurred in the post-progression state. However, the ERG highlighted that there was [redacted] and considered the manufacturer's approach for projecting long-term survival assuming a higher risk of death in the placebo arm compared with the pertuzumab arm to be inappropriate (see figure 9). The ERG rejected the parametric projections and applied the mortality trend from the Munich registry in both arms in the model. This change reduced the post-progression survival gain from [redacted] months as estimated by the manufacturer to less than [redacted]. The resulting ICER was £[redacted] per QALY gained. The ERG also estimated overall survival using the PFS estimates and adjusting them for any difference in the proportion of patients dying before disease progression. Specifically, it used the

estimated PFS gain and added to it the additional benefit post progression due to the small difference between the 2 treatment arms in the proportion of patients still alive following disease progression and assumed that the long-term post-progression hazard is the same in both arms. This approach reduced the overall survival gain from [redacted] months to [redacted] months and the discounted QALY gain from 0.83 to 0.45. The result of this analysis was an increase in the ICER to approximately £[redacted] per QALY gained (see table 8).

Figure 9 Kaplan-Meier plots for post-progression survival in the CLEOPATRA trial

[redacted]Source: ERG's report, figure 10, page 66

6.15 The ERG noted that the manufacturer did not include any subgroup analyses in the model despite the differences in the clinical results for some subgroups. The ERG noted that the manufacturer provided in its clarification response its discussion with the Committee for Medicinal Products for Human Use and additional time-to-event analyses for subgroups although the manufacturer did not use the method requested by the ERG. The ERG examined the Kaplan-Meier analyses for the subgroups of patients with visceral and non-visceral disease (see figure 10).

[redacted] In addition the ERG noted that the [redacted]. The ERG noted that these results suggest that [redacted]

[redacted]. The ERG suggested that if [redacted]

Figure 10 Kaplan-Meier cumulative hazard plots for PFS for subgroups of patients with visceral and non-visceral disease in the CLEOPATRA trial

[redacted]

Source: ERG's report, figure 9, page 64

6.16 The ERG agreed with the manufacturer that the addition of pertuzumab to trastuzumab and docetaxel resulted in an increase in PFS but considered that there was uncertainty around the size of this gain because of the bias shown in the final part of the PFS curve. The ERG conducted an exploratory analysis applying long-term linear hazard trends to both arms in the model from day 600 onwards. This analysis reduced the mean undiscounted PFS gain from [redacted] months to [redacted] months.

6.17 The ERG noted that the dose for the drugs used in the model were in line with their marketing authorisations but highlighted that capecitabine is routinely administered at a dose of 1000mg/m^2 in the UK. The ERG identified a number of minor errors in the model: errors in the formula for the estimation of utility values; the method for adjusting the dose of chemotherapy based on body surface area and weight of the patients; the sources for the calculation of chemotherapy acquisition and administration costs; inconsistencies between the incidence of adverse events shown in the CLEOPATRA clinical study report and those shown in the manufacturer's submission and the model; and the source of some adverse events costs. The ERG noted that treatment doses for trastuzumab, docetaxel and paclitaxel were calculated based on individual body weight and body surface area of the patients in the CLEOPATRA trial. The ERG highlighted that there were wide differences in body weight and body surface area for patients depending on the region and

considered that using the average characteristics of the patients in the CLEOPATRA trial was underestimating the doses that patients would receive in UK. The ERG used published survey estimates for England and Wales to calculate the doses needed and also used different sources for the acquisition costs of the drugs. These changes increased the ICER by less than £[redacted] per QALY gained. It was also noted that there was a coding error in the manufacturer's model related to the probabilistic sensitivity analysis when using the exponential distribution and that therefore all probabilistic sensitivity analyses using this distribution were not valid. The ERG conducted additional analyses to correct for these errors (see table 8) and concluded that the impact on the ICER was limited.

Table 8 Revised ERG's results

Adjustment	Trastuzumab + docetaxel			Pertuzumab + trastuzumab + docetaxel			Incremental				
	Cost	Survival[a] (months)	QALYs	Therapy cost	Survival[a] (months)	QALYs	Survival[a] (months)	Cost	QALYs	ICER (£/QALY)	ICER change
Original Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**0.833**	[redacted]	[redacted]
ERG utility values	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.828	[redacted]	[redacted]
ERG drug prices	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.833	[redacted]	[redacted]
ERG chemo admin costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.833	[redacted]	[redacted]
Munich survival estimates	[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]	**0.43**	[redacted]	[redacted]

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

Source: Adapted from ERG's report, table 36, page 71

7 End-of-life considerations

7.1 For treatments to be considered as life-extending, end of life treatments, they must be indicated for patients with a short life expectancy (less than 24 months), offer an extension to life (normally of at least an additional 3 months) and be licensed for a small patient population (less than 7000

for all licensed indications). Treatment with pertuzumab does not meet all the criteria for consideration as a life-extending, end-of-life treatment.

