NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer [ID767]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer [ID767]

Contents:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer

This premeeting briefing presents:

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

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

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies.

Key issues for consideration

Clinical

- Which patients with breast cancer are currently offered neoadjuvant chemotherapy in England?
- Do the patients in the NeoSphere trial reflect the HER2 positive population who would be considered for neoadjuvant treatment in England?
- The comparator in the scope (standard neoadjuvant therapy without pertuzumab for HER2-positive breast cancer) was broader than the comparator used by the company (neoadjuvant trastuzumab in combination with chemotherapy). The company data suggests around 75% of neoadjuvant treatment regiments contain trastuzumab in clinical practice. Can the results be generalised to the whole population in clinical practice?

- The company assume a relationship between pathological complete response and longer term survival outcomes:
  - What is the evidence that neoadjuvant therapy has a beneficial effect on event free survival and overall survival?
  - Is pathological complete response a reliable/ the best indicator of the long term benefit of neoadjuvant treatment?
  - If trying to establish a relationship between pathological complete response and long term benefit, is this best reflected by the whole population with breast cancer in the CTNeoBC meta-analysis, or in the HER2 positive subgroup only?
- Is there a length of disease free survival from diagnosis that indicates a cure in HER2 positive breast cancer?

Cost

- Is it reasonable to use a trastuzumab containing regimen as the sole comparator in the model?
- In March 2016 this technology received a negative recommendation from the Scottish Medicines Consortium (SMC) for the same drug in the same indication, based on an ICER submitted to the SMC by the company of £34,100 per QALY gained. However, the original base case ICER submitted by the company to NICE (£17,297) was substantially lower:
  - What are the reasons for these differences?
  - Are there differences in utility values and life expectancy in Scotland compared with England and how is the difference in QALY gains in the two submissions explained (0.26 and 0.31)?
- In the company model submitted to NICE, the incremental costs are less than half those submitted to SMC (£4,557 NICE submission, compared with £10,370 SMC). The model submitted to NICE includes the costs of follow-on treatments for metastatic disease which are currently funded in England by the Cancer Drugs Fund. Does this explain the difference, and is this reasonable?
- When predicting event free survival in the model, the company used a combination of event free survival curves taken from the CTNeoBC meta-analysis,

and NeoSphere trial data to adjust the curves depending on pathological complete response:

  - Is this the most appropriate approach? If so, is it robust enough for decision making?
  - How consistent are the results of this approach with the data on event free survival in NeoSphere?
  - If extrapolating curves from CTNeoBC, which data should be used – the whole population with breast cancer, or the population with HER2-positive disease only?

- The company assumes that after 7 years of event free survival, patients are cured of HER2-positive breast cancer. Is this a reasonable assumption?
- When taken with pertuzumab, trastuzumab can only be administered intravenously, however trastuzumab also has a licence for subcutaneous administration, which is available with a commercial discount to the NHS. What proportion of people use subcutaneous trastuzumab in clinical practice?

1 Remit and decision problems

1.1 The remit from the Department of Health for this appraisal was: to appraise the clinical and cost effectiveness of pertuzumab within its marketing authorisation for the neoadjuvant treatment of human epidermal growth factor receptor 2 (HER2) positive breast cancer.

Table 1 Decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
Pop.	Adults with HER2-positive breast cancer which is either; • locally advanced, or • inflammatory, or • early stage (at a high-risk of recurrence).		As scope.	Matches scope (although no economic analyses presented for subgroups).
Int.	Neoadjuvant pertuzumab in combination with trastuzumab and chemotherapy.		As scope.	Matches scope.

Com.	Standard neoadjuvant therapy without pertuzumab for HER2-positive breast cancer.	Neoadjuvant trastuzumab in combination with chemotherapy.		Scope comparator was broader. Most patients will receive trastuzumab regimen in clinical practice, but a small proportion will not (e.g. HER2 testing not available, frailty or cardiac co-morbidities). As no evidence has been provided for patients who would not receive trastuzumab, ERG assessment is limited to company population. NICE has not assessed treatments in neoadjuvant setting.
Out.	Overall survival (OS); disease free survival; surgical outcomes; pathological complete response (pCR); adverse effects of treatment; health-related quality of life	OS; event free survival (EFS); surgical outcomes; pCR; adverse effects of treatment; health-related quality of life	NeoSphere trial EFS is evaluated in same way as progression free survival. EFS is model endpoint	Primary outcome is pathological complete response. Trials included but not powered for OS and disease-free survival. OS not systematically reported within NeoSphere trial.

2 The technology and the treatment pathway

2.1 Breast cancer is the most common type of cancer in the UK; in 2011 there were approximately 42,000 diagnoses of breast cancer in England, and an estimated 10,000 deaths. It is estimated that approximately 15-25% of women with breast cancer will have human epidermal growth factor receptor 2 (HER2) positive tumours. HER2 is a receptor for a growth factor which occurs naturally in the body. When human epidermal growth factor attaches itself to HER2 receptors on breast cancer cells, it can stimulate the cells to divide and grow. Some breast cancer cells have more HER2 receptors than others; in these cases, the tumour is described as being HER2-positive, which is associated with a worse prognosis. Men are less likely to have HER2-positive breast cancers.

2.2 Breast cancer is described as 'early' if it is restricted to the breast, or the breast and nearby lymph nodes, and has not spread to other parts of the body (clinical stages 1 and 2). It is described as 'locally advanced' if the cancer is in a large part of the breast (more than 5 cm) but has not spread to other parts of the body (clinical stage 3), and described as 'advanced' if it has spread to other parts of the body and cannot be completely removed by surgery (clinical stage 4). Inflammatory breast cancer is a rare but aggressive type of breast cancer in which cancer cells grow along, and block the lymph nodes in the skin of the breast causing it to become inflamed and swollen. Inflammatory breast cancer affects the breast differently and usually the whole breast and the overlying skin are affected (clinical stage 3 or 4).

2.3 Pertuzumab (Perjeta, Roche Products) is a recombinant monoclonal antibody which targets HER2-positive breast tumours. It interrupts the activation of the HER2 intracellular signalling pathway, leading to cell growth arrest and apoptosis. It is administered by intravenous infusion. Pertuzumab has a marketing authorisation in the UK 'in combination with trastuzumab and chemotherapy for the neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence'. This marketing authorisation will be the subject of this appraisal. Pertuzumab also has a marketing authorisation 'in combination with trastuzumab and docetaxel in adult patients with HER2-positive metastatic or locally recurrent unresectable breast cancer who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease'. The company noted that the extension of the marketing authorisation for pertuzumab to treat neoadjuvant disease was granted with a number of conditions, in addition to those already in place for the metastatic indication. This included the submission of periodic safety reports, adherence to an agreed risk management plan, and conducting 2 post-authorisation trials: an efficacy trial, 'APHINTY' and a safety trial, 'BERENICE'. These trials are ongoing and are not considered in this appraisal.

2.4 NICE clinical guideline (CG) 80 recommends that early breast cancer can be treated with surgery (to remove the tumour) followed by chemotherapy (adjuvant) to reduce the risk of the cancer coming back (recurrence). In early stage breast cancer, risk assessment for recurrence depends upon tumour size, grade, hormone receptor status and lymph node involvement. Locally advanced and inflammatory breast cancers are considered to have a high-risk of recurrence. CG80 recommends trastuzumab as an adjuvant treatment for HER2-positive early invasive breast cancer, for 1 year or until disease progression. CG80 also recommends that systemic therapy can be offered before surgery (neoadjuvant) to people with early invasive, locally advanced, or inflammatory breast cancer who are considering breast conserving surgery that is not advisable at presentation. Although CG80 does not specify which neoadjuvant treatments should be given, the company for pertuzumab stated the commonly used regimens in clinical practice used as neoadjuvant therapy for HER2-positive breast cancer include fluorouracil, epirubicin and cyclophosphamide (or 'FEC') followed by docetaxel with trastuzumab. For people who cannot have an anthracycline (epirubicin) the neoadjuvant therapy comprises trastuzumab, docetaxel and carboplatin. The company stated that according to its own data, currently more than 75% of neoadjuvant treatment regimens contain trastuzumab. Clinical experts for the ERG confirmed this, noting that trastuzumab is recommended as an adjuvant treatment in CG80, and although it has not been evaluated by NICE in the neoadjuvant setting, trastuzumab is also being used in the earlier part of the pathway in clinical practice. The company and the ERG noted that a small proportion of patients would not receive trastuzumab, mainly because of HER2 testing results not being available, frailty or cardiac co-morbidities.

2.5 For advanced breast cancer, CG81 ('advanced breast cancer') recommends systemic chemotherapy for people for whom anthracyclines are not suitable, in the following sequence: first line: single-agent docetaxel; second line: single-agent vinorelbine or capecitabine; third line:

single-agent capecitabine or vinorelbine (whichever was not used as second line). TA34 recommends trastuzumab in combination with paclitaxel (as that was the licensed combination treatment at that time) as an option for HER2-positive metastatic breast cancer for people who have not received anthracyclines in the adjuvant setting, or trastuzumab monotherapy for people who have received at least two chemotherapy regimens for metastatic breast cancer. Additionally, pertuzumab is funded by the Cancer Drugs Fund (in combination with trastuzumab and docetaxel) for first line treatment of locally advanced or metastatic HER2 3+ or FISH positive breast cancer.

2.6 Figures 1 and 2 below show the proposed treatment pathway for breast cancer if pertuzumab neoadjuvant treatment is recommended for use in the NHS. Figure 1 is based on NICE pathways and therefore presents the pathway in terms of available NICE guidance. The company stated that the addition of pertuzumab would not change this existing treatment pathway, because it would be an add-on to the trastuzumab containing regimens currently used as a primary systemic treatment (figure 1) in UK clinical practice.

Figure 1: Treatment pathway 1: Current NICE guidance pathway

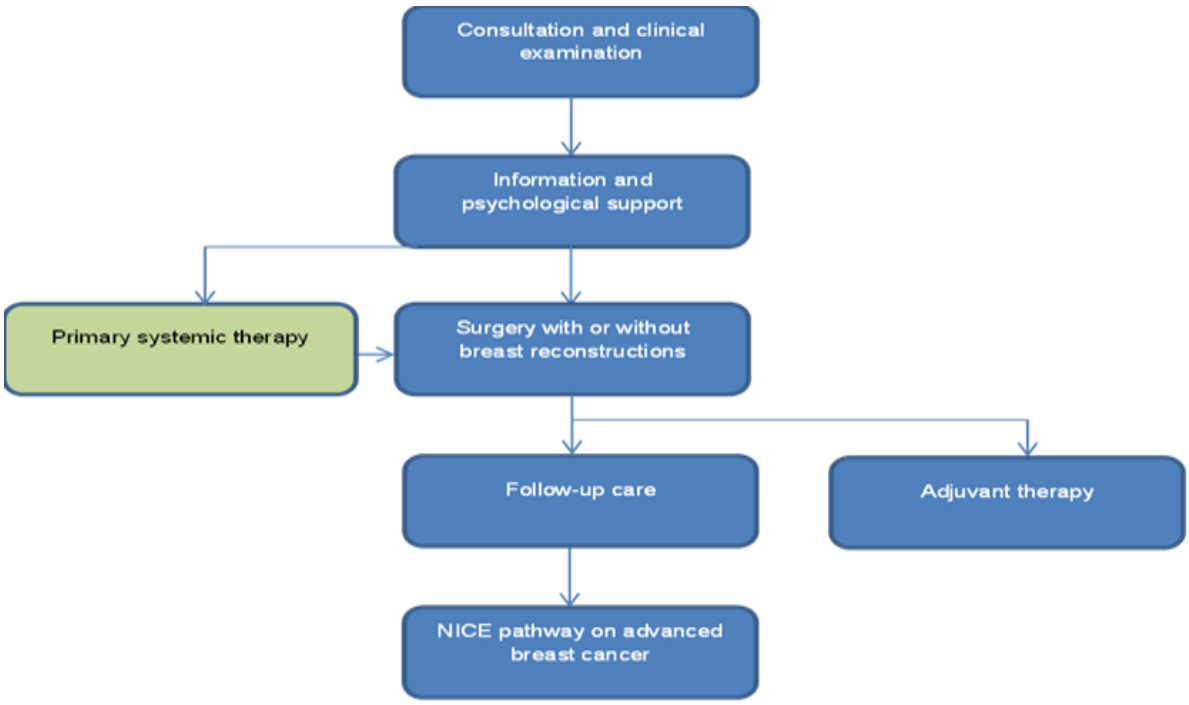


Figure 2: Treatment pathway 2: If pertuzumab is recommended

2.7 The company stated that there is variation in care across the UK: in whether patients are offered neoadjuvant treatment (the company stated that according to its own data 27% of people with HER2-positive disease receive neoadjuvant treatment); in the information available to clinicians when recommending a treatment plan; and in access to diagnosis of HER2 status. It received clinical expert opinion that the results of HER2-positive status may not be made available to patients and their clinicians before a decision on their treatment plan, which could delay their access to treatments with a license for HER2-positive disease only. The company also stated that there is likely to be variation in the appropriate tumour size to define HER2-positive early breast cancer patients who are at high risk of recurrence.

Table 2 Technology

	Pertuzumab	**Trastuzumab**	**Docetaxel**
Marketing authorisation	In combination with trastuzumab and chemotherapy for the neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence	Treatment of adult patients with HER2-positive early breast cancer in combination with neoadjuvant chemotherapy followed by adjuvant Herceptin therapy, for locally advanced (including inflammatory) disease or tumours > 2 cm in diameter.	Generically available. Licences do not specifically mention neoadjuvant treatment.
Administration method	Intravenous	Intravenous Subcutaneous (Pertuzumab is only licensed with intravenous trastuzumab)	Intravenous

	Initial loading dose 840 mg, followed by a maintenance dose of 420 mg every 3 weeks thereafter for 3 to 6 cycles. List price £2,395 per 420 mg vial. The company assumed costs of **£11,975** for 4 cycles	**Intravenous**: 3 weekly cycles: loading dose 8 mg/kg, maintenance dose of 6 mg/kg. Weekly cycles: loading dose of 4 mg/kg, maintenance dose 2 mg/kg every week concomitantly with paclitaxel following chemotherapy with doxorubicin and cyclophosphamide. For 1 year or until disease recurrence £407.40 per 150 mg vial. The company assumed costs of **£5,161** for 4 cycles. **Subcutaneous**: 600mg every 3 weeks for 1 year or until disease recurrence. £1222.20 per 600mg vial	When administered with pertuzumab the recommended initial dose of docetaxel is 75 mg/m2, administered thereafter on a 3 weekly schedule. The dose of docetaxel may be escalated to 100 mg/m2 on subsequent cycles if the initial dose is well tolerated (the docetaxel dose should not be escalated when used in combination with carboplatin, trastuzumab and pertuzumab). 80 mg/4ml - £25.73 per mg. The company estimated costs of **£215** for 4 cycles.

See summary of product characteristics for details on adverse reactions and contraindications.

3 Comments from consultees

3.1 The patient and professional groups described the treatment pathway for people with breast cancer. The patient organisation stated that surgery is usually the first option for women with primary or early breast cancer. Someone with advanced localised breast cancer may be offered neoadjuvant chemotherapy to shrink the size of the tumour, so that surgery can take place. The professional organisation stated that primary medical therapy consisted of anthracycline then taxane with trastuzumab, or docetaxel, carboplatin and trastuzumab, and in some sites pertuzumab is offered as a 'top-up' (and should only be prescribed by accredited breast cancer medical oncology and clinical oncology consultants and designated trainees, and delivered by systemic anti-cancer therapy delivery teams in NHS). It stated that pathological complete response with primary medical therapy is high, and response has a very strong

correlation with overall survival in HER2-positive breast cancer. If the patient has a response to neoadjuvant treatment, this can reduce the extent of surgery required, reducing morbidity and costs. Surgery may be followed by radiotherapy and/or chemotherapy depending on the balance of benefits and risks. The professional organisation stated that adjuvant treatment is usually anthracycline-based chemotherapy, followed by trastuzumab in combination with a taxane followed by trastuzumab alone or in combination with endocrine therapy if appropriate, or taxane-based chemotherapy in combination with trastuzumab from the outset.

3.2 The patient and professional groups described the patient experience for people with breast cancer. The patient organisation stated that the initial diagnosis of breast cancer can be very shocking and is likely to cause considerable anxiety to the patient as well as their family and friends. In the longer term, the fear of breast cancer spreading to other parts of the body such as the bone, lungs, liver and brain, or returning at a later date, can cause further anxiety. The patient organisation stated that treatment with chemotherapy usually has a range of unpleasant side-effects, which can have a significant impact on everyday activities, ability to work, social life and relationships. It stated that the best treatment outcome for patients with primary breast cancer is the complete eradication of their cancer to reduce the risk of recurrence or metastases. Any treatments that can effectively control the growth of the cancer or shrink the size of the tumour are also valued by the patient, as these can reduce the extent of surgery required. The professional organisation stated that HER2 positive breast cancer is considered to be one of the most aggressive types of breast cancer, and HER2 status is a significant predictor of both overall survival and time to relapse in patients with breast cancer.

3.3 The patient and professional groups considered the advantages of pertuzumab. The patient organisation stated that pertuzumab appears to be a promising treatment but that many benefits are hypothetical and require more research, because it has only recently been licensed for this indication and trial participants were small in number. It stated that based

on the results of the NeoSphere trial, pertuzumab increases the chances of complete eradication of the tumour. The side effects of pertuzumab are also usually much less severe than those associated with chemotherapy and may therefore be more appropriate for some patients, allowing them to lead more normal lives during their treatment. It also stated that there are several possible advantages to neoadjuvant treatment, because it may: reduce the extent of surgery, reducing the recovery time for the patient; allow less extensive surgery for example breast conserving surgery instead of a complete mastectomy (which can have beneficial psychological effects for some women); make the cancer operable which may not have been previously possible; and increase the chances of eradicating the tumour completely (and patients could therefore avoid surgery completely). The professional organisation stated that pertuzumab is a major advance and has huge potential to transform the outcomes and pathway for this group of patients. It stated that experts envisage that there would be no extra resources required, with healthcare workers already competent in administering this sort of treatment. It stated that there may be a need to educate people within the pathway, but that there would be a 'trade off' in any extra resource required, because there would be a reduction in people requiring surgical and medical treatment for HER2-positive metastatic breast cancer. The professional organisation also described the disadvantage of the *adjuvant* approach –there is no response data, treatment is essentially one size fits all, and there are data to show that delayed commencement of appropriate systemic anti-cancer therapy has a deleterious effect on survival.

3.4 The patient organisation described the disadvantages to pertuzumab. It stated that some patients may be weakened by chemotherapy pre-surgery, potentially increasing recovery time or complications associated with surgery. Some patients may also not respond to pertuzumab, and for these patients neoadjuvant treatment could unnecessarily delay surgery which could have been more effective if patients received it earlier. Patients with large tumours will often still need to have a complete

mastectomy anyway, which can have traumatic psychological effects. The patient organisation noted that the 2 clinical trials conducted to assess the effectiveness of pertuzumab (NeoSphere and TRYPHAENA) have not done a long-term follow up to ascertain the effect of neoadjuvant treatment on the risk of recurrence or long-term survival. It also stated that although the adverse effects from pertuzumab and trastuzumab alone are relative minor compared with chemotherapy, the effects may be worse when pertuzumab and trastuzumab are taken together. Furthermore, pertuzumab is administered intravenously ever 3 weeks for 3-6 cycles, which can be inconvenient for patients and cause discomfort (although the same is true for existing neoadjuvant standard of care trastuzumab). The professional organisation stated that there is some increase in moderate diarrhoea with pertuzumab, but adverse events are similar to those for treatments without pertuzumab, and easily manageable.

3.5 The patient organisation stated those with locally advanced disease or an inflammatory type of breast cancer will benefit the most from this treatment. Advanced localised disease may mean that the cancer is either inoperable or may require a complete mastectomy, whilst inflammatory breast cancer is usually aggressive and can therefore invade nearby tissue, also quickly making it inoperable or requiring extensive surgery. The increased effectiveness of pertuzumab in eliminating and shrinking the size of the tumour prior to surgery, than is possible with other current treatments, means that surgery may become possible in some cases or be less invasive, aiding a faster recovery time. The professional group stated that oestrogen receptor positive and negative breast cancer have different pathological complete response rates.

3.6 The patient and professional groups described variation in care. The professional organisation stated that for early breast cancer there is a huge variation across the UK in primary medical therapy compared with surgery for HER2-positive breast cancer despite the evidence that early anti-HER2 directed therapy improves survival in the metastatic and early breast cancer settings.

4 Clinical-effectiveness evidence

Overview of the clinical trials

4.1 The company conducted a systematic review of the literature to identify studies evaluating the clinical effectiveness and safety of pertuzumab added to trastuzumab and chemotherapy for the neoadjuvant treatment of human epidermal growth factor receptor 2 (HER2) positive locally advanced, inflammatory, or early stage breast cancer. The company identified 2 multicentre, open-label, randomised controlled trials conducted in this population: NeoSphere (efficacy trial, see section 4.2) and TRYPHAENA (safety trial, see section 4.3). The company also identified supporting evidence about the effectiveness and safety of pertuzumab: an ongoing clinical trial CLEOPATRA (conducted in a metastatic population, but used to present supporting data on treatment related adverse events, see section 4.5), and observational data from the Cleveland Clinical Registry (see section 4.6). Furthermore, the company presented a meta-analysis done by an international working group known as the Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC) group, which evaluated the relationship between pathological complete response and long-term outcomes in people with breast cancer, such as disease-free and overall survival (see section 4.7).

4.2 NeoSphere (n=417) was located in 59 centres in 16 countries including Australia, Austria, Brazil, and 2 centres in the UK. It randomised patients to 1 of 4 arms using different combinations of intravenous pertuzumab, trastuzumab and docetaxel, all administered intravenously and as described in their respective marketing authorisations: trastuzumab and docetaxel (Arm A, n=107), pertuzumab, trastuzumab and docetaxel (Arm B, n=107), pertuzumab and trastuzumab, (Arm C, n=107) and pertuzumab and docetaxel (Arm D, n=96). Please note that Arm C and D are not licensed combinations, therefore only results for Arm A and B are presented in this premeeting briefing document. In all arms, patients received treatment for 4 cycles (1 cycle = 3 weeks) before surgery. After

surgery, all patients received 3 cycles of adjuvant chemotherapy (Arms A and B received a regimen of 5-fluorouracil, epirubicin and cyclophosphamide ['FEC']). All patients received concomitant trastuzumab every 3 weeks as an adjuvant treatment to complete one year of treatment.

4.3 TRYPHAENA (n=225) was located in 44 centres in 19 countries including Brazil, Canada, Germany, and 3 centres in the UK. It randomised patients to 1 of 3 pertuzumab-containing treatment arms for 6 cycles before surgery (1 cycle = 3 weeks): pertuzumab and trastuzumab for all 6 cycles, with FEC chemotherapy for the first 3 cycles and docetaxel for the last 3 cycles (Arm A, n=73); FEC chemotherapy for the first 3 cycles, then docetaxel chemotherapy for the last 3 cycles, with pertuzumab and trastuzumab also for the last 3 cycles (Arm B, n=75); and pertuzumab, trastuzumab, docetaxel and carboplatin for all 6 cycles (Arm C, n=77). Patients were stratified by breast cancer type (operable, locally advanced, or inflammatory) and oestrogen receptor and/or progesterone-receptor positivity. After surgery, all patients received adjuvant trastuzumab every 3 weeks to complete a total of one year of treatment. Patients received further adjuvant treatment (radiotherapy, chemotherapy, hormonal treatment) according to local guidelines. Intravenous pertuzumab and trastuzumab were administered as described in their respective marketing authorisations.

4.4 The company stated that patient characteristics between treatment arms in both trials were generally well balanced. In both trials, median age was 49-50 years, median weight was 62-67kg, the majority of patients were white (64% to 75% in NeoSphere, 69% to 83% in TRYPHAENA), and disease type was classified as operable (60% to 73% across both trials), locally advanced (21% to 34% across both trials) or inflammatory (5% to 9% across both trials). In both trials the company used the 'intention to treat' populations (all randomised patients, regardless of whether or not they received study medication) for effectiveness outcomes, and the 'safety' populations (patients who received at least one dose of study

medication, and who had at least one safety assessment performed at baseline) for safety outcomes.

4.5 The CLEOPATRA trial was a double-blind, placebo-controlled clinical trial which enrolled 808 people with HER2 positive metastatic breast cancer. Although this was a different population to that specified in the scope, the company used the trial for data on treatment related adverse events. It randomised patients in a 1:1 ratio to 1 of 2 treatment arms: trastuzumab and docetaxel (n=396), or trastuzumab, docetaxel and pertuzumab (n=408). The primary outcome was progression-free survival.

4.6 The company identified registry data from the Cleveland Clinic Registry (Tiwari et al., 2015), which was a retrospective analysis of patients from a single centre in Cleveland in the US. The registry included 71 patients with HER2 positive non-metastatic breast cancer treated with neoadjuvant pertuzumab, trastuzumab, docetaxel, and carboplatin. Individual patient charts were reviewed to collect information about treatment received, cycle interruption, dose reductions and toxicity profile. Median age was 52.5 years, 100% were female, and 88.5% were white.

4.7 The company stated that neo-adjuvant trials for potentially curative treatments, such as the trials for pertuzumab, are not long enough to get robust evidence about survival outcomes. In the NeoSphere and TRYPHAENA trials, the company used pathological complete response to measure the effectiveness of pertuzumab. It therefore presented a meta-analysis done by the CTNeoBC group; established by the US Food and Drug Administration (FDA) to evaluate the relationship between long-term survival outcomes for breast cancer patients (such as disease free survival and overall survival) and 3 definitions of pathological complete response: pathological complete response in the breast (defined as absence of invasive tumour in the breast irrespective of ductal carcinoma in-situ or nodal involvement; total pathological complete response (absence of invasive tumour in breast and lymph nodes irrespective of ductal carcinoma in-situ); and German Breast Group pathological

complete response (absence of invasive cancer and in-situ cancer in the breast and axillary nodes). It included data from 11,955 patients (of whom 1,989 had HER2-positive disease) from 12 randomised neoadjuvant trials. The company used the results of this analysis to inform its economic model.

ERG comments

4.8 The ERG stated it was confident that all relevant controlled trials had been identified, and that NeoSphere and TRYPHAENA were of a reasonable methodological quality. However it was not confident that all relevant non-randomised and non-controlled studies had been identified because details of the systematic review process were lacking in the company submission.

Clinical trial results

Effectiveness evidence

4.9 The primary outcome in NeoSphere was pathological complete response in the breast, evaluated after surgery (please see section 4.7 for the different definitions of pathological complete response). However, after completion of the trial, the FDA and European Medicines Agency (EMA) proposed an alternative, preferred definition of response: total pathological complete response, based on the results of CTNeoBC. This meta-analysis demonstrated greater correlation between survival outcomes and pathological complete response when negative ipsilateral lymph nodes were included in the definition. The company therefore retrospectively collected data for this outcome also. The primary outcome in TRYPHAENA related to cardiac safety and is therefore presented in the section on adverse events, however TRYPHAENA also included pathological complete response as a secondary outcome (table 3).

Table 3: Pathological complete response in NeoSphere and TRYPHAENA

	NeoSphere		TRYPHAENA		
	Arm A (HD)	Arm B (PHD)	Arm A*	Arm B**	Arm C***
Pathological complete response in the breast (bpCR)					
%	29.0%	45.8%	61.6%	57.3%	66.2%
95% CI (%)	20.6; 38.5	36.1; 55.7	49.5; 72.8	45.4; 68.7	54.6; 76.6
Difference %	+16.8% (p=0.0141)		NA	NA	NA
Diff. 95% CI	3.5; 30.1		NA	NA	NA
Total pathological complete response (tpCR)					
%	21.5%	39.3%	56.2%	54.7%	63.6%
95% CI	14.1; 30.5	30.0; 49.2	44.1; 67.8	42.7; 66.2	51.9; 74.3
Difference %	+17.8% (p=0.0063)		NA	NA	NA
95% CI	5.7; 29.9		NA	NA	NA
German Breast Group pathological complete response (GBG pCR)					
%	12.1%	32.7%	50.7%	45.3%	51.9%
95% CI	6.6; 19.9	24.0; 42.5	38.7; 62.6	33.8; 57.3	40.3; 63.5
bpCR and no residual ductal and/or lobular carcinoma in situ at surgery					
%	16.8%	36.4%	NR	NR	NR

*FEC+H+P x3 / D+H+P x3; **FEC x3 / D+H+P x3; ***DCH+P x6

CI: confidence interval; D: docetaxel; DCH: docetaxel, carboplatin, trastuzumab; FEC: 5-flurouracil, epirubicin, and cyclophosphamide; H: trastuzumab; NA: not applicable; NR: not reported; P: pertuzumab.

4.10 Secondary outcomes in NeoSphere included disease-free and progression-free survival. However the company noted that these analyses were not designed or powered to test formal hypotheses and therefore the hazard ratios should be interpreted with caution. Five year progression free survival was 81% (95% confidence interval [CI] 71%–87%) for trastuzumab and docetaxel (Arm A), and 86% (95% CI 77%–91%) for pertuzumab, trastuzumab and docetaxel (Arm B), which generated a hazard ratio (HR) of 0.69 (95% CI 0.34-1.40). Five year disease free survival was 81% (95% CI 72%–88%) in the trastuzumab arm and 84% (95% CI 72%–91%) in the pertuzumab arm, generating a hazard ratio of 0.60 (95% CI 0.28–1.27). The company also analysed progression free survival by total pathological complete response. When combining all treatment arms, a higher progression free survival was

achieved in patients who had achieved total pathological complete response compared with those who did not (HR: 0.54 [95% CI: 0.29–1.00]). The company also presented the proportion of people who had breast conserving surgery instead of a planned mastectomy. The company described this as a "particularly important" secondary outcome, because it expected a high pathological complete response in the trial, leading to smaller tumours and more breast conserving surgery. In NeoSphere, rates were 22.6% and 23.2% in the trastuzumab and pertuzumab arms respectively. In TRYPHAENA, rates across the 3 pertuzumab arms ranged from 16.7% to 27%.

4.11 The company presented the observational data from the Cleveland registry. The pathological complete response rate was 52.8%.

Association of pathological complete response with survival

4.12 In CTNeoBC the authors performed a patient-level responder analysis, and a study level analysis, to investigate the relationship between pathological complete response compared with event free survival and overall survival. In patient level analyses for the HER2-positive subpopulation, patients who had total pathological complete response had improved event free survival (hazard ratio 0.39 (95% CI: 0.31-0.50) and overall survival (hazard ratio 0.34 (95% CI: 0.24-0.47) compared with those who did not. At study level, this relationship was not demonstrated; the R^2 value (coefficient of determination) showed a weak correlation between improvement in pathological complete response with both event free survival (0.03 (95% CI 0.00-0.25)) and overall survival (0.24 (95% CI 0.00-0.70).

Subgroups

4.13 In NeoSphere and TRYPHEANA, pathological complete response in the breast was analysed according to hormone-receptor status (hormone receptor positive and negative) and breast cancer type (operable, locally advanced and inflammatory), using the intention-to-treat population. The company stated that secondary endpoints were calculated and

summarised for descriptive purposes only. Please see company submission section 4.8 for results for subgroup analyses for NeoSphere and TRYPHAENA. The company also presented Cleveland registry data for the hormone-receptor status subgroup, please see table 36 of company submission.

ERG comments

4.14 The ERG stated that there are a number of limitations and uncertainties in the evidence base which warrant caution in its interpretation.

- Blinding: It was not possible to blind NeoSphere and TRYPHAENA, because of the nature of the interventions used (drug toxicity and administration methods), and this increased the risk of performance bias. However, it noted that in the trials most pathologists were not aware of the patient's treatment allocation, and that blinded outcome assessment can help to reduce bias.
- TRYPHAENA included pertuzumab in all arms and therefore could not provide evidence of comparative efficacy with treatments without pertuzumab
- Treatments other than trastuzumab may be used in practice and these are likely to be both less effective and less costly than trastuzumab. This was also demonstrated in market research data provided by the company, showing that 22% of patients in the UK receive non-trastuzumab based interventions, which include anthracycline as monotherapy or in combination with one of docetaxel, paclitaxel, or paclitaxel protein-bound. Also, trastuzumab plus docetaxel (with or without anthracyclines) was used in only 62% of patients eligible for neoadjuvant therapy, and therefore not all patients who received trastuzumab received it in combination with docetaxel.
- The trials were not designed or powered to test formal hypotheses for progression free survival, disease free survival and overall survival, or to determine the predictive role of pathological complete response according to hormone receptor status or breast cancer type. Also,

overall survival was not a protocol-defined secondary efficacy endpoint in the NeoSphere trial, therefore survival status was not systematically reported beyond progressive disease, disease recurrence or withdrawal.

4.15 The ERG stated that the key uncertainties in the evidence base relate to:

- The relationship between pathological complete response and survival outcomes. The CTNeoBC meta-analysis was unable to demonstrate a relationship between the effect of treatment on total pathological complete response, and event free survival and overall survival at the study level. Therefore, the predictive value of pathological complete response for estimating the long-term survival benefit in the target patient population is highly uncertain. The ERG reviewed further trials considering the association of pathological complete response and survival outcomes. It stated there is evidence at the patient level that response is associated with survival. However, the evidence that a positive treatment effect translates into a positive effect on overall survival was not convincing, and further study is needed.
- Lack of high quality randomised controlled and head-to-head trials.
- Generalisability to England. Only a few UK centres were included in the trials. Also, in the UK, 'FEC' is the most common chemotherapy regimen administered with trastuzumab as part of a neoadjuvant breast cancer treatment regimen. However, in the NeoSphere study the FEC component was administered as an adjuvant treatment. A clinical expert advised the ERG that this difference is not expected to impact the results.

Meta-analyses/indirect comparison/MTC

4.16 The company stated it was not possible to do a network meta-analysis, please see company submission section 4.9.

ERG comments

4.17 The ERG accepted that it was not possible to do a network meta-analysis because it was not possible to group chemotherapy treatments. However the ERG was concerned that this meant the evidence base for pertuzumab was limited to those receiving it in combination with trastuzumab and docetaxel, rather than trastuzumab and other chemotherapy agents.

Adverse effects of treatment

4.18 The company presented data on safety outcomes from NeoSphere and TRYPHAENA, and also supplementary data from CLEOPATRA (conducted in a metastatic population) and the Cleveland retrospective analysis of registry data. Across all 3 trials and the registry data, the most common adverse events were alopecia, neutropenia, leucopenia, rash, diarrhoea, nausea and fatigue. Adverse effects leading to treatment discontinuation during the neoadjuvant period of the trials were low (less than 3% and less than 8% in NeoSphere and TRYPHAENA respectively). There were 31 deaths reported in NeoSphere (1 death in neoadjuvant phase caused by fulminant hepatitis, and 30 during post-treatment follow-up); 13 deaths in TRYPHAENA (none in neoadjuvant phase and 13 during the adjuvant phase caused by progression/recurrence); and 1.2% and 1.5% of patients in the pertuzumab and placebo arms respectively had treatment related deaths in CLEOPATRA (caused by febrile neutropenia and/or infection). The company stated that safety data from the NeoSphere and TRYPHAENA trials were consistent with safety data previously observed from CLEOPATRA with no new safety signals identified.

4.19 The primary outcome of TRYPHAENA was cardiac safety (using safety population), measured as incidence of symptomatic cardiac events as assessed by the Investigator (Grade 3, 4 or 5 symptomatic left ventricular systolic dysfunction [LVSD]) and clinically significant decline in left ventricular ejection fraction (LVEF) over the course of the neoadjuvant

period (LVEF decline of ≥10% from baseline and to a value of <50%). NeoSphere also measured cardiac safety. The company noted that rates across arms were generally low (LVSD ranged from 0% to 2.7%, and decline in LVEF ranged from 0% to 12.3% across all relevant arms in both trials and in all time periods), however it stated that cardiac risk should be carefully considered and balanced against the medical need of the individual patient before use of pertuzumab in combination with trastuzumab and anthracyclines, because there are limited safety data available from TRYPHAENA and there are no safety data available concerning use of pertuzumab with doxorubicin. Please see table 15 of ERG report for cardiac outcome data in NeoSphere and TRYPHAENA.

ERG comments

4.20 The ERG stated that overall there did not appear to be any unacceptable additional toxicities or concerning differences in tolerability by adding pertuzumab to trastuzumab in the neoadjuvant setting.

5 Cost-effectiveness evidence

Model structure

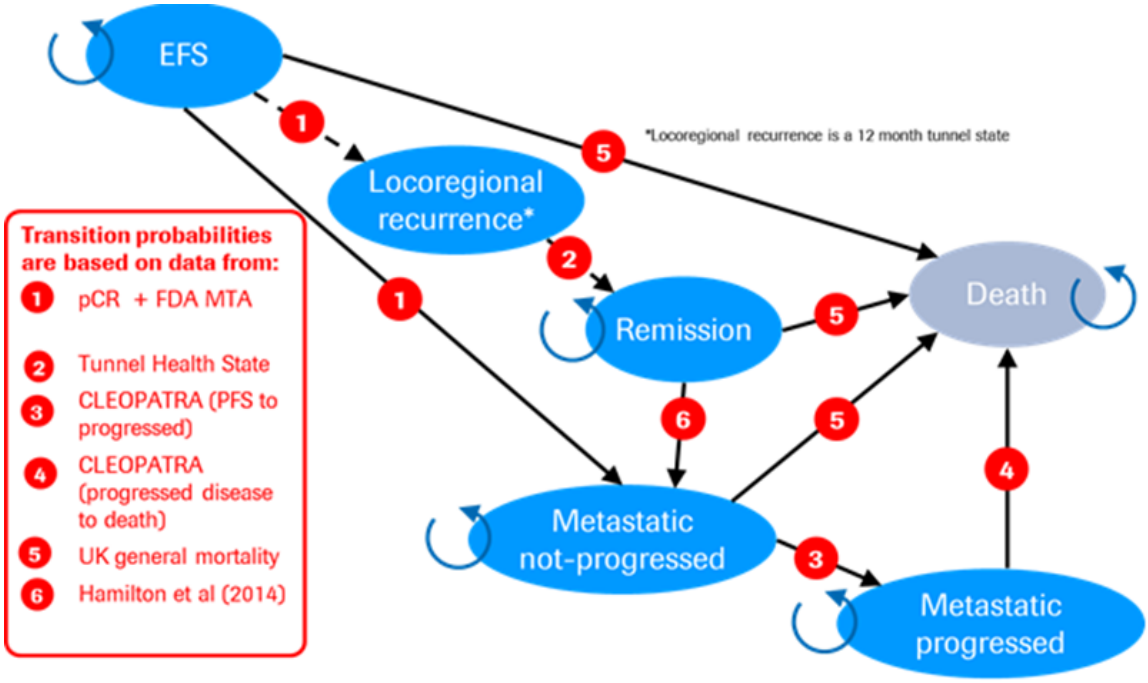
5.1 The company did a new Markov model to compare pertuzumab, trastuzumab and docetaxel, with trastuzumab and docetaxel, for treating adults with HER2-positive, locally advanced, inflammatory, or early stage breast cancer who had not previously received chemotherapy or HER2 directed treatment for their disease. It acknowledged that the chemotherapy regimens people receive are heterogeneous in clinical practice, but stated that the comparator chosen was the best representation of standard of care for this population, and it did not expect that using alternative comparators or changing concomitant chemotherapy to substantially change the ICER. The model included 5 health states plus a 'death' state: 'event free', locoregional recurrence', 'remission', 'metastatic not progressed', and 'metastatic progressed'. Within the locoregional recurrence health state, there were a series of 'tunnel states'

(where patients could only remain for a maximum of 1 cycle). The company stated this allowed patients to remain in the locoregional health state for 12 months whilst receiving further adjuvant treatment. Each health state was associated with costs and utility values. The cycle length was 4 weeks, the time horizon was 50 years (median age was 50; at the end of the time horizon, more than 99% of modelled patients had died), costs and benefits were discounted at 3.5%, and the analysis was done from the perspective of the NHS and personal social services.

5.2 At time zero all patients entered the model in the event free survival (EFS) health state. At the end of each cycle they could either remain within the same health state, or experience a worsening in their condition and transition to another health state. The company stated there were 2 distinct pathways for people who experienced a disease-related event:

- Locoregional recurrence: this led to a further 12 months of treatment with trastuzumab. After completion of treatment, modelled patients were assumed to be in remission and therefore transitioned to the 'remission' health state. If disease returned when in this health state, it was assumed to be metastatic (not-progressed).
- Metastatic event: patients transitioned to 'metastatic not-progressed', where they received first line treatment for metastatic breast cancer, and were at risk of transitioning to the 'metastatic progressed' health state to receive second line treatment for metastatic breast cancer.

Figure 3: Model structure



ERG comments

5.3 The ERG stated that the model was generally well described and justified, with no major errors. However, it noted that cost-effectiveness of pertuzumab, trastuzumab and docetaxel neoadjuvant treatment had only been measured compared with trastuzumab and docetaxel, and this did not include all possible comparators. Clinical experts advised the ERG that although most patients do receive trastuzumab, other treatments are also in use.

5.4 The ERG noted that the clinical data referred to 'disease free survival', whereas the cost effectiveness model used 'event free survival'. The ERG believed that these 2 terms referred to the same outcome.

Model details

Clinical effectiveness

5.5 The company used 2 main sources of data to model the effectiveness of neoadjuvant treatments in the model: NeoSphere (see section 4.2) and

the CTNeoBC meta-analysis (see section 4.7). The company stated that it did not include the TRYPHAENA trial because it was not powered to assess outcomes relevant to the economic case (pathological complete response, disease free survival, progression free survival, and overall survival), and because all arms were exposed to pertuzumab.

5.6 The company used a combination of NeoSphere trial data and the CTNeoBC meta-analysis to predict event free survival in the model. To do this, it first extrapolated event free survival curves from CTNeoBC for those with and without pathological complete response, irrespective of treatment. To estimate event free survival for the intervention and comparator arms, it weighted the extrapolated curves by the rate of pathological complete response or no response from the associated treatment arm in NeoSphere. The CTNeoBC analysis (see section 4.7) demonstrated that event free survival was more closely associated with total pathological complete response (a secondary outcome in the NeoSphere trial) than pathological complete response in the breast (primary outcome in NeoSphere), therefore the company used the former definition of response in its model. Total pathological complete response rates were 39.3% (CI: 30.0%–49.2%) for the intervention arm (based on Arm B of NeoSphere, pertuzumab, trastuzumab and docetaxel), and 21.5% [CI: 14.1%–30.5%] for the comparator arm (based on Arm A of NeoSphere, trastuzumab and docetaxel). Rates of no total pathological complete response were 60.7% in the intervention arm, and 78.5% in the comparator arm (calculated as 100% minus the NeoSphere rate of total pathological complete response). Based on visual inspection and goodness of fit statistics, the company chose the gamma function for extrapolation in the base case, and used other curves in scenario analyses.

5.7 Transition probabilities are described in table 4. The company noted the following:

- It had not included a transition from locoregional recurrence to death because locoregional recurrence was a series of tunnel states, and adding this transition would have been very complex. This exclusion slightly overestimated the number of people who remain in this state, overestimating the costs and QALYs in both modelled arms. However, the company stated that the expected impact of this was small because most mortality transitions were based on the relatively low UK general population mortality.
- After 7 years:
  - People who had not progressed were assumed to be event free, with a mortality rate equal to that of the age-matched general population. The company validated this assumption with clinical experts (who stated that most recurrences from progression free survival happen within 2 or 3 years).
  - The modelled treatment effect in both arms was equal, because the company assumed there was no additional benefit of adding pertuzumab to trastuzumab (the company stated it chose this timeframe because it only required what it considered to be a conservative assumption of treatment effect for 2 years after the NeoSphere follow-up data).
- There was uncertainty in the generalisability of the study by Hamilton et al. (table 4) (used to model the transition from remission to metastatic not progressed) to the model population, because patients in the study received radiation therapy. The company explored this transition probability in sensitivity analyses.

Table 4: Summary of the health state transitions used in the model

Transition	Transition probability	Source
EFS to EFS	Time dependent	NeoSphere and CTNeoBC
EFS to LR	42% of events	NeoSphere
EFS to MET-NP	58% of events	NeoSphere
LR to REM	100%	Assumption (validated by clinical experts)
REM to MET-NP	0.76 % per month	Hamilton 2014 (12,836 patients early breast cancer, estimated increased risk of 2nd malignancy with addition of regional radiation to local radiation).
MET- NP to MET-P	HD: 4.7% PHD: 3.17%	Weighted average (based on UK market share) of these values. Data from CLEOPATRA
MET-P to death	HD: 3.15% PHD: 2.73% Kad: 2.73%	Weighted average (based on UK market share) of these values. Data from CLEOPATRA
To death (other than MET-P and LR)	Age-dependent	UK general mortality (Ara and Brazier 2010). Transition to death from LR (series of tunnel states) not included because of added complexity
Health states: EFS: event free survival; LR: locoregional recurrence; MET (not prog): metastatic not progressed; REM: remission; MET (prog): metastatic progressed. Key: HD: trastuzumab docetaxel; PHD: pertuzumab, trastuzumab docetaxel, Kad: trastuzumab emtansine		

Utility values

5.8 The company stated that no health related quality of life data were available from the trials, and it could not identify any appropriate sources for utility values in a systematic review of the literature in the neoadjuvant setting. It therefore took utility values from 2 sources (but did not explain how these studies were identified). Lidgren et al. (2007) was a Swedish utility study for breast cancer that the company used for event free survival and metastatic not progressed health states. Metastatic progressed utility was derived from Lloyd et al. (2006) using a mixed model analysis (used in several other NICE technology appraisals in this disease area (TA257, TA263, and ID538). The company could not identify appropriate utility values to use for the locoregional or remission health states, therefore it made assumptions to estimate the value. The company also included a natural decline in quality of life for an aging population by assuming that patients could not have a higher utility value than the age-

matched general UK population, with UK general population utility values derived from Ara and Brazier (2010). Utility values are presented in table 5. Baseline quality of life was assumed to be similar in both treatment arms, and the company noted there was a low utility value in the event free survival first year state. It stated that this may be because of the negative effects of the surgery, treatment, the acknowledgement of a potentially fatal disease and the use taxanes.

Table 5: Utility values used in model

State	Utility	Source
Event free (first year)	0.696	Lidgren (2007): n=345 breast cancer, observational study in Sweden (mean age 57). EQ-5D and Time Trade Off
Event free (> first year)	0.779	
Metastatic not-progressed	0.685	
Metastatic progressed	0.452	Lloyd (2006): n=100 metastatic breast cancer. Standard Gamble
Locoregional (>first year)	0.696	Assumed same as event free; patients in remission would be disease free/ off treatment.
Remission	0.779	Assumed same as event free; patients receiving treatment and may experience similar adverse events

5.9 The company did not directly apply disutility values for adverse events to either arm in the neoadjuvant setting. It stated this was because pertuzumab in the neoadjuvant setting has a largely manageable safety profile with few life-threating events; that adverse events were similar in the intervention and comparator arm; and that the duration of treatment is very short (12 weeks). However, it stated that the utility values identified may already capture the disutility of treatment because they are derived from people who had already received treatment.

Costs and resource use

5.10 The model included the cost of treatments, treatment administration, selected adverse events, and supportive care. Resource use in each health state was primarily based on NICE clinical guideline (CG) 80 on early breast cancer.

5.11 Drug costs were based on either the British National Formulary (BNF, 2015) (for proprietary drug costs) or the Commercial Medicines Unit electronic Market Information Tool (CMU eMIT 2014) (for generic drugs). The company noted that for generic drugs, prices differed slightly between vial sizes, therefore it costed the most frequently used vial size. It also noted that for drugs requiring weight-based dosing, costs were based on UK average measures. The company assumed vial sharing of trastuzumab and generic medicines in the base case. If assuming no vial sharing, the company noted minor additional costs for the intervention arm of £41.60 for the initial cycle and £29.28 for subsequent cycles.

5.12 The company assumed there was a cost associated both with the pharmacy preparation and administration of intravenous drugs. The administration cost for each drug was based on NHS references costs 2013/14. Dispensing and preparation of treatments were assumed to take 12 minutes each, based on a prospective time-and-motion study which quantified the time taken to prepare and administer drugs for metastatic colorectal cancer in 2 NHS trusts (Millar et al, 2008). One hour of patient-related pharmacist time was assumed costing £48, taken from the Personal Social Services Research Unit (PSSRU). Therefore, the cost of dispensing of treatments in the economic model was estimated to be £9.60 per administration. In total administration costs for the first and subsequent cycles cost £326.60 and £174.60 respectively, based on chemotherapy delivery costs of £317 and £165 for the first and subsequent cycles respectively, plus £9.60 costs of pharmacy preparation. Table 6 shows treatment and administration costs for adjuvant and neoadjuvant treatment.

Table 6: Costs for neoadjuvant and adjuvant treatment

Items	Per dose	PHD	HD	Source
P (4 cycles neoadjuvant)	**Initial**: £4,790 (2x 420mg) **Cycle 2+**: £2,395 (1 x 420 mg)	£11,975	-	BNF
H (4 cycles neoadjuvant)	**Initial**: £1,588 (3.90 x 150 mg) **Cycle 2+**: £1,191 (2.92 x 150 mg)	£5,161		BNF
D (4 cycles neoadjuvant)	**Initial**: £43.09 (134.25 mg) **Cycle 2+**: £57.28 (179 mg)	£215		eMIT
FEC (3 cycles neoadjuvant)	£40.8	£122.4		eMIT
Administration Cost - 4 cycles neoadjuvant	**Initial**: £326 **Cycle 2+**: £174.60	£850.4		NHS ref. and PSSRU
Mean drug and admin cost neoadjuvant		**£18,324**	**£6,349**	
T (up to 13 cycles adjuvant)		£1,191 per cycle		BNF
Admin cost (up to 13 cycles adjuvant)		£174.6 per cycle		BNF
BNF: British National Formulary; D: docetaxel; eMIT: electronic market information tool; FEC: 5-flurouracil, epirubicin, and cyclophosphamide; H: trastuzumab P: pertuzumab; PSSRU: personal social services research unit				

5.13 Table 7 shows average monthly cost per patient in each health state. The company included post-progression treatment costs for people in the locoregional recurrence, metastatic not progressed and metastatic progressed health states. The company assumed that all patients in locoregional recurrence received trastuzumab and docetaxel, but it only included the cost of trastuzumab, because of the relatively small cost of docetaxel. For the metastatic not progressed state, patients could receive: trastuzumab and docetaxel; pertuzumab, trastuzumab and docetaxel; or trastuzumab and other (hormonal therapy with or without chemotherapy). For the metastatic progressed disease state, patients could receive: trastuzumab and a taxane; pertuzumab, trastuzumab and docetaxel; trastuzumab emtanzine; or capecitabine plus lapatinib. The dosages were assumed to be the same as for the neoadjuvant treatment doses, and

costs were estimated as a weighted average based on their UK market shares.

5.14 The company included supportive care costs to represent the services provided for people with cancer and their carers. These costs were derived from several sources and varied in each health state to reflect differing needs with disease progression. Supportive care included mammograms (with frequency based on CG80), cardiac assessment (based on NHS reference costs and applied every 3 months in both arms, using a weighted average cost of 30% multiple-gated acquisition [MUGA] scan and 70% echocardiogram), outpatient visits, CT scans, cardiac monitoring and health care practitioner time. The company assumed one CT scan (£91 based on NHS reference costs) and outpatient visit (£126 based on NHS reference costs) every three months during treatment.

Table 7: Summary of health state costs

Health states	Items	Average monthly cost per patient
Event Free Survival (Neoadjuvant treatment)	PHD and admin	**Initial cycle**: £6,748 **Cycle 2-4:** £3,818
	HD and admin	**Initial cycle**: £1,958 **Cycle 2-4:** £1,423
	SC* year 1+2	£67.85
	SC* year 3-5	£15.11
	SC* year 6 onwards	£3.83
Event Free Survival (Adjuvant treatment)	H, FEC and admin	**Cycle 5-7**: £1,407
	H and admin	**Cycle 8+:** £1,366
	SC* year 1+2	£67.85
	SC* year 3-5	£15.11
	SC* year 6 onwards	£3.83
Locoregional recurrence	Treatment (trastuzumab)	£1,365.60
	SC**	£75.53
Remission	SC**	£67.85
Metastatic not progressed	Treatment	£3,590.26
	SC***	£232.80
	Total	£3,823.06
Metastatic progressed	Treatment	£5,738
	SC***	£185.20
	Total	£5,923.20

*Includes GP visits (£46, 12-minute appointment), oncology specialist visits (£124), mammograms (£11.34) and cardiac monitoring (£65 ECHO/£234 MUGA).

**EFS supportive care plus CT scan (£91).

***Includes GP visits, oncology specialist visits, specialist nurse (£90), community nurse (£24.60, 20 min appointment), CT scans and cardiac monitoring.

FEC 5-fluorouracil, epirubicin, cyclophosphamide; D, docetaxel; H: trastuzumab; P: pertuzumab; SC: supportive care

5.15 The company only included adverse events occurring in more than 5% of cases or more in either arm of NeoSphere trial at grade 3, 4 or 5 severity. It stated that because 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. Adverse event costs were as follows: diarrhoea: £476; febrile neutropenia (grade 3 and 4): £8,662; leucopenia (grade 3): £155; and neutropenia (grade 3 and 4): £155. The company

noted that alopecia was not included in the model, because its cost was assumed to be incurred by the patient only. It also did not include adverse event costs for all progressive health states (loco-regional, metastatic not progressed and metastatic progressed), which it stated was a conservative assumption that underestimated the comparator arm costs and artificially increased the ICER.

ERG comments

5.16 The ERG considered the effectiveness assumptions in the model. It stated it had concerns about:

- The use of pathological complete response as a predictor of event free survival in the model, because it did not appear to be a good predictor in the NeoSphere trial. When comparing modelled and trial event free survival data in NeoSphere, modelled results substantially over predicted survival in both arms. The ERG stated that this led to uncertainty in the modelled results.
- The patient population used when extrapolating CTNeoBC event free survival data. The company had used all patients from CTNeoBC, rather than the HER2-positive subgroup. However the company did provide an updated base case analysis with this amended (see section 5.25).
- The applicability of the study by Hamilton et al. (2014, table 4) used to derive transition from remission to metastatic not progressed, because: all patients were treated with adjuvant chest wall radiation, it was located in 1 centre in Canada, and there were issues with heterogeneity within the study (it included female patients with stage I or II breast cancer, with HER2-positive, negative or unknown status, aged between 20 to 79 years, and diagnosed between 1989 and 2005).
- The assumption that patients who had not experienced locoregional or metastatic recurrence 7 years after treatment were cured, with a risk of mortality equal to the general population. The ERG stated that the reason for this cut off point was unclear, and clinical experts advised

the ERG that although this assumption may be reasonable for the hormone-receptor negative group, the hormone-receptor positive group are likely to continue to experience events and have a greater risk of mortality after 7 years than the general population.

5.17 The ERG noted the following issues about resource use in the model, which led to the ERG exploring these assumptions, either in sensitivity analyses, or by using different assumptions when deriving its own base case:

- The company base case assumed that all patients received intravenous trastuzumab. However, trastuzumab also has a license to be administered subcutaneously (although the pertuzumab license requires that it is used in combination with intravenous trastuzumab).
- In 'locoregional recurrence', patients received trastuzumab and docetaxel. However, clinical experts advised the ERG that there is limited data to support this assumption, and where possible locoregional recurrence is managed by surgery in clinical practice.
- In the metastatic health states, patients accrue treatment costs based on a weighted average of the cost of treatments used in clinical practice. However:
  - For 'metastatic not progressed', clinical experts advised the ERG that docetaxel, or other chemotherapies given in combination with trastuzumab or pertuzumab and trastuzumab, are likely to be discontinued after 6 cycles.
  - For 'metastatic progressed', treatments used in the calculation of costs included pertuzumab, trastuzumab and docetaxel. However, this is currently only approved by the Cancer Drugs Fund for people who have not previously received anti-HER2 treatment or chemotherapy.

5.18 The ERG reviewed the utility values used in the model. Clinical advisors to the ERG stated that pertuzumab would not impact health related quality of life substantially more than that associated with the chemotherapies

used within both arms. However, to explore the impact of any minor additional adverse events associated with trastuzumab and pertuzumab, the ERG did a sensitivity analyses reducing the quality of life within the first year of the event-free state. It also noted that it was not clear how the company had identified the 2 main sources of utility values used, and it also identified issues with these sources. It stated that Lidgren et al. appeared to have a heterogeneous population, with a wide age range (28 to 93 years old), with patients not split by HER2 status. Lloyd et al. included variables such as age, treatment response, disease progression and febrile neutropenia. However the company's calculations did not account for age or febrile neutropenia within the model. Because of these uncertainties the ERG undertook a sensitivity analysis around these utility values based upon a study by Essers et al. (2010, see section 5.30).

Company's base-case results and sensitivity analysis

Original base case

5.19 The company presented the results of its analyses. It first presented the results of its original base case. Following 2 issues identified by the ERG, the company provided 2 further sets of base case analyses, hereafter referred to as base case A and base case B. The original base case ICER was £17,297 per QALY gained.

Table 8: Company deterministic base case results (original base case)

	Total costs	Total QALYs	Inc. costs (£)	Inc QALYs	ICER
PHD	104,575	11.499	4,557	0.263	£17,297
HD	100,018	11.236			

HD: trastuzumab and docetaxel; ICER: incremental costs effectiveness ratio; Incr: incremental; PHD: pertuzumab, trastuzumab and docetaxel; LYG: life years gained; QALYs: Quality adjusted life years.

5.20 The company conducted probabilistic sensitivity analyses using 1,000 iterations, assigning probability distributions to various parameters including parametric distributions, utility values, and various resource costs (see table 101 company submission). In probabilistic analyses,

pertuzumab had a 64.1% chance of being cost-effective when assuming an ICER of £30,000 per QALY gained, and the probabilistic base-case ICER was £20,104.

5.21 The company did deterministic sensitivity analyses, changing the base case assumptions for parameters including parametric distributions (using Weibull, exponential, log-normal, log-logistic instead of gamma as assumed in the base case), utility values (increasing and decreasing values by 20% from base case), and various resource costs (including increasing and decreasing various costs by up to 40%). Most ICERs were below £20,000 per QALY gained, and the only scenarios that raised the ICER above £30,000 per QALY gained was the use of alternative value for the rate of pathological complete response: decreasing the rate of response of pertuzumab to 30% increased the ICER to £67,157 per QALY gained, and increasing the rate of response of trastuzumab to 30.5% resulted in an ICER of £64,416. For full results, please see table 103 of the company submission.

5.22 Although trastuzumab has a license to be administered both intravenously and subcutaneously, the company base case assumed all patients received intravenous trastuzumab (note: pertuzumab only has a license in combination with intravenous trastuzumab). It therefore presented a scenario analysis where 100% of patients in the comparator arm received subcutaneous rather than intravenous neoadjuvant trastuzumab (it stated that not all patients receive subcutaneous trastuzumab in clinical practice, therefore 100% was an overestimate). This did not affect the price of neoadjuvant treatment in the intervention arm because the license for pertuzumab only allows its use in combination with intravenous trastuzumab. This assumption increased the ICER to [redacted] per QALY gained, because it reduced the costs of neoadjuvant trastuzumab treatment in the comparator arm (the company for trastuzumab have a commercial agreement allowing it to be sold at reduced price of [redacted] per cycle, plus the company assumed 60% lower administration costs for the subcutaneous formulation).

Base case A

5.23 The ERG stated that the standard practice for the administration of trastuzumab was subcutaneous administration. The company therefore provided updated results using market research data to more accurately quantify the proportion of people receiving subcutaneous administration of trastuzumab than the 100% it had assumed in its scenario analysis for the original base case (see section 5.19). Its market research data showed that [redacted] of trastuzumab was administered intravenously and [redacted] subcutaneously, and it therefore included this assumption in its model.

Table 9: Company base case A

	Total costs	Total QALY	Incr costs	Incr QALY	ICER
PHD	£104,575	11.5	£5,253	0.26	£19,939
HD	£99,322	11.24	-	-	-

HD: trastuzumab and docetaxel; ICER: incremental costs effectiveness ratio; Incr: incremental; PHD: pertuzumab, trastuzumab and docetaxel; LYG: life years gained; QALYs: Quality adjusted life years.

5.24 The company provided sensitivity analyses based on its updated base case. Probabilistic sensitivity analyses using 1,000 iterations showed that pertuzumab, trastuzumab and docetaxel had a 62.1% chance of being cost-effective when assuming an ICER of £30,000 per QALY gained. The company also presented a probabilistic base case ICER of £21,869 per QALY gained. In deterministic sensitivity analyses varying the same assumptions used in the original base case (see section 5.21), the only analyses to increase the ICER above £30,000 per QALY gained were, as in the original base case, pathological complete response rates, which increased the ICER to approximately £70,000 per QALY gained when increasing and decreasing the comparator and intervention arm response rates respectively. The ERG also requested that the company present an additional analysis using event free survival data directly from NeoSphere, because of the uncertainty associated with using pathological complete response as a surrogate outcome in the model. The company fitted parametric curves to 5 year event free survival data from NeoSphere,

using a piecewise approach because no single curve fitted all of the data adequately. In this analysis, pertuzumab dominated trastuzumab (table 10). The company stated that these results should be considered with caution because immature event free survival data was used.

Table 10: Scenario analysis company base case A

	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
PHD	71,145	12.65			
HD	71,432	12.21	-287	0.43	-660
HD: trastuzumab and docetaxel; ICER: incremental costs effectiveness ratio; Incr: incremental; PHD: pertuzumab, trastuzumab and docetaxel; LYG: life years gained; QALYs: Quality adjusted life years.					

Base case B

5.25 The ERG identified that when using CTNeoBC to calculate the curve to extrapolate NeoSphere data (see section 5.6), the company had in error used data from the whole population, rather than the HER2-positive subpopulation. The company therefore redid the extrapolation explained in section 5.6 but using the HER2-positive population only. When using these results in its cost effectiveness analyses, this reduced its base case ICER (table 11).

Table 11: Company base case B

	Total costs (GBP)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
PHD	125,160	10.79	2,859	0.35	8,215
HD	122,301	10.44			
HD: trastuzumab and docetaxel; ICER: incremental costs effectiveness ratio; Incr: incremental; PHD: pertuzumab, trastuzumab and docetaxel; LYG: life years gained; QALYs: Quality adjusted life years.					

5.26 The company conducted probabilistic sensitivity analyses, showing that pertuzumab had an 82.9% chance of being cost-effective using ICERs of £30,000 per QALY gained. The probabilistic ICER was £9,047 per QALY

gained. It did not present any other sensitivity or scenario analyses for this base case.

ERG comments

5.27 The ERG noted that there were uncertainties in all of the company base case results. It had concerns about the use of pathological complete response to predict event free survival in the model, because response was a poor predictor of event free survival in the NeoSphere trial. It stated that the distribution parameters used in the probabilistic sensitivity analyses were neither presented nor justified. In addition, it noted that some uncertain model parameters were not explored with probability distributions, and where included, the values used to explore uncertainty for some model parameters appeared arbitrary. Overall, it stated that it preferred company base cases that did not assume 100% intravenous trastuzumab in the comparator arm, because this was not representative of current practice in England.

ERG exploratory analyses

5.28 The ERG did its own base case analysis, beginning with company base case B but changing several company base case assumptions. As done in company base case B, the ERG extrapolated CTNeoBC using the HER2-positive subpopulation (using lognormal curve), and assumed patients were at decreasing risk of recurrence over the lifetime of the model, rather than assuming a zero risk after 7 years as assumed in all company base cases. This increased the deterministic ICER to £23,467 per QALY gained for pertuzumab, trastuzumab and docetaxel compared with trastuzumab and docetaxel, which is similar to the probabilistic ICER of £23,264 per QALY gained. The ERG noted that individually the change in assumptions had a substantial impact, but because they changed the ICER in opposite directions, overall its base case was not substantially different to the company base case.

5.29 The ERG repeated the univariate sensitivity analysis done by the company but using the ERG base case. It noted most analyses did not

have a significant effect on the ICER. The only analyses that increased the ICER to over £30,000 per QALY gained were: using alternative parametric distributions for event free survival (increased the ICER to as much as £50,462 per QALY gained), decreasing and increasing the pathological complete response rates of pertuzumab and trastuzumab respectively (up to £76,515 per QALY gained), and assuming treatment effect in intervention and comparator arms was equal after 5 years rather than 7 years (£32,241 per QALY gained). For parametric distributions, the ERG noted that the various alternative curves used were less likely to be clinically appropriate than the lognormal distribution used in the ERG base case.

5.30 The ERG also did further sensitivity analyses based on key areas of uncertainty identified in the company model. These were:

- Number of cycles of pertuzumab: presented scenarios where pertuzumab was given for 3 cycles and for 6 cycles, based on the minimum and maximum number of cycles recommended in the marketing authorisation. The ERG did this in 3 different ways: changing the dosage only; changing the dosage and pathological complete response rates of the pertuzumab arm; and changing the dosage of pertuzumab and the pathological complete response rates of both arms.
- Alternative utility value: Used Essers et al. (2010), which reported utility values for HER2-positive breast cancer patients and was applicable to the UK setting
- Included disutility during treatment because of adverse events for pertuzumab and trastuzumab. It assumed the disutility was the same as chemotherapy because a lack of data for this value, estimated by the difference in utility between event free survival in first and subsequent years (-0.083). It also did another analysis halving this value.

- Used alternative metastatic treatment costs, using the least and most costly available treatments (rather than weighted costs based on market share)
- Varied the costs of locoregional recurrence. It included the costs of docetaxel in one analysis, and in another analysis only included a one-off cost of excision, because clinical experts advised the ERG local recurrence is managed by surgery where possible.
- Used event free survival data directly from NeoSphere.

Table 12: ERG scenario analysis utility values (derived from Essers et al. 2010)

	Company base case	Essers
EFS (first year)	0.696	0.749
EFS (subsequent years)	0.779	0.847
Locoregional recurrence	0.696	0.81
Remission	0.779	0.847
Metastatic not-progressed	0.685	0.484
Metastatic progressed	0.452	0.484

5.31 The only analyses that increased the ICER to over £30,000 per QALY gained were: decreasing the costs of the metastatic progressed health state (£33,755 per QALY gained), increasing the number of cycles of pertuzumab to 6 cycles (£43,203 per QALY gained), and including a quality of life decrement for adverse events in the first year of event free survival for pertuzumab only (£33,996 per QALY gained). Pertuzumab was dominant when using 3 cycles.

Innovation

5.32 Justifications for considering pertuzumab to be innovative:

- The company stated that based on trial data, similar pathological complete response rates were achieved with fewer cycles when using pertuzumab with trastuzumab, than with trastuzumab without pertuzumab. It also stated that pertuzumab is associated with more

breast conserving surgery, which is a substantial benefit that would unlikely be captured by the QALY.

- The company stated there would be wider societal benefits of pertuzumab because it is expected to extend long term survival. The median age of women in NeoSphere was 50, and within this age group it is more likely that premature death would have a substantial emotional and financial impact, including in terms of providing care to children and family members. Again the benefit of reducing these impacts would not be captured by the QALY.
- The patient organisation stated that it considered the treatment to be innovative, because it has an increased chance of completely eradicating the tumour, and this would be very beneficial for patients who could avoid surgery altogether. It was also stated that the side effects are much less severe than those associated with chemotherapy.

6 Equality issues

6.1 No equalities issues have been identified.

7 Authors

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with input from the Lead Team (David Thomson, Justin Daniels and Stephen Sharp).

Appendix A: Clinical efficacy section of the draft European public assessment report

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002547/WC500140980.pdf

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of pertuzumab within its marketing authorisation for the neoadjuvant treatment of human epidermal growth factor receptor 2 (HER2) positive breast cancer.

Background

Breast cancer is described as 'early' if it is restricted to the breast, or the breast and nearby lymph nodes, and has not spread to other parts of the body (clinical stages 1 and 2). It is described as 'locally advanced' if the cancer is in a large part of the breast (more than 5 cm) but has not spread to other parts of the body (clinical stage 3), and described as 'advanced' if it has spread to other parts of the body and cannot be completely removed by surgery (clinical stage 4).

Inflammatory breast cancer is a rare but aggressive type of breast cancer in which cancer cells grow along, and block the lymph nodes in the skin of the breast causing it to become inflamed and swollen. Inflammatory breast cancer affects the breast differently and usually the whole breast and the overlying skin are affected (clinical stage 3 or 4).

Human epidermal growth factor receptor 2 (HER2) is a receptor for a growth factor which occurs naturally in the body. When human epidermal growth factor attaches itself to HER2 receptors on breast cancer cells, it can stimulate the cells to divide and grow. Some breast cancer cells have more HER2 receptors than others. In this case, the tumour is described as being HER2-positive.

In 2011 in England, there were approximately 42,000 diagnoses of breast cancer with an estimated 10,000 deaths[1]. It is estimated that approximately 15-25% of women with breast cancer will have HER2-positive tumours. Men are less likely to have HER-2 positive breast cancers[2].

NICE clinical guideline 80 recommends that early breast cancer can be treated with surgery (to remove the tumour) followed by chemotherapy (adjuvant) to reduce the risk of the cancer coming back (recurrence).

Locally advanced and inflammatory breast cancers are considered to have a high-risk of recurrence. In early stage breast cancer, risk assessment for recurrence depends upon, tumour size, grade, hormone receptor status and

lymph node involvement. NICE clinical guideline 80 also recommends that systemic therapy could be offered before surgery (neoadjuvant) to people with early invasive, locally advanced, or inflammatory breast cancer who are considering breast conserving surgery that is not advisable at presentation. The commonly used neoadjuvant therapy for HER-2 positive breast cancer includes fluorouracil epirubicin and cyclophosphamide followed by docetaxel plus trastuzumab. For people who cannot have an anthracycline (epirubicin) the neoadjuvant therapy comprises trastuzumab, docetaxel and carboplatin.

The technology

Pertuzumab (Perjeta, Roche Products) is a recombinant monoclonal antibody which targets HER2-positive breast tumours. It interrupts the activation of the HER2 intracellular signalling pathway, leading to cell growth arrest and apoptosis. Pertuzumab is administered by intravenous infusion.

Pertuzumab has a marketing authorisation in the UK 'in combination with trastuzumab and chemotherapy for the neoadjuvant treatment of adult patients with HER-2 positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence'.

Intervention(s)	Neoadjuvant pertuzumab in combination with trastuzumab and chemotherapy.
Population(s)	Adults with HER2-positive breast cancer which is either; • locally advanced, or • inflammatory, or • early stage (at a high-risk of recurrence).
Comparators	Standard neoadjuvant therapy without pertuzumab for HER-2 positive breast cancer.
Outcomes	The outcome measures to be considered include: • overall survival • disease free survival • surgical outcomes • pathological complete response • adverse effects of treatment • health-related quality of life

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.
Other considerations	If the evidence allows the subgroups indicated in the 'population' section will be considered separately. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	Related Guidelines: 'Breast cancer (early & locally advanced): diagnosis and treatment' (2009) NICE guideline 80. Review date: June 2015. Related Quality Standards: 'Breast cancer quality standard' (2011) NICE quality standard 12. Related NICE Pathways: Early and locally advanced breast cancer (2015) NICE pathway: http://pathways.nice.org.uk/pathways/early-and-locally-advanced-breast-cancer
Related National Policy	Cancer Drugs Fund, NHS England. Updated March 2015. http://www.england.nhs.uk/wp-content/uploads/2015/03/ncdf-list-mar-15.pdf Department of Health, NHS Outcomes Framework 2014-2015, Nov 2013. Domains 1-5. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/256456/NHS_outcomes.pdf

References

1. Cancer Research UK (2011). Breast cancer incidence statistics. Accessed November 2015.

2. Macmillan. Information and support: HER-2 positive breast cancer. Accessed November 2015.

Appendix C

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer [ID767]

Matrix of consultees and commentators

Consultees	Commentators (no right to submit or appeal)
Company • Roche (Pertuzumab) Patient/carer groups • Black Health Agency • Breast Cancer Care • Breast Cancer UK • Cancer Black Care • Breast Cancer Now • Cancer Equality • HAWC • Helen Rollason Cancer Charity • Independent Cancer Patients Voice • Macmillan Cancer Support • Maggie's Centres • Marie Curie Cancer Care • Muslim Council of Britain • South Asian Health Foundation • Specialised Healthcare Alliance • Tenovus Cancer Care • Women's Health Concern Professional groups • Association of Anaesthetists • Association of Breast Surgery • Association of Cancer Physicians • Association of Surgeons of Great Britain & Ireland • British Association of Surgical Oncology • British Geriatrics Society • British Institute of Radiology • British Psychosocial Oncology Society	General • Allied Health Professionals Federation • Board of Community Health Councils in Wales • British National Formulary • Care Quality Commission • Department of Health, Social Services and Public Safety for Northern Ireland • Healthcare Improvement Scotland • Medicines and Healthcare products Regulatory Agency • National Association for Primary Care • National Pharmacy Association • NHS Alliance • NHS Commercial Medicines Unit • NHS Confederation • Scottish Medicines Consortium Comparator companies • None Relevant research groups • Against Breast Cancer • Breast Cancer Hope • Breast Cancer Research Trust • Cochrane Breast Cancer Group • Institute of Cancer Research • MRC Clinical Trials Unit • National Cancer Research Institute • National Cancer Research Network • National Institute for Health Research • Pro-Cancer Research Fund

Consultees	**Commentators (no right to submit or appeal)**
• Cancer Research UK • Royal College of Anaesthetists • Royal College of General Practitioners • Royal College of Nursing • Royal College of Pathologists • Royal College of Physicians • Royal College of Radiologists • Royal College of Surgeons • Royal Pharmaceutical Society • Royal Society of Medicine • Society and College of Radiographers • UK Clinical Pharmacy Association • UK Health Forum • UK Oncology Nursing Society <u>Others</u> • Department of Health • NHS England • NHS Hillingdon CCG • NHS Rushcliffe CCG • Welsh Government	<u>Associated Public Health Groups</u> • Public Health England • Public Health Wales

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and those who do not. Please let us know if we have missed any important organisations from the lists in the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

PTO FOR DEFINITIONS OF CONSULTEES AND COMMENTATORS

Definitions:

<u>Consultees</u>

National Institute for Health and Care Excellence
Matrix for the technology appraisal of pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer [ID767]

Organisations that accept an invitation to participate in the appraisal; the company that markets the technology; national professional organisations; national patient organisations; the Department of Health and the Welsh Government and relevant NHS organisations in England.

The company that markets the technology is invited to make an evidence submission, respond to consultations, nominate clinical specialists and has the right to appeal against the Final Appraisal Determination (FAD).

All non-company consultees are invited to submit a statement[1], respond to consultations, nominate clinical specialists or patient experts and have the right to appeal against the Final Appraisal Determination (FAD).

Commentators

Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement, are able to respond to consultations and they receive the FAD for information only, without right of appeal. These organisations are: companies that market comparator technologies; Healthcare Improvement Scotland; other related research groups where appropriate (for example, the Medical Research Council [MRC], National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Alliance and NHS Commercial Medicines Unit, and the *British National Formulary*.

All non-company commentators are invited to nominate clinical specialists or patient experts.

[1]Non-company consultees are invited to submit statements relevant to the group they are representing.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Neoadjuvant Perjeta▼ (pertuzumab) for the treatment of HER2-positive early breast cancer

Company evidence submission

Roche Products Limited

14th January 2016

File name	Version	Contains confidential information	Date
		Yes/no	14th Jan 2016

Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Please note that the information requirements for submissions are summarised in this template; full details of the requirements for pharmaceuticals and devices are in the user guide.

This submission must not be longer than 250 pages, excluding appendices and the pages covered by this template.

Companies making evidence submissions to NICE should also refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

Contents

Tables and figures

1. Executive summary

1.1 Introduction

Perjeta Neoadjuvant for early breast cancer patients

One in eight women in the UK will have to cope with a diagnosis of breast cancer (BC) during their lives, with diagnosis most common in women aged between 50-70 years (National Cancer intelligence). The incidence in the UK is the 6th highest in Europe while mortality rates in the UK are the 14th highest in Europe, with more than 50,000 women in the UK receiving a breast cancer diagnosis every year, of these approximately 11,000 women still die annually from this disease [Cancer Research UK].

It is estimated that 30% of women with early disease will eventually develop recurrent advanced BC or metastatic breast cancer (mBC), which is currently considered to be incurable [Gonzalez-Angulo, 2007]. .

Approximately 15% of women diagnosed with BC have HER2-positive disease (Ibrahim 2011; SEER 2011), which is associated with significantly worse prognosis [Wolf 2007; Fiszman 2011; Ross 2009]. Women with early HER2-positive disease have higher risk of disease recurrence than those with HER2-negative disease [Romond 2005; Smith 2007].

Effective treatment in the neoadjuvant setting provides the possibility of long term survival and potential cure. Neoadjuvant systemic chemotherapy has become a standard treatment option for early breast cancer (eBC) patients to shrink high risk tumours and render them operable and can increase the opportunity for breast conservation surgery (BCS) instead of mastectomy [FDA 2014; Cortazar 2014; EMA 2014; Gelber 2013].

The rate of breast conserving surgery was evaluated as a secondary endpoint in the Perjeta neoadjuvant studies. This was a particularly important endpoint as we expect a high proportion of patients treated with an effective neoadjuvant treatment to achieve a pathologic complete response (pCR), and have smaller tumours thus facilitating breast conserving surgery. Results from the National Surgical Adjuvant

Breast Project (NSABP) B-18 showed that breast conservation rates were higher in patients who received pre-operative therapy than those who had not (67.8% vs. 59.8%) [Wolmark 2001; Cortazar 2015; Fisher 1998].

Due to the potential curative nature of neoadjuvant treatment, trials are often not designed with durations which allow end points such as progression free survival (PFS) or event free survival (EFS) to reach median values. This is the case in the Perjeta neoadjuvant phase II study, NeoSphere, where at 5 years 80% of patients remained progression free. Pathological complete response (pCR) is increasingly becoming an efficacy endpoint commonly evaluated in neoadjuvant trials. Consequently pCR has been proposed as a surrogate for long-term outcome to expedite research and accelerate the assessment of new drugs.

pCR is associated with improved long-term outcomes, event free survival (EFS), and overall survival (OS), particularly in some tumour types including HER2-positive BC [Cortazar 2014; Wolmark 2001]. This association was accepted as a valid endpoint in granting marketing authorisation of Perjeta in the neoadjuvant setting by both the FDA and EMA (FDA 2014; EMA 2014).

There are three pCR sub categories: bpCR, tpCR,GBG pCR (see Table 1) The preferred FDA and EMA definition is tpCR [FDA 2014; EMA 2014]. Throughout the document pCR is used to cover the overarching concept, where a specific sub type is used it is mentioned specifically.

Table 1 Definitions of pathological complete response

Abbreviation	Definition
pCR	pathological complete response
bpCR	pathological complete response in the breast, defined as absence of invasive tumour in the breast irrespective of ductal carcinoma in-situ or nodal involvement (ypT0/is)
tpCR	total pathological complete response, defined as absence of invasive tumour in breast and lymph nodes irrespective of ductal carcinoma in-situ (ypT0/is ypN0)
GBG pCR	defined as absence of invasive cancer and in-situ cancer in the breast and axillary nodes (ypT0 ypN0)

Perjeta in Neoadjuvant breast cancer

Marketing authorisation

In July 2015 Perjeta received marketing authorisation from the EMA for use in combination with trastuzumab and chemotherapy for the neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence. This is in addition to the existing 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.

Place in the treatment pathway

Figure 1 Perjeta place in treatment pathway

NICE Clinical Guideline 80 (CG80) states that Neoadjuvant treatment can be offered to patients with eBC who are considering breast conserving surgery that is not advisable at presentation. Currently more than 75% of neoadjuvant treatment regimens contain Herceptin [Roche data on File RXUKPERT00220(1)].

Following NICE approval of Perjeta in combination with Herceptin and chemotherapy, it is anticipated that this regimen will be used as a first line neoadjuvant treatment for HER2-positive breast cancer as per marketing authorisation.

Unmet need

Despite the clinical benefits of Herceptin in this setting, there remains a large and urgent unmet need amongst patients with HER2-positive eBC. Five-year relapse rates, including distant recurrences, range up to 42% [Gianni 2014] and studies have shown that disease recurrence negatively impacts quality of life in patients with eBC.

An effective neoadjuvant treatment which provides women with an option to choose breast conservation instead of mastectomy could negate the emotional and physical impact experienced by women who undergo a mastectomy. Although not factored into this economic analysis it is hypothesised that BCS can provide an improved quality of life versus mastectomy [Curren 1998].

A positive recommendation by NICE for Perjeta as neoadjuvant therapy in early HER2-positive breast cancer would allow over 1400 patients per annum (see Table 5) with this form of hard-to-treat, aggressive cancer to benefit from an effective dual HER2 blockade therapy early in their treatment pathway. These woman are mothers, wives, sisters, aunties, daughters and friends, many have people that are

dependant upon them. The chance of stopping or delaying disease progression and achieving a cancer-free life expectancy is critically important.

1.2 Summary of the clinical effectiveness analysis

Include the studies and any meta-analyses or indirect comparisons that provide evidence of the clinical effectiveness and adverse reactions, a summary of the results and strengths and limitations of the evidence.

The addition of Perjeta to Herceptin and chemotherapy in the neoadjuvant treatment of HER2-positive, locally advanced, inflammatory, or early stage breast cancer has been studied in two key multicentre, international phase II open-label trials (NeoSphere [Gianni 2012] and TRYPHAENA [Schneeweiss 2013]). These studies had total enrollment of 417 and 225 patients, respectively. Both studies assessed pCR as the main efficacy outcome, although neither were powered to assess long-term outcomes such as disease-free survival (DFS) or overall survival (OS).

An international working group known as the Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC) group was established by the FDA to evaluate the relationship between definitions of pCR and long-term outcomes in breast cancer patients (e.g. DFS and OS). The group conducted a meta-analysis, which used primary source data from nearly 12,000 patients enrolled in published randomised neoadjuvant trials. The analysis at patient level found that patients who attained tpCR, defined as the absence of invasive cancer in the breast and axillary nodes, irrespective of ductal carcinoma *in situ* (DCIS), have improved survival compared to patients who did not achieve pCR. Tumour eradication from the breast alone was also associated with improved long-term outcomes, although to a lesser extent than eradication from both the breast and lymph nodes. The prognostic value of these responses is greatest in aggressive tumour subtypes, including HER2-positive breast cancer [Cortazar 2014]. Both the EMA and FDA therefore consider tpCR as an acceptable efficacy endpoint in neoadjuvant studies, which can help to expedite the approval of neoadjuvant systemic treatment for high-risk, early breast cancer patients [EMA 2014; FDA 2014].

In the NeoSphere study, rate of bpCR (primary endpoint) was significantly increased when Perjeta was added to a neoadjuvant regimen of Herceptin plus docetaxel

(45.8% [95% CI, 36.1–55.7] vs. 29.0% [20.6–38.5]; p=0.0141). These data, together with an associated increase in tpCR with the addition of Perjeta (39.3% [30.0–49.2] vs. 21.5% [14.1–30.5]), support the clinical benefit of dual HER2 blockade in the neoadjuvant treatment of HER2-positive early breast cancer [Gianni 2012]. Although not powered to assess long-term outcomes or subgroups, descriptive analyses after 5 years of follow-up were consistent with the primary analysis and, overall, patients who achieved tpCR had a reduced risk of a PFS or DFS event over 5 years of follow-up [Gianni 2015]. Additionally, 5-year PFS was improved in patients with a tpCR regardless of hormone receptor status [Gianni 2015]. The most common adverse events (AEs) of grade 3 or higher were neutropenia, febrile neutropenia and leucopenia, and the number of serious adverse events (SAEs) was similar across all arms that received chemotherapy. Cardiac feasibility was acceptable, with only one event of serious cardiac toxic effect (congestive heart failure in a woman with coronary stents and who was being treated for pre-existing cardiovascular disease) [Gianni 2012]. There was no change in the known safety profile with long-term follow-up over 5 years [Gianni 2015].

The primary aim of the TRYPHAENA study was to assess the tolerability of neoadjuvant treatment with Perjeta and Herceptin plus chemotherapy, with a focus on cardiac safety as the primary endpoint of the study. The study found that this treatment combination resulted in low rates (0.0-2.7%) of symptomatic left ventricular systolic dysfunction (LVSD), which were similar to rates observed in previous Perjeta studies. All treatment combinations were highly active – after 6 cycles of neoadjuvant treatment, pCR in the breast (57.3%–66.2%) and tpCR (45.3%–51.7%) rates were similar across the three treatment regimens, all of which contained Perjeta and Herceptin. Across the three treatment arms, 16.7%–27.0% of women with T2-3 tumours who had mastectomy planned were able to undergo breast conserving surgery (BCS) instead of mastectomy. Thus, TRYPHAENA found Perjeta and Herceptin plus chemotherapy to have an acceptable safety profile [Schneeweiss 2013], and supported the clinical efficacy of achieving pCR found in the NeoSphere study [Gianni 2012].

There is additional evidence to support the activity of dual HER2 blockade in early breast cancer as a neoadjuvant regimen from further studies (GeparSepto and

Cleveland Clinic Registry). The profile of Perjeta is also well-studied in metastatic disease, from the large phase III trial CLEOPATRA.

An investigator-initiated phase III study of nab-paclitaxel versus paclitaxel in the neoadjuvant setting enrolled 1,204 patients (GeparSepto study), and patients with HER2-positive disease (n=395) were treated with neoadjuvant Perjeta and Herceptin. GBG pCR rates were found to be 62% and 54%, respectively [Untch 2014]. Real-world evidence of the efficacy of dual HER2 blockade in the neoadjuvant setting comes from a retrospective analysis of registry data at a single centre in Cleveland, Ohio, where total pCR rates were similar to TRYPHAENA; 54% of the 71 patients in the registry had a pCR and no patients experienced symptomatic reductions in LVEF [Tiwari 2015].

CLEOPATRA, the pivotal phase III randomised double-blind placebo-controlled trial assessed the safety and efficacy of Perjeta in 808 patients with HER2-positive metastatic breast cancer. As well as meeting the primary study endpoint of PFS, safety analysis demonstrated that the most common adverse events (≥50%) with Perjeta treatment were diarrhoea, alopecia and neutropenia, and the combination of Perjeta and Herceptin plus docetaxel did not increase the incidence of cardiac adverse events, including LVSD, compared with the control arm [Swain 2013; Swain 2015].

The evidence supporting the use of Perjeta plus Herceptin and chemotherapy for neoadjuvant treatment of HER2-positive locally advanced, inflammatory, or early stage breast cancer is limited by the relatively small number of studies of Perjeta in the neoadjuvant setting, and the fact that these are phase II trials and not powered for assessing long-term outcomes. The phase II studies of neoadjuvant Perjeta used pCR as a primary measure of efficacy, which as shown by the CTNeoBC pooled analysis, is associated with improved survival [Cortazar 2014]. pCR has therefore been accepted by both the EMA and FDA as a valid and meaningful clinical endpoint, subject to agreed conditions for confirmatory study data with respect to DFS/OS [EMA, 2014; FDA, 2014]. The large phase III study APHINITY is currently ongoing, which will provide invasive disease-free survival (IDFS) data for adjuvant Perjeta with chemotherapy plus Herceptin versus placebo with chemotherapy plus

Herceptin for 1 year after surgery in more than 4,800 patients with HER2-positive non-metastatic breast cancer [von Minckwitz 2011].

The phase II neoadjuvant studies NeoSphere and TRYPHAENA support clinical benefits of adding Perjeta to a Herceptin-containing regimen as neoadjuvant treatment for HER2-positive early breast cancer [Gianni 2012; Schneeweiss 2013]. In addition, real-world data and data from an investigator-initiated trial reported similar rates of pCR [Tiwari 2015; Untch 2014]. Long-term survival benefits and safety profile have also been reported from the phase III CLEOPATRA study of Perjeta in HER2-positive metastatic breast cancer patients [Swain 2013].

In the context of the totality of the data, strong biological rationale for the combination and the efficacy and safety results from the metastatic setting, the efficacy of the addition of Perjeta to Herceptin and chemotherapy is considered established as a neoadjuvant treatment in HER2-positive early breast cancer. Perjeta is a valuable addition to the current treatment options available for the treatment of this cancer

1.3 Summary of the cost-effectiveness analysis

A cost utility analysis was conducted in order to evaluate the cost effectiveness of Perjeta, Herceptin and docetaxel compared with Herceptin and docetaxel for the neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence.

A six state transition Markov model with a 3-week cycle duration was constructed in Microsoft Excel® to explore the health outcomes and costs associated with the patient population defined in the scope. The health states are ‘event free’, ‘locoregional recurrence’, ‘remission’, ‘metastatic not-progressed‘, ‘metastatic progressed’ and ‘death’. A time horizon of 50 years is used to capture all costs and benefits associated with neoadjuvant treatment with Perjeta. Costs and utilities are discounted at 3.5%. The model structure was validated by an independent UK ad-board held in June 2015.

Clinical data sources

Two main sources of clinical data were used to model neoadjuvant treatment in the economic model.

The first is the pivotal NeoSphere study, where the primary endpoint of the study was pathological complete response rate in the breast (bpCR) at the time of surgery. tpCR was also collected prospectively for exploratory analysis.

The second source is CTneoBC group meta-analysis which evaluated the relationship (link) between the three pCR definitions (see Table 1 above) and long-term outcomes of event free survival (EFS) and overall survival (OS). tpCR showed a stronger link with EFS compared with bpCR and as such the tpCR data from NeoSphere is used in the economic model.

Patient level analyses (useful to compare the natural history and clinical outcomes of patients, with and without pCR, irrespective of treatment group) and trial-level analyses (useful for comparing treatment arms) were presented in the analysis. The CTneoBC group meta-analysis was not able to establish a link between EFS-tpCR at trial level. However, at patient level, the link between EFS-tpCR and OS-tpCR was established. Hence, for the purposes of the economic case, the natural course of pCR and non-pCR patients derived from the CTNeoBC analysis is considered appropriate to calculate the natural progression of HER2 early breast cancer patients as it enables a comparison of the progression of the two types of patients (pCR and no pCR patients).

Within the economic model, the CTNeoBC analysis was used to predict the natural course of the disease in terms of EFS, by fitting parametric curves calculated from the CTNeoBC analysis and using these to extrapolate pCR and no pCR KM (Kaplan Meier) data from NeoSphere beyond trial duration.

The primary aim of the TRYPHAENA study was to assess the tolerability of neoadjuvant treatment with Perjeta and Herceptin plus chemotherapy, with a focus on cardiac safety as the primary endpoint of the study. This study was not included in the economic analysis as it was not powered enough to address any of the relevant outcomes to the economic case (pCR, DFS, PFS, OS). Furthermore, as all

arms in the TRYPHAENA study were exposed to Perjeta, a comparator arm would have to be created hence increasing the uncertainty because of the assumptions that would have to be made.

Similarly to TRYPHAENA, all patients in the GeparSepto study were exposed to Perjeta hence the need to create a comparator arm also existed if this study was to be used. Moreover, the neoadjuvant treatment in GeparSepto was comprised of 10 cycles of Perjeta + Herceptin (2 cycles before biopsy and 8 cycles after the biopsy and before surgery). As the NeoSphere trial consisted of 4 neoadjuvant cycles only, an analysis with GeparSepto's 10 cycles would not be appropriate.For this reason, GeparSepto was not included in the economic case.

Thus, the economic modelling presented below is based on results from NeoSphere.

A systematic review was conducted to identify appropriate sources of utility values in the neoadjuvant setting for the model, however no studies were identified. Utilities were instead taken from two sources: a Swedish utility study in breast cancer (Lidgren 2007) provided the utilities for all health states except for the metastatic progressed state. The utility of the metastatic progressed health state was valued through Lloyds mixed model (Lloyd 2006) which has been applied in numerous NICE Technology Appraisals in this disease area (TA257, TA263, ID538). For some health states, (locoregional or remission) applicable utilities were not identified and hence assumptions were made to estimate these utilities (see section 5.4). The natural decline in QoL for an aging population was incorporated by using the Ara and Brazier 2010 study, which analysed the utilities of the general UK population.

Resource use in each health state was primarly based on NICE Clinical Guideline on Early Breast Cancer [NICE CG80]. Costs were taken from the British National Formulary (BNF 2015), Personal Social Services Research Unit (PSSRU 2014), NHS references costs 2013/14 and Commercial Medicines Unit 2014 electronic Market Information Tool (CMU eMIT).

The base case results indicate that Perjeta with Herceptin and docetaxel has an incremental cost and QALY of £4,557 and 0.263 respectively compared to Herceptin and docetaxel alone and an incremental cost effectiveness ratio (ICER) of £17,297 per QALY gained.

Table 2 Base case results

Technologies	Total costs (GBP)	Total LYG	Total QALYs	Incl costs (£)	Inc. LYG	Inc QALYs	Inc £/LYG	ICER (£/QALY))
PHD	104,575	16.719	11.499	4,557	0.365	0.263	£12,471	£17,297
HD	100,018	16.353	11.236					
PHD – Perjeta + Herceptin + docetaxel; HD - Herceptin + docetaxel; LYG – life years gained; QALYs – Quality adjusted life years; ICER – incremental costs effectiveness ratio								
Values in the table are discounted and 1/2 cycle corrected								

Extensive deterministic sensitivity analyses were conducted. Varying the individual paramers produced ICERs that remained below £23K per QALY gained in all cases but one. The exception being the proportion of patients achieving pCR in either arm. When the pCR rate is varied to the lower extremitiy of the confidence interval for Pejeta, Herceptin and docetaxel (PHD) only, the result is an ICER of £68K per QALY gained. This is a very conservative estimate which assumes that the rate of tpCR for PHD patients was 30% and Herceptin and docetaxel (HD) 21.5% (the base case tpCRresults are PHD 39.3% [CI: 30.25% – 48.63%] and HD 21.5% [CI: 14.28% - 29.72).

A 1,000 simulation probabilistic sensitivity analysis (PSA) was conducted in order to evaluate the uncertainty associated with the base-case estimate. The PSA indicates that Perjeta has a 64.1% chance of being cost-effective at a threshold of £30,000 per QALY gained with an ICER of £20,104.

Conclusion

The cost effectiveness analysis demonstrates that Perjeta as a neoadjuvant breast cancer treatment is a cost-effective use of NHS resources, and offers a potential cure to women who are at risk of progressing to metastatic breast cancer, for which there is currently no cure.

The NeoSphere clinical evidence demonstrates that Perjeta in combination with Herceptin and docetaxel is associated with a higher probability of achieveing tpCR than Herceptin and docetaxel alone (39.3% vs 21.5% respectively).

The economic analysis shows that the pCR rates seen within NeoSphere, taken in combination with parametric curves derived from the CTneoBC study, demonstrate

that Perjeta extends EFS by 7.2 months and OS by 4.2 months compared to Herceptin and Docetaxel alone.

An OS analysis from CTneoBC study was not used in this economic case but it also showed a positive trend between OS and EFS. Although the NeoSphere trial was not powered to detect statistically significant PFS, at the 5 year data cut, the Perjeta Herceptin and docetaxel arm had five patients more remaining in the PFS state than the Herceptin and docetaxel arm.

1.4 Statement of decision problem

Table 3 The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with HER2-positive breast cancer which is either; • locally advanced, or • inflammatory, or • early stage (at a high-risk of recurrence).	As scope	
Intervention	Neoadjuvant pertuzumab in combination with trastuzumab and chemotherapy	As scope	
Comparator (s)	Standard neoadjuvant therapy without pertuzumab for HER-2 positive breast cancer.	Neoadjuvant Herceptin in combination with chemotherapy.	
Outcomes	The outcome measures to be considered include: • overall survival • Disease free survival • surgical outcomes • pathological complete response • adverse effects of treatment • health-related quality of life	The outcome measures to be considered include: • overall survival • Event free survival • surgical outcomes • pathological complete response • adverse effects of treatment • health-related quality of life	In NeoSphere, EFS is evaluated in the same way as PFS. EFS is the endpoint used in the economic analysis
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	As scope. The time horizon in the economic model is 50 years. Costs and benefits are discounted at the rate of 3.5%.	

Subgroups to be considered	If the evidence allows the subgroups indicated in the 'population' section will be considered separately	As no statistically significant difference was seen between the sub groups no sub-group analysis is presented.	
Special considerations including issues related to equity or equality	No equality considerations have been identified.	As scope	

2. Description of the technology

2.1 Description of the technology

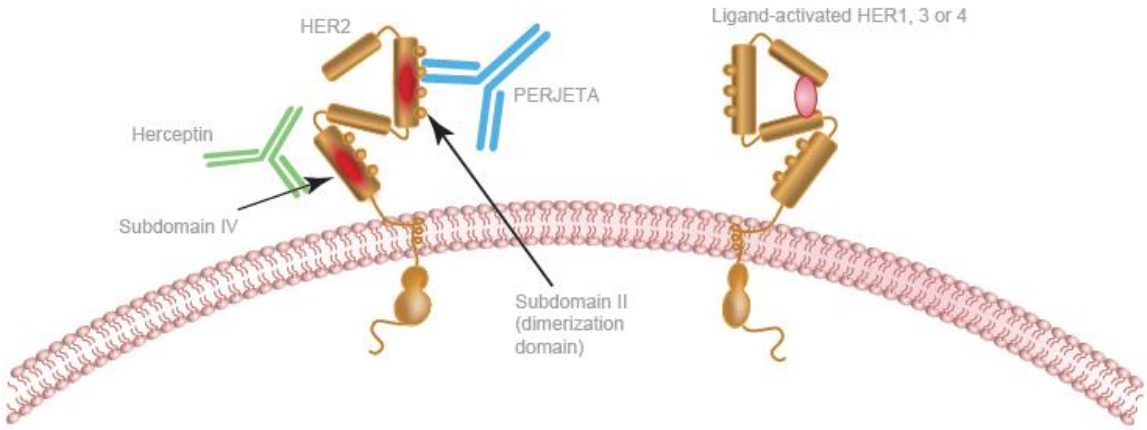
Brand name: Perjeta

Therapeutic class: ATC code: L01XC13

Perjeta, the first HER2 dimerisation inhibitor (HDI), is a recombinant humanised monoclonal antibody that specifically targets the extracellular dimerisation HER2 domain [Perjeta SmPC; Fendly 1990]. More specifically, it blocks ligand-dependent heterodimerisation of HER2 with other HER family members including EGFR, HER3, and HER4 [Perjeta SmPC; Franklin 2004]. As a result, Perjeta inhibits ligand-initiated intracellular signalling through two major signal pathways: mitogen-activated protein (MAP) kinase and phosphoinositide 3-kinase (PI3K). Inhibition of these signalling pathways can result in cell growth arrest and apoptosis respectively [Lewis 1996]. In addition, Perjeta mediates antibody-dependent cell-mediated cytotoxicity (ADCC) [Perjeta SmPC].

While Perjeta alone inhibits the proliferation of human tumour cells, the combination of Perjeta and trastuzumab (henceforth Herceptin) significantly augments anti-tumour activity in HER2-overexpressing xenograft models [Perjeta SmPC]. Perjeta and Herceptin both bind to the HER2-receptor but at distinct sites at the extracellular region of the HER2-receptor. Together, they show complementary mechanisms of action and provide a more comprehensive blockade of HER2-driven signalling [Nahta, 2004; Scheuer 2009].

Figure 2 - Mechanism of action of PERJETA



In summary, the mechanisms are as follows:

- Perjeta binds to HER2-receptor near the centre of subdomain II, sterically blocking a binding pocket necessary for ligand-dependent receptor dimerisation and signalling [Franklin 2004; Rajasekaran 2009].
- Herceptin binds to HER2 at the C-terminal portion of subdomain IV (Cho 2003). This link inhibits both ligand-independent HER2 signalling and HER2 extracellular region shedding [Junttila 2009].
- Perjeta and Herceptin flag cancer cells for destruction by antibody-dependent cell-mediated cytotoxicity (ADCC) [Scheuer 2009; El-Sahwi 2010].

2.2 Marketing authorisation/CE marking and health technology

2.2.1 Indicate whether the technology has a UK marketing authorisation/CE marking for the indications detailed in this submission. If so, give the date on which this was received. If not, state the current UK regulatory status, with relevant dates (for example, date of application and/or expected date of approval from the Committee for Human Medicinal Products).

A marketing authorisation was granted in July 2015 by the EMA.

With regards to Perjeta use for metastatic breast cancer (see indication in section 2.2.2) the marketing authorisation was granted by the EMA in March 2013.

2.2.2 Give the (anticipated) indication(s) in the UK. For devices, provide the date of (anticipated) CE marking, including the indication for use. If a submission is based on the company's proposed or anticipated marketing authorisation, the company must advise NICE immediately of any variation between the anticipated and the final marketing authorisation approved by the regulatory authorities

Perjeta has currently two marketing authorisations as follows:

Perjeta is indicated for use in combination with Herceptin and chemotherapy for the neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence.

Perjeta for use in combination with Herceptin 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.

2.2.3 Summarise any (anticipated) restrictions or contraindications that are likely to be included in the (draft) summary of product characteristics (SmPC).

Patients treated with Perjeta must have HER2-positive tumour status, defined as a score of 3+ by immunohistochemistry (IHC) and/or a ratio of ≥ 2.0 by in situ hybridisation (ISH) assessed by a validated test. As noted in the SmPC, this medicine is contraindicated to people who are hypersensitivity to Perjeta or to any of the excipients below:

- Acetic acid, glacial
- L-Histidine
- Sucrose
- Polysorbate 20
- Water for Injections

2.2.4 Include the (draft) SmPC for pharmaceuticals or information for use (IFU) for devices in an appendix

SmPC included in Appendix 1 Summary of Product Characteristics.

2.2.5 Provide the (draft) assessment report produced by the regulatory authorities (that is, the European public assessment report for pharmaceuticals) and a (draft) technical manual for devices in an appendix

European public assessment report is included in Appendix 2 EPAR Summary for the public.

2.2.6 Summarise the main issues discussed by the regulatory authorities (preferably by referring to the [draft] assessment report [for example, the European public assessment report]). State any special conditions attached to the marketing authorisation (for example, if it is a conditional marketing authorisation)

<u>European Public Assessment Report (EPAR)</u>

The assessment of Perjeta for a variation to its Marketing Authorisation (MA) resulted in the following recommended indication: **use in combination with Herceptin and chemotherapy for the neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence**. On granting the conditional variation in the MA for Perjeta, the CHMP accepted the positive clinical benefit-risk associated with the introduction of Perjeta and recognised the greater medical need in patients at high risk of recurrence [CHMP 2015].

The CHMP concluded that, “in the context of the totality of the data, in particular, the strong biological rationale for the combination, the compelling efficacy results in the metastatic setting, the acceptable toxicity assessment report profile, and the observed effect in terms of pCR, the efficacy is considered established”. After consultation with the SAG Oncology, the CHMP also recognised that, although not statistically significant, long-term efficacy outcome data (DFS and OS) from the NeoSphere Study showed a trend in favour of Perjeta, and that the survival benefit of adding Perjeta to Herceptin has been established in the metastatic setting, meaning

that it is reasonably likely that neoadjuvant treatment with Perjeta is associated with benefits in terms of DFS and OS [CHMP 2015].

With respect to HR-positive disease in the NeoSphere study, patients with HR-positive disease had lower pCR rates compared to patients with HR-negative disease and the difference between pCR rates was smaller in the HR-positive subgroup. Although the subgroup analysis of pCR rates in HR-positive disease is based on limited data, the CHMP considered that the effect on pCR was reasonably likely to be associated with a benefit in terms of long-term outcomes. Further understanding of the long-term effects of Perjeta for patients with HR-positive disease is expected from the APHINITY study in the adjuvant setting.

The APHINITY Study is a randomised multi-centre, double-blind, placebo-controlled comparison of chemotherapy plus Herceptin plus placebo versus chemotherapy plus Herceptin plus Perjeta as adjuvant therapy in patients with operable HER2-positive primary breast cancer (final clinical study report due May 2017), and has been included as a condition of the variation in the MA as a post-authorisation efficacy study. The APHINITY Study is expected to provide confirmatory data in terms of survival (DFS and OS) in the early breast cancer (adjuvant) setting. Further efficacy data in the neoadjuvant setting are expected from the post-authorisation safety study BERENICE, a multi-centre, multinational, phase II study to evaluate Perjeta in combination with Herceptin and standard neoadjuvant anthracycline-based chemotherapy in patients with HER2-positive, locally advanced, inflammatory, or early-stage breast cancer (safety and efficacy data from the neoadjuvant period are anticipated in May 2017) [CHMP, 2015].

Based on the available data, the CHMP suggested that Perjeta and Herceptin would increase the pCR rate as add-on to chemotherapy as demonstrated in both the NeoSphere Study (with docetaxel) and the TRYPHAENA Study (with three different chemotherapy regimens), and that data do not demonstrate a meaningful increase in cardiac toxicity when considering this combination. Therefore, the CHMP recommended that the indication include Perjeta as an add-on to Herceptin and chemotherapy rather than as an add-on to Herceptin and docetaxel [CHMP, 2015].

In terms of clinical safety, the CHMP concluded that “overall, the observed adverse events are well-characterised, clinically manageable and adequately reflected in the SmPC”. The post-authorisation safety study BERENICE has been included as a condition of granting the variation to the MA to ensure further characterisation of the long-term cardiac toxicity. In addition, safety data from the APHINITY Study and the final analysis of TRYPHAENA are expected to provide further evidence in the early (adjuvant and neoadjuvant) breast cancer setting with regard to this safety concern [CHMP 2015].

The CHMP considered the uncertainties with regard to safety were acceptable for patients who are at high risk of disease recurrence, which includes those with locally advanced or inflammatory breast cancer, and some with early breast cancer [CHMP 2015].

Conditions attached to the variation in the marketing authorisation for Perjeta

The variation to the MA was granted with a number of conditions, in addition to those already in place for the metastatic indication. These include the submission of periodic safety reports, adherence to the agreed risk management plan (RMP), and conducting the post-authorisation efficacy study (PAES) APHINTY and the post-authorisation safety study (PASS) BERENICE [CHMP 2015].

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

Perjeta was licenced in this indication in July 2015, and commercially launched at the end of September 2015.

2.2.8 State whether the technology has regulatory approval outside the UK. If so, please provide details.

After being approved in 2012 for the treatment of patients with advanced or late-stage (metastatic) HER2-positive breast cancer, Perjeta for neoadjuvant breast cancer was approved by the FDA in the US (through the Accelerated Approval Program) on 30th September 2013.

In the EU, Perjeta is already approved for neoadjuvant treatment of HER2-positive early breast cancer in 28 other countries including the following: Austria, Belgium, Bulgaria, Croatia, Republic ofCyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia,Slovenia, Spain, Sweden. Outside of the EU, Argentina, Chile, Peru, Uruguay, Aruba, Bolivia, Cuba, Costa Rica, Ecuador, Korea, Nicaragua, Philipines, Israel, Dominican Republic, El Salvador, Honduras, Jamaica, Guatemala, Singapore, Thailand, Kazahistan, Taiwan, Lebanon, Russia and Turkmenistan also have approved Perjeta for neoadjuvant treatment of HER2-positive early breast cancer.

2.2.9 State whether the technology is subject to any other health technology assessment in the UK. If so, give the timescale for completion

A Scottish Medicines Consortium (SMC) appraisal began in September 2015 for Perjeta in combination with trastuzumab and chemotherapy for the neoadjuvant treatment of adult patients with human epidermal growth factor receptor 2 (HER2)-positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence. Completion of this appraisal is expected in March 2016.

2.3 Administration and costs of the technology

2.3.1 For pharmaceuticals, complete the table 'Costs of the technology being appraised' in the company evidence submission template, including details of the treatment regimen and method of administration. Indicate whether the acquisition cost is list price or includes a patient access scheme, and the anticipated care setting. Specify the sources of information and data used to complete the table, for example SmPC or trial data. For more information see section 5.5 of the NICE guide to the methods of technology appraisal

Table 4 Costs of the intervention

	Cost	Source
Pharmaceutical formulation	Concentrate for solution for infusion.	Perjeta SmPC
Acquisition cost (excluding VAT) *	List prices **Perjeta** - £2,395 per 420 mg vial **Herceptin** - £407.4 per 150 mg vial **Docetaxel** 80 mg/4ml - £25.73 per mg **FEC** 5-Fluorouracil - £1.43 Epirubicin - £21.7 Cyclophosphamide - £17.67	Perjeta – BNF Herceptin – BNF 2015 Docetaxel - eMIT
Method of administration	Intravenous infusion.	
Doses	**Perjeta** Initial dose 840 mg Subsequent doses – 420 mg **Herceptin** 8mg/kg initial dose 6mg/kg cycle 2+ **Docetaxel** 75mg/m2 initial and cycle 2-4 Cycle 2+ can increase up to a maximum of 100mg/m^2 **FEC** 5-Fluorouracil - 600 mg/m^2 Epirubicin - 90 mg/m^2 Cyclophosphamide - 600 mg/m^2	NeoSphere study
Dosing frequency	Every three weeks (1 cycle = 3 weeks)	
Average length of a course of treatment	4 cycles in the base case The licence specifies 3-6 cycles	NeoSphere study Perjeta SmPC
Average cost of a course of treatment*	**PHD + FEC** £6,421 initial cycle (FEC included) £3,643.28 cycle 2+ **HD + FEC** £1,672 initial (FEC included) £1,248.28 cycle 2+	NeoSphere study
Anticipated average interval between courses of treatments	A person with HER2-positive early breast cancer will receive only one course of treatment with Perjeta before surgery and adjuvant treatment with Herceptin.	Perjeta SmPC

Anticipated number of repeat courses of treatments	A person with HER2-positive early breast cancer will receive only one course of treatment with Perjeta before surgery and adjuvant treatment with Herceptin.	Perjeta SmPC
Dose adjustments	Dose reductions are not recommended. Pertuzumab therapy should be discontinued if: • trastuzumab treatment was discontinued • symptomatic heart failure is confirmed. Pertuzumab and trastuzumab treatment should be withheld for at least 3 weeks if a patient develops signs and symptoms suggestive of congestive heart failure, a drop in left ventricular ejection fraction (LVEF) to <40% or a LVEF of 40-45% associated with a fall of ≥10% points below pre-treatment values. Pertuzumab and trastuzumab may be resumed if the LVEF has recovered to >40-45% associated with <10% points below pre-treatment value. • a patient experiences a NCI-CTCAE Grade 4 reaction (anaphylaxis), bronchospasm or acute respiratory distress syndrome	Perjeta SmPC
Anticipated care setting	Secondary care	
*Other treaments are possible for the neoadjuvant (see section 3.3.1)		

2.3.2 Provide details of any patient access scheme that has been referred to NICE for inclusion in the technology appraisal by ministers and formally agreed by the company with the Department of Health before the date of evidence submission to NICE for the technology. For more information see section 5 of the NICE guide to the processes of technology appraisal.

No patient access scheme has been referred to NICE.

2.3.3 For devices, provide the list price and average selling price in a table similar to the table presented in the template, 'Costs of the technology being appraised'. 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.

2.4 Changes in service provision and management

2.4.1 State whether additional tests or investigations are needed (for example, diagnostic tests to identify the population for whom the technology is indicated in the marketing authorisation) or whether there are particular administration requirements for the technology. For more information see section 5.9 of the NICE guide to the methods of technology appraisal

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 Perjeta based regimen, or prior to the administration of Perjeta.

2.4.2 Identify the main resource use to the NHS associated with the technology being appraised. Describe the location or setting of care (that is, primary and/ or secondary care, commissioned by NHS England specialised services and/or clinical commissioning groups), staff costs, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

For patients who are considering breast conserving surgery that is not advisable at presentation, a neoadjuvant therapy is an option (CG 80). Administration of this therapy takes place in a hospital with an established oncology unit, which has the staffing and infrastructure required for administration of cancer treatments. Perjeta will have minimal impact upon the current pathway, as it can be administered on the same treatment day as Herceptin IV (every 3 weeks).

The pivotal Herceptin NOAH study utilised 11 cycles of neoadjuvant treatment. Similar pCR rates were achieved with fewer cycles of neoadjuvant therapy in the NeoSphere and TRYPHAENA studies (3-6 cycles) therefore suggesting the lowering of resource requirements through use of neoadjuvant PHD.

Testing and monitoring of HER2-positive early breast cancer is outlined in CG80.

2.4.3 Specify if the technology requires additional infrastructure in the NHS to be put in place

No additional infrastructure is required.

2.4.4 State if and to what extent the technology will affect patient monitoring compared with established clinical practice in England

Minimal additional monitoring is required.

The SmPC requires that the assessment of left ventricular ejection fraction (LVEF) takes place prior to initiation of Perjeta and every 2 cycles of treatment in the neoadjuvant setting. For patients on Herceptin treatment in early breast cancer, cardiac assessments, as performed at baseline, should be repeated every 3 months during treatment and every 6 months following discontinuation of treatment until 24 months from the last administration of Herceptin.

2.4.5 State whether there are any concomitant therapies specified in the marketing authorisation or used in the key clinical trials (for example, for managing adverse reactions) administered with the technology

The safety of Perjeta has been evaluated in more than 600 people in the NeoSphere and TRYPHAENA trials.

The most common adverse reactions (grade 3, 4 or 5) which occurred in 5% or more trial participants were diarrhoea, neutropenia, febrile neutropenia and leucopenia.

In NeoSphere and TRYPHAENA, there were a number of concomitant therapies that were permitted such as:

- Antiemetics to control symptoms of sickness before and after chemotherapy treatment,
- Steroid tablets in the day before docetaxel and two days after to prevent allergic reactions and reduce other side effects,
- Acceptable methods of contraception for female patients or male partners who were not surgically sterilised or did not meet the study definition of postmenopausal.

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

2.5 Innovation

2.5.1 If you consider the technology to be innovative with potential to make a substantial impact on health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation:

- **State whether and how the technology is a 'step-change' in the management of the condition**
- **Provide a rationale to support innovation, identifying and presenting the data you have used.**

In 2008, Herceptin was licensed for use as part of a neoadjuvant regimen for HER2-positive early breast cancer, based on the clinical evidence from the NOAH study where patients assigned to the Herceptin arm received 11 cycles of neoadjuvant therapy followed by adjuvant therapy to complete 1 year of treatment. However, 42% of patients who received Herceptin relapsed after 5 years [Gianni 2014]. A new medicine was needed to meet these patient's expectations.

When Perjeta was introduced for use in mBC it was the first in class HER2 dimerisation inhibitor. In mBC the combination of Perjeta and Herceptin offers a comprehensive HER2 blockade and, when used with docetaxel, results in the inhibition of signalling pathways essential for tumour growth [Agus 2002].

The innovation of Perjeta as neoadjuvant treatment can be observed from the introduction of Perjeta to current Herceptin-containing regimens, based on the evidence from **TRYPHAENA** and **NeoSphere** studies. Similar pCR rates were achieved with fewer cycles of Perjeta, Herceptin and docetaxel therapy in the NeoSphere and TRYPHAENA studies (3-6 cycles) compared with NOAH (11 cycles).

A primary benefit of improved pCR that is unlikely to be captured in the QALY estimate is enabling more breast conservative surgery and/or breast conservation through shrinking of the tumour to facilitate surgery. Differences in surgical outcomes are difficult to capture in clinical trials, and as such are not able to be statistically powered in neoadjuvant clinical trial design. Despite these challenges, Perjeta is associated with more breast conservative surgery and/or breast conservation that will have a significant benefit to women. This benefit is not be captured in the economic model and QALY estimate.

Wider Societal Benefits

Within the Perjeta arm of the NeoSphere study, the median age of the women was 50 years old. [Gianni 2012] For this age group, any premature death will have a significant impact upon families and friends. Many women will be an income earner for their family and in addition a significant number will also play a pivotal role in the care and upbringing of children and /or care of other family members. Perjeta used in the neoadjuvant setting is expected to extend long term survival and grant women more time with their families.

We have previously observed a significant improvement in long-term outcomes with the addition of Perjeta to Herceptin and docetaxel in the metastatic HER2-positive breast cancer setting. [Baselga 2012; Swain 2013; Swain 2015a] Subsequently, efficacy results from NeoSphere, TRYPHAENA, GeparSepto and the Cleveland Clinic have also demonstrated an improvement in pCR rates with the addition of Perjeta to Herceptin and chemotherapy in the early HER2-positive early breast cancer setting. [Gianni 2012; Schneeweiss 2013]

Perjeta, when used in the neoadjuvant setting, provides an opportunity for breast cancer patients to benefit from dual HER2 blockade in the early stages of their disease, with an aim to extend the valuable time they have with their families.

This benefit is of consequence financially, socially and psychologically to patients through the ability to continue employment and to provide informal care and support to their families. In addition there is an adverse impact on caregivers, where studies have show a negative impact on their quality of life [Bukovic 2005, Wagner 2006], their ability to work and financial burden [Longo 2006]. These benefits are not captured in the QALY and should be considered by the Committee.

3. Health condition and position of the technology in the treatment pathway

3.1 Disease overview

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

One in eight women in the UK will have to cope with a diagnosis of breast cancer (BC) during their lives, with diagnosis most common in women aged between 50-70 years (National Cancer intelligence). The incidence and mortality rates in the UK are the 6th highest in Europe, with more than 50,000 women in the UK receiving a breast cancer diagnosis every year and with approximately 11,000 women still dying from this disease annually [Cancer Research UK].

It is estimated that 30% of women with early disease will eventually develop recurrent advanced BC or metastatic breast cancer (mBC), which is currently considered to be incurable [Gonzalez-Angulo 2007]. For these women, many of whom have children and other dependents, any chance of stopping or delaying progression to terminal metastatic breast and thereby achieve a cancer-free life expectancy is of critical importance.

Approximately 15% of women diagnosed with BC have HER2-positive disease [Ibrahim 2011; SEER 2011], which is associated with significantly worse prognosis [Wolf 2007; Fiszman 2011; Ross 2009]. Women with early HER2-positive disease have a higher risk of disease recurrence than those with HER2-negative disease [Romond 2005; Smith 2007]. For these patients, the current standard of care for neoadjuvant therapy consists of Herceptin plus chemotherapy prior to surgery for patients who are considering breast conserving surgery that is not advisable at presentation, followed by Herceptin therapy to complete 1 year of treatment after surgery [NICE CG80]. The NOAH study showed a remarkable clinical benefit in up to 11 cycles of neoadjuvant Herceptin plus chemotherapy prior to surgery; however 42% of patients who received Herceptin relapsed after 5 years [Gianni 2014]. This really exposes the large unmet need amongst early breast cancer patients.

Most women with breast cancer are diagnosed in early stages when the cancer is still confined to the breast, with or without loco-regional lymph node involvement. At this stage patients undergo a series of treatment stages (neoadjuvant, surgery, adjuvant) in an attempt to prevent disease progression. Yet, after these treatments the disease may either reappear in the ipsilateral preserved breast (local recurrence), or in the regional lymph nodes (regional recurrence). These types of recurrences may generally be termed as loco-regional recurrences. The disease can metastasise by spreading beyond the breast and lymph nodes. First line treatment for HER2-positive metastatic breast cancer would be chemotherapy with a Herceptin based regimen (PHD, HD and other treatments). When first line metastatic treatments are no longer effective, patients will have a second line of treatment with effective treatments such as Kadcyla. Further lines of treatments are possible when disease continues to progress.

The stages described above have an enormous impact on the QoL of patients (see section 5.4 related to QoL measures for these patients). Hence, an effective neoadjuvant treatment may provide women with an option to choose breast conservation instead of mastectomy and thereby mitigate its negative emotional and physical impact.

3.2 Effects of the disease on patients, carers and society

Patients with eBC, report lower Health Related QoL compared to the general population due to their treatment (most notably chemotherapy), independent of the method of measurement [Lidgren 2007].

QoL remains low even in BC survivors: in the US HEAL study, 41% of survivors were fatigued two to five years post-diagnosis, and this was significantly correlated with pain, cognitive problems, physical inactivity, weight gain/negative body image, and antidepressant use [Meeske 2007]. Evidence also suggests that BC survivors experience relative declines in physical functioning, bodily pain, general health and vitality, social functioning, and mental health, even many years after diagnosis. Women diagnosed with BC are ten times as likely to report a decline in self-rated health compared with age-matched controls [Trentham-Dietz 2008].

Women with BC are also more likely to experience specific comorbidities compared with the general population [Radice 2003; Bukovic 2005; Burgess 2005; Grabsch 2006; Kim 2007; Mehnert 2007; Morgan 2005; Paskett 2007], including fatigue, sexual dysfunction, and infertility. Even though many symptoms in eBC decline or disappear following treatment of BC, some of them, such as anticipatory nausea, weight gain, endocrine effects, disturbed sleep, and sexual dysfunction, may persist following treatment [Groenvold 2010]. However, a German population study found that fatigue was the strongest predictor of impact on QoL, explaining 30% to 50% of variability in terms of functional scores and overall QoL [Arndt 2006].

Lymphedema reportedly affects up to half of patients with both early and advanced-stage BC, [Grabsch 2006; Morgan 2005; Paskett 2007; Kissane 2007], although not all patients will experience persistent swelling [Paskett 2007]. This complication can be grossly disfiguring and may elicit emotional responses including shock, fear, annoyance, and frustration and can contribute to a negative body image, functional impairment, poorer psychological adjustment, anxiety, and depression.

Several studies have shown that there are many psychological issues associated with BC. Many patients experience anxiety, loneliness, depression, anger, guilt, fear of recurrence, and body image changes [Lidgren 2007; Burgess 2005; Grabsch 2006]. Depression and/or anxiety are experienced by up to 50% of women after a BC diagnosis, but this proportion decreases over time unless the disease recurs.

Breast cancer places a substantial burden not only on the patient but also on their caregivers. The burden on caregivers can be considered to include:

- Perceived burden
- Reduced QoL
- Psychological morbidity
- Adverse impact on work
- Financial burden

The Medical Outcomes Survey Short Form 36 (SF-36) was used to assess QoL for husbands of women with BC in the US [Wagner 2006]. Caregiver QoL can be negatively affected by the life-threatening nature of BC and the distressing side

effects of treatments that patients experience, resulting in a strain on the caregiver and their families [Bukovic 2005). Husbands of women with BC were shown by Wagner (2006) to score lower on general health, vitality, role-emotional, and mental health subscales compared with spouses of healthy women [Wagner 2006]. Reductions to a husband's QoL were not related to the clinical aspects of the patient's disease but were associated with less caregiver burden, lower use of emotion-focused coping, and higher social support.

An adverse impact on ability to work for the caregiver was also reported. A study of financial and family burden by Longo (2006) in 282 cancer patients (74 patients with BC) showed that for 36% of caregivers, time off work amounted to one-third of their working days in any given month [Longo 2006].

Besides the impact on patients and caregivers, this disease has an overarching impact on society. A 2012 study from Oxford University has shown that breast cancer alone accounts for an annual economic cost of £1.6 bn in the UK. An NCRI report showed that potential wage losses due to premature deaths, time off work , and unpaid care by friends and family accounted for 64% of all UK cancer costs in 2009 followed by healthcare costs and unpaid care to cancer patients by friends and family [NCRI, 2012].

3.3 Clinical pathway of care

Present the clinical pathway of care that shows the context of the proposed use of the technology. This information may be presented in a diagram. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this point should be consistent with the guideline and any differences should be explained.

3.3.1 Neoadjuvant treatments

NICE Clinical Guideline 80 [NICE CG80] includes recommendations on the diagnosis and treatment for people with HER2-positive early breast cancer. However, CG80 mainly includes recommendations for people who have undergone surgery (postoperative or adjuvant setting).

One of the exceptions, states that preoperative systemic treatment can be offered to patients with early invasive breast cancer who are considering breast conserving surgery that is not advisable at presentation. Over 75% of HER2-positive patients for whom a decision to administer neoadjuvant treatment has been made will receive a neoadjuvant regimen that contains Herceptin [Roche Data on File RXUKPERT00220(1)].

Although the pivotal study for Herceptin NOAH uses 11 cycles of chemotherapy consisting of doxorubicin and paclitaxel (for 3 cycles), followed by paclitaxel (for 4 cycles), and finally cyclophosphamide, methotrexate, and fluorouracil (for 3 cycles), there are other chemotherapy regimens (added to Herceptin neoadjuvant treatment) in UK practice. Typical chemotherapy components include [Roche Data on File RXUKPERT00220(1)]:

- Herceptin plus FEC-T: Anthracycline-based regimen of fluorouracil + epirubicin + cyclophosphamide for three cycles, followed by a taxane (e.g. docetaxel) for three cycles
- Herceptin plus TC: Taxane plus carboplatin for six cycles (anthracycline-free)

Administration of FEC chemotherapy at the start of the treatment regimen is commonly prescribed by clinicians in the UK as treatment that can be started for patients soon after diagnosis where tumour biology results may not be available, therefore avoiding delay in the treatment of occult micro-metastatic disease. In the NeoSphere trial, patients received FEC chemotherapy after surgery [Gianni 2012] as the objective was to isolate the effect of Perjeta in the neoadjuvant setting of HER2-positive eBC.

Following NICE approval of Perjeta as neoadjuvant treatment in HER2-positive early breast cancer, it is anticipated that Perjeta, in combination with Herceptin and chemotherapy (3-6 cycles), can be used as first line neoadjuvant treatment (prior to surgery) for the treatment of HER2-positive early breast cancer.

3.3.2 Adjuvant treatments

With regards to the postoperative setting (adjuvant treatment), NICE Technology Appraisal TA107 states that Herceptin, given at 3-week intervals for 1 year or until

disease recurrence (whichever is the shorter period), is recommended as a treatment option for women with early-stage HER2-positive breast cancer following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable). [NICE TA107] Since publication of TA107, the standard treatment of first line early breast cancer has changed to reflect the updated license of Herceptin in both the neoadjuvant and the adjuvant settings and this is clearly noted in the CG80.

As per the Perjeta product licence, Herceptin will need to be given at 3-weekly intervals post-surgery to complete 1 year of treatment.

3.3.3 Metastatic disease

The neoadjuvant and adjuvant treatments described above are related to pre-metastatic disease. For patients who progressed to metastatic disease, the NICE clinical guideline 81 (CG81) includes recommendations on the diagnosis and treatment for people with HER2-positive metastatic breast cancer. The algorithm within this guideline (page 7) states that Herceptin 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. However, after the acceptance of Perjeta for first line metastatic breast cancer patients by the Cancer Drugs Fund (CDF), the standard care for people with HER2-positive metastatic breast cancer is Perjeta in combination with Herceptin and docetaxel [Data on file RXUKPERT00252].

3.4 Life expectancy of people with the disease in England

Provide information about the life expectancy of people with the disease or condition in England Include the source of the data. Please provide information on the number of people with the particular therapeutic indication for which the technology is being appraised. If the marketing authorisation also includes other therapeutic indications for the technology, provide information about the numbers of people with these diseases or conditions in England and provide the source of the data. This is to assess whether the technology may be suitable for consideration as a 'life-extending treatment at

the end of life' as described in section 6.2.10 of the NICE guide to the methods of technology appraisal.

People with early breast cancer may live for many years after diagnosis. In England and Wales, Cancer Research UK notes that 99% of stage 1 and 90% of stage 2 breast cancer patients live for 5 years or more.

Patients eligible for Perjeta Neoadjuvant treatment in England and Wales are expected to be 1,380 see Table 5 below:

Table 5 Number of eligible people for Perjeta per annum

Step	Population	Proportion	No. Of People	Source
1	Total Population (UK)	100%	65,572,409	Office of National Statistics
2	Total Breast Cancer Incidence	0.07%	48,497 (2016)	IARC 2016
3	Early Stage Incident Population	94%	45,700	Seer 2015
4	HER2 Testing Rate	90%	41,130	Roche internal HER2-positive testing rate assumption of 90% for stage I-III and 80-90% for stage IV [data on file RXUKDONF00258]
5	HER2-positive	14.8%	6,087	Ibrahim 2011; SEER 2011
6	England Only	84%	5,113	Office for National Statistics ONS
7	Neoadjuvant Treatment Rate	27%	1,380	Data on File RXUKPERT00244

3.5 Guidance related to the condition

Provide details of any relevant NICE guidance, pathways or commissioning guides related to the condition for which the technology is being used. Specify whether any subgroups were explicitly addressed.

- **NICE Technology Appraisal (TA) No. 109 - Early node-positive breast cancer (September 2006)**

The appraisal recommends that docetaxel, when given concurrently with doxorubicin and cyclophosphamide (the TAC regimen) as per its licensed indication, is a treatment option for the adjuvant treatment of women with early node-positive breast cancer.

- **NICE TA No. 108 - Early node-positive breast cancer (September 2006)**

  The appraisal does not recommend paclitaxel for the adjuvant treatment of women with early node-positive breast cancer.

- **NICE TA No. TA107 - Early-stage HER2-positive breast cancer (August 2006)**

  The appraisal recommends Herceptin, given at 3-week intervals for 1 year or until disease recurrence (whichever is the shorter period), as a treatment option for women with early-stage HER2-positive breast cancer following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable).

- **NICE Clinical Guideline 80 - Early and locally advanced breast cancer (February 2009)**

  This clinical guidance recommends Herceptin, given at 3-week intervals for 1 year or until disease recurrence (whichever is the shorter period), as an adjuvant treatment to women with HER2-positive early invasive breast cancer following surgery, chemotherapy, and radiotherapy when applicable.

- **Treatment pathway (simplification from early and locally advanced breast cancer overview from NICE pathways)**

Figure 3 Treatment pathways

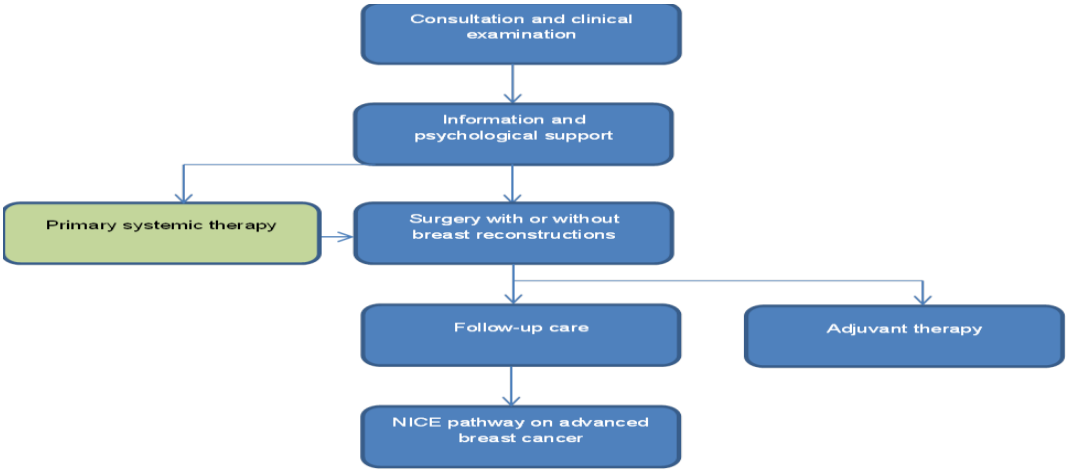


Figure 3 above shows that a primary systemic therapy can be administered before surgery (for patients who are considering BCS that is not advisable at presentation). For HER2-positive early breast cancer patients, primary systemic therapy typically involves Herceptin plus chemotherapy. Perjeta will be considered in this submission as an-add on to Herceptin plus chemotherapy neoadjuvant treatment, and therefore no change is expected to the current recommended treatment pathway.

3.6 Other clinical guidelines

Provide details of other clinical guidelines (for example, UK guidance from the royal societies or European guidance) and national policies

- **ESMO Clinical Practice Guidelines: Primary Breast Cancer 2015 [Senkus 2015]**

  The ESMO guidelines for primary breast cancer advises on the use of neoadjuvant systemic therapy for locally advanced and large 'operable' tumours, particularly when mastectomy is required, acknowledging that neoadjuvant therapy may enable operability and decreasing extent of surgery. The guideline notes that in the neoadjuvant setting, dual anti-HER2 blockade associated with chemotherapy (Herceptin + Perjeta) has led to improvements in the pCR rate when compared with chemotherapy associated with one anti-HER2 agent.

  The guideline also notes that regarding the PHD combination,the results of the large adjuvant APHINITY trial are needed before the combination is recommended for routine use. However, after reviewing potential risks and benefits (including the financial impact), in selected higher risk cases it can be considered an acceptable option as neoadjuvant therapy.

- **SIGN Guideline 134: Treatment of primary breast cancer (September 2013)**

  The guideline recommends that patients with HER2-positive primary breast cancer should receive Herceptin, either as adjuvant treatment or with non-anthracycline-based neoadjuvant chemotherapy.

- **St Gallen Expert Consensus Guidelines 2015 [Coates 2015]** The St Gallen international expert consensus guidelines for the management of early breast cancer supported dual anti-HER2 therapy with a taxane, Herceptin and Perjeta as an “acceptable regimen” for patients with stage 2 HER2-positive disease. The guidelines also stated “…there is increasing support for neoadjuvant … combined chemotherapy and anti-HER2 therapy in patients with HER2-positive disease and large tumours…” This is an advance upon the previous expert consensus guidelines from 2013 where the majority of the expert consensus recommended the use of chemotherapy plus Herceptin alone (without additional anti-HER agents).
- **National Comprehensive Cancer Network (NCCN) Guidelines for Invasive Breast Cancer, 2015**

  The guidelines advise the preferred regimens for HER2-positive disease are:

  - doxorubicin + cyclophosphamide followed by paclitaxel + Herceptin with/without Perjeta
  - docetaxel + carboplatin + Herceptin, with/without Perjeta

  Other regimens suggested are:

  - doxorubicin + cyclophosphamide followed by docetaxel + Herceptin with/without Perjeta
  - docetaxel + cyclophosphamide + Herceptin
  - FEC followed by docetaxel (or paclitaxel) + Herceptin + Perjeta
  - paclitaxel + Herceptin
  - Perjeta + Herceptin + docetaxel (or paclitaxel) followed by FEC

3.7 Issues relating to current clinical practice

Describe any issues relating to current clinical practice, including any variations or uncertainty about established practice.

There is likely to be heterogeneity in the treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer at high risk of

recurrence in clinical practice, as outlined below. There is variation across the UK in whether patients will be offered neoadjuvant treatment and in the information available to clinicians when recommending a treatment plan. However, if the decision is made to use a neoadjuvant treatment approach in patients with HER2-positive disease, then the neoadjuvant treatment regimen will typically involve Herceptin, used in combination with chemotherapy [Data on File: RXUKPERT00220(1)].

Identification of patients with HER2-positive disease: Despite recommendations by NICE that HER2 status be assessed and results made available within 2 weeks [NICE CG80; NICE 2011], the results of HER2 testing may not be available for all patients with HER2-positive disease prior to a decision on their treatment plan. Expert opinion from UK breast surgeons and oncologists suggests that UK clinical teams discussing patients' treatment plans do not always know the patients' HER2 status at the time of discussion. A patient with HER2-positive early breast cancer is only eligible to receive a Perjeta-based or Herceptin-based regimen if HER2-positivity is confirmed. As a result, HER2 test result turnaround times likely lead to variation in practice.

Definition of high risk of recurrence: There is also likely to be variation in the treatment decisions made by multidisciplinary teams (MDTs) at different UK centres in terms of defining HER2-positive early breast cancer patients who are at high risk of recurrence. As stated in the EPAR for Perjeta, locally advanced and inflammatory breast cancers are considered high-risk irrespective of hormone receptor status in the neoadjuvant setting [CHMP 2015]. In early stage breast cancer a number of factors are taken into consideration when determining whether a patient is at high risk of recurrence, including tumour size, grade, hormone receptor status and lymph node metastases [CHMP 2015]. However, there are differing views on the appropriate tumour size that is suitable for neoadjuvant treatment (ranging from ≥1 cm to ≥3 cm) [Data on File: RXUKPERT00246]; the views of oncologists and surgeons vary widely. In addition, UK expert opinion suggests that tumours may not always be graded at the outset. The key studies of Perjeta as neoadjuvant treatment included patients with locally advanced and inflammatory breast cancers, as well as those with early breast cancer of differing stages, ensuring that patients at high risk

of recurrence have been evaluated by the clinical study programme [see Section 4.8 [Gianni 2012; Schneeweiss 2013].

Selection of treatment strategy: Whether neoadjuvant treatment is offered (and which treatment) depends on characteristics of the tumour and the patient, including: assessment of the tumour in terms of size, spread, nodal involvement and pathology; how physically fit the patient is; and the surgical plan for the patient, e.g. whether breast conserving surgery (BCS) is preferred. Current data suggest that approximately 27% of patients with HER2-positive disease in the UK receive neoadjuvant treatment [Data on File: RXUKPERT00244].

Selection of (neoadjuvant) treatment regimen: Guidelines for the treatment of breast cancer, including early breast cancer, widely recommend the use of HER2-targeted therapies in those with HER2-positive disease [see 3.5 Guidance related to the condition and 3.6 Other clinical guidelines] [Coates 2015; NCCN 2015; NICE CG80]. As such, Herceptin-based regimens are considered the standard of care for the treatment of patients with HER2-positive early breast cancer, in both the neoadjuvant and adjuvant settings [Senkus 2015; Coates 2015]. The use of Herceptin in the neoadjuvant setting is based on the NOAH study, in which participants received 11 cycles of Herceptin prior to surgery [Gianni 2010 NOAH]. Herceptin-based neoadjuvant treatment can be given to patients before surgery, followed by adjuvant Herceptin to complete 1 year of treatment [Herceptin SmPC; Goldhirsch 2013; NCCN 2015; Senkus 2015]. Of those with HER2-positive early breast cancer who do receive neoadjuvant treatment, expert opinion suggests that the regimen will contain Herceptin in over 75% of cases [Data on File: RXUKPERT00220(1)].

Most commonly, the chemotherapy regimens administered with Herceptin as part of a neoadjuvant treatment regimen will include [Data on File: RXUKPERT00220(1)]:

- FEC-T: Anthracycline-based regimen of fluorouracil + epirubicin + cyclophosphamide (FEC) for three cycles, followed by a taxane (e.g. docetaxel; T) for three cycles
- Taxane plus carboplatin for six cycles (anthracycline-free)

These chemotherapy regimens closely resemble those assessed in the cardiac safety study TRYPHAENA, to which Perjeta was added. Patients in this study were assigned to one of the following regimens as neoadjuvant treatment [Schneeweiss 2013]:

- Arm A: Perjeta + Herceptin + FEC (3 cycles) followed by Perjeta + Herceptin + Docetaxel (3 cycles)
- Arm B: FEC (3 cycles) followed by Perjeta + Herceptin + Docetaxel (3 cycles)
- Arm C: Perjeta + Herceptin + Docetaxel + carboplatin (6 cycles)

4. Clinical effectiveness

4.1 Identification and selection of relevant studies

4.1.1 Methodology and objective

Advise whether a search strategy was developed to identify relevant studies for the technology. If a search strategy was developed and a literature search carried out, provide details under the subheadings listed in this section. Key aspects of study selection can be found in Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination).

A systematic literature review was conducted to identify all relevant published and unpublished randomised controlled trial (RCT) evidence relating to the use of Perjeta in combination with Herceptin and chemotherapy as neoadjuvant treatment in adults with HER2-positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence.

The systematic literature review was conducted according to the NICE guide to the methods of technology appraisal 2013 and therefore adhered to the Centre for Reviews and Dissemination guidance for undertaking systematic reviews in health care.

4.1.2 - Search strategy

Describe the search strategies used to retrieve relevant clinical data. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided so that the results may be reproduced. This includes a full list of all information sources and the full electronic search strategies for all databases, including any limits applied. The search strategies should be provided in an appendix

The complete search strategy for this review is provided in Appendix 5 Search strategy for systematic literature review of RCTs. The following sources were searched, using search terms that combined population, interventions and study types:

- Electronic databases were searched from database inception to 6th November 2015, except for Embase Alert which was searched to 17th November 2015:
    - Embase (Ovid SP)
    - MEDLINE and MEDLINE In-Process (Ovid SP)
    - Embase Alert (ProQuest)
    - Cochrane Central Library of Controlled Trials (Cochrane Library)
- Congress proceedings were also searched manually for the most recent 2 years:
    - American Society of Clinical Oncology (ASCO) Annual Meeting (2015 and 2014 meetings)
    - European Society for Medical Oncology (ESMO) Congress (2014 meeting)
    - American Society of Breast Surgeons (2015 and 2014 meetings)
    - American Society of Clinical Oncology (ASCO), Breast Cancer Symposium (2015 and 2014 meetings)
    - European Society for Medical Oncology (ESMO), IMPAKT Breast Cancer Conference (2015 and 2014 meetings)
    - San Antonio Breast Cancer Symposium (SABCS) (2014 and 2013 meetings)
    - St. Gallen International Breast Cancer Conference (2015 meeting)
- The reference lists of included articles were hand-searched for potentially relevant studies

4.1.3 Study selection

Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process in a table. Justification should be provided to ensure that the rationale for study selection is transparent.

4.1.3.1 Inclusion and exclusion criteria

The eligibility criteria used for the systematic review are presented in Table 6. No language restrictions were used.

Table 6 Eligibility criteria for systematic literature review of RCT evidence

Domain	Inclusion criteria	Exclusion criteria
Population	• Treatment-naïve adults (18 years and over) with HER2-positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence • Patients may have: o Operable stage I or II early breast cancer (T2-3, N0-1 [node negative or positive], M0) o Locally advanced stage III breast cancer (T2-3, N2-3, M0 or T4a-c, any N, M0) o Inflammatory breast cancer (T4d, any N, M0) • HER2-positive disease may be defined as: oHER2 over-expression 3+ by IHC oHER2 amplification by FISH* • Patients may be hormone receptor positive or negative and may be either pre- or post-menopausal	Studies that do not include the patient population of interest, or that do not present relevant outcomes for the population of interest separately to outcomes for other patients
Interventions	• Perjeta-based regimens used as neoadjuvant treatment	-
Comparators	• Any comparator regimen	-
Outcomes	• Progression-free survival • Event free survival • Disease-free survival • Overall survival • Pathological complete response (any definition)	• Pharmacokinetic outcomes
Study design	• Phase II, III or IV RCTs • Systematic reviews/meta-analyses of RCTs	• Phase I clinical trials • Narrative or non-systematic reviews • Case studies and case reports • Observational studies
Other considerations	• Only publications on human subjects will be included • No timeframe restrictions will be used • Articles can be in any language, with studies taking place in any country	-

*FISH, fluorescence *in situ* hybridisation; HER2, human epidermal growth receptor 2; IHC, immunohistochemistry; RCT, randomised controlled trial

4.1.3.2 Review strategy

The following review process was followed:

- Title/abstract review

  Each abstract was reviewed against the inclusion/exclusion criteria by two independent reviewers. Where the applicability of the inclusion criteria was unclear, the article was included at this stage in order to ensure that all potentially relevant studies were captured. Any discrepancies between the

two independent reviewers was resolved by a third independent reviewer making the final decision.

- Full-text review

  Each full-text article was reviewed against the inclusion/exclusion criteria by two independent reviewers, who came to a consensus on the included articles. In cases where the article did not give enough information to be sure if it met the inclusion criteria, the article was excluded to ensure that only relevant articles were ultimately included in the systematic review. The results of the two reviewers were compared and any disagreements resolved by discussion until a consensus was met.

