NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

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

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Contents

Contents 2
List of tables 2
List of figures 3
Executive summary 5
Section A – Decision problem 12
1 Description of technology under assessment 12
2 Context 17
4 Innovation 24
5 Statement of the decision problem 27
Section B – Clinical and cost effectiveness 28
6 Clinical evidence 29
7 Cost effectiveness 103
8 De novo analysis 106
Section C – Implementation 166
9 Assessment of factors relevant to the NHS and other parties 166
10 References 169
Appendices ..... **Error! Bookmark not defined.**
Related procedures for evidence submission .. **Error! Bookmark not defined.**

List of tables

Table 1 Base-case cost-effectiveness results 10
Table 2 Incremental cost-effectiveness results 10
Table 3 Additional evidence available within next 12 months 15
Table 4 Unit costs of technology being appraised 16
Table 5 Decision problem 27
Table 6 Elements of health technology assessment 28
Table 7 Details of CLEOPATRA 31
Table 8 CLEOPATRA inclusion criteria 37
Table 9 CLEOPATRA exclusion criteria 38
Table 10 Characteristics of participants in the RCTs across randomised groups 41
Table 11Statistical Power for final progression-free survival analysis 47
Table 12 Statistical Analyses of Efficacy Endpoints 47
Table 13 Sensitivity Analyses to Assess Robustness of progression-free survival Results 49
Table 14 Critical Appraisal of RCT 58
Table 15 Overview of Efficacy 62
Table 16 Comparison of paclitaxel and docetaxel 78
Table 17 Overview of Safety in CLEOPATRA 80
Table 18 Summary of adverse events with an incidence rate of >5% by trial treatment 84
Table 19 Inclusion and exclusion criteria for cost-effectiveness studies 104
Table 20 Key features of analysis 109
Table 22 Summary of variables applied in the economic model 125
Table 23 Summary of the 3 utility articles 131

Table 24 Results of the mixed model analysis 134
Table 25 Additional adverse events included in the model 136
Table 26 Summary of utility values for cost-effectiveness analysis..... 136
Table 27 Inclusion and exclusion criteria for resource utilisation studies 140
Table 28 Unit costs associated with the technology in the economic model 142
Table 29 Second line treatments in the economic model..... 148
Table 30 List of health states and associated costs in the economic model 148
Table 31 List of adverse events and summary of costs included in the economic model..... 152
Table 32 Deterministic sensitivity analysis 153
Table 33 Progression-free survival scenarios 155
Table 34 PSA distributions..... 155
Table 35 Summary of model results compared with clinical data 156
Table 36 Model outputs by clinical outcomes 157
Table 37 Summary of QALY gain by health state 157
Table 38 Summary of costs by health state 157
Table 39 Summary of predicted resource use by category of cost 158
Table 40 Base-case results 158
Table 41 Sensitivity Analysis..... 159
Table 42 Probabilistic sensitivity analysis results..... 161
Table 43 Progression-free survival extrapolation scenarios..... 162
Table 44 Eligible population by year 166
Table 45 Market share assumptions 167
Table 46 Budget impact by year 167

List of figures

Figure 1 Number of eligible people for pertuzumab per annum 19
Figure 2 PRISMA Statement Flow Diagram..... 30
Figure 3 Study Design: Patient Treatment and Assessment..... 35
Figure 4 Participant Flow 56
Figure 5 Progression-free survival (Independent Assessed 13 May 2011 data-cut) Kaplan-Meier Plots..... 63
Figure 6 Progression-free survival forest plot hazard (independent assess 13 May 2011)..... 65
Figure 7 Overall Survival (14 May 2012 data-cut) Kaplan-Meier Plots..... 67
Figure 8 Overall survival forest plot (Independent assessed 14 May 2012)... 69
Figure 9 Progression-free survival (Investigator Assessed 14 May 2012 data-cut) Kaplan-Meier Plots..... 71
Figure 10 Progression-free survival forest plot (Investigator assessed 14 May 2012)..... 72
Figure 11 FACT-B Kaplan-Meier plots 75
Figure 12 PRISMA Flow showing economic studies identified 105
Figure 13 Model structure 106
Figure 14 Progression-free survival Kaplan-Meier plots (14 May 2012 data) 110
Figure 15 Cumulative hazard plots of progression-free survival in the trastuzumab and docetaxel arm (14 May 2012 data)..... 112
Figure 16 Cumulative hazard plot of progression-free survival in pertuzumab, trastuzumab and docetaxel arm (14 May 2012 data)..... 113

Figure 17 Cumulative Hazard Plots of progression-free survival (14 May 2012 data) 114
Figure 18 Modelled progression-free survival - Scenario 1 116
Figure 19 Modelled progression-free survival - Scenario 2 117
Figure 20 Modelled progression-free survival - scenario 3 118
Figure 21 Modelled progression-free survival - scenario 4 119
Figure 22 Cumulative hazard plots of overall survival (14 May 2012 data) .. 120
Figure 23 Cumulative Hazard Plots of overall survival from month 8 onwards (14 May 2012 data) 120
Figure 24 Modelled overall survival 122
Figure 25 Cumulative hazard plot of Munich registry 122
Figure 26 Registry data of people with HER2-metastatic breast cancer 123
Figure 27 Tornado diagram 161
Figure 28 Cost-effectiveness acceptability curve 161

Executive summary

HER2-Positive metastatic breast cancer

Each year approximately 2,000 people in the United Kingdom (UK) die of HER2-positive metastatic breast cancer. The majority of the people diagnosed are women, with an average age at diagnosis of 55 years (Marty 2005, Baselga 2012).

With current treatments, 50% of women die within three years of developing metastatic disease.

The premature death of women with HER2-positive metastatic breast cancer has a significant impact upon society. A family will lose a key contributor to household income, a key contributor to informal care of both children and elderly parents and a key influencer upon their child's future development.

The primary objective of the management of HER2-positive metastatic breast cancer is to extend the person's length of life, whilst maintaining or improving quality of life – people with meastatic disease are unlikely to be cured.

There is a significant need for new treatments that extend the lives of women with HER2-positive metastatic breast cancer.

The current treatment algorithm

It is currently standard clinical practice to administer first line treatment with trastuzumab (Herceptin®) in combination with a taxane (docetaxel or paclitaxel) – a form of chemotherapy. Trastuzumab was NICE recommended for use in HER2-positive metastatic breast cancer in NICE TA34 (2002).

When first developed trastuzumab was regarded a step-change in the treatment of HER2-positive metastatic breast cancer. The addition of trastuzumab to docetaxel was demonstrated to increase the duration of median time to progression by 5.5 months (p=0.0001) and overall survival by 8.5 months (p=0.0325) (Marty 2005). A substantial survival gain considering

over 50% of people in the study control arm crossed over to receive trastuzumab upon disease progression.

Despite the improvement provided by trastuzumab approximately 50% of people with the disease will relapse within 12 months (Marty et al 2005) and 50% will be dead 3 years following diagnosis with metastatic disease (Swain 2012).

Pertuzumab is a step-change in the treatment of HER2-positive metastatic breast cancer

The addition of pertuzumab (Perjeta®) to trastuzumab and docetaxel in the first line treatment of HER2-positive metastatic breast cancer has been studied in a large, multinational phase III randomised controlled trial (RCT) (CLEOPATRA). A primary analysis of the study was conducted on 13 May 2011 with further analysis conducted on 14 May 2012.

This study demonstrates the addition of pertuzumab to the current standard of care results in a significant increase in overall survival (HR 0.66; CI 0.52, 0.84, p=0.0008), a significant increase in progression free survival (HR 0.69; CI 0.58, 0.81, p <0.0001) and a substantial improvement in response rates (over 80% of patients respond to pertuzumab combination therapy) (Swain 2012).

This efficacy gain is larger than that observed following the introduction of trastuzumab (Herceptin) – a treatment widely regarded as one of the biggest advances in the treatment of cancer. It represents a significant step forward for women with HER2-positive metastatic breast cancer, their families and for all those affected by the premature death of a woman with HER2-positive metastatic breast cancer.

Whilst median survival has been observed for patients in the control arm of the CLEOPATRA study (37.6 months) median survival for those receiving pertuzumab has not yet been observed. Over fifty percent of people randomised to pertuzumab were still alive at the point of data cut-off.

Modelling of the CLEOPATRA data suggests the median survival benefit associated with pertuzumab is likely to be between 12 and 16 months. A gain of this magnitude is comparable to that observed following the introduction of trastuzumab in the Marty 2005 study (in which a 14.6 month median overall survival gain was observed in patients who did not crossover to trastuzumab upon disease progression). A gain this large is likely to be highly valued by women affected by HER2-positive metastatic breast cancer.

Mode of Action

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 dimerisation. This leads to increased proliferation of tumour cells and disease progression. Activation of HER2 by HER3 is particularly potent.

Pertuzumab is first in a new class of targeted cancer treatments called “HER2 dimerisation inhibitors”. Pertuzumab is a monocloncal antibody that binds to HER2 receptors on the surface of tumours and prevents HER2 dimerising with other members of the HER family (HER1, HER3 and HER4). This results in the inhibition of signalling inside the cell which leads to tumour growth.

The combination of pertuzumab with trastuzumab, leads to a more comprehensive block of the signalling pathway. As a result there is reduced tumour proliferation and improved patient outcomes.

Safety

Pertuzumab is well tolerated. The incidence of adverse events of diarrhoea, rash, mucosal inflammation, febrile neutropenia, and dry skin was higher in the pertuzumab, trastuzumab and docetaxel arm compared with the trastuzumab and docetaxel arm. In contrast peripheral edema and constipation were more common in the trastuzumab and docetaxel arm. These side effects are similar to those observed with treatment with trastuzumab. They commonly occur in oncology, are generally manageable, and are typically not associated with increased mortality.

License

Pertuzumab is additive to the current standard of care (trastuzumab in combination with a taxane) and is administered intravenously once every three weeks. The initial dose of pertuzumab is 840 mg, followed by maintenance doses of 420 mg. Treatment with pertuzumab is continued until disease progression or unmanageable toxicity. The list price of one 420 mg vial is £2,395. On the basis of the results observed in CLEOPATRA, pertuzumab was granted European marketing authorisation in March 2013 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.

Cost-effectiveness

A cost utility analysis was conducted in order to evaluate the cost effectiveness of pertuzumab, trastuzumab and docetaxel compared with trastuzumab and docetaxel or trastuzumab and paclitaxel, in people with first line HER2-positive metastatic breast cancer.

The analysis was based on a three state partitioned survival model (progression-free survival, progressed disease, and death). The model took an England and Wales NHS PSS perspective, a 3.5% discount rate per annum for costs and QALYs, a 25 year time horizon, a one week cycle length and a half cycle correction where appropriate. Resource use in each health state was based on NICE Clinical Guideline on Advanced Breast Cancer (NICE CG81, 2009). Costs were taken from BNF 65, PSSRU 2012 and NHS references costs 2011/12. The utilities were based on a study by Lloyd et al (2006). The Lloyd mixed model analysis hasbeen applied in numerous NICE Technology Appraisals in this disease area (TA 257, TA 263, ID538).

The latest available data set from 14 May 2012 is used in the economic model. As the survival data observed is not complete, it was necessary to apply parametric extrapolation in order to derive mean survival with and without the intervention. In line with best practice in extrapolation, modelling

was informed via interpretation of the CLEOPATRA cumulative hazard plots, consultation with clinical and modelling experts (including a member of an ERG involved in the critique of manufacturer submissions) and validated through comparison with external data (see Section 8.2.1). The model has strong face validity when compared with the data available.

In order to inform the comparison of trastuzumab in combination with paclitaxel compared with pertuzumab in combination with trastuzumab and docetaxel, a search of the literature was undertaken and clinical experts were consulted. In light of the evidence demonstrated in Slamon et al, 2001, Marty et al, 2005 and Sparano, 2008, the opinion of clinical experts and the Appraisal Committee conclusion in TA 214, it is assumed the control arm of the CLEOPATRA study represents the outcomes that would be observed for people treated with trastuzumab in combination with weekly paclitaxel. The base-case cost-effectiveness results are presented in Table 1 and Table 2.

Table 1 Base-case cost-effectiveness results

	Pertuzumab, trastuzumab and docetaxel	Trastuzumab and docetaxel	Trastuzumab and paclitaxel
Technology acquisition cost	[redacted]	[redacted]	[redacted]
Other costs	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]
Difference in total costs	[redacted]	[redacted]	[redacted]
LYG	[redacted]	[redacted]	[redacted]
LYG difference	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
QALY difference	N/A	0.833	0.833
ICER	[redacted]	[redacted]	[redacted]

LYG, life years gained; QALY(s), quality-adjusted life year(s); ICER, incremental cost-effectiveness ratio.

Table 2 Incremental cost-effectiveness results

Technology (and comparators)	Total cost	Total QALY	Inc. cost	Inc. QALY	ICERs versus 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]	0.833	[redacted]	[redacted]

QALY, quality-adjusted life year; ICERs, incremental cost-effectiveness ratios.

The results indicate that treatment with trastuzumab and paclitaxel is dominated, that is, is more expensive and less effective than a combination of two other single-agent treatments (trastuzumab and docetaxel). Pertuzumab, trastuzumab and docetaxel compared with trastuzumab and docetaxel, is associated with an incremental cost effecitveness ratio (ICER) of [redacted] per QALY gained. Extensive deterministic sensitivity analyses were conducted – in each of these the ICER remained above [redacted] per QALY gained. These analyses indicate that the key drivers of the model are the cost of

pertuzumab, the long term projection of progression-free survival and overall survival and the utility values used. When the list price of pertuzumab is discounted by [redacted] (set to [redacted] per vial), the ICER remains above [redacted] per QALY gained.

A 5,000 simulation probabilistic sensitivity analysis was conducted in order to evaluate the uncertainty associated with the base-case estimate. The probabilisitic sensitivity analysis (PSA) indicates that pertuzumab has a 0% chance of being cost-effective at a threshold of £30,000 per QALY gained at the list price.

Conclusion

Pertuzumab offers a substantial gain in survival to a group of women with life threatening disease and an extremely poor prognosis. This gain is of prime importance to women with HER2-positive metastatic breast cancer, their families and society as a whole.

Pertuzumab is unlikely to be considered as being a ‘cost-effective’ use of NHS resources using NICE’s current methods and cost-effectiveness thresholds.

Section A – Decision problem

1 Description of technology under assessment

1.1 Give the brand name, approved name and, when appropriate, therapeutic class. For devices, provide details of any different versions of the same device.

Perjeta®, pertuzumab, antineoplastic agent, humanised monoclonal antibody, HER2 dimerisation inhibitor, ATC code: L01XC13.

1.2 What is the principal mechanism of action of the technology?

The human epidermal growth factor receptor (HER) family consists of four receptors (HER 1, 2, 3 and 4) which are found on the surface of cells. The receptors mediate cell growth, differentiation and survival (Sundaresan et al 1991; Yarden and Sliwkowski 2001).

Some breast cancers overexpress HER2 leading to the formation of HER2-containing pairs of receptors (called dimers) on the surface of cells. These dimers activate multiple signalling pathways within the cells resulting in an increase in their proliferation and a reduction in cell death. HER2:HER3 is the most potent receptor that drives tumour growth. Dimerisation of these two receptors leads to activation of cell proliferation and cell survival pathways (Jones et al 2006). Overexpression of HER2 is associated with more aggressive disease when compared with breast cancers that do not overexpress HER2 (Ross et al 2009).

Pertuzumab is the first in a new class of targeted cancer treatments called HER2 dimerisation inhibitors. By binding to HER2 receptors, pertuzumab prevents HER2 receptors dimerising with other members of the HER family. This results in the inhibition of signals that are essential for tumour growth. The mechanism of action of pertuzumab is complementary to that of trastuzumab which binds to a different domain of HER2 preventing receptor cleavage and associated signalling from activated receptor fragments. In

addition pertuzumab and trastuzumab both stimulate cell death by the activation of antibody-dependent cellular cytotoxicity.

1.3 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, give the date on which authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

A 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" was received in March 2013.

1.4 Describe the main issues discussed by the regulatory organisation (preferably by referring to the [draft] assessment report [for example, the EPAR]). If appropriate, state any special conditions attached to the marketing authorisation (for example, exceptional circumstances/conditions to the marketing authorisation).

Two potential issues were discussed by the Committee for Medicinal Products for Human Use (CHMP).

The first issue relates to the treatment history of participants in the pivotal CLEOPATRA trial. In CLEOPATRA a minority of participants received prior treatment with trastuzumab in the adjuvant setting. In current clinical practice trastuzumab is standard of care for the treatment of HER2-positive early breast cancer. The CHMP therefore questioned whether the population in CLEOPATRA were representative of people with HER2-positive metastatic breast cancer in clinical practice. Roche responded highlighting the rationale for the relatively low use of trastuzumab was reflective of the timing of trial recruitment and the global nature of the study. In the EU, trastuzumab was licenced for adjuvant use in mid-2006 and to be eligible for entry into CLEOPATRA participants had to complete any adjuvant treatment (typically

one year) and then have a disease-free interval of a minimum one year before relapse. Consequently, during the recruitment period (February 2008 – July 2010) there were relatively few eligible European participants who had received trastuzumab in the early breast cancer setting. Moreover, during the same time period, in some other regions of the world trastuzumab was unavailable. Following this response, and the comparable efficacy of pertuzumab in the trastuzumab naïve/trastuzumab experienced population, the CHMP concluded the evidence established the efficacy of pertuzumab in both groups.

The second issue considered by the CHMP was the hypothesis that pertuzumab is less efficacious in people with non-visceral disease compared to those with visceral disease. This issue was raised by the CHMP because the point estimate for the progression-free survival hazard ratio observed in the CLEOPATRA trial for the non-visceral disease subgroup was not as favourable as observed in the visceral disease subgroup. Roche responded to this question highlighting the small sample size in this patient population, the low event rate associated with this better prognosis population, the difficulties in measuring disease progression, and the wide confidence intervals surrounding this point estimate. The CHMP concluded the license for pertuzumab should not be restricted based on visceral disease status.

Both issues will be discussed in further detail in Section B of this submission.

1.5 What are the (anticipated) indication(s) in the UK? For devices, provide the (anticipated) CE marking, including the indication for use.

Pertuzumab is indicated 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.

1.6 Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

Table 3 Additional evidence available within next 12 months

Status	Details
Completed (Final overall survival data-cut expected to be available mid 2014)	**CLEOPATRA (WO20698)** - Phase III, randomised, double-blind, placebo-controlled, multicentre international clinical trial to evaluate pertuzumab in combination with trastuzumab and docetaxel compared with trastuzumab in combination with docetaxel in people with previously untreated HER2-positive metastatic breast cancer.
Ongoing (Safety data expected Q3 /4 2013)	**PERUSE (MO28047)** - Multicentre, open-label, single-arm study of pertuzumab in combination with trastuzumab and a taxane for the first line treatment of people with HER2-positive advanced (metastatic or locally advanced) breast cancer.

1.7 If the technology has not been launched, please supply the anticipated date of availability in the UK.

Pertuzumab has been available in England and Wales from March 2013.

1.8 Does the technology have regulatory approval outside the UK? If so, please provide details.

Pertuzumab was approved in the USA by the Food and Drug Administration (FDA) in June 2012, Switzerland in August 2012 and Mexico in September 2012. These approvals were for the same indication set out in section 1.5.

1.9 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

A Scottish Medicines Consortium (SMC) appraisal of pertuzumab will begin in May 2013. Advice is expected to be issued in September 2013.

1.10 For pharmaceuticals, please complete the table below. If the unit cost of the pharmaceutical is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Table 4 Unit costs of technology being appraised

Pharmaceutical formulation	Concentrate for solution for infusion.
Acquisition cost (excluding VAT)	£2,395 per 420 mg vial.
Method of administration	Intravenous Infusion.
Doses	Loading dose of 840 mg followed by a three-weekly maintenance dose of 420 mg.
Dosing frequency	Every three weeks.
Average length of a course of treatment	This will be evaluated formally in economic modelling. Median duration of treatment with pertuzumab in the CLEOPATRA study was 18.1 months (Baselga, 2012).
Average cost of a course of treatment	This will be evaluated formally in economic modelling.
Anticipated average interval between courses of treatments	A person with HER2-positive metastatic breast cancer will receive only one course of treatment with pertuzumab.
Anticipated number of repeat courses of treatments	A person with HER2-positive metastatic breast cancer will receive only one course of treatment with pertuzumab.
Dose adjustments	Dose reductions are not recommended.

1.11 For devices, please provide the list price and average selling price. If the unit cost of the device is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Not applicable.

1.12 Are there additional tests or investigations needed for selection, or particular administration requirements for this technology?

It is standard clinical practice to test the HER2 status of the tumours of people with breast cancer at the point of primary diagnosis (NICE CG80 and CG81). No additional tests are required to diagnose people for treatment with a pertuzumab based regimen, or prior to the administration of pertuzumab.

1.13 Is there a need for monitoring of patients over and above usual clinical practice for this technology?

Minimal additional monitoring is required.

According to the summary of product characteristics, the assessment of left ventricular ejection fraction (LVEF) should take place prior to initiation of pertuzumab and every three cycles of treatment (every 9 weeks). This is marginally more frequent than LVEF monitoring required with treatment with trastuzumab (every four cycles or 12 weeks).

1.14 What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

Pertuzumab is indicated for use in combination with trastuzumab and docetaxel.

Trastuzumab is recommended at an initial loading dose of 8 mg/kg of body weight administered as an intravenous infusion followed every three weeks thereafter by a maintenance dose of 6 mg/kg of body weight. If trastuzumab treatment is discontinued, treatment with pertuzumab should be discontinued.

Docetaxel is recommended at a dose of 75 mg/m^2 body surface area, administered every three weeks. The dose may be escalated to 100 mg/m^2 body surface area if the initial dose is well tolerated. If docetaxel is discontinued, treatment with pertuzumab and trastuzumab may continue until disease progression or unmanageable toxicity.

2 Context

2.1 Please provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.

Breast cancer is the most common malignancy affecting women in the UK. Approximately 50,000 people were diagnosed with breast cancer in the UK in 2010, of which 99.2% were women (CRUK 2012). Although advancements in the detection and management of early stage breast cancer have resulted in improvements in breast cancer mortality over recent years (Levi et al 2005,

Malvezzi et al 2011), metastatic breast cancer remains largely incurable, with the majority of people dying due to their disease.

Without targeted therapy, positive HER2 status is associated with poor survival (Chang 2003) and is present in approximately 23% of people with metastatic breast cancer (Roche data on file RXUKDON00258 - November 2012). HER2-positive metastatic breast cancer 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 (Borg et al 1990, Ross et al 1998, Menard et al 2001, Brown et al 2008, Crigliano et al 2009, Ross et al 2009 and Pauletti et al 2000). People with HER2-positive breast cancer are approximately five years younger than the general breast cancer population (Neven et al 2008; Kwan et al 2009).

Although recent advances in the treatment of HER2-positive metastatic breast cancer include the proven efficacy of trastuzumab and chemotherapy (Marty et al 2005), there still exists a significant need for new treatments that can increase response rates and increase the duration of progression-free survival and overall survival.

2.2 Please provide the number of patients covered by this particular therapeutic indication in the marketing authorisation and also including all therapeutic indications for the technology, or for which the technology is otherwise indicated, in England and Wales and provide the source of the data

Figure 1 Number of eligible people for pertuzumab per annum

Step	Population	Proportion	No of people	Source
1	Total population	100%	56,171,000	National Office of statistics – Mid 2011
2	Breast cancer disease		42,562	Methodology for calculating catchment incidence based on QOF, HES and NCIN data
3	Metastatic disease	25%	11,103	Roche commissioned analysis of the IMS Oncology Analyser (UK MAT Quarter 2 2012 – Nov 2012
4	HER tested	92%	10,193	Roche commissioned analysis of the IMS Oncology Analyser (UK MAT Quarter 2 2012 – Nov 2012
5	HER2-positive	23%	2,336	Roche commissioned analysis of the IMS Oncology Analyser (UK MAT Quarter 2 2012 – Nov 2012
6	% Non – clinical trial	92%	2,151	Assumption
7	Suitable for treatment	96%	2,058	Proportion of people receiving trastuzumab who are suitable for treatment – Roche Data July 2011
8	**Eligible for treatment**		**2,058**	

2.3 **Please provide information about the life expectancy of people with the disease in England and Wales and provide the source of the data.**

People with metastatic breast cancer have a poor prognosis. Median survival in the control arm in CLEOPATRA study was approximately three years.

2.4 Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed.

- NICE Technology Appraisal No. 34, March 2002, 'Trastuzumab for the treatment of advanced breast cancer'.

  TA 34 recommends trastuzumab for in combination with paclitaxel for women with tumours with excessive HER2 at levels of 3+ who have not had chemotherapy for metastatic breast cancer and for whom anthracycline treatment is inappropriate. It is recommended for women with tumours with excessive HER2 at levels of 3+ who have had at least two chemotherapy treatments for metastatic breast cancer. Previous chemotherapy must have included at least an anthracycline drug and a taxane drug where these treatments are appropriate. It should also have included hormonal therapy in patients sensitive to oestrogen.

- NICE Technology Appraisal No. 257. April 2012, 'Lapatinib and trastuzumab in combination with an aromatase inhibitor for the first-line treatment of metastatic hormone receptor positive breast cancer which over-expresses HER2'.

  TA257 does not recommend lapatinib or trastuzumab in combination with an aromatase inhibitor for women who have been through the menopause and who have metastatic breast cancer that is hormone receptor and HER2 positive.

- Clinical Guideline No. 81, February 2009, 'Advanced breast cancer: diagnosis and treatment'

- Breast cancer follow-up and management after primary treatment: American Society of Clinical Oncology Clinical Practice Guideline Update - Posted ahead of print on www.jco.org on November 5, 2012

- American Society of Clinical Oncology-College of American Pathologists Guideline Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer - Published in JCO 2007; 25:118-145.
- AGO Recommendations for Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer. Update 2011.
- NCCN Clinical Practice Guidelines in Oncology – Breast Cancer V. 3.2012 dated 09/10/12
- SIGN Guideline 84: Management of breast cancer in women. A national clinical guideline. December 2013.
- Locally recurrent or metastatic breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Published in Ann Oncol (2012) 23 (suppl 7): vii11-vii19.

2.5 Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.

NICE Clinical Guideline 81 (CG81) includes recommendations on the diagnosis and treatment for people with HER2-positive metastatic breast cancer. The guideline recommends assessment of HER2 status at the time of disease recurrence if receptor status was not assessed at the time of initial diagnosis.

Treatment of HER2-positive metastatic breast cancer is outlined in a treatment algorithm in CG81 (CG81, Page 24). The algorithm states that trastuzumab in line with TA34 is the standard first line treatment of HER2-positive metastatic breast cancer for people who have not received anthracyclines in the adjuvant setting. Following CG81, the vast majority people currently receive anthracyclines in the adjuvant setting. Since

publication of TA34, the standard treatment of first line metastatic breast cancer has changed to reflect the updated licence of trastuzumab. The licence now also includes trastuzumab in combination with docetaxel, in addition to trastuzumab in combination with paclitaxel for people that have not received chemotherapy for their HER2-positive metastatic breast cancer. Standard care of people for their HER2-positive metastatic breast cancer is now trastuzumab in combination with docetaxel or paclitaxel, as acknowledged in the NICE final scope. The algorithm also recommends treatment with vinorelbine or capecitabine for the second line treatment of people with HER2-positive metastatic breast cancer.

Following NICE approval of pertuzumab our clinical experts anticipate that pertuzumab will be given in combination with trastuzumab and docetaxel as a first line treatment for HER2-positive metastatic breast cancer.

2.6 Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

There is minimal variation or uncertainty about best practice in the treatment of HER2-positive metastatic breast cancer.

2.7 Please identify the main comparator(s) and justify their selection.

Comparator 1: Trastuzumab in combination with docetaxel

Comparator 2: Trastuzumab in combination with paclitaxel

These two regimens are those most commonly given for the first line treatment of HER2-positive metastatic breast cancer and are set out as the comparators in the final scope for this appraisal.

2.8 Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

The safety of pertuzumab has been evaluated in more than 1,400 people in the pivotal trial CLEOPATRA and in phase I and II trials.

In the pivotal trial CLEOPATRA the most common adverse reactions (grade 3, 4 or 5) which occurred in 10% or more trial participants were neutropenia, febrile neutropenia and leukopenia.

Adverse reactions were reported less frequently after discontinuation of docetaxel treatment (Summary of Products Characteristics).

The cost associated with treatment of adverse events will be considered in the economic analysis.

2.9 Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

It is standard NHS practice to give people with HER2-positive metastatic breast cancer an intravenous infusion of trastuzumab every 21 days. This infusion typically takes place in a hospital with an established oncology unit, which has the staffing and infrastructure required for administration of cancer treatments. Pertuzumab will have minimal impact upon the current pathway, as it can be administered on the same treatment day as trastuzumab (every 21 days).

Testing and monitoring of HER2-positive metastatic breast cancer is outlined in CG81.

2.10 Does the technology require additional infrastructure to be put in place?

No.

3 Equality

2.11 Identification of equality issues

2.11.1 Please let us know if you think that this appraisal:

- **could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;**
- **could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology**
- **could lead to recommendations that have any adverse impact on people with a particular disability or disabilities**

Please provide us with any evidence that would enable the Committee to identify and consider such impacts.

No equality issues have been identified.

2.11.2 How has the analysis addressed these issues?

No equality issues have been identified.

4 Innovation

2.11.3 Discuss whether and how you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits, and whether and how the technology is a 'step-change' in the management of the condition.

Pertuzumab is a step change in the treatment of HER2-positive metastatic breast cancer

For more than a decade trastuzumab in combination with a taxane (docetaxel or paclitaxel) has remained the standard of care with no significant advances in the treatment of people with this disease.

Pertuzumab is a first-in-class HER2 dimerisation inhibitor. The combination of pertuzumab and trastuzumab offers a comprehensive HER2 blockade and,

when used with docetaxel, results in the inhibition of signalling pathways essential for tumour growth (Agus et al 2002). The result is an innovative breakthrough treatment significantly improving outcomes of people with this disease.

This innovation is demonstrated by the substantial improvement in outcomes seen in the pivotal CLEOPATRA trial. When compared to trastuzumab and docetaxel alone, pertuzumab is associated with a greater proportion of people responding to treatment (objective response rate of 80.2% compared with 69.3%), a statistically significant and clinically important increase in median progression-free survival of 6.3 months (from 12.4 to 18.7 months) and a statistically significant and marked increase in overall survival with a 34% reduction in the risk of death (Baselga et al 2012, Swain et al 2012).

2.11.4 Discuss whether and how you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation.

Wider Societal Benefits

The median age of women in the pertuzumab arm of the CLEOPATRA study was only 53 years old.

The premature death of these women can have a significant impact upon families. A family may lose a key contributor to household income, a key contributor to informal care of both children and elderly parents and a key influencer upon their child's future development.

Pertuzumab can extend survival and grant women more time to contribute to their families (both financially and via informal care).

This issue is <u>not</u> currently captured in the NICE process and should be considered be the Committee.

The Differential Value of QALYs Gained in Differential Circumstances

HER2-positive metastatic breast cancer is associated with a significant burden of illness. These women die approximately 30 years earlier than an equivalent healthy woman (ONS Interim Life Tables 2008-2010).

It is a widely held view that society places a preference upon QALYs gained by people in these circumstances (a view shared by the government in its consultations on “Value Based Pricing”). This preference is not captured in a simple QALY calculation and is not captured by the use of an arbitrarily defined ‘End of Life criteria’.

We believe the Committee should carefully consider societies potential preference of QALYs gained in areas of a higher burden of disease.

2.11.5 Please identify the data you have used to make these judgements, to enable the Appraisal Committee to take account of these benefits.

Societies preference for QALYs gained in people with a high burden of illness is being investigated in an on-going study commissioned by the Department of Health commissioned study. We hope the results of this study will be published prior to the conclusion of this Appraisal.

5 Statement of the decision problem

Table 5 Decision problem

	Final scope issued by NICE	**Decision problem addressed in the submission**	**Rationale if different from scope**
Intervention	Pertuzumab (in combination with trastuzumab and docetaxel)	As per NICE scope	N/A
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	As per NICE scope	N/A
Comparator(s)	Trastuzumab in combination with a taxane (docetaxel or paclitaxel)	As per NICE scope	N/A
Outcomes	-progression free survival -overall survival -response rate -adverse effects of treatment -health-related quality of life	As per NICE scope	N/A
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	N/A
Subgroups to be considered	No subgroups identified	As per NICE scope	N/A
Special considerations including equity or equality issues	No potential equity or equality issues identified	As per NICE scope	N/A

Section B – Clinical and cost effectiveness

Table 6 Elements of health technology assessment

Element of health technology assessment	Reference case	Section in 'Guide to the methods of technology appraisal'
Defining the decision problem	The scope developed by NICE	5.2.5 and 5.2.6
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	5.2.5 and 5.2.6
Perspective costs	NHS and PSS	5.2.7 to 5.2.10
Perspective benefits	All health effects on individuals	5.2.7 to 5.2.10
Type of economic evaluation	Cost-effectiveness analysis	5.2.11 and 5.2.12
Synthesis of evidence on outcomes	Based on a systematic review	5.3
Measure of health effects	QALYs	5.4
Source of data for measurement of HRQL	Reported directly by patients and carers	5.4
Source of preference data for valuation of changes in HRQL	Representative sample of the public	5.4
Discount rate	An annual rate of 3.5% on both costs and health effects	5.6
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	5.12
HRQL, health-related quality of life; NHS, National Health Service; PSS, personal social services; QALY(s), quality-adjusted life year(s)		

6 Clinical evidence

6.1 Identification of studies

6.1.1 Describe the strategies used to retrieve relevant clinical data, both from the published literature and from unpublished data that may be held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 10.2, appendix 2.

A systematic review was undertaken in order to identify all randomised evidence relevant do the decision problem.

Searches used index and text words which included pertuzumab, trastuzumab, docetaxel and breast cancer as descriptors. The search was restricted to include only documents relating to humans and clinical trials, and excluded reviews when the inclusion criteria were not met. Only publications written in English were assessed. The search was restricted to metastatic or advanced breast cancer. The search was further restricted manually according to inclusion/exclusion criteria in Section 10.2.6.

Full details of the searches conducted and terms used are provided in Appendix 10.2. Details of the search outputs/records obtained and reasons for exclusion/inclusion of records are also provided in Section 10.2.7.