7.2 The manufacturer noted that the majority of people with HER2-positive metastatic breast cancer are women with an average age at diagnosis of 55 years and that with current treatments, 50% of women die within 3 years of developing metastatic disease. The manufacturer noted that median survival in patients who receive treatment with trastuzumab plus docetaxel in the CLEOPATRA trial was 37.6 months. The manufacturer highlighted that this means that HER2-positive metastatic breast cancer is associated with a significant burden of illness and that women with the condition die approximately 30 years earlier than an equivalent healthy woman (ONS Interim Life Tables 2008-2010). The manufacturer further noted that this premature death has a significant impact upon society because family will lose a key contributor to household income and to informal care of both children and elderly parents, and also a key influencer upon their children's future development. The manufacturer noted that the society places a preference upon QALYs gained by people with a high burden of illness and that this preference is not captured in the QALY calculation either by the use of the end of life criteria specified by NICE for appraising life-extending, end of life treatments. The manufacturer highlighted that there is a significant need for new treatments that extend the lives of women with HER2-positive metastatic breast cancer because it is an incurable disease.

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	The manufacturer noted that median survival in patients who receive treatment with trastuzumab plus docetaxel in the CLEOPATRA trial was 37.6 months.
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	The manufacturer noted that in the CLEOPATRA trial, at the time of the second interim analysis (May 2012) median overall survival had not been reached in the pertuzumab arm and median overall survival was 37.6 months in the control arm, resulting in a statistically significant increase in median overall survival (HR 0.66, 95% CI 0.52 to 0.84, p=0.0008). The manufacturer estimated in its economic model a difference of [redacted] months in overall survival favouring pertuzumab plus trastuzumab and docetaxel compared with tratuzumab plus docetaxel based on the CLEOPATRA trial. The ERG estimated this overall survival gain to be [redacted] months based on CLEOPATRA trial and trends observed in the Munich registry data. The ERG also estimated overall survival using the PFS estimates and adjusting them for any difference in the proportion of patients dying before disease progression, and assuming the same long-term post-progression hazard in both arms. This approach reduced the overall survival gain from [redacted] months to [redacted] months
The treatment is licensed or otherwise indicated for small patient populations	In 2010, there were 44,226 people diagnosed with breast cancer and over 10,000 people died in England and Wales. It has been estimated that 5% of women initially presenting with breast cancer have locally advanced disease or distant metastases. Approximately 20–30% of people with metastatic breast cancer have HER2-positive tumours The manufacturer estimated that there are 2336 people with HER2-positive metastatic breast cancer (Roche commissioned analysis of the IMS Oncology Analyser (UK MAT Quarter 2 2012 – Nov 2012) of which 2058 people are eligible for treatment with pertuzumab per annum (Proportion of people receiving trastuzumab who are suitable for treatment – Roche Data July 2011).

8 Equalities issues

8.1 No equality issues were identified during scoping consultation or in the evidence submitted.

9 Innovation

9.1 The manufacturer stated that pertuzumab significantly improves outcomes of people with HER2-positive metastatic breast cancer and mentioned that this innovation is demonstrated in the CLEOPATRA trial with a greater proportion of people responding to treatment, a statistically significant increase in median progression-free survival and a statistically significant increase in median overall survival. Pertuzumab offers a HER2 blockade and, when used with docetaxel, results in the inhibition of signalling pathways essential for tumour growth. Therefore, the manufacturer considered that pertuzumab provides an innovative step-change in the management of HER2-positive metastatic breast cancer.

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Appendix A: Supporting evidence

Related NICE guidance

Published

- Advanced breast cancer: diagnosis and treatment. NICE clinical guideline 81 (2009).
- Trastuzumab for the treatment of advanced breast cancer. NICE technology appraisal guidance 34 (2002).
- Bevacizumab in combination with a taxane for the first-line treatment of metastatic breast cancer (replaces NICE technology appraisal guidance 147). NICE technology appraisal guidance 214 (2011).
- Lapatinib or trastuzumab in combination with an aromatase inhibitor for the first-line treatment of metastatic hormone-receptor-positive breast cancer that overexpresses HER2. NICE technology appraisal guidance 257 (2012).
- Bevacizumab in combination with capecitabine for the first line treatment of metastatic breast cancer. NICE technology appraisal guidance 263 (2012).

Under development

NICE is developing the following guidance (details available from www.nice.org.uk):

- Trastuzumab emtansine for treating unresectable metastatic HER2-positive breast cancer after treatment with trastuzumab and a taxane. NICE technology appraisal. August 2014

NICE pathways

- There is a NICE pathway on advanced breast cancer overview, which is available from http://pathways.nice.org.uk/pathways/advanced-breast-cancer.

Appendix B: European public assessment report

The European public assessment report for pertuzumab was published on 4 March 2013 and is available from:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002547/human_med_001628.jsp&mid=WC0b01ac058001d124