- Data extraction

  The methods and results of all included studies were extracted into pre-specified data extraction tables in Microsoft Word by a single reviewer who also assessed study quality. A second independent reviewer then independently verified the extracted information, checked that no relevant information had been missed and also assessed study quality. Any discrepancies or missing information identified by the second individual were discussed by both individuals until a consensus was reached on the information that should be presented in the extraction tables.

4.1.4 Search results

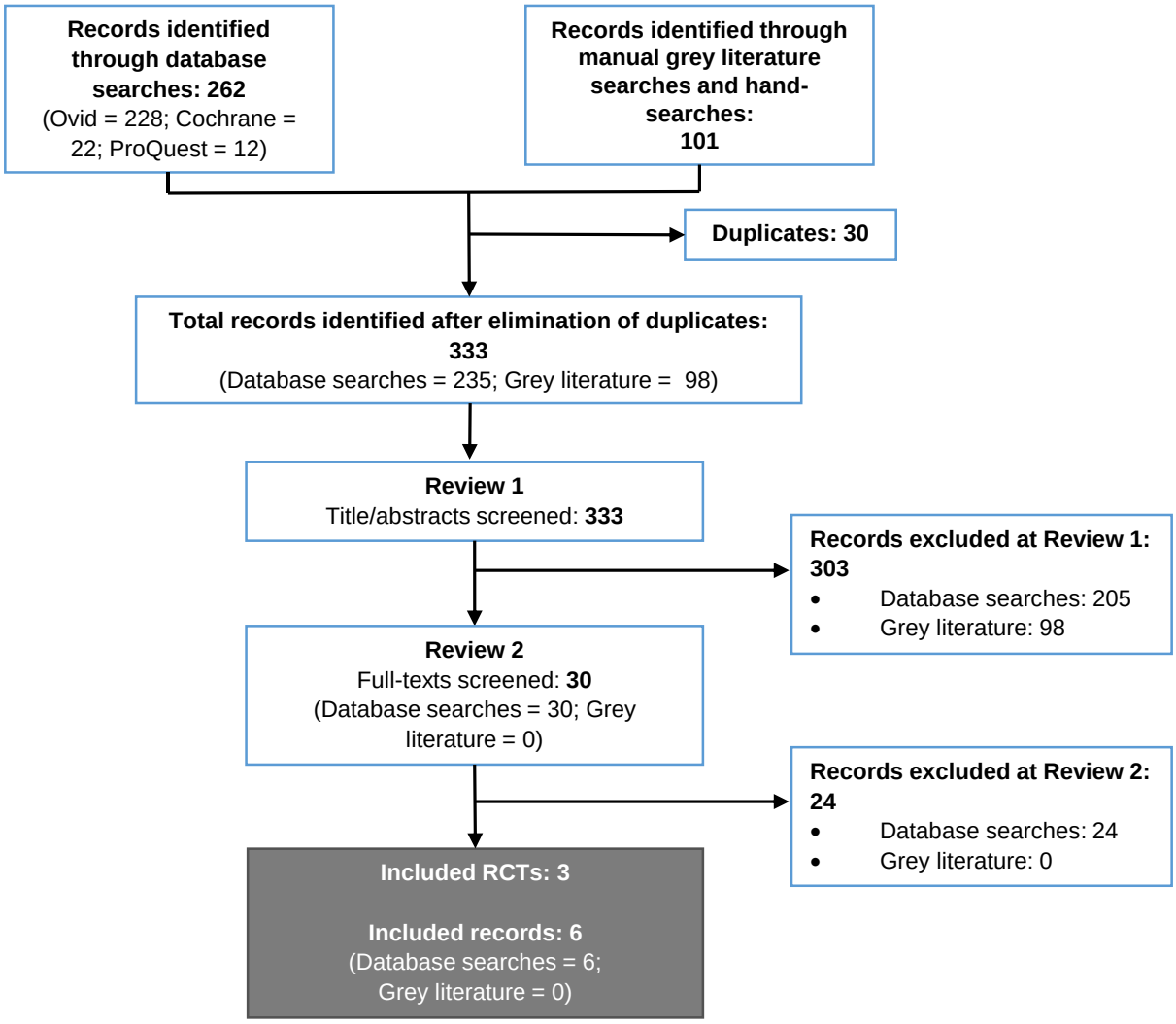
A flow diagram of the numbers of studies included and excluded at each stage should be provided using a validated statement for reporting systematic reviews and meta-analyses, such as the PRISMA flow diagram**. The total number of studies in the statement should equal the total number of studies listed in section 4.2.**

When data from a single study have been drawn from more than 1 source (for example, a poster and a published report) or when trials are linked (for example, an open-label extension to a randomised controlled trial [RCT]), this should be clearly stated.

Provide a complete reference list for excluded studies in an appendix.

The electronic database search (accessed 6th or 17th November 2015; see Appendix 5 Search strategy for systematic literature review of RCTs) identified 262 records and searches of conference proceedings and reference lists identified 101 records; in total, 333 records (235 database abstracts, 98 conference abstracts) were screened after de-duplication of results. Of these, 303 records were excluded based on the screening of the title/abstract. On re-application of the review eligibility criteria to the remaining full-text articles, six records were ultimately included in the review, which reported outcomes of three RCTs (NeoSphere, TRYPHAENA and GeparSepto; see Table 120 in Appendix 6 Records included in the systematic literature review of RCTs). The 24 records excluded from the systematic review at the full-text review stage can also be found listed in Table 121 in Appendix 6 Records included in the systematic literature review of RCTs with the reason for exclusion.

Figure 4 PRISMA diagram for systematic literature review of RCTs (search cut-off date: 6th or 17th November 2015)



RCT, randomised controlled trial

4.2 List of relevant randomised controlled trials

4.2.1 In a table, present the list of relevant RCTs comparing the intervention with other therapies (including placebo) in the relevant patient group. Highlight which studies compare the intervention directly with the appropriate comparator(s) with reference to the decision problem. If there are none, state this.

4.2.2 When the RCTs listed above have been excluded from further discussion, justification should be provided to ensure that the rationale for

doing so is transparent. For example, when RCTs have been identified, but there is no access to the level of data required, this should be stated.

The efficacy and safety of Perjeta in combination with Herceptin and chemotherapy have been studied in two key phase II, randomised, active-controlled trials (NeoSphere, and TRYPHAENA). Data from these studies are supported further by early analysis of the HER2-positive subpopulation in the phase III, randomised active-controlled trial GeparSepto. This study assessed the efficacy and safety of paclitaxel or nab-paclitaxel, in addition to chemotherapy and, if disease was HER2-positive, Perjeta and Herceptin were added to the chemotherapy regimen.

The GeparSepto study will not be considered as a key trial in this submission because currently available data for the HER2-positive subpopulation in this trial are very limited (primary endpoint of pCR only). Furthermore, no safety data were presented for the HER2-positive patient subgroup in the interim analysis.

No further randomised controlled trials comparing the efficacy and safety of Perjeta in combination with Herceptin and chemotherapy as neoadjuvant treatment of HER2-positive breast cancer were found. A summary of the identified RCTs is provided in Table 7.

Table 7 List of relevant RCTs

Trial number (name)	Sponsor	Intervention	Comparator	Population	Primary study reference
NCT00545688 (NeoSphere)	F Hoffmann-La Roche	Arm A: H plus T Arm B: P and H plus T Arm C: P and H (no chemotherapy) Arm D: P plus T After completion of neoadjuvant treatment, eligible patients underwent surgery and adjuvant chemotherapy. All patients received concomitant H for 1 year.	N/A	Female patients aged ≥18 years with centrally confirmed HER2-positive operable (T2–3, N0–1, M0), locally advanced (T2–3, N2–3, M0 or T4a–c, any N, M0), or inflammatory (T4d, any N, M0) breast cancer with primary tumours >2 cm in diameter and who had not received any previous cancer therapy.	Gianni et al. 2012 [Gianni 2012]: data cut-off date: December 2009 Additional reference: Gianni et al. 2011 [Gianni 2011]: data cut-off date: December 2009 Five-year analysis: Gianni et al. 2015 [Gianni 2015]
NCT00976989 (TRYPHAENA)	F. Hoffmann-La Roche Ltd, Basel, Switzerland	Arm A: FEC followed by T, with H and P given concurrently throughout (FEC + H + P x 3→T + H + P x 3) Arm B: FEC followed by T + H+ P (FEC x 3→T + H+ P x 3) Arm C: T, carboplatin, H with P (TCH+P ×6)	N/A	Female patients aged ≥18 years with operable (T2-3, N0-1, M0), locally advanced (T2-3, N2 or N3, M0; T4a-c, any N, M0), or inflammatory (T4d, any N, M0) HER2-positive breast cancer and a primary tumour size >2 cm.	Schneeweiss et al. 2013 [Schneeweiss 2013]: data cut-off: July 2012
NCT01583426 (GeparSepto)	Financially supported by Roche and Celgene	Nab-paclitaxel (125 mg/m^2) q1w for 12 weeks followed by 4 cycles of conventionally dosed EC (E, 90 mg/m^2; C, 600 mg/m^2) q3w HER2-positive patients received H (loading dose 8 mg/kg; 6 mg/kg) plus P (loading dose 840 mg; 420 mg) q3w concomitantly	Paclitaxel (80 mg/m^2) q1w for 12 weeks followed by 4 cycles of conventionally dosed EC (E, 90 mg/m^2; C 600 mg/m^2) q3w HER2-positive patients received H (loading dose 8 mg/kg; 6 mg/kg) plus P (loading dose 840 mg; 420 mg) q3w concomitantly	Patients with untreated, histologically confirmed uni- or bilateral, cT2- cT4d carcinoma, and no clinically relevant cardiovascular and other co-morbidities.	Untch et al. 2015 (oral presentation at 2014 San Antonio Breast Cancer Symposium) [Untch 2015] Protocol amendment 3 (version 10.06.2015) available online [GeparSepto protocol] ClinicalTrials.gov was used to supplement the information available in the primary reference.

C, cyclophosphamide; E, epirubicin; FEC, 5-fluorouracil, epirubicin and cyclophosphamide; H, Herceptin; HER2, human epidermal growth factor receptor 2; N/A, not applicable; P, Perjeta; q1w, once weekly; q3w, every three weeks; T, docetaxel; TCH, docetaxel, carboplatin and Herceptin

4.3 Summary of methodology of the relevant randomised controlled trials

4.3.1 Items 3 to 6b of the CONSORT checklist should be provided for all RCTs listed:

4.3.2 Provide a comparative summary of the methodology of the RCTs in a table.

The regulatory submission, which forms the basis of the EMA's regulatory approval for Perjeta in combination with Herceptin and chemotherapy for the neoadjuvant treatment of adult patients with HER2-positive early breast cancer, is based primarily on the two pivotal studies, NeoSphere and TRYPHAENA.

The analyses of NeoSphere and TRYPHAENA studies are listed in Table 8, whilst the methodology of the supportive study GeparSepto is presented in Appendix 3 Summary of the GeparSepto study.

Table 8 Analyses and data cut-off dates for NeoSphere and TRYPHAENA (CSRs)

Trial	Outcome (data cut-off date)	Description
NeoSphere	Primary endpoint - pCR (22 December 2009)	• Measured when all patients had received neoadjuvant treatment and had either undergone primary surgery or withdrawn from the study • Included safety data for the neoadjuvant period, as well as available safety data for the adjuvant period
	Additional safety data (9 March 2012)	• Additional safety data following the completion of all study treatment, including complete safety data for the adjuvant period
	Further safety data (12 July 2013)	• The second update CSR provided new safety data reported during the post-treatment follow-up period between the second (9 March 2012) and the third (12 July 2013) clinical cut-off dates
	Progression-free survival (PFS) and updated safety data (20 October 2014)	• Provided updated safety data, and the first (and final) efficacy data on progression-free survival (PFS) • Final safety data reported during the post-treatment follow-up period were also presented
TRYPHAENA	Primary analysis (cardiac safety) (21 June 2011)	• Measured when patients had (whichever occurred earlier): ○ received six cycles of neoadjuvant treatment, or ○ undergone surgery and had all necessary samples taken, or ○ withdrawn from the study
	Updated safety data (04 July 2012)	• Occurred once all patients had received a total of 17 cycles of Herceptin
	Additional safety data (22 July 2013)	• The second update CSR provided additional safety data reported during the post-treatment follow-up period (i.e., data from patients who completed neoadjuvant and adjuvant treatment, or who withdrew from treatment but were still on study)

Key aspects of methodology for the relevant RCTs (NeoSphere and TRYPHAENA) have been detailed below using items 3 to 6b of the CONSORT checklist. Each study is presented fully in turn.

Following the presentation of the methodology of the studies, the meta-analysis sponsored by US Food and Drug Administration (FDA) is presented as evidence of validity to evaluate the use of pathological complete response (pCR) as an acceptable clinical endpoint in neoadjuvant breast cancer trials. [Cortazar 2014] This meta-analysis of nearly 12,000 patients also evaluated the relationship between three pCR definitions (bpCR, tpCR and GBG pCR) and long-term outcomes. Please be aware that some of these neoadjuvant trials from this meta-analysis are not summarised in this submission with respect to methodology as they do not fall within the scope of the decision problem.

4.3.1 Key aspects of methodology for the relevant RCTs

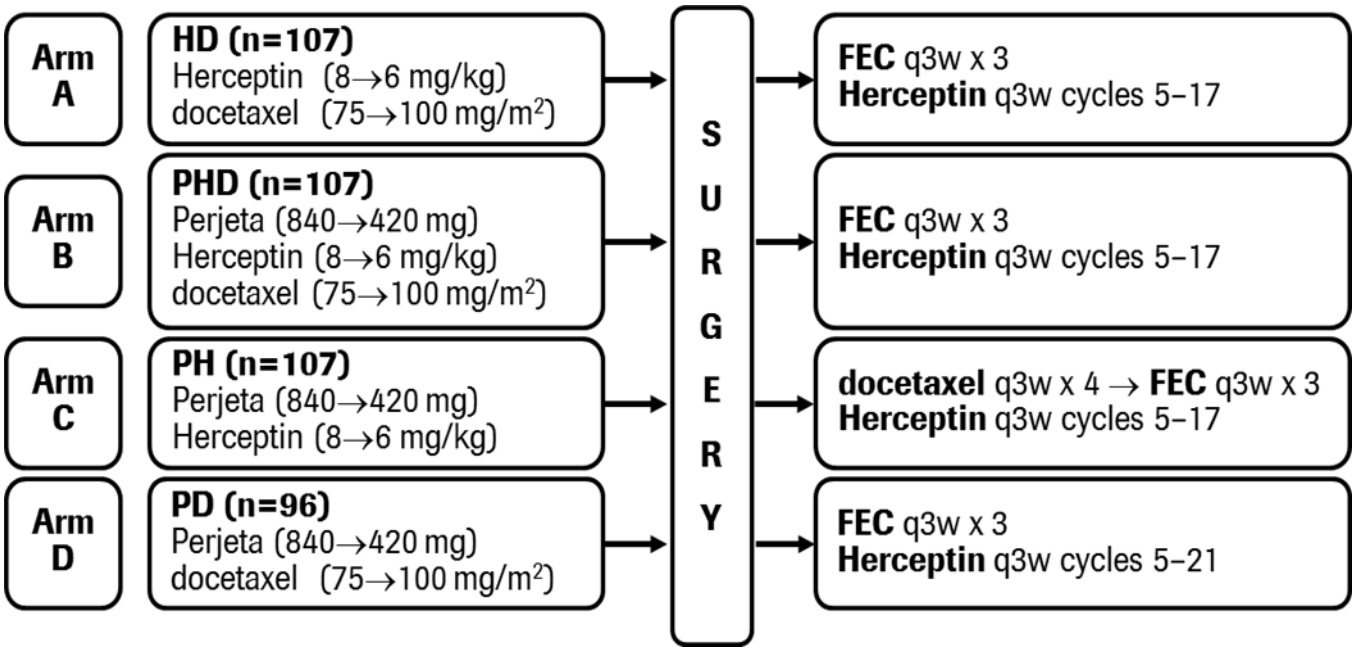
The NeoSphere study [Gianni 2012; NeoSphere Primary CSR]

Trial design: NeoSphere is a phase II, multicentre, multinational, randomised, four-arm trial to investigate the efficacy and safety of Perjeta in combination with Herceptin and docetaxel in the neoadjuvant setting in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer. The study enrolled 417 patients. [Gianni 2012]

All patients received neoadjuvant treatment every three weeks for four cycles before surgery, according to the treatment arm to which they were randomised. Pathological complete response (pCR) was evaluated after surgery. Following surgery, patients received three cycles of adjuvant FEC therapy (5-fluorouracil + epirubicin + cyclophosphamide). Patients in Arm C received four cycles of docetaxel before FEC. All patients received concomitant Herceptin every three weeks as an adjuvant treatment to complete one year of treatment. [Gianni 2012]

The study design is shown in Figure 5.

Figure 5 Study schematic for NeoSphere study



HD, Herceptin + docetaxel; PHD, Perjeta + Herceptin + docetaxel; PH, Perjeta + Herceptin; PD, Perjeta + docetaxel; FEC, 5-fluorouracil + epirubicin + cyclophosphamide; q3w, every three weeks

Eligibility criteria: Table 9 contains details of the key inclusion and exclusion criteria for the study.

Table 9 Key inclusion/exclusion criteria for NeoSphere study [Gianni 2012; Primary CSR]

Inclusion criteria	Exclusion criteria
• Female patients aged ≥18 years • Centrally confirmed HER2-positive operable (T2-3, N0-1, M0), locally advanced (T2-3, N2-3, M0 or T4a-c, any N, M0), or inflammatory (T4d, any N, M0) breast cancer • Primary tumour >2 cm in diameter • HER2-positive as determined by immunohistochemistry (IHC) score of 3+ or 2+, and positive for fluorescence or chromogenic in-situ hybridisation (FISH/CISH) • Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 • Baseline left ventricular ejection fraction (LVEF) of ≥55% as measured by echocardiography (ECHO) or multiple gated acquisition (MUGA) • No previous cancer therapy	• Metastatic disease (stage IV), bilateral breast cancer, or other malignancies (except for carcinoma in situ of the cervix or basal cell carcinoma) • Inadequate bone marrow or renal function • Impaired liver function • Impaired cardiac function • Uncontrolled hypertension • Severe uncontrolled systemic disease (e.g., hypertension, clinically significant cardiovascular, pulmonary, metabolic, wound-healing, ulcer, or bone fracture) • Pregnancy • Refusal to use contraception

Settings and locations where the data were collected: From 17 December 2007 to 22 December 2009, patients were enrolled across 59 centres in 16 countries. [Gianni 2012] Patients were enrolled at centres in Australia, Austria, Brazil, Canada, Italy, Mexico, Peru, Poland, Republic of Korea, Russian Federation, Spain, Sweden, Switzerland, Taiwan, Thailand, and the United Kingdom. There were two centres in the UK. [NeoSphere Primary CSR]

Trial drugs and concomitant medications: Prior to surgery, trial treatments were given according to treatment arm as follows:

- Perjeta was administered intravenously every three weeks. A fixed loading dose of 840 mg was administered at cycle 1; fixed maintenance doses of 420 mg were given at each cycle thereafter.

- Herceptin was administered intravenously every three weeks. A weight-based loading dose of 8 mg/kg was administered at cycle 1; weight-based maintenance doses of 6 mg/kg were given at each cycle thereafter.

- Docetaxel was administered intravenously every three weeks. The initial dose was 75 mg/m^2; the dose could then be escalated to 100 mg/m^2 as tolerated.

After completion of four cycles of neoadjuvant treatment, eligible patients underwent surgery and received three cycles of adjuvant FEC therapy. Patients in Arm C received four cycles of docetaxel before FEC. The FEC regimen consisted of:

- 5-flurouracil 600 mg/m² intravenously every three weeks
- epirubicin 90 mg/m² intravenously every three weeks
- cyclophosphamide 600 mg/m² intravenously every three weeks

Herceptin was administered to all patients to complete one year of therapy (every three weeks for cycles 5-17; patients in Arm D received Herceptin in cycles 5-21). [Gianni et al, 2012]

Permitted/excluded concomitant medications are listed in Table 10.

Table 10 Permitted/excluded concomitant medications in NeoSphere study [Primary CSR]

Permitted therapies	Excluded therapies
• H1 and H2 antagonists (e.g., diphenhydramine, cimetidine) • Analgesics (e.g., paracetamol, meperidine, acetaminophen, opioids) • Corticosteriods to treat or prevent allergic or infusion reactions • Antiemetics (approved prophylactic serotonin antagonists, benzodiazepines, ondansetron etc.) • Medication to treat diarrhoea (e.g., loperamide) • Colony stimulating factors (e.g., granulocyte colony-stimulating factor [G-CSF]) • Oestrogen receptor antagonists (e.g., tamoxifen) or aromatase inhibitors (e.g., anastrazole, exemestane) after completion of post-operative chemotherapy as per local practice • Acceptable methods of contraception, mandatory for female patients or male partners who were not surgically sterilised or did not meet the study definition of postmenopausal (≥ 12 months of amenorrhoea)	• Anti-cancer therapies other than those administered in this study, including cytotoxic chemotherapy, radiotherapy (except for adjuvant radiotherapy for breast cancer after completion of chemotherapy), immunotherapy, and biological anti-cancer therapy • Any targeted therapy • Treatment with steroids except for thyroid hormone replacement therapy and short term corticosteroids, in order to treat or prevent allergic or infusion reactions • High doses of systemic corticosteroids. High dose was considered as >20 mg of dexamethasone a day (or equivalent) for >7 consecutive days • Any investigational agent, except for those used for this study • Initiation of herbal remedies. Herbal remedies initiated prior to study entry and continuing during the study were permitted • Any oral, injected or implanted hormonal methods of contraception

Primary outcome:

The primary endpoint was pCR rate in the breast (bpCR) at the time of surgery.

- pCR was defined as an absence of invasive neoplastic cells at microscopic examination of the tumour remnants after surgery following neoadjuvant therapy

- The bpCR rate is the proportion of the intent-to-treat (ITT) population that achieved a bpCR

In addition, tpCR[1] data were collected prospectively in order to conduct exploratory analyses on clinical efficacy.

Pathologists at participating centres followed guidelines for the assessment of pathological complete response on serial sections of the surgical specimen. Blinded pathology data were reviewed by a consultant pathologist at regular intervals to ensure consistency. [Gianni 2012]

Secondary outcomes [NeoSphere Primary CSR]:

- **Progression-free survival (PFS):** the time from the date of randomisation to the first documentation of progressive disease (PD) or death. Contralateral in-situ disease was not considered as PD in this definition.

- **Disease-free survival (DFS):** the time from the first date of no disease (i.e., the date of surgery) to the first documentation of PD or death. Contralateral in-situ disease was not considered as PD in this definition.

- **Clinical response rate (CRR):** best tumour responses were recorded as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD) and were identified as per local practice based on RECIST criteria. Clinical response rate (CRR) was the proportion of patients who achieved a clinical response (CR or PR) during cycles 1–4 (pre-surgery). Clinical response was required to be assessed by clinical breast examination (CBE), at each cycle between days 15–21 or on study day 1 of the next cycle, and by mammography at baseline and cycle 4. Mammography and/or other conventional methods could also be used as per local medical practice; however a mammogram was only mandatory at baseline and after completion of neoadjuvant therapy. The same techniques were to be used for evaluating the target lesion for all assessments throughout the treatment period.

  For simplicity, some important modifications to RECIST criteria were employed for each of the following categories:

[1] total pathological complete response, defined as absence of invasive tumour in breast and lymph nodes irrespective of ductal carcinoma in-situ (ypT0/is ypN0).

- Primary lesion: RECIST criteria were applied in terms of percentage, but the sum of lesions was not used: only the size of the primary breast lesion by method of assessment was entered to determine response.

- Overall response: the sizes would only be summed if the method of assessment was the same for all lesions (breast and nodes). For example, if the patient had a breast lesion measured by mammogram and lymph nodes assessed by ultrasound, each would only be summed within that method of assessment. Therefore, care should be taken when interpreting these results.

- **Time to clinical response:** the time from the date of first dose received to the date of assessment of clinical response.

- **Rate of breast-conserving surgery:** for all patients with T2–3 tumours (i.e. excluding patients with inflammatory breast cancer) for whom mastectomy was planned at diagnosis. (NB: patients with inflammatory disease received mastectomy irrespective of their response to neoadjuvant treatment.)

- **Evaluation of biomarkers:** those that may be associated with primary and secondary efficacy endpoints in accordance with each treatment arm.

It is important to note that the protocol required individual patient follow-up as follows:

"After completion of the study treatment, patients will be followed up for progression free survival (PFS) until disease progression or until five years after randomisation of the last patient, whichever is earlier".

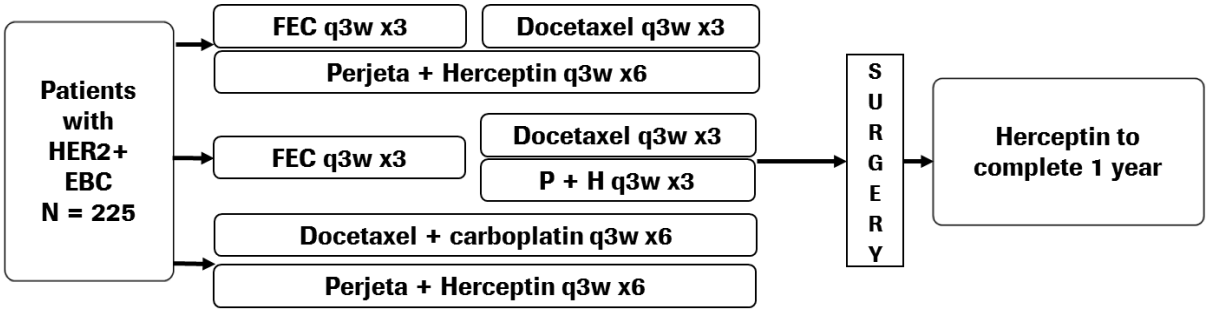
Survival status was also collected for patients, but only when available. Overall survival was not a protocol-defined secondary efficacy endpoint and, therefore, survival status was not systematically reported beyond progressive disease, disease recurrence or withdrawal.

TRYPHAENA [Schneeweiss 2013] [Primary CSR]

Trial Design: TRYPHAENA is a phase II, multinational, multicentre, randomised, three-arm open-label study designed to primarily evaluate the tolerability and cardiac safety of Perjeta when added to Herceptin in combination with anthracycline- or carboplatin-based neoadjuvant systemic chemotherapy in patients with HER2-positive operable, locally advanced, or inflammatory primary breast cancer with a primary tumour size >2 cm.

Patients were randomly allocated to receive one of three neoadjuvant treatment regimens for six cycles prior to surgery. Following surgery, all patients received adjuvant Herceptin every three weeks to complete a total of one year of treatment. Patients received further adjuvant treatment (radiotherapy, chemotherapy, hormonal treatment) according to local guidelines. [Schneeweiss 2013] Figure 6 shows the overall schema of the study design.

Figure 6 Study schematic for TRYPHAENA study



x3, for three cycles; x6, for six cycles; EBC, early breast cancer; FEC, 5-flurouracil + epirubicin + cyclophosphamide; q3w, every three weeks; P, Perjeta; H, Herceptin

Eligibility criteria: Table 11 contains details of the key inclusion and exclusion criteria for the study.

Table 11 Key inclusion/exclusion criteria for TRYPHAENA study [Schneeweiss 2013]

Trial	Inclusion criteria	Exclusion criteria
TRYPHAENA	• Female patients aged ≥18 years • Operable (T2-3, N0-1, M0), locally advanced (T2-3, N2 or N3, M0; T4a-c, any N, M0), or inflammatory (T4d) primary breast cancer • Primary tumour ≥2 cm. Tumors had to be HER2 3+ by immunohistochemistry (IHC) or fluorescent in situ hybridisation (FISH)/chromogenic in situ hybridisation (CISH) positive. FISH/CISH positivity mandatory for HER2 2+ tumours • Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 • Left ventricular ejection fraction (LVEF) ≥55% at baseline	• Metastatic disease (stage IV) or bilateral breast cancer • Previous systemic local anti-cancer therapy • Other malignancy • Inadequate bone marrow, liver or renal function • Uncontrolled hypertension or history of myocardial infarction within 6 months of enrolment

Settings and locations where the data were collected: From December 2009 to January 2011, patients were recruited from 44 centres in 19 countries. [Schneeweiss 2013] Patients were enrolled at centres in the Bahamas, Bosnia & Herzegovina, Brazil, Canada, Croatia, Germany, Italy, Mexico, New Zealand, Portugal, Republic of China, Republic of Korea, Republic of Serbia, Romania, South Africa, Spain, Sweden, Switzerland and the United Kingdom. There were three centres in the UK. [TRYPHAENA Primary CSR]

Trial drugs and concomitant medications: Prior to surgery, trial treatments were given according to treatment arm as follows: [Schneeweiss 2013]

All study drugs were administered intravenously on a 3-weekly schedule. Patients received six cycles of neoadjuvant treatment.

- Perjeta was administered intravenously every three weeks. A fixed loading dose of 840 mg was administered at cycle 1; fixed maintenance doses of 420 mg were given at each cycle thereafter.

- Herceptin was administered intravenously every three weeks. A weight-based loading dose of 8 mg/kg was administered at cycle 1; weight-based maintenance doses of 6 mg/kg were given at each cycle thereafter.

- The FEC regimen (Arms A and B[1]) consisted of:

    - 5-fluorouracil 500 mg/m² intravenously every three weeks
    - epirubicin 100 mg/m² intravenously every three weeks
    - cyclophosphamide 600 mg/m² intravenously every three weeks

- In Arms A and B, docetaxel was given at an initial dose of 75 mg/m^2 in cycle 4, and escalating to 100 mg/m^2 in subsequent cycles if tolerated. In Arm C, docetaxel was given at 75 mg/m^2 (no dose escalation allowed)

- In Arm C, carboplatin was administered at a dose of AUC6 (area under the plasma concentration-time curve)

Dose modifications were not permitted for Perjeta or Herceptin. Docetaxel could be reduced to 75 mg/m^2 then to 60 mg/m^2 (re-escalation was not permitted). Dose modifications for FEC and carboplatin were permitted as per local prescribing information. [Schneeweiss et al, 2013]

Permitted/excluded concomitant medications are listed in Table 12.

[1] Arm A: FEC+Herceptin+Perjeta x3 cycles → Docetaxel+Herceptin+Perjeta x3 cycles
Arm B: FEC x3cycles → docetaxel+Herceptin+Perjeta x3 cycles
Arm C: Perjeta+docetaxel+carboplatin+Herceptin x6 cycles

Table 12 Key inclusion/exclusion criteria for TRYAPHENA study [Schneeweiss 2013]

Trial	Inclusion criteria	Exclusion criteria
TRYPHAENA	• Acceptable methods of contraception when the female patient or male partner was not surgical sterilised or did not meet the study definition of post-menopausal (≥12 months of amenorrhoea). • H1 and H2 antagonist (e.g. diphenhydramine, cimetidine) • Analgesics (e.g. paracetamol, meperidine, opioids) • Short term use of corticosteroids to treat or prevent allergic or infusion reactions • Antiemetics (approved prophylactic serotonin-antagonists, benzodiazepines, ondansetron etc.) • Medication to treat diarrhoea (e.g., loperamide) • Colony stimulating factors (e.g., G-CSF) • Oestrogen receptor antagonist (e.g., tamoxifen) or aromatase inhibitors (e.g., anastrazole, exemestane) after completion of post-operative chemotherapy as per local practice.	• Anti-cancer therapies other than those administered in this study, including cytotoxic chemotherapy, radiotherapy, (except for adjuvant radiotherapy for breast cancer after completion of chemotherapy or additional adjuvant chemotherapy immediately post-surgery, if deemed necessary) immunotherapy, and biological anti-cancer therapy • Any targeted therapy • Treatment with steroids except for thyroid hormone replacement therapy and short term corticosteroid, in order to treat or prevent allergic or infusion reactions • High doses of systemic corticosteroids. High dose is considered as >20 mg of dexamethasone a day (or equivalent) for >7 consecutive days. • Any investigational agent, except for those used for this study • Initiation of herbal remedies • Any oral, injected or implanted hormonal methods of contraception

Outcomes

The outcomes and endpoints employed in TRYPHAENA are commonly used in neoadjuvant breast cancer studies.

Primary outcomes [TRYPHAENA Primary CSR]

The primary outcomes were:

- Incidence of symptomatic left ventricular systolic dysfunction (LVSD)
- Incidence of decline in left ventricular ejection fraction (LVEF) of ≥10% from baseline to <50%, during neoadjuvant treatment

LVEF was measured by multiple-gated acquisition (MUGA) or echocardiography (ECHO) – the same method was required to be used throughout the study for an individual patient. The assessments were carried out: at baseline; at cycles 2, 4 and 6; prior to cycle 7; at cycles 10, 12, 15 and 18; and at the final visit (or withdrawal). Copies of ECHO and MUGA scans were assessed by a central laboratory; patient medical management was based on local ECHO readings. LVSD was reported as a serious adverse event (SAE).

Adverse events were graded for intensity according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0.

Secondary outcomes:

Secondary endpoints investigated activity and safety during neoadjuvant and adjuvant treatment.

- **Pathological complete response:** assessed locally, defined as absence of invasive neoplastic cells at microscopic examination of the primary tumour in the breast at surgery (bpCR) or in both the breast and lymph nodes (tpCR).

- **Clinical response rate (CRR):** the proportion of patients who achieved a complete or partial response at any time before surgery.

  Tumour assessments were carried out at baseline, after cycle 6 (before surgery), and at the final visit (or withdrawal from study). Patients underwent clinical breast examination (CBE), mammogram or magnetic resonance imaging (MRI).

  Investigator assessment of overall tumour response was assessed at every cycle and at the final visit (or withdrawal from study). Patients underwent CBE and/or mammography or other conventional methods as per local practice, such as magnetic resonance imaging (MRI), ultrasound, X-rays, or computed tomography (CT).

- **Time to clinical response:** the time from the date of first dose received to the first date of assessment of clinical response.

- **Rate of breast-conserving surgery (BCS):** in patients for whom a mastectomy had been planned prior to treatment (T2–3). This was defined as the proportion of patients who achieved breast-conserving surgery out of the ITT population without inflammatory breast cancer (these patients received mastectomy irrespective of their response to neoadjuvant treatment).

- **Disease-free survival (DFS):** defined as the time from the first date of no disease (i.e., date of surgery) to the first documentation of progressive disease (PD) or death. Any evidence of contralateral disease in situ was not considered as PD. DFS was described separately in patients who achieved a pCR from those who did not. DFS was also described for the overall intention-to-treat (ITT) population. Patients who were withdrawn from the study without documented PD were censored at the date of the last assessment when the patient was known to be disease-free.

- **Progression-free survival (PFS):** defined as the time from the date of randomisation to the first documentation of PD or death. Patients who were withdrawn from the study without documented PD were censored at the date of the last assessment when the patient was known to be free from PD. Patients without post-baseline assessments but known to be alive were censored at the time of randomisation plus one day.

- **Overall survival (OS):** defined as the time from randomisation to the date of death from any cause. Patients who were alive or lost to follow-up were censored at the last known alive date. Patients with no post-baseline information were censored at the date of randomisation plus one day.

Evidence for the reliability, validity and current status of pathological complete response (pCR) as an outcome measure

Meta-analysis investigating the predictive value of pCR to DFS, PFS and OS outcomes

An international working group known as the Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC) group was established by the FDA specifically to evaluate the relationship between three pCR definitions (see Table 13 below) and long-term outcomes (e.g. EFS and OS). [Cortazar 2014]

Table 13 Definitions of pathological complete response

Abbreviation	Definition
pCR	pathological complete response
bpCR	pathological complete response in the breast, defined as absence of invasive tumour in the breast irrespective of ductal carcinoma in-situ or nodal involvement (ypT0/is)
tpCR	total pathological complete response, defined as absence of invasive tumour in breast and lymph nodes irrespective of ductal carcinoma in-situ (ypT0/is ypN0)
GBG pCR	defined as absence of invasive cancer and in-situ cancer in the breast and axillary nodes (ypT0 ypN0)

The meta-analysis used primary source data from nearly 12,000 patients enrolled in published randomised neoadjuvant trials. PubMed, Embase and Medline were searched for reports of clinical trials of neoadjuvant treatment of breast cancer published between 1 January 1990 and 1 August 2011. [Cortazar 2014]

To be included in the analysis each trial had to have:

- ≥200 patients with eBC treated with neoadjuvant chemotherapy followed by surgery

- Data available for pCR, EFS and OS
- Median follow up of ≥3 years

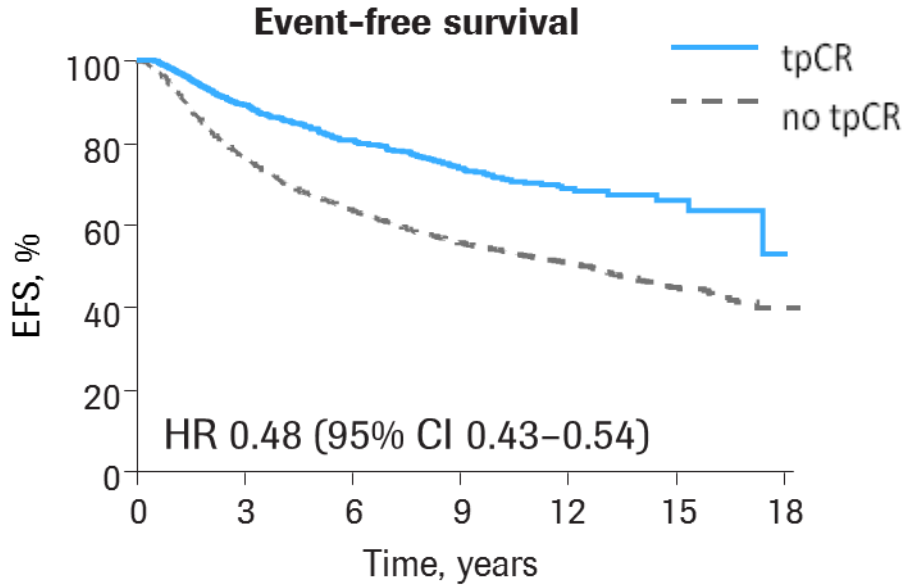
The following trials were identified for this analysis:

- AGO 1, [Untch 2009 AGO]
- ECTO, [Gianni 2009 ECTO]
- EORTC 10994/BIG 1-00, [Bonnefoi 2011]
- GeparDuo, [von Minckwitz 2005 GeparDuo]
- GeparQuattro, [von Minckwitz 2010 GeparQuattro] [Untch 2010 GeparQuattro]
- GeparTrio, [von Minckwitz 2008 GeparTrio] [von Minckwitz 2008a GeparTrio]
- GeparTrio Pilot, [von Minckwitz 2005 GeparTrio pilot]
- NOAH, [Gianni 2010 NOAH]
- NSABP B-18, [Wolmark 2001 NSABP B18] [Rastogi 2008 NSABP B18&B27]
- NSABP B-27, [Rastogi 2008 NSABP B18&B27] [Bear 2003 NSABP B27]
- PREPARE, [Untch 2011 PREPARE] [Untch 2011a PREPARE]
- TECHNO [Untch 2011 TECHNO]

The CTNeoBC group looked at the three most commonly used definitions of pCR (bpCR, tpCR,GBG pCR). tpCR and GBG pCR were better associated with improved EFS and OS than bpCR. Associations with EFS and OS were similar for tpCR and GBG pCR, and therefore the tpCR definition was used for subsequent analyses by clinical tumour subtype.

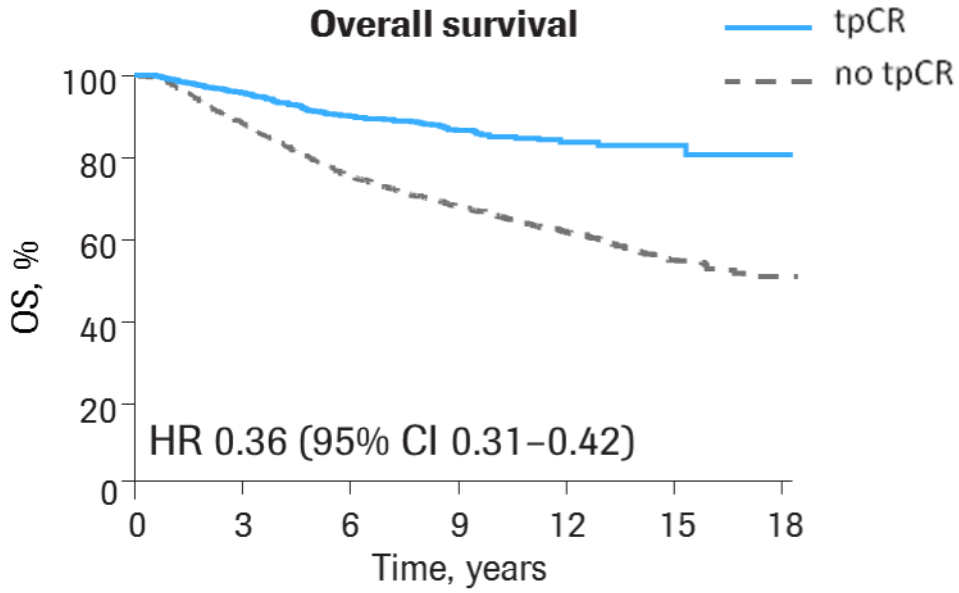
Patients who achieved tpCR had improved EFS (hazard ratio [HR] 0.48, [95% CI: 0.43-0.54], p<0.001) and OS (HR 0.36; [95% CI: 0.31-0.42], p<0.001) compared with those who did not achieve tpCR. See Figure 7 and Figure 8.

Figure 7 Kaplan-Meier plot of association between tpCR and EFS [Cortazar 2014]



n at risk							
tpCR	2,131	1,513	583	337	124	35	2
no tpCR	9,824	6,169	2,674	1,523	525	165	1

Figure 8 Kaplan-Meier plot of association between tpCR and OS [Cortazar 2014]



n at risk							
tpCR	2,131	1,618	640	383	145	43	3
no tpCR	9,824	7,119	3,173	1,859	659	209	3

The strongest association was seen in patients with more aggressive tumour types where pCR rates were the highest such as patients with HER2-positive, hormone receptor-negative tumours who received Herceptin (pCR rate = 50.3 [95 % CI 45.0–55.5]) patients with HER2-negative hormone receptor-positive disease, and triple negative breast cancer. For patients with HER2-positive hormone-receptor negative tumours, risk of death was reduced by 92% (95% CI: 78–97%) for patients achieving pCR, compared with those who did not achieve pCR. [Cortazar 2015].

Despite the association between pCR and long-term outcome observed, the absolute magnitude of improvement in pCR rate needed to affect long-term outcome was not formally established in this meta-analysis. This was thought to be primarily due to insufficient information (although a large number of patients were included, the meta-analysis included patients with heterogeneous tumour types and only 1989 patients were known to have HER2-positive disease). However, a modest correlation between change in pCR and change in EFS was observed for the subgroup of patients with HER2-positive disease. The authors suggested that the low overall pCR rates, heterogeneous patient populations, and/or inclusion of only a single study (NOAH; Gianni 2010) designed to evaluate the effects of a targeted therapy in the meta-analysis may have hindered their ability to establish a predictive correlation. [Cortazar 2014]

4.3.2 Comparative tabulated summary of the methodology of the RCTs

Table 14 provides a side-by-side comparison of the methodology of the two neoadjuvant studies. Details for GeparSepto are provided in Appendix 3 Summary of the GeparSepto study.

Table 14 Comparative summary of the methodology of the neoadjuvant trials

Trial name	NeoSphere	TRYPHAENA
Location	Multicentre	Multicentre
Trial design	Phase II, multinational, multicentre, randomised, four-arm study to investigate the efficacy and safety of Perjeta in combination with Herceptin and docetaxel in the neoadjuvant setting in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer	Phase II, multinational, multicentre, randomised, three-arm open-label study designed to primarily evaluate the tolerability and cardiac safety of Perjeta when added to Herceptin in combination with anthracycline- or carboplatin-based neoadjuvant systemic chemotherapy in patients with HER2-positive operable, locally advanced, or inflammatory primary breast cancer
Eligibility criteria for trial participants	HER2-positive early breast cancer • Operable (T2–3, N0–1, M0), or • Locally advanced (T2–3, N2–3, M0; T4a–c, any N, M0), or • Inflammatory (T4d, any N, M0) Primary tumour ≥2 cm	HER2-positive early breast cancer • Operable (T2–3, N0-1, M0), or • locally advanced (T2–3, N2–3, M0; T4a–c, any N, M0), or • Inflammatory (T4d, any N, M0) Primary tumour ≥2 cm
Settings and locations where the data were collected	59 centres in 16 countries Australia, Austria, Brazil, Canada, Italy, Mexico, Peru, Poland, Republic of Korea, Russian Federation, Spain, Sweden, Switzerland, Taiwan, Thailand, United Kingdom (2 centres)	44 centres in 19 countries Bahamas, Bosnia & Herzegovina, Brazil, Canada, Croatia, Germany, Italy, Mexico, New Zealand, Portugal, Republic of China, Republic of Korea, Republic of Serbia, Romania, South Africa, Spain, Sweden, Switzerland, United Kingdom (3 centres)
Trial drugs and concomitant medications	Arm A: Before surgery: Herceptin + docetaxel every three weeks for four cycles After surgery: FEC every three weeks for three cycles + Herceptin every three weeks for 13 cycles Arm B: Before surgery: Perjeta + Herceptin + docetaxel every three weeks for four cycles After surgery: FEC every three weeks for three cycles + Herceptin every three weeks for 13 cycles Arm C: Before surgery: Perjeta + Herceptin every three weeks for four cycles After surgery: Docetaxel every three weeks for four cycles, then FEC every three weeks for three cycles) + Herceptin every three weeks for 13 cycles	Arm A: Before surgery: FEC + Herceptin + Perjeta every three weeks for three cycles, then docetaxel + Herceptin + Perjeta every three weeks for three cycles After surgery: Herceptin every three weeks for 11 cycles Arm B: Before surgery: FEC every three weeks for three cycles, then docetaxel + Herceptin + Perjeta every three weeks for three cycles After surgery: Herceptin every three weeks for 14 cycles Arm C: Before surgery: docetaxel + carboplatin + Herceptin + Perjeta every three weeks for six cycles After surgery: Herceptin every three weeks for 11 cycles

	Arm D: Before surgery: Perjeta + docetaxel every three weeks for four cycles After surgery: FEC every three weeks for three cycles + Herceptin every three weeks for 17 cycles	
	<u>Study drug doses</u> Perjeta: 840 mg IV loading dose followed by 420 mg IV q3w Herceptin: 8 mg/kg body weight IV loading dose followed by 6 mg/kg body weight q3w Docetaxel: initial dose 75 mg/m^2; the dose could then be escalated to 100 mg/m^2 as tolerated FEC: 5-fluorouracil 600 mg/m² IV q3w epirubicin 90 mg/m² IV q3w cyclophosphamide 600 mg/m² IV q3w	<u>Study drug doses</u> Perjeta: 840 mg IV loading dose followed by 420 mg IV q3w Herceptin: 8 mg/kg IV loading dose followed by 6 mg/kg q3w Docetaxel: • Arms A and B, docetaxel was given at an initial dose of 75 mg/m^2 in cycle 4, and escalating to 100 mg/m^2 in subsequent cycles if tolerated. • Arm C, docetaxel was given at 75 mg/m^2 (no dose escalation allowed) FEC: 5-fluorouracil 500 mg/m² IV q3w epirubicin 100 mg/m² IV q3w cyclophosphamide 600 mg/m² IV q3w Carboplatin: administered at a dose of AUC6 (area under the plasma concentration-time curve)

	Permitted concomitant therapies • H1 and H2 antagonists • Analgesics • Corticosteriods • Antiemetics • Anti-diarrhoeals • Colony stimulating factors • Oestrogen receptor antagonists • Acceptable methods of contraception Excluded concomitant therapies • Anti-cancer therapies • Any targeted therapy • Steroids • High doses of systemic corticosteroids • Any investigational agent • Initiation of herbal remedies • Oral, injected or implanted hormonal methods of contraception	Permitted concomitant therapies • H1 and H2 antagonist • Analgesics • corticosteroids • Antiemetics • Anti-diarrhoeals • Colony stimulating factors • Oestrogen receptor antagonist • Acceptable methods of contraception Excluded concomitant therapies • Anti-cancer therapies • Any targeted therapy • Steroids • High doses of systemic corticosteroids • Any investigational agent, • Initiation of herbal remedies • Any oral, injected or implanted hormonal methods of contraception
Primary outcome(s)	pCR rate in the breast (bpCR) at the time of surgery	Incidence of symptomatic left ventricular systolic dysfunction (LVSD) Incidence of decline in left ventricular ejection fraction (LVEF) of ≥10% from baseline to <50%, during neoadjuvant treatment
Secondary outcomes	• Progression-free survival (PFS) • Disease-free survival (DFS) • Clinical response rate (CRR) • Time to clinical response • Rate of breast-conserving surgery (BCS) • Evaluation of biomarkers	• Pathological complete response • Clinical response rate (CRR) • Time to clinical response • Rate of breast-conserving surgery (BCS) • Disease-free survival (DFS) • Progression-free survival (PFS) • Overall survival (OS)
Pre-planned sub-groups	Subgroups included stratification by: • Hormone status • Breast cancer type: operable, locally advanced and inflammatory breast cancer	• pCR rate endpoint was analysed by breast cancer type (operable, locally advanced, inflammatory) • pCR rate endpoint was analysed by hormone receptor status (positive or negative)

4.4 Statistical analysis and definition of study groups in the relevant randomised controlled trials

4.4.1 During completion of this section consider items 7a (sample size), 7b (interim analyses and stopping guidelines), 12a (statistical methods used to compare groups for primary and secondary outcomes) and 12b (methods for additional analyses, such as subgroup analyses and adjusted analyses) of the CONSORT checklist.

4.4.2 For each trial listed, provide details of the trial population included in the primary analysis of the primary outcome and methods used to take account of missing data (for example, a description of the intention-to-treat analysis carried out, including censoring methods, or whether a per-protocol analysis was carried out).

4.4.3 For each trial, provide details of the statistical tests used in the primary analysis. Also provide details of the primary hypothesis or hypotheses under consideration, the power of the trial and a description of sample size calculation, including rationale and assumptions in a table. If the outcomes were adjusted for covariates, provide the rationale.

Key aspects of the statistical analysis for the relevant RCTs have been detailed below using items 7a (sample size), 7b (interim analyses and stopping guidelines), 12a (statistical methods used to compare groups for primary and secondary outcomes) and 12b (methods for additional analyses) of the CONSORT checklist. Details of the trial population included in the primary analysis of the primary outcome for each RCT have been provided.

The NeoSphere study [Gianni 2012; NeoSphere Primary CSR]

Statistical hypotheses: Three individual hypotheses were tested using a two-sided Cochrane Mantel-Haenszel test at an alpha level of 0.2. (A two-sided test was appropriate because it was not known *a priori* with confidence in which direction the difference would lie for all comparisons).

The comparisons were stratified by operable, locally advanced, and inflammatory breast cancer, and hormone receptor positivity.

Table 15 Study hypotheses [NeoSphere Primary CSR]

	Arm A vs Arm B	Arm A vs arm C	Arm D vs arm B
Null hypothesis	pCR A rate = pCR B rate	pCR A rate = pCR C rate	pCR D rate = pCR B rate
Alternative hypothesis	pCR A rate ≠ pCR B rate	pCR A rate ≠ pCR C rate	pCR D rate ≠ pCR B rate
Arm A: Herceptin + docetaxel; Arm B: Perjeta + Herceptin + docetaxel Arm C: Perjeta + Herceptin; Arm D: Perjeta + docetaxel			

Arm D was added to the study following a protocol amendment; thus, formal comparison of Arm D with Arm A was not pre-specified and not powered to test the hypotheses. [Gianni 2012]

As there were three individual comparisons a Simes multiplicity adjustment was applied to the individual p-values obtained at the end of the study to maintain the overall false positive risk at 0.2.

Sample size: 400 patients were planned to be randomised into the study (approximately 100 per treatment arm). With 400 patients and an overall alpha level of 0.2 the study would have 80% power to detect an absolute percentage increase of 15% between each of the three primary comparisons. [Gianni 2012]

A total of 417 patients were eligible for randomisation into the four treatment arms.

Analysis populations:

The intention-to-treat (ITT) population is defined as all randomised patients, regardless of whether or not they received study medication. Data for patients in the ITT population are grouped according to the study treatment arm to which they were assigned.

The per protocol (PP) population is a sub-set of the ITT population. It excludes patients who were deemed to have major protocol violations prior to the adjuvant phase of the study. Data for patients in the PP population are grouped according to the study treatment arm to which they were assigned.

The safety population includes patients who received at least one dose of study medication, and who had at least one safety assessment performed at baseline. Data for patients in the safety population are grouped according to the treatment they actually received. NeoSphere Primary CSR]

Interim analysis

No interim analyses of the primary endpoint (pCR) were planned or performed.

A pre-planned descriptive follow-up analysis in the ITT population conducted at five years after randomisation of the last patient. This analysis focused on PFS and DFS. Cardiac function and LVEF data were presented. [Gianni 2015]

Primary endpoint analysis

The pCR rate was calculated for each arm by dividing the number of patients achieving pCR by the ITT population.

pCR rate for the Perjeta + Herceptin + docetaxel arm (Arm B) and the Perjeta + Herceptin arm (Arm C) were each compared to the Herceptin + docetaxel arm (Arm A). pCR rate for Perjeta + docetaxel (Arm D) was compared to the Perjeta + Herceptin + docetaxel arm (Arm B). All three comparisons were of equal importance. The comparisons were made using a Cochrane Mantel-Hansel test, stratified by:

- operable breast cancer (T2–3, N0–1, M0)
- locally advanced breast cancer (T2–3, N2, M0; T4a–c, any N, M0)
- inflammatory breast cancer (T4d, any N, M0)
- oestrogen and/or progesterone positivity (either positive vs both negative)

In order to assess the robustness of the primary analysis based on the ITT population, the primary analysis was repeated for the safety population. The primary analysis was also repeated on only the patients who were randomised into the study. [NeoSphere Primary CSR]

Secondary endpoint analyses

The following secondary endpoints were calculated and summarised for descriptive purposes only:

- best tumour response (tabulated)
- clinical response rate (tabulated)
- time to clinical response
- proportion of patients with T2-3 tumours achieving breast conserving surgery (tabulated)
- progressive disease

Best tumour response: Tumour response was assessed during Cycles 1–4 (pre-surgery) - at each cycle, between Days 15–21 or on Study Day 1 of the next cycle. The response was calculated separately for each assessment modality, for patients with evaluable results. The best tumour response was defined separately for the primary, secondary breast lesions, all breast tumours, axillary nodes, ipsilateral supraclavicular nodes and for all nodes examined as being the best tumour response (CR>PR>SD>PD[1]) a patient achieved during the neoadjuvant period.

Time to clinical response: The Kaplan-Meier approach was used to estimate median time to clinical response for each treatment arm. The Cox proportional hazard model, stratified by operable, locally advanced, inflammatory breast cancer and oestrogen and/or progesterone receptor positivity was used to estimate the hazard ratio (HR; i.e., the magnitude of treatment effect) and its 95% confidence interval (CI), for description purposes only.

PFS and DFS: Patients who withdrew from the study without documented progression and for whom there was evidence that evaluations were made, were censored at the date of the last assessment when the patient was known to be free from PD. Patients without post-baseline assessments but known to be alive were

[1] CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease

censored at the time of randomisation. DFS is described separately in patients who achieved a pCR from those who did not. Patients who had surgery but did not achieve a pCR were censored at date of surgery. Patients who withdrew from the study without documented progression and for whom there was evidence that evaluations were made, were censored at the date of the last assessment when the patient was known to be disease-free. [NeoSphere Primary CSR]

The TRYPHAENA study [Schneeweiss 2013; TRYPHAENA Primary CSR]

Statistical hypotheses

No formal hypothesis testing was planned or carried out, and no statistical comparison was made between the treatment arms. Therefore, secondary endpoints were calculated and summarised only for descriptive purposes. However:

- For the assessment of incidence of symptomatic LVSD, if the true underlying incidence was 3%, the probability of observing more than five such events in a treatment arm was 0.025. 95% confidence intervals were calculated for incidence of LVSD and incidence of LVEF decline equal or greater than 10% from baseline to <50%.

- Expectations for bpCR rates were: Arm A[1]: 50%; Arm B: 45%; Arm C: 40%. With a planned sample size of 225 patients, if these response rates were observed, the minimum true efficacy (lower bound of 95% CI) of the estimates would be Arm A: 38.9%; Arm B: 33.8%; Arm C: 28.9%

Sample size

The sample size was based on the primary (safety) endpoint. Approximately 75 patients per arm were planned to be recruited into the study (225 patients in total).

[1] Arm A: FEC+Herceptin+Perjeta x3 cycles → Docetaxel+Herceptin+Perjeta x3 cycles
Arm B: FEC x3 cycles → docetaxel+Herceptin+Perjeta x3 cycles
Arm C: Perjeta+docetaxel+carboplatin+Herceptin x6 cycles

Analysis populations

The intent-to-treat population is defined as all patients randomised, regardless of whether they received any study medication. All efficacy outputs were produced for the ITT population. Data for patients in the ITT population are grouped according to the study treatment arm to which they were assigned.

The safety population included patients who received any amount of study medication. Data for patients in the safety population are grouped according to the treatment they actually received.

Interim analyses

No interim analyses were planned or performed.

A post-hoc exploratory analysis was performed, refining the analysis to patients achieving a pCR in the absence of both positive lymph nodes and ductal carcinoma in situ / lobular carcinoma in situ (DCIS/LCIS).

DFS, PFS and OS will be reported after all patients have completed adjuvant treatment.

Primary endpoint analysis

The primary objective of the study was to describe the tolerability of the treatment regimens in Arms, A[1], B and C during neoadjuvant treatment. Therefore, the primary endpoint of this study did not relate to efficacy. The following safety endpoints were of primary importance for the evaluation of the primary objective:

- Incidence of symptomatic cardiac events as assessed by the Investigator (Grade 3, 4 or 5 symptomatic LVSD)
- Clinically significant LVEF declines over the course of the neoadjuvant period (LVEF decline of ≥10% from baseline and to a value of <50%)

[1] Arm A: FEC+Herceptin+Perjeta x3 cycles → Docetaxel+Herceptin+Perjeta x3 cycles
Arm B: FEC x3cycles → docetaxel+Herceptin+Perjeta x3 cycles
Arm C: Perjeta+docetaxel+carboplatin+Herceptin x6 cycles

The primary endpoint was assessed using the safety population. All safety parameters were summarised and presented in tables. The primary safety endpoints were summarised for each treatment arm, along with their associated 95% CIs.

For selected events of particular interest, symptomatic LVSD, and asymptomatic decline in LVEF requiring treatment or leading to discontinuation of Perjeta and Herceptin, summary tables for time to first onset of the event and for the total number of episodes are presented. Every occurrence of an event in any patient was counted in the total number of episodes. However, successive reports of an identical event in the same period (i.e., neoadjuvant or adjuvant) were combined into one episode if:

- the end date of the earlier event was the same as the start date of the later event, or
- if the end date of the earlier event was missing

Secondary endpoint analysis

Secondary endpoints were calculated and summarised for descriptive purposes only.

pCR was defined at the time of surgery and the rate is the proportion of the ITT population that achieved a pCR. A 95% confidence interval (CI) was calculated around the observed pCR rate for each treatment arm in order to show the variability associated with the point estimate.

Clinical response rate and the proportion achieving BCS in each treatment arm were tabulated, together with their associated 95% CIs. The Kaplan-Meier approach was used to estimate median time to clinical response for each treatment arm. The Cox proportional hazards model, (stratified by, operable, locally advanced, inflammatory breast cancer and oestrogen and or progesterone receptor positivity) was used to estimate the Hazard Ratio (HR, i.e., the magnitude of treatment effect) and its 95% CI, for descriptive purposes only.

Summary of statistical analyses in the RCTs

Details of the statistical tests used in the primary analysis for each RCT is provided, including details of the primary hypothesis or hypotheses under consideration, the power of the trial and a description of sample size calculation, including rationale and assumptions. (Details for GeparSepto are provided in Appendix 3 Summary of the GeparSepto study)

Table 16 Summary of the statistical analyses in the neoadjuvant studies

Trial name	NeoSphere	TRYPHAENA
Hypothesis objective	• To determine whether Perjeta + Herceptin + docetaxel (Arm B) is superior to Herceptin + docetaxel (Arm A), or Perjeta + docetaxel (Arm D) • To determine whether Perjeta + Herceptin (Arm C) is superior to Herceptin + docetaxel (Arm A) H_0: pCR rate (Arm A) = pCR rate (Arm B) vs H_1: pCR rate (Arm A) ≠ pCR rate (Arm B) H_0: pCR rate (Arm A) = pCR rate (Arm C) vs H_1: pCR rate (Arm A) ≠ pCR rate (Arm C) H_0: pCR rate (Arm D) = pCR rate (Arm B) vs H_1: pCR rate (Arm D) ≠ pCR rate (Arm B) Three individual hypotheses were tested using a two-sided Cochrane Mantel-Haenszel test at an alpha level of 0.2. As there were three individual comparisons a Simes multiplicity adjustment was applied to the individual p-values obtained at the end of the study to maintain the overall false positive risk at 0.2.	Exploratory: The aim of this study was to explore and make a preliminary assessment of the tolerability of neoadjuvant treatment with the combination of Perjeta and Herceptin when given with either anthracycline or non-anthracycline based chemotherapy. No formal hypothesis testing was planned or carried out, and no statistical comparison was made between the treatment arms. Therefore, secondary endpoints were calculated and summarised only for descriptive purposes. However: • For the assessment of incidence of symptomatic LVSD, if the true underlying incidence was 3%, the probability of observing more than five such events in a treatment arm was 0.025. 95% confidence intervals were calculated for incidence of LVSD and incidence of LVEF decline equal or greater than 10% from baseline to <50%. • Expectations for bpCR rates were: ○ Arm A[1]: 50% ○ Arm B: 45% ○ Arm C: 40% With a planned sample size of 225 patients, if these response rates were observed, the minimum true efficacy (lower bound of 95% CI) of the estimates would be ○ Arm A: 38.9% ○ Arm B: 33.8% ○ Arm C: 28.9%
Statistical analysis	All the efficacy analyses were carried out in the ITT population.	The primary endpoint for this study is safety

[1] Arm A: FEC+Herceptin+Perjeta x3 cycles → Docetaxel+Herceptin+Perjeta x3 cycles
Arm B: FEC x3cycles → docetaxel+Herceptin+Perjeta x3 cycles
Arm C: Perjeta+docetaxel+carboplatin+Herceptin x6 cycles

	The primary endpoint of pCR rate was calculated for each arm by dividing the number of patients achieving pCR by the ITT population. pCR rate for treatment arm B (Perjeta + Herceptin + docetaxel) and treatment arm C (Perjeta + Herceptin) were each compared to treatment arm A (Herceptin + docetaxel). pCR rate for treatment arm D (Perjeta + docetaxel) was compared to treatment arm B (Perjeta + Herceptin + docetaxel). All three comparisons were of equal importance. The comparisons were made using a Cochrane Mantel-Hansel test, stratified by: • operable breast cancer (T2–3, N0–1, M0) • locally advanced breast cancer (T2–3, N2, M0; T4a–c, any N, M0) • inflammatory breast cancer (T4d, any N, M0) • oestrogen and/or progesterone positivity (either positive vs both negative) The following secondary endpoints were calculated and summarised for descriptive purposes only: • best tumour response (tabulated) • clinical response rate (tabulated) • time to clinical response • proportion of patients with T2-3 tumours achieving breast conserving surgery (tabulated) • progressive disease	• Incidence of symptomatic cardiac events as assessed by the Investigator (Grade 3, 4 or 5 symptomatic LVSD) • Clinically significant LVEF declines over the course of the neoadjuvant period (LVEF decline of ≥10% from baseline and to a value of <50%) The primary endpoint was assessed using the safety population. All safety parameters were summarised and presented in tables. The primary safety endpoints were summarised for each treatment arm, along with their associated 95% CIs. pCR was defined at the time of surgery and the rate is the proportion of the ITT population that achieved a pCR. A 95% confidence interval (CI) was calculated around the observed pCR rate for each treatment arm in order to show the variability associated with the point estimate. Secondary endpoints were calculated and summarised for descriptive purposes only. Clinical response rate and the proportion achieving BCS in each treatment arm were tabulated, together with their associated 95% CIs. The Kaplan-Meier approach was used to estimate median time to clinical response for each treatment arm. The Cox proportional hazards model, (stratified by, operable, locally advanced, inflammatory breast cancer and oestrogen and or progesterone receptor positivity) was used to estimate the Hazard Ratio (HR, i.e., the magnitude of treatment effect) and its 95% CI, for descriptive purposes only.
Sample size, power calculation	400 patients were planned to be randomised into the study (approximately 100 per treatment arm). With 400 patients and an overall alpha level of 0.2 the study would have 80% power to detect an absolute percentage increase of 15% between each of the three primary comparisons.	The sample size was based on the primary (safety) endpoint. Approximately 75 patients per arm were planned to be recruited into the study (225 patients in total).
Data management, patient withdrawals	The intention-to-treat (ITT) population is defined as all randomised patients, regardless of whether they received study medication. Data for patients in the ITT population are grouped according to the study treatment arm to which they were assigned.	The intent-to-treat population is defined as all patients randomised, regardless of whether they received study medication. All efficacy outputs were produced for the ITT population. Data for patients in the ITT population are grouped according to the study treatment arm to which they were assigned.

	The per-protocol (PP) population is a sub-set of the ITT population. It excludes patients who were deemed to have major protocol violations prior to the adjuvant phase of the study. Data for patients in the PP population are grouped according to the study treatment arm to which they were assigned. The safety population includes patients who received at least one dose of study medication, and who had at least one safety assessment performed at baseline. Data for patients in the safety population are grouped according to the treatment they actually received. <u>Arm A (Herceptin + docetaxel):</u> 107 patients were randomised to receive this treatment (ITT population). One patient withdrew prior to treatment. One patient randomised to Arm B (Perjeta + Herceptin + docetaxel) actually received treatment for Arm A. Therefore, the safety population for Arm A included 107 patients. Four patients withdrew from neoadjuvant treatment. <u>Arm B Perjeta + Herceptin + docetaxel:</u> 107 patients were randomised to receive this treatment (ITT population). One patient randomised to Arm B actually received treatment for Arm A. One patient randomised to Arm D (Perjeta + docetaxel) actually received treatment for Arm B. Therefore, the safety population for Arm B included 107 patients. Five patients withdrew from neoadjuvant treatment. <u>Arm C Perjeta + Herceptin:</u> 107 patients were randomised to receive this treatment (ITT population). One patient randomised to Arm D (Perjeta + docetaxel) actually	The safety population includes patients who received at least one dose of study medication. Data for patients in the safety population are grouped according to the treatment they actually received. <u>Arm A:</u>[1] 73 patients were randomised to receive this treatment (ITT population). One patient withdrew prior to treatment. Therefore, the safety population for Arm A included 72 patients. Four patients withdrew from neoadjuvant treatment (three for safety reasons; one for non-safety reasons). <u>Arm B:</u> 75 patients were randomised to receive this treatment (ITT population). There were no withdrawals prior to treatment; therefore, there were 75 patients in the safety population for Arm B. Ten patients withdrew from neoadjuvant treatment (four for safety reasons; six for non-safety reasons). <u>Arm C:</u> 77 patients were randomised to receive this treatment (ITT population). One patient withdrew prior to treatment. Therefore, the safety population for Arm C included 76 patients. Nine patients withdrew from neoadjuvant treatment (five for safety reasons; four for non-safety reasons).

[1] Arm A: FEC+Herceptin+Perjeta x3 cycles → Docetaxel+Herceptin+Perjeta x3 cycles
Arm B: FEC x3cycles → docetaxel+Herceptin+Perjeta x3 cycles
Arm C: Perjeta+docetaxel+carboplatin+Herceptin x6 cycles

	received treatment for Arm C. Therefore, the safety population for Arm C included 108 patients. 14 patients withdrew from neoadjuvant treatment. <u>Arm D Perjeta + docetaxel:</u> 96 patients were randomised to receive this treatment (ITT population). One patient randomised to Arm D actually received treatment for Arm B (Perjeta + Herceptin + docetaxel). One patient randomised to Arm D actually received treatment for Arm C (Perjeta + Herceptin). Therefore, the safety population for Arm D included 94 patients. Six patients withdrew from neoadjuvant treatment.	

4.5 Participant flow in the relevant randomised controlled trials

4.5.1 Provide details of the numbers of participants who were eligible to enter the trials. Include the number of participants randomised and allocated to each treatment. Provide details of and the rationale for participants who crossed over treatment groups, were lost to follow-up or withdrew from the RCT. Provide a CONSORT diagram showing the flow of participants through each stage of each of the trials.

4.5.2 In a table describe the characteristics of the participants at baseline for each of the trials. Provide details of baseline demographics, including age, gender and relevant variables describing disease severity and duration and if appropriate previous treatments and concomitant treatment. Highlight any differences between trial groups.

For NeoSphere and TRYPHAENA, details of the numbers of participants who were eligible to enter the studies are provided, including numbers of patients randomised and allocated to treatment. A CONSORT diagram for NeoSphere and TRYPHAENA is provided, showing the flow of participants through each stage of each of the study including reasons for any patient withdrawals.

The characteristics of the patients at baseline for each of the studies are provided in table format for each of the studies, including baseline demographics (age, disease characteristics etc.)

As GeparSepto has not been fully published, no CONSORT diagram is available for this study. Baseline characteristics of the HER2-postive sub-group were not reported in the available publications. Therefore, we have presented the baseline characteristics of the whole population of GeparSepto: refer to Appendix 3 Summary of the GeparSepto study.

The NeoSphere study [Gianni et al, 2012; NeoSphere Primary CSR]

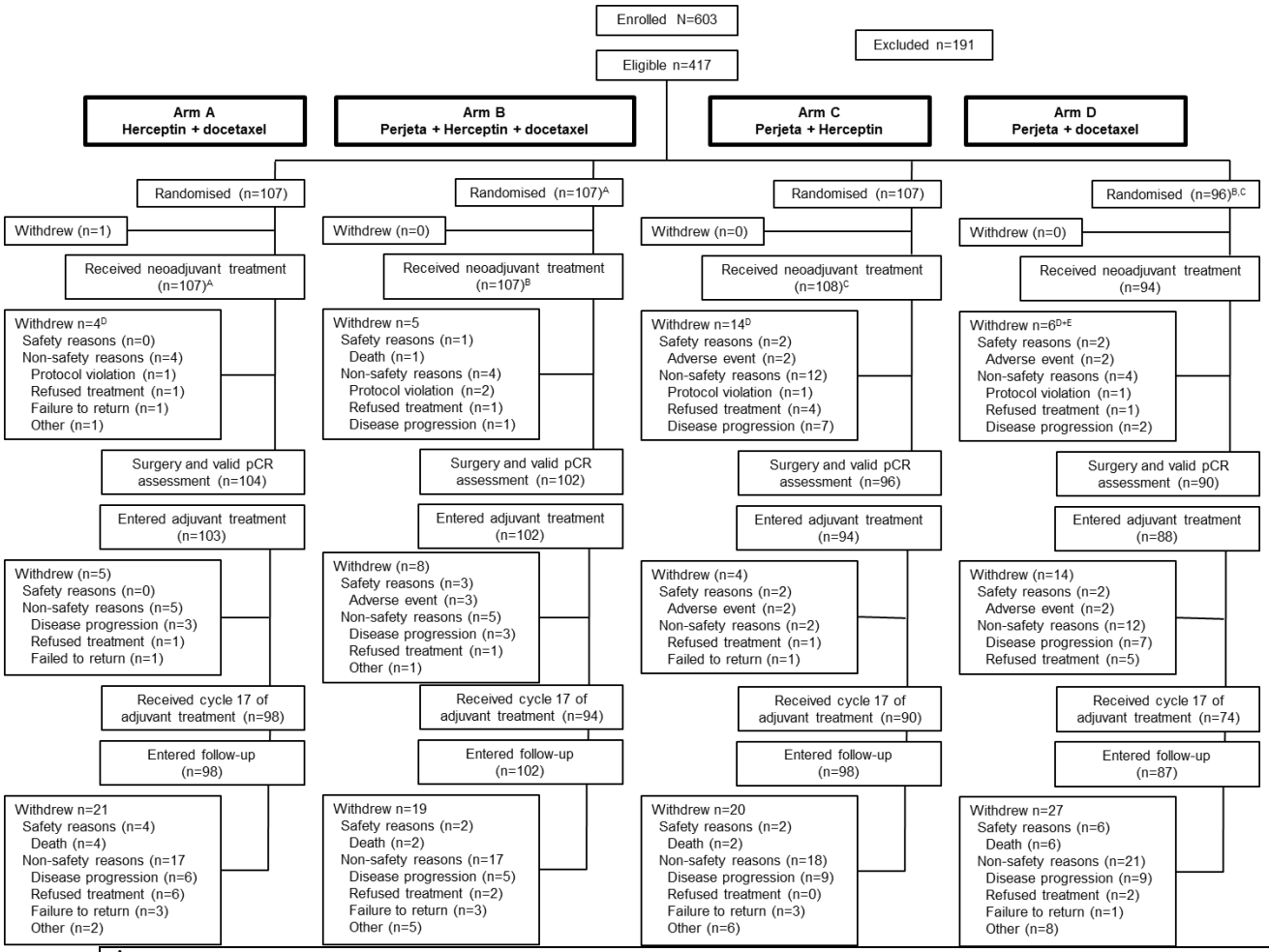
A total of 603 patients were screened, and 417 patients with HER2-positive early breast cancer were randomly assigned to receive study treatment.

The ITT population consisted of 107 patients in the Herceptin + docetaxel arm (Arm A), 107 patients in the Perjeta + Herceptin + docetaxel arm (Arm B), 107 patients in the Perjeta + Herceptin arm (Arm C) and 96 patients in the Perjeta + docetaxel arm (Arm D).

The safety population consisted of 107 patients in the Herceptin + docetaxel arm (Arm A), 107 patients in the Perjeta + Herceptin + docetaxel arm (Arm B), 108 patients in the Perjeta + Herceptin arm (Arm C) and 94 patients in the Perjeta + docetaxel arm (Arm D).

The consort diagram Figure 9 shows patient flow in the study.

Figure 9 CONSORT diagram for NeoSphere study [Gianni 2012; NeoSphere Final CSR]



[A] One patient randomly assigned to Arm B received Arm A treatment
[B] One patient randomly assigned to Arm D received Arm B treatment
[C] One patient randomly assigned to Arm D received Arm C treatment
[D] One patient withdrew from adjuvant treatment due to an adverse event of left ventricular dysfunction, incorrectly reported as interruption of study treatment

Withdrawals from neoadjuvant treatment were generally low, but were greater in the Perjeta + Herceptin arm (Arm C), primarily due to more patients in this arm reporting progressive disease or refusing treatment. Withdrawals from adjuvant treatment were also generally low; however, the Perjeta + docetaxel arm (Arm D) had a higher number of withdrawals in the adjuvant period due to more patients in this arm reporting progressive disease or refusing treatment. There were very few withdrawals (0-3 per arm) for safety reasons in the neoadjuvant and adjuvant periods.

Of the 31 deaths in the study, 30 occurred during post-treatment follow up. No patients died during the adjuvant period. [Final CSR]

One patient in the Perjeta + Herceptin + docetaxel arm (Arm B) died during the neoadjuvant treatment: death caused by fulminant hepatitis, possibly related to treatment. (Comorbidities: high body-mass index, hypertension, type 2 diabetes.) [Gianni 2012]

One patient in the Perjeta + docetaxel arm (Arm D) died after disease progression at cycle 3. This was mistakenly reported as withdrawal due to death (i.e. death during neoadjuvant treatment); however the patient was withdrawn from the study due to disease progression, and subsequently died (i.e. death during follow-up). [Final CSR]

Twenty-three of the deaths in the post-treatment follow-up period were due to disease progression, four had no cause of death reported, two were due to colorectal carcinoma and one was due to cerebrovascular accident.

TRYPHAENA [Schneeweiss et al, 2013]

300 patients were screened, and 225 patients with HER2-positive early breast cancer were randomly assigned to receive study treatment.

The majority of patients completed neoadjuvant treatment, and had surgery plus a valid pCR assessment (89%–95% of patients across arms).

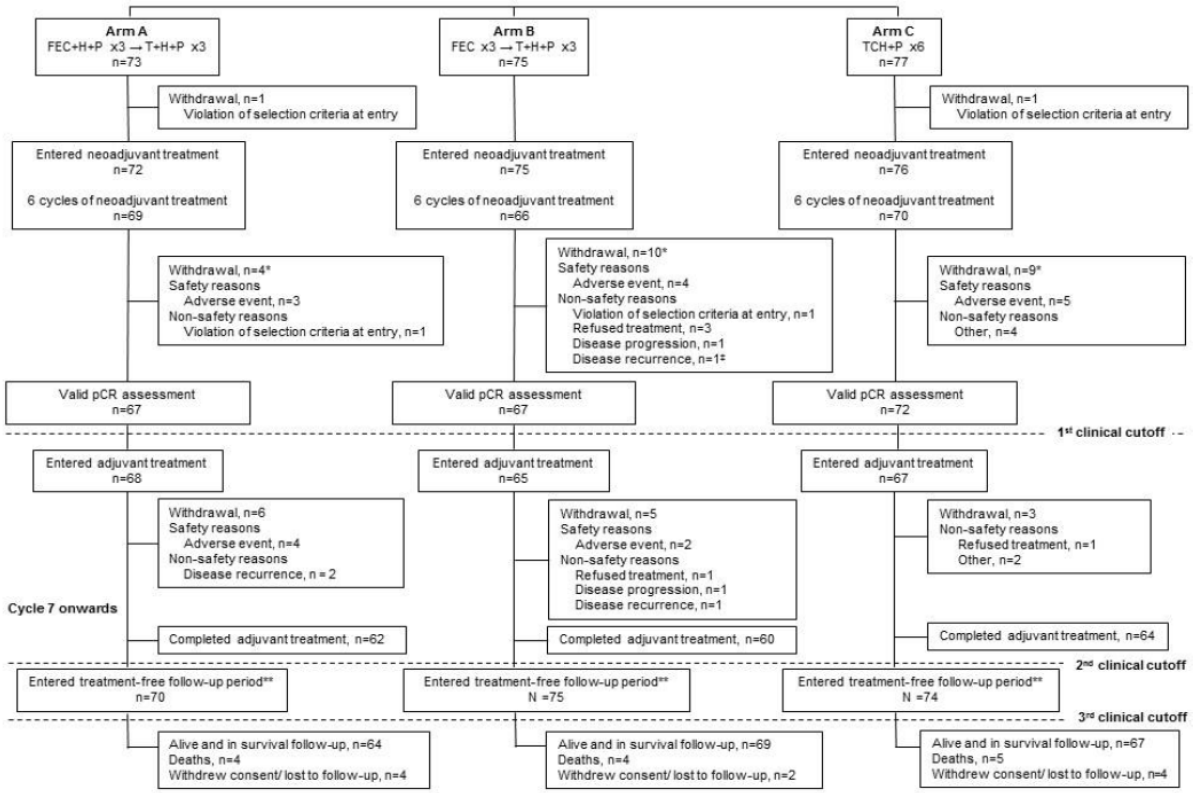
The consort diagram Figure 10 shows the patient flow in the study.

The ITT population consisted of 73 patients in Arm A[1], 75 patients in Arm B, and 77 patients in Arm C.

The safety population consisted of 72 patients in Arm A, 75 patients in Arm B and 76 patients in Arm C.

[1] Arm A: FEC+Herceptin+Perjeta x3 cycles → Docetaxel+Herceptin+Perjeta x3 cycles
Arm B: FEC x3cycles → docetaxel+Herceptin+Perjeta x3 cycles
Arm C: Perjeta+docetaxel+carboplatin+Herceptin x6 cycles

Figure 10 CONSORT diagram for TRYPHAENA study [2nd update CSR]



*Patients could withdraw from neoadjuvant treatment, but still have on-study surgery and enter adjuvant treatment; 'Other' and 'Refused treatment' withdrawals include 'Withdrew consent'.
**Includes all patients, i.e., those who withdrew during neoadjuvant and adjuvant periods, as well as those who completed study treatment)
FEC, 5-fluorouracil + epirubicin + cyclophosphamide; H, Herceptin; P, Perjeta; T, docetaxel; C, carboplatin

There were fewer withdrawals from neoadjuvant treatment in Arm A[1] than Arms B and C. Two patients were withdrawn in Arm B for disease progression and disease recurrence respectively; no patients were withdrawn from Arms A or C for these reasons. Few patients withdrew from neoadjuvant treatment due to AEs (3–5 patients per arm) and no patients died during the neoadjuvant treatment period.

Withdrawals from adjuvant treatment were also low: there were fewer withdrawals from adjuvant treatment in Arm C than in Arms A and B. In Arm C, there were no withdrawals for either safety reasons or disease progression. No patients died during the adjuvant treatment period.

Of the 13 deaths reported in the study, 12 were caused by disease progression and occurring during the post-treatment follow up period. The other death (a patient in Arm A) was due to the adverse event 'metastatic neoplasm' during the adjuvant treatment period. It should be noted that progressive disease was not to be routinely recorded as an AE, if consistent with the natural course of the disease, however, in this case, the site preferred to report the adverse event on Study Day 314, and disease recurrence in the lung and bone was confirmed on Study Day 321. The patient died on Study Day 337.

Baseline characteristics

The baseline characteristics of each study is described in turn. (Details for GeparSepto are provided in Appendix 3 Summary of the GeparSepto study)

NeoSphere: The treatment arms were generally well balanced with respect to the baseline demography (age, weight, height, ECOG status, race and reproductive status), and with respect to differentiation status of the primary tumours and to the type of breast cancer (Gianni, 2012). Median age was 49–50 years, and median weight was 62–67 kg. There were fewer Caucasian patients in the Perjeta + docetaxel arm (Arm D) compared to other arms. The proportion of patients with an ECOG status of 0 was greater in the Herceptin + docetaxel arm (Arm A) than in other arms. Baseline characteristics are summarised in Table 17.

[1] Arm A: FEC+Herceptin+Perjeta x3 cycles → Docetaxel+Herceptin+Perjeta x3 cycles
Arm B: FEC x3cycles → docetaxel+Herceptin+Perjeta x3 cycles
Arm C: Perjeta+docetaxel+carboplatin+Herceptin x6 cycles

The baseline demographic and disease characteristics of the per-protocol (PP) population closely matched those of the ITT population. [Primary CSR]

Table 17 Baseline characteristics in the NeoSphere study [Gianni 2012; NeoSphere Primary CSR]

	Arm A HD (n=107)	Arm B PHD (n=107)	Arm C PH (n=107)	Arm D PD (n=96)
Median age (range), years	50 (32–74)	50 (28–77)	49 (22–80)	49 (27–70)
ECOG PS 0, %	94*	90	86	83
ECOG PS 1, %	6*	10	14	17
Black, %	0	2	1	3
White, %	75	72	74	64
Asian, %	23	21	21	26
Other, %	2	5	5	7
ER+ or PR+ or both, %	47	47	48*	48
ER– and PR–, %	53	53	52*	52
Disease type, %				
Operable,	60	61	61	63
Locally advanced,	34	30	33	32
Inflammatory	7	9	7	5
Histological grade, %				
Well differentiated	1	2	3	4
Moderately differentiated	35	31	26	26
Poorly differentiated	29	21	36	35
Anaplastic	-	-	1	-
Unknown	36	36	34	33
Not known	-	-	1	1
HER2 status by IHC, %				
2+	7	6	12	4
3+	93	94	88	96
HER2 status by FISH, %				
Positive	95	95	95	100
Unknown	5	5	4	-
Lymph node status, %				
N0	30	29*	30	29
N1	45	50*	43	43
N2	21	21*	22	23
N3	5	0	5	5
Median tumour size at CBE, mm (range)	50 (20-200)	55 (20-150)	50 (20-200)	50 (0-180)

Arm A: HD, Herceptin + docetaxel; Arm B: PHD, Perjeta + Herceptin + docetaxel
Arm C: PH, Perjeta + Herceptin; Arm D: PD, Perjeta + docetaxel
CBE, clinical breast examination; ER, oestrogen receptor negative; ER+, oestrogen receptor positive; ECOG PS, Eastern Cooperative Oncology Group performance status; PR, progesterone receptor negative; PR+, progesterone receptor positive
*Data missing for one patient

TRYPHAENA: Randomisation was stratified by breast cancer type (operable, locally advanced, or inflammatory) and oestrogen receptor (ER) and/or progesterone-receptor (PR) positivity. Baseline characteristics are summarised in Table 18. Further data regarding grading of breast cancers at baseline, as well as cardiac risk factors and cardiac medication are in Appendix 4 Additional baseline characteristics of the TRYPHAENA study.

Baseline demographics were generally balanced across arms with respect to age, weight, height, European Cooperative Oncology Group performance status (ECOG PS), race, and smoking status; however, there were some exceptions:

- More white patients were randomised to Arm C[1]
- The proportion of patients with operable breast cancer was lower in Arm C. Correspondingly, more patients in Arm C presented with locally advanced disease
- More patients in Arm B presented with hormone receptor-negative tumours
- The proportion of patients with HER2 IHC 2+ tumours was higher in Arm A

[1] Arm A: FEC+Herceptin+Perjeta x3 cycles → Docetaxel+Herceptin+Perjeta x3 cycles
Arm B: FEC x3cycles → docetaxel+Herceptin+Perjeta x3 cycles
Arm C: Perjeta+docetaxel+carboplatin+Herceptin x6 cycles

Table 18 Baseline characteristics in the TRYPHAENA study [Schneeweiss et al, 2013]

	Arm A FEC+H+P x3 → D+H+P x3 (n=73)	Arm B FEC x3 → D+H+P x3 (n=75)	Arm C DCH+P x6 (n=77)
Median age, years (range)	49.0 (27-77)	49.0 (24-75)	50.0 (30-81)
Median weight, kg (range)	63.3 (44-111)	64.9 (42-112)	66.5 (45-128)
Race, n (%)			
Black	4 (5.5)	3 (4.0)	2 (2.6)
White	56 (76.7)	52 (69.3)	64 (83.1)
Oriental	12 (16.4)	18 (24.0)	11 (14.3)
Other	1 (1.4)	2 (2.7)	0 (0.0)
ECOG PS, n (%)			
0	66 (90.4)	66 (88.0)	68 (88.3)
1	6 (8.2)	9 (12.0)	9 (11.7)
Unknown	1 (1.4)	0 (0.0)	0 (0.0)
Histological grade			
Well differentiated	3 (4.1)	2 (2.7)	2 (2.6)
Moderately differentiated	28 (38.4)	34 (45.3)	32 (41.6)
Poorly differentiated	25 (34.2)	26 (34.7)	27 (35.1)
Unknown	17 (23.3)	13 (17.3)	16 (20.8)
ER-positive and/or PgR-positive, n (%)	39 (53.4)	35 (46.7)	40 (51.9)
ER-negative and PgR-negative, n (%)	34 (46.6)	40 (53.3)	37 (48.1)
Disease type, n (%)			
Operable	53 (72.6)	54 (72.0)	49 (63.6)
Locally advanced	15 (20.5)	17 (22.7)	24 (31.2)
Inflammatory	5 (6.8)	4 (5.3)	4 (5.2)
HER2 status by IHC, n (%)			
0 and 1+	1 (1.4)	0 (0.0)	0 (0.0)
2+	5 (6.8)[a]	1 (1.3)[a]	2 (2.6)[a]
3+	67 (91.8)	74 (98.7)	75 (97.4)
HER2 status by FISH, n (%)			
Positive	69 (94.5)	69 (92.0)	73 (94.8)
Negative	0 (0.0)	1 (1.3)	2 (2.6)
Unknown	4 (5.5)	5 (6.7)	2 (2.6)
Primary tumour size at baseline by clinical breast examination, mm			
Median (range)	53 (10-220)	49 (19-120)	50 (15-200)

[a] All patients with HER2 IHC 2+ status had FISH-positive status
ECOG PS- European Cooperative Oncology Group performance status; FISH, fluorescence in situ hybridisation; IHC, immunohistochemistry; ITT, intent-to-treat;
FEC, 5-fluorouracil + epirubicin + cyclophosphamide; H, Herceptin; P, Perjeta; D, docetaxel; C, carboplatin

There were few differences in the populations for the two studies:

- A slightly greater percentage of patients in the NeoSphere study had operable disease compared with patients in the TRYPHAENA study (60–63% vs 63–73%, respectively)
- A slightly greater percentage of patients in the NeoSphere study had locally advanced disease compared with patients in the TRYPHAENA study (30–34% vs 21–32%, respectively)

4.6 Quality assessment of the relevant randomised controlled trials

4.6.1 The validity of the results of an individual RCT will depend on the robustness of its overall design and execution, and its relevance to the decision problem. The quality of each RCT identified in section 4.2 should be appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies. The quality assessment will be validated by the Evidence Review Group.

4.6.2 Describe the methods used for assessing risk of bias and generalisability of individual RCTs (including whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.

- **The following are the minimum criteria for assessment of risk of bias and generalisability in parallel group RCTs, but the list is not exhaustive:**
    - **Was the randomisation method adequate?**
    - **Was the allocation adequately concealed?**
    - **Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?**
    - **Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blind to treatment allocation, what might be the likely impact on the risk of bias (for each outcome)?**
    - **Were there any unexpected imbalances in drop outs between groups? If so, were they explained or adjusted for?**
    - **Is there any evidence to suggest that the authors measured more outcomes than they reported?**
    - **Did the analysis include an intention to treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?**

- **Consider how closely the RCT(s) reflects routine clinical practice in England.**

- **In addition to parallel group RCTs, there are other randomised designs (for example, randomised crossover trials and randomised cluster trials) in which further quality criteria may need to be considered when assessing bias. Key aspects of quality to be considered can be found in Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination).**

4.6.3 If there is more than 1 RCT, tabulate a summary of the responses applied to each of the quality assessment criteria. A suggested table format for the quality assessment results is presented below.

Critical appraisal of the included RCTs was performed using the format provided in the NICE submission template which adhered to the Centre for Reviews and Dissemination (CRD), University of York guidance (Centre for Reviews and Dissemination (CRD) 2008). A summary is presented in Table 19, and the full appraisals can be found in Appendix 7 Quality appraisal of the RCTs identified in the SLR. The studies were of high quality based on the respective responses for each category, where judgement was possible using the available information, thus indicating low risk of bias in study conduct and design. Information about the GeparSepto Study was only available in a congress abstract and presentation, with some information available via ClinicalTrials.gov.

Table 19 Quality assessment of the identified RCTs

Study Question	Grade (Yes/No/ Not Clear/N/A)		
	NeoSphere (NCT00545688)	**TRYPHAENA (NCT00976989)**	**GeparSepto (NCT01583426)**
Was randomisation carried out appropriately?	Yes	Yes	Not clear
Was the concealment of treatment allocation adequate?	Yes	Yes	Not clear
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	Yes	Not clear
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)?	No	No	No
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Not clear	Not clear	Not clear
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Not clear	Not clear	Yes
Did the analysis include an intent-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Not clear	Yes	Not clear

NeoSphere: The study was undertaken in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided written informed consent. Approvals for the study protocol (and any modifications thereof) were obtained from independent ethics committees. [Gianni 2012]

TRYPHAENA: The study was conducted in full accordance with the guidelines for Good Clinical Practice and the Declaration of Helsinki. Written informed consent was obtained from each participant. Approval for the protocol and for any modifications was obtained from independent ethics committees. [Schneeweiss 2013]

4.7 Clinical effectiveness results of the relevant randomised controlled trials

The efficacy data from NeoSphere and TRYPHAENA respectively were analysed from the intent-to-treat (ITT) population.

The primary analysis for NeoSphere took place with a clinical data cut-off of 22 December 2009, which took place once all patients had received neoadjuvant treatment and had either undergone primary surgery or withdrawn from the study. It included the primary endpoint, pathological complete response (pCR) analysis and safety data for the neoadjuvant period, as well as available safety data for the adjuvant period. The efficacy data on progression-free survival (PFS) and disease-free survival (DFS) was provided from the final analysis.

The primary analysis for TRYPHAENA took place with a clinical cut-off of 21 June 2011, once all patients had received six cycles of neoadjuvant treatment, undergone surgery and had all necessary samples taken, or had withdrawn from the study, whichever occurred earlier. Cardiac safety was also evaluated at this time point. The final analysis, in which PFS and DFS data will be reported, has not yet been conducted.

GeparSepto is currently on-going, and as such, preliminary data have been presented at congress. We present for this submission the efficacy results for the HER2-positive subgroup.

For the purpose of this submission, the following definitions of pathological complete response have been used:

Table 20 Definitions of pathological complete response

Abbreviation	Definition
pCR	pathological complete response
bpCR	pathological complete response in the breast, defined as absence of invasive tumour in the breast irrespective of ductal carcinoma in-situ or nodal involvement (ypT0/is)
tpCR	total pathological complete response, defined as absence of invasive tumour in breast and lymph nodes irrespective of ductal carcinoma in-situ (ypT0/is ypN0)
GBG pCR	defined as absence of invasive cancer and in-situ cancer in the breast and axillary nodes (ypT0 ypN0)

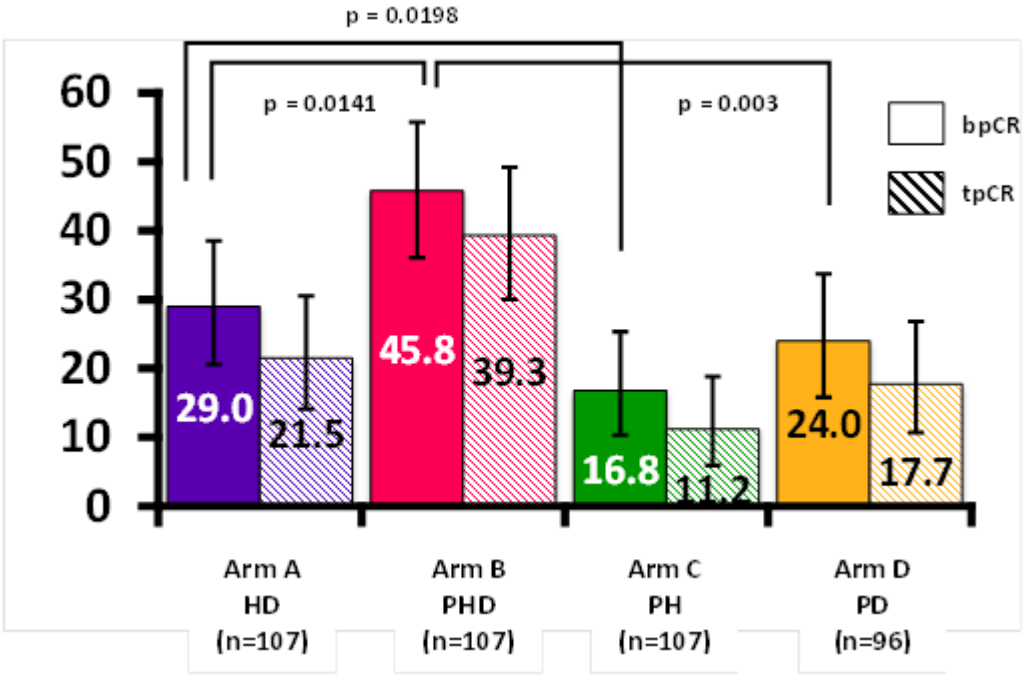
NeoSphere

Primary outcomes

The study met its primary endpoint: pathological complete response in the breast (bpCR). Total pathological complete response (tpCR) (the definition of pCR preferred by the FDA and EMA) rates were collected retrospectively. It should be noted that the tpCR definition closely reflects the definition ‘pCR with negative lymph nodes at surgery’ in the NeoSphere study.

pCR outcomes in ITT population: At the time of surgery, a statistically significant improvement in bpCR rate was observed in patients receiving Perjeta + Herceptin plus docetaxel (Arm B) compared to patients receiving Herceptin + docetaxel (Arm A), respectively; p=0.0141). The trend was similar for tpCR rates. [Gianni 2012] bpCR and tpCR rates in each treatment arm are shown graphically in Figure 11 and are tabulated in Table 21.

Figure 11 bpCR and tpCR at surgery in NeoSphere [adapted from Gianni 2012]



Arm A: HD, Herceptin + docetaxel; Arm B: PHD, Perjeta + Herceptin + docetaxel
Arm C: PH, Perjeta + Herceptin; Arm D: PD, Perjeta + docetaxel

tpCR rates: An overview of tpCR rates between all treatment arms is presented in Table 21. The majority of patients who achieved bpCR had negative lymph nodes at surgery and thus achieved tpCR. The pattern of tpCR between treatment arms in patients who achieved pCR closely matched that of the overall population. More patients in the Perjeta + Herceptin + docetaxel arm (Arm B) achieved tpCR than in other treatment arms. [Primary CSR]

pCR rate by ductal carcinoma in situ (DCIS) and/or lobular carcinoma in situ (LCIS) at surgery:

DCIS and/or LCIS are non-invasive but could develop into invasive cancer.

It should be noted that these results relate to bpCR with residual DCIS/LCIS at surgery. This does not reflect the definition presented by the German Breast Group (GBG). (GBG pCR requires negative nodal status at surgery as well as eradication of in situ disease – effectively tpCR with no residual DCIS/LCIS).

From Table 21, more patients in the Perjeta + Herceptin + docetaxel arm (Arm B; 36%) achieved bpCR and additionally had no residual DCIS/LCIS than in any other treatment arm (Herceptin + docetaxel [Arm A] 17%; Perjeta + Herceptin [Arm C] 9%; Perjeta + docetaxel [Arm D] 18%). Of note, a higher proportion of the patients in the Herceptin + docetaxel arm (Arm A) and in the Perjeta + Herceptin arm (Arm C) who achieved bpCR still had residual DCIS/LCIS at surgery compared to the proportions in the Perjeta + Herceptin + docetaxel arm (Arm B) and the Perjeta + docetaxel arm (Arm D). [Primary CSR]

Table 21 Pathological complete responses in the ITT population [Gianni 2012] [Primary CSR]

	Arm A HD (n=107)	Arm B PHD (n=107)	Arm C PH (n=107)	Arm D PD (n=96)
bpCR (overall)				
bpCR, n (%) [95% CI][a]	31 (29.0) [20.6–38.5]	49 (45.8) [36.1–55.7]	18 (16.8) [10.3–25.3]	23 (24.0) [15.8–33.7]
Difference in bpCR rates[b] [95% CI][c]	-	+16.8 % [3.5–30.1]	-12.2 % [-23.8–0.5]	-21.8 % [-35.1–8.5]
p-value (with Simes corr. for CMH test)[d]		p=0.0141 vs Arm A	p=0.0198 vs Arm A	p=0.003 vs Arm B
tpCR				
tpCR achieved, n (%) [95% CI]	23 (21.5) [14.1–30.5]	42 (39.3) [30.0–49.2]	12 (11.2) [5.9–18.8]	17 (17.7) [10.7–26.8]
bpCR by residual DCIS/LCIS at surgery				
bpCR achieved and no residual DCIS/LCIS at surgery, n (%)	18 (16.8)	39 (36.4)	10 (9.3)	17 (17.7)

Arm A: HD, Herceptin + docetaxel; Arm B: PHD, Perjeta + Herceptin + docetaxel;
Arm C: PH, Perjeta + Herceptin; Arm D: PD, Perjeta + docetaxel
[a] 95% CI for one sample binomial using Pearson-Clopper method
[b] Treatment Arm B and Arm C are compared to Arm A, while Arm D is compared to Arm B
[c] Approximate 95% CI for difference of two response rates using Hauck-Anderson method
[d] p-value from Cochran-Mantel-Haenszel test, with Simes multiplicity adjustment

Secondary efficacy outcomes

Best tumour response: An overview of best tumour response (where clinical breast examination [CBE] was used to assess the primary lesion) is given in Table 22. The majority of patients achieved an unconfirmed clinical response (i.e., complete response or partial response) in the primary lesion. The clinical response rate (CRR) was highest in the Perjeta + Herceptin + docetaxel arm (Arm B; 88.1%), followed by the Herceptin + docetaxel arm (Arm A; 79.8%). [Primary CSR]

Table 22 Overview of tumour response and CRR after 12 weeks of neoadjuvant therapy assessed by CBE [Primary CSR]

	Arm A HD (n=107)	Arm B PHD (n=107)	Arm C PH (n=107)	Arm D PD (n=96)
Best tumour response*, n	99	101	102	91
CR, n (%)	23 (23.2)	31 (30.7)	17 (16.7)	19 (20.9)
PR, n (%)	56 (56.6)	58 (57.4)	52 (51.0)	46 (50.5)
SD, n (%)	20 (20.2)	12 (11.9)	31 (30.4)	26 (28.6)
PD, n (%)	0 (0)	0 (0)	2 (2.0)	0 (0)
CRR*, n (%)	79 (79.8)	89 (88.1)	69 (67.6)	65 (71.4)
Median time to clinical response (weeks) (80% CI	6.3 [6–7]	6.3 [4–7]	6.9 [6–9]	7.3 [6–9]

*in primary breast lesion; defined as CR + PR
Arm A: HD, Herceptin + docetaxel; Arm B: PHD, Perjeta + Herceptin + docetaxel
Arm C: PH, Perjeta + Herceptin; Arm D: PD, Perjeta + docetaxel
CR, complete response; CRR, clinical response rate; PR, partial response; SD, stable disease; PD, progressive disease

Time to clinical response: Time to response as assessed by CBE was similar across the treatment arms. However, median time to response was slightly shorter in the Herceptin + docetaxel arm and the Perjeta + Herceptin + docetaxel arms (Arms A and B respectively) than in the Perjeta + Herceptin and the Perjeta + docetaxel arms (Arms C and D respectively). [Primary CSR]

Table 23 Time to first clinical response in NeoSphere

	Arm A HD (n=107)	Arm B PHD (n=107)	Arm C PH (n=107)	Arm D PD (n=96)
Patients included in analysis	99	101	102	91
Patients with response*, n (%)	79 (79.8)	89 (88.1)	69 (67.6)	65 (71.4)
Median time to clinical response (weeks)	6.3	6.3	6.9	7.3
80% CI for median	[6–7]	[4–7]	[6–9]	[6–9]
Range (weeks)	3–13	3–13	3–13	3–13

*in primary breast lesion, during neoadjuvant treatment
Arm A: HD, Herceptin + docetaxel; Arm B: PHD, Perjeta + Herceptin + docetaxel
Arm C: PH, Perjeta + Herceptin; Arm D: PD, Perjeta + docetaxel

Breast-conserving surgery (BCS): Just over half the patients on study were originally planned to undergo a mastectomy. However, between 18-32% of those patients who were planned to undergo mastectomy were able to have BCS (defined as quadrantectomy or lumpectomy). Rates of BCS were broadly balanced across the Herceptin + docetaxel arm, the Perjeta + Herceptin + docetaxel arm and the Perjeta + Herceptin arm (Arms A, B and C; 18-23%), with a higher rate reported in the Perjeta + docetaxel arm, (Arm D; 32%). [Primary CSR]

Table 24 Patients achieving breast conserving surgery in the ITT population inNeoSphere [Primary CSR]

	Arm A HD (n=107)	**Arm B PHD (n=107)**	**Arm C PH (n=107)**	**Arm D PD (n=96)**
Patients with T2-3 tumours and planned mastectomy, n	62	56	61	60
Patients with T2-3 tumours achieving BCS for whom mastectomy was planned, n (%)	14/62 (22.6)	13/56 (23.2)	11/61 (18.0)	19/60 (31.7)
Arm A: HD, Herceptin + docetaxel; Arm B: PHD, Perjeta + Herceptin + docetaxel Arm C: PH, Perjeta + Herceptin; Arm D: PD, Perjeta + docetaxel BCS, breast conserving surgery; ITT, intent-to-treat				

Progression-free survival (PFS) and disease-free survival (DFS): PFS and DFS analyses were not designed or powered to test formal hypotheses and are for descriptive purposes only. The hazard ratio and confidence intervals in each respect should be interpreted with care. Five-year PFS and DFS in Arm A (Herceptin plus docetaxel) and Arm B (Perjeta, Herceptin and docetaxel) and respective HRs are shown in Table 25.

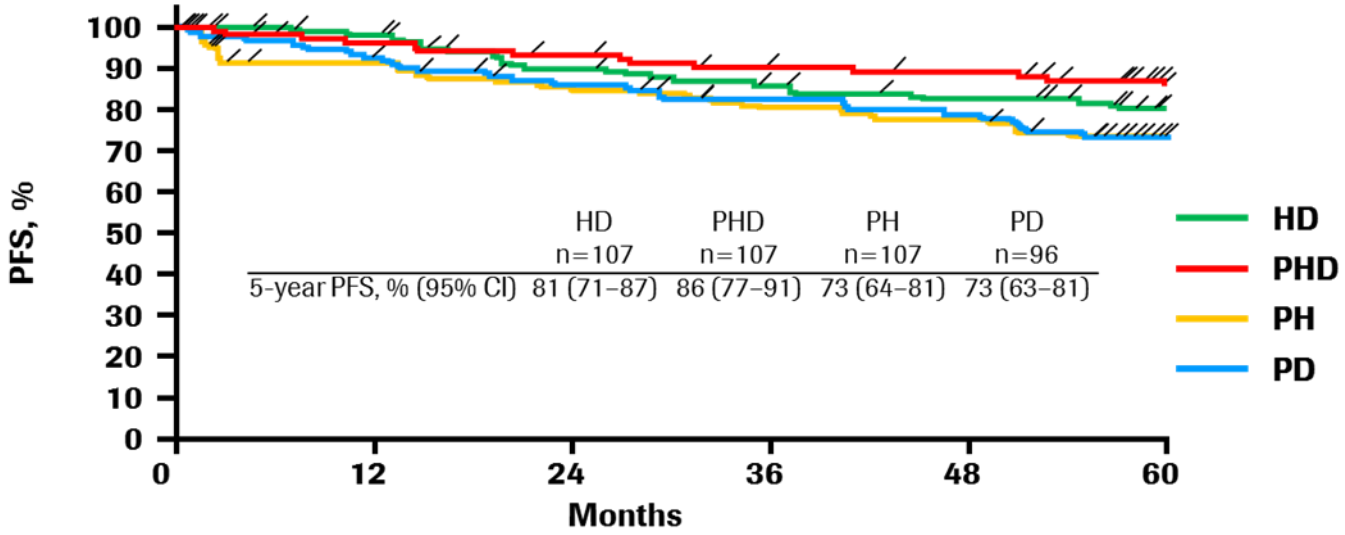
Table 25 Five-year PFS and DFS in the ITT population for Arm A versus Arm B [Gianni 2015]

	Arm A HD (n=107)	**Arm B PHD (n=107)**	**HR (95% CI)**
5-year PFS, % (95% CI)	81 (71–87)	86 (77–91)	0.69 (0.34-1.40)
5-year DFS, % (95% CI)	81 (72–88)	84 (72–91)	0.60 (0.28–1.27)
Arm A: HD, Herceptin + docetaxel; Arm B: PHD, Perjeta + Herceptin + docetaxel CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat			

Patients who received the triple combination with Perjeta, Herceptin and docetaxel (Arm B) showed higher 5-year PFS than the conventional Herceptin and docetaxel combination (Arm A). A higher 5-year DFS was achieved with the triple combination in comparison to conventional therapy, despite the only difference being the addition of Perjeta for four cycles in the neoadjuvant period. [Gianni 2015]

Figure 12 illustrates the PFS in all arms of therapy in the ITT population. The triple combination of Perjeta + Herceptin + docetaxel exhibited the highest 5-year PFS probability at 86% compared to other treatment arms. [Gianni 2015]

Figure 12 PFS in the ITT population in NeoSphere [Gianni 2015]



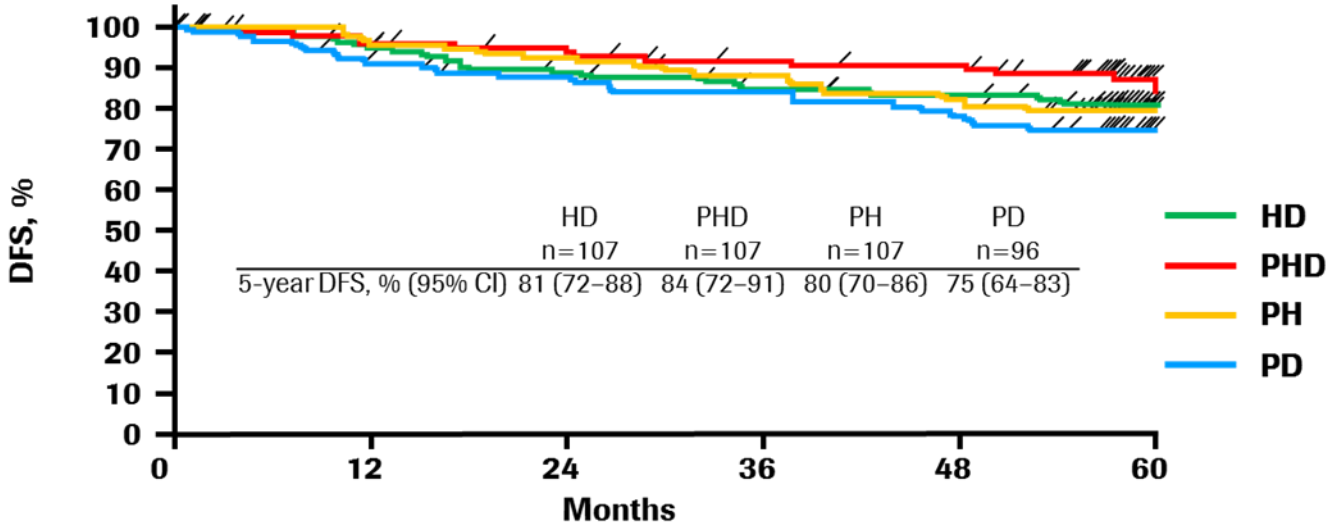
n at risk						
HD	107	101	89	83	78	58
PHD	107	99	94	88	86	63
PH	107	93	86	80	77	55
PD	96	85	76	72	69	57

Arm A: HD, Herceptin + docetaxel; Arm B: PHD, Perjeta + Herceptin + docetaxel
Arm C: PH, Perjeta + Herceptin; Arm D: PD, Perjeta + docetaxel
CI, confidence interval; ITT, intent-to-treat; PFS, progression-free survival

Figure 13 illustrates the DFS in all arms of therapy in the ITT population. Again, the triple combination of Perjeta + Herceptin + docetaxel showed the highest 5-year DFS probability at 84%, in spite of the fact that the chemotherapy backbone and the

HER2-directed adjuvant therapy was the same in the 4 arms of therapy. [Gianni 2015]

Figure 13 DFS in the ITT population in NeoSphere [Gianni 2015]



n at risk

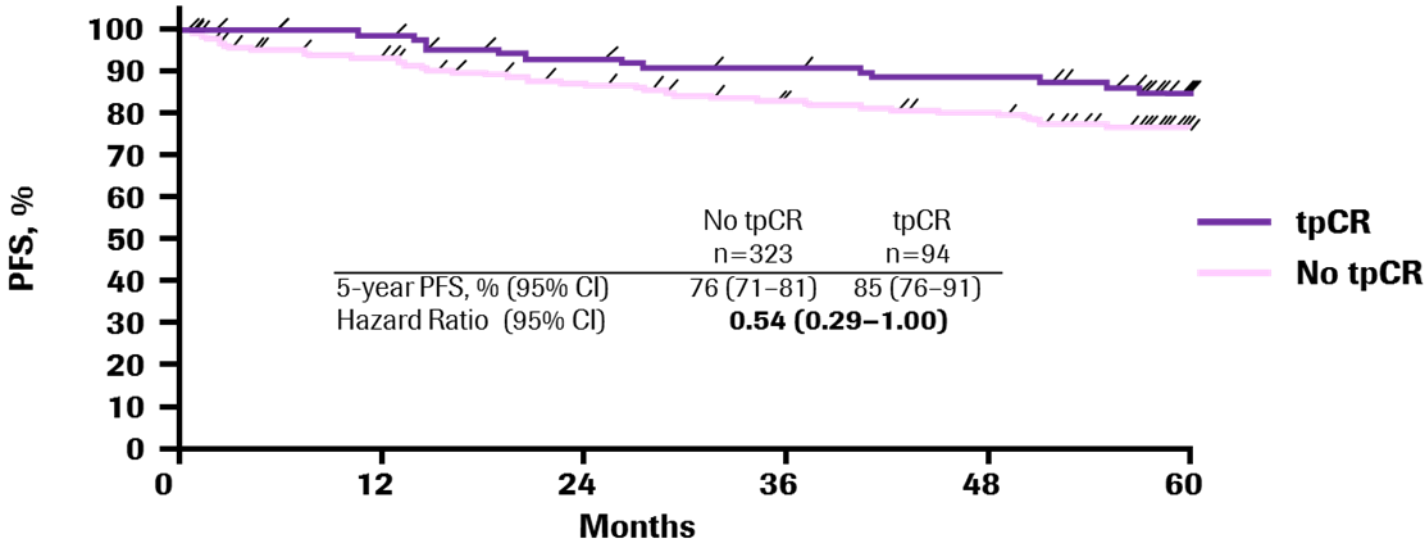
HD	103	92	85	79	77	12
PHD	101	96	92	88	85	17
PH	96	91	87	81	75	10
PD	92	81	76	72	66	29

Arm A: HD, Herceptin + docetaxel; Arm B: PHD, Perjeta + Herceptin + docetaxel
Arm C: PH, Perjeta + Herceptin; Arm D: PD, Perjeta + docetaxel
CI, confidence interval; DFS, disease-free survival; ITT, intent-to-treat

PFS Analyses by tpCR Status

When combining all treatment arms, a higher PFS was achieved in patients who had achieved tpCR versus those who did not achieve tpCR: patients who achieved tpCR were 46% less likely to experience disease worsening, recurrence or death (HR: 0.54 [95% CI: 0.29–1.00]). [Gianni 2015] See Figure 14.

Figure 14 PFS by tpCR: all treatment arms combined (ITT population) in NeoSphere [Gianni 2015]

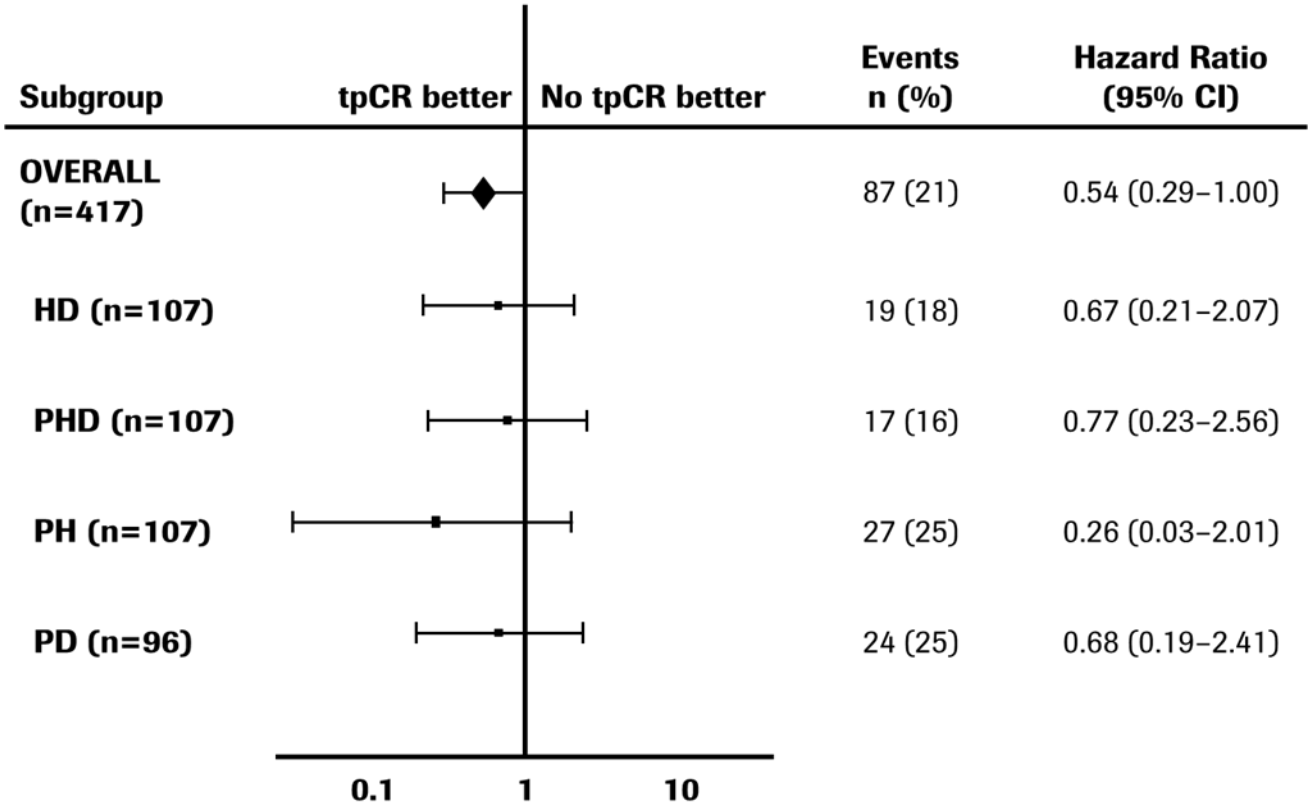


n at risk						
tpCR	94	91	83	79	76	55
no tpCR	323	287	262	244	234	178

CI, confidence interval; ITT, intent-to-treat; PFS, progression-free survival; tpCR, total pathological complete response, defined as no invasive tumour in the breast and lymph nodes

A subgroup analysis for PFS was performed for patients that had achieved a tpCR versus patients who had not achieved tpCR in order to see whether pCR rates have any association to PFS. The analysis was conducted on patients in the intent-to-treat population. Figure 15 below shows that a higher PFS was observed in patients who achieved tpCR in all four treatment arms. Given the small sample sizes, the 95% CI are large and cross the unit line for each individual group. [Gianni 2015]

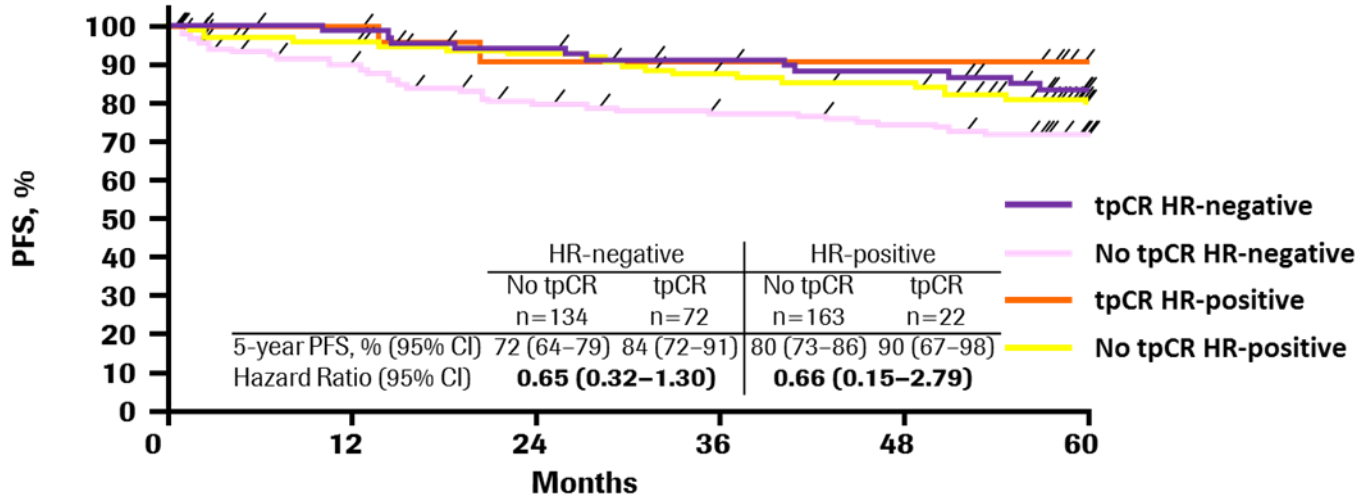
Figure 15 PFS for tpCR vs no tpCR: subgroup analysis (ITT population) [Gianni 2015]



Arm A: HD, Herceptin + docetaxel; Arm B: PHD, Perjeta + Herceptin + docetaxel
Arm C: PH, Perjeta + Herceptin; Arm D: PD, Perjeta + docetaxel
CI, confidence interval; PFS, progression free survival; tpCR, total pathological complete response, defined as no invasive tumour in the breast and lymph nodes

Further analysis of PFS by tpCR and hormone receptor status demonstrated an improved 5-year PFS for patients with HR-negative tumours who achieved tpCR compared with those who did not achieve tpCR. This trend was also observed for patients with HR-positive tumours. [Gianni 2015] These results are shown in Figure 16.

Figure 16 PFS for tpCR and no tpCR by hormone receptor status (ITT population) in NeoSphere [Gianni 2015]



n at risk						
tpCR HR-	72	69	64	60	58	43
no tpCR HR-	147	125	108	102	97	82
tpCR HR+	22	22	19	19	18	12
no tpCR HR+	175	161	153	142	137	96

CI, confidence interval; HR, hormone receptor; ITT, intent-to-treat; PFS, progression free survival; tpCR, total pathological complete response, defined as no invasive tumour in the breast and lymph nodes

TRYPHAENA

The primary endpoint was to evaluate safety and tolerability of Perjeta during neoadjuvant treatment, of which results are provided in section 4.12 of this document.

Clinical efficacy was assessed by pathological complete response in the breast (bpCR) and was a secondary endpoint in the TRYPHAENA study. Total pathological complete response (tpCR) is the definition of pCR included in the FDA and EMA guidance [FDA] [EMA], and thus is also presented here as tpCR rates (ypT0/is ypNo) from the TRYPHAENA study.

No formal hypothesis testing for efficacy parameters was carried out, and no statistical comparisons were made between arms to assess clinical efficacy. Secondary efficacy endpoints are summarised below for descriptive purposes only.

Pathological Complete Response: Results from the TRYPHAENA study demonstrate that the majority of patients in all arms (~60%) in the ITT population achieved bpCR after neoadjuvant treatment; see Table 26. Of those patients, the majority also achieved tpCR. The pattern of tpCR responses was comparable across all treatment arms.

Table 26 pCR in the ITT population in TRYPHAENA [Primary CSR]

pCR	Arm A FEC+H+P x3 → D+H+P x3 (n=73)	Arm B FEC x3 → D+H+P x3 (n=75)	Arm C DCH+P x6 (n=77)
bpCR, n (%) [95% CI]	45 (61.6) [49.5–72.8]	43 (57.3) [45.4–68.7]	51 (66.2) [54.6–76.6]
tpCR, n (%)	41 (56.2)	41 (54.7)	49 (63.6)
bpCR, pathological complete response, defined as no invasive tumour in the breast; tpCR, total pathological complete response, defined as no invasive tumour in the breast and lymph nodes; FEC, 5-fluorouracil + epirubicin + cyclophosphamide; D, docetaxel, H, Herceptin; P, Perjeta; C, carboplatin			

Clinical Response: The majority of patients responded clinically to treatment when assessed by physical examination. Clinical responses during neoadjuvant treatment for each arm are listed in Table 27. Patients in Arm B achieved a lower complete CR rate than the patients in Arm A and Arm C[1].

Table 27 Clinical responses during neoadjuvant treatment in ITT population in TRYPHAENA [Schneeweiss 2013 Suppl. S7]

	Arm A FEC+H+P x3 → D+H+P x3 (n=73)	Arm B FEC x3 → D+H+P x3 (n=75)	Arm C DCH+P x6 (n=77)
Objective response rate, n (%)	67 (91.8)	71 (94.7)	69 (89.6)
Complete response rate	37 (50.7)	21 (28.0)	31 (40.3)
Partial response rate	30 (41.1)	50 (66.7)	38 (49.4)
Stable disease, n (%)	3 (4.1)	1 (1.3)	5 (6.5)
Progressive disease, n (%)	0 (0.0)	1 (1.3)	0 (0.0)
No assessment, n (%)	3 (4.1)	2 (2.7)	3 (3.9)
ITT, intent-to-treat; FEC, 5-fluorouracil + epirubicin + cyclophosphamide; H, Herceptin; P, Perjeta; D, docetaxel, C, carboplatin			

[1] Arm A: FEC+Herceptin+Perjeta x3 cycles → Docetaxel+Herceptin+Perjeta x3 cycles
Arm B: FEC x3cycles → docetaxel+Herceptin+Perjeta x3 cycles
Arm C: Perjeta+docetaxel+carboplatin+Herceptin x6 cycles

Time to clinical response: Median time to clinical response was shortest in Arm A (3.6 weeks) followed by Arm C (4.9 weeks), however, the range in time to response was wide (between 1 and 18-20 weeks across all arms). These findings are consistent with the high response rates seen in these two treatment arms and suggest that earlier initiation of Perjeta and Herceptin may contribute to shorter time to clinical response as seen in Arms A and C compared with Arm B.[1]

Table 28 Time to clinical response in TRYPHAENA [Primary CSR]

	Arm A FEC+H+P x3 → D+H+P x3 (n=73)	**Arm B FEC x3 → D+H+P x3 (n=75)**	**Arm C DCH+P x6 (n=77)**
Number of patients with a clinical response	67	71	69
Time to clinical response			
Patients included in analysis*, n	70	73	74
Median[a], weeks (range[b])	3.6 (3–18)	6.9 (3–20)	4.9 (3–18)

*Number of patients in the respective treatment arms who are actually included in the analysis (patients for which records in the event data set are available, time-to-event is not negative and not missing and censoring variable it not missing
[a]Kaplan-Meier estimates
[b]Includes censored observations
ITT, intent-to-treat; FEC, 5-fluorouracil + epirubicin + cyclophosphamide; H, Herceptin; P, Perjeta; D, docetaxel; C, carboplatin

Breast conserving surgery (BCS): The majority of patients for whom a mastectomy was planned were eligible to have BCS following neoadjuvant treatment, if they wished. It should be noted, however, that some of the sensitivity of this analysis is lost since patients could opt to go ahead with a full mastectomy even if this was not the clinical recommendation. Thus, the proportion of patients eligible for BCS who actually underwent BCS was between 16–27% across the three treatment arms. Patients with T2–3

[1] Arm A: FEC+Herceptin+Perjeta x3 cycles → Docetaxel+Herceptin+Perjeta x3 cycles
Arm B: FEC x3cycles → docetaxel+Herceptin+Perjeta x3 cycles
Arm C: Perjeta+docetaxel+carboplatin+Herceptin x6 cycles

tumours in Arm B for whom a mastectomy was planned were less likely to undergo BCS than patients in Arms A and C.

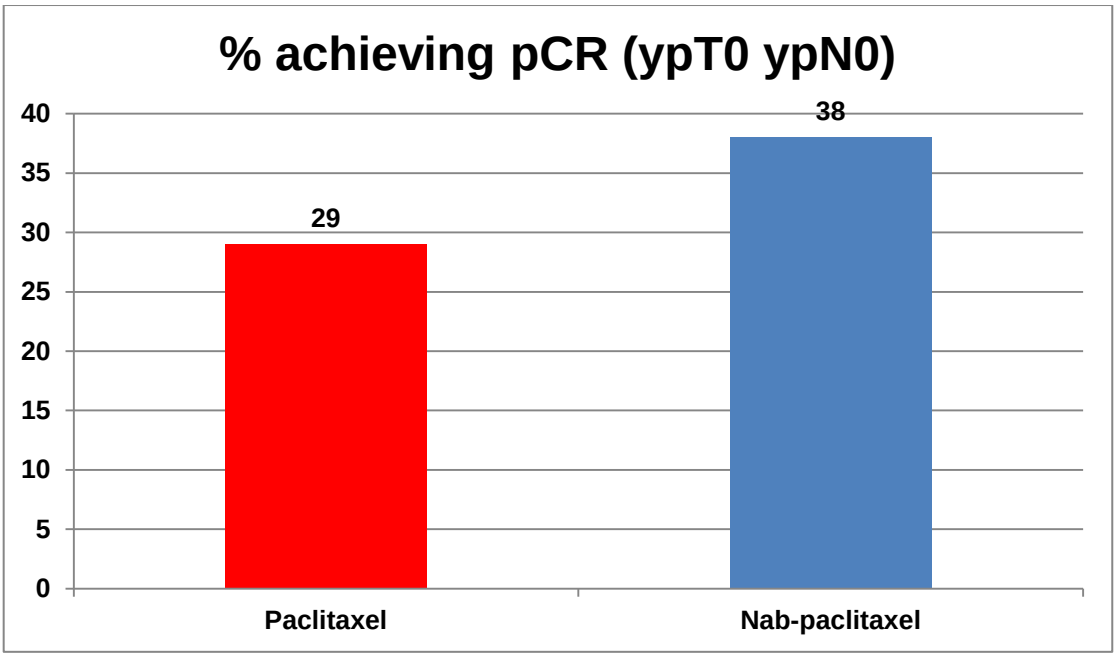
Table 29 Patients achieving breast conserving surgery in ITT population in TRYPHAENA [Primary CSR]

	Arm A FEC+H+P x3 → D+H+P x3 (n=73)	**Arm B FEC x3 → D+H+P x3 (n=75)**	**Arm C DCH+P x6 (n=77)**
Patients with T2-3 tumours and planned mastectomy, n	61	63	58
Patients with T2-3 tumours eligible for BCS following neoadjuvant treatment, n (%)	46/61 (75.4)	36/63 (57.1)	37/58 (63.8)
Patients that underwent BCS, n (%) [95% CI]	10/46 (21.7) [10.9–36.4]	6/36 (16.7) [6.4–32.8]	10/37 (27.0) [13.8–44.1]
FEC, 5-fluorouracil + epirubicin + cyclophosphamide; H, Herceptin; P, Perjeta; D, docetaxel; C, carboplatin BCS, breast conserving surgery; ITT, intent-to-treat			

GeparSepto Study

The efficacy results for the overall study population showed a greater percentage of patients treated with nab-paclitaxel achieved GBG pCR than for those patients treated with paclitaxel (38% vs 29%; p=0.01). See Figure 17.

Figure 17 Efficacy results for overall population of the GeparSepto study [adapted from Untch 2014]



The efficacy results presented for the HER2-positive subgroup of this study are shown below, using the definition of GBG pCR.

Table 30 Efficacy results for the HER2-positive subgroup of the GeparSepto Study [Untch 2014]

Trial name (number)	**GeparSepto (NCT01583426)**	
Study arm	**Paclitaxel**	**Nab-paclitaxel**
	n=196	**n=199**
GBG pCR (ypT0 ypN0), %	54.1	61.8
GBG pCR (ypT0 ypN0), odds ratio (95% CI)	1.37 (0.920–20.5)	
p-value for comparison	p=0.120	
CI, confidence interval; pCR, pathological complete response		

4.8 Subgroup analysis

NeoSphere

The primary endpoint of bpCR, in NeoSphere was analysed according to

- hormone-receptor status subgroups (hormone receptor positive and hormone receptor negative), and
- breast cancer types (operable breast cancer, locally advanced breast cancer and inflammatory breast cancer)

The comparisons between the treatment arms were made using a Cochrane Mantel-Hansel test.

The subgroup analysis of the secondary endpoints in NeoSphere (clinical response, tumour response, and breast conserving surgery) was exploratory in nature and conducted for descriptive purposes only. The Kaplan-Meier approach was used to estimate median time to clinical response for each treatment arm. The Cox proportional hazard model was used to estimate the hazard ratio and its 95% confidence interval (CI), for description purposes only. The subgroup analyses for the secondary endpoints were conducted on the intent-to-treat (ITT) population and are reported in summary here.

pCR outcomes by hormone receptor status: The analysis showed that pathological complete response (pCR) rates were higher for hormone receptor (HR)-negative tumours than HR-positive tumours. Patients in the Perjeta + Herceptin + docetaxel arm (Arm B) had the highest pCR rates regardless of hormone receptor status. pCR rate was notably low in hormone receptor-positive patients in the Perjeta + Herceptin arm (Arm C). tpCR rates according to hormone receptor status were not reported. See Table 31.

Table 31 pCR according to hormone receptor status in the ITT population in NeoSphere

	Arm A HD (n=107)	Arm B PHD (n=107)	Arm C PH (n=107)	Arm D PD (n=96)
bpCR				
bpCR, n (%) [95% CI][a]	31 (29.0) [20.6–38.5]	49 (45.8) [36.1–55.7]	18 (16.8) [10.3–25.3]	23 (24.0) [15.8–33.7]
pCR by hormone-receptor status				
HR-negative[b]	(n=57)	(n=57)	(n=55)	(n=50)
bpCR, n (%) [95% CI]	21 (36.8) [24.4–50.7]	36 (63.2) [49.3–75.6]	16 (29.1) [16.1–41.0]	15 (30.0) [17.9–44.6]
tpCR, n (%)	17 (29.8)	31 (54.4)	11 (20.0)	13 (26.0)
HR-positive[c]	(n=50)	(n=50)	(n=51)	(n=46)
bpCR, n (%) [95% CI]	10 (20.0) [10.0–33.7]	13 (26.0) [14.6–40.3]	3 (5.9) [1.2–16.2]	8 (17.4) [7.8–31.4]
tpCR, n (%)	6 (12.0)	11 (22.0)	1 (2.0)	4 (8.7)

Arm A: HD, Herceptin + docetaxel; Arm B: PHD, Perjeta + Herceptin + docetaxel
Arm C: PH, Perjeta + Herceptin; Arm D: PD, Perjeta + docetaxel
bpCR, pathological complete response in the breast
tpCR, total pathological complete response
[a] 95% CI for one sample binomial using Pearson-Clopper method
[b] Oestrogen receptor negative and progesterone receptor negative
[c] Oestrogen receptor and/or progesterone receptor positive

pCR outcomes by breast cancer type: pCR rates across the treatment arms in patients with operable breast cancer closely matched those in the ITT population. For patients with locally advanced cancer, patients in the Herceptin + docetaxel arm and the Perjeta + Herceptin + docetaxel arm (Arms A and B respectively) had a similar pCR rate (41.7% and 43.8% respectively), which were higher than the Perjeta + Herceptin arm and the Perjeta + docetaxel arm (Arms C and D; 14.3% and 16.1% respectively). There were too few patients with inflammatory breast cancer to draw any firm conclusions, but the pCR rate for patients with this breast cancer type was highest in patients receiving regimens including both Perjeta and docetaxel. See Table 32. [Primary CSR]

Table 32 pCR according to breast cancer type in the ITT population in NeoSphere [Gianni 2012; Primary CSR]

	Arm A HD (n=107)	Arm B PHD (n=107)	Arm C PH (n=107)	Arm D PD (n=96)
Overall bpCR				
bpCR, n (%) [95% CI][a]	31 (29.0) [20.6–38.5]	49 (45.8) [36.1–55.7]	18 (16.8) [10.3–25.3]	23 (24.0) [15.8–33.7]
bpCR by breast cancer type				
Operable breast cancer	(n=64)	(n=65)	(n=65)	(n=60)
n (%) [95% CI][a]	15 (23.4) [13.8–35.7]	31 (47.7) [35.1–60.5]	12 (18.5) [9.9–30.0]	16 (26.7) [16.1–39.7]
Locally advanced breast cancer	(n=36)	(n=32)	(n=35)	(n=31)
n (%) [95% CI][a]	15 (41.7) [25.5–59.2]	14 (43.8) [26.4–62.3]	5 (14.3) [4.8–30.3]	5 (16.1) [5.5–33.7]
Inflammatory breast cancer	(n=7)	(n=10)	(n=7)	(n=5)
n (%) [95% CI][a]	1 (14.3) [0.4–57.9]	4 (40.0) [12.2–73.8]	2 (28.6) [3.7–71.0]	2 (40.0) [5.3–85.3]

Arm A: HD, Herceptin + docetaxel; Arm B: PHD, Perjeta + Herceptin + docetaxel
Arm C: PH, Perjeta + Herceptin; Arm D: PD, Perjeta + docetaxel
bpCR, pathological complete response in the breast
tpCR, total pathological complete response
[a] 95% CI for one sample binomial using Pearson-Clopper method

Clinical response, tumour response, and breast conserving surgery [Primary CSR]

(These subgroup analyses were exploratory in nature; therefore, a summary of the findings has been provided below.)

Clinical response and tumour response endpoints were assessed by various methods including clinical breast examination (CBE) and were analysed by breast cancer type. In general, the response rates of patients classified with operable cancer, or those with locally advanced cancer, followed patterns consistent with the response rates for the overall population. Patients in the Perjeta + Herceptin + docetaxel arm (Arm B) had the highest CR rate

compared to other treatment arms, while the Perjeta + Herceptin arm (Arm C) had the lowest rate.

The number of patients with inflammatory breast cancer was too low (between 5–10 patients per arm) to allow meaningful comparisons across the treatment arms.

Rates of breast conserving surgery (BCS) in patients with breast cancer classified as operable reflects the rates seen in the overall T2–3 tumour population, with the highest rate in the Perjeta + docetaxel arm (Arm D) and the lowest in the Perjeta + Herceptin arm (Arm C). BCS rates were similar across the arms in patients with locally advanced disease.

TRYPHAENA

In TRYPHAENA, the main efficacy endpoint of bpCR (a secondary endpoint in the study), like NeoSphere, was analysed according to **hormone-receptor status subgroups** (hormone receptor positive and hormone receptor negative), and according to **breast cancer types** (operable breast cancer, locally advanced breast cancer and inflammatory breast cancer). Secondary endpoints were calculated and summarised for descriptive purposes only. The subgroup analyses were conducted on the intent-to-treat (ITT) population.

pCR outcomes by hormone receptor status

A breakdown of bpCR and tpCR rates in the ITT population according to hormone receptor (HR) status is summarised in Table 33. All three treatment regimens from the TRYPHAENA study achieved clinically important bpCR/tpCR rates regardless of hormone receptor status. However, patients with hormone receptor-negative tumours achieved higher rates of tpCR compared with patients with hormone receptor-positive tumours. Of note is the fact that patients in Arm B received Herceptin and Perjeta in only three of

the six cycles (and six cycles of chemotherapy), while patients in Arms A[1] and C received Herceptin and Perjeta in all six cycles of the neoadjuvant phase.

Table 33 pCR according to hormone receptor status in the ITT population in TRYPHAENA [Primary CSR] [MAA]

pCR	Arm A FEC+H+P x3 → D+H+P x3 (n=73)	Arm B FEC x3 → D+H+P x3 (n=75)	Arm C DCH+P x6 (n=77)
pCR			
bpCR, n (%) [95% CI][a]	45 (61.6) [49.5–72.8]	43 (57.3) [45.4–68.7]	51 (66.2) [54.6–76.6]
tpCR, n (%)	41 (56.2)	41 (54.7)	49 (63.6)
bpCR by hormone-receptor status			
HR-negative[b]	(n=34)	(n=40)	(n=37)
bpCR, n (%) [95% CI]	27 (79.4) [62.1–91.3]	26 (65.0) [48.3–79.4]	31 (83.8) [68.0–93.8]
tpCR, n (%)	25 (73.5)	25 (62.5)	30 (81.1)
HR-positive[c]	(n=39)	(n=35)	(n=40)
bpCR, n (%) [95% CI]	18 (46.2) [30.1–62.8]	17 (48.6) [31.4–66.0]	20 (50.0) [33.8–66.2]
tpCR, n (%)	16 (41.0)	16 (45.7)	19 (47.5)

FEC, 5-fluorouracil + epirubicin + cyclophosphamide; D, docetaxel, H, Herceptin; P, Perjeta; C, carboplatin; bpCR, pathological complete response, defined as no invasive tumour in the breast; tpCR, total pathological complete response, defined as no invasive tumour in the breast and lymph nodes
NB: the definition of tpCR in the TRYPHAENA study closely reflects the definition by the FDA and EMA
[a] 95% CI for one sample binomial using Pearson-Clopper method
[b] Oestrogen receptor negative and progesterone receptor negative
[c] Oestrogen receptor and/or progesterone receptor positive

bpCR outcomes according to breast cancer type

Within the subgroup of patients with operable breast cancer, bpCR rates were comparable with those in the ITT population. Within the subgroup of patients with locally advanced breast cancer, the bpCR rate was also comparable to the ITT population; however, patient numbers for this subgroup were too low to allow firm conclusions. There were also too few patients with inflammatory

[1] Arm A: FEC+Herceptin+Perjeta x3 cycles → Docetaxel+Herceptin+Perjeta x3 cycles
Arm B: FEC x3cycles → docetaxel+Herceptin+Perjeta x3 cycles
Arm C: Perjeta+docetaxel+carboplatin+Herceptin x6 cycles

disease (n = 4-5 across arms) to give a meaningful analysis. See Table 34. tpCR rates according to breast cancer type were not reported.

Table 34 pCR according to breast cancer type in the ITT population in TRYPHAENA [Primary CSR] [MAA]

pCR	Arm A FEC+H+P x3 → D+H+P x3 (n=73)	Arm B FEC x3 → D+H+P x3 (n=75)	Arm C DCH+P x6 (n=77)
pCR			
bpCR, n (%) **[95% CI][a]**	45 (61.6) [49.5–72.8]	43 (57.3) [45.4–68.7]	51 (66.2) [54.6–76.6]
tpCR, n (%)	41 (56.2)	41 (54.7)	49 (63.6)
bpCR by breast cancer type			
operable **n (%)** **[95% CI][a]**	(n=53) 34 (64.2) [49–76.9]	(n=54) 29 (53.7) [39.6–67.4]	(n=49) 32 (65.3) [50.4–78.3]
locally advanced **n (%)** **[95% CI][a]**	(n=15) 8 (53.3) [26.6–78.7]	(n=17) 13 (76.5) [50.1–93.2]	(n=24) 15 (62.5) [40.6–81.2]
inflammatory **n (%)** **[95% CI][a]**	(n=5) 3 (60.0) [14.7–94.7]	(n=4) 1 (25.0) [0.6–80.6]	(n=4) 4 (100.0) [39.8–100.0]

FEC, 5-fluorouracil + epirubicin + cyclophosphamide; D, docetaxel, H, Herceptin; P, Perjeta; C, carboplatin; bpCR, pathological complete response, defined as no invasive tumour in the breast; tpCR, total pathological complete response, defined as no invasive tumour in the breast and lymph nodes

NB: the definition of tpCR in the TRYPHAENA study closely reflects the definition by the FDA and EMA

[a] 95% CI for one sample binomial using Pearson-Clopper method

4.9 Meta-analysis

The inclusion of Tryphaena or GeparSepto trials in a meta-analysis was not possible for the following reasons:

TRYPHAENA

The primary endpoints included the incidence of symptomatic cardiac events and clinically significant LVEF declines over the course of the neoadjuvant treatment period. The endpoints of interest for this submission were analysed as secondary endpoints (bpCR, clinical response rate, DFS, PFS, OS) and therefore the study was not powered enough to address them. Furthermore,

as all arms in the TRYPHAENA study were exposed to pertuzumab, a comparator arm would have to be created hence increasing the uncertainty as a result of the assumptions that would have to be made.