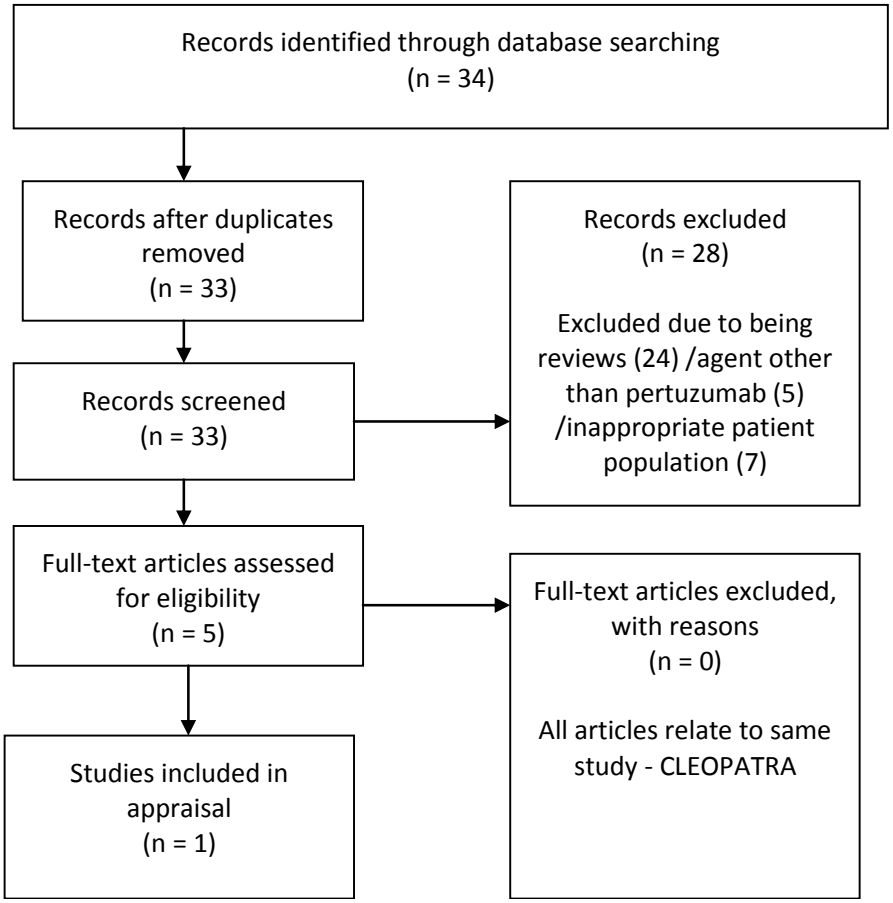
6.2 Study selection

6.2.1 Inclusion and exclusion selection criteria

See section 10.2.6

6.2.2 Flow diagram of the number of studies included and excluded at each stage

Figure 2 PRISMA Statement Flow Diagram



6.2.3 When data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or when trials are linked (for example, an open-label extension to an RCT), this should be made clear.

One RCT was identified – the CLEOPATRA study. Section 6.2.4 lists all publications founded upon this study.

Complete list of relevant RCTs

6.2.4 Provide details of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by

independent searches conducted by the Evidence Review Group

Table 7 Details of CLEOPATRA

Trial number (acronym)	Intervention	Comparator	Population	Primary study reference
CLEOPATRA (WO20698)	Pertuzumab in combination with trastuzumab and docetaxel (n=402). Pertuzumab fixed loading dose of 840mg followed by 420mg every 3 weeks. Trastuzumab loading dose of 8mg/kg bodyweight followed by a maintenance dose of 6mg/kg every 3 weeks. Docetaxel at a starting dose of 75mg/m^2 every 3 weeks (at discretion of the investigator could be increased to 100mg/m^2 if the side-effect profile was acceptable.	Placebo in combination with trastuzumab and docetaxel (n=406). Placebo fixed dose of 840mg followed by 420mg every 3 weeks. Trastuzumab loading dose of 8mg/kg bodyweight followed by a maintenance dose of 6mg/kg every 3 weeks. Docetaxel at a starting dose of 75mg/m^2 every 3 weeks (at discretion of the investigator could be increased to 100mg/m^2 if the side-effect profile was acceptable.	People with HER2-positive metastatic breast cancer who had not received chemotherapy or biologic therapy for their metastatic disease.	The full study was published by Baselga J et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. NEJM 2012; 366(2):109-119. And in Swain et al.

CLEOPATRA is a phase III, randomised, double-blind, placebo-controlled clinical trial to evaluate the efficacy and safety of pertuzumab in combination with trastuzumab and docetaxel compared with placebo, trastuzumab and docetaxel in people with previously untreated HER2-positive metastatic breast cancer.

The following articles and abstracts have been published:

Baselga J & Swain SM. CLEOPATRA: A Phase III Evaluation of Pertuzumab and Trastuzumab for HER2-Positive Metastatic Breast Cancer. *Clinical Breast Cancer 2010;* 10(6): 489-491

J Baselga et al. Pertuzumab plus Trastuzumab plus Docetaxel for Metastatic Breast Cancer. N Engl J Med 2012;366:109-19. (This is the first publication to feature results from the CLEOPATRA study – the 13th May 2011 data-cut.)

Swain S, et al. Confirmatory overall survival analysis of CLEOPATRA: A randomized, double-blind, placebo-controlled phase III study with pertuzumab, trastuzumab, and docetaxel in patients with HER2-positive first-line metastatic breast cancer. CTRC-AACR San Antonio Breast Cancer Symposium 2012. Abstract P5-18-26. (This poster presented the final overall survival analysis prior to participant crossover being permitted in the study.)

PFS Concordance

Miles D, Swain S, Im Y-H, Knott A, Ross G, Clark E, Benyunes M, Baselga J. Concordance between independently and investigator-assessed progression-free survival in CLEOPATRA. ASCO Annual Meeting 2012. Abstract e11055

Adverse events

Baselga J, Cortés J, Im S-A, Pivot X, Clark E, Knott A, Ross G, Swain SM Adverse events with pertuzumab and trastuzumab: Evolution during treatment with and without docetaxel in CLEOPATRA. ASCO Annual Meeting 2012. Abstract 597

Cardiac tolerability

Ewer MS, Baselga J, Clark E, Benyunes MC, Ross G, Swain SM
Cardiac tolerability of pertuzumab, trastuzumab and docetaxel in patients with HER2-positive metastatic breast cancer in the CLEOPATRA study. ASCO Annual Meeting 2012. Abstract 533

Health-related quality of life/health outcomes

Cortés J, Baselga J, Im Y-H, Ross G, Clark E, Knott A, Swain SM
Quality of life assessment in CLEOPATRA, a Phase III study combining pertuzumab with trastuzumab and docetaxel in metastatic breast cancer. ASCO Annual Meeting 2012. Abstract 598

Pharmacokinetics

J Cortés, SM Swain, I Kudaba, M Hauschild, T Patel, E Grincuka, N Masuda, V McNally, J Visich, J Baselga. Pharmacokinetics of pertuzumab with trastuzumab and docetaxel in HER2-positive first-line metastatic breast cancer: Results from the phase III trial CLEOPATRA. ESMO Congress 2012. Abstract 344P.

Elderly participants

D Miles, J Baselga, D Amadori, P Sunpaweravong, V Semiglazov, A Knott, E Clark, G Ross, and SM Swain. Pertuzumab (P) in combination with trastuzumab (T) and docetaxel (D) in elderly patients with HER2-positive metastatic breast cancer in the CLEOPATRA stud. CTRC-AACR San Antonio Breast Cancer Symposium 2012. Abstract P5-18-01.

Biomarker analyses

J Baselga, J Cortés, S-A Im, E Clark, A Kiermaier, G Ross, and SM Swain. Biomarker analyses in CLEOPATRA: A phase III, placebo-controlled study of pertuzumab in HER2-positive, first-line metastatic breast cancer. CTRC-AACR San Antonio Breast Cancer Symposium 2012. S5-1

6.2.5 Please highlight which of the RCT is identified above compares the intervention directly with the appropriate comparator(s) with references to the decision problem. If there are none, please state this.

CLEOPATRA is a randomised placebo-controlled double-blind clinical trial comparing the intervention of interest with a trastuzumab in combination with a taxane (docetaxel). This study is directly relevant to the decision problem.

6.2.6 When studies identified above have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. For example, when studies have been identified but there is no access to the level of trial data required, this should be indicated.

No identified studies have been excluded.

List of relevant non-RCTs

6.2.7 Please provide details of any non-RCTs (for example experimental and observational data) that are considered relevant to the decision problem and a justification for their inclusion. Full details should be provided in section 6.8 and key details should be presented in a table; the following is a suggested format.

Due to the availability of randomised placebo-controlled double-blind data on the relative efficacy directly relevant to the decision problem no non-RCT evidence has been presented in this submission.

6.3 Summary of methodology of relevant RCTs

6.3.1 As a minimum, the summary should include information on the RCT(s) under the subheadings listed in this section. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (www.consort-statement.org). It is expected that all key aspects of methodology will be in the public domain; if a manufacturer or sponsor wishes to submit aspects of the methodology in confidence, prior agreement must be requested from NICE. When there is more than one RCT, the information should be tabulated.

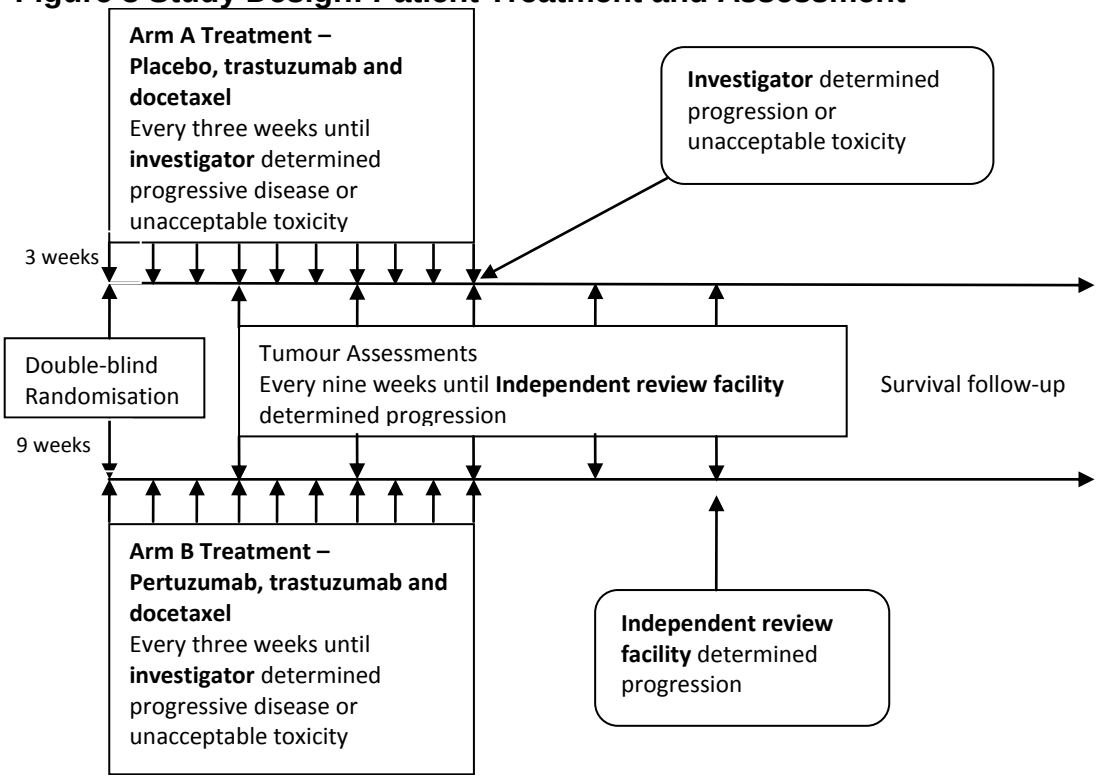
Methods

6.3.2 Describe the RCT(s) design (for example, duration, degree and method of blinding, and randomisation) and interventions. Include details of length of follow-up and timing of assessments. The following tables provide a suggested format for when there is more than one RCT.

Summary of the CLEOPATRA study

CLEOPATRA is a phase III, randomised, double-blind, placebo-controlled, international, multicentre clinical trial, designed to evaluate the efficacy and safety of pertuzumab, trastuzumab and docetaxel compared with trastuzumab and docetaxel in people with previously untreated HER2-positive metastatic breast cancer.

Figure 3 Study Design: Patient Treatment and Assessment



The study enrolled 808 people with HER2-positive metastatic breast cancer randomised in a 1:1 ratio to one of two treatment arms (see Table 7 for details of the two arms). Treatment in the study is given until investigator-assessed radiographic or clinical progressive disease (unacceptable toxicity or withdrawal of patient consent). Participants are withdrawn from the study if pertuzumab or placebo and/or trastuzumab are permanently discontinued or withheld for more than two cycles of treatment. Docetaxel was permanently discontinued for unacceptable toxicity.

Treatment arm A - Trastuzumab and docetaxel

- Pertuzumab placebo: IV infusion every 3 weeks (q3w)

- Trastuzumab: loading dose of 8 mg/kg IV infusion, followed by 6 mg/kg IV infusion q3w
- Docetaxel dose of 75 mg/m^2 IV infusion q3w for at least six cycles

Treatment arm B - Pertuzumab, trastuzumab and docetaxel

- Pertuzumab: loading dose of 840 mg/kg IV infusion, followed by 420 mg/kg IV q3w
- Trastuzumab: loading dose of 8 mg/kg IV infusion, followed by 6 mg/kg IV q3w
- Docetaxel dose of 75 mg/m^2 IV infusion q3w for at least six cycles (may be increased to 100 mg/m^2 at the investigators discretion)

Scans, medical photography and other relevant data relating to disease assessments were sent to the independent review facility on an on-going basis. Once a participant was assessed to have progressed by the investigator, the independent review facility was notified. If progression was confirmed by the independent review facility, the Investigator was notified that the participant no longer required tumour assessments in the study. If progression was not confirmed, the investigator was informed that the patient continue to be scanned every 9 weeks, as per protocol.

The primary analysis of efficacy is progression-free survival based on tumour assessments by an independent review facility. This was scheduled to take place when approximately 381 independent review facility assessed progression-free survival events (corresponding to approximately 448 investigator-assessed events) occurred. An interim analysis of overall survival was planned to take place at the same time, along with other analyses of safety and efficacy.

The primary efficacy analysis was performed from a clinical data cut-off on 13 May 2011 (follow up of 19.4 months). During the review process, the regulatory authorities requested a further analysis for overall survival. This was carried out with an additional year of data from a clinical data cut-off on 14 May 2012 (30 months follow up). After this analysis, as per protocol, the

study was fully unblinded and crossover permitted for those patients in the control arm whose disease had not yet progressed and who were still receiving treatment with trastuzumab. The trial will end when approximately 385 deaths have been reported unless terminated early by the sponsor. At this time, the final overall survival analysis will be reported, along with updated safety and selected efficacy parameters, although it should be noted that these results will be compounded by crossover.

Participants

6.3.3 Provide details of the eligibility criteria (inclusion and exclusion) for the trial.

The study population for this trial comprised participants aged at least 18 years with previously, untreated (in the metastatic setting), HER2-positive, metastatic or locally recurrent, unresectable breast cancer. This population included people who had not received chemotherapy and/or biologic therapy for their metastatic disease. Participants were allowed prior adjuvant hormonal therapy and one line of hormonal therapy for metastatic disease. People with stage IV disease at initial disease presentation or 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 population for the study reflects people who would normally be eligible for trastuzumab-based treatment outside of the clinical trial setting. See Table 8 and Table 9 for full details of the inclusion exclusion criteria for the study.

Table 8 CLEOPATRA inclusion criteria

Inclusion criteria
• Histologically or cytologically confirmed adenocarcinoma of the breast with locally recurrent or metastatic disease, and candidate for chemotherapy. • People with measurable and/or non-measurable disease were eligible. • People with bone only metastases were eligible provided they had some bone metastases that had not been previously irradiated and had tumour tissue samples from the primary tumour available for central HER2 testing and subsequent biomarkers analysis. • Locally recurrent disease must not be amenable to resection with curative intent. • People with de-novo Stage IV disease were eligible. • HER2-positive (defined as 3+ IHC or FISH amplification ratio ≥ 2.0) metastatic breast cancer confirmed by a sponsor-designated central laboratory. It was strongly

recommended that a formalin-fixed paraffin-embedded (FFPE) tissue block from the primary tumour (or metastatic if the primary was not available) be submitted for central laboratory confirmation of HER2 eligibility; however, if that was not possible, 25 unstained and freshly cut slides were to be submitted. The tissue was used subsequently for assessment of biomarkers.

- Age ≥ 18 years.
- LVEF ≥ 50% at baseline (within 42 days of randomisation) as determined by either ECHO or MUGA (ECHO being the preferred method. If the patient was randomised to the study, the same method of LVEF assessment, ECHO or MUGA, was to be used throughout the study, and to the extent possible, be obtained at the same institution). All available historic LVEF values during and post-trastuzumab adjuvant treatment for people who received such adjuvant therapy prior to enrolment into the study were collected.
- Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1.
- For women of childbearing potential and men with partners of childbearing potential, agreement to use a highly effective, non-hormonal form of contraception or two effective forms of non-hormonal contraception by the patient and/or partner. Contraception use was to continue for the duration of study treatment and for at least 6 months after the last dose of study treatment. Males whose partners were pregnant should use condoms for the duration of the pregnancy.

Table 9 CLEOPATRA exclusion criteria

Exclusion criteria

• Cancer-related exclusion criteria:
• History of anti-cancer therapy for metastatic breast cancer (with the exception of one prior hormonal regimen for metastatic breast cancer, which had to be stopped prior to randomization).
• Anti-cancer therapy for metastatic breast cancer included any EGFR or anti-HER2 agents or vaccines, cytotoxic chemotherapy, or more than one prior hormonal regimen for metastatic breast cancer.
• One prior hormonal 'regimen' for metastatic breast cancer could have included more than one hormonal therapy. If a patient switched therapy due to toxicity or local standard practice, and not due to progression, this was counted as one 'regimen'.
• If a patient received hormonal therapy for metastatic breast cancer and switched to a different hormonal therapy due to progression, this was counted as two 'regimens' and the patient was not eligible.
• History of approved or investigative tyrosine kinase/HER inhibitors for breast cancer in any treatment setting, except trastuzumab used in the neoadjuvant or adjuvant setting.
• History of systemic breast cancer treatment in the neoadjuvant or adjuvant setting with a disease-free interval from completion of the systemic treatment (excluding hormonal therapy) to metastatic diagnosis of < 12 months.
• History of persistent NCI-CTCAE, version 3.0 grade ≥ 2 hematologic toxicity resulting from previous adjuvant therapy.
• Current peripheral neuropathy of Grade ≥ 3 at randomization.
• History of other malignancy within the last 5 years, except for carcinoma in situ of the cervix, basal cell carcinoma or squamous cell carcinoma of the skin that was previously treated with curative intent.
• Current clinical or radiographic evidence of central nervous system (CNS) metastases. CT or MRI scan of the brain was mandatory (within 28 days of randomization) in cases of clinical suspicion of brain metastases.
 	
• History of exposure to the following cumulative doses of anthracyclines:
  o doxorubicin or liposomal doxorubicin > 360 mg/m^2
  o epirubicin > 720 mg/m^2
  o mitoxantrone > 120 mg/m^2 and idarubicin > 90 mg/m^2
  o other (ie liposomal doxorubicin or other anthracycline > the equivalent of 360 mg/m^2 of doxorubicin)
  o if more than one anthracycline was used, then the cumulative dose must not exceed the equivalent of 360 mg/m^2 of doxorubicin.

- Exclusion criteria related to hematological, biochemical, and organ function parameters:
  - Current uncontrolled hypertension (systolic > 150 mmHg and/or diastolic > 100 mmHg) or unstable angina.
  - History of congestive heart failure (CHF) of any New York Heart Association (NYHA) criteria, or serious cardiac arrhythmia requiring treatment (exception: atrial fibrillation, paroxysmal supraventricular tachycardia).
  - History of myocardial infarction within 6 months of randomization.
  - History of LVEF decline to below 50% during or after prior trastuzumab neoadjuvant or adjuvant therapy.
  - Current dyspnoea at rest due to complications of advanced malignancy, or other diseases requiring continuous oxygen therapy.

- General exclusion criteria:
  - Inadequate organ function, evidenced by the following laboratory results within 28 days of randomization:
  - Absolute neutrophil count (ANC) < 1,500 cells/mm3
  - Platelet count < 100,000 cells/mm3
  - Haemoglobin < 9 g/dL
  - Total bilirubin > upper limit of normal (ULN) (unless the patient had documented Gilbert's syndrome)
  - AST (SGOT) or ALT (SGPT) > 2.5 × ULN
  - AST (SGOT) or ALT (SGPT) > 1.5 × ULN with concurrent serum alkaline phosphatase > 2.5 × ULN. Serum alkaline phosphatase may have been > 2.5 × ULN only if bone metastases were present and AST (SGOT) and ALT (SGPT) < 1.5 × ULN
  - Serum creatinine > 2.0 mg/dL or 177μmol/L
  - International normalized ratio (INR) and activated partial thromboplastin time or partial thromboplastin time (aPTT or PTT) > 1.5 × ULN (unless on therapeutic coagulation).
  - Current severe, uncontrolled systemic disease (eg, clinically significant cardiovascular, pulmonary, or metabolic disease; wound healing disorders; ulcers; or bone fractures).
  - Major surgical procedure or significant traumatic injury within 28 days of study treatment start or anticipation of the need for major surgery during the course of study treatment.
  - Pregnant or lactating women.
  - History of receiving any investigational treatment within 28 days of randomization.
  - Current known infection with HIV, HBV, or HCV.
  - Receipt of IV antibiotics for infection within 14 days of randomization.
  - Current chronic daily treatment with corticosteroids (dose of > 10 mg/day methylprednisolone equivalent) (excluding inhaled steroids).
  - Known hypersensitivity to any of the study drugs.
  - Assessed by the investigator as unable or unwilling to comply with the requirements of the protocol.
  - Participation in concurrent interventional or non-interventional studies was not permitted

6.3.4 Describe the patient characteristics at baseline. Highlight any differences between study groups.

The treatment groups were generally comparable with respect to demographic characteristics (see Table 10 for more details).

The median age in both treatment arms was 54 years, with over 80% of people in both arms aged less than 65 years (339 people [83.5%] in the

trastuzumab and docetaxel arm and 342 people [85.1%] in the pertuzumab, trastuzumab and docetaxel arm). The age of this recruited population is comparable to the ages of participants recruited in previous trastuzumab studies (Marty et al 2005, Slamon et al 2001) and younger than the general breast cancer population (Neven et al 2008; Kwan et al 2009). The majority of people were categorised as either White (235 people [57.9%] in the trastuzumab and docetaxel arm compared with 245 people [60.9%] in the pertuzumab, trastuzumab and docetaxel arm) or Asian (far east) (133 people [32.8%] in the trastuzumab and docetaxel compared with 128 people [31.8%] in the pertuzumab, trastuzumab and docetaxel arm).

Prior treatment status was also well balanced between treatment arms. Approximately 50% of people in each treatment group had received prior adjuvant or neoadjuvant therapy (192 people [47.3%] in the trastuzumab and docetaxel arm compared with 184 people [45.8%] in the pertuzumab, trastuzumab and docetaxel arm). The remaining people had a de novo diagnosis of metastatic or locally advanced unresectable breast cancer.

The only baseline characteristic for which the treatment arms were imbalanced was baseline ECOG status. With fewer participants in the trastuzumab and docetaxel arm with an ECOG performance status of 0 (248 people [61.1%] compared with 274 people [68.2%] in the pertuzumab, trastuzumab and docetaxel arm.

Table 10 Characteristics of participants in the RCTs across randomised groups

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

Outcomes

6.3.5 Provide details of the outcomes investigated and the measures used to assess those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of health-related quality of life (HRQL), and any arrangements to measure compliance. Data provided should be from pre-specified outcomes rather than post-hoc analyses. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within UK clinical practice).

This study was conducted in full conformance with the principles of the Declaration of Helsinki and its subsequent amendments or with the laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the individual. The study adhered to the principles outlined in the Guideline for Good Clinical Practice ICH Tripartite Guideline (January 1997) or with local law if it afforded greater protection to the subject. In other countries where guidelines for good clinical practice existed, the sponsor and the investigators were to strictly ensure adherence to the stated provisions. The study was designed by the senior academic authors and representatives of the sponsor. The data were collected and analysed by the sponsor in collaboration with senior academics, who confirm the completeness and accuracy of the data and analyses, and the fidelity of the study to the protocol.

Primary endpoint

Progression-free survival

The primary efficacy endpoint was progression-free survival based on tumour assessments by an independent review facility.

Progression-free survival was defined as the time from randomisation to the first documented progressive disease, as determined by the independent review facility using RECIST (Response Evaluation Criteria in Solid Tumours) or death from any cause (within 18 weeks of last tumour assessment), whichever occurred first.

The RECIST criteria are the standard method of classifying tumour response to chemotherapy trials. Assessment of progression was based on a review of radiographic (eg MRI, CT, bone scans, chest x-ray), as well as cytologic (eg relevant cytology reports documenting malignant pleural effusions, bone marrow aspirations, cerebral spinal fluid), and photographic data, if available.

Progression-free survival is a valid primary endpoint in this study as the effect of first line treatment can be accurately investigated.

Secondary endpoints

Overall survival

Overall survival is defined as the time from the date of randomization to the date of death from any cause.

Progression-free survival based on investigator assessments

Investigator assessed progression-free survival is defined as the time from randomisation to the first documented radiographic progression, as determined by the investigator using RECIST, or death from any cause, whichever occurs first.

Overall response rate

Overall response rate (ORR) is defined as a complete response (CR), or partial response (PR) determined by the independent review facility using RECIST on two consecutive occasions ≥ 4 weeks apart (people without measurable disease or with disease localised only to the bone were not included in the analysis of objective response).

Duration of objective response

Duration of objective response is defined as the period from the date of initial confirmed partial or complete response until the date of progression or death from any cause (tumour responses were based on independent review facility evaluations using RECIST).

Health-related quality of life - Time to symptom progression

The study used the Functional Assessment of Cancer Therapy-Breast (FACT-B), Version 4 questionnaire to assess participant-reported quality of life. The FACT-B questionnaire provides a total quality of life score in addition to information about physical well-being, social/family well-being, functional well-being, and disease-specific concerns.

Time to symptom progression is defined as the time from randomisation to the first symptom progression as measured by the FACT TOI-PFB—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 was considered to be clinically meaningful and thus to be symptom progression. Compliance with the completion of the FACT-B questionnaire was assessed by deriving the number and percentage of patients with a valid questionnaire at each scheduled visit at which the questionnaire is expected to be completed (every 9 weeks).

<u>Exploratory efficacy endpoints</u>

Time to response

Time to first response is defined as the period from randomisation to the date of initial confirmed PR or CR (i.e. the date of tumour assessment at which response (PR or CR) was first detected by the independent review facility or the investigator). All responses were verified four weeks later. People who did not respond were censored at the last valid tumour assessment

Clinical benefit response rate

Clinical benefit response (CBR) rate is defined as the percentage of people who demonstrated an objective response (CR or PR confirmed a minimum of four weeks later), or stable disease (SD) maintained for at least 180 days.

Safety parameters

Safety analyses included the following:

• Incidence and severity of adverse events (AEs) and serious adverse events (SAEs)

• Incidence of symptomatic left ventricular systolic dysfunction (congestive heart failure [CHF]) and asymptomatic left ventricular systolic dysfunction events

• Left ventricular ejection fraction (LVEF) measurements over the course of the study

• Laboratory test abnormalities

All of the outcomes assessed in the study considered to be relevant to the decision problem are discussed further, with regards to their relevance to UK clinical practice and benefits to people with the disease.

Statistical analysis and definition of study groups

6.3.6 State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken).

<u>Primary Efficacy Analysis</u>

Progression-Free Survival

The difference in primary endpoint, independent review facility assessed progression-free survival, between the two treatment arms was compared using a two-sided log-rank test at 5% significance level, stratified by prior treatment status (*de novo* and prior adjuvant or neoadjuvant therapy) and region (Europe, North America, South America, and Asia). The null hypothesis (H0) is that the survival distribution of progression-free survival (S) in the two treatment groups is the same. The alternative hypothesis (H1) is that the survival distributions of progression-free survival in the treatment and the control arms are different:

H_0: S<pertuzumab> = S<placebo> vs H_1: S<pertuzumab> ≠ S<placebo>

Additional tests were performed to compare whether the distributions or the key summary statistics of the secondary endpoints between the two treatment arms were the same at a two-sided alpha level of 5%. The overall type I error rate for the analysis of primary endpoint of progression-free survival, overall survival, and objective response rate (ORR) was controlled at 5% using the fixed-sequence testing procedure. The three variables were each tested at an overall two-sided 5% significance level in the order specified.

The primary analysis of progression-free survival was planned for when approximately 381 independent review facility-assessed progression-free survival events had occurred. It was estimated that a total of 381 independent review facility-assessed progression-free survival events would provide approximately 80% power to detect a 33% improvement in median progression-free survival (hazard ratio [HR] of 0.75 with a two-sided significance level of 5%). In designing the study, median progression-free survival for the control group was assumed to be 10.5 months, improving to 14 months with the addition of pertuzumab, assuming that progression-free survival is exponentially distributed.

An interim analysis of overall survival was performed at the time of the primary analysis of progression-free survival. To account for this interim analysis of overall survival, a Lan−deMets α-spending function with the O'Brien−Fleming

stopping boundary was applied to the overall survival analyses. The protocol estimated that approximately 50% of the total 385 required deaths (193 deaths) would have occurred at the time of the primary analysis of progression-free survival (under this assumption the alpha level for the first overall survival analysis would be 0.0031).

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.

The final analysis of overall survival is planned to take place after 385 deaths have occurred, which will provide 80% power to detect a 33% improvement in overall survival (median overall survival for the control group is assumed to be 36 months). The table below lists the power for final progression-free survival analysis at the two-sided significance level of 5% with 381 independent review facility assessed progression-free survival events.

Table 11Statistical Power for final progression-free survival analysis

Effect size	Power for Log-Rank Test of PFS
40% improvement in PFS	90%
33% improvement in PFS	80%
PFS, Progression-free survival	

A data cut-off date was determined when the required number of progression-free survival events was reached, and the clinical data on or prior to the data cut-off date were thoroughly cleaned. The treatment assignment was unblinded and the analyses described below were performed.

Efficacy analysis

Efficacy analyses are based on the ITT population with people included under the treatment arm to which they were randomised. The statistical tests employed for each type of endpoint in the study are summarized in Table 12.

Table 12 Statistical Analyses of Efficacy Endpoints

Variable	Test	Stratification*
Primary endpoint:	Log-rank	prior treatment status,

independent review facility - assessed progression-free survival		region
Secondary endpoints: time-to-event: investigator-assessed progression-free survival, overall survival, time to symptom progression, duration of response	Cox regression	prior treatment status, region
Objective response rate	Mantel–Haenszel χ^2	prior treatment status, region
	Fisher's exact	unadjusted (sensitivity)
* Strata: Prior treatment status: de novo vs prior (neo)adjuvant therapy; Region: Europe, North America, South America, and Asia.		

The following fixed-sequence testing hierarchy was used at the time of the primary progression-free survival analysis to adjust for multiple statistical testing of independent review facility assessed progression-free survival, overall survival and ORR for the purposes of confirmatory statistical testing:

1. Test the primary endpoint independent review facility assessed progression-free survival, at a two-sided 5% significance level. If positive, continue to Step 2; otherwise, stop.

2. Test overall survival at an overall two-sided 5% significance level. If positive, continue to Step 3; otherwise, stop.

3. Test ORR at a two-sided 5% significance level.

Primary Endpoint

The primary endpoint was independent review facility assessed progression-free survival. The log-rank test, stratified by prior treatment status (*de novo* and prior adjuvant or neoadjuvant therapy) and region (Europe, North America, South America, and Asia), was used to compare progression-free survival between the two treatment arms. The unstratified log-rank test results are also provided as a sensitivity analysis.

The Kaplan-Meier approach was used to estimate median progression-free survival for each treatment arm and the Cox proportional hazard model, stratified by prior treatment status and region was used to estimate the HR

between the two treatment arms (ie, the magnitude of treatment effect) and its 95% confidence interval (CI).

The analyses were performed in pre-defined demographic subgroups as appropriate provided there was a reasonable sample size.

Univariate and multivariate cox regression analyses were also performed, to investigate the association between the pre-defined stratification and baseline prognostic covariates with progression-free survival.

Sensitivity Analyses on progression-free survival

Six sensitivity analyses were planned to account for the potential impact of the following factors on progression-free survival calculations:

1. A possible difference between investigator and independent review facility tumour assessments

2. Censoring at the time of next-line anti-cancer therapy (NACT)

3. Independent review facility -assessed progression-free survival on treatment

4. Potential bias introduced by varied tumour assessment intervals as a result of missed visit(s)

5. Timing of death, including all deaths occurring more than 18 weeks after last tumour assessment as an event

6. Controlling for treatment withdrawals due to toxicity

Details of these analyses are in the below table. All sensitivity analyses were stratified by prior treatment status and region, and based on the ITT population.

Table 13 Sensitivity Analyses to Assess Robustness of progression-free survival Results

	Factor Assessed	Censoring Rules

1	Possible differences between investigator and independent review facility tumour assessments	The earliest progression date as assessed by either the independent review facility or the investigator was used as the date of the progression-free survival event.
2	Censoring at the time of next-line anti-cancer therapy (NACT)	People who started NACT prior to either independent review facility assessed progression, death (within 18 weeks of last tumour assessment) or last independent review facility evaluable tumour assessment were censored at the date of the last independent review facility evaluable tumour assessment prior to the start of NACT.
3	Independent review facility assessed progression-free survival during treatment	Only independent review facility assessed progression-free survival events occurring no later than 42 days after the last administration of any study treatment were included in the analysis.
4	Potential bias introduced by varied tumour assessment intervals as a result of a missing visit(s)	The missing assessment (or earliest missing assessment if more than one was missed) was replaced by an assessment of progression and the time to event was set as the expected day of the missing scheduled visit. If no assessment was missed, then the first progression date as assessed by the independent review facility was used as the date of the event. In the case of death without prior progression within 18 weeks of the last tumour assessment, where death was preceded by a missing assessment, the missing assessment was replaced by an assessment of progression.
5	Timing of death	All deaths, including those occurring 18 weeks after the last tumour assessment, were included as events in the analysis.
6	People stopping treatment early due to toxicity	People who discontinued tumour all study treatment due to toxicity were censored at their last independent review facility assessed tumour assessment on or before their treatment discontinuation date

Secondary Endpoints

Overall survival: Analysis methods were the same as those described for the primary endpoint.