GeparSepto

The GeparSepto is currently on-going and only preliminary data and information have been presented to date. Current available data for the HER2-positive subpopulation in this study are limited to efficacy alone (pCR), no safety data for the HER2-positive subpopulation are available for inclusion in this meta-analysis.

4.10 Indirect and mixed treatment comparisons

See response 4.9 above.

4.11 Non-randomised and non-controlled evidence

Provide details fo the non-randomised and non-controlled studies that provide additional evidence to supplement RCT data. Provide a list of the relevant studies and summarise the methodology, statistical analyses, participant flow and quality assessment for each. Briefly summarise the resutls of the non-randomised and non-controlled studies.

We are aware of real-world evidence from a retrospective analysis, as detailed below.

Cleveland Clinic experience [Tiwari 2015]

Rationale and methodology

The aim was to evaluate the safety and efficacy of neoadjuvant docetaxel + carboplatin + Herceptin + Perjeta (TCH-P) in women with HER2-positive non-metastatic breast cancer in a non-clinical trial setting.

A cancer data registry was used to identify all patients with HER2-postive non-metastatic breast cancer treated at the Cleveland Clinic (Ohio, USA) with

neoadjuvant TCH-P (docetaxel: 75 mg/m^2; carboplatin: AUC 6; Herceptin: 8 mg/kg loading dose, 6 mg/kg maintenance; Perjeta: 840 mg loading dose, 420 mg maintenance dose; 6 cycles q3w). Individual patient charts were reviewed to collect accurate information regarding treatment received, cycle interruption, dose reductions and toxicity profile.

pCR was defined as the absence of invasive tumour in both breast and lymph nodes. No statistical analyses were reported.

Participant flow

The study identified 71 patients. The patient demographics are shown in Table 35.

Table 35 Characteristics of patients included in the Cleveland Clinic retrospective analysis

Study name	**Cleveland Clinic retrospective analysis n=71**
Age, median	52.5 years
Sex, n % Female Male	 70 (100) 0 (0%)
Race, n (%) Caucasian African American Asian Other	 62 (88.5) 3 (4.2) 4 (5.7) 2 (2.8)
ECOG status, n (%) 0 1	 28 (40) 30 (42.8)
ER / PR status, n (%) Positive Negative	 41 (58.5) 29 (41.4)
Clinical stage, n (%) Stage I Stage II Stage III	 8 (11.4) 46 (65.7) 16 (22.8)
ECOG, Eastern Cooperative Oncology Group; ER, oestrogen receptor; PR, progesterone receptor	

Efficacy

The overall observed pCR (ypT0 ypN0) rate for neoadjuvant TCH-P was 52.8% (Table 36). The pCR (ypT0 ypN0) rate was higher in patients with hormone receptor (HR)-negative breast cancer than in those with HR-positive disease: 68.9% vs. 41.4%, respectively (Table 36).

Table 36 pCR rates in the patients included in the Cleveland Clinic retrospective analysis

Study name	Cleveland Clinic retrospective analysis
pCR (ypT0 ypN0), n/N (%)	37 / 70 (52.8%)
pCR (ypT0 ypN0) by ER / PR status, n/N (%) Positive Negative	 17 /41 (41.4%) 20 / 29 (68.9%)
ER, oestrogen receptor; PR, progesterone receptor	

Adverse events

21.4% (15/71) of patients required a dose reduction. No patients had symptomatic cardiac toxicity with TCH-P, with only 4% of patients having an asymptomatic reduction in left ventricular ejection fraction (LVEF) >10%. Adverse events reported are shown in Table 37.

Table 37 Adverse event reporting from the Cleveland Clinic retrospective analysis

Study name	Cleveland Clinic retrospective analysis			
Event, %	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Diarrhoea	32.8	7.1	5.7	1.4
Fatigue	42.8	1.4	1.4	0
Myalgia	15.7	0	0	0
Neuropathy	17.1	7.1	2.8	0
Cytopenias	2.8	4.2	1.4	2.8
Nausea / vomiting	27.1	1.4	1.4	1.4
Rash	8.5	1.4	0	0

4.12 Adverse reactions

4.12.1 Evidence from comparative RCTs and regulatory summaries is preferred, but findings from non comparative trials may sometimes be relevant. For example, post marketing surveillance data may demonstrate that the technology shows a relative lack of adverse reactions commonly associated with the comparator, or that the occurrence of adverse reactions is not statistically significantly different to those associated with other treatments.

4.12.2 In a table, summarise adverse reactions reported in the studies listed in section 4.2. For each intervention group, give the number with the adverse reaction and the frequency, the number in the group, and the percentage with the reaction. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse reaction.

The safety of Perjeta has been evaluated in more than 1600 patients in randomised trials [Perjeta SPC]

The following studies are included in this section:

- NeoSphere and TRYPHAENA, two studies which provided safety data in 532 patients treated with neoadjuvant Perjeta in combination with Herceptin and chemotherapy (e.g., docetaxel, FEC or TCH). This included safety data from 309 patients in the NeoSphere study and 223 patients in the TRYPHAENA study. Safety data from these two studies are summarised below. TRYPHAENA investigated the safety profile for Perjeta in the neoadjuvant setting as the primary objective. NeoSphere investigated efficacy as the primary objective, with safety as a secondary objective.

- In the metastatic breast cancer setting, CLEOPATRA provided safety data from 408 patients, who were treated with Perjeta in combination with Herceptin and docetaxel, the same regimen used during the neoadjuvant phase in Arm B of the NeoSphere study and part of the

neoadjuvant regimen used in two of the treatment arms in the TRYPHAENA study (Arms A and B).The primary objective was efficacy, with safety as a secondary objective. Safety data from the CLEOPATRA study is summarised here to provide further evidence to support the safety and tolerability of Perjeta.

The GeparSepto Study has not yet been fully published. Data presented at the San Antonio Breast Cancer Symposium in 2014 included adverse events (AEs) for the entire study population and did not report AEs in the HER2-positive subpopulation. [Untch 2015] Please refer to Appendix 3 Summary of the GeparSepto study.

The safety of Perjeta administered for more than 6 cycles in the neoadjuvant setting has not been established.

Very common adverse events reported in ≥10% of Perjeta-treated patients in the metastatic and neoadjuvant setting include: [Perjeta SmPC]

- Upper respiratory tract infection, nasopharyngitis
- Neutropenia, anaemia, leucopenia, febrile neutropenia*
- Hypersensitivity/anaphylactic reaction**, infusion reaction/cytokine release syndrome***
- Decreased appetite†
- Insomnia
- Peripheral neuropathy, headache†, dysgeusia
- Cough†
- Diarrhoea†, vomiting†, nausea†, constipation†, stomatitis, dyspepsia
- Alopecia, rash†, nail disorder
- Myalgia, arthralgia
- Fatigue†, asthenia†, oedema†, mucositis/mucosal inflammation, pyrexia, pain†

*Including an adverse reaction with a fatal outcome.
**Hypersensitivity/anaphylactic reaction is based on a group of terms.
***Infusion reaction/cytokine release syndrome includes a range of different terms within a time window.
†Except for febrile neutropenia, neutropenia, leucopenia, and alopecia, all events were also reported in at least 1% of patients participating in Perjeta monotherapy trials, although not necessarily considered causally related to Perjeta by the investigator. Very common events (reported in ≥10% of Perjeta monotherapy-treated patients) are marked with a †.

Cardiac dysfunction has been associated with the use of anti-HER2 targeted therapy Herceptin due to the effect of HER2 signalling on myocardial homeostasis. [Siedman 2002] [Slamon 2011] Therefore, cardiac safety results will also be discussed specifically from the NeoSphere and TRYPHAENA studies.

The ten most common adverse events in the neoadjuvant period for each of the two neoadjuvant studies (NeoSphere and TRYPHAENA) are listed below. Following this, the adverse event profile of each study is presented in turn.

Table 38 Ten most common adverse events in the neoadjuvant period in NeoSphere [Primary CSR]

Adverse event, n (%)	Arm A HD (n=107)	Arm B PHD (n=107)	Arm C PH (n=108)	Arm D PD (n=94)
Total patients with ≥1 AE	105 (98.1)	105 (98.1)	78 (72.2)	93 (98.9)
Total no. of AEs	806	803	326	765
Alopecia	70 (65.4)	68 (63.6)	1 (0.9)	63 (67.0)
Neutropenia	67 (62.6)	54 (50.5)	1 (0.9)	59 (62.8)
Diarrhoea	36 (33.6)	49 (45.8)	30 (27.8)	51 (54.3)
Nausea	39 (36.4)	41 (38.3)	15 (13.9)	34 (36.2)
Fatigue	29 (27.1)	28 (26.2)	13 (12.0)	24 (25.5)
Rash	23 (21.5)	28 (26.2)	12 (11.1)	27 (28.7)
Mucosal inflammation	23 (21.5)	28 (26.2)	3 (2.8)	24 (25.5)
Myalgia	24 (22.4)	24 (22.4)	10 (9.3)	19 (20.2)
Asthenia	19 (17.8)	22 (20.6)	3 (2.8)	15 (16.0)
Headache	12 (11.2)	12 (11.2)	15 (13.9)	12 (12.8)
Arm A: HD, Herceptin + docetaxel; Arm B: PHD, Perjeta + Herceptin + docetaxel Arm C: PH, Perjeta + Herceptin; Arm D: PD, Perjeta + docetaxel				

Table 39 Ten most common adverse events in the neoadjuvant period in TRYPHAENA

Adverse event, n (%)	Arm A FEC+H+P x3 / D+H+P x3 (n=72)	Arm B FEC x3 / D+H+P x3 (n=75)	Arm C DCH+P x6 (n=76)
Total patients with ≥1 AE	72 (100.0)	72 (96.0)	76 (100.0)
Total no. of AEs	781	685	935
Diarrhoea	44 (61.1)	46 (61.3)	55 (72.4)
Alopecia	35 (48.6)	39 (52.0)	41 (53.9)
Nausea	38 (52.8)	40 (53.3)	34 (44.7)
Neutropenia	37 (51.4)	35 (46.7)	37 (48.7)
Vomiting	29 (40.3)	27 (36.0)	30 (39.5)
Fatigue	26 (36.1)	27 (36.0)	32 (42.1)
Anaemia	14 (19.4)	6 (8.0)	28 (36.8)
Mucosal inflammation	17 (23.6)	15 (20.0)	13 (17.1)
Constipation	13 (18.1)	17 (22.7)	12 (15.8)
Dyspepsia	18 (25.0)	6 (8.0)	17 (22.4)

NeoSphere

Safety and tolerability data from the neoadjuvant period of the study will be presented here: adverse events of all grades, grade ≥3, serious adverse events and deaths. This reflects the period in which neoadjuvant Perjeta was given. For the adjuvant period and follow-up period in NeoSphere, serious adverse events and deaths will be presented, to demonstrate the safety of Herceptin as a single anti-HER2 therapy, which is well established from previous phase III studies and real word clinical experience. [Piccart-Gebhart 2005; Jackisch 2015; Slamon 2011; Slamon 2015; Romond 2005; Perez 2014] As expected, there were no new safety concerns identified in the adjuvant period of the NeoSphere study.

The safety population consisted of 107 patients in the Herceptin + docetaxel arm (Arm A), 107 patients in the Perjeta + Herceptin + docetaxel arm (Arm B), 108 patients in the Perjeta + Herceptin arm (Arm C) and 94 patients in the Perjeta + docetaxel arm (Arm D). One extra patient has been included in the safety population in the Perjeta + Herceptin arm (in relation to the efficacy population), due to that patient who was randomly assigned to Perjeta + docetaxel (Arm D) receiving Perjeta + Herceptin (Arm C) treatment. Please refer to the CONSORT diagram in Figure 9 for further details.

Extent of exposure to neoadjuvant study treatment (Perjeta)

In the NeoSphere study, between 93-95% of patients in the Perjeta + Herceptin + docetaxel arm, the Perjeta + Herceptin arm, and the Perjeta + docetaxel arm (Arms B, C and D) received the full 4 cycles of neoadjuvant Perjeta. Between 90-93% of cycles of Perjeta were administered without the need for delay, interruption, modification or discontinuation. The doses received are summarised in Table 40:

Table 40 Summary of Neoadjuvant Perjeta received [Primary CSR]

Total dose received, mg	Arm B PHD (n=107)	Arm C PH (n=108)	Arm D PD (n=94)
Patients receiving scheduled number of cycles	95%	93%	94%
Number of cycles administered per patient, n			
Mean	3.9	3.9	3.9
SD	0.47	0.42	0.48
Median	4.0	4.0	4.0
Range	1-4	2-4	1-4
Total dose received, mg			
Mean	2059.6	2047.7	2051.0
SD	280.79	177.57	202.74
Median	2100.0	2100.0	2100.0
Range	300-2940	1260-2100	840-2100

Arm B: PHD, Perjeta + Herceptin + docetaxel; Arm C: PH, Perjeta + Herceptin
Arm D: PD, Perjeta + docetaxel
Arm A not included here as treatment arm does not include Perjeta
SD – standard deviation

Adverse events of any grade in the neoadjuvant period

The majority of patients experienced at least one adverse event in the neoadjuvant period. See Table 41. The majority of AEs were of grades 1-2 in severity. [Primary CSR]

Table 41 Summary of adverse events in the neoadjuvant period (treatment cycles 1-4) of NeoSphere [Primary CSR]

	Arm A HD (n=107)	Arm B PHD (n=107)	Arm C PH (n=108)	Arm D PD (n=94)
Total patients with at least one adverse event, n (%)	105 (98.1)	105 (98.1)	78 (72.2)	93 (98.9)
Total number of adverse events, n	806	803	326	765
Arm A: HD, Herceptin + docetaxel; Arm B: PHD, Perjeta + Herceptin + docetaxel Arm C: PH, Perjeta + Herceptin; Arm D: PD, Perjeta + docetaxel				

The ten most common adverse events of any grade are presented in Table 42. Adverse events of grade ≥3 are presented in Table 43.

Table 42 Ten most common adverse events (any grade) in the neoadjuvant period of NeoSphere [Primary CSR]

Adverse event, n (%)	Arm A HD (n=107)	Arm B PHD (n=107)	Arm C PH (n=108)	Arm D PD (n=94)
Alopecia	70 (65.4)	68 (63.6)	1 (0.9)	63 (67.0)
Neutropenia	67 (62.3)	54 (50.5)	1 (0.9)	59 (62.8)
Diarrhoea	36 (33.6)	49 (45.8)	30 (27.8)	51 (54.3)
Nausea	39 (36.4)	41 (38.3)	15 (13.9)	34 (36.2)
Fatigue	29 (27.1)	28 (26.2)	13 (12.0)	24 (25.5)
Rash	23 (21.5)	28 (26.2)	12 (11.1)	27 (28.7)
Mucosal inflammation	23 (21.5)	28 (26.2)	3 (2.8)	24 (25.5)
Myalgia	24 (22.4)	24 (22.4)	10 (9.3)	19 (20.2)
Asthenia	19 (17.8)	22 (20.6)	3 (2.8)	15 (16.0)
Headache	12 (11.2)	12 (11.2)	15 (13.9)	12 (12.8)
Arm A: HD, Herceptin + docetaxel; Arm B: PHD, Perjeta + Herceptin + docetaxel Arm C: PH, Perjeta + Herceptin; Arm D: PD, Perjeta + docetaxel				

Adverse events grade ≥3 in the neoadjuvant period

The proportion of patients experiencing grade ≥3 adverse events were similar in the Herceptin + docetaxel arm, the Perjeta + Herceptin + docetaxel arm, and the Perjeta + docetaxel arm (Arms A, B and D, respectively), but were notably lower in the Perjeta + Herceptin arm (Arm C), where docetaxel was not administered. The most common Grade ≥3 AEs were neutropenia, febrile neutropenia, and leucopenia, and were as expected in the treatment arms containing docetaxel. See Table 43. One patient in arm C experienced grade ≥3 congestive heart failure (CHF).

Table 43 Grade ≥3 Adverse Events occurring in ≥1 patient in the neoadjuvant period in NeoSphere [Primary CSR; Gianni 2012]

Grade ≥3 AE, n (%)	Arm A HD (n=107)	Arm B PHD (n=107)	Arm C PH (n=108)	Arm D PD (n=94)
Total patients with ≥1 grade ≥3 AE, n (%)	78 (72.9)	67 (62.6)	7 (6.5)	66 (70.2)
Neutropenia	61 (57.0)	48 (44.9)	1 (0.9)	52 (55.3)
Leucopenia	13 (12.1)	5 (4.7)	0	7 (7.4)
Febrile neutropenia	8 (7.5)	9 (8.4)	0	7 (7.4)
Granulocytopenia	1 (0.9)	1 (0.9)	0	2 (2.1)
Alopecia	1 (0.9)	5 (4.7)	0	4 (4.3)
Rash	2 (1.9)	2 (1.9)	0	1 (1.1)
Diarrhoea	4 (3.7)	6 (5.6)	0	4 (4.3)
Urinary tract infection	2 (1.9)	2 (1.9)	0	1 (1.1)
Irregular menstruation	1 (0.9)	1 (0.9)	0	4 (4.3)
Asthenia	0	2 (1.9)	0	2 (2.1)
Mucosal inflammation	0	2 (1.9)	0	0
ALT increase	3 (2.8)	0	0	1 (1.1)
AST increase	2 (1.9)	0	0	1 (1.1)
Transaminases increase	0	2 (1.9)	0	0
Nervous system disorders	2 (1.9)	1 (0.9)	0	1 (1.1)
Drug hypersensitivity	0	1 (0.9)	2 (1.9)	0
Congestive heart failure (CHF)	0	0	1 (0.9)	0

Arm A: HD, Herceptin + docetaxel; Arm B: PHD, Perjeta + Herceptin + docetaxel
Arm C: PH, Perjeta + Herceptin; Arm D: PD, Perjeta + docetaxel
ALT=alanine aminotransferase
AST=aspartate aminotransferase
Multiple occurrences of the same adverse event in one individual counted only once.
Adverse events occurring in only one patient across treatment arms are not shown here (except for CHF).

Cardiac safety

The number of patients with cardiac dysfunction AEs in NeoSphere was low, but was greater in arm B (Perjeta + Herceptin + docetaxel) than arms A (Herceptin + docetaxel), C (Perjeta + Herceptin), and D (Perjeta + docetaxel) for the neoadjuvant and the adjuvant periods. Despite incidence of cardiac dysfunction being slightly greater in Arm B than the other arms, incidence was still low (3-6% across the treatment periods) and there were no incidences of left ventricular systolic dysfunction in Arm B.

Incidence of left ventricular systolic dysfunction is shown in Table 44. One patient in Arm C (Perjeta + Herceptin) experienced congestive heart failure (CHF). Study treatment was discontinued and the patient received medication for the event. The event resolved after 5 days. This patient had a history of hypertension and angina pectoris, had a coronary arterial stent in situ and was receiving medication with digoxin at baseline. This patient's enrolment into the study was a protocol violation. No further events of symptomatic LVSD were reported in NeoSphere. [Gianni 2012]

The mean maximum decrease in LVEF measurement during the neoadjuvant period was low (4–5%) and was balanced across the treatment arms. The maximum decrease did not alter greatly when the adjuvant treatment period was also taken into account (mean maximal decrease was 6% across all arms). No patient reported an LVEF decrease to below 40% at any time in the study. It should be noted that LVEF assessments were not scheduled for every cycle, and were therefore performed routinely only at certain cycles or as warranted clinically. [Gianni 2012]

Declines in LVEF of at least 10 percentage points to less than 50% of baseline are shown in Table 44. Of the patients in the neoadjuvant period, all had improved to greater than 50% and less than a 10% decrease by cycle 4, with the exception of the patient in Arm C (Perjeta + Herceptin), who discontinued treatment due to CHF. [Gianni 2012]

Table 44 Left ventricular dysfunction and left ventricular ejection fraction declines in the safety population in NeoSphere [Gianni 2013]

Cardiac event n (%) [95% CI]	Arm A HD	Arm B PHD	Arm C PH	Arm D PD
Neoadjuvant period Symptomatic LVSD LVEF decline	(n=107) 0 (0.0) [0.0-3.4] 1 (0.9) [0.0-5.1]	(n=107) 0 (0.0) [0.0-3.4] 3 (2.8) [0.6-8.0]	(n=108) 1 (0.9) [0.0-5.1] 1 (0.9) [0.0-5.1]	(n=94) 0 (0.0) [0.0-3.8] 1 (1.1) [0.0-5.8]
Adjuvant period Symptomatic LVSD LVEF decline	(n=99) 0 (0.0) [0.0–3.5] 1 (1.0) [0.0–5.3]	(n=98) 0 (0.0)[0.0–3.6] 6 (5.9) [2.2–12.4]	(n=92) 0 (0.0) [0.0–3.8] 0 (0.0) [0.0–3.8]	(n=84) 0 (0.0) [0.0–4.1] 5 (5.7) [1.9–12.8]
Follow-up period Symptomatic LVSD LVEF decline	(n=97) 0 (0.0) [0.0–3.7] 0 (0.0) [0.0–3.7]	(n=99) 0 (0.0) [0.0–3.7] 4 (4.0) [1.1–10.0]	(n=96) 0 (0.0) [0.0–3.8] 1 (1.0) [0.0–5.7]	(n=86) 0 (0.0) [0.0–4.2] 3 (3.5) [0.7–9.9]
Arm A: HD, Herceptin + docetaxel; Arm B: PHD, Perjeta + Herceptin + docetaxel Arm C: PH, Perjeta + Herceptin; Arm D: PD, Perjeta + docetaxel LVEF, left ventricular ejection fraction (decline = decline ≥10% points to <50%) LVSD, left ventricular systolic dysfunction (grade ≥3)				

Serious Adverse Events (SAEs)

Neoadjuvant period: The number of patients who experienced at least one SAE was lower in the Perjeta plus Herceptin arm (Arm C; 4% of patients) than the other three treatment arms (10–17% of patients). Neutropenia and febrile neutropenia were the most frequent SAEs in any treatment arm. See Table 45

One patient in the Perjeta + Herceptin + docetaxel arm (Arm B) experienced an SAE of fulminant hepatitis that was fatal. One patient in the Perjeta + Herceptin arm (Arm C) experienced an SAE of congestive cardiac failure. [Primary CSR]

Adjuvant period: The number of patients who experienced at least one SAE was lower in the Herceptin + docetaxel arm (Arm A) (4% of patients) that the other three treatment arms (11-18%). The incidence was highest in the Perjeta + Herceptin arm (Arm C). Most of the serious adverse events in the Perjeta + Herceptin arm were events known to be associated with docetaxel

(neutropenia, febrile neutropenia, and neutropenic infection); therefore, the higher incidence in the Perjeta + Herceptin arm was likely due to the administration of docetaxel during the adjuvant period in this arm (all other arms received docetaxel in the neoadjuvant period only. [1st update CSR] Three patients in the Perjeta + Herceptin + docetaxel arm (Arm B) reported cardiac SAEs: two cases of left ventricular dysfunction and one case of angina pectoris. [Primary CSR] See Table 46

Following completion of adjuvant chemotherapy, a total of 10 patients experienced serious adverse events during adjuvant Herceptin therapy (4 [3.9%] in the Perjeta + Herceptin + docetaxel arm (Arm B), 5 [5.3%] in the Perjeta + Herceptin arm (Arm C), and 1 [1.1%] in the Perjeta + docetaxel arm (Arm D)), all of which resolved with no sequelae. Left ventricular dysfunction was reported in 2 patients (2.0%) in the Perjeta + Herceptin + docetaxel arm (Arm B); all other serious adverse events were experienced by 1 patient per treatment arm. [1st update CSR]

Follow-up period: two SAEs were reported during the post-treatment follow-up period. One patient in the Perjeta + Herceptin + docetaxel arm (Arm B) experienced cerebrovascular accident, which resulted in death. One patient in the Perjeta + docetaxel arm (Arm D) experienced myeloproliferative disorder. [Final CSR]

Table 45 SAEs in the neoadjuvant setting NeoSphere [Primary CSR; Gianni 2012]

SAE, n (%)	Arm A HD (n=107)	Arm B PHD (n=107)	Arm C PH (n=108)	Arm D PD (n=94)
No. of patients ≥1 SAE	18 (16.8)	11 (10.3)	4 (3.7)	16 (17.0)
Total SAEs, n	20	15	4	16
Febrile neutropenia	7 (6.5)	6 (5.6)	0	6 (6.4)
Neutropenia	1 (0.9)	4 (3.7)	0	6 (6.4)
Neutropenic infection	0	1 (0.9)	0	0
Neutropenic sepsis	1 (0.9)	0	0	0
Pyrexia	1 (0.9)	1 (0.9)	0	0
Diarrhoea	2 (1.9)	0	0	1 (1.1)
Congestive heart failure	0	0	1 (0.9)	0
Fulminant hepatitis	0	1 (0.9)*	0	0
Other	8 (7.5)	2 (1.9)	3 (2.8)	3 (3.2)
Deaths	0	1 (1)†‡	0	1 (1)♯

Arm A: HD, Herceptin + docetaxel; Arm B: PHD, Perjeta + Herceptin + docetaxel
Arm C: PH, Perjeta + Herceptin; Arm D: PD, Perjeta + docetaxel
*Resulted in patient's death
†Died from fulminant hepatitis. Death occurred in the neoadjuvant setting on Day 70
‡Docetaxel is associated with a rare incidence of fatal hepatitis
♯Died of lung metastases and progressive disease in the adjuvant setting on Day 116
Multiple occurrences of the same adverse event in one individual counted only once

Table 46 SAEs in the adjuvant setting NeoSphere [1st update CSR]

SAE, n (%)	Arm A HD (n=103)	Arm B PHD (n=102)	Arm C PH (n=94)	Arm D PD (n=88)
No. of patients ≥1 SAE	5 (4.9)	11 (10.8)	17 (18.1)	11 (12.5)
Total SAEs, n	5	15	20	12
Febrile neutropenia	3 (2.9)	2 (2.0)	4 (4.3)	8 (9.1)
Neutropenia	0	2 (2.0)	3 (3.2)	0
Neutropenic infection	1 (1.0)	0	1 (1.1)	0
Pyrexia	0	0	2 (2.1)	1 (1.1)
Left ventricular dysfunction	0	2 (2.0)	0	0
Others	1 (1.0)	9 (8.8)	10 (10.6)	3 (3.4)
Arm A: HD, Herceptin + docetaxel; Arm B: PHD, Perjeta + Herceptin + docetaxel Arm C: PH, Perjeta + Herceptin; Arm D: PD, Perjeta + docetaxel N = Number of patients who started adjuvant treatment Multiple occurrences of the same adverse event in one individual counted only once				

Deaths

Of the 31 deaths in the study, 30 occurred during post-treatment follow up. No patients died during the adjuvant period. [Final CSR]

One patient in the Perjeta + Herceptin + docetaxel arm (Arm B) died during neoadjuvant treatment: death caused by fulminant hepatitis, possibly related to treatment. (Comorbidities: high body-mass index, hypertension, type 2 diabetes.) [Gianni et al, 2012]

One patient in the Perjeta + docetaxel arm (Arm D) died after disease progression at cycle 3. This was mistakenly reported as withdrawal due to death (i.e. death during neoadjuvant treatment); however the patient was withdrawn from the study due to disease progression, and subsequently died (i.e. death during follow-up). [Final CSR]

Twenty-three of the deaths in the post-treatment follow-up period were due to disease progression, four had no cause of death reported, two were due to colorectal carcinoma and one was due to cerebrovascular accident.

Discontinuation or modification of treatment [Primary CSR]

Five patients discontinued from a study treatment in the neoadjuvant period due to an adverse event. Four were possibly related to treatment.

- Two patients (one in the Perjeta + Herceptin + docetaxel arm (Arm B), one in the Perjeta + Herceptin (Arm C[1])) discontinued docetaxel due to drug hypersensitivity
- One patient in the P (Arm C) withdrew from all medication due to congestive heart failure (CHF)
- One patient in the Perjeta + docetaxel arm (Arm D) withdrew from Perjeta and docetaxel due to neutropenia
- One patient in the Perjeta + docetaxel arm (Arm D) discontinued due to ulcerative colitis – this was considered unrelated to treatment by the investigators. This patient did complete all neoadjuvant treatment cycles, but the adverse event meant that FEC (5-fluorouracil + epirubicin + cyclophosphamide) was discontinued before the first cycle of adjuvant therapy was actually received; therefore this discontinuation was assigned to the neoadjuvant period

The number of patients who experienced an adverse event in the neoadjuvant period that required treatment interruption or modification was highest in the Perjeta + docetaxel arm (Arm D; 44%) and lowest in the Perjeta + Herceptin

[1] This patient had been randomised to, and included in the ITT population of the Perjeta + Herceptin + docetaxel arm (Arm B), but did not receive a full dose of docetaxel, since infusion was quickly discontinued (within 5 minutes) as a result of a hypersensitivity reaction. The patient was therefore assigned to the Perjeta + Herceptin arm (Arm C) for the purpose of the safety population.

arm (Arm C; 15%). The Herceptin + docetaxel and the Perjeta + Herceptin + docetaxel arms (Arms A and B, respectively) were comparable (35% and 33% respectively). The most frequently reported AEs (in at least five patients in any arm) requiring dose modification are shown in Table 47. Three patients in the Perjeta + Herceptin + docetaxel arm (Arm B) experienced left ventricular dysfunction leading to dose modification during the neoadjuvant period. All three events were assessed as possibly related to study treatment, and resolved without sequelae.

Table 47 Most frequent adverse events leading to dose modifications [Primary CSR]

Adverse event	Arm A HD (n=107)	Arm B PHD (n=107)	Arm C PH (n=108)	Arm D PD (n=94)
Neutropenia	9.3	5.6	0.9	16
Infusion-related reaction	4.7	3.7	2.8	4.3
Diarrhoea	0.9	7.5	0	6.4
Febrile neutropenia	6.5	3.7	0	4.3
Drug hypersensitivity	0.9,	1.9	4.6	4.3
Arm A: HD, Herceptin + docetaxel; Arm B: PHD, Perjeta + Herceptin + docetaxel Arm C: PH, Perjeta + Herceptin; Arm D: PD, Perjeta + docetaxel				

TRYPHAENA

TRYPHAENA was a safety study, which investigated specific cardiac function parameters as its primary endpoints.

Cardiac tolerability data from the neoadjuvant period, adjuvant period and follow-up period will be presented here from the TRYPHAENA study. Adverse events of all grades, grade ≥3, serious adverse events and deaths will be presented for the neoadjuvant and adjuvant periods.

The combination of Perjeta and Herceptin with chemotherapy was associated with no new safety signals, which is consistent with the safety profile observed

with the use of Perjeta in combination with Herceptin and docetaxel from the CLEOPATRA study in the metastatic setting.

The safety population consisted of 72 patients in Arm A[1], 75 patients in Arm B and 76 patients in Arm C.

Extent of exposure to study treatment

The extent of exposure to Perjeta in the neoadjuvant period of the study is summarised in Table 48.

Table 48 Extent of exposure to Perjeta in the neoadjuvant period of TRYPHAENA [Primary CSR]

	Arm A FEC+H+P x3 / D+H+P x3 (n=72)	**Arm B FEC x3 / D+H+P x3 (n=75)**	**Arm C DCH+P x6 (n=76)**
Patients receiving scheduled number of cycles, %	91.7	88.0	92.1
Number of cycles administered per patient, n			
Mean	5.8	2.9	5.7
SD	0.78	0.42	1.02
Median (range)	6.0 (1-6)	3.0 (1-3)	6.0 (1-6)
Total dose received, mg			
Mean	2875.8	1637.8	2823.9
SD	328.1	177.3	458.0
Median (range)	2940.0 (840–3360)	1680.0 (840–1680)	2940.0 (420–2940)

FEC, 5-flurouracil + epirubicin + cyclophosphamide; P, Perjeta; H, Herceptin; D, docetaxel
SD, standard deviation

Cardiac safety in TRYPHAENA

Incidence of symptomatic left ventricular systolic dysfunction (LVSD) and significant decline in left ventricular ejection fraction (LVEF) were primary

[1] Arm A: FEC+Herceptin+Perjeta x3 cycles → Docetaxel+Herceptin+Perjeta x3 cycles
Arm B: FEC x3 cycles → docetaxel+Herceptin+Perjeta x3 cycles
Arm C: Perjeta+docetaxel+carboplatin+Herceptin x6 cycles

endpoints of the study. The study investigated concurrent versus sequential administration of Perjeta and Herceptin with anthracycline-containing chemotherapy regimens, and compared these against Perjeta and Herceptin with a non-anthracycline-containing carboplatin-based chemotherapy regimen.

Neoadjuvant period

- Two patients (2.7%) in Arm B[1] experienced symptomatic LVSD during neoadjuvant treatment. However, one of these patients experienced the event during the administration of the FEC-only period of their neoadjuvant treatment: the other patient experienced LVSD after their fourth cycle of Perjeta. Therefore, only one out of 223 patients (0.4%) from the safety population, who received Perjeta and Herceptin with standard chemotherapy developed symptomatic LVSD during the neoadjuvant period. The events for both these patients resolved after study treatment discontinuation and medication for the event. No symptomatic LVSD events were experienced by patients in the other two arms in the neoadjuvant period. [2nd update CSR]

The incidence of LVEF decline of ≥10% points from baseline to <50% was low for all three treatment arms; see Table 49. These measurements had improved to ≥50% in all but two patients at the first data cut-off (i.e. data cut following completion of neoadjuvant period). Measurements for the remaining two patients had improved to ≥50% by the second data cut (i.e. following completion of adjuvant period) [1st update CSR]

[1] Arm A: FEC+Herceptin+Perjeta x3 cycles → Docetaxel+Herceptin+Perjeta x3 cycles
Arm B: FEC x3 cycles → docetaxel+Herceptin+Perjeta x3 cycles
Arm C: Perjeta+docetaxel+carboplatin+Herceptin x6 cycles

Adjuvant period

- One patient in Arm C experienced symptomatic LVSD during adjuvant treatment, whilst receiving Herceptin-only therapy. The patient received treatment for the event, and the event resolved 24 days after onset. Herceptin therapy was temporarily interrupted for two cycles during the event, but was then resumed. No symptomatic LVSD events were experienced by patients in the other two arms in the adjuvant period. [2nd update CSR]

- Incidence of significant LVEF declines in the adjuvant period was highest in Arm B (12.3%) and lower in Arms A[1] and C (5.9% and 4.5% respectively). All of these declines had improved to ≥50% at the second data cutoff (i.e. after completion of adjuvant period). [2nd update CSR]

Follow-up period

- One patient in Arm B experienced symptomatic LVSD in the follow-up period. This patient had received four cycles of neoadjuvant therapy in the study, and was then withdrawn due to pneumonitis. The investigator considered the LVSD event related to off-study adjuvant Herceptin treatment (which was subsequently discontinued). No details on the outcome of the event are available as the patient withdrew consent. No symptomatic LVSD events were experienced by patients in the other two arms in the follow-up period. [2nd update CSR]

- During follow-up, nine patients (two [2.9%] in Arm A, five [6.7%] in Arm B, two [2.7%] in Arm C) experienced significant LVEF declines. LVEF values had improved to ≥50% in 7/9 patients at the third data cut off (i.e. after the follow-up period). [2nd update CSR]

[1] Arm A: FEC+Herceptin+Perjeta x3 cycles → Docetaxel+Herceptin+Perjeta x3 cycles
Arm B: FEC x3 cycles → docetaxel+Herceptin+Perjeta x3 cycles
Arm C: Perjeta+docetaxel+carboplatin+Herceptin x6 cycles

In addition to the symptomatic LVSD events shown in Table 49 a serious adverse event of LVSD was reported during neoadjuvant treatment for one patient in Arm A.

Table 49 Left ventricular systolic dysfunction and left ventricular ejection fraction declines in the safety population in TRYPHAENA [2nd update CSR]

Cardiac event **n (%)** **[95% CI]**	**Arm A** **FEC+P+D x3 /** **D+P+D x3**	**Arm B** **FEC x3 /** **D+P+D x3**	**Arm C** **DCH+P x6**
Neoadjuvant period	**n=72**	**n=75**	**n=76**
LVSD (all grades)	4 (5.6) [1.5–13.6]	3 (4.0) [0.8–11.2*]	2 (2.6) [0.3–9.2]
Symptomatic LVSD (Grade ≥3)	0 (0.0) [0.0–5.0]	2 (2.7) [0.3–9.3 *]	0 (0.0) [0.0–4.7]
LVEF decline ≥10% points to <50%	4 (5.6) [1.5–13.6]	4 (5.3) [1.5–13.1]	3 (3.9) [0.8–11.1]
Adjuvant period	**n=68**	**n=65**	**n=67**
LVSD (all grades)	4 (5.9) [1.6–14.4]	5 (7.7) [2.5–17.0]	3 (4.5) [0.9–12.5]
Symptomatic LVSD (Grade ≥3)	0 (0.0) [0.0–5.3]	0 (0.0) [0.0–5.5]	1 (1.5) [0.0–8.0]
LVEF decline ≥10% points to <50%	4 (5.9) [1.6–14.4]	8 (12.3) [5.5–22.8]	3 (4.5) [0.9–12.5]
Follow-up period	**n=70**	**n=75**	**n=74**
LVSD (all grades)	1 (1.4) [0.0–7.7]	2 (2.7) [0.3–9.3]	1 (1.4) [0.0–7.3]
Symptomatic LVSD (Grade ≥3)	0 (0.0) [0.0–5.1]	1 (1.3) [0.0–7.2]	0 (0.0) [0.0–4.9]
LVEF decline ≥10% points to <50%	3 (4.3) [0.9–12.0]	4 (5.3) [1.5–13.1]	2 (2.7) [0.3–9.4]
FEC, 5-flurouracil + epirubicin + cyclophosphamide; P, Perjeta; H, Herceptin; D, docetaxel * Patient who had symptomatic LVSD during FEC and prior to the administration of PHD is excluded			

Non-cardiac safety

Adverse events of any grade in the neoadjuvant period

The vast majority of patients experienced at least one adverse event in the neoadjuvant period (96–100% across arms), with patients in Arm C reporting the greatest total number of adverse events. [Primary CSR] Diarrhoea, alopecia and nausea (all grades) were reported in >50% of patients across all arms. The ten most common adverse events of any grade in the neoadjuvant period are listed in Table 50 [Schneeweiss 2013]

Table 50 Ten most common AEs (any grade) in the neoadjuvant period in TRYPHAENA [Schneeweiss 2013]

Adverse event, n (%)	Arm A FEC+H+P x3 / D+H+P x3 (n=72)	Arm B FEC x3 / D+H+P x3 (n=75)	Arm C DCH+P x6 (n=76)
Diarrhoea	44 (61.1)	46 (61.3)	55 (72.4)
Alopecia	35 (48.6)	39 (52.0)	41 (53.9)
Nausea	38 (52.8)	40 (53.3)	34 (44.7)
Neutropenia	37 (51.4)	35 (46.7)	37 (48.7)
Vomiting	29 (40.3)	27 (36.0)	30 (39.5)
Fatigue	26 (36.1)	27 (36.0)	32 (42.1)
Anaemia	14 (19.4)	6 (8.0)	28 (36.8)
Mucosal inflammation	17 (23.6)	15 (20.0)	13 (17.1)
Constipation	13 (18.1)	17 (22.7)	12 (15.8)
Dyspepsia	18 (25.0)	6 (8.0)	17 (22.4)

FEC, 5-flurouracil + epirubicin + cyclophosphamide; P, Perjeta; H, Herceptin; D, docetaxel

Adverse events of grade ≥3 in the neoadjuvant period

Table 51 Ten most common Grade ≥3 AEs in the neoadjuvant period in TRYPHAENA [Schneeweiss 2013]

Grade ≥3 AE, n (%)	Arm A FEC+H+P x3 / D+H+P x3 (n=72)	Arm B FEC x3 / D+H+P x3 (n=75)	Arm C DCH+P x6 (n=76)
Total patients with ≥1 grade ≥3 AE	50 (69.4)	45 (60.0)	56 (73.7)
Neutropenia	34 (47.2)	32 (42.7)	35 (46.1)
Febrile neutropenia	13 (18.1)	7 (9.3)	13 (17.1)
Leucopenia	14 (19.4)	9 (12.0)	9 (11.8)
Diarrhoea	3 (4.2)	4 (5.3)	9 (11.8)
Anaemia	1 (1.4)	2 (2.7)	13 (17.1)
Thrombocytopenia	0	0	9 (11.8)
Vomiting	0	2 (2.7)	4 (5.3)
Drug hypersensitivity	2 (2.8)	0	2 (2.6)
Fatigue	0	0	3 (3.9)
ALT increase	0	0	3 (3.9)

FEC, 5-flurouracil + epirubicin + cyclophosphamide; P, Perjeta; H, Herceptin; D, docetaxel
ALT, alanine aminotransferase

Serious adverse events in the neoadjuvant phase

The incidence of SAEs was highest in Arm C (35.5%), followed by Arm A (27.8%) and Arm B (20.0%). Febrile neutropenia was the most common SAE. The most common SAEs are shown in Table 52. All other SAEs occurred in ≤2 patients in any arm. [Primary CSR]

A total of five patients reported cardiac disorder SAEs. These were:

- Three reports of left ventricular systolic dysfunction (LVSD) (one in Arm A; two in Arm B which were grade 3). The three LSVD SAEs led to discontinuation of study treatment
- One report of cardiovascular disorder in Arm C
- One report of conduction disorder in Arm C

Table 52 Serious adverse events in ≥2 patients per arm in the neoadjuvant phase in TRYPHAENA [Primary CSR]

SAE, %	Arm A FEC+H+P x3 / D+H+P x3 (n=72)	Arm B FEC x3 / D+H+P x3 (n=75)	Arm C DCH+P x6 (n=76)
Total patients with at least one SAE n (%)	20 (27.8)	15 (20.0)	27 (35.5)
Total number of SAEs	27	24	
Febrile neutropenia, %	13.9	5.3	14.5
Neutropenia, %	2.8	4.0	1.3
Diarrhoea, %	1.4	4	5.3
FEC, 5-flurouracil + epirubicin + cyclophosphamide; P, Perjeta; H, Herceptin; D, docetaxel SAE, serious adverse event			

Serious adverse events in the adjuvant period

In the adjuvant period 5, 4 and 6 patients in Arms A[1], B and C, respectively, had at least one SAE. [1st update CSR]

[1] Arm A: FEC+Herceptin+Perjeta x3 cycles → Docetaxel+Herceptin+Perjeta x3 cycles
Arm B: FEC x3 cycles → docetaxel+Herceptin+Perjeta x3 cycles

Table 53 Serious adverse events in the adjuvant period in TRYPHAENA [1st update CSR]

	Arm A FEC+H+P x3 / D+H+P x3 (n=68)	Arm B FEC x3 / D+H+P x3 (n=65)	Arm C DCH+P x6 (n=67)
Total patients with at least one SAE n (%)	5 (7.4)	4 (6.2)	6 (9.0)
Total number of SAEs, n	5	5	6
	pneumonia x2 cystitis vaginal haemorrhage metastatic neoplasm	appendicitis device-related sepsis infection seroma ovarian cyst	pyelonephritis wound infection post-procedural haematoma left ventricular dysfunction chest pain anaphylactic reaction
FEC, 5-flurouracil + epirubicin + cyclophosphamide; P, Perjeta; H, Herceptin; D, docetaxel N = number of patients entering adjuvant period Multiple occurrences of the same adverse event in one individual counted only once SAE, serious adverse event			

Deaths

No death was reported during neoadjuvant treatment. During adjuvant treatment, one patient in Arm A[1] presented with malignant neoplasm and withdrew from study treatment. This disease progression was reported as an adverse event, and the patient died on study day 337 during follow-up. [Schneeweiss 2013] An additional 12 deaths during follow-up were due to disease recurrence (Arm A: 3, Arm B: 4, Arm C: 5). [2nd update CSR]

Discontinuation or modification of treatment in the neoadjuvant phase

The number of patients discontinuing any study medication was low across all the arms (4, 5 and 6 patients in Arms A, B and C, respectively). In the majority of cases, all study treatments being received were discontinued

Arm C: Perjeta+docetaxel+carboplatin+Herceptin x6 cycles
[1] Arm A: FEC+Herceptin+Perjeta x3 cycles → Docetaxel+Herceptin+Perjeta x3 cycles
Arm B: FEC x3 cycles → docetaxel+Herceptin+Perjeta x3 cycles
Arm C: Perjeta+docetaxel+carboplatin+Herceptin x6 cycles

simultaneously. Adverse events leading to discontinuation in more than one patient were left ventricular systolic dysfunction (LVSD), drug hypersensitivity and neutropenia.

Dose modifications were common in all arms, and were primarily performed in order to manage blood and lymphatic disorders (see Table 54). A total of 36%, 29% and 50% of patients in Arms A, B and C respectively had adverse events that led to some study treatment modification in the neoadjuvant period.

- The majority of Herceptin infusions in the neoadjuvant treatment phase were given without dose modification or discontinuation. More cycles of Herceptin were modified, delayed or discontinued due to an AE in Arm C (14%) than in Arm A (6%) or Arm B (5%). Of those patients who did experience some form of dose modification (13–20% across arms), the vast majority did so for only one cycle of treatment, and nearly all dose delays lasted for 14 days or less
- The proportion of cycles of docetaxel that were modified, delayed or discontinued was 18– 27% across arms. A higher proportion of these in Arm C[1] (18%) were due to an AE than in Arm A (10%) or Arm B (9%). Of those patients who did experience some form of dose modification, the majority of patients in Arms A and B did so for only one cycle of treatment, but there were more patients in Arm C who experienced modification at multiple cycles (likely due to the greater number of cycles received). One patient experienced modifications in all six cycles. Nearly all dose delays lasted for 14 days or less. Three patients (1 in Arm A, 2 in Arm C) had one cycle of docetaxel discontinued.
- The majority of patients did not require any dose modifications for FEC, and of those that did (between 7–17%) this occurred for only one cycle. The proportion of patients with AEs leading to dose modifications of

[1] Arm A: FEC+Herceptin+Perjeta x3 cycles → Docetaxel+Herceptin+Perjeta x3 cycles
Arm B: FEC x3 cycles → docetaxel+Herceptin+Perjeta x3 cycles
Arm C: Perjeta+docetaxel+carboplatin+Herceptin x6 cycles

any or all of the three treatments was higher in Arm A (13%–14 %) than in Arm B (3%).

- A total of 29% of patients required dose modifications for carboplatin, of which the majority were due to AEs. For most patients with a dose modification, this was required at only one cycle.

Table 54 Most frequent adverse events (in ≥5% patients) leading to dose modifications [Primary CSR]

Adverse event, n (%)	Arm A FEC+H+P x3 / D+H+P x3 (n=72)	Arm B FEC x3 / D+H+P x3 (n=75)	Arm C DCH+P x6 (n=76)
Neutropenia	10 (13.9)	11 (14.7)	11 (14.5)
Anaemia	2 (2.8)	-	16 (21.1)
Thrombocytopenia	-	-	12 (15.8)
Febrile neutropenia	4 (5.6)	2 (2.7)	2 (2.6)
Investigations (for laboratory abnormalities)	3 (4.2)	1 (1.3)	8 (10.5)
Diarrhoea	-	4 (5.3)	3 (3.9)
FEC, 5-flurouracil + epirubicin + cyclophosphamide; P, Perjeta; H, Herceptin; D, docetaxel			

4.12.3 CLEOPATRA

The phase III CLEOPATRA study evaluated the efficacy and safety of dual anti-HER2 blockade, Perjeta + Herceptin, in combination with docetaxel, in patients with metastatic breast cancer. These patients received median of 24 cycles and had more advanced disease than patients in the NeoSphere and TRYPHAENA studies.

CLEOPATRA is therefore included in this section of the submission to provide further safety data with the use of Perjeta, observed from a large phase III study in patients with metastatic HER2-positive breast cancer.

Safety data from the NeoSphere and TRYPHAENA neoadjuvant studies were consistent with safety data previously observed from the CLEOPATRA study.

No new safety signals were identified. [Gianni 2012; Schneeweiss 2013; Baselga 2012]

The CLEOPATRA study was a randomised, double-blind, placebo-controlled clinical trial which enrolled 808 people with HER2-positive metastatic breast cancer randomised in a 1:1 ratio to one of two treatment arms: Herceptin (8 mg/kg loading dose, 6 mg/kg maintenance) plus docetaxel (starting dose 75 mg/m^2) or Herceptin plus docetaxel plus Perjeta (840 mg loading dose, 420 mg maintenance dose). The primary endpoint of the study was progression-free survival (PFS), defined as the time from randomisation to the first documented radiographic evidence of progressive disease (PD).

Treatment groups in the study were generally comparable with respect to baseline characteristics. However, there are a few notable differences compared to patients enrolled into the neoadjvant studies; the proportion of Caucasian patients was lower in CLEOPATRA (and the proportion of Asian patients was higher) and, as expected due to the course of their disease, the proportion of patients in CLEOPATRA with an Eastern Cooperative Oncology Group performance status (ECOG PS) of zero was lower that that seen in the neoadjuvant studies.

The trial methodology for CLEOPATRA (location, trial design, eligibility criteria, settings & location, outcomes, statistical analysis), baseline characteristics and patient flow are presented in Appendix 8 CLEOPATRA study in metastatic breast cancer.

Safety in the CLEOPATRA study

Extent of exposure to Perjeta in CLEOPATRA

In the CLEOPATRA study, patients received Perjeta + Herceptin + docetaxel or Herceptin + docetaxel every three weeks until progression of disease, withdrawal or unacceptable toxicity. Patients were exposed to Perjeta for a

median of 24 cycles. A summary of the number of treatment cycles received in the study is shown in Table 55 [CLEOPATRA2nd update CSR]

Table 55 Summary of total dose of Perjeta / Placebo received [CLEOPATRA2nd update]

	Perjeta + Herceptin + docetaxel (n=408)	Placebo + Herceptin + docetaxel (n=396)
Median number of treatment cycles (range)	24* (1-96)	15 (1-67)
Median number of docetaxel cycles (range)	8 (1-52)	8 (1-42)
*Patients who crossed over to the Perjeta group received a median of 22.5 cycles of Perjeta (range 1-28)		

Adverse events of any grade

100% of patients in the Perjeta + Herceptin + docetaxel arm experienced at least one adverse event of any grade, compared with 98.7% of patients in the placebo + Herceptin + docetaxel arm. The majority of the adverse events experienced in both treatment arms were grade 1-2 in severity (89%) and occurred during docetaxel administration and declined after discontinuation. A list of the most common adverse events (all Grades) that occurred with ≥ 25% incidence or at a difference of ≥ 5% between groups overall is shown in Table 56.

Table 56 Adverse events with an incidence rate of ≥25% in either arm or a difference of >5% between arms [2nd update CSR]

Adverse event, n (%)	Perjeta + Herceptin + docetaxel (n=408)	Placebo + Herceptin + docetaxel (n=396)
Total patients with ≥1 AE	408 (100.0)	391 (98.7)
Alopecia	248 (60.8)	240 (60.6)
Diarrhoea	279 (68.4)	193 (48.7
Neutropenia	218 (53.4)	198 (50.0)
Nausea	183 (44.9)	168 (42.4)
Fatigue	155 (38.0)	148 (37.4)
Rash	153 (37.5)	95 (24.0)
Asthenia	113 (27.7)	122 (30.8)
Decreased appetite	121 (29.7)	106 (26.8)
Peripheral oedema	98 (24.0)	111 (28.0)
Vomiting	106 (26.0)	97 (24.5)
Myalgia	99 (24.3)	99 (25.0)
Mucosal inflammation	111 (27.2)	79 (19.9)
Headache	105 (25.7)	76 (19.2)
Constipation	65 (15.9)	101 (25.5)
Upper respiratory tract infection	85 (20.8)	57 (14.4)
Pruritus	72 (17.6)	40 (10.1)
Febrile neutropenia	56 (13.7)	30 (7.6)
Dry skin	46 (11.3)	24 (6.1)
Muscle spasms	42 (10.3)	20 (5.1)
Multiple occurrences of the same adverse event in one individual were counted only once. Data reported prior to the date of first crossover treatment were included under Placebo +Herceptin + Docetaxel for patients who crossed over from placebo to Perjeta.		

Adverse events of grade ≥3

The incidence of grade ≥3 adverse events was similar in both treatment arms (77.2% in the Perjeta + Herceptin + docetaxel arm and 73.5% in Herceptin + docetaxel arm). The most common grade ≥3 AEs (incidence ≥5%) are shown in Table 57. The frequency of all AEs, including rash and diarrhoea, fell considerably after discontinuation of docetaxel, with no further episodes of febrile neutropenia reported in either treatment group. [2nd update CSR]

Table 57 Grade ≥3 Adverse events with an incidence rate of ≥ 5% [2nd update CSR]

Adverse event, n (%)	PHD (n=408)	HD (n=396)
Total patients with ≥1 grade ≥3 AE	315 (77.2)	291 (73.5)
Neutropenia	200 (49.0)	183 (46.2)
Leucopenia	50 (12.3)	59 (14.9)
Febrile neutropenia	56 (13.7)	30 (7.6)
Diarrhoea	38 (9.3)	20 (5.1)
Multiple occurrences of the same adverse event in one individual were counted only once. Data reported prior to the date of first crossover treatment were included under Placebo +Herceptin + Docetaxel for patients who crossed over from placebo to Perjeta.		

Serious adverse events

The overall incidence of SAEs was higher in the Perjeta + Herceptin + docetaxel arm (36.5%) than in the Herceptin + docetaxel arm (29.3%).

Table 58 Ten most common serious adverse events by body system

SAE, n (%)	PHD (n=408)	HD (n=396)
Total patients with ≥1 SAE	149 (36.5)	116 (29.3)
Blood and lymphatic system disorders	65 (15.9)	42 (10.6)
Infections and infestations	51 (12.5)	34 (8.6)
Gastrointestinal disorders	22 (5.4)	18 (4.5)
General disorders and administration site conditions	14 (3.4)	9 (2.3)
Respiratory, thoracic and mediastinal disorders	14 (3.4)	9 (2.3)
Cardiac disorders	8 (2.0)	14 (3.5)
Immune system disorders	7 (1.7)	4 (1.0)
Injury, poisoning and procedural complications	9 (2.2)	3 (0.8)
Musculoskeletal and connective tissue disorders	6 (1.5)	3 (0.8)
Nervous system disorders	4 (1.0)	5 (1.3)

Cardiac safety

There was no significant increase in cardiac adverse events or left ventricular dysfunction (LVD) with Perjeta + Herceptin + docetaxel compared with

Herceptin + docetaxel alone and no evidence to suggest cumulative or late toxic effects.

- The rate of left ventricular dysfunction (LVD), as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 (NCI-CTCAE v.3), and the New York Heart Association, was somewhat lower in the Perjeta + Herceptin + docetaxel arm than in the Herceptin + docetaxel arm (6.6% [27 of 408 patients] vs. 8.6% [34 of 396 patients]). Rates of grade ≥3 LVD were 1.5% vs 3.3% respectively
- 8 patients (2.0%) in the Herceptin + docetaxel arm and 7 patients (1.7%) in the Perjeta + Herceptin + docetaxel arm had experienced SAEs suggestive of congestive heart failure (CHF), most commonly LVD
- Reductions in the LVEF of 10% or more from baseline to an absolute value of less than 50% occurred in 24 of 394 patients (6.1%) in the Perjeta + Herceptin + docetaxel arm and 28 of 378 patients (7.4%) in the Herceptin + docetaxel arm. Declines were reversed in 21 of 24 patients (87.5%) in the Perjeta + Herceptin + docetaxel arm and 22 of 28 patients (78.6%) in the Herceptin + docetaxel arm. [Swain 2015a]

Deaths

From the first patient enrolled in February 2008 until the data cut-off date of 11 February 2014 (at five-year follow-up), 217/396 (54.8%) in the Herceptin + docetaxel arm and 169/408 (41.4%) patients in the Perjeta + Herceptin + docetaxel arm had died.

Table 59 Causes of death in the CLEOPATRA study [Swain 2015a]

	Perjeta + Herceptin + docetaxel (n=408)	Herceptin + docetaxel (n=396)
Disease progression, %	36.8	49.5
Febrile neutropenia or infection, %	1.7	1.5
Other/unknown, %	2.9	3.8

4.12.3 Overview of the safety of the technology in relation to the decision problem

The tolerability of Perjeta + Herceptin + docetaxel in NeoSphere was comparable with that of Herceptin + docetaxel in terms of the incidence and severity of AEs and related AEs, discontinuations due to AEs, dose interruptions or modifications due to AEs, and frequency of AEs requiring treatment or leading to death. No new or unexpected safety signals were identified with the addition of Perjeta to Herceptin and docetaxel compared to Herceptin and docetaxel alone. No significant increase in cardiac risk was identified with the Perjeta-containing treatment arms in NeoSphere over a course of four cycles of neoadjuvant therapy.

At 5-year follow-up, the safety data for Perjeta in combination with Herceptin and docetaxel in the NeoSphere study was consistent with that observed previously with Perjeta in the metastatic breast cancer setting. No new or unexpected safety signals were identified, with the addition of Perjeta to Herceptin and chemotherapy in both NeoSphere and TRYPHAENA. [Gianni 2015] [Schneeweiss 2013]

The most common adverse events of any grade in NeoSphere were alopecia, neutropenia, diarrhoea, nausea, fatigue, rash, and mucosal inflammation. However, in Arm C (Perjeta + Herceptin) of the NeoSphere study, there were only two cases of alopecia and neutropenia (one case each) in the neoadjuvant period (in the absence of docetaxel).

When comparing Arm A (Herceptin + docetaxel) with Arm D (Perjeta + docetaxel) in NeoSphere, a similar safety profile was observed, with the notable exception of diarrhoea, which occurred at a higher incidence in Arm D than Arm A (54.3% vs 33.6%). Diarrhoea was consistently observed at a higher incidence in Perjeta-containing regimens compared with non-Perjeta-containing regimens in NeoSphere and TRYPHAENA and as such is considered to be treatment-related. (Incidence and management of diarrhoea is discussed in more detail later in this section.)

Overall, there were no new or unexpected toxicities by adding Perjeta to Herceptin in the neoadjuvant period of NeoSphere. The safety profile was slightly altered in the adjuvant period compared to the neoadjuvant period. The majority of patients received Herceptin for up to one year in the adjuvant period: FEC chemotherapy was also administered for three cycles in the adjuvant period, and patients in Arm C also received 4 cycles of docetaxel. Nausea, neutropenia, vomiting, fatigue and diarrhoea were the most frequent adverse events in the adjuvant period. Incidence of alopecia in Arm A (Herceptin +docetaxel), Arm B (Perjeta + Herceptin + docetaxel) and Arm D (Perjeta + docetaxel) was low (2–8%), but occurred in 59.6% of the patients in Arm C (Perjeta + Herceptin). It is important to note that patients in Arm C received docetaxel in the adjuvant setting, whereas patients in Arms A, B and D did not.

The combination of Perjeta and Herceptin with chemotherapy was well tolerated in the TRYPHAENA study. The most frequent adverse events in the neoadjuvant setting in Arm A[1] and B were similar, which is expected as FEC chemotherapy was administered to the patients in both arms. In Arm C, where patients received the non-anthracycline regimen (Perjeta + docetaxel + carboplatin + Herceptin) incidence of myelotoxic-related adverse events (anaemia, thrombocytopenia, etc.) was greater than in Arms A and B, due to the toxic effects on the bone marrow of the carboplatin and docetaxel regimen in Arm C. However, these AEs are clinically manageable by dose delay/modification: no patients required discontinuation of study medication for anaemia or thrombocytopenia, and only 2 patients in Arm C required discontinuation of study medication for neutropenia.

The majority of patients received Herceptin up to one year in the adjuvant setting in TRYPHAENA. Adverse events occurred less frequently in the non-anthracycline arm (Arm C). There were only slight differences between Arm A

[1] Arm A: FEC+Herceptin+Perjeta x3 cycles → Docetaxel+Herceptin+Perjeta x3 cycles
Arm B: FEC x3 cycles → docetaxel+Herceptin+Perjeta x3 cycles
Arm C: Perjeta+docetaxel+carboplatin+Herceptin x6 cycles

and B, except for a relevant difference in upper respiratory tract infections (2 [2.9%] vs. 8 [12.3%]). However, all events were mild to moderate.

Grade ≥3

The number of patients experiencing adverse events of Grade ≥3 in the neoadjuvant period in NeoSphere was lowest in the Perjeta + Herceptin arm (Arm C) (7% of patients). The overall incidence of grade ≥3 AEs was consistent with the Herceptin + docetaxel arm, the Perjeta + Herceptin + docetaxel arm and the Perjeta + docetaxel arm (Arms A, B and D respectively) in NeoSphere (63%–73% of patients). The most common Grade ≥3 AEs in the neoadjuvant period occurred in the blood and lymphatic system (neutropenia, febrile neutropenia, and leucopenia): these occurred in Arms A, B and D (where patients received docetaxel in the neoadjuvant period) and were virtually absent in Arm C (no docetaxel in the neoadjuvant period). The incidence of febrile neutropenia was similar in arms A, B and D (8-9%) and absent in Arm C. Neutropenia is a well-known and well-characterised adverse event of special interest (AESI) already listed in the Perjeta SmPC.

Overall, there were fewer Grade ≥ 3 adverse events in Arm B[1] in the TRYPHAENA study, but the overall incidence of adverse events was comparable between treatment arms. The predominant grade ≥3 AEs in TRYPHAENA were within the blood and lymphatic system, such as neutropenia, febrile neutropenia, leucopenia and anaemia. There were slightly more Grade 4 adverse events in Arm C than in Arms A and B (41 patients, vs 30 and 31 patients respectively), mostly in the “blood and lymphatic system disorders” class, predominantly manifesting as neutropenia. This is a well-known risk of chemotherapy and it is clinically manageable (as mentioned previously, by dose modification). There were no Grade 5 adverse events.

[1] Arm A: FEC+Herceptin+Perjeta x3 cycles → Docetaxel+Herceptin+Perjeta x3 cycles
Arm B: FEC x3 cycles → docetaxel+Herceptin+Perjeta x3 cycles
Arm C: Perjeta+docetaxel+carboplatin+Herceptin x6 cycles

Cardiac events

In both neoadjuvant studies, NeoSphere and TRYPHAENA, the rate of symptomatic left ventricular systolic dysfunction (LVSD) was low (even in the presence of anthracyclines, in TRYPHAENA). In TRYPHAENA, the incidence of symptomatic LVSD and significant declines in left ventricular ejection fraction in the three treatment arms were similar and low, regardless of whether Perjeta + Herceptin were given sequentially or concomitantly with anthracycline-based chemotherapy, or with a carboplatin-based chemotherapy regimen. [Schneeweiss et al, 2013]

- There was only one incidence of symptomatic left ventricular systolic dysfunction in NeoSphere; this occurred in a patient in Arm C (Perjeta + Herceptin), who experienced congestive heart failure (CHF). (This patient had a history of hypertension and angina pectoris, had a coronary arterial stent in situ and was receiving medication with digoxin at baseline.)
- There were very few cases of symptomatic LVSD in TRYPAHENA (two in Arm B in the neoadjuvant period, and one in Arm A in the adjuvant period)

An increased incidence of significant LVEF declines was observed in patients in the NeoSphere study treated with Perjeta + Herceptin + docetaxel (Arm B) and Perjeta + docetaxel (Arm D), than those treated with Herceptin + docetaxel (Arm A). However, LVEF declines were generally low across all treatment arms in all periods of the study (>6%). LVEF recovered to ≥50% in all patients. In TRYPHAENA, there were slightly more patients with LVEF decline in Arms B[1] and C. LVEF values recovered to ≥50% in all patients with significant LVEF declines by the end of study treatment or following the data cut-off in the follow-up period.

[1] Arm A: FEC+Herceptin+Perjeta x3 cycles → Docetaxel+Herceptin+Perjeta x3 cycles
Arm B: FEC x3 cycles → docetaxel+Herceptin+Perjeta x3 cycles
Arm C: Perjeta+docetaxel+carboplatin+Herceptin x6 cycles

Very few patients discontinued treatment due to cardiac events.

A direct comparison between the neoadjuvant and metastatic studies is not appropriate since the patient populations and the eligibility criteria differ. However, the frequency of grade ≥ 3 LVSD, LVEF decline and CHF appear consistent between the Perjeta + Herceptin + docetaxel arm in the NeoSphere study and the Perjeta + Herceptin + docetaxel arm in the CLEOPATRA study. Thus, the use of Perjeta in the neoadjuvant setting did not lead to excess of cardiac toxicity. This is also supported by results from the TRYPHAENA study.

Left ventricular dysfunction is a well-known risk with the use of anti-HER2 targeted therapies. Therefore, this adverse event is also listed in the Perjeta SmPC: LVEF declines to <40% or by 40%–45% associated with ≥10% points below the baseline value may be managed by withholding Perjeta and Herceptin treatment until LVEF improves. LVEF should be assessed prior to initiation of Perjeta and during treatment with Perjeta (every 3 cycles in the metastatic setting and every 2 cycles in the neoadjuvant setting) to ensure that LVEF is within the institution's normal limits [SmPC]. The APHINITY and BERENICE trials and the final analysis of TRYPHAENA should provide further evidence with regard to characterising cardiac safety with Perjeta in early breast cancer.

SAEs

In the NeoSphere study, most SAEs occurred in Arm A (Herceptin + docetaxel) and D (Perjeta + docetaxel) in the neoadjuvant period. Most frequent SAEs in all treatment arms were neutropenia and febrile neutropenia. The pattern of SAEs was consistent with the Perjeta + Herceptin + docetaxel arm in the CLEOPATRA study. In the neoadjuvant period of the TRYPHAENA study, most SAEs occurred in the non-anthracycline arm (Arm C[1]). Across all

[1] Arm A: FEC+Herceptin+Perjeta x3 cycles → Docetaxel+Herceptin+Perjeta x3 cycles
Arm B: FEC x3 cycles → docetaxel+Herceptin+Perjeta x3 cycles
Arm C: Perjeta+docetaxel+carboplatin+Herceptin x6 cycles

three arms in the TRYPHAENA study, diarrhoea, neutropenia and gastrointestinal disorders occurred most frequently. All are reflected in the SmPC. Very few SAEs were observed in the adjuvant and post-treatment follow-up period in the TRYPHAENA study.

Adverse events of special interest (AESI)

Infusion reactions: In the NeoSphere and TRYPHAENA studies in the neoadjuvant setting, Perjeta was administered on the same day as the other study treatment drugs in all cycles. In the CLEOPATRA study, Perjeta was administered the day before other study drugs in cycle 1, and then on the same day as other study drugs in subsequent cycles. In all three studies, the majority of infusion-related reactions starting during a Perjeta infusion were grade 1 or 2 and occurred at the first cycle. There were very few grade ≥3 infusion related reactions in the three studies. Infusion reactions in the two neoadjuvant studies were consistent with those observed in CLEOPATRA at the cycles when Perjeta was given on the same day as Herceptin and docetaxel.

Hypersensitivity and anaphylaxis: In NeoSphere and TRYPHAENA, hypersensitivity/anaphylaxis events were consistent with those observed in CLEOPATRA in terms of incidence and severity:

- In NeoSphere, incidence of hypersensitivity and anaphylaxis events was 5.6% in Arms B (Perjeta + Herceptin + docetaxel) and C (Perjeta + Herceptin), 6.4% in Arm D (Perjeta + docetaxel) and 1.9% in Arm A (Herceptin + docetaxel). The majority of the cases were Grade 1-2. Only three patients experienced a Grade 3 hypersensitivity event (2 events were attributed to docetaxel; one to Perjeta and/or Herceptin). In Arms B and D the majority of hypersensitivity reactions were specifically attributed to docetaxel, whereas in arm C the majority were attributed to Perjeta. [Primary CSR]

- In TRYPHAENA, the incidence of hypersensitivity and anaphylaxis events was lowest in Arm B[1] (one event; 1.3%), compared with Arm A (7 [9.7%]) and Arm C (10 [13.2%]). Patients in Arm B received only three doses of Perjeta and Herceptin, which may explain the incidence rate. One patient in Arm A and two in Arm C had Grade ≥ 3 events. [Primary CSR]

- In CLEOPATRA, incidence of hypersensitivity events was 10.8% in the Perjeta + Herceptin + docetaxel arm (vs 9.1% in the Herceptin + docetaxel arm). Almost all patients experiencing an AE of hypersensitivity or anaphylaxis continued study medication in spite of the event and some experienced these reactions on more than one occasion. The majority of reactions were mild and did not require dose modification to study medication and/or were not considered by the Investigators to be related to Perjeta. [Primary CSR]

Leucopenic events: Overall, there is no indication of any excess cases of neutropenia or febrile neutropenia by adding Perjeta to Herceptin in the neoadjuvant setting. As in the CLEOPATRA trial, a higher incidence of neutropenia and febrile neutropenia was observed in Asian patients compared with other patients in both neoadjuvant trials.

- In the NeoSphere trial, a slightly higher incidence of 8.4% of patients treated with neoadjuvant Perjeta + Herceptin + docetaxel experienced febrile neutropenia compared with 7.5% of patients treated in Arm A (Herceptin and docetaxel) and 7.4% in Arm D (Perjeta + docetaxel). No patients in Arm C (Perjeta + Herceptin; i.e. no docetaxel) experienced febrile neutropenia. However, very few infections were reported indicating that the episodes were clinically manageable. Neutropenia occurred in 63% of patients in Arm A (Herceptin + docetaxel) and Arm

[1] Arm A: FEC+Herceptin+Perjeta x3 cycles → Docetaxel+Herceptin+Perjeta x3 cycles
Arm B: FEC x3 cycles → docetaxel+Herceptin+Perjeta x3 cycles
Arm C: Perjeta+docetaxel+carboplatin+Herceptin x6 cycles

D (Perjeta + docetaxel) and in 51% patients in Arm B (Perjeta + Herceptin + docetaxel); only one case occurred in Arm C (no docetaxel). [Primary CSR]

- In the TRYPHAENA trial, the majority of patients had at least one leucopenic AE in the neoadjuvant period. The most common leucopenic AE was neutropenia (47% - 51% of patients), followed by leucopenia (16% - 22%), then febrile neutropenia (9% in Arm B, 18%, 17% in Arms A, C). The incidence of grade ≥3 febrile neutropenia was higher in patients who received six cycles of Perjeta (Arms A and C; 17-18%) compared with patients who received three cycles of Perjeta (Arm B; 9%), independent of the chemotherapy given [Primary CSR]

- In the CLEOPATRA trial, the overall incidence of leucopenic events was comparable between the two arms. The incidence of neutropenia and febrile neutropenia in the Perjeta + Herceptin + docetaxel arm in CLEOPATRA were consistent with the Perjeta + Herceptin + docetaxel arm in the NeoSphere study.

Rash: The incidence of all-grade rash events in the neoadjuvant trials was consistent with the Perjeta + Herceptin + docetaxel arm in the CLEOPATRA trial: no increased risk of rash was seen when adding Perjeta to Herceptin + chemotherapy in the neoadjuvant setting.

- The incidence of rash events in NeoSphere was lowest (18.5%) in Arm C (Perjeta + Herceptin) where no docetaxel was given, and highest in the treatment arms where Perjeta was given with docetaxel: 40.2% and 40.4% for Arm B (Perjeta + Herceptin + docetaxel) and Arm D (Perjeta + docetaxel) respectively. In the Herceptin + docetaxel arm (Arm A) the incidence of rash was 29.0%. [Primary CSR]

- In TRYPHAENA, there were more patients reporting rash events in Arm C[1] (36.8%) than in Arms A and B (27.8% and 20.0% respectively). The incidence of rash was higher in patients who received six cycles of Perjeta compared with patients who received three cycles of Perjeta, independent of the chemotherapy given. [Primary CSR]

- In CLEOPATRA, the incidence of rash events was higher in the Perjeta + Herceptin + docetaxel arm (45.2%) than in the Herceptin + docetaxel arm (36.0%) [Primary CSR]

Diarrhoea: Diarrhoea was one of the most common AEs reported in Perjeta-containing regimens in the neoadjuvant studies. However, only a minority of episodes of diarrhoea in the neoadjuvant studies were of grade 3-4 and none lead to treatment discontinuation. Cases of diarrhoea in NeoSphere and TRYPHAENA were managed by interruptions/modifications (occurring in ≤8% of patients across NeoSphere, TRYPHAENA), and/or treatment with anti-diarrhoeals (most commonly loperamide). Patients who had dose delays (interruptions/modifications) due to diarrhoea were subsequently maintained on Perjeta. In CLEOPATRA, cases of diarrhoea were also managed by interruptions/modifications, and/or with anti-diarrhoeals. Additionally, 2% of patients in the Perjeta + Herceptin + docetaxel arm discontinued a study drug due to diarrhoea (vs 0.5% of patients in the Herceptin + docetaxel arm). [Swain 2015b]

- In the neoadjuvant period of the NeoSphere trial, the incidence of diarrhoea was higher in the Perjeta + Herceptin + docetaxel arm (Arm B; 45.8%) and the Perjeta + docetaxel arm (Arm D; 54.3%) than in the Herceptin + docetaxel arm (Arm A; 33.6%) and the Perjeta + Herceptin arm (Arm C; 27.8%). Most events were mild to moderate in severity. The majority of episodes occurred in the first 2 treatment cycles, with few patients reporting diarrhoea at cycle 4. The incidence of grade ≥ 3

[1] Arm A: FEC+Herceptin+Perjeta x3 cycles → Docetaxel+Herceptin+Perjeta x3 cycles
Arm B: FEC x3 cycles → docetaxel+Herceptin+Perjeta x3 cycles
Arm C: Perjeta+docetaxel+carboplatin+Herceptin x6 cycles

diarrhoea was low and comparable across treatment arms. No grade 4 cases were reported throughout the neoadjuvant period. [Primary CSR]

- In the TRYPHAENA trial, diarrhoea was the most common AE in the neoadjuvant period and had a higher incidence in Arm C[1] (72%) than in Arms A and B (61% each). In all three arms, diarrhoea AEs were most common during the first cycle of Perjeta and Herceptin treatment, and incidence progressively declined thereafter. Most events were mild to moderate in severity; grade 3 cases were experienced by 4%, 5% and 12% of patients in Arms A, B and C, respectively. [Primary CSR]

- In CLEOPATRA, the incidence of diarrhoea was higher in the Perjeta + Herceptin + docetaxel arm (68.1%) than the Herceptin + docetaxel arm (46.3%), and was often observed in the first cycle. Incidence of grade 3 diarrhoea was low; only one grade 4 event occurred (in the Herceptin + docetaxel arm). [Primary CSR]

Laboratory abnormalities: Incidence of grade 3-4 neutropenia in the neoadjuvant studies was consistent with that seen in the CLEOPATRA study.

- In the NeoSphere trial, the incidence of NCI-CTCAE v.3 grade 3-4 neutropenia was 74.5% in patients treated with neoadjuvant Perjeta + Herceptin + docetaxel (Arm B) compared with 84.5% in patients treated with Herceptin + docetaxel (Arm A), including 50.9% and 60.2% Grade 4 neutropenia, respectively [Primary CSR]
- In the TRYPHAENA trial, the incidence of NCI-CTCAE v.3 grade 3-4 neutropenia was 92.9% in Arm A, 77.0% in Arm B and 85.3% in Arm C, including 59.5%, 66.7% and 70.4% grade 4 neutropenia, respectively [Primary CSR]
- In CLEOPATRA, incidence of grade 3-4 neutropenia was 85.9% in the Perjeta + Herceptin + docetaxel arm and 86.6% in the Herceptin +

[1] Arm A: FEC+Herceptin+Perjeta x3 cycles → Docetaxel+Herceptin+Perjeta x3 cycles
Arm B: FEC x3 cycles → docetaxel+Herceptin+Perjeta x3 cycles
Arm C: Perjeta+docetaxel+carboplatin+Herceptin x6 cycles

docetaxel arm (including 61.0% and 64.3% grade 4 neutropenia respectively) [Primary CSR]

Mucositis: Mucositis is a common AESI, and occurred with an incidence of 50% in the Perjeta + Herceptin + docetaxel arm of the CLEOPATRA study. [2nd update CSR] In the neoadjuvant studies, the incidence was 9%–46%. Mucositis occurred much less frequently in the Perjeta + Herceptin arm (Arm C) of the NeoSphere study, than the other three treatment arms (see below), thus indicating that it may be closely associated with chemotherapy. Mucosal inflammation and stomatitis were the most frequently reported events in that class in the neoadjuvant studies.

- In NeoSphere, mucositis was common during the neoadjuvant treatment period (33.6% of patients in the Herceptin + docetaxel arm [Arm A], 45.8% in the Perjeta + Herceptin + docetaxel arm [Arm B], 9.3% in the Perjeta + Herceptin arm [Arm C] and 43.6% in the Perjeta + docetaxel arm [Arm D] respectively). Only two patients experienced Grade ≥ 3 mucositis (1 in the Perjeta + Herceptin + docetaxel arm and 1 in the Perjeta + docetaxel arm). Mucositis was also common in the adjuvant period. [Primary CSR]

- In the neoadjuvant period of TRYPHAENA, 45.8% of patients in Arm A[1], 41.3% of patients in Arm B and 34.2% of patients in Arm C experienced mucositis. Most of these were Grade 1–2 in severity. Grade 3 mucositis events were experienced by one patient in Arm A, two patients in Arm B and one patient in Arm C. [CHMP 2015]

[1] Arm A: FEC+Herceptin+Perjeta x3 cycles → Docetaxel+Herceptin+Perjeta x3 cycles
Arm B: FEC x3 cycles → docetaxel+Herceptin+Perjeta x3 cycles
Arm C: Perjeta+docetaxel+carboplatin+Herceptin x6 cycles

Summary

Overall, the addition of Perjeta to Herceptin in the neoadjuvant setting did not lead to unexpected safety findings, as observed in the NeoSphere and TRYPHAENA studies. This is supported by the safety profile seen from the CLEOPATRA study. The TRYPHAENA study also provided further evidence with regards to cardiac safety in the neoadjuvant setting: there were no new cardiac safety concerns or differences in tolerability seen with the addition of Perjeta to an existing anti-HER2 regimen with Herceptin, used with either an anthracycline-containing or anthracycline-free regimen, in HER2 positive early breast cancer.

However, cardiac risk should be carefully considered and balanced against the medical need of the individual patient before use of Perjeta in combination with Herceptin and anthracyclines. There are limited safety data available from the TRYPHAENA study concerning sequential or concomitant administration of Perjeta with epirubicin, as part of the FEC regimen. There are no safety data available concerning use of Perjeta with doxorubicin [Perjeta SmPC].

Based on the pharmacological actions of Perjeta and anthracyclines, an increased risk of cardiac toxicity might be expected from concomitant use of these agents compared with sequential administration, although this was not seen in the TRYPHAENA study. [Perjeta SmPC]

4.13 Interpretation of clinical effectiveness and safety evidence

4.13.1 A statement of the principal findings from the clinical evidence highlighting the clinical benefits and harms of the technology

Understanding the development and treatment of early breast cancer requires clinical investigations in the adjuvant and neoadjuvant settings. Historically, trials in the adjuvant setting focused on definitive endpoints such as relapse/progression and disease-free survival (DFS) / event free survival

(EFS). Trials in the neoadjuvant setting, by definition, need to employ alternative intermediate endpoints, as long-term efficacy data from 'traditional' endpoints such as DFS, EFS and overall survival (OS) are typically not yet available. Additionally, these traditional endpoints only represent one of the goals of neoadjuvant treatment and do not reflect tumour re-staging or improved cosmesis. For example, neoadjuvant treatment has been shown to downstage tumours and facilitate breast conserving surgery. [Hawkesford 2014] The evaluation of novel breast cancer therapies in the neoadjuvant setting thus depends on improvements in intermediate endpoints transforming into clinically meaningful increases in survival rates.

In early breast cancer neoadjuvant trials, pathological complete response (pCR) is commonly used as a clinical endpoint. The standard definition proposed by the EMA and FDA for regulatory purposes is 'absence of any residual invasive cancer on hematoxylin and eosin evaluation of the resected breast specimen and all sampled lymph nodes following completion of neoadjuvant systemic therapy. [EMA guidance] [FDA guidance] (Both the FDA and EMA guidances recognised the findings from Cortazar's publication that eradication of tumour from both breast and lymph nodes has been shown to be associated with better event free survival (EFS) and overall survival (OS) compared with eradication in only the breast.) This definition was evaluated in both NeoSphere and TRYPHAENA (referred to as tpCR). Advantages of assessing pCR in neoadjuvant trials include:

- time-to-event for a given therapy is assessed at an earlier time point (over DFS) to potentially accelerate approval in areas of unmet need [FDA guidance]
- tpCR is associated with good patient outcomes and reasonable likelihood to predict clinical benefit (i.e. EFS, DFS and OS) in patients with high-risk early stage disease (including inflammatory breast cancer) within several months of initiation of trial. [Wolmark 2001] [Cortazar 2014]

Several factors have been correlated with increased likelihood of attaining pCR, including HER2-positivity [Loibl 2014]. Virtually all studies examining the impact of pCR after neoadjuvant chemotherapy have demonstrated an association with improved survival. [Teshome 2014] Randomised trials have suggested that pCR may predict DFS and OS in patients receiving neoadjuvant systemic therapy of patients with HER2-positive, locally advanced, inflammatory, or early-stage BC.

Despite the clinical benefit of up to 11 cycles of neoadjuvant Herceptin plus chemotherapy prior to surgery, observed in the NOAH study, there remains a large unmet need amongst patients with HER2-positive early breast cancer. At five-year follow-up, 49 out of 117 (42%) patients who received Herceptin in the NOAH study had relapsed. [Gianni 2014] This highlights the need for new agents with greater efficacy in this setting.

Perjeta and Herceptin have complementary mechanisms of action and, when used together, provide dual blockade of HER2 signalling [Baselga 2012] [Franklin 2004], which is more effective than either agent alone. [Scheuer 2009] [Lee-Hoeflich 2008]

In the pivotal phase III CLEOPATRA study Perjeta in combination with Herceptin and docetaxel was compared with Herceptin and docetaxel alone and demonstrated significant clinical benefit in HER2-positive metastatic breast cancer. [Baselga 2012] The introduction of Perjeta with Herceptin-based regimens as neoadjuvant therapy is based on the evidence from two open-label phase II studies (NeoSphere [Gianni 2012] and TRYPHAENA [Schneeweiss 2013]) both of which were international, randomised, multicentre trials. Both studies had similar patient populations; however they differ slightly in the main objectives of the study and treatment regimens used.

The NeoSphere trial compared three neoadjuvant Perjeta-containing regimens to a comparator neoadjuvant regimen of Herceptin + docetaxel. In this study, FEC (5-fluorouracil + epirubicin + cyclophosphamide) chemotherapy was given after surgery in order to isolate the effect of Perjeta in the neoadjuvant setting of HER2-positive eBC. Patients given Perjeta,

Herceptin and docetaxel had a significantly improved bpCR (primary endpoint), compared with those given Herceptin plus docetaxel, without substantial differences in tolerability. The proportion of patients who achieved tpCR were highest in the Perjeta, Herceptin, and docetaxel regimen (39.3% [95% confidence interval (CI): 30.0–49.2]), with the Herceptin and docetaxel arm following behind (21.5%, [95% CI: 14.1–30.5]). [Gianni 2012] Normally FEC (anthracycline-based) chemotherapy would be given prior surgery to achieve higher pCR rates compared to FEC given after surgery, this study design was considered acceptable from a scientific endpoint given the supportive evidence from CLEOPATRA and anticipated confirmatory results from APHINITY. [CHMP 2015]

Recent data from the NeoSphere study also showed that in the DFS and PFS analyses, the respective hazard ratios for Arm B to Arm A are 0.69 and 0.60 (see table below), demonstrating a lower risk of DFS and progression-free survival (PFS) events in patients treated with Perjeta in combination with Herceptin and docetaxel versus treatment with Herceptin and docetaxel alone. The PFS and DFS results are also supportive of the benefit shown from the addition of Perjeta to Herceptin plus docetaxel in the primary analysis of pCR. [Gianni 2015]

Table 60 5-year PFS and DFS, and tpCR rates from NeoSphere [Gianni 2015]

	Arm A HD (n=107)	**Arm B PHD (n=107)**	**Arm C PH (n=107)**	**Arm D PD (n=96)**
Outcome, HR (95% CI)				
5-year PFS (from ITT population)	-	0.69 (0.34–1.40)	1.25 (0.68–2.30)	2.05 (1.07–3.93)
5-year DFS (from ITT population)	-	0.60 (0.28–1.27)	0.83 (0.42–1.64)	2.16 (1.08–4.32)
tpCR rates*, % (95% CI)				
tpCR at surgery	21.5 (14.1–30.5)	39.3 (30.0–49.2)	11.2 (5.9–18.8)	17.7 (10.7–26.8)

Arm A: HD, Herceptin + docetaxel; Arm B: PHD, Perjeta + Herceptin + docetaxel
Arm C: PH, Perjeta + Herceptin; Arm D: PD, Perjeta + docetaxel
CI, confidence interval; DFS- disease-free survival; HR, hazard ratio; ITT- intent-to-treat; PFS- progression-free survival
*tpCR rate is provided as this is the preferred definition used by FDA and EMA

The safety findings from NeoSphere showed that the addition of Perjeta to Herceptin and docetaxel were similar in tolerability to Herceptin and docetaxel alone. As expected, bone-marrow toxic effects and febrile neutropenia occurred in all treatment arms that included docetaxel. Diarrhoea occurred in 51.4% of patients who received Perjeta + Herceptin + docetaxel (Arm B); most events were mild to moderate in severity. [Gianni 2012]

Results from the TRYPHAENA study demonstrated that the majority of patients achieved tpCR after neoadjuvant treatment in all three arms. [Schneeweiss 2013] The regimens used in the TRYPHAENA study also reflect closely to the UK practice of neoadjuvant regimens used in early breast cancer. [Roche Data on File - RXUKPERT00220(1).] Results from 225 patients showed that the incidence of symptomatic LVSD and significant declines in LVEF (≥10% points from baseline to <50%) was low across all arms. The combination of Perjeta and Herceptin was generally well-tolerated regardless of whether it was administrated with anthracycline-based or carboplatin-based chemotherapy. [Schneeweiss 2013]

The safety data from NeoSphere and TRYPHAENA were therefore consistent with safety findings observed with previous Perjeta clinical studies (CLEOPATRA) and **no new safety signals were identified.**

Perjeta is currently licensed in the US and EU for use in combination with Herceptin and docetaxel (US) or chemotherapy (EU) as neoadjuvant therapy in HER2-positive early breast cancer, based on demonstration of an improvement in pathological complete response rate from NeoSphere and TRYPHAENA, therefore all regimens evaluated in these two studies can be considered as neoadjuvant treatment for HER2-positive early breast cancer within the product licence.

4.13.2 A discussion of the strengths and limitations of the clinical evidence base for the technology

Several attempts have been made to investigate the predictive value of pathological complete response (pCR). There is evidence to shows that patients who achieve tpCR have improved survival. The prognostic value of tpCR is greatest in aggressive tumour sub-types (e.g. HER2-positive). However from the FDA-sponsored meta-analysis (Cortazar 2014), it was not possible to establish the magnitude of pCR benefit that would translate into a definitive improvement in EFS, DFS, or OS. The potential explanations for this included the heterogeneity of cancer tumour subtypes in women enrolled in the clinical trials included in the Cortazar meta-analysis, which may obscure the correlation between pCR and survival if women responded differently to the same treatment. Differences in treatment effects of the various trials in the Cortazar meta-analysis also made it difficult to determine this correlation. Trials that included targeted therapies such as NOAH (use of Herceptin for HER2-positive early breast cancer [Gianni 2010]) resulted in pCR rates as high as 20% compared to chemotherapy, however the majority of trials included were comparisons between chemotherapy treatments with an absolute difference of approximately 1–11%, which were generally low. [Cortazar 2104]

The magnitude of benefit with Perjeta in the neoadjuvant setting, in terms of DFS/PFS or OS, therefore cannot be definitively measured from the observed pCR effect. Despite of this, it is acknowledged that tpCR is reasonably likely to predict long-term outcomes of EFS, DFS, or OS [Cortazar 2014] [Rastogi 2008], as seen from the patient level analyses in the Cortazar meta-analysis. The strength of the association increased with Herceptin treatment, which emphasised the importance of targeted therapy for treatment of specific cancer subtypes.

The Cortazar meta-analysis also showed that the eradication of tumour from both the breast and axillary lymph nodes (tpCR) was more closely associated with improved EFS and OS than eradication of invasive tumour from the

breast alone (bpCR). With the ultimate aim to bring novel therapies earlier to the market for the benefit of patients, a final guidance from FDA [FDA guidance] and a draft guidance from EMA [EMA guidance] has been issued to guide the process of approval of promising drugs in early breast cancer based on the use of tpCR with some consideration such as well-designed trials, established mechanism of action, etc. Both NeoSphere and TRYPHAENA have evaluated tpCR as an efficacy clinical endpoint on the basis of these regulatory guidance papers.

The NeoSphere study was designed to compare the efficacy and safety of Perjeta + Herceptin + docetaxel (Arm B) versus Herceptin + docetaxel (Arm A). Perjeta + Herceptin (Arm C) was an exploratory arm to evaluate the activity of two monoclonal antibodies without chemotherapy. Perjeta and docetaxel (Arm D) was included to address the regulatory question of the activity of Perjeta without Herceptin. The study was also powered to test for efficacy of both Arm C and Arm D compared with Arm B respectively. [Primary CSR]

Results demonstrated that the bpCR rate for Arm C was significantly lower than for Arm A (p=0.0198), highlighting the synergistic effect of anti-HER2 agents when combined with chemotherapy. [Primary CSR]

When evaluating the efficacy of Perjeta with chemotherapy (Arm D), the bpCR rates showed meaningful activity, but was significantly less than the regimen containing Perjeta, Herceptin and docetaxel (Arm B), 24 vs. 46%, respectively, p=0.003. The bpCR rates of Perjeta and chemotherapy (Arm D) was similar to Herceptin and chemotherapy (Arm A), 24% vs. 29%, respectively; p=0.0030. However, this comparison was not predefined and the study was not sufficiently powered to exclude a true difference between these two regimens. The majority of patients who achieved bpCR also achieved tpCR (Arm A: 23/31; Arm B: 42/49; Arm C: 12/19; Arm D: 17/23). [Primary CSR] **These results highlight the importance and additional benefit of dual blockade with anti-HER2 agents in breast cancer, as previously demonstrated in**

CLEOPATRA; the combination of two antibodies (Perjeta + Herceptin) is more active than either antibody alone with chemotherapy**.**

The NeoSphere study also investigated DFS and PFS as exploratory endpoints, therefore these endpoints were not designed or powered to test formal hypotheses and the data presented are for descriptive purposes only. Nonetheless, the lowest risk of DFS and PFS events were observed in patients who received Perjeta + Herceptin + docetaxel (Arm B) compared to the other treatment arms; patients who achieved pCR have longer DFS and PFS versus those who did not achieve pCR, therefore these results also support the benefit shown with the addition of Perjeta to Herceptin plus docetaxel in the primary analysis of pCR. [Gianni 2015]

TRYPHAENA was an open-label, phase II study which evaluated three Perjeta-containing regimens: two anthracycline-based chemotherapy regimens with Herceptin and one anthracycline-free chemotherapy regimen with Herceptin. All three regimens in the TRYPHAENA study contained Perjeta (i.e. no control arm); therefore, TRYPHAENA was not designed as a comparative study. The primary endpoint for TRYPHAENA was to assess cardiac safety and tolerability; tpCR rates were evaluated as a secondary endpoint, therefore the study was not powered to test for formal hypotheses on efficacy. Despite of these limitations, response rates observed were encouraging with consistently high bpCR and tpCR rates across all treatment arms in the TRYPHAENA study (57–66% and 45–52% respectively), therefore there is an added benefit of combining Perjeta with FEC + Herceptin neoadjuvant therapy for either 3 to 6 cycles. [Schneeweiss 2013]

In the context of the totality of the data, strong biological rationale for the combination, efficacy and safety results from the metastatic setting, the efficacy on the addition of Perjeta in combination with Herceptin and chemotherapy is considered established.

The headings listed below provide further information on the interpretation of the data from the subgroup analyses.

Pathological Response Rates stratified by Hormone status

The following figures show the pCR rates when stratified by hormone status in NeoSphere and TRYPHAENA.

Patients with HER2-positive early breast cancer who are also hormone receptor (HR)-positive generally achieve a lower pCR rate than those patients who are hormone negative.

Figure 18 pCR rates when stratified by subgroups in NeoSphere [adapted from Gianni 2012]

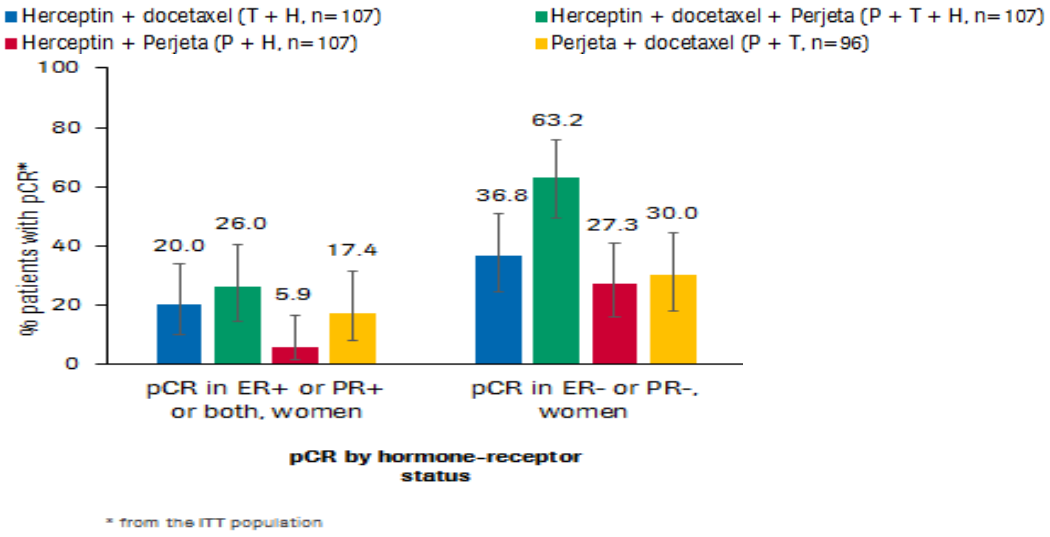
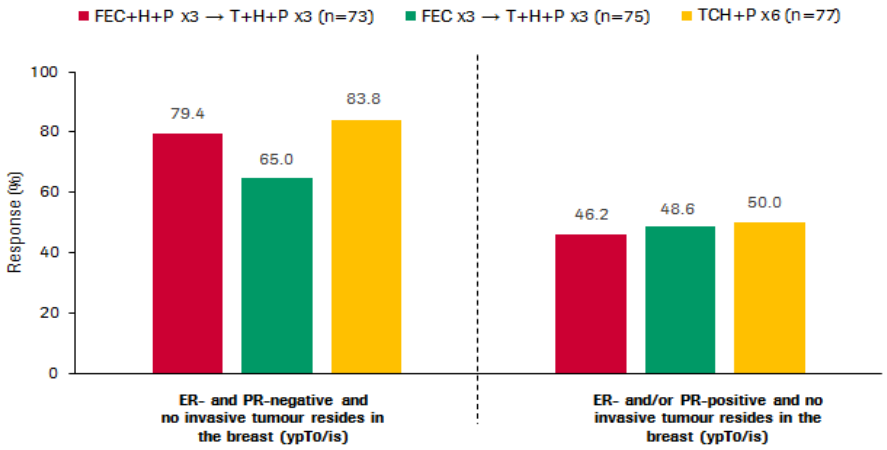


Figure 19 pCR rates when stratified by subgroups in TRYPHAENA [adapted from Schneeweiss 2013]



However, in NeoSphere, there was a 10% increase in tpCR rate in the HR-positive subgroup treated with Perjeta + Herceptin + docetaxel (Arm B)

compared with the Herceptin + docetaxel (Arm A), at 22% versus 12%; this is also associated with encouraging PFS/DFS (see Table 61).

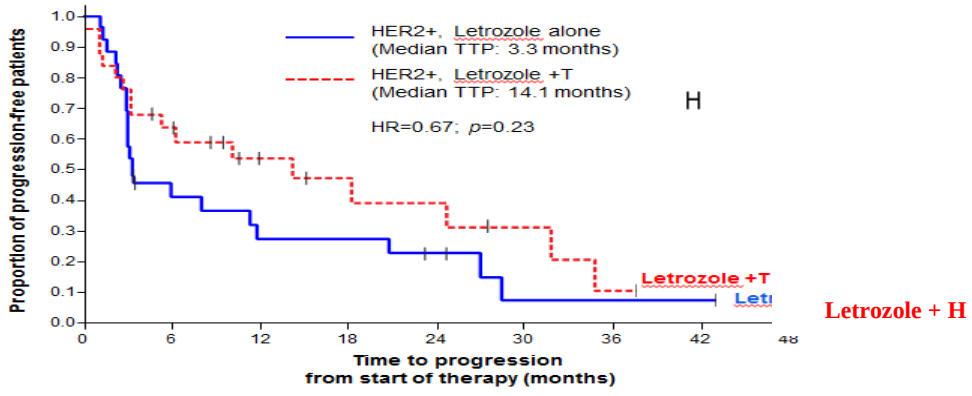
Table 61 Differences in HR-positive subgroup in PHD (Arm B) versus HD (Arm A)

	ITT population	Hormone receptor positive subgroup
tpCR rate	Δ=17.8%	Δ=10.0%
PFS Hazard Ratio	0.69	0.86
DFS Hazard Ratio	0.60	0.82
D, docetaxel; DFS, disease-free survival; H, Herceptin; ITT, intent-to-treat; P, Perjeta; PFS, progression-free survival; tpCR, total pathological complete response		

A similar trend was also observed in TRYPHAENA where tpCR rates in HR-positive subgroup fall between 41.0% - 47.5% dependent on treatment arm. The tpCR rates achieved in the Perjeta-containing neoadjuvant regimens from the GeparSepto study [Untch 2015] supports the TRYPHAENA results.

Patients who are HER2-positive/HR-positive are also at high risk of local recurrence; HER2 antibody therapy provides an additive mode of action to hormone therapy. The ELECTRA study [Huober 2012], although evaluated patients in the metastatic setting, showed that HER2-positive/HR-positive patients treated with Herceptin plus hormone therapy respond better (higher PFS rates) than those who were treated with hormone therapy alone.

Figure 20 PFS results from ELECTRA study [Huober 2012]



H- Herceptin; HR- hazard ratio; TTP, time to progression

The clinical effectiveness of anti-HER2 targeted therapy in HER2-positive/HR-positive patients can be observed with:

Herceptin treatment in early breast cancer from large, randomised phase III studies such as NOAH, which demonstrated EFS and DFS benefit greater than HR-negative/HER2-positive patients, see Table 62.

Table 62 EFS and DFS results from NOAH [Gianni 2010]

Trial	Hazard Ratio	ITT population	Hormone receptor negative	Hormone receptor positive
NOAH	EFS	0.59	0.46	0.87

Dual anti-HER2 blockade with Perjeta and Herceptin in CLEOPATRA significantly improves PFS and OS in HR-positive mBC, see Table 63.

Table 63 PFS and OS results from CLEOPATRA [Baselga 2012] [Swain 2015a]

	All patients	Hormone receptor negative	Hormone receptor positive
PFS Hazard Ratio	0.62	0.55	0.72
OS Hazard Ratio	0.68	0.61	0.71

Hormone therapy alone has limited efficacy in HER2-positive and HR-positive disease [Huober 2012]; therefore, anti-HER2 therapies add to the positive benefits of achieving pCR and likelihood of positive clinical outcomes. Safety data from NeoSphere and TRYPHAENA has shown that there were no new safety concerns when Perjeta was added to a Herceptin-containing regimen in eBC, therefore supporting the efficacy to achieve pCR in HER2-positive/HR-positive eBC subgroup.

Pathological Response Rates stratified by Disease Stage/Type [CHMP 2015)]

In both NeoSphere and TRYPHAENA, pCR rates were similar in patients with operable versus locally advanced breast cancer (LABC). [NeoSphere Primary CSR] [TRYPHAENA Primary CSR]

In NeoSphere, pCR rates were highest in Arm B (Perjeta + Herceptin + docetaxel) and Arm D (Perjeta + docetaxel) in patients with inflammatory breast cancer (IBC); however, there were too few patients (between 5-10 per arm) to draw firm conclusions. For LABC, patients in Arm A (Herceptin + docetaxel) and Arm B has similar pCR rate (41.7% and 43.8% respectively), which were higher than Arm C (Perjeta + Herceptin) and Arm D (Perjeta + docetaxel), at 14.3% and 16.1% respectively. [NeoSphere Primary CSR]

Secondary Endpoint: Breast Conservation Surgery (BCS)

A secondary endpoint that was also evaluated from TRYPHAENA and NeoSphere study respectively were breast conservation rates from the Perjeta-containing neoadjuvant regimens.

In NeoSphere, rates of BCS achieved were broadly balanced across arms A (Herceptin + docetaxel), B (Perjeta + Herceptin + docetaxel) and C (Perjeta + Herceptin) (18-23%), with a higher rate reported in Arm D (Perjeta + docetaxel; (32%). [NeoSphere Primary CSR]

Table 64 Patients undergoing breast-conserving surgery in NeoSphere [NeoSphere Primary CSR]

	Arm A HD (n=107)	**Arm B PHD (n=107)**	**Arm C PH (n=107)**	**Arm D PD (n=96)**
Patients with T2-3 tumours and planned mastectomy, n	62	56	61	60
Patients with T2-3 tumours achieving BCS for whom mastectomy was planned, n (%)	14/62 (22.6%)	13/56 (23.2%)	11/61 (18.0%)	19/60 (31.7%)
Arm A: HD, Herceptin + docetaxel; Arm B: PHD, Perjeta + Herceptin + docetaxel Arm C: PH, Perjeta + Herceptin; Arm D: PD, Perjeta + docetaxel BCS, breast conserving surgery; ITT, intent-to-treat				

It should be noted that:

- a patient could be counted in more than one category if they underwent multiple procedures
- Patients with inflammatory breast cancer received mastectomy irrespective of their response to neoadjuvant treatment and therefore were excluded from this analysis[NeoSphere Primary CSR]

In TRYPHAENA, BCS rate was observed within a range of 16% - 27% across all treatment arms. It should again be noted, that some of the sensitivity of this analysis is lost since patients could opt to go ahead with a full mastectomy even if this was not the clinical recommendation. [TRYPHAENA Primary CSR]

Table 65 BCS rates in TRYPHAENA [Schneeweiss 2013] [Primary CSR]

	Arm A FEC+H+P x3 → D+H+P x3	**Arm B FEC x3 → D+H+P x3**	**Arm C DCH+P x6**
T2/3 patients planned for mastectomy	61	63	58
Eligible for BCS following neoadjuvant treatment, n (%)	46/61 (75.4)	36/63 (57.1)	37/58 (63.8)
Patients that underwent BCS, n (%), [95% CI]	10 (21.7) [10.9, 36.4]	6 (16.7) [6.4, 32.8]	10 (27.0) [13.8, 44.1]
FEC, 5-fluorouracil + epirubicin + cyclophosphamide; H, Herceptin; P, Perjeta; D, docetaxel; C, carboplatin; BCS, breast conserving surgery			

Both NeoSphere and TRYPHAENA studies were not designed to show a difference in BCS. [NeoSphere Primary CSR] [TRYPHAENA Primary CSR] Despite the higher pCR rate in the Herceptin + docetaxel arm and Perjeta + Herceptin + docetaxel arm, seen from the NeoSphere study, no firm conclusions can be drawn on the BCS.

Considering these data, it is worth noting that clinical opinion clearly supports the fact that improving the rates of pCR in HER2-positive patients will increase the proportion eligible for BCS. This is important as BCS is associated with equivalent or better survival outcomes compared to mastectomy [van Maaren 2015] and is likely less costly in total than mastectomy and reconstruction

[Smith 2015]. In combination with the widely acknowledged quality of life benefits of BCS, the benefits of more patients achieving pCR through effective neoadjuvant treatment should not be understated. In addition to these points, the principle reason BCS is not more common in the UK are the high rates of re-excision of up to 30% [MacNeill 2015] which drive the cost of the intervention up and are mainly due to a lack of clear margins achieved in BCS. Neoadjuvant treatment that facilitates tumour restaging and increased pCR rates in HER2-positive patients will necessarily improve the ability to achieve clear margins. Therefore, neoadjuvant treatment will reduce the need for re-excision and make BCS (and all the benefits discussed previously) a more preferable intervention.

This technology does not meet the end-of-life criteria because patients with early breast cancer are expected to have life expectancy beyond 24 months.

Table 66 End-of-life criteria

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	No – In England and Wales, Cancer Research UK notes that 99% of stage 1 and 90% of stage 2 breast cancer patients live for 5 years or more
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	The base case economic results show an additional benefit of 0.365 LYG that corresponds to 4.38 months OS (section 5.7.2)
The treatment is licensed or otherwise indicated for small patient populations	The population of patients receiving neoadjuvant treatment for HER2-positive breast cancer in England is 1,457 (see Table 5)

4.14 Ongoing studies

APHINITY is a randomised, double-blind, placebo-controlled, two-arm trial with the objective to evaluate adjuvant Perjeta with chemotherapy plus Herceptin vs chemotherapy with Herceptin plus placebo for 1 year after surgery in patients with HER2-positive breast cancer in more than 4800 patients. After surgery, patients will be randomised to receive either Perjeta or placebo intravenously (IV) every 3 weeks for one year, in addition to 6-8

cycles of chemotherapy and 1 year of Herceptin IV every 3 weeks. This trial has completed its recruitment and is on-going at the time of this NICE submission (Clinical trials.gov identifier: NCT01358877).

The final analysis of invasive disease-free survival (IDFS) from the phase III APHINITY study will provide confirmation of the clinical benefits of Perjeta in the early breast cancer setting as we have already seen in the NeoSphere and TRYPHAENA studies. This fulfils the consideration from EMA guidance, where approval based on pCR is acceptable in neoadjuvant breast cancer clinical trials.

DFS was evaluated as a secondary endpoint of efficacy in TRYPHAENA, however this data was not sufficiently mature at the time of submission. This data will be reported when all patients have completed adjuvant treatment and is anticipated in 2016.

5 Cost effectiveness

5.1 Published cost-effectiveness studies

5.1.1 Identification of studies

Describe the strategies used to retrieve cost-effectiveness studies relevant to decision-making in England from published NICE technology appraisals, the published literature and from unpublished data held by the company. Justify the methods used with reference to the decision problem and the NICE reference case. Provide sufficient detail to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used. Provide the search strategy used in an appendix

Search strategy development

The search strategy was developed using a combination of free text, Medical Subject Headings (MeSH) and EMBASE EMTREE terms, as appropriate for the databases included. Briefly, the search terms in the strategy included:

- Disease state terms; and
- Economic terms

Restrictions were incorporated in the search strategy, including:

- Limited to English language publications; and
- Removal of animal studies.

The full search strategy, including number of hits returned from each step, is available in Appendix 9 Search strategy for the systematic literature review for the economic model.

Data sources

In keeping with the requirements of major health technology assessment (HTA) bodies, and recommended by the Centre for Reviews and Dissemination (CRD) and Cochrane Collaboration [CHSRI 2011; CRD 2009], the following databases were searched for relevant studies:

- MEDLINE® and MEDLINE® in-process (OVID SP)

- EMBASE (OVID SP)
- NHS Economic Evaluations Database (NHS EED)
- EconLit

Search strategies for MEDLINE® and EMBASE were implemented using the OVID portal to access the electronic databases. Full search strategies are presented in Appendix 9 Search strategy for the systematic literature review for the economic model.

Search implementation date and span

The date span of the search strategies, and the date the searches were conducted are described in Table 67.

Table 67 Search span and dates of search strategy implementation for the CEA, costs and resource use SLR

Database	Date of Search	Dates Span of Search
Medline® and Medline® In-Process	12 Nov 2015	1946 to 10 Nov 2015
EMBASE	12 Nov 2015	1974 to 10 Nov 2015
EconLit	12 Nov 2015	1886 to Oct 2015
Cochrane Library	12 Nov 2015	NR

Study selection process

To identify and retrieve relevant cost-effectiveness and cost-utility analyses, a double, independent review of publications was conducted in a two phase approach. The first phase consisted of a title and abstract review of all publications identified from the search strategy. Reviewers categorised each publication as either 'included' or 'excluded'. All publications deemed 'included' were reviewed in the second phase, and all publications that were 'rejected' were excluded from further review. The second phase consisted of a full-text review of articles, with reviewers classifying each publication as 'included' or 'excluded'. Reasons for exclusion during the full-text review were recorded.

Discrepancies between reviewers were resolved by consensus. In cases where a decision could not be agreed upon by both reviewers, a third reviewer acted as adjudicator; the judgment of the third reviewer was considered final.

As recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, [Moher 2010] the study selection process was documented in a flow diagram.

Inclusion criteria

The inclusion criteria were defined using an adaptation of the PICOS framework, as described in The Cochrane Collaboration Handbook (Table 68).

Table 68 Inclusion criteria

	Inclusion criteria
Population	Adults with HER2-positive, locally advance, inflammatory, or early stage breast cancer
Intervention	Any neoadjuvant or adjuvant therapy
Outcomes	N/A
Study design	Full economic evaluations
Abbreviations: **HER2** – human epidermal growth factor receptor 2; **N/A** – not applicable.	

In addition to the PICOS criteria stated, articles were included if they were a primary publication in the English language article published in a peer-reviewed journal.

Exclusion criteria

Publications were excluded based on the following criteria:

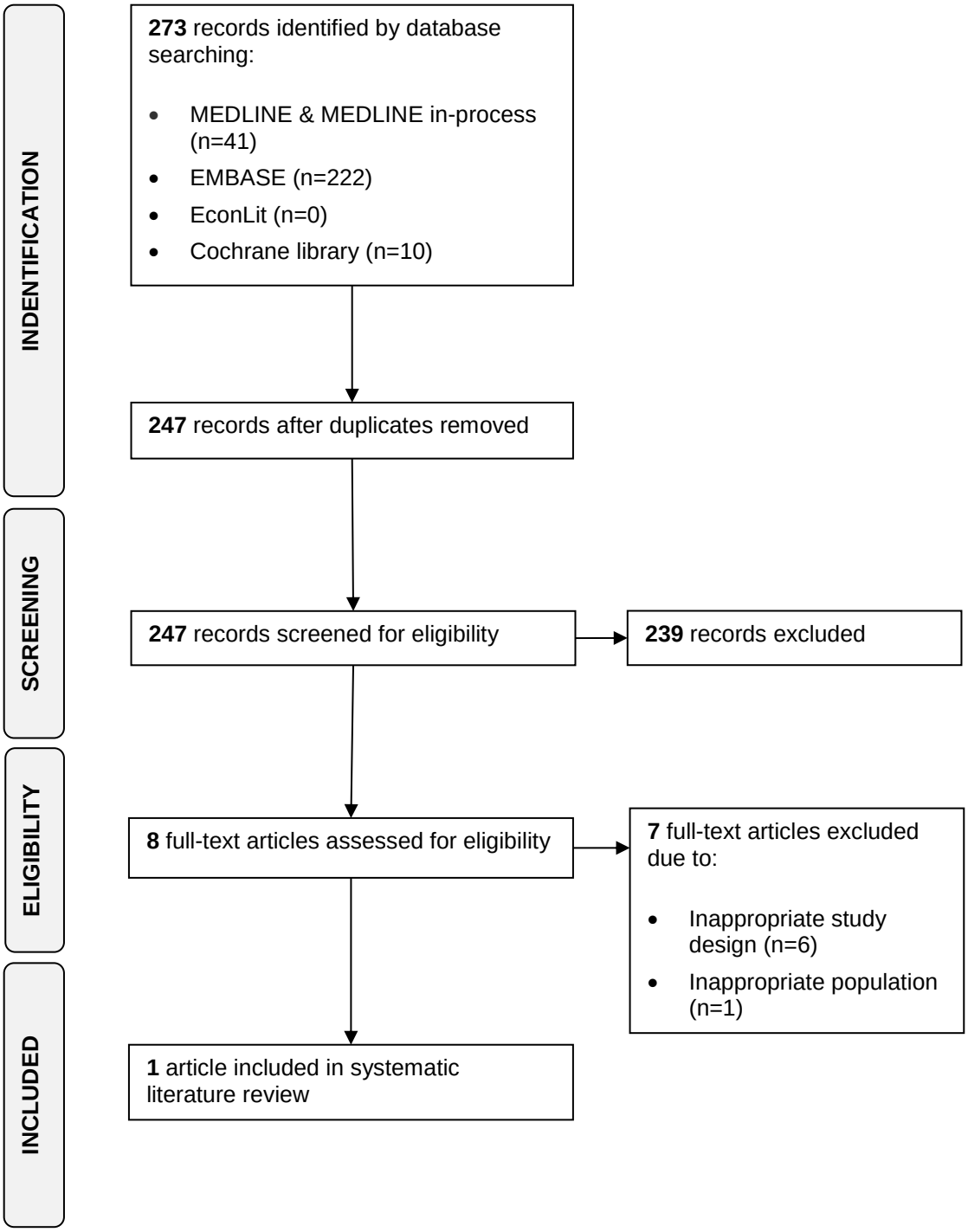
- Disease area not of interest;
- Study design or publication format not of interest, including:
    - Secondary publications;
    - Review articles, systematic literature reviews or meta-analyses;
    - Editorials or notes or letters to the editor;
    - Conference proceedings; and
    - Studies containing no primary data.

5.1.2 Description of studies

Provide a brief overview of each cost-effectiveness study only if it is relevant to decision-making in England. Describe the aims, methods and results for each study. Each study's results should be interpreted with reference to a critical appraisal of its methodology. When studies have been identified and not included, justification for this should be provided. If more than 1 study is identified, please present the information in a table as suggested below

The PRISMA flow-diagram outlining the study selection process is presented in Figure 21. The search strategy identified a total of 247 articles for review. During the first study selection phase, 239 articles were excluded; of the remaining eight articles, seven were excluded during the second study selection phase, resulting in one article identified for extraction. The most common reason for exclusion during the second study selection phase was inappropriate study design (85.7% of excluded articles).

Figure 21 PRISMA diagram depicting study selection process of cost-effectiveness studies



Description of Attard et al [Attard 2015]

The single study identified for inclusion was a cost-utility analysis (CUA) assessing the benefits, costs, and cost-effectiveness of neoadjuvant therapy

from the Canadian healthcare payer perspective over a 28 year time horizon in patients with locally advanced, inflammatory, or early HER2-positive breast cancer. Two base-case analyses were modelled in this analysis, however only the intervention arm informed by the NeoSphere trial met the eligibility criteria for extraction and will be discussed further (Table 69).

A Markov model comparing neoadjuvant PHD vs. HD was developed. The model incorporated previously published direct medical costs and health state utility value (HSUV) estimates. Indirect costs were not incorporated in the model. Further model details can be found in Table 69 and Table 70.

The model reported gains in life years and QALYs among patients in the Perjeta containing arm. The discounted cost/QALY reported was $25,388 (2014 CAD). Sensitivity analysis of model inputs reported a range of cost/QALY from $9,230 (2014 CAD) to $38,419 (2014 CAD).

Table 69 Neoadjuvant CEA study characteristics

Study	Interventions [a]	Type of analysis	Type of model	Health states included	Source of transition probabilities	Cycle length	Time horizon	Discount rate [b]	Perspective
Attard (2014)	Perjeta Herceptin FEC and docetaxel vs. Herceptin, FEC and docetaxel	CEA/CUA	Markov	• Event free year 1 • Event free year 2+ • Local recurrence • Relapsed • Dead	Digitalised EFS and OS curves [c]	1 month	28 years	5%	Canadian healthcare payer, with Ontario as a reference province

Abbreviations: **CEA** – cost-effectiveness analysis; **CUA** – cost-utility analysis; **EFS** – event free survival; **FEC** – fluorouracil, epirubicin and cyclophosphamide; **OS** – overall survival.
[a] The following drug doses were used: Perjeta loading dose of 840 mg and maintenance doses of 420 mg; Herceptin loading dose of 8 mg/kg, maintenance doses of 6 mg/kg; docetaxel was given at an initial dose of 75 mg/m2, with dose escalation to 100 mg/m2 permitted, if tolerated; FEC in the NeoSphere trial was 600 mg/m2 5-fluorouracil, 90 mg/m2 epirubicin, 600 mg/m2 cyclophosphamide.
[b] Discount rate applied to costs and health effects.
[c] Source: Kim (2013)

Table 70 Summary of CEA inputs and estimated ICERs

Study	Summary of model	Patients	Utility values	QALYs gained	Total Costs	ICER
Attard (2014)	CEA of standard neoadjuvant chemotherapy with Perjeta vs without Perjeta in patients with breast cancer	Patients with early stage breast cancer with a median age of 50 years	Event free, year 1: 0.97 Event free, year 2+: 0.99 Local recurrence: 0.75 Metastatic disease: 0.65 Weighted utility for relapsed: 0.68 [a]	QALYs With Perjeta: 11.0 Without Perjeta: 10.7	With Perjeta: $125,518 Without Perjeta: $117,638 (Costs in 2014 CAD).	$25,388 per QALY gained

Abbreviations: **CAD** – Canadian dollar; **CEA** – cost-effectiveness analysis; **ICER** – incremental cost-effectiveness ratio; **QALY** – quality adjusted life-year.
[a] Source: Hedden (2012)

5.1.1 Provide a complete quality assessment for each relevant cost-effectiveness study identified. Use an appropriate and validated instrument, such as those of Drummond and Jefferson (1996)[2] or Philips (2004)[3]. Please provide these assessments in an appendix.

The quality of the Attard cost-effectiveness study was assessed using the Drummond and Jefferson (Drummond 1996) checklist. Of the 36 items measured in the checklist, the Attard study met 28 items (see Table 133). Reporting of the study was well defined, including a clearly stated research question, the treatment arms being compared, the primary outcomes evaluated, an overview of the sensitivity analysis conducted, and conclusions offered. For complete details of the quality assessment checklist, please see Appendix 9 Search strategy for the systematic literature review for the economic model.

5.2 De novo analysis

5.2.1 Patient population

State which patient groups are included in the economic evaluation and how they reflect the population defined in the scope and decision problem for the NICE technology appraisal, marketing authorisation/CE marking, and the population from the trials. If there are differences, please provide the rationale. Explain the implications of this for the relevance of the evidence base to the decision problem. For example, indicate if the population in the economic model is different from that described in the (draft) summary of product characteristics (SmPC) or information for use (IFU) and included in the trials

An economic model was constructed to assess the clinical and cost effectiveness of Perjeta in combination with Herceptin and docetaxel in adults with HER2-positive, locally advanced, inflammatory, or early stage breast cancer who have not previously received chemotherapy or HER2 directed treatment for their disease. The model captures the key outcomes from the ITT population of the NeoSphere study. The patient group included in the economic model reflects that of the decision problem and scope for the NICE appraisal and that of the Perjeta SmPC (adults with

HER2-positive breast cancer which is either locally advanced, or inflammatory, or early stage (at a high-risk of recurrence)).

Compared to the five health state model from Attard, this de novo model is believed to better reflect the natural course of the disease. The Attard model included a 'Relapsed' health state that was felt to not appropriately describe the different benefits and costs experieced by a patient between EFS and the death state. Within the de novo model it was decided to divide this health state into three (locoregional recurrence, metastatic not progressed and metastatic progressed). These health states will be further discussed in subsequent sections.

Model structure

5.2.2 Model structure

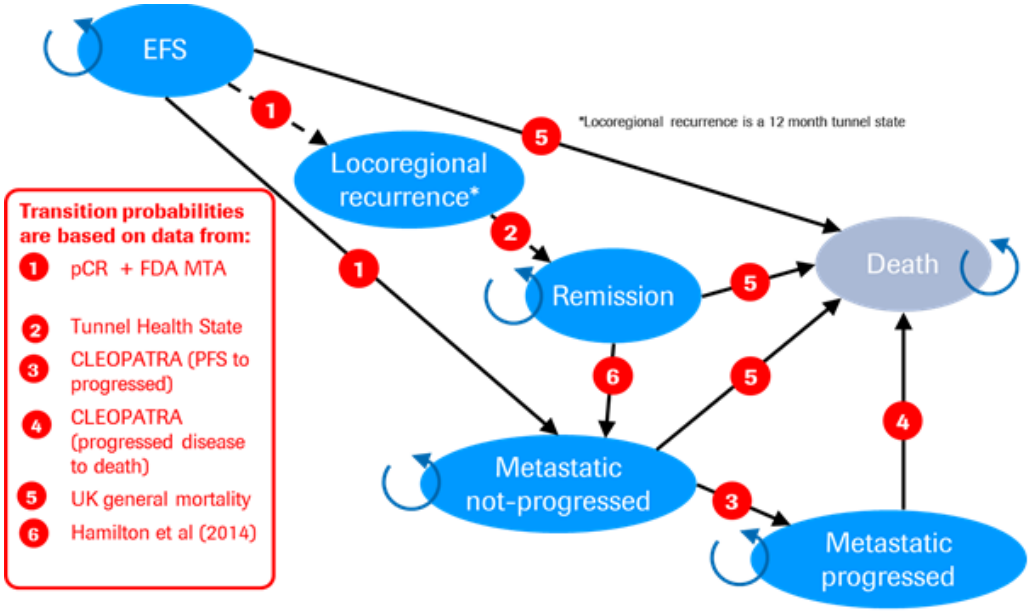
Describe the model structure and provide a diagram of the model submitted, including the following:

- **Type of de novo analysis (for example, decision tree, Markov model, discrete event simulation model).**
- **Justification of the chosen structure in line with the clinical pathway of care described in section 3.3.**
- **How the model structure and its health states capture the disease or condition for patients identified in section 3.3.**
- **Where appropriate, state the cycle length and whether a half-cycle correction has been applied.**

A Markov model was created in Excel® with the following health states: 'event free', 'locoregional recurrence', 'remission', 'metastatic not-progressed', 'metastatic progressed' and 'death' which is an absorbing state. At each 3-week cycle, people can transition between the health-states described in Figure 22. Each health state is then assigned a specific cost and a health state utility.

The model structure differs from a typical three health state model frequently used in oncology. The model structure allows costs and utilities to be distinguished between different types of events i.e. metastatic and non-metastatic events (locoregional recurrences) which better reflect the disease pathway.

Figure 22 Model structure



A series of 12 tunnel states are used to model the locoregional recurrence health state. Markov models are 'memoryless' so cannot determine how long an individual may spend in a certain health state. Adding tunnel states is a way of implementing time-dependency. This enables people to remain in the locoregional recurrence state for 12 months whilst receiving further adjuvant therapy.

Transitions between health states

At time zero all patients enter the model in event free survival (EFS) health state. At the end of each monthly cycle they may either remain within the same health state or experience an event (i.e. locoregional, metastatic or death due to natural causes) and move to a worse health state.

There are two distinct pathways for people who experience a disease-related event:

1) In the event of a locoregional recurrence, this will lead to a further 12 months of treatment with Herceptin. Upon completion of treatment, people are assumed to be in remission and transition to the remission state. If an individual's disease returns whilst in the remission health state it is assumed to be a metastatic event.

2) The other possible type of progression is a metastatic event, where a first line treatment for metastatic breast cancer is administered. In the 'metastatic not

progressed' health state there is a risk of disease progression and movement to the 'metastatic progressed' health state, where individuals are administered a second line treatment for their metastatic breast cancer.

The split between people who transition into 'metastatic non-progressed' or 'locoregional recurrence' health state is based on the results from NeoSphere study.

The probability of moving to the 'metastatic not progressed' health state is expected to be higher from the 'remission' state than from EFS. It is expected that if a person has already had a "locoregional recurrence" their chance of having a further recurrence is higher. This was verified at a Roche advisory board in held June 2015 with English and Scottish oncologists.

If a patient's breast cancer becomes metastatic the patient moves into the 'metastatic not-progressed' health state. The transition probabilities in the metastatic disease are based on transition probabilities observed in the clinical trial CLEOPATRA which evaluated the clinical efficacy and safety of Perjeta in combination with Herceptin and docetaxel, compared with placebo plus Herceptin plus docetaxel, as first-line treatment for patients with HER2-positive mBC.

People can transition into the 'death' state from all stages of the model except the 'locoregional recurrence' state which is a 12 month tunnel state. 'Death' is an absorbing state. Adding a transition to 'death' from the tunnel states would make the model very complex. Excluding this transition slightly overestimates the number of people who remain in locoregional recurrence, which overestimates the QALYS and costs associated with this health state in both arms.

The impact of exclusion this is expected to be small because mortality from all health states except metastatic disease is modelled as UK general population mortality. which is relatively low.

The model structure was considered by clinicians at the Roche advisory board and was thought to reflect the disease pathway of people receiving neoadjuvant therapy.

5.2.3 Features of the de novo analysis

Complete the table below presenting the features of the de novo analysis. Compare and justify your chosen values with the methods specified by NICE in the reference case (see the NICE guide to the methods of technology appraisal, section 5, table 5.1).

Table 71 Features of the de novo analysis

Factor	Chosen values	Justification
Time horizon (years)	50	Patients are relatively young and may have a life expectancy equal to the general population. A 45 year time horizon was used in TA107 Herceptin adjuvant early breast cancer.
Were health effects measured in QALYs; if not, what was used?	Yes	In accordance with NICE methods guide
Discount of 3.5% for utilities and costs	3.5%	In acordance with NICE methods guide
Perspective (NHS/PSS)	Yes	In acordance with NICE methods guide
PSS, personal social services; QALYs, quality-adjusted life years; NHS, National Health Service		

Intervention technology and comparators

5.2.4 If the intervention and comparator(s) are not implemented in the model as per their marketing authorisations/CE marking, describe how and why there are differences. Make it clear whether the intervention and comparator(s) included in the model reflect the decision problem. If not, briefly describe how and why, cross-referencing to the decision problem section in your submission

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 5.5.

5.2.5 If a treatment continuation rule has been assumed for the intervention and comparator(s), provide the rationale for the continuation rule and where it is referenced (for example, [draft] SmPC, European public assessment report, comparator use, clinical practice, or

clinical trial protocols). Please note that this refers to clinical continuation rules and not patient access schemes. If a treatment continuation rule is included in the model that is not stated in the (draft) SmPC or information for use (IFU), this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following:

- **the costs and health consequences of implementing the continuation rule (for example, any additional monitoring required)**
- **the robustness and plausibility of the end point on which the rule is based**
- **whether the 'response' criteria defined in the rule can be reasonably achieved**
- **the appropriateness and robustness of the time at which response is measured**
- **whether the rule can be incorporated into routine clinical practice**
- **whether the rule is likely to predict those people for whom the technology is particularly cost effective**
- **Issues about withdrawal of treatment for people whose disease does not respond and other equity considerations.**

Treatment continuation rules have not been applied in the economic model.

5.3 Clinical parameters and variables

5.3.1 Describe how the clinical data were incorporated into the model, also commenting on the following factors:

- **Whether intermediate outcome measures were linked to final outcomes (for example, if a change in a surrogate outcome was linked to a final clinical outcome). If so, explain how the relationship was estimated, what sources of evidence were used, and what other evidence there is to support it.**

- **Whether costs and clinical outcomes are extrapolated beyond the trial follow-up period(s). If so, explain and justify the assumptions that underpin this extrapolation, particularly the assumption that was used about the longer-term difference in effectiveness between the intervention and its comparator. For the extrapolation of clinical outcomes, present graphs of any curve fittings to patient-level data or Kaplan–Meier plots and the methods and results of any internal and external validation exercises. The NICE Decision Support Unit[4] has published technical support document 14, which provides additional information on the implementation of methods and reporting standards for extrapolation with patient level data.**

Due to the potential curative nature of neoadjuvant treatment, PFS or EFS as endpoints do not reach median values during the trial duration (low number of events). This is the case in NeoSphere where at 5 years 80% of patients had not progressed. Powering of NeoSphere to detect a statistically significant 5 year PFS would have required a study size of 677 per arm. Therefore, often pCR is primarily used as an efficacy endpoint in neoadjuvant clinical trials. pCR was accepted as a valid endpoint by both the FDA and EMA during regulatory filing. The correlation between EFS and pCR will be further explored below.

Clinical inputs from NeoSphere

The key effectiveness input in the model is tpCR (ypT0/is ypN0). tpCR is the secondary endpoint measured in NeoSphere, it has been used as an endpoint in a number of trials of neoadjuvant systemic therapy for early breast cancer and is reported at surgery. Despite being a primary endpoint in NeoSphere, bpCR was not used in the economic model as the CTNeoBC analysis which quantified the link between pCR and EFS found that the link tpCR-EFS was stronger than bpCR-EFS.

Given the improvement in survival for individual patients who attain tpCR (Gianni 2012), a novel agent that produces a marked absolute increase in tpCR rate compared with standard therapy alone in the full intent-to-treat population is likely to result in long-term improvements in EFS or OS. Although it is possible that different breast cancer subtypes will require different magnitudes of improvement in tpCR

rates to translate into superior EFS or OS, therapies that modestly increase tpCR rates are unlikely to improve long-term outcomes in any subtype (FDA 2014).

Table 72 below presents the proportion of patients who achieved tpCR with confidence intervals based in NeoSphere (data cut-off at surgery or withdrawal). These values were used in the submission.

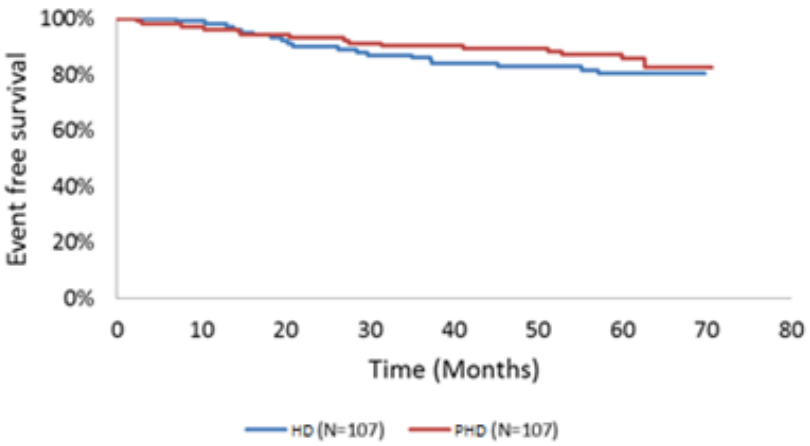
Table 72 tpCR rates from NeoSphere (clinical cut off 22 December 2009)

	Herceptin + docetaxel tpCR (95% CI)	Perjeta + Herceptin + docetaxel tpCR (95 %CI)
NeoSphere	21.5% (CI: 14.1%–30.5%)	39.3% (CI: 30.0%–49.2%)

End-points other than pCR were also collected in NeoSphere including EFS and DFS, but the trial was not powered to show a statistical difference for these variables. Figure 23 shows the Kaplan Meier EFS data for arms A and B.

Five years of EFS follow-up data was available at the time of the analysis, however, EFS was collected in the trial as an exploratory endpoint hence a small number of events were observed in the NeoSphere trial and the data is immature.

Figure 23 Kaplan-Meier estimate of EFS - PHD vs HD



As noted in section 5.2.2, patients who progress from EFS will either transition into ‘metastatic non-progressed’ or ‘locoregional recurrence’ health states. These transitions are based on the tpCR results from Arms A and B of NeoSphere (39.3% (CI: 30.0%–49.2%) and 21.5% (CI: 14.1%–30.5%) for PHD and HD arm

respectively). In the trial 58% of observed disease progression was to the metastatic health state and the remaining 42% of progressions were locoregional (clinical cut off 20 October 2014).

The HERA trial (Goldhirsch 2013) offers an alternative source to inform this split between these types of recurrence which is explored in sensitivity analyses (70% PHD and 30% HD respectively). HERA is a randomised, open-label, multicentre, phase III trial investigating the efficacy of Herceptin for 1 and 2 years with observation after standard neoadjuvant chemotherapy, adjuvant chemotherapy, or both in HER2-positive early breast cancer patients. This may provide more accurate results as more people have experienced events than in the NeoSphere data.

Clinical inputs from CTNeoBC meta analysis – The link between pCR and EFS

To establish the impact of achieving tpCR on a patients long term outcomes, an additional data source is required. Cortazar (2014) analysed the results from an FDA sponsored group - The Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC). This analysis was published in the Lancet journal and investigated the association between pCR and long-term outcomes (OS and EFS) in a pooled analysis of neoadjuvant trials [Cortazar 2014]. In this study, PubMed, Embase and Medline were searched for reports of clinical trials of neoadjuvant treatment of breast cancer published between 1 January 1990 and 1 August 2011. The pooled analysis included 11,955 patients from 12 trials.

Outcomes were measured at patient and trial level:

- Patient level analyses compare clinical outcomes in patients with pCR versus those without pCR, irrespective of treatment group. Such analyses can predict improved survival for patients who have pCR and can provide insight into the natural history of an individual's disease, which can help to guide patient information and counselling.

- Trial-level analyses are useful for predicting population treatment benefits and help to explore the role of pCR as a surrogate endpoint in neoadjuvant trials. The trial level analysis included 10 international randomised trials (excluding

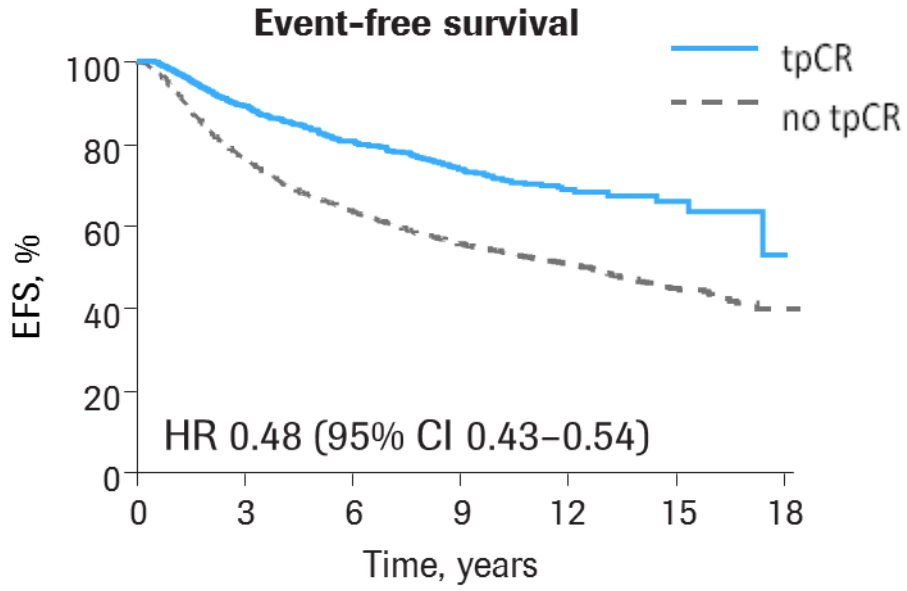
non-randomised groups or those receiving additional adjuvant taxane therapy, because effect size could not be calculated).

Results from CTNeoBC meta analysis [Cortazar 2014, Cortazar 2015]

- **Patient level analyses**

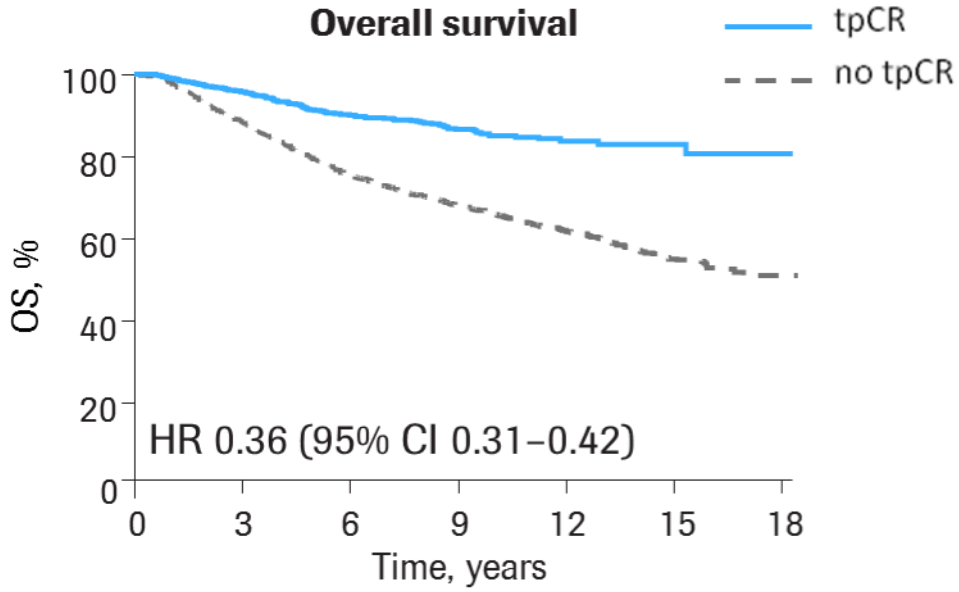
In the pooled patient level analysis, patients who achieved pCR irrespective of definition had longer EFS and OS than patients who did not achieve pCR (see Figure 24 and Figure 25 below). tpCR had a higher association with improved EFS and OS than bpCR.

Figure 24 Kaplan-Meier plot of association between tpCR and EFS [Cortazar 2014]



n at risk							
tpCR	2,131	1,513	583	337	124	35	2
no tpCR	9,824	6,169	2,674	1,523	525	165	1

Figure 25 Kaplan-Meier plot of association between tpCR and OS [Cortazar 2014]

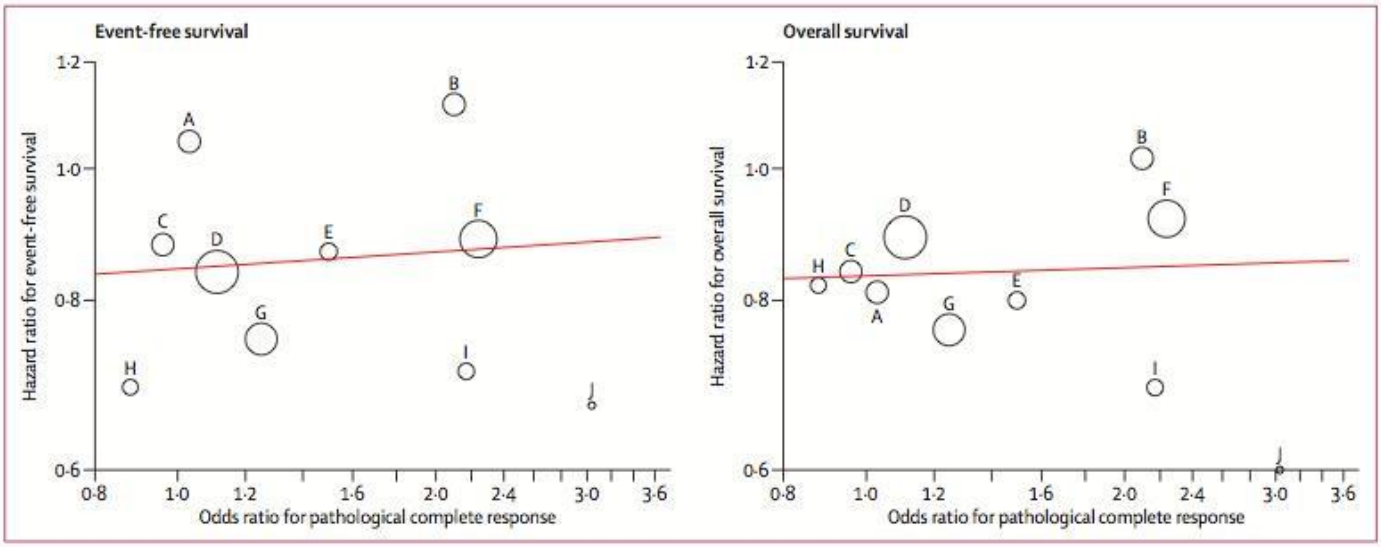


n at risk							
tpCR	2,131	1,618	640	383	145	43	3
no tpCR	9,824	7,119	3,173	1,859	659	209	3

- **Trial level analyses**

For the trial level analysis, the odds ratio for pCR in each trial was plotted against the hazard ratio for EFS and OS in turn. This is shown graphically below (Figure 26): each circle represents one randomised trial; the size of the circle represents the sample size. At a trial level, there was only a weak association between frequency of tpCR and the treatment's effect on EFS or OS. Coefficient of determination (R^2) between improvement in pCR and EFS was 0.03 (95% CI 0.00-0.25); for OS it was 0.24 (95% CI 0.00-0.70). Thus, the trial level analysis could not establish the magnitude of increase in pCR rate that would be needed to predict a survival benefit from treatment.

Figure 26 Trial-level correlation between treatment effect on tpCR and EFS or OS



Key:
A: GeparQuatro; **B:** GeparDuo; **C:** GeparQuatro; **D:** EORTC10994; **E:** PREPARE; **F:** NSABP B27; **G:** Responders in GeparTrio;
H: Non-responders in GeparTrio; **I:** AGO; **J:** NOAH

A possible explanation for the lack of clear correlation (from a trial level perspective) could be the fact that the studies enrolled women with a heterogeneous mix of tumour sub-types: this potentially masked associations between pCR and EFS or

OS, since the absolute difference in pCR rates between treatment arms in the studies was low (111% - Cortazar 2015).

Ideally, a surrogate endpoint should correlate with outcomes at both the individual and the trial levels. The analyses could not validate pCR as a surrogate endpoint for improved EFS and OS at a trial level but the correlation between tpCR and PFS and OS was seen at an individual level. Nonetheless, the authors concluded that the survival benefits associated with tpCR in individual patients encourage confidence in a relationship between marked tpCR in the intention-to-treat population and long-term improvements in outcomes.

- **Applications to the economic case**

The CTNeoBC patient level analysis provided the natural history of the disease regardless of treatment. It was used in the model to determine the progression over time of patients who achieved pCR those that did not regardeless of treatment.

Trial level analysis did not find a strong correlation between EFS and pCR and provide comment that "In the HER2-positive subgroup, we noted that the addition of one trial with increased treatment effects (NOAH) decreased the slope of the curve, suggesting a trial-level correlation between frequency of pathological complete response and long-term outcome could be identified in future trials with more homogeneous populations and incorporation of targeted therapies"

Only the natural history of pCR and no pCR patients – patient level analysis fits the purposes of the submission.

The CTNeoBC meta-analysis KM data were digitized using Grafula 3 (version 2.10). The digitized data was used to reconstruct the individual patient level data (IPD) using the algorithm by Guyott [Guyott 2012]. A number of parametric functions (i.e. exponential, weibull, log-logistic, log-normal, Gompertz and gamma) were then fitted to the generated IPD data.

Table 73 below contains the parameters used for extrapolation of event free survival; based upon the CTNeoBC meta-analysis. The impact on the ICER of using different parametric functions was explored in the sensitivity analysis.

Table 73 Parameters for extrapolation of Event Free Survival depending on pCR status

	Lambda	Gamma	Delta	AIC (rank)
Not having achieved pCR				
Exponential	0.006	NA	NA	4,182 (5)
Weibull	0.003	1.171	NA	4,173 (4)
Lognormal	4.683	1.380	NA	4,132 (2)
Loglogistic	0.002	1.312	NA	4,157 (3)
Gamma	4.114	1.747	-1.314	4,116 (1)
Having achieved pCR				
Exponential	0.003	NA	NA	1,001 (5)
Weibull	0.001	1.370	NA	995 (4)
Lognormal	5.366	1.345	NA	985 (2)
Log-logistic	0.001	1.455	NA	993 (3)
Gamma	3.721	1.775	-4.304	974 (1)

Selection of parametric function

In order to determine the most appropriate parametric function to extrapolate the EFS data, the shape of the cumulative hazard plots and goodness of fit were considered (both visually and using goodness of fit statistics).

- **Log-cumulative hazard plots and Log-odds plots**

Log-cumulative hazard plots allow a close inspection of whether hazards are monotonic, non-monotonic or constant and where significant changes in the observed hazard occur by plotting the log of the negative log of the survival function versus the log of time. In particular, they allow for the testing of the suitability of the Weibull and exponential distributions. In addition, such plots allow an evaluation of whether the proportional hazards assumption holds.

When a sample follows a Weibull distribution, the log-cumulative hazard plot describes a straight line (if the gradient is one then it can be assumed to follow an exponential distribution). Furthermore, two samples that describe parallel straight lines follow a Weibull distribution and have proportional hazards. Figure 27 below

depicts the log-cumulative hazards of the pCR and no pCR arms of the CTNeoBC analysis.

Log-cumulative hazard plots: The log-cumulative hazard plots of the EFS data from the CTNeoBC analysis by tpCR and no tpCR are presented in Figure 27.

Figure 27 Log-cumulative hazard plot of EFS from the CTNeoBC analysis split by individuals achieving a tpCR and no tpCR

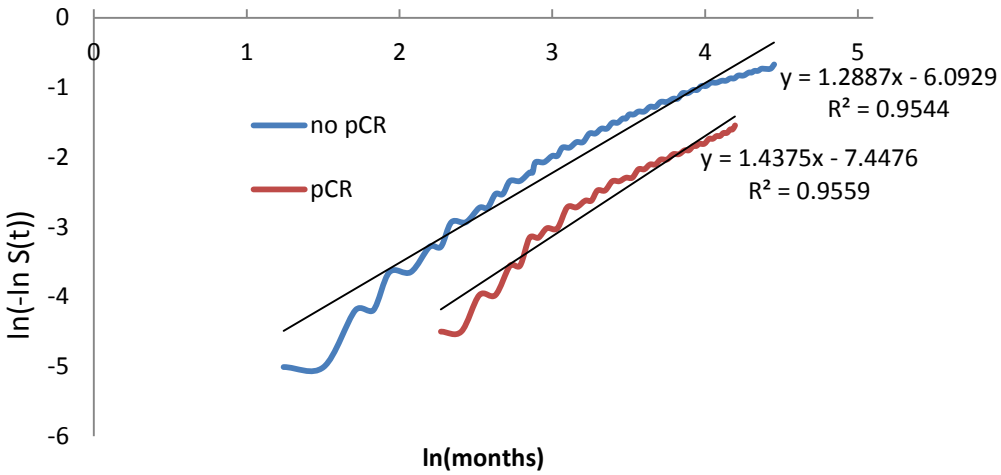


Figure 27 shows that pCR and no pCR trendlines have slightly different gradients (suggesting that the proportional hazards assumption may not hold). The figure also suggests that the hazard ratio is not constant as the plot produced a straight line. Further investigation may be needed to explore other distributions that may fit the data better.

A log-odds plot is a simple plot that depicts the log of the odds of surviving beyond time *t* ($\ln(\frac{S(t)}{1-S(t)})$) against the log of time (ln(t)).

Figure 28 Log-odds plot of event free survival from the CTNeoBC analysis split by individuals achieving a tpCR and no tpCR

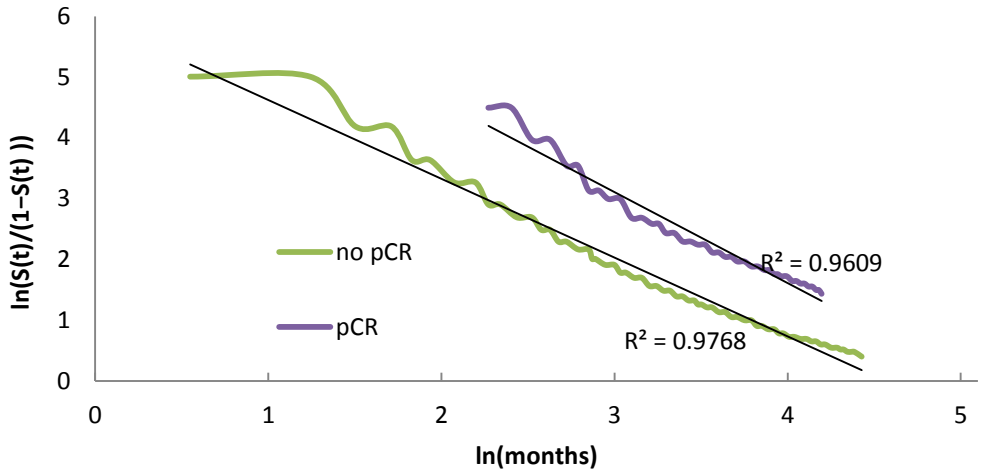


Figure 28 above again shows that pCR and no pCR trendlines have slightly different gradients (suggesting that the proportional hazards assumption may not hold). Furthermore, the trendline regression coefficients for the log-cumulative hazards plot are lower than those for the log-odds plot. This suggests that the log-logistic distribution (and possibly other Accelerated Time Failure models (AFTs) such as log-normal or the Gamma distribution) may fit the data better than parametric proportional hazard models such as the Weibull.

Overall the analyses above suggests that the hazard ratios of either the pCR and no pCR are not constant (they are diminishing as the time passes), and the pCR explanatory variable of the trendline is higher than that of no pCR suggesting that the risk of progressing is lowering faster in the pCR arm (see Figure 27). These facts suggest that AFTs (such as log-logistic, log-normal or gamma distributions) should fit the data better than the Weibull or the exponential distributions. Further methods to confirm these conclusions are described below.

- **Goodness of fit**

The AIC and BIC are criteria for model selection that considers the statistical fit of the parametric function to the KM data. The parametric function with the lowest AIC and BIC is preferred.

Table 74 Summary of parametric functions' goodness of fit for EFS

	no tpCR		*tpCR*		*Rank*
Parametric Model (EFS)	***AIC***	***BIC***	***AIC***	***BIC***	
exponential	4182	4187	1001	1005	6
weibull	4173	4184	995	1003	4
lognormal	4132	4142	985	994	2
loglogistic	4157	4168	993	1001	3
gompertz	4184	4186	1002	1004	5
gamma	4116	4120	974	976	1

The parametric function with the best statistical fit is the gamma followed by the log normal function in both arms. These results support the hypothesis noted in the section above, that in this situation, proportional hazard models show worse fits than more flexible models.

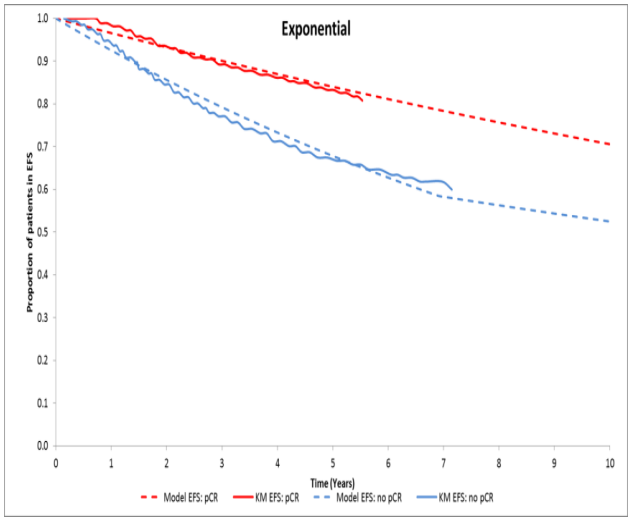
- **Visual inspection**

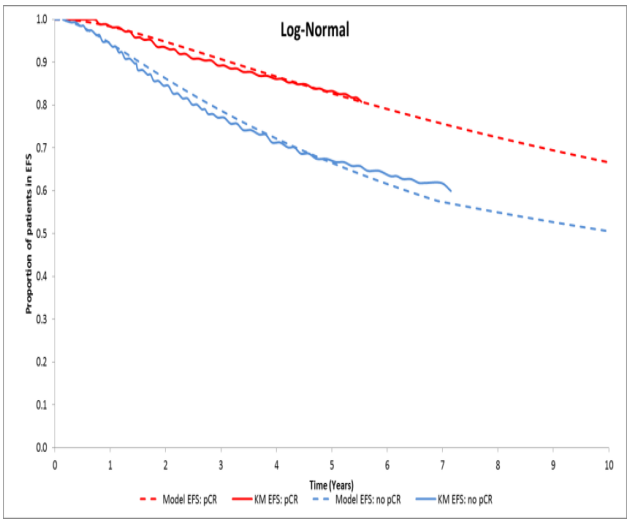
A range of possible parametric extrapolations of the EFS data was considered. These are shown in Figure 29. The parametric functions are used in the model to estimate estimate the fit in the first years of EFS, as such the figures focus on these sections of the curves. Figure 30 shows the modelled estimation of EFS by treatment arm for the different parametric functions for the time horizon. Note that each arm is a weighted average of the tpCR and no tpCR curves. This weighting is based on the tpCR results from NeoSphere (39.3% (CI: 30.0% – 49.2%) and 21.5% (CI: 14.1%-30.5%) for PHD and HD arm respectively). The no tpCR rates are the balance up to 100% i.e PHD 60.7% and HD 78.5%.

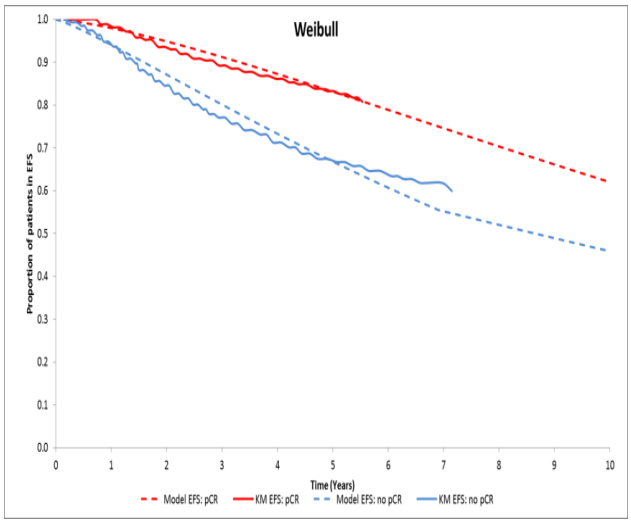
Since there are no long-term follow-up data for eBC patients receiving Perjeta, it is challenging to validate the model predictions of event free survival beyond 5 years (see section 5.3.3 for further explanation).

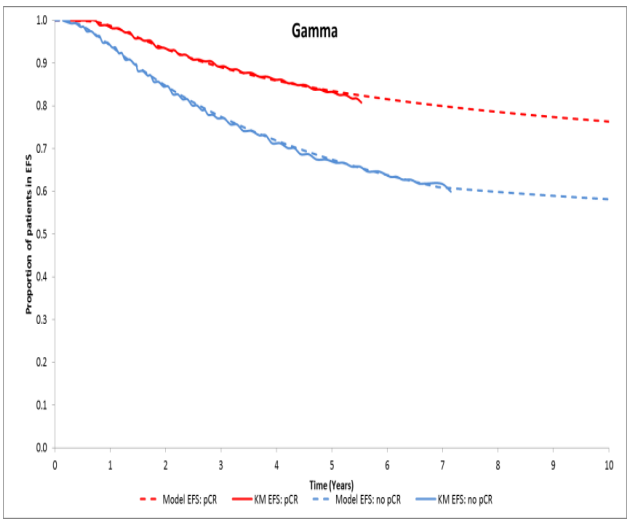
Following the observation of the relatively stable flattening curves seen in both arms and the AIC/BIC statistics, it is hypothesised that the data supports the use of a gamma function when extrapolating the KM curves from the CTNeoBC analysis. Alternative parametric curves are explored in sensitivity analysis.

Figure 29 CTNeoBC Parametric survival curves fitted in NeoSphere EFS KM data









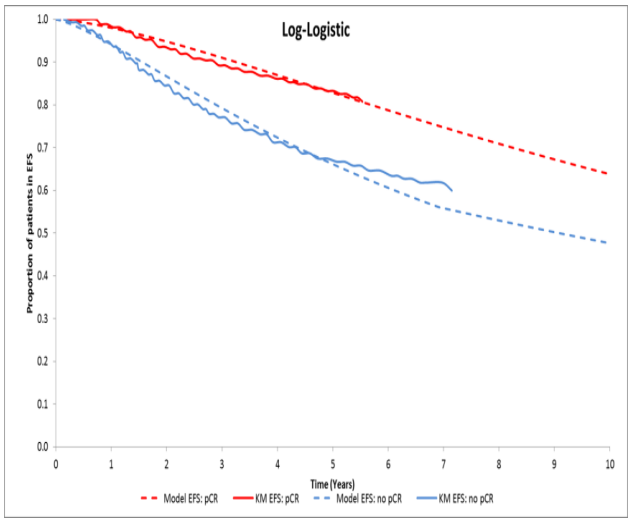
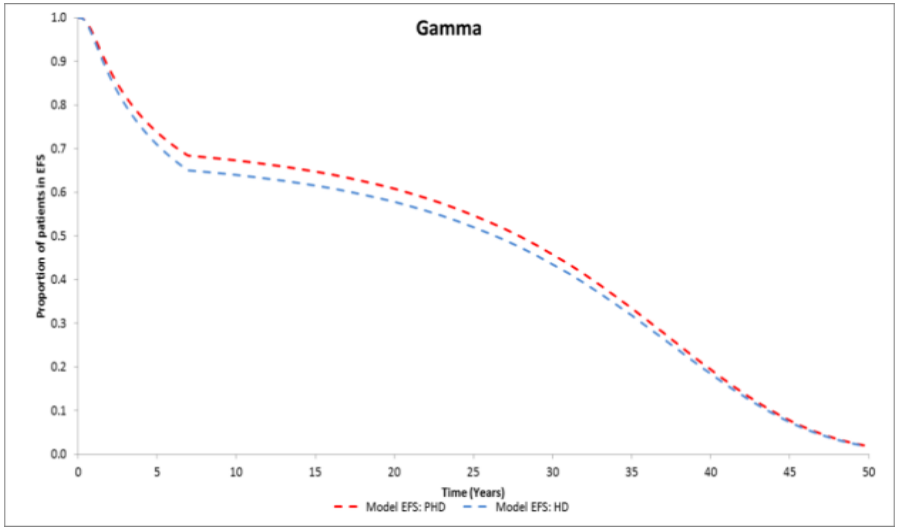
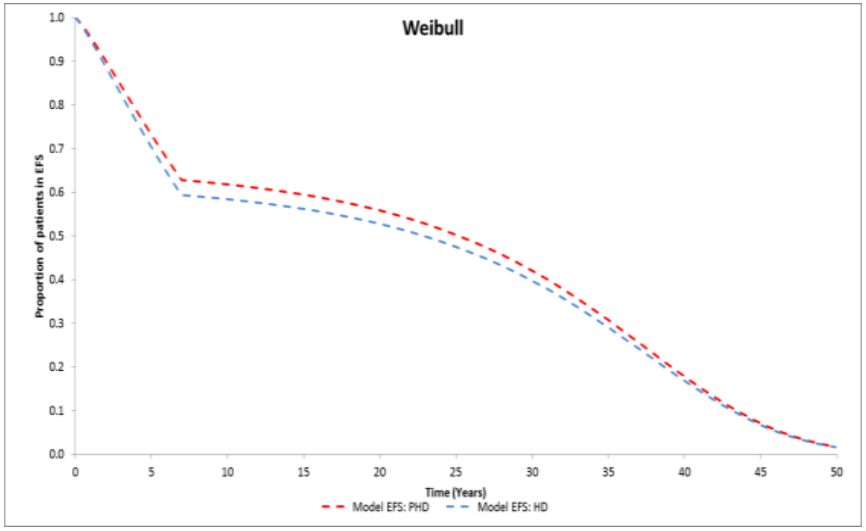
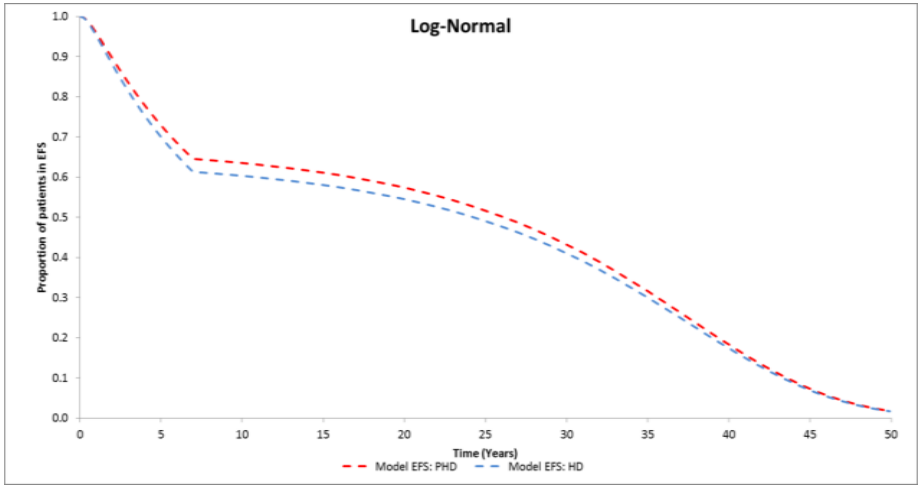
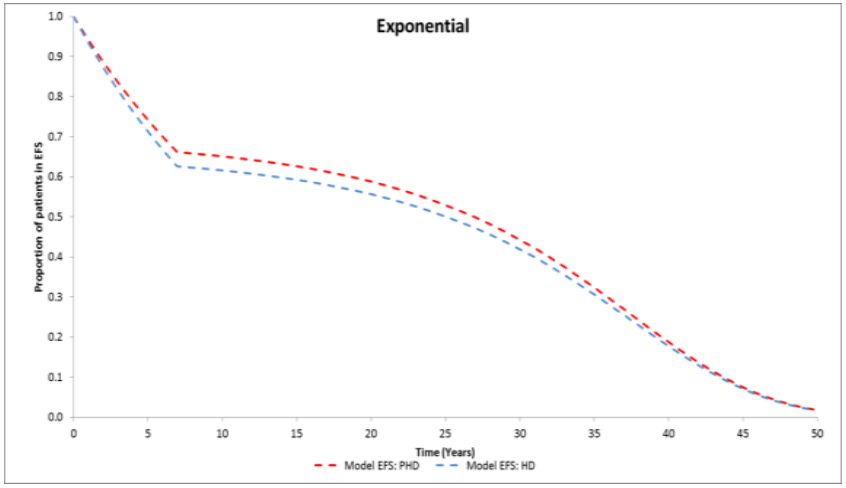


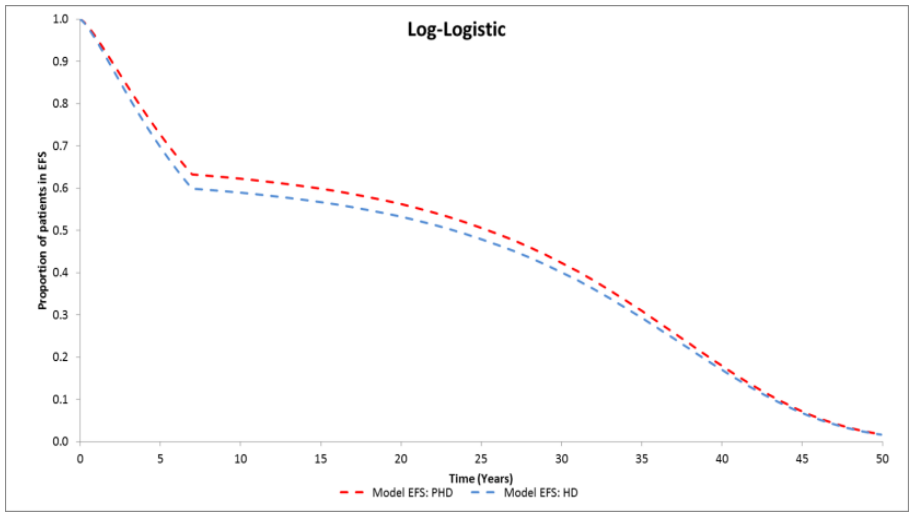
Figure 30 Model estimation of EFS using different parametric curves










Log-Logistic
Proportion of patients in EFS
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
5
10
15
20
25
30
35
40
45
50
Time (Years)
Model EFS: PHD
Model EFS: HD

Other clinical data

- **Hamilton 2014**

The risk of a second malignancy (progressing from the 'remission' to the 'metastatic non-progressed' state) was based upon Hamilton 2014. This study included a cohort of 12,836 early breast cancer patients and estimated the risk of a second malignancy after adjuvant therapy. The mean time until a progression was 7.6 years and this value was converted into a monthly transition probability of 0.76%. As there are a number of differences between the NeoSphere population and Hamilton 2014 (i.e. patients were treated with radiation) the value of this transition is explored in the sensitivity analysis

- **CLEOPATRA – metastatic states**

The risk of progressing once being diagnosed with metastatic disease is based upon the CLEOPATRA trial [Swain 2015a], which compared PHD vs HD in first line metastatic disease. A substantial difference in the monthly risk of progression between PHD (3.17%), and HD (4.70%) arms was reported. To fairly reflect these differences the monthly transition probability used in the model is a weighted average (based on UK market shares – see Table 75 below).

The risk of dying due to metastatic disease was also based upon the CLEOPATRA trial. There was a difference in the mortality risk between the HD (3.15%) and PHD (2.73%) arms. Trastuzumab emtansine (Kadcyla) mortality risk (2.73%) was conservatively assumed to be equal to Perjeta's mortality risk. The monthly risk of dying due to the disease was also calculated as a weighted average (based on their UK market shares – see Table 75) between PHD and HD.

Table 75 Metastatic treatments (first and second line)

First line metastatic	Market shares	Source
Herceptin	20%	Data on file RXUKPERT00252
PHD	44%	
Herceptin + other	36%	
Second line metastatic*		
Capectiabine + lapatinib	4%	
Herceptin + capecitabine	7%	
Kadcyla	50%	
PHD	27%	
PHD Perjeta Herceptin docetaxel PH Perjeta Herceptin *Second line market shares sum to 88%, the remaining 12% comprise a range of treatments comprising small percentages of market share each, these have not been included in the economic analysis. Therefore the 4 regimens above summing to 88% are scaled up to 100% for use within the model		

- **TRYPHAENA and GeparSepto**

The primary aim of the TRYPHAENA study was to assess the tolerability of neoadjuvant treatment with Perjeta and Herceptin plus chemotherapy, with a focus on cardiac safety as the primary endpoint of the study. This study was not included in the economic analysis as it was not powered to address any of the outcomes relevant to the economic case (pCR, DFS, PFS, OS). Furthermore, as all arms in the TRYPHAENA study were exposed to Perjeta, a comparator arm would have to be created, increasing the level of uncertainty as a result of the assumptions that would have to be made.

Similarly to TRYPHAENA, all patients in the GeparSepto study were exposed to Perjeta hence the issue of creating a comparator arm also existed. Moreover, the neoadjuvant treatment in GeparSepto was comprised of 10 cycles of Perjeta + Herceptin (2 cycles before biopsy and 8 cycles after the biopsy and before surgery), which does not allow comparison against 4 cycles of treatment within NeoSphere.

For the above reasons, TRYPHAENA and GeparSepto were not included in the economic case.

Table 76 below contains a summary of all the transitions used in the model and the sources/assumptions for each value. Each transition probability and its sources) is later described in more detail.

Table 76 Summary of the health state transitions used in the model

Transition	Transition probability	Source
EFS to EFS	Time dependent	Based upon tpCR observed in NeoSphere. Combined with long-term data from CTneoBC (Table 73)
EFS to LR	42% of events	Split observed in NeoSphere
EFS to MET (not prog.)	58% of events	Split observed in NeoSphere
LR to REM	100%	Assumption (was validated by an advisory board of clinical experts)
REM to MET (not prog.)	0.76 % per month	Hamilton 2014
MET (not prog.) to MET (prog.)	TD: 4.7% PHD: 3.17% (these values are weighted averages according to the individual market shares)	CLEOPATRA, weighted average between Perjeta and Herceptin (Calculation included in the economic model)
MET (prog.) to death	TD: 3.15% PHD: 2.73% Kad: 2.73% (these values are weighted averages according to the individual market shares)	CLEOPATRA, weighted average between Perjeta and Herceptin (Calculation included in the economic model)
Health states to death (excluding MET (prog.))	Age-dependent	UK general mortality (Ara and Brazier (2010)
Health states: EFS Event free survival, LR locoregional reccurance, MET (not prog) metastatic not progressed, REM remission MET (prog) metastatic progressed		

5.3.2 Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix and describe the details of the transformation of clinical outcomes or any other relevant details here

The hazards estimated using data from CTNeoBC meta-analysis and all other transition probabilities are described in Section 5.3.1

5.3.3 If there is evidence that (transition) probabilities may change over time for the treatment effect, condition or disease, confirm whether this has 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 cumulative hazard plots from the CTNeoBC analysis reveal that eBC patients progress monotonically at a diminishing rate (the slope of the cumulative hazards plot diminishes in both the pCR and no pCR arms) regardless of treatment.

An assumption in the economic base case is that people who have not progressed after 7 years would be considered event free and assumed to have a mortality rate equal to that of the age-matched general population. A Roche advisory board of UK clinicians confirmed that most recurrences from PFS happen within 2 or 3 years. This assumption results in a flattening of the EFS curve starting from the 7th year (see Figure 30). Furthermore, it is assumed that after 7 years the treatment effect in both arms is equal and there is no further benefit from receiving Perjeta. This timeframe was chosen as it only requires a conservative assumption of treatment effect for 2 years after the NeoSphere follow-up data. This conservative assumption reduces the need to predict the treatment effects beyond the duration of the CTNeoBC analysis data.

5.3.4 If clinical experts have assessed the applicability of the clinical parameters or approximated any of the clinical parameters, provide the following details:

- **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 whose opinion was sought**
- **the background information provided and its consistency with all 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).**

A Roche advisory board consisting of three clinicians and two health economists were consulted in the development of this submission and economic model.

The advisors noted that it was very positve that CTNeoBC study was sponsored by the FDA and had been published in the Lancet.

The assumption that patient's who did not progress after 7 years could be considered event free and therefore have the same mortality as the general population was also commented on by the experts, who noted that most recurrences occur within 2 or 3 years.

Finally, the advisory board also validated some of the resource use and health related costs. Where this is the case it is stated in the relevant section.

5.4 Measurement and valuation of health effects

Health-related quality-of-life data from clinical trials

5.4.1 If health-related quality-of-life (HRQL) data were collected in the clinical trials identified in section 4, comment on whether the data are consistent with the reference case. Consider the following points, but note that this list is not exhaustive:

- **method of elicitation**
- **method of valuation**
- **point when measurements were made**
- **consistency with reference case**
- **appropriateness for cost-effectiveness analysis**

- **results with confidence intervals**

The NeoSphere and TRYPHAENA studies did not collect quality of life measures. The phase III CLEOPATRA study, collected disease specific quality of life measurements (FACT-B), but could not be used as no mapping function exists for FACT-B to EQ-5D.

Mapping

5.4.2 If applicable, describe the mapping methods used to estimate health state utility values from the quality-of-life data collected in clinical trials. Please include the following information:

- **which tool was mapped from and onto which other tool (for example, SF–36 to EQ–5D)**
- **details of the methodology used**
- **details of validation of the mapping technique**
- **if the mapping technique is published or has been used in other NICE technology appraisals for similar diseases or health conditions.**

Please see above.

Health-related quality-of-life studies

5.4.3 Describe how systematic searches for relevant HRQL data were done. Consider published and unpublished studies, including any original research commissioned for the 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 an appendix

Search strategy development

The search strategy was developed using a combination of free text, MEDLINE MeSH and EMBASE EMTREE terms, as appropriate for the databases included. Briefly, the search terms in the strategy included:

- Disease state terms; and
- Health-related quality of life (HRQoL) or health state utility (HSUV) terms.

Restrictions were incorporated in the search strategy, including:

- Limited to English language publications.

Data sources

The following databases were searched, in line with best practices [CHSRI 2011; CRD 2009]:

- MEDLINE® and MEDLINE® in-process (OVID SP); and
- EMBASE (OVID SP).
- NHS Economic Evaluations Database (NHS EED); and
- EconLit.

Search strategies for MEDLINE® and EMBASE were implemented using the OVID portal to access the electronic databases. Full search strategies are presented in Appendix 9 Search strategy for the systematic literature review for the economic model.

Search implementation date and span

The date span of the search strategies, and the date the searches were conducted are described in Table 77 below:

Table 77 Search span and dates of search strategy implementation for the HRQoL and HSUV SLR

Database	Date of Search	Dates Span of Search
Medline® and Medline® In-Process	12 Nov 2015	1946 to 10 Nov 2015
EMBASE	12 Nov 2015	1974 to 10 Nov 2015
EconLit	12 Nov 2015	1886 to Oct 2015
Cochrane Library	12 Nov 2015	NR

Study selection process

A review of publications by two independent reviewers was conducted, consisting of a title and abstract review, and a further review of full-text articles that were not excluded during the title and abstract review phase. Full-text articles were reviewed until all articles were classified as either ‘included’ or ‘excluded’ in the same manner as described in Section 5.1.1. Reasons for exclusion during the full-text review were

recorded and documented in a PRISMA flow diagram, as recommended by the PRISMA guidelines. [Moher 2010]

Discrepancies between reviewers were resolved by consensus or by a third party adjudicator if consensus could not be reached.

Inclusion criteria

Table 78 outlines the inclusion criteria for the HRQoL and HSUV review, as defined using an adaptation of the PICOS framework [CHSRI 2011].

Table 78 Inclusion criteria

	Inclusion criteria
Population	Adults with HER2-positive, locally advance, inflammatory, or early stage breast cancer
Intervention	Neoadjuvant therapy
Outcomes	HRQoL, reported utilities or scores derived using preference based measures of health as measured using generic instruments (SF-36, HUI II/III, EQ-5D)
Study design	Only primary publications will be considered

Abbreviations: **EQ-5D** – EuroQol 5 Dimensions; **HER2** – human epidermal growth factor receptor 2; **HRQoL** – health-related quality of life; **HUI** – Health Utility Index; **N/A** – not applicable; **SF-36** – Short Form 36.

In addition articles were included if they were published in the English language.

Exclusion criteria

Publications were excluded based on the following criteria:

- Disease area not of interest;
- Study design or publication format not of interest, including:
    - Secondary publications;
    - Review articles, systematic literature reviews or meta-analyses;
    - Editorials or notes or letters to the editor;
    - Conference proceedings; and
    - Studies containing no primary data.

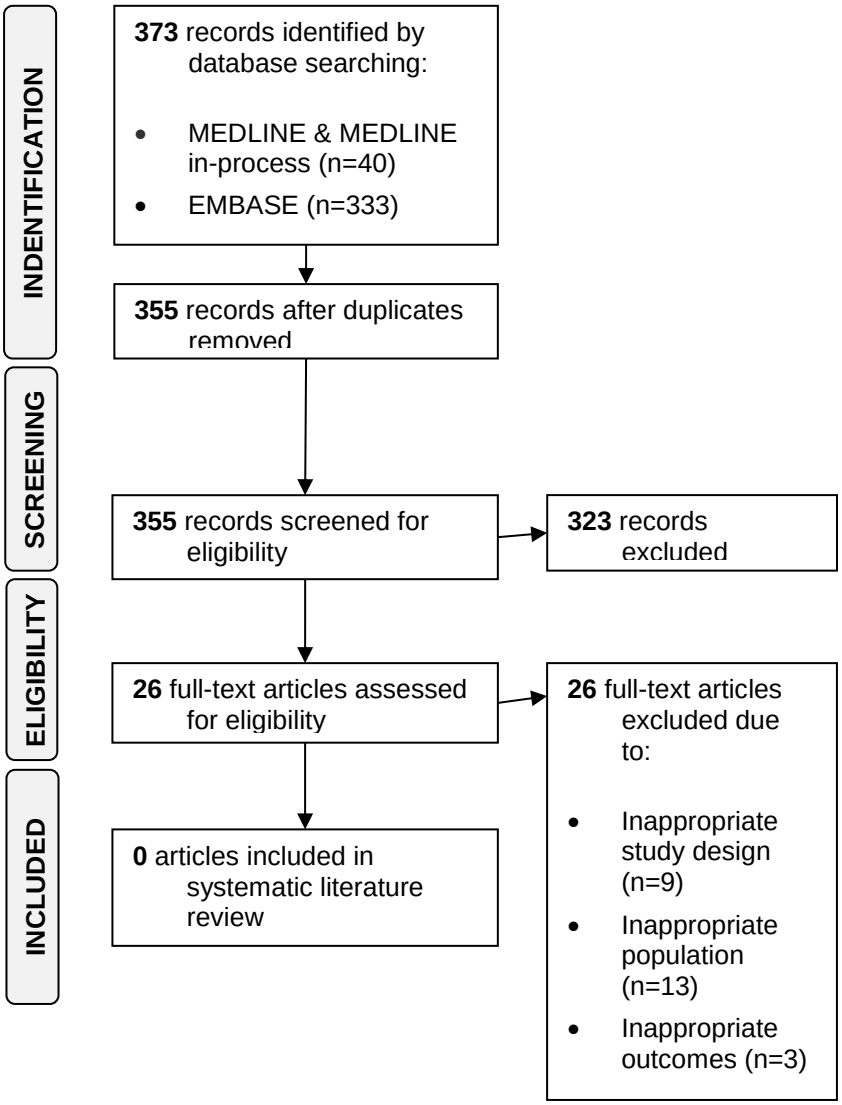
Details of included studies

No studies identified from the search strategy and reviewed met the eligibility criteria for inclusion (Figure 31). Additionally, the HSUV used in the Attard CEA (refer to

section 5.1) described HSUV during adjuvant chemotherapy [Hillner 1991; Smith 1993; Hristova 1997], and therefore did not meet the eligibility criteria for inclusion.

Lidgren 2007 was not was identified in the search strategy although it is a relevant study (that was included in the economic analysis). The reason for this being that the article title/abstract do not include the relevant expressions from the search strategy (i.e. neoadjuvant). The only mention that relates it to eBC is the expression “Patients in their first year after a primary breast cancer…”.

Figure 31 PRISMA diagram depicting study selection process of HRQoL and HSUV studies



5.4.4 Tabulate the details of the studies in which HRQL was measured. Include the following, but note that this list is not exhaustive:

- **population in which health effects were measured**
- **information on recruitment (for example, participants of a clinical trial, approximations from clinical experts, utility elicitation exercises including members of the general public or patients)**
- **interventions and comparators**
- **sample size**
- **response rates**
- **description of health states**
- **adverse reactions**
- **appropriateness of health states given the condition and treatment pathway**
- **method of elicitation**
- **method of valuation**
- **mapping**
- **uncertainty around values**
- **consistency with reference case**
- **appropriateness for cost-effectiveness analysis**
- **results with confidence intervals**
- **Appropriateness of the study for cost-effectiveness analysis.**

No studies were selected from the systematic literature review as noted on the PRISMA diagram on section 5.4.3.

5.4.5 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 derived/mapped from the NeoSphere, TRYPHAENA or CLEOPATRA studies.

Adverse reactions

5.4.6 Describe how adverse reactions affect HRQL. The effect of adverse reactions on HRQL should be explored regardless of whether they are included in a cost-effectiveness analysis in the base-case analysis. Any exclusion of the effect of adverse reactions on HRQL in the cost-effectiveness analysis should be fully justified.

Perjeta in the neoadjuvant setting has a largely manageable safety profile with very few life-threatening adverse events. AEs were similar between the intervention and comparator arm and disutilities for AEs were therefore not applied to either arm of the decision analytic model. Moreover, the treatment duration is very short (12 weeks) and therefore any disutilities would have a very limited impact on the economic results, or if taken into account across the whole time horizon could result in flawed economic results.

In relation to metastatic progressed patients, the Lloyd's mixed model (that estimates independent predictors of utilities such as AEs) was used for this health state (Lloyd 2006 will be further discussed in the next section).

The Lidgren study utilised data from early breast cancer patients and so can be assumed to capture within the utlity values the impact of adverse events. This study informs the utility estimates for EFS, and metastatic not progressed health states.

Health-related quality-of-life data used in cost-effectiveness analysis

5.4.7 Define what a patient experiences in the health states in terms of HRQL in the cost-effectiveness analysis. Explain how this relates to the aspects of the disease or condition that most affect patients' quality of life.

Patient experience is described in section 3.2.

5.4.8 Clarify whether HRQL is assumed to be constant over time in the cost-effectiveness analysis. If not, provide details of how HRQL changes over the course of the disease or condition.

The model predicts the cost-effectiveness of PHD over a long time horizon. The utility value in the general population decreases with increasing age, as a result of increasing number of comorbidities. Utility values of the general UK population [Ara

and Brazier 2010] were used to capture this natural decline. The minimal method was used to adjust the utilities. In this method, the utility for each health state is caped to the UK background utility values for a certain age as it is assumed that patients cannot have a higher utility than the general population.

5.4.9 If appropriate, describe whether the baseline HRQL assumed in the cost-effectiveness analysis is different from the utility values used for each of the health states. State whether quality-of-life events were taken from this baseline.

The baseline quality of life has been assumed similar in both treatment arms of the economic evaluation.

5.4.10 If the health state utility values used in the cost-effectiveness analysis have been adjusted, describe how and why they have been adjusted, including the methodologies used.

Health state utilities were not adjusted.

5.4.11 Identify any health effects found in the literature or clinical trials that were excluded from the cost effectiveness analysis and explain their exclusion.

No studies were identified.

5.4.12 In a table, summarise the utility values chosen for the cost-effectiveness analysis, referencing values obtained in sections 5.4.1–5.4.6. Justify the choice of utility values, giving consideration to the reference case. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed. See below for a suggested table format.

No article evaluating the quality of life of breast cancer patients in the neoadjuvant setting was identified in the systematic literature review. Two utility studies were identified that were used in previously published cost-effectiveness studies and were used within the economic model. Details of the studies are summarised in Table 79.

Table 79 Utility studies in early and metastatic breast cancer

	Lidgren 2007	Lloyd 2006
Population	345 patients in a cross-sectional observational study in Sweden (mean age 57 years old)	100 general UK public
Elicitation methods	EQ-5D index and Time Trade Off	Standard Gamble
Data set	Patient groups defined by disease status	Vignettes of metastatic breast cancer with different responses and side effects.
Disease area/treatment	Breast cancer	Metastatic breast cancer
Utility estimate	• First year after primary breast cancer = 0.696 (95% CI: 0.634–0.747) • First year after breast cancer recurrence = 0.779 (95% CI: 0.700–0.849) • Second or consecutive year after diagnosis or recurrence = 0.779 (CI: 0.745–0.811) • metastatic disease = 0.685 (95% CI: 0.620–0.735)	Progression-free survival stable = 0.715, treatment response = +0.075, disease progression = -0.272, and other decrements for side effects.

The utilities used in this model derived from two sources depending on the health states. Lidgren (2007) provided the utilities for the 'event free', 'locoregional', and 'metastatic non-progressed' health states. Lloyd (2006) provided the utility for the metastatic progressed health state. An assumption was made regarding the utility of the 'remission' state. Each of the studies/assumptions is described below:

Lidgren (2007)

Lidgren used the EQ-5D index and a direct Time Trade-off (TTO) questionaire to measure the preferences of 345 patients in a cross-sectional observational study in at one study site in Sweden. The utilities used in the model are as follows:

- 'Event free' state (first year) – Lidgren (2007) reported a mean utility value of 0.696 (95% CI: 0.634–0.747) for patients who were diagnosed with breast

cancer and had no metastatic disease of recurrence within one year or less prior to answering a questionnaire. The negative effects of the surgery, treatment and the acknowledgement of a potentially fatal disease that follow in the first year after a primary breast cancer (or recurrence) may justify this low QoL. The use of taxanes may also contribute to this lower utility.

- 'Event free' state (after first year) – A mean utility of 0.779 (95% CI: 0.700–0.849) was reported in Lidgren at al. (2006) which averaged the utility scores of patients that experienced at least one recurrence, had no metastatic disease, and were treated with adjuvant chemotherapy, with those that had been diagnosed with a primary breast cancer, no-metastatic disease and received adjuvant hormone treatment.

- 'Metastatic not-progressed' state – Lidgren (2007) assigned a utility value of 0.685 (95% CI: 0.620–0.735) for patients in a 'metastatic' state. The study noted that the adverse effects and the psychological aspects that follow the acknowledgement of being diagnosed with metastatic cancer and the effects of treatment were expected to negatively impact the HRQoL compared to both the general population as well as patients in previous health states.

Assumptions based on Lidgren (2007)

- 'Remission' state – A utility of 0.779 (95% CI: 0.700–0.849) is assigned to this health state assuming it is as that of the 'Event free' state (after first year) state. This utility value is chosen as patients in remission are thought to be disease free and off treatment. Hence, the utility is assumed to be similar to those patients in the 'Event free' state (after first year) state.

- 'Locoregional recurrence' state - It was assumed that patients in this health state had the same utility of the 'event free' state at the first year (0.696; 95% CI: 0.634–0.747), as patients in the 'locoregional recurrence' health state are undergoing a treatment (e.g. with taxanes) they may experience similar AEs to patients in the 'event free' (first year) state.

Lloyd (2006)

Lloyd (2006) reports the results of 100 participants asked to value various health states and side effects associated with metastatic breast cancer using the Standard Gamble technique. 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 previous NICE Technology Appraisals in metastatic breast cancer (Fleeman 2010).

As previously noted, the utility for the progressed metastatic health state was calculated through the results of the mixed model analysis presented by Lloyd. The central estimates of the parameter coefficients (and their standard errors) for the Lloyds model are listed below in Table 80.

Table 80 Lloyd's model parameter coefficients

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

- 'Metastatic progressed' state – a utility of 0.452 was calculated using the mixed model from Lloyd (2006).

The utility values used in the model are summarised in Table 81.

Table 81 Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)
HS: Event free (first year)	0.696	0.634–0.747	Lidgren (2007)
HS: Event free (after first year)	0.779	0.700-0.849	Lidgren (2007)
HS: Locoregional (after first year)	0.696	0.634–0.747	Assumption
HS: Remission	0.779	0.700-0.849	Assumption
HS: Metastatic not-progressed	0.685	0.634–0.747	Lidgren (2007)
HS: Metastatic progressed	0.452	-	Lloyd (2006)

Adverse events

Utilities have not been adjusted to account for the incidence of adverse events; for two reasons. Firstly, most AEs reported in the NeoSphere trial were primarily associated with chemotherapy and therewas only a small difference in the incidence of adverse events between treatment arms; hence, adjusting for utilities would only have had a small impact on the results. Secondly, the values by Lidgren et al were collected in breast cancer patients who had undergone treatment and therefore experienced AEs. It is therefore most likely that these values already capture the effect of adverse events.

5.5 Cost and healthcare resource use identification, measurement and valuation

Resource identification, measurement and valuation studies

5.5.1 All parameters used to estimate cost effectiveness should be presented clearly in a table with details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

5.5.2 Describe how relevant cost and healthcare resource use data for England were identified. Include the search strategy and inclusion criteria, and consider published and unpublished studies to demonstrate how

relevant cost and healthcare resource use data for England were identified. The search strategy used should be provided in an appendix. If the systematic search yields limited

- **data for England, the search strategy may be extended to capture data from**
- **other countries. Please give the following details of included studies:**
- **country of study**
- **date of study**
- **applicability to clinical practice in England**
- **cost valuations used in the study**
- **costs for use in the economic analysis**
- **technology costs.**

A systematic literature review was conducted to identify relevant UK-specific costs or resource use estimates that could be included in the CEA.

Systematic literature review of cost and resource utilisation

Search strategy development

Due to similarities in search terms and selection criteria, the search strategy employed was the same as the search strategy described in Section 5.1. The search strategy consisted of a combination of free text, MEDLINE MeSH and EMBASE EMTREE terms, as appropriate for the databases included. Briefly, the search terms in the strategy included:

- Relevant medicinal products (Perjeta);
- Disease state terms; and
- Economic terms.

Restrictions included:

- Limited to English language publications; and

- Removal of animal studies.

The full search strategy, including number of hits returned from each step, is available in Appendix 9 Search strategy for the systematic literature review for the economic model.

Data sources

In keeping with the recommendations and requirements of major HTA bodies, the CRD and Cochrane Collaboration practices [CHSRI 2011; CRD 2009], the following databases were searched for relevant studies:

- MEDLINE® and MEDLINE® in-process (OVID SP);
- EMBASE (OVID SP);
- NHS Economic Evaluations Database (NHS EED); and
- EconLit.

Search strategies for MEDLINE® and EMBASE were implemented using the OVID portal to access the electronic databases. Full search strategies are presented in Appendix 9 Search strategy for the systematic literature review for the economic model.

Search implementation date and span

The date span of the search strategies, and the date the searches were conducted are described in Table 82 .

Table 82 Search span and dates of search strategy implementation for the CEA, costs and resource use SLR

Database	Date of Search	Dates Span of Search
Medline® and Medline® In-Process	12 Nov 2015	1946 to 10 Nov 2015
EMBASE	12 Nov 2015	1974 to 10 Nov 2015
EconLit	12 Nov 2015	1886 to Oct 2015
Cochrane Library	12 Nov 2015	NR

Study selection process

Two independent reviewers conducted the review of identified articles, consisting of a title and abstract review, and a further review of full-text articles that were not excluded during the title and abstract review phase. Full-text articles were reviewed

until all articles were classified as either 'included' or 'excluded' in the same manner as described in Section 5.1.1. Reasons for exclusion during the full-text review were recorded and documented in a PRISMA flow diagram, as recommended by the PRISMA guidelines. [Moher 2010].

Discrepancies between reviewers were resolved by consensus or by a third party adjudicator if consensus could not be reached.

Inclusion criteria

The inclusion criteria were defined using an adaptation of the PICOS framework, as described in The Cochrane Collaboration Handbook (Table 83) (CHSRI 2011).

Table 83 Inclusion criteria for the Cost and Resource use Systematic review

	Inclusion criteria
Population	Adults with HER2-positive, locally advance, inflammatory, or early stage breast cancer
Intervention	Any neoadjuvant or adjuvant therapy
Outcomes	UK-specific resource use; UK-specific direct medical costs; UK-specific direct non-medical costs; UK-specific indirect costs.
Study design	Full economic evaluations
Abbreviations: **HER2** – human epidermal growth factor receptor 2; **N/A** – not applicable.	

Additionally, articles were required to be a primary publication in the English language article published in a peer-reviewed journal.

Exclusion criteria

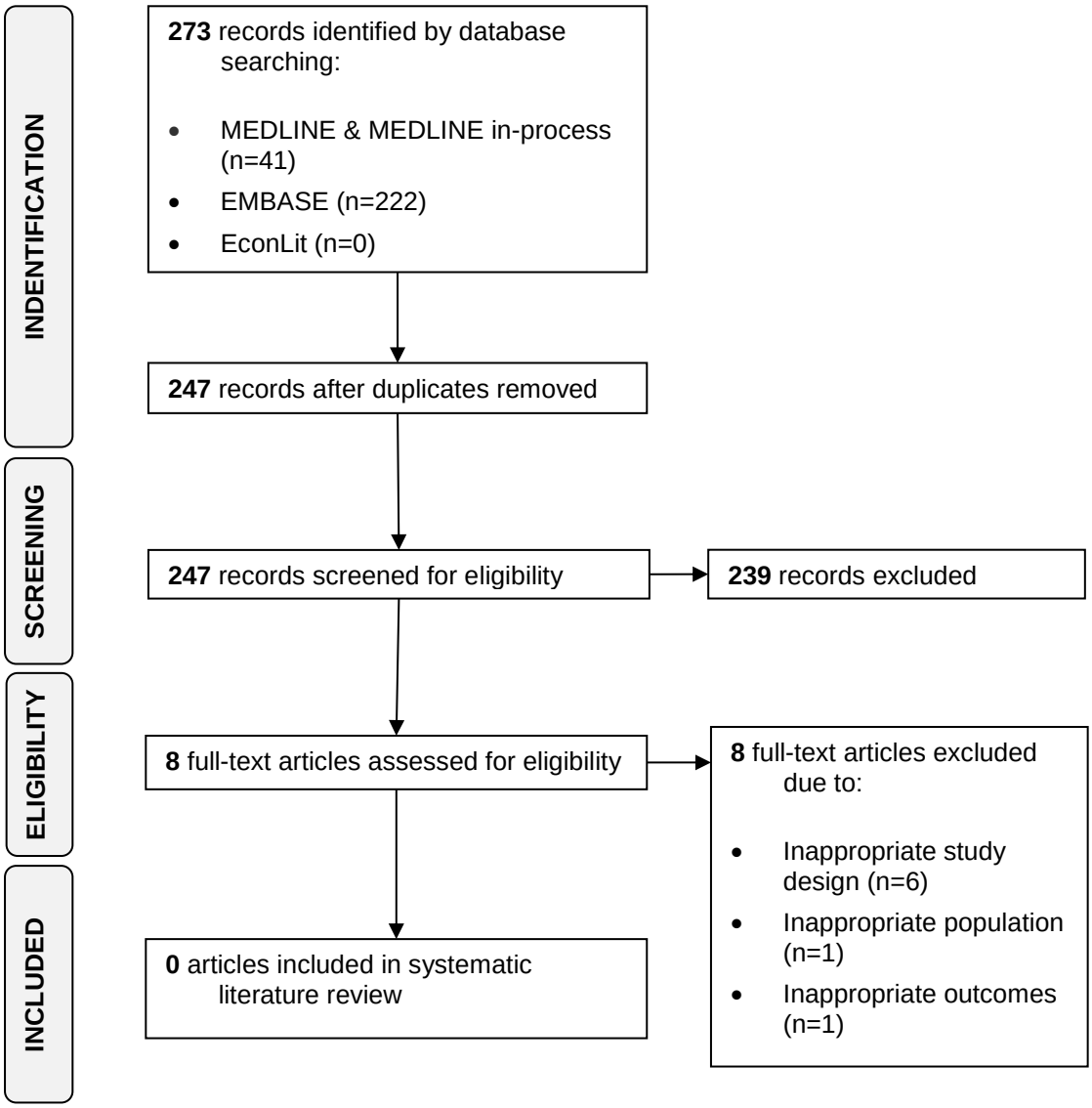
Publications were excluded based on the following criteria:

- Disease area not of interest;
- Study design or publication format not of interest, including:
    - Secondary publications;
    - Review articles, systematic literature reviews or meta-analyses;
    - Editorials or notes or letters to the editor;
    - Conference proceedings; and
    - Studies containing no primary data.

Details of included studies

The search conducted for cost and resource use outcomes did not yield any eligible articles for inclusion (Figure 32). One CEA fitting the inclusion criteria was identified; however, it was conducted in a Canadian setting and did not report UK-specific costs or resource use.

Figure 32 PRISMA diagram for costs and resource use SLR



5.5.3 When describing how relevant unit costs were identified, comment on whether NHS reference costs or payment-by-results (PbR) tariffs are appropriate for costing the intervention being appraised. Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the PbR tariff. Provide the relevant

Healthcare ResourceGroups and PbR codes and justify their selection with reference to section 2.

Treatment pathways, including follow up care, for people with early and locally advanced breast cancer are described in NICE guideline CG80 (2009). Management of advanced breast cancer is described in NICE guideline CG81 (2009 updated 2014). NHS reference costs and unit costs are therefore the most appropriate source of cost data for this appraisal for drug administration cost (see Table 86, Table 88 and Table 89) and supportive care (Table 90, Table 91, Table 92 and Table 93).

5.5.4 If clinical experts assessed the applicability of the cost and healthcare resource use values available, or approximated any of the values used in the cost-effectiveness analysis, provide the details (see section 5.3.4).

Where clinical experts commented on the relevance of costs and resources this is noted within the each individual section of the submission.

Intervention and comparators' costs and resource use

5.5.5 In a table, summarise the cost and associated healthcare resource use of each treatment. A suggested format for a table is provided below. Cross refer to other sections of the submission; for example, drugs costs should be cross-referenced to section 2.3.1. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 5.2.2.

The costs for drug acquisition, drug administration and monitoring for neoadjuvant and adjuvant treatment are summarised in Table 84 below.

Table 84 Costs for neoadjuvant and adjuvant treatment

Items	Intervention: (PHD)	Comparator: (HD)	Reference in submission
Perjeta (4 cycles neoadjuvant treatment)	£11,975	-	Table 85 section 2.3.1
Herceptin (4 cycles neoadjuvant)	£5,161	£5,161	Table 85
Docetaxel (4 cycles neoadjuvant)	£215	£215	Table 85
3 cycles of FEC (Fluoruracil, Epirubicin and Cyclophosphamide) neoadjuvant	£122.4	£122.4	Table 85
Administration Cost - 4 cycles neoadjuvant	£850.4	£850.4	Table 86
Mean drug and administration cost of neoadjuvant treatment treatment	£18,324	£6,349	Sum of above
Herceptin – up to 13 cycles adjuvant	£1,191 per cycle	£1,191 per cycle	Table 85
Administration Cost – up to 13 cycles adjuvant	£174.6 per cycle	£174.6 per cycle	Table 86
PHD Perjeta, Herceptin, docetaxel, HD Herceptin, docetaxel			

Drug acquisition costs

Brand-name drugs costs were taken from British National Formulary (BNF 2015). Acquisition costs for generic drugs are obtained from the Commercial Medicines Unit 2014 electronic Market Information Tool (CMU eMIT 2014). 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 prices reported in the CMU eMIT differ slightly between vial sizes. The price used in the model is based on the vial size that is reported as used most frequently.

Drug costs are based on the UK average measures (weight of 73.10kg, height of 162.8cm and consequent BSA of 1.79m^2). As Perjeta is a flat dose and many of the drugs are generic the effect of varying the weight and height has a very small impact on the cost effectiveness results. A summary of the per-cycle drug costs for neoadjuvant and adjuvant treatment is presented in Table 85.

Table 85 Drug costs for neoadjuvant and adjuvant treatments

	Per cycle £ (vial share) BASE CASE	**Per cycle £ (no vial share)**	**Dose based on / no of cycles**
Perjeta	£4,790 initial (2x 420 mg) £2,395 cycle 2+(1 x 420 mg)	Equal to base case	Flat dosing q3w Initial dose 840mg, cycle 2+ 420mg
Herceptin	£1588 initial (3.90 x 150 mg) £1,191 cycle 2+ (2.92 x 150 mg)	£1,629.6 initial (4 x 150 mg) £1,222.2 cycle 2 +(3 x 150 mg)	8mg/kg initial dose 6mg/kg cycle 2+ q3w
Docetaxel (generic)	£43.09 initial (134.25 mg) £57.28 cycle 2+ (179 mg)	£43.09 initial (134.25 mg) £57.28 cycle 2 + (179 mg)	75mg/m^2 initial and cycle 2-4 Cycle 2+ can increase up to a maximum of 100mg/m^2 q3w
PHD + FEC **total**	£6,421 initial cycle (FEC included) £3,643.28 cycle 2+	£6,462.6 initial £3,674.48 cycle 2+	
Herceptin + docetaxel + FEC **total**	£1672 initial (FEC included) £1248.28 cycle 2+	£1672.6 initial £1279.48 cycle 2+	
FEC total (generic) 5-Fluorouracil Epirubicin Cyclophosphamide	£40.8 £1.43 £21.7 £17.67	£40.8 £1.43 £21.7 £17.67	3 cycles 600 mg/m^2 90 mg/m^2 600 mg/m2
PHD Perjeta, Herceptin, docetaxel PH Perjeta, Herceptin			

Perjeta costs £2,395 per 420 mg vial (BNF, 2015). It is given as a flat dose and administered as IV infusion. As in the NeoSphere trial, it is assumed that PHD would be administered as a day case for four cycles prior to surgery. The recommended initial dose is 840 mg and costs £4,790. Subsequent doses are recommended to be 420 mg costing £2,395. Four cycles of neoadjuvant treatment costs are therefore £11,975.

Herceptin costs £407.40 for 150 mg vial (BNF, 2015). As in the NeoSphere trial, it is assumed that Herceptin would be administered as a day case for four cycles prior to surgery in both arms. A further 13 cycles of Herceptin would be administered post-surgery a part of the adjuvant therapy (to bring the total Herceptin received pre- and post-surgery to a full year). The recommended initial loading dose of Herceptin is 8 mg/kg. The recommended maintenance dose at three-weekly intervals is 6 mg/kg body weight, beginning three weeks after the loading dose (CMU SPC, 2015). Based on the average patient weight, the mean number of vials is 3.9 x 150 mg vials for initial dose and 2.92 x 150 mg vials for maintenance, respectively.

Due to the volume of Herceptin utilisation within the early and locally advanced adjuvant (NICE TA 107), it is assumed that the majority of centres will vial share and thus keep wastage to a minimum. Discussions with clinical experts indicate that many centres currently use vial sharing practices to eliminate wastage. Given the current economic pressures facing the NHS it is anticipated that these vial sharing programs will continue to expand as health boards seek to make the efficiency savings required of them.

The cycle costs as per license are £1,588.32 for the initial dose and £1,191.24 for the subsequent doses as part of eBC treatment.

Docetaxel is a generic drug. The initial recommended dose of docetaxel is 75 mg/m^2. Subsequent doses may be escalated to 100 mg/m^2. In NeoSphere subsequent doses were escalated to 100 mg/m^2 if no limiting toxicity occurred. As in the NeoSphere trial, it is assumed that docetaxel would be administered as an outpatient for four cycles prior to surgery in both arms. The price used in the model is £0.32 per mg (national product code DHC029). The mean cycle cost as per license is £43.09 for the initial dose and £57.28 for subsequent doses.

FEC (5-fluoruracil + epirubicin and cyclophosphamide). In addition to receiving Herceptin + docetaxel or Perjeta + Herceptin + docetaxel, people in the UK are typically given 3 cycles of FEC (5-fluoruracil + epirubicin and cyclophosphamide) either pre- or post-surgery as part of their treatment for early breast cancer. As in NeoSphere, it is assumed that patients would receive 3 cycles of FEC post-surgery

alongside Herceptin. It is also possible that three cycles of FEC are administered prior to surgery.

5-fluorouracil is a generic drug. The recommended dose of fluorouracil is 600mg/m^2. The cost used in the model is £0.001 per mg (national product code DHA265). The mean cycle cost as per license is £1.

Epirubicin is a generic drug. The recommended dose of epirubicin is 90 mg/m^2. The cost used in the model is £0.14 per mg (national product code DHA086). The mean per cycle cost as per license is £21.7.

Cyclophosphamide is a generic drug. The recommended dose of cyclophosphamide is 600 mg/m^2. The cost per mg is £0.02 (national product code DHA014). The mean per cycle cost as per license is £17.67.

In the base case it has been assumed that vial sharing occurs for Herceptin and also for the generic medicines as these are in regular use. Since Perjeta is a flat dose independent of patient weight or BSA, vial sharing is irrelevant. Table 85 shows that assuming no vial sharing of Herceptin has a minimal impact on cost and increases the cost of a cycle of PHD by £41.6 for the initial cycle and £29.28 for subsequent cycles.

Administration and Pharmacy costs

There is a cost associated with both the pharmacy preparation of the infusion and the administration of the technologies. The administration cost of the first cycle for each technology is based on NHS Reference costs 2013/14 (SB13Z): Deliver more Complex Parenteral Chemotherapy at First Attendance (Chemotherapy Delivery: Day case and Regular Day / Night). The administration cost of subsequent cycles is obtained from NHS Reference costs 2013/14 (SB12Z): Deliver simple Parenteral Chemotherapy at First Attendance (Chemotherapy Delivery: Outpatient). It is assumed that all technologies are administered under the same NHS Reference cost code for subsequent cycles.

The dispensing and preparation of the treatments within the economic model is assumed to take 12 minutes each. This is based on a prospective time-and-motion

study conducted in two UK secondary care NHS Trusts, which quantified the time taken to prepare and administer XELOX (capecitabine in combination with oxaliplatin) and FOLFOX-6 (5-FU in combination with folinic acid and oxaliplatin) in metastatic colorectal cancer (Millar 2008). The results of the study indicate that dispensing of capecitabine and preparation of oxaliplatin (administered intravenously) requires an average of 12 minutes each.

One hour of pharmacist time performing patient related activities (accounting for overheads, qualifications, and salary on costs) costs £48. The cost of dispensing of treatments in the economic model is estimated to be £9.60 (£48 x12 / 60) per administration, based on 12 minutes of pharmacist preparation time.

Administration costs for 1st and subsequent cycles are summarised in Table 86.

Table 86 Administration costs of chemotherapy

	1st cycle	**NHS reference costs 2013/14**	**2+ cycle**	**NHS reference costs 2013/14**
Chemotherapy delivery	£317	SB13Z Deliver complex parenteral chemotherapy (daycase)	£165	SB12Z Deliver simple parenteral chemotherapy (outpatient)
Pharmacy preparation	£9.60	PSSRU 2014 pharmacist time £48/hour 12m x £48/60m	£9.60	PSSRU 2014 pharmacist time £48/hour 12m x £48/60m
Total	**£326.60**		**£174.60**	

Health-state unit costs and resource use

5.5.6 Summarise and tabulate the costs included in each health state. A suggested format for a table is provided below. Cross refer 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 5.2.2.

Table 87 contains a summary of the health state costs in the model. Details are described in the following sections.

Table 87 Summary of health state costs

Health states	Items	Average monthly cost per patient	Reference in submission
Event Free Survival (Neoadjuvant treatment)	PHD + FEC + administration costs	£6,107	Table 85 & Table 86
	HD + FEC + administration costs	£2,129.6	Table 85 & Table 86
	Supportive care† year 1+2	£67.85	Table 90
	Supportive care† year 3-5	£15.11	Table 90
	Supportive care† year 6 onwards	£3.83	Table 90
Event Free Survival (Adjuvant treatment)	H + administration costs	£1,365.6	Table 85 & Table 86
	Supportive care† year 1+2	£67.85	Table 90
	Supportive care† year 3-5	£15.11	Table 90
	Supportive care† year 6 onwards	£3.83	Table 90
Locoregional recurrence	Treatment (Herceptin)	£1,365.6	Table 88
	Supportive care††	£75.53	Table 91
Remission	Supportive care†	£67.85	Same as Supportive care EFS Y1
Metastatic not progressed	Treatment	£3,590,26	Table 88
	Supportive care†††	£232.8	Table 92
	Total	£3,823.06	
Metastatic progressed	Treatment	£5,738	Table 89
	Supportive care†††	£185.20	Table 93
	Total	£5,923.20	

† Includes GP visits, oncology specialist visits, mammograms and cardiac monitoring.
†† EFS supportive care plus CT scan.
††† Includes GP visits, oncology specialist visits, specialist nurse, community nurse, CT scans and cardiac monitoring.
PHD Perjeta, Herceptin, docetaxel HD Herceptin, docetaxel FEC 5-fluorouracil, Epirubicin, Cyclophosphamide

Post-Progression Treatments

Post-progression treatments are applied in both arms of the model in the locoregional recurrence, metastatic not progressed and metastatic progressed health states

Locoregional recurrence

The model assumes 100% of patients with locoregional recurrence receive Herceptin and Docetaxel. The model conservatively accounts for the cost of Herceptin only since the cost of docetaxel comprises a very small proportion of the cost.

Metastatic not progressed

In England, people routinely receive the following treatment options as first line (metastatic not progressed) therapy for their metastatic breast cancer regardless of prior treatment.

- Herceptin + docetaxel (HD)
- Perjeta with Herceptin and docetaxel (PHD)
- Herceptin + other (hormone with or without chemo)
- Costs for administration are included in the model.

Perjeta: dosing in mBC setting is identical to the neoadjuvant and adjuvant setting. Refer to drug cost section above for the per cycle cost of Perjeta (Table 84). It is assumed that Perjeta is given every 3 weeks until progression.

Herceptin: dosing in mBC setting is identical to the neoadjuvant and adjuvant setting. Refer to drug cost section above for the per cycle cost of Herceptin (Table 84). It is assumed that Herceptin is given until progression.

Docetaxel: Docetaxel costs have not been included in the locoregional health state and therefore the analysis may be conservative as the HD arm contributes with more patients to this health state

The costs of treatment for locoregional recurrence or metastatic not progressed disease per 21 day cycle and per month are summarised in Table 88.

Table 88 Drug and administration costs for locoregional recurrence and metastatic not progressed health states

	Per 21 day cycle	Source/Dose
Herceptin	£1,191 cycle 2+	Refer to Table 85 costs for neoadjuvant treatments
Herceptin + Docetaxel (HD)	£1,248.28	Refer to Table 85 costs for neoadjuvant treatments
PHD (PHD)	£3,643.27	Refer to Table 85 costs for neoadjuvant treatments
Administration costs	£174.6	PSSRU 2014 (based on 12 minutes of pharmacist time to dispense) NHS reference costs SB12Z Table 86
Treatment costs HD (treatment + administration costs)	£1,422.6	Calculated
Treatment costs PHD	£3,818	Calculated
	Per month	
Herceptin (locoregional recurrence)	£1,758	based on 12 month treatment (17.4 cycles).
Treatment costs mBC not progressed HD (treatment + administration costs)	£1,151	Calculated based on 21 day cycle length and weighted for market share of this regimen* (Table 75)
Treatment costs mBC not progressed PHD (treatment + administration costs)	£2,438	Calculated based on 21 day cycle length and and weighted for market share of this regimen* (Table 75)
Average treatment costs mBC not progressed (administration costs included)	£3,589	Calculated based on weighted for market shares for these regimens*
PHD Perjeta, Herceptin, docetaxel HD Herceptin docetaxel Market share information [data on file RXUKPERT00252] see Table 75		

Metastatic Progressed

If a person's metastatic disease progresses, treatment options costed in the model are:

- Herceptin with a taxane (docetaxel)
- Perjeta with Herceptin and docetaxel
- Kadcycla
- Capecitabine + Lapatinib

In addition to Perjeta, Herceptin and Docetaxel, Kadcyla was considered as an additional option in calculating the cost of treatment regimens for metastatic progressed disease.

Kadcyla: the recommended dose is 3.6 mg/kg bodyweight administered as an intravenous infusion every 3 weeks (21-day cycle). Patients are assumed to be treated until disease progression. Kadcyla is available as 100mg vials and 160 mg vials at list price of £1,641.01 and £2,625.62, respectively. Based on 73.10 kg average patient weight, the cost of one 21 day cycle are £4,318.5 (assuming vial sharing). Kadcyla is currently funded by the Cancer Drug Fund with a confidential discount to the list price.

The costs of treatment for metastatic progressed disease per 21 day cycle and per month are summarised in Table 89. The monthly cost is calculated using a weighted average according to the proportion of patients assumed to receive each of the treatments [Data on file RXUKPERT00252].

Lapatinib: The recommended dose of lapatinib is 1250 mg per day. The cost used in the model is £11.49 per 250mg tablet. The mean per cycle cost as per license is £2,155.21.

Capecitabine: is a generic drug. The recommended dose of capecitabine for a BSA of 1.79m2 is 2150mg twice daily for 14 days in each 21 day cycle. The mean per cycle cost as per license is £39.17. It is assumed that capecitabine is given until progression.

Table 89 Drug and administration costs for metastatic progressed heath state

	Per 21 day cycle	Proportion of patients (weight*)	Weighted average monthly costs (incl. administration)	Source/Dose
Herceptin + capecitabine	£1,233.2	7%	£157	Refer to Table 85
Perjeta, Herceptin, docetaxel	£3,643.3	27%	£1,707	Refer to Table 85
Kadcyla	£4,318.50	50%	£3,740	Based on 1.79m^2 BSA
lapatinib + capecitabine	£2,194.38	4%	£134	Lapatinib 1250mg per day Capecitabine 2150mg twice daily
Total Weighted average treatment costs			£5,738	Calculated
*Weighting from data on file RXUKPERT00252				

The first cycle administration costs within both progressed and not progressed metastatic health states were not included in the economic analysis. If included, these would have a minimal effect to lower the ICER.

Health state costs: Supportive care costs represent the services that are provided to patients with cancer and their carers throughout the patient pathway, from pre-diagnosis onwards. As patient's needs change with disease progression, these costs are based on several sources depending on the health states, e.g. 'event free', 'metastatic not progressed' and 'metastatic progressed' (an advisory board confirmed that it is reasonable to assume that costs in the locoregional recurrence and in the remissions states were similar to those in the first year 'event free' state).

Event free survival Costs: Family Practice visits (i.e. GP visits), Oncology Specialist visits, mammograms, and cardiac monitoring and have been applied in the

model for this health state. The cost of primary breast surgery which is undergone after neaoadjuvant therapy is not included in the economic analysis as this cost is assumed to be the same in both arms.

The frequency of mammograms was based on Clinical Guidance 80 from NICE that includes recommendations to the diagnosis and treatment of early and locally advanced breast cancer. In relation to cardiac assessment's costs, these are applied every 3 months in both arms and used in a weighted average of 30% MUGA scan (NHS Reference Cost 2013/14 - RA37Z: Nuclear Medicine – Category 3 Outpatient) and 70% ECHO scan (NHS Reference Cost 2013/14 - RA60A: Simple Echocardiogram, 19 years and over). Family practice visits and Oncologist Specialist visits are assumptions. Table 90 summarises the EFS costs.

Table 90 Event Free survival - Supportive Costs

Items	Frequency year 1&2 (annual)	Frequency year 3-5 (annual)	Subsequent years (annual)	Unit Cost per contact	Proportion treated (%)	Sources	
						Cost	Resource use
Oncologist Medical Specific Re-assessment	2	1	0	£124	100	*Service code 800	Assumption
Family Practice General Re-assessment	2	1	1	£46 (per 11.7 minute contact)	100	PRSSU 2014 Section 10.8B	Assumption
Mammogram	1	1	0	£11.34	100	NHS BSP	Clinical guideline 80
Cardiac Monitoring - ECHO Scan	4	0	0	£65	70	*RA60A code	**
Cardiac Monitoring- MUGA Scan	4	0	0	£234	30	*RA37Z code	**
Average monthly supportive care cost	**£67.85**	**£15.11**	**£3.83**				

References
*NHS Reference cost 2013/14
Service code 800 - Consultant Led: Follow up Attendance Non-Admitted Face to Face: clinical oncology
RA60A Simple Echocardiogram
RA37Z Nuclear Medicine Category 3
**NICE clinical guidelines CG 80, 30% MUGA:70% ECHO assumption + every 3 months and CT Scan every 3 months (assumption from LRiG TA257 - Table 25)

NHSBSP NHS Breast Screening Programme

These health state costs were also verified by clinicians at a Roche advisory board.

Locoregional recurrence health state costs: It is assumed that the supportive care costs are the same as those incurred in year 1 of EFS but with an additional cost of a CT scan (as shown in Table 91).

Table 91 Locoregional recurrence supportive costs

Items	Frequency (annual)	Unit Cost per contact (£)	Proportion of patients treated (%)	Cost Sources	Resource use sources
CT Scan	1	91	75	NHS Reference cost 2013/14 RA08A code	Advisory board; clinical guidance 81
Average monthly supportive care cost*	**73.97**				
*This cost is based on the average monthly cost of conducting a CT scan plus the average monthly cost of supportive care in year 1 if EFS (£67.85) RA08A Computerised Tomography Scan, one area, no contrast, 19 years and over					

In addition, it is assumed that people in the locoregional recurrence state would receive a further 12 months of Herceptin.

Remission health state cost: It is assumed that people in remission would incur the same health state costs as those in year 1-2 of EFS.

Metastatic health states (progressed and not-progressed) costs: Response to treatment is monitored and assessed via outpatient visits, CT scans, cardiac monitoring and health care practitioner time. These costs have been applied in the model. Furthermore, in clinical trials a CT scan is typically conducted every three months to assess whether a person's disease has progressed. Advice from clinicians indicated that the frequency of CT scans may be different in different centres. In light of this, and the assumptions made in previous NICE MTA Technology Appraisals and SMC Submissions, the model applies a conservative estimate of one CT scan and outpatient visit every three months during treatment. A CT scan in the model is associated with a cost of £91 (NHS Reference Cost 2013/14 (RA12Z: Computerised Tomography – two areas with contrast - Outpatient)) and the cost of an outpatient visit is £126 (NHS Reference Cost 2013/14 (service code 800: Consultant Led: Follow up Attendance Non-Admitted Face to Face: clinical oncology)).

The cost of cardiac assessment was calculated through 2 weighted averages. The first relates to the length of the interval of first line assessment needs (e.g. 9 and 12 months for the Perjeta and Herceptin arms respectively) from CLEOPATRA study. The second weighted average relates to the cost of cardiac assessments that were applied as a weighted average of 30% MUGA scan (NHS Reference Cost 2013/14 - RA37Z: Nuclear Medicine – Category 3 Outpatient) and 70% ECHO scan (NHS

Reference Cost 2013/14 - RA60A: Simple Echocardiogram, 19 years and over). This is based on previous clinical specialist advice to the Evidence Review Group in NICE MTA Technology Appraisal 257 - Lapatinib or trastuzumab in combination with an aromatase inhibitor for the first-line treatment of metastatic hormone-receptor-positive breast cancer that overexpresses HER2.

The supportive care costs for metastatic not progressed and metastatic progressed disease are summarised in Table 92 and Table 93, respectively.

Table 92 Metastatic not progressed supportive care cost

Items	Frequency (yearly)	Unit Cost per contact (£)	Proportion of patients treated (%)	Cost Sources	Resource use sources
Family Practice General Re-assessment	12	£46 (per 11.7 minute contact)	100	PRSSU 2014 Section 10.8B	Assumption
Cardiac Monitoring -ECHO Scan	4	£65	70	*RA60A code	**
Cardiac Monitoring-MUGA Scan	4	£234	30	*RA37Z code	**
CT Scan	Once only	£91	75	*RA08A code	Advisory board (March 2013); clinical guidance 81
Clinical nurse specialist	12	£90	100	PSSRU 2014 Section 10.7	Clinical guideline 81
Community Nurse (home visit)	22	£24.6 (20 minute contact)	100	PSSRU 2014 Section 10.4	Assumption
Social worker	1hr once	£79	100	PSSRU 2014	Assumption
Average monthly supportive care cost	**£232**				

References:
*NHS Reference cost 2013/14
RA60A Simple echocardiogram
RA08A Computerised Tomography Scan, one area, no contrast, 19 years and over
RA37Z Nuclear medicine category 3
**NICE clinical guideline 81, 30% MUGA:70% ECHO assumption + every 3 months and CT Scan every 3 months (assumption from LRiG TA257 - Table 25)

Table 93 Metastatic progressed supportive care cost

Items	Frequency (annual)	Unit Cost per contact (£)	Proportion of patients treated (%)	Cost Sources	Resource use sources
Family Practice General Re-assessment	12	£46 (per 11.7 minute contact)	100	PSSRU 2014 Section 10.8B	Assumption
Clinical nurse specialist	12	£90	100	PSSRU 2014 Section 10.8 B	Assumption
Community Nurse (home visit)	24	£24.6 (20 minute contact)	100	PSSRU 2014 Section 10.4	Assumption
Average monthly supportive care cost	**£185**				

Adverse reaction unit costs and resource use

5.5.7 Summarise and tabulate the costs for each adverse reaction listed in section 4.12 and included in the de novo cost-effectiveness analysis. These should include the costs of therapies identified in section 2.3. A suggested format for a table is provided below. Cross refer to other sections of the submission for the resource costs.

The number of surgical procedures related to breast cancer (excluding primary surgery) performed was 13 for the Herceptin + docetaxel arm and 11 surgeries for the PHD arm (data on file, CSR page 850).

Only adverse events occurring in more than 5% or more in either arm of NeoSphere trial at grade 3, 4 or 5 severity are incorporated into the model. 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. The cost associated with adverse events that occur in 5% or more people in either arm of the NeoSphere trial at grade 3, 4 or 5 severity are incorporated are outlined in Table 94 below:

Table 94 Adverse event costs included in the model

Adverse reactions	Grade	% people in PHD arm	% people in HD arm	Unit cost per episode	Reference: NHS reference costs 2013/2014
Diarrhoea (Grade 3)	3	6.54%	4.67%	£476	Malignant Breast Disorders with Major CC (reduced short stay emergency tariff) JA12E
Febrile Neutropenia (Grade 3 and 4)	3&4	7.48%	6.54%	£8,662	Febrile Neutropenia with Malignancy - Elective Inpatient HRG Data: PA45Z
Leucopenia (Grade 3)	3	7.48%	16.82%	£155	High Cost Drugs: Outpatient - Neutropenia Drugs, Band 1 XD25Z
Neutropenia (Grade 3 and 4)	3&4	67.29%	82.24%	£155	High Cost Drugs: Outpatient - Neutropenia Drugs, Band 1 XD25Z
Alopecia		5.61%	0.93%	£0	Not included (see explanation in text below)
PHD Perjeta Herceptin docetaxel HD Herceptin docetaxel					

The cost of managing Alopecia is assumed to be incurred only by the patient experiencing this adverse event and that no additional cost is incurred to the NHS. Therefore the cost of managing Alopecia is not included in the economic model.

Finally, adverse event costs for all progressive health states (loco-regional, metastatic not progressed and metastatic progressed were not included in the model. This is a conservative analysis that understimates the comparator arm costs and therefore artificially increases the ICER.

Miscellaneous unit costs and resource use

5.5.8 Describe and tabulate any additional costs and healthcare resource use that have not been covered elsewhere (for example, costs relating to subsequent lines of therapy received after disease progression, personal and social services costs). If none, please state.

None

5.6 Summary of base-case de novo analysis inputs and assumptions

Summary of base-case de novo analysis inputs

5.6.1 Tabulate all variables included in the cost-effectiveness analysis, detailing the values used, range (for example, confidence interval, standard error or distribution) and source. Cross refer to other parts of the submission. Complete the table below that summarises the variables applied in the economic model.

5.6.2 For the base-case de novo analysis the company should ensure that the cost-effectiveness analysis reflects the NICE reference case as closely as possible. Describe the rationale if an input chosen in the base-case de novo analysis:

- **deviates from the NICE reference case or**
- **is taken from other sources (such as the published literature) rather than data from clinical trials of the technology (when available).**

Table 95 Summary of variables applied in the economic model

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Source	Reference to section in submission
Demographics				
Age	50 years		NeoSphere trial	4.4.3
Weight	73.1 kg	SE 0.59	Health & Social Care Information Centre. Available at: http://www.hscic.gov.uk/catalogue/PUB16077 Based on women aged 45 – 54	5.5.5
Height	162.8 cm*	SE 0.22	Health & Social Care Information Centre. Available at: http://www.hscic.gov.uk/catalogue/PUB16077 Based on women aged 45 – 54	5.5.5
Model structure				
Time horizon	50 years	Not applied	Assumption	1.4 5.2.3 5.7.4
Discount rate for costs and outcomes	3.50%		NICE single technology appraisal user guide 2015	5.2.3
Time point when setting treatment effect equal	7 years		Assumption	5.3.3
Time point when switching to background mortality	7 years		Assumption	5.3.3
Transition probabilities				
Proportion of progressions that are loco-regional recurrences	42%	Beta distribution	NeoSphere trial	5.3.1
Proportion of progressions that are metastatic (distant recurrences)	58%	Beta distribution	NeoSphere trial	5.3.1
Met. (not progressed) to met progressed	TD: 4.70% PHD: 3.17%	Beta distribution	CLEOPATRA TRIAL	5.3.2

Met. Progressed to death	TD: 3.15% PHD: 2.73% KAD: 2.73%	Beta distribution	CLEOPATRA TRIAL Kadcyla probability of death as an assumption of equivalence to Perjeta	5.3.2
Risk of metastatic event for patients in remission	0.76%	SE 0.0012 (Beta) (Override SE 0.05)	Hamilton 2014	5.3.2
Patients achieving tpCR Herceptin, docetaxel	21.5%	CI: 14.1% - 30.5% (Beta)	NeoSphere trial	5.3.2 4.13 2.5.1 1.3
Patients achieving tpCR Perjeta, Herceptin and docetaxel	39.3%	CI:30% - 49.2% (Beta)	NeoSphere trial	5.3.2 4.13 2.5.1 1.3
Market shares				
First Line: metastatic not progressed				
Herceptin + docetaxel	20%	Not applied	Data on file RXUKPERT00252	5.5.6 5.3.1
Perjeta + Herceptin + docetaxel	44%			
Herceptin + other	36%			
Second Line: metastatic progressed				
Capectiabine + Lapatinib	4%	Not applied	Data on file RXUKPERT00252	5.5.6 5.3.1
Herceptin + capecitabine	7%			
Kadcyla	50%			
Perjeta + Herceptin + docetaxel	27%			
Locoregional treatment market share				
Herceptin + docetaxel	100.0%	Not applied	Assumption (validated at advisory board)	
Cost and resource use				
Metastatic not progressed supportive care cost (unit costs)				
Family Practice General	£46 (per 11.7	Not applied	PRSSU 2014 Section 10.8B	5.5.6

Re-assessment	minute contact)			
Cardiac Monitoring - ECHO Scan	£65		*RA60A code Simple echocardiogram	5.5.6
Cardiac Monitoring- MUGA Scan	£234		*RA37Z code Nuclear medicine category 3	5.5.6
CT Scan	£91		*RA08A code Computerised Tomography Scan, one area, no contrast, 19 years and over	5.5.6
Clinical nurse specialist	£90		PSSRU 2014 Section 10.8B	5.5.6
Community Nurse (home visit)	£24.6 (20 minute contact)		PSSRU 2014 Section 10.4	5.5.6
Social worker	£79		PSSRU 2014 Section 11.2	5.5.6
Metastatic progressed supportive care cost (unit costs)				
Family Practice General Re-assessment	£46 (per 11.7 minute contact)	Not applied	PSSRU 2014 Section 10.8B	5.5.6
Clinical nurse specialist	£90		PSSRU 2014 Section 10.8B	5.5.6
Community Nurse (home visit)	£24.6 (20 minute contact)		PSSRU 2014 Section 10.4	5.5.6
Locoregional recurrence supportive costs				
CT Scan	£91		NHS Reference cost 2013/14 RA08A code Computerised Tomography Scan, one area, no contrast, 19 years and over	
Event Free survival - Supportive Costs (unit costs)				
Oncologist Medical Specific Re-assessment	£124	25% to the mean Log normal distribution	*Service code 800 Consultant Led: Follow up Attendance Non-Admitted Face to Face: clinical oncology	
Family Practice General Re-assessment	46 (per 11.7 minute contact)		PRSSU 2014 Section 10.8B	
Mammogram	£11.34		NHS Breast Screening Programme	
Cardiac Monitoring -	£65		*RA60A code Simple echocardiogram	

ECHO Scan				
Cardiac Monitoring-MUGA Scan	£234		*RA37Z code code Nuclear medicine category 3	
Drug costs (unit costs)				
Perjeta per vial	£2,395	Not applied	BNF 2015 (branded medicines) CMU eMIT 2014 (generic)	5.5.5
Herceptin per vial	£407.4			
Docetaxel (generic) per mg	£0.32			
Fluorouracil per mg	£0.001			
Epirubicin per mg	£0.14			
Lapatinib per 250mg	£11.49			
Capecitabine per mg	£0.001			
Cyclophosphamide per mg	£0.02			
Adverse Events				
Diarrhoea (Grade 3)	£476	Log Normal distribution	*JA12E Malignant Breast Disorders with Major CC (reduced short stay emergency tariff)	5.5.7
Febrile Neutropenia (Grade 3 and 4)	£8,662		PA45Z Febrile Neutropenia with Malignancy - Elective Inpatient HRG Data. Health and Social Care Information Centre 2013/14	
Leukopenia (Grade 3)	£155		*XD25Z High Cost Drugs: Outpatient - Neutropenia Drugs, Band 1	
Neutropenia (Grade 3 and 4)	£155		*XD25Z High Cost Drugs: Outpatient - Neutropenia Drugs, Band 1	
Alopecia	£0		Not included (see explanation in 5.5.7)	
Utilities				

1st year after prim breast cancer	0.696	SE 0.06 (Beta)	Lidgren 2007	5.4
1st year after recurrence	0.779	SE 0.03 (Beta)	Lidgren 2007	5.4
Locoregional recurrence	0.696	SE 0.03 (Beta)	Lidgren 2007	5.4
Non-progressive metastatic disease	0.685	SE 0.06 (Beta)	Lidgren 2007	5.4
Progressive metastatic disease	0.452		Lloyd 2004	5.4
Remission	0.779	SE 0.03 (Beta)	Lidgren 2007	5.4
Outcomes				
Survival function used for PFS in both arms for base case	Gamma	Weibull Log-logistic Exponential Log Normal		5.3.1 5.8.6
CI, confidence interval *NHS Reference costs 2013/14				

Assumptions

5.6.3 Provide a list of all assumptions used in the de novo economic model and justify each assumption

A number of assumptions are required to make modelling this disease area feasible and to model beyond the existing data. Below is a list of the key assumptions made when constructing this model:

Table 96 Key assumptions in the model

Variable	Assumption	Justification/notes
Utilities	Patients cannot have a higher utility than the general population	The UK population QoL is usually expected be higher than that of a patient as they are assumed to be healthier
	The 'Remission' state utility (0.779) is assumed to be the same as the utility for the 'event free' after first year state.	Patients in remission are thought to be disease free and off treatment which is similar to those patients in the EFS after year 1 health state.
	The 'Locoregional recurrence' state utility (0.696) is assumed to be equal to that of the 'event free' state at the first year	Patients in the 'locoregional recurrence' health state are undergoing a treatment (e.g. with taxanes) and may experience similar AEs to patients in the 'event free' (first year) state
Costs and resource use	100% of patients with locoregional recurrence receive Herceptin and Docetaxel.	This assumption was validated by an advisory board The model conservatively accounts for the cost of Herceptin only.
	Patients in remission incur the same supportive health costs than those in year 1-2 EFS	Patients in this health state are assumed to be disease free and therefore have the same supportive care costs as EFS year 1-2 patients
	Supportive care costs for a patient in locoregional recurrence are the same as those incurred in year 1 of EFS but with an additional cost of a CT scan	This assumption was validated by an advisory board
	Cost of primary breast surgery is not included in the economic analysis	Cost is assumed to be the same in both arms
	Vial sharing occurs for Herceptin and also the generic medicines as these are in regular use.	Discussions with clinical experts indicate that many centres currently use vial sharing practices to reduce wastage. It is anticipated that these vial sharing programs will continue to expand as

		health boards seek to make the efficiency savings required of them Since Perjeta is a flat dose independent of patient weight or BSA, vial sharing is not relevant.
	As in the NeoSphere trial, it is assumed that PHD and HD would be administered as day cases for four cycles prior to surgery	HD is currrently administered as a day case. PHD is an add-on and should be administered likewise
	Dispensing and preparation of the treatments within the economic model is assumed to take 12 minutes	Based on a prospective time-and-motion study conducted in two UK secondary care NHS Trusts, which quantified the time taken to prepare and administer XELOX (capecitabine in combination with oxaliplatin) and FOLFOX-6 (5-FU in combination with folinic acid and oxaliplatin) in metastatic colorectal cancer (Millar 2008). The results of the study indicate that dispensing of capecitabine and preparation of oxaliplatin (administered intravenously) requires an average of 12 minutes each
	As in NeoSphere, it is assumed that patients would receive 3 cycles of FEC post-surgery alongside Herceptin	It is also possible that three cycles of FEC are administered prior to surgery.
Transitions	Patients cannot die during the locoregional recurrence tunnel states	Adding this probability would add complexity to the model. It is not expected that this simplification would have any impact in the economic results as the mortality would be that of UK general population, which is relatively low
	Upon completion of treatment for a locoregional recurrence, people are assumed to transition to the remission state. If an individual's disease returns whilst in the remission health state it is assumed to be a metastatic event	This was supported by an Advisory board
	All patients who experienced a locoregional recurrence would undergo one year of treatment with Herceptin and thereafter enter the remission state	This assumption was validated by an advisory board of clinical experts.
Efficacy	The efficacy of first line mBC	Other treatment efficacy data was not

	Herceptin + other treatments was similar to that of Herceptin + docetaxel	available therefore it was assumed the same efficacy of HD
	The probability of dying while on second line mBC Kadcyla was similar to that of second line Herceptin + docetaxel	Dataon the probability of dying available from EMILIA trial (that compared Kadcyla with Lapatinib and Capecitabine) for second line mBC produced very low ICERs. Given that there might be some heterogeneity, this probability was not included in the economic case. This analysis is conservative as Kadcyla extends overall survival compared to Herceptin and docetaxel
	mBC treatments are assumed to be administered every 3 weeks until progression	As per SmPC for Perjeta and Herceptin
	People only experience breast cancer related mortality once their disease has progressed in the metastatic phase; as a result death due to the disease only occurs from the 'metastatic progressed' health state.	The rate of dying from breast cancer observed in CLEOPATRA is used to model this transition probability. This assmption was made to simplify the model.
	After 7 years, the treatment effect in both arms is equal and there is no further benefit of receiving Perjeta.	This timeframe was chosen as it only requires conservative assumption of treatment effect for 2 years after the NeoSphere follow-up data. This assumption, reduces the need to predict the treatment effects beyond the CTNeoBC analysis data.
	Patients who have not progressed after 7 years are considered event free and assumed to have a mortality rate equal to that of the age-matched general population	An advisory board noted that after 8 years there are few recurrences (most occur within 2-3 years)

5.7 Base-case results

5.7.1 Provide the results of the analysis. In particular, results should include, but are not limited to, the following:

- **the link between clinical- and cost-effectiveness results**

- **costs, quality-adjusted life years (QALYs) and incremental cost per QALY**
- **disaggregated results such as life years gained, costs associated with treatment,**
- **costs associated with adverse reactions, and costs associated with follow-up or subsequent treatment.**

Base-case incremental cost effectiveness analysis results

5.7.2 When presenting the results of the base case incremental cost effectiveness analysis in the table below, list the interventions and comparator(s) from least to most expensive. Present incremental cost-effectiveness ratios (ICERs) compared with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance. If the company has formally agreed a patient access scheme with the Department of Health, present the results of the base-case incremental cost-effectiveness analysis with the patient access scheme

The cost-effectiveness results are presented **Error! Not a valid bookmark self-reference.** below

Table 97 Deterministic basecase results

Technologies	Total costs (GBP)	Total LYG	Total QALYs	Incl costs (£)	Inc. LYG	Inc QALYs	Inc £/LYG	ICER (£/QALY))
PHD	104,575	16.719	11.499	4,557	0.365	0.263	£12,471	£17,297
HD	100,018	16.353	11.236					
PHD – Perjeta + Herceptin + docetaxel; HD - Herceptin + docetaxel; LYG – life years gained; QALYs – Quality adjusted life years; ICER – incremental costs effectiveness ratio								
Values in the table are discounted and 1/2 cycle corrected								

Clinical outcomes from the model

5.7.3 For the outcomes highlighted in the decision problem (see section 3), provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials, as suggested in the table below. Discuss reasons for any differences between the modelled results in the cost-effectiveness analysis and the observed results in the clinical trials (for example, adjustment for crossover).

In order to compare the relative treatment in PFS (in terms of difference in log-survival) between model and trial, the survival rates at time(t) of PHD or HD obtained from the model and trial (NeoSphere) respectively ($S^{\mathrm{Mod}}_{\mathrm{PHD/HD}}(t)$ and $S^{\mathrm{Trial}}_{\mathrm{PHD/HD}}(t)$) were used as follows:

The difference in log-survival was defined as

$$\Delta_{\mathrm{Trial}}(t) = \log\left(S^{\mathrm{Trial}}_{\mathrm{PHD}}(t)\right) - \log\left(S^{\mathrm{Trial}}_{\mathrm{HD}}(t)\right) \quad (1)$$

and

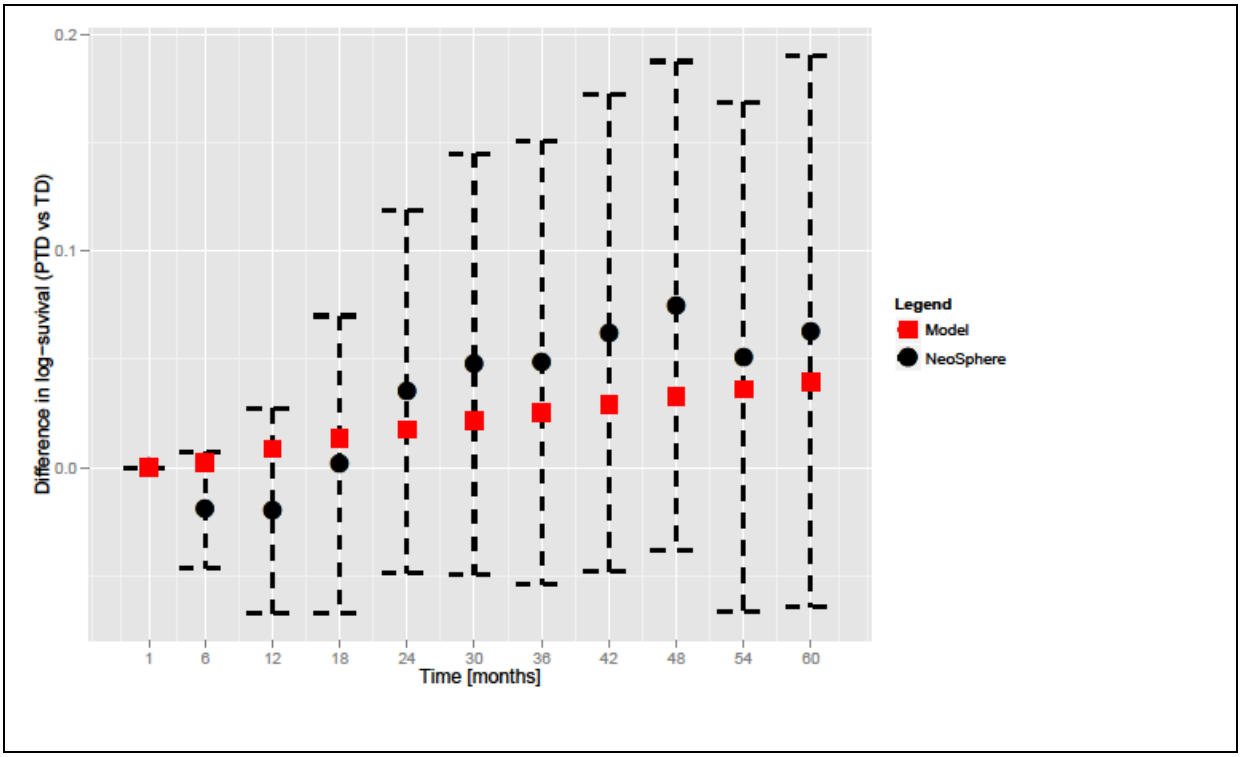
$$\Delta_{\mathrm{Mod}}(t) = \log\left(S^{\mathrm{Mod}}_{\mathrm{PHD}}(t)\right) - \log\left(S^{\mathrm{Mod}}_{\mathrm{HD}}(t)\right). \quad (2)$$

Point-wise confidence intervals for $\Delta_{\mathrm{Trial}}(t)$ can be obtained as

$$\Delta_{\mathrm{Trial}}(t) \mp 1.96\sqrt{\mathrm{se}^2\left\{\log\left(S^{\mathrm{Trial}}_{\mathrm{X}}(t)\right)\right\} + \mathrm{se}^2\left\{\log\left(S^{\mathrm{Trial}}_{\mathrm{X}}(t)\right)\right\}}. \quad (3)$$

Figures 33 below show the differences in log-survival for the model, $\Delta_{\mathrm{Mod}}(t)$, and the trial, $\Delta_{\mathrm{Trial}}(t)$, along with point-wise confidence intervals. Confidence intervals are very large in both cases (few PFS events in trials). In NeoSphere, model and trial give similar results in terms of difference in log-survival (the model results are within the trial confidence intervals). From 24 months onwards there is a trend that the model is slightly conservative in the difference in log-survival.

Figure 33 Model prediction vs trial data (NeoSphere)



5.7.4 Provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying 1 for each comparator.

The model runs for 50 years on a monthly cycle length. Reproducing the Markov trace would substantially lengthen the submission and thus 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.

5.7.5 Provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

See response 5.7.4.

Disaggregated results of the base case incremental cost effectiveness analysis

5.7.6 Provide details of the disaggregated QALYs and costs by health state, and of resource use predicted by the model in the base case incremental

cost effectiveness analysis by category of cost. The tables that should be completed summarising the disaggregated results (for example, QALY gain by health state, costs by health state, predicted resource use by category of cost) are presented below.

The incremental costs and QALYs are negative in some health states. This is due to more people in those states in the control arm than the intervention arm. In the intervention arm individuals progress slower and as a result do not incur as high costs or gain as many QALYs in the progressed states.

Table 98 Summary of QALY gain by health state

Outcome	Therapy	QALYs	PHD vs. HD	Absolute QALY gain	% absolute QALY gain
EFS	PHD	10.18			
	HD	9.76	0.42	0.42	72.4%
Locoreg. Recurr.	PHD	0.08			
	HD	0.09	-0.01	0.01	1.7%
Remission	PHD	0.66			
	HD	0.74	-0.08	0.08	13.8%
Met. (not progressed)	PHD	0.31			
	HD	0.35	-0.04	0.04	6.9%
Met. (progressed)	PHD	0.268			
	HD	0.299	-0.031	0.03	5.2%
Total	**PHD vs. HD**		**0.263**	**0.58**	**100%**
PHD Perjeta Herceptin docetaxel PH Perjeta Herceptin					

Table 99 Summary of Costs by health state

Outcome	Therapy	Total Cost	Cost PHD vs. HD	Absolute incremental cost	% absolute COST difference
EFS	PHD	£38,308			
	HD	£26,122	£12,185	£12,185	61.5%
Locoreg. Recurr.	PHD	£2516.16			
	HD	£2805.66	£-289.50	£289.5	1.5%
Remission	PHD	£690			
	HD	£769	£-79	£79	<1%
Met. (not progressed)	PHD	£20,950			
	HD	£23,361	£-2,412	£2,412	12.2%
Met. (progressed	PHD	£42,122			
	HD	£46,960	£-4,848	£4,848	24.5%
Total	**PHDvs. HD**		**£4,557**	**£19813.5**	**100%**
PHD Perjeta Herceptin docetaxel PH Perjeta Herceptin					

Table 100 Summary of predicted resource use by category of cost

EFS					
Item	**Cost PHD**	**Cost HD**	**Cost PHD vs. HD**	**Absolute Cost difference**	**% absolute C difference (by state)**
Perjeta	£11,971	£0	£11,971	£11,971	98%
Herceptin	£20,380	£20,271	£108	£108	<1%
Docetaxel	£215	£215	£0	£0	<1%
FEC	£122	£122	£0	£0	<1%
Drug Administration	£3,081	£3,065	£16	£16	<1%
Adverse Events	£795	£742	£52	£52	<1%
Supportive Care Cost	£1,744	£1,706	£38	£38	<1%
EFS Total	**£38,308**	**£26,122**	**£12,185**	**£12,185**	
LocoRegional					
Herceptin	£2,415	£2,693	£-278	£278	96%
Docetaxel	£0	£0	£0	£0	<1%
Drug Administration	£0	£0	£0	£0	<1%
Adverse Events	£0	£0	£0	£0	<1%
Supportive Care Cost	£101	£113	£-12	£12	<1%
LocoRegional Total	**£2,516**	**£2,806**	**£-290**	**£290**	
Remission					
Supportive Care Cost	£689.50	£769	£79.5	£79.5	100%
Remission Total	**£689.50**	**£769**	**£79.5**	**£79.5**	**100%**
First Line metastatic treatment costs					
Perjeta plus Herceptin plus Docetaxel	£13,365	£14,904	£-1,539	£1,539	63.8%
Herceptin	£2,244	£2,502	£-258	£258	10.7%
Herceptin plus other treatments	£4,069	£4,538	£-468	£468	19.4%
Supportive Care Cost	£1,271	£1,418	£-146	£146	6.05%
Metastatic not progressed Total	**£20,950**	**£23,361**	**£-2,412**	**£2,412**	**100%**
Second Line metastatic treatment costs					
Capectiabine + lapatinib	£953	£1,063	£-110	£110	2.3%
Herceptin + capecitabine	£1,119	£1,248	£-129	£129	2.7%
Kadcyla	£26,591	£26,652	£-3,061	£3,061	63.1%
PHD	£12,133	£13,530	£-1,397	£1,397	28.8%
Supportive Care Cost	£1,317	£1,468	£-152	£152	3.2%
Metastatic Progressed Total	**£42,122**	**£46,960**	**£-4,848**	**£4,848**	**100%**
Values in the table are discounted and 1/2 cycle corrected					

5.8 Sensitivity analyses

Probabilistic sensitivity analysis

5.8.1 All inputs used in the analysis will be estimated with a degree of imprecision. As specified in the NICE guide to the methods of technology appraisal, probabilistic sensitivity analysis is preferred for translating the imprecision in all input variables into a measure of decision uncertainty in the cost effectiveness of the options being compared. In non-linear decision models, probabilistic methods provide the best estimates of mean costs and outcomes. The mean value, distribution around the mean, and the source and rationale for the supporting evidence should be clearly described for each parameter included in the model. The distributions for probabilistic sensitivity analysis should not be arbitrarily chosen, but should represent the available evidence on the parameter of interest, and their use should be justified.

Provide the information specified in sections 5.8.2–5.8.4.

5.8.2 The distributions and their sources for each parameter should be clearly stated if different from those presented in section 5.5, including the derivation and value of 'priors'. If any parameters or variables were omitted from the probabilistic sensitivity analysis, please provide the rationale for the omission(s).

All model variables which had a distribution assigned are presented in Table 101.

Table 101 Parameters included in the PSA

Parameter	Uncertainty	Distribution
pCR rates from NeoSphere	SE as reported	Beta
Parametric distributions	SE	Multivariate Normal
Utility, Lidgren 2006 and Lloyds 2004 and overwritten utilities	SE	Beta
AE (%)	SE	LogNormal
AE (cost)	10% of the mean	LogNormal
Administration cost	10% of the mean	LogNormal
Pharmacy time required for IV preparation	20% of the mean	LogNormal
Supportive care cost	25% of the mean	LogNormal
Split between locoregional and metastatic	SE	Beta
Risk of recurrence from remission	SE	Beta
Risk of progression	SE	Multivariate Normal
Risk of death due to metastatic disease	SE	Multivariate Normal

5.8.3 Present the incremental cost effectiveness results of a probabilistic sensitivity analysis (including 95% confidence intervals). Include scatter plots and cost-effectiveness acceptability curves showing the probability that the treatment is cost effective if the incremental cost-effectiveness ratio ICER is £20,000 to £30,000 per QALY gained. Describe how the probabilistic ICER(s) were calculated and provide the rationale.

A 1,000 iteration probabilistic sensitivity analysis was conducted in order to determine the uncertainty surrounding the base-case ICERs.

Figure 34 PSA results (incremental cost effectiveness plane)

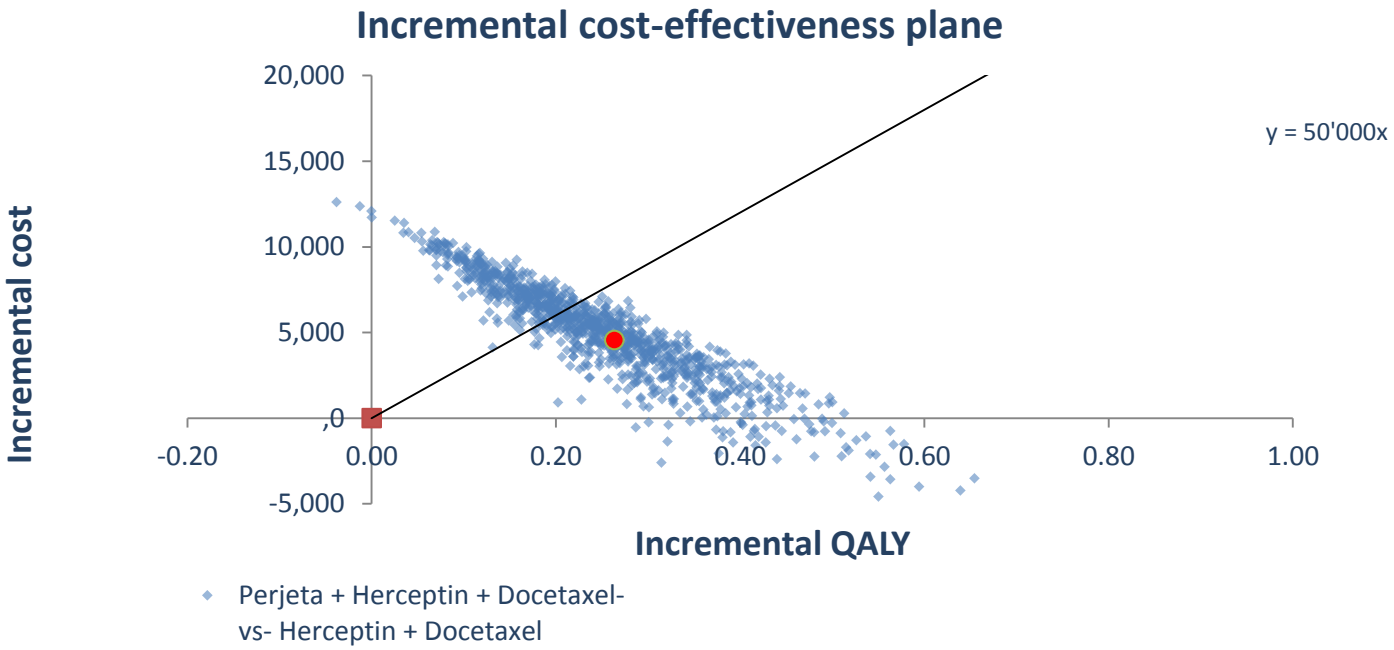
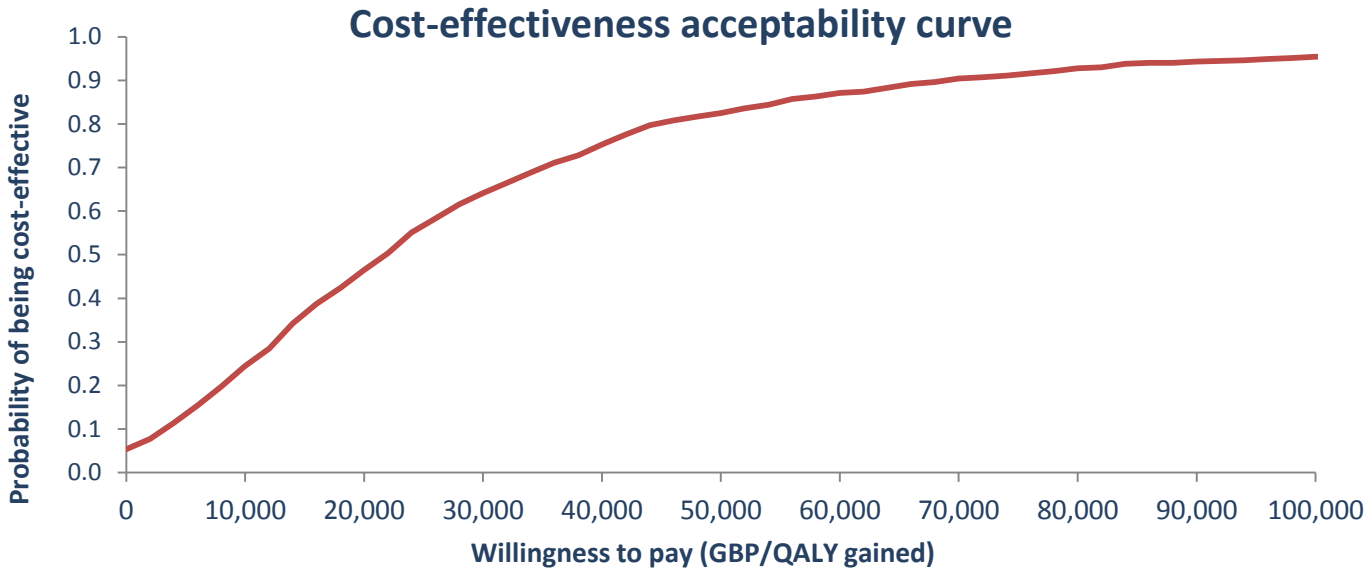


Figure 35 PSA results (Cost effectiveness acceptability curve)



This analysis indicated that Perjeta in combination had a 64.1% chance of being cost-effective treatment at a threshold of £30,000/QALY gained. The probabilistic base-case ICER was comparable to the deterministic base-case at £17,297/QALY gained. The PSA resulted in a probabilistic ICER of £20,104.

5.8.4 Describe and explain, if any, the variation between the incremental cost effectiveness analysis results estimated from the base-case analysis (section 5.6) and the probabilistic sensitivity analysis.

Deterministic and probabalistic sensitivity analyses results are approximately comparable

5.8.5 Identify which variables were subject to deterministic sensitivity analysis, how they were varied, and the rationale behind this. If any parameters or variables listed in section 5.6.1 were omitted from sensitivity analysis, please provide the rationale.

Deterministic sensitivity analysis was carried out on the parameters listed in Table 103(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 event free survival and overall survival on the ICERs was explored. The discount rate for costs and outcomes was varied according to standard methods and the time horizon altered.

Utilities

Two different sets of utility values have been explored in the sensitivity analysis. Firstly the utility values used in the base case are varied up and down by 20%. The utility values used in source 2 are shown in Table 102.

Table 102 Utility values of source 2 used in sensitivity analysis

Health State	Utility Value	Source
Event free (first year)	0.696	Lidgren [2006]
Event free (subsequent years)	0.85	Ara and Brazier [2010]
Locoregional recurrence	0.696	Assumption
Remission	0.85	Ara and Brazier [2010]
Metastatic not-progressed	0.685	Lidgren [2006]
Metastatic progressed	0.5	Lloyd [2006]

The utility values use different values from the base case for the EFS after year 1 and remission health states only. In these health states the utility values reflect the utility of the general UK population (at age 50-55). As patients in remission are considered to be disease free and are not receiving any treatment it may be

reasonable to assume that their quality of life is the same as that of the general population. The sensitivity of using these alternative sources is shown in Table 103.

Table 103 Sensitivity analysis for base case

	Base case value (BCV)	High Value	Low value
Costs			
Vial sharing assumptions	Vial sharing assumed	No vial sharing assumed	
Administration cost (monthly)	£326.60 (1st treatment) £174.60 (for subsequent treatment)	457.24 (BCV x 1.4) 244.44 (BCV x 1.4)	195.96 (BCV x 0.6) 104.76 (BCV x 0.6)
Pharmacy cost	£9.60 per 12 minutes	£13.44 (BCV x 1.4)	£5.76 (BCV x 0.6)
Event free survival supportive care cost (monthly)	£67.85 (year 1-2) £15.11 (year 3-5) £3.83 (year 5+)	£84.81 (BCV x 1.25) £18.89 (BCV x 1.25) £4.79 (BCV x 1.25)	£50.88 (BCV x 0.75) £11.33 (BCV x 0.75) £2.88 (BCV x 0.75)
LR supportive care costs health state costs	£74	£103.60 (BCV x 1.4)	£44.40 BCV x 0.6)
Metastatic not progressed supportive care costs (monthly)	£232	£324.8 (BCV x 1.4)	£139.20 (BCV x 0.6)
Metastatic progressed disease supportive care cost (monthly)	£185	£259 (BCV x 1.4)	£111 (BCV x 0.6)
Cardiac assessment proportion	30%/70% (MUGA/ECHO) proportion	10%/90% (MUGA/ECHO) proportion	50%/50% (MUGA/ECHO) proportion
Proportion receiving capecitabine and vinorelbine in metastatic progressed	60%/40% (capecitabine/vinorelbine)	80%/20%	40%/60%
Adverse event costs (per course of treatment)	£794.66 (PHD arm) £742.47 (HD arm)	£1112.52 (BCV x 1.4) £1039.46 (BCV x 1.4)	£476.79 (BCV x 0.6) £445.48 (BCV x 0.6)
Utility			
Source1 EFS (first year) EFS (subsequent years) Locoregional recurrence Remission Metastatic not-progressed Metastatic progressed	 0.696 0.779 0.696 0.779 0.685 0.5	 0.8352 (BCV x 1.2) 0.9348 (BCV x 1.2) 0.8352 (BCV x 1.2) 0.9348 (BCV x 1.2) 0.822 (BCV x 1.2) 0.6 (BCV x 1.2)	 0.5568 (BCV x 0.8) 0.6232 (BCV x 0.8) 0.5568 (BCV x 0.8) 0.6232 (BCV x 0.8) 0.548 (BCV x 0.8) 0.4 (BCV x 0.8)
Source 2 EFS (first year) EFS (subsequent years) Locoregional recurrence Remission Metastatic not-progressed Metastatic progressed	 As above	 0.696 0.85 0.696 0.85 0.685 0.452	
Outcomes			
Split between metastatic and local regional recurrence	58% and 42% (Source: NeoSphere)	(70% and 30%) (Source: Goldhirsch 2013)	
Transition probability of moving from metastatic not progressed to death (HD)	3.15%	3.78% (BCV x 1.2)	2.52% (BCV x 0.8)
Transition probability of moving from metastatic not progressed to death (PHD)	2.73%	3.82% (BCV x 1.2)	2.18% (BCV x 0.8)

Perjeta pCR	39.25%	49.2%	30.0%
Comparator pCR	21.5%	30.5%	14.1%
Monthly risk of a second malignancy	0.76%	1.52% (BCV x 2)	0.38% (BCV x 0.5)
Parametric functions			
Parametric fit	Gamma	(1) Weibull (2) Exponential (3) Log-logistic (4) Log normal	
Other			
Time horizon	50	30	50
PHD- Perjeta, Herceptin and docetaxel; HD- Herceptin and docetaxel; Both arms- PHD and HD arms BCV – Base Case Value LR Locoregional Recurrence AE Adverse Event			

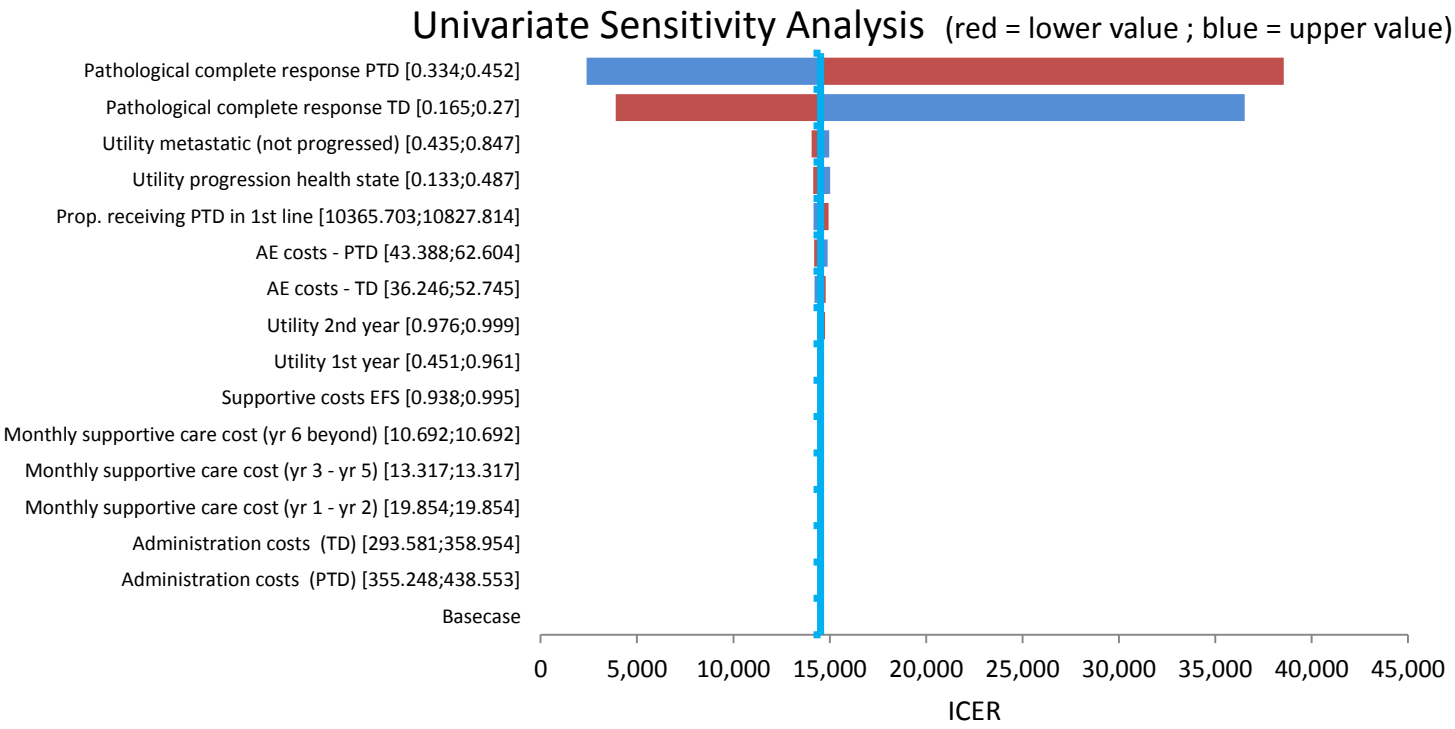
5.8.6 Results of deterministic sensitivity analysis.

Table 104 Deterministic sensitivity analysis for base case

Base case ICER £17,133					
Parameter modified	**Base value**	**High Value**	**Low Value**	**ICER High**	**ICER Low**
LR supportive care costs health state costs	£74	£103.60	£44.40	£17,279	£17,314
Log-Logistic parametric function		Log-logistic		£17,381	
Pharmacy cost	£10	£13.44	£5.76	£17,268	£17,326
Cardiac assessment proportion	30/70 (MUGA/ECHO) proportion	10/90 (MUGA/ECHO) proportion	50/50 (MUGA/ECHO) proportion	£17,324	£17,270
Event free survival supportive care cost (monthly)	£67.85 (year 1-2), £15.11 (year 3-5), £3.83 (year 5+)	BCVs x 1,25	BCVs x 0,75	£17,248	£17,346
AE cost	£794.66 (PHD Arm), £742.47 (HD Arm)	£1112.52 (BCV x 1.4), £1039.46 (BCV x 1.4)	£476.79 (BCV x 0.6), £445.48 (BCV x 0.6)	£17,374	£17,218
Metastatic not progressed supportive care costs (monthly)	£232	£324.8 (BCV x 1.4)	£139.20 (BCV x 0.6)	£17,075	17,519
Administration cost (monthly)	£326.60 (for 1st treatment), £174.60 (for subsequent treatment)	£457.24 £244.44	£195.96 £104.76	£16,765	£17,829
Metastatic progressed disease supportive care cost (monthly)	£185	£259 (BCV x 1.4)	£111 (BCV x 0.6)	£17,068	£17,527
Weibull parametric fit	Gamma	Weibull		£16,612	
Log-Normal parametric function	Gamma	Log normal		£18,897	
Exponential parametric function	Gamma	Exponential		£15,281	
Split between metastatic and local regional recurrence	58% and 42% (Source: NeoSphere)	70% and 30% (Source: HERA)		£15,156	
Transition probability of moving from metastatic not progressed to death (HD)	3.15%	3.78% (BCV x 1.2)	2.52% (BCV x 0.8)	£17,935	£16,602
Transition probability of moving from metastatic not progressed to death (PHD)	2.73%	3.82% (BCV x 1.2)	2.18% (BCV x 0.8)	£20,799	£14,535

PHD pCR	39.25%	49.2%	30.0%	£841	£67,157
HD pCR	21.5%	30.5%	14.1%	£64,416	£3,831
Monthly risk of a second malignancy	0.76%	1.52% (BCV x 2)	0.38% (BCV x 0.5)	£14,183	£22,022
Utility Values Source 2	See Table 103	See Table 103		£17,764	
Time horizon	50	50	30	£21,242	
Utility Values Source 1	See Table 103	See Table 103	see table 14	£14,222	£21,894
Vial sharing assumptions (Herceptin only)	Vial sharing	No Vial Sharing		£17,280	
BCV – Base Case Value PHD Perjeta, Herceptin, docetxel HD Herceptin, docetaxel AE Adverse Event LR Locoregional recurrence					

Figure 36 Tornado plot for base case



5.8.7 For technologies whose final price or acquisition cost has not been confirmed, sensitivity analysis should be done over a plausible range of prices. This may also include the price of a comparator that includes a confidential patient access scheme.

Due to commercial in confidence discounts for [redacted].

Scenario analysis

5.8.8 Sensitivity analysis should be used to explore uncertainty around the structural assumptions used in the analysis. Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

Herceptin subcutaneous formulation (Herceptin SC) is also provided by the NHS to early breast cancer patients for neoadjuvant treatment. Hence, an analysis of PHD

vs. HD, with Herceptin in the comparator arm as a SC formulation is provided. The features of this analysis are the following:

- The price of Herceptin SC (600mg/5ml fixed dose) was set to [redacted] per cycle on the HD arm only, this price includes a confidential discount.
- Herceptin SC administration costs are lower than those of Herceptin IV, a 60% reduction in the administration costs were assumed
- The Herceptin SC adverse event costs were assumed to be similar to those of Herceptin IV.

This analysis assumes that all patients treated with HD, receive Herceptin SC formulation, this overestimates the numbers of patients who receive this formulation by approximately 50%. Follow on treatments with Herceptin are assumed to be delivered by IV. This is considered reasonable since the treatments in each arm are the same, therefore factoring in Herceptin SC would make marginal difference to the ICER

5.8.9 Present the results of scenario analysis. Include details of structural sensitivity analysis.

Table 105 Scenario 1 results

Technologies	Total costs (GBP)	Total LYG	Total QALYs	Incl costs (£)	Inc. LYG	Inc QALYs	Inc £/LYG	ICER (£/QALY))
PHD	104,575	16.719	11.499	[redacted]	0.365	0.263	[redacted]	[redacted]
HD SC	[redacted]	16.353	11.236					
PHD – Perjeta + Herceptin + docetaxel; HD - Herceptin + docetaxel; LYG – life years gained; QALYs – Quality adjusted life years; ICER – incremental costs effectiveness ratio								
Values in the table are discounted and 1/2 cycle corrected								

The ICER increase was expected as the lower administration and preparation costs of Herceptin SC (compared to Herceptin IV) lowered the costs of the comparator arm. The incremental costs increase from

Summary of sensitivity analyses results

5.8.10 Describe the main findings of the sensitivity analyses, highlighting the key drivers of the cost-effectiveness results.

As expected, the deterministic sensitivity analyses (see section 5.8.6) demonstrate that pCR values for PHD and HD are the most important drivers in the model. Nevertheless, it was reassuring to see that for all other parameters, the ICER remains below £23k.

5.9 Subgroup analysis

5.9.1 Types of subgroups that are not considered relevant are those based solely on the following factors:

- **Individual utilities for health states and patient preference.**
- **Different treatment costs for individuals according to their social characteristics.**
- **Subgroups specified according to the costs of providing treatment in different locations in England (for example, when the costs of facilities available for providing the technology vary according to location).**

5.9.2 Please specify whether analysis of subgroups was carried out and how these subgroups were identified, referring to the scope and decision problem specified for the NICE technology appraisal. When specifying how subgroups were identified, confirm whether they were identified based on a prior expectation of different clinical or cost effectiveness because of known, biologically plausible mechanisms, social characteristics or other clearly justified factors. Cross refer to the clinical effectiveness section 4.7.

No subgroup analysis was undertaken.

5.9.3 Clearly define the characteristics of patients in the subgroup.

See question 5.9.2

5.9.4 Describe how the statistical analysis was carried out.

See question 5.9.2

5.9.5 If subgroup analyses were done, please present the results in tables similar to those in section 5.7.

See question 5.9.2

5.9.6 Identify any obvious subgroups that were not considered and explain why. Please refer to the subgroups identified in the decision problem in section 3.

As noted at the Perjeta SmPC, pCR rates were similar in patients with operable versus locally advanced disease. There were too few patients with inflammatory breast cancer to draw any firm conclusions but the pCR rate was higher in patients who received Perjeta plus Herceptin and docetaxel. Please see Table 106 below with NeoSphere trial results:

Table 106 Patient numbers (%) by subgroups

Treatment	Operable Breast Cancer	Locally advanced breast cancer	Inflammatory breast cancer
PHD	26 (40.0%)	13 (40.6%)	3 (30.0%)
HD	12 (18.8%)	10 (27.8%)	1 (14.3%)

5.10 Validation

Validation of de novo cost-effectiveness analysis

5.10.1 When describing the methods used to validate and quality assure the model, provide:

- **the rationale for using the chosen methods**
- **references to the results produced and cross-references to the evidence identified in the clinical evidence, measurement and valuation of health effects, and cost and healthcare resource sections.**

See section 5.7.3.

5.11 Interpretation and conclusions of economic evidence

5.11.1 When interpreting and concluding your economic evidence, consider the following:

- **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?**
- **Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem?**
- **How relevant (generalisable) is the analysis to clinical practice in England?**
- **What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?**
- **What further analyses could be carried out to enhance the robustness or completeness of the results?**

Conclusion of the economic evidence

The NeoSphere trial demonstrated a statistical improvement in tpCR for patients receiving Perjeta, Hercetin and docetaxel compared to Herceptin + docetaxel (39.3% vs. 21.5%). tpCR is validated as a surrogate for EFS and was accepted as a valid endpoint by both the FDA and EMA during regulatory filing.

Approval of Perjeta would give patients access to a medicine early on in the disease pathway where treatment is most effective. Patients could be administered dual HER2 blockade therapy which has also proven effective in the mBC setting.

The results of the de novo cost effectiveness analysis of Perjeta in combination with Herceptin and docetaxel, show that it is both more effective (0.263 QALY gain) and more costly (£4557 incremental costs) than Herceptin and docetaxel alone as a neoadjuvant treatment, with a base case ICER presented of £17,297.

This conclusion has been tested during extensive sensitivity analysis. Deterministic sensitivity analysis produced results where, the majority of ICERs fall in the range of

£14,222 to £22,022 per QALY. The two exceptions are; is pCR rates at the limits of the confidence intervals moves the ICER between £841 to £67,157. Secondly use of Herceptin subcutaneous administration was considered as a scenario analysis and resulted in an ICER of £21,454.

The economic model is most sensitive to the pCR rates. Probabilistic sensitivity analysis was run for 1000 simulations and produced an ICER of £20,104 per QALY The probability of being cost effective at a willingness to pay threshold of £30k is 64.1%

Treatment in the neoadjuvant breast cancer setting is given with a curative intent, as a result, the average patient age at diagnosis is only 50 years, there is an unavoidable degree of uncertainty in the modelling of long term survival.

Consistency *of results to previous economic analysis*

Only one study was identified through the systematic literature review [Attard 2014]. This analysis had significant differences from the economic case within this submission (for more differences and reasons for exclusion of this study please refer to Appendix 9 Search strategy for the systematic literature review for the economic model.

- The discount rate for costs and benefits was 5%
- The utilities were in general higher
- The model had only 5 health states compared to this model that has 6 health states

These changes produced different ICERs that ranged between $9,230 (2014 CAD) and $38,419 (2014 CAD)

Relevance to the licensed patient population

The economic evaluation is based on the NeoSphere trial which is representative of the licensed patient population

Generalisability to the UK

All resource use, costs and utility values were taken from English relevant sources. The NICE's 'Single technology appraisal: User guide for company evidence submission template' and the 'Guide to the methods of technology appraisal 2013' were followed throughout. Every step possible was taken to ensure that the analysis undertaken was as pragmatic as possible and accurately estimated the likely costs and health outcomes associated with an average English breast cancer patient's disease progression. The results produced therefore have strong applicability to an English clinical setting.

The NeoSphere trial contained a comparator arm which is not exactly equivalent to the neoadjuvant breast cancer treatment in England. FEC is administered as a neoadjuvant treatment in England while in NeoSphere it was administered as an adjuvant treatment. This difference is not expected to impact the clinical results as noted by an Advisory Board of British clinicians.

In additional, in clinical practice in the UK some patients receive Herceptin as a subcutaneous formulation which produces a saving in administration time. This was not factored into the base case analysis but was explored as a scenario.

Strengths of the economic evaluation

- The economic model is based upon the NeoSphere trial, which was a robust and well conducted study in a patient population which is representative of the licensed indication

- NeoSphere trial included a comparator arm which is applicable to England thus no indirect treatment comparison or network meta-analysis was required

- Progression from EFS was modelled using a robust FDA sponsored meta-analysis (CTNeoBC study) that analysed 11955 patients (which included 2000 HER-2 positive patients) to establish if pCR (tpCR) has validity as a surrogate for EFS for neoadjuvant treatments. The EMA accepted pCR to be used as a valid study endpoint during the regulatory approval of Perjeta. This meta-analysis concluded that a link between pCR and EFS could not be stablished

at trial level, due to heterogeneity between patient types and treatments. However, at patient level a positive correlation between pCR and EFS was noted in which patients who achieved pCR were associated with higher probabilities of achieving EFS and OS

- Extensive sensitivity analysis has been performed on the model parameters

Areas of weakness or uncertainty

- The CTNeoBC study concluded that there was tendency for patients who achieved pCR to remain in EFS for longer, this effect was found at the patient level and not at the trial level. With regards to the economic case, trial level analysis would not fit the purposes as a comparison between the different treatments from the pooled analysis would not inform this model (furthermore the trial level analysis is biased due to heterogeneity). Only patient level analysis could be used in this model as it informs the natural history of pCR and non-pCR patients.

- Within the economic model a tunnel state was used for locoregional recurrence to allow patients to receive 12 months of Herceptin. In order to retain a workeable model structure it was necessary to assume that patients cannot die during the locoregional recurrence tunnel states. To reflect reality, patients should be able to move to the death health state from all health states. A death rate from this locoregional health state would be all cause mortality, similar to the other non-metastatic health states. As such, it would be low and not likely to impact the cost effectiveness results in a significant way.

- It has been assumed that the comparator in the model is the best representation of the SOC in England and Wales (FEC followed by HD/PHD). However, the chemotherapy regimens patients currently receive is heterogeneous (in some areas paclitaxel is administered and not docetaxel). Changes in the comparator arm or concomitant therapies may change the ICER but it is not expected to bring it up to prohibitive levels nor drastically reduce it.

Potential for further analysis

- Longer term follow up from NeoSphere would allow the validation of longer term treatment effect of PHD, and reduce uncertainty.

- Utility values in the base case are taken from Lidgren. These are real world EQ-5D values collected for breast cancer. The study was carried out in Sweden and as such patient characteristics may vary from the English population. Collection of EQ-5D values from participants in the trial or from a UK breast cancer population would improve the quality of life estimates within the event free survival and progressed health states.

- If the FDA meta analysis were to be updated and include more HER2 positive patients, the authors note that this may establish a stronger link between EFS-tpCR or this sub-type at trial level.

- It can also be seen that between year 1 and year 2, EFS KM curves cross in the trial. This is due to very low number of events observed in the trial and these results reinforce the use of pCR from CTNeoBC data as a more reliable source to stablish the link between EFS and tpCR.

6 Assessment of factors relevant to the NHS and other parties

6.1 The purpose of this section is to provide an analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical and cost effectiveness. This will allow subsequent evaluation of the budget impact analysis. Such factors might include issues relating to service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers. Provide the information specified in sections 6.2–6.10.

6.2 State how many people are eligible for treatment in England. Present results for the full marketing authorisation or CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

It is estimated that approximately 1,380 people per annum will be eligible to receive PHD. The derivation of this number is provided in Table 107 and adjusted accordingly for the population of England and Wales. At a population growth rate of 0.5% per annum this results in the following yearly eligible populations.

Table 107 Eligible population by year

Year	2016	2017	2018	2019	2020
Eligible population	1,380	1,387	1,394	1,401	1,408

6.3 Explain any assumptions that were made about current treatment options and uptake of technologies.

The analysis considers only the absolute budget impact of Perjeta as it is an add-on treatment and hence no technologies are displaced.

6.4 When relevant, explain any assumptions that were made about market share in England.

It is assumed that 30% of eligible people in the year following NICE approval would receive Perjeta with that figure rising to 70% in the fifth year following approval. The market share figures used are presented in Table 108.

Table 108 Market share assumptions by year

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

6.5 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, administration costs, monitoring costs and the costs of managing adverse reactions).

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

6.6 State what unit costs were assumed and how they were calculated. If unit costs used in health economic modelling were not based on national reference costs or the payment-by-results tariff, explain how a cost for the activity was calculated

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

6.7 If there were any estimates of resource savings, explain what they were and when they are likely to be made.

No.

6.8 State the estimated annual budget impact on the NHS in England.

Table 109 Budget impact by year

Year	1	2	3	4	5
Budget impact - drug cost	£4,957,650	£6,643,251	£8,345,584	£10,064,774	£11,800,948
Budget impact - non-drug cost	-	-	-	-	-
Total budget impact	**£4,957,650**	**£6,643,251**	**£8,345,584**	**£10,064,774**	**£11,800,948**

6.9 Identify any other opportunities for resource savings or redirection of resources that it has not been possible to quantify.

No.

6.10 Highlight the main limitations within the budget impact analysis

No important limitations were noted.

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Appendices

Appendix 1 Summary of Product Characteristics

Summary of Product Characteristics Updated 24-Sep-2015 | Roche Products Limited

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Perjeta 420 mg concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One 14 ml vial of concentrate contains 420 mg of pertuzumab at a concentration of 30 mg/ml.

After dilution, one ml of solution contains approximately 3.02 mg of pertuzumab for the initial dose and approximately 1.59 mg of pertuzumab for the maintenance dose (see section 6.6).

Pertuzumab is a humanised IgG1 monoclonal antibody produced in mammalian (Chinese hamster ovary) cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear to slightly opalescent, colourless to pale yellow, liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Metastatic Breast Cancer
Perjeta is indicated for use in combination with trastuzumab and docetaxel in adult patients with HER2-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease.

Neoadjuvant Treatment of Breast Cancer
Perjeta is indicated for use in combination with trastuzumab and chemotherapy for the neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence (see section 5.1)

4.2 Posology and method of administration

Perjeta is subject to restricted medical prescription and therapy should only be initiated under the supervision of a physician experienced in the administration of anti-cancer agents. Perjeta should be administered by a healthcare professional prepared to manage anaphylaxis and in an environment where full resuscitation facilities are immediately available.

Patients treated with Perjeta must have HER2-positive tumour status, defined as a score of 3+ by immunohistochemistry (IHC) and/or a ratio of ≥ 2.0 by in situ hybridisation (ISH) assessed by a validated test.

To ensure accurate and reproducible results, the testing must be performed in a specialised laboratory, which can ensure validation of the testing procedures. For full instructions on assay performance and interpretation please refer to the package leaflets of validated HER2 testing assays.

Posology
The recommended initial loading dose of Perjeta is 840 mg administered as a 60 minute intravenous infusion, followed every 3 weeks thereafter by a maintenance dose of 420 mg administered over a period of 30 to 60 minutes.

When administered with Perjeta the recommended initial loading dose of trastuzumab is 8 mg/kg body weight administered as an intravenous infusion followed every 3 weeks thereafter by a maintenance dose of 6 mg/kg body weight.

When administered with Perjeta the recommended initial dose of docetaxel is 75 mg/m2, administered thereafter on a 3 weekly schedule. The dose of docetaxel may be escalated to 100 mg/m2 on subsequent cycles if the initial dose is well tolerated (the docetaxel dose should not be escalated when used in combination with carboplatin, trastuzumab and Perjeta).

The medicinal products should be administered sequentially and not mixed in the same infusion bag. Perjeta and trastuzumab can be given in any order. When the patient is receiving docetaxel, this should be administered after Perjeta and trastuzumab. An observation period of 30 to 60 minutes is recommended after each Perjeta infusion and before commencement of any subsequent infusion of trastuzumab or docetaxel (see section 4.4).

Metastatic Breast Cancer
Patients should be treated with Perjeta and trastuzumab until disease progression or unmanageable toxicity.

Neoadjuvant Treatment of Breast Cancer
Perjeta should be administered for 3 to 6 cycles in combination with neoadjuvant trastuzumab and chemotherapy, as part of a treatment regimen for early breast cancer. Following surgery, patients should be treated with adjuvant trastuzumab to complete 1 year of treatment (see section 5.1).

Delayed or missed doses
If the time between two sequential infusions is less than 6 weeks, the 420 mg dose of Perjeta should be administered as soon as possible without regard to the next planned dose.

If the time between two sequential infusions is 6 weeks or more, the initial loading dose of 840 mg Perjeta should be re-administered as a 60-minute intravenous infusion followed every 3 weeks thereafter by a maintenance dose of 420 mg administered over a period of 30 to 60 minutes.

Dose modification
Dose reductions are not recommended for Perjeta.

Patients may continue therapy during periods of reversible chemotherapy-induced myelosuppression but they should be monitored carefully for complications of neutropenia during this time. For docetaxel and other chemotherapy dose modifications, see relevant summary of product characteristics (SmPC).

For trastuzumab, dose reductions are not recommended, see trastuzumab summary of product characteristics (SmPC).

If trastuzumab treatment is discontinued, treatment with Perjeta should be discontinued.

If docetaxel is discontinued, treatment with Perjeta and trastuzumab may continue until disease progression or unmanageable toxicity in the metastatic setting.

Left ventricular dysfunction
Perjeta and trastuzumab should be withheld for at least 3 weeks for any of the following:

- signs and symptoms suggestive of congestive heart failure (Perjeta should be discontinued if symptomatic heart failure is confirmed)
- a drop in left ventricular ejection fraction (LVEF) to less than 40%
- a LVEF of 40%-45% associated with a fall of ≥ 10% points below pre-treatment values.

Perjeta and trastuzumab may be resumed if the LVEF has recovered to > 45% or 40-45% associated with < 10% points below pretreatment value.

If after a repeat assessment within approximately 3 weeks, the LVEF has not improved, or has declined further, discontinuation of Perjeta and trastuzumab should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks (see section 4.4).

Infusion reactions
The infusion rate may be slowed or interrupted if the patient develops an infusion reaction (see section 4.8). The infusion may be resumed when symptoms abate. Treatment including oxygen, beta agonists, antihistamines, rapid i.v. fluids and antipyretics may also help alleviate symptoms.

Hypersensitivity reactions/anaphylaxis
The infusion should be discontinued immediately if the patient experiences a NCI-CTCAE Grade 4 reaction (anaphylaxis), bronchospasm or acute respiratory distress syndrome (see section 4.4).

Elderly patients
Limited data are available on the safety and efficacy of Perjeta in patients ≥ 65 years of age. No significant differences in safety and efficacy of Perjeta were observed between elderly patients aged 65 to 75 years and adult patients aged < 65 years. No dose adjustment is necessary in the elderly population ≥ 65 years of age. Very limited data are available in patients > 75 years of age.

Patients with renal impairment
Dose adjustments of Perjeta are not needed in patients with mild or moderate renal impairment. No dose recommendations can be made for patients with severe renal impairment because of the limited pharmacokinetic data available (see section 5.2).

Patients with hepatic impairment
The safety and efficacy of Perjeta have not been studied in patients with hepatic impairment. No specific dose recommendations can be made.

Paediatric population
The safety and efficacy of Perjeta in children and adolescents below 18 years of age have not been established. There is no relevant use of Perjeta in the paediatric population in the indication of breast cancer.

Method of administration
Perjeta is administered intravenously by infusion. It should not be administered as an intravenous push or bolus. For instructions on dilution of Perjeta prior to administration, see sections 6.2 and 6.6.

For the initial dose, the recommended infusion period is 60 minutes. If the first infusion is well tolerated, subsequent infusions may be administered over a period of 30 minutes to 60 minutes (see section 4.4).

4.3 Contraindications

Hypersensitivity to pertuzumab or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

In order to improve traceability of biological medicinal products, the tradename and batch number of the administered product should be clearly recorded (or stated) in the patient file.

Left ventricular dysfunction (including congestive heart failure)
Decreases in LVEF have been reported with medicinal products that block HER2 activity, including Perjeta. Patients who have received prior anthracyclines or prior radiotherapy to the chest area may be at higher risk of LVEF declines. In the pivotal trial CLEOPATRA in patients with metastatic breast cancer, Perjeta in combination with trastuzumab and docetaxel was not associated with a greater incidence of symptomatic left ventricular systolic dysfunction (LVD) or LVEF declines compared with placebo and trastuzumab and docetaxel (see section 4.8).

In the neoadjuvant setting (NEOSPHERE) the incidence of LVD was higher in the Perjeta–treated groups than in those who did not receive Perjeta. An increased incidence of LVEF declines was also observed in patients treated with Perjeta in combination with trastuzumab and docetaxel; LVEF recovered to ≥50% in all patients.

Perjeta has not been studied in patients with: a pre-treatment LVEF value of ≤ 50%; a prior history of congestive heart failure (CHF); LVEF declines to < 50% during prior trastuzumab adjuvant therapy; or conditions that could impair left ventricular function such as uncontrolled hypertension, recent myocardial infarction, serious cardiac arrhythmia requiring treatment or a cumulative prior anthracycline exposure to > 360 mg/m2 of doxorubicin or its equivalent.

Assess LVEF prior to initiation of Perjeta and during treatment with Perjeta (every 3 cycles in the metastatic setting and every 2 cycles in the neoadjuvant setting) to ensure that LVEF is within the institution's normal limits. If LVEF is < 40% or 40%-45% associated with ≥ 10% points below the pretreatment value, Perjeta and trastuzumab should be withheld and a repeat LVEF assessment performed within approximately 3 weeks. If the LVEF has not improved, or has declined further, discontinuation of Perjeta and trastuzumab should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks (see section 4.2).

Cardiac risk should be carefully considered and balanced against the medical need of the individual patient before use of Perjeta with an anthracycline. There are limited safety data available from the TRYPHAENA study concerning sequential or concomitant administration of Perjeta with epirubicin, as part of the FEC regimen (see sections 4.8 and 5.1). There are no safety data available concerning use of Perjeta with doxorubicin.

Based on the pharmacological actions of pertuzumab and anthracyclines an increased risk of cardiac toxicity might be expected from concomitant use of these agents compared with sequential use, although not seen in the TRYPHAENA study. In this study, only chemotherapy-naive subjects, not receiving additional chemotherapy after surgery, were treated with low cumulative dose of epirubicin, i.e. up to 300 mg/m2.

Infusion reactions
Perjeta has been associated with infusion reactions (see section 4.8). Close observation of the patient during and for 60 minutes after the first infusion and during and for 30-60 minutes after subsequent infusions of Perjeta is recommended. If a

significant infusion reaction occurs, the infusion should be slowed down or interrupted and appropriate medical therapies should be administered. Patients should be evaluated and carefully monitored until complete resolution of signs and symptoms. Permanent discontinuation should be considered in patients with severe infusion reactions. This clinical assessment should be based on the severity of the preceding reaction and response to administered treatment for the adverse reaction (see section 4.2).