Progression-free survival based on investigator assessments: Data for people without documented progression or who did not die within 18 weeks of the last tumour assessment were censored at the time of the last investigator tumour assessment (or, if no tumour assessments are performed after the baseline visit, at 1 day). Analysis methods were same as for the primary endpoint.

Objective response: Only people with independent review facility determined measurable disease at baseline were included in the analysis of the objective response. Objective response was based on the best overall response recorded from the start of trial treatment until independent review facility assessed progression, death or first administration of NACT, whichever occurs earliest. People without a post-baseline independent review facility assessed tumour assessment were considered to be non-responders.

An estimate of the objective response rate and its 95% CI was calculated for each treatment arm. The Mantel-Haenszel $\chi 2$ test stratified by prior treatment status and region was used to compare the objective response rate between the two treatment arms. An unadjusted Fisher's exact test result was provided as a sensitivity analysis.

As a sensitivity analysis, Investigator-assessed objective response was evaluated, based on people with Investigator-determined measurable disease at baseline.

Duration of objective response: Duration of objective response was based on independent review facility assessments. No formal hypothesis testing was performed on this endpoint, as the subgroup of people with objective response is not a randomised subset. Median duration of objective response for each treatment arm was estimated using the Kaplan-Meier approach. The hazard ratio between the two treatment arms was estimated using Cox regression.

As a sensitivity analysis, duration of objective response was repeated based on Investigator assessments.

Time to symptom progression: Please see Section on Health-Related Quality of Life below.

Health-related Quality of Life Analysis

Time to symptom progression was evaluated using the Functional Assessment of Cancer Therapy-for people with Breast Cancer (FACT-B)

questionnaire with the Trial Outcomes Index-Physical/Functional/Breast (TOI-PFB) subscale. Female people completed questionnaires every 9 weeks (within three days prior to each tumour assessment) until independent review facility determined progression. Importantly, people were to complete the assessment on schedule even if study therapy was no longer being administered due to toxicity or investigator-determined progression (assessments stopped at independent review facility determined progression). Analysis methods were the same as those described for the primary efficacy endpoint (independent review facility determined progression-free survival). Time to event analysis using Kaplan Meier methodology tested the hypothesis that the addition of pertuzumab to the treatment regimen does not have a significant impact on Health-related quality of life.

The TOI-PFB is a 24-item subscale generated using three subsections of the FACT-B questionnaire (physical and functional well-being and additional concerns for people with breast cancer (breast cancer subscale [BCS]). All items in the questionnaire were rated by the patient on a five-point scale ranging from 0 (“not at all”) to 4 (“very much”). The higher subscale score indicates better perceived quality of life. A decrease of five points or more in the TOI PFB score from baseline was considered to be a clinically meaningful change (i.e. indicative of symptom progression).

Exploratory efficacy analysis

The following endpoints, which were not specified as planned endpoints within the Study Protocol, were evaluated as exploratory analyses:

1. Time to Response (independent review facility and Investigator assessed)

2. Clinical Benefit Response (independent review facility and Investigator assessed)

Time to Response: Time to response was summarised based on both the independent review facility and Investigator tumour assessments and was defined as the period (weeks) from randomisation to the date of initial confirmed PR or CR (defined as the date of tumour assessment at which the

PR/CR was first detected by the independent review facility /Investigator). Time to response was based on tumour assessments up to independent review facility /Investigator-assessed progression (as appropriate to the endpoint), death or NACT, whichever occurs earlier.

People in the ITT population with measurable disease at baseline (according to the independent review facility or Investigator, as appropriate) were included in the analysis of time to response. People who do not respond and do not experience disease progression or death (within 18 weeks of last tumour assessment) will be censored at the date of their last tumour assessment (independent review facility -assessed or Investigator-assessed as appropriate). People who do not respond and who experience disease progression or death (within 18 weeks of the last tumour assessment) or start NACT (next line anti-cancer therapy) were censored at their date of progression (independent review facility or Investigator assessed, as appropriate) date of death, or the last TA prior to onset of NACT, whichever is earlier. People with no tumour assessments after baseline will be censored at 1 day.

No hypothesis testing was performed on this endpoint as the analysis was considered to be exploratory.

Clinical Benefit Response: Clinical benefit response (CBR) was evaluate based on the independent review facility and Investigator tumour assessments of progression (as appropriate to the endpoint), death or NACT, whichever occurred earlier. People were defined as showing clinical benefit if they have had an objective response (CR or PR subsequently confirmed a minimum of 4 weeks later), or stable disease (SD) that was maintained for at least 180 days.

The analysis of the CBR was based on the ITT population. It was not necessary to restrict the analysis of CBR to people with measurable disease, as done for the analysis of ORR, because it is possible to observe clinical benefit in people with non-measurable disease, in the form of stable disease. People with a best overall response (BOR) of CR or PR, confirmed at least 4

weeks apart, or with SD maintained for at least 180 days were classified as demonstrating clinical benefit. All other people, including people with no post-baseline tumour assessments, were classified as non-responders with respect to clinical benefit.

The analysis was descriptive, with no hypothesis testing performed, as this was an exploratory endpoint. An estimate of the CBR and 95% CI using the Pearson-Clopper method was calculated for each treatment arm.

SAFETY ANALYSIS

6.3.7 People who received any amount of any component of study treatment were included in safety analyses (safety analysis population), this will be discussed in Section 6.9**Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc.**

Subgroup analyses were pre-planned for the study. Analyses for independent review facility determined progression-free survival were performed for the following pre-defined categorical covariates:

• Prior Treatment Status (stratification factor)

• Region (stratification factor)

• Age-group (< 65, ≥ 65 years)

• Age-group (<75, ≥ 75 years)

• Race (White, Black, Asian, Other)

• Disease type (Visceral disease vs. non-visceral disease)

• IHC HER2 Status (3+)

• FISH (positive)

• ER/PgR Status (ER and PgR negative vs ER and/or PgR positive)

Forest plots of the HR and corresponding (1-α) % CI were produced for all subgroups.

Post database lock, further subgroup analyses of progression-free survival were defined for the following subgroups:

• HER2 IHC 2+

• Baseline ECOG (0 vs. 1+)

• People with prior neoadjuvant or adjuvant treatment, split into people who had received prior trastuzumab and people who had not received prior trastuzumab

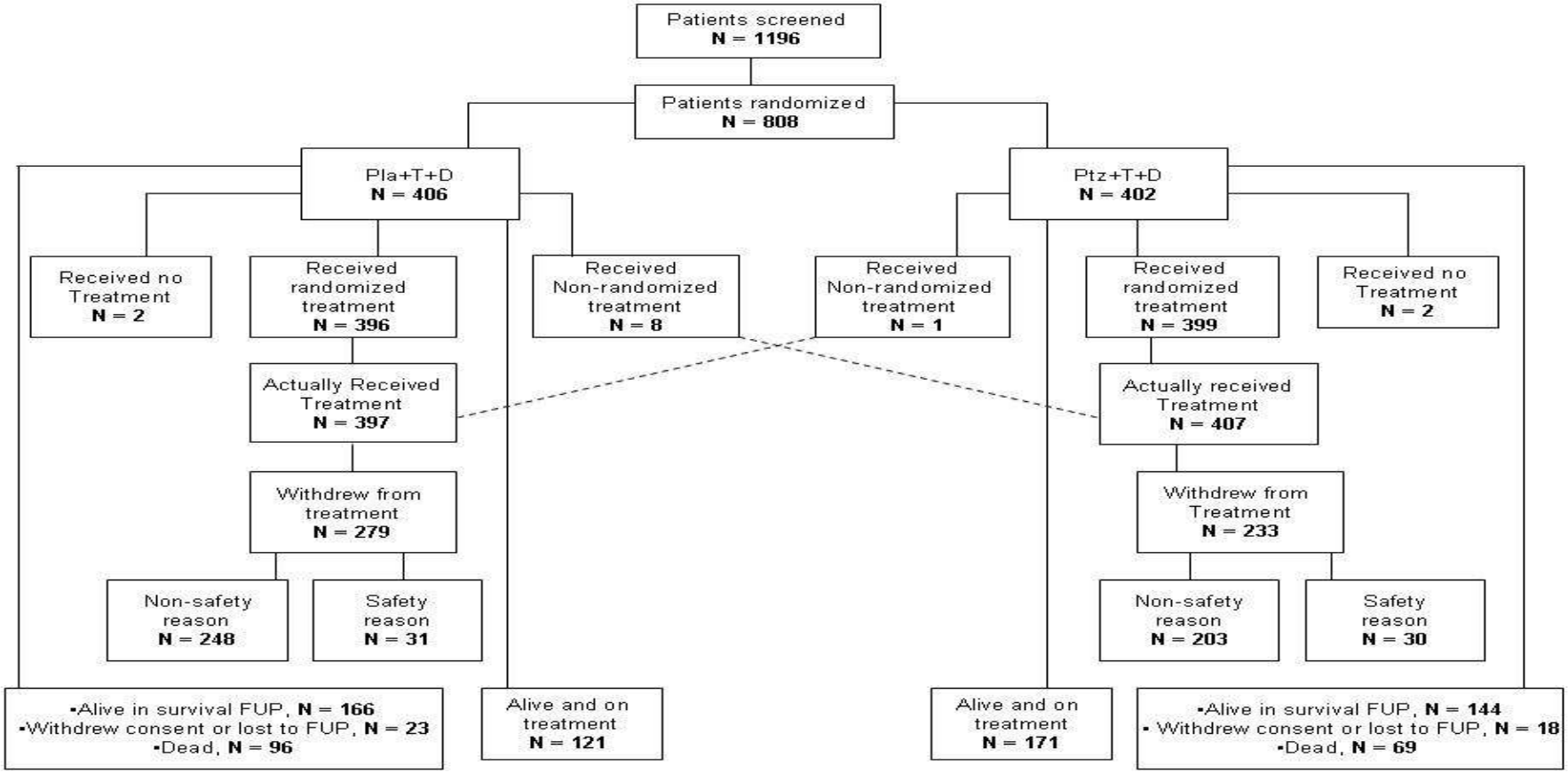
• Docetaxel dose escalation to 100mg/m^2 (Yes vs. No).

For the post-database lock subgroup analyses, the summary table produced for the primary analysis was repeated for each subgroup level, rather than presenting the additional subgroup data in a Forest plot

Participant flow

6.3.8 Provide details of the numbers of patients who were eligible to enter the RCT(s), randomised, and allocated to each treatment. Provide details of and the rationale for, patients who crossed over treatment groups and/or were lost to follow-up or withdrew from the RCT

Figure 4 Participant Flow



6.4 Critical appraisal of relevant RCTs

- **The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study that meets the criteria for inclusion should therefore be critically appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies. The critical appraisal will be validated by the ERG.**

Data for this study were recorded through an electronic data capture system using eCRFs. Exceptions to this procedure included films for radiographic tumour assessment, ECHO/MUGA cardiac assessments, and paper quality-of-life questionnaires completed by participants and data on HER2 status. Accurate and reliable data collection was assured by verification and cross-checking of the eCRFs against the investigator's records by the study monitor (source document verification), and by the maintenance of a drug-dispensing log by the investigator. A comprehensive validation check program utilising front-end checks in the eCRF and back-end checks in the Roche database was used to verify the data, and discrepancy reports were generated accordingly. These were transferred electronically to the eCRF at the site for resolution by the investigator.

Table 14 Critical Appraisal of RCT

Study ID or acronym		
Study question	How is the question addressed in the study?	Grade (yes/no/not clear/N/A)
Was randomisation carried out appropriately?	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).	Yes
Was the concealment of treatment allocation adequate?	A double-blind placebo control was used to minimise any bias.	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	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.	Yes
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)?	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.	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	There were no unexpected imbalances in drop outs	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	There is no evidence to suggest this	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	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	Yes
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

6.4.1 Please provide as an appendix a complete quality assessment for each RCT. See section 10.3, appendix 3 for a suggested format.

See section 10.3, appendix 3

6.4.2 If there is more than one RCT, tabulate a summary of the responses applied to each of the critical appraisal criteria. A suggested format for the quality assessment results is shown below.

Not appropriate as there is only one RCT.

6.5 Results of the relevant RCTs

6.5.1 Provide the results for all relevant outcome measure(s) pertinent to the decision problem. Data from intention-to-treat analyses should be presented whenever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given. If there is more than one RCT, tabulate the responses.

6.5.2 The information may be presented graphically to supplement text and tabulated data. If appropriate, please present graphs such as Kaplan–Meier plots.

6.5.3 For each outcome for each included RCT, the following information should be provided.

- **The unit of measurement.**
- **The size of the effect; for dichotomous outcomes, the results ideally should be expressed as both relative risks (or odds ratios) and risk (or rate) differences. For time-to-event analysis, the hazard ratio is an equivalent statistic. Both absolute and relative data should be presented.**
- **A 95% confidence interval.**
- **Number of participants in each group included in each analysis and whether the analysis was by 'intention to treat'. State the results in absolute numbers when feasible.**

- **When interim RCT data are quoted, this should be clearly stated, along with the point at which data were taken and the time remaining until completion of those RCT. Analytical adjustments should be described to cater for the interim nature of the data.**
- **Other relevant data that may assist in interpretation of the results may be included, such as adherence to medication and/or study protocol.**
- **Discuss and justify definitions of any clinically important differences.**

  Report any other analyses performed, including subgroup analysis and adjusted analyses, indicating those pre-specified and those exploratory.

The primary analysis took place with a clinical data cut-off of 13 May 2011.Following the primary progression-free survival analysis, a formal request was received from regulatory authorities for an additional analysis of overall survival prior to the planned protocol-specified final analysis. This second interim analysis of overall survival was conducted with data cut-off date of 14 May 2012.This second interim analysis provided updated investigator assessed progression-free survival and safety data. Subsequent to the second interim analysis, as per protocol, patient crossover has been permitted; therefore any data obtained in future will be compounded by crossover. The results, presented below, for each of the outcome measures all refer to their respective most recent analysis with the relevant data cut-off dates (13 May 2011 or 14 May 2012) clearly stated.

Primary Endpoint (Data cut-off 13 May 2011)

The study met its primary endpoint. Treatment with pertuzumab, trastuzumab and docetaxel resulted in a statistically significant improvement in independent review facility assessed progression-free survival (HR=0.62, 95% CI [0.51, 0.75], p <0.0001) with an increase in median progression-free survival of 6.1 months (median progression-free survival of 12.4 months in

the trastuzumab and docetaxel arm compared with 18.5 months in the pertuzumab, trastuzumab and docetaxel arm).

Key Secondary Endpoints (Data cut-off 13 May 2011)

Median time to investigator-assessed progression-free survival was significantly improved in the pertuzumab, trastuzumab and docetaxel arm compared with trastuzumab and docetaxel arm (18.5 months compared with 12.4 months), with a hazard ratio of 0.65 [0.54, 0.78], $p<0.0001$. The results were comparable with those observed for independent review facility assessed progression-free survival and were updated in the second interim analysis (data cut-off 14 May 2012, discussed later in this section).

A strong trend towards an overall survival benefit was observed in the pertuzumab arm (hazard ratio of 0.64 [0.47, 0.8, $p=0.005$). However the estimated hazard ratio did not meet the O'Brien-Fleming stopping boundary of the Lan-DeMets α-spending function for this interim analysis of survival and was therefore not deemed statistically significant. The subsequent second interim analysis (data cut-off 14 May 2012) with an additional year of data, however, was found to be statistically significant (discussed later in this section).

A higher percentage of people receiving pertuzumab achieved an objective response (complete response or partial response), as assessed by the independent review facility (233 participants [69.3%] in the trastuzumab and docetaxel arm compared with 275 participants [80.2%] in the pertuzumab, trastuzumab and docetaxel arm.

The duration of response was longer in people receiving pertuzumab, trastuzumab and docetaxel compared with trastuzumab and docetaxel (87.6 week median overall response duration in the pertuzumab, trastuzumab and docetaxel arm compared with 54.1 weeks in the trastuzumab and docetaxel).

There was no evidence to suggest that addition of pertuzumab to trastuzumab and docetaxel had a detrimental effect on patient-reported outcomes based on the comparable time to symptom progression between treatment arms, as measured by the change in TOI_PFB (median 18.3 weeks in the trastuzumab and docetaxel arm compared with 18.4 weeks in the pertuzumab, trastuzumab and docetaxel arm).

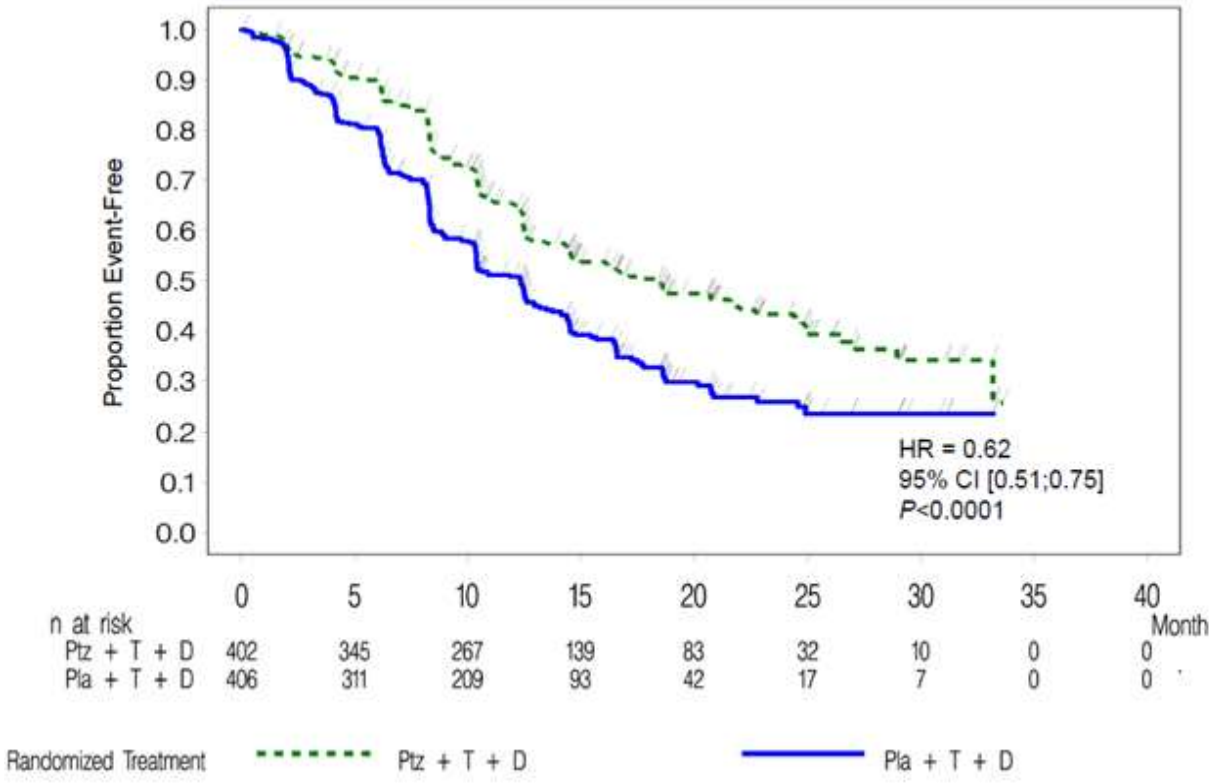
Table 15 Overview of Efficacy

	Trastuzumab and docetaxel arm (n=406)	Pertuzumab, trastuzumab and docetaxel (n=402)	Hazard Ratio, P-Value. Confidence Interval
Primary Endpoint **Independent review facility assessed progression-free survival (data cut-off 13 May 2011)**			
n No (%) people with event Median time to event (months)	406 242 (59.6%) 12.4	402 191 (47.5%) 18.5	p-value - <0.0001 HR 0.62 CI [0.51, 0.75)
Key Secondary Endpoints **Investigator-Assessed progression-free survival (data cut-off 14 May 2012)**			
n No (%) people with event Median time to event (months)	406 296 (72.9%) 12.4	402 257 (63.9%) 18.7	p-value- <0.0001 HR 0.69 CI [0.58; 0.81]
Overall Survival (data cut-off 14 May 2012)			
n No (%) of deaths Median time to event (months)	406 154 (37.9%) 37.6	402 113 (28.1%) Median not reached	HR 0.66 CI [0.52; 0.84]
Objective Response Rate (data cut-off 13 May 2011)			
n Responders 95% CI for Objective Response Rate Complete response Partial response Stable disease Progressive disease	336 233 (69.3%) [64.1; 74.2] 14 (4.2%) 219 (65.2%) 70 (20.8%) 28 (8.3%)	343 275 (80.2%) [75.6; 84.3] 19 (5.5%) 256 (74.6%) 50 (14.6%) 13 (3.8%)	
Duration of Response (data cut-off 13 May 2011)			
n Median duration of response (weeks) 95% CI for Median	233 54.1 [46;64]	275 87.6 [71;106]	
Time to Symptom Progression (FACT-B) (data cut-off 13 May 2011)			
n Number (%) people with event Median time to symptom progression (weeks) 95% CI for Median	404 229 (56.7%) 18.3 [18;27]	402 239 (59.5%) 18.4 [18;27]	
HR, Hazard Ratio (Log-Rank test, stratified **); P-Value, P-Value (Log-Rank test, stratified **), CI, Confidence Interval 95%			

Primary Efficacy Parameter – Independent Review Facility assessed Progression-free survival (Data cut-off 13 May 2011)

Independent review facility assessed progression-free survival was significantly improved for people in the pertuzumab, trastuzumab and docetaxel arm compared with people receiving trastuzumab and docetaxel (HR = 0.62, p < 0.0001), with an increase in median progression-free survival of 6.1 months (median 12.4 for trastuzumab and docetaxel compared with 18.5 months for pertuzumab, trastuzumab and docetaxel). The Kaplan-Meier curve (Figure 5) shows an early separation beginning at the first tumour assessment (9 weeks), which is maintained from this point onwards. The curves remain separate and do not cross.

Figure 5 Progression-free survival (Independent Assessed 13 May 2011 data-cut) Kaplan-Meier Plots

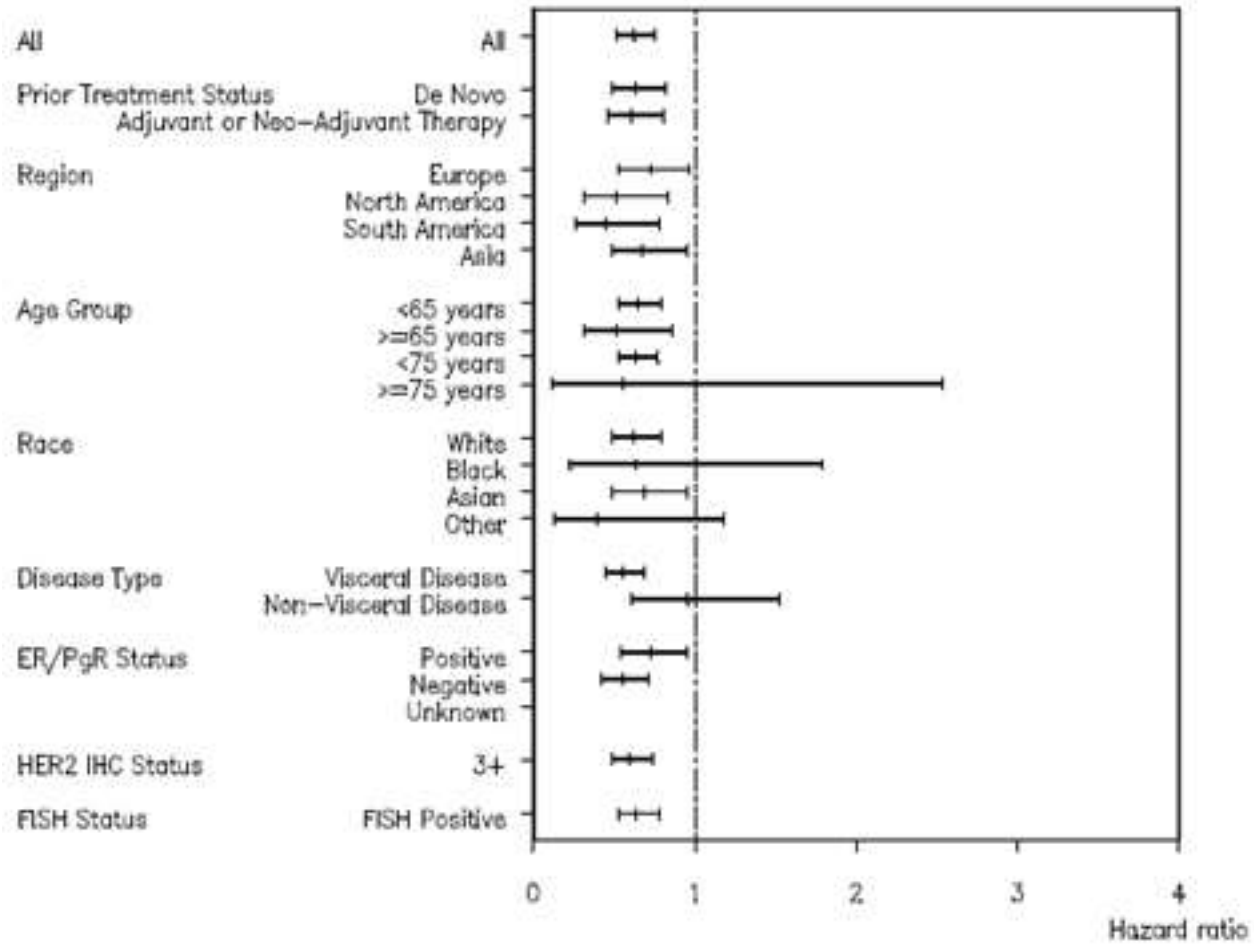


Progression-free survival events were defined as progressed disease or death within 18 weeks of the person's last tumour assessment. The progression-free survival event was progressed disease in 226 people (55.7%) in the trastuzumab and docetaxel arm and 180 people (44.8%) in the pertuzumab, trastuzumab and docetaxel arm. Death within 18 weeks of the

person's last independent review facility assessed tumour assessment made up the remaining events.

Subgroup analyses for independent review facility assessed progression survival were performed on a set of covariates, as pre-specified in the study statistical analysis plan. The results of the subgroup analyses were generally consistent with the results seen in the study population. The benefit associated with pertuzumab was seen in all of the subgroups tested, with point estimates of the hazard ratio all less than 1.0. Furthermore, in the majority of subgroups tested, the hazard ratio was comparable to the overall hazard ratio observed in the study population (HR = 0.63, unstratified analysis). Moreover, the upper 95% CI for the HR was below 1 in the majority of subgroups indicating all sub-groups benefitted from pertuzumab- based treatment.

Figure 6 Progression-free survival forest plot hazard (independent assess 13 May 2011)



Category	Subgroup	N	Lower confidence limit	Estimate	Upper confidence limit
All	All	808	0.52	0.63	0.76
Prior Treatment Status	De Novo	432	0.49	0.63	0.82
	Adjuvant or Neo-Adjuvant Therapy	376	0.46	0.61	0.81
Region	Europe	306	0.53	0.72	0.97
	North America	135	0.31	0.51	0.84
	South America	114	0.27	0.46	0.78
	Asia	253	0.48	0.68	0.95
Age Group	<65 years	681	0.53	0.65	0.80
	>=65 years	127	0.31	0.52	0.86
	<75 years	789	0.53	0.64	0.78
	>=75 years	19	0.12	0.55	2.54
Race	White	480	0.49	0.62	0.80
	Black	30	0.23	0.64	1.79
	Asian	261	0.49	0.68	0.95
	Other	37	0.13	0.39	1.18
Disease Type	Visceral Disease	630	0.45	0.55	0.68
	Non-Visceral Disease	178	0.61	0.96	1.52
ER/PgR Status	Positive	388	0.55	0.72	0.95
	Negative	408	0.42	0.55	0.72
	Unknown	12	0.00	179E6	.
HER2 IHC Status	3+	721	0.49	0.60	0.74
FISH Status	FISH Positive	767	0.53	0.64	0.78

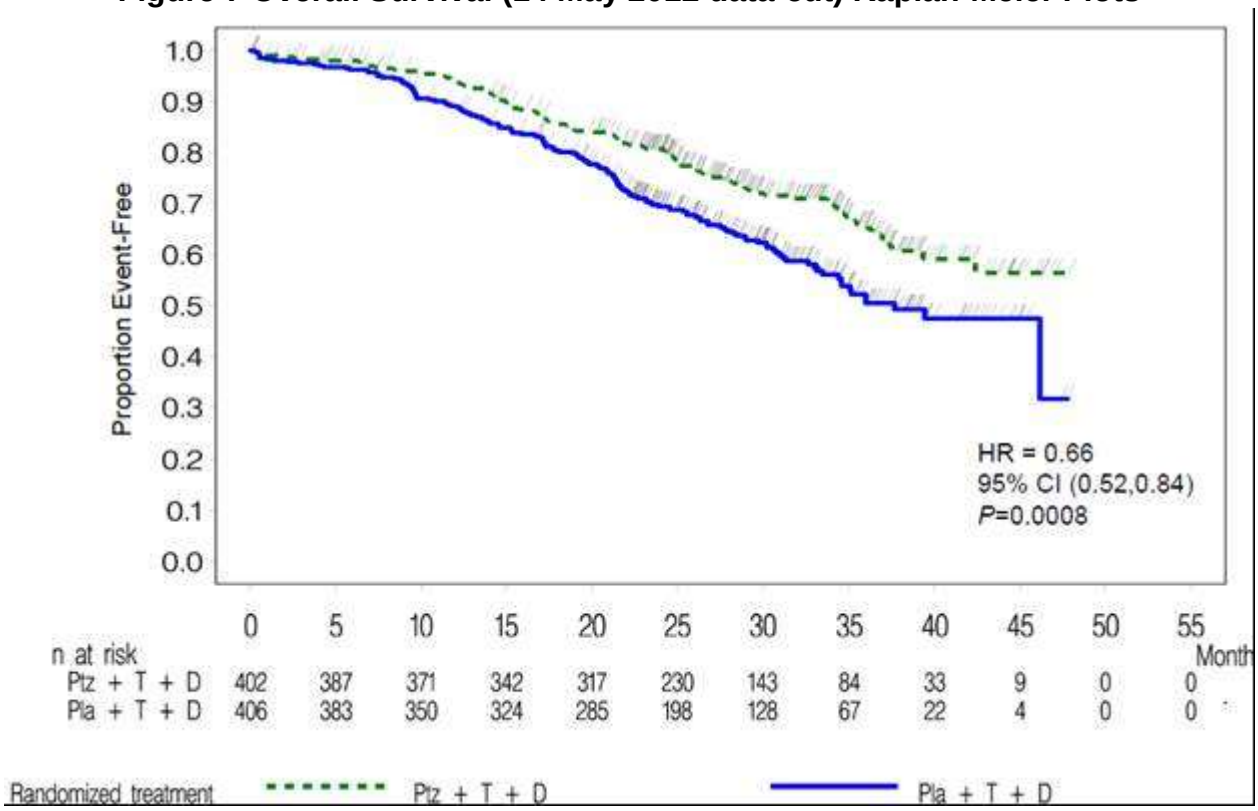
Secondary efficacy parameters

Overall Survival (Data cut-off 14 May 2012)

At the time of the clinical data cut-off for the second interim overall survival analysis (14 May 2012), 267 deaths had occurred, with more deaths in the trastuzumab and docetaxel arm (154 deaths [37.9% of people]) than in the pertuzumab, trastuzumab and docetaxel arm (113 deaths [28.1%]). This analysis included an additional 102 deaths (58 deaths in the trastuzumab and docetaxel arm and 44 deaths in the pertuzumab, trastuzumab and docetaxel arm) compared with the first interim analysis of overall survival. The clinical data cut-off occurred approximately 22 months after the last patient was randomised in the study; median survival follow-up was 30 months in both arms. The Kaplan−Meier analysis of time to censoring for overall survival shows that the pattern of survival follow-up is similar for both arms). The overall survival result for this analysis (HR = 0.66, 95% CI: 0.52, 0.84; p = 0.0008; stratified by prior treatment status and region) crosses the pre-defined O'Brien−Fleming stopping boundary for the Lan−DeMets α-spending function (HR ≤ 0.739, p ≤ 0.0138) and therefore demonstrates a statistically significant survival benefit for people randomised to pertuzumab, trastuzumab and docetaxel. Median survival has been reached in the trastuzumab and docetaxel arm (37.6 months) but has not been reached in the pertuzumab, trastuzumab and docetaxel arm.

The Kaplan-Meier curves demonstrate an early separation at approximately 4 months that continues over time (see Figure 7). The absolute difference between the two arms was 5% at 1 year, 11% at 2 years and 16% at 3 years.

Figure 7 Overall Survival (14 May 2012 data-cut) Kaplan-Meier Plots



A series of sensitivity analyses were conducted to assess the robustness of this analysis, as described below, all are supportive of this latest overall survival analysis:

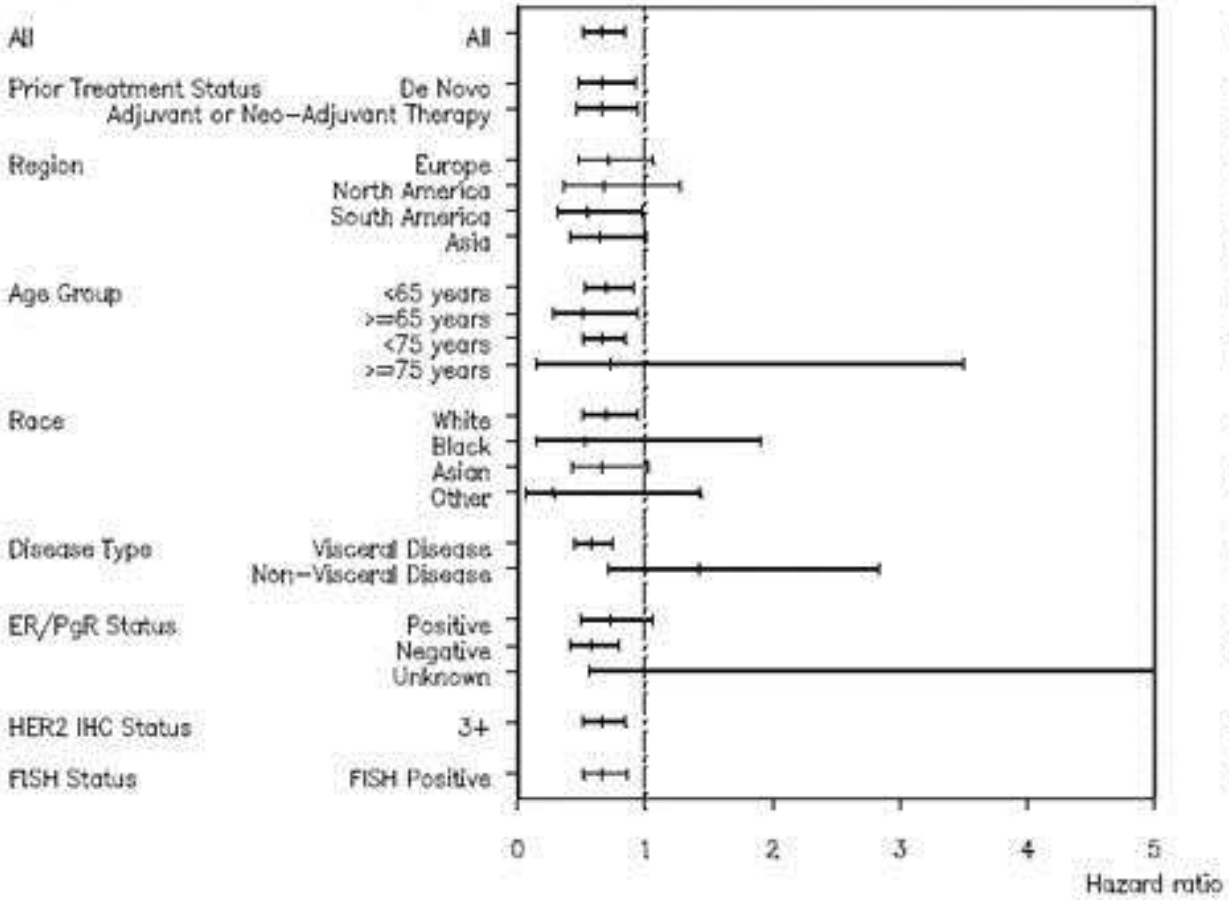
- An unstratified analysis provided identical results (HR=0.66, p=0.0008)
- Additionally, the overall survival curves were compared using the Wilcoxon test, which is an alternative to the log-rank test for comparing survival distributions. This analyses provided identical results (p=0.0008)

Subgroup analyses of overall survival were performed using the same pre-specified covariates as defined for the progression-free survival analysis. In general, the subgroup analysis results, based on the observed hazard ratios and 95% confidence intervals (CIs), are consistent with those for the overall study population and indicate a consistent survival benefit with pertuzumab.

The hazard ratio for the subgroup of people with non-visceral disease was estimated to be 1.42. However, it should be noted that there was a low number of people in this subgroup and a low number of deaths (33 deaths in 178 people [18.5%]), with high 1-year survival rates in both treatment arms

(0.93−0.95). Consequently, the variability around this estimated HR was high (95% CI: 0.71, 2.84). The CHMP concluded the relatively small sample size of this subgroup and low event rate may have affected the probability to detect a true treatment effect and consequently did not advise a restriction of indication of pertuzumab to this subgroup.

Figure 8 Overall survival forest plot (Independent assessed 14 May 2012)



Category	Subgroup	N	Lower confidence limit	Estimate	Upper confidence limit
All	All	808	0.52	0.66	0.84
Prior Treatment Status	De Novo	432	0.47	0.66	0.93
	Adjuvant or Neo-Adjuvant Therapy	376	0.46	0.66	0.94
Region	Europe	306	0.48	0.72	1.07
	North America	135	0.36	0.68	1.28
	South America	114	0.31	0.55	0.98
	Asia	253	0.41	0.64	1.00
Age Group	<65 years	681	0.53	0.70	0.91
	>=65 years	127	0.27	0.51	0.95
	<75 years	789	0.52	0.66	0.85
	>=75 years	19	0.15	0.72	3.50
Race	White	480	0.51	0.70	0.95
	Black	30	0.14	0.52	1.91
	Asian	261	0.43	0.66	1.03
	Other	37	0.06	0.29	1.43
Disease Type	Visceral Disease	630	0.44	0.57	0.74
	Non-Visceral Disease	178	0.71	1.42	2.84
ER/PgR Status	Positive	388	0.50	0.73	1.06
	Negative	408	0.41	0.57	0.79
	Unknown	12	0.56	8.94	143.6
HER2 IHC Status	3+	721	0.51	0.66	0.85
FISH Status	FISH Positive	767	0.52	0.67	0.86

Cox Regression Analyses for Overall Survival

Exploratory univariate and multivariate Cox regression analyses were performed on the updated overall survival.

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 overall survival analysis. In addition, the key covariates identified as potential prognostic factors remained consistent, compared to the analyses reported in the primary data data-cut.

Investigator-Assessed Progression-Free Survival (Data-cut 14 May 2012)

At the time of the second clinical data-cut (14 May 2012), 1553 people (68% of 808 people randomised) were reported to have had a progression-free survival event according to investigator assessment. More people in the trastuzumab and docetaxel arm (296 of 406 people [73%]) had had a progression-free survival event than in the pertuzumab, trastuzumab and docetaxel arm (257 of 402 people [64%]). The HR was 0.69 (95% CI: 0.58, 0.81) and the increase in median progression-free survival was 6.3 months from 12.4 months for trastuzumab and docetaxel compared with 18.7 months for pertuzumab, trastuzumab and docetaxel. These results are consistent with those from the primary analysis, demonstrating a durable clinical benefit.

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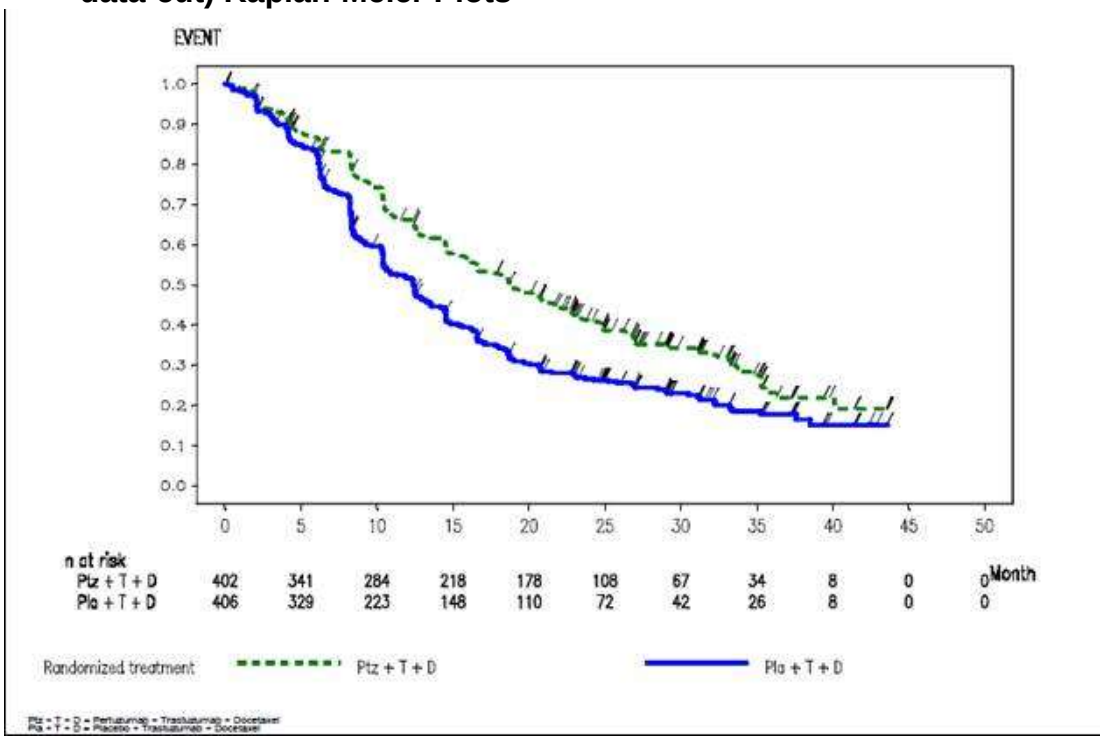
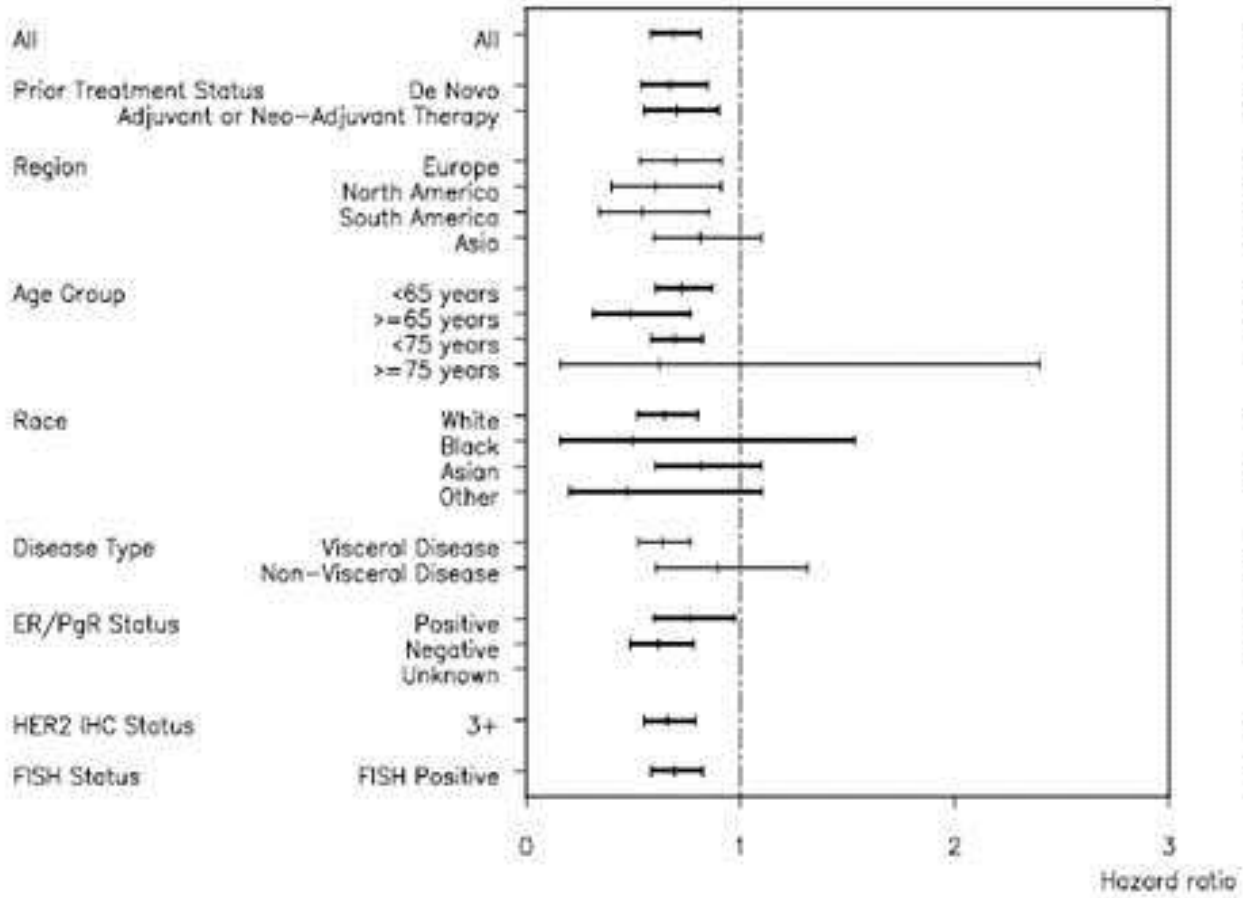
Figure 9 Progression-free survival (Investigator Assessed 14 May 2012 data-cut) Kaplan-Meier Plots



Exploratory subgroup analyses of investigator-assessed progression-free survival were performed for the baseline characteristics used in the primary analysis of independent review facility assessed progression-free survival. The results of these subgroup analyses are consistent with both the overall progression-free survival result for the updated analysis and with the subgroup results presented in the primary analysis (data-cut 13 May 2011) independent review facility assessed progression-free survival. The benefit associated with pertuzumab-based treatment is maintained in all of the subgroups explored, with point estimates of the hazard ratio consistently below 1.0.

Figure 10 Progression-free survival forest plot (Investigator assessed 14 May 2012)



Category	Subgroup	N	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

Objective Response (Data-cut 13 May 2011)

The results of the independent review facility assessed objective response support the results of the primary endpoint, with a higher percentage of people in the pertuzumab, trastuzumab and docetaxel arm (275 people [80.2%]) achieving an objective response, compared with those on the trastuzumab and docetaxel arm (233 people [69.3%]), p = 0.0011, stratified analysis. Complete response was achieved by 14 people (4.2%) in the trastuzumab and docetaxel arm and 19 people (5.5%) in the pertuzumab, trastuzumab and docetaxel arm, and partial response by 219 people (65.2%) compared with 256 people (74.6%) respectively.

Objective response based on investigator assessment was also investigated as a sensitivity analysis. The analysis was based on the subset of the ITT population with investigator-determined measurable disease (n = 371 for the trastuzumab and docetaxel arm, n = 367 for the pertuzumab, trastuzumab and docetaxel arm). The results were broadly similar to the results from the independent review facility assessed objective response, with 253 people (68.2%) in the trastuzumab and docetaxel arm and 284 people (77.4%) in the pertuzumab, trastuzumab and docetaxel arm achieving an objective response (p = 0.0049, stratified analysis).

Duration of Objective Response (Data-cut 13 May 2011)

The median duration of response was 54.1 weeks in the trastuzumab and docetaxel arm compared with 87.6 weeks in the pertuzumab, trastuzumab and docetaxel arm (HR = 0.66, 95% CI [0.51, 0.85]). Comparable results were observed in the analysis of investigator-assessed duration of objective response (median 54.0 in the trastuzumab and docetaxel arm compared with 73.7 weeks in the pertuzumab, trastuzumab and docetaxel arm, HR = 0.67 [0.52, 0.85]).

Time to Symptom Progression According to FACT-B Quality of Life Questionnaire (Data-cut 13 May 2011)

Only females completed the FACT-B questionnaire as planned. This resulted in 806 of the 808 ITT population included in the FACT-B analyses (404 people in the trastuzumab and docetaxel arm and 402 people in the pertuzumab, trastuzumab and docetaxel arm). Symptom progression according to FACT-B was defined as a decrease from baseline in the TOI-PFB score of five points or more. The TOI-PFB is a composite score derived from the physical wellbeing, functional wellbeing and additional concerns subscales.

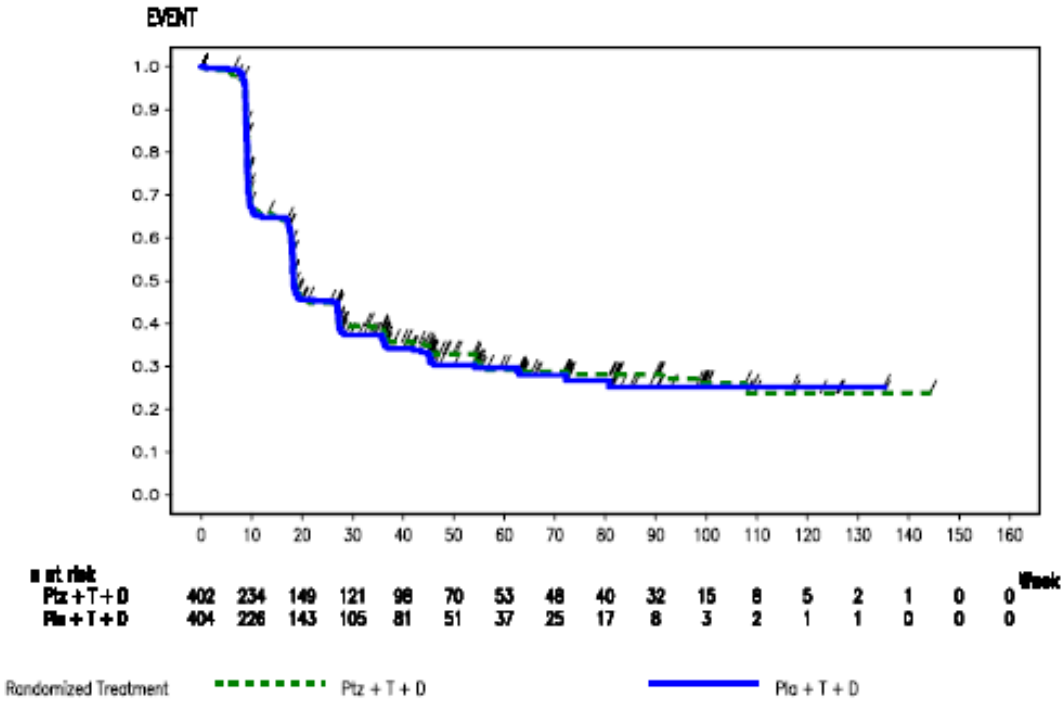
There was no evidence that the addition of pertuzumab to trastuzumab and docetaxel led to a detrimental effect on quality of life, with 229 people (56.7%) in the trastuzumab and docetaxel arm and 239 people (59.5%) in the pertuzumab, trastuzumab and docetaxel arm experiencing symptom progression based on the TOI-PFB. The median time to event was 18.3 weeks compared with 18.4 weeks, representing approximately 6 treatment cycles, with a HR of 0.97 [0.81,1.16]. The upper limit of the confidence interval for the HR indicates that a true worsening of more than 16% can be ruled out with 95% confidence. The Kaplan-Meier curves for the two treatment arms are similar, with clear steps corresponding to the scheduled 9-weekly intervals indicating good compliance with the timing of the assessments. The results are supported by the unstratified analysis which also produced a HR of 0.97.

A summary of the mean change from baseline in TOI-PFB is presented by cycle and graphically. At Cycle 6, the mean reduction in TOI-PFB score from baseline was -3.5 in the trastuzumab and docetaxel arm compared with -3.0 in the pertuzumab, trastuzumab and docetaxel arm. However, at subsequent cycles the mean reductions were smaller (for example at cycle 9 the mean reduction in TOI-PFB score from baseline was -2.0 compared with -0.8) suggesting that TOI-PFB scores improved after an initial reduction. Overall the mean changes tended to be small in both treatment arms. It is important to

note the questionnaires were scheduled to be completed every three cycles. Data are included for the interim cycles (such as cycles 1, 2, and 4) if, for example, a patient completed a questionnaire at an unscheduled visit. Caution should therefore be applied in interpreting the data at the interim cycles, due to the small sample sizes. The data were further summarized by scheduled visit, and a consistent profile was observed.

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. The percentage of people completing FACT-B questionnaires at each 9-weekly interval was also consistent with the percentage of people undergoing tumour assessments on schedule (at least 75% in each arm for the first year) providing further evidence that compliance was high.

Figure 11 FACT-B Kaplan-Meier plots



6.6 Meta-analysis

6.6.1 The following steps should be used as a minimum when presenting a meta-analysis.

- **Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate that the RCT results are heterogeneous, try to provide an explanation for the heterogeneity.**
- **Statistically combine (pool) the results for both relative risk reduction and absolute risk reduction using both the fixed effects and random effects models (giving four combinations in all).**
- **Provide an adequate description of the methods of statistical combination and justify their choice.**
- **Undertake sensitivity analysis when appropriate.**
- **Tabulate and/or graphically display the individual and combined results (such as through the use of forest plots).**

A meta-analysis was not considered necessary given that only one relevant trial was identified.

6.7 Indirect and mixed treatment comparisons

6.7.1 Describe the strategies used to retrieve relevant clinical data on the comparators and common references both from the published literature and from unpublished data. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 10.4, appendix 4.

Trastuzumab in combination with a taxane is currently standard of care for people with previously untreated HER2-positive metastatic breast cancer who

are suitable for chemotherapy in Europe, the US and many other countries (Aebi et al, 2010; Cardoso et al 2010; Goldhirsch et al, 2007; Goldhirsch et al, 2009; Carlson et al, 2011).

There are two taxanes that are routinely used in clinical use in combination with trastuzumab; paclitaxel and docetaxel. There is no head to head evidence that compares the efficacy of pertuzumab in combination with trastuzumab and docetaxel compared with trastuzumab in combination with paclitaxel. As a result an indirect comparison to paclitaxel is required in order to fulfill the decision problem.

Paclitaxel is available as a weekly or three-weekly regimen. Weekly paclitaxel is associated with higher response rates and increased time to disease progression compared with three-weekly paclitaxel (Seidman et al 2008). In addition, data indicates that weekly paclitaxel is the standard dosing schedule for paclitaxel for people with locally advanced or metastatic HER2-positive breast cancer (Verrill et al Abstract LBA1005 ASCO 2007).

The issue of the relative efficacy of docetaxel and paclitaxel (albeit as monotherapies) was discussed in detail in the NICE Technology Appraisal of bevacizumab in combination with a taxane (NICE TA 214). In this appraisal the Appraisal Committee stated that whilst there is no head to head evidence evaluating the relative efficacy of three weekly docetaxel and weekly paclitaxel in the metastatic setting, the totality of evidence available strongly indicates these regimens are clinically equivalent (an assumption made when conducting the economic evaluation within TA 214). The rationale for this is outlined below.

Evidence that weekly paclitaxel and three-weekly docetaxel are equivalent

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 (Slamon et al, 2001; Marty et al, 2005). See Table 16 for a comparison of the two regimens used in combination with trastuzumab and alone in Slamon et al (2001) and Marty et al (2005).

Table 16 Comparison of paclitaxel and docetaxel

	Marty et al (2005)		**Slamon et al (2001)**	
	Trastuzumab and docetaxel	Docetaxel	Trastuzumab and paclitaxel	Paclitaxel
Median time to progression	11.7	6.1	6.9	3
Objective response	61	34	38	16
Median overall survival	22.7	31.2	22.1	18.4

A study by Sparano et al (2008) provides head to head evidence on the relative efficacy of several taxane regimens (paclitaxel weekly, paclitaxel three-weekly, docetaxel weekly and docetaxel three-weekly) in the adjuvant breast cancer setting. Although the study evaluated the relative efficacy of these agents in the adjuvant treatment for HER2-negative early disease, breast cancer is recognized as a disease continuum from the early to the advanced setting and comparable treatment efficacy has been shown for numerous agents, from tamoxifen to trastuzumab, in the early and advanced breast cancer setting. This large study in 4950 people demonstrates that docetaxel three-weekly and paclitaxel weekly at the doses used were the most effective regimens. Paclitaxel weekly was associated with 5-year disease-free survival of 81.5% and overall survival of 89.7%, comparable to that of docetaxel three-weekly (5-year disease-free survival of 81.2% and overall survival of 87.3%).

In light of the lack of head to head 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 our clinical experts and the Appraisal Committee discussion in TA 214, it is assumed the control arm of the CLEOPATRA study represents the outcomes that would be observed for people treated with trastuzumab in combination with weekly paclitaxel.

6.8 Non-RCT evidence

6.8.1 If non-RCT evidence is considered (see section 6.2.7), please repeat the instructions specified in sections 6.1 to 6.5 for the identification, selection and methodology of the trials, and the presentation of results. For the quality assessments of non-RCTs, use an appropriate and validated quality assessment instrument. Key aspects of quality to be considered can be found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 10.6 and 10.7, appendices 6 and 7.

There are no non-RCTs which are relevant to the decision problem.

6.9 Adverse events

6.9.1 If any of the main trials are designed primarily to assess safety outcomes (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse event), please repeat the instructions specified in sections 6.1 to 6.5 for the identification, selection, methodology and quality of the trials, and the presentation of results. Examples for search strategies for specific adverse effects and/or generic adverse-effect terms and key aspects of quality criteria for adverse-effects data can found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 10.8 and 10.9, appendices 8 and 9.

Safety was an endpoint in the CLEOPATRA study. In light of this no additional searches have been undertaken.

6.9.2 Please provide details of all important adverse events for each intervention group. For each group, give the number with the adverse event, the number in the group and the percentage with the event. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse event. A suggested format is shown below.

An overview of the cumulative safety data reported at the time of the primary data-cut (13 May 2011) and the latest clinical data-cut (14 May 2012) is provided in Table 17**Error! Reference source not found.**.

Table 17 Overview of Safety in CLEOPATRA

	Trastuzumab and docetaxel		**Pertuzumab, trastuzumab and docetaxel**	
	13 May 2011 N=397	14 May 2012 N = 396	13 May 2011 N = 407	14 May 2012 N = 408
Adverse events				
Any grade	391 (98.5%)	391 (98.7%)	406 (99.8%)	408 (100%)
Grade 3 ≥	289 (72.8%)	291 (73.5%)	302 (74.2%)	311 (76.2%)
Related	382 (96.2%)	381 (96.2%)	396 (97.3%)	397 (97.3%)
Serious AE	104 (26.2%)	115 (29.0%)	140 (24.4%)	148 (36.3%)
AE leading to discontinuation of any study medication	110 (27.7%)	114 (28.8%)	119 (29.2%)	125 (30.6%)
AE leading to dose interruption or modification	211 (53.1%)	215 (54.3%)	244 (60.0%)	252 (61.8%)
AE resulting in death	10 (2.5%)	12 (3.0%)	8 (2.0%)	8 (2.0%)
People with events to monitor				
Symptomatic LVSD adjudicated by the CRC	4 (1.0%)	4 (1.0%)	4 (1.0%)	4 (1.0%)
Grade 3 ≥	0	0	3 (0.7%)	3 (0.7%)
Symptomatic LVSD assessed by the investigator	7 (1.8%)	7 (1.8%)	4 (1.0%)	5 (1.2%)
Grade 3 ≥	4 (1.0%)	4 (1.0%)	3 (0.7%)	3 (0.7%)
Left ventricular dysfunction	33 (8.3%)	34 (8.6%)	18 (4.4%)	22 (5.4%)
Grade 3 ≥	11 (2.8%)	13 (3.3%)	5 (1.2%)	5 (1.2%)
SAE suggestive of CHF	7 (1.8%)	8 (2.0%)	4 (1.0%)	6 (1.5%)

Grade 3 ≥	7 (1.8%)	7 (1.8%)	4 (1.0%)	5 (1.2%)
AE during placebo or pertuzumab infusion	20 (5.0%)	20 (5.1%)	36 (8.8%)	39 (9.6%)
Grade 3 ≥	1 (0.3%)	1 (0.3%)	1 (0.2%)	2 (0.5%)
Diarrhoea	184 (46.3%)	191 (48.2%)	272 (66.8%)	278 (68.1%)
Grade 3 ≥	20 (5.0%)	20 (5.1%)	32 (7.9%)	37 (9.1%)
Rash	143 (36.0%)	144 (36.4%)	184 (45.2%)	194 (47.5%)
Grade 3 ≥	5 (1.3%)	5 (1.3%)	11 (2.7%)	12 (2.9%)
Leukopenia	231 (58.2%)	231 (58.2%)	254 (62.4%)	255 (62.5%)
Grade 3 ≥	211 (53.1%)	211 (53.1%)	237 (58.2%)	238 (58.3%)
Leukopenia infection	39 (9.8%)	38 (9.6%)	51 (12.5%)	52 (12.7%)
Grade 3 ≥	9 (2.3%)	9 (2.3%)	19 (4.7%)	19 (4.7%)
Febrile neutropenia infection	3 (0.8%)	3 (0.8%)	14 (3.4%)	14 (3.4%)
Grade 3 ≥	1 (0.3%)	1 (0.3%)	6 (1.5%)	6 (1.5%)
Anaphylaxis and hypersensitivity	36 (9.1%)	36 (9.1%)	44 (10.8%)	45 (11.0%)
Grade 3 ≥	10 (2.5%)	10 (2.5%)	8 (2.0%)	8 (2.0%)
Interstitial lung disease	6 (1.5%)	6 (1.5%)	9 (2.2%)	10 (2.5%)
Grade 3 ≥	2 (0.5%)	2 (0.5%)	3 (0.7%)	3 (0.7%)
QT prolongation	5 (1.3%)	5 (1.3%)	8 (2.0%)	9 (2.2%)
Grade 3 ≥	1 (0.3%)	1 (0.3%)	4 (1.0%)	4 (1.0%)
Mucositis	147 (37.0%)	150 (37.9%)	198 (48.6%)	203 (49.8%)
Grade 3 ≥	7 (1.8%)	8 (2.0%)	12 (2.9%)	13 (3.2%)
Drug-related hepatic disorder	40 (10.1%)	43 (10.9%)	39 (9.6%)	42 (10.3%)
Grade 3 ≥	5 (1.3%)	5 (1.3%)	7 (1.7%)	7 (1.7%)

Overall, the results were similar between the two data-cuts. No major changes in incidence, severity, or specificity of AEs were observed, and no new safety concerns were identified based on the latest clinical data-cut.

In summary:

- As reported at the primary clinical data-cut, the tolerability of pertuzumab, trastuzumab and docetaxel was broadly comparable with that of trastuzumab and docetaxel in terms of the incidence and severity of AEs, discontinuations due to AEs, and AEs leading to death.
- Similar to findings at the primary clinical cut-off, the incidence of serious adverse events was lower in the trastuzumab and docetaxel arm (29.0%) than in the pertuzumab, trastuzumab and docetaxel arm (36.3%) with the difference mainly due to febrile neutropenia.
- More deaths occurred in the trastuzumab and docetaxel arm (152 of 396 people; 38.4%) compared with the pertuzumab, trastuzumab and

docetaxel arm (113 of 408 people; 27.7%), and the majority of deaths in both arms were due to progression.

- Two additional people in the trastuzumab and docetaxel arm had Grade ≥ 3 LVD and 1 additional patient in the pertuzumab, trastuzumab and docetaxel arm had a Grade ≥ 3 CHF event reported since the primary clinical cut-off.
- The incidence of the AEs of diarrhoea, rash, mucosal inflammation, febrile neutropenia, and dry skin was higher (≥ 5% difference) in the pertuzumab, trastuzumab and docetaxel arm compared with the trastuzumab and docetaxel arm, whereas peripheral edema and constipation were more common in the trastuzumab and docetaxel arm. This was similar to what was previously reported. At the latest data cut-off, pruritus was the only additional AE that occurred at a difference in frequency of ≥ 5% in the pertuzumab, trastuzumab and docetaxel arm compared with the trastuzumab and docetaxel arm.

Since people in the pertuzumab, trastuzumab and docetaxel arm were in the study and on study treatment longer than people in the trastuzumab and docetaxel arm, a higher incidence of AE and serious adverse events would be expected because of the longer exposure to treatment and the longer AE and serious adverse events reporting period.

Common Adverse Events

At the time of the data cut-off of 14 May 2012, the most common AEs by MedDRA PT in both treatment arms remained alopecia, diarrhoea, neutropenia, nausea, fatigue, rash, asthenia, decreased appetite, vomiting, peripheral oedema, myalgia, and mucosal inflammation (see Table below).

The incidence of diarrhoea, rash, mucosal inflammation, pruritus, febrile neutropenia, and dry skin was higher (≥ 5% difference) in the pertuzumab, trastuzumab and docetaxel arm compared with the trastuzumab and docetaxel arm, whereas the incidence of peripheral oedema and constipation was higher (≥ 5% difference) in the trastuzumab and docetaxel arm compared with the pertuzumab, trastuzumab and docetaxel arm.

These findings are similar to those reported at the time of the primary analysis. The overall incidence of most AEs did not increase by more than 2%. The only exception was headache, which increased by a similar extent in the two treatment arms (16.9% incidence at the time of the primary analysis and 18.9% at the time of the latest data cut-off in the trastuzumab and docetaxel arm; 20.9% and 23.8%, respectively, in the pertuzumab, trastuzumab and docetaxel arm). AEs with a difference in incidence between the two arms of ≥ 5% at the time of the primary analysis also did not change at the latest data cut-off, apart from the addition of pruritus. The difference in incidence of pruritus between the two arms was less than 5% at the primary data cut-off (10.1% of people in the trastuzumab and docetaxel arm vs. 14.0% of people in the pertuzumab, trastuzumab and docetaxel arm), and this difference increased very slightly (10.1% vs. 16.7%, respectively) at the time of the latest data cut off.

Overall, these data suggest that the pattern of adverse events has remained stable with the additional year of safety data collection, and most AEs occurred during the initial cycles of treatment.

Table 18 Summary of adverse events with an incidence rate of >5% by trial treatment

Adverse Event	Trastuzumab and docetaxel (n=396)		Pertuzumab, trastuzumab and docetaxel (n=408)	
	No.	%	No.	%
Alopecia	240	60.6	248	60.8
Diarrhoea	191	48.2	278	68.1
Neutropenia	197	49.7	216	52.9
Nausea	168	42.4	179	43.9
Fatigue	148	37.4	155	38.0
Rash	95	24.0	149	36.5
Asthenia	121	30.6	110	27.0
Decreased Appetite	105	26.5	121	29.7
Oedema Peripheral	122	30.8	101	24.8
Vomiting	97	24.5	104	25.5
Myalgia	97	24.5	97	23.8
Mucosal Inflammation	79	19.9	112	27.5
Nail Disorder	92	23.2	94	23.0
Anaemia	77	19.4	96	23.5
Cough	78	19.7	94	23.0
Headache	75	18.9	97	23.8
Peripheral Neuropathy	79	19.9	88	21.6
Constipation	101	25.5	63	15.4
Leukopenia	82	20.7	75	18.4
Pyrexia	72	18.2	78	19.1
Stomatitis	62	15.7	81	19.9
Arthraligia	66	16.7	75	18.4
Dysgeusia	62	15.7	76	18.6
Upper Respiratory Tract Infection	56	14.1	74	18.1
Pain in extremity	51	12.9	71	17.4
Dyspnoea	63	15.9	57	14.0
Nasopharyngitis	58	14.6	61	15.0
Insomnia	55	13.9	62	15.2
Lacrimation increased	55	13.9	58	14.2
Abdominal pain	49	12.4	61	15.0
Dizziness	52	13.1	58	14.2
Back pain	47	11.9	61	15.0
Peripheral sensory neuropathy	58	14.6	50	12.3
Pruritus	40	10.1	68	16.7
Dyspepsia	48	12.1	54	13.2
Oedema	49	12.4	47	11.5
Febrile neutropenia	30	7.6	56	13.7
Abdominal pain upper	42	10.6	42	10.3
Paraesthesia	41	10.4	38	9.3
Hypertension	32	8.1	43	10.5
Epistaxis	35	8.8	39	9.6

Musculoskeletal pain	37	9.3	36	8.8
Bone pain	34	8.6	37	9.1
Dry skin	23	5.8	44	10.8
Urinary tract infection	30	7.6	35	8.6
Oropharyngeal pain	26	6.6	32	7.8
Hypokalaemia	20	5.1	37	9.1
Left ventricular dysfunction	34	8.6	22	5.4
Muscle spasms	18	4.5	36	8.8
Weight decreased	17	4.3	36	8.8
Rhinorrhoea	23	5.8	29	7.1
Palmar-Plantar Erythrodysaesthesia Syndrome	22	5.6	28	6.9
Chills	15	3.8	34	8.3
Pain	22	5.6	26	6.4
Hypersensitivity	20	5.1	27	6.6
Influenza	22	5.6	24	5.9
Depression	19	4.8	26	6.4
Erythema	20	5.1	24	5.9
Hot flush	21	5.3	23	5.6
Paronychia	14	3.5	30	7.4
Pleural effusion	23	5.8	21	5.1
Conjunctivitis	17	4.3	26	6.4
Lymphoedema	16	4.0	23	5.6
Rhinitis	22	5.6	17	4.2
Chest pain	22	5.6	14	3.4
Weight increased	22	5.6	14	3.4
Dysuria	10	2.5	22	5.4
Dry Eye	7	1.8	23	5.6
Influenza-like Illness	9	2.3	21	5.1

During the one year between the primary and the latest clinical cut-off date, fewer AEs were reported in the trastuzumab and docetaxel arm (91 people [23.0%] reported 368 AEs) compared with the pertuzumab, trastuzumab and docetaxel arm (140 people [34.3%] reported 651 AEs). This may be at least partly due to the longer exposure to treatment and the longer adverse event and serious adverse events reporting period for people in the pertuzumab, trastuzumab and docetaxel arm.