Hypersensitivity reactions/anaphylaxis
Patients should be observed closely for hypersensitivity reactions. Severe hypersensitivity, including anaphylaxis, has been observed in clinical trials with Perjeta (see section 4.8). Medications to treat such reactions, as well as emergency equipment, should be available for immediate use. Perjeta must be permanently discontinued in case of NCI-CTCAE Grade 4 hypersensitivity reactions (anaphylaxis), bronchospasm or acute respiratory distress syndrome (see section 4.2). Perjeta is contraindicated in patients with known hypersensitivity to pertuzumab or to any of its excipients (see section 4.3).

Febrile neutropenia
Patients treated with Perjeta, trastuzumab and docetaxel are at increased risk of febrile neutropenia compared with patients treated with placebo, trastuzumab and docetaxel, especially during the first 3 cycles of treatment (see section 4.8). In the CLEOPATRA trial in metastatic breast cancer, nadir neutrophil counts were similar in Perjeta-treated and placebo-treated patients. The higher incidence of febrile neutropenia in Perjeta-treated patients was associated with the higher incidence of mucositis and diarrhoea in these patients. Symptomatic treatment for mucositis and diarrhoea should be considered. No events of febrile neutropenia were reported after cessation of docetaxel.

Diarrhoea
Pertuzumab may elicit severe diarrhoea. In case of onset of severe diarrhoea an anti-diarrhoeal treatment should be instituted and interruption of the treatment with pertuzumab should be considered if no improvement of the condition is achieved. When the diarrhoea is under control the treatment with pertuzumab may be reinstated.

4.5 Interaction with other medicinal products and other forms of interaction

No pharmacokinetic (PK) interactions were observed between pertuzumab and trastuzumab, or between pertuzumab and docetaxel in a sub-study of 37 patients in the randomised, pivotal trial CLEOPATRA in metastatic breast cancer. In addition, in the population PK analysis, no evidence of a drug-drug interaction has been shown between pertuzumab and trastuzumab or between pertuzumab and docetaxel. This absence of drug-drug interaction was confirmed by pharmacokinetic data from the NEOSPHERE trial in the neoadjuvant setting.

Four studies have evaluated the effects of pertuzumab on the PK of co-administered cytotoxic agents, docetaxel, gemcitabine, erlotinib and capecitabine. There was no evidence of any PK interaction between pertuzumab and any of these agents. The

PK of pertuzumab in these studies was comparable to those observed in single-agent studies.

4.6 Fertility, pregnancy and lactation

Contraception
Women of childbearing potential should use effective contraception while receiving Perjeta and for 6 months following the last dose of Perjeta.

Pregnancy
There is limited amount of data from the use of pertuzumab in pregnant women.

Studies in animals have shown reproductive toxicity (see section 5.3).

Perjeta is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding
Because human IgG is secreted in human milk and the potential for absorption and harm to the infant is unknown, a decision should be made to discontinue breast-feeding or to discontinue treatment, taking into account the benefit of breast-feeding for the child and the benefit of Perjeta therapy for the woman (see section 5.2).

Fertility
No specific fertility studies in animals have been performed to evaluate the effect of pertuzumab. Only very limited data are available from repeat-dose toxicity studies with respect to the risk for adverse effects on the male reproductive system. No adverse effects were observed in sexually mature female cynomolgus monkeys exposed to pertuzumab.

4.7 Effects on ability to drive and use machines

On the basis of reported adverse reactions, Perjeta is not expected to influence the ability to drive or use machines. Patients experiencing infusion reactions should be advised not to drive and use machines until symptoms abate.

4.8 Undesirable effects

Summary of the safety profile
The safety of Perjeta has been evaluated in more than 1,600 patients in the randomized trials CLEOPATRA (n=808), NEOSPHERE (n=417) and TRYPHAENA (n=225) and in Phase I and phase II trials conducted in patients with various malignancies and predominantly treated with Perjeta in combination with other antineoplastic agents. The safety of Perjeta in Phase I and II studies was generally consistent with that observed in the CLEOPATRA, NEOSPHERE and TRYPHAENA trials, although the incidence and most common adverse drug reactions (ADRs) varied depending on whether Perjeta was administered as monotherapy or with concomitant anti-neoplastic agents.

Metastatic Breast Cancer

In the pivotal clinical trial CLEOPATRA, 408 patients received at least one dose of Perjeta in combination with trastuzumab and docetaxel. The most common ADRs (≥ 50%) seen with Perjeta in combination with trastuzumab and docetaxel were diarrhoea, alopecia and neutropenia. The most common NCI-CTCAE v.3 Grade 3-4 ADRs (> 10%) were neutropenia, febrile neutropenia and leucopenia, and the most common serious adverse events were febrile neutropenia, neutropenia and diarrhoea. Treatment-related deaths occurred in 1.2% of patients in the Perjeta-treated group and 1.5% of patients in the placebo-treated group and were mainly due to febrile neutropenia and/or infection.

In the pivotal trial CLEOPATRA, ADRs were reported less frequently after discontinuation of docetaxel treatment. After discontinuation of docetaxel, ADRs in the Perjeta and trastuzumab treated group occurred in < 10% of patients with the exception of diarrhoea (28.1%), upper respiratory tract infection (18.3%), rash (18.3%), headache (17.0%), fatigue (13.4%), nasopharyngitis (17.0%), asthenia (13.4%), pruritus (13.7%), arthralgia (11.4%), nausea (12.7%), pain in extremity (13.4%), back pain (12.1%) and cough (12.1%).

Neoadjuvant Treatment of Breast Cancer

In the neoadjuvant trial NEOSPHERE, the most common ADRs (≥50%) seen with Perjeta in combination with trastuzumab and docetaxel were alopecia and neutropenia. The most common NCI-CTCAE v.3 Grade 3-4 ADR (≥10%) was neutropenia.

In the neoadjuvant trial TRYPHAENA, when Perjeta was administered in combination with trastuzumab and FEC (5-fluorouracil, epirubicin, cyclophosphamide) for 3 cycles followed by 3 cycles of Perjeta, trastuzumab and docetaxel, the most common ADRs (≥50%) were neutropenia, diarrhoea and nausea. The most common NCI-CTCAE v.3 Grade 3-4 ADRs (≥10%) were neutropenia, febrile neutropenia and leucopenia. When Perjeta was administered in combination with trastuzumab and docetaxel for 3 cycles following 3 cycles of FEC (5-fluorouracil, epirubicin, cyclophosphamide), the most common ADRs (≥50%) were diarrhoea, nausea and alopecia. The most common NCI-CTCAE v.3 Grade 3-4 ADRs (≥10%) were neutropenia and leucopenia. Similarly, when Perjeta was administered in combination with TCH (docetaxel, carboplatin and trastuzumab) for 6 cycles, the most common ADRs (≥50%) were diarrhoea and alopecia. The most common NCI-CTCAE v.3 Grade 3-4 ADRs (≥10%) were neutropenia, febrile neutropenia, anaemia, leucopenia and diarrhoea. The safety of Perjeta administered for more than 6 cycles in the neoadjuvant setting has not been established.

Tabulated list of adverse reactions

Table 1 summarizes the ADRs from the pivotal trial CLEOPATRA, in which Perjeta was given in combination with docetaxel and trastuzumab to patients with metastatic breast cancer, and from the neoadjuvant trials NEOSPHERE and TRYPHAENA, in which Perjeta was given in combination with trastuzumab and chemotherapy to patients with early breast cancer. As Perjeta is used with trastuzumab and chemotherapy, it is difficult to ascertain the causal relationship of an adverse event to a particular medicinal product.

The ADRs are listed below by MedDRA system organ class (SOC) and categories of frequency:

- Very common (≥ 1/10)
- Common (≥ 1/100 to < 1/10)
- Uncommon(≥ 1/1,000 to < 1/100)
- Rare (≥ 1/10,000 to < 1/1,000)
- Very rare (< 1/10,000)
- Not known (cannot be estimated from the available data)

Within each frequency grouping and SOC, adverse reactions are presented in the order of decreasing seriousness.

Table 1 Summary of ADRs in patients treated with Perjeta in the metastatic and neoadjuvant setting^

System organ class	***Very Common***	***Common***	***Uncommon***
Infections and infestations	Upper respiratory tract infection Nasopharyngitis	Paronychia	
Blood and lymphatic system disorders	Febrile neutropenia* Neutropenia Leucopenia Anaemia		
Immune system disorders	Hypersensitivity/ anaphylactic reaction° Infusion reaction/cytokine release syndrome°°		
Metabolism and nutrition disorders	Decreased appetite †		
Psychiatric disorders	Insomnia		
Nervous system disorders	Neuropathy peripheral Headache † Dysgeusia	Peripheral sensory neuropathy Dizziness	
Eye disorders		Lacrimation increased	
Cardiac disorders		Left ventricular dysfunction † (including congestive heart failure)**	
Respiratory, thoracic and mediastinal disorders	Cough †	Pleural effusion Dyspnoea †	Interstitial lung disease
Gastrointestinal disorders	Diarrhoea † Vomiting † Stomatitis Nausea † Constipation † Dyspepsia		
Skin and subcutaneous tissue disorders	Alopecia Rash † Nail disorder	Pruritus Dry skin	
Musculoskeletal and connective tissue disorders	Myalgia Arthralgia		
General disorders and administration site conditions	Mucositis/mucosal inflammation Pain † Oedema † Pyrexia Fatigue † Asthenia †	Chills	

^ Table 1 shows pooled data from the overall treatment period in CLEOPATRA (data cutoff 11 February 2014; median number of cycles of Perjeta was 24); and from the neoadjuvant treatment period in NEOSPHERE (median number of cycles of Perjeta was 4, across all treatment arms) and TRYPHAENA (median number of cycles of Perjeta was 3 – 6 across treatment arms)

* Including adverse reactions with a fatal outcome.

** For the overall treatment period across the 3 studies.

† Except for febrile neutropenia, neutropenia, leucopenia, lacrimation increased, interstitial lung disease, paronychia, and alopecia, all events in this table were also reported in at least 1% of patients participating in Perjeta monotherapy trials, although not necessarily considered causally related to Perjeta by the investigator. Very common events (reported in ≥ 10% of Perjeta monotherapy-treated patients) are marked in the Table with a †.

° Hypersensitivity/anaphylactic reaction is based on a group of terms.

°° Infusion reaction/cytokine release syndrome includes a range of different terms within a time window, see “Description of selected adverse reactions” below.

Description of selected adverse reactions

Left ventricular dysfunction
In the pivotal trial CLEOPATRA in metastatic breast cancer, the incidence of LVD during study treatment was higher in the placebo-treated group than in the Perjeta-treated group (8.6% and 6.6%, respectively). The incidence of symptomatic LVD was also lower in the Perjeta-treated group (1.8% in the placebo-treated group vs. 1.5% in the Perjeta-treated group) (see section 4.4).

In the neoadjuvant trial NEOSPHERE , in which patients received 4 cycles of Perjeta as neoadjuvant treatment, the incidence of LVD (during the overall treatment period) was higher in the Perjeta, trastuzumab and docetaxel-treated group (7.5%) compared to the trastuzumab and docetaxel-treated group (1.9%). There was one case of symptomatic LVD in the Perjeta and trastuzumab-treated group.

In the neoadjuvant trial TRYPHAENA, the incidence of LVD (during the overall treatment period) was 8.3% in the group treated with Perjeta plus trastuzumab and FEC (followed by Perjeta plus trastuzumab and docetaxel); 9.3% in the group treated with Perjeta plus trastuzumab and docetaxel following FEC; and 6.6% in the group treated with Perjeta in combination with TCH. The incidence of symptomatic LVD (congestive heart failure) was 1.3% in the group treated with Perjeta plus trastuzumab and docetaxel following FEC (this excludes a patient who experienced symptomatic LVD during FEC treatment prior to receiving Perjeta plus trastuzumab and docetaxel) and also 1.3% in the group treated with Perjeta in combination with TCH. No patients in the group treated with Perjeta plus trastuzumab and FEC followed by Perjeta plus trastuzumab and docetaxel experienced symptomatic LVD.

Infusion reactions
An infusion reaction was defined in the pivotal trial CLEOPATRA in metastatic breast cancer as any event reported as hypersensitivity, anaphylactic reaction, acute infusion reaction or cytokine release syndrome occurring during an infusion or on the same day as the infusion. In the pivotal trial CLEOPATRA, the initial dose of Perjeta was given the day before trastuzumab and docetaxel to allow for the examination of Perjeta-associated reactions. On the first day when only Perjeta was administered, the overall frequency of infusion reactions was 9.8% in the placebo-treated group and 13.2% in the Perjeta-treated group, with the majority of infusion reactions being mild or moderate. The most common infusion reactions (≥ 1.0%) in the Perjeta-

treated group were pyrexia, chills, fatigue, headache, asthenia, hypersensitivity and vomiting.

During the second cycle when all medicinal products were administered on the same day, the most common infusion reactions in the Perjeta-treated group (≥ 1.0%) were fatigue, dysgeusia, drug hypersensitivity, myalgia and vomiting (see section 4.4).

In the NEOSPHERE and TRYPHAENA trials in the neoadjuvant setting, Perjeta was administered on the same day as the other study treatment drugs in all cycles. Infusion reactions were consistent with those observed in CLEOPATRA at the cycles when Perjeta was given on the same day as trastuzumab and docetaxel, with a majority of reactions being mild or moderate.

Hypersensitivity reactions/anaphylaxis
In the pivotal trial CLEOPATRA in metastatic breast cancer, the overall frequency of investigator reported hypersensitivity/anaphylaxis events during the entire treatment period was 9.3% in the placebo-treated group and 11.3% in the Perjeta-treated group, of which 2.5% and 2.0% were NCI-CTCAE Grade 3-4, respectively. Overall, 2 patients in the placebo-treated group and 4 patients in the Perjeta-treated group experienced events described as anaphylaxis by the investigator (see section 4.4).

Overall, the majority of hypersensitivity reactions were mild or moderate in severity and resolved upon treatment. Based on modifications made to the study treatment, most reactions were assessed as secondary to docetaxel infusions.

In NEOSPHERE and TRYPHAENA trials in the neoadjuvant setting, hypersensitivity/anaphylaxis events were consistent with those observed in CLEOPATRA. In NEOSPHERE, two patients in the Perjeta and docetaxel-treated group experienced anaphylaxis. In TRYPHAENA, the overall frequency of hypersensitivity/anaphylaxis was highest in the Perjeta and TCH treated group (13.2%), of which 2.6% were NCI-CTCAE v.3 Grade 3-4.

Febrile neutropenia
In the pivotal trial CLEOPATRA, the majority of patients in both treatment groups experienced at least one leucopenic event (63.0% of patients in the Perjeta-treated group and 58.3% of patients in the placebo-treated group), of which the majority were neutropenic events. Febrile neutropenia occurred in 13.7% of Perjeta-treated patients and 7.6% of placebo-treated patients. In both treatment groups, the proportion of patients experiencing febrile neutropenia was highest in the first cycle of therapy and declined steadily thereafter. An increased incidence of febrile neutropenia was observed among Asian patients in both treatment groups compared with patients of other races and from other geographic regions. Among Asian patients, the incidence of febrile neutropenia was higher in the Perjeta-treated group (25.8%) compared with the placebo-treated group (11.3%).

In the NEOSPHERE trial, 8.4% of patients treated with neoadjuvant Perjeta, trastuzumab and docetaxel experienced febrile neutropenia compared with 7.5% of patients treated with trastuzumab and docetaxel. In the TRYPHAENA trial, febrile neutropenia occurred in 17.1% of patients treated with neoadjuvant Perjeta + TCH, and 9.3% of patients treated with neoadjuvant Perjeta, trastuzumab and docetaxel

following FEC. In TRYPHAENA, the incidence of febrile neutropenia was higher in patients who received six cycles of Perjeta compared with patients who received three cycles of Perjeta, independent of the chemotherapy given. As in the CLEOPATRA trial, a higher incidence of neutropenia and febrile neutropenia was observed among Asian patients compared with other patients in both neoadjuvant trials. In NEOSPHERE, 8.3% of Asian patients treated with neoadjuvant Perjeta, trastuzumab and docetaxel experienced febrile neutropenia compared with 4.0% of Asian patients treated with neoadjuvant trastuzumab and docetaxel.

Diarrhoea
In the pivotal trial CLEOPATRA in metastatic breast cancer, diarrhoea occurred in 68.4% of Perjeta-treated patients and 48.7% of placebo-treated patients. Most events were mild to moderate in severity and occurred in the first few cycles of treatment. The incidence of NCI-CTCAE Grade 3-4 diarrhoea was 9.3% in Perjeta-treated patients vs 5.1% in placebo-treated patients. The median duration of the longest episode was 18 days in Perjeta-treated patients and 8 days in placebo-treated patients. Diarrhoeal events responded well to proactive management with anti-diarrhoeal agents.

In the NEOSPHERE trial, diarrhoea occurred in 45.8% of patients treated with neoadjuvant Perjeta, trastuzumab and docetaxel compared with 33.6% of patients treated with trastuzumab and docetaxel. In the TRYPHAENA trial, diarrhoea occurred in 72.3% of patients treated with neoadjuvant Perjeta+TCH and 61.4% of patients treated with neoadjuvant Perjeta, trastuzumab and docetaxel following FEC. In both studies most events were mild to moderate in severity.

Rash
In the pivotal trial CLEOPATRA in metastatic breast cancer, rash occurred in 51.7% of Perjeta-treated patients, compared with 38.9% of placebo-treated patients. Most events were Grade 1 or 2 in severity, occurred in the first two cycles, and responded to standard therapies, such as topical or oral treatment for acne.

In the NEOSPHERE trial, rash occurred in 40.2% of patients treated with neoadjuvant Perjeta, trastuzumab and docetaxel compared with 29.0% of patients treated with trastuzumab and docetaxel. In the TRYPHAENA trial, rash occurred in 36.8% of patients treated with neoadjuvant Perjeta + TCH and 20.0% of patients treated with neoadjuvant Perjeta, trastuzumab and docetaxel following FEC. The incidence of rash was higher in patients who received six cycles of Perjeta compared with patients who received three cycles of Perjeta, independent of the chemotherapy given.

Laboratory abnormalities
In the pivotal trial CLEOPATRA in metastatic breast cancer, the incidence of NCI-CTCAE v.3 Grade 3-4 neutropenia was balanced in the two treatment groups (86.3% of Perjeta-treated patients and 86.6% of placebo-treated patients, including 60.7% and 64.8% Grade 4 neutropenia, respectively).

In the NEOSPHERE trial, the incidence of NCI-CTCAE v.3 Grade 3-4 neutropenia was 74.5% in patients treated with neoadjuvant Perjeta, trastuzumab and docetaxel compared with 84.5% in patients treated with trastuzumab and docetaxel, including

50.9% and 60.2% Grade 4 neutropenia, respectively. In the TRYPHAENA trial, the incidence of NCI-CTCAE v.3 Grade 3-4 neutropenia was 85.3% in patients treated with neoadjuvantPerjeta + TCH and 77.0% in patients treated with neoadjuvant Perjeta, trastuzumab and docetaxel following FEC, including 66.7% and 59.5% Grade 4 neutropenia, respectively.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions (see details below).

Ireland

HPRA Pharmacovigilance

Earlsfort Terrace

IRL - Dublin 2

Tel: +353 1 6764971

Fax: +353 1 6762517

Website: www.hpra.ie

e-mail: medsafety@hpra.ie

Malta

ADR Reporting

Website: www.medicinesauthority.gov.mt/adrportal

United Kingdom

Yellow Card Scheme

Website: www.mhra.gov.uk/yellowcard

4.9 Overdose

The maximum tolerated dose of Perjeta has not been determined. In clinical trials, single doses higher than 25 mg/kg (1727 mg) have not been tested.

In case of overdose, patients must be closely monitored for signs or symptoms of adverse reactions and appropriate symptomatic treatment instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies, ATC code: L01XC13

Mechanism of action
Perjeta is a recombinant humanised monoclonal antibody that specifically targets the extracellular dimerisation domain (subdomain II) of the human epidermal growth factor receptor 2 protein (HER2), and thereby, blocks ligand-dependent heterodimerisation of HER2 with other HER family members, including EGFR, HER3 and HER4. As a result, Perjeta inhibits ligand-initiated intracellular signalling through two major signal pathways, mitogen-activated protein (MAP) kinase and phosphoinositide 3-kinase (PI3K). Inhibition of these signalling pathways can result in cell growth arrest and apoptosis, respectively. In addition, Perjeta mediates antibody-dependent cell-mediated cytotoxicity (ADCC).

While Perjeta alone inhibited the proliferation of human tumour cells, the combination of Perjeta and trastuzumab significantly augmented antitumour activity in HER2-overexpressing xenograft models.

Clinical efficacy and safety
The efficacy of Perjeta in HER2-positive breast cancer is supported by a randomised phase III comparative trial in metastatic breast cancer and two phase II studies (one single-arm trial in metastatic breast cancer and one randomised comparative trial in the neoadjuvant setting).

Metastatic breast cancer

Perjeta in combination with trastuzumab and docetaxel
CLEOPATRA (WO20698) is a multicentre, randomised, double-blind, placebo-controlled phase III clinical trial conducted in 808 patients with HER2-positive metastatic or locally recurrent unresectable breast cancer. Patients with clinically important cardiac risk factors were not included (see section 4.4). Due to the exclusion of patients with brain metastases no data are available on Perjeta activity on brain metastases. There is very limited data available in patients with unresectable locally recurrent disease. Patients were randomized 1:1 to receive placebo + trastuzumab + docetaxel or Perjeta + trastuzumab + docetaxel.

Perjeta and trastuzumab were given at standard doses in a 3-weekly regimen. Patients were treated with Perjeta and trastuzumab until disease progression, withdrawal of consent or unmanageable toxicity. Docetaxel was given as an initial dose of 75 mg/m2 as an intravenous infusion every three weeks for at least 6 cycles. The dose of docetaxel could be escalated to 100 mg/m2 at the investigator's discretion if the initial dose was well tolerated.

The primary endpoint of the study was progression-free survival (PFS) as assessed by an independent review facility (IRF) and defined as the time from the date of randomization to the date of disease progression or death (from any cause) if the

death occurred within 18 weeks of the last tumour assessment. Secondary efficacy endpoints were overall survival (OS), PFS (investigator-assessed), objective response rate (ORR), duration of response, and time to symptom progression according to the FACT B Quality of Life questionnaire.

Approximately half the patients in each treatment group had hormone receptor-positive disease (defined as estrogen receptor (ER) positive and/or progesterone receptor (PgR) positive) and approximately half of the patients in each treatment group had received prior adjuvant or neoadjuvant therapy. Most of these patients had received prior anthracycline therapy and 11% of all patients had received prior trastuzumab. A total of 43% of patients in both treatment groups had previously received radiotherapy. Patients' median LVEF at baseline was 65.0% (range 50% – 88%) in both groups.

The efficacy results from the CLEOPATRA study are summarised in Table 2. A statistically significant improvement in IRF-assessed PFS was demonstrated in the Perjeta-treated group compared with the placebo-treated group. The results for investigator-assessed PFS were similar to those observed for IRF-assessed PFS.

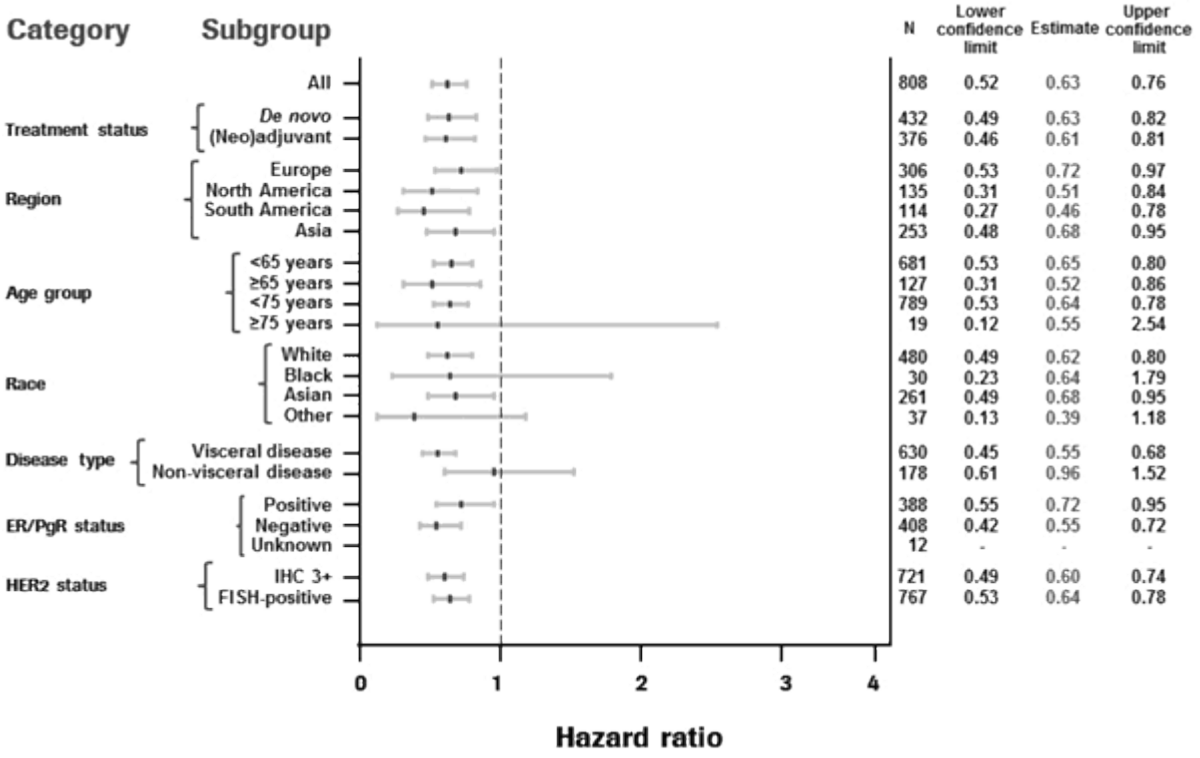
Table 2 Summary of efficacy from CLEOPATRA study

Parameter	**Placebo+ trastuzumab + docetaxel n=406**	**Perjeta+ trastuzumab + docetaxel n=402**	**HR (95% CI)**	**p-value**
Progression-Free Survival (independent review) – primary endpoint*				
no. of patients with an event	242 (59%)	191 (47.5%)	0.62	<0.0001
Median months	12.4	18.5	[0.51;0.75]	
Overall Survival - secondary endpoint**				
no. of patients with an event	221 (54.4%)	168 (41.8%)	0.68	0.0002
Median months	40.8	56.5	[0.56;0.84]	
Objective Response Rate (ORR)^ - secondary endpoint				
no. of patients with measurable disease	336	343	Difference in ORR:	0.0011
Responders***	233 (69.3%)	275 (80.2%)	10.8%	
95% CI for ORR	[64.1; 74.2]	[75.6; 84.3]	[4.2,17.5]%	
Complete response (CR)	14 (4.2%)	19 (5.5%)		
Partial Response (PR)	219 (65.2%)	256 (74.6%)		
Stable disease (SD)	70 (20.8%)	50 (14.6%)		
Progressive disease (PD)	28 (8.3%)	13 (3.8 %)		
Duration of Response †^				
n=	233	275		
Median weeks	54.1	87.6		
95% CI for Median	[46;64]	[71;106]		

* Primary progression-free survival analysis, cutoff date 13th May 2011.
** Final analysis of overall survival, cutoff date 11th February 2014.
*** Patients with best overall response of confirmed CR or PR by RECIST.
† Evaluated in patients with Best Overall Response of CR or PR.
^ Objective response rate and duration of response are based on IRF-assessed tumour assessments.

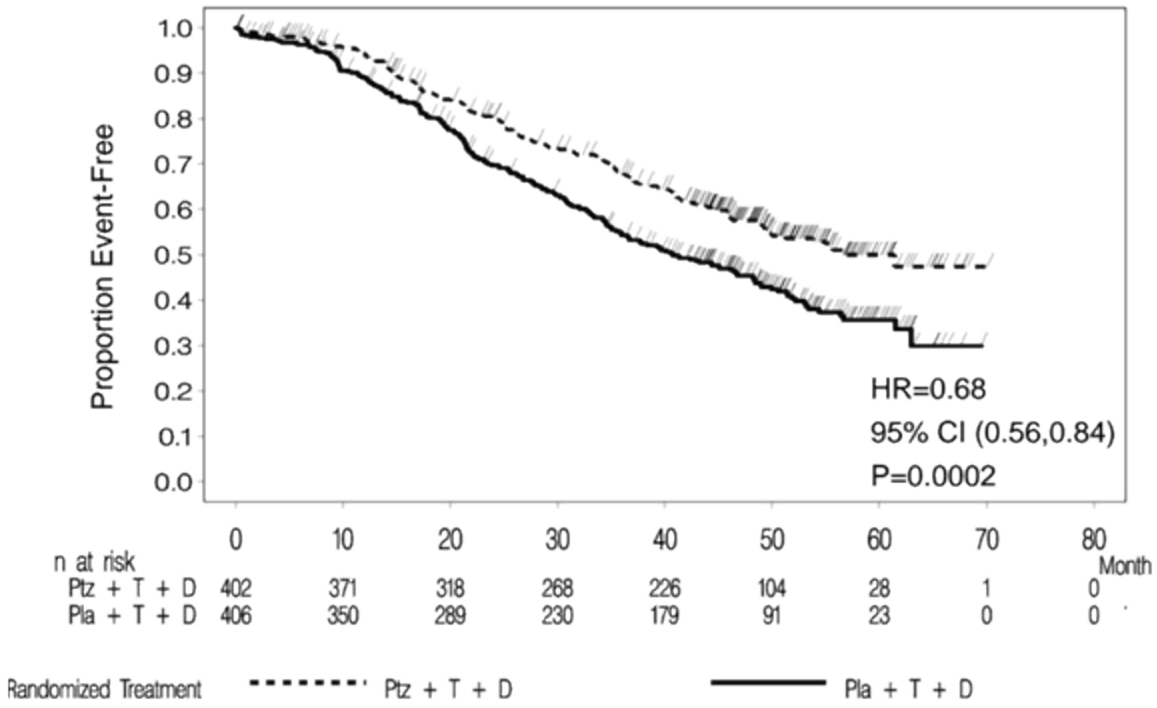
Consistent results were observed across pre-specified patient subgroups including the subgroups based on stratification factors of geographic region and prior adjuvant/neoadjuvant therapy or de novo metastatic breast cancer (see Figure 1). A post hoc exploratory analysis revealed that for patients who had received prior trastuzumab (n = 88), the hazard ratio for IRF-assessed PFS was 0.62 (95% CI 0.35, 1.07), compared with 0.60 (95% CI 0.43, 0.83) for patients who had received prior therapy which did not include trastuzumab (n = 288).

Figure 1 IRF-assessed PFS by patient subgroup



The final analysis of OS was performed when 389 patients had died (221 in the placebo-treated group and 168 in the Perjeta-treated group). The statistically significant OS benefit in favour of the Perjeta-treated group, previously observed at an interim analysis of OS (performed one year after the primary analysis), was maintained (HR 0.68, p = 0.0002 log-rank test). The median time to death was 40.8 months in the placebo-treated group and 56.5 months in the Perjeta-treated group (see Table 2, Figure 2).

Figure 2 Kaplan-Meier Curve of Overall Survival



HR= hazard ratio; CI= confidence interval; Pla= placebo; Ptz= pertuzumab (Perjeta); T= trastuzumab (Herceptin); D= docetaxel.

No statistically significant differences were found between the two treatment groups in Health Related Quality of Life as assessed by FACT-B TOI-PFB scores.

Additional supportive clinical trial information

BO17929 - single-arm trial in metastatic breast cancer

BO17929 was a phase II, non-randomised study in patients with metastatic breast cancer whose tumours had progressed during treatment with trastuzumab. Treatment with Perjeta and trastuzumab resulted in a response rate of 24.2%, with a further 25.8% of patients experiencing stabilisation of disease lasting at least 6 months, indicating that Perjeta is active following progression on trastuzumab.

Neoadjuvant Treatment of Breast Cancer

In the neoadjuvant setting, locally advanced and inflammatory breast cancers are considered as high-risk irrespective of hormone receptor status. In early stage breast cancer, tumor size, grade, hormone receptor status and lymph node metastases should be taken into account in the risk assessment.

The indication in the neoadjuvant treatment of breast cancer is based on demonstration of an improvement in pathological complete response rate, and trends to improvement in disease-free survival that nevertheless do not establish or precisely measure a benefit with regard to long-term outcomes, such as overall survival or disease-free survival.

NEOSPHERE (WO20697)

NEOSPHERE is a phase II, multicentre, multinational randomized controlled trial with Perjeta and was conducted in 417 adult female patients with newly diagnosed, early, inflammatory or locally advanced HER2-positive breast cancer (T2-4d; primary tumour > 2cm in diameter) who had not received prior trastuzumab, chemotherapy or radiotherapy. Patients with metastases, bilateral breast cancer, clinically important cardiac risk factors (see section 4.4) or LVEF < 55% were not included.The majority of patients were less than 65 years old.

Patients were randomised to receive one of the following neoadjuvant regimens for 4 cycles prior to surgery:

- Trastuzumab plus docetaxel
- Perjeta plus trastuzumab and docetaxel
- Perjeta plus trastuzumab
- Perjeta plus docetaxel.

Randomisation was stratified by breast cancer type (operable, locally advanced, or inflammatory) and ER or PgR positivity.

Perjeta was given intravenously at an initial dose of 840 mg, followed by 420 mg every three weeks. Trastuzumab was given intravenously at an initial dose of 8 mg/kg, followed by 6 mg/kg every three weeks. Docetaxel was given intravenously at an initial dose of 75 mg/ m2 followed by 75 mg/ m2 or 100 mg/ m2 (if tolerated) every 3 weeks. Following surgery all patients received 3 cycles of 5-fluorouracil (600 mg/m2), epirubicin (90 mg/m2), cyclophosphamide (600 mg/m2) (FEC) given intravenously every three weeks, and trastuzumab administered intravenously every three weeks to complete one year of therapy. Patients who only received Perjeta plus trastuzumab prior to surgery subsequently received both FEC and docetaxel post surgery.

The primary endpoint of the study was pathological complete response (pCR) rate in the breast (ypT0/is). Secondary efficacy endpoints were clinical response rate, breast conserving surgery rate (T2-3 tumours only), disease-free survival (DFS), and PFS. Additional exploratory pCR rates included nodal status (ypT0/isN0 and ypT0N0).

Demographics were well balanced (median age was 49-50 years, the majority were caucasian (71%)) and all patients were female. Overall 7% of patients had inflammatory breast cancer, 32% had locally advanced breast cancer and 61% had operable breast cancer. Approximately half the patients in each treatment group had hormone receptor-positive disease (defined as ER positive and/or PgR positive).

The efficacy results are presented in Table 3. A statistically significant improvement in pCR rate (ypT0/is) was observed in patients receiving Perjeta plus trastuzumab and docetaxel compared to patients receiving trastuzumab and docetaxel (45.8% vs 29.0%, p value = 0.0141). A consistent pattern of results was observed regardless of pCR definition. The difference in pCR rate is considered likely to translate into a

clinically meaningful difference in long term outcomes and is supported by positive trends in PFS (HR 0.69, 95% CI 0.34, 1.40) and DFS (HR 0.60, 95% CI 0.28, 1.27).

The pCR rates as well as the magnitude of benefit with Perjeta (Perjeta plus trastuzumab and docetaxel compared to patients receiving trastuzumab and docetaxel) were lower in the subgroup of patients with hormone receptor-positive tumours (difference of 6% in pCR in the breast) than in patients with hormone receptor-negative tumours (difference of 26.4% in pCR in the breast).

pCR rates were similar in patients with operable versus locally advanced disease. There were too few patients with inflammatory breast cancer to draw any firm conclusions but the pCR rate was higher in patients who received Perjeta plus trastuzumab and docetaxel.

TRYPHAENA (BO22280)

TRYPHAENA is a multicentre, randomised phase II clinical trial conducted in 225 adult female patients with HER2-positive locally advanced, operable, or inflammatory breast cancer (T2-4d; primary tumour > 2cm in diameter) who had not received prior trastuzumab, chemotherapy or radiotherapy. Patients with metastases, bilateral breast cancer, clinically important cardiac risk factors (See section 4.4) or LVEF <55% were not included. The majority of patients were less than 65 years old. Patients were randomised to receive one of three neoadjuvant regimens prior to surgery as follows:

- 3 cycles of FEC followed by 3 cycles of docetaxel, all given concurrently with Perjeta and trastuzumab
- 3 cycles of FEC alone followed by 3 cycles of docetaxel, with trastuzumab and Perjeta given concurrently
- cycles of TCH in combination with Perjeta.

Randomisation was stratified by breast cancer type (operable, locally advanced, or inflammatory) and ER and /or PgR positivity.

Perjeta was given intravenously at an initial dose of 840 mg, followed by 420 mg every three weeks. Trastuzumab was given intravenously at an initial dose of 8 mg/kg, followed by 6 mg/kg every three weeks. FEC (5-fluorouracil [500 mg/m^2], epirubicin [100 mg/m^2], cyclophosphamide [600 mg/m^2]) were given intravenously every three weeks for 3 cycles. Docetaxel was given as an initial dose of 75 mg/m^2 IV infusion every three weeks with the option to escalate to 100 mg/m^2 at the investigator's discretion if the initial dose was well tolerated. However, in the group treated with Perjeta in combination with TCH, docetaxel was given intravenously at 75 mg/m^2 (no escalation was permitted) and carboplatin (AUC 6) was given intravenously every three weeks. Following surgery all patients received trastuzumab to complete one year of therapy.

The primary endpoint of this study was cardiac safety during the neoadjuvant treatment period of the study. Secondary efficacy endpoints were pCR rate in the breast (ypT0/is), DFS, PFS and OS.

Demographics were well balanced between arms (median age was 49-50 years, the majority were Caucasian [77%]) and all patients were female. Overall 6% of patients had inflammatory breast cancer, 25% had locally advanced breast cancer and 69% had operable breast cancer. Approximately half the patients in each treatment group had ER-positive and/or PgR-positive disease.

Compared with published data for similar regimens without pertuzumab, high pCR rates were observed in all 3 treatment arms (see Table 3). A consistent pattern of results was observed regardless of pCR definition used. The pCR rates were lower in the subgroup of patients with hormone receptor-positive tumours (range 46.2% to 50.0%) than in patients with hormone receptor-negative tumours (range 65.0% to 83.8%).

pCR rates were similar in patients with operable and locally advanced disease. There were too few patients with inflammatory breast cancer to draw any firm conclusions.

Table 3 NEOSPHERE (WO20697) and TRYPHAENA (BO22280): Overview of efficacy (Intent to Treat Population)

	NEOSPHERE (WO20697)				TRYPHAENA (BO22280)	
Parameter	**Trastuzumab +Docetaxel N=107**	**Perjeta+ Trastuzumab+ Docetaxel N=107**	**Perjeta+ Trastuzumab N=107**	**Perjeta +Docetaxel N=96**	**Perjeta+ Trastuzumab+ FEC → Perjeta+ Trastuzumab+ Docetaxel N=73**	**FEC → Perjeta+ Trastuzumab+ Docetaxel N=75**
pCR rate in the breast (ypT0/is) n (%) [95% CI][1]	31 (29.0%) [20.6; 38.5]	49 (45.8%) [36.1; 55.7]	18 (16.8%) [10.3; 25.3]	23 (24.0%) [15.8; 33.7]	45 (61.6%) [49.5; 72.8]	43 (57.3%) [45.4; 68.7]
Difference in pCR rates[2] [95% CI][3]		+16.8 % [3.5; 30.1]	-12.2 % [-23.8; -0.5]	-21.8 % [-35.1; -8.5]	NA	NA
p-value (with Simes corr. for CMH test)[4]		0.0141 (vs. Trastuzumab+ Docetaxel)	0.0198 (vs. Trastuzumab + Docetaxel)	0.0030 (vs Perjeta+ Trastuzumab + Docetaxel)	NA	NA
pCR rate in the breast and lymph node (ypT0/is N0) n (%) [95% CI]	23 (21.5%) [14.1; 30.5]	42 (39.3%) [30.3; 49.2]	12 (11.2%) [5.9; 18.8]	17 (17.7%) [10.7; 26.8]	41 (56.2%) [44.1; 67.8]	41 (54.7%) [42.7; 66.2]
ypT0 N0 n (%) [95% CI]	13 (12.1%) [6.6; 19.9]	35 (32.7%) [24.0; 42.5]	6 (5.6%) [2.1; 11.8]	13 (13.2%) [7.4; 22.0]	37 (50.7%) [38.7; 62.6]	34 (45.3%) [33.8; 57.3]
Clinical Response[5]	79 (79.8%)	89 (88.1%)	69 (67.6%)	65 (71.4%)	67 (91.8%)	71 (94.7%)

FEC: 5-fluorouracil, epirubicin, cyclophosphamide; TCH: docetaxel, carboplatin and trastuzumab, CMH: Cochran–Mantel–Haenszel

1. 95% CI for one sample binomial using Pearson-Clopper method.

2. Treatment Perjeta+Trastuzumab+Docetaxel and Perjeta+Trastuzumab are compared to Trastuzumab+ Docetaxel while Perjeta+Docetaxel is compared to Perjeta+Trastuzumab+Docetaxel.

3. Approximate 95% CI for difference of two response rates using Hauck-Anderson method.

4. p-value from Cochran-Mantel-Haenszel test, with Simes multiplicity adjustment.

5. Clinical response represents patients with a best overall response of CR or PR during the neoadjuvant period (in the primary breast lesion).

Immunogenicity

Patients in the pivotal trial CLEOPATRA were tested at multiple time-points for anti-therapeutic antibodies (ATA) to Perjeta. Approximately 2.8% (11/386 patients) of Perjeta-treated patients and 6.2% (23/372 patients) of placebo-treated patients tested positive for ATAs. Of these 34 patients, none experienced severe (NCI-CTCAE Grade 4) infusion or hypersensitivity reactions (anaphylaxis) that were clearly related to ATA. However, Grade 3 hypersensitivity reactions associated with detectable ATAs occurred in 2 of 366 Perjeta-treated patients (0.5%) in phase I and II studies. There are currently insufficient data to evaluate the effects of ATA on the efficacy of Perjeta in combination with trastuzumab and docetaxel.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Perjeta in all subsets of the paediatric population in breast cancer (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

A population pharmacokinetic analysis was performed with data from 481 patients across different clinical trials (phase I, II and III) with various types of advanced malignancies who had received Perjeta as a single agent or in combination at doses ranging from 2 to 25 mg/kg administered every 3 weeks as a 30-60 minutes intravenous infusion.

Absorption

Perjeta is administered as an intravenous infusion. There have been no studies performed with other routes of administration.

Distribution

Across all clinical studies, the volume of distribution of the central (Vc) and the peripheral (Vp) compartment in the typical patient, was 3.11 litres and 2.46 litres, respectively.

Biotransformation

The metabolism of Perjeta has not been directly studied. Antibodies are cleared principally by catabolism.

Elimination

The median clearance (CL) of Perjeta was 0.235 litres/day and the median half-life was 18 days.

Linearity/non-linearity

Perjeta displayed linear pharmacokinetics within the recommended dose range.

Elderly patients
Based on the population pharmacokinetic analysis, no significant difference was observed in the pharmacokinetics of Perjeta between patients < 65 years (n=306) and patients ≥ 65 years (n=175).

Patients with renal impairment
No dedicated renal impairment trial for Perjeta has been conducted. Based on the results of the population pharmacokinetic analysis, Perjeta exposure in patients with mild (creatinine clearance [CLcr] 60 to 90 ml/min, N=200) and moderate renal impairment (CLcr 30 to 60 ml/min, N=71) was similar to that in patients with normal renal function (CLcr greater than 90 ml/min, N=200). No relationship between CLcr and Perjeta exposure was observed over the range of CLcr (27 to 244 ml/min).

Other special populations
The population PK analysis suggested no PK differences based on age, gender and ethnicity (Japanese versus non-Japanese). Baseline albumin and lean body weight were the most significant covariates influencing CL. CL decreased in patients with higher baseline albumin concentrations and increased in patients with greater lean body weight. However sensitivity analyses performed at the recommended dose and schedule of Perjeta showed that at the extreme values of these two covariates, there was no significant impact on the ability to achieve target steady-state concentrations identified in preclinical tumour xenograft models. Therefore, there is no need to adjust the dosage of Perjeta based on these covariates.

The PK results of pertuzumab in the NEOSPHERE study are consistent with the predictions from the previous population PK model.

5.3 Preclinical safety data

No specific fertility studies in animals have been performed to evaluate the effect of pertuzumab. No definitive conclusion on adverse effects can be drawn on the male reproductive organs in cynomolgus monkey repeated dose toxicity study.

Reproductive toxicology studies have been conducted in pregnant cynomolgus monkeys (Gestational Day (GD) 19 through to GD 50) at initial doses of 30 to 150 mg/kg followed by bi-weekly doses of 10 to 100 mg/kg. These dose levels resulted in clinically relevant exposures of 2.5 to 20-fold greater than the recommended human dose, based on Cmax. Intravenous administration of pertuzumab from GD19 through GD50 (period of organogenesis) was embryotoxic, with dose-dependent increases in embryo-foetal death between GD25 to GD70. The incidences of embryo-foetal loss were 33, 50, and 85% for pregnant female monkeys treated with bi-weekly pertuzumab doses of 10, 30, and 100 mg/kg, respectively (2.5 to 20-fold greater than the recommended human dose, based on Cmax). At Caesarean section on GD100, oligohydramnios, decreased relative lung and kidney weights and microscopic evidence of renal hypoplasia consistent with delayed renal development were identified in all pertuzumab dose groups. In addition, consistent with foetal growth restrictions, secondary to oligohydramnios, lung hypoplasia (1 of 6 in 30 mg/kg and 1 of 2 in100 mg/kg groups), ventricular septal defects (1 of 6 in 30 mg/kg group), thin ventricular wall (1 of 2 in 100 mg/kg group) and minor skeletal defects (external - 3 of 6 in 30 mg/kg group) were also noted. Pertuzumab exposure was reported in

offspring from all treated groups, at levels of 29% to 40% of maternal serum levels at GD100.

In cynomolgus monkeys, weekly intravenous administration of pertuzumab at doses up to 150 mg/kg/dose was generally well tolerated. With doses of 15 mg/kg and higher, intermittent mild treatment-associated diarrhoea was noted. In a subset of monkeys, chronic dosing (7 to 26 weekly doses) resulted in episodes of severe secretory diarrhoea. The diarrhoea was managed (with the exception of euthanasia of one animal, 50 mg/kg/dose) with supportive care including intravenous fluid replacement therapy.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Acetic acid, glacial
- L-Histidine
- Sucrose
- Polysorbate 20
- Water for Injections

6.2 Incompatibilities

No incompatibilities between Perjeta and polyvinylchloride (PVC) or non-PVC polyolefin bags including polyethylene have been observed. Glucose (5%) solution should not be used to dilute Perjeta since it is chemically and physically unstable in such solutions.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial
2 years.

Diluted solution
Chemical and physical in-use stability has been demonstrated for 24 hours at 30°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2°C-8°C).

Do not freeze.

Keep the vial in the outer carton in order to protect from light.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Vial (Type I glass) with a stopper (butyl rubber) containing 14 ml of solution.

Pack of 1 vial.

6.6 Special precautions for disposal and other handling

Perjeta does not contain any antimicrobial preservative. Therefore, care must be taken to ensure the sterility of the prepared solution for infusion and should be prepared by a healthcare professional.

Perjeta is for single use only and is administered intravenously by infusion.

The vial must not be shaken. 14 ml of Perjeta concentrate should be withdrawn from the vial and diluted into a 250 ml PVC or non-PVC polyolefin infusion bag of sodium chloride 9 mg/ml (0.9%) solution for infusion. After dilution, one ml of solution should contain approximately 3.02 mg of pertuzumab (840 mg/278 ml) for the initial dose where two vials are required and approximately 1.59 mg of pertuzumab (420 mg/264 ml) for the maintenance dose where one vial is required.

The bag should be gently inverted to mix the solution in order to avoid foaming.

Parenteral medicinal products should be inspected visually for particulates and discolouration prior to administration. If particulates or discoloration are observed, the solution should not be used. Once the infusion is prepared it should be administered immediately (see section 6.3).

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/813/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 4th March 2013

10. DATE OF REVISION OF THE TEXT

18 September 2015

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

Appendix 2 EPAR Summary for the public

EMA/589130/2015
EMEA/H/C/002547

PERJETA

This is a summary of the European public assessment report (EPAR) for Perjeta. It explains how the Committee for Medicinal Products for Human Use (CHMP) assessed the medicine to reach its opinion in favour of granting a marketing authorisation and its recommendations on the conditions of use for Perjeta.

What is Perjeta?

Perjeta is a cancer medicine that contains the active substance pertuzumab. It is available as a concentrate to be made into a solution for infusion (drip) into a vein.

What is Perjeta used for?

Perjeta is used to treat adults with breast cancer which is 'HER2-positive' (where a specific protein called 'HER2' is found on the surface of the cancer cells).

Perjeta can be used to treat metastatic breast cancer (cancer that has spread to other parts of the body) that has not already been treated with chemotherapy medicines or medicines designed to attach to HER2, or breast cancer that has come back after treatment and cannot be removed by surgery. In these cases, Perjeta is used together with trastuzumab and docetaxel (other cancer medicines).

Perjeta can also be used to treat earlier stages of breast cancer at high risk of coming back (i.e. locally advanced, inflammatory or early stage breast cancer), before the patient undergoes surgery. In these cases, Perjeta is used with trastuzumab and chemotherapy.

The medicine can only be obtained with a prescription.

How is Perjeta used?

Treatment with Perjeta should only be started under the supervision of a doctor who is experienced in using cancer medicines and in a hospital setting where resuscitation equipment is available. The HER2-positive status of the patient's cancer must be determined in advance of treatment with Perjeta by suitable tests.

Perjeta is given by infusion into a vein. The recommended first dose is 840 mg given over a period of one hour. This is followed by a dose of 420 mg every three weeks given over a period of half an hour to one hour. When used in the earlier stages of breast cancer, treatment with Perjeta should continue until the patient undergoes surgery. For metastatic cancer, treatment should continue until the disease gets worse or the side effects become unmanageable. Treatment should be temporarily interrupted if the patient experiences certain side effects.

How does Perjeta work?

The active substance in Perjeta, pertuzumab, is a monoclonal antibody. A monoclonal antibody is an antibody (a type of protein) that has been designed to recognise and attach to a specific structure (called an antigen) that is found on certain cells in the body. Pertuzumab has been designed to recognise and attach to HER2, a protein found on the surface of HER2-positive cancer cells. By attaching to HER2, pertuzumab stops HER2 producing signals that cause the cancer cells to grow. It also activates cells of the immune system, which then kill the cancer cells.

How has Perjeta been studied?

Perjeta has been studied in one main study involving 808 adults with previously untreated HER2-positive metastatic breast cancer. The effects of Perjeta were compared with placebo (a dummy treatment) when given together with other cancer medicines (trastuzumab and docetaxel). The patients were treated until their disease got worse or the side effects of treatment became unmanageable. The main measure of effectiveness was progression free survival (how long the patients lived without their disease getting worse).

Perjeta has also been studied in two main studies involving a total of 642 patients with earlier stages of breast cancer who were to undergo surgery. In these studies, Perjeta was given with trastuzumab and/or chemotherapy. The studies looked at how many patients responded to treatment (i.e. patients who had no cancer cells in the breast after surgery).

What benefit has Perjeta shown during the studies?

In the study in metastatic disease, patients treated with Perjeta lived for longer without their disease getting worse than patients given placebo. On average, patients treated with Perjeta lived for 18.5 months without their disease getting worse, compared with 12.4 months for patients given placebo.

In the studies in patients with earlier stages of breast cancer who were to undergo surgery, Perjeta was shown to improve response to treatment. In the first study, 46% of the patients treated with Perjeta plus trastuzumab and docetaxel responded to treatment, compared with 29% of patients who received trastuzumab and docetaxel alone. Response to treatment was also high in the second study (ranging from 57% to 66%) where Perjeta was given with trastuzumab and different chemotherapy medicines.

What is the risk associated with Perjeta?

The most common side effects with Perjeta given with trastuzumab and chemotherapy are diarrhoea, alopecia (hair loss), nausea (feeling sick) and neutropenia (low levels of neutrophils, a type of white blood cell important for fighting infections), which were experienced by more than half of all patients. The most common serious side effects include febrile neutropenia (low levels of neutrophils with fever), serious diarrhoea, leucopenia (low white blood cell counts) and neutropenia. Several other side effects are seen in more than 1 patient in 10.

For the full list of all side effects and restrictions with Perjeta, see the package leaflet.

Why has Perjeta been approved?

The CHMP noted that HER2-positive breast cancer is an aggressive form of breast cancer which occurs in around one in five cases. The Committee considered that Perjeta has been shown to benefit patients with metastatic cancer by extending the amount of time patients lived without their disease getting worse as well as how long they lived. It considered that this would provide an additional benefit when added to other medicines for HER2-positive cancer, notably trastuzumab. Perjeta has also been shown to improve the outcome of patients with earlier stages of breast cancer, when used with trastuzumab and chemotherapy.

The CHMP considered that, despite the side effects reported with Perjeta, the overall safety profile was acceptable. Therefore the CHMP decided that Perjeta's benefits are greater than its risks and recommended that it be given marketing authorisation.

What measures are being taken to ensure the safe and effective use of Perjeta?

A risk management plan has been developed to ensure that Perjeta is used as safely as possible. Based on this plan, safety information has been included in the summary of product characteristics and the package leaflet for Perjeta, including the appropriate precautions to be followed by healthcare professionals and patients.

In addition, the company that markets Perjeta will carry out two studies to assess the effects of using Perjeta and trastuzumab together with two different types of cancer medicine, in patients with HER2-positive breast cancer that is metastatic or has come back after treatment.

The company will also carry out two further studies to look into the long-term benefits and safety of Perjeta when used in patients with earlier stages of breast cancer.

Other information about Perjeta

The European Commission granted a marketing authorisation valid throughout the European Union for Perjeta on 4 March 2013.

The full EPAR for Perjeta can be found on the Agency's website:

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

For more information about treatment with Perjeta, read the package leaflet (also part of the EPAR) or contact your doctor or pharmacist.

This summary was last updated in 07-2015.

Appendix 3 Summary of the GeparSepto study

Trial design including method of randomisation: Randomised, multicentre, open-label, active-controlled, phase III study

Patients were randomised 1:1. It is not clear how patients were randomised or how the randomisation schedule was developed. Randomisation was stratified by centrally-assessed HER2, ER, PR, Ki67 and SPARC status.

Patients with HER2-positive breast cancer were simultaneously randomised 1:1:1 to receive two cycles of Herceptin, or Perjeta, or Herceptin and Perjeta prior to study entry (i.e. prior to receiving nab-paclitaxel or paclitaxel).

Duration of study: Patients were enrolled between July 2012 and January 2014. The data cut-off date for the primary analysis was not reported. However, it was planned to take place in July 2014.

Method of blinding: Blinding was not used in this study.

Interventions and comparators:

Table 110 Interventions and comparators in GeparSepto [Untch 2015]

Paclitaxel arm (n=598)	Nab-paclitaxel arm (n=606)	All arms
Paclitaxel weekly for 12 weeks followed by 4 cycles of conventionally dosed epirubicin + cyclophosphamide every three weeks.	Nab-paclitaxel weekly for 12 weeks followed by 4 cycles of conventionally dosed epirubicin + cyclophosphamide every three weeks.	HER2-positive patients (n=196 in the paclitaxel arm; n=199 in the nab-paclitaxel arm) received Herceptin plus Perjeta every three weeks concomitantly.

Eligibility criteria

Table 111 Eligibility criteria for GeparSepto study [Untch 2015]

Inclusion criteria	Exclusion criteria
Written informed consent according to local regulatory requirements prior to beginning specific protocol procedures Complete baseline documentation sent to GBG Forschungs GmbH Unilateral or bilateral primary carcinoma of the breast, confirmed histologically by core biopsy. Fine-needle aspiration alone was not sufficient and incisional biopsy was not allowed. In case of bilateral cancer, the investigator had to decide prospectively which side would be evaluated for the primary endpoint Tumour lesion in the breast with a palpable size of ≥2 cm or a sonographical size of ≥1 cm in maximum diameter. The lesion had to be measurable in two dimensions, preferably by sonography. In case of inflammatory disease, the extent of inflammation could be used as a measurable lesion Patients had to be in the following stages of disease: - cT2 - cT4a-d or cT1c and cN+ or - cT1c and pNSLN+ or - cT1c and ER-negative and PR-negative or - cT1c and Ki67 > 20% cT1c and HER2-positive In patients with multifocal or multicentric breast cancer, the largest lesion should be measured Centrally confirmed ER/PR/HER2, Ki67 and SPARC status detected on core biopsy. ER/PR positive was defined as >1% stained cells and HER2-positive was defined as IHC 3+ or *in situ* hybridisation (ISH) ratio >2.0. Formalin-fixed, paraffin-embedded breast tissue from core biopsy therefore had to be sent to the Dept. of Pathology at the Charité, Berlin, prior to randomisation Female aged ≥18 years	Prior chemotherapy for any malignancy Prior radiation therapy for breast cancer Pregnant or lactating patients. Patients of childbearing potential had to implement adequate non-hormonal contraceptive measures (barrier methods, intrauterine contraceptive devices, sterilisation) during study treatment Inadequate general condition (not fit for anthracycline-taxane targeted agents based chemotherapy) Previous malignant disease without being disease-free for less than 5 years (except carcinoma in situ of the cervix and non-melanomatous skin cancer) Known or suspected congestive heart failure (>NYHA I) and/or coronary heart disease, angina pectoris requiring antianginal medication, previous history of myocardial infarction, evidence of transmural infarction on ECG, uncontrolled or poorly controlled arterial hypertension (ie. BP >160/90 mm Hg under treatment with two antihypertensive drugs), rhythm abnormalities requiring permanent treatment, or clinically significant valvular heart disease History of significant neurological or psychiatric disorders including psychotic disorders, or dementia or seizures that would prohibit the understanding and giving of informed consent Persons who have been admitted to an institution by order of jurisdictional or governmental grounds Pre-existing motor or sensory neuropathy of grade 2 or more by NCICTC criteria v4.0 Currently active infection Definite contraindications for the use of corticosteroids Known hypersensitivity reaction to one of the compounds or incorporated substances used in this protocol Concurrent treatment with:

Karnofsky Performance status index ≥80% Normal cardiac function confirmed by ECG and cardiac ultrasound (LVEF or shortening fraction) within 3 months prior to randomisation. Results above the normal limit of the institution. For patients with HER2-positive tumours, LVEF ≥55% Laboratory requirements Haematology: absolute neutrophil count (ANC) ≥2.0 x 109/L and platelets ≥100 x 109/L and haemoglobin ≥10 g/dL (≥6.2 mmol/L) Hepatic function: total bilirubin <1.5x UNL; AST and ALT ≤1.5x UNL; and alkaline phosphatase ≤2.5x UNL Negative pregnancy test (urine or serum) within 14 days prior to randomisation for all women of childbearing potential Complete staging workup within 3 months prior to randomisation. All patients had to have had bilateral mammography, breast ultrasound (≤21 days), breast MRI (optional), chest X-ray (posterior-anterior and lateral), abdominal ultrasound or CT scan or MRI, and bone scan. In case of positive bone scan, bone X-ray was mandatory. Other tests could be performed as clinically indicated Patients had to be available and compliant for central diagnostics, treatment and follow-up	Chronic corticosteroids unless initiated >6 months prior to study entry and at low dose (10 mg or less methylprednisolone or equivalent) Sex hormones. Prior treatment must be stopped before study entry Other experimental drugs or any other anti-cancer therapy Participation in another clinical trial with any investigational, not marketed drug within 30 days prior to study entry Male patients

Trial drugs and concomitant medications

Neoadjuvant treatment

Paclitaxel arm

Paclitaxel infusion (80 mg/m^2) weekly for 12 weeks followed by 4 cycles of conventionally dosed EC (epirubicin, 90 mg/m^2; cyclophosphamide 600 mg/m^2) q3w (every three weeks).

Nab-paclitaxel arm

Nab-paclitaxel infusion (125 mg/m^2) weekly for 12 weeks followed by 4 cycles of conventionally dosed EC (epirubicin, 90mg/m^2; cyclophosphamide 600 mg/m^2) q3w.

Concomitant medications

The protocol for permitted concomitant therapy was not detailed in the study publications. However, HER2-positive patients received Herceptin plus Perjeta q3w (every three weeks) concomitantly. Herceptin was administered as a loading dose of 8 mg/kg followed by dosing at 6 mg/kg q3w. Perjeta was administered as a loading dose of 840 mg followed by dosing at 420 mg q3w.

Adjuvant treatment

After surgery, patients were to be treated according to Arbeitsgemeinschaft Gynäkologische Onkologie (German Gynaecological Oncology Group; AGO) Guidelines, with Herceptin if HER2-positive, and with tamoxifen and aromatase inhibitors if HR-positive.

Primary outcome: Pathological complete response (pCR) rate, defined as ypT0 ypN0, at Week 24.

Secondary outcomes:

- Rates of ypT0/is ypN0; ypT0 ypN0/+; ypT0/is ypN0/+; ypT(any) ypN0, and regression grade at Week 24
- Clinical and imaging response of the breast tumour ad axillary nodes at Week 24, based on physical examination and imaging tests (sonography, mammography, or MRI) after treatment in both arms
- Tolerability and safety at Week 24, with descriptive statistics for the 4 treatments (each taxane +/anti-HER2 treatment) on the number of patients whose treatment had to be reduced, delayed or permanently stopped
- pCR rates per treatment arm at Week 24
- Breast conservation rate at Week 24
- Onset of grade 3 neuropathy at Week 24
- Resolution of grade 3/4 neuropathy to at least grade 1 at Week 24
- Regional recurrence-free survival in patients with initial node-positive axilla, measured until event occurs (no event for cured patients)
- pCR rate and local recurrence free survival at Week 24 in patients with a clinical complete response (cCR) and a negative core biopsy

- Examination and comparison of molecular markers at baseline, Week 12 and Week 24
- Loco-regional invasive recurrence free survival in both arms and according to stratified subpopulations after 5 years (to be analysed after the end of the study), defined as the time period between registration and first event
- Distant disease-free survival (DFS) in both arms and according to stratified subpopulations after 5 years (to be analysed after the end of the study), defined as the time period between registration and first event
- Invasive disease-free survival in both arms and according to stratified subpopulations after 5 years (to be analysed after the end of the study), defined as the time period between registration and first event
- Overall survival in both arms and according to stratified subpopulations after 5 years (to be analysed after the end of the study), defined as the time period between registration and first event

Sub-studies

- CTC Substudy: Assess, characterise, and correlate circulating tumour cells and proteins with the effect of treatment (baseline, Week 12 and Week 24)
- Pharmacogenetic substudy: Correlate Single Nucleotide Polymorphisms (SNPs) of genes with the associated toxicity and histologically assessed treatment effect (baseline, Week 12 and Week 24)
- Ovarian substudy: Assess ovarian function measured by amenorrhea rate in correlation with changes in oestradiol, follicle stimulating hormone, luteinizing hormone, anti-Müller hormone, ultrasound follicle count in patients aged <45 years (baseline, 6 months, 12 months, 18 months, 24 months and 30 months)
- Surgical substudy in patients with high probability for pCR if it can be shown at an interim analysis that the positive predictive value for a pCR of a negative (≥3) core biopsies before surgery in patients with complete clinical response is >90%, these patients might opt for having no further breast surgery (baseline, after 4 cycles and before surgery)

Pre-planned subgroups: The study planned to analyse pCR outcomes by disease subgroups, including HER2 status (positive or negative), hormone receptor (HR) status (positive or negative), HER2 and HR status (four subgroups), Ki67 status (≤20% or >20%) and SPARC status (positive or negative).

Duration of follow-up: The study planned to follow-up patients for 5 years. However, the primary outcome was measured at Week 24.

Hypothesis objective: To compare the pCR (ypT0 ypN0) rates of neoadjuvant treatment of nab-paclitaxel with solvent-based paclitaxel as part of neoadjuvant treatment of operable or locally advanced primary breast cancer

A window of opportunity study was integrated to investigate response to anti-HER2 treatment without chemotherapy, HER2-positive patients were randomised to receive 6 weeks of either Herceptin, Perjeta or the combination with biomaterial collection at the start and the end of the window, before they received paclitaxel or nab-paclitaxel.

Statistical analysis: Two stage sequential testing was used, first to exclude 10% non-inferiority margin, and second, if positive, a superiority test with 2-sided α=0.05, ß=0.8.

The populations used in the outcome analyses were not reported in the available publications.

Sample size, power calculation: To increase the pCR rate from 33% with paclitaxel to 41% with nab-paclitaxel, corresponding to an odds ratio of 1.41 with an alpha of 0.05 and a power of 80%, 1,200 patients would be needed, of which 400 were to be HER2-positive.

Data management and patient withdrawals: The data management approach was not described in the available publications and withdrawals were not reported for the HER2-positive subgroup specifically.

- Paclitaxel arm
  598 patients were allocated to this study arm. 516 completed the allocated cycles of neoadjuvant Paclitaxel. 37 patients discontinued due to AEs, 30 due

to disease progression, 6 withdrew consent, 7 were withdrawn by Investigators, 1 patient died and 1 withdrew for unknown reasons.

- Nab-paclitaxel arm
  606 patients were allocated to the nab-paclitaxel arm. 479 patients completed the allocated cycles of neoadjuvant nab-paclitaxel. 103 patients discontinued due to AEs, 10 due to disease progression, 7 withdrew consent, 6 were withdrawn by Investigators and 1 withdrew for unknown reasons.

Quality assessment: The quality of the identified study was assessed according to the criteria outlined in the User Guide and shown in Table 112. Information about the GeparSepto Study was only available in a congress abstract and presentation, with some information available via ClinicalTrials.gov.

Table 112 Quality assessment of GeparSepto

Study Question	Grade (Yes/No/ Not Clear/N/A
Was randomisation carried out appropriately?	Not clear
Was the concealment of treatment allocation adequate?	Not clear
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Not clear
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)?	No
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Not clear
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Yes
Did the analysis include an intent-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Not clear

Baseline characteristics: Baseline characteristics of the HER2-postive sub-group were not reported in the available publications. Therefore, Table 113 shows the baseline characteristics of the whole population.

Table 113 Characteristics of participants in the GeparSepto Study across treatment groups

Trial name (number)	**GeparSepto (NCT01583426)**	
Study arm	**Paclitaxel**	**Nab-paclitaxel**
	n=598	**n=606**
Age in years, median (range)	48 (22–76)	49 (21–75)
Palpable tumour size in mm, median (range)	30 (5–150)	30 (4–150)
cT3 / 4, n (%)	86 (16.6)	82 (16.0)
cN+, n (%)	264 (45.1)	275 (46.3)
G 3, n (%)	336 (56.2)	318 (52.5)
Breast cancer subtype, n (%)		
HER2-negative	402 (67.2)	407 (67.1)
HER2-positive	**196 (32.7)**	**199 (32.8)**
Ki67 >20%, n (%)	414 (69.2)	418 (69.0)
SPARC positive, n (%)	94 (15.7)	97 (16.0)

HER2, human epidermal growth receptor 2; SPARC, secreted protein acidic and rich in cysteine protein

Appendix 4 Additional baseline characteristics of the TRYPHAENA study

Further details of the baseline characteristics of the patients in the TRYPHAENA study are provided here:

Detailed breakdown of the grading of breast cancer in each of the subgroups (operable, locally advanced, and inflammatory breast cancer) is presented in Table 114

The cardiac risk factors of the safety population are presented in Table 115.

Cardiac medications received by patients in the ITT population are presented in Table 116

Table 114 Grading of breast cancer at baseline in TRYPHAENA

Study arm	Arm A FEC+H+P x3 → T+H+P x3 n = 73	Arm B FEC x3 → T+H+P x3 n = 75	Arm C TCH+P x6 n = 77
Operable breast cancer, n (%)	n = 53	n = 54	n = 49
T2 N0 M0	9 (17.0)	20 (37.0)	19 (38.8)
T2 N1 M0	18 (34.0)	15 (27.8)	19 (38.8)
T3 N0 M0	6 (11.3)	5 (9.3)	4 (8.2)
T3 N1 M0	20 (37.7)	14 (25.9)	7 (14.3)
Locally advanced breast cancer, n (%)	n = 15	n = 17	n = 24
T2 N2 M0	3 (20.0)	3 (17.6)	2 (8.3)
T2 N3 M0	0 (0.0)	0 (0.0)	3 (12.5)
T3 N2 M0	4 (26.7)	4 (23.5)	4 (16.7)
T3 N3 M0	1 (6.7)	2 (11.8)	0 (0.0)
T4b N0 M0	1 (6.7)	1 (5.9)	0 (0.0)
T4c N0 M0	0 (0.0)	0 (0.0)	1 (4.2)
T4a N1 M0	1 (6.7)	0 (0.0)	1 (4.2)
T4b N1 M0	1 (6.7)	2 (11.8)	6 (25.0)
T4c N1 M0	0 (0.0)	1 (5.9)	1 (4.2)
T4a N2 M0	0 (0.0)	0 (0.0)	1 (4.2)
T4b N2 M0	2 (13.3)	2 (11.8)	3 (12.5)
T4c N2 M0	0 (0.0)	0 (0.0)	1 (4.2)
T4b N3 M0	0 (0.0)	2 (11.8)	0 (0.0)
T4c N3 M0	1 (6.7)	0 (0.0)	1 (4.2)
Unknown	1 (6.7)	0 (0.0)	0 (0.0)
Inflammatory breast cancer, n (%)	n = 5	n = 4	n = 4
T4d N0 M0	2 (40.0)	0 (0.0)	0 (0.0)
T4d N1 M0	2 (40.0)	0 (0.0)	4 (100.0)
T4d N2 M0	0 (0.0)	1 (25.0)	0 (0.0)
T4d N3 M0	1 (20.0)	2 (50.0)	0 (0.0)
T4d N3 M1*	0 (0.0)	1 (25.0)	0 (0.0)
*The inclusion of 1 patient in Arm B with T4d N3 M1 was a protocol violation. The patient received study treatment and was withdrawn after 2 cycles			

Table 115 Cardiac risk factor characteristics of participants in the TRYPHAENA study across treatment groups (safety population)

Study arm	Arm A FEC+H+P x3 → T+H+P x3 n = 72	Arm B FEC x3 → T+H+P x3 n = 75	Arm C TCH+P x6 n = 76
Baseline LVEF (central readings) Median (range)	71.6 (55−89)	72.0 (50−88)	72.9 (51−88)
Smoking status, n (%) Current smoker Never smoked Past smoker	 8 (11.1) 53 (73.6) 11 (15.3)	 10 (13.3) 56 (74.7) 9 (12.0)	 14 (18.4) 51 (67.1) 11 (14.5)
Atrial fibrillation, n (%) Previous Current	 0 (0.0) 0 (0.0)	 1 (1.3) 0 (0.0)	 0 (0.0) 1 (1.3)
Myocardial infarction, n (%) Previous Current	 1 (1.4)[a] 0 (0.0)	 0 (0.0) 0 (0.0)	 0 (0.0) 0 (0.0)
Myocardial ischaemia, n (%) Previous Current	 0 (0.0) 0 (0.0)	 1 (1.3) 0 (0.0)	 0 (0.0) 0 (0.0)
Arrhythmia, n (%) Previous Current	 0 (0.0) 1 (1.4)	 0 (0.0) 0 (0.0)	 0 (0.0) 0 (0.0)
Bundle branch block left, n (%) Previous Current	 0 (0.0) 0 (0.0)	 0 (0.0) 1 (1.3)	 0 (0.0) 0 (0.0)
Palpitations, n (%) Previous Current	 0 (0.0) 0 (0.0)	 0 (0.0) 0 (0.0)	 0 (0.0) 1 (1.3)
Tachyarrhythmia, n (%) Previous Current	 0 (0.0) 1 (1.4)	 0 (0.0) 0 (0.0)	 0 (0.0) 0 (0.0)
Hypertension, n (%) Previous Current	 0 (0.0) 13 (18.1)	 1 (1.3) 17 (22.7)	 0 (0.0) 15 (19.7)
Diabetes, n (%) Previous Current	 0 (0.0) 3 (4.2)	 1 (1.3) 3 (4.0)	 0 (0.0) 2 (2.6)
Hypothyroidism, n (%) Previous Current	 0 (0.0) 2 (2.8)	 0 (0.0) 2 (2.7)	 0 (0.0) 3 (3.9)
Hyperthyroidism, n (%) Previous Current	 0 (0.0) 1 (1.4)	 0 (0.0) 0 (0.0)	 0 (0.0) 1 (1.3)
Goiter, n (%) Previous Current	 0 (0.0) 2 (2.8)	 0 (0.0) 0 (0.0)	 0 (0.0) 1 (1.3)

Oedema, n (%)			
Previous	0 (0.0)	0 (0.0)	0 (0.0)
Current	0 (0.0)	1 (1.3)	0 (0.0)
Oedema peripheral, n (%)			
Previous	0 (0.0)	1 (1.3)	0 (0.0)
Current	0 (0.0)	0 (0.0)	0 (0.0)
Hypercholesterolaemia, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Previous	1 (1.4)	1 (1.3)	1 (1.3)
Current			
Hyperlipidaemia, n (%)			
Previous	0 (0.0)	0 (0.0)	0 (0.0)
Current	0 (0.0)	1 (1.3)	0 (0.0)
Blood triglycerides increased, n (%)			
Previous	0 (0.0)	0 (0.0)	0 (0.0)
Current	1 (1.4)	0 (0.0)	0 (0.0)

[a] Occurred during screening and patient exited the study before start of study treatment
FEC, 5-fluorouracil, epirubicin and cyclophosphamide; H, Herceptin; LVEF, left ventricular ejection fraction; P, Perjeta; T, docetaxel; C, carboplatin

Table 116 Cardiac medication in the TRYPHAENA study across treatment groups (ITT population)

Study arm	Arm A FEC+H+P x3 → T+H+P x3	Arm B FEC x3 → T+H+P x3	Arm C TCH+P x6
Previous medication, n (%)	n = 73	n = 75	n = 77
Alpha-adrenoreceptor antagonists	0 (0.0)	0 (0.0)	0 (0.0)
Angiotensin-converting enzyme inhibitors	4 (5.5)	7 (9.3)	5 (6.5)
Angiotensin-II receptor antagonists	4 (5.5)	4 (5.3)	2 (2.6)
Beta-adrenoceptor blocking agents	4 (5.5)	1 (1.3)	3 (3.9)
Calcium channel blockers	4 (5.5)	2 (2.7)	4 (5.2)
Antihypertensive agents	0 (0.0)	0 (0.0)	2 (2.6)
Statins	1 (1.4)	1 (1.3)	2 (2.6)
Anticoagulants	1 (1.4)	1 (1.3)	1 (1.3)
Platelet aggregation inhibitors	1 (1.4)	0 (0.0)	0 (0.0)
Thiazide and related diuretics	5 (6.8)	4 (5.3)	4 (5.2)
Loop diuretics	0 (0.0)	0 (0.0)	0 (0.0)
Thrombolytic agent	0 (0.0)	0 (0.0)	0 (0.0)
Medication during[a] neoadjuvant treatment, n (%)	n = 73	n = 75	n = 77
Alpha-adrenoreceptor antagonists	0 (0.0)	0 (0.0)	0 (0.0)
Angiotensin-converting enzyme inhibitors	0 (0.0)	1 (1.3)	2 (2.6)
Angiotensin-II receptor antagonists	0 (0.0)	2 (2.7)	0 (0.0)
Beta-adrenoceptor blocking agents	2 (2.7)	3 (4.0)	2 (2.6)
Calcium channel blockers	1 (1.4)	1 (1.3)	0 (0.0)
Antihypertensive agents	0 (0.0)	0 (0.0)	0 (0.0)
Statins	0 (0.0)	0 (0.0)	0 (0.0)
Anticoagulants	7 (9.6)	4 (5.3)	6 (7.8)
Platelet aggregation inhibitors	0 (0.0)	1 (1.3)	0 (0.0)
Thiazide and related diuretics	1 (1.4)	3 (4.0)	1 (1.3)
Loop diuretics	4 (5.5)	1 (1.3)	3 (3.9)
Thrombolytic agent	2 (2.7)	3 (4.0)	3 (3.9)
Medication during[a] adjuvant treatment, n (%)	n = 68	n = 65	n = 67
Alpha-adrenoreceptor antagonists	1 (1.5)	0 (0.0)	0 (0.0)
Angiotensin-converting enzyme inhibitors	4 (5.9)	2 (3.1)	0 (0.0)
Angiotensin-II receptor antagonists	2 (2.9)	1 (1.5)	0 (0.0)
Beta-adrenoceptor blocking agents	2 (2.9)	4 (6.2)	0 (0.0)
Calcium channel blockers	2 (2.9)	2 (3.1)	0 (0.0)
Antihypertensive agents	0 (0.0)	1 (1.5)	0 (0.0)
Statins	0 (0.0)	1 (1.5)	0 (0.0)
Anticoagulants	3 (4.4)	3 (4.6)	3 (4.5)
Platelet aggregation inhibitors	0 (0.0)	0 (0.0)	0 (0.0)
Thiazide and related diuretics	1 (1.5)	2 (3.1)	0 (0.0)
Loop diuretics	0 (0.0)	1 (1.5)	0 (0.0)

Thrombolytic agent	1 (1.5)	0 (0.0)	0 (0.0)

[a] Defined as the interval beginning 7 days prior to the patient's recruitment and continuing through the study.
FEC, 5-fluorouracil, epirubicin and cyclophosphamide; H, Herceptin; ITT, intent-to-treat; P, Perjeta; T, docetaxel; C, carboplatin

Appendix 5 Search strategy for systematic literature review of RCTs

The search terms for each database searched can be found in the following tables. No limits were applied to any of the searches.

Table 117: MEDLINE, MEDLINE In-Process and Embase via Ovid SP

Table 118: Embase Alert via ProQuest

Table 119: Cochrane Library Databases via the Wiley Online platform

Table 117 Search terms for the RCT search of MEDLINE, MEDLINE In-Process and Embase (searched simultaneously via the Ovid SP platform)

Term group	#	Terms	No. results
Disease area: HER2-positive breast cancer	1	exp breast neoplasms/	640,822
	2	exp breast tumor/	640,822
	3	exp breast cancer/	571,654
	4	((breast or mammary) adj5 (tumo* or cancer* or neoplasm* or adenocarcinoma* or carcinoma* or malignan* or sarcoma*)).mp.	788,835
	5	Or/1-4	793,095
	6	exp Neoadjuvant Therapy/	122,251
	7	(neoadjuvant* or pathologic* or pCR or tpCR or bpCR or operable or early or inflammatory or "locally advanced" or preoperative or "pre-operative" or "pre-surgery" or "before surgery").mp.	5,911,760
	8	((preliminary or primary) adj3 (therapy or treatment or chemotherapy or systemic or target?ed)).mp.	121,546
	9	Or/6-8	6,057,379
	10	5 and 9	193,234
Drugs	11	(pertuzumab or perjeta* or RG1273 or 2C4).tw.	1,534
RCTs	12	exp Randomized Controlled Trials as Topic/	19,911
	13	exp Randomized Controlled Trial/	805,637
	14	exp Random Allocation/	155,405
	15	exp Randomization/	155,405
	16	exp Double Blind Method/	262,864
	17	exp Single Blind Method/	42,774
	18	exp Cross-over Procedure/	45,083
	19	((singl* or doubl* or treb* or tripl*) adj (blind*3 or mask*3)).tw.	323,396
	20	exp Clinical Trial/	1,914,045
	21	clinical trial, phase ii.pt.	25,790
	22	clinical trial, phase iii.pt.	10,942
	23	clinical trial, phase iv.pt.	1,095
	24	exp Phase 2 Clinical Trial/ or exp Clinical trial, phase II/	76,576
	25	exp Phase 3 Clinical Trial/ or exp Clinical trial, phase III/	32,682
	26	exp Phase 4 Clinical Trial/ or exp Clinical trial, phase IV/	3,035
	27	controlled clinical trial.pt.	91,996
	28	randomized controlled trial.pt.	415,160
	29	clinical trial.pt.	507,464
	30	comparative study.pt.	1,746,867
	31	exp Clinical Trials as Topic/	473,857
	32	Trial*.ti.	463,314
	33	(clinical adj trial*).tw.	584,465
	34	exp Placebos/	312,774
	35	placebo*.ti,ab.	403,920
	36	randomly allocated.tw.	43,674
	37	(allocated adj2 random*).tw.	49,610
	38	random allocation.tw.	2,779
	39	random assignment.tw.	4,076
	40	randomi?ed.ti,ab.	1,016,502
	41	randomi?ation.tw.	59,430
	42	randomly.ti,ab.	552,033
	43	RCT.tw.	29,809
	44	Or/12-43	4,959,516
Exclusion terms	45	Animals/ not humans/	5,264,218
	46	(comment or editorial or "case reports").pt.	3,213,056
	47	(case stud* or case report*).ti.	490,653
	48	Or/45-47	8,739,680
Combined	49	10 and 11 and 44	291
	50	49 not 48	288
	51	Remove duplicates from 50	228

Table 118 Search terms for the RCT search of Embase Alert (searched via the ProQuest platform)

Term group	#	Terms	No. results
Disease area: HER2-positive breast cancer	S1	EMB.EXACT.EXPLODE("breast tumor")	14,827
	S2	(breast or mammary) near/5 (tumo* or cancer* or neoplasm* or adenocarcinoma* or carcinoma* or malignan* or sarcoma*)	16,970
	S3	S1 or S2	17,061
	S4	EMB.EXACT.EXPLODE("adjuvant therapy")	4,981[o]
	S5	(neoadjuvant* or pathologic* or pCR or tpCR or bpCR or operable or early or inflammatory or "locally advanced" or preoperative or "pre-operative" or "pre-surgery" or "before surgery")	142,726
	S6	(preliminary or primary) near/3 (therapy or treatment or chemotherapy or systemic or target?ed)	4,288[o]
	S7	S4 or S5 or S6	147,755
	S8	S3 and S7	5,362
Drugs	S9	pertuzumab or perjeta* or RG1273 or 2C4	472[o]
RCTs	S10	EMB.EXACT.EXPLODE("randomized controlled trials (topic)")	0
	S11	EMB.EXACT.EXPLODE("Randomized Controlled Trial")	8,448
	S12	EMB.EXACT.EXPLODE("Randomization")	2,027[o]
	S13	EMB.EXACT.EXPLODE("double blind procedure")	865[o]
	S14	EMB.EXACT.EXPLODE("single blind procedure")	106[o]
	S15	EMB.EXACT.EXPLODE("Cross-over Procedure")	0
	S16	(singl* or doubl* or treb* or tripl*) near/0 (blind*3 or mask*3)	6,747
	S17	EMB.EXACT.EXPLODE("Clinical Trial")	20,299
	S18	EMB.EXACT.EXPLODE("Clinical trial (topic)")	15,974
	S19	TI("Trial*")	15,421
	S20	clinical near/0 trial*	23,356
	S21	EMB.EXACT.EXPLODE("Placebo")	8,194
	S22	TI("placebo") or AB("placebo")	8,709
	S23	randomly allocated	1,465[o]
	S24	allocated near/2 random*	1,421[o]
	S25	random near/0 (allocation or assignment)	132[o]
	S26	randomi?ed or randomi?ation or randomly or random	49,440
	S27	RCT	1,615[o]
	S28	S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27	70,486
Exclusion terms	S29	RTYPE.EXACT("editorial" or "case reports")	9,069
	S30	TI("case stud*" or "case report*")	8,226
	S31	S29 or S30	17,272
Combined	S32	S8 and S9 and S28	12[o]
	S33	S32 not S31	12[o]

Table 119 Search terms for the RCT search of the Cochrane Library Databases (searched simultaneously via the Wiley Online platform)

Term group	#	Terms	No. results
Disease area: HER2-positive breast cancer	1	[mh “Breast neoplasms”]	9,107
	2	((breast or mammary) near/5 (tumo* or cancer* or neoplasm* or adenocarcinoma* or carcinoma* or malignan* or sarcoma*))	21,419
	3	#1 or #2	21,419
	4	[mh “Neoadjuvant therapy”]	124,154
	5	neoadjuvant* or pathologic* or *pCR or operable or early or inflammatory or "locally advanced" or preoperative or "pre-operative" or "pre-surgery" or "before surgery"	11,193
	6	(preliminary or primary) near/3 (therapy or treatment or chemotherapy or systemic or targeted or targetted)	11,193
	7	{or #4-#6}	131,948
	8	#3 and #7	7,109
Drugs	9	pertuzumab or perjeta* or RG1273 or 2C4	156
RCTs	10	[mh “Randomized controlled trials as topic”]	21,239
	11	[mh “Random allocation”]	20,486
	12	[mh “Randomized controlled trial”]	169
	13	[mh “Randomization”]	20,486
	14	[mh “Double-blind method”]	107,319
	15	[mh “Single-blind method”]	12,974
	16	[mh “Clinical trial”]	201
	17	[mh “Clinical trial, phase II”]	0
	18	[mh “Clinical trial, phase III”]	1
	19	[mh “Clinical trial, phase IV”]	0
	20	[mh “Clinical Trials as Topic”]	56,864
	21	[mh “Placebos”]	22,192
	22	controlled clinical trial:pt	357,862
	23	randomized controlled trial:pt	357,572
	24	clinical trial:pt	365,862
	25	clinical trial, phase ii:pt	6,272
	26	clinical trial, phase iii:pt	7,373
	27	clinical trial, phase iv:pt	422
	28	(singl* OR doubl* OR treb* OR tripl*) next (blind* OR mask*)	213,746
	29	trial*:ti	170,041
	30	clinical next trial*	437,731
	31	placebo*:ti,ab	158,539
	32	“randomly allocated”	20,707
	33	allocated near/2 random*	23,690
	34	“random allocation”	27,096
	35	“random assignment”	2,713
	36	randomi?ed:ti,ab	374,603
	37	randomi?ation	37,456
	38	randomly:ti,ab	123,696
	39	RCT	225,293
	40	{or #10-#39}	828,311
Combined	41	#8 and #9 and #40	22
	42	#41 in Cochrane Reviews (Reviews only), Other Reviews and Trials	22

Appendix 6 Records included in the systematic literature review of RCTs

A summary of the records included at the full-text review stage of the systematic review to identify RCT evidence is presented in Table 120, and those excluded are presented in Table 121.

Table 120 Records included in the systematic literature review of RCTs

Citation	Study	Comments
Gianni 2012. "Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): A randomised multicentre, open-label, phase 2 trial." *Lancet Oncology*. 13(1):25-32.	NeoSphere	Primary data source; peer-reviewed publication.
Gianni 2011. "Addition of pertuzumab (P) to trastuzumab (H)-based neoadjuvant chemotherapy significantly improves pathological complete response in women with HER2-positive early breast cancer: Result of a randomised phase II study (NEOSPHERE)." *Breast*. 20(suppl. 1): S73.	NeoSphere	Secondary data source; congress poster from 12th St Gallen International Breast Cancer Conference and published abstract reporting additional outcomes compared to the primary publication.
Gianni 2015. "Five-year analysis of the phase II NeoSphere trial evaluating four cycles of neoadjuvant docetaxel (D) and/or trastuzumab (T) and/or pertuzumab (P)." *Journal of Clinical Oncology*. 33(15 suppl): 505.	NeoSphere	Secondary data source; congress oral presentation from American Society of Clinical Oncology (ASCO) 2015 Annual Meeting and published abstract reporting longer-term follow-up compared with the primary data source.
Schneeweiss 2013. "Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: A randomized phase II cardiac safety study (TRYPHAENA)." *Annals of Oncology*. 24(9): 2278-2284.	TRYPHAENA	Primary data source; peer-reviewed publication.
Schneeweiss 2012. "Pertuzumab and trastuzumab in combination with an anthracycline-containing or an anthracycline-free standard chemotherapy in the neoadjuvant treatment of HER2-positive breast cancer (TRYPHAENA)." *European Journal of Cancer*. 48(suppl 1): S96.	TRYPHAENA	Secondary data source; congress poster from 8th European Breast Cancer Conference and published abstract reporting additional outcomes compared to the primary publication.
Untch 2015. "A randomized phase III trial comparing neoadjuvant chemotherapy with weekly nanoparticle-based paclitaxel with solvent-based paclitaxel followed by anthracyline/cyclophosphamide for patients with early breast cancer (GeparSepto); GBG 69." *Cancer Research*. 75(9 suppl): Abstract S2-07.	GeparSepto	Primary data source; congress oral presentation from 2014 San Antonio Breast Cancer Symposium and published abstract. Supplemented with information from study record on ClinicalTrials.gov.

Table 121 Records excluded at the full-text review stage of the SLR of RCTs

Citation	Study	Reason for exclusion
2012. Neoadjuvant pertuzumab (P) and trastuzumab (H): Biomarker analyses of a 4-arm randomized phase II study (NeoSphere) in patients (Pts) with HER2-positive breast cancer (BC). *Clinical Advances in Hematology & Oncology*. 10(2 suppl 2): 10–11.	NeoSphere	Congress presentation review. The outcomes have been reported in a peer-reviewed manuscript.
2012. Neoadjuvant pertuzumab and trastuzumab concurrent or sequential with an anthracycline-containing or concurrent with an anthracycline-free standard regimen: A randomized phase II study (TRYPHAENA). *Clinical Advances in Hematology & Oncology*. 10(2 suppl 2): 9–10.	TRYPHAENA	Congress presentation review. The outcomes have been reported in a peer-reviewed manuscript.
Bria 2012. "A treatment-interaction analysis balancing pathological complete responses (PCR) and cardiotoxicity of single-(S)/dual-(D) HER2 inhibition and neoadjuvant chemotherapy (CT) backbone in operable/locally advanced breast cancer (O/LABC) patients." *Annals of Oncology*. 23(suppl 9): ix117-ix118.	Review	The publication did not report comparative data for Perjeta-based regimens. The publication incorporated 8 RCTs, however it as unclear which RCTs were included.
Capelan 2012. "Pertuzumab: New hope for patients with HER2-positive breast cancer." *Annals of Oncology*. 24(2): 273-282.	Review	Narrative review reporting on NeoSphere and TRYPHAENA.
DeMichele 2013. "Rationale of the design of the I-SPY trial." *European Journal of Cancer*. 49(suppl 4): S2.	I-SPY	Study protocol; no outcomes reported.
Dent 2013. "HER2-targeted therapy in breast cancer: A systematic review of neoadjuvant trials." *Cancer Treatment Reviews*. 39(6): 622-631.	Systematic review	The relevant RCT identified (NeoSphere) was already included in the review, and no additional information was reported.
Drucker 2012. "Risk of rash with the anti-HER2 dimerization antibody pertuzumab: A meta-analysis." *Breast Cancer Research and Treatment*. 135(2): 347-354.	Meta-analysis	The meta-analysis included a mixed population, including breast, prostate and ovarian cancers. Outcomes were not reported separated for breast cancer.
Furlanetto 2012. "Impact of single/dual HER2 inhibition and chemotherapy (CT) backbone upon pathologic complete response (pCR) in patients receiving neoadjuvant CT for operable/locally advanced breast cancer (O/LABC): A treatment-interaction analysis of randomized trials." *Journal of Clinical Oncology*. 30(15 suppl): 630.	Interaction analysis	The publication did not report comparative data for Perjeta-based regimens. The publication incorporated 7 RCTs, however it as unclear which RCTs were included.
Gianni 2011. "Neoadjuvant Pertuzumab (P) and Trastuzumab (H): Biomarker analyses of a 4-arm randomized phase II study (NeoSphere) in patients (pts) with HER2-Positive Breast Cancer (BC)." *Cancer Research*. 71(24 suppl): Abstract S5-1.	NeoSphere	No additional information was reported compared to the peer-reviewed publication.
Gianni 2013. "Cardiac safety of pertuzumab-and trastuzumab-based therapy: Neosphere and tryphaena joint analysis." *Breast*. 22(suppl 1): S102.	NeoSphere / TRYPHAENA	Pooled analysis two relevant RCTs (NeoSphere and TRYPHAENA) that were already included in this SLR.

Gianni 2010. "Neoadjuvant Pertuzumab (P) and Trastuzumab (H): Antitumor and Safety Analysis of a Randomized Phase II Study ('NeoSphere')."*Cancer Research.* 70(24 suppl): Abstract S3-2.	NeoSphere	No additional information was reported compared to the peer-reviewed publication.
Jackisch 2013. "A randomized phase III trial comparing nanoparticle-based paclitaxel with solvent-based paclitaxel as part of neoadjuvant chemotherapy for patients with early breast cancer (GeparSepto): GBG 69." *Journal of Clinical Oncology*. 31(15 suppl): Abstract TPS1141.	GeparSepto	Study protocol; no outcomes reported.
Kumler 2014. "A systematic review of dual targeting in HER2-positive breast cancer." *Cancer Treatment Reviews*. 40(2): 259-270.	Systematic review	The relevant RCT identified (NeoSphere) was already included in the review, and no additional information was reported.
Martin 2013. "Neoadjuvant trastuzumab emtansine and docetaxel, with or without pertuzumab, in patients with HER2-positive early-stage breast cancer: Results from a phase 1b/2a study." *Cancer Research*. 73(24 suppl): Abstract P4-12-07.	BP22572	Not a RCT.
Mates 2015. "Systemic targeted therapy for HER2-positive early female breast cancer: A systematic review of the evidence for the 2014 cancer care Ontario systemic therapy guideline." *Current Oncology*. 22(suppl 1): S114-S122.	Systematic review	The relevant RCT identified (NeoSphere) was already included in the review, and no additional information was reported.
Nagayama 2014. "Comparative effectiveness of neoadjuvant therapy for HER2-positive breast cancer: A network meta-analysis." *Journal of the National Cancer Institute*. 106(9): dju203	NMA	The relevant RCT identified (NeoSphere) was already included in the review, and no additional information was reported.
Schneeweiss 2012. "Biomarker (BM) analyses of a phase II study of neoadjuvant pertuzumab and trastuzumab with and without anthracycline (ATC)-containing chemotherapy for treatment of HER2-positive early breast cancer (BC) (TRYPHAENA)." *Annals of Oncology*. 23(suppl 9). Abstract 202P.	TRYPHAENA	No additional information of interest to this SLR was reported compared to the peer-reviewed publication; biomarker analyses were not an outcome of interest.
Schneeweiss 2011. "Neoadjuvant pertuzumab and trastuzumab concurrent or sequential with an anthracycline-containing or concurrent with an anthracycline-free standard regimen: A randomized phase ii study (TRYPHAENA)." *Cancer Research*. 71(24 suppl): Abstract S5–6.	TRYPHAENA	No additional information was reported compared to the peer-reviewed publication.
Schneeweiss 2015. "A randomized phase III trial comparing two dose-dense dose-intensified approaches (EPC and PM(Cb)) for neoadjuvant treatment of patients with high-risk early breast cancer (GeparOcto)." *Journal of Clinical Oncology*. 33(15 suppl): TPS1101.	GeparOcto;	Study protocol; no outcomes reported for the HER2-positive subpopulation.
Sendur 2012. "Pertuzumab in HER2-positive breast cancer." *Current Medical Research and Opinion*. 28(10): 1709-1716.	Review	Narrative review.

Untch 2012. "A randomized phase III trial comparing nanoparticle-based paclitaxel with solvent-based paclitaxel as part of neoadjuvant chemotherapy for patients with early breast cancer (geparsepto) gbg 69." *Cancer Research*. 72(24 suppl): Abstract OT3-3-11.	GeparSepto;	Study protocol; no outcomes reported for the HER2-positive subpopulation.
Van Ramshorst 2013. "Optimizing neoadjuvant systemic treatment in HER2 positive breast cancer-The TRAIN-2 study." *Cancer Research*. 73(24 suppl): Abstract OT1-1-01.	TRAIN-2	Study protocol; no outcomes reported.
Walshe 2006. "A phase II trial with trastuzumab and pertuzumab in patients with HER2-overexpressed locally advanced and metastatic breast cancer." *Clinical Breast Cancer*. 6(6): 535-539.	*No study name or number reported*	Not neoadjuvant treatment and not a RCT; single-arm, single-centre study.
Zagouri 2013. "Pertuzumab in breast cancer: A systematic review." *Clinical Breast Cancer*. 13(5): 315-324.	Systematic review	The relevant RCT identified (NeoSphere) was already included in the review, and no additional information was reported.

Appendix 7 Quality appraisal of the RCTs identified in the SLR

The full quality appraisals for the RCTs identified in the SLR can be found here:

NeoSphere (Table 122)

TRYPHAENA (Table 123)

GeparSepto (Table 124)

Table 122 Quality assessment of the NeoSphere Study

Study Question	NeoSphere (NCT00545688)	
	How is the Question Addressed in the Study?	Grade (Yes/No/ Not Clear/N/A)
Was randomisation carried out appropriately?	Patients were centrally randomly assigned (1:1:1:1) to receive 1 of the 4 neoadjuvant treatments. An interactive voice response system was used to obtain screening information for every patient. Patients were randomly assigned treatment by a central randomisation procedure with the adaptive randomisation method and stratified by operable, locally advanced, and inflammatory breast cancer, and by positivity for oestrogen or progesterone receptors. It is not clear from the information provided how the randomisation scheme was generated.	Yes
Was the concealment of treatment allocation adequate?	Patients were centrally randomly assigned (1:1:1:1) via an interactive voice response system.	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	The study publication stated that baseline demographics were balanced across arms.	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)?	Blinding was not used in this study. In terms of the primary outcome, pathologists at study centres followed guidelines for the assessment of pCR on serial sections of the surgical specimen. In addition to this, blinded pathology data were reviewed by a consultant pathologist at regular intervals to ensure consistency, therefore reducing the risk of bias in primary outcome results.	No
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	A higher proportion of patients in Arm C withdrew from neoadjuvant study treatment; 4/107, 5/107, 14/107 and 6/96 patients in Groups A, B, C and D, respectively, withdrew from neoadjuvant study treatment. It is not clear whether this imbalance was unexpected. In the primary manuscript, however, it is noted that 6% (25/417) of patients, mostly in the chemotherapy-free group (Arm C), did not undergo surgery as planned, mainly due to failure to achieve a sufficient therapeutic response. This is acknowledged as a potential limitation of the study.	Not clear
Is there any evidence to suggest that the authors measured more outcomes than they reported?	The primary endpoints and most of the secondary endpoints were reported in the primary manuscript (time to clinical response and breast-conserving surgery rate we not reported in the primary manuscript). A congress abstract/presentation has reported longer-term analyses. Some exploratory biomarker analyses have been presented at congresses. Further outcomes were available in the Study CSR.	N/A (CSR available)

Did the analysis include an intent-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	The primary manuscript stated that efficacy analyses were carried out in the intent-to-treat population. Further information on the methods used to account of missing data are not reported in the primary manuscript. However, more details were provided in the Study CSR. Patients who received study treatment were included in the safety analysis.	Not clear

Table 123 Quality assessment of the TRYPHAENA Study

Study Question	TRYPHAENA (NCT00976989)	
	How is the Question Addressed in the Study?	**Grade (Yes/No/ Not Clear/N/A)**
Was randomisation carried out appropriately?	Patients were centrally randomised 1 : 1 : 1 via an interactive voice response system. Treatment allocation was dynamic and stratified by operable, locally advanced and inflammatory breast cancer and by hormone receptor positivity. It is not clear from the information provided how the randomisation scheme was generated.	Yes
Was the concealment of treatment allocation adequate?	Patients were centrally randomised 1 : 1 : 1 via an interactive voice response system.	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	The study publication stated that baseline demographics were generally balanced across arms, with the following exceptions: • More white patients were randomised to Arm C • The proportion of patients with operable breast cancer was lower in Arm C. Correspondingly, more patients in Arm C presented with locally advanced disease • More patients in Arm B presented with hormone receptor-negative tumours • The proportion of patients with HER2 IHC 2+ tumours was higher in Arm A	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)?	Blinding was not used in this study.	No
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	A higher number of patients who entered neoadjuvant treatment in Arm B and Arm C did not complete neoadjuvant treatment compared to Arm A; 3/72, 9/75 and 6/76 patients in Arm A, Arm B and Arm C, respectively, did not receive all 6 cycles of neoadjuvant treatment. It is not clear whether this imbalance was unexpected. Similar proportions of patients who entered adjuvant treatment did not complete the adjuvant treatment period; 6/68, 5/65 and 3/67 patients in Arm A, Arm B and Arm C, respectively, completed adjuvant treatment.	Not clear
Is there any evidence to suggest that the authors measured more outcomes than they	The primary, secondary and safety outcomes were reported in the primary manuscript. Some exploratory biomarker analyses have been presented at congress. Further outcomes were available in the Study CSR.	N/A (CSR available)

reported?		
Did the analysis include an intent-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	The publication stated that all randomised patients were included in the intent-to-treat population, which was used to assess pCR rates. Patients who received at least one study treatment were included in the safety analysis.	Yes
HER2, human epidermal growth receptor 2; IHC, immunohistochemistry; pCR, pathological complete response		

Table 124 Quality assessment of the GeparSepto Study

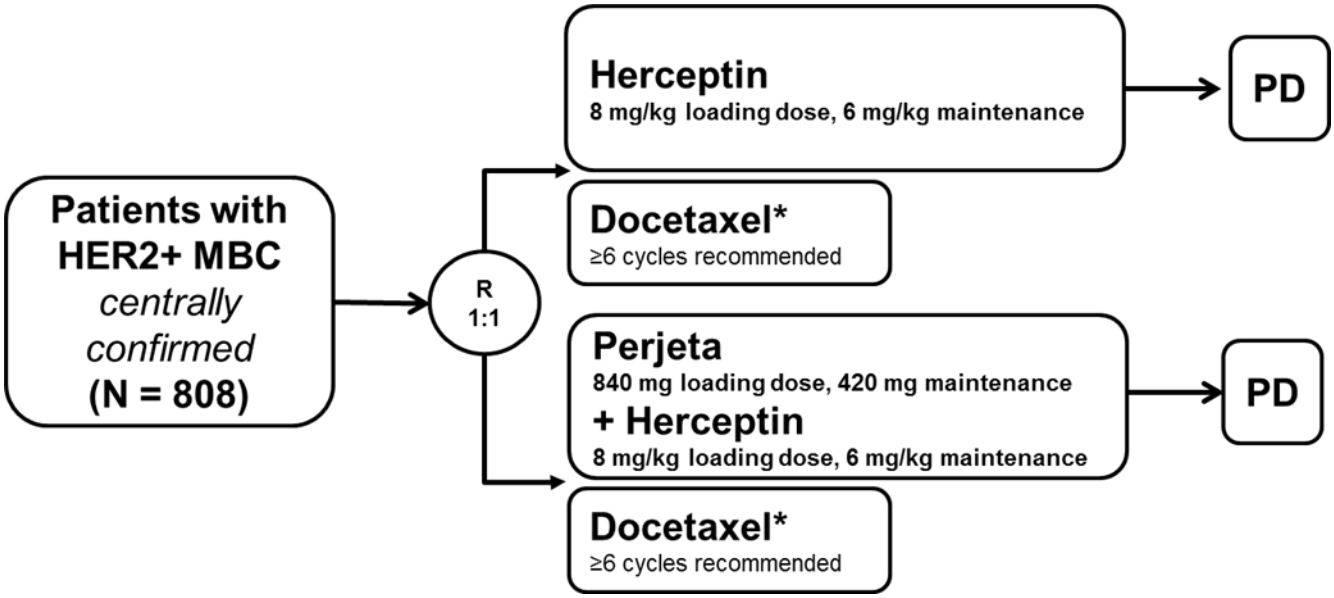
Study question	How is the Question Addressed in the Study?	Grade (Yes/No/ Not Clear/N/A)
Was randomisation carried out appropriately?	The method of randomisation was not reported (congress proceeding and presentation only).	Not clear
Was the concealment of treatment allocation adequate?	The method of concealment of treatment allocation was not reported (congress proceeding and presentation only).	Not clear
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	The baseline characteristics for the HER2-positive subpopulation were not reported separately. However, the baseline characteristics of the whole population was similar.	Not clear
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)?	Blinding was not used in the study.	No
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Drop-outs for the HER2-positive subpopulation were not reported separately. However, overall there was a statistically significant difference in discontinuation between the treatment arms; more patients discontinued in the nab-paclitaxel arm ($p<0.001$). Reasons for discontinuation were reported.	Not clear
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Information on the clinicaltrials.gov website suggests further outcomes than reported in the congress presentation were assessed. Only pCR was reported for the HER2-positive subpopulation.	Yes
Did the analysis include an intent-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	The populations used in the analyses were not reported (congress proceeding and presentation only).	Not clear
HER2, human epidermal growth receptor 2		

Appendix 8 CLEOPATRA study in metastatic breast cancer

The trial methodology for CLEOPATRA (location, trial design, eligibility criteria, settings & location, outcomes, statistical analysis), baseline characteristics and patient flow are presented here (as was done in sections 4.3-4.5 for the neoadjuvant studies. The safety data for the CLEOPATRA study follows thereafter.

Trial Design: The CLEOPATRA study was a randomised, double-blind, placebo-controlled clinical trial which enrolled 808 people with HER2-positive metastatic breast cancer randomised in a 1:1 ratio to one of two treatment arms. The study design is shown in Figure 37.

Figure 37 Study schema for the CLEOPATRA trial [Baselga 2012]



PD=progressive disease
*<6 cycles allowed for unacceptable toxicity or PD; >6 cycles allowed at investigator discretion; docetaxel starting dose 75mg/m^2

Eligibility criteria: Table 125 and Table 126 contain details of the key inclusion and exclusion criteria for the study. As in NeoSphere and TRYPHAENA, patients had to be 18 years of age or over, have left ventricular ejection fraction of ≥50%, and an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1.

Table 125 Key inclusion criteria specific to the metastatic setting in the CLEOPATRA study [CLEOPATRA Primary CSR]

Inclusion criteria
• Locally recurrent, unresectable, or centrally confirmed metastatic HER2-postive breast cancer • No more than one hormonal treatment for metastatic disease • Adjuvant or neoadjuvant chemotherapy with or without Herceptin before randomisation was allowed, with an interval of ≥12 months between completion of adjuvant or neoadjuvant therapy and the diagnosis of metastatic breast cancer

Table 126 Key exclusion criteria in the CLEOPATRA study [CLEOPATRA Primary CSR]

Exclusion criteria
• History of anticancer therapy for metastatic breast cancer (with the exception of one previous hormonal regimen) • History of approved or investigative tyrosine kinase/HER inhibitors for breast cancer in any treatment setting, except Herceptin 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 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 • Evidence of central nervous system metastases • LVEF <50% during or after previous Herceptin therapy • Cumulative exposure >360 mg/m^2 of doxorubicin or its equivalent • Inadequate cardiac function, haematological, biochemical, and organ function parameters (as specified in the study protocol)

Settings and locations where the data were collected: Between February 2008 and July 2010, a total of 808 patients were enrolled at 204 centres in 25 countries. Patients were enrolled at centres in Argentina, Brazil, Costa Rica, China, Croatia, Ecuador, Finland, France, Germany, Guatemala, Italy, Japan, Latvia, Macedonia, Mexico, Philippines, Poland, Republic of Korea, Russia, Singapore, Spain, Taiwan, Thailand, USA, United Kingdom. There were 10 centres in the UK. [CLEOPATRA Primary CSR]

Trial drugs and concomitant medications

Perjeta and Herceptin were administered at the same doses and schedules as in the NeoSphere study (see Table 14) Perjeta and Herceptin were continued until disease progression or unacceptable side effects.

- Docetaxel was administered intravenously every three weeks. The initial dose was 75 mg/m^2; the dose could then be escalated to 100 mg/m^2 as tolerated. The investigator could reduce the dose by 25% from 100 mg/m^2 to 75 mg/m^2, or from 75 mg/m^2 to 55 mg/m^2 if the patient was not tolerating the dose. It was recommended that patients should be given at least six cycles of docetaxel. Docetaxel could be discontinued at the investigator's discretion: the two antibodies (Perjeta and Herceptin) could still be continued, until disease progression.

Permitted concomitant medications included many of those permitted in NeoSphere and TRYPHAENA. Additional permitted therapies for CLEOPATRA included bisphosphonates as well as palliative surgical procedures. Excluded therapies were consistent with those listed for NeoSphere and TRYPHAENA.

Primary outcome: The primary efficacy endpoint was progression free survival (PFS) based on assessment of tumours by an independent review facility. PFS was defined as the time from randomisation to the first documented radiographic evidence of progressive disease (PD), as determined by the independent review facility using RECIST (Response Evaluation Criteria in Solid Tumours: the standard method of classifying tumour response to chemotherapy trials) or death from any

cause (within 18 weeks of last tumour assessment), whichever occurred first. [Baselga et al, 2012] Assessment of PD was based on a review of radiographic (magnetic resonance imaging [MRI], computed tomography [CT], bone scans, chest x-ray, etc.), as well as cytologic (e.g. relevant cytology reports documenting malignant pleural effusions, bone marrow aspirations, cerebral spinal fluid, etc.), and photographic data, if available.

Secondary outcomes:

Secondary outcomes were:

- **Overall survival:** defined as the time from the date of randomisation to the date of death from any cause
- **Investigator-assessed PFS**, defined as the time from randomisation to the first documented radiographic PD, as determined by the investigator using RECIST, or death from any cause, whichever occurred first.
- **Objective response rate:** defined as a complete response [CR], or partial response [PR] determined by the IRF using RECIST on two consecutive occasions ≥ 4 weeks apart (patients without measurable disease or with disease localised only to the bone were not included in the analysis of objective response)
- **Duration of objective response**, defined as the period from the date of initial confirmed partial or complete response until the date of PD or death from any cause (tumour responses were based on IRF evaluations using RECIST)
- **Time to symptom progression:** defined as the time from randomisation to the first symptom progression as measured by the 'Functional assessment of cancer therapy - Trial outcome index–physical/functional/breast' (FACT TOI-PFB) a 24-item subscale generated using three subsections from the 'Functional assessment of cancer therapy – breast' (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

- **Safety**
- **Time to response**: defined as the period from randomisation to the date of initial confirmed PR or CR (i.e., the date of tumour assessment at which PR/CR was first detected by the IRF/investigator).
- **Clinical benefit response (CBR):** defined as the percentage of patients 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.

Statistical hypotheses

The difference in primary endpoint, independent review facility (IRF)-assessed progression-free survival (PFS), 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 (H_0) is that the survival distributions of PFS (S) in the two treatment groups is the same. The alternative hypothesis (H_1) is that the survival distributions of PFS in the treatment and the control arms are different:

$$H_0: S_{<Perjeta>} = S_{<placebo>} \text{ vs } H_1: S_{<Perjeta>} \neq S_{<placebo>}$$

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 PFS, overall survival (OS), 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. [Primary CSR]

Sample size

The primary analysis of PFS was planned for when approximately 381 IRF-assessed PFS events had occurred. It was estimated that a total of 381 IRF-assessed PFS

events would provide approximately 80% power to detect a 33% improvement in median PFS (hazard ratio [HR] of 0.75 with a two-sided significance level of 5%). In designing the study, median PFS for the control group was assumed to be 10.5 months, improving to 14 months with the addition of Perjeta, assuming that PFS is exponentially distributed.

Table 127 lists the power for final PFS analysis at the two-sided significance level of 5% with 381 IRF-assessed PFS events.

Table 127 Statistical power for final PFS analysis in the CLEOPATRA study

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

A data cut-off date was determined when the required number of PFS 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.

Analysis populations

The intent-to-treat population includes all patients randomised to treatment.

Other Analysis Populations: For objective response and time to response, only patients with measurable disease at baseline were included in the analysis. For duration of response, only responders were included in the analysis. For time to symptom progression based on the FACT-B questionnaire, only female patients were included in the analysis.

The safety analysis population includes all patients who received any amount of any component of study treatment.

Interim analysis

An interim analysis of OS was performed at the time of the primary analysis of PFS. To account for this interim analysis of OS, a Lan−deMets α-spending function with

the O'Brien−Fleming stopping boundary was applied to the OS 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 PFS (under this assumption the alpha level for the first OS analysis would be 0.0031).

The final analysis of OS was planned to take place after 385 deaths have occurred, which will provide 80% power to detect a 33% improvement in OS (median OS for the control group was assumed to be 36 months).

Endpoint analysis

Since the CLEOPATRA study is included here for the purpose of providing supportive information on the safety and tolerability of Perjeta, a description of the analysis of efficacy endpoints (primary or secondary) are not detailed here.

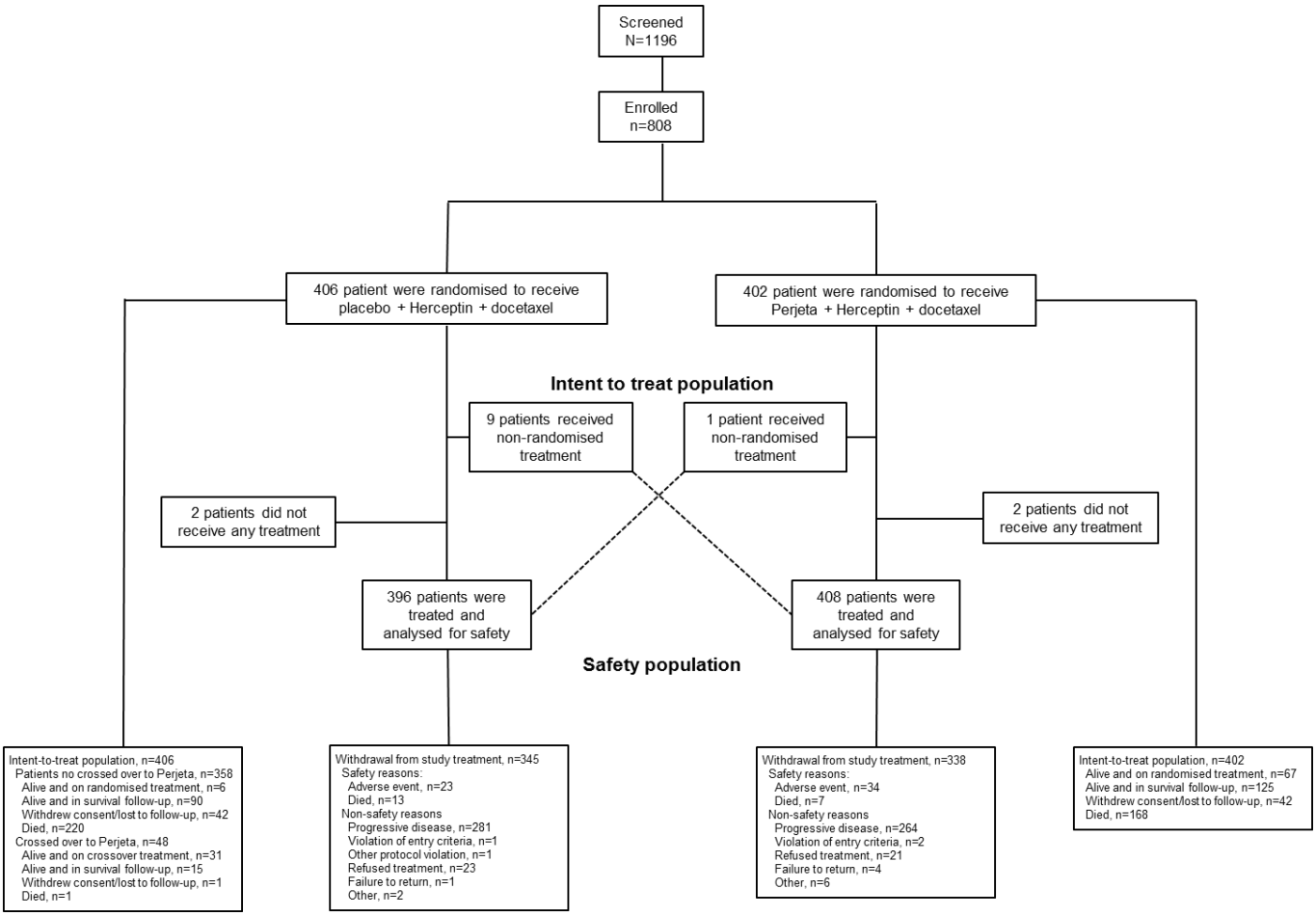
Patients who received any amount of any component of study treatment were included in safety analyses (safety analysis population). Safety results are summarised by the actual treatment patients received.

If a patient had repeated episodes of a particular adverse event, only the most severe episode or the episode with the strongest causal relationship to the trial drug was counted.

Patient flow

A total of 1196 patients were screened for the study, and a total of 808 patients were randomised to one of two treatment arms: 406 patients to the Herceptin + docetaxel arm and 402 patients to the Perjeta + Herceptin + docetaxel arm. [2nd update CSR] See the CONSORT diagram in Figure 38.

Figure 38 Participant flow in the CLEOPATRA study



As shown, the majority of patients in both arms withdrew from study treatment due to disease progression, (281 patients [71.0%] in the Herceptin + docetaxel arm and 264 patients [64.7%] in the Perjeta + Herceptin + docetaxel arm). A similar proportion of patients in both treatment arms withdrew due to safety reasons: 36 patients (9.1%) in the Herceptin + docetaxel arm and 41 patients (10.0%) in the Perjeta + Herceptin + docetaxel arm. [2nd update CSR]

Baseline characteristics

The treatment groups were generally comparable with respect to demographic characteristics. The median age in both treatment arms was 54 years, and over 80% of patients in both arms were aged <65 years. Two male patients took part in the study, both of whom were randomised to the Herceptin + docetaxel arm. [Primary CSR]

The proportion of white patients in CLEOPATRA differed from that in the neoadjuvant studies (58-61% in CLEOPATRA vs 64-83% in the neoadjuvant studies). The proportion of Asian patients also differed: 32-33% in CLEOPATRA vs 14-26% in the neoadjuvant studies. Median age in the CLEOPATRA and neoadjuvant studies were similar. The proportion of patients with a HER2 status of 3+ by immunohistochemistry or positive by in situ hybridisation was similar between the three studies. The proportion of patients in the CLEOPATRA study with an Eastern Cooperative Oncology Group Performance Status of zero was lower than for the neoadjuvant studies, as would be expected due to the course of their disease. 61-68% of patients in CLEOPATRA had an ECOG PS of 0; 31-39% of patients had an ECOG PS of 1. In the neoadjuvant studies, 83-94% of patients had ECOG PS of 0; 6-17% had ECOG PS of 1. The split of hormone receptor positivity versus negativity was similar between the three studies.

Table 128 Baseline patient demographics and tumour characteristics in the CLEOPATRA study [Baselga 2012] [Primary CSR]

Baseline characteristic, n (%)	Perjeta + Herceptin + docetaxel (n=402)	Placebo + Herceptin + docetaxel (n=406)
Age (years)		
Median (range)	54.0 (22-82)	54.0 (27-89)
<65	342 (85.1%)	339 (83.5%)
≥65	60 (14.9%)	67 (16.5%)
<75	397 (98.8%)	392 (96.6%)
≥75	5 (1.2%)	14 (3.4%)
Disease type at screening		
Non-visceral	88 (21.9%)	90 (22.2%)
Visceral	314 (78.1%)	316 (77.8%)
Prior adjuvant or neoadjuvant chemo		
No	218 (54.2%)	214 (52.7%)
Yes	184 (45.8%)	192 (47.3%)
Anthracycline	150 (37.3%)	164 (40.4%)
Hormone	106 (26.4%)	97 (23.9%)
Taxane	91 (22.6%)	94 (23.2%)
Herceptin	47 (11.7%)	41 (10.1%)

Appendix 9 Search strategy for the systematic literature review for the economic model

Table 129 MEDLINE® and MEDLINE in process® database CEA and costs and resource use search strategy

#	Searches	Results
1	exp Neoplasms/	2805544
2	(cancer* or malignanc* or tumor* or tumour* or carcinoma* or neoplasm*).ti,ab.	2379773
3	1 or 2	3386564
4	Breast/	30591
5	(breast or mamma*).ti,ab.	641600
6	4 or 5	646418
7	3 and 6	330311
8	Breast Neoplasms/	237458
9	7 or 8	364520
10	Neoadjuvant Therapy/	13163
11	((neoadjuvant or neo adjuvant) adj2 (treatment or therap*)).ti,ab.	7180
12	10 or 11	17142
13	9 and 12	3898
14	"costs and cost analysis"/ or cost-benefit analysis/	106868
15	quality-adjusted life years/	8131
16	markov chains/	11096
17	monte carlo method/	22270
18	Decision Trees/ec	1
19	(cost$ adj3 (estimate? or variable? or effective$ or unit? or benefit or utility or analys$ or minimi?ation or consequence)).ti.	27222
20	(cost$ adj3 (estimate? or variable? or unit? or benefit or utility or analys$ or minimi?ation or consequence)).ab.	39097
21	(qoly? or hrqol or hrql or qaly? or qale? or qald?).ti,ab.	18096
22	(economic$ or price$ or pricing or pharmacoeconomic$).ti.	44431
23	(sensitivity adj analys#s).ti,ab.	18855
24	(willing$ adj2 pay).ti,ab.	3580
25	quality adjusted life.ti,ab.	7780
26	(decision adj1 (tree$ or analy$ or model$)).ti,ab.	11829
27	(perspective adj2 (societal or nhs or health service)).ti,ab.	2636
28	time horizon.ti,ab.	1871
29	budget impact analys#s.ti,ab.	288
30	monte carlo.ti,ab.	33233
31	markov chain.ti,ab.	3757
32	(resource adj2 "use").ti,ab.	5964
33	(resource adj3 (allocation$1 or utilit$)).ti,ab.	5674
34	"cost of illness"/	20219
35	(economic adj3 (evaluation$ or model or analys$)).ti,ab.	14403
36	exp models, economic/	11282
37	(cost or costs or costing$1).ti.	81533
38	(cost$1 adj2 (direct or indirect)).ti,ab.	10580
39	Health Resources/	9706
40	Economics, Nursing/	3956
41	exp Economics, Hospital/	20912
42	exp Economics, Pharmaceutical/	2651
43	exp Economics, Medical/	14109
44	exp "Fees and Charges"/	28010
45	exp Health Care Costs/	51437
46	burden.ti.	16413
47	(burden adj3 (disease or illness)).ab.	16318
48	or/14-47	388596

49	13 and 48	43
50	limit 49 to english language	41

Table 130 Embase database CEA and costs and resource search strategy

#	Searches	Results
1	exp *neoplasm/	2808580
2	(cancer* or malignanc* or tumor* or tumour* or carcinoma* or neoplasm*).ti,ab.	3030791
3	1 or 2	3845627
4	*breast/	19377
5	(breast or mamma*).ti,ab.	761771
6	3 or 4	3854148
7	3 and 6	3845627
8	*breast cancer/	167211
9	7 or 8	3845627
10	*adjuvant therapy/	4736
11	((neoadjuvant or neo adjuvant) adj2 (treatment or therap*)).ti,ab.	12766
12	10 or 11	16307
13	9 and 12	15361
14	exp *economic evaluation/	40724
15	exp health economics/	673996
16	quality adjusted life year/	14924
17	*probability/	4458
18	Monte Carlo method/	26152
19	"decision tree"/	7115
20	(cost$ adj3 (estimate? or variable? or effective$ or unit? or benefit or utility or analys$ or minimi?ation or consequence)).ti.	37355
21	(cost$ adj3 (estimate? or variable? or unit? or benefit or utility or analys$ or minimi?ation or consequence)).ab.	56212
22	(qoly? or hrqol or hrql or qaly? or qale? or qald?).ti,ab.	28594
23	(economic$ or price$ or pricing or pharmacoeconmic$).ti.	53829
24	(sensitivity adj analys#s).ti,ab.	27364
25	(willing$ adj2 pay).ti,ab.	5217
26	quality adjusted life.ti,ab.	10841
27	(decision adj1 (tree$ or analy$ or model$)).ti,ab.	16094
28	(perspective adj2 (societal or nhs or health service)).ti,ab.	3940
29	time horizon.ti,ab.	3825
30	budget impact analys#s.ti,ab.	731
31	monte carlo.ti,ab.	32006
32	markov chain.ti,ab.	3923
33	(economic adj3 (evaluation$ or model or analys$)).ti,ab.	19554
34	(resource adj2 "use").ti,ab.	8431
35	(resource adj3 (allocation$1 or utilit$)).ti,ab.	6919
36	(cost or costs or costing$1).ti.	105555
37	(cost$1 adj2 (direct or indirect)).ti,ab.	16207
38	(burden adj3 (disease or illness)).ab.	23131
39	burden.ti.	22817
40	exp *economic aspect/	378731
41	or/14-40	997897
42	13 and 41	459
43	limit 42 to english language	437
44	conference.so.	2063092
45	43 not 44	222

Database(s): Embase 1974 to 2015 November 10

Table 131 EconLit database CEA and costs and resource search strategy

#	Searches	Results
1	((breast or mamma*) adj3 (cancer* or malignanc* or tumor* or tumour* or carcinoma* or neoplasm*)).ti,ab.	247
2	(neoadjuvant or neo adjuvant).ti,ab.	1
3	1 and 2	0

Database(s): Econlit 1886 to October 2015

Table 132 NHS EED database CEA and costs and resource search strategy

ID	Search	Hits
#1	MeSH descriptor: [Neoplasms] explode all trees	54662
#2	cancer* or malignanc* or tumor* or tumour* or carcinoma* or neoplasm*:ti,ab,kw	116204
#3	#1 or #2	119507
#4	MeSH descriptor: [Breast] explode all trees	634
#5	breast or mamma*:ti,ab,kw	28460
#6	#4 or #5	28464
#7	#3 and #6	22313
#8	MeSH descriptor: [Breast Neoplasms] explode all trees	9107
#9	#7 or #8	22313
#10	MeSH descriptor: [Neoadjuvant Therapy] explode all trees	780
#11	(neoadjuvant or neo adjuvant) near/2 (treatment or therap*):ti,ab,kw	1355
#12	#10 or #11	1355
#13	#9 and #12 in Technology Assessments and Economic Evaluations	10

Table 133 Quality assessment of included CEA study using Drummond et al. checklist

CEA quality assessment questions	
1. Was the research question stated?	Yes
2. Was the economic importance of the research question stated?	Yes
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes
5. Were the alternatives being compared clearly described?	Yes
6. Was the form of economic evaluation stated?	Yes
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes
8. Was/were the source(s) of effectiveness estimates used stated?	Yes
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	No
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes
12. Were the methods used to value health states and other benefits stated?	Yes
13. Were the details of the subjects from whom valuations were obtained given?	Yes
14. Were productivity changes (if included) reported separately?	No
15. Was the relevance of productivity changes to the study question discussed?	No
16. Were quantities of resources reported separately from their unit cost?	No
17. Were the methods for the estimation of quantities and unit costs described?	Yes
18. Were currency and price data recorded?	Yes
19. Were details of price adjustments for inflation or currency conversion given?	Yes
20. Were details of any model used given?	Yes
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes
22. Was the time horizon of cost and benefits stated?	Yes
23. Was the discount rate stated?	Yes
24. Was the choice of rate justified?	No
25. Was an explanation given if cost or benefits were not discounted?	No
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No

27. Was the approach to sensitivity analysis described?	Yes
28. Was the choice of variables for sensitivity analysis justified?	Yes
29. Were the ranges over which the parameters were varied stated?	Yes
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes
31. Was an incremental analysis reported?	Yes
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes
33. Was the answer to the study question given?	Yes
34. Did conclusions follow from the data reported?	Yes
35. Were conclusions accompanied by the appropriate caveats?	Yes
36. Were generalisability issues addressed?	No

Abbreviations: **CEA** – cost effectiveness analysis

Table 134 MEDLINE® and MEDLINE in process® database HRQoL and HSUV search strategy

#	Searches	Results
1	exp Neoplasms/	2805544
2	(cancer* or malignanc* or tumor* or tumour* or carcinoma* or neoplasm*).ti,ab.	2379773
3	1 or 2	3386564
4	Breast/	30591
5	(breast or mamma*).ti,ab.	641600
6	4 or 5	646418
7	3 and 6	330311
8	Breast Neoplasms/	237458
9	7 or 8	364520
10	Neoadjuvant Therapy/	13163
11	((neoadjuvant or neo adjuvant) adj2 (treatment or therap*)).ti,ab.	7180
12	10 or 11	17142
13	9 and 12	3898
14	"Quality of Life"/	133724
15	quality of life.ti.	46781
16	(hql or hrql or hrqol or hqol).ti,ab.	12115
17	quality of life index.ti,ab.	1293
18	qwb.ti,ab.	190
19	quality of well being.ti,ab.	363
20	quality of wellbeing.ti,ab.	11
21	(hui or hui 2 or hui2 or hui 3 or hui3).ti,ab.	1046
22	(time trade off or time tradeoff or tto).ti,ab.	1370
23	(utilit$ adj2 (value$1 or cost$1 or health or analys$ or index)).ti,ab.	6784
24	health state$1.ti,ab.	4338
25	(hye or healthy year$1 equivalent$).ti,ab.	66
26	standard gamble$.ti,ab.	744
27	discrete choice experiment$.ti,ab.	649
28	conjoint analysis.ti,ab.	443
29	(euroqol or euroquol or EQ 5D or eq5d).ti,ab.	5325
30	visual analog$ scale$.ti,ab.	34340
31	(sf 36 or sf36 or sf thirtysix or sf thirty six or short form 36 or short form thirty six or shortform thirty six or shortform 36).ti,ab.	18593
32	(sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or short form six or shortform six).ti,ab.	1531
33	(sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or short form twelve or shortform twelve).ti,ab.	3474
34	or/14-33	189944
35	13 and 34	44
36	limit 35 to english language	40

Database(s): Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present

Table 135 Embase database HRQoL and HSUV search strategy

#	Searches	Results
1	exp *neoplasm/	2808580
2	(cancer* or malignanc* or tumor* or tumour* or carcinoma* or neoplasm*).ti,ab.	3030791
3	1 or 2	3845627
4	*breast/	19377
5	(breast or mamma*).ti,ab.	761771
6	3 or 4	3854148
7	3 and 6	3845627
8	*breast cancer/	167211
9	7 or 8	3845627
10	*adjuvant therapy/	4736
11	((neoadjuvant or neo adjuvant) adj2 (treatment or therap*)).ti,ab.	12766
12	10 or 11	16307
13	9 and 12	15361
14	exp "quality of life"/	320068
15	quality of life.ti.	66190
16	(hql or hrql or hrqol or hqol).ti,ab.	18200
17	quality of life index.ti,ab.	1729
18	qwb.ti,ab.	211
19	quality of well being.ti,ab.	397
20	quality of wellbeing.ti,ab.	22
21	(hui or hui 2 or hui2 or hui 3 or hui3).ti,ab.	1501
22	(time trade off or time tradeoff or tto).ti,ab.	1816
23	(utilit$ adj2 (value$1 or cost$1 or health or analys$ or index)).ti,ab.	10229
24	health state$1.ti,ab.	6732
25	(hye or healthy year$1 equivalent$).ti,ab.	104
26	standard gamble$.ti,ab.	859
27	discrete choice experiment$.ti,ab.	931
28	conjoint analysis.ti,ab.	600
29	(euroqol or euroquol or EQ 5D or eq5d).ti,ab.	9291
30	visual analog$ scale$.ti,ab.	47224
31	*visual analog scale/	583
32	(sf 36 or sf36 or sf thirtysix or sf thirty six or short form 36 or short form thirty six or shortform thirty six or shortform 36).ti,ab.	27607
33	(sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or short form six or shortform six).ti,ab.	1667
34	(sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or short form twelve or shortform twelve).ti,ab.	5423
35	or/14-34	380546
36	13 and 35	652
37	limit 36 to english language	605
38	conference.so.	2063092
39	37 not 38	333

Database(s): Embase 1974 to 2015 November 10

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Single Technology Appraisal (STA)

Pertuzumab for the neoadjuvant treatment of HER2 positive breast cancer [ID767]

Dear Denzyl,

The Evidence Review Group, School of Health and Related Research (ScHARR), and the technical team at NICE have now had an opportunity to take a look at the submission received on the 14th January 2016 by Roche Products. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **5pm** on 18th February 2016. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be uploaded to NICE Docs/Appraisals via this link: https://appraisals.nice.org.uk/request/11031.

If you have any further queries on the technical issues raised in this letter then please contact [redacted], Technical Lead [redacted]. Any procedural questions should be addressed to [redacted] Project Manager [redacted] in the first instance.

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Yours sincerely

Joanna Richardson
Technical Adviser – Appraisals
Centre for Health Technology Evaluation

Section A: Clarification on effectiveness data

Treatment pathway

A1. **Priority question:** Please provide further details on the strength and robustness of the evidence (e.g. whether this is based on expert opinion, survey of experts etc) for the following statements in the company submission:

- 'Current data suggest that approximately 27% of patients with HER2-positive disease in the UK receive neoadjuvant treatment (p49)
- 'Currently more than 75% of neoadjuvant treatment regimens contain Herceptin' (p13). Also please provide further details on neoadjuvant treatments that do not contain trastuzumab that are used within the UK.

A2. Please provide further details on the clinical pathway of care for HER2-positive neoadjuvant patients who do not receive trastuzumab?

A3. Please clarify if the marketing authorisation for pertuzumab limits its use to 6 cycles. If it does not, please comment on the potential implications for clinical practice in England (including the expected maximum number of cycles people would have). In addition, is the variation in pertuzumab cycles dependent on the co-administrative treatment? If so, please provide further details.

A4. Please provide evidence to support the use of FEC (5-Flurouracil, Epirubicin and Cyclophosphamide) therapy before surgery and its impact on outcomes given that NeoSphere is based on the use of FEC therapy after surgery. What are the potential implications to UK clinical practice? For example, is there any difference in clinical outcomes if FEC is taken before or after surgery).

Literature searching

A5. Search filters have been used to identify RCTs and economic and QOL studies; however no sources are provided for these. Please indicate in each case whether a published, validated filter was used and give details of any amendments made.

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Systematic review process

A6. Please provide further details on how systematic reviews/meta-analyses of RCTs (Table 6, p53) were identified and included in the company's systematic literature review.

Quality assessment, data synthesis and analysis

A7. **Priority Question:** Please provide further details on the strengths, robustness and limitations/criticisms of the CTneoBC group meta-analysis (Cortazar et al. 2014) which evaluated the relationship between pathological complete response and long term clinical benefit. In addition, please comment on the following papers by Berrutti et al. 2014 (J Clin Oncol, 32: 3883-3891) and Korn et al. 2016 (Annals of Oncology 27: 10-15) which appear to contradict the findings from the CTneoBC group meta-analysis.

A8. Please comment on the crossing of the survivor functions between 10 and 20 months (Figure 23 Kaplan-Meier estimate of event free survival [EFS] for Perjeta (pertuzumab) + Herceptin (trastuzumab) + docetaxel compared with Herceptin + docetaxel only) and whether this might be indicative of groups of patients at higher versus lower risk of event free survival (EFS).

A9. Please provide the mean age of patients and mean tumour size in the NeoSphere trial and TRYPHAENA study.

A10. Please provide further details on the method for determining clinical response rate (p66-67) in the NeoSphere trial and why the RECIST criteria were modified? What is the expected impact of the modifications to the RECIST criteria impact on the results?

A11. Please confirm if there are (and provide if available) any long term survival data available from the Cleveland Clinic Cancer registry (section 4.11, p129-131).

Mixed treatment comparison

A12. **Priority question:** Please clarify why an indirect and mixed treatment comparison was not deemed possible (section 4.10, p129). Given that other neoadjuvant treatments for HER2-positive breast cancer may be deemed to be valid comparators, please provide results of such an analysis. If this is not possible, please provide comments on the network meta-analysis by Nagayama et al. 2014 (J Natl Cancer Inst, 106(9)) and its relevance to the current submission.

<u>Section B: Clarification on cost-effectiveness data</u>

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Literature searching

B1. Please clarify why different (fewer) disease area terms have been used in the cost searches (Tables 129-132 and 134-135, p365-372) compared with the clinical searches (Tables 117-119, p344-346). In addition, the EMBASE searches for the economic studies and health-related quality of life (HRQoL) evidence (Table 135) both appear to contain a logic error at line 6, where lines "3 or 4" have been combined instead of "4 or 5".Please comment on the implications of these issues for the findings of the respective reviews (and/or re-run the searches).

B2. The ERG notes that the company's HRQoL searches did not find the study by Lidgren 2007. Given that this article is indexed in MEDLINE and EMBASE, both of which were searched, did the company perform any follow up searches in light of this. How confident is the company that no similar studies of potential relevance have been missed?

B3. Please explain how the study by Hamilton 2014 was identified to inform the monthly transition from remission to metastatic non-progressed health states. Are there other relevant studies from which data could be used within the sensitivity analysis rather than doubling and halving the figure from Hamilton 2014?

Cost effectiveness review

B4. Very little detail is provided for the one study included in the cost-effectiveness review (Attard et al.) (p192-193). Please provide a more complete description and critical review of this study, for example: What were the health states? How were trial outcomes extrapolated? What were the model/ data limitations? What were the key drivers of the model results?

Health economic model

B5. **Priority question:** As referred to on page 13 of the company submission, some HER2-positive breast cancer patients who would receive neoadjuvant treatment within England may not receive trastuzumab. Could you please incorporate these additional comparators within the economic model (see point A13 for clarification around the inclusion of a mixed treatment comparison). If you do not consider this to be feasible within the current timescales, as a minimum please describe the potential implications of doing this upon your findings. Please consider including the cost of surgery if it is expected that this would differ substantially between interventions.

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B6. **Priority question:** Please present a figure comparing the currently predicted event free survival (EFS) within the model with the trial EFS curves for each arm (HD and PHD), accompanied by a discussion of the fit and implications for the modelling.

B7. **Priority question:** Given the limitations and uncertainty associated with the use of tpCR (total pathological complete response) as a predictor for EFS, please could you undertake additional analyses within the model using the EFS trial outcomes from the NeoSphere trial? For example by using the Kaplan-Meier curves from the trial within the model directly and fitting appropriate parametric distributions to the Kaplan-Meier data for each arm. Please provide the output files containing the parameters, their confidence intervals and the variance-covariance matrix for each of the parametric distributions. Please analyse which of them provides a best fit to the Kaplan–Meier data using the AIC, BIC and visual fit criteria and present the associated ICERs.

B8. **Priority question:** In section 5.3.1 of the submission (Table 73 and Table 74), the following 5 parametric distributions were analysed for best fit to the Kaplan–Meier data (patients with pCR and patients without pCR) using the AIC, BIC and visual fit criteria: Exponential; Weibull; Log-normal; Log-logistic; Gamma.

- Please clarify why a Gompertz distribution was not analysed or presented in this analysis.
- Please provide the output files containing the parameters, their confidence intervals and the variance-covariance matrix for each of the distributions listed above.

B9. Please provide an assessment of the relationship between tpCR and EFS within the NeoSphere study? Please comment how this relationship compares with that observed in the CTneoBC group meta-analysis (Cortazar et al. 2014).

B10. Please comment on the clinical plausibility of the extrapolated survivor functions for event free survival (Figure 30) and the implied hazard rates for each treatment group over time.

B11. Given that the Kaplan Meier data from the CTNeoBC meta-analysis was used to estimate the EFS in the model for patients with and without pCR, please justify why the overall survival (OS) in the model was not estimated in the same manner? That is, modelling the OS from the CTNeoBC meta-analysis

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which provides KM data of OS for patients with and without pCR (Figure 2, Cortazar et al 2014 - the same figure as that of the EFS).

B12. Please explain the calculations used to adjust the EFS survival in columns P and Y of the 'Extrapolation' sheet of the model.

B13. The model uses a monthly cycle length. Please explain why a 3-weekly cycle has not been used within the model given that the key clinical events (e.g. treatment cycles, cardiovascular checks) happen in 3-weekly intervals? Please also check that this is consistent throughout the company submission, since in some parts of the submission (p17, p196) it is suggested that 3-weekly cycles are used for the modelling.

B14. The ERG and their clinical advisers understand that the use of subcutaneous trastuzumab is now standard practice in England. Please include the cost for subcutaneous trastuzumab within the base case rather than in a scenario analysis, or present evidence to justify why intravenous trastuzumab was used in the base case.

B15. Please clarify the cost of docetaxel; within the report (Table 85), the cost is £43.09 initial dose, £57.28 cycle 2+; within the model the cost that is used appears to be £43.09 initial dose, £57.46 cycle 2+; and on the 'vial sharing' sheet in the model (that does not seem to be used to estimate the base case results), the cost is estimated to be £32.37 with vial sharing. Please also clarify the average monthly cost per patient of PHD + FEC + administration cost and HD + FEC + administration cost as this seems inconsistent between Table 85/ 86, Table 87 and the values used within the model. If the values within the model are incorrect, then please correct these and recalculate the model results.

B16. Please clarify why the supportive care resource use, and associated costs, in the metastatic not progressed state (Table 92) are greater than that in the metastatic progressed state (Table 93).

B17. The costs and mortality risk for patients taking treatments for metastatic disease are calculated based on a weighted average of different treatments (see Table 75, p216). Please clarify if in UK practice any individual patient can get any of these treatments or if the choice depends upon what they had for neoadjuvant/adjuvant treatment? If the latter, please present the cost effectiveness results using appropriate treatments for metastatic disease for each of the arms in the model (as opposed to using a weighted average).

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B18. Please clarify why the mortality risk in the metastatic progressed state only uses the data for HD and PHD (cell F122 of 'Supportive Care' sheet) while the costs are estimated using all treatments including Kadcyla and Capecitabine + lapatinib (cell K91 of 'Supportive Care' sheet)? Please also comment on the applicability of these treatments for metastatic disease to the UK setting, with reference to current NICE guidance for metastatic HER2 positive breast cancer treatment. Where this differs please assess the impacts of these parameters on the model results within sensitivity analysis.

B19. The results of the subgroup analysis suggest that pertuzumab may be more effective in the operable group than in the locally advanced breast cancer group (see Table 32, p125). Please assess the cost-effectiveness of pertuzumab within each of these subgroups within the model.

B20. The assumption that if patients do not progress after seven years they would be event free and follow the general population OS is questionable according to the ERG's clinical advisers, particularly in the hormone receptor (HR)-positive group. Please test this assumption within a sensitivity analysis and present the impact upon the model results.

B21. Please provide the values of all PSA parameters in the probability distributions (Table 101).

B22. Please clarify how the beta parameters to estimate the uncertainty around the tpCR rates from NeoSphere (cells D18 and E18 in Efficacy Data sheet) were estimated within the model.

B23. The incremental cost-effectiveness plane (Figure 34) suggests that there is a strong negative relationship between the incremental costs and QALYs. Please comment on this in relation to the distributions used within the PSA?

B24. The Cost Effectiveness Acceptability Curve (CEAC) should detail the probability of each intervention being the most cost-effective, and therefore the summation of the individual probabilities should equal 100%. Please correct the CEAC (Figure 35) to include both/all the interventions being compared.

B25. For completeness, please present all of the results of the sensitivity analyses described within Table 103 within the tornado diagram (Figure 36).

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B26. Page 262/263: Please generate from the model the predictive distribution for the (log) difference in survival rates between treatments and compare this with the observed result from NeoSphere (i.e. cross validation).