The incidence of cardiac disorders changed very little in both treatment arms since the primary clinical cut-off; 17.4% of people in the trastuzumab and docetaxel arm (69 people) and 15.4% of people in the pertuzumab,

trastuzumab and docetaxel arm (63 people) experienced cardiac disorders. The most frequently reported cardiac-related AE was LVSD, with 1 additional case in the trastuzumab and docetaxel arm and 3 additional cases in the pertuzumab, trastuzumab and docetaxel arm at the latest clinical cut-off (i.e., a total of 34 people [8.6%] in the trastuzumab and docetaxel arm vs. 22 people [5.4%] in the pertuzumab, trastuzumab and docetaxel arm).

Serious Adverse Events

The incidence of serious adverse events was higher in the pertuzumab, trastuzumab and docetaxel arm (36.3%) than in the trastuzumab and docetaxel arm (29.0%). Although people in the pertuzumab, trastuzumab and docetaxel arm received more infusions after the primary clinical cut-off than people in the trastuzumab and docetaxel arm, the rates of serious adverse events reported after the primary data cut-off were low for each of the treatment arms (14 [3.5%] in the trastuzumab and docetaxel arm vs. 15 [3.7%] in the pertuzumab, trastuzumab and docetaxel arm).

Serious adverse events coded to the SOC Blood and Lymphatic System Disorders were the most frequently reported serious adverse events in both treatment arms; these occurred in 15.9% of people in the pertuzumab, trastuzumab and docetaxel arm and 10.6% of people in the trastuzumab and docetaxel arm, with an incidence similar to that observed at the primary clinical cut-off. The difference between the two treatment arms was mainly due to the incidence of febrile neutropenia in the pertuzumab, trastuzumab and docetaxel arm, 11.3% of people compared with 5.1% of people in the trastuzumab and docetaxel arm, the same incidence as previously reported.

The next most frequently reported SOC was Infections and Infestations. With events being reported in 11.8% of people in the pertuzumab, trastuzumab and docetaxel arm and 8.6% of people in the trastuzumab and docetaxel arm. However, no single event accounted for the difference in incidence between the two arms.

Although the incidence of gastrointestinal serious adverse events was balanced between the two treatment arms, diarrhoea was observed in 3.2% of people in the pertuzumab, trastuzumab and docetaxel arm and 1.3% of people in the trastuzumab and docetaxel arm.

Cardiac serious adverse events occurred in 3.5% of people in the trastuzumab and docetaxel arm and in 1.7% of people in the pertuzumab, trastuzumab and docetaxel arm.

6.9.3 Give a brief overview of the safety of the technology in relation to the decision problem.

The safety evaluation of pertuzumab has been based on data from the pivotal CLEOPATRA study and 16 other phase I and II studies. In total, these 17 studies provide data on 1412 people exposed to pertuzumab.

The safety profile for all people exposed to pertuzumab was consistent with that observed in the key CLEOPATRA study, bearing in mind that 57.7% of the 1412 people received concurrent chemotherapy (with or without trastuzumab) and that it was expected the safety profile of pertuzumab would be dominated by the toxicity of any concurrent chemotherapy.

Some of the key findings across these studies were:

- There was no evidence that pertuzumab exacerbates the cardiac toxicity associated with trastuzumab.
- Overall, pertuzumab treatment was associated with increases in common docetaxel-related toxicities (diarrhoea, neutropenia, and mucositis) but these events were mainly mild to moderate in severity, easily managed and rarely led to discontinuation of all treatment.
- Pertuzumab infusions were generally well-tolerated and most infusion associated events were mild to moderate in severity. There was no evidence of an increased risk of hypersensitivity reactions with pertuzumab.

- Exploratory subgroup analyses were conducted for potential risk factors. Concurrent chemotherapy was identified as the major risk factor for leukopenia

The side-by-side comparison of both treatment arms in the pivotal study is considered of major importance as they reflect the proposed population for pertuzumab.

In CLEOPATRA, overall, the tolerability of the pertuzumab-based regimen was comparable to that of trastuzumab and docetaxel alone in terms of the severity of AEs, discontinuations due to AEs and AEs leading to death.

Most AEs were mild to moderate in severity and decreased in frequency after discontinuation of docetaxel treatment. The most common AEs (all grades of severity, regardless of causality) in both arms were alopecia, diarrhoea, neutropenia, nausea and fatigue. The incidence of diarrhoea, rash, mucosal inflammation, febrile neutropenia, pruritus and dry skin was higher (> 5% difference) in the pertuzumab based arm than in the trastuzumab and docetaxel arm of the study. Peripheral oedema and constipation, however, were more common in the trastuzumab and docetaxel arm and more people died in that arm, mainly due to progressive disease.

The incidence of diarrhoea in the pertuzumab based regimen group was 66.8% compared with 46.3% the trastuzumab and docetaxel group, The majority of diarrhoea experienced in both arms was mild to moderate in severity, and the difference in incidence of severe diarrhoea between the treatment arms was small; only 5.0% of people in the trastuzumab and docetaxel group experienced severe diarrhoea compared with 7.9% of people in the pertuzumab based arm. Moreover, the majority of 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 and prolonged in the pertuzumab based arm than the trastuzumab and docetaxel group, it was generally manageable and had no major impact on participants' ability to continue study treatment.

The incidence of rash in the pertuzumab based arm was 45.2% compared with 36.0% in the trastuzumab and docetaxel arm. The majority of rashes were mild to moderate in severity and only 11 people (2.7%) in the pertuzumab based arm and 5 people (1.3%) in the trastuzumab and docetaxel arm experienced severe events. Most rash events were reported 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 based arm and 1.6% of people in the trastuzumab and docetaxel arm, and to discontinuation of study medication in 2.5% and 0.3% of participants, respectively.

Mucositis was experienced by 48.6% of people in the pertuzumab based arm of the study compared with 37.0% of people in the trastuzumab and docetaxel group. The great majority of events were mild to moderate in severity with severe events occurring in only 2.9% of people in the pertuzumab based arm and 1.8% of people in the trastuzumab and docetaxel group. Of the 198 people in the pertuzumab based arm and the 147 people in the trastuzumab and docetaxel arm who experienced mucositis during the study, only 16.7% of people in the pertuzumab based arm and 8.2% of people in the trastuzumab and docetaxel arm developed mucositis after discontinuation of docetaxel suggesting that docetaxel was a major contributor to mucositis. In the pivotal study for trastuzumab, M77001, the addition of trastuzumab to docetaxel also increased the incidence of stomatitis (from 14% with docetaxel alone to 20% with trastuzumab and docetaxel), suggesting that general HER2 pathway inhibition may play a part (Marty et al, 2005) and that it is not a pertuzumab-specific event,

Febrile neutropenia occurred in 13.8% of the people in the pertuzumab based arm compared with 7.6% of people in the trastuzumab and docetaxel arm although the incidence of leukopenia and neutropenia based on laboratory values was similar in both arms. It is important to note that no febrile neutropenia events occurred after docetaxel discontinuation in the pivotal study. Moreover, participants from Asia in the study experienced notably more

febrile neutropenia, in the pertuzumab based regimen arm 25.6% of people from Asia experienced febrile neutropenia compared with 8.5% of people from the rest of the world. This finding may be due to the observations that docetaxel is associated with more neutropenia in Asian people compared with Western people (Fujiwara et al, 1999; Sato et al, 2006) possibly related to the fact that docetaxel clearance is reduced in people with low body surface area (Clark & Rivory, 1999; Engels et al, 2005). Consequently the overall rates of febrile neutropenia seen in the study are likely to be greater than the potential rates to be expected for the UK population.

In summary, these data indicate that pertuzumab in combination with trastuzumab and docetaxel is well tolerated with manageable additional toxicity. Additionally, despite targeting the same HER2 receptor pathway as trastuzumab, pertuzumab appears to add no significant cardiac toxicity when given with trastuzumab. No new or unexpected toxicities were encountered other than those that are known for agents that target the HER family of receptors including the current standard of care trastuzumab-based regimen and consequently they are not expected to add any significant burden to people, their healthcare professionals or cost to the NHS.

6.10 Interpretation of clinical evidence

6.10.1 Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.

Since the introduction of trastuzumab, there have been no significant advances in the treatment of people with HER2-positive metastatic breast cancer comparable with the results from the CLEOPATRA study. Trastuzumab has resulted in significant improvements in treatment and prognosis of people with HER2-positive breast cancer (Nahta and Esteva, 2007). The addition of trastuzumab to standard therapy has been shown to significantly improve progression-free-, disease-free-, and overall survival in people with HER2-positive breast cancer in a range of settings (Slamon et al, 2001; Marty et al, 2005; Piccart-Gebhart et al, 2005; Romond et al, 2005; Kaufman et al, 2009; Gianni et al, 2010; Slamon et al, 2011). Trastuzumab-

based therapy is now the recommended treatment for almost all people with HER2-positive breast cancer, who do not have a contraindication to its use (Aebi et al, 2010; Cardoso et al 2010; Goldhirsch et al, 2007; Goldhirsch et al, 2009; Carlson et al, 2011). Despite this, approximately 50% of people with HER2-positive metastatic disease will experience disease progression within a year of initiating treatment (Marty et al 2005).

In the key M77001 trastuzumab licencing study, the combination of trastuzumab and docetaxel compared with docetaxel alone resulted in an improvement in median time to progression (TTP), from 6.1 months to 11.7 months and overall survival from 22.7 months to 31.2 months. A comparable magnitude of benefit has now been demonstrated in the CLEOPATRA study with pertuzumab, trastuzumab and docetaxel compared with trastuzumab and docetaxel alone. It should also be noted that the CLEOPATRA study has demonstrated a significant overall survival benefit in a clinical setting with relatively few previous positive studies.

Pertuzumab is the first in a new class of targeted cancer treatments called HER2 dimerisation inhibitors. By targeting and binding to the subdomain 2 of the extracellular domain of HER2, pertuzumab prevents heterodimerisation of HER2 with other members of the HER family (HER1, HER3 and HER4). As a result, ligand-activated downstream signaling is blocked by pertuzumab. Pertuzumab is also capable of activating antibody-dependent cell-mediated cytotoxicity (ADCC).

In the CLEOPATRA study the first efficacy analysis (data cut-off 13 May 2011) showed that the combination of pertuzumab, trastuzumab and docetaxel resulted in a clinically meaningful and statistically significant improvement in progression-free survival. The independently assessed median progression-free survival increased from 12.4 months in the trastuzumab and docetaxel arm to 18.5 months in the pertuzumab based arm, an increase of 6.1 months (HR 0.62, 95%CI: 0.51, 0.75, $p<0.0001$). At the second analysis (data cut-off 14 May 2012) with an additional 12 months of data, the progression-free survival benefit was shown to be confirmed and maintained with the result based on Investigator assessment. The updated data showed the median

progression-free survival to have increased by 6.3 months, from 12.4 months in the trastuzumab and docetaxel arm to 18.7 months with the pertuzumab based regimen. The associated HR of 0.69 (95%CI: 0.58, 0.81) represents a 31% reduction in the relative risk of disease progression. This Investigator assessed progression-free survival analysis is considered to be of greater relevance to routine clinical practice and, subsequently, was used in the health economic models.

This magnitude of improvement in progression-free survival seen in CLEOPATRA is comparable with the pivotal trastuzumab licencing study for people with HER2-positive metastatic breast cancer where the median time to disease progression was shown to increase by 5.6 months, from 6.1 months with docetaxel alone to 11.7 months with trastuzumab and docetaxel (p=0.0001) (Marty et al, 2005).

The latest efficacy analysis (data cut-off 14 May 2012) for CLEOPATRA also showed a significant overall survival benefit for people randomised to receive pertuzumab. The median survival was 37.6 months in the trastuzumab and docetaxel arm but people in the pertuzumab based arm had fared so well that the median in that arm had not been reached at the time of data cut-off. The associated HR of 0.66 (95% CI: 0.52; 0.84, p< 0.0008) shows a 34% reduction in the relative risk of death. Survival rates showed a sustained survival advantage in the pertuzumab based arm with 94% of people still alive after one year compared to 89% in the trastuzumab and docetaxel arm, an absolute difference of 5%. This difference in survival then continued to increase over the course of the study with an absolute difference of 12% between the groups at two years and 16% at three years, all in favour of the pertuzumab based regimen arm.

After this latest efficacy analysis (data cut-off 14 May 2012), as per study protocol, crossover between the two study arms has been permitted in patients whose disease has not progressed and who are still receiving treatment with trastuzumab. Consequently, any future analysis of overall survival will be compounded by crossover.

In addition to the significant improvements in both progression-free and overall survival, the pertuzumab based arm had a statistically significant greater objective response rate with 80.2% of people in the pertuzumab based arm experiencing a complete or partial response (as per RECIST criteria) to treatment compared to 69.3% in the trastuzumab and docetaxel arm, a difference of 10.8% (95% CI: 4.2, 17.5; p=0.001).

The safety profile of the pertuzumab-based regimen was generally comparable to that of the trastuzumab and docetaxel arm. Importantly, there was no increase in cardiac-related adverse events with the pertuzumab based regimen and the monitoring required was similar to that in routine, current practice with trastuzumab based treatment. Most AEs were mild to moderate in severity. Diarrhoea, rash, mucosal inflammation, febrile neutropenia, pruritus and dry skin occurred at a higher incidence (> 5% difference) in the pertuzumab based arm than in the trastuzumab and docetaxel arm of the study. The majority of these events occurred during docetaxel treatment and once this ended, the incidence of these events decreased significantly. The pertuzumab based arm had a greater incidence of febrile neutropenia, especially in Asian people and during the first three cycles of treatment, but no events of febrile neutropenia were reported after cessation of docetaxel. Moreover, it should be noted that use of granulocyte colony stimulating factor (G-CSF) was not permitted for the first cycle of treatment in the study. This is likely to have contributed to the incidence of febrile neutropenia seen in association with the first cycle of treatment together with the increase in the overall observed rate caused by the high rates in the Asian population in the trial mean the overall observed rate may be higher than and of the incidence in routine clinical practice in the UK.

Importantly, based on the patient-completed FACT-B questionnaire, no differences in quality of life between the two treatment arms were observed.

Conclusion

CLEOPATRA demonstrates that pertuzumab offers substantial and consistent clinically relevant benefits as a first-line therapy for locally recurrent

unresectable or metastatic HER2-positive breast cancer. These benefits included significant improvements in the proportions of people responding to treatment, progression-free survival and overall survival. Minimal added toxicity was observed, the safety profile was manageable and the quality of life of people in the study was maintained.

These people represent a great unmet medical need as the HER2-positive status of their breast cancer is associated with aggressive disease and approximately 50% of people with HER2-positive metastatic breast cancer progress within one year of starting treatment (Marty et al 2005). Moreover, they are likely to present at a younger age than the general breast cancer population (Neven et al 2008; Kwan et al 2009) representing a potentially greater burden of illness with consequential wider societal impacts. These encompass effects on family life including changes in roles and responsibilities within families; relationships with partners, children and close family and friends; and concerns regarding becoming dependent and care requirements (Breast Cancer Care 2013). Financial and social impacts include the potential loss of income due to changes in working patterns, increased costs of living with an increased reliance on benefits.

6.10.2 Please provide a summary of the strengths and limitations of the clinical-evidence base of the intervention.

Strengths - The CLEOPATRA study is a robust, high quality, adequately powered, placebo-controlled, double blind centrally randomised trial that compared the intervention directly with current standard of care.

The study was developed with the aid of EMA scientific advice, Investigator feedback, early phase studies and published data. It was conducted in 204 centres in 25 countries with a total of 808 people randomised (406 into the trastuzumab and docetaxel arm and 402 into the pertuzumab based arm). The study incorporated many of the standard features of clinical studies in people with advanced breast cancer, but differed from many previous studies in that it was placebo-controlled and blinded, with additional features such as central confirmation of a positive HER2 status (the key biomarker, selective of

patients most likely to receive benefit from treatment), and additional safety measures for monitoring cardiac safety. The safety of participants was overseen by an independent Data Monitoring Committee (DMC) with input from an independent Cardiac Review Committee (CRC).

The International nature of the study ensured that all major race groups and ages were enrolled. Benefit with the pertuzumab based treatment was seen across these groups and this would be expected in the clinical setting.

The comparator treatment in the study is a licenced and regimen and was, at the time, considered to be standard of care and the most effective treatment for HER2 positive metastatic breast cancer.

The primary efficacy parameter, progression-free survival, was determined by an Independent Review Facility with investigator assessed progression-free survival a secondary efficacy endpoint, which is considered to be of more relevance to routine clinical practice in the UK. The data from independent review and investigator assessment were very similar, indicative of the quality of data collection.

In addition to the independent review of the primary endpoint, other potential sources of bias were reduced by the double-blind, placebo-controlled design of the study; by use of standardized definitions (RECIST 1.0 criteria) for assessing response and progression; by use of an identical schedule of assessments in the two treatment arms, fixed in time; and importantly, by continuation of tumour assessments until Independent Review Facility confirmation of progression (in the event that this was after the investigator's assessment). Strict maintenance of the blind and explicit protocol stipulations that cross-over would not be allowed also helped remove any (conscious or subconscious) incentive to guess treatment allocation and/or diagnose disease progression early in the hope of obtaining access to the experimental treatment. In addition, the use of a placebo increased the reliability of safety comparisons between the two treatment arms by removing subjectivity in safety assessments.

Blinding in the study was rigorously maintained even after the results of the primary efficacy analysis (13 May 2011) were known and crossover did not occur until the overall survival benefit of the pertuzumab-based regimen was shown to be statistically significant after the second efficacy analysis (14 May 2012).

Unblinding was only allowed for individual people who were reported to have a serious, unexpected, suspected adverse reaction (SUSAR). Safety data from the two arms of the study, particularly on the first day of study treatment (when pertuzumab or placebo were given alone), were similar. It is therefore unlikely that investigators could have deduced which arm a patient was in based on the adverse events seen.

In terms of withdrawals from the study, most of the premature withdrawals from treatment were due to disease progression (235 people in the pertuzumab based regimen group and 271 people in the trastuzumab and docetaxel group). The incidence of early treatment withdrawal for reasons other than disease progression was low and comparable between the two study arms (65 people in the pertuzumab based regimen arm and 61 people in the trastuzumab and docetaxel arm). An equivalent percentage of people in each arm withdrew from study treatment for safety reasons (37 people in the pertuzumab based group and 36 people in the trastuzumab and docetaxel group).

The data collection allowed efficacy analysis of the intervention, the first in a new class of targeted cancer treatments, for people who currently have an unmet clinical need and require new treatment options. The CHMP concluded the CLEOPATRA study is a well-designed and well-conducted trial.

Limitations – Although people were permitted by the protocol to have received prior neoadjuvant treatment, including trastuzumab, they were required to have had a disease-free interval of at least 12 months from the completion of adjuvant therapy and disease recurrence. This requirement was incorporated into the protocol at the request of the Regulatory authorities to ensure the prognosis of people would be more uniform across the study by

excluding people who were less likely to respond to re-challenge with trastuzumab and/or taxanes. Related to this was the fact that relatively few people enrolled in the study had received prior trastuzumab for early breast cancer and this is discussed further in section 6.10.4. However, this was mitigated by study WO17929 which showed that patients who failed prior treatment with trastuzumab responded to pertuzumab. In that study patients were able to switch to pertuzumab 4 weeks (or greater) after their last dose of trastuzumab.

The protocol selected people with good cardiac function but this was done to limit the possible occurrence of any cardiac toxicity as people would potentially be receiving both pertuzumab and trastuzumab. Reassuringly, there was no increase in cardiac adverse events with the pertuzumab based regimen when compared to trastuzumab and docetaxel alone and this is expected in the clinic. The cardiac safety monitoring plan for the study was developed with the aid of the Regulatory authorities**.**

6.10.3 Please provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

The primary and secondary outcomes adopted to assess efficacy and safety in the pivotal study have been well established in oncology, are familiar to oncologists, and are relevant to people with metastatic disease.

The main treatment challenge in clinical practice is how to manage people who have disease progression whilst receiving trastuzumab. Oncologists are anxious to observe quickly if a new treatment is effective. Response rates are accepted as being an early indicator of efficacy of a treatment for metastatic breast cancer. The high objective response rate (80.2%) and clinical benefit rate (94.8%) are very reassuring to oncologists. Such a high response rate demonstrates the benefit of a targeted treatment which allowed treatment of only those people most likely to benefit.

Once a person has responded to treatment the next important outcome is the duration of response which was shown to be 87.6 weeks in the pertuzumab based arm compared with 54.1 weeks in the trastuzumab and docetaxel group (HR=0.66, 95%CI 0.51, 0.85).

The primary efficacy endpoint of the pivotal study, progression-free survival, as determined by an IRF using Response Evaluation Criteria in Solid Tumors (RECIST), has been accepted as an endpoint for registration of products for the treatment of metastatic breast cancer and is considered clinically relevant if the prolongation in progression-free survival is long, ie, >~5 months (Tuma, 2009**;** Burzykowski et al, 2008; Fleming et al, 2009). Prolongation of progression-free survival in itself provides a meaningful clinical benefit to people by extending the time without disease progression and its associated symptoms, and by delaying the need for further toxic chemotherapy. The durability of response has translated into an unprecedented 18.7 months progression-free survival, an improvement of 6.3 months over best current standard of care.

The secondary outcome of overall survival is arguably the outcome of greatest relevance to the treatment of all people with cancer. The improved response rate and progression-free survival seen with pertuzumab which has ultimately resulted in the greatest overall survival seen in HER2 positive metastatic breast cancer (a relative improvement of 33%). These improvements have been seen with little impact on patient safety and no impact on quality of life. Other secondary endpoints such as objective response rate and quality of life are highly pertinent to people and their clinicians when discussing treatment options at the onset of HER2-positive metastatic disease.

The outcomes assessed in CLEOPATRA, therefore, are expected to have a significant beneficial effect on people in clinical practice as the pertuzumab based regimen has been shown to increase the proportion of breast cancers responding to treatment (the highest response seen in HER2-positive metastatic breast cancer studies) and that this response is durable as seen by the significant increases in progression-free survival with an associated significant increase in overall survival. For people with breast cancer being

treated with the pertuzumab based regimen, this would mean a higher likelihood of their disease responding, the disease being controlled for a longer period of time and a subsequently longer life expectancy.

6.10.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select patients for whom treatment would be suitable based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?

Overall CHMP concluded the study population is representative of people with HER2-positive metastatic breast cancer who could be considered as candidates for further HER2-targeted treatment and, overall, the demographics of enrolled participants are considered to be reflective of the proposed population in the UK.

One concern was that only about 10% of people (10.1% in the trastuzumab and docetaxel arm compared with 11.7% in the pertuzumab based arm) had received prior trastuzumab in the (neo-) adjuvant setting. This was partly due to a generally lower usage of trastuzumab in the EU in this setting the beginning of the recruitment period (February 2008 – July 2010) compared to the present and to the requirement of a disease-free interval of at least one year between adjuvant therapy and relapse. Supporting study BO17929 had previously demonstrated activity of the pertuzumab-trastuzumab combination in people previously treated with trastuzumab in the metastatic setting. In CLEOPATRA the randomisation of participants were stratified according to prior treatment status (de novo and prior adjuvant or neo-adjuvant therapy), and the two study arms were well balanced for these parameters. Reassuringly, an exploratory *post-hoc* subgroup analysis showed similar efficacy progression-free survival outcomes for people who received prior trastuzumab, HR 0.62 (95% CI: 0.35; 1.07), compared with the overall

participant population, HR 0.62 (95% CI: 0.51; 0.75). Moreover, this was supported by the updated overall survival results with the prior trastuzumab subgroup, HR 0.68 (95% CI: 0.30; 1.55), comparable with the study population, HR 0.66 (95% CI: 0.52, 0.84).

The CHMP concluded these data support the efficacy of pertuzumab in people pre-treated with trastuzumab.

Another issue related to the subgroup analysis that detected seemingly limited efficacy in people with non-visceral disease, HR 0.96 (95%CI: 0.61, 1.52 (n=178)) for progression-free survival and HR 1.42 (95% CI: 0.71, 2.84) for overall survival. The CHMP considered that the relatively small sample size and biological nature of non-visceral disease resulting in a lower event rate may have affected the large variability of the point estimate and the probability to capture a true treatment effect. Consequently the CHMP concluded the licence for pertuzumab should not be restricted based on visceral disease status.

As CLEOPATRA was a global, multicentre study, the treatments that people received, once their disease had progressed and they had stopped study treatment, was not necessarily reflective of current UK practice. Importantly, however, the subsequent breast cancer therapies were generally balanced between both arms and treatment with pertuzumab was not permitted prior to study unblinding.

What proportion of the evidence base is for the dose(s) given in the SPC?

In the intervention arm of CLEOPATRA, the pertuzumab, trastuzumab and docetaxel doses administered in the CLEOPATRA study are identical to the dose specified in the pertuzumab SPC.

In the comparator arm of CLEOPATRA, trastuzumab was administered as per the trastuzumab SPC. Docetaxel was not administered as per the docetaxel SPC due to the blinded nature of the study.

In Europe, the licensed dose of docetaxel is 100 mg/m^2 when used in combination with trastuzumab for people with HER2-positive breast cancer. However due to its toxicity many clinicians prefer to use lower doses. In the US the approved dose of docetaxel for metastatic breast cancer is 60 mg/m^2 to 100 mg/m^2 and a range of doses (60-100 mg/m^2) is also recommended by the NCCN Guidelines (Carlson et al, 2011). In many Asian countries, including Japan, doses lower than 100 mg/m^2 are registered, following observations that docetaxel is associated with more neutropenia in Asian people compared with Western people (Fujiwara et al, 1999; Sato et al, 2006). In one randomised study in Western people, there was a trend towards better outcomes with higher doses of docetaxel (60, 75 and 100 mg/m^2) (Harvey et al, 2006). However, there was a marked increase in toxicity, especially neutropenia and febrile neutropenia, with increasing doses.

When the CLEOPATRA study was designed, the licensed doses of docetaxel globally, published data, investigator feedback, and EMA Scientific Advice were all considered. An initial docetaxel dose of 75 mg/m^2 was chosen for both arms of the study with an option to dose escalate to 100 mg/m^2 after the first dose. This approach was widely acceptable to investigators and was seen as compatible with routine clinical practice and with docetaxel license recommendations globally

This dosing regimen is considered representative of routine NHS clinical practice, where a docetaxel dose of 100 mg/m^2 is associated with a significant burden of adverse events, giving a tolerability profile which UK clinicians do not regarded as appropriate in the palliative treatment of most first-line metastatic breast cancers. Clinicians generally treat first-line metastatic breast cancer with docetaxel 75 mg/m^2 three-weekly for a maximum of 6 or, in exceptional cases, 8 cycles (protocols in many tertiary centres, including Royal Marsden Hospital).

Hospital sales data from IMS show that the average planned docetaxel treatment for metastatic breast cancer in UK is 6.13 cycles three weekly, at an average planned dose of 150mg (or 79 mg/m^2 for an average 1.9 m^2 patient).

In the study itself, 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 (125 mg in the trastuzumab and docetaxel arm compared with 123 mg in the pertuzumab based arm) and a very similar median dose intensity per week (24.8 mg/m^2 per week in the trastuzumab and docetaxel arm compared with 24.6 mg/m^2 per week in the pertuzumab based arm).

7 Cost effectiveness

7.1 Published cost-effectiveness evaluations

Identification of studies

7.1.1 Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided as in section 10.10, appendix 10.

Embase (EMYY), Embase Alert (EMBA), Medline (MEYY) and NHS EED were searched for studies assessing the cost-effectiveness of pertuzumab relevant to the decision problem. The search was designed to evaluate whether de novo modelling was necessary in order to answer the decision problem. More details on the search are provided in Appendix 10.

Key word strategies were developed using key references retrieved through initial scoping searches. ProQuest was used to search EMYY, EMBA and MEYY whilst NHS EED was searched using The Centre for Reviews and Dissemination's website (University of York 2011) on 25th October 2012. Each search result's title and abstract were assessed for relevance according to pre-defined inclusion and exclusion criteria (See Table 19).

Table 19 Inclusion and exclusion criteria for cost-effectiveness studies

Parameter	Inclusion Criteria	Exclusion Criteria
Population	Female, HER2-positive advanced or metastatic breast cancer patients	Non breast cancer patients, Non HER2-positive 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

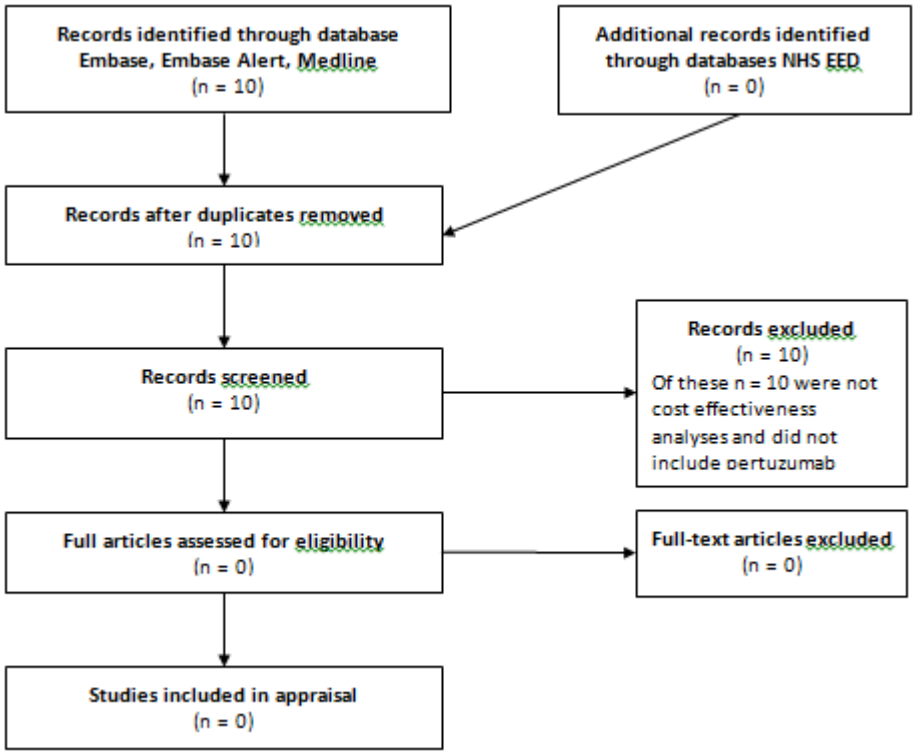
The above methodology is based upon the methods outlined in the CRD's 'Guidance for undertaking reviews in health care' (2008). The objectives of the search, and the inclusion criteria and exclusion criteria defined as a product of those objectives, were clearly aligned with the decision problem.

Description of identified studies

7.1.2 Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. When studies have been identified and not included, justification for this should be provided. If more than one study is identified, please present in a table as suggested below.

No studies were identified in the search, see Figure 12 and Appendix 10 for more details on the search.

Figure 12 PRISMA Flow showing economic studies identified



8 De novo analysis

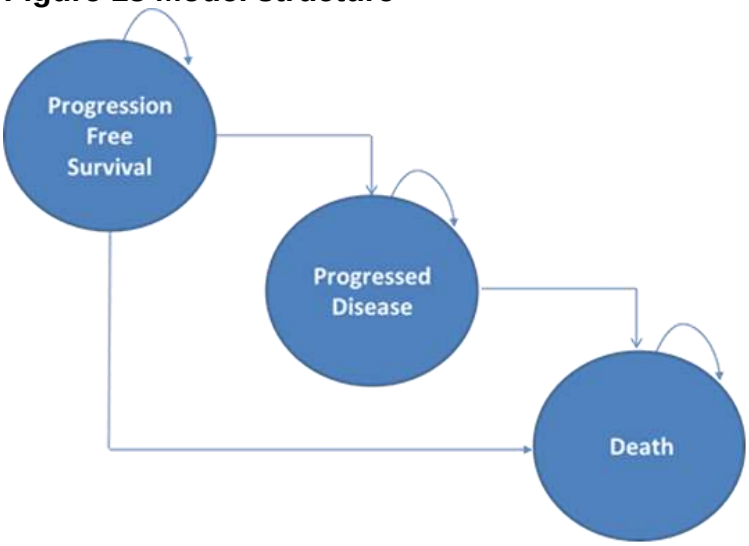
8.1.1 What patient group is included in the economic evaluation? Do they reflect the licensed indication/CE marking or the population from the trials in sections 1.3 and 6.3.3, respectively? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem? For example, the population in the economic model is more restrictive than that described in the (draft) SPC/IFU and included in the trials.

As a result of no cost-effectiveness identified in the search outlined in Section 7, an economic model was constructed to assess the clinical and cost effectiveness of pertuzumab in combination with trastuzumab and docetaxel in people with HER2-positive metastatic breast cancer who have not previously received chemotherapy or HER2 directed treatment for their metastatic disease. The model captures the key outcomes from the ITT population of the CLEOPATRA trial.

Model structure

8.1.2 Please provide a diagrammatical representation of the model you have chosen.

Figure 13 Model structure



8.1.3 Please justify the chosen structure in line with the clinical pathway of care identified in section 2.5.

The model is constructed using Excel® featuring three health states; progression-free, progressed and death. The health states mirrored the main endpoints measured in the CLEOPATRA trial. The structure of stratifying the clinical outcomes of people with cancer into progression-free, progression, and death is common practice in the economic evaluation of oncology interventions. The health states align with one of the key objectives of treatment within this disease area: to extend duration of progression-free survival for as long as possible. The progressed health state represents the duration from first treatment relapse until death and therefore includes the possible sequence of remission and relapse of second line treatments common to metastatic breast cancer. Disease progression is represented in the model by people who are no longer classified as “progression free”, as defined by the CLEOPATRA protocol

8.1.4 Please define what the health states in the model are meant to capture.

All people in the model start in the progression-free health state. At the end of each discrete weekly cycle a person either remains in progression-free survival or move to the progressed health state or dies. Once a person is within the progressed health state, they may remain in that health state or die at the end of each weekly cycle. People cannot move from the progressed health state back to progression-free survival health state in the model. Death is an absorbing health state in the model.

The model uses a partitioned survival approach, in which inputs are taken as estimated parametric survival functions for both overall survival and progression-free survival. The proportion of the initial cohort in the progressed state at each cycle is the difference between the proportion that is alive and the proportion that is progression-free. The area between these two curves is the mean life-years of people with progressed metastatic disease. This

approach allows the model to be accurately calibrated with the trial results for progression-free survival and overall survival.

8.1.5 How does the model structure capture the main aspects of the condition for patients and clinicians as identified in section 2 (Context)? What was the underlying disease progression implemented in the model? Or what treatment was assumed to reflect underlying disease progression?

The three health states within the model capture most conditions relevant to the decision problem. A limitation of this modelling approach is that it is not aligned with the available utilities data in the setting of metastatic breast cancer. Utility values in metastatic breast cancer are typically distinguished by the health states of response, stable disease, and progression; where response and stable disease are classified as progression-free survival. Due to the misalignment in model structure (which is driven by the endpoint of progression-free survival) and available utilities data in metastatic breast cancer (which is focused on understanding how different response states impact on quality of life), the model adjusts for the observed differences in utility values that occur within a single health state (see section 8.3.5 for more details on the utilities used in the model).

8.1.6 Please provide a table containing the following information and any additional features of the model not previously reported.

Table 20 Key features of analysis

Factor	Chosen values	Justification	Reference
Time horizon	Lifetime (equating to a maximum of 25 years)	NICE reference case	NICE methods guide
Cycle length	1 week	The three-weekly administration of drugs in the model supports the use of a weekly cycle length.	NICE methods guide
Half-cycle correction	Yes (half cycle correction is not applied to drug, administration and pharmacy costs)	NICE reference case	NICE methods guide
Were health effects measured in QALYs; if not, what was used?	QALY	NICE reference case	NICE methods guide
Discount rate for utilities and costs	3.5%	NICE reference case	NICE methods guide
Perspective (NHS/PSS)	NHS/PSS	NICE reference case	NICE methods guide
NHS, National Health Service; PSS, personal social services; QALYs, quality-adjusted life years			

Technology

8.1.7 Are the intervention and comparator(s) implemented in the model as per their marketing authorisations/CE marking and doses as stated in sections 1.3 and 1.5? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specified decision problem?

The intervention and comparators are in line with the decision problem set out in the NICE scope, and have been implemented as per their marketing

authorisations. More details on the implementation of the technologies within the models can be found in Section 8.3.20.

8.1.8 Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed?

No treatment continuation rule has been applied in the economic model.

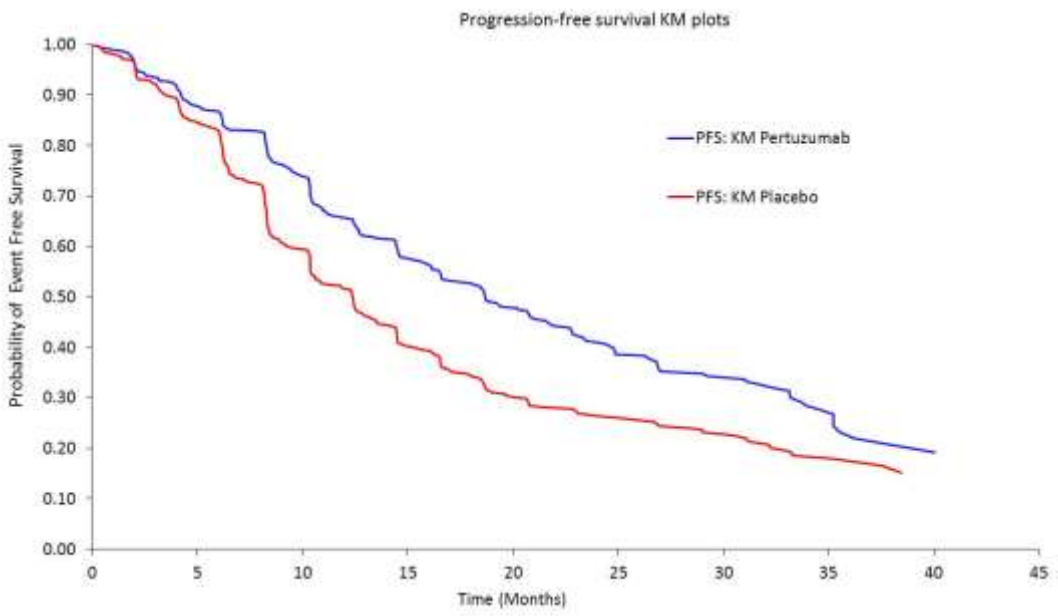
8.2 Clinical parameters and variables

8.2.1 Please demonstrate how the clinical data were implemented into the model.

The model is a partitioned survival model which treats progression-free survival and overall survival as individual entities (i.e no assumption is made about the relationship between the two). The proportion of people in the progression-free survival health state is derived using the hazard rates observed in the pertuzumab, trastuzumab and docetaxel and trastuzumab and docetaxel arms of the CLEOPATRA trial.

The model was developed using the 14 May 2012 cut of the CLEOPATRA data. This cut of data features investigator assessed progression-free survival. The progression-free survival Kaplan-Meier curves are presented in Figure 14.

Figure 14 Progression-free survival Kaplan-Meier plots (14 May 2012 data)



Cumulative hazard plots

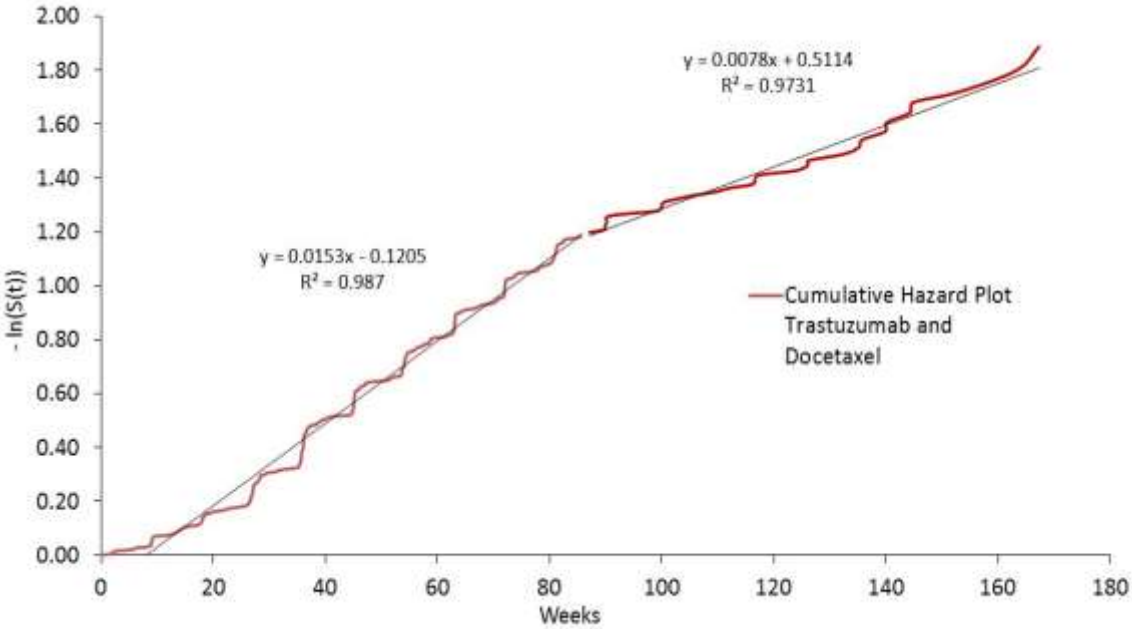
Whilst survival data is typically presented in the form of Kaplan-Meier plots (such as in Figure 14), the production of cumulative hazard plots allows simple examination of the trends in the data that can be difficult to interpret using Kaplan-Meier data alone. The slope of the cumulative hazard plot at any point in time can be interpreted as the hazard of the event of interest occurring at that point in time. The steeper a cumulative hazard plot is the higher the hazard of the event occurring and the flatter a cumulative hazard plot is the lower the hazard of the event occurring is. This property allows consideration of how the risk of an event occurring changes over time (i.e. *how does the slope change over time)* and the way in which the impact of some intervention changes over time (i.e. *how much does the ratio of the two slopes (the hazard ratio) change over time).* This method of analysing the data is important when considering extrapolation as it can inform both the extrapolation of the baseline risk without the intervention (i.e. *if the slope (hazard) of the cumulative hazard plot for the non-intervention curve has been straight for the period observed it may be reasonable to continue with a straight hazard beyond this point in time*) and how the intervention arm may differ from that baseline risk if further follow-up were available (i.e*. if the ratio of the two*

slopes (hazard ratio) has been constant throughout the data it may be reasonable to continue that ratio beyond the period of follow-up).

Cumulative hazard plot: trastuzumab and docetaxel arm

The cumulative hazard plot for the trastuzumab and docetaxel arm is presented in Figure 15. It is clear from the plots observed in Figure 15 that the cumulative hazard is high (the curve is steep) for the first 86 weeks for people treated with trastuzumab and docetaxel. The cumulative hazard then appears to lower for the remaining period in the trial arm represented by a flatter curve (this may be due to prognostic or responsive heterogeneity in the population in CLEOPATRA or spurious due to low numbers of people (109 people remained in the trastuzumab and docetaxel at week 86 – at which point only 20% of people are remaining in the arm). These periods are associated with two distinct constant linear hazards. Up to week 86 there is a constant linear hazard of 0.153, (with an extremely high r^2 value of 0.987), and from week 87 onwards there is another constant linear hazard of 0.0078, (with a similarly higher^2 value of 0.9731).

Figure 15 Cumulative hazard plots of progression-free survival in the trastuzumab and docetaxel arm (14 May 2012 data)

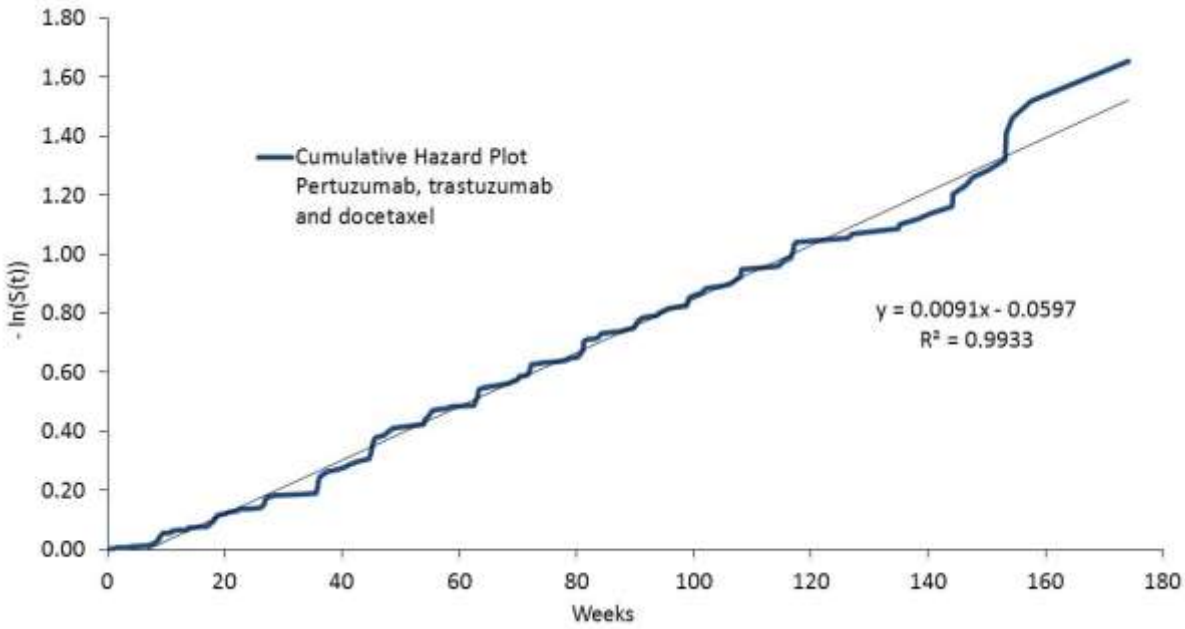


The observation that the hazard rate appears to be somewhat improved from week 87 onwards is potentially important when extrapolating the data. As two defined constant hazard periods are observed (i.e the curve appears to be a joining of two straight lines with different slope) and, if this “hinge” is considered as being real and not spurious, it may be appropriate to utilise two exponential functions with the latter ‘stabilised’ hazard used for extrapolation (i.e if there is a ‘hinge’ in the curve, we would extrapolate with the straight line observed after the hinge).

Cumulative hazard plot: pertuzumab, trastuzumab and docetaxel arm

From looking at the Figure 16 it is clear that pertuzumab, trastuzumab and docetaxel is associated with a low average hazard of a progression-free survival event (progression or death) occurring.

Figure 16 Cumulative hazard plot of progression-free survival in pertuzumab, trastuzumab and docetaxel arm (14 May 2012 data)

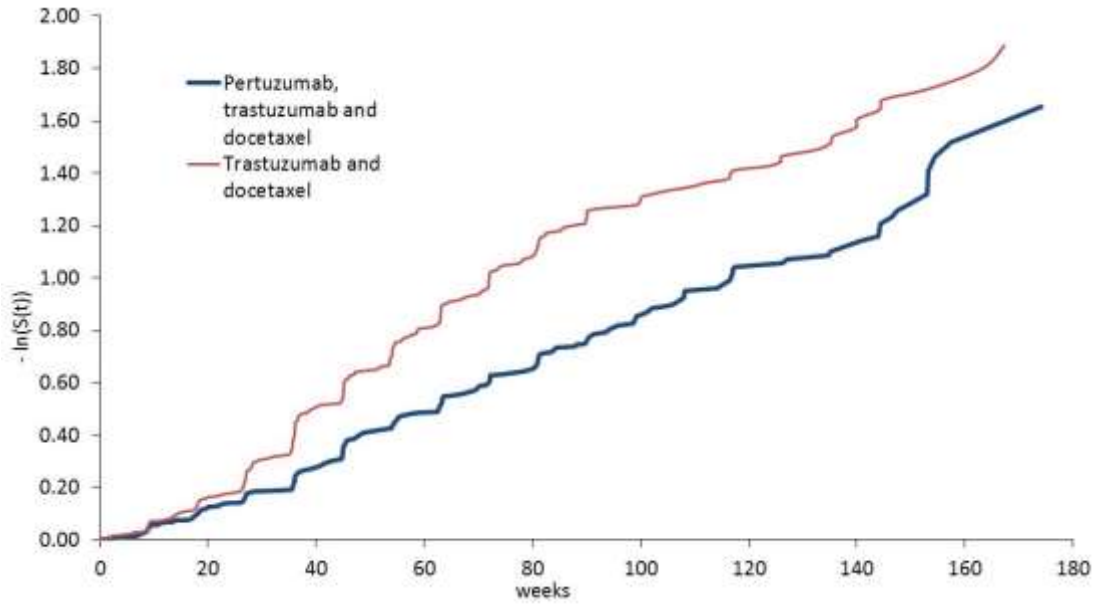


The cumulative hazard plot in Figure 16 demonstrates the constant low linear hazard of 0.0091, r^2 0.9933 observed for the whole period in the pertuzumab, trastuzumab and docetaxel arm.

Cumulative hazard plots: pertuzumab, trastuzumab and docetaxel and trastuzumab and docetaxel arms

When the two cumulative hazard plots are combined (see Figure 17), we can see that pertuzumab, trastuzumab and docetaxel is associated with a lower average hazard of a progression-free survival event (progression or death) occurring compared with if treated with trastuzumab and docetaxel as demonstrated by the average of the slope of the blue line being lower than the average of the slope of the red line.

Figure 17 Cumulative Hazard Plots of progression-free survival (14 May 2012 data)



The ratio of the two curves is lower from week 87 onwards than in the first 86 weeks (i.e the hazard ratio is still lower than 1 but not as low as it was in the previous period).

As noted previously and see in Figure 15, there appear to be two distinct hazard rates observed in the trastuzumab and docetaxel arm (the trastuzumab and docetaxel cumulative hazard is high for the first 86 weeks, and then flattens for the remaining period). If these periods are considered

separately with separate exponential hazard rates estimated for each period, the progression-free survival hazard ratio from weeks 0 to 86 is 0.60. The ratio of the two curves is higher from week 87 onwards compared with the first 86 weeks. The ratio of the two curves clearly demonstrates the efficacy of pertuzumab, trastuzumab and docetaxel and its ability to delay progression (i.e the hazard ratio is still lower than 1 but not as low as it was in the previous period).

Following the observation that the trastuzumab and docetaxel arm hazard is relatively stable from week 87 onwards it is hypothesised that the data supports the use of an exponential function derived using data from week 87 onwards when extrapolating this curve (i.e using the hazard shown in Figure 15 above). In light of the trends observed in the cumulative hazard plots, a number of possible scenarios reflecting different assumptions are outlined below:

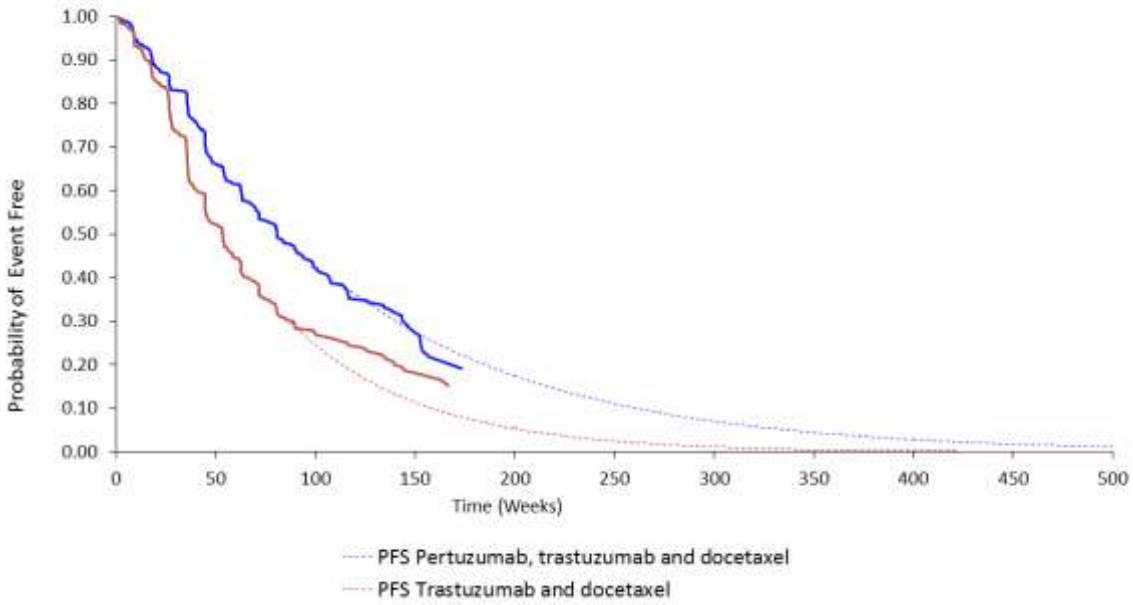
Scenario 1: Straight up

One possible explanation for the flattening of the curve in the trastuzumab and docetaxel arm is it is due to small number of remaining participants in that arm. If this is believed the case, then it can be assumed the steep part of the curve reflects the true hazard rate of people treated with trastuzumab and docetaxel. This approach supports the use of utilising the probability of remaining in progression-free survival observed up to week 86 (0.0151), after which the survival curve is extrapolated according to an exponential function.

Given the probability of remaining in progression-free survival in the pertuzumab, trastuzumab and docetaxel arm is stable (i.e the cumulative hazard plot is straight), then it is appropriate to extrapolate the pertuzumab, trastuzumab and docetaxel survival curve according to an exponential function. Week 117 is considered a transition point from using Kaplan-Meier data and the exponential tail in the pertuzumab, trastuzumab and docetaxel arm as that is point at which the observed Kaplan-Meier data remains reliable (i.e. the curve was yet to become erratic). The weekly transition probability

applied is 0.0091. The resulting progression-free survival extrapolation is outlined in Figure 18.

Figure 18 Modelled progression-free survival - Scenario 1

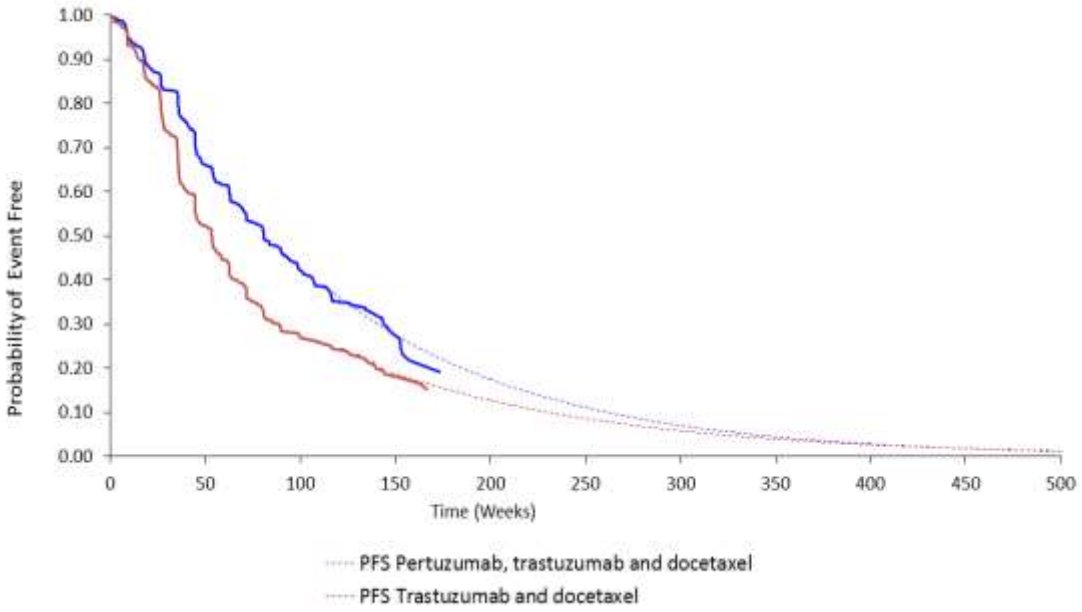


Scenario 2: Comparator hinge

Another possible explanation for the flattening of the curve is that it reflects the true probability of remaining in progression-free survival for people treated with trastuzumab and docetaxel. If this if this is the case then in order to accurately model the observed time spent in progression-free survival it is assumed the cumulative hazard plot for the trastuzumab and docetaxel arm is composed of two curves. This approach allows for the noticeable change in slope seen at approximately week 86 and includes the behaviour observed for the participants remaining in progression-free survival at week 86. A weekly transition probability of 0.0079 is applied to the trastuzumab and docetaxel arm from week 152 onwards, due to week 152 being the last point at which the observed Kaplan-Meier data remains reliable.

Similarly to scenario 1, this scenario assumes an exponential function for the pertuzumab, trastuzumab and docetaxel arm from Week 117 onwards, and applies a weekly transition probability of 0.009, as illustrated in Figure 19:

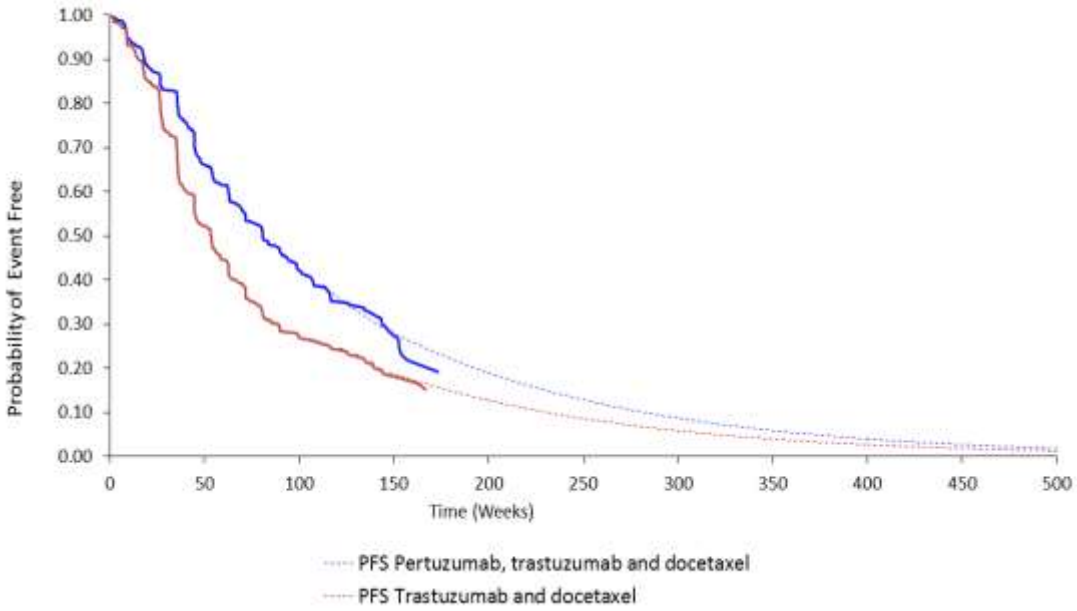
Figure 19 Modelled progression-free survival - Scenario 2



Scenario 3: Both hinge

It may be the case that if participants in the pertuzumab, trastuzumab and docetaxel arm were followed up over a longer time period the curve would experience a flattening similar to that seen in the trastuzumab and docetaxel curve. This flattening would then represent a separate clinically distinct cohort of people found in both study arms that respond better to treatment than those in the steeper part of the curve. This scenario applies the same weekly transition probability (0.0077) used to extrapolate the flattened area of the trastuzumab and docetaxel curve, to the pertuzumab, trastuzumab and docetaxel curve from Week 117 onwards. Week 117 was considered as a transition point from using Kaplan-Meier data and the exponential tail in the pertuzumab, trastuzumab and docetaxel arm as that is the point at which the observed Kaplan-Meier data flattens slightly before rising sharply (which would be expected to be seen if there are two clinically distinct cohorts of people in the arm).

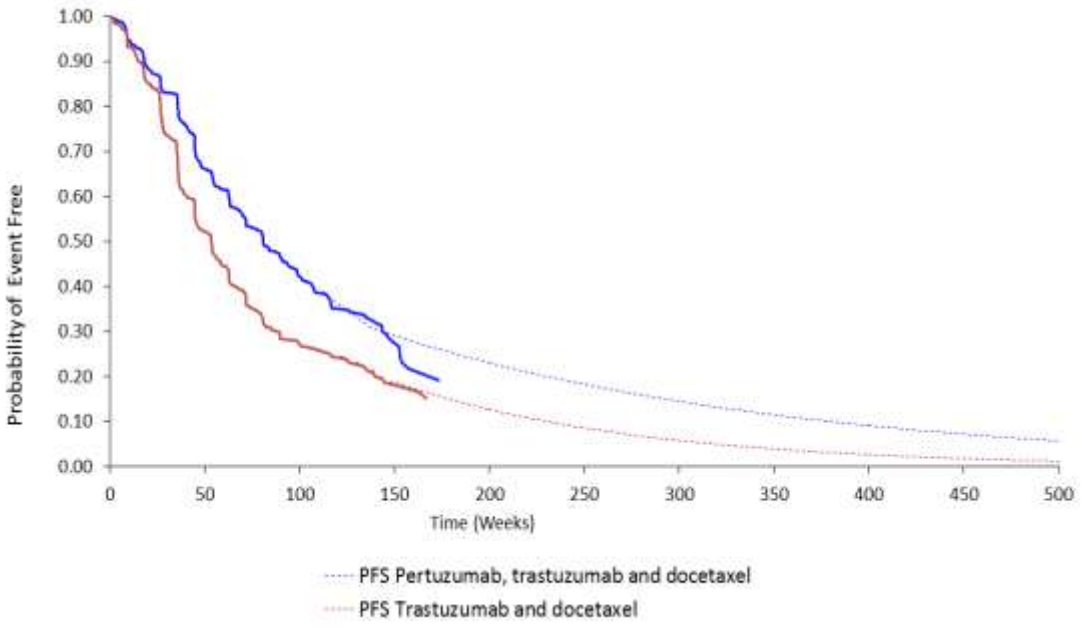
Figure 20 Modelled progression-free survival - scenario 3



Scenario 4: Informed hinge

If the flattening represents a separate clinically distinct cohort of people found in both study arms that respond better to treatment than those in the steeper part of the curve, then it may be the case that the treatment benefit associated with pertuzumab, trastuzumab and docetaxel observed in the trial would also be observed if the participants in the trial were followed for a longer duration. If this is the case, the relative treatment effect associated with pertuzumab, trastuzumab and docetaxel up to week 139 would be applied throughout the extrapolated period. This approach multiplies the hazard rate observed on the flat plat of the trastuzumab and docetaxel curve by the hazard ratio observed for the steep parts of both arms (0.0078 x (0.0091 / 0.0153)). The resulting hazard rate is converted to a weekly transition probability and applied to the pertuzumab, trastuzumab and docetaxel arm from week 139 onwards.

Figure 21 Modelled progression-free survival - scenario 4



Whilst this scenario appears to have the poorest face validity due to the seemingly erratic flattening in the intervention arm it should be noted that the observed data in the comparator arm features a similarly erratic flattening.

Progression-free survival base case

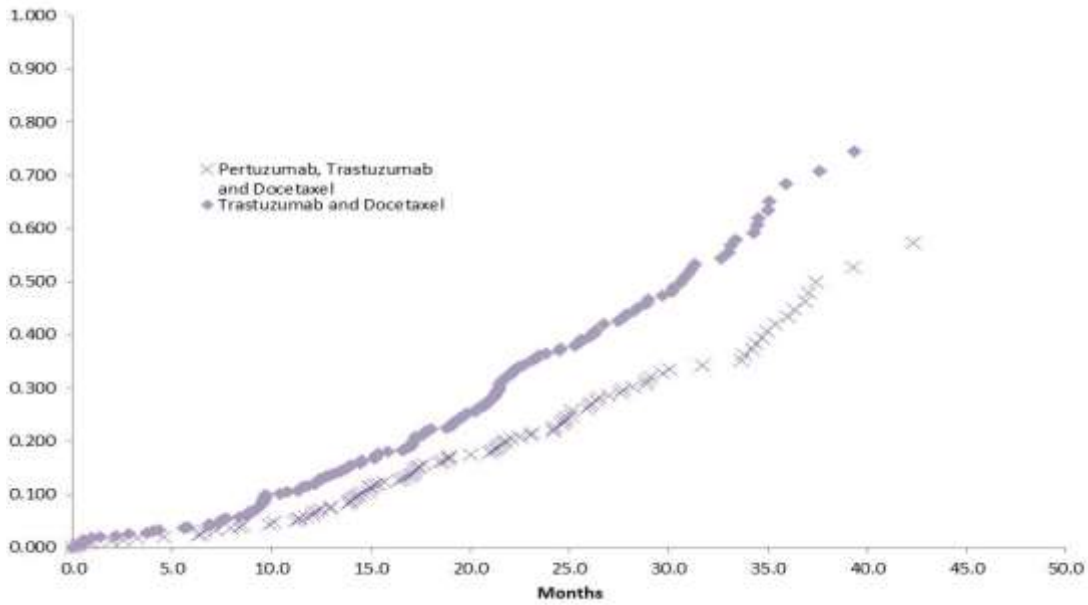
Data from the CLEOPATRA trial suggests the risk of progression appears to decline over time (if it is believed that the flattening of the curve is real). Clinicians at two advisory board meetings stated that in clinical practice there are a group of people that have a long-term response to treatment with trastuzumab, and that it is clinically plausible the addition of pertuzumab results in a longer duration of response compared with trastuzumab alone. The clinical specialists referred to the Kaplan-Meier curves observed for the primary data-cut of 13 May 2011 (see Figure 5), which show a significant flattening in the pertuzumab arm - similar to that observed in the trastuzumab and docetaxel arm in the secondary data-cut of 14 May 2012 (see Figure 9). As a result of this and clinical specialist opinion, scenario 3 was chosen as the base case in the economic model.

Overall survival

The model uses overall survival data from the data-cut of 14 May 2012 of the CLEOPATRA trial (see Figure 7 for Kaplan-Meier plots of overall survival for 14 May 2012 data-cut), in which median overall survival was reached in the trastuzumab and docetaxel arm but not the pertuzumab, trastuzumab and docetaxel arm. Given that the most recent overall survival data is censored in CLEOPATRA, the data has been extrapolated to capture the costs and benefits for the expected duration of people's lifetime.