B27. Please clarify the purpose of each of the following sheets for the modelling since they do not appear to impact upon the base case model results: Drug cost; BSA; Vial Sharing; BL Char; KM EFS; Cumulative Hazard Plots EFS; EFS extrapolation FDA; Chart Data.

Section C: Textual clarifications and additional points

C1. Please clarify how many patients will be eligible for pertuzumab in England as there is discrepancy between Table 5 which suggests 1380 patients in England and the text on page 13 which suggests over 1400 patients.

Section A: Clarification on effectiveness data

Treatment pathway

A1. Priority question: *Please provide further details on the strength and robustness of the evidence (e.g. whether this is based on expert opinion, survey of experts etc) for the following statements in the company submission:*

- *'Current data suggest that approximately 27% of patients with HER2-positive disease in the UK receive neoadjuvant treatment (p49)*
- *'Currently more than 75% of neoadjuvant treatment regimens contain Herceptin' (p13). Also please provide further details on neoadjuvant treatments that do not contain trastuzumab that are used within the UK.*

The data which supports the above two items of evidence was collected as part of a regular market research project, funded by Roche and implemented using a market research agency. The research conforms to Market Research Society regulations as well as BHBIA, and ABPI conduct, and the Data Protection Act. The survey is conducted to better understand current drug usage in the treatment of breast cancer and explores awareness, opinions and hypothetical usage of potential new products in development for breast cancer.

The respondents are anonymous but include consultant oncologists (mix of medical and clinical) and oncology surgeons from across the UK. Research was carried out via an on-line survey. The UK data is from entirely UK based respondents, 62 respondents took part for both surveys.

We consider this data to be robust market research, which provides reliable data on neoadjuvant treatments used in clinical practice.

Further detail on the survey can be provided if required.

A2. *Please provide further details on the clinical pathway of care for HER2-positive neoadjuvant patients who do not receive trastuzumab?*

The efficacy and safety of Herceptin in HER2-positive breast cancer has been established in several large, randomised, Phase III pivotal trials, in both early (HERA, NSABP B-31, NCCTG N-9831, BCIRG 006, NOAH & HannaH)[1-6] and metastatic[7-10] breast cancer, including long-term follow-up[11,12]. The clinical benefit observed with the addition of Herceptin to adjuvant and/or neoadjuvant chemotherapy in pivotal studies reinforces the importance of HER2 as a therapeutic target, with Herceptin now well established as the standard-of-care for the treatment of HER2 positive, early breast cancer.

Various UK[13,14], EU[15,16] and US[17] guidelines have also recommended the use of anti-HER2 targeted therapy for the treatment in early HER2-positive breast cancer. Currently in the UK, patients with HER2-positive early breast cancer who require neoadjuvant treatment would be expected to receive anti-HER2 targeted treatment with Herceptin in combination with chemotherapy.

We acknowledge that not all patients will receive Herceptin treatment; this will be at the clinician's discretion. Some of these reasons may be due to:

- HER2-testing results not available for treatment decisions at multidisciplinary team (MDT) meeting
- Previous cardiac dysfunction (e.g. from previous anthracycline therapy, symptomatic left ventricular systolic dysfunction (LVSD), left ventricular ejection fraction (LVEF) < 55%)

Patients not eligible for anti-HER2 targeted treatment may be considered for alternative treatments such as chemotherapy

Overall, information based on market research and insights from UK clinicians suggest that treatment with Herceptin and chemotherapy, as the only reimbursed HER2 targeted regimen, would normally be prescribed for eligible patients who require neoadjuvant treatment in early HER2-positive breast cancer in the UK.

A3. *Please clarify if the marketing authorisation for pertuzumab limits its use to 6 cycles. If it does not, please comment on the potential implications for clinical practice in England (including the expected maximum number of cycles people would have). In addition, is the variation in pertuzumab cycles dependent on the co-administrative treatment? If so, please provide further details.*

Yes, the marketing authorisation limits the use of Perjeta to 6 cycles. Safety for more than 6 cycles in the neoadjuvant setting has not been established. (Perjeta Summary of Product Characteristics, July 2015)

Perjeta is indicated for use in combination with trastuzumab and chemotherapy for the neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence. This is based on the regimens investigated from the 2 pivotal studies, NeoSphere and TRYPHAENA, which evaluated the combination of Perjeta with Herceptin and different chemotherapy regimens as neoadjuvant treatment. These regimens include:

<u>NeoSphere (prior to surgery)</u>

- Perjeta + Herceptin + docetaxel (every 3 weeks) x 4 cycles

After surgery, patients will receive FEC (5-fluorouracil, epirubicin, cyclophosphamide) every 3 weeks for 3 cycles in combination with Herceptin (every 3 weeks) to complete one year of treatment

TRYPHAENA (prior to surgery)

- FEC (5-fluorouracil, epirubicin, cyclophosphamide) x 3 cycles followed by Perjeta + Herceptin + docetaxel x 3 cycles
- Perjeta +Herceptin + FEC x 3 cycles followed by Perjeta + Herceptin + docetaxel x 3 cycles
- Perjeta + Herceptin + docetaxel + carboplatin x 6 cycles

After surgery, patients will receive adjuvant Herceptin to complete one year of treatment.

A4. *Please provide evidence to support the use of FEC (5-Flurouracil, Epirubicin and Cyclophosphamide) therapy before surgery and its impact on outcomes given that NeoSphere is based on the use of FEC therapy after surgery. What are the potential implications to UK clinical practice? For example, is there any difference in clinical outcomes if FEC is taken before or after surgery).*

Administration of FEC to patients at the start of the treatment regimen is commonly prescribed by clinicians as it can be given immediately after diagnosis and staging without the need for tumour testing, and avoiding delay in the treatment of occult micro-metastatic disease.

In the NeoSphere trial, patients received FEC chemotherapy after surgery, in order to isolate the effect of Perjeta in the neoadjuvant setting of HER2-positive eBC in the NeoSphere study. FEC chemotherapy after surgery is also most reflective to the standard treatment in the USA.

In the UK, FEC-T (anthracycline-based regimen of fluorouracil + epirubicin + cyclophosphamide for three cycles, followed by a taxane (e.g. docetaxel; T) for three cycles) is one of the most common chemotherapy regimens administered with Herceptin as part of a neoadjuvant treatment regimen in the UK[18].

A meta-analysis by Mauri et al[19] and NSABP-18[20] study compared the outcomes after neoadjuvant treatment versus adjuvant treatment regardless of the additional surgery and/or radiation used. Both these studies demonstrated that the outcomes to neoadjuvant treatment have not been shown to be inferior to outcomes associated with adjuvant therapy in terms of death, disease progression or distance recurrence. The clinical timings are therefore not expected to differ based on FEC administration (neoadjuvant vs. adjuvant therapy).

Literature searching

A5. *Search filters have been used to identify RCTs and economic and QOL studies; however no sources are provided for these. Please indicate in each case whether a published, validated filter was used and give details of any amendments made.*

Randomised Controlled Trial (RCT) Terms

The search filters for RCTs used in the clinical evidence systematic literature review (SLR) to identify Phase 2, 3 and 4 RCTs were based on the SIGN search filter set, with a number of modifications as detailed below. Compared to the SIGN set, all MeSH and Emtree terms used were exploded.

Table 1 - RCT search terms used in the SLR for RCT evidence (MEDLINE and Embase search via Ovid platform)

Term group	#	Terms	SIGN filter set	Comments
RCTs	12	exp Randomized Controlled Trials as Topic/	MEDLINE	
	13	exp Randomized Controlled Trial/	MEDLINE and Embase	
	14	exp Random Allocation/	MEDLINE	
	15	exp Randomization/	Embase	
	16	exp Double Blind Method/	MEDLINE	Synonymous with "Double blind procedure/" (SIGN Embase)
	17	exp Single Blind Method/	MEDLINE	Synonymous with "Single blind procedure/" (SIGN Embase)
	18	exp Cross-over Procedure/	Embase	
	19	((singl* or doubl* or treb* or tripl*) adj (blind*3 or mask*3)).tw.	MEDLINE	Also picks up "Single blind$.tw.", "Double blind$.tw." and "((treble or triple) adj (blind$).tw." (SIGN Embase)
	20	exp Clinical Trial/	MEDLINE and Embase	
	21	Clinical trial, phase ii.pt.	MEDLINE	
	22	Clinical trial, phase iii.pt.	MEDLINE	
	23	Clinical trial, phase iv.pt.	MEDLINE	
	24	exp Phase 2 Clinical Trial/ or exp Clinical trial, phase II/	-	Additional term
	25	exp Phase 3 Clinical Trial/ or exp Clinical trial, phase III/	-	Additional term
	26	exp Phase 4 Clinical Trial/ or exp Clinical trial, phase IV/	-	Additional term
	27	Controlled clinical trial.pt.	MEDLINE	
	28	Randomized controlled trial.pt.	MEDLINE	
	29	Clinical trial.pt.	MEDLINE	
	30	Comparative study.pt.	-	Additional term
	31	exp Clinical Trials as Topic/	MEDLINE	
	32	Trial*.ti.	-	Additional term
	33	(clinical adj trial$).tw.	MEDLINE	
	34	exp Placebos/	MEDLINE	Synonymous with "Placebo/" (SIGN

				Embase)
	35	Placebo*.ti,ab.	-	Subset of "placebo$.tw." (SIGN MEDLINE and Embase)
	36	randomly allocated.tw.	MEDLINE and Embase	
	37	(allocated adj2 random*).tw.	MEDLINE and Embase	
	38	random allocation.tw.	Embase	
	39	random assignment.tw.	-	Additional term
	40	randomi?ed.ti,ab.	-	Additional term; some overlap with "randomi?ed controlled trial$.tw." (SIGN Embase)
	41	randomi?ation.tw.	-	Additional term
	42	randomly.ti,ab.	-	Additional term; some overlap with "allocated randomly.tw." (SIGN Embase)
	43	RCT.tw.	Embase	
	44	Or/16-43		

RCT search terms used in the SLR for RCT evidence (MEDLINE and Embase search via Ovid platform)

The following terms for RCTs from the SIGN filter set were not included in the search strategy:

- Clinical trial, phase i.pt (SIGN MEDLINE); note that Phase 1 clinical trials were not of interest to the review
- Multicenter study.pt (SIGN MEDLINE)
- Prospective study/ (SIGN Embase)
- Placebo$.tw. (SIGN MEDLINE and Embase); note that placebo*.ti,ab. was included in the search strategy
- Randomi?ed controlled trial$.tw (SIGN MEDLINE and Embase); note that randomi?ed.ti,ab. was included in the search strategy
- Allocated randomly.tw. (SIGN MEDLINE and Embase); note that randomly.ti,ab. was included in the search strategy

Exclusion Terms

The exclusion filters used differed from validated sets, as shown below.

Table 2 - Exclusion terms used in the SLR for RCT evidence (MEDLINE and Embase search via Ovid platform)

Term group	#	Terms	SIGN filter set	Comments
Exclusion terms	45	Animals/ not humans/	-	BMJ "(animals not humans).sh." Cochrane "Exp animals/ not exp humans/"
	46	(comment or editorial or "case reports").pt.	-	BMJ filter set excludes "comment or editorial.pt." amongst others; SIGN MEDLINE and Embase filters exclude "case report.tw."
	47	(case stud* or case report*).ti.	-	SIGN MEDLINE and Embase filters exclude "case report.tw."
	48	Or/45-47		

Exclusion terms used in the SLR for RCT evidence (MEDLINE and Embase search via Ovid platform)

The following exclusion terms from the SIGN filter set were not used in the search strategy:

- Letter/ (SIGN MEDLINE)
- Historical article/ (SIGN MEDLINE)
- Case study/ (SIGN Embase)
- Abstract report/ or letter (SIGN Embase)

The filters used for the economic and HRQoL systematic reviews were internally developed by a vendor specialising in systematic review. These are based on published economic filters by SIGN (economic studies) and BMC Health Services Research (McKinlay et al. 2006), terms were adapted from the published filters to provide as broad but specific filter to identify economic models, cost and resource use data.

Systematic review process

A6. *Please provide further details on how systematic reviews/meta-analyses of RCTs (Table 6, p53) were identified and included in the company's systematic literature review.*

In the clinical evidence systematic literature review (SLR) to identify evidence for the clinical efficacy and safety of Perjeta in HER2-positive early breast cancer from Phase 2, 3 and 4 RCTs, no specific terms were included in the search strategy to identify systematic reviews or meta-analyses. Instead, it was assumed that any systematic review or meta-analysis of RCTs would be tagged or use words that were in the RCT search terms.

Any systematic literature reviews, pooled analyses or meta-analyses identified were to be screened according to the eligibility criteria. The RCTs identified by systematic reviews, pooled analyses and meta-analyses that passed the title/abstract screening stage were cross-checked against the list of included and excluded RCTs to ensure that no potentially relevant RCTs identified in other systematic reviews were missed.

The RCTs identified by 11 systematic reviews, pooled analyses or meta-analyses were cross-checked against the list of included studies, and were then excluded from this review because they did not contain any novel RCTs meeting the eligibility criteria of this review. These articles were detailed in Table 121 (Appendix 6) of the submission document.

Quality assessment, data synthesis and analysis

A7. *Priority Question:* *Please provide further details on the strengths, robustness and limitations/criticisms of the CTNeoBC group meta-analysis (Cortazar et al. 2014) which evaluated the relationship between pathological complete response and long term clinical benefit. In addition, please comment on the following papers by Berrutti et al. 2014 (J Clin Oncol, 32: 3883-3891) and Korn et al. 2016 (Annals of Oncology 27: 10-15) which appear to contradict the findings from the CTneoBC group meta-analysis.*

The **CTNeoBC study** is a meta-analysis (sponsored by the FDA) of 12 neoadjuvant trials in early breast cancer, conducted by **Cortazar et al (Lancet 2014; 384: 164–72)**. The objective of this meta-analysis was to determine if there is a correlation (i.e. surrogacy) between pathological complete response (pCR) and improvements in long term clinical outcomes such as event-free survival (EFS) and overall survival (OS) after neoadjuvant treatment in early breast cancer. Investigators from identified trials were invited to participate in a collaborative analysis and also agreed to provide individual patient data from the identified studies. Results of the meta-analysis demonstrated 4 main results:

1. **It established pCR definitions that correlated best with long-term outcome.** Eradication of tumour from both the breast and axillary lymph nodes with or without residual carcinoma in situ (ypT0 ypN0 or ypT0/is ypN0 respectively) had a stronger association with improvements in EFS and OS than tumour eradication from the breast alone (ypT0/is). Associations with EFS and OS were similar for eradication of tumour with residual carcinoma in situ (ypT0 ypN0) and without residual carcinoma in situ (ypT0/is ypN0). The associations were consistent when adjusted for baseline factors using multivariable Cox models, therefore the authors proposed the definition ypT0/is ypN0 (no invasive tumour in the breast and lymph nodes, irrespective of ductal carcinoma in situ) to be used for subsequent analyses in this study.

2. **It demonstrated better long-term outcomes for individual patients who attained a pCR compared with those without a pCR.** The CTNeoBC meta-analysis investigated the association between pCR and improved clinical outcomes at both trial and patient level analysis (also known as responder level analysis). Patient level analysis was conducted to investigate the clinical outcomes of patients who achieved pCR versus the patients who didn't achieve pCR, irrespective of treatment group. Patient level analysis is important and clinically meaningful as it helps predict probability of survival in patients who had achieved pCR after neoadjuvant treatment. Although the benefits of patient who achieve pCR was seen in relation to long-term clinical and survival outcomes, as the responder analysis was independent of treatment groups, no conclusions can be drawn from these results for trial-level analysis.

3. **It found that the prognostic value of pCR was greatest in patients with aggressive tumour subtypes**, such as HER-positive and triple-negative breast cancer. A strong association between pathological complete response and long-term outcomes was observed in patients in the HER2-positive subgroup irrespective of hormone receptor status (EFS: HR 0·39, 95% CI 0·31–0·50; OS: 0·34, 0·24–0·47). The strength of the association was increased in HER2-positive disease treated with an anti-HER2 targeted therapy. The CTNeoBC meta-analysis of 12 neoadjuvant trials demonstrated that the most incremental benefit observed with pCR to improved survival outcomes was the NOAH study, which evaluated the use of anti-HER2 targeted therapy Herceptin (trastuzumab), in combination with chemotherapy, as neoadjuvant treatment in early HER2-positive breast cancer.

4. **It demonstrated a weak association between long-term outcome and the magnitude of improvement in pCR rate between treatment arms (trial-level correlation).** Potential explanations for the lack of trial-level correlation between achieving pCR to improvements in long-term clinical outcomes include:
   - Heterogeneity of cancer subtypes in women enrolled in the clinical trials evaluated in this meta-analysis; the prognostic value of pCR can be obscured if women responded differently to the same treatment.
   - Differences in treatment effects from the various trials had made it difficult to determine a correlation between pCR and long term outcomes from this meta-analysis. Trials that included targeted therapies such as NOAH resulted in pCR rates up to 20% compared to chemotherapy; however the majority of trials included were comparisons between chemotherapy treatments, which were generally low, with an absolute difference of approximately 1-11%.

A meta-analyis conducted by **Berutti et al (J Clin Onc 2014; 22(24): 3883-94)** also investigated the role of pCR as a potential surrogate endpoint (trial-level correlation) for long-term clinical outcomes such disease-free survival (DFS) and OS in neoadjuvant breast cancer trials. The meta-analysis included 29 studies (12 studies which were evaluated in the CTNeoBC meta-analysis were also included in this meta-analysis), with a total just over 14000 patients; the Berutti meta-analysis also employed similar statistical methods to those used in the CTNeoBC analysis. One difference to note is that *Berruti et al* reviewed the data based on the outcomes from literature identified, whereas in CTNeoBC meta-analysis, individual patient-level data was obtained from the investigators of the trials identified and as such can be considered a more robust analyses.

The results from the Berutti meta-analysis, like the results from the CTNeoBC meta-analysis, demonstrated a weak association between the treatment effects on pCR and improvement in long-term clinical outcomes such as DFS and OS, therefore pCR does not meet the criteria as a surrogate endpoint for DFS and OS. However, the authors had acknowledged that:

- The Berutti meta-analysis had 'substantially reproduced' the patient level analysis observed from the CTNeoBC analysis
- Potential limitations when trying to establish surrogacy of pCR in meta-analyses of published studies, which were also observed with this meta-analysis, include:

    - Heterogeneity of patient populations and response to treatment
    - Difference in pCR definitions adopted in various trials
    - Different regimens were used
    - Use of additional therapies after surgery (e.g. chemotherapy and hormone therapy)

- The Berutti meta-analysis also excluded exploratory analysis with the HER2-positive subtype as only 2 trials were identified in this meta-analysis where anti-HER2 targeted treatments were studied. Despite of this, the authors acknowledged that the probability of achieving pCR can differ in different tumour subtypes; they also noted that the probability of achieving pCR is most likely to be observed in triple negative and HER2-positive disease, which was also consistent with the results from the CTNeoBC meta-analysis. This is further supported by the 5 year follow up results seen in the NOAH[1] study, which demonstrated improvements in survival in patients who achieved pCR after treatment with Herceptin and chemotherapy versus patients treated with chemotherapy alone. Adjuvant randomised controlled studies (such as HERA[2]) also demonstrated improvements in survival in patients treated with an anti-HER2 target therapy regimen (such as Herceptin) compared with chemotherapy alone.

The publication by ***Korn et al*** **(Annals of Oncology 2016; 27: 10-15)** is a commentary where the authors discuss the differences between individual-level versus trial-level surrogacy and the importance of establishing trial-level surrogacy to confirm pCR as a valid endpoint for survival improvements. The authors provided not only hypothetical scenarios to assess the lack of trial-level correlation between pCR and long term outcomes, they also re-analysed the evidence published from the meta-analyses CTNeoBC and by Berutti et al respectively, via various methods such as

- Illustrating the plots which showed the association between odds ratio (OR) for pCR and EFS and OS effect (as hazard ratios (HR)
- Utilising formal models of surrogacy such as those developed by Buyse to determine why trial-level surrogacy between pCR and long-term outcomes could not be established. The authors confirmed, as demonstrated in both CTNeoBC and Berutti et al meta-analyses respectively, that trial-level correlation was not seen, therefore the magnitude of benefit could not be established in patients who achieved pCR to long term clinical outcomes.

The Korn commentary, although supportive of the results for lack of trial correlation of pCR and long term clinical outcome observed from CTNeoBC and Berutti meta-analyses respectively, the analysis and the results from this publication should be considered as the authors' views on this subject matter only; there was no explanation on formal statistical analyses and their methodology had not been validated. As noted by Korn et al, acquiring more trial data and restriction of patient populations may demonstrate the correlation between pCR and long term outcomes, however unlike the CTNeoBC and Berutti meta-analyses respectively, there was no investigation into specific subgroups that may indicate the association of pCR to long term clinical outcomes. In terms of robustness of the study, this would be considered as low level of evidence.

In summary, we acknowledge from both the Berutti meta-analysis and Korn publication that trial-level correlation between pCR and long-term clinical outcomes could not be established. Strength of the CTNeoBC meta-analysis was that patient level data was evaluated (responder analysis) which demonstrated an association between patients who achieved pCR had improved clinical outcomes between the 12 trials evaluated. These results are important as this had been recognised by the FDA that an uncertainty still remains regarding the validity of utilising pCR to predict the magnitude of benefit in long-term clinical outcomes. Given the unmet need in high-risk breast cancer, which includes HER2-positivity, the FDA and EMA had granted accelerated approval of Perjeta in both the US and EU as neoadjuvant treatment in early HER2-positive breast cancer as high-risk disease, pending on confirmatory data from a large adjuvant study (APHINITY).

Table 3 - Characteristics of the studies

Study	Number of patients	Trial and/or individual level correlation investigated	Type of evidence	Strengths of study	Limitations of study	Quality (level of evidence)
Cortazar	11955	Trial and individual	Meta-analysis	- Analysis of individual patient data - Validated statistical analysis - PICO question established as objectives and investigated	- Heterogeneity of populations in the trials analysed - Assessment of treatment effects difficult from the studies in the meta-analysis - Women with same cancer subtype may respond differently to the same treatment	High
Berruti	14641	Trial	Meta-analysis	- Validated statistical analysis - PICO question established as objectives and investigated	- Heterogeneity of patient populations and differing responses to treatment - Difference of pCR definitions used in the various trials - Different regimens used for same cancer subtype - Use of additional therapies after surgery - Exclusion of HER2-positive breast cancer subgroup in the analysis - analysis of outcomes from data in publication **i.e. not individual patient data**	High
Korn	N/A	trial	Commentary	- Used the data from Cortazar and Berutti	- Statistical analysis not validated - Authors' views only - No investigation into subgroups	Low

In summary, we believe that the Cortazar represents the best evidence available as it provides clinical evidence that highlights the strengths of pCR as a surrogate for long term outcomes; it also underlines from the uncertainties surrounding pCR and tries to explain them.

A8 *Please comment on the crossing of the survivor functions between 10 and 20 months (Figure 23 Kaplan-Meier estimate of event free survival [EFS] for Perjeta (pertuzumab) + Herceptin (trastuzumab) + docetaxel compared with Herceptin + docetaxel only) and whether this might be indicative of groups of patients at higher versus lower risk of event free survival (EFS).*

As noted in the submission, EFS (evaluated as PFS in NeoSphere) data were collected as an exploratory endpoint. All patients from their randomisation date until their first documentation of a progressive disease (PD), recurrence or death were included in this analysis and data was collected via electronic case report form (eCRF). These data were captured in a Kaplan-Meier curve which demonstrated that the number of EFS events in the overall analysis was low at 5 years follow-up. One explanation for the crossover may be due to the low patient numbers in each arm analysed (677 patients per arm would be required to power EFS to detect a statistically significant difference in NeoSphere), but caution should be taken as the EFS analyses in NeoSphere are for descriptive purposes only (i.e. these endpoints were not powered to test for formal hypotheses). The low number of events highlights the uncertainty surrounding an analysis of EFS rather than pCR and it justifies pCR as a primary endpoint in neoadjuvant studies.

As the number of patients in each arm and EFS events that occurred were low in the PHD and HD arms respectively, conclusions cannot be drawn on the subgroups that may be at higher risk of a PFS event. As noted in the tpCR data, there were too few patients in the cancer subgroups (operable, inflammatory and locally advanced) to draw firm conclusions.

A9 *Please provide the mean age of patients and mean tumour size in the NeoSphere trial and TRYPHAENA study.*

Please find this information in the table below.

Table 4 – NeoSphere and TRYPHAENA patient characteristics

	NeoSphere (n=417)				TRYPHAENA (N=223)		
Mean age (years)	49.8 (22-80)				50.2 (24-81)		
Mean tumour size (mm)	Arm A H+T 50 (20-200)	Arm B P+H+D 55 (20-150)	Arm C P+H 50 (20-200)	Arm D P+T 50 (0-18)	Arm A (n=68) FEC+P+H x 3 / P+H+Tx3 12.03 (0.0-120.0)	Arm B (n=71) FEC x 3 / P+H+Tx3 8.25 (0.0-80.0)	Arm C (n=75) TCH+P x6 11.37 (0.0-140.0)
	At clinical breast examination (CBE)						
P- Perjeta, H- Herceptin, FEC - 5-fluorouracil, epirubicin, cyclophosphamide, T- docetaxel, C- carboplatin							

A10 *Please provide further details on the method for determining clinical response rate (p66-67) in the NeoSphere trial and why the RECIST criteria were modified? What is the expected impact of the modifications to the RECIST criteria impact on the results?*

Clinical response was required to be assessed by clinical breast examination (CBE), at each cycle between days 15-21 or on study day 1 of the next cycle, and by mammography at baseline and cycle 4. Clinical response is defined as complete response (CR), partial response (PR) stable disease (SD) and progressive disease (PD), which were identified as per local practice based on RECIST criteria, but with some important modifications that were required due to the study design and electronic case report form (eCRF) used to capture tumour assessment data. For simplicity, these modifications were employed for each of the following categories:

Primary lesion- For the primary lesion in the breast, RECIST criteria were applied in terms of percentage, but the sum of lesions was not used: only the size of the primary breast lesion by method of assessment was entered to determine response.

Overall response- Only if the method of assessment was the same for all lesions (breast and nodes) would the sizes is summed. For example, if the patient had a breast lesion measured by mammogram and lymph nodes assessed by ultrasound, each would only be summed within that method of assessment. Therefore, care should be taken when interpreting these results.

Often due to other variables which can affect tumour response, the current WHO and RECIST criteria do not accurately assess anti-tumour therapies which do not reduce the size of the tumour (seen in other non-breast cancer tumours such as hepatocellular carcinoma (HCC), therefore the RECIST criteria is sometimes modified in clinical trials to more accurately assess specific tumour types in practice.

A11 *Please confirm if there are (and provide if available) any long term survival data available from the Cleveland Clinic Cancer registry (section 4.11, p129-131).*

No further data is available for the Cleveland study other than the abstract provided with the submission.

Mixed treatment comparison

A12 ***Priority question:*** *Please clarify why an indirect and mixed treatment comparison was not deemed possible (section 4.10, p129). Given that other neoadjuvant treatments for HER2-positive breast cancer may be deemed to be valid comparators, please provide results of such an analysis. If this is not possible, please provide comments on the network meta-analysis by Nagayama et al. 2014 (J Natl Cancer Inst, 106(9)) and its relevance to the current submission.*

The feasibility assessment of pharmacological interventions for the treatment of neoadjuvant HER2-positive breast cancer concluded that meta-analysis was not feasible. The primary reason for this was the inability to group chemotherapy treatments to allow the formation of connected evidence networks. The treatments of interest, pertuzumab, trastuzumab, and lapatinib, are given in combination with a chemotherapy regimen. The various clinical studies identified during the systematic review used different chemotherapy regimens, and as such, the majority of treatment arms could not be compared across trials.

The chemotherapy treatments that were not considered equivalent are as follows:

- paclitaxel 80 mg, 175 mg and 255 mg could *not* be considered equivalent
- docetaxel and paclitaxel could not be considered equivalent, at any dose
- all other chemotherapy treatments could *not* be considered as equivalent.

Only docetaxel 75 mg and 100 mg could be considered equivalent

As noted in question A2, Perjeta is an add-on to Herceptin and because Herceptin is the current standard of care treatment in the UK for HER2-positive eBC patients, the combination of Herceptin and docetaxel is considered an appropriate comparator.

Following from above, the Nagayama et al. 2014 publication was reviewed and in this study the neoadjuvant monotherapy and combination chemotherapies were considered comparable and grouped as 'chemotherapy'. Notably, docetaxel and paclitaxel were considered comparable and the publication does not indicate that any of the assumptions for grouping chemotherapies regardless of agent and regimen has been clinically validated.

Moreover, a review of the methods presented indicates heterogeneity in terms of outcome definition and treatment duration as follows:

- The publication states that for the outcome of pathologically complete response (pCR) "other definitions of pCR were substituted if not reported."
- The follow up time of the studies included in the meta-analysis ranged from 12-30 weeks and all outcome data were analysed as dichotomous outcomes. This would require an assumption that treatment duration beyond 12 weeks would make no difference to trial-level relative treatment effects, and this was not stated within the publication.
- The study does not provide a qualitative discussion of heterogeneity, although it highlights heterogeneity as a limitation in the discussion

The assessment of inconsistency presented in the publication is the main area of concern regarding the approach to forming the evidence networks and the validity of the analyses presented. The network meta-analysis publication notes that

“statistically significant inconsistency was identified” in the four main outcomes of interest (pCR, treatment completion, diarrhoea and neutropenia). Statistical inconsistency may be considered as a form of heterogeneity from the variation of effect modifiers across treatment comparisons. If data are inconsistent it may not be suitable to form the basis for a coherent model.

In summary, the Nagayama et al., 2014 publication and the detection of inconsistency within the evidence networks highlights that combining studies and treatment nodes inappropriately in this indication may result in unreliable network meta-analysis.

Section B: Clarification on cost-effectiveness data

Literature searching

B1. *Please clarify why different (fewer) disease area terms have been used in the cost searches (Tables 129-132 and 134-135, p365-372) compared with the clinical searches (Tables 117-119, p344-346). In addition, the EMBASE searches for the economic studies and health-related quality of life (HRQoL) evidence (Table 135) both appear to contain a logic error at line 6, where lines "3 or 4" have been combined instead of "4 or 5".Please comment on the implications of these issues for the findings of the respective reviews (and/or re-run the searches).*

The economic search terms are more focused on terms for neoadjuvant treatment, this was a conscious decision to identify the specific types of study of interest. Although there are differences in disease terms, the economic searches retrieve a greater number of "breast cancer" related publication than the clinical search.

- Lines 1-5 in clinical search = 323951
- Lines 1-9 in economic search = 357853

The search is made narrower because of the terms used for neoadjuvant treatment for which only terms outlined in the MeSH entry were used (https://www.nlm.nih.gov/cgi/mesh/2016/MB_cgi). These terms should fully capture the relevant studies reporting the use of neoadjuvant treatment in a more focused way that the terms used in the clinical search.

Regarding the terms outlined below, we only included breast cancer terms included in the MeSH entry terms and Emtree entry terms (https://www.nlm.nih.gov/cgi/mesh/2016/MB_cgi)

- "tumo" > this is captured by the 2 terms included in the economic search “tumour*” and “tumor*”
- "adernocarcinoma" > “carcinoma” would capture this.

- "malignan" > “malignanc*” would capture the majority of these, it is acknowledged that the we should probably have taken the “c” off the end to be more inclusive.
- "sarcoma” > is not an entry term for breast cancer (see MeSH browser link above)

We acknowledge that there is a logic error in line 6 of the EMBASE searches for economic studies and HRQoL. The searches have been re-run with the logic error corrected, with the following results:

The HRQoL studies results identified an additional 321 abstracts, which were reviewed by their titles and abstract if they appeared relevant. None were identified as relevant for inclusion.

The economic studies identified 76 less abstracts. No further analyses of these were carried out.

We do not believe that the logic error has affected the final search results as it is likely that the majority of studies not captured in the Embase Utility search would have been captured in the searches conducted in other databases and the correction of the economic studies search produced few results.

B2. *The ERG notes that the company’s HRQoL searches did not find the study by Lidgren 2007. Given that this article is indexed in MEDLINE and EMBASE, both of which were searched, did the company perform any follow up searches in light of this. How confident is the company that no similar studies of potential relevance have been missed?*

Lidgren 2007 study was not identified by the HRQoL searches, because the search was specific in looking for breast cancer and neoadjuvant treatment. The term neoadjuvant was not mentioned within the Lidgren publication.

Although we are not aware of any additional sources, there is potential that similar studies may be available which do not specifically reference neoadjuvant treatment, but do relate to early breast cancer (as per Lidgren).

B3. *Please explain how the study by Hamilton 2014 was identified to inform the monthly transition from remission to metastatic non-progressed health states. Are there other relevant studies from which data could be used within the sensitivity analysis rather than doubling and halving the figure from Hamilton 2014?*

Hamilton 2014 was identified through a targeted search on PubMed. We are not aware of any other studies which could be used. In the absence of other supporting data the decision was made to double and half the figures to produce the sensitivity analysis.

Cost effectiveness review

B4. *Very little detail is provided for the one study included in the cost-effectiveness review (Attard et al.) (p192-193). Please provide a more complete description and critical review of this study, for example:*

What were the health states?

The model by Attard et al contained only 3 health states as follows: event-free (with utilities for the first year and for subsequent years), relapse (local or metastatic) and death.

How were trial outcomes extrapolated?

Attard et al used the overall survival and event-free survival from a retrospective study reported by Kim et al (study that determined the prognostic value of pathologic response to neoadjuvant chemotherapy with concurrent Herceptin). This patient level data was estimated based upon the Kaplan-Meier estimates from the publication using the algorithm published by Guyot et al.

What were the model/ data limitations?

The main limitations from Attard are as follows:

- the data was derived from a single centre,
- The number of patients with HER2-positive breast cancer very low (only 229)
- The publication by Kim et al does not present number at risk over time, therefore more assumptions are required to run the algorithm by Guyot (an algorithm that maps digitised curves back to Kaplan-Meier data by finding numerical solutions to the inverted Kaplan-Meier equations, using where available information on number of events and numbers at risk) leading to potentially less robust results.
- No long-term data is reported on patients treated with neoadjuvant Perjeta.

What were the key drivers of the model results?

The key drivers of the model are the discount rate, absolute difference in pCR and cost of subsequent treatments.

Health economic model

B5. ***Priority question:*** *As referred to on page 13 of the company submission, some HER2-positive breast cancer patients who would receive neoadjuvant*

treatment within England may not receive trastuzumab. Could you please incorporate these additional comparators within the economic model (see point A13 for clarification around the inclusion of a mixed treatment comparison). If you do not consider this to be feasible within the current timescales, as a minimum please describe the potential implications of doing this upon your findings. Please consider including the cost of surgery if it is expected that this would differ substantially between interventions.

As noted in question A2, the relevant Perjeta patient population is equivalent to that of Herceptin (since Perjeta is an add-on to Herceptin). As Herceptin is the standard of care in the UK for neoadjuvant treatment (used by more than 75% of patients [Roche data on File RXUKPERT00220(1)], it was felt that it is the only appropriate comparator to include in the economic model.

With regards to the inclusion of surgery, Breast Conservation Surgery rates are similar between both arms in NeoSphere. Therefore its inclusion would be expected to have limited impact in the model results. Moreover, the choice of the type surgery is multifactorial and consequently its inclusion would increase the complexity of the model.

B6. ***Priority question:*** *Please present a figure comparing the currently predicted event free survival (EFS) within the model with the trial EFS curves for each arm (HD and PHD), accompanied by a discussion of the fit and implications for the modelling.*

Figure 1 below depicts the comparison between the predicted piecewise exponential fit (further detailed below) of NeoSphere EFS survival vs. the predicted NeoSphere EFS survival from CTNeoBC analysis. It can be seen that the model under-predicts the EFS survival in both arms. A discussion of the fit is detailed in question B7 below.

Figure 2 (taken from page 263 of the submission) and Table 5 below shows the difference in log survival between PHD and HD (the incremental treatment effect), and it can be seen that the model is underestimating the incremental treatment effect (even though the model estimates are within the confidence interval seen in NeoSphere Kaplan-Meier analysis). In this sense the model may be considered conservative.

Figure 1- Predicted EFS (NeoSphere) vs. Predicted EFS (CTNeoBC data)

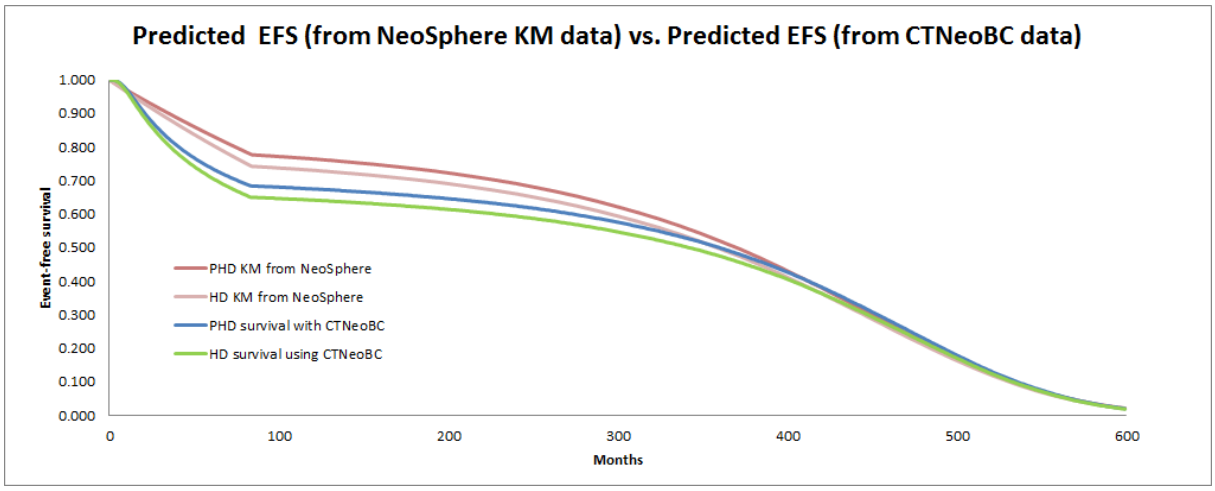
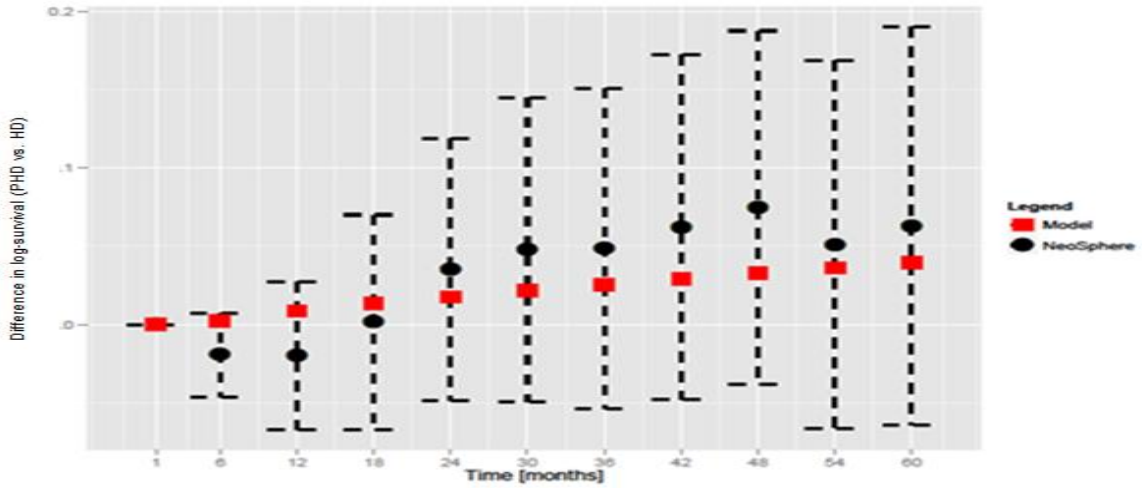


Figure 2 – Incremental EFS survival from NeoSphere vs. Incremental EFS survival from the model



Time [months]	Delta_trial (95% confidence interval)	Delta_model
1	0 (0,0)	0
6	-0.019 (-0.046,0.007)	0.002
12	-0.02 (-0.067,0.027)	0.009
18	0.001 (-0.067,0.07)	0.013
24	0.035 (-0.049,0.119)	0.018
30	0.048 (-0.049,0.145)	0.022
36	0.049 (-0.053,0.151)	0.025
42	0.062 (-0.048,0.172)	0.029
48	0.075 (-0.038,0.188)	0.033
54	0.051 (-0.067,0.168)	0.036
60	0.063 (-0.064,0.19)	0.039

The EFS curves modelling and fit from NeoSphere trial are further detailed in the following question.

B7. ***Priority question:*** *Given the limitations and uncertainty associated with the use of tpCR (total pathological complete response) as a predictor for EFS, please could you undertake additional analyses within the model using the EFS trial outcomes from the NeoSphere trial? For example by using the Kaplan-Meier curves from the trial within the model directly and fitting appropriate parametric distributions to the Kaplan-Meier data for each arm. Please provide the output files containing the parameters, their confidence intervals and the variance-covariance matrix for each of the parametric distributions. Please analyse which of them provides a best fit to the Kaplan–Meier data using the AIC, BIC and visual fit criteria and present the associated ICERs.*

The scenario below uses the 5 year event-free data from NeoSphere, which was collected in the trial as an exploratory endpoint. Parametric survival functions were fitted to this data and incorporated in the model.

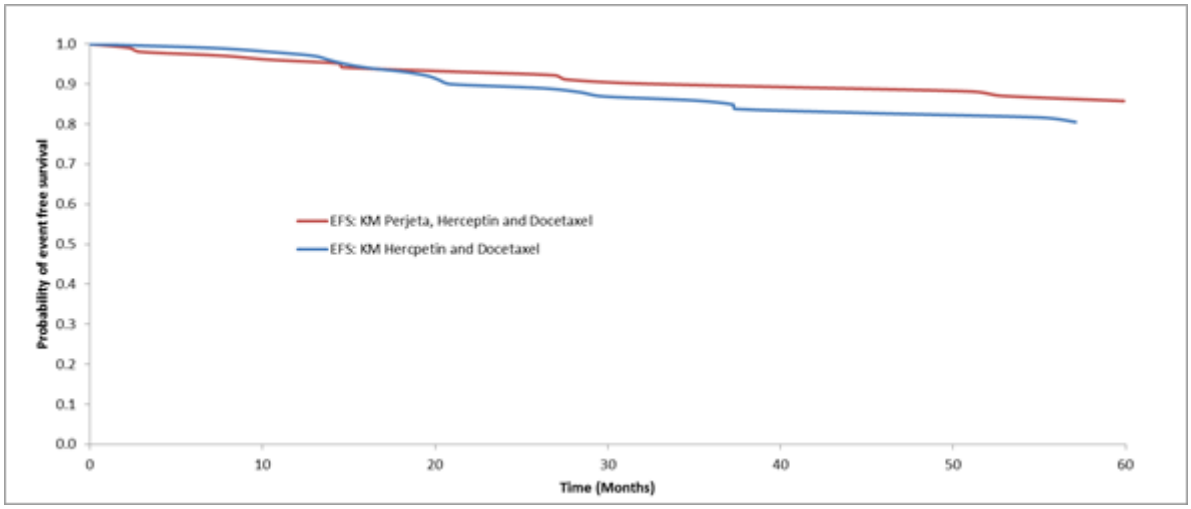
The relative strengths and weaknesses of the differing methods used in the base case and this scenario (EFS Scenario) are presented below.

Table 6 - Strengths and weaknesses of methods to estimate EFS

	Base Case: tpCR + CTNeoBC analysis	**EFS Scenario: EFS from NeoSphere**
Is trial data from NeoSphere used?	Yes, but CTNeoBC analysis is also required	Yes, used directly
Do the results use valid endpoint from the trial?	tpCR is the secondary endpoint in NeoSphere. EFS is a primary endpoint in CTNeoBC analysis	EFS is a secondary endpoint. This endpoint is an exploratory analysis and was not powered to test for formal hypotheses of efficacy.
How reliable is the data source?	FDA data includes a large number of events and is more mature	Data includes a small number of events and is less mature.
Are any assumptions required to predicted EFS?	Assumption required about the link between tpCR and EFS	No Assumption required, EFS data is used directly from trial
How long is the follow-up?	Follow up is between 5.4 and 6.6 years for no tpCR and tpCR arm respectively	5 years

The Kaplan-Meier data in Figure 3 shows the EFS data split by treatment arm. The Kaplan-Meier plots in both arms are relatively flat reflecting the small number of events that have occurred over the 5 year (60 month) period.

Figure 3- Kaplan-Meier curves from NeoSphere



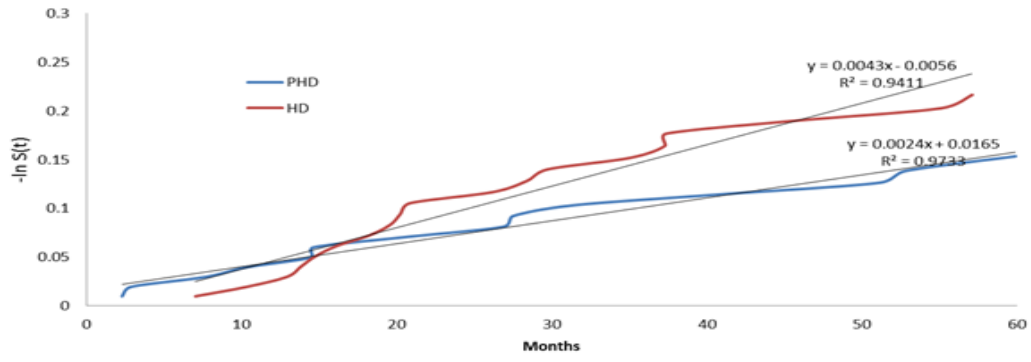
Selection of parametric function

In order to determine the most appropriate parametric function to extrapolate the EFS data, the shape of the cumulative hazard plots and goodness of fit was considered (both visually and using goodness of fit statistics).

- **Cumulative hazard plots for EFS Scenario**

Figure 4 shows that individuals in the PHD arm have a lower risk of a progressing compared with individuals in the HD arm. This is demonstrated by the average of the slope of the HD line being steeper than the average of the slope of the PHD line.

Figure 4 - Cumulative hazard plots from NeoSphere



Parametric survival functions (i.e. exponential, Weibull, log-logistic, log-normal, Gompertz and gamma) were fitted to the EFS data. Only four out of the six tested survival functions converged or produced an appropriate covariance matrix due to the low patient number and observed events (see appendix A for the covariance matrix). Parameters are displayed in Table 7.

Functions were fitted as independent of shape (i.e. one curve for the HD and one for PHD) because treatment curves were crossing around month 15. None of the estimated survival functions fitted the data adequately, as assessed by visual inspection (see section below) of the fit to the Kaplan-Meier curves.

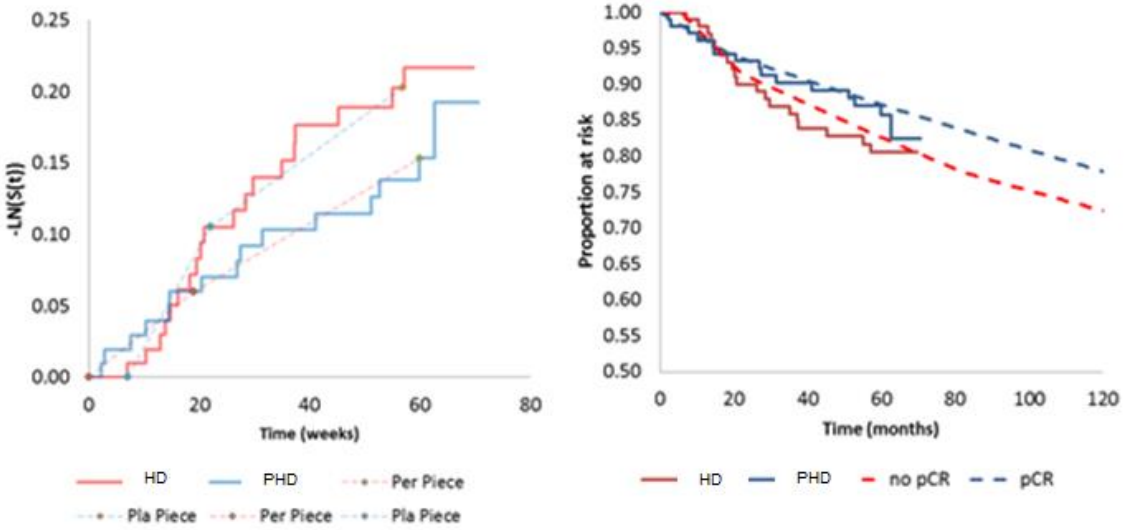
Table 7 - Parameters for extrapolation of Event-Free Survival by treatment arm

	Lambda	Gamma	AIC (rank)	BIC (rank)
Treated with HD				
Exponential	0.004		135.3 (2)	137.9784
Weibull	0.002	1.124	137.0 (4)	142.3706
Lognormal	5.436	1.571	134.4 (1)	139.7868
Log-logistic	0.002	1.197	136.4 (3)	141.7941
Treated with PHD				
Exponential	0.003		127.3 (1)	129.9554
Weibull	0.002	1.064	129.2 (2)	134.5586
Lognormal	6.016	1.962	130.1 (4)	135.4719
Log-logistic			129.5 (3)	134.878
The generalized gamma or Gompertz distributions were not included as they did not converge. An estimated theta of 0.0000001, and a non-sensible covariance matrix for the gamma function				

Piecewise exponential

The Kaplan-Meier for HD and PHD arms are crossing as indicated in Figure 3 at around month 15, meaning that the proportional hazards assumption was violated; a piecewise approach was therefore also explored.

Figure 5 - (left) Hazard plot with exponential pieces (right) predicted EFS by piece-wise versus Kaplan-



In a piecewise exponential approach exponential pieces were fitted to the hazard, see left figure in Figure 5. The first objective was to determine where there was a change in hazards. Two exponential pieces were fitted to each hazard curve, for the HD arm a change in the hazard was seen at 22 months. Since no events occurred in the HD arm for the first 7 months the piece did not start until month 7 and incorporated the same way in the CE-model. For PHD one piece was fitted for the first 19 months and then a second piece, from month 22 to 60. The right plot in Figure 5 shows the estimated piecewise extrapolation better fits the observed Kaplan-Meier.

Table 8 - Time interval and estimated hazard for the fitted pieces

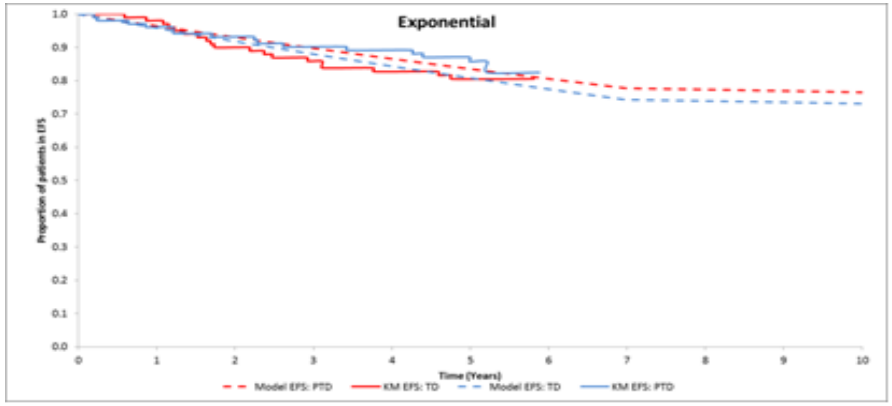
PHD – Breakpoints (months)	PHD – Hazard	HD – Breakpoints (months)	HD – Hazard
0-19	0.0032	7* – 22	0.0054
19-60	0.0019	22 – 57	0.0127
*No events were observed before 7 months for HD, therefore implemented in the same way in the model			

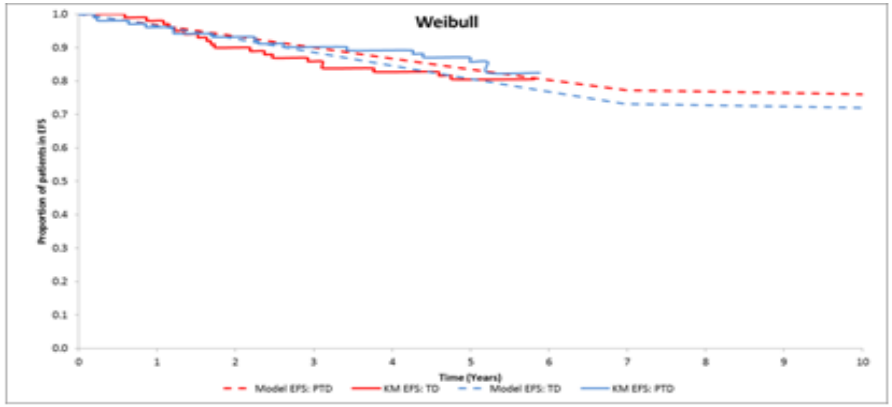
The parametric function with the best statistical fit is the piece-wise exponential function for the PHD arm and exponential and log-normal functions for the HD arm.

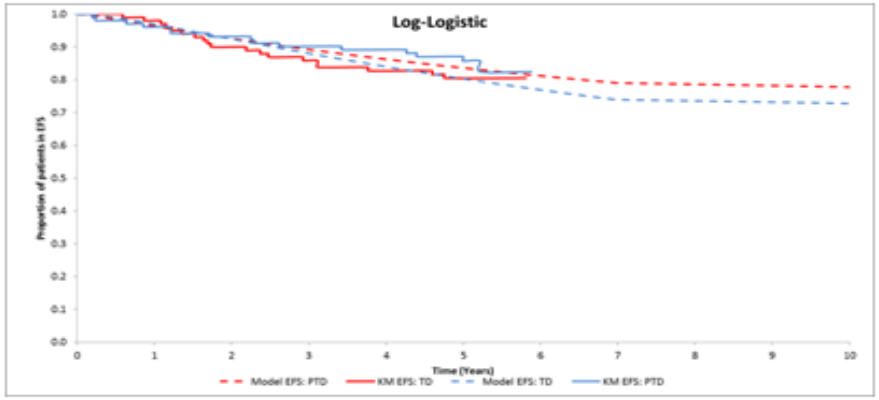
Visual inspection: a range of possible parametric extrapolation of the EFS data was considered (these are shown in Figure 6). The parametric functions are used in the model to estimate the first 7 years of EFS only as such the figures focus the

first 7 years. Figure 7 shows the modelled estimates of EFS by treatment arm for the different parametric functions.

Figure 6 - Parametric survival curves for EFS (compared to observations) in NeoSphere







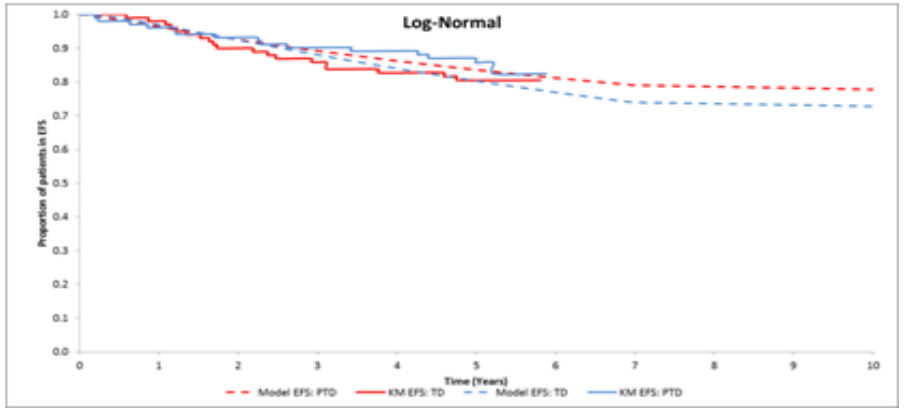
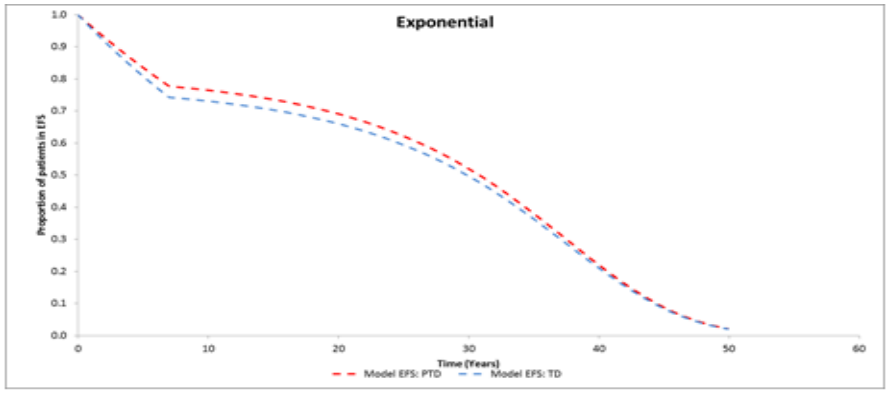
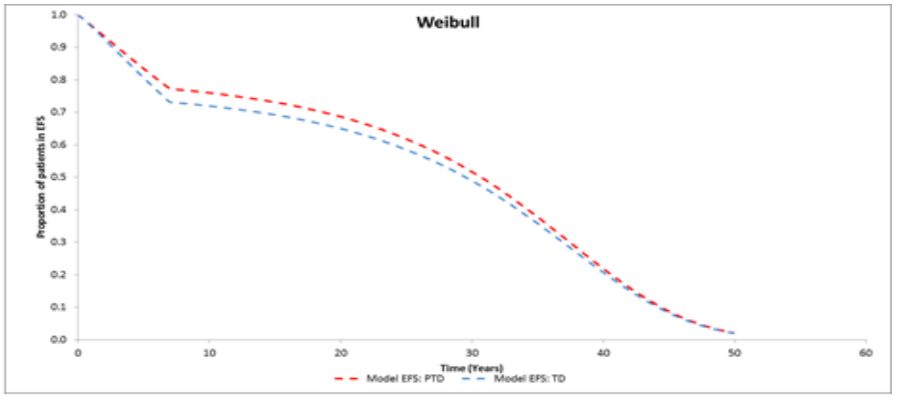
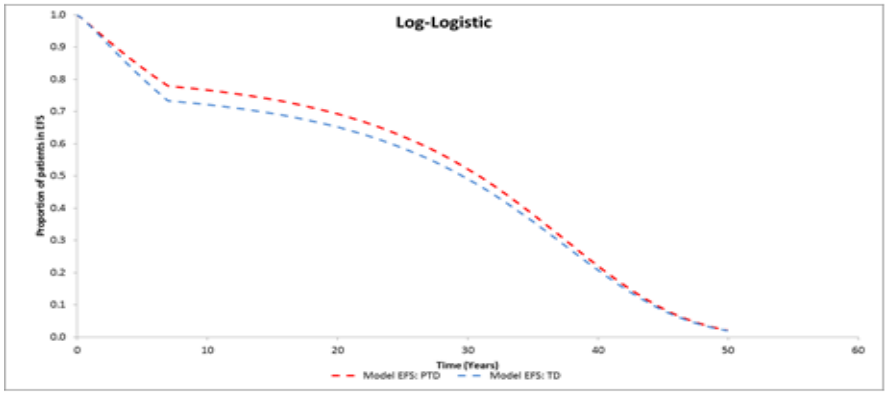
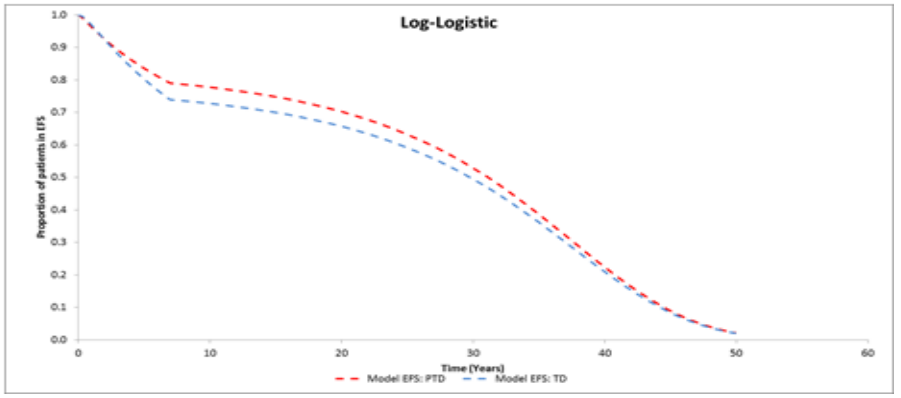


Figure 7 - Model estimation of EFS using different parametric curves









Based on the results from the AIC/BIC and on the visual inspection of the curves, the piece-wise exponential parametric function is the one that better fits the data and therefore is used in the EFS Scenario.

Table 9 - Deterministic EFS scenario results

Technologies	Total costs (GBP)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	Inc. £/LYG	ICER (£/QALY)
PHD	71,145	18.31	12.65					
HD	71,432	17.71	12.21	-287	0.6	0.43	-476	-660
PHD – Perjeta + Herceptin + docetaxel; HD - Herceptin + docetaxel; LYG – life years gained; QALYs – Quality adjusted life years; ICER – incremental costs effectiveness ratio								
Values in the table are discounted and 1/2 cycle corrected								

It should be noted that these results should be considered with caution as immature EFS data was used to calculate the ICER.

B8. ***Priority question:*** *In section 5.3.1 of the submission (Table 73 and Table 74), the following 5 parametric distributions were analysed for best fit to the Kaplan–Meier data (patients with pCR and patients without pCR) using the AIC, BIC and visual fit criteria: Exponential; Weibull; Log-normal; Log-logistic; Gamma.*

Please clarify why a Gompertz distribution was not analysed or presented in this analysis.

Six different parametric survival extrapolations were explored, including Gompertz. As can be seen in the table below a negative scale parameter was estimated for the Gompertz scale for EFS no pCR. This non-sensible value suggests that the model did not converge and was therefore excluded from the analysis. See table below.

Please provide the output files containing the parameters, their confidence intervals and the variance-covariance matrix for each of the distributions listed above.

The parameters and their confidence intervals are as follows:

Table 10 – CTNeoBC parametric functions and confidence intervals

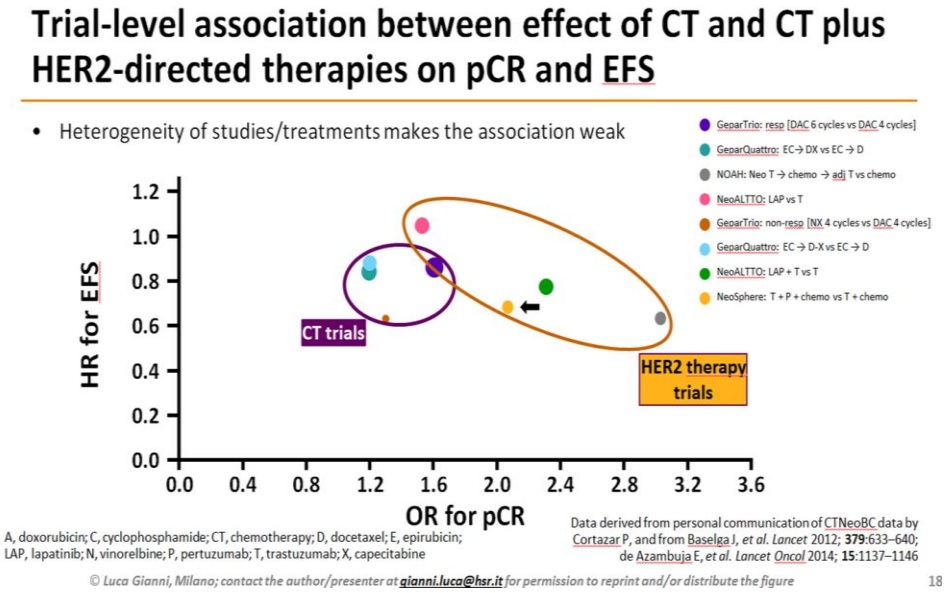
Subgroup	Endpoint	Distribution	intercept	scale	shape	AIC	BIC	log_likelihood
no pCR	EFS	exponential	5.041	1.000	NA	4182	4187	-2090.0
no pCR	EFS	weibull	4.870	0.854	NA	4173	4184	-2084.6
no pCR	EFS	lognormal	4.683	1.380	NA	4132	4142	-2063.8
no pCR	EFS	loglogistic	4.605	0.762	NA	4157	4168	-2076.7
no pCR	EFS	gompertz	0.007	-0.001	NA	4184	4186	-2090.0
no pCR	EFS	gamma	4.114	1.747	-1.314	4116	4120	-2055.1
pCR	EFS	exponential	5.842	1.000	NA	1001	1005	-499.4
pCR	EFS	weibull	5.327	0.730	NA	995	1003	-495.3
pCR	EFS	lognormal	5.366	1.345	NA	985	994	-490.6

pCR	EFS	loglogistic	5.177	0.688	NA	993	1001	-494.3
pCR	EFS	gompertz	0.002	0.006	NA	1002	1004	-499.0
pCR	EFS	gamma	3.721	1.775	-4.304	974	976	-484.0

Please find the output files containing the parameters, their confidence intervals and the variance-covariance matrix in appendix B.

B9. *Please provide an assessment of the relationship between tpCR and EFS within the NeoSphere study? Please comment how this relationship compares with that observed in the CTneoBC group meta-analysis (Cortazar et al. 2014).*

HER2-positive targeted trials (NeoALLTO and NeoSphere) were not included in the meta-analysis by CTNeoBC. If these two trials were added and the analysis was restricted to HER2-positive targeted therapies only, a substantially stronger association between pCR (odds ratio) versus EFS (hazard ratio) compared to non-targeted treatments would be shown. See figure below (Gianni 2015 ASCO):



B10. *Please comment on the clinical plausibility of the extrapolated survivor functions for event free survival (Figure 30) and the implied hazard rates for each treatment group over time.*

All plots from figure 30 of the submission (see example of the Gamma distribution below) can be divided into two time periods as follows:

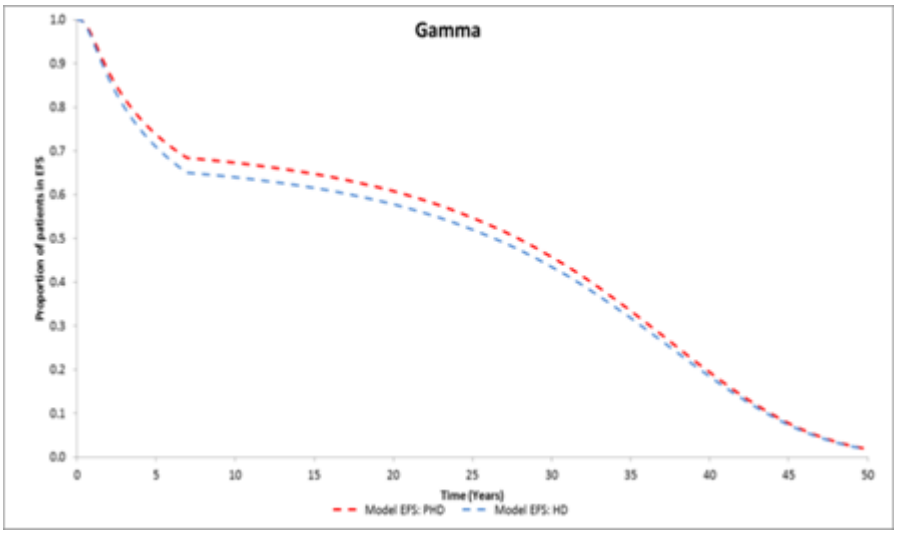
Period one (from year 0 to year 7): This period represents the first 7 years of progression and is informed by the tpCR rates from NeoSphere and by the CTNeoBC meta-analysis (which had duration of approximately 7 years). In the base

case this period was modelled with a Gamma function that implied a diminishing risk of progression. This assumption is supported with the opinions of an advisory board of clinicians that noted that most recurrences may happen within 2-3 years and then the risk diminishes.

Period two (from year 7 to end of time horizon): After 7 years, patients would not progress to other disease health states and were assumed to have the UK background mortality rates. Therefore, after year 7 patients can only progress to the death state due to natural causes. This explains the flattening of the EFS curve starting from the 7th year.

It is acknowledged that the shape of the curves may not be seen in clinical practice (especially the shape of the curve around year 7 as such change in the hazard would not be so rapid). However, the shape results from conservative assumptions (i.e. null incremental efficacy after year 7) and from the assumption of general UK mortality after year 7 for patients in the EFS state. It should be noted that the incremental OS is not expected to be overestimated.

Figure 8 - Gamma distribution of the CTNeoBC data



B11. *Given that the Kaplan Meier data from the CTNeoBC meta-analysis was used to estimate the EFS in the model for patients with and without pCR, please justify why the overall survival (OS) in the model was not estimated in the same manner? That is, modelling the OS from the CTNeoBC meta-analysis which provides KM data of OS for patients with and without pCR (Figure 2, Cortazar et al 2014 - the same figure as that of the EFS).*

Cortazar presents EFS data for HER2-positive specific subgroup. However, the article does not present the OS data for HER2-positive subgroup (it presents for all breast cancer patients). There is a large difference in survival between with HER2-positive and HER2-negative and as only 1989 out of the 11955 breast cancer

patients were confirmed HER2-positive (17% of the patients) this data was not used in the model to estimate the OS.

B12. *Please explain the calculations used to adjust the EFS survival in columns P and Y of the 'Extrapolation' sheet of the model*.

The calculations in these columns can be explained as follows:

Not achieved pCR (column P)

- The model allows the user to determine when there is no longer a negative effect of not having achieved pCR (i.e. no pCR) on EFS.
- If it is within the aforementioned timeframe the model uses the highest risk of the following two alternatives a locoregional /metastatic event or risk of death for the general population.
- If it is beyond the aforementioned timeframe the model uses the same values as for pCR.

Achieved pCR (column Y)

- The maximum value is used of the probability of leaving EFS and the probability of dying in accordance with the general mortality

B13. *The model uses a monthly cycle length. Please explain why a 3-weekly cycle has not been used within the model given that the key clinical events (e.g. treatment cycles, cardiovascular checks) happen in 3-weekly intervals? Please also check that this is consistent throughout the company submission, since in some parts of the submission (p17, p196) it is suggested that 3-weekly cycles are used for the modelling.*

The model was developed with a monthly cycle length primarily because the duration of neoadjuvant treatment is relatively short and given that the model utilises a 50 year time horizon, it was felt that a monthly cycle was appropriate to capture costs and utilities over the lifetime of the model.

We acknowledge that a three week cycle length could also have been used and that this may have simplified application of costs in the initial time period of the model, for the reasons outlined above.

B14. *The ERG and their clinical advisers understand that the use of subcutaneous trastuzumab is now standard practice in England. Please include the cost for subcutaneous trastuzumab within the base case rather than in a scenario analysis, or present evidence to justify why intravenous trastuzumab was used in the base case.*

The base case has been adapted for the split in usage of Herceptin IV and Herceptin Subcutaneous (SC) formulations. Market research data shows that the ratio of Herceptin containing regimens is [redacted] and [redacted] for Herceptin SC and Herceptin IV respectively. It should be noted that Herceptin SC is not licensed for use with Perjeta, and as such the cost of Herceptin SC is factored in only into the comparator arm. Therefore, these results are different from those in scenario 1 in the submission which made the simplistic assumption that all patients received Herceptin SC in the comparator arm.

An analysis with the above IV/SC split was undertaken with the following results:

Table 11 – Updated deterministic base-case results

Technologies	Total costs	Total LYG	Total QALYs	Incr costs	Incr LYG	Incr QALYs	Incr cost/ LYG	ICER incr (QALYs)
PHD	£104,575	16.72	11.50	-	-	-	-	-
HD	[redacted]	16.35	11.24	-	-	-	-	-
PHD vs. HD	-	-	-	[redacted]	0.37	0.26	[redacted]	[redacted]
Values in the table are discounted and 1/2 cycle corrected								

Table 12 - Summary of QALY gain by health state

Outcome	**Therapy**	**QALYs**	**PHD vs HD**	**Absolute QALY gain**	**% Absolute QALY gain**
EFS	PHD	10.18			
	HD	9.76	0.42	0.42	73.21%
Locoreg. Recurr.	PHD	0.08			
	HD	0.09	-0.01	0.01	1.62%
Remission	PHD	0.66			
	HD	0.74	-0.08	0.08	13.39%
Met. (not progressed)	PHD	0.31			
	HD	0.35	-0.04	0.04	6.35%
Met. (progressed)	PHD	0.27			
	HD	0.30	-0.03	0.03	5.43%
Total	**PHD vs. HD**		**0.26**	**0.57**	**100%**

Table 13 - Summary of Costs by health state

Outcome	Therapy	Total Cost (£)	Cost PHD vs HD (£)	Absolute incremental cost (£)	% Absolute COST difference
EFS	PHD	38,308			
	HD	[redacted]	[redacted]	[redacted]	[redacted]
Locoreg. Recurr.	PHD	2,516			
	HD	2,805	-289.50	289.50	[redacted]
Remission	PHD	690			
	HD	769	-79	79	[redacted]
Met. (not progressed)	PHD	20,950			
	HD	23,361	-2,412	2,412	[redacted]
Met. (progressed)	PHD	42,112			
	HD	46,960	-4,848	4,848	[redacted]
Total	**PHD vs. HD**		[redacted]	[redacted]	**100%**

A 1,000 iteration probabilistic sensitivity analysis was conducted in order to determine the uncertainty surrounding the base-case ICERs.

Figure 9 - Incremental Cost Effectiveness Plane

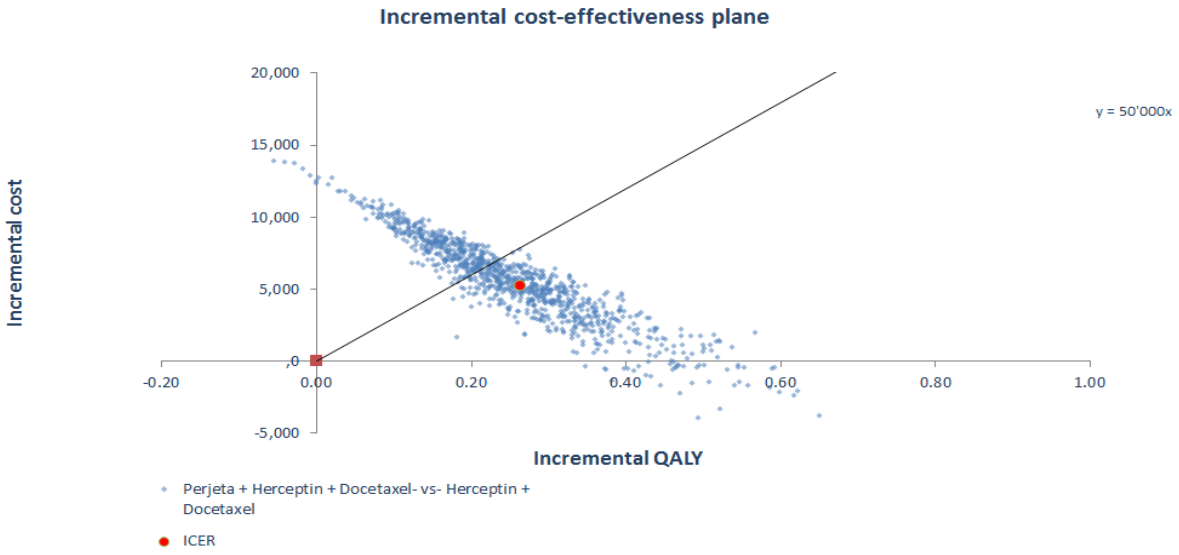
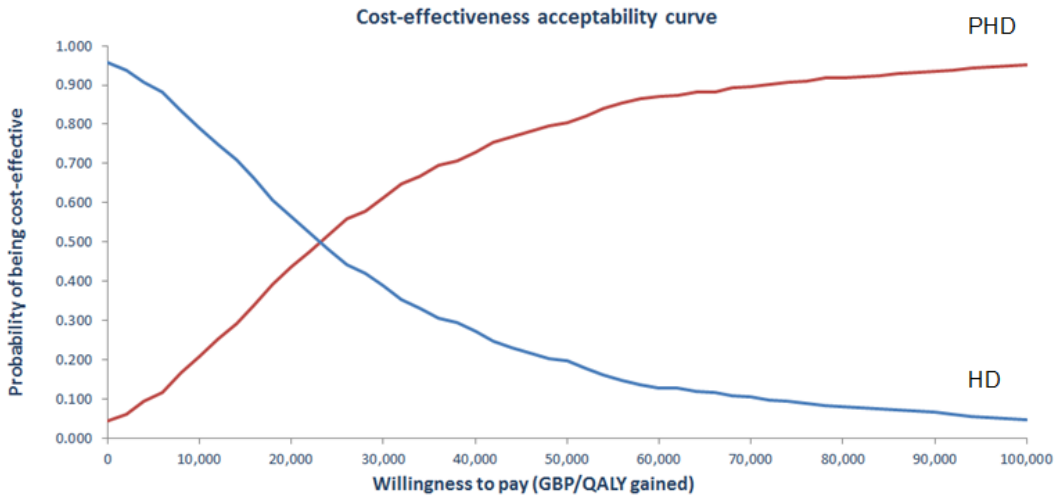


Figure 10 - Cost Effectiveness Acceptability Curve



This analysis indicated that Perjeta in combination with Herceptin had a 62.1% chance of being cost-effective treatment at a threshold of £30,000/QALY gained. The probabilistic base-case ICER of £21,869 was comparable to the deterministic base-case ICER [redacted]).

Table 14 - Deterministic sensitivity analysis for base case

Base case ICER [redacted]					
Parameter modified	**Base value (£)**	**High Value**	**Low Value**	**ICER High (£ per QALY)**	**ICER Low (£ per QALY)**
LR supportive care costs health state costs	£74	£103.60	£44.40	£19,921	£19,956
Log-Logistic parametric function		Log-logistic			£20,021
Pharmacy cost	£10	£13.44	£5.76	£19.909	£19,968
Cardiac assessment proportion	30/70 (MUGA/ECHO) proportion	10/90 (MUGA/ECHO) proportion	50/50 (MUGA/ECHO) proportion	£19,966	£19,912
Event free survival supportive care cost (monthly)	£67.85 (year 1-2), £15.11 (year 3-5), £3.83 (year 5+)	BCVs x 1,25	BCVs x 0,75	£19,889	£19,988
AE cost	£794.66 (PHD Arm), £742.47 (HD Arm)	£1112.52 (BCV x 1.4), £1039.46 (BCV x 1.4)	£476.79 (BCV x 0.6), £445.48 (BCV x 0.6)	£20,018	£19,859
Metastatic not progressed supportive care costs (monthly)	£232	£324.8 (BCV x 1.4)	£139.20 (BCV x 0.6)	£17,716	£20,161
Administration cost (monthly)	£326.60 (for 1st treatment),	£457.24 £244.44	£195.96 £104.76	£19,880	£20,675

	£174.60 (for subsequent treatment)				
Metastatic progressed disease supportive care cost (monthly)	£185	£259 (BCV x 1.4)	£111 (BCV x 0.6)	£19,709	£20,169
Weibull parametric fit	Gamma	Weibull		£19,212	
Log-Normal parametric function	Gamma	Log normal		£21,624	
Exponential parametric function	Gamma	Exponential		£17,803	
between metastatic and local regional recurrence	58% and 42% (Source: NeoSphere)	70% and 30% (Source: HERA)		£17,602	
Transition probability of moving from metastatic not progressed to death (HD)	3.15%	3.78% (BCV x 1.2)	2.52% (BCV x 0.8)	£20,565	£19,257
Transition probability of moving from metastatic not progressed to death (PHD)	2.73%	3.82% (BCV x 1.2)	2.18% (BCV x 0.8)	£23,375	£17,229
PHD pCR	39.25%	49.2%	30.0%	£2,534	£72,673
HD pCR	21.5%	30.5%	14.1%	£69,776	£5,696
Monthly risk of a second malignancy	0.76%	1.52% (BCV x 2)	0.38% (BCV x 0.5)	£16,588	£24,987
Utility Values Source 2	See Table 103	See Table 103		£20,477	
Time horizon	50	50	30	£24,608	
Utility Values Source 1	See Table 103	See Table 103	see table 14	£16,394	£25,237
Vial sharing assumptions (Herceptin only)	Vial sharing	No Vial Sharing			£20,248
Time point when switching to background mortality (only)	7	5	6	£27,726	£22,994
BCV – Base Case Value PHD Perjeta, Herceptin, docetaxel HD Herceptin, docetaxel AE Adverse Event LR Locoregional recurrence					

B15. *Please clarify the cost of docetaxel; within the report (Table 85), the cost is £43.09 initial dose, £57.28 cycle 2+; within the model the cost that is used*

appears to be £43.09 initial dose, £57.46 cycle 2+; and on the 'vial sharing' sheet in the model (that does not seem to be used to estimate the base case results), the cost is estimated to be £32.37 with vial sharing. Please also clarify the average monthly cost per patient of PHD + FEC + administration cost and HD + FEC + administration cost as this seems inconsistent between Table 85/ 86, Table 87 and the values used within the model. If the values within the model are incorrect, then please correct these and recalculate the model results.

Tables 85-87 (table numbers from the submission) are corrected and presented below. Please note that errors were made in the completing the tables only and not in the economic modelling and as such no updates to the model results are necessary.

The tables should have read PHD (+ Administration cost) and not include the cost of FEC. In the economic model PHD is given for 4 cycles followed by FEC for 3 cycles. As FEC and PHD are not administered in the same cycle these should not have been presented as a per cycle cost. The cost of HD with FEC has been corrected and updated in the table. Please see corrected tables below with changes are highlighted in yellow.

The vial sharing tab is not used in the submission.

Table 85 Drug costs for neoadjuvant and adjuvant treatments

	Per cycle £ (vial share) BASE CASE	**Per cycle £ (no vial share)**	**Dose based on / no of cycles**
Perjeta	£4,790 initial (2x 420 mg) £2,395 cycle 2+(1 x 420 mg)	Equal to base case	Flat dosing q3w Initial dose 840mg, cycle 2+ 420mg
Herceptin	£1588 initial (3.90 x 150 mg) £1,191 cycle 2+ (2.92 x 150 mg)	£1,629.6 initial (4 x 150 mg) £1,222.2 cycle 2 +(3 x 150 mg)	8mg/kg initial dose 6mg/kg cycle 2+ q3w
Docetaxel (generic)	£43.09 initial (134.25 mg) £57.28 cycle 2+ (179 mg)	£43.09 initial (134.25 mg) £57.28 cycle 2 + (179 mg)	75mg/m^2 initial and cycle 2-4 Cycle 2+ can increase up to a maximum of 100mg/m^2 q3w
PHD Total	£6,421 initial cycle £3,643 cycle 2-4	£6,462 initial £3,674 cycle 2-4	
HD Total	£1673 initial £1248 cycle 2-4	£1673 initial £1279 cycle 2-4	
H + FEC Total	£1232 cycle 5-7	£1232 cycle 5-7	
FEC total (generic) 5-Fluorouracil Epirubicin Cyclophosphamide	£40.8 £1.43 £21.7 £17.67	£40.8 £1.43 £21.7 £17.67	3 cycles 600 mg/m^2 90 mg/m^2 600 mg/m2
PHD Perjeta, Herceptin, docetaxel PH Perjeta, Herceptin			

Table 86 Administration costs of chemotherapy

	1st cycle	NHS reference costs 2013/14	2+ cycle	NHS reference costs 2013/14
Chemotherapy delivery	£317	SB13Z Deliver complex parenteral chemotherapy (daycase)	£165	SB12Z Deliver simple parenteral chemotherapy (outpatient)
Pharmacy preparation	£9.60	PSSRU 2014 pharmacist time £48/hour 12m x £48/60m	£9.60	PSSRU 2014 pharmacist time £48/hour 12m x £48/60m
Total	**£326.60**		**£174.60**	

Table 87 Summary of health state costs

Health states	Items	Average monthly cost per patient	Reference in submission
Event Free Survival (Neoadjuvant treatment)	PHD + administration costs	£6,748 initial cycle £3,818 Cycle 2-4	Table 85 & Table 86
	HD + administration costs	£1,958 initial cycle £1,423 Cycle 2-4	Table 85 & Table 86
	Supportive care† year 1+2	£67.85	Table 90
	Supportive care† year 3-5	£15.11	Table 90
	Supportive care† year 6 onwards	£3.83	Table 90
Event Free Survival (Adjuvant treatment)	H + FEC + Administration costs	£1,407 cycle 5-7	Table 85 & Table 86
	H + administration costs	£1,366 cycle 8+	Table 85 & Table 86
	Supportive care† year 1+2	£67.85	Table 90
	Supportive care† year 3-5	£15.11	Table 90

	Supportive care† year 6 onwards	£3.83	Table 90
Locoregional recurrence	H + Administration costs	£1,366	Table 88
	Supportive care††	£75.53	Table 91
Remission	Supportive care†	£67.85	Same as Supportive care EFS Y1
Metastatic not progressed	Treatment	£3,590,26	Table 88
	Supportive care†††	£232.8	Table 92
	Total	£3,823.06	
Metastatic progressed	Treatment	£5,738	Table 89
	Supportive care†††	£185.20	Table 93
	Total	£5,923.20	

† Includes GP visits, oncology specialist visits, mammograms and cardiac monitoring.
†† EFS supportive care plus CT scan.
††† Includes GP visits, oncology specialist visits, specialist nurse, community nurse, CT scans and cardiac monitoring.
PHD Perjeta, Herceptin, docetaxel HD Herceptin, docetaxel FEC 5-fluorouracil, Epirubicin, Cyclophosphamide

B16. *Please clarify why the supportive care resource use, and associated costs, in the metastatic not progressed state (Table 92) are greater than that in the metastatic progressed state (Table 93).*

It was assumed that CT scans and cardiac assessment is only carried out while patients are on treatment and therefore these costs are not factored into the metastatic progressed supportive care costs.

However within our model patients are receiving second line mBC treatment in the metastatic progressed health state and it would be plausible that supportive care costs are at a similar level during this health state as during metastatic not progressed. If the per month costs for metastatic progressed are increased to be in line with metastatic not progressed, this has a minimal effect of reducing the ICER by less than £200.

B17. *The costs and mortality risk for patients taking treatments for metastatic disease are calculated based on a weighted average of different treatments (see Table 75, p216). Please clarify if in UK practice any individual patient can get any of these treatments or if the choice depends upon what they had for neoadjuvant/adjuvant treatment? If the latter, please present the cost*

effectiveness results using appropriate treatments for metastatic disease for each of the arms in the model (as opposed to using a weighted average).

There are stipulations within the licensed indications for metastatic treatments which have an impact on the sequence of therapies that a patient can receive. For example as per the Kadcyla mBC license, patients must have received Herceptin plus a taxane as a prior line of therapy. However the choice of mBC treatments are not dependant on the neo-adjuvant or adjuvant therapies received, i.e. whether patients were given the intervention or comparator arm as neoadjuvant therapy, choice of anti-HER2 targeted treatment for these patients who progressed to metastatic disease should not differ between the treatment groups.

The weighted average approach was taken as a pragmatic solution to simplify the model. The weightings are informed from market research data which identified treatment regimens used in clinical practice, these do not necessarily adhere to the licensed indications.

B18. *Please clarify why the mortality risk in the metastatic progressed state only uses the data for HD and PHD (cell F122 of 'Supportive Care' sheet) while the costs are estimated using all treatments including Kadcyla and Capecitabine + lapatinib (cell K91 of 'Supportive Care' sheet)? Please also comment on the applicability of these treatments for metastatic disease to the UK setting, with reference to current NICE guidance for metastatic HER2 positive breast cancer treatment. Where this differs please assess the impacts of these parameters on the model results within sensitivity analysis.*

Kadcyla and Capecitabine + lapatinib risks of mortality were not included in the model (data from EMILIA) as there are significant differences between CLEOPATRA and EMILIA population. Hence, it was decided to include their costs but with the conservative assumption that their risk of mortality is similar to PHD/HD.

The creation of the Cancer Drugs Fund opened the possibility for patients to access some of the most effective treatments for metastatic breast cancer (i.e. Perjeta and Kadcyla). Table 75 of the submission highlights the range of medicines used within clinical practice. Hence, despite Kadcyla, Perjeta and Capecitabine/Lapatinib not being recommended treatments by NICE, these are used in the UK clinical practice. Hence their presence in the model is justifiable. Should there be a change in the reimbursement situation for any of these treatments funded through the Cancer Drugs Fund it would be appropriate to amend the metastatic treatments contained within the model.

B19. *The results of the subgroup analysis suggest that pertuzumab may be more effective in the operable group than in the locally advanced breast cancer*

group (see Table 32, p125). Please assess the cost-effectiveness of pertuzumab within each of these subgroups within the model.

Table 15 below shows the tpCR results and its associated uncertainty by sub group. The p-values shown are very high due to the very low number patient numbers in each sub group. Therefore a sub group analysis was felt not to be appropriate.

Table 15 - NeoSphere tpCR analysis by sub-group

	PHD	**HD**	***Relative risk 95% CI***	**p-value**
Operable	n=65 40.0	n=64 18.8	1.18-3.85	0.0119
Locally Advanced	n=32 40.6	n=36 27.8	0.75-2.87	0.2682
Inflammatory	n=10 30.0	n=7 14.3	0.27-16.26	0.4774

B20. *The assumption that if patients do not progress after seven years they would be event free and follow the general population OS is questionable according to the ERG's clinical advisors, particularly in the hormone receptor (HR)-positive group. Please test this assumption within a sensitivity analysis and present the impact upon the model results.*

As noted in the submission, this timeframe was chosen as requires the conservative assumption of treatment effect for 2 years after the NeoSphere follow-up data. This assumption reduces the need to predict the treatment effects beyond the CTNeoBC analysis data that showed an increasing incremental efficacy until approximately year 7 among HER2-positive patients.

Table 16: Switch to background mortality analysis

Parameter modified	**Base value**	**Alternative 1**	**Alternative 2**
Time point (years) when switching to background mortality	7	6	5
ICER	[redacted]	[redacted]	[redacted]

B21. *Please provide the values of all PSA parameters in the probability distributions (Table 101).*

The PSA parameters and the probabilities distributions are as follows:

Table 17 - PSA parameters and the probabilities distributions

Parameter		Value	Parameters	Distribution
pCR rates from NeoSphere	PHD	39.25%	alpha = 42, beta = 65	Beta
	HD	21.50%	alpha = 23, beta = 84	Beta
Administration cost				
Overhead Time/Administration	1st cycle	317.00	se = 0.1482	LogNormal
	subsequent cycles	165.00	se = 0.2136	LogNormal
	1st cycle	9.60	se = 0.1482	LogNormal
	subsequent cycles	9.60	se = 0.2136	LogNormal
Probability of an AE (%)				
	Alopecia	0.562%	sd = 0.2311	Normal
	Diarrhoea	0.661%	sd = 0.2484	
	Febrile Neutropenia	0.766%	sd = 0.2643	
	Leukopenia	0.755%	sd = 0.4493	
	Neutropenia	6.409%	sd = 0.9593	
Event free survival - no pCR				
	Distribution used	Gamma		
	Lambda	12.78	Covariance matrix	Normal
	Gamma	0.58		
	Delta	-0.75		
Event free survival - pCR				
	Distribution used	Gamma		
	Lambda	447.76	Covariance matrix	Normal
	Gamma	0.05		
	Delta	-2.42		
Split between metatstatic and non-metastatic events				
	Metastatic	54.43%	alpha = 47, beta = 34	Beta
	Local recurrence	45.57%		
	Risk of recurrence	0.76%	se = 0.0012	Beta
Utilities				
	EFS (first year)	0.673	se = 0.0577	Beta
	Loco-regional recurrence	0.673	se = 0.0337	
	EFS (Subsequent years)	0.775	se = 0.076	
	Metastatic not-progressed	0.685	se = 0.0587	
	Remission	0.775	se = 0.076	
	Metastatic progressed	0.522		
Supportive care cost				
	Year 1-2 after treatment	67.85	se = 0.1277	LogNormal
	Year 3 - 5	15.11	se = 0.1277	
	Beyond 5 years	3.83	se = 0.1277	
	Remission	61.15	se = 0.1277	
Market shares in 1st line*				
	Herceptin + taxane	19.48%		Dirchlet
	Perjeta + Herceptin + docetaxel	40.60%		

	Herceptin + other	39.93%		
Market shares in 2nd line*				
	Capectiabine + lapatinib	4.37%		Dirchlet
	Herceptin + capecitabine	12.49%		
	Kadcyla	54.88%		
	Perjeta + Herceptin + docetaxel	28.26%		
Prob. of moving from non-progressed to progressed				
	Distribution used	Exponential		
	PHD	3.451	Covariance matrix	Normal
	HD	3.058		
Prob. of death in progressed metastatic				
	Distribution used	Exponential		
	PHD	3.601	Covariance matrix	Normal
	HD	3.458		

B22. *Please clarify how the beta parameters to estimate the uncertainty around the tpCR rates from NeoSphere (cells D18 and E18 in Efficacy Data sheet) were estimated within the model.*

The alpha represents the number of patients who experienced a total pCR in NeoSphere (42 and 23 patients respectively). The betas are the number of people who did not experience a pCR (total number of patients per arm (107) minus alpha).

B23. *The incremental cost-effectiveness plane (Figure 34) suggests that there is a strong negative relationship between the incremental costs and QALYs. Please comment on this in relation to the distributions used within the PSA?*

The negative correlation in the incremental cost-effectiveness plane is due to the importance of pCR. A large difference in pCR between treatments leads to lower number of events and consequently to both higher QoL **and** higher cost savings, due to patients avoiding the metastatic health states. It should be noted that this negative correlation was also noted in the Attard et al study.

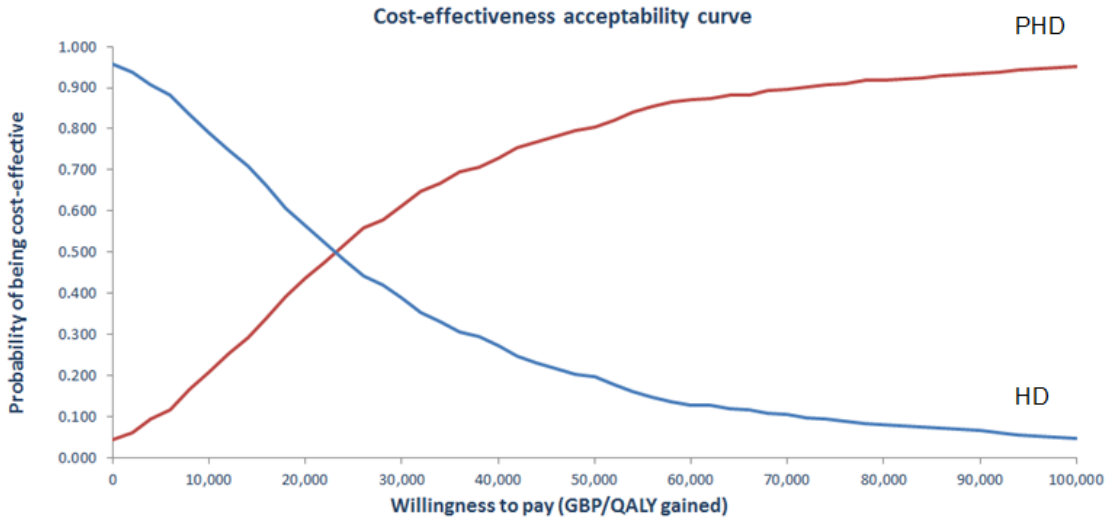
B24. *The Cost Effectiveness Acceptability Curve (CEAC) should detail the probability of each intervention being the most cost-effective, and therefore the summation of the individual probabilities should equal 100%. Please correct the CEAC (Figure 35) to include both/all the interventions being compared.*

The updated base case incorporates Herceptin subcutaneous in use in the comparator arm for neoadjuvant treatment. The updated base case ICER is [redacted]. This makes an assumption that [redacted] of Herceptin use in neo-adjuvant is

subcutaneous formulation and [redacted] remains IV usage. This data is derived from market research which showed that of [redacted].
Since patients who are not suitable for Herceptin are not relevant to this analysis, the Herceptin total use of [redacted] was used to calculate the split between subcutaneous and IV formulations.

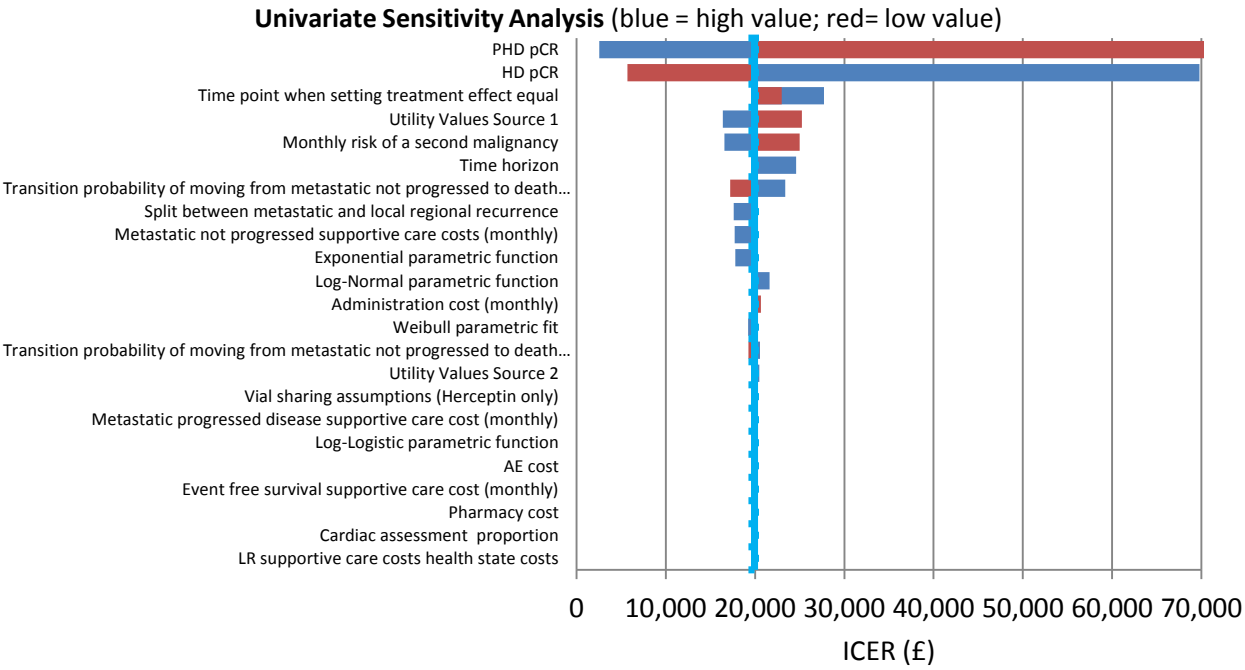
Please find below the updated CEAC, which includes both the intervention and comparator arms. At a willingness to pay threshold of £30,000 per QALY gained Perjeta, Herceptin and docetaxel has a 61.2% chance of being cost effective.

Figure 11 - Cost Effectiveness Acceptability Curve



B25. *For completeness, please present all of the results of the sensitivity analyses described within Table 103 within the tornado diagram (Figure 36).*

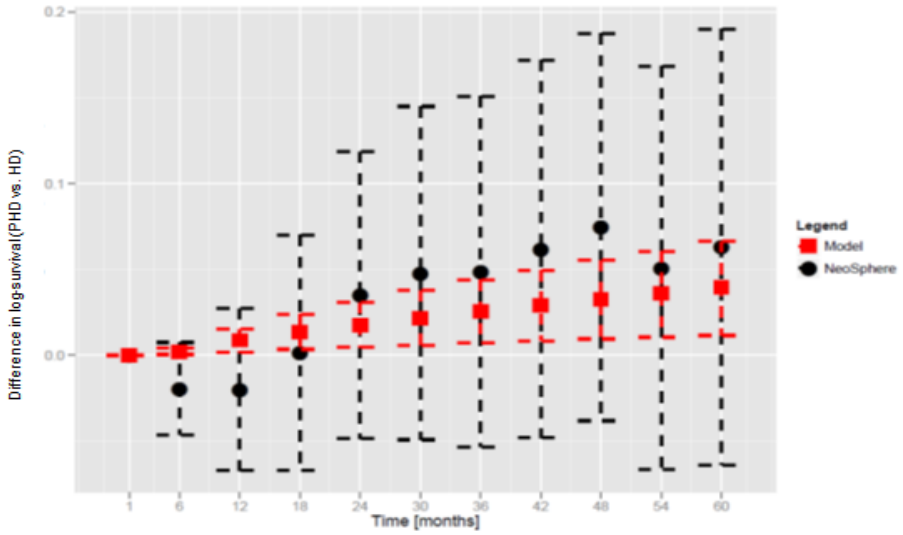
Figure 36 (updated) Tornado diagram of univariate sensitity analysis



B26. *Page 262/263: Please generate from the model the predictive distribution for the (log) difference in survival rates between treatments and compare this with the observed result from NeoSphere (i.e. cross validation).*

Figure 12: Differences in log-survival function (PHD vs HD)Figure 12 depicts the incremental efficacy from the NeoSphere trial and the incremental efficacy estimated from the model. It can be seen that the model estimates are within the NeoSphere data confidence interval.

Figure 12: Differences in log-survival function (PHD vs HD)



B27. *Please clarify the purpose of each of the following sheets for the modelling since they do not appear to impact upon the base case model results: Drug cost; BSA; Vial Sharing; BL Char; KM EFS; Cumulative Hazard Plots EFS; EFS extrapolation FDA; Chart Data*.

Only the Drug costs and the BSA tabs are required for the model to work. All other mentioned tabs can be disregarded.

Section C: Textual clarifications and additional points

C1. *Please clarify how many patients will be eligible for pertuzumab in England as there is discrepancy between Table 5 which suggests 1380 patients in England and the text on page 13 which suggests over 1400 patients.*

Table 5 contains the correct estimation of patient numbers, at approximately 1380 patients in England.

References

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2. Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med 2005;353:1673-1684.
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6. Perez EA, Romond EH, Suman VJ, et al. Trastuzumab plus adjuvant chemotherapy for human epidermal growth factor receptor 2-positive breast cancer: planned joint analysis of overall survival from NSABP B-31 and NCCTG N9831. J Clin Oncol. E-pub Date: [published online ahead of print] 2014. DOI # 10.1200/JCO.2014.55.5730. http://www.ncbi.nlm.nih.gov/pubmed/25332249
7. Cobleigh et al., JCO 1999; 17(9): 2639-48
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9. Marty et al., JCO 2005; 23:4265-74 (M77001)
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11. 11.Goldhirsch A, Piccart-Gebhart M, de Azambuja E et al. HERA trial: 2 years versus 1 year of trastuzumab after adjuvant chemotherapy in women with HER2-positive early breast cancer at 8 years of median follow up. Presented at the European Society for Medical Oncology in Vienna, Austria; September 28 - October 2, 2012. ESMO Oral presentation #LBA6.
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14. SIGN Guideline 134: Treatment of primary breast cancer (September 2013)
15. Senkus E, Kyriakides S, Ohno S et al. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 2015; 26 (Supplement 5): v8–v30
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on the Primary Therapy of Early Breast Cancer 2015. Annals of Oncology 2015; 00:1-14 (St Gallen Expert Consensus Guidelines 2015)
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22. Goldhirsch A, Gelber RD, Piccart-Gebhart MJ et al. 2 years versus 1 year of adjuvant trastuzumab for HER2-positive breast cancer (HERA): an open-label, randomised controlled trial. Lancet 2013; 382: 1021–28.

Appendix A

Table 18 - Variance-Covariance tables

Study name	Subgroup	Endpoint	Distribution	intercept	scale	shape	treatment	aic	bic	log_likelihood
CTNeoBC	no pCR	EFS	exponential	5.041	1.000	NA	NA	4182	4187	-2090.0
CTNeoBC	no pCR	EFS	weibull	4.870	0.854	NA	NA	4173	4184	-2084.6
CTNeoBC	no pCR	EFS	lognormal	4.683	1.380	NA	NA	4132	4142	-2063.8
CTNeoBC	no pCR	EFS	loglogistic	4.605	0.762	NA	NA	4157	4168	-2076.7
CTNeoBC	no pCR	EFS	gompertz	0.007	-0.001	NA	NA	4184	4186	-2090.0
CTNeoBC	no pCR	EFS	gamma	4.114	1.747	-1.314	NA	4116	4120	-2055.1
CTNeoBC	pCR	EFS	exponential	5.842	1.000	NA	NA	1001	1005	-499.4
CTNeoBC	pCR	EFS	weibull	5.327	0.730	NA	NA	995	1003	-495.3
CTNeoBC	pCR	EFS	lognormal	5.366	1.345	NA	NA	985	994	-490.6
CTNeoBC	pCR	EFS	loglogistic	5.177	0.688	NA	NA	993	1001	-494.3
CTNeoBC	pCR	EFS	gompertz	0.002	0.006	NA	NA	1002	1004	-499.0
CTNeoBC	pCR	EFS	gamma	3.721	1.775	-4.304	NA	974	976	-484.0
NeoSphere	no pCR	EFS	exponential	5.382	1.000	NA	NA	532	536	-265.1
NeoSphere	no pCR	EFS	weibull	5.722	1.249	NA	NA	530	537	-262.9
NeoSphere	no pCR	EFS	lognormal	5.745	2.304	NA	NA	529	536	-262.3
NeoSphere	no pCR	EFS	loglogistic	5.456	1.170	NA	NA	530	537	-262.8
NeoSphere	no pCR	EFS	gompertz			NA	NA			
NeoSphere	no pCR	EFS	gamma				NA			
NeoSphere	pCR	EFS	exponential	5.885	1.000	NA	NA	102	104	-49.8
NeoSphere	pCR	EFS	weibull	5.415	0.742	NA	NA	102	107	-49.2
NeoSphere	pCR	EFS	lognormal	5.539	1.434	NA	NA	101	107	-48.7
NeoSphere	pCR	EFS	loglogistic	5.301	0.714	NA	NA	102	107	-49.2
NeoSphere	pCR	EFS	gompertz			NA	NA			
NeoSphere	pCR	EFS	gamma				NA			
NeoSphere	TD	EFS	exponential	5.642	1.000	NA	NA	135	138	-66.7
NeoSphere	TD	EFS	weibull	5.462	0.889	NA	NA	137	142	-66.5

NeoSphere	TD	EFS	lognormal	5.436	1.571	NA	NA	134	140	-65.2
NeoSphere	TD	EFS	loglogistic	5.273	0.835	NA	NA	136	142	-66.2
NeoSphere	TD	EFS	gompertz			NA	NA			
NeoSphere	TD	EFS	gamma				NA			
NeoSphere	PTD	EFS	exponential	5.809	1.000	NA	NA	127	130	-62.6
NeoSphere	PTD	EFS	weibull	5.704	0.940	NA	NA	129	135	-62.6
NeoSphere	PTD	EFS	lognormal	6.016	1.962	NA	NA	130	135	-63.1
NeoSphere	PTD	EFS	loglogistic	5.578	0.910	NA	NA	130	135	-62.8
NeoSphere	PTD	EFS	gompertz			NA	NA			
NeoSphere	PTD	EFS	gamma				NA			

Appendix B

Table 19 - Variance-covariance tables for EFS analysis

Study name	Subgroup	Endpoint	Distribution	row_name	column_name	row_num	col_num	value
CTNeoBC	no pCR	EFS	exponential	intercept	intercept	1	1	0.003
CTNeoBC	no pCR	EFS	weibull	intercept	intercept	1	1	0.004
CTNeoBC	no pCR	EFS	weibull	intercept	scale	2	1	0.002
CTNeoBC	no pCR	EFS	weibull	scale	intercept	1	2	0.002
CTNeoBC	no pCR	EFS	weibull	scale	scale	2	2	0.002
CTNeoBC	no pCR	EFS	lognormal	intercept	intercept	1	1	0.005
CTNeoBC	no pCR	EFS	lognormal	intercept	scale	2	1	0.003
CTNeoBC	no pCR	EFS	lognormal	scale	intercept	1	2	0.003
CTNeoBC	no pCR	EFS	lognormal	scale	scale	2	2	0.003
CTNeoBC	no pCR	EFS	loglogistic	intercept	intercept	1	1	0.004
CTNeoBC	no pCR	EFS	loglogistic	intercept	scale	2	1	0.001
CTNeoBC	no pCR	EFS	loglogistic	scale	intercept	1	2	0.001
CTNeoBC	no pCR	EFS	loglogistic	scale	scale	2	2	0.001
CTNeoBC	no pCR	EFS	gompertz	intercept	intercept	1	1	0.000
CTNeoBC	no pCR	EFS	gompertz	intercept	scale	2	1	0.000
CTNeoBC	no pCR	EFS	gompertz	scale	intercept	1	2	0.000
CTNeoBC	no pCR	EFS	gompertz	scale	scale	2	2	0.008
CTNeoBC	no pCR	EFS	gamma	intercept	intercept	1	1	0.032
CTNeoBC	no pCR	EFS	gamma	intercept	scale	1	2	-0.001
CTNeoBC	no pCR	EFS	gamma	intercept	shape	1	3	0.052
CTNeoBC	no pCR	EFS	gamma	scale	intercept	2	1	-0.001
CTNeoBC	no pCR	EFS	gamma	scale	scale	2	2	0.002
CTNeoBC	no pCR	EFS	gamma	scale	shape	2	3	-0.006
CTNeoBC	no pCR	EFS	gamma	shape	intercept	3	1	0.052
CTNeoBC	no pCR	EFS	gamma	shape	scale	3	2	-0.006
CTNeoBC	no pCR	EFS	gamma	shape	shape	3	3	0.100
CTNeoBC	pCR	EFS	exponential	intercept	intercept	1	1	0.014
CTNeoBC	pCR	EFS	weibull	intercept	intercept	1	1	0.027
CTNeoBC	pCR	EFS	weibull	intercept	scale	2	1	0.010
CTNeoBC	pCR	EFS	weibull	scale	intercept	1	2	0.010

CTNeoBC	pCR	EFS	weibull	scale	scale	2	2	0.006
CTNeoBC	pCR	EFS	lognormal	intercept	intercept	1	1	0.033
CTNeoBC	pCR	EFS	lognormal	intercept	scale	2	1	0.020
CTNeoBC	pCR	EFS	lognormal	scale	intercept	1	2	0.020
CTNeoBC	pCR	EFS	lognormal	scale	scale	2	2	0.016
CTNeoBC	pCR	EFS	loglogistic	intercept	intercept	1	1	0.025
CTNeoBC	pCR	EFS	loglogistic	intercept	scale	2	1	0.009
CTNeoBC	pCR	EFS	loglogistic	scale	intercept	1	2	0.009
CTNeoBC	pCR	EFS	loglogistic	scale	scale	2	2	0.005
CTNeoBC	pCR	EFS	gompertz	intercept	intercept	1	1	0.000
CTNeoBC	pCR	EFS	gompertz	intercept	scale	2	1	-0.001
CTNeoBC	pCR	EFS	gompertz	scale	intercept	1	2	-0.001
CTNeoBC	pCR	EFS	gompertz	scale	scale	2	2	0.041
CTNeoBC	pCR	EFS	gamma	intercept	intercept	1	1	0.212
CTNeoBC	pCR	EFS	gamma	intercept	scale	1	2	0.057
CTNeoBC	pCR	EFS	gamma	intercept	shape	1	3	0.627
CTNeoBC	pCR	EFS	gamma	scale	intercept	2	1	0.057
CTNeoBC	pCR	EFS	gamma	scale	scale	2	2	0.021
CTNeoBC	pCR	EFS	gamma	scale	shape	2	3	0.151
CTNeoBC	pCR	EFS	gamma	shape	intercept	3	1	0.627
CTNeoBC	pCR	EFS	gamma	shape	scale	3	2	0.151
CTNeoBC	pCR	EFS	gamma	shape	shape	3	3	2.000

4th March update
Additional Clarification question – A1 treatment pathway

We note that in your response to clarification question A1 you said that more information could be provided on the market research survey if needed. The ERG have contacted NICE and said that it would be incredibly useful if you could provide results from this survey of the proportions of patients receiving docetaxel, paclitaxel and other chemotherapies in clinical practice (both alongside trastuzumab and instead of trastuzumab). If these data are available please could you submit these, with any necessary confidentiality marking and upload to the NICE docs https://appraisals.nice.org.uk/request/11031 by 1st March 2016

Roche response from the 23rd February

The detail that we currently have available concerning regimens in use in the UK for HER2-positive neoadjuvant therapy are incorporated in the Data on File RXUKPERT00220(1) that was provided with the submission.

We have made a request to the market research agency for any additional granularity captured within the survey. Apologies that we have yet to have a response to this question, therefore we will update this response as soon as we have further clarity.

Roche response from 4th March

Market research data for the full year of 2015 (see Table 1 below) shows that docetaxel was the most commonly used taxane with 68% of the market share (compared with paclitaxel 8%).

The market research data shows that Herceptin is included in 79% of neoadjuvant treatments. Herceptin/docetaxel (with or without anthracyclines), is used in 62% of patients.

Table 1 – Neoadjuvant treatment regimens in HER2-positive early breast cancer (2015)

	2015				
Neoadjuvant treatments	**Q1**	**Q2**	**Q3**	**Q4**	**Average Q1-Q4**
H+Docetaxel + Anthracyclines +/- other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
H+Docetaxel (without Anthracycline) +/- other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel +/- Anthracycline, other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
H+Paclitaxel + Anthracyclines +/- other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

H+Paclitaxel (without Anthracycline) +/- other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Paclitaxel +/- Anthracycline, other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
H + Abraxane +/- Anthracycline , other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
H + Anthracycline +/- other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
H mono	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
H + other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abraxane +/-Anthracycline, other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anthracycline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
n	[redacted]	[redacted]	[redacted]	[redacted]	
Key H - Herceptin					

4th March

Additional clarification question – Cortazar modelling

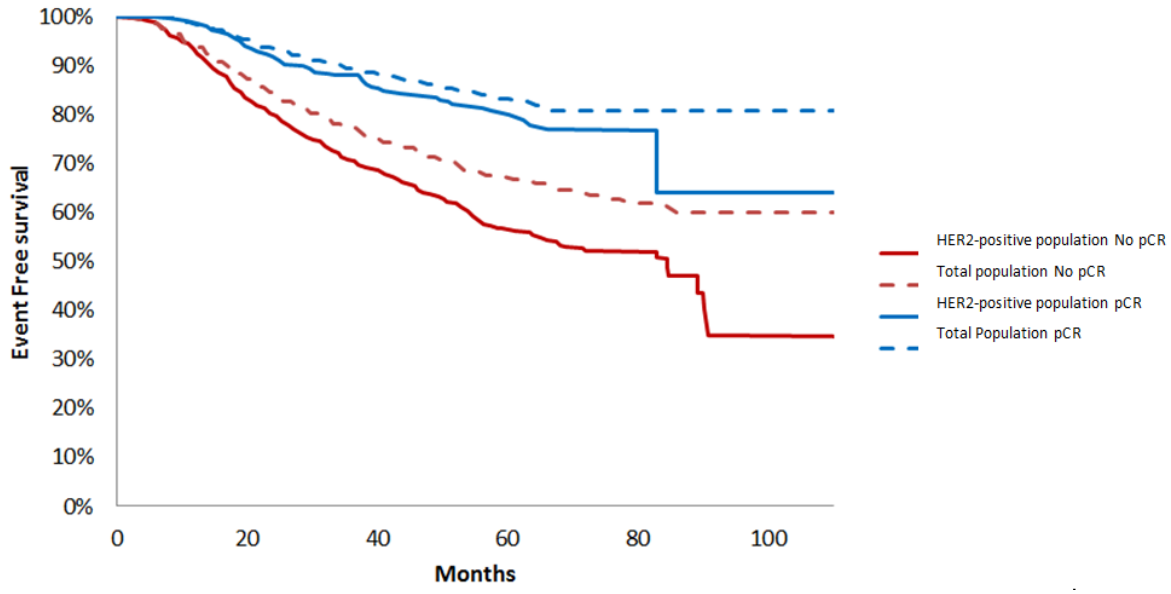
It appears that the company have used the curve from all breast cancer patients within the Cortazar paper, but only up to the point that follow up stops for the HER2 positive subgroup (approx 9 years). The company also appear to have inconsistently used the numbers at risk from the HER2 positive subgroup. Please can the company clarify whether it intended to use data from the HER2 positive subgroup or all breast cancer patients or if there is some other explanation for the inconsistencies within the analysis? Please can the company justify its analysis, or redo it if it agrees that it is incorrect. If the company does redo the analysis, the ERG suggests that data should have been used from the HER2 positive subgroup given that the patient numbers are reasonable and the relationship seems to be stronger for this group.

The intention was to use the HER2-positive subgroup to model EFS progression. However the whole population EFS data from Cortezar (2014) was used in error. The ERG are correct that the HER2-positive sub group from Cortezar shows a stronger tpCR-EFS link and demonstrates the superior impact on the clinical benefit of targeted therapies.

Following from the above, the analysis was re-run using the Guyot algorithm to estimate new parameters (for both pCR and no pCR parameters of the HER2-positive subgroup) to feed into the economic model.

A comparison between the Kaplan Meier (KM) curves for the whole population (dotted lines denote) and the KM curves from HER2-positive population, (denoted by solid lines) are shown below.

Figure 1 - Comparison of the pCR and no pCR Kaplan Meier EFS curves for total population and HER2-positive



A new analysis of the HER2-positive KM curves fit has been undertaken as follows:

Table 1: Parameters for extrapolation of Event Free Survival for no-pCR status (HER2-positive sub-population only)

Distribution	Intercept	Scale	Shape	AIC	BIC
Exponential	4.727	1.000	NA	5500	5505
Weibull	4.580	0.820	NA	5477	5488
Log-normal	4.297	1.209	NA	5414	5425
Log-logistic	4.266	0.695	NA	5447	5457
Gompertz	0.002	0.008	NA	5501	5503
Gamma	3.835	1.406	-1.072	**5398**	**5395**

Table 2: Parameters for extrapolation of Event Free Survival for pCR status (HER2-positive sub-population only)

Distribution	Intercept	Scale	Shape	AIC	BIC
Exponential	5.618	1.000	NA	1246	1250
Weibull	5.179	0.729	NA	1237	1245
Log-normal	5.103	1.253	NA	1224	1232
Log-logistic	4.989	0.670	NA	1233	1242
Gompertz	0.006	0.003	NA	1246	1248
Gamma	3.884	1.616	-3.100	**1214**	**1212**

The parametric function with the best statistical fit is the gamma followed by the log normal function in both arms in the HER2-positive sub-population. This is the same as for the total population.

The re-stated economic results are as follows:

Table 3: Updated Deterministic base-case results

Technologies	Total costs (GBP)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	Inc. £/LYG	ICER (£/QALY)
PHD	125,160	15.74	10.79	2,859	0.48	0.35	5,922	8,215
HD	122,301	15.25	10.44					

PHD – Perjeta + Herceptin + docetaxel; HD - Herceptin + docetaxel; LYG – life years gained; QALYs – Quality adjusted life years; ICER – incremental costs effectiveness ratio

Values in the table are discounted and 1/2 cycle corrected

The ICER is reduced since there is a large difference in patients who do not achieve pCR between the whole population and the HER2-positive sub-population.

A 1,000 iteration probabilistic sensitivity analysis was conducted in order to determine the uncertainty surrounding the base-case ICERs.

Figure 2: PSA results (incremental cost effectiveness plane)

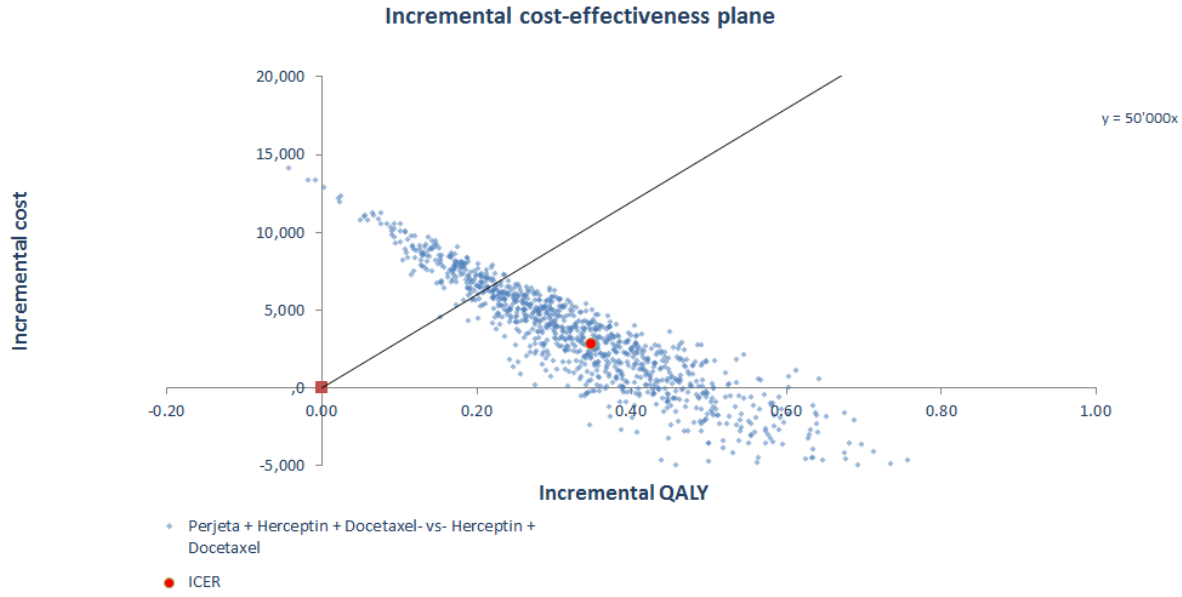
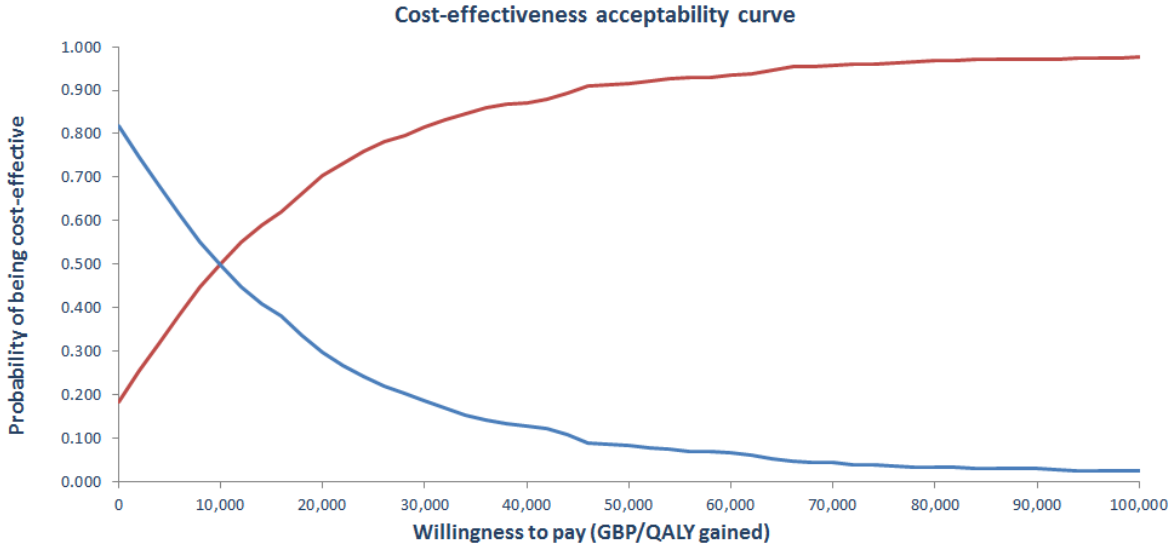


Figure 3: PSA results (incremental cost effectiveness plane)



This analysis indicated that Perjeta in combination with Herceptin and docetaxel has a 82.9% chance of being cost-effective at a threshold of £30,000/QALY gained. The PSA resulted in a probabilistic ICER of £9,047.

Please advise if additional analysis is required.

References

Cortazar et al, Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet. 2014 Jul 12;384(9938):164-72

29th March

Additional clarification question – Perjeta Neoadjuvant SMC and NICE submission differences

"It has come to our attention that the Scottish Medicines Consortium (SMC) published advice on pertuzumab for the neoadjuvant treatment of HER2 positive breast cancer earlier this month following a full submission assessed under the orphan medicine process. In reviewing this document we were surprised to see that the incremental cost effectiveness ratio for the addition of pertuzumab to a neoadjuvant regimen of trastuzumab and docetaxel differed markedly from the results submitted to us.

Given the similarity of Scottish and English healthcare systems, we find this difference disconcerting and would like to explore the reasons for the discrepancy. Please could you provide a detailed description of the cost effectiveness analysis supplied to SMC with particular reference to any differences between the model used in the SMC submission and that supplied to us?"

Response:

The error that was identified by the ERG during clarification questions regarding the population used to model EFS progression was also present in the SMC submission and not identified during the course of the appraisal. The published SMC ICER is calculated using the total population from Cortezar (2014). Correction of this error would reduce the ICER by approximately £10k, similar to we saw with the correction to the NICE base case.

The model structure and assumptions used within the SMC model are aligned with those used in the initial submission to NICE, with a few exceptions.

The major driver of the ICER difference between the SMC and NICE is in regard to the metastatic breast cancer treatments that are considered to be standard of care in either country. Scotland does not benefit from the Cancer Drugs Fund (CDF) and therefore trastuzumab emtansine (Kadcyla) and pertuzumab (Perjeta) are not regularly used to treat metastatic breast cancer. In England these regimens have become standard of care since their introduction to the CDF and are included in the economic model to NICE.

Inclusion of Kadcyla and Perjeta increases the costs of metastatic treatments and also the time that patients spend in the metastatic health states. When Perjeta is used as 1L metastatic treatment this prolongs the time that patients remain in the metastatic not progressed health state. Similarly the risk of death for metastatic progressed health state is lower.

General population mortality values differ between countries which marginally impacts the LYG and QALY values. There were in addition some minor corrections and updates made to the model for the NICE submission, for example to add an age restriction on utilities so that the utility value can never be higher than the general population value for the same age.

Table 1 below shows a comparison of the discounted LYG and costs for the SMC base case and NICE updated base case.

The SMC report on this appraisal is available on their website. If you require any further information, we are happy to provide further detail if required.

Table 1: Comparison of SMC and NICE base case LYG and Costs

	SMC Base Case	NICE updated Base Case
Incremental LYG		
EFS	0.579	0.597
Loco regional recurrence	-0.013	-0.013
Remission	-0.097	-0.098
Metastatic not progressed	-0.045	-0.053
Metastatic progressed	-0.062	-0.068
Total incremental LYG	0.362	0.365
Incremental Costs		
EFS	£12,184	£12,881
Loco regional recurrence	£-291	£-290
Remission	£-79	-£79
Metastatic not progressed	£-1250	£-2,412
Metastatic progressed	£-194	-£4,848
Total incremental costs	£10,370	£5,253
ICER	**£34,100**	**£19,939**

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (STA)

Pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer [ID767]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages.

1. About you and your organisation

Your name: [redacted]

Name of your organisation: Breast Cancer Now

Your position in the organisation: Senior Policy Officer

Brief description of the organisation: Breast Cancer Now is the UK's largest breast cancer charity, dedicated to funding ground-breaking research into the disease. Our ambition is that by 2050, everyone who develops breast cancer will live. We're bringing together all those affected by the disease to improve the way we prevent, detect, treat and stop breast cancer. And we're committed to working with the NHS and governments across the UK to ensure that breast cancer services are as good as they can be, and that breast cancer patients benefit from advances in research as quickly as possible.

This submission reflects the views of Breast Cancer Now, based on our experience of working with people who are affected by breast cancer. We know that access to effective drugs is hugely important to our supporters and that quality of life is valued just as much as length of life.

However, we want to stress that it was very difficult to find patients who had been treated, or are currently being treated, with Perjeta (pertuzumab) in the neoadjuvant setting. This is perhaps unsurprising given that the drug was only recently licensed for this indication, and that the patients enrolled in the two clinical trials were small in number and spread across many different countries. We therefore wish to caveat our response by saying that, although we think this is a potentially promising treatment, we would strongly support the collection of more evidence as many of the benefits we cite are hypothetical.

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: none

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

A new diagnosis of breast cancer is likely to cause considerable anxiety to the patient as well as their family and close friends. The initial diagnosis can be very shocking and in the longer-term, the fear of breast cancer spreading to other parts of the body such as the bone, lungs, liver and brain (known as secondary breast cancer, which is incurable) or returning at a later date can cause considerable anxiety for both the patient and their loved ones.

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

The best treatment outcome for patients with primary breast cancer is the complete eradication of their cancer. If it is not possible to eradicate the cancer, the disease can recur and metastasise, spreading to distant parts of the body, and making the cancer incurable. Any treatments that can effectively control the growth of the cancer or shrink the size of the tumour are also valued by the patient, as these can reduce the extent of surgery required.

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?

Surgery is usually the first option for women with primary or early breast cancer. Someone with advanced localised breast cancer may be offered neoadjuvant chemotherapy to shrink the size of the tumour, so that surgery can take place. Surgery may be followed by radiotherapy and/or chemotherapy depending on the balance of benefits and risks. Treatment with chemotherapy usually has a range of unpleasant side-effects, which can have a significant impact on everyday activities, ability to work, social life and relationships.

4. What do patients or carers consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment being appraised.

The treatment being assessed increases the chances of complete eradication of the tumour. The NeoSphere study found that patients given Perjeta, Herceptin and docetaxel had a significantly improved pathological complete response rate (pCR; defined as the absence of invasive tumour tissue in the affected breast at the time of surgery) compared with those given Herceptin plus docetaxel. The treatment can also be effective if given without chemotherapy: 17% of patients given Herceptin and Perjeta in the study had a complete response rate. The side effects of Perjeta are also usually much less severe than those associated with chemotherapy and may therefore be more appropriate for some patients, allowing them to lead more normal lives during their treatment.

Since the treatment being assessed would be given prior to surgery, it may also reduce the extent of surgery, thus also reducing the recovery time for the patient. Less extensive surgery, such as breast conserving surgery instead of a complete mastectomy, may also have beneficial psychological effects on some women, who struggle to come to terms with their new body image post-surgery.

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

In some cases, this treatment might shrink or eradicate the tumour thereby reducing the need for surgery or the extent of surgery needed to remove the cancer. For patients with advanced localised tumours, using Perjeta may enable these patients to have surgery to remove the tumour, where this may not have otherwise been possible.

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

We are not aware of any differences of opinion between patients.

5. What do patients and/or carers consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns patients or carers have about current NHS treatments in England.

Patients who have locally advanced disease may not be able to have surgery, due to the spread of the cancer. In these cases patients may be given chemotherapy pre-surgery to attempt to shrink the tumour. However, this is not effective for all patients and may weaken them prior to surgery, thereby potentially increasing recovery time or complications associated with surgery. Patients, whose tumours are large, will often need to undergo a complete

mastectomy. Some women find that the psychological effect of having a complete mastectomy is traumatic: "I also clearly remember waking up in recovery and being so aware that my breast had gone, it felt so empty. No-one had talked to or prepared me for this feeling. I cried for hours post-op".

Please list any concerns patients or carers have about the treatment being appraised.

It is important to note that the two clinical trials conducted to assess the effectiveness of Perjeta (NeoSphere and TRYPHAENA) have not done a long-term follow up to ascertain the effect of neoadjuvant treatment on the risk of recurrence or long-term survival. Furthermore, there is a chance that Perjeta might not be effective for a particular patient. Therefore taking it prior to surgery may delay effective treatment for some patients, who may otherwise have benefited from earlier surgery. Lastly, whilst side effects from Perjeta and Herceptin can be relatively minor compared to chemotherapy, these side effects are likely to be combined as the two drugs need to be taken together to be effective.

In the NeoSphere study, Perjeta was delivered intravenously every 3 weeks for 12 weeks (ie four cycles of treatment). This could cause some patients discomfort and they may find it an inconvenience (in terms of both time and expense) to have to travel to hospital. However, this would also be true if Herceptin and docetaxel were given alone because they are administered in the same way.

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

We are not aware of any differences in opinion.

6. Patient population

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

Perjeta is a targeted treatment, which would only benefit patients with HER2-positive breast cancer. This type of breast cancer is present in around 1 in 5 women who are diagnosed with breast cancer.

Those patients who also have HER2-positive breast cancer and locally advanced disease or an inflammatory type of breast cancer will benefit the most from this treatment. Advanced localised disease may mean that the cancer is either inoperable or may require a complete mastectomy, whilst inflammatory breast cancer is usually aggressive and can therefore invade nearby tissue, also quickly making it inoperable or requiring extensive surgery. The increased effectiveness of Perjeta in eliminating and shrinking the size of the tumour prior to surgery, than is possible with other current treatments, therefore means that surgery may become possible in some cases or be less invasive, aiding a faster recovery time.

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

The treatment may not work effectively on all HER2-positive patients, but it is impossible to tell who these patients are in advance from the information available from clinical trials.

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment?

Yes

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment as part of their routine NHS care reflects the experiences of patients in the clinical trials.

The treatment is not yet available to patients receiving routine care.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

The clinical trials include some data on the number and severity of side effects experienced by patients, receiving different combinations or neoadjuvant drugs. This allows comparison on the level of side effects, which we know can affect the quality of life experienced by a cancer patient.

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

This treatment is not available in the NHS.

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

☐ No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having 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 treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

Not that we are aware of.

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

Not that we are aware of.

9. Other issues

Do you consider the treatment to be innovative?

☐ Yes

If yes, please explain what makes it significantly different from other treatments for the condition.

The treatment, when taken in combination with Herceptin, has an increased chance of eradicating a tumour completely, compared to patients receiving Herceptin and a chemotherapy drug alone. In the best cases, this would be hugely beneficial for patients, who may therefore be able to avoid surgery completely. Moreover, the side effects of the treatment being assessed are much less severe than those associated with chemotherapy.

Are there any other issues that you would like the Appraisal Committee to consider?

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- The promising potential of this drug to either shrink or completely eradicate the tumour prior to surgery is innovative and beneficial to patients with HER2-positive breast cancer
- Patients with locally advanced or inflammatory disease, which may be inoperable, would benefit the most from this treatment.
- Compared to chemotherapy, which may sometimes be given prior to surgery, this treatment has fewer side effects associated with treatment, thereby improving quality of life for the patient.
- The lack of long term follow up and lack of assessment of the risk of disease recurrence is a concern, as the current clinical trials conducted were not designed to demonstrate disease-free survival.

- The treatment may not work effectively for all patients.

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer [ID767]

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name:
Comments submitted by [redacted] on behalf of:

Name of your organisation: NCRI/RCP/RCR/ACP

Comments coordinated by [redacted]

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology?

- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?

- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer [ID767]

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

HER-2 positive breast cancer is considered to be one of the most aggressive types of breast cancer. HER-2 amplification is a significant predictor of both overall survival and time to relapse in patients with breast cancer. Trastuzumab has revolutionised the outlook for HER-2 positive breast cancer. Other anti-HER-2 therapies have added to the benefit of trastuzumab.

For early breast cancer there is a huge variation across the UK with respect to primary medical therapy versus surgery for HER-2 positive breast cancer despite the evidence that early commencement of anti-HER-2 directed therapy improves survival in the metastatic and EARLY breast cancer settings.

At the UKBCM last year attend by over 200 non-surgical breast cancer oncologists the response to the following question was

1. What proportion of patients with HER2 positive breast cancer receive primary medical therapy? (Multiple Choice)

Responses		
	Percent	Count
<10%	6%	8
10-25%	24%	31
26-50%	28%	36
51-75%	22%	28
>75%	20%	26
Totals	100%	129

Adjuvant treatment is usually anthracycline-based chemotherapy, followed by trastuzumab in combination with taxane followed by trastuzumab alone or in combination with endocrine therapy if appropriate, or taxane-based chemotherapy in combination with trastuzumab from the outset. Treatment choice is often based on patient factors and also some cancer related factors (stage). There may still be some use of sequential trastuzumab after chemotherapy which is probably not optimal. The disadvantage of the adjuvant approach is that there is no response data and treatment is essentially one size fits all. Also there are data that delayed commencement of appropriate systemic anti-cancer therapy has a deleterious effect on survival.

Primary medical therapy in the HER2 arena is usually anthracycline → taxane + trastuzumab or Docetaxel Carboplatin Trastuzumab. With the European license for Pertuzumab some sites are offering Pertuzumab as top up. Primary medical therapy has the advantage of understanding the response of the cancer to the treatment. The pathological complete response is high. Pathological complete response is associated with a very strong correlation with overall survival in HER2 positive breast cancer (Cortazar et al). Pathological complete response from neoadjuvant therapy also enables downstaging of the surgical treatment of the

cancer. This has the potential to minimise the extent of surgery required, and reduce both morbidity and costs associated with surgery.

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Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer [ID767]

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

OESTROGEN RECEPTOR+ and OESTROGEN RECEPTOR-ve breast cancer have different pathological complete response rates. They are both high pathological complete response rates in high risk breast cancer

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

Specialist clinics should deliver systemic anti-cancer therapy, as is the current situation.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Some experts are offering Pertuzumab (as top up self-funded) to patients receiving primary medical therapy. It is always used within its licensed indications

Please tell us about any relevant clinical guidelines and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

It will need to be added to the early breast cancer guidance. It will be essential that all patients are discussed with a non-surgical oncologist before surgical treatment.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

It is a major advance and has huge potential to transform the outcomes and pathway for this group of patients. We are developing a platform to investigate discontinuation of treatment if pathological complete response achieved and the role of new treatments eg (Trastuzumab-Emtansine (TDM-1, Kadcyla)) if a complete response is not achieved within NCRI BCSG

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer [ID767]

Needs to be restricted to prescription by accredited breast cancer medical oncology and clinical oncology consultants and designated trainees and delivered by systemic anti-cancer therapy delivery teams in NHS

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

Yes we were involved in NEOSPHERE - both this and TRYPHAENA are consistent with UK practice (with the addition of Pertuzumab)

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Adverse events are similar to those without Pertuzumab. There is some increase in moderate diarrhoea but all AEs are typical of those we usually encounter with systemic anti-cancer therapy and easily manageable

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Implementation issues

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within
3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer [ID767]

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Guidance and pathway for these patients would need to be written. There would be an opportunity to develop trials that could have a major impact on duration of treatment and effectiveness of treatment with much better patient outcomes.

No specific extra training would be required

No, our experts would envisage that the trade-off would be with requiring less (surgical and medical) treatment for HER-2 positive metastatic breast cancer.

The people delivering the technology would already be competent. There would be a need to educate some people within the pathway

Equality
NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. 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;
Not any more than they may already be.

- 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;

Not any more than they may already be

- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Not any more than they may already be

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer [ID767]

Appendix K – clinical expert statement declaration form

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer [ID767]

Please sign and return via NICE Docs/Appraisals.

I confirm that:

- I agree with the content of the submission provided by **[insert name of nominating organisation]** and consequently I will not be submitting a personal statement.

Name: .....

Signed: .....

Date: 24 March 2016

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer [ID767]

Please sign and return via NICE Docs/Appraisals.

I confirm that:

- I agree with the content of the submission provided by **The Royal College of Physicians** and consequently I will not be submitting a personal statement.

Name: ....[redacted].....

Signed: .....

Date: .....21/03/2016.....

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer expert statement (STA)

Pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer [ID767]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, including health-related quality of life)
- preferences for different treatments and how they are given
- expectations about the risks and benefits of the treatment.

We have already asked your nominating organisation to provide an organisation's view. We are asking you to give your views as an individual whether you are:

- a patient
- a carer (who may be voicing views for a patient who is unable to) or
- somebody who works or volunteers for a patient organisation.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The response area will expand as you type. The length of your response should not normally exceed 10 pages.

1. About you

Your name: [redacted]

Name of your nominating organisation: Breast Cancer Now

Do you know if your nominating organisation has submitted a statement?
Yes

Do you wish to agree with your nominating organisation's statement?
Yes
(We would encourage you to complete this form even if you agree with your nominating organisation's statement.)

Are you:

- a patient with the condition?

Yes – diagnosed with HER2+ locally advanced primary breast cancer in September 2013. Docetaxel, Herceptin and Perjeta treatment started in September 2013, 6 rounds were completed in January 2014, a simple mastectomy was carried out in February 2014 followed by 15 sessions of radiotherapy in March 2014 and 12 further rounds of Herceptin and Perjeta which finished in October 2014.

- a carer of a patient with the condition?

No

- a patient organisation employee or volunteer?

No

Do you have experience of the treatment being appraised?
Yes
If you wrote the organisation submission and do not have anything to add, tick here ☐ (If you tick this box, the rest of this form will be deleted after submission.)

2. Living with the condition

What is your experience of living with the condition as a patient or carer?

I am a 42 year old female living in Northumberland. I am married and have two boys aged 13 and 11. I was diagnosed with locally advanced stage 3 primary breast cancer on 4th September 2013 having been to my GP on 2nd September. I had 3 tumours (each between 7mm and 10mm in size) in my right breast, located close to the skin but spread over a 6cm area and my lymph nodes were also involved. My cancer was HER2+ and my Oncologist (Dr Branson at North Tyneside General Hospital) recommended Docetaxal chemotherapy prior to surgery alongside the drug Herceptin and the drug Perjeta which he would apply for via the Cancer Drugs Fund. I was the first patient at North Tyneside General Hospital to be given this drugs combination.

I was given an MRI scan after three rounds of the drugs combination and was told the drugs were working well. Following six rounds of this drug combination I was given another MRI scan. Dr Branson could not be sure all of the cancer was gone and because of the number of tumours, their location, and at that point in time the lack of data relating to the success of the drug combination, I was advised by my surgeon to have a simple mastectomy which I had on 4th February 2014. After the operation I was informed that I had had a complete response to the drugs and that no cancer remained. I commenced the remaining twelve rounds of Herceptin and Perjeta on 26th February 2014 and began twenty one sessions of radiotherapy on 17th March 2014. I finished active medical treatment in October 2014.

3. Current practice in treating the condition

Which treatment outcomes are important to you? (That is, what would you like treatment to achieve?) Which of these are most important? If possible, please explain why.

The main outcome that I wanted treatment to achieve was the complete eradication of my cancer. I was warned from the outset that following initial chemotherapy and targeted treatment I would most likely require a mastectomy due to multiple tumours being present and the large area they were spread over. I am aware that in time it is hoped that this treatment combination may remove the need for surgery in some cases which would be wonderful however from my point of view I was comfortable with the mastectomy as an extra insurance policy to eradicate the cancer given that there was very little data to confirm whether or not surgery would always be required or not. A reduction in unpleasant side effects is also an important outcome as this helps maintain a relatively normal life given the circumstances.

What is your experience of currently available NHS care and of specific treatments? How acceptable are these treatments – which did you prefer and why?

I am aware that Perjeta is not a standard treatment and that my Oncologist applied for my treatment via the Cancer Drugs Fund. I am extremely grateful that he was able to do this and it would therefore be great if everybody who was diagnosed with HER2+ breast cancer was able to receive this treatment, especially if it has an excellent complete response rate. I am also aware that Perjeta is only available to those diagnosed with HER2+ breast cancer so not all breast cancer patients would be able to receive it, but at the same time many of these patients can be given other drugs to help them that are not available to HER2+ patients. It is good that there are a number of specialist drugs available to treat the many different types of breast cancer.