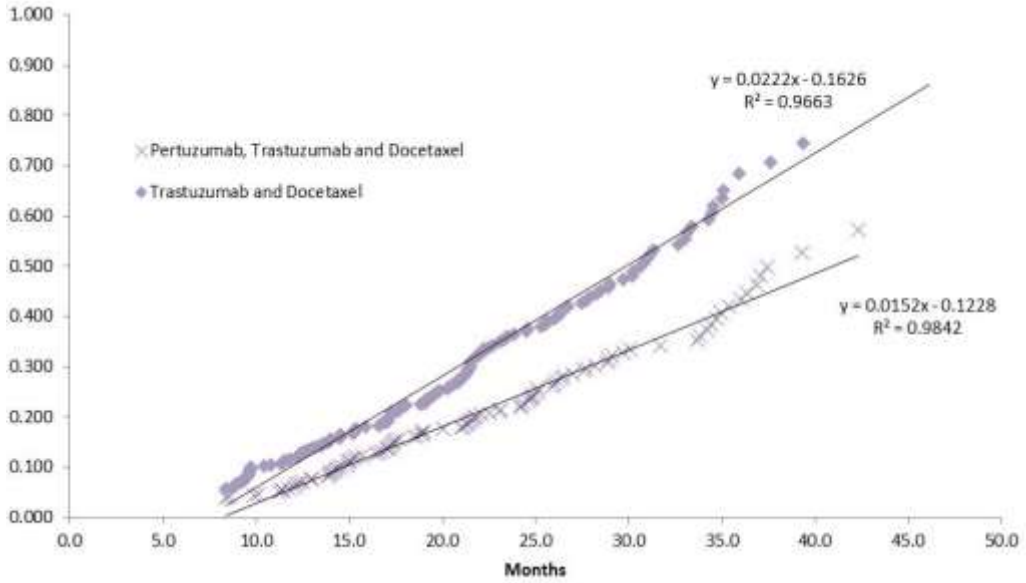
In order to inform extrapolation of this data, cumulative hazard plots were produced and examined (see Table 20). This exercise revealed that the hazard of death in each arm appears to be low for the first 8 months followed by a period of increased, but constant hazard (i.e. the cumulative hazard plots get steeper and then remain at the same gradient). Clinical specialists indicate the initial low hazard period may be due to the exclusion criteria preventing people who are at immediate risk of death from being included in the trial.

Figure 22 Cumulative hazard plots of overall survival (14 May 2012 data)



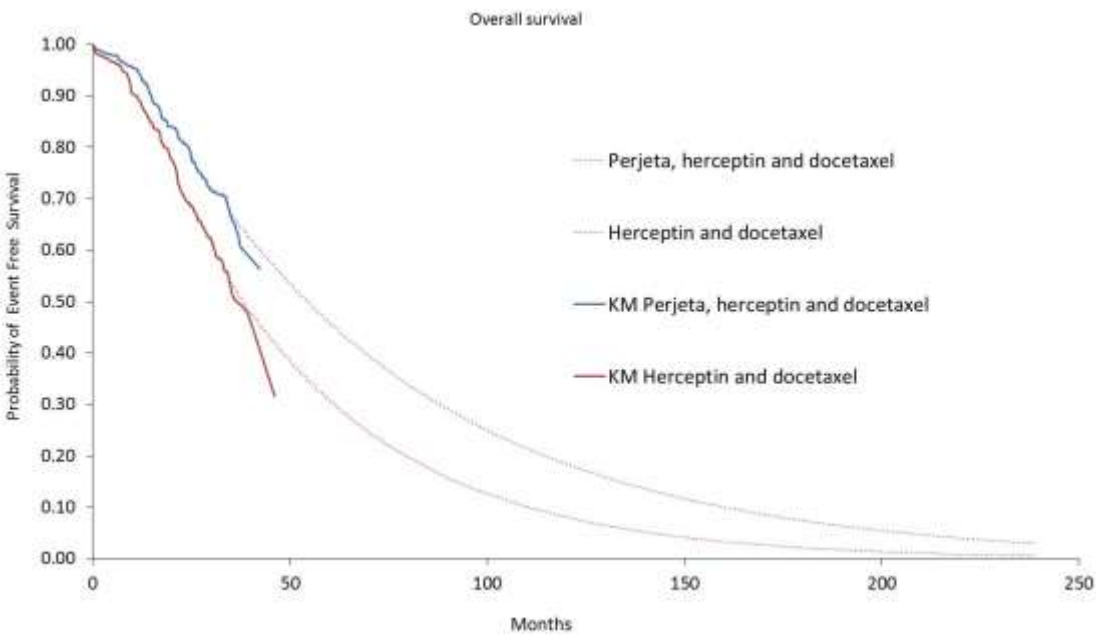
In light of this it is hypothesised that extrapolation of the CLEOPATRA data should be based upon the stabilised overall survival hazard observed from month 8 onwards.

Figure 23 Cumulative Hazard Plots of overall survival from month 8 onwards (14 May 2012 data)



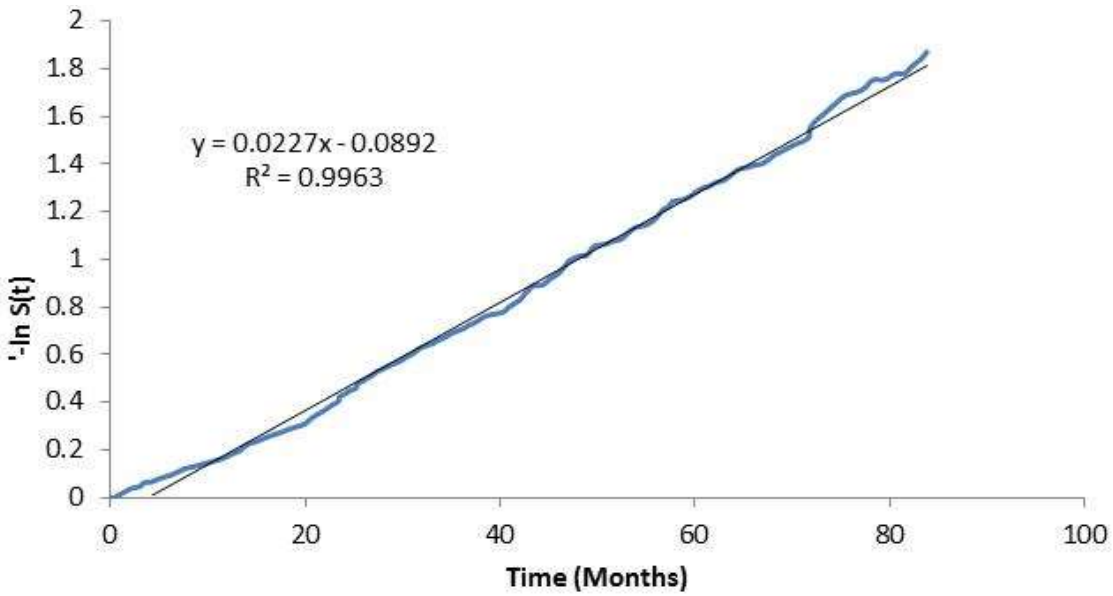
The hazard period in each arm from month 8 onwards appears constant as seen in Figure 23 (0.0222 in the trastuzumab and docetaxel arm, and 0.0152 in the pertuzumab, trastuzumab and docetaxel arm). Linear trend lines when fitted to both curves are associated with extremely high r^2 values (0.96 in the control arm and 0.98 in the intervention arm). In order to evaluate the plausibility of this extrapolation, the above hazards were incorporated within the model using Kaplan-Meier data up to month 35 (the point of last concordance between the trend and the observed data before the cumulative hazard plot became erratic) with constant hazards used from that point onwards. The modelled overall survival is presented in Figure 24.

Figure 24 Modelled overall survival



The external validity of the resultant curves was then assessed comparing the modelled survival of people observed in a registry of 523 people diagnosed with HER2-positive metastatic breast cancer between 2002 and 2009 in Munich, Germany (Tumorregister-Muenchen, 2012). The cumulative hazard plot for the Munich registry data are presented in Figure 25.

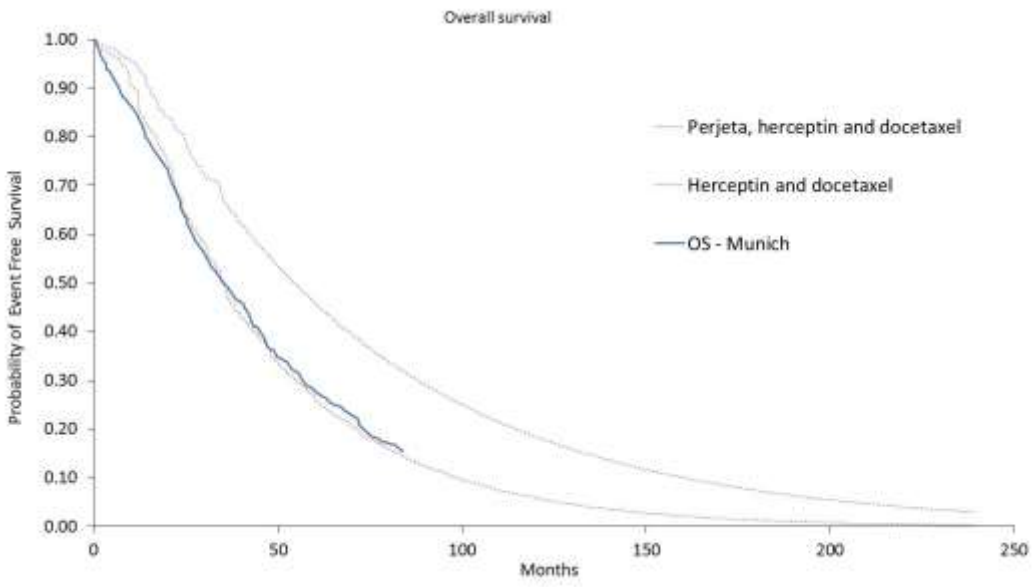
Figure 25 Cumulative hazard plot of Munich registry



The cumulative hazard plots observed in the Munich registry data indicate a constant linear hazard that supports the use of an exponential function when

extrapolating the data. Figure 26 shows the Munich registry curve overlaid against the extrapolated CLEOPATRA curves.

Figure 26 Registry data of people with HER2-metastatic breast cancer



The data demonstrates that the model has extremely strong face validity compared to external data. Whilst it is not possible to validate the modelling of the pertuzumab arm using external data (as the most mature data that exists is from the CLEOPATRA study) it is nevertheless reassuring that the modelling undertaken for the trastuzumab alone arm using the same approach used for pertuzumab has strong external validity.

The above rationale and resultant survival curves were discussed with a group of UK clinical experts in January 2013. The clinical specialists acknowledged the resultant curves had strong face validity and stated they should form the base-case of any modelling undertaken. The curves were also presented to an academic health economist (an ERG member) experienced in the critique of oncology models submitted to NICE's STA programme. The health economist noted the extrapolation and the rationale for employing the extrapolation based upon interpretation of the overall survival cumulative hazard plots appear reasonable.

Alternative extrapolation approaches (i.e. use of time variant hazards) was tested in sensitivity analysis (see Section 8.5.7).

8.2.2 Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here.

The hazards estimated using data from CLEOPATRA were converted into weekly probabilities prior to inclusion in the model, as described in Section 8.2.1.

8.2.3 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

The data from the CLEOPATRA trial suggests that the risk of progression appears to decline over time (if it is believed that the flattening of the curve is real). Clinicians at the advisory board acknowledged the trends seen in the data, stating that in clinical practice there are a group of people that have a long-term response to treatment with trastuzumab, and that it is clinically plausible that this group of people would have a longer response when pertuzumab is added to trastuzumab compared with trastuzumab alone.

8.2.4 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

No, progression free survival and overall survival were modelled individually and no relationship between the two was specified.

8.2.5 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[1]:

Clinical specialists were consulted in two advisory boards in the development of the submission and economic model. The clinical experts gave their opinion on the validity of the extrapolation conducted and the resource use and costing assumptions applied in the model based on their specialist knowledge of the subject.

Summary of selected values

8.2.6 Please provide a list of all variables included in the cost-effectiveness analysis, detailing the values used, range (distribution) and source. Provide cross-references to other parts of the submission. Please present in a table, as suggested below.

Table 21 Summary of variables applied in the economic model

Variable	Value	Reference to section in submission
Transition Probabilities		
Progression-free survival weekly hazard in PTD (week 117 to 139)	0.00906	Section 8.2.1
Progression-free survival weekly hazard in PTD (week 139 onwards)	0.00770	Section 8.2.1
Progression-free survival weekly hazard in TD (week 152 onwards	0.00770	Section 8.2.1
Overall survival weekly hazard in TD (month 32 onwards)	0.00220	Section 8.2.1
Overall survival weekly hazard in PTD (month 32 onwards)	0.01520	Section 8.2.1
Utility Values		
Progression-free survival TD (during docetaxel or paclitaxel)	0.769	Section 8.3.9
Progression-free survival PTD (during docetaxel or paclitaxel)	0.772	Section 8.3.9
Progression-free survival TD (after docetaxel or paclitaxel)	0.777	Section 8.3.9
Progression-free survival PTD (after docetaxel or paclitaxel)	0.785	Section 8.3.9
Progressed in both arms	0.500	Section 8.3.9
Costs (£)		

[1] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

MUGA Scan cost (per scan)	£238	Section 8.3.21
ECHO Scan cost (per scan)	£84	Section 8.3.21
MUGA and ECHO scan proportion	30%:70%	Section 8.3.21
Best supportive care costs (per month)	£157	Section 8.3.21
End of life costs (applied last week of life)	£3,608.69	Section 8.3.21
Administration costs (£)		
First cycle	£248	Section 8.3.20
Subsequent cycles	£197	Section 8.3.20
Pharmacy costs per dispensing	£9.40	Section 8.3.20
Adverse event costs (£)		
Anaemia	£331	Section 8.3.22
Diarrhoea	£391	Section 8.3.22
Fatigue	£391	Section 8.3.22
Febrile Neutropenia	£10,799	Section 8.3.22
Leukopenia	£215	Section 8.3.22
Peripheral Neuropathy	£319	Section 8.3.22
Neutropenia	£215	Section 8.3.22
Drug costs(£)		
Pertuzumab	£2,395 (420 mg vial)	Section 8.3.20
Trastuzumab	£407.40 (150 mg vial)	Section 8.3.20
Paclitaxel	£7 (80 mg vial) £6.30 (20 mg vial)	Section 8.3.20
Docetaxel	£20 (100 mg vial) £5 (30 mg vial)	Section 8.3.20
Discount rate (%)		
Costs	3.5	NICE Methods Guide
QALYs	3.5	NICE Methods Guide
Patient characteristics		
Age (years)	53.50	CLEOPATRA
Weight (kg)	66.60	CLEOPATRA
Body surface area (m^2)	1.68	CLEOPATRA

8.2.7 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer term difference in effectiveness between the intervention and its comparator?

See section 8.2.1 for details of how the extrapolation was conducted.

8.2.8 Provide a list of all assumptions in the de novo economic model and a justification for each assumption.

Assumption 1: All treatments are administered under the same NHS reference cost code (except for the first administration). This is based on clinical specialist advice from two advisory board meetings.

Assumption 2: Febrile Neutropenia events only take place during docetaxel or paclitaxel treatment. This is based on data from the CLEOPATRA trial in which no events of febrile neutropenia were reported after cessation of docetaxel (see Section 6.9.2 for more details of the adverse events observed in the CLEOPATRA trial).

Assumption 3: CT scan and outpatient visit applied every three months in both arms of the model. However, clinical advice confirms the frequency of assessing treatment with a CT scan (and an associated outpatient visit) varies across centres in England and Wales. In light of this, and the assumptions made in previous NICE Technology Appraisals, the model applies a conservative estimate of a CT scan and outpatient visit every three months during treatment. The effect of varying this assumption is explored in the deterministic sensitivity analysis.

Assumption 4: Cardiac assessment (MUGA or ECHO) are applied as a weighted average of 30% MUGA and 70% ECHO. This is based on clinical advice the ERG received in TA 257. The effect of varying this assumption is explored in the deterministic sensitivity analysis.

Assumption 5: Trastuzumab and docetaxel progression free survival curve and overall survival curves are assumed to be a reasonable proxy for the one weekly paclitaxel comparator. (Based on NICE Appraisal Committee conclusion in TA 214) and data from studies outlined in section 6.6.1.

Assumption 6: Only adverse events with over 2% incidence in either treatment arm of CLEOPATRA were assumed to have resource use and quality of life impact.

8.3 Measurement and valuation of health effects

Patient experience

8.3.1 Please outline the aspects of the condition that most affect patients' quality of life.

Studies have found that cancer survivors whose disease recurs have a worse quality of life in most indices than those who remain disease-free (Helgeson & Tomich 2005) and the most important distress factor among people with cancer has been found to be the fear of disease progression (Herschback, Keller, Knight, Huber, enrich & Marten-Mittag 2004).

8.3.2 Please describe how a patient's HRQL is likely to change over the course of the condition.

Health-related quality of life is expected to decrease with each line of treatment failure due to disease progression.

HRQL data derived from clinical trials

8.3.3 If HRQL data were collected in the clinical trials identified in section 6 (Clinical evidence), please comment on whether the HRQL data are consistent with the reference case.

A disease specific measurement (FACT-B) collected changes in quality of life in the CLEOPATRA study. The NICE reference case specifies use of a generic quality of life measurement, preferably EQ-5D, to capture changes in quality of life.

Mapping

8.3.4 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.

- **Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.**
- **Details of the methodology used.**
- **Details of validation of the mapping technique.**

As no mapping function exists for FACT-B to EQ-5D, quality of life data collected in the CLEOPATRA trial could not be used in the economic model.

HRQL studies

8.3.5 Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in section 10.12, appendix 12.

Embase (EMYY), Embase Alert (EMBA), Medline (MEYY), Medline in Process (MEIP) and NHS EED were searched for studies assessing utility values for different health states in metastatic breast cancer. The search was designed to evaluate all potentially relevant utility scores that have been used in metastatic breast cancer health technology evaluations. The complete search strategy is provided in section 11.12. The methodology used was based upon on the methods outlined in the CRD‟s "Guidance for undertaking reviews in health care‟ (2008).

As a similar search was conducted for a recent NICE Technology Appraisal of bevacizumab in combination with capecitabine (TA263) the search conducted was not completely *de novo* but an update of that search designed to identify any newly published utility values (with the search therefore limited from 2nd December 2011 – the date the TA263 search was conducted).

If a record was deemed potentially relevant it was retrieved in full and re-assessed against the inclusion/exclusion criteria.

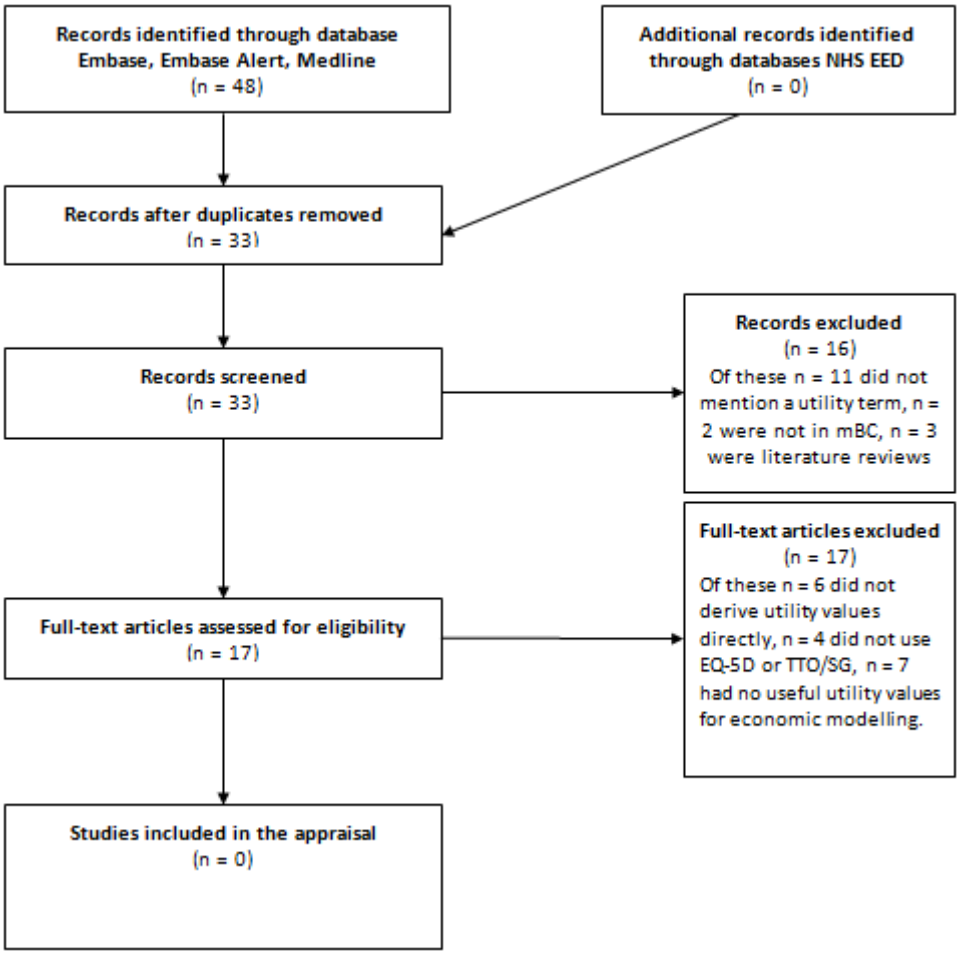
Table 18: Inclusion and exclusion criteria for utility studies

Inclusion Criteria	Exclusion Criteria
Metastatic or advanced breast cancer	Review of studies already included

Health related quality of life QALY or quality adjusted life year SF-36 OR SF-12 OR EQ-5D OR EQ-5D-5L OR EUROQOL Utilities Time Trade Off or Standard Gamble	Not quality of life studies Utility value not elicited by the general public Not in metastatic/advanced setting No useful health-related quality of life/Utility values for economic modelling

In total 48 records were identified from 4 databases. Of these, 16 were excluded by the independent reviewers and 17 were deemed potentially relevant and read in full. Of these, all were excluded after being assessed against the exclusion criteria.

Figure 16: PRISMA flow for utility studies identified through database searching



8.3.6 Provide details of the studies in which HRQL is measured.

The search in TA263 found three studies that measured utility values directly and that could potentially be used in the economic model. The table below summarises the main characteristics of the three articles. A critical appraisal of the three studies was undertaken in TA263, and is summarized below.

Table 22 Summary of the 3 utility articles

	(Dranitsaris, Leung, Mather, & Oza 2000)	**(Leung, Tannock, Oza, Puodziunas, & Dranitsaris 1999)**	**(Lloyd, Nafees, Narewska, Dewilde, & Watkins 2006)**
Population	25 general public, 25 female health care professionals	25 health care workers and 25 breast cancer patients	100 general public completed study
Elicitation methods	TTO	TTO	SG
Data set	Vignettes of progression free survival	Vignettes of 3 treatments for metastatic breast	Vignettes of metastatic breast cancer with different

		cancer and side effects	responses and side effects
Disease area/treatment	Advanced breast cancer	Metastatic breast cancer	Metastatic breast cancer
Utility estimate	Progression-free survival response to an AI public average = 0.8, nurse average = 0.74. Progression-free survival response to megestrol acetate = 0.8, nurse 0.67	Progression-free survival response to paclitaxel = 0.62 (0.61), response to docetaxel = 0.51 (0.49) and response to vinorelbine = 0.8 (0.77) *patients values in parentheses	Progression-free survival stable = 0.715, treatment response = +0.075, disease progression = -0.272, and other decrements for side effects.

Dranistaris et al. provide utility values from the TTO methods, for (1) progression free survival estimates for 2 aromatase inhibitors and megestrol acetate, for (2) response to treatment, (3) no response to treatment but response to chemotherapy, (4) no response to treatment and (5) progression during chemotherapy. The notable values that could potentially be used in the model come from response to treatment which were 0.8 when valued by the public, and varied considerably when valued by health care professionals (0.78 for letrozole, 0.72 for anastrozole and 0.67 for megestrol acetate). Utility values are provided for non-response to one of the three drugs (letrozole, anastrozole or megestrol) but having responded to subsequent chemotherapy - 5-fluorouracil, doxorubicin and cyclophosphamide (FAC). These treatments would not be useful for our model as we have no data on subsequent response rate to such chemotherapies within the CLEOPATRA study. Furthermore, the sample used is small, resulting in the robustness of the 0.8 value estimated by the public for response to treatment not sufficiently validated.

Leung et al. provide utility values for people with metastatic breast cancer' in progression-free survival having responded to three different treatment (paclitaxel, docetaxel and vinorelbine) (Leung, Tannock, Oza, Puodziunas, & Dranitsaris 1999). Given that there is considerable variation in the values estimated for the three treatments, and that none of the three treatments are the focus of this submission, using an average of these utility values in the model would lack validity. Similarly to Dranistaris et al, the sample used is small, leading to a lack of robustness of utility values.

Lloyd 2006 report the results of 100 participants asked to value various health states and side effects associated with metastatic breast cancer using the Standard Gamble technique (Lloyd et al 2006). An overall value for progression-free survival is found, and then deviations from this value (such as response to treatment, and progression of disease) are reported as incremental changes from this baseline utility value. The utility values from this study have been used in numerous NICE Technology Appraisals in metastatic breast cancer (Fleeman et al 2010).

8.3.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

No utility values were taken from CLEOPATRA (directly via EQ-5D or via mapping of FACT-B).

Adverse events

8.3.8 Please describe how adverse events have an impact on HRQL.

Pertuzumab has a largely manageable safety profile with very few life-threatening adverse events. Grade 1 and 2 adverse events were not included in the model as these were not associated with significant disutilities according clinical specialists opinion. The disutilities associated with treatment-related grade 3, 4 and 5 adverse events were included in the model. Adverse events were included based on incidence in the CLEOPATRA trial. The adverse events that have a significant quality of life impact are: febrile neutropenia, diarrhoea and vomiting, fatigue, anaemia and peripheral neuropathy. It is assumed that the type and frequency of adverse events observed in the trastuzumab and docetaxel arm of the CLEOPATRA trial can be applied to treatment with trastuzumab and paclitaxel.

Quality-of-life data used in cost-effectiveness analysis

8.3.9 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing

values obtained in sections 7.4.3 to 7.4.8. Justify the choice of utility values, giving consideration to the reference case.

There is a dearth of relevant utility studies appropriate to this appraisal and conforming to the NICE recommended approach (UK data capturing population preferences using EQ-5D or either time-trade off or standard gamble methodology).

The utility values used in the economic model have been estimated using the statistical model detailed in a study by Lloyd et al (see Section 8.3.6 for more details of the study). The study considered health states and a limited set of treatment-related adverse events specific to metastatic breast cancer and developed a mixed model using data collected from a sample of 100 UK residents broadly similar in age and sex to the general population. The Lloyd model includes age and treatment response as model variables and features several factors including the rate of response to chemotherapy and the exposure to a set of important adverse events. It has been used in previous NICE Technology Appraisals and is the best source currently available (TA257, TA263).

It is important to note that the relevant age used in the mixed model is not that of the patient but of the study participant. An average age of respondents to the original multi-vessel disease study of 47 years is used in arriving at utility parameter values. This is to ensure consistency with the UK EQ-5D standard value scheme and is the mean age of population taking part in the original Kind et al study.

Utilities were calculated from the results of the mixed model analysis presented by Lloyd et al. The central estimates of the parameter coefficients (and their standard errors) are listed in Table 23.

Table 23 Results of the mixed model analysis

Parameter	Parameter estimate	Standard error
intercept	0.008871	0.3196
age	0.0239	0.006946
treatment response	0.4063	0.05521
disease progression	-1.1477	0.1031

febrile neutropenia	-0.6603	0.08501
diarrhoea and vomiting	-0.4629	0.09929
hand-foot syndrome	-0.5184	0.09929
stomatitis	-0.6634	0.09929
fatigue	-0.5142	0.09929
hair loss	-0.5086	0.09929

For people who are in the progression free survival state it is necessary to calculate a treatment-specific weighted average of the model values for stable disease and treatment response, based on the reported overall response rate (79.59% for pertuzumab, trastuzumab and docetaxel, 69.37% for trastuzumab and docetaxel) to verify in the CLEOPATRA trial. For people in the progressed health state, a common health state utility value of 0.5 was obtained for use in both treatment arms.

All adverse events affecting more than 2% of participants in either treatment arm and which were deemed to affect quality of life according to clinical opinion, were used to calculate utility values (see Table 30 for a list of the adverse events of more than 2% incidence). No disutility decrement was applied to incidences of neutropenia and leukopenia as they are lab abnormalities and have no direct impact on quality of life. The utility decrement for febrile neutropenia is applied only during treatment with docetaxel or paclitaxel. This is based on data from the CLEOPATRA in which incidents of febrile neutropenia only occurred during treatment with docetaxel (see Section 6.9.2 for more details on the adverse events in the trial). The utility decrements for peripheral neuropathy and anaemia have been taken from NICE Technology Appraisal 250 and from the ERG report on the on-going NICE Technology Appraisal of bevacizumab for the treatment of recurrent advanced ovarian cancer. Table 24 lists the disutilities applied in economic model, additional to those in the Lloyd model.

Table 24 Additional adverse events included in the model

Adverse event	Disutility	Source
Anaemia	-0.120	TA 250 and ERG report of on-going NICE Technology Appraisal of bevacizumab for the treatment of recurrent advanced ovarian cancer
Peripheral Neuropathy	-0.120	TA 250 and ERG report of on-going NICE Technology Appraisal of bevacizumab for the treatment of recurrent advanced ovarian cancer

The utility values based on the Lloyd mixed model when supplemented with the disutilities associated with anaemia and peripheral neuropathy, and adjusted for response rate and age are listed in Table 25.

Table 25 Summary of utility values for cost-effectiveness analysis

State	Utility value	Reference in submission	Justification
Progression-free survival TD (during docetaxel or paclitaxel)	0.769	Section 8.3.9	Utility values determined to be appropriate for use in metastatic breast cancer by Fleeman et al 2010 in NICE TA257.
Progression-free survival PTD (during docetaxel or paclitaxel)	0.772		
Progression-free survival TD (after docetaxel or paclitaxel)	0.777		
Progression-free survival PTD (after docetaxel or paclitaxel)	0.785		
Progressed	0.769		
PTD, pertuzumab, trastuzumab and docetaxel; TD, trastuzumab and docetaxel; TP, trastuzumab and paclitaxel.			

8.3.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[2]:

[2] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

- **the criteria for selecting the experts**
- **the number of experts approached**
- **the number of experts who participated**
- **declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought**
- **the background information provided and its consistency with the totality of the evidence provided in the submission**
- **the method used to collect the opinions**
- **the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)**
- **the questions asked**
- **whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).**

Clinical specialists were consulted upon in the development of this submission and economic model. The specialists indicated the utility values are a conservative estimate of the quality of life with people with the disease, and that they would expect to see a higher quality of life in the progressed disease health state. The clinical specialists stated the calculation of utility values include all adverse events that have a significant impact on quality of life of people with the condition. The impact of varying utility values on the ICER has been explored in the sensitivity analysis.

8.3.11 Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

Patient experience is described in section 8.1.5.

8.3.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

All relevant health effects identified in the literature have been taken into account.

8.3.13 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

The baseline quality of life has been assumed to be different in the two treatment arms of the economic evaluation. People in the progression-free survival health state are characterised as either responders, who have a slightly improved quality of life, or have stable disease. All people in the progressed health state are characterised as being progressed.

8.3.14 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

Health related quality of life changes over time in the model according to health state and taxane use. The utility decrement for febrile neutropenia is applied only during treatment with docetaxel or paclitaxel. This is due to febrile neutropenia only being present during treatment with docetaxel in the CLEOPATRA trial (see Section 6.9.2 for more details of the adverse events in the CLEAPATRA trial).

8.3.15 Have the values in sections 7.4.3 to 7.4.8 been amended? If so, please describe how and why they have been altered and the methodology.

The methodology used to analyse the published coefficients is described in Section 8.3.9.

Resource identification, measurement and valuation

NHS costs

8.3.16 Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff. Provide the relevant

Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to section 2.

The process for the clinical management of advanced breast cancer is recommended in NICE clinical guideline CG81 (2009).CG81 has formed the basis of the costing assumptions for disease management in the model.

8.3.17 Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.

NHS reference costs are the most appropriate source of cost data for this appraisal.

Resource identification, measurement and valuation studies

8.3.18 Please provide a systematic search of relevant resource data for the UK. Include a search strategy and inclusion criteria, and consider published and unpublished studies. The search strategy used should be provided as in section 10.13, appendix 13. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources. Please give the following details of included studies:

- **country of study**
- **date of study**
- **applicability to UK clinical practice**
- **cost valuations used in study**
- **costs for use in economic analysis**
- **technology costs.**

Embase (EMYY), Embase Alert (EMBA), Medline (MEYY), Medline in Process (MEIP) and NHS EED were searched for studies assessing utility values for different health states in metastatic breast cancer. The complete search strategy is provided in section 11.13. The methodology used was based upon on the methods outlined in the CRD"s "Guidance for undertaking reviews in health care" (2008).

Similarly to the search of health related quality of life, as a comparable search was conducted for a recent NICE Technology Appraisal of bevacizumab in combination with capecitabine (TA263) the search conducted in this submission was not completely *de novo* but an update of the search in TA263 designed to identify any newly published resource use data (with the search therefore limited from 1st January 2011 – the date the TA263 search was conducted).

Keyword strategies were developed using key references retrieved through initial scoping searches. A date limit was set to retrieve records since January 1st 2011. ProQuest Dialogue was used to search EMYY, EMBA and MEYY whilst NHS EED was searched using The Centre for Reviews and Dissemination's website http://www.crd.york.ac.uk/crdweb/SearchPage.asp and ECON LIT was searched using (The American Economic Association & EconLIT 2011), accessed 15th March 2013. Titles and abstracts were assessed for relevance according to the pre-defined inclusion and exclusion criteria.

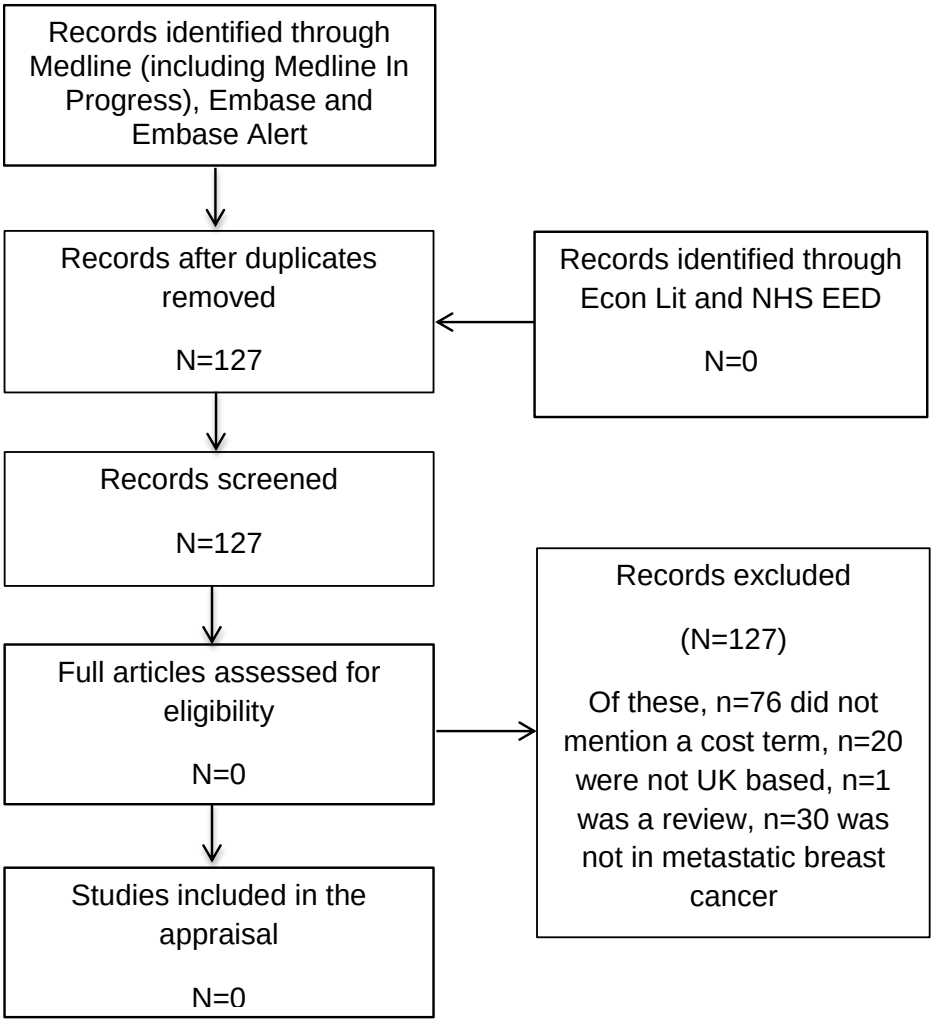
If a record was deemed potentially relevant it was retrieved in full and re-assessed against the inclusion/exclusion criteria are listed in Table 26.

Table 26 Inclusion and exclusion criteria for resource utilisation studies

Inclusion criteria	Exclusion criteria
Advanced or metastatic breast cancer Resource utilisation from a UK NHS Perspective	Early breast cancer Resource utilisation from a private/US setting and any other non-UK country. Costs derived from studies more than 5 years old.

In total 130 records were identified from 3 databases. Of these, all were excluded by the independent reviewers (see figure below for details of reasons for exclusion). Since no studies were identified in TA 263, resource use in the model is based on relevant clinical guidelines, previous NICE appraisals and clinical specialist and health economist opinion from two advisory board meetings.

Figure 16: PRISMA flow for resource utilisation studies identified through database searching



8.3.19 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[3]:

- **the criteria for selecting the experts**
- **the number of experts approached**
- **the number of experts who participated**

[3] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

- **declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought**
- **the background information provided and its consistency with the totality of the evidence provided in the submission**
- **the method used to collect the opinions**
- **the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)**
- **the questions asked**
- **whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).**

Clinical specialists were consulted upon in the development of this submission and economic model, and indicated that the resource use inputs and assumptions are appropriate.

Intervention and comparators' costs

8.3.20 Please summarise the cost of each treatment in the following table.

Table 27 Unit costs associated with the technology in the economic model

Items	Pertuzumab	Trastuzumab	Docetaxel	Paclitaxel	Ref. in submission
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)	8.3.20
Administration cost (first)	£248	£248	£248	£248	8.3.20
Administration cost (subsequent	£197 for all subsequent administrations				8.3.20
Pharmacy cost	£9.40	£9.40	£9.40	£9.40	8.3.20

Pertuzumab drug cost:

Pertuzumab is administered by intravenous infusion once every 3 weeks at an initial dose of 840 mg, followed by a maintenance dose of 420 mg.

Pertuzumab can be purchased in a 420 mg vial for £2,395. This equates to a cost of £4,790 for the initial dose, followed by £2,395 for subsequent doses.

Trastuzumab drug cost:

Trastuzumab is administered by intravenous infusion once every three weeks at a dose of 8 mg/kg for initial dose, followed by a 3 weekly maintenance dose of 6 mg/kg. The cost of trastuzumab in the model is based on the distribution of body weight of participants in the CLEOPATRA trial. This is instead of using an average body weight of participants in the trial.

Based on the distribution of body weight in the CLEOPATRA trial, the mean patient weight is 66.59 kg. Based on the distribution of patient weight, the mean initial dose is 532.75 mg/kg, and maintenance dose is 399.56 mg/kg.

Trastuzumab can be purchased in a powder for reconstruction of 150 mg vial (Joint Formulary Committee 2012):

150 mg vial = £407.40

Based on the distribution of patient weight, the mean number of vials is 4.02 x 150 mg vials for initial dose, and 3.15 x 150 mg vials (if no vial sharing is assumed) or 3.55 x 150 mg vials for initial dose, and 2.66 x 150 mg vials (if vial sharing is assumed and the centre uses the remaining trastuzumab in the vial). For the purpose of the base case, it is assumed that no vial sharing will take place.

The mean per protocol per cycle cost of treatment with trastuzumab including consideration of wastage and based on the distribution of patient weight is £1,629.60 for the initial dose and £1,222.20 for the maintenance dose.

Docetaxel drug cost:

Docetaxel was administered every three weeks at a dose of 75 mg/m^2 body surface area (calculated using the Du Bois formula). The cost of docetaxel in the model is based on the distribution of body surface area of participants in the CLEOPATRA trial.

As docetaxel is a generic drug the base case applies acquisition costs of docetaxel obtained from the Commercial Medicines Unit 2012 electronic Market Information Tool (CMU eMIT) (Commercial Medicines Unit 2012). The CMU eMit is an online source of information on the historical average price paid for a product. The estimates provided are derived from data collected via a system covering approximately 95% of English NHS Trusts. The lowest price per mg of docetaxel obtained from CMU eMIT is £0.25 per mg (National Product Code – DHC035). Based on costs from the CMU eMIT, the mean per protocol per cycle cost of treatment with docetaxel including based on the distribution of patient body surface area is £35.

The impact of applying acquisition costs of docetaxel obtained from the Joint Formulary Committee on the ICER is explored in sensitivity analysis. Docetaxel can be purchased in 6 pack sizes of 10 mg/ml or 20 mg/ml concentration (Joint Formulary Committee 2012):

10 mg/ml concentration:

2 ml (20 mg) vial = 162.75

8 ml (80 mg) vial = 534.75

16 ml (160 mg) vial = 1069.50

20 mg/ml concentration

1 ml (20 mg) vial = 154.61

4 ml (80 mg) vial = 508.01

7 ml (140 mg) vial = 720.10.

Paclitaxel drug cost:

The model applies paclitaxel for 18 cycles at a weekly dose of 90 mg/m^2 body surface area (see Section 6.7 for an explanation as to the use of weekly regimen of paclitaxel in the model). Similarly to other technologies in the model, paclitaxel drug costs are based on the distribution of body surface area of participants in the CLEOPATRA trial calculated using the Du Bois formula. Based on the distribution of body surface area in the CLEOPATRA trial the mean dose required is 150.83.

As paclitaxel is a generic drug the base case applies acquisition costs of paclitaxel obtained from the CMU eMIT (Commercial Medicines Unit 2012). The lowest price per mg of paclitaxel obtained from CMU eMIT is £0.07 per mg (National Product Code – DHA297). Based on costs from the CMU eMIT, the mean per protocol per cycle of treatment with paclitaxel based on the distribution of body surface area is £19.60.

The impact of applying acquisition costs of paclitaxel obtained from the Joint Formulary Committee on the ICER is explored in sensitivity analysis. Paclitaxel can be purchased in four pack sizes at 6 mg/ml concentration (Joint Formulary Committee 2012):

5 ml (30 mg) vial = £66.85

16.7 ml (100 mg) vial = £200.35

25 ml (150 mg) vial = £300.52

50 ml (150 mg) vial = £601.03

Administration and pharmacy cost

Pertuzumab and trastuzumab are administered by intravenous infusion in a hospital on the first day of each 21 day cycle. There is a cost associated with both the pharmacy preparation of the infusion and the administration of the technologies (typically within a hospital setting). The administration cost of the first cycle for each technology is based on NHS Reference costs 2011/12 (SB13Z): Deliver more Complex Parenteral Chemotherapy at First Attendance (Chemotherapy Delivery: Daycase and Regular Day / Night). It is assumed that all technologies are administered under the same NHS Reference cost code for subsequent cycles. The administration cost of subsequent cycles is obtained from NHS Reference costs 2011/12 (SB12Z): Deliver simple Parenteral Chemotherapy at First Attendance (Chemotherapy Delivery: Outpatient).

A prospective time-and-motion study was conducted in two UK secondary care NHS Trusts to quantify time taken with the preparation and administration of XELOX (capecitabine in combination with oxaliplatin) and

FOLFOX-6 (5-FU in combination with folinic acid and oxaliplatin) in metastatic colorectal cancer (Millar et al. 2008). The results of the study indicate that dispensing of capecitabine and preparation of oxaliplatin (administered intravenously) requires an average of 12 minutes each. It is assumed that the dispensing of treatments in the economic model takes 12 minutes each.

One hour of pharmacist time performing patient related activities (accounting for overheads, qualifications, and salary on costs) costs £47 (PSSRU, 2012). The cost of dispensing of treatments in the economic model is estimated to be £9.40 (£47 x12 / 60) per administration, based on 12 minutes of pharmacist preparation time.

Duration of first line treatment

A proportion of people cease treatment prior to disease progression (i.e due to adverse event or patient preference) it is therefore essential to consider the distinction between progression-free survival and treatment cessation when evaluating the real incremental cost of treatments. In order to account for this disparity, patient level data on treatment duration was used to produce time to off treatment Kaplan-Meier curves that could be applied to determine the proportion of people still receiving pertuzumab, trastuzumab and docetaxel or trastuzumab and docetaxel in each week within the model. This fitting was conducted in the same manner as described for progression-free survival, that is, the time to off treatment modeling is determined by the modeling of progression-free survival used in each arm in the model. The model was half cycle corrected and the time-to-off-treatment was capped at the progression-free survival rate to avoid more people being on treatment than being progression free. The impact on the ICER of applying time to off treatment equal to progression-free survival is explored in the sensitivity analysis.

Second line treatment cost

Second line treatments applied in the model are vinorelbine and capecitabine, based on the treatment algorithm in Table 26 of NICECG81. As vinorelbine is a generic drug, acquisition costs of vinorelbine are obtained from the CMU eMIT (Commercial Medicines Unit 2012). The lowest price per mg of

vinorelbine obtained from CMU eMIT is £0.42 per mg (National Product Code – DHA220).

The model estimates the cost of vinorelbine by applying a weekly loading dose of 25 mg/m^2 body surface area for three weeks, followed by a weekly maintenance dose of 25 mg/m^2 body surface area. The price per mg of vinorelbine obtained from CMU eMIT is then multiplied by the average body surface area (calculated using the Du Bois formula) of participants in the CLEOPATRA trial. As vinorelbine is intravenously administered, a first cycle administration cost based on NHS Reference costs 2011/12 (SB13Z): Deliver more Complex Parenteral Chemotherapy at First Attendance (Chemotherapy Delivery: Daycase and Regular Day / Night), has been applied. Subsequent administrations of vinorelbine have an associated cost based on NHS Reference costs 2011/2012 (SB12Z): Deliver simple Parenteral Chemotherapy at First Attendance (Chemotherapy Delivery: Outpatient).

The model applies capecitabine at a dose of 1250 mg/m^2 body surface area given twice daily for 14 days followed by a 7 day treatment gap.

Capecitabine can be purchased in tablet form in two pack sizes (Joint Formulary Committee 2012):

150 mg (60 tab pack) = £40.02

500 mg (120-tab pack) = £265.55

The cost per 150 mg tablet is 0.66p (60 / £40.02) and per 500 mg tablet is £2.21 (120 / £265.55). Administration costs are only applied to treatments delivered by injection or infusion, therefore no administration costs have been applied to treatment with capecitabine as it is available in tablet form.

Table 28 Second line treatments in the economic model

Second line treatment	Dose	Frequency	Weekly cost (£)	Source
Vinorelbine (IV)	25 mg/m² loading dose	Once weekly (first three weeks)	17.71	Commercial Medicines Unit 2012
Vinorelbine (IV) maintenance dose	30 mg/m² maintenance dose	Once weekly (subsequent weeks)	21.25	Commercial Medicines Unit 2012
Capecitabine	1250 mg/m^2	Twice daily for 14 days followed by a 7-day rest period	134.98 (during treatment weeks)	BNF 65

The model applies the cost of second line treatments to the progressed health state for 4.3 months. This is based on a study by Cameron et al (2008) in which people with metastatic breast cancer whose disease had progressed following treatment with trastuzumab were treated with capecitabine for an average 4.3 months. An average of the total cost of both treatments given for 4.3 months (including administration costs) are multiplied by the proportion of people transitioning to the progression health state at each week in each arm in the model. Due to complexity in modelling the deaths which may occur during this period when applying the one-off cost, deaths have not been accounted for in this analysis. This is likely to lead to the overestimation of the cost of second line treatment.

Health-state costs

8.3.21 Please summarise, if appropriate, the costs included in each health state. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model. The health states should refer to the states in section 7.2.4.

As the model runs on a weekly cycle length, monthly costs were split into weekly costs prior to being applied in the model. Best supportive care costs are based on a package of care described in NICE CG81.

Table 29 List of health states and associated costs in the economic model

Health states	Items	Frequency	Unit cost (£)	Total Cost (£)	Reference in submission
Progression-free survival best supportive care	Community Nurse (home visit)	20 mins every 2 weeks	61 (per hour)	40.66	Section 8.3.21
	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**	
End of life care cost				3,608.69	

Given uncertainty as to which package of care is appropriate for inclusion and the contents of packages, Roche approached the health economist who developed the economic model used in CG81. The health economist confirmed that ‘package 1’ is applied during chemotherapy treatment up until a patient receives only supportive and palliative care, irrespective of the line of treatment, and the cost of a social worker is applied only once per line of treatment.

In order to assess response to treatment, outpatient visits and CT scans have been applied in the model. In clinical trials a CT scan is typically conducted every three months to assess whether a person's disease has progressed. Clinical advice confirms the frequency of assessing treatment with a CT scan varies across centres – some only scan at the presence of symptoms of progression due to the view that it is inefficient to assess without signs of progression. In contrast other centres scan frequently (no more than every three months), but at a decreasing rate throughout treatment. In light of this and the assumptions made in previous NICE Technology Appraisals the model applies a conservative estimate of a CT scan and outpatient visit every three months during treatment. A CT scan in the model is associated with a cost of £125 (NHS Reference Cost 2011/12 (RA12Z: Computerised Tomography – two areas with contrast - Outpatient)) and the cost of an outpatient visit is £113 (NHS Reference Cost 2011/12 (service code 800: Consultant Led: Follow up Attendance Non-Admitted Face to Face: clinical oncology)). The impact of applying alternative frequencies of CT scan and outpatient visits on the ICER is explored in sensitivity analysis.

An additional cost of cardiac assessment is applied during the progression-free health state. These assessments are applied every 9 months in the pertuzumab, trastuzumab and docetaxel arm and every 12 months in the trastuzumab and docetaxel arm, as specified in licensed indication for these technologies. The cost of cardiac assessments are applied as a weighted average of 30% MUGA scan (NHS Reference Cost 2011/12 - RA37Z: Nuclear Medicine – Category 3 Outpatient) and 70% ECHO scan (NHS Reference Cost 2011/12 - RA60A: Simple Echocardiogram, 19 years and over). This is based on clinical specialist advice to the Evidence Review Group in NICE TA 257. The impact of applying alternative frequencies of cardiac assessments, and of alternative proportions of MUGA and ECHO scans, on the ICER is explored in sensitivity analysis

The cost of palliative care is included within the model through application of costs from Guest et al (2006). Guest et al examined the treatment patterns and corresponding costs of healthcare resource use associated with palliative

care for people with different types of advanced cancer; from initiation of strong opioid treatment until death. Resource utilisation data associated with palliative care were obtained from the DIN-LINK database; DIN-LINK is an anonymised database of individual primary care records in the UK, from general practices that use a health information systems software program (iSOFT, formerly Torex; iSOFT Group, plc, Manchester, UK). Palliative care costs for breast cancer were estimated to be £2,482 per patient using costs from 2000–2001. This cost was inflated to current prices (£3,608.69) using inflation indices for Hospital and Community Health Services (PSSRU). The cost of palliative care cost is applied as one lump sum upon death in the model. This approach to modelling end of life costs is consistent with several recent oncology NICE Technology Appraisals (particularly those in metastatic non-small-cell lung cancer such as TA 258).

Adverse-event costs

8.3.22 Please summarise the costs for each adverse event listed in section 6.9 (Adverse events). These should include the costs of therapies identified in sections 2.7 and 2.8. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2.

Only adverse events occurring in 2% or more people in either arm of the CLEOPATRA trial at grade 3, 4 or 5 severity are incorporated into the model. In all instances the most recent NHS reference costs are used in the model (Department of Health 2012). Given that adverse events typically occur during the beginning of treatment, the cost of adverse events were applied in week one in the model and so were not discounted. It is assumed that treatment regimens of trastuzumab and docetaxel, and trastuzumab and paclitaxel have the same toxicity profile. This is likely to overestimate the adverse event incidence and costs associated with paclitaxel given that clinical specialist opinion indicates that weekly paclitaxel is slightly better tolerated than three-weekly docetaxel. The impact on the ICER of assuming a lower incidence of adverse events for treatment with paclitaxel is explored in the sensitivity

analysis. The cost associated with adverse events that occur in 2% or more people in either arm of the CLEOPATRA trial at grade 3, 4 or 5 severity are incorporated are outlined in Table 30.

Table 30 List of adverse events and summary of costs included in the economic model

Adverse events	% people in PTD arm	% people in TD arm	Cost per episode (£)	Source (NHS reference cost 2011/12)
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
PTD, Pertuzumab, trastuzumab and docetaxel: TD, Trastuzumab and docetaxel.				

Miscellaneous costs

8.3.23 Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.

None

8.4 Sensitivity analysis

8.4.1 Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated,

including a description of the alternative scenarios in the analysis.

The three state model structure used in this model has been used in previous NICE Technology Appraisals in metastatic oncology and is accepted as the appropriate method of modelling metastatic breast cancer, therefore no structural sensitivity analysis of the model has been undertaken.

8.4.2 Which variables were subject to deterministic sensitivity analysis? How were they varied and what was the rationale for this? If any parameters or variables listed in section 7.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.

Deterministic sensitivity analysis was carried out on the parameters listed in Table 31 (note: all costs are monthly costs unless otherwise stated). Significant costs were varied and the impact of varying utility values individually as well as in combination with the others was explored. The impact of using different parametric functions used to model progression-free survival and overall survival on the ICER were explored. The discount rate for costs and outcomes was varied according to standard methods and the time horizon altered.

Table 31 Deterministic sensitivity analysis

	Base case value (BCV)	**High value**	**Low value**
Costs			
Administration subsequent cost (monthly)	£197	£275.80 (BCV x1.4)	£118.20 (BCV x 0.6)
Progression-free survival supportive care cost (monthly)	£157.66	£220.72 (BCV x1.4)	£94.59 (BCV x 0.6)
Progressed disease supportive care cost (monthly)	£157.66	£220.72 (BCV x1.4)	£94.59 (BCV x 0.6)
Cardiac assessment frequency	Every 9 weeks in PTD Every 12 weeks in TD	Every 9 weeks both arms	Every 12 weeks both arms
Cardiac assessment	30/70 (MUGA/ECHO)	10/70 (MUGA/ECHO)	50/50 (MUGA/ECHO)

proportion	proportion	proportion	proportion
CT scan and outpatient visit frequency	Every 3 months	CT scan and outpatient visit once at week 12 and once at progression	Every 6 months
Second line treatment duration	4.3 months	12 months	2 months
Docetaxel	CMU eMIT	BNF 65 (see Section 8.3.20)	
Paclitaxel	CMU eMIT	BNF 65 (see Section 8.3.20)	
First line treatment duration	Actual Treatment duration observed in the trial	To Progression-free survival	
Outcomes			
Progression-free survival utility (during docetaxel)	Different values in arms	Same values based on PTD arm	Same values based on TD arm
Progression-free survival utility (after docetaxel)	Different values in arms	Same values based on PTD arm	Same values based on TD arm
Progression-free survival utility (during docetaxel)	See Table 25	BCV +0.2 for both arms	BCV -0.2 for both arms
Progression-free survival utility (after docetaxel)	See Table 25	BCV +0.2 for both arms	BCV -0.2 for both arms
Progressed utility	See Table 25	BCV +0.2 for both arms	BCV -0.2 for both arms
Adverse event incidence of paclitaxel	Assume same as docetaxel in CLEOPATRA	Total number of people and occurrences of adverse events reduced by 50% (Impacts cost of AE and utilities in TP arm)	
Parametric functions			
Parametric fit	Kaplan-Meier data with piecewise exponential tail	Kaplan-Meier data with non-piecewise tails (1) Weibull (2) Exponential (3) Log-logistic (4) Log normal (5) Gamma	
Overall survival	Kaplan-Meier data with piecewise exponential tail	Kaplan-Meier data with non-piecewise tails (1) Weibull (2) Exponential (3) Log-logistic (4) Log normal (5) Gamma	
Other			
Cost discount rate	3.5%	6%	0
Health outcomes discount rate	3.5%	6%	0
Health and cost discount rates	3.5% both arms	6% both arms	0% both arms
Time horizon	25	20	30
PTD, pertuzumab, trastuzumab and docetaxel; TD, trastuzumab and docetaxel; TP, trastuzumab and paclitaxel; Both arms, PTD and TD arms.			

In addition to the sensitivity analysis in Table 31, the impact of alternative progression-free survival scenarios on the ICER was explored.

Table 32 Progression-free survival scenarios

Progression-free survival scenario	Source
Scenario 1 with exponential tail	See section 8.2.1 for an explanation of the various progression-free survival scenarios
Scenario 2 with exponential tail	
Scenario 4 with exponential tail	

8.4.3 Was PSA undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated if different from those in section 7.3.6, including the derivation and value of 'priors'. If any parameters or variables were omitted from sensitivity analysis, please provide the rationale for the omission(s).

A PSA was undertaken. The distributions used are listed in Table 33.

Table 33 PSA distributions

	Distribution
Utilities	
PFS PTD (During docetaxel	Beta (77.210, 22.790)
PFS PTD (After docetaxel)	Beta (78.667, 21.333)
PFS TD (During docetaxel)	Beta (76.853, 23.147)
PFS TD (After docetaxel)	Beta (77.589, 22.411)
PD	Beta (50.000, 50.000)
Costs	
Best supportive care Both arms and PFS and PD	Lognormal (36,24, 0.5243)
Second line treatment costs	Lognormal (6,046.54, 0.0719)
PFS, Progression-free survival; PD, Progressed disease; PTD, pertuzumab, trastuzumab and docetaxel; TD, trastuzumab and docetaxel.	

8.5 Results

Clinical outcomes from the model

8.5.1 For the outcomes highlighted in the decision problem (see section 5), please provide the corresponding outcomes from

the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

Table 34 Summary of model results compared with clinical data

Outcome	Clinical trial result	Model result
Pertuzumab, trastuzumab and docetaxel		
Progression-free survival	Median = 18.6 months	Median = 18.6 months
Overall response Rate	79%	79%
Trastuzumab and docetaxel		
Progression-free survival	Median = 12.4 months	Median = 12.4 months
Overall survival	Median = 37.5 months	Median = 38 months
Response Rate	69%	69%

Table 34 indicates the model predicts median progression-free survival observed in the CLEOPATRA trial. This is due to the response rates taken from the study and applied in the model as an input and the progression-free survival curves from the study used directly in the model until the start of extrapolation (which began after median progression-free survival).

8.5.2 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

The model runs for 25 years on a weekly cycle length (1,297 cycles). Reproducing the Markov trace would require approximately 30 pages of the submission. As this submission is already approximately 200 pages long, this information is has not been reproduced within the template. The trace is available within the model and can be provided as a separate appendix document if required.

8.5.3 Please provide details of how the model assumes QALYs accrued over time.

See response to 8.5.2.

8.5.4 Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results.

Table 35 Model outputs by clinical outcomes

Technologies	Outcome	LY	QALY
Pertuzumab, trastuzumab and docetaxel	Progression-free survival	[redacted]	[redacted]
	Progressed disease	[redacted]	[redacted]
	Overall survival	[redacted]	[redacted]
Trastuzumab and docetaxel	Progression-free survival	[redacted]	[redacted]
	Progressed disease	[redacted]	[redacted]
	Overall survival	[redacted]	[redacted]
Trastuzumab and paclitaxel	Progression-free survival	[redacted]	[redacted]
	Progressed disease	[redacted]	[redacted]
	Overall survival	[redacted]	[redacted]
LY, life years; QALY, quality-adjusted life year			

8.5.5 Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost.

Table 36 Summary of QALY gain by health state

Technologies	Progression-free survival	Increment (% absolute increment)	Progressed	Increment (% absolute increment)
Trastuzumab and docetaxel	[redacted]	[redacted]	[redacted]	
Trastuzumab and paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]
Pertuzumab, trastuzumab and docetaxel	[redacted]	[redacted]	[redacted]	[redacted]

Table 37 Summary of costs by health state

Technologies	Progression-free survival	Increment (% absolute increment)	Progressed	Increment (% absolute increment)
Trastuzumab and docetaxel	[redacted]	[redacted]	[redacted]	
Trastuzumab and paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]
Pertuzumab, trastuzumab and docetaxel	[redacted]	[redacted]	[redacted]	[redacted]

Table 38 Summary of predicted resource use by category of cost

Technology	Mean treatment cost (£)	Increment (%)	Admin cost (£)	Increment (%)	Supportive care cost (£)	Increment (%)
Trastuzumab and docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Trastuzumab and paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pertuzumab, trastuzumab and docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% = (% absolute increment)						

Base-case analysis

8.5.6 Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance.

Table 39 Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
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.							

Sensitivity analyses

8.5.7 Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.

The results of the deterministic sensitivity analysis are presented in Table 40.

Table 40 Sensitivity Analysis

	Base case value (BCV)	**High value**	**Low value**
Costs			
Administration subsequent cost (monthly)	£197	£275.80 (BCV x1.4)	£118.20 (BCV x 0.6)
	[redacted]	[redacted]	[redacted]
Progression-free survival supportive care cost (monthly)	£157.66	£220.72 (BCV x1.4)	£94.59 (BCV x 0.6)
	[redacted]	[redacted]	[redacted]
Progressed disease supportive care cost (monthly)	£157.66	£220.72 (BCV x1.4)	£94.59 (BCV x 0.6)
	[redacted]	[redacted]	[redacted]
Cardiac assessment frequency	Every 9 weeks in PTD Every 12 weeks in TD	Every 9 weeks both arms	Every 12 weeks both arms
	[redacted]	[redacted]	[redacted]
Cardiac assessment proportion	30/70 (MUGA/ECHO) proportion	10/70 (MUGA/ECHO) proportion	50/50 (MUGA/ECHO) proportion
	[redacted]	[redacted]	[redacted]
CT scan and outpatient visit frequency	Every 3 months	CT scan and outpatient visit once at week 12 and once at progression	Every 6 months
	[redacted]	[redacted]	[redacted]
Second line treatment duration	4.3 months	12 months	2 months
	[redacted]	[redacted]	[redacted]
Docetaxel	CMU eMIT	BNF 65	
	[redacted]	[redacted]	
Paclitaxel	CMU eMIT	BNF 65	
	[redacted] (vrs TP)	[redacted] (comparison with PTD)	
First line treatment duration	Actual Treatment duration observed in the trial	To progression-free survival	
	[redacted]	[redacted]	
Outcomes			
Progression-free survival utility (during docetaxel)	Different values in arms	PTD arm values in both arms	TD arm values in both arms
	[redacted]	[redacted]	[redacted]
Progression-free survival utility (after docetaxel)	Different values in arms	PTD arm values in both arms	TD arm values in both arms
	[redacted]	[redacted]	[redacted]
Progression-free survival utility (during docetaxel)	See Table 25	BCV +0.2 for both arms	BCV -0.2 for both arms
	[redacted]	[redacted]	[redacted]

Progression-free survival utility (after docetaxel)	See Table 25	BCV +0.2 for both arms	BCV -0.2 for both arms
	[redacted]	[redacted]	[redacted]
Progressed utility	See Table 25	BCV +0.2 for both arms	BCV -0.2 for both arms
	[redacted]	[redacted]	[redacted]
Adverse event incidence of paclitaxel		Total number of people and occurrences of adverse events reduced by 50% (Impacts cost of AE and utilities in TP arm).	
	[redacted] (vrs TP)	[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]
Time horizon	25	20	30
	[redacted]	[redacted]	[redacted]
PTD, pertuzumab, trastuzumab and docetaxel; TD, trastuzumab and docetaxel; TP, trastuzumab and paclitaxel; Both arms, PTD and TD arms.			

Deterministic sensitivity analysis demonstrates the model is most sensitive to the long term extrapolation of progression-free survival and overall survival. The model is also sensitive to the utility values in progression-free survival (after docetaxel treatment) and progression health states, and the discount rate for health outcomes and costs - these are displaced graphically in Figure 27.

Figure 27 Tornado diagram

[redacted]

8.5.8 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

The results of the PSA are presented in Table 41.

Table 41 Probabilistic sensitivity analysis results

Technology (and comparators)	Total cost £	Total QALY	Inc. cost £	Inc. QALY	ICERs versus 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]
QALY, quality-adjusted life year; ICERs, incremental cost-effectiveness ratios.						

The results of the PSA indicate that pertuzumab, trastuzumab and docetaxel has a 0% probability of being cost-effective at a willingness-to-pay of £30,000 per QALY gained, see Figure 28 for a graphical representation of the cost-effectiveness acceptability curve.

Figure 28 Cost-effectiveness acceptability curve

[redacted]

[redacted]

8.5.9 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

Results of different progression-free survival scenarios are presented in Table 42. See Section 8.2.1 for a description of the different scenarios.

Table 42 Progression-free survival extrapolation scenarios

Scenario	Incremental costs (£)	Incremental QALYs	ICER (£)
Base Case (Scenario 3)	[redacted]	0.833	[redacted]
PFS scenario 1 with exponential tail	[redacted]	0.899	[redacted]
PFS scenario 2 with exponential tail	[redacted]	0.860	[redacted]
PFS scenario 4 with exponential tail	[redacted]	0.942	[redacted]
PFS, Progression-free survival			

8.5.10 What were the main findings of each of the sensitivity analyses?

[redacted].

The deterministic sensitivity analysis demonstrates the model is most sensitive to the long term extrapolation of progression-free survival and overall survival. The model is also sensitive to the utility values in progression-free

survival (after docetaxel treatment) and progression health states, and the discount rate for health outcomes and costs.

8.5.11 What are the key drivers of the cost-effectiveness results?

The key drivers of the model are the cost of pertuzumab, the long term projection of progression-free survival and overall survival and the utility values used.

8.6 Validation

8.6.1 Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical, quality of life and resources sections.

The model was validated at two advisory board meetings and by a health economics consultancy. The model functionality was checked and the clinical inputs and assumptions were validated.

The extrapolation conducted was discussed with an academic health economist and two panels of clinicians. All noted that whilst subject to uncertainty the extrapolation approach employed appeared reasonable given the evidence currently available.

8.7 Subgroup analysis

8.7.1 Please specify whether analysis of subgroups was undertaken and how these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical or cost effectiveness because of known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section 6.3.7.

No subgroup analysis was undertaken.

8.8 Interpretation of economic evidence

8.8.1 Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

There are no economic evaluations in this indication and patient population with which these results may be compared (see Section 7 for more details of the search of cost-effectiveness studies undertaken).

8.8.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 5?

The evaluation is founded upon the CLEOPATRA trial and so should be representative of all people who participated in the CLEOPATRA trial.

8.8.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

Strengths

1. The model uses data from the pivotal clinical trial (CLEOPATRA) wherever possible, and resource use and costs based on recent NICE clinical guidelines.

2. CLEOPATRA is a robust and well conducted study in people broadly representative of the population expected to be treated in England and Wales.

3. The model uses costs and utilities that have been applied and accepted as appropriate in previous NICE Technology Appraisals in metastatic breast cancer where appropriate.

4. The extrapolated overall survival curves demonstrate strong external validity when compared against registry data of people with HER2-positive metastatic breast cancer.

Weaknesses

1. The model is heavily reliant upon long-term projection of overall survival.

2. A minority of participants in the ITT population of the CLEOPATRA trial received prior treatment with trastuzumab in the adjuvant setting. However data from CLEOPATRA suggests the efficacy of pertuzumab in the trastuzumab naïve and the trastuzumab experienced populations is similar (see Section 1.4 for more details).

8.8.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

Key drivers in the model are the extrapolation of overall survival and progression-free survival, and the utility values used to estimate the quality of life of people with the disease. Robustness of the model would be improved by the incorporation of more mature data on the baseline risk of death and the longer term treatment effect associated with pertuzumab. Collection of EQ-5D values from participants in the trial would improve the estimates of the quality of life impact within the progression-free survival and progressed health states.

Section C – Implementation

9 Assessment of factors relevant to the NHS and other parties

9.1 How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

It is estimated that approximately 2,058 people per annum will be eligible to receive pertuzumab for first line treatment of HER2-positive metastatic breast cancer. The derivation of this number is provided in Figure 1. At a population growth rate of 0.5% per annum this results in the following yearly eligible populations

Table 43 Eligible population by year

Year	1	2	3	4	5
Eligible Population	2,058	2,068	2,078	2,088	2,098

9.2 What assumption(s) were made about current treatment options and uptake of technologies?

Trastuzumab in combination with a taxane is considered to be the standard of care and therefore the most likely treatment option.

9.3 What assumption(s) were made about market share (when relevant)?

It is assumed that 30% of eligible people in the year following NICE approval would receive pertuzumab with that figure rising to 70% in the fifth year following approval. The market share figures used are presented in Table 44.

Table 44 Market share assumptions

Year	1	2	3	4	5
% people treated with pertuzumab	30%	40%	50%	60%	70%

9.4 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

The budget impact calculations include all the additional costs of treatment with pertuzumab as included in the de novo economic model and discussed in the cost-effectiveness section.

9.5 What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?

The budget impact calculations are based upon the output of the economic model.

9.6 Were there any estimates of resource savings? If so, what were they?

No.

9.7 What is the estimated annual budget impact for the NHS in England and Wales?

Table 45 Budget impact by year

Year	1	2	3	4	5
Budget Impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

9.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

No.

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