4. What do you consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that you expect to gain from using the treatment being appraised.

The main benefit for me was that the treatment I had prior to surgery completely eradicated my tumours. I am not 100% sure which physical symptoms I could put down solely to Perjeta as I was given this alongside two other drugs. Symptoms I did notice were diarrhoea approximately 2-3 days after treatment although this was easily treated with over the counter medication and continued until the end of the additional 12 rounds Perjeta and Herceptin treatment. I had bone pain during the initial 6 rounds of Docetaxel, Herceptin and Perjeta but this disappeared once the Docetaxel was finished.

During the first round of Perjeta I developed small white headed spots on my face and was given a cream by my hospital. These cleared quite easily when washed with warm water and a flannel. During the second round the spots moved to cover where my hair had been, they were larger and tougher than the ones that had appeared on my face and were again treated with the cream. I was informed by my hospital that this was a result of the Perjeta rather than the Docetaxel and Herceptin and that they would peak at round 2. This was indeed the case as they did not return after this.

I could not say I experienced any pain from Perjeta, I do not consider myself to have a disability so it had no impact on this. It did not affect my mental health which remained fine throughout treatment and had no real impact on my quality of life or that of my family.

I received treatment in hospital as Perjeta needed to be administered via an IV drip and I did not have a problem with this. I was happy to travel to hospital to receive treatment and was always confident that I was in the right place should there have been a problem.

My heart was monitored before and during treatment and I was lucky enough to suffer no adverse reactions. Towards the last few rounds of treatment I felt myself start to become slightly out of breath and a little tired if I exerted myself, my heart remained fine and I simply put this down to a build-up of the drugs and it had very little impact on my life.

Please explain any advantages that you think this treatment has over other NHS treatments in England.
The main advantage is that this treatment targets a different area of the tumours to that targeted by Herceptin which can only be a good thing as it is hopefully increasing patient's chances of a successful outcome. I believe I was able to have a slightly lower dose of Docetaxel as I was having it alongside Herceptin and Perjeta. I believe I coped well with the effects of chemotherapy and it may well be that this was due to the slightly lower dose.

If you know of any differences in opinion between you and other patients or carers about the benefits of the treatment being appraised, please tell us about them.
I was the first patient at North Tyneside General Hospital to receive Perjeta for treatment for locally advanced primary breast cancer and was not in contact with any other patients receiving this combination so I feel unable to comment on any differences of opinions as I have not heard any.

5. What do you consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns you have about current NHS treatments in England.

The limited availability of certain drugs is a worry as it means patients are perhaps missing out on treatment which may increase their chances of survival.

Please list any concerns you have about the treatment being appraised.

There is always the worry that treatment may not work and that patients suffer side effects that they are unable to tolerate which I expect would then have an effect on their families too. The fact that it must be administered by IV may have an impact on those who struggle with IV cannulas or those who might be unable to travel to hospital for personal or financial reasons. I personally found that my hair took a very long time to grow back compared to those I know who had had treatments (not the same treatment) at the same time as me. I could put this side effect down to Perjeta?

Personally none of the above were a concern for me (other than the initial worry that it may not work). I was extremely grateful for any treatment offered to me and was happy to accept everything I was given no matter where or how it was given.

If you know of any differences in opinion between you and other patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

Again as I was the first patient at North Tyneside General Hospital to receive Perjeta for treatment for primary breast cancer and was not in contact with any other patients receiving this combination I feel unable to comment on any differences of opinions as I have not heard any.

6. Patient population

Do you think some patients might benefit more from the treatment than others? If so, please describe them and explain why.
Whilst I am aware Perjeta is only available to patients with HER2+ breast cancer I believe this is a decision that can only be made by a medical practitioner.

Do you think some patients might benefit less from the treatment than others? If so, please describe them and explain why.
Again I believe this is a decision that can only be made by a medical practitioner.

7. Research evidence on patient or carer views of the treatment

Are you familiar with the published research literature for the treatment?
Yes

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether your experience of using the treatment as part of routine NHS care reflects the experience of patients in the clinical trials.
I am aware of the NeoSphere trial and the side effects detailed in this. Personally I suffered some of the side effects listed but not all of them and could not say that they affected me greatly or impacted hugely on my everyday life. I would assume they are a good reflection of patient experience as not everybody reacts in the exact same way to treatments.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?
Yes as they have warned patients of the chances of possible side effects.

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?
In my own personal experience there were no side effects that were not detailed in the clinical trials or the information I was given from my hospital.

Are you aware of any relevant research on patient or carer views of the condition or existing treatments?
No

If yes, please provide references to the relevant studies.
N/A

8. Equality

NICE is committed to promoting equality of opportunity and eliminating discrimination. Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, who they are and why.
None that I am aware of

9. Other issues

Do you consider the treatment to be innovative?
Yes

If yes, please explain what makes it significantly different from other treatments for the condition.
The fact that this treatment works alongside Herceptin to target a different area in tumours is a very good thing. My complete response to the treatment filled me with confidence that I was being successfully treated which I believe helped my mental health as I was able to think positively throughout my treatment.

Is there anything else that you would like the Appraisal Committee to consider?

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- The idea that Perjeta can completely eradicate tumours or shrink them considerably prior to surgery can only be seen as a good thing.
- The side effects appear to be less harsh that those that typically arise from chemotherapy and even if given alongside chemotherapy the overall combination may reduce the typical chemotherapy side effects.
- The hope that in the future there is enough data to suggest that surgery may not always be needed after this treatment may help many patients facing breast cancer.
- The theory that the drug is targeted specifically to switch off the actual cells that switch the cancer on in the first place will give greater hope to patients like myself, particularly in the early days of a diagnosis.

Pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer

Produced by School of Health and Related Research (ScHARR), The University of Sheffield

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Declared competing interests of the authors

None of the authors have any conflicts of interest to declare.

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Hazel Squires was the project lead. Abdullah Pandor and Eva Kaltenthaler summarised and critiqued the clinical effectiveness data reported within the company's submission. Praveen Thokala and Hazel Squires critiqued the health economic analysis submitted by the company. John Stevens critiqued the statistical elements of the company submission. Mark Clowes critiqued the company's search strategy. All authors were involved in drafting and commenting on the final report.

CONTENTS

TABLES

FIGURES

LIST OF ABBREVIATIONS

ALT	Alanine aminotransferase
APHINITY	Adjuvant Pertuzumab and Herceptin in Initial TherapY
AST	Aspartate aminotransferase
BCV	Base case value
BERENICE	A Study Evaluating Perjeta (Pertuzumab) Combined With Herceptin (Trastuzumab) and Standard Anthracycline-based Chemotherapy in Patients With HER2-positive Locally Advanced, Inflammatory, or Early-stage Breast Cancer
bpCR	pathological complete response in the breast
CDF	Cancer Drugs Fund
CI	Confidence interval
CMH	Cochran–Mantel–Haenszel
CRD	Centre for Reviews and Dissemination
CS	Company's submission to NICE
DCH	Docetaxel, carboplatin, trastuzumab
DFS	Disease-free survival
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EFS	Event-free survival
EMA	European Medicines Agency
ER	Oestrogen ('Estrogen') receptor (status)
ER+ / ER-	Oestrogen receptor positive/negative status
ERG	Evidence Review Group
FDA	Food and Drug Administration
FEC	5-fluorouracil, epirubicin, cyclophosphamide
GeparSepto	Nab-paclitaxel versus solvent-based paclitaxel in neoadjuvant chemotherapy for early breast cancer
HD	Trastuzumab plus docetaxel
HER2	Human epidermal growth factor
HER2-positive	Overexpression of HER2
HR	Hazard ratio
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
LVEF	Left Ventricular Ejection Fraction
LVSD	Left Ventricular Systolic Dysfunction
LY	Life Year
MeSH	Medical subject headings

NeoSphere	Neoadjuvant Study of Pertuzumab and Herceptin in an Early Regimen Evaluation
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OS	Overall survival
pCR	Pathological complete response
PFS	Progression-free survival
PHD	Pertuzumab plus trastuzumab plus docetaxel
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSS	Personal Social Services
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RECIST	Response evaluation criteria in solid tumours
SAE	Serious adverse event
SE	Standard error
tpCR	Total pathological complete response
TRYPHAENA	ToleRabilitY of Pertuzumab, Herceptin and AnthracyclinEs in NeoAdjuvant breast cancer

1 SUMMARY

1.1 Critique of the decision problem in the company's submission

The decision problem addressed by the company's submission (CS) was generally in line with the final scope issued by the National Institute for Health and Care Excellence (NICE).

The target population was adults with HER2-positive breast cancer which is either locally advanced, or inflammatory, or early stage (at a high-risk of recurrence). The intervention is pertuzumab which can be used within its licensed indication to treat this patient population before they undergo surgery, to be used together with trastuzumab and chemotherapy. The comparator described within the company's statement of the decision problem is 'neoadjuvant trastuzumab in combination with chemotherapy', whilst the comparator within the final NICE scope was more broadly described as 'standard neoadjuvant therapy without pertuzumab for HER-2 positive breast cancer'. NICE guidance does not currently recommend which treatments to provide within the neoadjuvant setting for these patients. Whilst the company's market research and the ERG's clinical experts suggest that most patients in England would be given the combination regimen of 5-fluorouracil, epirubicin and cyclophosphamide (FEC) followed by a taxane alongside trastuzumab, some patients may receive alternative therapies. Since no evidence around effectiveness and cost-effectiveness has been provided by the company for patients who would not receive trastuzumab, this assessment is limited to those patients who will receive trastuzumab as neoadjuvant therapy. It should also be noted that none of these therapies have previously been evaluated by NICE within the neoadjuvant setting.

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

The description of the decision problem within the CS does not highlight any equity issues and a Patient Access Scheme has not been proposed for neoadjuvant pertuzumab.

1.2 Summary of clinical effectiveness evidence submitted by the company

The CS included a systematic review of clinical effectiveness evidence of neoadjuvant pertuzumab. The main supporting evidence was derived from two company-sponsored, multi-country, multi-centre, randomised, open-label, active controlled trials assessing the efficacy and safety of neoadjuvant pertuzumab in combination with trastuzumab and chemotherapy for the treatment of HER2-positive early breast cancer.

The NeoSphere trial (a proof of concept study) was a four arm, Phase II trial that randomised 417 treatment-naïve women, (aged over 18 years) with operable, locally advanced or inflammatory centrally confirmed HER2-positive breast cancer (primary tumours >2 cm in diameter) to receive four neoadjuvant cycles of trastuzumab plus docetaxel (Arm A, n=107); pertuzumab plus trastuzumab plus docetaxel (Arm B, n=107); pertuzumab plus trastuzumab (Arm C, n=107) or pertuzumab plus docetaxel (Arm D, n=96). Pertuzumab was administered at a loading dose of 840mg, followed by a 420mg dose every 3 weeks. Trastuzumab was administered at a loading dose of 8mg/kg, followed by a 6mg/kg dose every 3 weeks. Docetaxel was administered at a dose of 75mg/m^2 (with escalation to 100mg/m^2, if tolerated) every 3 weeks. Following surgery, all patients received three cycles of adjuvant chemotherapy with the FEC regimen (5-fluorouracil, 600mg/m^2; epirubicin, 90mg/m^2; and cyclophosphamide, 600mg/m^2 administered intravenously every 3 weeks) and trastuzumab every 3 weeks to complete 1 year of therapy. The primary endpoint was pathological complete response in the breast (bpCR).Total pathological complete response (tpCR) was also reported. It is noteworthy, that the marketing authorisation for pertuzumab in the neoadjuvant setting is restricted to use in combination with trastuzumab and chemotherapy only; hence Arm C and Arm D of the NeoSphere trial are not relevant to this appraisal.

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

In general, the bpCR rate (trial definition of pCR [absence of invasive tumour in the breast irrespective of ductal carcinoma in-situ or nodal involvement, ypT0/Tis]) in the NeoSphere study was significantly higher in Arm B (combination of pertuzumab, trastuzumab and docetaxel, 45.8%) compared with Arm A (combination of trastuzumab plus docetaxel, 29.0%), with a difference of 16.8% (p=0.0141). The rate of tpCR (EMA and FDA preferred definition of pCR [absence of invasive tumour in breast and lymph nodes irrespective of ductal carcinoma in-situ, ypT0/is ypN0]) was broadly similar (Arm B, 39.3% versus Arm A, 21.5%; difference of 17.8%, p=0.0063). In the TRYPHAENA study, bpCR and tpCR were consistently high and similar across all treatment groups (approximately 60%).

Although the NeoSphere study was not powered to assess long-term outcomes or subgroups (thus data should be treated with caution), 5-year progression-free survival (PFS) was 86% for Arm B (95% CI: 77 to 91) compared with 81% (95% CI: 71 to 87), 73% (95% CI: 64 to 81), and 73% (95% CI: 63 to 81), for Arms A, C, and D, respectively. The hazard ratio for PFS for Arm B versus Arm A was 0.69 (95% CI: 0.34 to 1.40; p= not reported). The 5-year disease-free survival (DFS) data were 81%, 84%, 80%, and 75%, in the A, B, C, and D arms, respectively. The DFS hazard ratio for Arm B versus Arm A was 0.60 (95% CI: 0.28 to 1.27; p= not reported). In the TRYPHAENA study, DFS data were not sufficiently mature at the time at which the CS was submitted. Data relating to health related quality-of-life (HRQoL) were not collected in either study.

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

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

The systematic review process followed by the company was reasonably comprehensive. Despite minor limitations in the company's search strategy, the ERG is confident that all relevant controlled studies of pertuzumab in combination with trastuzumab and chemotherapy for the treatment of HER2-positive early breast cancer were included in the CS, including data from ongoing or planned studies. However, the ERG is not confident that all relevant non-randomised and non-controlled studies have been identified and included in the CS, as details of the systematic review process (e.g. identification, selection, data extraction, quality assessment and analysis and interpretation) were lacking in the CS. The specified inclusion and exclusion criteria were mostly appropriate and generally reflect the decision problem set out in the final NICE scope. The validity assessment tool used to appraise the included studies (NeoSphere andTRYPHAENA) was considered appropriate by the ERG.

Although the efficacy (measured in terms of pCR response [using various definitions]) and safety of pertuzumab in combination with trastuzumab and chemotherapy compared with trastuzumab and chemotherapy was positively demonstrated in the key included studies, there are a number of limitations and uncertainties in the evidence base which warrant caution in its interpretation. The main evidence in the CS was derived from two, Phase II, randomised, open-label, active controlled studies. As with many cytotoxic cancer drugs, the nature of the interventions precludes blinding and is almost universally absent from oncology trials; however, blinded outcome assessment can enhance bias reduction. The TRYPHAENA study was a cardiac safety study and included pertuzumab in all arms, could not provide evidence of comparative efficacy with treatments without pertuzumab. The company did not present a network meta-analysis.

The key uncertainties in the evidence base relate to the use of pCR as a surrogate endpoint for survival outcomes (including magnitude of benefit in survival) in the neoadjuvant treatment of breast cancer, the lack of high quality Phase III RCTs in this patient population, and the generalisability of the trial results to England.

1.4 Summary of cost effectiveness submitted evidence by the company

The company identified one existing economic evaluation of pertuzumab for early stage breast cancer. This was developed by the company and is similar to the model within the CS. The company undertook model-based economic evaluation of neoadjuvant pertuzumab plus trastuzumab and docetaxel compared with neoadjuvant trastuzumab and docetaxel over a lifetime horizon from the perspective of the NHS and PSS. The company's *de novo* model adopts a cohort level state transition approach based on six health states: event-free, locoregional recurrence, remission, metastatic not-progressed, metastatic progressed and death. Costs and outcomes are evaluated using a monthly cycle length. Due to the immature event-free survival (EFS) data within the key clinical trials, the company

used pCR to estimate EFS within the model. A meta-analysis of 12 neoadjuvant studies investigating the relationship between pCR and EFS by the Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC) group was used to extrapolate the outcomes reported in the NeoSphere trial. The EFS curves for patients who achieved a pCR and did not achieve a pCR from the CTNeoBC meta-analysis were extrapolated. The EFS for each treatment arm in the model was then estimated by multiplying these by the proportions of patients achieving pCR and no pCR patients in the respective arms in the NeoSphere trial. A utility was assigned to each health state according to published data. Disutilities for adverse events were not applied. The model includes costs associated with drug acquisition, drug administration, the treatment of selected adverse events; supportive care; and treatment within the post-progression state. The company reported a probabilistic ICER within their original submission of £20,104 per QALY gained for pertuzumab alongside trastuzumab and docetaxel compared with trastuzumab and docetaxel, which was revised to £21,869 per QALY gained following the clarification process. After the clarification process, the ERG highlighted an error around the digitised curves which resulted in a new company probabilistic ICER of £9,047 per QALY gained for pertuzumab alongside trastuzumab and docetaxel compared with trastuzumab and docetaxel.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The *de novo* model developed is generally appropriate for the decision problem defined in the final scope, though not all possible comparators have been included. The perspective, outcomes, discount rate, and measurement and valuation of costs and outcomes adhere to the NICE Reference Case. The model was generally well described within the CS. There are uncertainties associated with the use of pCR as a surrogate measure for EFS and it does not appear to be a good predictor of the EFS data from the NeoSphere trial. The one-way sensitivity analysis suggests that the key driver of the model results is the pCR rates. The uncertainty around the model parameters for the PSA is inadequately characterised. An alternative analysis was undertaken by the company using the EFS data from the NeoSphere trial directly within the analysis, which suggested that pertuzumab, trastuzumab and docetaxel is dominating (i.e. is more effective and less costly) compared with trastuzumab and docetaxel alone.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

The company undertook a reasonably comprehensive systematic review of pertuzumab (in combination with trastuzumab and chemotherapy) for the treatment of HER2-positive early breast cancer. No major limitations were noted. The NeoSphere and TRYPHAENA trials were of a reasonable methodological quality (with some limitations) and measured a range of clinically relevant outcomes.

The health economic model submitted by the company was generally well described and justified, with no major errors.

1.6.2 Weaknesses and areas of uncertainty

The key area of uncertainty in the clinical evidence concerned the validity of pCR as a surrogate endpoint for long-term outcomes. There is insufficient robust evidence at present that an effect on pCR translates into effects on long-term clinical outcomes. There may also be differential relationships depending on treatment and cancer subtypes. However, pCR was accepted for accelerated approval by both the European and US licensing authorities as a valid and meaningful clinical endpoint for regulatory approval of neoadjuvant breast cancer studies, subject to the need to collect long-term clinical outcomes data. Although there is no high quality evidence from prospective, Phase III controlled trials, data from a post-authorisation efficacy trial, APHINITY, is expected to help address this concern. However, it is due for completion in December 2023 with a primary analysis expected to take place in 2016 and the final clinical study report is expected in May 2017.

The extrapolation of the outcomes from the NeoSphere trial is highly uncertain, leading to uncertainty around the economic model results. The choice of parametric distribution used for extrapolation impacts upon the model results substantially and there is limited longer term data within this patient population to be able to satisfactorily validate this choice. The use of pCR as a surrogate outcome to predict EFS within the health economic model is a poor predictor of the EFS within the NeoSpere trial, irrespective of which parametric distribution is chosen. However, the company did also undertake an analysis using the EFS data directly from the NeoSphere trial which suggested that the pertuzumab arm dominates (i.e. is more effective and less costly than the comparator).

It should also be noted that the only comparator included within the economic evaluation is trastuzumab and docetaxel.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG produced a revised base case which was similar to the company's base case resulting from the clarification process. The ERG corrected an error in the digitisation of the curves and modified the clinically inappropriate assumption that the probability of recurrence is zero after seven years. Whilst these changes individually impacted upon the ICER substantially, because they acted in different directions, when incorporated together they do not have a substantial impact on the company's results. The ERG-preferred probabilistic ICER for pertuzumab in combination with trastuzumab plus docetaxel compared with trastuzumab plus docetaxel is estimated to be £23,264 per QALY gained. Similarly, the ERG's deterministic base case ICER is estimated to be £23,467 per QALY gained. The

univariate sensitivity analysis suggested that the key drivers of the model results are: the relative pCR rates associated with the interventions; the parametric distribution employed for extrapolation of EFS; whether the treatment effect is assumed to continue beyond the trial follow-up duration; the number of cycles of pertuzumab administered and health utility values.

2. BACKGROUND

2.1 Critique of company's description of underlying health problem

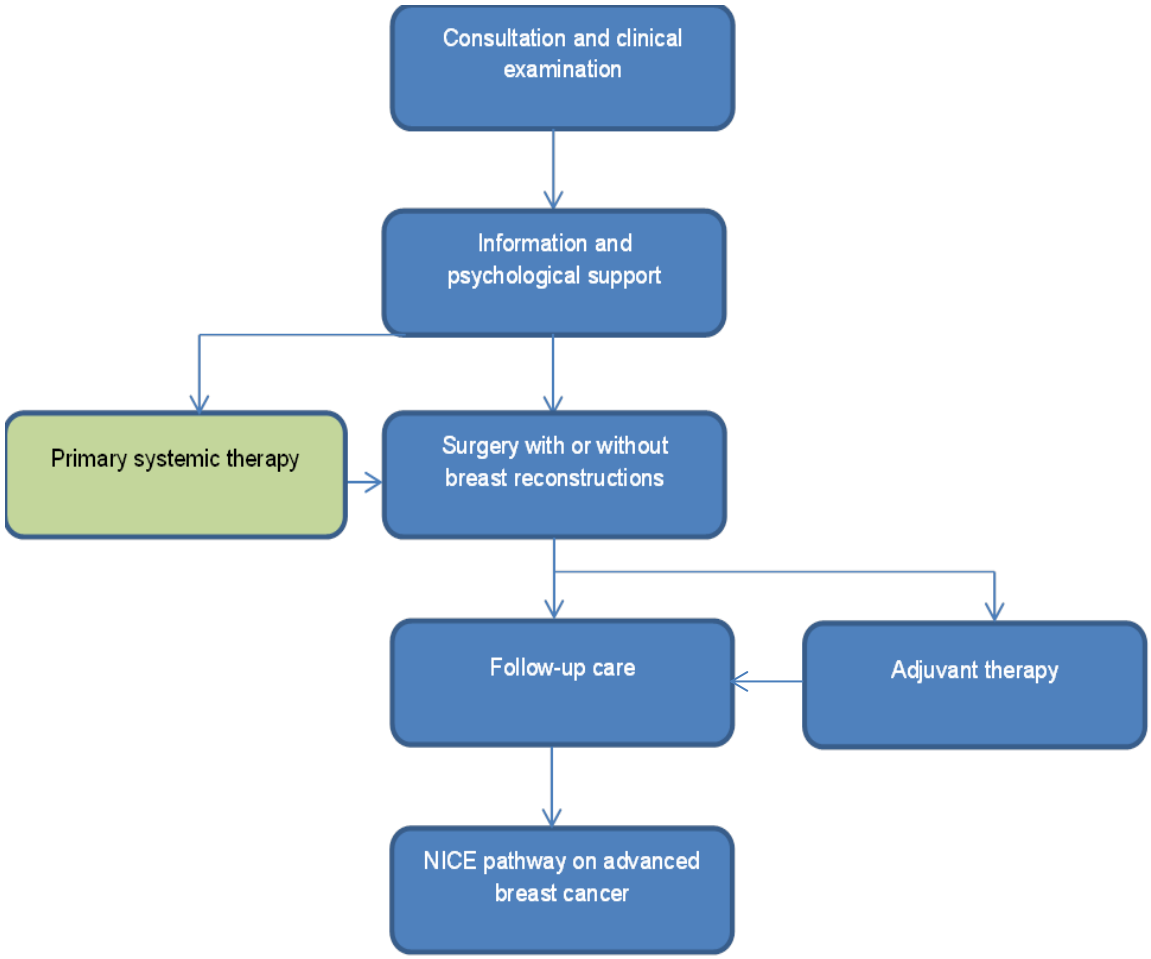
Pertuzumab is licensed for the treatment of early stage HER2-positive breast cancer at high risk of recurrence (locally advanced, inflammatory or early stage breast cancer). The company's description of HER2-positive breast cancer is brief, although appropriate and relevant to the decision problem. The company submission (CS) highlights that HER2-positive breast cancer is associated with a significantly worse prognosis and higher recurrence rate than other breast cancers. The CS contains some discussion around the definition of 'high risk of recurrence.' This suggests that locally advanced and inflammatory breast cancers are considered to be 'high risk' irrespective of other factors, whereas a subjective clinical judgement is made for early stage breast cancer, depending on a number of adverse risk factors including large tumour size, increasing tumour grade, absence of hormone receptors, lymph node metastases and HER2 over-expression or amplification.

In the CS (p44), data on the number of people who would be eligible for treatment with neoadjuvant pertuzumab was based on a mixture of published evidence and company data on file. Based on published evidence, the CS estimates that each year there are 5,113 patients with newly diagnosed HER2-positive breast cancer in England. Of these, 27% of patients (based on the company's market research data) would receive neoadjuvant therapy, resulting in 1,380 newly eligible patients per annum. Clinical advisors to the ERG suggest that whilst there is some uncertainty around these estimates, the proportions used within the calculations seem reasonable.

2.2 Critique of company's overview of current service provision

The CS suggests that NICE clinical guidelines[1] recommend the use of neoadjuvant therapy and provide a simplified version of NICE pathways (see Figure 1).

Figure 1. Simplified version of NICE pathways provided in the CS [Figure 3, p45][a]



The CS suggests that pertuzumab will be considered as an additional neoadjuvant treatment for use in combination with trastuzumab plus chemotherapy, and therefore no change is expected to the current recommended treatment pathway. However, the NICE Early and Locally Advanced Breast Cancer guidelines,[1] recommend that *"for patients considering breast conserving surgery that is not advisable at presentation: Preoperative systemic therapy[b] can be offered."* No recommendations are provided by NICE around which neoadjuvant therapies to provide for breast cancer patients.

Trastuzumab is recommended as an adjuvant treatment within the NICE guidelines, which state: "*Offer trastuzumab, given at 3-week intervals for 1 year or until disease recurrence (whichever is the shorter period), as an adjuvant treatment to women with HER2-positive early invasive breast cancer following surgery, chemotherapy and radiotherapy when applicable."* Trastuzumab as a neoadjuvant therapy has not been evaluated by NICE. A license extension for trastuzumab for HER2-positive early

[a] The ERG notes that if there is no recurrence then patients will not continue to the NICE pathway on advanced breast cancer
[b] Otherwise termed neoadjuvant therapy

breast cancer patients was granted in 2012 to include neoadjuvant use in combination with chemotherapy followed by adjuvant trastuzumab.[2] Clinical advisors to the ERG suggest that after trastuzumab was recommended by NICE as an adjuvant therapy, clinicians began using trastuzumab within the neoadjuvant setting and completing the usual one year treatment schedule after surgery.

The company submitted data on the current use of neoadjuvant therapies within the UK for HER2-positive breast cancer patients (company data on file). It included questionnaire results from Quarter 4 2014 and Quarter 1 2015 given to a sample of 62 and 39 people respectively (it is unclear what skills the participants had or how they were identified), and market research data based upon interviews and questionnaires with 10 oncologists and 7 surgeons treating early HER2-positive breast cancer within different centres in England. This evidence suggests that there are a range of neoadjuvant therapies in use within England including trastuzumab, taxanes (including docetaxel and paclitaxel), fluorouracil plus epirubicin plus cyclophosphamide (FEC), other anthracycline based regimens, other chemotherapies (including carboplatin) and hormone therapies. Based upon these data, the company suggest that trastuzumab would be given to approximately 75% of these patients. Following an additional clarification request from the ERG, the company provided updated market research data from all of 2015, which suggests that 79% of these patients receive trastuzumab in practice. This also suggests that approximately 62% of these patients receive trastuzumab alongside docetaxel in practice. Clinical advisors to the ERG also suggest that most HER2-positive breast cancer patients for whom neoadjuvant treatment is appropriate would receive trastuzumab. However, there may be a small proportion of patients in current practice who would not receive trastuzumab as neoadjuvant therapy, mainly due to HER2 testing results not being available, frailty or cardiac co-morbidities. In addition, whilst the ERG's clinical advisors suggest that most patients in the neoadjuvant setting receive FEC followed by a taxane plus trastuzumab, there is some variation around adjunctive treatments and there may also be some variation around whether FEC would be provided before or after surgery (see Section 4.2.3 for further discussion around this issue).

A discussion of the appropriateness of the comparator within the decision problem addressed by the company is included in Section 3.3.

The CS suggests that treatment following progression to metastatic disease would be chemotherapy with a trastuzumab-based regimen, as recommended within NICE guidelines for patients who have not received anthracyclines in the adjuvant setting.[1] The company suggests that in clinical practice, pertuzumab may also be provided. NICE has not published any final recommendations for pertuzumab for metastatic breast cancer; however, it is currently funded by the Cancer Drugs Fund (CDF), and clinical advisors to the ERG agree that this treatment is used in practice for the treatment of metastatic disease. The CS states that further lines of treatment are possible following disease

progression. A range of metastatic treatment options are included within the economic model based upon the company's data on file describing current practice in England (see Section 5.2.6.2).

3. CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

3.1 Population

The patient population addressed by the company's statement of the decision problem matches that described in the final NICE scope. The patient population is adults with HER2-positive breast cancer which is either locally advanced, or inflammatory, or early stage (but at a high-risk of recurrence). Clinical evidence was available on this population, which reflects the characteristics of the patient population in England who are eligible for treatment. The CS also presents the pathological complete response (pCR) rates within the clinical section of the submission according to the following subgroups:

- breast cancer type (operable, locally advanced, inflammatory)
- hormone receptor status (positive or negative)

However, the company states that since no statistically significant difference was seen between these subgroups, no subgroup analysis is presented within the health economic modelling.

3.2 Intervention

The intervention addressed by the company's statement of the decision problem matches that described in the final NICE scope. The intervention is pertuzumab (Perjeta®) which can be used within its licensed indication to treat early stage HER-2 positive breast cancer at high risk of recurrence (locally advanced, inflammatory or early stage breast cancer), before the patient undergoes surgery, to be used together with trastuzumab and chemotherapy.[3] Although outside the remit of this appraisal, pertuzumab is also indictaed for use in combination with trastuzumab and docetaxel in adult patients with HER2- positive metastatic or locally recurrent unresectable breast cancer, who have not received previous antiHER2 therapy or chemotherapy for their metastatic disease. Pertuzumab is given by intravenous infusion. The recommended first dose is 840mg, followed by a dose of 420mg every three weeks until the patient undergoes surgery, which will be between 3 and 6 doses. The marketing authorisation limits the use of pertuzumab to 6 cycles since safety for a greater number of cycles has not been established.[3] Within the two key clinical trials,[4, 5] three to six cycles of pertuzumab were given. Clinical advisors to the ERG suggest that in practice most patients are likely to receive four cycles of pertuzumab as it will be administered as part of the four cycles of trastuzumab.

3.3 Comparators

The comparator described within the company's statement of the decision problem is 'neoadjuvant trastuzumab in combination with chemotherapy', whilst the comparator within the final NICE scope was more broadly described as 'standard neoadjuvant therapy without pertuzumab for HER-2 positive breast cancer.' Within the NeoSphere trial,[4] the pivotal trial of efficacy for pertuzumab which was

used to inform the company's economic model within the CS, the comparator was trastuzumab plus docetaxel. As discussed in Section 2.2, a range of other neoadjuvant chemotherapy regimens available for this patient group including taxanes (including docetaxel and paclitaxel), FEC, other anthracycline combinations, and other agents including carboplatin with a taxane. Clinical advisors to the ERG agree that most patients would be given FEC followed by a taxane alongside trastuzumab; however, none of these regimens have previously been evaluated by NICE within the neoadjuvant setting.

In their response to a request for clarification from the ERG (question A2), the company acknowledge that *"…not all patients will receive trastuzumab; this will be at the clinician's discretion. Some of these reasons may be due to:*

- *HER2-testing results not available for treatment decisions at multidisciplinary team (MDT) meeting*
- *Previous cardiac dysfunction (e.g. from previous anthracycline therapy, symptomatic left ventricular systolic dysfunction (LVSD), left ventricular ejection fraction (LVEF) < 55%)*
- *Patients not eligible for anti-HER2 targeted treatment may be considered for alternative treatments such as chemotherapy."*

These alternative treatments are likely to be both less effective and less costly than trastuzumab.

Since no evidence has been provided by the company for patients who would not receive other regimens, the evidence contained within the CS is restricted only to those patients who receive trastuzumab as neoadjuvant therapy. It should be noted that whilst trastuzumab has not been evaluated in terms of cost-effectiveness in this population, clinical advisors to the ERG suggest that trastuzumab as adjuvant therapy (which has been assessed and recommended by NICE[1]) has simply been moved to an earlier stage in the patient pathway. The cost of trastauzumab in the neoadjuvant setting should be equivalent to that within the adjuvant setting and it is expected to be at least as effective in the neoadjuvant setting.

3.4 Outcomes

The final scope lists the following outcome measures:

- Overall survival (OS)
- Disease-free survival (DFS)
- Surgical outcomes
- Pathological complete response (pCR)
- Adverse effects of treatment
- Health-related quality of life

The CS includes evidence relating to all of these outcomes. Within the statement of the decision problem, event-free survival (EFS) is listed rather than disease free survival; however, within the clinical effectiveness section of the CS, DFS and PFS are presented. The US Food and Drug Administration (FDA) suggest that for neoadjuvant trials, long-term clinical benefits should be termed EFS, whilst for adjuvant trials, long-term clinical benefit should be termed DFS. Although OS is listed in the CS as an outcome, it was not a protocol-defined secondary efficacy endpoint in the NeoSphere trial, and thus survival status was not systematically reported beyond progressive disease, disease recurrence or withdrawal.[4]

The health economic outcome employed is the incremental cost per QALY gained, as set out within the NICE Reference Case.

3.5 Other relevant factors

The description of the decision problem within the CS does not highlight any equity issues. However, within the description of the technology section, the CS highlights that HER2-positive breast cancer is more aggressive than other types of breast cancer and that the median age of women affected is 50 years. The company suggests that this leads to increased broader societal impacts of the disease including effects on family life, as well as personal and societal financial implications. The company also highlights the adverse effects of the disease upon carers which will not be captured within the QALY measure.

At the time of writing, a Patient Access Scheme for pertuzumab had not been proposed by the company.

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4. CLINICAL EFFECTIVENESS

This chapter presents a review of evidence relating to the clinical effectiveness of pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer. Section 4.1 presents a critique of the company's systematic review and Section 4.2 provides a discussion on the validity of pCR as a surrogate for log-term clinical outcomes, a summary of the clinical effectiveness results (efficacy and safety) and critique of included pertuzumab studies. Sections 4.3 and 4.4 provide a discussion of the potential use of a network meta-analysis, whilst Section 4.5 clarifies that no additional work on the clinical effectiveness was undertaken by the ERG. Finally, Section 4.6 provides the conclusions of the clinical effectiveness section.

4.1 Critique of the methods of review(s)

4.1.1 Searches

The searches undertaken by the company to identify all relevant RCTs were conducted in November 2015. The search strategy utilised appropriate free text and medical subject heading terms to identify the condition (breast cancer), the intervention (pertuzumab) and the type of evidence (RCTs). Several electronic bibliographic databases (MEDLINE, MEDLINE in Process, EMBASE, EMBASE Alert and the Cochrane Library) were searched and no date or language restrictions were applied. Although research registers such as ClinicalTrials.gov and the International Standard Randomised Controlled Trial Number Register were not searched, seven conference proceedings (American Society of Clinical Oncology Annual Meeting, European Society for Medical Oncology Congress, American Society of Breast Surgeons, American Society of Clinical Oncology Breast Cancer Symposium, European Society for Medical Oncology IMPAKT Breast Cancer Conference, San Antonio Breast Cancer Symposium and the St. Gallen International Breast Cancer Conference) were reviewed for relevant abstracts presented at meetings held between 2013 to 2015. Supplementary searches such as scanning of bibliographies of included studies was also undertaken.

In general, the searches for the systematic literature review of RCTs in the CS were conducted in a systematic fashion and according to a clear protocol based on an explicit Population, Intervention, Comparator, Outcomes and Study design question. However, in a systematic literature search it is customary to search each database separately in order to: (a) increase transparency by indicating how many records were returned from each, and; (b) allow for the optimisation of the search strategy for each database by choosing the most appropriate subject headings, field codes and limits. Every database has a different thesaurus and indexing hierarchy. Records imported from MEDLINE into EMBASE are automatically re-indexed to Emtree but the process is unmediated and can result in sub-headings losing their original context and being treated as free-standing subject headings. For this

reason, the ERG considers that searching EMBASE and MEDLINE together (known as multi-file searching) is not optimal.

Multi-file searching requires particular care and attention to include appropriate subject headings for *each* database searched (in this case, MeSH and Emtree). The ERG recognises that on this occasion considerable care has been taken to include headings from both indices, but still notes certain omissions among the headings used - for example, in line 11 of the multi-file search, terms for pertuzumab are searched in titles and abstracts only (using the suffix ".tw."). Since pertuzumab is additionally available as an Emtree heading, it would have been more appropriate to use the suffix ".mp." or ".af." as this would have the added benefit of finding studies where pertuzumab was one of a number of neoadjuvant therapies in use.

No acknowledgement was provided in the CS for the RCT filter that was applied to the MEDLINE / EMBASE searches. In response to a request for clarification from the ERG (question A5), the company acknowledged that they had used a hybrid filter derived from the Scottish Intercollegiate Guidelines Network filters designed for each database. The ERG notes that modifying a published filter for use on additional databases to those for which it was designed can be hazardous. Moreover, the company indicated that they also intended to identify systematic reviews of RCTs and that *"...it was assumed that any systematic review or meta-analysis of RCTs would be tagged or use words that were in the RCT search terms"* (see clarification question A6). The ERG did not have time to test this assumption, but is doubtful of its accuracy, particularly as the free text search terms used were far from comprehensive (for example, we found nearly twice as many results on MEDLINE / EMBASE simply by searching for "(RCT or RCTs).tw." instead of "RCT.tw."). Since numerous validated filters are available for the purpose of identifying systematic reviews on various databases, it would have been more appropriate to use one of these in addition to the RCT filter used, combining the sets with OR in order to find all relevant reviews as well as RCTs in this area.

The ERG also has some reservations concerning the use of an RCT filter in the Cochrane Library search. The Cochrane Library is a collection of several study specific databases. For example the Cochrane Central Register of Controlled Trials is a highly concentrated resource of randomised and quasi-randomised controlled trials, whilst the Cochrane Database of Systematic Reviews and the Database of Abstracts of Reviews of Effects are leading resources for systematic reviews in health care. As such, the ERG believes that the use of an RCT filter is unnecessary and argues that a simpler search using drug terms alone would have offered higher sensitivity without retrieving an unmanageable number of results.

Despite the limitations noted above, the ERG considers all the search strategies for the RCT evidence

to be sufficiently comprehensive to retrieve important citations relating to all eligible studies of which the ERG and its clinical advisors are aware. No relevant published controlled studies are likely to have been missed. However, as no search details/strategies for non-randomised and non-controlled studies were provided in the CS, it is unclear whether all relevant non-randomised and non-controlled studies have been identified and included in the CS.

4.1.2 Inclusion criteria

The CS describes an appropriate method of identifying and screening references for inclusion of RCT evidence in the systematic review of pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer. Two independent reviewers applied pre-specified inclusion and exclusion criteria (via a two-stage sifting process) to citations identified by the searches. Any differences in the selection process were resolved through discussion between reviewers or consultation with a third reviewer, if required (see CS, p53-54). A summary of the inclusion and exclusion criteria, as reported in the CS (p53), is reproduced (with minor changes) in Table 1.

The specified inclusion and exclusion criteria were appropriate and generally reflect the decision problem. It is noteworthy that the reporting of clinical harms is often inadequate in controlled clinical trial publications because they exclude patients at high (or even medium) risk from harms,[6, 7] they may be too short to identify long-term or delayed harms, or they may have insufficient sample sizes to detect rare events.[7, 8] Supplementary sources of evidence may provide additional supporting evidence concerning safety considerations.[9] The CS (p29) states that the variation to the marketing authorisation was granted with a number of conditions and included the following: periodic safety reports, adherence to the agreed risk management plan, and conducting the post-authorisation efficacy study APHINITY and the post-authorisation safety study BERENICE.[3] Both of these studies are currently ongoing: the primary analysis and the final clinical study report of the APHINITY trial and the safety and efficacy data from the neoadjuvant period of the BERENICE study are expected in the next two years.[3]

Whilst additional evidence from a review of non-randomised and non-controlled studies on the efficacy and safety of pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer was reported in the CS (p129-131), the CS did not provide details on how these were identified and which inclusion/exclusion criteria were applied during the study selection process.

Table 1. Inclusion/exclusion criteria used to select studies of pertuzumab in the CS (reproduced from CS, Table 6, p53)

Criteria	Inclusion criteria	Exclusion criteria
Population	• Treatment-naïve adults (aged 18 years and over) with HER2-positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence • Patients may have: o *Operable stage I or II early breast cancer* (T2-3, N0-1 [node negative or positive], M0) o *Locally advanced stage III breast cancer* (T2-3, N2-3, M0 or T4a-c, any N, M0) o *Inflammatory breast cancer* (T4d, any N, M0) • HER2-positive disease may be defined as: o *HER2 over-expression 3+ by IHC* o *HER2 amplification by FISH* • Patients may be hormone receptor positive or negative and may be either pre- or post-menopausal	• Studies that do not include the patient population of interest, or that do not present relevant outcomes for the population of interest separately to outcomes for other patients
Interventions	• Pertuzumab-based regimens used as neoadjuvant treatment	• None specified
Comparators	• Any comparator regimen	• None specified
Outcomes	• Progression-free survival • Event-free survival • Disease-free survival • Overall survival • Pathological complete response (any definition) • Response rate • Surgical outcomes e.g. breast-conserving surgery • Adverse effects of treatment • Health-related quality of life	• Pharmacokinetic outcomes
Study design	• Phase II, III or IV RCTs • Systematic reviews/meta-analyses of RCTs	• Phase I clinical trials • Narrative or non-systematic reviews • Case studies and case reports • Observational studies
Other considerations	• Publication type – humans only • Publication timeframe - none • Language restrictions – none	• None specified

FISH, fluorescence *in situ* hybridisation; HER2, human epidermal growth receptor 2; IHC, immunohistochemistry; RCTs, randomised controlled trials

4.1.3 Critique of data extraction

The data extracted and presented in the clinical section of the CS for the systematic review of RCT evidence appears to be appropriate and comprehensive. As noted in the CS (p54), all relevant data were extracted by a single reviewer into a pre-defined data extraction table. All extractions were then checked for accuracy by a second independent reviewer. Any discrepancies were resolved through discussion between reviewers. For the review of non-randomised and non-controlled evidence, the CS did not provide any information on the data extraction process.

4.1.4 Quality assessment

In the systematic review of RCT evidence, the validity assessment tool used to appraise the included studies in the CS (p105-106) was based on the minimum criteria for assessment of risk of bias in RCTs, as suggested by the Centre for Reviews and Dissemination (CRD) guidelines for undertaking reviews in health care.[7] As noted in the CS (p54), methodological quality assessment of included studies was performed by one researcher and checked by a second researcher. The ERG acknowledges that the validity assessment tool used in the CS was appropriate. For the review of non-randomised evidence, details of the methodological quality assessment process were lacking in the CS.

4.1.5 Evidence synthesis

The company did not undertake a formal meta-analysis. Whilst the CS (p128-129) provided various explanations for not undertaking a meta-analysis (some of which the ERG consider to be questionable), the ERG notes that the main reason that a meta-analysis was not possible was because studies compared different treatments with different comparators in the included trials (NEOSPHERE,[4] TRYPHAENA[5] and GeparSepto[10]). Instead, the company undertook a narrative synthesis of the evidence; however, no explicit details were provided on how this approach was undertaken. Ideally, a narrative synthesis approach should be pre-specified, justified, rigorous (i.e. describe results without being selective or emphasising some finding over others) and transparent to reduce potential bias.[7, 8] Despite the lack of transparency in the CS, the ERG acknowledges that the narrative synthesis approach undertaken by the company was acceptable.

In response to a request for clarification from the ERG (see clarification response, question A12), the company provided a justification for not conducting a network meta-analysis (NMA). The company argued that such an analysis was not feasible due to the *"…inability to group chemotherapy treatments to allow the formation of connected evidence networks. The treatments of interest, pertuzumab, trastuzumab, and lapatinib, are given in combination with a chemotherapy regimen. The various clinical studies identified during the systematic review used different chemotherapy regimens,*

and as such, the majority of treatment arms could not be compared across trials." Further details and the ERG's critique of the NMA section of the CS can be found in Sections 4.3 and 4.4 respectively.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

4.2.1 Studies included in/excluded from the submission

The company's Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram relating to the literature searches does not conform exactly to the PRISMA statement flow diagram (http://www.prisma-statement.org/). Despite this, the flow diagram presented by the company represents the identification and selection of all relevant RCTs (see CS, p56) of pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer and appears to be an adequate record of the literature searching and screening process. The ERG notes that details of the company's review of non-randomised and non-controlled evidence was lacking.

The company's systematic review of RCTs of pertuzumab identified and included three relevant studies. Of these, the NeoSphere trial (Neoadjuvant Study of Pertuzumab and Herceptin in an Early Regimen Evaluation)[4] and the TRYPHAENA study (ToleRabilitY of Pertuzumab, Herceptin and AnthracyclinEs in NeoAdjuvant breast cancer)[5] were completed Phase II, randomised active controlled trials assessing the efficacy and safety of neoadjuvant pertuzumab in combination with trastuzumab and chemotherapy for the treatment of HER2-positive early breast cancer. Further details of these two key studies are provided as the main supporting evidence in this section. The GeparSepto study[10] is a Phase III, randomised, active controlled trial assessing the efficacy and safety of neoadjuvant paclitaxel or nab-paclitaxel in combination with chemotherapy for early breast cancer. Patients with HER2-positive breast cancer also received pertuzumab and trastuzumab throughout the course of neoadjuvant chemotherapy. The CS (p57) states that *"the GeparSepto study will not be considered as a key trial in this submission because currently available data for the HER2-positive subpopulation in this trial are very limited (primary endpoint of pCR only). Furthermore, no safety data were presented for the HER2-positive patient subgroup in the interim analysis."* As a result, further details of this study (including the interim results) are presented as additional supportive evidence in Section 4.2.4.3.

The company's review of non-randomised and non-controlled evidence included one study that provides retrospective analysis data from a cancer data registry on the efficacy and safety of neoadjuvant pertuzumab-based combination treatment in women with HER2-positive non-metastatic breast cancer. The ERG is unclear about how this study was identified. Further details of the review of non-randomised and non-controlled evidence are presented in Section 4.2.4.3.

4.2.1.1 Main supporting evidence (pivotal studies)

A summary of the study design and population characteristics of the two main supporting studies is provided in Table 2.

Table 2. Characteristics of the key included studies - NeoSphere[4] and TRYPHAENA[5] (adapted from CS, Table 14, p78-80)

Study	Location (sites)	Design	Population	Interventions	Primary outcome measures	Duration
NeoSphere[4] (NCT00545688, WO20697) Proof of concept study funded by F. Hoffman-La Roche Ltd	59 centres in 16 countries (including 2 sites in the UK, n= unclear)[b]	Phase II, randomised (1:1:1:1), four-arm open-label, active-controlled trial (n=417)	Patients (aged ≥ 18 years) with confirmed HER2-positive operable, locally advanced, inflammatory or early-stage breast cancer with primary tumours ≥2cm in diameter, treatment naïve, ECOG PS 0 or 1 and LVEF ≥55%	*Neoadjuvant phase*: Arm A: Trastuzumab plus docetaxel (n=107) Arm B: Pertuzumab plus trastuzumab plus docetaxel (n=107) Arm C: Pertuzumab plus trastuzumab (no chemotherapy) (n=107) Arm D: Pertuzumab plus docetaxel (n=96) Following neoadjuvant therapy (a total of 4 preoperative treatment cycles), all eligible patients in Arms A, B and D received postoperative adjuvant chemotherapy with the FEC regimen whereas Arm C received docetaxel followed by FEC. All Arms also received concomitant trastuzumab to complete 1 year of treatment.	Pathological complete response in the breast (defined as the absence of invasive neoplastic cells in the breast at microscopic examination of the tumour remnants after surgery following neoadjuvant therapy)	Neoadjuvant treatment for 4 cycles (12 weeks) followed by surgery and post-operative treatment for 1 year. Follow-up for 5 years or until disease progression or death[11]
TRYPHAENA[5] (NCT00976989, BO22280) Cardiac safety study funded by F. Hoffman-La Roche Ltd	44 centres in 19 countries (including 3 sites in the UK, n= not reported)	Phase II, randomised (1:1:1), three-arm open-label, active-controlled trial (n=225)	Patients (aged ≥ 18 years) with confirmed HER2-positive operable, locally advanced, inflammatory or early-stage breast cancer with primary tumours ≥ 2cm in diameter, treatment naïve, ECOG PS 0 or 1 and LVEF ≥55%	*Neoadjuvant phase*: Arm A: 5-fluorouracil, epirubicin, cyclophosphamide (FEC) followed by docetaxel, with pertuzumab and trastuzumab given concurrently with all cycles (n=73) Arm B: FEC followed by docetaxel with pertuzumab and trastuzumab (given concurrently with docetaxel only) (n=75) Arm C: Pertuzumab, trastuzumab, docetaxel, and carboplatin given concurrently (n=77) Following neoadjuvant therapy (a total of 6 preoperative cycles), patients underwent surgery and continued trastuzumab to complete 1 year of treatment.	Incidence of symptomatic left ventricular systolic dysfunction and decline in LVEF of ≥10% points from baseline to <50%, during adjuvant treatment	Neoadjuvant treatment for 6 cycles, followed by surgery and post-operative treatment for 1 year. Follow-up for 5 years or until disease progression or death[12]

HER2, HER2, human epidermal growth receptor 2; ECOG PS, Eastern Cooperative Oncology Group Performance Status; LVEF, Left ventricular ejection fraction

[a] One patient randomly assigned to Arm B received Arm A treatment. One patient randomly assigned to Arm D received Arm B treatment. One patient randomly assigned to Arm D received Arm C treatment

[b] Enrolment data by country were reported in the U.S. Food and Drug Administration Medical review of pertuzumab (p53).[13] This data suggest that the number of patients in each study group from the UK sites were as follows: Arm A, n=1; Arm B, n=0; Arm C: n=0; Arm D, n=88 (the ERG notes that the data appear to be incorrect for Arm C and D).

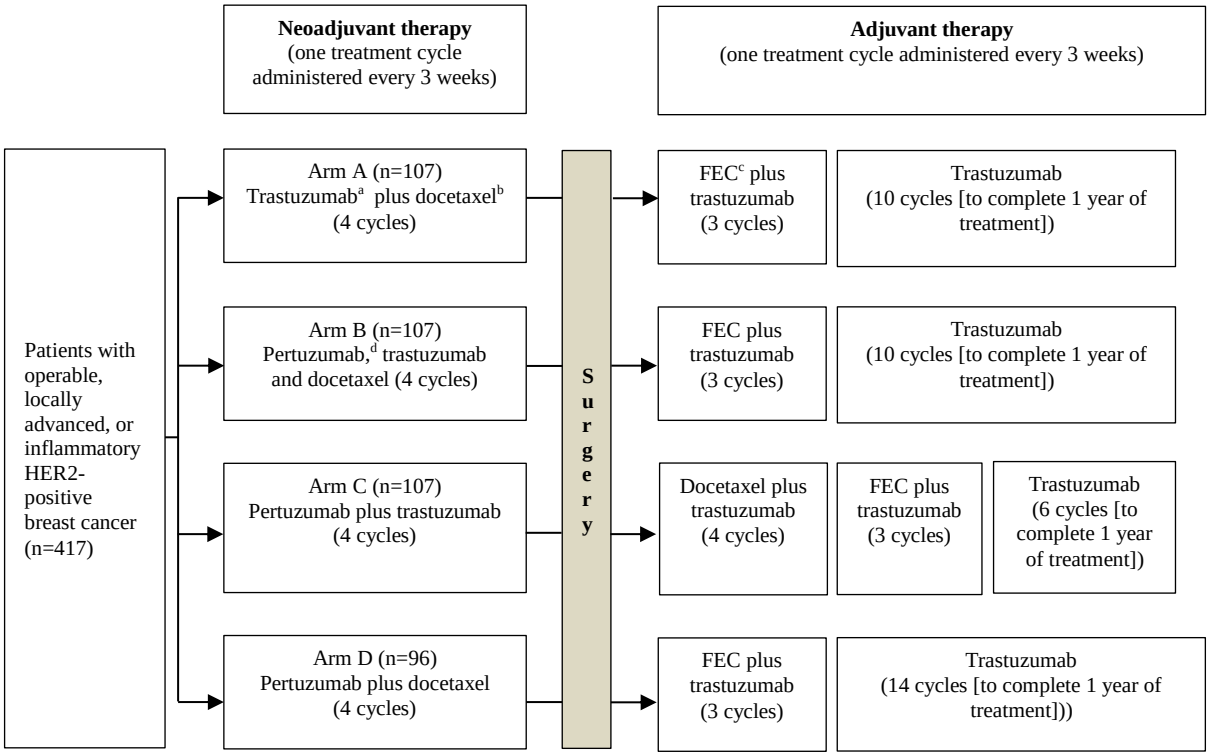
- *NeoSphere trial*

The NeoSphere trial[4] was a Phase II, company-sponsored, randomised, open-label, active-controlled, multicentre study designed to evaluate four neoadjuvant regimens in 417 treatment-naïve women, aged over 18 years (mean age 49.8 years and 71% were Caucasian) with operable (T2-3, N0-1, M0; 61% of study population), locally advanced (T2-3, N2-3, M0 or T4a-c, any N, M0; 32% of study population) or inflammatory (T4d, any N, M0; 7% of study population) HER2-positive breast cancer. The study included patients from 59 centres in 16 countries including two sites the UK. Eligible patients were enrolled between December 2007 and December 2009 and needed to have: a baseline Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 (88% of study population) or 1 (12% of study population); baseline left ventricular ejection fraction (LVEF) of ≥55% as measured by echocardiography or multiple gated acquisition and primary tumours had to be over 2cm in diameter (median size was at least 50mm across all study groups); and centrally confirmed as HER2-positive (immunohistochemistry score of 3+ or 2+, and positive for fluorescence or chromogenic in-situ hybridisation). The key exclusion criteria included metastatic disease (Stage IV), bilateral breast cancer, other malignancies, inadequate bone marrow or renal function, impaired liver function, impaired cardiac function, uncontrolled hypertension, pregnancy, and refusal to use contraception. The ERG note that the study population was limited to females and it is unclear why males were excluded.

Patients were randomly allocated to receive one of four neoadjuvant treatments: trastuzumab plus docetaxel (Arm A, n=107), pertuzumab plus trastuzumab and docetaxel (Arm B, n=107), pertuzumab plus trastuzumab without chemotherapy (Arm C, n=107), or pertuzumab plus docetaxel (Arm D, n=96). Randomisation was stratified by breast cancer type (operable, locally advanced, or inflammatory) and hormone receptor status. It is noteworthy, that the neoadjuvant licence indication for pertuzumab is restricted for use in combination with trastuzumab and chemotherapy only; hence Arm C and Arm D are not relevant to this appraisal but are reported here for completeness. Treatment in Arm B included four neoadjuvant cycles of pertuzumab, trastuzumab, and docetaxel administered by intravenous infusion every 3 weeks. Patients received an initial fixed loading dose of pertuzumab, 840mg, as a 60-minute infusion followed every 3 weeks thereafter by a fixed maintenance dose of 420mg, administered over a period of 30 to 60 minutes. Trastuzumab was administered at an initial dose of 8mg/kg, followed by 6mg/kg every 3 weeks. Docetaxel was administered at an initial dose of 75mg/m^2 (with escalation to 100mg/m^2 if the initial dose was well tolerated). Following surgery, all patients received three cycles of adjuvant chemotherapy with the FEC regimen (5-fluorouracil, 600mg/m^2; epirubicin, 90mg/m^2; and cyclophosphamide, 600mg/m^2 administered intravenously every 3 weeks) and trastuzumab (6mg/kg) every three weeks to complete one year of therapy. Radiotherapy and standard hormone treatment for patients positive for oestrogen receptor were prescribed as per

local guidelines. The treatment regimens in Arm A were identical to Arm B except for the omission of pertuzumab. A summary of the NeoSphere trial schema is presented in Figure 2.

Figure 2. NeoSphere trial[4] schema (adapted from CS, Figure 5, p62)



[a] Trastuzumab dosing: 8 mg/kg loading dose, then 6 mg/kg for subsequent cycles

[b] Docetaxel dosing: 75 mg/m^2 at cycle 1, then increased to 100 mg/m^2 at investigator's discretion if initial dose was well tolerated

[c] FEC dosing: 5-fluorouracil (600 mg/m^2), epirubicin (90 mg/m^2), and cyclophosphamide (600 mg/m^2)

[d] Pertuzumab dosing: 840 mg loading dose, then 420 mg for subsequent cycles

The primary endpoint was pCR in the breast, defined as an absence of invasive neoplastic cells in the breast only (ypT0/is) on histopathologic examination of the surgical specimen following primary systemic therapy. Secondary endpoints included clinical response rate, time to clinical response, safety profile, progression-free survival (PFS), disease-free survival (DFS), rate of breast-conserving surgery and biomarker assessment.

- *TRYPHAENA trial*

The TRYPHAENA trial[5] was undertaken to assess the tolerability, with particular focus on cardiac safety, of pertuzumab and trastuzumab with chemotherapy as a neoadjuvant treatment in patients with HER2-positive primary breast cancer. This was a company sponsored Phase II, randomised, open-

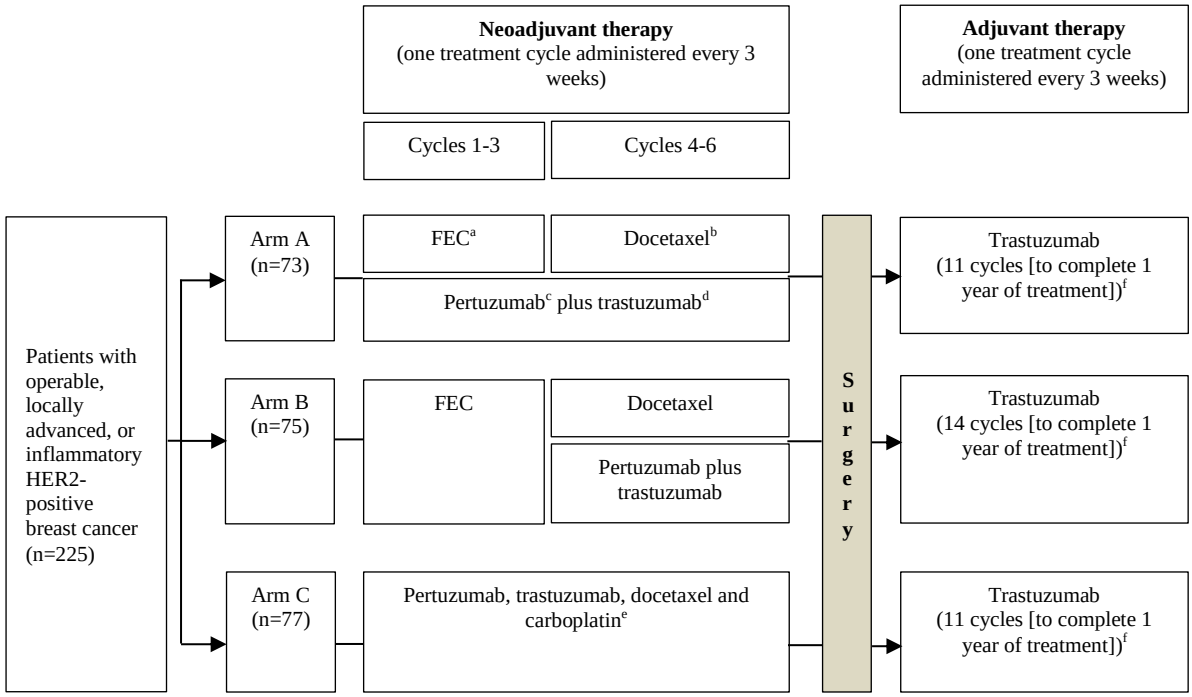
label, active-controlled, multicentre study in 225 treatment-naïve women, aged over 18 years (mean age 50.2 years and 76% were Caucasian) with operable (T2-3, N0-1, M0; 69.3% of study population), locally advanced (T2-3, N2-3, M0 or T4a-c, any N, M0; 24.9% of study population) or inflammatory (T4d, any N, M0; 5.8% of study population) HER2-positive breast cancer. The study included 44 centres in 19 countries including three sites in the UK. Eligible patients were enrolled between December 2009 and January 2011 and needed to have: a baseline ECOG PS of 0 (88.9% of study population) or 1 (10.7% of study population); baseline LVEF of ≥55% and primary tumours had to be over 2cm in diameter (median size was at least 49mm across all study groups); and centrally confirmed as HER2-positive (immunohistochemistry score of 3+ or 2+, and positive for fluorescence or chromogenic in-situ hybridisation). A summary of the study design and population characteristics is provided in Table 2. The key exclusion criteria included metastatic disease (Stage IV), bilateral breast cancer, other malignancies, inadequate bone marrow, liver or renal function, uncontrolled hypertension or history of myocardial infarction within 6 months of enrolment. The ERG note that the study population was limited to females and it is unclear why males were excluded.

Patients were randomly allocated to receive one of three neoadjuvant treatments: Arm A (n=73) included pertuzumab and trastuzumab in cycles 1 to 6 plus FEC in cycles 1 to 3 (5-fluorouracil, 500mg/m^2; epirubicin, 100mg/m^2 and cyclophosphamide 500mg/m^2) and docetaxel in cycles 4 to 6 (75 mg/m^2 increased to 100mg/m^2 if tolerated); Arm B (n=75) included FEC alone in cycles 1 to 3 followed by pertuzumab, trastuzumab and docetaxel in cycles 4 to 6 (75mg/m^2 increased to 100mg/m^2 if tolerated); Arm C (n=77) included pertuzumab, trastuzumab, docetaxel (75mg/m^2 with no dose escalation) and carboplatin in cycles 1 to 6 (administered at a dose of area under the plasma concentration–time curve of six). All regimens were given intravenously every 3 weeks to a total of six neoadjuvant cycles. Following surgery, all patients received trastuzumab every 3 weeks to complete 1 year of therapy. Further adjuvant treatment (radiotherapy, chemotherapy and hormonal treatment) was given according to local guidelines if considered necessary by the study investigators. Pertuzumab and trastuzumab were administered according to the same doses as those used in the NeoSphere study.[4] A summary of the TRYPHAENA trial schema is presented in Figure 3. It is noteworthy that all arms in the TRYPHAENA study[5] received pertuzumab. Consequently, this study does not provide evidence of the comparative efficacy of pertuzumab in combination with trastuzumab and chemotherapy versus trastuzumab and chemotherapy without pertuzumab.

The primary safety endpoint included: (1) incidence of symptomatic cardiac events (grade 3, 4 or 5 symptomatic left ventricular systolic dysfunction as assessed by the investigator); and (2) clinically significant LVEF declines over the course of the neoadjuvant period (LVEF decline of ≥10% from baseline to <50%). Secondary endpoints included pCR rates in the breast (ypT0/is), clinical response rate, time to clinical response, rate of breast-conserving surgery, DFS, PFS and overall survival.

However, as noted in the CS (p85 and p118), no formal hypothesis testing was planned or carried out, and no statistical comparisons were made between the treatment arms. Secondary efficacy endpoints were calculated and summarised for descriptive purposes only. In addition, the CS (p108 and p187) notes that the PFS and DFS data were not sufficiently mature at the time of submission.

Figure 3. TRYPHAENA trial schema (adapted from CS, Figure 6, p68)



[a] FEC dosing: 5-fluorouracil (500 mg/m^2), epirubicin (100 mg/m^2), and cyclophosphamide (600 mg/m^2)

[b] Docetaxel dosing: in Arm A and B, initial dose of 75 mg/m^2 in cycle 4, then increased to 100 mg/m^2 at investigator's discretion if initial dose was well tolerated. In Arm C, docetaxel given at 75 mg/m^2 and no dose escalation was allowed

[c] Pertuzumab dosing: 840 mg loading dose, then 420 mg for subsequent cycles

[d] Trastuzumab dosing: 8 mg/kg loading dose, then 6 mg/kg for subsequent cycles

[e] Carboplatin dosing: administered at a dose of AUC6 (area under the plasma concentration-time curve of six)

[f] Patients received additional radiotherapy, chemotherapy, hormone treatment post-surgery and during adjuvant trastuzumab treatment according to local guidelines if considered necessary by the investigator

4.2.1.2 Ongoing studies of pertuzumab in combination with trastuzumab plus chemotherapy

Several ongoing studies were noted in the CS (p28-29 and p186-187); however, full and clear explicit details on study characteristics were lacking. A summary of the key studies that may provide some evidence within the timeframe of this submission is provided in Table 3.

Table 3. List of key ongoing studies of pertuzumab

Criteria	APHINITY study[14] (Post-authorisation efficacy study)	BERENICE study[15] (Post-authorisation safety study)
Title (official)	A randomised, multicentre, double-blind, placebo-controlled comparison of chemotherapy plus trastuzumab plus placebo versus chemotherapy plus trastuzumab plus pertuzumab as adjuvant therapy in patients with operable HER2-positive primary breast cancer	A multicentre, multinational, phase II study to evaluate pertuzumab in combination with trastuzumab and standard neoadjuvant anthracycline-based chemotherapy in patients with HER2-positive, locally advanced, inflammatory, or early-stage breast cancer
Study ID number	Clincinaltrials.gov: NCT01358877 Other: BO25126, TOC4939G, 2010-022902-41, BIG 04-11	Clincinaltrials.gov: NCT02132949 Other: WO29217
Sponsors and collaborators	Sponsor: Hoffmann-La Roche Collaborators: Genentech, Inc. and Breast International Group	Sponsor: Hoffmann-La Roche
Study objective	To assess the safety and efficacy of pertuzumab in addition to chemotherapy plus trastuzumab as adjuvant therapy in patients with operable HER2-positive primary breast cancer.	To evaluate the safety and efficacy of pertuzumab in combination with trastuzumab and anthracycline-based chemotherapy as neoadjuvant treatment in patients with HER2-based locally advanced, inflammatory, or early-stage breast cancer
Study design	Phase III, randomised, double-blind, placebo-controlled trial.	Phase II, non-randomised, open-label study.
Study location	Multinational (approximately 42 countries, including 26 centres in the UK)	Multinational (approximately 13 countries, including 8 centres in the UK
Study population	4805 adult patients (male and female aged ≥ 18 years) with non-metastatic primary invasive HER2-positive carcinoma of the breast that is adequately excised and that is node-positive. Additional inclusion criteria include Eastern Cooperative Oncology Group Performance Status of 0 or 1, baseline left ventricular ejection fraction ≥55 and known receptor status (oestrogen receptor and progesterone receptor)	400 (planned) adult patients (male and female aged ≥ 18 years) with locally advanced, inflammatory, or early-stage, unilateral, and histologically confirmed invasive breast cancer. Additional inclusion criteria include Eastern Cooperative Oncology Group Performance Status of 0 or 1, baseline left ventricular ejection fraction ≥55, primary tumours over 2cm in diameter or over 5mm in diameter and node-positive and HER2-positive breast cancer confirmed by a central laboratory
Study interventions	After surgery, patients will be randomised to receive either pertuzumab or placebo intravenously every 3 weeks for one year, in addition to 6-8 cycles of chemotherapy and 1 year of trastuzumab intravenously every 3 weeks. Anticipated time on study treatment is 52 weeks. Further details of the treatments are provided below: • Pertuzumab: 840 mg intravenous loading dose in cycle 1, followed by 420 mg intravenous every 3 weeks for 52 weeks	Each investigator will choose a treatment regimen (A or B) for all their patients to follow (delivered intravenously). Treatment A (Cohort A): Patients will first be given doxorubicin (60 mg/m^2 every 2 weeks for 8 weeks [cycles 1-4]) and cyclophosphamide (600 mg/m^2 every 2 weeks for 8 weeks [cycles 1-4]). This will be followed by administration of paclitaxel (80 mg/m^2 given weekly for 12 weeks [cycles 5-8]), pertuzumab (420 mg [840 mg first dose] every 3 weeks [cycles 5-8]) and trastuzumab (6 mg/kg [8mg/k first dose] every 3 weeks [cycles 5-8]) treatment for four cycles.

Criteria	APHINITY study[14] (Post-authorisation efficacy study)	BERENICE study[15] (Post-authorisation safety study)
	• Chemotherapy: 6-8 cycles of standard chemotherapy (non-anthracycline based or anthracycline-based) • Trastuzumab: 8 mg/kg intravenous loading dose in cycle 1, followed by 6 mg/kg intravenous every 3 weeks for 52 weeks • Placebo: Intravenously every 3 weeks for 52 weeks Follow-up time frame is up to 13 years.	Treatment B (Cohort B): Patients will first receive 5-fluorouracil (500 mg/m^2 [cycles 1-4]), epirubicin (100 mg/m^2 [cycles 1-4]), and cyclophosphamide (600 mg/m^2 [cycles 1-4]). This is to be followed by docetaxel (100 mg/m^2 [75 mg/m^2 first dose] in cycles 5-8), pertuzumab (420 mg [840 mg first dose] in cycles 5-8) and trastuzumab (6 mg/kg [8mg/kg first dose] in cycles 5-8). All regimens in cohort B will be delivered every three weeks for four cycles Patients in both cohorts will subsequently undergo surgical treatment and then resume pertuzumab and trastuzumab treatment. Total time on treatment is expected to last 1 year and patients will be followed-up for a further 4 years.
Study outcomes	*Primary outcome* • Invasive disease-free survival (time-frame: up to 13 years) *Secondary outcomes* • Invasive disease-free survival including second non-breast cancer • Disease-free survival including second non-breast cancer or contralateral or ipsilateral ductal carcinoma in situ • Overall survival • Recurrence-free interval (defined as time between randomisation and local, regional or distant breast cancer recurrence) • Distant recurrence-free interval (defined as time between randomisation and distant breast cancer recurrence) • Cardiac and overall safety (incidence of adverse events) • Quality of life	*Primary outcome* (time-frame: approximately 5 years) • Incidence of cardiac events • Changes in left ventricular ejection fraction *Secondary outcomes* (time-frame: approximately 5 years) • Incidence of adverse events • Incidence of anti-therapeutic antibodies to pertuzumab • Total pathological complete response • Clinical response • Event-free survival (defined as time from enrolment to first occurrence of progressive disease, relapse, or death from any cause) • Invasive disease-free survival (defined as the time from the first date of no disease to the first documentation of progressive invasive disease, relapse, or death from any cause) • Overall survival (defined as the time from enrolment to death from any cause)
Start date	November 2011	July 2014
Expected completion date	December 2023 (primary analysis expected to take place in 2016 and the final clinical study report expected in May 2017)[3]	November 2020 (safety and efficacy data from the neoadjuvant period expected in May 2017)[3]

4.2.2 Details of relevant studies not included in the submission

The ERG is confident that all relevant published controlled studies were included in the CS and details of ongoing trials that are likely to be reporting additional evidence in the future were reported. However, as no search details/strategies for non-randomised and non-controlled studies were provided in the CS, the ERG is not confident that all relevant non-randomised and non-controlled studies have been identified and included in the CS.

4.2.3 Summary and critique of the company's analysis of validity assessment

The company provided a formal appraisal of the validity of the included pertuzumab RCTs using standard and appropriate criteria for assessing the risk of bias in RCTs, as suggested by the CRD guidelines for undertaking reviews in health care.[7] The completed validity assessment tool for the two pivotal trials, as reported in the CS, is reproduced (with minor changes) in Table 4.

Table 4. Quality assessment results for included RCTs as assessed by the company (adapted from CS, Table 19, p106)

Quality assessment criteria	Trials			
	NeoSphere (NCT00545688)[4]		TRYPHAENA (NCT00976989)[5]	
	Company Assessment	ERG Assessment	Company Assessment	ERG Assessment
Was randomisation carried out appropriately?	Yes	Yes	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	Yes	Yes	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)?	No	No	No	No
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Not clear	No [a]	Not clear	No [a]
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Not clear	No [b]	Not clear	No [b]
Did the analysis include an intent-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Not clear	Yes [c]	Yes	Yes

[a] ERG assessment: No (full details and reasons of dropouts were provided in the published papers[4, 5] and all patients were accounted for)
[b] ERG assessment: No
[c] ERG assessment: Yes (the published paper[4] and the CS [p82-86 and p90] suggest that efficacy analyses were conducted using the intention-to-treat approach)

Whilst the method of randomisation was not reported in the CS, the CS (p352-353) states that in the NeoSphere and TRYPHAENA studies,[4, 5] randomisation was performed centrally using an interactive voice response system and treatment allocation was dynamic and stratified by operable, locally advanced and inflammatory breast cancer and by hormone receptor positivity. However, it should be noted that the dynamic allocation method (a form of minimisation used to achieve balance across several factors simultaneously) is not truly random, and can potentially be subverted because of difficulties in concealing the allocation sequence. It is therefore theoretically possible that some patients may have been deliberately allocated to one or other treatment group on the basis of prognostic factors; however, the ERG has no reason to believe that this was the case.

In the open-label NeoSphere and TRYPHAENA trials,[4, 5] patients and investigators were all unblinded to the assigned treatment. Double-blinding protects against performance bias and measurement bias[16] and its absence in RCTs tends to result in larger treatment effects.[17] With many cytotoxic cancer drugs, the nature of the intervention precludes blinding (i.e. drug toxicities or manner of administration) for the practical and ethical reason that informed dose monitoring and adjustment is required. Although it is almost universally absent from oncology trials, blinded outcome assessment can enhance bias reduction.[18] As noted in the European Public Assessment Report (published by the European Medicines Agency, EMA),[19] most pathologists were not aware of the patient's treatment allocation (results of a survey performed by the marketing authorisation holder suggest that pathologists were only aware of treatment arms in 19 (4.6%) patients in the NeoSphere study and 22 (9.8%) patients in the TRYPHAENA study. Thus, the likelihood of biased reviews of pathology slides/specimens in these trials was considered to be very low by the EMA.[19]

The CS (p54-55) states that baseline demographics were generally well balanced across arms. In addition, the CS (p99-101) reported slight imbalances between treatment groups for white ethnicity and ECOG PS in the NeoSphere study[4] whereas in the TRYPHAENA study,[5] slight imbalances between treatment groups were noted for white ethnicity, operable breast cancer, locally advanced disease, hormone receptor-negative tumours and the proportion of patients with HER2 immunohistochemistry 2+ tumours. Statistically, studies should be analysed according to the way in which they were randomised; if the randomisation included stratification factors then the analysis should be adjusted for these irrespective of baseline balance. Furthermore, all relevant prognostic factors should be defined a priori and included as covariates in an analysis. In the case of linear models such as when comparing treatment means, the inclusion of covariates will increase the precision of the treatment effect even when there is perfect balance between treatments in the covariates responses. In the case of non-linear models such as when estimating odds ratios, the inclusion of covariates is not predictable and may increase the uncertainty associated with the treatment effect.

The CS (p136) suggests that the majority of patients in the NeoSphere trial (between 93% to 95%)[4] and the TRYPHAENA study (between 88% to 92%)[5] received the scheduled cycles of neoadjuvant pertuzumab and less than 20% of participants in each study (and by each treatment arm during the neoadjuvant or adjuvant phases) were reported to have been lost to follow-up. In general, the validity of a study may be threatened if attrition is more than 20%.[20] In both studies,[4, 5] all patients were accounted for and efficacy analyses were conducted according to the intention-to-treat (ITT) principle (see CS, p82-86 and p90). Overall, attrition bias should be low in the NeoSphere and TRYPHAENA studies.[4, 5]

The ERG notes that the quality assessment section of the CS (p104-106) failed to provide details on how closely the RCTs reflect routine clinical practice in England (a criteria suggested in the Single Technology Appraisal user guide for company evidence).[21] Nevertheless, as noted in the CS (p177 and p282) and the company's clarification response (question A4), the NeoSphere trial[4] contained a comparator arm (e.g. use of FEC chemotherapy after surgery [adjuvant treatment]), which was not comparable to routine clinical practice in England. FEC-T (anthracycline-based regimen of fluorouracil, epirubicin and cyclophosphamide for three cycles, followed by a taxane [e.g. docetaxel; T] for three cycles) is the most common chemotherapy regimen administered with trastuzumab as part of a neoadjuvant treatment regimen for breast cancer in the UK (see CS, p177). In the TRYPHAENA study[5] (a cardiac safety study where all treatment arms received pertuzumab), FEC therapy was administered as a neoadjuvant treatment and was considered by the company to closely reflect UK practice (see CS, p177). In addition, many patients in clinical practice in the UK now receive trastuzumab as a subcutaneous formulation (which produces a saving in administration time [see CS, p282]) compared with an intravenous infusion as used in the NeoSphere and TRYPHAENA studies.[4, 5] This issue is discussed further in Section 5.2 in terms of the assumptions employed within the company's health economic model.

Due to the differences in the use of FEC in UK practice (i.e. before surgery) and in the pivotal NeoSphere study (i.e. after surgery), the company's clarification response (question A4) noted that a systematic review and meta-analysis of nine RCTs by Mauri *et al*.[22] and a study by Wolmark *et al*.[23] demonstrated that the outcomes to neoadjuvant treatment have not been shown to be inferior to outcomes associated with adjuvant therapy in terms of death, disease progression or distant recurrence. Mauri *et al*.[22] identified 12 studies of neoadjuvant versus adjuvant therapy, although one study was excluded because no peer reviewed report had been produced and two studies were ongoing. Eighty-five patients across four studies did not have analysable data. In these studies, the mean or median age of the patients was reported and these ranged between 43 and 56 years. The inclusion criteria varied in terms of stage of breast cancer, tumour size and lymph node status. Several treatment regimens were used but only van der Hage *et al*.[24] used FEC. The number of treatment courses in the neoadjuvant treatment arms varied between one and six. In four studies, patients in the neoadjuvant arms received some courses before surgery and some courses after surgery. In the remaining five studies, patients received all courses of neoadjuvant treatment before surgery. There was no evidence of heterogeneity between studies in terms of the relative risk of death. The relative risk of death was 1.0 (95% CI: 0.90, 1.12). Only five studies provided information on pathological response. Differences in the rates of pathological response in these studies were low but significantly heterogeneous. The authors concluded that overall survival is not affected by the timing of chemotherapy (i.e. whether it was administered before or after surgery). They also concluded the equivalence of adjuvant and neoadjuvant treatments in terms of survival based on a difference of up to

12% in the relative risk of death RR=1 (95%: 0.90, 1.12). The ERG notes that similar conclusions were also found in a more recent systematic review and meta-analysis of 14 RCTs by van der Hage *et al*.[24] As a result, the company's clarification response (question A4) states that *"the clinical timings are therefore not expected to differ based on FEC administration (neoadjuvant vs. adjuvant therapy)."*

4.2.4 Summary and critique of results

This section presents the main results from the NeoSphere and TRYPHAENA trials,[4, 5] based on information reported in the CS and the company's clarification response. As the neoadjuvant licence indication for pertuzumab is restricted for use in combination with trastuzumab and chemotherapy only, data from Arm C (pertuzumab in combination with trastuzumab) and Arm D (pertuzumab in combination with docetaxel) of the NeoSphere trial[4] are not relevant to this appraisal but are reported in the ERG report for completeness. In the NeoSphere study,[4] the data cut-off for the primary analysis was 22 December 2009, which occurred when all patients had received neoadjuvant treatment and had either undergone surgery or withdrawn from the study. The final cut-off date for the PFS and DFS outcomes was 20 October 2014 (see CS, p60). In the TRYPHAENA study,[5] the data cut-off for the primary analysis was 21 June 2011, which occurred when all patients received neoadjuvant treatment and had either undergone surgery or withdrawn from the study. The final analysis, in which PFS and DFS data will be reported, has not yet been conducted (see CS, p108). Additional information, not reported in the CS, was provided by the company in their response to the clarification questions raised by the ERG. Where appropriate, data have been re-tabulated by the ERG to provide further clarity.

4.2.4.1 Efficacy

- pCR (main efficacy outcome)

Pertuzumab is a licensed drug approved by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) for neoadjuvant treatment of breast cancer. Approval was granted based on two phase II trials[4, 5] that used a novel surrogate endpoint - pCR. Study investigators in both studies[4, 5] defined pCR as the absence of invasive neoplastic cells at microscopic examination of the primary tumour at surgery following primary systemic therapy (bpCR, ypT0/is). However, after the completion of these trials, an alternate definition of pCR was proposed by the EMA[25] (and the FDA)[26] in 2014 for regulatory purposes. This was defined as *"the absence of any residual invasive cancer on hematoxylin and eosin evaluation of the resected breast specimen and all sampled ipsilateral lymph nodes following completion of the neoadjuvant systemic therapy."*[25, 26] This recommendation was based on a meta-analysis by Cortazar *et al*,[27] that found greater correlation between survival outcomes and pCR when negative ipsilateral lymph nodes were included in the definition. Further discussion and critique on the validity of pCR as a surrogate marker is provided below. On the basis of these regulatory guidance papers,[25, 26] both the NeoSphere and TRYPHAENA studies evaluated tpCR rate

(defined as absence of invasive tumour in breast and lymph nodes irrespective of ductal carcinoma in situ, ypT0/is ypN0) (collected retrospectively) as a clinical efficacy endpoint.[13, 19] A summary of results using various pCR definitions is summarised in Table 5.

Table 5. Summary of pCR by different definitions in the ITT populations (adapted from CS, Table 21, p111 and Table 26, p119)

	NeoSphere[4]				TRYPHAENA[5]		
	Arm A HD (n=107)	**Arm B PHD (n=107)**	**Arm C PH (n=107)**	**Arm D PD (n=96)**	**Arm A FEC+H+P x3 / D+H+P x3 (n=73)[a]**	**Arm B FEC x3 / D+H+P x3 (n=75)**	**Arm C DCH+P x6 (n=77)[a]**
bpCR (ypT0/is) - Trial pCR definition							
n (%)	31 (29.0%)	49 (45.8%)	18 (16.8%)	23 (24.0%)	45 (61.6%)	43 (57.3%)	51 (66.2%)
95% CI[b]	20.6 to 38.5	36.1 to 55.7	10.3 to 25.3	15.8 to 33.7	49.5 to 72.8	45.4 to 68.7	54.6 to 76.6
Difference of response, %[c]	-	+16.8%	-12.2%	-21.8%	NA	NA	NA
95% CI[d]		3.5 to 30.1	-23.8 to -0.5[a]	-35.1 to -8.5[a]	NA	NA	NA
Adjusted CMH *p*-value[e]		*p*=0.0141 vs Arm A	*p*=0.0198 vs Arm A	*p*=0.003 vs Arm B[f]	NA	NA	NA
tpCR (ypT0/is ypN0) - EMA and FDA preferred pCR definition							
n (%)	23 (21.5%)	42 (39.3%)	12 (11.2%)	17 (17.7%)	41 (56.2%)	41 (54.7%)	49 (63.6%)
95% CI	14.1 to 30.5	30.0 to 49.2	5.9 to 18.8	10.7 to 26.8	44.1 to 67.8[g]	42.7 to 66.2[g]	51.9 to 74.3[g]
Difference of response , %		+17.8%[h]	-10.3%[h]	+21.5%[h]	NA	NA	NA
95% CI		5.7 to 29.9[h]	-20.1 to -0.47[h]	9.6 to 33.5[h]	NA	NA	NA
Adjusted CMH *p*-value		*p*=0.0063 vs Arm A[h]	NR	NR	NA	NA	NA
German Breast Group pCR definition (ypT0 ypN0)							
n (%)	13 (12.1%)	35 (32.7%)	6 (5.6%)	13 (13.2%)	37 (50.7%)[g]	34 (45.3%)[g]	40 (51.9%)[g]
95% CI	6.6 to 19.9	24.0 to 42.5	2.1 to 11.8	7.4 to 22.0	38.7 to 62.6[g]	33.8 to 57.3[g]	40.3 to 63.5[g]
Difference of response , %	NR	NR	NR	NR	NA	NA	NA
bpCR (ypT0 ypN0) and no residual ductal carcinoma in situ and/or lobular carcinoma in situ at surgery							
n (%)	18 (16.8%)	39 (36.4%)	10 (9.3%)	17 (17.7%)	NR	NR	NR
95% CI	NR	NR	NR	NR	NR	NR	NR
Difference of response , %	NR	NR	NR	NR	NA	NA	NA

bpCR, pathological Complete Response (no invasive tumour) in the breast; CI, confidence interval; CMH, Cochran–Mantel–Haenszel; EMA, European Medicines Agency; FDA, US Food and Drug Administration, NA, not applicable; NR, not reported; tpCR, total pathological Complete Response (no invasive tumour in the breast and lymph nodes); FEC, 5-flurouracil, epirubicin, cyclophosphamide; P, Pertuzumab; H, trastuzumab; D, docetaxel; DCH, docetaxel, carboplatin, trastuzumab

[a] Data incorrectly presented in Table 21 (p111) of the CS. Corrected data from the Summary of Product Characteristics (p320, CS) is presented in this Table

[b] 95% CI for one sample binomial using Pearson-Clopper method

[c] NeoSphere study: Treatment Arm B and Arm C are compared to Arm A, while Arm D is compared to Arm B

[d] Approximate 95% CI for difference of two response rates using Hauck-Anderson method

[e] p-value from Cochran-Mantel-Haenszel test, with Simes multiplicity adjustment

[f] Ad hoc exploratory treatment comparison of A vs D, p=0.3263 (data from EPAR, p29)[19]

[g] Data from EPAR (p44)[19]

[h] Data from U.S. Food and Drug Administration Medical review of pertuzumab (p57)[13]

In general, the bpCR rate (trial definition) in the NeoSphere study[4] was statistically significantly higher in Arm B (combination of pertuzumab, trastuzumab and docetaxel) at 45.8% compared with Arm A (combination of trastuzumab plus docetaxel) at 29.0%, with a difference of 16.8% (p=0.0141). The rate of tpCR (EMA and FDA preferred pCR definition) was also higher in Arm B (Arm B, 39.3% versus Arm A, 21.5%; difference of 17.8%, p=0.0063). Comparable results were also observed using other pCR definitions. In the TRYPHAENA study,[5] bpCR and tpCR were consistently high and similar across all treatment groups (approximately 60%). As noted in the EPAR,[19] the higher rate of pCR in the TRYPHAENA study reflects the higher number cycles of neoadjuvant treatment and the use of the combination of pertuzumab, trastuzumab and chemotherapy in all three treatment arms.

Critique of pCR as a surrogate marker for long-term clinical outcomes

pCR has been used by the company as a surrogate endpoint for long-term survival outcomes, although its validity has been questioned and assessed by the EMA, FDA and others. The ERG identified, based upon an informal search, four published studies evaluating the relationship of pCR as a surrogate marker for long-term outcomes: Cortazar *et al*.[27], Berrutti *et al*.[28], Korn *et al*.[29] and Broglio *et al*.[30]

The FDA and EMA both accept pCR as a surrogate endpoint in neoadjuvant treatment for high risk early stage breast cancer, although the FDA acknowledges that there is uncertainty regarding the validity of pCR as a surrogate for long-term clinical outcomes and requires long-term follow-up data to confirm the effect of treatment on EFS and OS.[13, 25] The FDA and EMA acceptance of the surrogate is based on work by the Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC) Group established by the FDA.[27] The CTNeoBC Group compared the three most commonly used definitions of pCR (ypT0/Tis (absence of invasive cancer in the breast), ypT0/Tis ypN0 (absence of invasive cancer in the breast and axillary nodes), and ypT0 ypN0 (absence of invasive and in situ cancer in the breast and axillary nodes)) and their relationship with long-term outcomes. Patients in neoadjuvant studies all have invasive cancer at randomisation and the FDA recommend that long-term clinical benefit is defined as EFS or OS. EFS is, for regulatory purposes, defined as the time from randomisation to one of: progression of disease that precludes surgery, local or distant recurrence or death from any cause.

Cortazar *et al*.[27] performed a patient-level responder analysis and a study-level analysis to investigate the relationship between pCR compared with EFS and OS. The authors identified 12 neoadjuvant studies: AGO 1 (n=668), ECTO (n=1,355), EORTC 10,994/BIG 1-00 (n=1856), GeparDuo (n=907), GeparQuattro (n=1495), GeparTrio (n=2,072), GeparTrio-Pilot (n=285), NOAH (n=334), NSABP B-18 (n=1,523), NSABP B-27 (n=2,411), PREPARE (n=733), and TECHNO (n=217). All studies except for NOAH and TECHNO included heterogeneous patients; NOAH and TECHNO were limited

to patients with HER2-positive locally advanced or inflammatory breast cancer. 11,955 patients were included in the responder analysis and 9,440 patients were included in the study-level analysis. 1,989 (17%) patients were HER-2 positive. In all patients, this analysis suggested that patients who achieved pCR defined as absence of invasive cancer in the breast and axillary nodes had a reduced risk of EFS (Hazard Ratio (HR) 0.48 95% CI: 0.43, 0.54) and OS (HR 0.36 95% CI: 0.31, 0.42) compared to those who did not have a pathological complete response. Pathological complete response was associated with long-term outcome in the HER2 positive patients (EFS: HR 0.39 95% CI 0.31, 0.50; OS: 0.34 0.24, 0.47). The greatest association was in patients with HER2-positive, hormone receptor-negative tumours who received trastuzumab (EFS: 0.15 95% CI: 0.09, 0.27; OS: 0.08 95% CI: 0.03, 0·22) and those in the triple-negative subgroup. However, the analysis was unable to demonstrate a relationship between the effect of treatment on pCR (estimated using an odds ratio) and the effect of treatment on EFS and OS (estimated using a hazard ratio) at the study level. The authors suggested that the reasons why an increase in pCR rate did not translate into an improvement in long-term outcome might be because: (1) most of the studies included women with heterogeneous breast cancer tumour subtypes which is expect to dilute the association; (2) trastuzumab targeted to a specific tumour subtype was used only in three studies (GeparQuattro, NOAH and TECHNO) and as an adjunct to chemotherapy in only the NOAH study; (3) absolute differences in pCR rates in the studies were low (1-11%) but was as high as 20% in the NOAH study, and; (4) there may be factors unrelated to primary tumour response.

Berrutti *et al.*[28] also considered the potential role of pCR as a surrogate for DFS and OS. This meta-analysis included 29 studies (12 of which were included in the Cortazar analysis). In this study, the authors were unable to demonstrate a relationship between pCR and long-term outcomes and suggested that some reasons for this include: (1) heterogeneity between patient populations and their response to treatment; (2) differences in pCR definitions used in the studies; (3) differences in treatment regimens; (4) the use of additional therapies after surgery. As highlighted by the company within their clarification response to question A7, Berrutti *et al.*[28] noted that the probability of achieving pCR can differ in different tumour subtypes and that the probability of achieving pCR is most likely to be achieved in triple negative and HER2-positive patients.

Korn *et al.*[29] subsequently discussed the statistical issues involved in establishing whether an endpoint can be used as a study-level surrogate with particular reference to the use of pCR in early stage breast cancer. They concluded that there is no evidence to suggest that study-level effects on pCR is associated with improvements in long-term clinical outcomes. In addition, they noted some difficulties in relating treatment effects on surrogate outcomes to survival outcomes, including that there may be different relationships depending on the class of treatment being evaluated and that the use of subsequent lines of treatment may lead to a dilution in the observed effect on survival

irrespective of the treatments being compared. Indeed, the effect on survival outcomes may not be constant over time, hence attempting to relate an odds ratio to a hazard ratio may be inappropriate without allowing for a time-dependence in the treatment effect.

In another recent article, Broglio *et al.*[30] assessed the association of pCR to neoadjuvant therapy in HER2-positive breast cancer with long-term outcomes. They included cohort studies in addition to studies included in the Cortazar[27] analysis, which was taken as a single study for the purpose of the patient-level analysis. The authors concluded that an increase in pCR rate is associated with a positive HR in terms of EFS and OS. In addition, they showed that a beneficial pCR odds ratio is associated with a positive HR on EFS but not on OS. They suggest that the relationship between the absolute improvement in pCR and HR for EFS and OS may be more relevant for designing clinical trials, although the assumed relationship may differ according to the specific treatment administered.

In summary, the findings of Cortazar *et al.*,[27] Berrutti *et al.*[28] and Broglio *et al.*[30] are generally consistent. The ERG accepts that there is evidence at the patient-level that a pCR responder is associated with a lower risk of EFS and OS. However, the evidence that a positive treatment effect translates into a positive effect on OS is not convincing. Coupled with the fact that it has been suggested that the relationship may depend on the specific treatment being administered leads the ERG to conclude that the evidence for a positive relationship between an effect on pCR and an effect on OS is not proven in general or for a specific treatment and that it is necessary to confirm this relationship in studies of HER2-positive breast cancer patients treated with regimens tailored to the specific subtype.

The ERG also notes that in the EPAR for neoadjuvant pertuzumab,[19] a Scientific Advisory Group (SAG) on Oncology was consulted on whether the difference in tpCR rate of 17.8% between Arm A and B in the NeoSphere study was sufficiently large enough to translate into a significant difference in DFS and OS. The EPAR[19] stated that "*Given the existing uncertainty about pCR as a surrogate for DFS and OS, the SAG concluded that a difference of 18% does not allow to automatically conclude a significant difference with regard to long-term benefit. In addition NEOSPHERE design was not optimal to address this question of surrogacy (not all major treatments were given in the neoadjuvant setting, e.g., anthracyclines, and this may lead to overestimating the treatment effect of the experimental drug pertuzumab). However, the SAG agreed that in the context of the totality of the data, in particular, the strong biological rationale for the combination, the compelling efficacy results in the metastatic setting, the acceptable toxicity profile and the observed effect in terms of pCR, it is reasonably likely that neoadjuvant treatment with pertuzumab is associated with a benefit in terms of DFS and OS. A precise estimation of the expected long-term benefit is currently not possible based on the available data"*[19]

- Other outcomes

A range of secondary endpoints were evaluated in the NeoSphere and TRYPHAENA studies.[4, 5] A summary of the results from both studies is presented in Table 6 and 7. In both studies, the majority of patients achieved a clinical response in the primary lesion, as assessed by clinical breast examination. In the NeoSphere study,[4] the highest overall response (complete and partial response) was observed in Arm B (88.1%), whereas all three arms in the TRYPHAENA study[5] had similarly high overall response rates. Very few patients experienced disease progression during neoadjuvant treatment in either study (<2%). Median time to clinical response was around 6 to 7 weeks in all arms in the NeoSphere study,[4] whereas in the TRYPHAENA study,[5] median time to clinical response varied between 3.6 weeks in Arm A to 6.9 weeks in Arm B.

In the NeoSphere study,[4] over 50% of patients with T2-3 tumours were originally planned to undergo mastectomy; and only between 18% to 32% of these patients actually underwent breast conserving surgery (defined as quadrantectomy or lumpectomy). Similar rates of breast conserving surgery were observed in the TRYPHAENA study[5] (between 16% to 27% across the three treatment arms). As noted in the EPAR,[19] *"the NEOSPHERE and TRYPHAENA studies were not designed to show a difference in breast conserving surgery and the reasons for choosing mastectomy or breast conserving surgery were not collected. Thus… no firm conclusions can be drawn…"*

Although DFS was evaluated as a secondary endpoint in the TRYPHAENA study, these data were not sufficiently mature at the time of the CS; data will be reported when all patients have completed adjuvant treatment and is anticipated in 2016 (see CS, p187). The NeoSphere study also investigated DFS and PFS as secondary endpoints; however, the CS (p113) states that these endpoints were not designed or powered to test formal hypotheses and were presented for descriptive purposes only. As a result, the summary results of the hazard ratios and confidence intervals presented in Table 7 should be treated with caution. In the NeoSphere study,[31] at the time of the final cut-off (20 October 2014), 5-year PFS was 86% for Arm B (95% CI: 77 to 91) compared with 81% (95% CI: 71 to 87), 73% (95% CI: 64 to 81), and 73% (95% CI: 63 to 81), for Arms A, C, and D, respectively (see Table 6). The hazard ratio for PFS for Arm B versus Arm A was 0.69 (95% CI, 0.34 to 1.40; *p*= not reported). The 5-year DFS findings were 81%, 84%, 80%, and 75%, in Arms A, B, C, and D, respectively. The DFS hazard ratio for Arm B versus Arm A was 0.60 (95% CI: 0.28 to 1.27; *p*= not reported). The ERG note that although OS is listed in the CS (Table 3, p22) as an outcome, it was not a protocol-defined secondary efficacy endpoint in the NeoSphere trial, and thus survival status was not systematically reported beyond progressive disease, disease recurrence or withdrawal.[4] As concluded in the EPAR,[19] "*Although not statistically significant, efficacy outcome data (DFS and OS) from the NeoSphere study*

shows a trend in favour of pertuzumab… Confirmatory study data in terms of DFS and OS are considered necessary to address long-term efficacy of pertuzumab in the neoadjuvant setting."

Table 6. Summary of secondary endpoints from the NeoSphere and TRYPHAENA studies (adapted from CS, Tables 22-24 and 27-29)

	NeoSphere[4]				TRYPHAENA[5]		
	Arm A HD (n=107)	**Arm B PHD (n=107)**	**Arm C PH (n=107)**	**Arm D PD (n=96)**	**Arm A FEC+H+P x3 / D+H+P x3 (n=73)**	**Arm B FEC x3 / D+H+P x3 (n=75)**	**Arm C DCH+P x6 (n=77)**
Best tumour response in primary breast lesion with clinical breast examination							
Patients included, n	99	101	102	91	73	75	77
Complete response, n (%)	23 (23.2%)	31 (30.7%)	17 (16.7%)	19 (20.9%)	37 (50.7%)	21 (28.0%)	31 (40.3%)
Partial response, n (%)	56 (56.6%)	58 (57.4%)	52 (51.0%)	46 (50.5%)	30 (41.1%)	50 (66.7%)	38 (49.4%)
Stable disease, n (%)	20 (20.2%)	12 (11.9%)	31 (30.4%)	26 (28.6%)	3 (4.1%)	1 (1.3%)	5 (6.5%)
Progressive disease, n (%)	0	0	2 (2.0)	0	0	1 (1.3)	0
No assessment, n (%)	NR	NR	NR	NR	3 (4.1%)	2 (2.7%)	3 (3.9%)
Clinical response rate in primary breast lesion with clinical breast examination							
Complete or partial, n (%)	79 (79.8%)	89 (88.1%)	69 (67.6%)	65 (71.4%)	67/73 (91.8%)	71/75 (94.7%)	69/77 (89.6%)
Time to response							
Weeks	6.3	6.3	6.9	7.3	3.6	6.9[b]	4.9
80% CI for median[a]	6 to 7	4 to 7	6 to 9	6 to 9	3 to 18	3 to 20	3 to 18
Range	3 to 13	3 to 13	3 to 13	3 to 13			
Breast conserving surgery							
Patient's with T2-3 tumours achieving BCS for whom mastectomy was planned, n (%)	14/62 (22.6%)	13/56 (23.2%)	11/61 (18.0%)	19/60 (31.7%)	10/46 (21.7%) [c]	6/36 (16.7%) [c]	10/37 (27%) [c]

BCS, breast conserving surgery; CI, confidence interval; NR, not reported; EPAR, European Public Assessment Report; FEC, 5-flurouracil, epirubicin, cyclophosphamide; P, Pertuzumab; H, trastuzumab; D, docetaxel; DCH, docetaxel, carboplatin, trastuzumab

[a] Kaplan-Meier estimates (information from EPAR[19]

[b] Data discrepancy - reported as 6.3% in EPAR (p54)[19]

[c] Expressed as a percentage of patients with T2-3 tumours and eligible for BCS (planned mastectomy: Arm A, n=61; Arm B, n=63; Arm C, n=58)

Table 7. Summary of PFS and DFS from the NeoSphere (adapted from CS, Table 60, p176)

Outcomes	NeoSphere[4]			
	Arm A HD (n=107)	**Arm B PHD (n=107)**	**Arm C PH (n=107)**	**Arm D PD (n=96)**
	Hazard ratio (95% CI)			
5-year PFS (from ITT population)	-	0.69 (0.34 to 1.40; *p*= not reported)	1.25 (0.68 to 2.30; *p*= not reported)	2.05 (1.07 to 3.93; *p*= not reported)
5-year DFS (from ITT population)	-	0.60 (0.28 to 1.27; *p*= not reported)	0.83 (0.42 to 1.64; *p*= not reported)	2.16 (1.08 to 4.32; *p*= not reported)

FEC, 5-flurouracil, epirubicin, cyclophosphamide; P, Pertuzumab; H, trastuzumab; D, docetaxel; DFS, disease-free survival; HR, hazard ratio; ITT, intention-to-treat; PFS, progression-free survival

- Subgroup analyses

In the NeoSphere and TRYPHAENA studies,[4, 5] breast cancer status (operable, locally advanced, and inflammatory) and hormone receptor status (hormone receptor positive and hormone receptor negative) were used as stratification factors at baseline. A summary of the pCR results according to hormone receptor status and breast cancer type is presented in Table 8. Whilst it is unclear from the CS, the ERG assumes that these analyses were pre-specified. In general, pCR rates in both studies were lower in the subgroup of patients with hormone-receptor-positive (HR+) tumours compared with hormone-receptor-negative (HR-) tumours. The ERG notes that in the EPAR,[19] the SAG Oncology states that *"…the lower pCR rates observed in patients with HR+ tumours adds to the uncertainty with regard to long-term benefit. However, the subgroup analysis is based on very limited data and it is difficult to rule out the play of chance."*

Within the subgroup of patients with operable breast cancer, bpCR rates were similar to those in the ITT population of the NeoSphere and TRYPHAENA studies.[4, 5] In the NeoSphere study, patients with locally advanced cancer had a similar bpCR rates in Arm A (41.7%) and Arm B (43.8%), whereas in the TRYPHAENA study, data were too limited to draw any firm conclusions. Data for patients with inflammatory breast cancer were too limited in both studies to provide a meaningful analysis.

Table 8. Subgroup analysis - pCR according to hormone-receptor status and breast cancer type in the ITT populations (adapted from CS, Table 31-34, p124-128)

	NeoSphere				TRYPHAENA		
	Arm A HD (n=107)	**Arm B PHD (n=107)**	**Arm C PH (n=107)**	**Arm D PD (n=96)**	**Arm A FEC+H+P x3 / D+H+P x3 (n=73)**	**Arm B FEC x3 / D+H+P x3 (n=75)**	**Arm C DCH+P x6 (n=77)**
pCR by hormone-receptor status							
HR-negative[a]	(n=57)	(n=57)	(n=55)	(n=50)	(n=34)	(n=40)	(n=37)
bpCR (ypT0/is)							
n (%)	21 (36.8%)	36 (63.2%)	16 (29.1%)	15 (30.0%)	27 (79.4%)	26 (65.0%)	31 (83.8%)
95% CI[b]	24.4 to 50.7	49.3 to 75.6	16.1 to 41.0	17.9 to 44.6	62.1 to 91.3	48.3 to 79.4	68.0 to 93.8
tpCR (ypT0/is ypN0)							
n (%)	17 (29.8%)	31 (54.4%)	11 (20.0%)	13 (26.0%)	25 (73.5%)	25 (62.5%)	30 (81.1%)
95% CI	NR	NR	NR	NR	NR	NR	NR
HR-positive[c]	(n=50)	(n=50)	(n=51)	(n=46)	(n=39)	(n=35)	(n=40)
bpCR (ypT0/is)							
n (%)	10 (20.0%)	13 (26.0%)	3 (5.9%)	8 (17.4%)	18 (46.2%)	17 (48.6%)	20 (50.0%)
95% CI	10.0 to 33.7	14.6 to 40.3	1.2 to 16.2	7.8 to 31.4	30.1 to 62.8	31.4 to 66.0	33.8 to 66.2
tpCR (ypT0/is ypN0)							
n (%)	6 (12.0%)	11 (22.0%)	1 (2.0%)	4 (8.7%)	16 (41.0%)	16 (45.7%)	19 (47.5%)
95% CI	NR	NR	NR	NR	NR	NR	NR
bpCR by breast cancer type							
Operable breast cancer	(n=64)	(n=65)	(n=65)	(n=60)	(n=53)	(n=54)	(n=49)
n (%)	15 (23.4%)	31 (47.7%)	12 (18.5%)	16 (26.7%)	34 (64.2%)	29 (53.7%)	32 (65.3%)
95% CI	13.8 to 35.7	35.1 to 60.5	9.9 to 30.0	16.1 to 39.7	49 to 76.9	39.6 to 67.4	50.4 to 78.3
Locally advanced breast cancer	(n=36)	(n=32)	(n=35)	(n=31)	(n=15)	(n=17)	(n=24)
n (%)	15 (41.7%)	14 (43.8%)	5 (14.3%)	5 (16.1%)	8 (53.3%)	13 (76.5%)	15 (62.5%)
95% CI	25.5 to 59.2	26.4 to 62.3	4.8 to 30.3	5.5 to 33.7	26.6–78.7	50.1–93.2	40.6–81.2
Inflammatory breast cancer	(n=7)	(n=10)	(n=7)	(n=5)	(n=5)	(n=4)	(n=4)
n (%)	1 (14.3%)	4 (40.0%)	2 (28.6%)	2 (40.0%)	3 (60.0%)	1 (25.0%)	4 (100%)
95% CI	0.4 to 57.9	12.2 to 73.8	3.7 to 71.0]	5.3 to 85.3	14.7 to 94.7	0.6 to 80.6	39.8 to 100

bpCR, pathological Complete Response (no invasive tumour) in the breast; CI, confidence interval; CMH, Cochran–Mantel–Haenszel; tpCR, total pathological Complete Response (no invasive tumour in the breast and lymph nodes); FEC, 5-flurouracil, epirubicin, cyclophosphamide; P, Pertuzumab; H, trastuzumab; D, docetaxel; DCH, docetaxel, carboplatin, trastuzumab

[a] Oestrogen receptor negative and progesterone receptor negative

[b] 95% CI for one sample binomial using Pearson-Clopper method

[c] Oestrogen receptor and/or progesterone receptor positive

The CS also presents further subgroup analyses from the NeoSphere study. These include an exploratory descriptive analysis (no tabulated data was provided) of clinical response, tumour response and breast conserving surgery. Further details are available in the CS (p125-126). In addition, the CS provides data for PFS by tpCR status based on an exploratory analysis (see CS, p115-118); this suggests higher PFS was observed in patients who achieved tpCR in all four treatment arms (hazard ratio, 0.54; 95% CI: 0.29 to 1.00; *p*= not reported). Further analysis[31] of PFS by tpCR and hormone-receptor status showed statistically non-significant improvements in 5-year PFS for patients with hormone-receptor negative-tumours (hazard ratio, 0.65; 95% CI: 0.32 to 1.30; *p*= not reported) who achieved tpCR compared with those who did not. Similar trends were observed for patients with hormone-receptor-positive tumours (hazard ratio, 0.66; 95% CI: 0.15 to 2.79; *p*= not reported).

4.2.4.2 Safety and tolerability

This section provides the main safety evidence from all participants who received at least one dose of study medication within the NeoSphere and TRYPHAENA trials. As noted in the CS (p136), safety and tolerability data for the neoadjuvant period of the studies is presented for: adverse events of all grades, grade ≥3 adverse events, serious adverse events and deaths. For the adjuvant and follow-up period, data relating to serious adverse events and deaths are also reported. Additional safety data were reported from two additional studies - a registry based observational study of neoadjuvant treatment in patients with HER2-positive breast cancer[32] and a Phase III trial in patients with metastatic breast cancer.[33-35]

- *Extent of exposure, discontinuation or modification of study treatment*

In the NeoSphere study,[4] 416 patients received at least one cycle of treatment (Arm A, n=107 [control arm without pertuzumab]; Arm B, n=107; Arm C, n=108 [one extra patient was included in Arm C as the patient who was randomly assigned to Arm D received Arm C treatment] and Arm D, n= 94). Pertuzumab was only administered in the neoadjuvant period. As noted in Section 4.2.1.1, the neoadjuvant licence indication for pertuzumab is restricted for use in combination with trastuzumab and chemotherapy (Arm B); hence Arm C and Arm D are not relevant to this appraisal but are reported for completeness. In this study, between 93% and 95% of patients received the full four cycles of neoadjuvant pertuzumab and between 90% and 93% of pertuzumab cycles were administered without the need for delay, interruption, modification or discontinuation (see CS, p136). In the TRYPHAENA study (a cardiac safety study),[5] 223 patients received at least one cycle of treatment (Arm A, n=72; Arm B, n=75, and; Arm C, n=76). Pertuzumab was administered to all treatment arms (for either 3 or 6 cycles) in the neoadjuvant period. In this study, the majority of patients received all scheduled cycles of neoadjuvant treatment. A summary of patient exposure to neoadjuvant study treatment in the two trials is provided in Table 9.

Table 9. Summary of neoadjuvant pertuzumab exposure in the NeoSphere and TRYPHAENA trials (adapted from CS, Table 40, p137 and Table 48, p147)

	NeoSphere[4]				**TRYPHAENA**[5]		
	Arm A HD (n=107)	**Arm B PHD (n=107)**	**Arm C PH (n=108)**	**Arm D PD (n=94)**	**Arm A FEC+H+P x3 / D+H+P x3 (n=72)**	**Arm B FEC x3 / D+H+P x3 (n=75)**	**Arm C DCH+P x6 (n=76)**
Patients receiving scheduled number of pertuzumab cycles	N/A	95%	93%	94%	91.7	88.0	92.1
Mean (±SD) number of pertuzumab cycles, mg	N/A	3.9 (±0.47)	3.9 (±0.42)	3.9 (±0.48)	5.8 (± 0.78)	2.9 (± 0.42)	5.7 (± 1.02)
Median number of pertuzumab cycles, mg (range)	N/A	4.0 (1 to 4)	4.0 (2 to 4)	4.0 (1 to 4)	6.0 (1 to 6)	3.0 (1 to 3)	6.0 (1 to 6)
Mean (±SD) pertuzumab dose received, mg	N/A	2059.6 (±280.79)	2047.7 (±177.57)	2051.0 (±202.74)	2875.8 (±328.1)	1637.8 (±177.3)	2823.9 (±458.0)
Median pertuzumab dose received, mg (range)	N/A	2100.0 (300 to 2940)	2100.0 (1260 to 2100)	2100.0 (840 to 2100)	2940.0 (840 to 3360)	1680.0 (840 to 1680)	2940.0 (420 to 2940)

FEC, 5-flurouracil, epirubicin, cyclophosphamide; P, Pertuzumab; H, trastuzumab; D, docetaxel; DCH, docetaxel, carboplatin, trastuzumab; SD, standard deviation

During the neoadjuvant period of the NeoSphere study, seven patients discontinued from any study treatment due to an adverse event (Arm A, n=0; Arm B, n=2 [1.9%]; Arm C, n=3 [2.8%] and Arm D, n=2 [2.1%]).[19] The EPAR[19] states that *"all adverse events leading to treatment discontinuation were considered possibly related to treatment, with the exception of the ulcerative colitis, which was assessed as unrelated by the investigators."* Similarly, very few patients discontinued treatment in the TRYPHAENA study[5] (Arm A, n= 4 [5.6%]; Arm B, n= 5 [6.7%] and Arm C, n= 6 [7.9%]) in the neoadjuvant period (n=15) and in the majority of cases, all study treatments were discontinued simultaneously (see CS, p153-154).[19]

The number of patients who experienced an adverse event in the neoadjuvant period that required treatment interruption or modification in the NeoSphere study[4] was highest in Arm D (44%) and lowest in Arm C (15%). Arms A and B were comparable (35% and 33% respectively). The CS (p146) notes that three patients in Arm B experienced left ventricular dysfunction leading to dose modification during the neoadjuvant period. All 3 events were assessed as possibly related to study treatment, and resolved without sequelae. In the TRYPHAENA study,[5] dose modifications were common in all neoadjuvant arms and were primarily performed in order to manage blood and lymphatic disorders (Arm A, 36%; Arm B, 29% and Arm C, 50%) in the neoadjuvant period. A summary of the most frequently reported adverse events requiring dose modification in both studies is provided in Table 10. It should be noted that statistical comparisons were not reported in the CS for either study.

Table 10. Most frequent adverse events (≥5% of patients in any arm) leading to dose modifications in the NeoSphere and TRYPHAENA trials (adapted from CS, Table 47, p146 and Table 54, p155)

Adverse event	NeoSphere[4a]				TRYPHAENA[5]		
	Arm A HD (n=107)	Arm B PHD (n=107)	Arm C PH (n=108)	Arm D PD (n=94)	Arm A FEC+H+P x3 / D+H+P x3 (n=72)	Arm B FEC x3 / D+H+P x3 (n=75)	Arm C DCH+P x6 (n=76)
Neutropenia	10 (9.3%)	6 (5.6%)	1 (0.9%)	15 (16%)	10 (13.9%)	11 (14.7%)	11 (14.5%)
Infusion-related reaction	5 (4.7%)	4 (3.7%)	3 (2.8%)	4 (4.3%)	-	-	-
Diarrhoea	1 (0.9%)	8 (7.5%)	0	6 (6.4%)[b]	-	4 (5.3%)	3 (3.9%)
Febrile neutropenia	7 (6.5%)	4 (3.7%)	0	4 (4.3%)	4 (5.6%)	2 (2.7%)	2 (2.6%)
Drug hypersensitivity	1 (0.9%)	2 (1.9%)	5 (4.6%)	4 (4.3%)			
Anaemia	-	-	-	-	2 (2.8%)	-	16 (21.1%)
Investigations (for laboratory abnormalities)	-	-	-	-	3 (4.2%)	1 (1.3%)	8 (10.5%)

FEC, 5-flurouracil, epirubicin, cyclophosphamide; P, Pertuzumab; H, trastuzumab; D, docetaxel; DCH, docetaxel, carboplatin, trastuzumab

[a] All n's were calculated by the ERG based on the numbers (identified as percentages in the EPAR) [19] reported in Table 47 of the CS (p146)

[b] Data reported as 4.3% in the EPAR[19]

- *Adverse events of any grade in the neoadjuvant period*

The majority of patients in the NeoSphere[4] and TRYPHAENA[5] trial experienced at least one adverse event during the neoadjuvant period. The most frequently occurring adverse events in the NeoSphere study[4] were alopecia, neutropenia, diarrhoea, nausea, fatigue, rash and mucosal inflammation. Most of these were grade 1 or 2 in severity (according to the National Cancer Institute Common Terminology Criteria [NCICTC] for Adverse Events version 3.0) and nearly all were deemed to be possibly related to study treatment.[4] In the TRYPHAENA study,[5] similar common adverse events were reported with the exception of rash. A summary of the most common adverse events (any grade) in the neoadjuvant periods of the two studies is shown in Table 11. The ERG notes that further details of additional adverse events (incidence rate of at least 5% in any arm) from the NeoSphere study[4] can be found in the EPAR (Table 35, p65).[19]

Table 11. Ten most common adverse events (any grade) in the neoadjuvant period of the NeoSphere or TRYPHAENA study (adapted from CS, Table 38 and 39, p135)

	NeoSphere[4]				TRYPHAENA[5]		
	Arm A HD (n=107)	**Arm B PHD (n=107)**	**Arm C PH (n=108)**	**Arm D PD (n=94)**	**Arm A FEC+H+P x3 / D+H+P x3 (n=72)**	**Arm B FEC x3 / D+H+P x3 (n=75)**	**Arm C DCH+P x6 (n=76)**
Total patients with ≥1 adverse events	105 (98.1%)	105 (98.1%)	78 (72.2%)	93 (98.9%)	72 (100%)	72 (96.0%)	76 (100%)
Total number of adverse events	806	803	326	765	781	685	935
Most common adverse events (all grades)							
Alopecia	70 (65.4%)	68 (63.6%)	1 (0.9%)	63 (67.0%)	35 (48.6%)	39 (52.0%)	41 (53.9%)
Neutropenia	67 (62.6%)	54 (50.5%)	1 (0.9%)	59 (62.8%)	37 (51.4%)	35 (46.7%)	37 (48.7%)
Diarrhoea	36 (33.6%)	49 (45.8%)	30 (27.8%)	51 (54.3%)	44 (61.1%)	46 (61.3%)	55 (72.4%)
Nausea	39 (36.4%)	41 (38.3%)	15 (13.9%)	34 (36.2%)	38 (52.8%)	40 (53.3%)	34 (44.7%)
Fatigue	29 (27.1%)	28 (26.2%)	13 (12.0%)	24 (25.5%)	26 (36.1%)	27 (36.0%)	32 (42.1%)
Rash	23 (21.5%)	28 (26.2%)	12 (11.1%)	27 (28.7%)	NR[b]	NR[b]	NR[b]
Mucosal inflammation	23 (21.5%)	28 (26.2%)	3 (2.8%)	24 (25.5%)	17 (23.6%)	15 (20.0%)	13 (17.1%)
Myalgia	24 (22.4%)	24 (22.4%)	10 (9.3%)	19 (20.2%)	NR[b]	NR[b]	NR[b]
Asthenia	19 (17.8%)	22 (20.6%)	3 (2.8%)	15 (16.0%)	NR[b]	NR[b]	NR[b]
Headache	12 (11.2%)	12 (11.2%)	15 (13.9%)	12 (12.8%)	NR[b]	NR[b]	NR[b]
Vomiting	13 (12.1%)[a]	14 (13.1%)[a]	5 (4.6%)[a]	15 (16.0%)[a]	29 (40.3%)	27 (36.0%)	30 (39.5%)
Anaemia	7 (6.5%)[a]	3 (2.8%)[a]	5 (4.6%)[a]	6 (6.4%)[a]	14 (19.4%)	6 (8.0%)	28 (36.8%)
Constipation	8 (7.5%)[a]	8 (7.5%)[a]	3 (2.8%)[a]	3 (3.2%)[a]	13 (18.1%)	17 (22.7%)	12 (15.8%)
Dyspepsia	NR	NR	NR	NR	18 (25.0%)	6 (8.0%)	17 (22.4%)

FEC, 5-flurouracil, epirubicin, cyclophosphamide; P, Pertuzumab; H, trastuzumab; D, docetaxel; DCH, docetaxel, carboplatin, trastuzumab

[a] Reported as common adverse events in the TRYPHAENA study,[5] thus corresponding data (reported in the EPAR)[19] for NeoSphere study are reported here

[b] Reported as common adverse events in the NeoSphere study;[4] however, corresponding data from the TRYPHAENA study[5] were not reported in the CS

- *Adverse events of grade ≥3 in the neoadjuvant period*

The most common grade ≥3 adverse events in the neoadjuvant period of the NeoSphere study[4] were neutropenia, febrile neutropenia and leucopenia, as would be expected from the use of treatment with docetaxel. In the TRYPHAENA study,[5] similar frequent grade ≥3 adverse events were observed across treatment arms. A summary of the most common grade ≥3 adverse events in the neoadjuvant periods of the two studies is shown in Table 12.

Table 12. Grade ≥3 adverse events occurring in ≥1 patient in the neoadjuvant period of the NeoSphere or TRYPHAENA study (adapted from CS, Table 43, p139 and Table 51, p151)

	NeoSphere[4]				TRYPHAENA[5]		
	Arm A HD (n=107)	**Arm B PHD (n=107)**	**Arm C PH (n=108)**	**Arm D PD (n=94)**	**Arm A FEC+H+P x3 / D+H+P x3 (n=72)**	**Arm B FEC x3 / D+H+P x3 (n=75)**	**Arm C DCH+P x6 (n=76)**
Total patients with ≥1 grade ≥3 adverse events	78 (72.9%)	67 (62.6%)	7 (6.5%)	66 (70.2%)	50 (69.4%)	45 (60.0%)	56 (73.7%)
Adverse events (grade ≥3 in ≥1 patient)							
Neutropenia	61 (57.0%)	48 (44.9%)	1 (0.9%)	52 (55.3%)	34 (47.2%) [a]	32 (42.7%) [a]	35 (46.1%) [a]
Leucopenia	13 (12.1%)	5 (4.7%)	0	7 (7.4%)	14 (19.4%) [a]	9 (12.0%) [a]	9 (11.8%) [a]
Febrile neutropenia	8 (7.5%)	9 (8.4%)	0	7 (7.4%)	13 (18.1%) [a]	7 (9.3%)	13 (17.1%) [a]
Granulocytopenia	1 (0.9%)	1 (0.9%)	0	2 (2.1%)	-	-	-
Alopecia	1 (0.9%)	5 (4.7%)	0	4 (4.3%)	-	-	-
Rash	2 (1.9%)	2 (1.9%)	0	1 (1.1%)	-	-	-
Diarrhoea	4 (3.7%)	6 (5.6%)	0	4 (4.3%)	3 (4.2%) [a]	4 (5.3%) [a]	9 (11.8%) [a]
Urinary tract infection	2 (1.9%)	2 (1.9%)	0	1 (1.1%)	-	-	-
Irregular menstruation	1 (0.9%)	1 (0.9%)	0	4 (4.3%)	-	-	-
Asthenia	0	2 (1.9%)	0	2 (2.1%)	-	-	-
Mucosal inflammation	0	2 (1.9%)	0	0	-	-	-
ALT increase	3 (2.8%)	0	0	1 (1.1%)	0 [a]	0 [a]	3 (3.9%) [a]
AST increase	2 (1.9%)	0	0	1 (1.1%)	-	-	-
Transaminases increase	0	2 (1.9%)	0	0	-	-	-
Nervous system disorders	2 (1.9%)	1 (0.9%)	0	1 (1.1%)	-	-	-
Drug hypersensitivity	0	1 (0.9%)	2 (1.9%)	0	2 (2.8%) [a]	0 [a]	2 (2.6%) [a]
Congestive heart failure	0	0	1 (0.9%)	0	-	-	-
Anaemia	-	-	-	-	1 (1.4%) [a]	2 (2.7%) [a]	13 (17.1%) [a]
Thrombocytopenia	-	-	-	-	0 [a]	0 [a]	9 (11.8%) [a]
Vomiting	-	-	-	-	0 [a]	2 (2.7%) [a]	4 (5.3%) [a]
Fatigue			-	-	0 [a]	0 [a]	3 (3.9%) [a]

ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; FEC, 5-flurouracil, epirubicin, cyclophosphamide; P, Pertuzumab; H, trastuzumab; D, docetaxel; DCH, docetaxel, carboplatin, trastuzumab

[a] Reported as common adverse events in the TRYPHAENA study[5]

- *Serious adverse events*

In the neoadjuvant setting of NeoSphere study,[4] neutropenia and febrile neutropenia were the most frequently reported serious adverse events in any treatment arm. One patient in Arm B experienced a serious adverse event of fulminant hepatitis that was fatal and one patient in Arm C experienced a serious adverse event of congestive cardiac failure. In the TRYPHAENA study,[5] febrile neutropenia was the most common serious adverse event. Moreover, a total of five patients reported cardiac disorder serious adverse events: three reports of left ventricular systolic dysfunction (Arm A, n=1; Arm B, n=2 [grade 3]), one report of cardiovascular disorder in Arm C and one report of conduction disorder in Arm C). A summary of the most common serious adverse events in the neoadjuvant periods of the two studies is shown in Table 13.

During the adjuvant period of the NeoSphere study,[4] febrile neutropenia was the most frequently reported serious adverse event in any treatment arm. The incidence of serious adverse events was highest in Arm C and was likely due to the administration of docetaxel in the neoadjuvant period in this arm (all other arms received docetaxel in the neoadjuvant period only). In the TRYPHAENA study,[5] 15 patients experienced at least one serious adverse event (Arm A, n=5 [7.4%]; Arm B, n=4 [6.2%] and Arm C, n=6 [9.0%]). A summary of the most common serious adverse events in the adjuvant periods of the two studies is shown in Table 14.

Following completion of adjuvant chemotherapy, a total of 10 patients experienced serious adverse events in the NeoSphere trial[4] (Arm B, n=4 [3.9%]; Arm C, n=5 [5.3%] and Arm D, n=1 [1.1%]) all of which were resolved without sequelae. During the post-treatment follow-up period, one patient in Arm B experienced a cerebrovascular accident and died, whereas another patient in Arm D experienced a myeloproliferative disorder (it is unclear in the CS whether this was fatal or non-fatal). In the TRYPHAENA study,[5] two patients in Arm B experienced treatment-related serious adverse events in the post post-treatment follow-up period. The ERG notes that although colony stimulating factors were permitted therapies (e.g. granulocyte colony-stimulating factor) in both studies, its use was not reported in the CS.

Table 13. Serious adverse events in the neoadjuvant setting of the NeoSphere and TRYPHAENA trials (adapted from CS, Table 45, p143 and Table 52, p152)

	NeoSphere[4]				TRYPHAENA[5a]		
	Arm A HD (n=107)	**Arm B PHD (n=107)**	**Arm C PH (n=108)**	**Arm D PD (n=94)**	**Arm A FEC+H+P x3 / D+H+P x3 (n=72)**	**Arm B FEC x3 / D+H+P x3 (n=75)**	**Arm C DCH+P x6 (n=76)**
No. of patients ≥1 serious adverse event	18 (16.8%)	11 (10.3%)	4 (3.7%)	16 (17.0%)	20 (27.8)	15 (20.0)	27 (35.5)
Total serious adverse events, n	20	15	4	16	27	24	NR
Febrile neutropenia	7 (6.5%)	6 (5.6%)	0	6 (6.4%)	10 (13.9%) [b]	4 (5.3%) [b]	11 (14.5%) [b]
Neutropenia	1 (0.9%)	4 (3.7%)	0	6 (6.4%)	2 (2.8%) [b]	3 (4.0%) [b]	1 (1.3%) [b]
Neutropenic infection	0	1 (0.9%)	0	0	-	-	-
Neutropenic sepsis	1 (0.9%)	0	0	0	-	-	-
Pyrexia	1 (0.9%)	1 (0.9%)	0	0	-	-	-
Diarrhoea	2 (1.9%)	0	0	1 (1.1%)	1 (1.4%) [b]	4 (4.0%) [b]	4 (5.3%) [b]
Congestive heart failure	0	0	1 (0.9%)	0	-	-	-
Fulminant hepatitis	0	1 (0.9%)[c]	0	0	-	-	-
Other	8 (7.5%)	2 (1.9%)	3 (2.8%)	3 (3.2%)	-	-	-
Deaths	0	1 (1)[d,e]	0	1 (1)[f]	-	-	-

FEC, 5-flurouracil, epirubicin, cyclophosphamide; P, Pertuzumab; H, trastuzumab; D, docetaxel; DCH, docetaxel, carboplatin, trastuzumab

[a] Serious adverse events in ≥2 patients per arm in the neoadjuvant phase in TRYPHAENA study[5]

[b] All n's were calculated by the ERG based on the percentages reported in the CS (Table 52, p152)

[c] Resulted in patient's death

[d] Died from fulminant hepatitis. Death occurred in the neoadjuvant setting on Day 70

[e] Docetaxel is associated with a rare incidence of fatal hepatitis

[f] Died of lung metastases and progressive disease in the adjuvant setting on Day 116

(note: multiple occurrences of the same adverse event in one individual counted only once)

Table 14. Serious adverse events in the adjuvant setting of the NeoSphere and TRYPHAENA trials (adapted from CS, Table 46, p144 and Table 53, p153)

	NeoSphere[4]				**TRYPHAENA**[5]		
	Arm A HD (n=103)	**Arm B PHD (n=102)**	**Arm C PH (n=94)**	**Arm D PD (n=88)**	**Arm A FEC+H+P x3 / D+H+P x3 (n=68)**	**Arm B FEC x3 / D+H+P x3 (n=65)**	**Arm C DCH+P x6 (n=67)**
No. of patients ≥1 serious adverse event	5 (4.9%)	11 (10.8%)	17 (18.1%)	11 (12.5%)	5 (7.4%)	4 (6.2%)	6 (9.0%)
Total serious adverse events, n	5	15	20	12	5 [a]	5 [b]	6
Febrile neutropenia	3 (2.9%)	2 (2.0%)	4 (4.3%)	8 (9.1%)	-	-	-
Neutropenia	0	2 (2.0%)	3 (3.2%)	0	-	-	-
Neutropenic infection	1 (1.0%)	0	1 (1.1%)	0	-	-	-
Pyrexia	0	0	2 (2.1%)	1 (1.1%)	-	-	-
Left ventricular dysfunction	0	2 (2.0%)	0	0	-	-	-
Others	1 (1.0%)	9 (8.8%)	10 (10.6%)	3 (3.4%)	-	-	-

FEC, 5-flurouracil, epirubicin, cyclophosphamide; P, Pertuzumab; H, trastuzumab; D, docetaxel; DCH, docetaxel, carboplatin, trastuzumab

[a] Pneumonia (n=2), cystitis (n=1), vaginal haemorrhage (n=1), metastatic neoplasm n=1)

[b] Appendicitis (n=1), device-related sepsis (n=1), infection (n=1), seroma (n=1), ovarian cyst (n=1)

[c] Pyelonephritis (n=1), wound infection (n=1), post-procedural haematoma(n=1), left ventricular dysfunction (n=1), chest pain (n=1), anaphylactic reaction (n=1)

- *Deaths*

There were 31 deaths reported in the NeoSphere study,[4] 30 of which occurred during post-treatment follow-up period. One patient in the NeoSphere trial died due to fulminant hepatitis during the neoadjuvant phase. In the TRYPHAENA study,[5] no deaths were reported during the neoadjuvant phase; however, 13 deaths due to disease progression/recurrence were observed during the adjuvant phase.

- *Cardiac safety*

Cardiac toxicity is a recognised adverse event associated with HER-2 targeted treatments.[13] This was measured in the trials using left ventricular ejection fraction (LVEF) decline and left ventricular systolic dysfunction (LVSD). In the NEOSPHERE study,[4] the number of patients with cardiac dysfunction adverse events was low in all trial arms; the incidence of this adverse event was highest in Arm B (3% to 6% across the treatment periods). Similarly, in the TRYPHAENA study,[5] the incidence of symptomatic LVSD and significant declines in LVEF (≥10% points from baseline to <50%) were low across all trial arms but were highest in Arm B (1.3% to 12.3% across the treatment periods). Table 15 shows LVSD and LVEF decline in the safety populations from the NEOSPHERE and TRYPHAENA trials.

Table 15 Left ventricular dysfunction and left ventricular ejection fraction declines in the safety population of the NeoSphere and TRYPHAENA trials (adapted from CS, Table 44, p141 and Table 49, p150)

Cardiac event	NeoSphere[4]				TRYPHAENA[5]		
	Arm A HD	**Arm B PHD**	**Arm C PH**	**Arm D PD**	**Arm A FEC+P+D x3 / D+P+D x3**	**Arm B FEC x3 / D+P+D x3**	**Arm C DCH+P x6**
Neoadjuvant period	(n=107)	(n=107)	(n=108)	(n=94)	(n=72)	(n=75)	(n=76)
Symptomatic LVSD							
n (%)	0	0	1 (0.9%)	0	0	2 (2.7%)	0
95% CI	0.0 to 3.4	0.0 to 3.4	0.0 to 5.1	0.0 to 3.8	0.0 to 5.0	0.3 to 9.3 [a]	0.0 to 4.7
LVEF decline							
n (%)	1 (0.9%)	3 (2.8%)	1 (0.9%)	1 (1.1%)	4 (5.6%)	4 (5.3%)	3 (3.9%)
95% CI	0.0 to 5.1	0.6 to 8.0	0.0 to 5.1	0.0 to 5.8	1.5 to 13.6	1.5 to 13.1	0.8 to 11.1
Adjuvant period	(n=99)	(n=98)	(n=92)	(n=84)	(n=68)	(n=65)	(n=67)
Symptomatic LVSD							
n (%)	0	0	0	0	0	0	1 (1.5%)
95% CI	0.0 to 3.5]	0.0 to 3.6]	0.0 to 3.8	0.0 to 4.1	0.0 to 5.3	0.0 to 5.5	0.0 to 8.0
LVEF decline							
n (%)	1 (1.0%)	6 (5.9%)	0	5 (5.7%)	4 (5.9%)	8 (12.3%)	3 (4.5%)
95% CI	0.0 to 5.3	2.2 to 12.4	0.0 to 3.8	1.9 to 12.8	1.6 to 14.4	5.5 to 22.8	0.9 to 12.5
Follow-up period	(n=97)	(n=99)	(n=96)	(n=86)	(n=70)	(n=75)	(n=74)
Symptomatic LVSD							
n (%)	0	0	0	0	0	1 (1.3%)	0
95% CI	0.0 to 3.7	0.0 to 3.7	0.0 to 3.8	0.0 to 4.2	0.0 to 5.1	0.0 to 7.2	0.0 to 4.9
LVEF decline							
n (%)	0	4 (4.0%)	1 (1.0%)	3 (3.5%)	3 (4.3%)	4 (5.3%)	2 (2.7%)
95% CI	0.0 to 3.7	1.1 to 10.0	0.0 to 5.7	0.7 to 9.9	0.9 to 12.0	1.5 to 13.1	0.3 to 9.4

LVEF, left ventricular ejection fraction (decline = decline ≥10% points to <50%); LVSD, left ventricular systolic dysfunction (grade ≥3); FEC, 5-flurouracil, epirubicin, cyclophosphamide; P, Pertuzumab; H, trastuzumab; D, docetaxel; DCH, docetaxel, carboplatin, trastuzumab

[a] Patient who had symptomatic LVSD during FEC and prior to the administration of PHD is excluded

4.2.4.3. Supplementary evidence

The CS included additional supporting evidence from the ongoing, Phase III GeparSepto trial[10] (preliminary efficacy data only) and the Cleveland clinic registry (safety data)[32] to support the activity of dual HER2 blockade in early breast cancer as a neoadjuvant regimen. Safety data were also presented from the large Phase III CLEOPATRA study.[34, 35] Further details, in brief, are provided below.

- *GeparSepto trial*[10]

The GeparSepto trial is a large investigator-initiated (German Breast Group and the Arbeitsgemeinschaft Gynäkologische Onkologie—Breast Investigators) open-label, randomised, multicentre, Phase III study (of reasonable methodological quality) that evaluated nab-paclitaxel versus paclitaxel as neoadjuvant treatment for patients with early breast cancer. A total of 1,206 patients were included (started treatment) in this study of whom 396 patients had HER2-positive disease. Patients received nab-paclitaxel 125mg/m^2 continuous weekly (reduced from the initial dose of 150 mg/m^2 after a protocol amendment due to neurotoxicity) or solvent based paclitaxel 80mg/m^2 continuous weekly, each followed by epirubicin/cyclophosphamide. Patients with HER2-positive tumours also received trastuzumab and pertuzumab throughout treatment. Patients received 10 cycles of pertuzumab with trastuzumab (two cycles before biopsy and eight after biopsy and before surgery).

In the overall study population, pCR (German Breast Group definition, ypT0 ypN0) occurred more frequently in the nab-paclitaxel group (233/606 [38%, 95% CI: 35 to 42] patients) than in the solvent-based paclitaxel group (174/600 [29%, 95% CI: 25 to 33] patients; odds ratio, 1·53; 95% CI: 1·20 to 1·95; unadjusted p=0·00065). This effect was consistent irrespective of the pCR definition and patient subgroup. In patients with HER2-positive tumours, 123 (62%) of 199 patients achieved a pCR (ypT0 ypN0) with nab-paclitaxel compared with 106 (54%) of 197 patients with solvent-based paclitaxel (odds ratio, 1·39; 95% CI: 0·931 to 2·07; p=0.11). Adverse event data for the HER2-positive subpopulation are currently not available. Full details of the GeparSepto study are provided in Untch *et al.*[10] and in Appendix 3 of the CS. It is noteworthy that one of the ERGs clinical advisors notes that nab-paclitaxel is not approved in the EU for use in any breast cancer setting and is more expensive than docetaxel/paclitaxel which are generic. Moreover, nab-paclitaxel is only used in patients with intolerance to solvent based taxanes.

- *Cleveland Clinic Registry*

The aim of the Cleveland Clinic Registry was to evaluate the safety and efficacy of neoadjuvant docetaxel + carboplatin + trastuzumab + pertuzumab in women with HER2-positive non-metastatic breast cancer in a non-clinical setting. Data were obtained from a retrospective analysis of registry

data at a single centre in Cleveland, Ohio, USA. Total pCR rates were similar to TRYPHAENA; 53% of the 71 patients in the registry had a pCR (see CS, CS).

Adverse event data from the Cleveland Clinic retrospective analysis are summarised in Table 16. The results of this analysis were presented in a conference poster[32] and were described as a retrospective review of individual patient charts from 71 patients. Patients received neoadjuvant pertuzumab in combination with trastuzumab, carboplatin and docetaxel. Exact dosing of pertuzumab was unclear from the poster (where these results were presented) although it appears that patients received six cycles of treatment and 15 of 71 (21.4%) of patients required a dose reduction. No patients had symptomatic cardiac toxicity and only 4% of patients had asymptomatic reduction in LVEF>10%.[32] Toxicity was considered manageable and reported adverse events were similar to those reported in the NeoSphere and TRYPHAENA trials.

Table 16. Adverse event reporting from the Cleveland Clinic retrospective analysis (reproduced [with minor changes] from CS, Table 37, p131)

Adverse event	Grade severity (%)			
	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhoea	32.8	7.1	5.7	1.4
Fatigue	42.8	1.4	1.4	0
Myalgia	15.7	0	0	0
Neuropathy	17.1	7.1	2.8	0
Cytopenias	2.8	4.2	1.4	2.8
Nausea / vomiting	27.1	1.4	1.4	1.4
Rash	8.5	1.4	0	0

- *CLEOPATRA trial*[33-35]

The CLEOPATRA study was a pivotal Phase III randomised, double-blind, placebo-controlled trial designed to assess the safety and efficacy of pertuzumab in patients with HER2-positive metastatic breast cancer. A total of 808 patients were randomised in a 1:1 ratio to one of two treatment arms: pertuzumab (840mg loading dose, 420mg maintenance dose) in combination with trastuzumab (8mg/kg loading dose, 6mg/kg maintenance) and docetaxel (starting dose 75mg/m^2) or trastuzumab plus docetaxel. The primary endpoint of the study was PFS (defined as the time from randomisation to the first documented radiographic evidence of progressive disease) or death from any cause (within 18 weeks of last tumour assessment), whichever occurred first.

The CLEOPATRA trial provided safety data from 408 patients who were treated with pertuzumab in combination with trastuzumab and docetaxel in the metastatic breast cancer setting. The median number of pertuzumab treatment cycles was 24 (range: 1-96). The most common adverse events were

alopecia, diarrhoea, neutropenia, nausea and fatigue. Grade ≥ 3 adverse events included neutropenia, leucopenia, febrile neutropenia and diarrhoea. The overall incidence of serious adverse events was higher in the treatment arm containing pertuzumab (36.5%) than in the arm without it (29.3%). There was no significant increase in cardiac adverse events or left ventricular dysfunction in the patients receiving pertuzumab compared to the group not receiving pertuzumab and no evidence to suggest cumulative or late toxic effects. The safety profile seen in the CLEOPATRA study is in line with the safety findings observed in the NeoSphere and TRYPHAENA studies. Further details of the CLEOPATRA study can be found in the CS (see CS, Table 57 and Appendix 8).

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The company did not define a full *comparator decision set*. The CS argues that because the NeoSphere study included a comparator arm which they considered to be applicable to England, no indirect treatment comparison or network meta-analysis was required.

4.4 Critique of the indirect comparison and/or multiple treatment comparison

The CS did not include a standard pairwise meta-analysis or include a network meta-analysis (NMA) of potentially relevant treatments in the comparator decision set. The appropriateness of performing a standard pairwise meta-analysis and NMA was only considered by the company with respect to the relevance of including the TRYPHAENA and GeparSepto studies. In terms of TRYPHAENA, the company argued that the endpoints of interest in this submission were analysed as secondary endpoints in the study and were not appropriately powered to compare them. The ERG does not consider this to be sufficient justification for not making use of all available information and quantifying the extent of the uncertainty about treatment effects of interest. In terms of GeparSepto, the CS suggests that, although the study is ongoing, there is evidence on the effect of pCR for the HER2-positive subpopulation. However, the ERG notes that there is no common treatment arm in the NeoSphere, TRYPHAENA and GeparSepto studies hence the studies cannot be linked in a conventional NMA.

In their clarification questions to the company, the ERG suggested that other neoadjuvant treatments for HER2-positive breast cancer may be deemed to be valid comparators and asked the company to provide results of such an analysis and to provide comments on the NMA of comparative effectiveness of neoadjuvant therapy for HER2-positive breast cancer by Nagayama *et al*.[36] and its relevance to the current submission (question A12). Nagayama *et al*.[36] is a systematic review and NMA of neoadjuvant therapy for HER2-positive breast cancer patients. Ten studies were included in the analysis. Cytotoxic regimens were considered as a single group. The authors found that cytotoxic

regimens plus trastuzumab plus pertuzumab had the highest probability of being the most effective treatment in terms of pCR.

The company suggested that a NMA was not considered feasible and stated that "*The primary reason for this was the inability to group chemotherapy treatments to allow the formation of connected evidence networks… …The chemotherapy treatments that were not considered equivalent are as follows:*

- *paclitaxel 80 mg, 175 mg and 255 mg could not be considered equivalent*
- *docetaxel and paclitaxel could not be considered equivalent, at any dose*
- *all other chemotherapy treatments could not be considered as equivalent.*

Only docetaxel 75 mg and 100 mg could be considered equivalent"

It is generally accepted that grouping different treatments in a NMA is not a good thing to do. Where different treatments are associated with different treatment effects this may introduce heterogeneity which, in a NMA, can manifest itself as inconsistency between direct and indirect estimates of treatment effect. However, a consequence of not grouping the chemotherapy treatments is that the evidence presented within the CS about the effectiveness and cost-effectiveness of pertuzumab may be limited to those patients who would receive trastuzumab and docetaxel and may not be generalisable to those patients receiving trastuzumab and paclitaxel or other chemotherapy treatments. The company highlighted within their response that since pertuzumab is an add-on to trastuzumab, the combination of trastuzumab and docetaxel is considered an appropriate comparator. Whilst the ERG agrees that a trastuzumab-based regimen is an appropriate comparator because patients would need to be eligible for trastuzumab in order to receive pertuzumab according to its licensed indication, the additional treatment is unspecified within the licensing for pertuzumab. In response to a follow up clarification question around current neoadjuvant treatment in the UK, the company submitted data on file based upon their market research which suggested that an estimated 62% of patients receiving neoadjuvant treatment in 2015 had received trastuzumab and docetaxel, whilst an estimated 78% of patients had received trastuzumab plus any other treatment (such as paclitaxel or docetaxel). The clinical advisors for the ERG suggested that these other treatments are essentially comparable; however the company's response suggests that the evidence provided in the CS may not be generalised to those patients not receiving docetaxel.

It should be noted that the ERG had their own concerns with the NMA conducted by Nagayama *et al*.[36] In particular:

- the duration of the studies included in the NMA varied between 12 and 30 weeks with the duration of studies being said to be unreported,
- using an odds ratio as the measure of the treatment effect may be inappropriate if the response rate in each treatment group is expected to increase with longer follow-up,
- the Bayesian NMA is inadequately reported because it does not present the prior distributions that were used for the uncertain parameters nor does it describe how burn-in to the stationary posterior distributions was assessed,
- the reported results do not include the estimate and 95% credible internal for the between-study standard deviation or discuss the impact of any heterogeneity on the conclusions,
- inconsistency between direct and indirect estimates of treatment effects does not appear to have been assessed correctly; nevertheless, the authors claim that there was an inconsistency between the direct and indirect estimates of treatment effect for pCR but they do not discuss the implications of this on the conclusions.

Given the ERG's uncertainty with the assessment of inconsistency by Nagayama et al.,36 it would ideally suggest verifying the results in a reanalysis. If inconsistencies between direct and indirect estimates were found, this could be explored, and ideally dealt with, through potential treatment effect modifiers. If it is possible to explain the inconsistencies, then the analysis could report the extent of the between-study heterogeneity which would quantify and incorporate an element of potential differences in treatment effect arising from different chemotherapies; inferences and uncertainty about inputs to the economic model would be based on the predictive distribution of effect in a new study. The ERG was unable to undertake this analysis within the timeframe of the STA.

4.5 Additional work on clinical effectiveness undertaken by the ERG

The ERG did not undertake any additional work to assess the clinical effectiveness of neoadjuvant pertuzumab.

4.6 Conclusions of the clinical effectiveness section

The main supporting evidence was derived from two Phase II, company-sponsored, multi-country, multi-centre, randomised, open-label, active controlled trials assessing the efficacy and safety of neoadjuvant pertuzumab in combination with trastuzumab and chemotherapy in people with operable, locally advanced or inflammatory centrally confirmed HER2-positive breast cancer (primary tumours >2 cm in diameter).

In general, the bpCR rate (trial definition of pCR) in the NeoSphere study[4] (which used a median of 4 pertuzumab cycles in each of the four treatment arms [data from Arm C and Arm D are not relevant to

this appraisal as they are not part of the licence indication for neoadjuvant pertuzumab] was statistically significantly higher in Arm B (combination of pertuzumab, trastuzumab and docetaxel) at 45.8% compared with Arm A (combination of trastuzumab plus docetaxel) at 29.0%, with a difference of 16.8% (p=0.0141). The rate of tpCR (EMA and FDA preferred pCR definition) was also higher in Arm B (Arm B, 39.3% versus Arm A, 21.5%; difference of 17.8%, p=0.0063). Comparable results were also observed using other pCR definitions. In the TRYPHAENA study,[5] (which used a median of 3 to 6 cycles across the three pertuzumab containing arms), bpCR and tpCR were consistently high and similar across all pertuzumab treatment groups (approximately 60%). Despite these favourable findings, the ERG notes the validity of pCR as a surrogate endpoint for long-term outcomes is uncertain (see section 4.6.3). Although the NeoSphere study was not powered to assess long-term outcomes (thus data should be treated with caution), 5-year PFS data were 86% for Arm B (95% CI: 77 to 91) compared with 81% (95% CI: 71 to 87) for Arm A. The hazard ratio for PFS for Arm B versus Arm A was 0.69 (95% CI: 0.34 to 1.40; p= not reported). The 5-year DFS data were 84% and 81% in Arms B and A, respectively (hazard ratio, 0.60; 95% CI: 0.28 to 1.27; p= not reported). In the TRYPHAENA study, DFS data were not sufficiently mature at the time at which the CS was submitted. Data relating to HRQoL were not collected in either study.

During the neoadjuvant period of the NeoSphere (<3% across all arms) and TRYPHAENA studies (<8% across all arms), adverse events leading to treatment discontinuation were generally low. In the neoadjuvant phase of the NeoSphere study, grade ≥3 neutropenia was numerically higher in patients who received docetaxel (Arm A, 57.0%; Arm B, 44.9%; Arm D, 55.3%) than in patients who did not receive docetaxel (Arm C, 1%). The other most common grade ≥3 adverse events were febrile neutropenia (range 7.4% to 8.4% in docetaxel arms and none in the arm without docetaxel) and leucopenia (range 5% to 12% in the docetaxel arms and none in the arm without docetaxel). In the TRYPHAENA study, similar incidences of grade ≥3 adverse events were observed (neutropenia, range 46.1% to 47.2%; febrile neutropenia, range 9.3% to 18.1%; leucopenia, range 11.8% to 19.4%). In the NEOSPHERE study, the number of patients with cardiac dysfunction adverse events was low in all trial arms; this was highest in Arm B (3% to 6% across the treatment periods). Similarly, in the TRYPHAENA study, incidence of symptomatic LVSD and significant declines in LVEF (≥10% points from baseline to <50%) were low across all trial arms but highest in Arm B (1.3% to 12.3% across the treatment periods). Additional supporting safety evidence from a retrospective analysis of data from the Cleveland Clinic registry[32] and from a large Phase III CLEOPATRA study,[34, 35] suggest that adverse events were similar to those reported in the NeoSphere and TRYPHAENA trials. In addition, as noted in the EPAR,[19] there is currently no indication of any concerning differences in tolerability associated with adding pertuzumab to trastuzumab and anthracyclines or carboplatin in the neoadjuvant period.

4.6.1 Completeness of the CS with regard to relevant clinical studies and relevant data within those studies

The clinical evidence in the CS is based on a systematic review of pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer. The ERG is confident that all relevant controlled trials (published and unpublished) were included in the CS, including data from ongoing/planned studies. However, the ERG is not confident that all relevant non-randomised and non-controlled studies have been identified and included in the CS, as details of the systematic review process (e.g. identification, selection, data extraction, quality assessment and analysis and interpretation) were lacking in the CS.

4.6.2 Interpretation of treatment effects reported in the CS in relation to relevant population, interventions, comparator and outcomes

The evidence submitted in the CS included two pivotal studies trials - the NeoSphere trial (a Phase II proof of concept study)[4] and the TRYPHAENA study (a Phase II trial, designed primarily to assess cardiac safety),[5] which formed the basis of the EMA's regulatory approval[19] for the use of pertuzumab in combination with trastuzumab and chemotherapy for the neoadjuvant treatment of adult patients with HER2-positive early breast cancer.

A key issue that may limit the robustness of the efficacy and safety data reported in the CS relates to the design of NeoSphere and the TRYPHAENA trials, both of which were open-label active controlled trials.[4, 5] Double blinding protects against performance bias and measurement bias[16] and its absence in RCTs tends to result in larger treatment effects.[17] With many cytotoxic cancer drugs, the nature of the interventions precludes blinding (i.e. drug toxicities or manner of administration) for the practical and ethical reason that informed dose monitoring and adjustment is required. Although it is almost universally absent from oncology trials, blinded outcome assessment can enhance bias reduction.[18] As noted in the EPAR,[19] most pathologists were not aware of the patient's treatment allocation thus the likelihood of biased reviews of pathology slides/specimens in these trials was considered by the EMA[19] to be minimal.

In the final NICE scope, the comparator was defined as standard neoadjuvant therapy. In the CS, the comparator was defined as neoadjuvant trastuzumab in combination with chemotherapy. The only arm within the reported clinical trials that does not include pertuzumab, consists of treatment with FEC, trastuzumab and docetaxel. Other neoadjuvant therapies may be used in practice and these are likely to be less effective (and less costly) than trastuzumab. Since these have not been considered in the CS, this assessment is limited to those patients who will receive trastuzumab as neoadjuvant therapy.

Another issue that may limit the robustness of the efficacy evidence relates to PFS, DFS or OS data between treatment arms in the NeoSphere study. These endpoints were not designed or powered to test formal hypotheses. Similarly, the NeoSphere trial was not powered to determine the predictive role of pCR according to hormone receptor status or breast cancer type. Moreover, OS was not a protocol-defined secondary efficacy endpoint in the NeoSphere trial, and thus survival status was not systematically reported beyond progressive disease, disease recurrence or withdrawal.[4] As a result, these data should be treated with caution.

4.6.3 Uncertainties surrounding the reliability of the clinical effectiveness evidence

The key uncertainties in the evidence base relate to the use of pCR as a surrogate endpoint for survival outcomes in the neoadjuvant treatment of breast cancer, the lack of high quality phase III RCTs in this patient population, and the generalisability of the trial results to England and Wales.

- *Use of pCR as a surrogate endpoint*

Pertuzumab in combination with trastuzumab and chemotherapy is a licensed drug approved by the EMA (and the FDA) for neoadjuvant treatment of breast cancer. Approval was granted based on the acceptance that pCR was an acceptable surrogate efficacy endpoint for long-term outcomes in neoadjuvant studies, which can help to expedite the approval of neoadjuvant systemic treatment for high-risk, early breast cancer patients.[13, 19] This link was based on a meta-analysis by Cortazar *et al.*[27] that found that patients who achieved tpCR had longer survival than patients who did not achieve tpCR at the patient level. However, Cortazar *et al.*[27] were unable to demonstrate a relationship between the effect of treatment on tpCR (estimated using an odds ratio) and the effect of treatment on EFS and OS (estimated using a hazard ratio) at the study level. Due to a lack of correlation with outcomes (such as EFS) at both the individual and the trial levels, there is some controversy regarding the acceptability of pCR as a surrogate marker in this study population.[28] Therefore, the predictive value of pCR for estimating the long-term survival benefit in the target patient population is highly uncertain.

- *Lack of high quality Phase III RCTs and head-to-head trials*

Although there is no high quality evidence from prospective, Phase III controlled trials, data from a post-authorisation efficacy trial, APHINITY,[**14**] is expected to help to address this concern. This study is an ongoing randomised, multicentre, double-blind, placebo-controlled study comparing pertuzumab in combination with trastuzumab and chemotherapy with trastuzumab, chemotherapy and placebo as adjuvant therapy in patients with operable HER2-positive primary breast cancer. However, it is due for completion in December 2023 with a primary analysis expected to take place in 2016. The final

clinical study report is expected in May 2017.[3] In addition, there is an absence of head-to-head trials of pertuzumab containing regimens compared with other neoadjuvant therapies that are currently used in the UK.

- *Generalisability to England*

In the UK, FEC-T is the most common chemotherapy regimen administered with trastuzumab as part of a neoadjuvant breast cancer treatment regimen. However, in the pivotal NeoSphere study the FEC component was administered as an adjuvant treatment. The meta-analysis by Mauri *et al*.[22] found no evidence of a significant difference between adjuvant and neoadjuvant treatment, although differences of up to 12% could not be ruled out. Although there is some uncertainty as to whether or not the use of FEC in the neoadjuvant setting is equivalent to the use of FEC in the adjuvant setting with regard to outcomes, one of the ERGs clinical advisors and the CS suggest that this difference is not expected to impact the results. In addition, only a few centres from the UK were included within the pivotal studies.

5. COST EFFECTIVENESS

This chapter presents a review of evidence relating to the cost-effectiveness of pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer. Section 5.1 presents a critique of the company's systematic review and Section 5.2 provides a summary and critique of the company's submitted economic evaluation. Section 5.3 presents the ERG's suggested base case and the additional sensitivity analyses undertaken by the ERG. Finally, Section 5.4 provides the conclusions of the cost-effectiveness section.

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

5.1.1 Searches for economic studies

The searches undertaken for the published economic studies were conducted in November 2015. Several electronic bibliographic databases (MEDLINE, MEDLINE in Process, EMBASE, EconLit and NHS EED) were searched from inception; however, searches were restricted to English language studies (the CS did not provide any justifications for using this limit). Published filters were adapted and applied for the MEDLINE and EMBASE searches; the ERG notes that any changes made to a published filters risks reducing its proven effectiveness. All database searches undertaken by the company are reported in detail; however, the ERG notes that for these searches a substantively different approach was taken to defining the population (breast cancer) compared with the clinical effectiveness searches; the cost-effectiveness searches were narrowed by including the concept of neoadjuvant treatment. Whilst the company argues that it was necessary to focus the reviews on neoadjuvant rather than other stages of treatment, the methods used appear to be less than comprehensive. Although some of the appropriate subject headings were used, in EMBASE "adjuvant therapy/" was not exploded to include the narrower heading "cancer adjuvant therapy/". The free text searches only covered titles and abstracts and used a highly restrictive search string "((neoadjuvant or neo adjuvant) adj2 (treatment or therap*).ti,ab.". This would not find other variant phrases such as "neoadjuvant chemotherapy". In addition, the operator "adj2" seems excessively precise.

There are several inconsistencies between the searches applied in the different databases. Whilst it is often sensible to modify search strategies, the reasons for doing this in the CS are sometimes unclear. For example, in the EMBASE search (but not those for other databases) many of the Emtree headings included have been "focussed" (i.e. results would only be found if the heading selected was one of the major headings for the article). This is a risky strategy as a "major heading" status is only usually given where a concept occurs prominently in the title or abstract (fields which have already been searched). To search for a term in titles and abstracts but then ignore records where it is a minor heading seems somewhat inconsistent. It would also have been advisable to explode more of the

headings which were included; for example, "breast cancer/" could have been exploded to include narrower headings such as "breast carcinoma/" and "inflammatory breast cancer/", or the broader heading "breast tumor" might have been used in its exploded form (as was done for the clinical effectiveness search).

In line 18 of the MEDLINE search, rather than using the MeSH heading "Decision Trees/", the company have selected the subheading "Decision Trees/ec", which has only found 1 study, whereas the EMBASE search used the subject heading "decision tree/", and found 7,115 results. Since an estimated 50% of articles are inadequately or incorrectly indexed by subheading,[37] it is inadvisable to use subheadings instead of the full MeSH heading.

There is a significant logic error common to both the EMBASE searches (for evidence relating to cost & resource use and HRQoL) at line 6, where lines "3 or 4" are combined rather than lines "4 or 5". Whilst the company stated within the clarification letter that correcting this error produced a net decrease in the final number of cost-effectiveness articles, and an increase of only 321 results in the HRQoL search (none of which met their inclusion criteria), the ERG observes that the impact would have been greater had the searches been run in accordance with the other recommendations of the ERG. The ERG re-ran the EMBASE CEA and cost/resource use strategy with all the amendments suggested above (on 28th January 2016) and found significantly more results (n=1,708).

5.1.2 Inclusion/ exclusion criteria

The company stated (see CS, Table 68) that their intention was to identify all previously published full economic evaluations of adjuvant and neoadjuvant therapies in adults with HER2-positive, locally advance, inflammatory, or early stage breast cancer. However, the search strategy provided in Appendix 9 of the CS included only economic analyses of neoadjuvant therapies. Nevertheless, the ERG considers this to be appropriate.

5.1.3 Included economic studies

The company's economic review identified only one study by Attard *et al*.[38] As described in Section 5.1.1, other relevant economic studies may not have been identified. Also, there is a lack of detail in the reporting of the results of the review. There is no description of the eight studies that were excluded at the full text sifting stage. In addition, the CS provides very little description or interpretation of the economic evidence. Whilst a summary of some of the key aspects of the economic analysis of Attard *et al*.[38] was tabulated by the company (Table 70, CS), there is no description of the model (e.g. methods used to extrapolate trial outcomes), and no discussion of the model/data limitations or the implications of the economic analysis for the company's *de novo* model.

Given that the company did not provided a detailed discussion of the study in their submission; the ERG provides a brief summary of Attard *et al*.[38] below.

Attard *et al*.[38] performed a cost-effectiveness analysis of neoadjuvant pertuzumab and trastuzumab therapy for locally advanced, inflammatory, or early HER2-positive breast cancer, from the perspective of the Canadian healthcare payer, using a 28-year time horizon. A three state Markov model ('event-free', 'relapsed', and 'dead') was developed. Published EFS and OS data for patients who achieved/ did not achieve pCR based on Kim *et al*.[39] were used in combination with the percentage achieving pCR in the pertuzumab trials to estimate survival. The modelled costs included costs of drugs, treatment administration, management of adverse events, supportive care, and subsequent therapy. Utility values were sourced from published literature. Two separate analyses were conducted based on the pCR data from the NeoSphere and TRYPHAENA trials. The incremental cost per QALY (in Canadian $) ranged from $25,388 (NeoSphere analysis) to $46,196 (TRYPHAENA analysis).

The EFS and OS for each treatment arm were modelled by multiplying the survival curves for patients with pCR and no pCR, extrapolated from Kim *et al*.[39], by the proportion of patients achieving a pCR and no pCR in the respective arms. Kim *et al*.[39] analysed survival outcomes for patients achieving pCR (n = 114) or not (n = 115) over a median follow-up of 63 (range 53–77) months. Data from Kim *et al*.[39] were digitised and parametric survivor functions were chosen based on how well they fitted the Kaplan-Meier curves. Proportional hazards were assumed and the published hazard ratios for EFS (4.09; 95% CI: 1.67 to 10.04) and OS (4.15; 95% CI: 1.39 to 12.38) from Kim *et al*.[39] were applied to the survival functions of the pCR curve to generate the survival functions of the no pCR curve. There was a lack of detail provided about the methods used for extrapolation of EFS and OS. No detail was provided about whether the fit was assessed visually or using formal goodness of fit statistics. Also, it is unclear whether the appropriateness of the proportional hazards assumption was explored (e.g. looking at the log cumulative hazard plots). General population mortality rates were used for surviving patients after ten years, thereby assuming cure i.e. after 10 years patients were assumed not to experience disease-related progression or relapse.

The utility values in the model are estimated by applying multipliers to Canadian age- and sex-matched general population utilities. The multipliers for the event-free state were based on data from Hedden *et al*.[40] however, these appear to be implausibly high (0.97 for event-free year 1 and 0.99 for event-free, year 2 onwards). The utility multiplier for the relapsed state (0.68) was calculated as a weighted average, assuming that 25% of relapsed patients have a local recurrence and 75% have

metastatic disease, with the utility multipliers of 0.65 and 0.75 respectively, based on Hedden *et al*.[40] This model did not include utility decrements for adverse events.

The model reported by Attard *et al*.[38] is broadly similar to the company's submitted model. Whilst the cost and utility data are different (and specific to Canada), a similar methodology for extrapolating trial outcomes based on pCR data was used. The results of the Attard *et al*.[38] study, which was funded by Roche, are similar to those generated using the company's model (0.31 incremental QALYs in Attard *et al*.[38] compared with 0.26 QALYs in company's model).

As part of the clarification process for this appraisal, the ERG asked the company to provide a critical review of the Attard *et al*.[38] study. In response to this request (question B4), the company noted the following limitations of the Attard *et al*. study:[38]

a) *The data were derived from a single centre,*
b) *The number of patients with HER2-positive breast cancer was very low (n=229)*
c) *No long-term data are reported for patients treated with neoadjuvant pertuzumab.*
d) *The publication by Kim et al.[39] does not present the number of patients at risk over time, therefore more assumptions are required to run the algorithm by Guyot et al.[41] (an algorithm that maps digitised curves back to Kaplan-Meier data by finding numerical solutions to the inverted Kaplan-Meier equations, using information on number of events and numbers at risk where available) leading to potentially less robust results.*

It should be noted that limitations (a) to (c) are also applicable to the company's submitted model.

5.2 Summary and critique of company's submitted economic evaluation by the ERG

As part of their submission to NICE, the company submitted a cohort state transition model implemented in Microsoft Excel® together with a detailed description of the economic analysis.

Overview of model

A six state transition model including (i) event-free; (ii) locoregional recurrence; (iii) remission; (iv) metastatic not-progressed; (v) metastatic progressed, and; (vi) death states was constructed, using a monthly time cycle and a 50-year time horizon (see Section 5.2.2 for more details). The model compares neoadjuvant pertuzumab in combination with trastuzumab and docetaxel with neoadjuvant trastuzumab and docetaxel for adults with HER2-positive, locally advanced, inflammatory, or early stage breast cancer, from a NHS and PSS perspective (see Sections 5.2.3 to 5.2.5 for more details and critique). The EFS for each treatment arm was modelled by multiplying the EFS curves for patients with pCR and no pCR extrapolated from the CTNeoBC meta-analysis[27], by the proportions of patients experiencing pCR and no pCR in the respective arms. The transitions from event-free state to other

states were based on transition probabilities extracted from the NeoSphere trial[4] and other published sources. The patients who are event free after seven years from treatment initiation are assumed to be cured, with only the risk of general population mortality (treatment effectiveness and extrapolation is described and critiqued in Section 5.2.6). Utilities and costs for each health state are based on published sources (described and critiqued in Sections 5.2.7 and 5.2.8 respectively).

The model was generally well developed with few errors and the company's cost-effectiveness section was well described. However, there are some issues with the company's economic analysis, as described in the sections below.

Methods for ERG critique

The ERG employed a number of approaches to explore, interrogate and critically appraise the company's submitted economic evaluation and the underlying health economic model upon which this was based. These included:

- Examination of correspondence between the description of the model reported within the CS and the executable model.
- Scrutiny of the company's model by health economic modellers and discussion of issues identified amongst the members of the ERG.
- The use of extreme values (e.g. zero for utilities/costs) to check for errors in the programming and logic of the model
- The use of expert clinical input to judge the clinical credibility of the company's economic evaluation and assumptions underlying the company's model.
- Comparison of the EFS estimated from the model to published EFS outcomes from Cortazar *et al*.[42] to check for their appropriateness.

5.2.1 NICE reference case checklist

The company's economic evaluation generally follows the NICE Reference Case, although not all relevant comparators are included within the economic evaluation, as shown in Table 17.

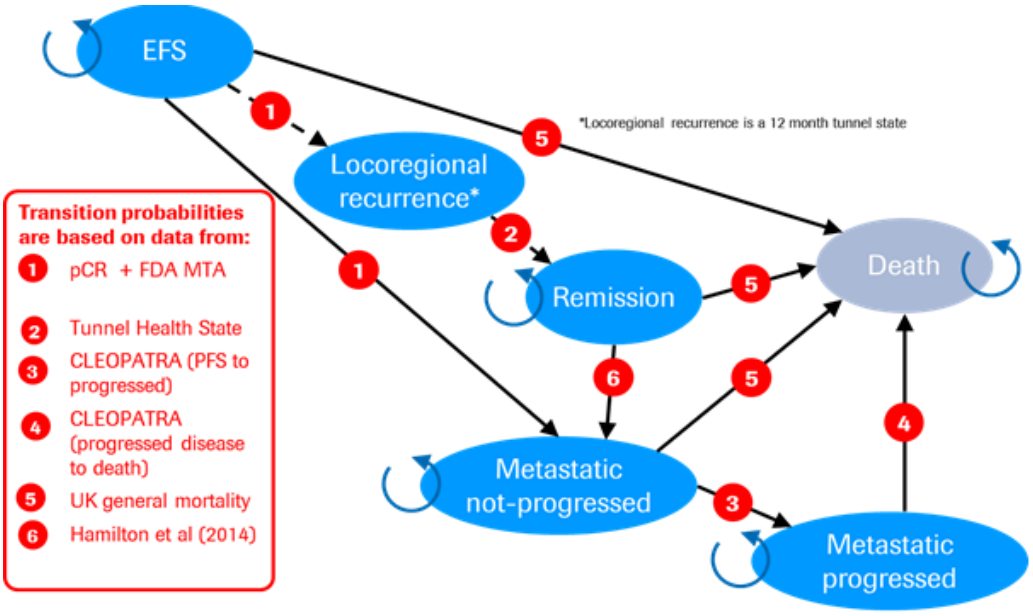
Table 17. Adherence of the CS to the NICE Reference Case

Element of health technology assessment	**Reference Case**	**Does the submission adequately address the Reference Case?**
Defining the decision problem	The scope developed by the Institute	Not all relevant comparators are included (see Sections 3.3, 4.4 and 5.2.4)
Comparator	Therapies routinely used in the National Health Service (NHS), including technologies regarded as current best practice	
Perspective on costs	NHS and Personal Social Service (PSS)	Yes
Perspective on outcomes	All health effects on individuals	Yes
Type of economic evaluation	Cost-effectiveness analysis	Yes
Synthesis of evidence on outcomes	Based on a systematic review	Yes, but the reviewing methods may be flawed (see Section 4.1.2) and there is no NMA (see Section 4.4). The treatment effect is modelled using pCR which is a surrogate endpoint.
Measure of health effects	QALYs	Yes
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	Yes
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	Yes
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes

5.2.2 Model structure

The company's model includes six health states: (i) event-free; (ii) locoregional recurrence; (iii) remission; (iv) metastatic not-progressed; (v) metastatic progressed, and; (vi) death. The possible transitions between modelled health states are shown in Figure 4. A monthly time cycle is used.

Figure 4. Model structure (reproduced from CS, Figure 22, p197)



Patients in the event-free state can transit to locoregional recurrence, the metastatic not-progressed state or death. Patients spend 12 months in locoregional recurrence (which is modelled as a tunnel state without the possibility of transitioning to death), after which they transition to the remission state. Patients in the remission state can transition to the metastatic not-progressed state or death. Patients in the metastatic not-progressed state can transition to the metastatic progressed state or death. Patients in the metastatic progressed state can transition only to death.

5.2.3 Population

The population within the model is adults with HER2-positive, locally advanced, inflammatory, or early stage breast cancer who have not previously received chemotherapy or HER2-directed treatment for their disease. This is consistent with the final NICE scope.[43] The patients simulated in the model were assumed to be aged 50 years at the first cycle, based on the median age of the patients in the NeoSphere trial[4].

5.2.4 Interventions and comparators

The CS assessed the intervention pertuzumab in combination with trastuzumab and docetaxel with the comparator trastuzumab and docetaxel in the neoadjuvant setting. The NICE scope specified the comparator as standard neoadjuvant therapy, which the company defined as trastuzumab and docetaxel in their submission. However, clinical advice to the ERG suggested that whilst most patients in England currently receive FEC followed by trastuzumab and docetaxel, other neoadjuvant therapies are also in use. This is acknowledged in the CS (p13), which states that 25% of HER2-positive breast cancer patients who would receive neoadjuvant treatment in England may not receive trastuzumab. The market research data provided by the company as part of an additional clarification question response (company data on file) suggests that 22% of these patients in the UK receive non-trastuzumab based interventions, which include: Docetaxel+/- anthracycline; Paclitaxel+/- anthracycline; Paclitaxel protein-bound+/- anthracycline; Anthracycline; and other treatments. These treatments are likely to be less effective and less costly than trastuzumab based treatments. The cost-effectiveness of pertuzumab is therefore assessed only in a population of patients for whom trastuzumab would be provided as neoadjuvant therapy. In response to a request for clarification from the ERG (question B5), the company acknowledged that the relevant patient population for pertuzumab is equivalent to that of the patient population eligible for neoadjuvant trastuzumab, given that the marketing authorisation for pertuzumab requires that it is given in combination with trastuzumab and chemotherapy.

However, it should also be noted that the market research data suggested that trastuzumab plus docetaxel (with or without anthracyclines), is used in only 62% of patients eligible for neoadjuvant therapy. The company suggested within the clarification response (question A12) that docetaxel is not comparable to paclitaxel or other chemotherapies (see Section 4.4). The extent of which the outcomes of this analysis can be generalised to patients who do not receive docetaxel in addition to trastuzumab is therefore unclear.

5.2.5 Perspective, time horizon and discounting

The economic analysis undertaken by the company adopts a NHS and PSS perspective; this is in line with the NICE Reference Case. Patients are followed over 50 years within the company's base case (effectively a lifetime horizon). By the end of the 50 year time horizon, more than 99% of modelled patients have died. In line with the NICE Reference Case, costs and health outcomes are discounted at 3.5% per annum.

5.2.6 Treatment effectiveness and extrapolation

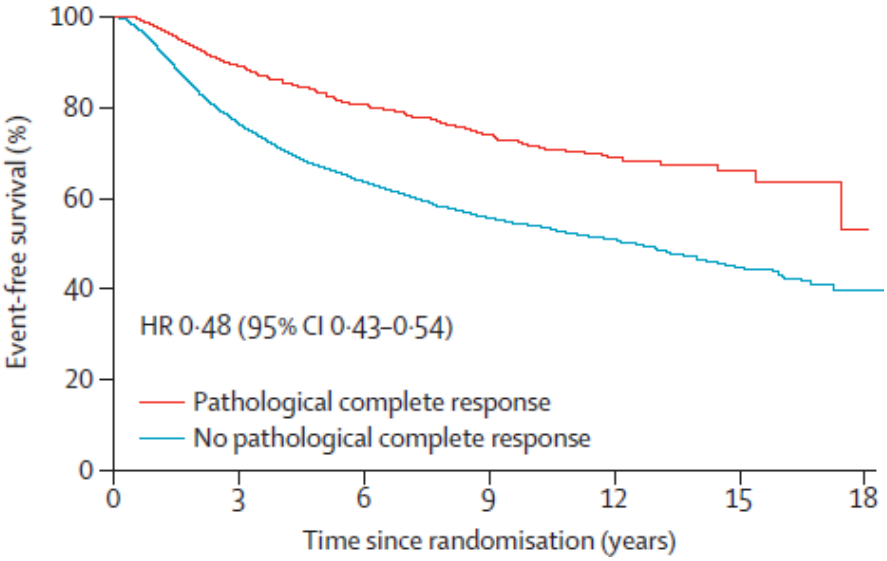
5.2.6.1 Event free survival

Although the company use the term DFS within the clinical effective section of the CS, they use EFS within the cost-effectiveness section. The ERG believes that the company's intention is that these terms be considered synonymous, reflecting the same clinical endpoint (see Section 3.4).

The company used data from the CTNeoBC meta-analysis[27] for the extrapolation of EFS for patients with pCR and no pCR, and the EFS for each arm was weighted using the proportion of patients experiencing pCR and no pCR from Arm A (pertuzumab, trastuzumab and docetaxel) and Arm B (trastuzumab and docetaxel) from the Neosphere trial.[4] The company digitised the EFS Kaplan-Meier data from the CTNeoBC meta-analysis using Grafula 3 (version 2.10) and used it to replicate the individual patient data (IPD) for patients achieving pCR or not achieving pCR patients, using the algorithm reported by Guyot *et al*.[41]

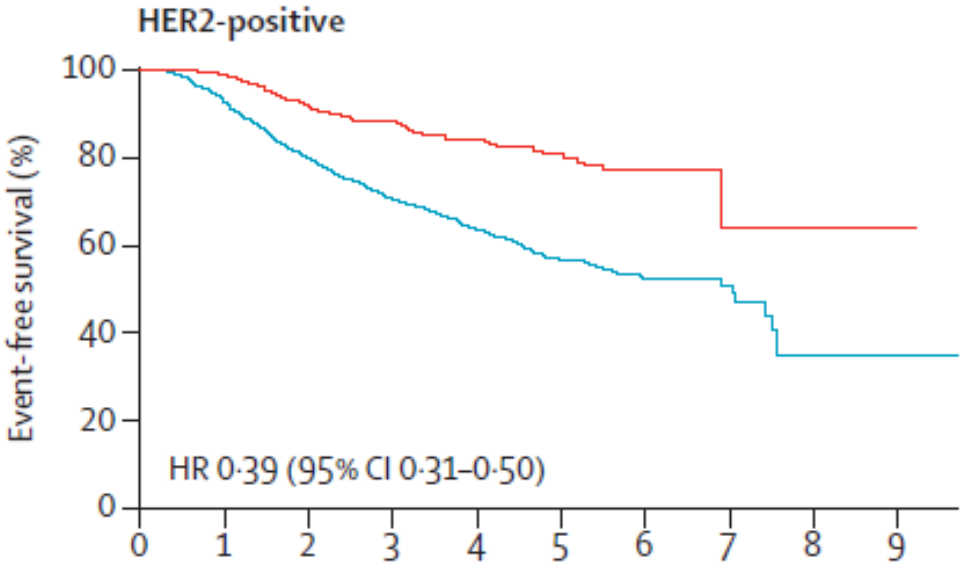
It is unclear from the CS whether the company had planned to use the EFS data from the CTNeoBC meta-analysis for all breast cancer patients or for the HER2-positive subgroup. In the model, the company appear to have used the data from all breast cancer patients up until around 9 years (the length of follow up available for the HER2-positive subgroup, rather than the 18 year follow up available for all breast cancer patients), alongside the numbers at risk from the HER2-positive subgroup. The ERG believes that this was done in error by the company. In order to illustrate this issue, Figures 5 and 6 show the CTNeoBC EFS Kaplan-Meier functions and numbers at risk for all breast cancer patients and for the HER2-positive subgroup, respectively. The ERG has digitised these curves from the CTNeoBC meta-analysis for all breast cancer patients and the HER2-positive subgroup, and combined them with the Kaplan-Meier curves digitised by the company, shown in Figure 7.

Figure 5. **Kaplan-Meier plot of association between tpCR and EFS for all breast cancer patients (reproduced from Cortazar *et al.*[42])**



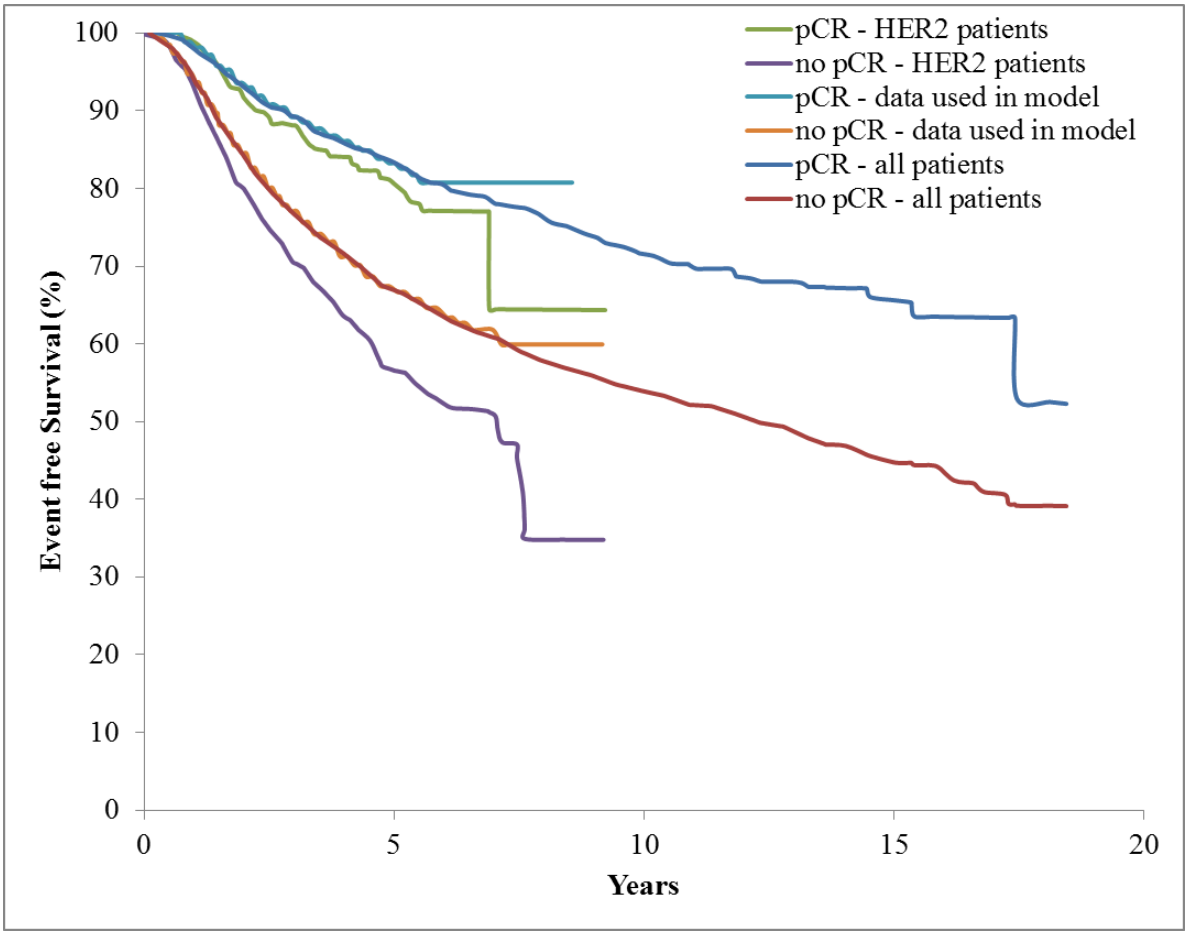
n at risk							
tpCR	2,131	1,513	583	337	124	35	2
no tpCR	9,824	6,169	2,674	1,523	525	165	1

Figure 6. **Kaplan-Meier plot of association between tpCR and EFS for the HER2-positive subgroup (reproduced from Cortazar *et al.*[42])**



n at risk										
tpCR	586	527	454	371	212	120	37	4	2	1
no tpCR	1403	1157	918	713	436	269	106	33	3	1

Figure 7. Comparison of the company's digitised curves with the CTNeoBC meta-analysis curves digitised by the ERG



The company fitted a number of parametric functions (exponential, Weibull, log logistic, log normal, Gompertz and Generalised gamma) to the replicated IPD data, and assessed the best fit using visual inspection and Akaike information criterion (AIC)/ Bayesian information criterion (BIC) statistics. In the base case analysis, the company used gamma distributions for patients achieving pCR and for patients not achieving pCR. The impact of using alternative parametric curves on the cost-effectiveness of pertuzumab was explored in the company's sensitivity analysis. The Gompertz distribution was not analysed or presented in the CS. When queried as part of the clarification response (question B7), the company provided the explanation that *"a negative scale parameter was estimated for the Gompertz scale for EFS no pCR. This non-sensible value suggests that the model did not converge and was therefore excluded from the analysis."*

The proportions of patients who achieved pCR in each arm were based on the NeoSphere trial (data cut-off at surgery or withdrawal), as presented in Table 18. These values were used in the model to weight the parametric EFS curves for those patients achieving pCR and for those not achieving pCR to estimate the overall EFS distribution for the intervention and comparator arms.

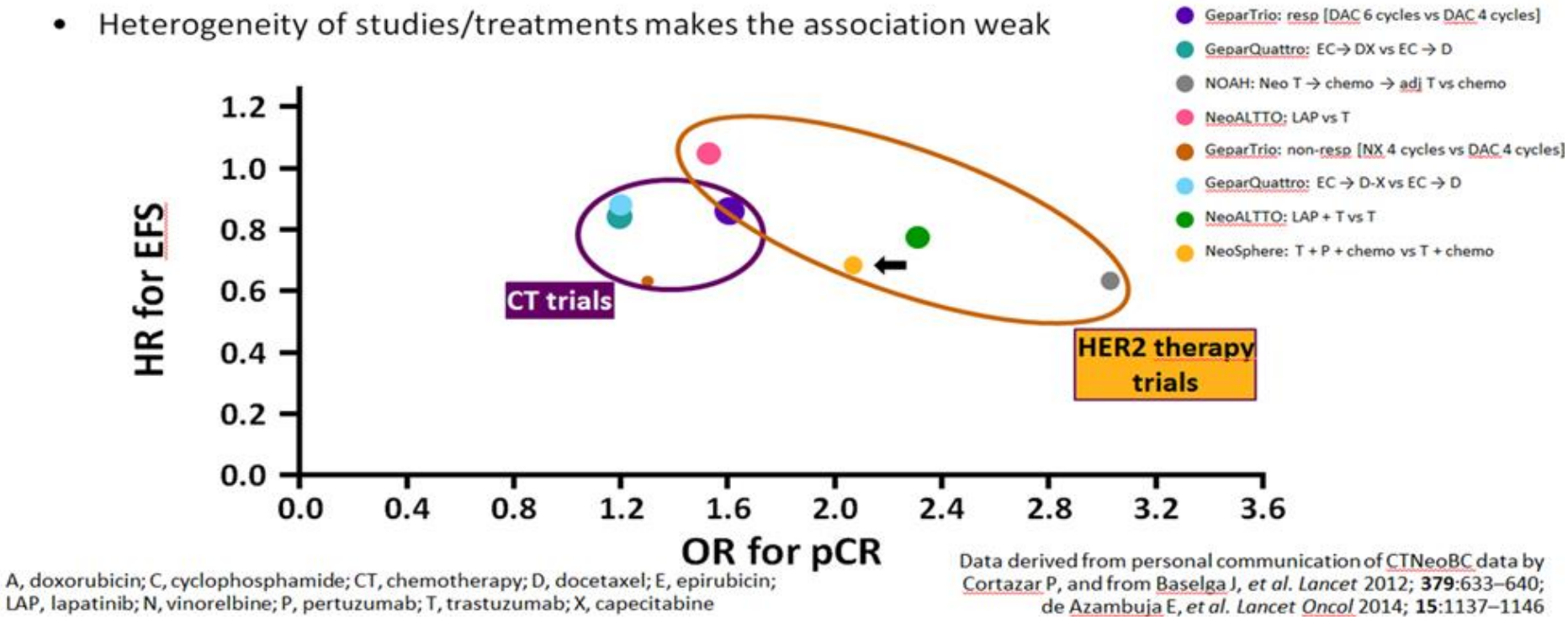
Table 18. tpCR rates from NeoSphere (reproduced from CS Table 72, p201)

	Trastuzumab + docetaxel tpCR (95% CI)	Pertuzumab + Trastuzumab + docetaxel tpCR (95 % CI)
NeoSphere	21.5% (CI: 14.1 to 30.5)	39.3% (CI: 30.0 to 49.2)

Although pCR has been used as a surrogate outcome for regulatory approval, the ERG has concerns about the use of pCR as a predictor of EFS. The CTNeoBC analyses found a correlation between pCR and EFS at the individual level, but could not validate pCR as a surrogate endpoint for improved EFS at the trial-level. The relationship is assumed to be the same for all treatments, including pertuzumab (see Section 4.2.4.1 for a detailed discussion of the use of this surrogate outcome).

As part of the clarification process (question B9), the ERG requested that the company provide an assessment of the relationship between tpCR and EFS within the NeoSphere study, including a commentary on how this relationship compares with that observed in the CTneoBC group meta-analysis. The company responded that "*HER2-positive targeted trials (NeoALLTO and NeoSphere) were not included in the meta-analysis by CTNeoBC and if these two trials were added and the analysis was restricted to HER2-positive targeted therapies only, a substantially stronger association between pCR (odds ratio) versus EFS (hazard ratio) compared to non-targeted treatments would be shown. See Figure [8] below:*[31]"

Figure 8. Trial-level associations between effect of chemotherapy and chemotherapy plus HER2-directed therapies on pCR and EFS (replicated from clarification letter, question B9)



A, doxorubicin; C, cyclophosphamide; CT, chemotherapy; D, docetaxel; E, epirubicin; LAP, lapatinib; N, vinorelbine; P, pertuzumab; T, trastuzumab; X, capecitabine

Data derived from personal communication of CTNeoBC data by Cortazar P, and from Baselga J, *et al. Lancet* 2012; **379**:633–640; de Azambuja E, *et al. Lancet Oncol* 2014; **15**:1137–1146

In addition, as part of a response to a clarification question (question B7), the company provided a table of the strengths and weaknesses of the use of pCR as a surrogate outcome versus the use of EFS directly from the NeoSphere trial to model EFS. This is replicated in Table 19 below. Given the data available, the ERG also prefers the use of pCR as a surrogate outcome due to the low number of patients progressing in both arms of the trial.

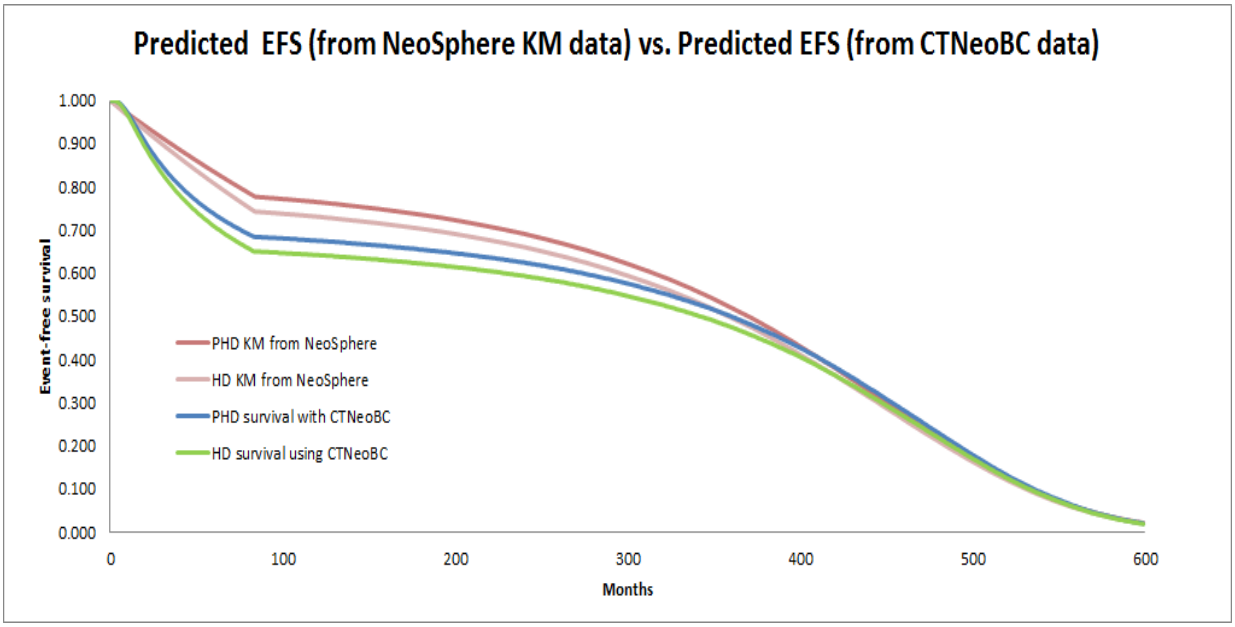
Table 19. Strengths and weaknesses of methods to estimate EFS (replicated from clarification response, Table 6)

	Use of tpCR surrogate outcome and CTNeoBC analysis	**Use of EFS from NeoSphere**
Is trial data from NeoSphere used?	Yes, but CTNeoBC analysis is also required	Yes, used directly
Do the results use valid endpoint from the trial?	tpCR is the secondary endpoint in NeoSphere. EFS is a primary endpoint in CTNeoBC analysis.	EFS is a secondary endpoint. This endpoint is an exploratory analysis and was not powered to test for formal hypotheses of efficacy.
How reliable is the data source?	FDA data includes a large number of events and is more mature	Data includes a small number of events and is less mature.
Are any assumptions required to predicted EFS?	Assumption required about the link between tpCR and EFS	No assumption required, EFS data is used directly from trial
How long is the follow-up?	Follow up is between 5.4 and 6.6 years for no tpCR and tpCR arm respectively	5 years

Given the concerns with the surrogate outcome, the ERG asked the company to provide a graph comparing the EFS outcomes from the NeoSphere trial with the model-predicted EFS (question B6). The ERG also requested that the company use the Kaplan-Meier curves from the trial in the model directly within an additional analysis, fitting appropriate parametric distributions to the Kaplan-Meier data for each arm (question B7). The company performed these analyses using piecewise exponential parametric functions to predict EFS (see Section 5.2.10) and presented a comparison of the predicted piecewise exponential fit of NeoSphere EFS survival vs. the predicted NeoSphere EFS survival from CTNeoBC analysis, replicated in Figure 9 below. The company did not include the original Kaplan-Meier curves from the trial within their figure, but the comparison presented by the company showed

that the model substantially over-predicts EFS outcomes in both arms compared to the CTNeoBC analysis.

Figure 9. Predicted EFS using the EFS data directly and the pCR surrogate (reproduced from company's clarification response, Figure 1, p19)



Within the model it was assumed that the treatment effect persists for seven years. The company also assumed that after seven years from treatment initiation, patients who have not experienced locoregional or metastatic recurrence are assumed to be cured, with only the risk of general population mortality. The justification for selecting this cut-off point is unclear from the CS. Clinical advisors to the ERG suggest that whilst this may be reasonable for the hormone receptor (HR)-negative group, HR-positive patients are likely to continue to experience events and have greater mortality beyond seven years following treatment initiation compared with the general population. Since the clinical advisors to the ERG suggested that this is not clinically plausible, this assumption is amended in the ERG's base case analysis (see Section 5.3 for details).

5.2.6.2 Disease progression

Patients in the event-free state can transition to locoregional recurrence, the metastatic not-progressed state or death. Patients spend 12 months in locoregional recurrence (which is modelled as a tunnel state without the possibility of transitioning to death), after which they transition to the remission state. Patients in the remission state can transition to the metastatic not-progressed state or death. Patients in the metastatic not-progressed state can transition to the metastatic progressed state or

death. Patients in the metastatic progressed state can transition only to death. The probabilities used in the model for each of these transitions are described below.

The company used the proportions of patients with metastatic and locoregional recurrence observed in the NeoSphere trial to model the progression of patients from EFS to these health states; 58% of observed disease progression was to metastatic disease and the remaining 42% of progression events were locoregional recurrence. Clinical advice received by the ERG suggests that this split is broadly reflective of what is typically observed in clinical practice.

Patients within the model spend 12 months in the locoregional recurrence health state before transitioning to the remission state. During this 12 month period, in order to simplify the model, the company assumes that there are no transitions to death or to the metastatic health state. Whilst this is unrealistic, clinical advice received by the ERG suggested that very few patients would progress or die during the first 12 months following a locoregional recurrence. Thus, it is unlikely to impact substantially on the cost-effectiveness results.

The monthly transition probability from the 'remission' to the 'metastatic non-progressed' state in the model was 0.76% based on Hamilton *et al.*,[44] a study of 12,836 early breast cancer patients which estimated the risk of a second malignancy after adjuvant therapy. The company explored the impact of this transition probability in the sensitivity analysis by doubling and halving the figures reported by Hamilton *et al*. As part of the clarification process, the ERG queried how the study by Hamilton *et al*.[44] was identified and whether there were other relevant studies reporting data which could have been used within the sensitivity analysis (question B3). In response, the company stated that *"Hamilton 2014 was identified through a targeted search on PubMed. We are not aware of any other studies which could be used. In the absence of other supporting data the decision was made to double and half the figures to produce the sensitivity analysis."* The ERG was not provided with the search strategy so are unable to verify whether this was reasonable; however the ERG has some concerns about the applicability of Hamilton *et al.*[44]. The patients in this study were heterogeneous as they included stage I/II female breast cancer patients (with HER2 positive, negative or unknown status), ranging between 20 to 79 years of age, diagnosed between 1989 and 2005. Furthermore, they were all treated with adjuvant chest wall radiation and were from one institution in Canada.

The transition probability from the metastatic not progressed state to the metastatic progressed state was modelled as a weighted average of the monthly risk of progression from the pertuzumab in combination with trastuzumab plus docetaxel (3.17%) arm, and trastuzumab plus docetaxel (4.70%) arm of the CLEOPATRA trial[35] and the UK market share data for first-line treatments for metastatic

disease (company data on file, brief details in Section 2.2). UK market shares are reported in the CS as: trastuzumab, 20%; pertuzumab with trastuzumab plus docetaxel, 44%; and trastuzumab plus other, 36%.

The monthly risk of dying due to metastatic disease was also modelled as a weighted average of the monthly risk of progression from the CLEOPATRA trial (trastuzumab plus docetaxel 3.15%; pertuzumab plus trastuzumab plus docetaxel 2.73% and trastuzumab emtansine, 2.73% (assumed to be the same as pertuzumab plus trastuzumab plus docetaxel)) and the UK market share data for second-line treatments for metastatic disease. UK market share estimates are reported in the CS as: capecitabine plus lapatinib, 4%; trastuzumab plus capecitabine, 7%; trastuzumab emtansine, 50%; and pertuzumab plus trastuzumab plus docetaxel, 27%. The company scaled up these four regimens (summing to 88%) to 100% for use within the model, stating that the remaining 12% include a range of treatments comprising small percentages of the market share each, and hence they are excluded in the economic analysis.

As part of the clarification process, the ERG asked the company whether the choice of metastatic treatment for a patient depended on their neoadjuvant treatment (question B17). The company responded that *"the choice of metastatic breast cancer treatments are not dependent on the neoadjuvant or adjuvant therapies received, i.e. whether patients were given the intervention or comparator arm as neoadjuvant therapy, choice of anti-HER2 targeted treatment for these patients who progressed to metastatic disease should not differ between the treatment groups. The weighted average approach was taken as a pragmatic solution to simplify the model. The weightings are informed from market research data which identified treatment regimens used in clinical practice, these do not necessarily adhere to the licensed indications."* It should be noted that whilst both trastuzumab emtansine and pertuzumab are not recommended by NICE in the metastatic setting, they are currently available in England due to funding through the CDF. However, the indication for pertuzumab in the CDF is for patients who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease. Thus it should not be provided as a second line anti-HER2 therapy in the metastatic setting. Due to these issues the ERG has undertaken a sensitivity analysis around this (see Section 5.3.3).

5.2.7 Health related quality of life

The company stated that no HRQoL data were available from the pertuzumab trials and conducted a search of published literature to identify relevant studies for use in the model.

5.2.7.1 Search strategies

The HRQoL searches share many of the same problems as those for the economic model review (e.g. the logic error at line 6 of the EMBASE searches; the focussing of Emtree headings, and the narrow definition of the disease area using limited terms for neoadjuvant therapy). This last issue is however of particular significance in a quality of life search whereby it is conventional to concentrate on the condition rather than interventions (even where an intervention is being used as a means of defining the disease stage). Indeed, the company appear to have realised this by the inclusion of a study (Lidgren *et al*.[45]) which was beyond the scope of their search. The ERG notes that Lidgren *et al*.[45] is indexed in MEDLINE and EMBASE, both of which were searched. This would only have been found by substantially broadening the disease area (for example by searching for "primary breast cancer" and "quality of life").

The ERG ran an additional HRQoL search (see Appendix A for search strategy) to identify studies of possible relevance which might have been missed by the company's searches. Owing to time constraints, this search was run only on EMBASE (chosen because the company's search of this source had contained the largest number of errors).

In addition to correcting the logic error and focussed headings, the ERG included the search string used in the clinical effectiveness search to define neoadjuvant therapy (rather than the narrower string used in the CEA/HRQoL searches). In order to make the search more precise (for pragmatic reasons) terms were introduced relating to HER2 breast cancer. This search retrieved an additional 203 studies. Following sifting of these studies, only one study was identified that reported utilities for HER2-positive breast cancer patients applicable to the UK setting.[46] The CS did not report a search to identify utilities for the metastatic setting.

5.2.7.2 Study selection

The company stated (see CS, Table 78) that their intention was to identify studies containing HRQoL outcomes i.e. utilities or scores derived using preference-based measures of HRQoL as measured using generic instruments (SF-36, HUI II/III, EQ-5D). The intervention included neoadjuvant therapies and the population was adults with HER2-positive, locally advanced, inflammatory, or early stage breast cancer. The company reported that none of the studies identified from the search strategy met the eligibility criteria for inclusion. The data from Lidgren *et al*.[45] were included in the economic analysis although it was not identified in the search strategy.

5.2.7.3 Utilities used in the model

The utilities used in the company's model are based on two studies as summarised in Table 20. Lidgren *et al*.[45] provided the utilities for the 'event-free', 'locoregional', and 'metastatic non-

progressed' health states. A study by Lloyd *et al.*[47] was used to inform the utility value for the metastatic progressed health state. As discussed in Section 5.2.7.1, it is unclear how these studies were identified. The utility in the locoregional recurrence state was assumed to be the same as the utility in the 'event-free' state at the first year and the utility in the remission state was assumed to be the same as that within the 'event-free' state after the first year. The ERG also notes that the utilities used within the model are assumed to be the same for both treatment options within the model.

Table 20. Summary of utility values for cost-effectiveness analysis (reproduced from CS, Table 81, p230)

Health State	Utility value: mean	95% confidence interval	Source
Event-free (first year)	0.696	0.634–0.747	Lidgren *et al.*[45]
Event-free (after first year)	0.779	0.700-0.849	Lidgren *et al.*[45]
Locoregional (after first year)	0.696	0.634–0.747	Assumption
Remission	0.779	0.700-0.849	Assumption
Metastatic not-progressed	0.685	0.634–0.747	Lidgren *et al.*[45]
Metastatic progressed	0.452	-	Lloyd *et al.*[47]

Lidgren *et al.*[45] is a study based on 361 consecutive breast cancer patients attending a breast cancer outpatient clinic in Stockholm between April and May 2005. EQ-5D self-classifier and a direct Time Trade Off (TTO) question were used to estimate the HRQoL for patients classified into different breast cancer disease states, which include ''First year after primary breast cancer'', ''First year after recurrence'', ''Second and following years after primary breast cancer or recurrence'' and ''Metastatic disease''. The patients appear to be heterogeneous with a wide age range (28 to 93 years old) and they do not seem to be split by HER2 status.

Lloyd *et al.*[47] is a mixed model analysis based upon a sample of 100 people from the general population of England and Wales who were asked to value different health states and adverse events associated with metastatic breast cancer using the standard gamble technique. The variables included are: age; treatment response; disease progression; febrile neutropenia; diarrhoea and vomiting; hand-foot syndrome; stomatitis; fatigue; and hair loss. However, it seems that the company's calculations do not account for age or febrile neutropenia within the model.

The company undertook some sensitivity analyses around these utility values; however, given all of these issues, the ERG also undertook a sensitivity analysis around these utility values based upon a

study by Essers *et al*.,[46] identified via the corrected search undertaken by the ERG (see Section 5.2.7.1). The methods and results of this analysis are described in Sections 5.3.3 and 6.2 respectively.

There are no disutilities associated with adverse events explicitly included in the model; however, the utilities are estimated for patients receiving chemotherapy such that the impact of adverse events will already be reflected to some degree. Clinical advisors to the ERG suggest that pertuzumab would not substantially impact upon utility over and above the reduction in HRQoL associated with the chemotherapies used within both arms. However, to explore the impact upon the model results of any minor impacts of additional adverse events associated with (a) trastuzumab and (b) pertuzumab, the ERG has undertaken sensitivity analyses reducing the quality of life within the first year of the event-free state. The methods and results of this analysis are described in Sections 5.3.3 and 6.2 respectively.

5.2.8 Resources and costs

The company's health economic model includes: the cost of the treatments; the cost of administration; the cost of treating a selection of adverse events (occurring in more than 5% of patients in either arm of the NeoSphere trial at grade 3, 4 or 5 severity); supportive care costs; and costs of treatment associated with progressed disease. The company sifted the studies identified from the systematic search of the cost-effectiveness review (see Section 5.1.1) but did not identify any studies reporting UK specific resource use and cost data.

5.2.8.1 Cost of the treatments

The unit costs of the brand-name drugs, pertuzumab and trastuzumab, were taken from the British National Formulary [48] whilst the costs of the generic drugs (docetaxel, 5-fluorouracil, epirubicin and cyclophosphamide) were taken from the Commercial Medicines Unit 2014 electronic Market Information Tool.[49]

The dosage of pertuzumab is fixed and is consistent with the recommended dose within the British National Formulary. The dosages of trastuzumab, docetaxel and FEC are each dependent upon the weight or body surface area of the patient. The model uses drug costs based on the UK average measures (weight of 73.10kg, height of 162.8cm and consequent body surface area of 1.79m^2). The company's base case analysis assumes vial sharing for all treatments without a fixed dose.

For pertuzumab, patients require 840mg for the initial dose, followed by a dose of 420mg for the subsequent cycles. Within the model, it is assumed that three more cycles (i.e. a total of four cycles) will be provided, which is consistent with the NeoSphere trial (see Section 4.2.1.1). However, there

may be some variation in practice around this according to the clinical advisors for the ERG. Given that the unit cost of pertuzumab is £2,395 per 420mg vial, treatment costs for four cycles of neoadjuvant pertuzumab are £11,975.

For intravenous trastuzumab, patients require 8mg/kg for the initial dose, followed by a three-weekly maintenance dose of 6mg/kg. The model includes costs of trastuzumab administered for four cycles prior to surgery and a further 13 cycles to be administered post-surgery as adjuvant therapy. It should be noted that in current practice in England, trastuzumab can also be administered subcutaneously. However, when used in combination with pertuzumab, trastuzumab would be given via infusion. This would lead to a difference in the costs associated with trastuzumab between the comparator and intervention arm. In the original CS, the impact of this is tested within a scenario analysis (see Section 5.2.10 for details), by assuming that all patients in the trastuzumab arm receive trastuzumab subcutaneously. However, in their response to clarification queries (question B14), the company amended their base case analysis by costing trastuzumab using the split in usage of infusional ([redacted]) and subcutaneous ([redacted]) formulations of trastuzumab, based on their market research data. The results of the company's new base case analysis are presented in Section 5.2.9. In the model, a 600mg/5ml fixed dose is used for subcutaneous trastuzumab costing [redacted] per cycle, which includes a confidential discount.

For docetaxel, the initial recommended dose is 75mg/m^2 after which subsequent doses may be escalated to 100mg/m^2. The unit cost is £0.32 per mg and the model includes four cycles of docetaxel prior to surgery. This results in a mean cycle cost of £43.09 for the initial dose and £57.28 for subsequent doses.

The model also includes 3 cycles of FEC (5-fluoruracil plus epirubicin and cyclophosphamide) administered post-surgery. This is consistent with the NeoSphere trial, though in practice FEC is likely to be administered in the neoadjuvant setting (at the same cost). The unit cost of 5-fluoruracil is £0.001 per mg (national product code DHA265) and the model uses the recommended dose of 600mg/m^2, resulting in a mean cycle cost of £1.00. The unit cost of epirubicin is £0.14 per mg (national product code DHA086) and the model uses a dose of 90mg/m^2, resulting in a mean cycle cost of £21.70. The unit cost of cyclophosphamide is £0.02 per mg (national product code DHA014) and the model uses a dose of 600mg/m^2, resulting in a mean cycle cost of £17.67. The total cost per cycle of FEC used in the model is therefore £40.80.

5.2.8.2 Cost of administration

The cost of administration includes the pharmacy costs and the costs of administering the treatments. The unit costs are £48 per hour for a pharmacist, based upon Personal Social Services Research Unit (PSSRU) 2014 costs.[50] The model assumes 12 minutes preparation and dispensation time for each patient, resulting in pharmacy costs of £9.60 per administration. The costs of administration are based on NHS Reference Costs 2013/14;[51] £317 for the first cycle (SB13Z code - deliver complex parenteral chemotherapy day case) and £165 for subsequent cycles (SB12Z code - deliver simple parenteral chemotherapy outpatient). The ERG considers these costs to be appropriate.

5.2.8.3 Costs of treatment within progressed disease state

The model includes the costs of treatments associated with 'locoregional recurrence', 'metastatic not progressed' and 'metastatic progressed' health states. The model assumes that all patients experiencing locoregional recurrence receive trastuzumab and docetaxel, but only includes the cost of trastuzumab, stating that the cost of docetaxel comprises a very small proportion of the cost; hence, this cost has been excluded. The clinical advisors to the ERG suggest that locoregional recurrence is managed by surgery where possible, and there is limited data to suggest that trastuzumab and docetaxel should be provided at this point in the patient pathway. Therefore, the ERG has undertaken a sensitivity analysis around this cost.

For the 'metastatic not progressed' state, patients may receive: trastuzumab and docetaxel; pertuzumab with trastuzumab and docetaxel; or trastuzumab and other (hormonal therapy with or without chemotherapy). The dosages for these treatments are assumed to be the same as for the neoadjuvant treatment doses. The costs in the model are £3,589 per month until progression or death, estimated as a weighted average of these treatments based on their UK market shares for first-line treatments for metastatic disease (see Section 5.2.6.2). The clinical advisors to the ERG suggest that chemotherapy is likely to be discontinued after six cycles; however, due to the low costs of docetaxel (or other chemotherapy), the ERG does not expect this to substantially impact upon the ICER. Due to the uncertainty and variability in the costs of metastatic first line treatment, the ERG has undertaken sensitivity analyses around this cost (see Section 5.3.1).

Similarly, for the 'metastatic progressed disease' state, based upon the company's market research, patients in the model may receive: trastuzumab with a taxane; or pertuzumab with trastuzumab and docetaxel; or trastuzumab emtansine; or capecitabine plus lapatinib. The costs in the model are £5,738 per month, estimated as a weighted average of these treatments based on their UK market shares for the second-line treatments for metastatic disease (see Section 5.2.6.2). The indication for pertuzumab in the CDF is for patients who have not received previous anti-HER2 therapy or chemotherapy for

their metastatic disease. Since all patients are assumed to be treated with an anti-HER2 therapy for first line metastatic disease, the ERG has undertaken a sensitivity analysis varying this cost (see Section 5.3.1).

5.2.8.4 Supportive care costs

Supportive care costs were applied to all health states. Supportive costs in the event-free state were assumed to be £67.85 in the first two years, £15.11 in years three to five and £3.83 in subsequent years. Supportive care costs in the locoregional recurrence and remissions states were assumed to be made up of the supportive care costs in the first year of the 'event free' state plus the additional cost of a CT scan (£73.97). Supportive care costs in the remission state were assumed to be similar to those in years 1-2 of the 'event free' state. Supportive care costs in the 'metastatic not progressed' state and the 'metastatic progressed' state were assumed to be £232 and £185, respectively. Clinical advisors to the ERG suggest that these assumptions are reasonable.

5.2.8.5 Cost of adverse events

Only adverse events occurring in more than 5% of patients in either arm of the NeoSphere trial at grade 3, 4 or 5 severity are included in the model. These include diarrhoea (grade 3), febrile neutropenia (grade 3 and 4), leucopenia (grade 3), and neutropenia (grade 3 and 4). The company assumed that each adverse event was associated with a code from the NHS Reference Costs, though these may not always map precisely to each of the included adverse events. The adverse event costs are applied in the first cycle of the model and assumed to occur only once.

The company did not include the adverse event costs associated with the progressive health states ('loco-regional', 'metastatic not progressed' and 'metastatic progressed') in the model, stating that this was a conservative analysis that underestimates the comparator arm costs.

Summary of model parameters

Table 21 presents a summary of the variables used in the model along with their sources.

Table 21. Summary of variables applied in the economic model

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Source
Outcomes			
Survival function used for PFS in both arms for base case	Gamma	Weibull Log-logistic Exponential Log Normal	CTNeoBC analysis[42]
Mortality	General population mortality	None	ONS
Transition probabilities			
Proportion of progressions that are loco-regional recurrences	42%	Beta distribution	NeoSphere trial[4]
Proportion of progressions that are metastatic (distant recurrences)	58%	Beta distribution	NeoSphere trial[4]
Met. (not progressed) to met progressed	TD: 4.70% PHD: 3.17%	Beta distribution	CLEOPATRA trial[34, 35]
Met. Progressed to death	TD: 3.15% PHD: 2.73% KAD: 2.73%	Beta distribu etion	CLEOPATRA trial[34, 35] Trastuzumab emtansine probability of death as an assumption of equivalence to pertuzumab
Risk of metastatic event for patients in remission	0.76%	SE 0.0012 (Beta) (Override SE 0.05)	Hamilton *et al.* 2014[44]
Patients achieving tpCR Trastuzumab, docetaxel	21.5%	CI: 14.1% - 30.5% (Beta)	NeoSphere trial[4]
Patients achieving tpCR Pertuzumab, Trastuzumab and docetaxel	39.3%	CI:30% - 49.2% (Beta)	NeoSphere trial[4]
Utilities			
1st year after prim breast cancer	0.696	SE 0.06 (Beta)	Lidgren *et al.* 2007[45]
1st year after recurrence	0.779	SE 0.03 (Beta)	Lidgren *et al.* 2007[45]
Locoregional recurrence	0.696	SE 0.03 (Beta)	Lidgren *et al.* 2007[45]
Non-progressive metastatic disease	0.685	SE 0.06 (Beta)	Lidgren *et al.* 2007[45]
Progressive metastatic disease	0.452		Lloyd *et al.* 2004[47]
Remission	0.779	SE 0.03 (Beta)	Lidgren *et al.* 2007[45]
Market shares			
First Line: metastatic not progressed			
Trastuzumab + docetaxel	20%	Not applied	Company data on file
Pertuzumab + Trastuzumab + docetaxel	44%		

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Source
Trastuzumab + other	36%		
Second Line: metastatic progressed			
Capectiabine + Lapatinib	4%	Not applied	Company data on file
Trastuzumab + capecitabine	7%		
Trastuzumab emtansine	50%		
Pertuzumab + Trastuzumab + docetaxel	27%		
Locoregional treatment market share			
Trastuzumab + docetaxel	100.0%	Not applied	Company's assumption (from advisory board)
Cost and resource use			
Drug costs (unit costs)			
Pertuzumab per vial	£2,395	Not applied	British National Formulary 2015 (branded medicines) CMU eMIT 2014 (generic)
Trastuzumab per vial	£407.4		
Docetaxel (generic) per mg	£0.32		
Fluorouracil per mg	£0.001		
Epirubicin per mg	£0.14		
Lapatinib per 250mg	£11.49		
Capecitabine per mg	£0.001		
Cyclophosphamide per mg	£0.02		
Adverse Events			
Diarrhoea (Grade 3)	£476	Log Normal distribution	*JA12E Malignant Breast Disorders with Major CC (reduced short stay emergency tariff)
Febrile Neutropenia (Grade 3 and 4)	£8,662		PA45Z Febrile Neutropenia with Malignancy - Elective Inpatient HRG Data. Health and Social Care Information Centre 2013/14
Leukopenia (Grade 3)	£155		*XD25Z High Cost Drugs: Outpatient - Neutropenia Drugs, Band 1
Neutropenia (Grade 3 and 4)	£155		*XD25Z High Cost Drugs: Outpatient - Neutropenia Drugs, Band 1
Alopecia	£0		Not included (see explanation in Section 5.5.7)
Metastatic not progressed supportive care cost (unit costs)			
Family Practice General Re-assessment	£46 (per 11.7 minute contact)	Not applied	PSSRU 2014 Section 10.8B
Cardiac Monitoring - ECHO Scan	£65		*RA60A code Simple echocardiogram

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Source
Cardiac Monitoring-MUGA Scan	£234		*RA37Z code Nuclear medicine category 3
CT Scan	£91		*RA08A code Computerised Tomography Scan, one area, no contrast, 19 years and over
Clinical nurse specialist	£90		PSSRU 2014 Section 10.8B
Community Nurse (home visit)	£24.6 (20 minute contact)		PSSRU 2014 Section 10.4
Social worker	£79		PSSRU 2014 Section 11.2
Metastatic progressed supportive care cost (unit costs)			
Family Practice General Re-assessment	£46 (per 11.7 minute contact)	Not applied	PSSRU 2014 Section 10.8B
Clinical nurse specialist	£90		PSSRU 2014 Section 10.8B
Community Nurse (home visit)	£24.6 (20 minute contact)		PSSRU 2014 Section 10.4
Locoregional recurrence supportive costs			
CT Scan	£91		NHS Reference cost 2013/14 RA08A code Computerised Tomography Scan, one area, no contrast, 19 years and over
Event Free survival - Supportive Costs (unit costs)			
Oncologist Medical Specific Re-assessment	£124	25% to the mean Log normal distribution	*Service code 800 Consultant Led: Follow up Attendance Non-Admitted Face to Face: clinical oncology
Family Practice General Re-assessment	46 (per 11.7 minute contact)		PRSSU 2014 Section 10.8B
Mammogram	£11.34		NHS Breast Screening Programme
Cardiac Monitoring - ECHO Scan	£65		*RA60A code Simple echocardiogram
Cardiac Monitoring-MUGA Scan	£234		*RA37Z code code Nuclear medicine category 3

CI, confidence interval

*NHS Reference costs 2013/14

5.2.9 Cost-effectiveness results

The company's base case deterministic cost-effectiveness results, as presented in the original CS, are reproduced in Table 22. This suggests that pertuzumab leads to an additional 0.26 QALYs at an additional cost of £4,557 on average per person. The cost per QALY gained for pertuzumab, trastuzumab and docetaxel in comparison to trastuzumab and docetaxel is estimated to be £17,297.

The company presented a similar probabilistic base case ICER of £20,104 per QALY gained, with an estimated 64.1% chance of being considered to be cost-effective at a threshold of £30,000 per QALY gained.

Table 22. Deterministic cost-effectiveness analysis results from company's base case analysis in the original submission (reproduced from CS, Table 97, p261)

Technologies	Total costs	Total LYG	Total QALYs	Incr costs	Incr LYG	Incr QALYs	Incr LYG	ICER (£/QALY)
PHD	£104,575	16.72	11.50	£4,557	0.37	0.26	£12,471	£17,297
HD	£100,018	16.35	11.24					

PHD – Pertuzumab + Trastuzumab + docetaxel; HD - Trastuzumab + docetaxel; LYG – life years gained; QALYs – Quality adjusted life years; ICER – incremental costs effectiveness ratio

In the clarification responses (question B14), the company amended their base case analysis by costing trastuzumab using the split in usage of intravenous trastuzumab ([redacted]) and subcutaneous trastuzumab ([redacted]) formulations, based on their market research data. The results of the new base case analysis are presented in Table 23. Again, the probabilistic ICER was similar, estimated at £21,869 per QALY gained for pertuzumab, trastuzumab and docetaxel in comparison to trastuzumab and docetaxel, with a 62.1% chance of being considered to be cost-effective at a threshold of £30,000 per QALY gained.

Table 23. Reproduced deterministic base-case results presented in company's clarification response (question B14)

Technologies	Total costs	Total LYG	Total QALYs	Incr costs	Incr LYG	Incr QALYs	Incr LYG	ICER (£/QALY)
PHD	£104,575	16.72	11.50	£5,253	0.37	0.26	£14,375	£19,939
HD	£99,322	16.35	11.24	-	-	-	-	-

PHD – Pertuzumab + Trastuzumab + docetaxel; HD - Trastuzumab + docetaxel; LYG – life years gained; QALYs – Quality adjusted life years; ICER – incremental costs effectiveness ratio

The ERG prefers the base case from the clarification response as it is more representative of current practice in England. On this basis, only the results of the sensitivity analyses reported in the company's clarification response are presented in the subsequent section.

It should be noted that the ERG raised a concern with the company via NICE after the response to clarification questions had been received (26th Feb 2016) about the potential error relating to the digitisation of the CTNeoBC meta-analysis, set out in Section 5.2.6.1. The response from the company (received by the ERG on 14th March 2016) acknowledged the error and presented a revised deterministic base case of £8,215 per QALY gained for pertuzumab, trastuzumab and docetaxel in comparison to trastuzumab and docetaxel. The revised probabilistic base case ICER was estimated to be £9,047, with an 82.9% chance of being the most cost-effective option at £30,000 per QALY gained. An updated one-way sensitivity analysis was not presented using this revised base case.

5.2.10 Sensitivity analyses

The company undertook probabilistic sensitivity analysis (PSA) and univariate sensitivity analyses. However, both sets of analyses contain weaknesses. The company also undertook scenario analyses using: (a) different trastuzumab costs (using subcutaneous trastuzumab instead of intravenous trastuzumab), and; (b) EFS data from the NeoSphere trial directly. In addition, within the original CS, the company undertook a threshold analysis around commercial-in-confidence price discounts for metastatic treatment costs.

PSA

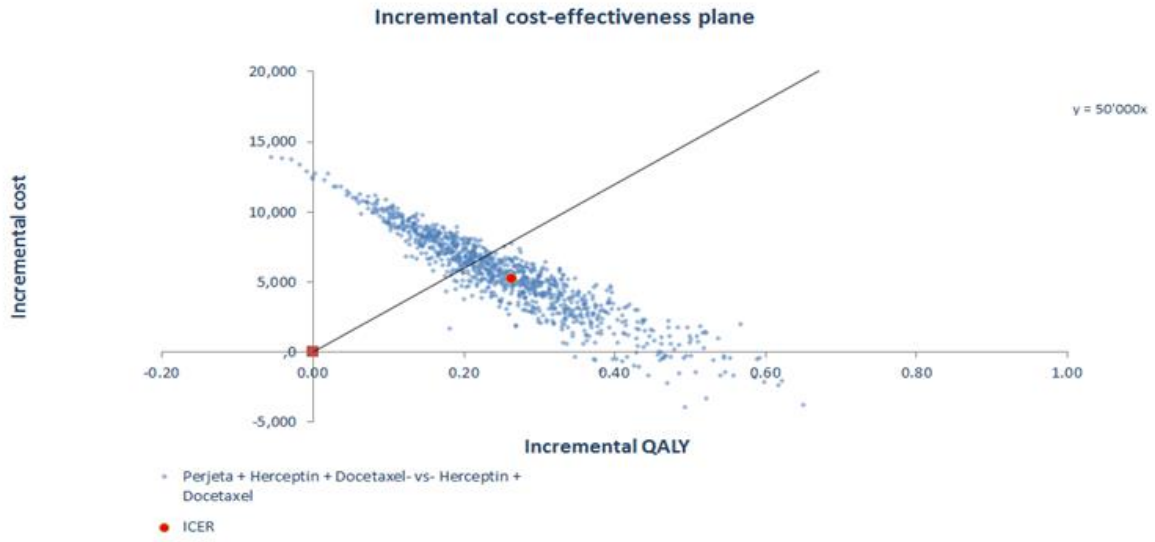
Within the CS, the distribution parameters used in the PSA are neither presented nor justified. In addition, the ERG notes that some uncertain model parameters are not characterised by probability distributions, and where included, the characterisation of uncertainty surrounding some model parameters appears arbitrary. For example, the parameterisation of uncertainty in adverse event cost, administration cost, pharmacy time required for intravenous preparation and supportive care cost is arbitrary i.e. the standard error is assumed to be a proportion (typically 10-25%) of the mean.

Tabled results of the PSA are not presented by the company. As part of the clarification process (question B21), the ERG requested that the company provide a table with values of all PSA parameters and their probability distributions. However, the numbers provided do not match with those used in the model. The ERG assumes that the parameters in the model are correct as the model results based on these distributions are consistent with the results presented in the company's clarification response. In relation to the issues described above, as part of the clarification process (question B8), the company provided the EFS distribution parameters and covariance matrices for each of the parametric distributions.

Figures 9 and 10 show the company's incremental cost-effectiveness plane and cost-effectiveness acceptability curves (CEACs). Figure 10 suggests that there is a strong negative relationship between the incremental costs and QALYs. As part of the clarification process (question B23), the ERG asked

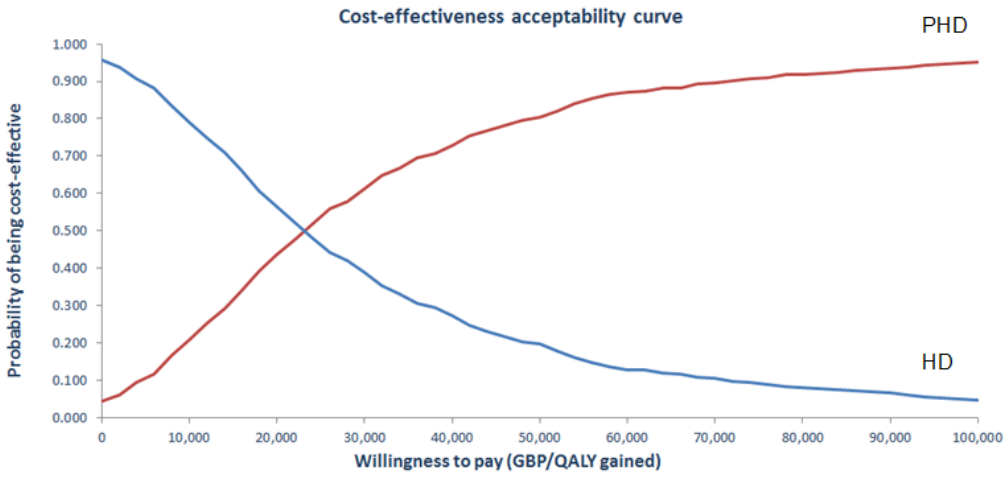
the company to comment on this in relation to the distributions used within the PSA. The company responded that *"The negative correlation in the incremental cost-effectiveness plane is due to the importance of pCR. A large difference in pCR between treatments leads to lower number of events (in the treatment group) and consequently to both higher QoL* ***and*** *higher cost savings, due to patients avoiding the metastatic health states. It should be noted that this negative correlation was also noted in the Attard et al study."* The ERG considers this to be a reasonable explanation.

Figure 10. Company's incremental cost effectiveness plane (reproduced from CS clarification response, Figure 9)



The company's CEAC in the original submission only included the pertuzumab arm. CEACs should detail the probability of each intervention being the most cost-effective, and therefore the summation of the individual probabilities should equal to 1. The ERG requested that the company correct the CEAC to include both the intervention and the comparator (question B24). The CEAC presented in the company's clarification response is presented in Figure 11. This suggests that there is around a 62% probability of the pertuzumab arm being the most cost effective option at £30,000 per QALY gained; however, this is based on arbitrary figures to quantify the uncertainty for many of the model parameters.

Figure 11. **Company's Cost Effectiveness Acceptability Curve** (reproduced from clarification response, Figure 11)



PHD – Pertuzumab plus trastuzumab plus docetaxel, HD – Trastuzumab plus docetaxel

Univariate sensitivity analyses

The results of the company's univariate sensitivity analyses are provided in Table 24.

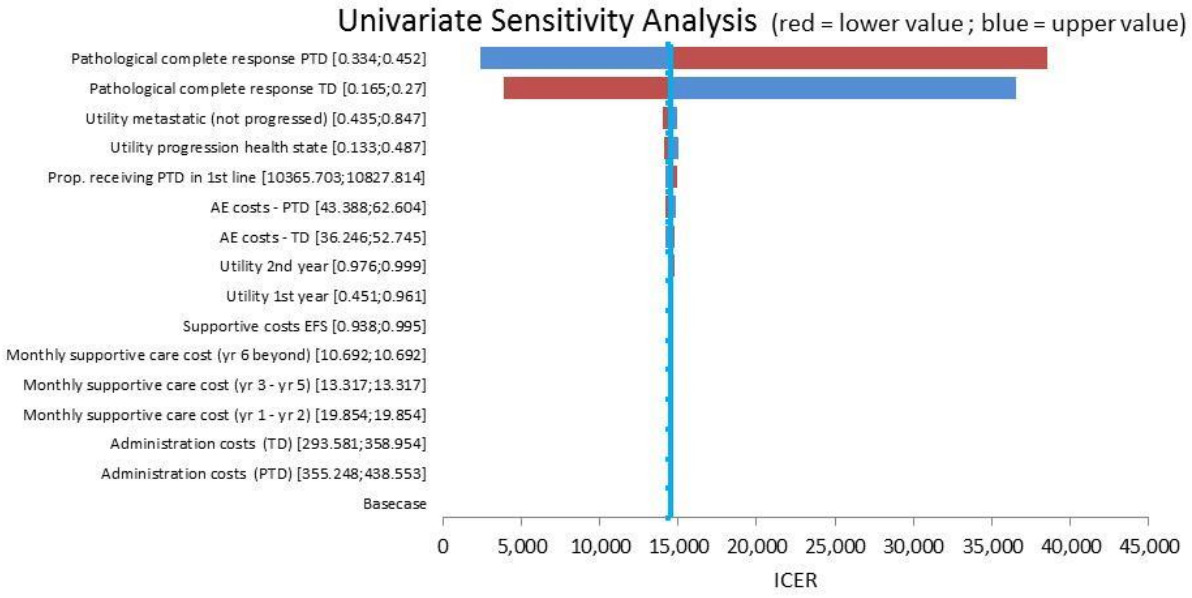
Table 24. Company's deterministic univariate sensitivity analysis (reproduced from clarification response, Table 14)

Base case ICER £19,939					
Parameter modified	**Base value (£)**	**High value**	**Low value**	**ICER high (£ per QALY)**	**ICER low (£ per QALY)**
LR supportive care costs health state costs	£74	£103.60	£44.40	£19,921	£19,956
Log-Logistic parametric function		Log-logistic		£20,021	
Pharmacy cost	£10	£13.44	£5.76	£19.909	£19,968
Cardiac assessment proportion	30/70 (MUGA/ECHO) proportion	10/90 (MUGA/ECHO) proportion	50/50 (MUGA/ECHO) proportion	£19,966	£19,912
Event free survival supportive care cost (monthly)	£67.85 (year 1-2), £15.11 (year 3-5), £3.83 (year 5+)	BCVs x 1,25	BCVs x 0,75	£19,889	£19,988
AE cost	£794.66 (PHD Arm), £742.47 (HD Arm)	£1112.52 (BCV x 1.4), £1039.46 (BCV x 1.4)	£476.79 (BCV x 0.6), £445.48 (BCV x 0.6)	£20,018	£19,859
Metastatic not progressed supportive care costs (monthly)	£232	£324.8 (BCV x 1.4)	£139.20 (BCV x 0.6)	£17,716	£20,161
Administration cost (monthly)	£326.60 (for 1st treatment), £174.60 (for subsequent treatment)	£457.24 £244.44	£195.96 £104.76	£19,880	£20,675
Metastatic progressed disease supportive care cost (monthly)	£185	£259 (BCV x 1.4)	£111 (BCV x 0.6)	£19,709	£20,169
Weibull parametric fit	Gamma	Weibull		£19,212	
Log-Normal parametric function	Gamma	Log normal		£21,624	
Exponential parametric function	Gamma	Exponential		£17,803	

Base case ICER £19,939					
Parameter modified	**Base value (£)**	**High value**	**Low value**	**ICER high (£ per QALY)**	**ICER low (£ per QALY)**
Split between metastatic and local regional recurrence	58% and 42%	70% and 30%		£17,602	
Transition probability of moving from metastatic not progressed to death (HD)	3.15%	3.78% (BCV x 1.2)	2.52% (BCV x 0.8)	£20,565	£19,257
Transition probability of moving from metastatic not progressed to death (PHD)	2.73%	3.82% (BCV x 1.2)	2.18% (BCV x 0.8)	£23,375	£17,229
PHD pCR	39.25%	49.2%	30.0%	£2,534	£72,673
HD pCR	21.5%	30.5%	14.1%	£69,776	£5,696
Monthly risk of a second malignancy	0.76%	1.52% (BCV x 2)	0.38% (BCV x 0.5)	£16,588	£24,987
Utility Values Source 2	See Table 103	See Table 103		£20,477	
Time horizon	50	50	30	£24,608	
Utility Values Source 1	See Table 103	See Table 103	see table 14	£16,394	£25,237
Vial sharing assumptions (trastuzumab only)	Vial sharing	No Vial Sharing			£20,248
Time point when switching to background mortality (only)	7	5	6	£27,726	£22,994
BCV, Base Case Value; PHD, pertuzumab, trastuzumab, docetaxel; HD, trastuzumab, docetaxel; AE, Adverse Event; LR, Locoregional recurrence; ECHO, echocardiography; MUGA, multiple gated acquisition					

In the original CS, the company presented only a selection of these one way sensitivity analyses in the form of a tornado diagram. As part of the clarification process (question B25), the ERG requested that the company present all of the results of the sensitivity analyses described within Table 23 within the tornado diagram. The figure presented by the company is shown in Figure 12.

Figure 12. Company's univariate sensitivity analysis (reproduced from clarification response, Figure 36)



The key driver of the model is the pCR rates for the treatment and comparator, with ICERs ranging from £2,534 per QALY gained to £72,673 per QALY gained, depending on the pCR values chosen for the analysis. The rest of the parameters chosen do not have a significant impact on the ICER and the company stated that this sensitivity analysis suggests that the ICER is robust to many of the parameters within the model. However, this is applicable only within the ranges selected for the univariate analyses and the parameters chosen by the company for analysis. The ERG notes that although varying the parametric distribution for EFS and the time point for switching to background mortality do not individually have a sizeable impact on the model results, varying these parameters simultaneously may substantially increase the ICER (see Section 6.1). The ERG have included other plausible one way sensitivity analyses which have a greater impact upon the model results (see Section 5.3.3 and Section 6.2 for a description of the analysis and results respectively).

Scenario analysis

The company undertook two additional scenario analysesrelating to (i) the use of subcutaneous trastuzumab only, and; (ii) the use of EFS directly from NeoSphere trial. The latter analysis was not undertaken in the CS, but was provided in response to a request for clarification from the ERG (question B7).

Subcutaneous trastuzumab

The company, in their original submission, undertook a scenario analysis assuming that all patients receive trastuzumab subcutaneously rather than intravenously. This included amending the price of subcutaneous trastuzumab (600mg/5ml fixed dose) to [redacted] per cycle (which includes a confidential discount) for the trastuzumab plus docetaxel arm only. A 60% reduction in administration costs were assumed, whilst the trastuzumab subcutaneous adverse event costs were assumed to be similar to those for intravenous trastuzumab. Follow-on treatments including trastuzumab were assumed to be delivered by intravenous administration. The results from this scenario analysis are replicated below in Table 25. The results suggest the costs for the pertuzumab plus trastuzumab plus docetaxel arm are the same as base case analysis (see Table 21) but the costs of the trastuzumab plus docetaxel arm are lower, thus resulting in an increased ICER.

Table 25. Results of the company's scenario analysis (reproduced from CS, Table 105, p277)

Technologies	Total costs	Total LYG	Total QALYs	Incr costs (£)	Incr LYG	Incr QALYs	Incr £/LYG	ICER (£/QALY))
PHD	£104,575	16.719	11.499	[redacted]	0.365	0.263	[redacted]	[redacted]
HD SC	[redacted]	16.353	11.236					

PHD, Pertuzumab+ Trastuzumab+ docetaxel; HD, Trastuzumab+ docetaxel; LYG,life years gained; QALYs, Quality adjusted life years; ICER, incremental costs effectiveness ratio

EFS data from the NeoSphere trial

Given the uncertainties associated with pCR as a surrogate outcome (discussed in detail in Section 4.2.4.1) and the poor prediction of EFS from the NeoSphere trial based on this surrogate, (see Section 5.2.6.1), the ERG asked the company to undertake an additional analysis using the EFS data directly from the NeoSphere trial.[4] In the response to this request, the company fitted different parametric curves to the Kaplan-Meier data for each arm of the trial assuming independent hazards; different functional forms were used for each arm since the Kaplan-Meier curves were crossing at around month 15. The company reported that none of the estimated survivor functions fitted the data adequately, as assessed by visual inspection of the fit to the Kaplan-Meier curves. Instead, the company used a piecewise approach whereby two exponential pieces were fitted to each hazard curve from the NeoSphere trial. For the trastuzumab and docetaxel arm, a change in the hazard rate was observed at 22 months. The company reported that no events occurred in this arm for the first 7 months and thus, the exponential distribution is not used until month 7. For the pertuzumab, trastuzumab and docetaxel arm, one piece was fitted for the first 19 months and then a second piece

was fitted from month 19 to 60 (see Table 26). The company has not presented the figure comparing the fitted piece-wise exponential curves against the Kaplan-Meier trial data.

Table 26. Time interval and estimated hazard for the fitted pieces

PHD – Breakpoints (months)	PHD – Hazard	HD – Breakpoints (months)	HD – Hazard
0-19	0.0032	7* – 22	0.0054
19-60	0.0019	22 – 57	0.0127
PHD, Pertuzumab+ Trastuzumab+ docetaxel; HD, Trastuzumab+ docetaxel * The company reported that no events occurred in this arm for the first 7 months and thus, the exponential distribution is not used until month 7			

The deterministic results are presented in Table 27. These suggest that the pertuzumab, trastuzumab and docetaxel arm dominates i.e. it is less costly and more effective than the trastuzumab and docetaxel arm. The company highlights that these results should be interpreted with caution as the EFS data were immature. The ERG agree with the company that this analysis has limitations due to the small number of events at the 5-year follow up point, but consider that it is useful to include the results of this approach for comparison.

Table 27. Reproduced deterministic EFS scenario results from company's clarification response (question B7)

Technologies	Total costs (GBP)	Total LYG	Total QALYs	Incr costs (£)	Incr LYG	Incr QALYs	Incr £/LYG	ICER (£/QALY)
PHD	£71,145	18.31	12.65					
HD	£71,432	17.71	12.21	-£287	0.60	0.43	-£476	-£660
PHD, Pertuzumab+ Trastuzumab+ docetaxel; HD, Trastuzumab+ docetaxel; LYG, life years gained; QALYs, Quality adjusted life years; ICER, incremental costs effectiveness ratio								

Threshold analysis in the original submission

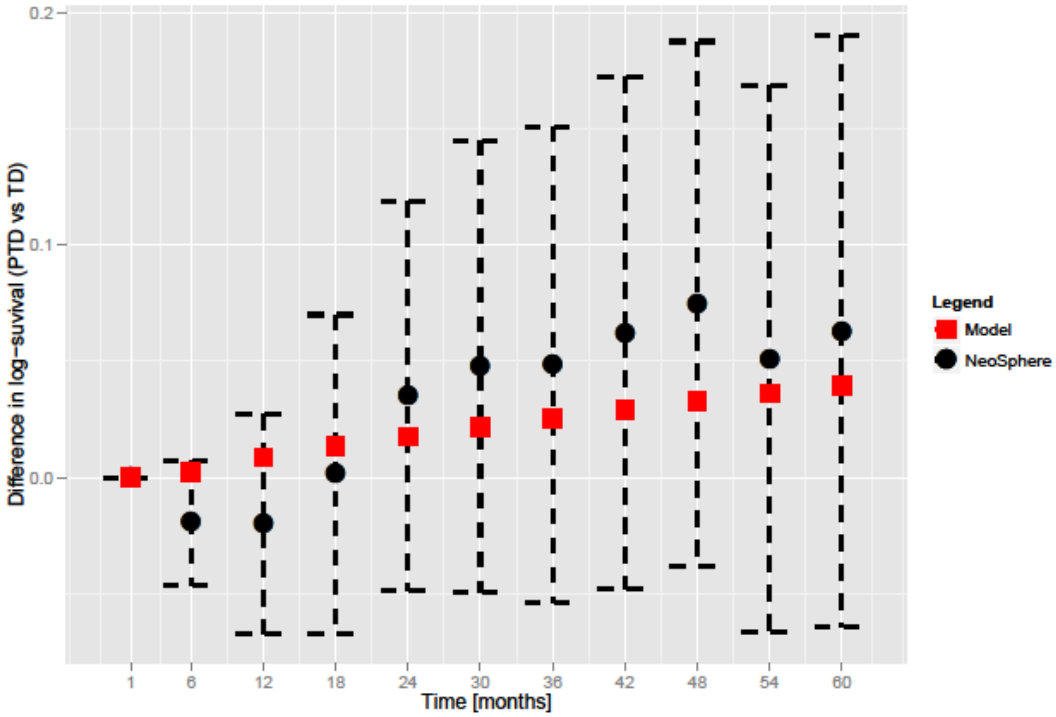
The company stated that the discounts (which are commercial in confidence) for metastatic treatment costs contained within the economic [redacted]. It should be noted that a threshold analysis was not performed by the company using the updated base case model in the clarification responses (question B14).

5.2.11 Model validation and face validity check

The CS included an assessment of the validity of the model. This is based on the survivor functions estimated by the company, although the ERG believed, and the company later verified, that the analysis was based on the CTNeoBC meta-analysis for all breast cancer patients (See Section 5.2.6.1).

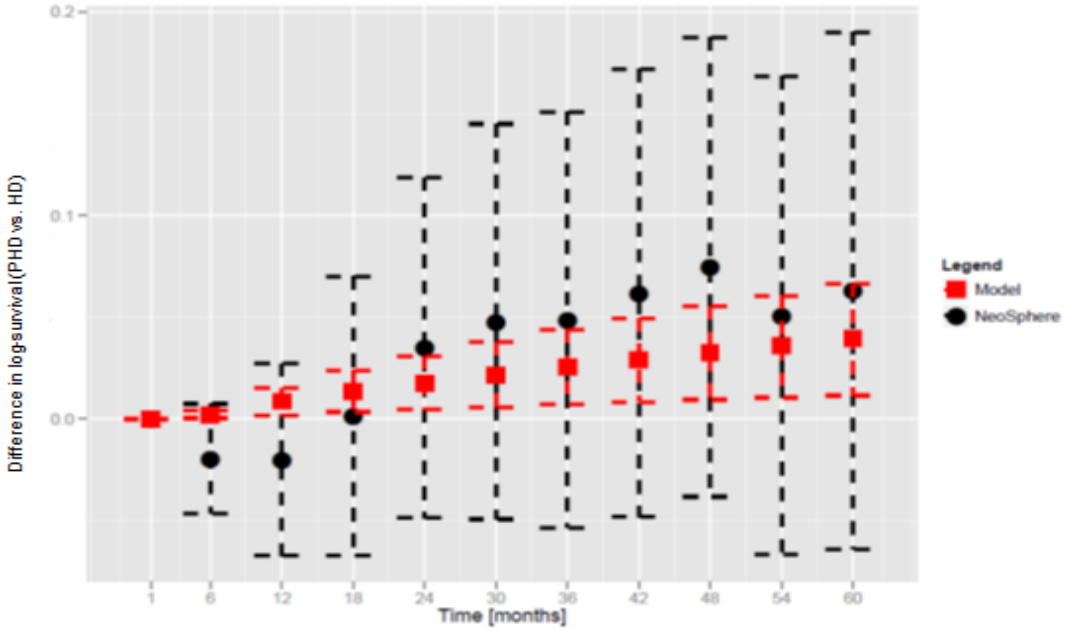
In order to explore model validity, the company generated 95% confidence intervals for the difference in the survival rates between treatments on the log scale at 6-monthly intervals in the NeoSphere study and compared this with the model predictions (see Figure 13); the figure is labelled "survival" although this is actually described as PFS within the CS, which is assumed by the ERG to be synonymous with EFS.

Figure 13. Company's model prediction vs NeoSphere trial data (reproduced from CS, Figure 33, p263)



As part of the clarification process (question B26), the ERG asked the company to use the model to generate the predictive distribution for the (log) difference in survival rates between treatments and compare this with the observed result from the NeoSphere study (in other words, to generate realisations of different studies of identical size to NeoSphere given the assumed underlying model and its uncertainty – a form of cross validation). The ERG is unable to verify whether the company did this correctly; however, based on the results provided by the company, shown in Figure 14, it appears that the model is not a good representation of the data generated in the NeoSphere study; however this appears to be due to the model underestimating the treatment effects.

Figure 14. Differences in log-survival function of PHD vs HD (reproduced from company's clarification response, B26)



5.3 Exploratory and sensitivity analyses undertaken by the ERG

5.3.1 The ERG's suggested base case

Based upon the critique of the company's economic model, the ERG have identified one model error (around EFS extrapolation) and one assumption which is not clinically valid according to the ERGs clinical advisors (patients that are event free at 7 years assumed to be cured). Both these have been amended within the ERG's preferred base case analysis and thus the ERG's suggested base case includes:

1) Using parametric distributions from the ERG's survival analysis

As described in Section 5.2.6.1, the company has used approximately the first 9 years of data (out of 18 years follow-up) from all breast cancer patients for the CTNeoBC meta-analysis for fitting the parametric distributions to predict long-term EFS, alongside the numbers at risk from the HER2-positive subgroup. The ERG believes that the company has made an error when digitising the curves.

Given that HER2-positive breast cancer patients have a worse prognosis than other breast cancer, and given that the CTNeoBC meta-analysis showed a stronger relationship between pCR and EFS for the HER2-positive subgroup, the ERG considered that using the subgroup of HER2-positive breast cancer patients from the CTNeoBC meta-analysis was appropriate. The uncertainty resulting from the smaller numbers at risk within this subgroup can be reflected within the probabilistic sensitivity

analysis. The ERG digitised the Kaplan-Meier EFS data for HER2-positive patients from CTNeoBC meta-analysis using Enguage Digitizer (version 4.1) and used the Guyot *et al*.[41] algorithm to reconstruct the IPD for patients achieving pCR and patients not achieving pCR. The ERG assessed a number of parametric functions (exponential, weibull, log-logistic, log-normal, Gompertz and Generalised gamma) fitted to the generated IPD data using visual inspection, consideration of the AIC/BIC statistics and clinical plausibility.

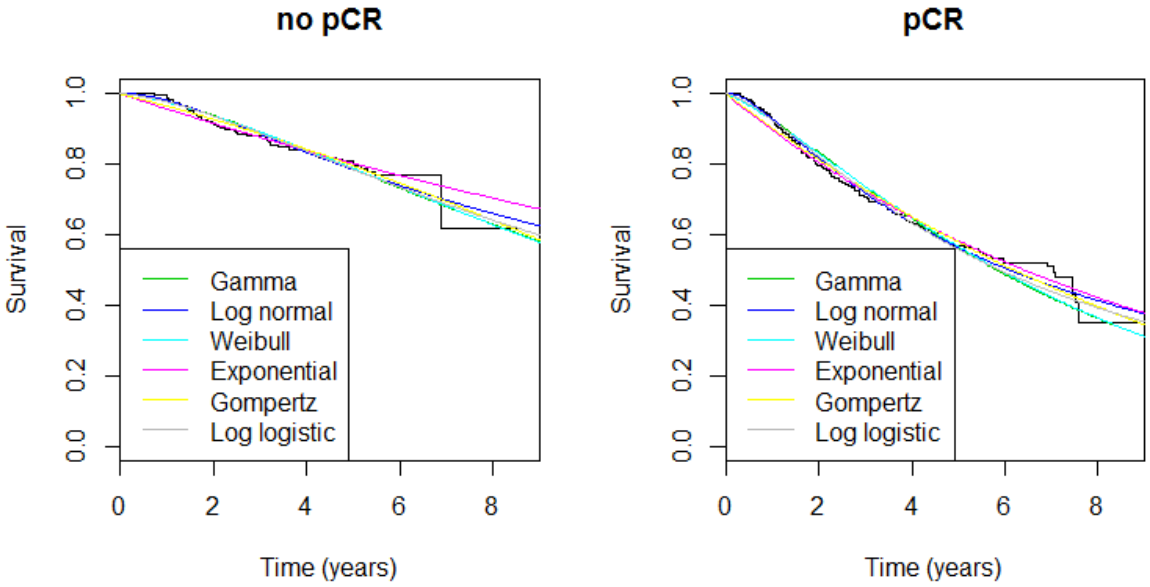
The parameters and their confidence intervals are shown in Table 28.

Table 28. Parametric functions and confidence intervals fitted to HER2 patients in CTNeoBC

Subgroup	Distribution	intercept	scale	shape	AIC	BIC
no pCR	Exponential	0.108			3034.653	3045.146
	Weibull	7.926	1.225		2990.189	3000.682
	Lognormal	1.8076	1.231		3019.448	3029.941
	Loglogistic	5.8878	1.424		3065.816	3076.308
	Gompertz	0.09954	0.037		3042.928	3053.421
	Generalised gamma	1.43	1.440	-0.905	2978.033	2970.839
pCR	Exponential	0.043			723.637	732.383
	Weibull	13.705	1.426		714.329	723.067
	Lognormal	2.595	1.247		723.248	731.994
	Loglogistic	11.72	1.52		735.265	744.012
	Gompertz	0.033	0.117		725.694	734.440
	Generalised gamma	1.102	1.518	-3.992	700.418	720.731
AIC, Akaike information criterion; BIC, Bayesian information criterion						

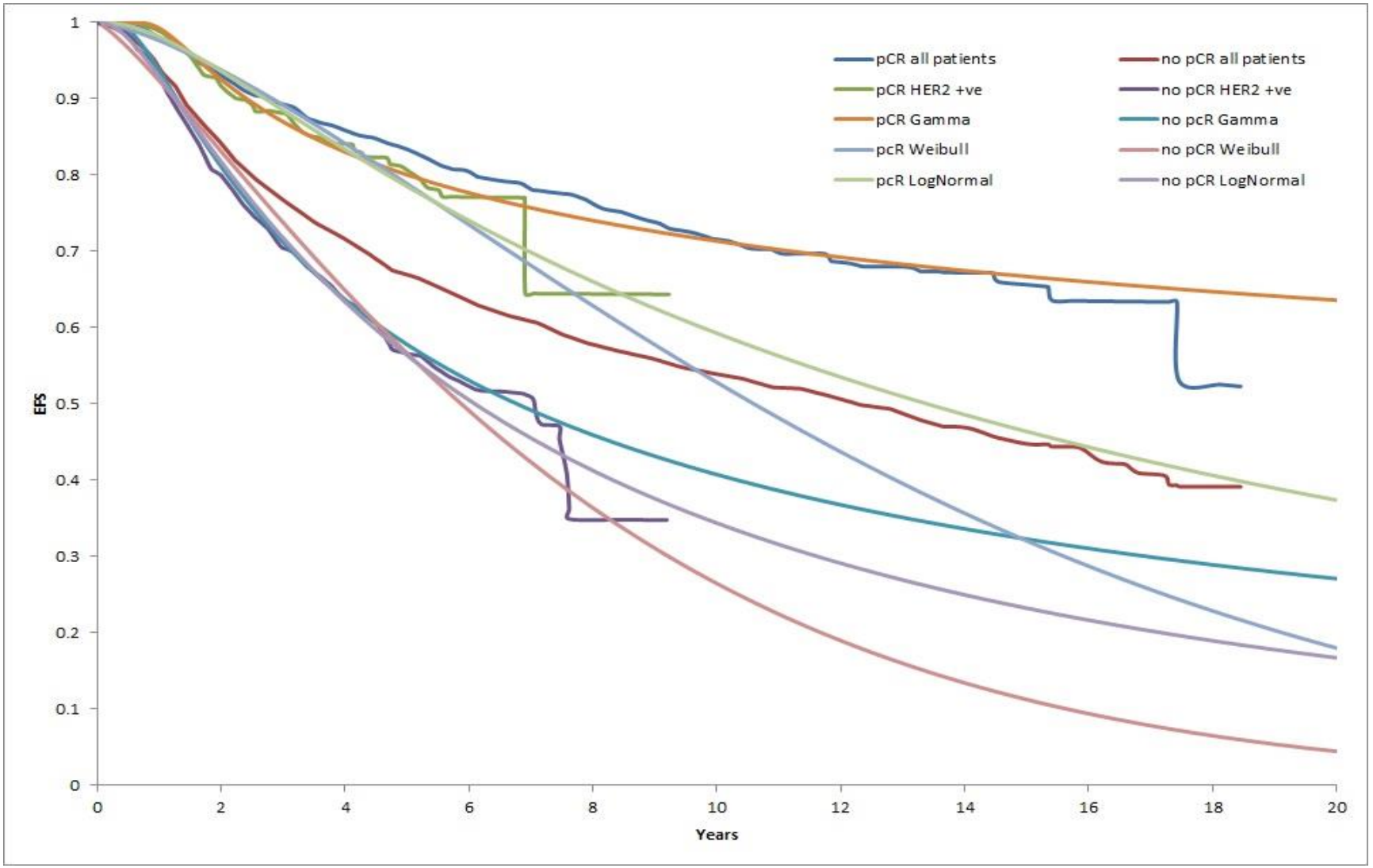
The output files containing the parameters, their confidence intervals and the variance-covariance matrices for multi-parameter models are presented in Appendix B. The different parametric distributions for the extrapolation of the EFS data were plotted against the digitised Kaplan-Meier data, as shown in Figure 15.

Figure 15. Parametric survival curves for EFS



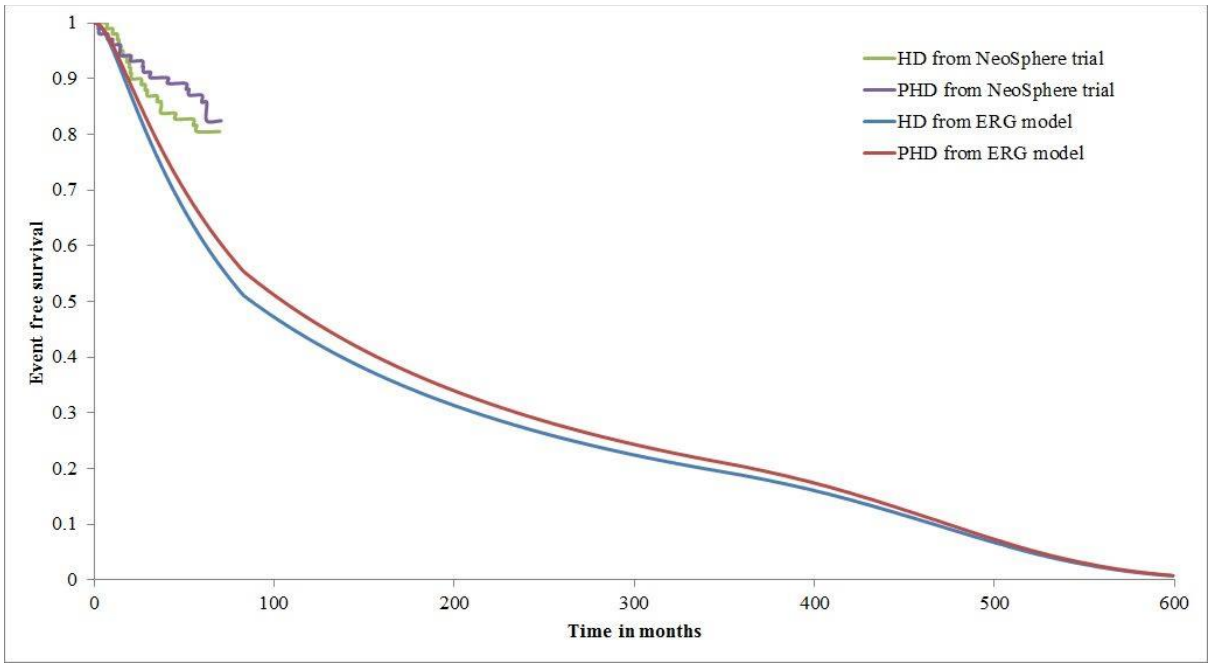
Both visual inspection and AIC/BIC statistics suggest that the generalised gamma, Weibull and lognormal parametric distributions provide the best fit to the data. A study by Perez *et al*.[52] has been identified by the ERG as presenting the longest follow up for HER2-positive patients, with a 10 year follow up of EFS. This study suggests that the risk of recurrence persists beyond seven years (the cut-off assumed in the company's model). The ERG digitised the curves from Perez *et al*.[52] and estimated that around 6% of patients progress between years 7 to 10. The lognormal distribution predicts the proportion progressing to be about 10% from years 7 to 10. This is a slight overestimate compared with the data from Perez *et al*.[52] but the other parametric distributions apart from the generalised gamma predict a more rapid drop. The curves predicted by the generalised gamma and the lognormal were plotted alongside the curves for all cancer patients from the CTNeoBC meta-analysis and the generalised gamma resulted in higher EFS curves than those of all breast cancer patients beyond around 10 years (i.e. there were fewer events over time in the HER2 group, using the generalised gamma distribution), as shown in Figure 16. Based upon this comparison, the lognormal distribution was chosen to be a reasonable fit to the data with the most clinical plausibility over time to be used within the ERG's base case.

Figure 16. ERG parametric survival curves and Kaplan-Meier curves from Cortazar *et al*.[42]



It is important to note that, as for the company's CTNeoBC meta-analysis, this extrapolation results in a substantial underestimate of the EFS curves from the NeoSphere trial, as shown within Figure 17. Given the available trial data, the only other option for extrapolating outcomes over the long-term is to use the EFS data directly, which is associated with other major limitations (see Section 5.2.6.1 for a comparison of the two approaches). However, since pCR is a poor predictor of EFS for the NeoSphere data, the ERG has also undertaken an additional analysis using the EFS data from the NeoSphere trial directly within a scenario analysis (see Section 5.3.3).

Figure 17. EFS predictions based on the pCR surrogate and the NeoSphere trial



2) EFS extrapolation for life time (rather than seven years).

As described within Section 5.2.6.1, the company used the EFS estimates only until seven years after treatment initiation, after which the patients are assumed to be cured, with only the risk of general population mortality. Clinical advisors to the ERG suggested that the assumption that the hazard of recurrence beyond seven years is zero is not clinically valid.[52] The ERG amended this assumption within the base case analysis by using the log normal distribution estimated for the HER2-positive patients for the whole time horizon of 50 years. Using the lognormal distribution, recurrence rates slow down over time but do not stop, as could be expected in practice.

5.3.2 Probabilistic sensitivity analysis

Section 5.2.10 described the limitations in the company's implementation of the PSA. The ERG considers that informed distributions for the uncertainty around some parameters (e.g. costs and utilities) need to be used. However, given the substantial resources that would be required in delivering the above, the ERG's exploratory analyses focus on including the parametric distributions estimated from reanalysed survival data in the base case analysis and undertaking extensive one-way sensitivity analyses using the deterministic model to describe the key drivers of the model results.

5.3.3 Univariate sensitivity analysis

The ERG have repeated the univariate sensitivity analyses run by the company using the ERG's preferred base case, and have also undertaken further sensitivity analyses based upon key areas of uncertainty identified within the ERG's critique of the company's model. These are:

1) Number of cycles of pertuzumab

Given that the marketing authorisation includes a minimum of three cycles and a maximum of six cycles of pertuzumab (clarification question A3), the ERG performed sensitivity analyses using the costs for three and six cycles of pertuzumab. These analyses are performed: (a) by changing the dosage only; (b) by changing the dosage and pCR rates of the pertuzumab arm; and (c) by changing the dosage of pertuzumab and the pCR rates of both arms. In analysis (b), the pCR rates for the pertuzumab arm were changed to those achieved in the TRYPHAENA trial (63.6 % for six cycles of pertuzumab and 54.7% three cycles of pertuzumab) and the pCR rates for the trastuzumab arm were unchanged (i.e. 21.5% based on Neosphere trial). In analysis (c), the pCR rates for the pertuzumab arm were changed to those achieved in the TRYPHAENA trial and the pCR rates for the trastuzumab arm were estimated (as 45.8% and 36.9%, respectively) assuming the same absolute difference in pCR observed between treatment regimens with and without pertuzumab in the NeoSphere study (17.8%).

2) Utility values based on Essers et al.[46]

The HRQoL search conducted by the ERG identified one study (Essers *et al.*[46]) which reported utility values for HER2-positive breast cancer patients which was applicable to the UK setting (see Table 30, Section 6.2, for utility values). This was therefore used within a sensitivity analysis.

3) Incorporating disutility during treatment

The ERG performed exploratory analysis around the impact of incorporating disutility due to adverse events for a) trastuzumab and b) pertuzumab during treatment. Given the lack of data around this, the ERG assumed that this disutility is the same as the disutility due to chemotherapy, which can be

estimated from the model as the difference between the EFS utility in the first year and EFS utility in subsequent years (-0.083). The ERG also performed another sensitivity analysis using half this disutility value (i.e. -0.0415). For the analysis assuming disutility for trastuzumab, the disutility is assumed to last for the whole year and is applied in both arms of the model. For the analysis assuming disutility for pertuzumab, the disutility is applied in only the pertuzumab arm of the model and two different analyses are performed assuming the disutility lasts for whole year and only for the first three months (i.e. treatment duration of pertuzumab).

4) Cost of metastatic treatment

Owing to uncertainty surrounding the use of alternative metastatic treatments within England and the effect of the CDF on current therapy use, the ERG performed sensitivity analyses amending the cost of metastatic treatments (both first and second line treatments). The cost of metastatic treatments, which are currently estimated in the model as a weighted average of costs of different treatments based on market share research undertaken by the company (company data on file), are amended to the most costly and least costly treatment regimens in order to assess the impact of changes to these assumptions upon the model results.

5) Cost of locoregional recurrence

The costs associated with docetaxel were not included in the costs for the locoregional recurrence state which assumes patients are treated with trastuzumab and docetaxel i.e. only the costs of trastuzumab are included due to the minimal costs of docetaxel (see Section 5.2.8.3). In addition, the clinical advisors to the ERG suggest that locoregional recurrence is managed by surgery where possible, and there is limited data to suggest that trastuzumab and docetaxel should be provided at this point in the patient pathway. Therefore, the ERG performed sensitivity analysis to assess the impact of variations to this cost upon the model results, by (a) including the costs of docetaxel in the costs of locoregional recurrence; and (b) including only a one off cost of excision based upon a study by Rafia *et al.*[53] and no costs associated with trastuzumab and docetaxel.

6) *Analysis with the company's model based on NeoSphere trial*

The company performed analysis using the EFS data directly from the NeoSphere trial as part of their clarification response (question B7). However, the analysis was based on the assumption that the patients that are event free at seven years are assumed to be cured (see Section 5.3.1). The ERG revised this assumption to be consistent with their base case to assess the impact upon the model results.

The parameters and the results of the company's sensitivity analyses repeated by the ERG are presented in Table 30 and the parameters and results of the additional analyses undertaken by the ERG outlined above are presented in Table 31.

5.4 Conclusions of the cost effectiveness section

The *de novo* model developed is generally appropriate for the decision problem defined in the final NICE scope, though it should be noted that the only comparator tested within the economic evaluation was trastuzumab alongside docetaxel. The model was well described within the report. The company reported a probabilistic ICER within their original submission of £20,104 per QALY gained for pertuzumab alongside trastuzumab and docetaxel compared with trastuzumab and docetaxel, which was revised to £21,869 per QALY gained following the clarification process. After the clarification process, the ERG highlighted an error around the digitised curves which resulted in a new probabilistic ICER of £9,047 per QALY gained for pertuzumab alongside trastuzumab and docetaxel compared with trastuzumab and docetaxel.

There are uncertainties associated with the use of pCR as a surrogate measure for EFS and it does not appear to be a good predictor of the EFS data from the NeoSphere trial. The one-way sensitivity analysis suggests that the key driver of the model results is the pCR rates; however there are areas of uncertainty which have not been explored by the company within their analyses. The uncertainty around the model parameters for the PSA is inadequately characterised. An alternative analysis was undertaken by the company using the EFS data from the NeoSphere trial directly within the analysis, which suggested that pertuzumab, trastuzumab and docetaxel dominates (i.e. is more effective and less costly) compared with trastuzumab and docetaxel.

6. IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

6.1 ERG's base case ICER

The ERG's base case ICER is developed in stages in Tables 29 and 30. Table 29 shows the model results when the curves from the HER2-positive subgroup of the CTNeoBC meta-analysis were re-digitised by the ERG and the lognormal parametric distribution from the ERG's survival analysis was used for predicting EFS (see Section 5.3.1 for details). The incremental life years gained and QALYs gained are 0.471 and 0.340 respectively. The deterministic ICER estimated is £9,235 per QALY gained for pertuzumab, trastuzumab and docetaxel compared with trastuzumab and docetaxel, which is approximately consistent with the estimate from the company once they had corrected this error after the clarification process. The ERG's probabilistic ICER is estimated to be £9,897 per QALY gained, which is similar to the deterministic results.

Table 29. PSA results of the analysis using HER2-positive subgroup of the CTNeoBC and log normal distribution

Technologies	Total costs	Total LYG	Total QALYs	Incr costs (£)	Incr LYG	Incr QALYs	Incr £/LYG	ICER (£/QALY)
PHD	£132,782	15.39	10.54	£3,174	0.47	0.339	£6,752	£9,355
HD	£129,608	14.92	10.20					

PHD, Pertuzumab+ Trastuzumab+ docetaxel; HD, Trastuzumab+ docetaxel; LYG, life years gained; QALYs, Quality adjusted life years; ICER, incremental costs effectiveness ratio

Table 30 shows the model results when the lognormal parametric distribution from the ERG's survival analysis was used for predicting EFS for the whole life time horizon of 50 years. The incremental life years gained and QALYs are 0.365 and 0.262, respectively. These are lower than those in Table 29 as expected, because the patients progress according to the log normal distribution beyond seven years (as opposed to the assumption that they are cured in the earlier analysis). This increases the deterministic ICER to £23,467 per QALY gained for pertuzumab, trastuzumab and docetaxel compared with trastuzumab and docetaxel, which is similar to the probabilistic ICER of £23,264 per QALY gained.

Table 30. PSA results of the analysis using ERG's log normal distribution for the whole time horizon

Technologies	Total costs	Total LYG	Total QALYs	Incr costs (£)	Incr LYG	Incr QALYs	Incr £/LYG	ICER (£/QALY)
PHD	£171,401	14.03	9.53	£6,284	0.36	0.255	£17,578	£24,640
HD	£165,117	13.67	9.27					

PHD, Pertuzumab+ Trastuzumab+ docetaxel; HD, Trastuzumab+ docetaxel; LYG, life years gained; QALYs, Quality adjusted life years; ICER, incremental costs effectiveness ratio

6.2 Univariate sensitivity analysis

The incremental cost per QALYs from the ERG's univariate sensitivity analyses are shown within Table 31 below.

Table 31. Replication of the company's sensitivity analysis using the ERG's deterministic base case

Base case ICER £23,467/QALY					
Parametric distributions	**Base distribution**	**Alternate distribution**		ICER (£ per QALY)	
EFS curves	LogNormal parametric distribution	Log-Logistic parametric function		£27,291	
		Weibull parametric function		£39,282	
		Gompertz parametric function		£50,462	
		Exponential parametric function		£19,268	
		Generalised Gamma distribution		£23,467	
Parameter modified	**Base value (£)**	**High Value**	**Low Value**	**ICER High (£ per QALY)**	**ICER Low (£ per QALY)**
Transition probabilities and pCR parameters					
Split between metastatic and local regional recurrence	58% and 42% (Source: NeoSphere)	70% and 30% (Source: HERA)		£21,183	
Transition probability of moving from metastatic not progressed to death (HD)	3.15%	3.78% (BCV x 1.2)	2.52% (BCV x 0.8)	£24,014	£22,872
Transition probability of moving from metastatic not progressed to death (PHD)	2.73%	3.82% (BCV x 1.2)	2.18% (BCV x 0.8)	£26,473	£21,107
PHD pCR	39.25%	49.2%	30.0%	£5,959	£76,515
HD pCR	21.5%	30.5%	14.1%	£73,605	£9,139
Monthly risk of a second malignancy	0.76%	1.52% (BCV x 2)	0.38% (BCV x 0.5)	£20,185	£28,577
Model assumptions					
Vial sharing assumptions (Trastuzumab only)	Vial sharing	No Vial Sharing		£23,640	
Time horizon	50	50	30	£23,467	£26,416
Time point when setting treatment effect equal	7	6	5	£27,010	£32,241
Utilities					
Source1				£19,104	£29,335
EFS (first year)	0.696	0.8352	0.557		
EFS (subsequent years)	0.779	0.935	0.623		
Locoregional recurrence	0.696	0.835	0.557		
Remission	0.779	0.935	0.623		
Metastatic not-progressed	0.685	0.822	0.548		
Metastatic progressed	0.452	0.542	0.362		

		All values are BCV x 1.2	All values are BCV x 0.8		
Source 2 EFS (first year) EFS (subsequent years) Locoregional recurrence Remission Metastatic not-progressed Metastatic progressed	As above	 0.696 0.85 0.696 0.85 0.685 0.452		£24,044	
Costs					
LR supportive care costs health state costs	£74	£103.60	£44.40	£23,452	£23,483
Pharmacy cost	£10	£13.44	£5.76	£23,482	£23,453
Cardiac assessment proportion	30/70 (MUGA/ECHO) proportion	10/90 (MUGA/ECHO) proportion	50/50 (MUGA/ECHO) proportion	£23,498	£23,437
Event free survival supportive care cost (monthly)	£67.85 (year 1-2), £15.11 (year 3-5), £3.83 (year 5+)	BCVs x 1,25	BCVs x 0,75	£23,457	£23,478
AE cost	£794.66 (PHD Arm), £742.47 (HD Arm)	£1112.52 (BCV x 1.4), £1039.46 (BCV x 1.4)	£476.79 (BCV x 0.6), £445.48 (BCV x 0.6)	£23,547	£23,388
Metastatic not progressed supportive care costs (monthly)	£232	£324.8 (BCV x 1.4)	£139.20 (BCV x 0.6)	£23,269	£23,666
Administration cost (monthly)	£326.60 (for 1st treatment), £174.60 (for subsequent treatment)	£457.24 £244.44	£195.96 £104.76	£24,294	£22,640
Metastatic progressed disease supportive care cost (monthly)	£185	£259 (BCV x 1.4)	£111 (BCV x 0.6)	£23,261	£23,673
BCV, Base Case Value; PHD, pertuzumab, trastuzumab, docetaxel; HD, trastuzumab, docetaxel; AE, Adverse Event; LR, Locoregional recurrence					

Table 32. Additional sensitivity analysis undertaken by the ERG

Parameter modified	Base value (£)	High Value	Low Value	ICER High (£ per QALY)	ICER Low (£ per QALY)
Costs of metastatic treatments					
costs of 'metastatic not progressed' state	£3,822	£5,759 (Source: CS model)	£2,292 (Source: CS model)	£17,070	£26,827
costs of 'metastatic progressed' state	£5,923	£6,689 (Source: CS model)	£2,223 (Source: CS model)	£21,336	£33,755
Number of cycles of pertuzumab					
Only costs amended (pCR rates same as NeoSphere trial)	4 (Source: NeoSphere)	6 (Source: TRYPHAENA)	3 (Source: TRYPHAENA)	£42,995	£14,353
Costs and pCR rates amended (for pertuzumab arm only using TRYPHAENA trial)	4 (Source: NeoSphere)	6 (Source: TRYPHAENA)	3 (Source: TRYPHAENA)	£3,517	Dominant
Costs and pCR rates amended (for both arms, based on TRYPHAENA and absolute differences from Neopshere trial)	4 (Source: NeoSphere)	6 (Source: TRYPHAENA and NeoSphere)	3 (Source: TRYPHAENA and NeoSphere)	£43,203	£14,228
Cost of locoregional recurrence					
Costs replaced to surgery costs	£1,831	£2,519 (Source: Rafia *et al.*[53])		£23,105	
including Docetaxel costs in locoregional recurrence costs	0	43.9 (Source: CS model)		£23,424	

Parameter modified	Base value (£)	High Value	Low Value	ICER High (£ per QALY)	ICER Low (£ per QALY)
Utilities					
EFS (first year) EFS (subsequent years) Locoregional recurrence Remission Metastatic not-progressed Metastatic progressed	0.696 0.779 0.696 0.779 0.685 0.452	0.749 0.847 0.810 0.847 0.484 0.484 (Source: Essers *et al.* [46])		£21,023	
QoL decrement due to adverse events in first year of EFS					
Trastuzumab	0	-0.083	-0.0415	£28,665	£25,776
Pertuzumab only	0	-0.083	-0.0415	£33,996	£27,767
Pertuzumab only (3 months)	0	-0.083	-0.0415	£25,481	£24,433
Using EFS curves directly from NeoSphere					
Structural change based on company's additional analysis				£3,792	

Table 31 suggests that the parametric distribution chosen for extrapolation of EFS has the biggest impact on the ICER. The ICER varied from £50,462 per QALY gained when a Gompertz function was used compared to £8,816 per QALY gained when a Generalised gamma distribution was used. However, these curves are less likely to be clinically appropriate over the long-term compared with the curve based on the lognormal distribution (see Section 5.3.1).

Among the sensitivity analyses replicated using the parameters and ranges chosen by the company, the other key drivers of the model are the pCR rates for the treatment and comparator, with ICERs ranging from £5,959 per QALY gained to £76,515 per QALY gained, depending on the pCR values chosen for analysis. The choice of time point at which the treatment effect is assumed to become equal also has a substantial impact upon the model results, with ICERs of £27,010 per QALY gained and £32,241 per QALY gained for 6 and 5 years, respectively. The rest of the parameters chosen by the company do not have a significant impact on ICER.

In the additional sensitivity analyses performed by the ERG (see Table 32), the costs of second line metastatic treatment had the biggest impact upon the model results, with the ICER ranging from £21,336 per QALY gained to £33,765 per QALY gained depending on which treatment cost is used. Increasing the number of cycles of pertuzumab (but assuming the pCR rates remain the same) and assuming disutility for pertuzumab (for a whole year) also increase the ICERs to £42,995 per QALY gained and £33,996 per QALY gained respectively.

When the ERG replicated the analysis using the EFS data directly from the NeoSphere trial, the ICER was £3,792/QALY.

7. END OF LIFE

The CS does not propose a case for meeting End of Life criteria.

To meet NICE End of Life criteria all of the below must be satisfied:

1) The treatment is indicated for patients with a short life expectancy, normally less than 24 months and;
2) There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment, and;
3) The treatment is licensed or otherwise indicated, for small patient populations.

The trials were not powered to estimate OS because few patients die within the trial follow up period of 5 years. Fewer than 8% of the patients died at the end of follow-up in the trastuzumab plus docetaxel and pertuzumab plus trastuzumab plus docetaxel arms of the NeoSphere trial.[4]

The model predicts that more than 99% of patients will be alive at 24 months within both the comparator and treatment arms. The company estimated that the eligible population would be approximately 1,380 patients per year. Thus, the ERG believes that criterion 3 for end of life may be met by neoadjuvant pertuzumab for this patient group; however, criteria 1 and 2 would not be met.

8. OVERALL CONCLUSIONS

Clinical effectiveness

The efficacy (in terms of pCR response [using various definitions]) and safety of pertuzumab in combination with trastuzumab and chemotherapy was positively demonstrated (compared with trastuzumab and chemotherapy) in the key included studies. However, there are a number of limitations and uncertainties in the evidence base which warrant caution in its interpretation. Due to the phase II, open-label design, treatment effects (including magnitude) may be confounded. The key uncertainties in the evidence base relate to the use of pCR as a surrogate endpoint for survival outcomes (including magnitude of benefit) in the neoadjuvant treatment of breast cancer, the lack of results from high quality phase III RCTs, and the generalisability of the trial results to England.

Cost effectiveness

The *de novo* model developed is generally appropriate for the decision problem defined in the final scope, , though it should be noted that the only comparator tested within the economic evaluation was trastuzumab alongside docetaxel. The model was generally well described within the report. The model structure was considered by the ERG to be reasonable, however there are uncertainties associated with the use of pCR as a surrogate measure for EFS and it does not appear to be a good predictor of the EFS data from the NeoSphere trial. The company's probabilistic ICER using this surrogate outcome is £20,104 per QALY gained for pertuzumab alongside trastuzumab and docetaxel compared with trastuzumab and docetaxel, which was revised to £21,869 per QALY gained following the clarification process. The ERG have corrected an error in the digitisation of the curves and modified the clinically inappropriate assumption that recurrence is zero after 7 years. Whilst these changes individually impact upon the ICER substantially, because they act in different directions, incorporated together they do not alter the model results provided by the company substantially. The ERGs probabilistic base case is £23,264 per QALY gained. An alternative analysis was undertaken by the company using the EFS data from the NeoSphere trial directly within the analysis, which suggested that pertuzumab, trastuzumab and docetaxel dominates (i.e. is more effective and less costly) compared with trastuzumab and docetaxel alone. The univariate sensitivity analysis suggested that the key drivers of the model results are: the relative pCR rates associated with the interventions; the parametric distribution employed for extrapolation of EFS; whether the treatment effect is assumed to continue beyond the trial follow-up duration; the number of cycles of pertuzumab administered and health utility values.

8.1 Implications for research

As highlighted in the report (section 4.2.4.1), the validity of pCR as a surrogate endpoint for long-term disease outcomes (including magnitude of benefit in survival) remains uncertain. Further meta-analyses of neoadjuvant treatment trials in breast cancer are needed to more reliably assess the relationships between pCR and EFS and OS across the different subtypes of breast cancer.

There are no prospective phase III trials either planned or in progress comparing the clinical and cost effectiveness of pertuzumab containing regimens in the neoadjuvant setting with the current chemotherapy plus trastuzumab standard of care regimens used in England. However, it is expected that the large phase III APHINITY study[14] of chemotherapy and trastuzumab plus or minus pertuzumab in the postoperative adjuvant setting, which is currently in follow up and expected to report first findings in 2017, will largely address this issue.

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10. APPENDICES

Appendix 1 ERG's amended search strategy for HRQoL data

Database: Embase <1974 to 2016 February 12>
Search Strategy:
---

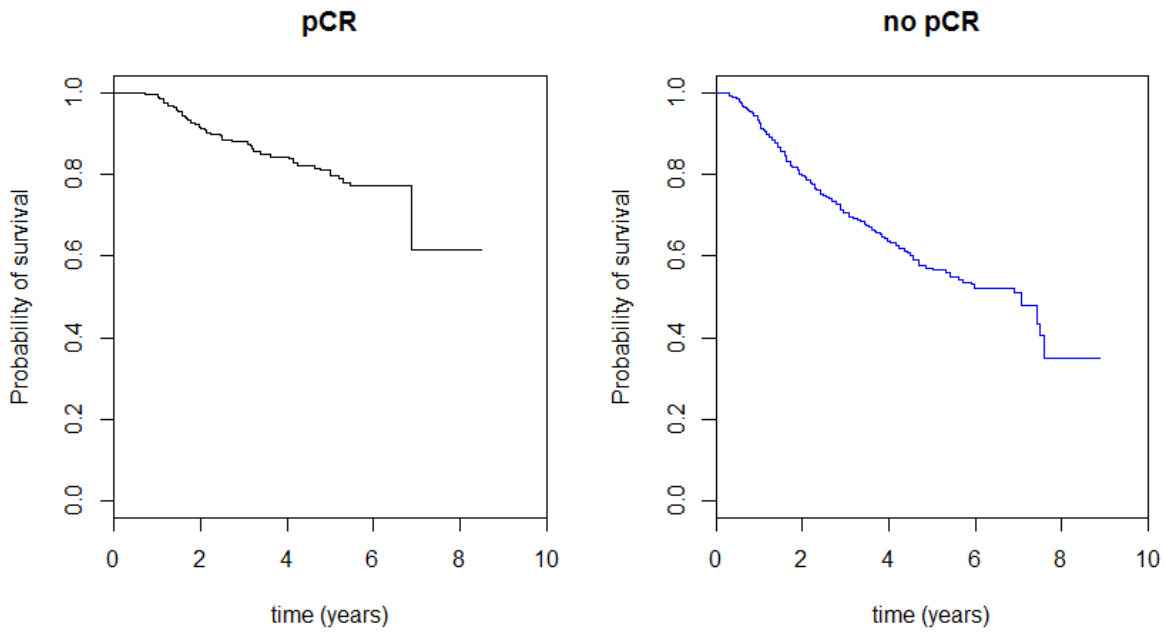
1 exp neoplasm/ (3583377)
2 (cancer* or malignanc* or tumor* or tumour* or carcinoma* or neoplasm*).ti,ab. (3077460)
3 1 or 2 (4243762)
4 breast/ (79265)
5 (breast or mamma*).ti,ab. (770434)
6 4 or 5 (781910)
7 3 and 6 (434357)
8 exp breast cancer/ or exp breast tumor/ (405660)
9 7 or 8 (510344)
10 exp "quality of life"/ (327902)
11 quality of life.ti. (67552)
12 (hql or hrql or hrqol or hqol).ti,ab. (18814)
13 quality of life index.ti,ab. (1761)
14 qwb.ti,ab. (213)
15 quality of well being.ti,ab. (400)
16 quality of wellbeing.ti,ab. (22)
17 (hui or hui 2 or hui2 or hui 3 or hui3).ti,ab. (1510)
18 (time trade off or time tradeoff or tto).ti,ab. (1873)
19 (utilit$ adj2 (value$1 or cost$1 or health or analys$ or index)).ti,ab. (10657)
20 health state$1.ti,ab. (6976)
21 (hye or healthy year$1 equivalent$).ti,ab. (105)
22 standard gamble$.ti,ab. (873)
23 discrete choice experiment$.ti,ab. (1011)
24 conjoint analysis.ti,ab. (610)
25 (euroqol or euroquol or EQ 5D or eq5d).ti,ab. (9815)
26 visual analog$ scale$.ti,ab. (48439)
27 visual analog scale/ (47994)
28 (sf 36 or sf36 or sf thirtysix or sf thirty six or short form 36 or short form thirty six or shortform thirty six or shortform 36).ti,ab. (28276)
29 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or short form six or shortform six).ti,ab. (1696)
30 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or short form twelve or shortform twelve).ti,ab. (5604)
31 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 (402641)
32 conference.so. (2176547)
33 9 and 31 (16271)
34 limit 33 to english language (15048)
35 34 not 32 (10998)
36 (neo-adjuvant* or neoadjuvant* or pathologic* or pCR or tpCR or bpCR or operable or early or inflammatory or "locally advanced" or preoperative or "pre-operative" or "pre-surgery" or "before surgery").mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (3367339)
37 ((preliminary or primary) adj3 (therapy or treatment or chemotherapy or systemic or target?ed)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (72295)

38 36 or 37 (3420639)
39 epidermal growth factor receptor 2/ or oncogene neu/ (33517)
40 (HER2* or HER 2* or HER-2* or "Human epidermal growth factor receptor 2" or "erbB-2" or "erbB2" or "erbB 2").mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (48551)
41 39 or 40 (59328)
42 35 and 38 and 41 (205)
43 remove duplicates from 42 (203)

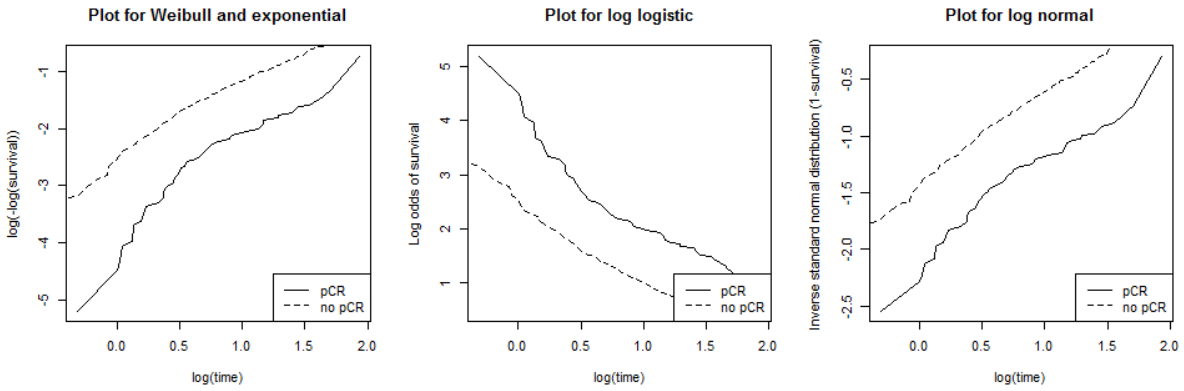
Appendix 2. ERG's statistical analyses from Cortazar meta-analysis (HER2 positive patients only)

Fitting survival curves

Plot of KM survival estimates after reconstructing digitized KM plots for HER2 patients only from Cortazar meta analysis:



Exploratory plots to indicate which model may be appropriate:



Fitting independent parametric models to the data

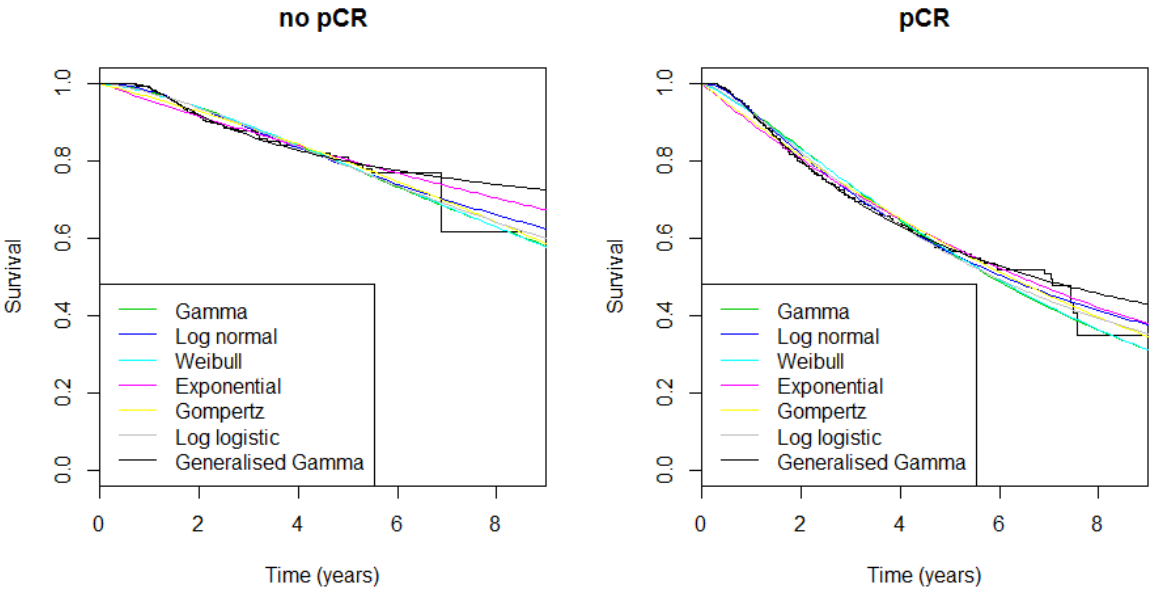
Parameter estimates

Subgroup	Distribution	scale	shape	intercept
no pCR	exponential	0.10809(rate)		
no pCR	weibull	7.926	1.225	
no pCR	lognormal	1.8076(mean)	1.2314(sd)	
no pCR	loglogistic	5.8878	1.4246	
no pCR	gompertz	0.09954(rate)	0.03707	
no pCR	gamma	0.1804 (rate)	1.3646	
no pCR	Generalised Gamma	1.4300	1.4405	-0.9057
pCR	exponential	0.04391		
pCR	weibull	13.705	1.426	
pCR	lognormal	2.595(mean)	1.247(sd)	
pCR	loglogistic	11.72	1.52	
pCR	gompertz	0.03347	0.11732	
pCR	gamma	0.1186 (rate)	1.5965	
pCR	Generalised Gamma	1.102	1.518	-3.992

Goodness of fit information

	pCR		**no pCR**	
	AIC	**BIC**	**AIC**	**BIC**
Gamma	723.6371	732.383728	3034.653	3045.146
Log normal	714.3209	723.067493	2990.189	3000.682
Log logistic	723.2482	731.994864	3019.448	3029.941
Gompertz	735.2654	744.012072	3065.816	3076.308
Weibull	725.6942	734.44084	3042.928	3053.421
Exponential	736.3581	740.731424	3065.593	3070.839
Generalised gamma	700.4181	713.538	2978.0326	2993.772

Plots of survival functions:



Variance-covariance matrices:

1) Exponential

No pCR	pCR
rate rate 0.002105263	rate rate 0.01123595

2) Weibull

No pCR	pCR
shape scale shape 0.001532528 -0.001007871 scale -0.001007871 0.002065702	shape scale shape 0.008606957 -0.009960131 scale -0.009960131 0.017052516

3) Log-normal

No pCR	pCR
meanlog sdlog meanlog 0.002575455 0.001070277 sdlog 0.001070277 0.001255281	meanlog sdlog meanlog 0.02090215 0.010373134 sdlog 0.01037313 0.007298785

4) Log-logistic

No pCR	pCR
shape scale shape 0.0014872561 -0.0008746562 scale -0.0008746562 0.0021300747	shape scale shape 0.008405826 -0.009091639 scale -0.009091639 0.015763528

5) Gompertz

No pCR	pCR
shape rate shape 0.000761342 -0.001729505 rate -0.001729505 0.006034100	shape rate shape 0.004301095 -0.01058182 rate -0.010581823 0.03727127

6) Gamma

No pCR	pCR
shape rate shape 0.002755620 0.004304484 rate 0.004304484 0.008097849	shape rate shape 0.01364608 0.02584618 rate 0.02584618 0.05439356

7) Generalised gamma

No pCR	pCR
mu sigma Q mu 0.016405821 -0.001185631 0.028511351 sigma -0.001185631 0.001543638 -0.004756796 Q 0.028511351 -0.004756796 0.059544503	mu sigma Q mu 0.10527128 0.03428597 0.32611263 sigma 0.03428597 0.01559347 0.09426122 Q 0.32611263 0.09426122 1.12193081