NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Pertuzumab for adjuvant treatment of HER2-positive early breast cancer [ID1192]

Committee Papers

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Pertuzumab for adjuvant treatment of HER2-positive early breast cancer [ID1192]

Contents:

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

Pre-meeting briefing

Pertuzumab for the adjuvant treatment of HER2-positive breast cancer

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- 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

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting

Key decision points

1. The APHINITY trial did not include people who had prior neoadjuvant therapy (biologic or chemo) - how generalizable are the results of the APHINITY trial?
2. Is invasive disease-free survival (IDFS) a reliable surrogate outcome for overall survival (OS)?
3. Does adding pertuzumab to trastuzumab and chemotherapy result in a meaningful clinical benefit?
4. Are node positive patients (included in company's main economic analysis) a clinically relevant subgroup? Do they experience greater treatment benefit?
5. Are hormone receptor negative patients a clinically relevant subgroup?
6. Are there any other subgroups who fall within marketing authorisation (MA) that are clinically relevant/might be expected to experience greater treatment benefit (the exclusion of other subgroups was not justified)

Preview: Clinical effectiveness and treatment pathway issues

- Does the committee believe that the available evidence from the APHINITY trial is generalizable to English setting given that the patients receiving pertuzumab had not received any prior neoadjuvant treatment despite being considered high risk?
- Is the evidence presented for treatment benefit and health-related quality of life impact in the ITT population robust?
- Does the committee accept the methodology used by the company to explore the treatment effect in different subgroups?
- Does the committee accept that pertuzumab has a greater treatment effect in the lymph-node positive population compared to:
  - The overall HER2+ population?
  - Other subgroups?

Preview: Cost-effectiveness issues

- Does the committee accept the company's approach to modelling the cost effectiveness of pertuzumab? Specifically, does it accept the way in which IDFS outcome data from the APHINITY study has been extrapolated/adjusted in the company's model?
- What is the appropriate length of treatment effect?

Early or locally advanced breast cancer

- Breast cancer arises from the tissues of the ducts or lobules of the breast.
  - Approximately 46,500 people diagnosed with breast cancer in England in 2014
  - Third most common cause of cancer death in 2014.
- Terminology and clinical staging:
  - ‘Early’ breast cancer describes tumours that are restricted to the breast, or the breast and nearby lymph nodes and have not spread to other parts of the body (clinical stages 1 and 2)
  - ‘Locally advanced’ breast cancer describes tumours larger than 5 cm that may have grown into the skin or muscle of the chest or nearby lymph nodes but have not spread to other parts of the body (clinical stage 3)
  - Around 35% of those with early or locally advanced disease will progress to metastatic breast cancer. 5 year survival rate for metastatic breast cancer in England is 15%

Human epidermal growth factor receptor 2 (HER2)

- Human epidermal growth factor is a naturally occurring protein in the body that attaches itself to HER2 receptors on breast cancer cells, it can stimulate the cancer cells to divide and grow.
- Some breast cancer cells overexpress HER2 receptors and are described as HER2-positive.
- 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).
- HER2-positive tumours:
  - are associated with aggressive disease and poor prognosis, and,
  - patients are ~5 years younger than the average breast cancer population

Patient perspective

"All treatments have side effects. Treatment with chemotherapy usually has a number of unpleasant side effects which can have a significant impact on everyday activities, ability to work, social life and relationships. Hormone therapy can also have unpleasant menopausal side effects that can make it difficult for women to complete the recommended course of therapy. Targeted therapies for HER2 breast cancer tend to be better tolerated"

"A diagnosis of breast cancer will cause considerable anxiety to the patient as well as their family and friends. The initial diagnosis can be shocking and in the longer-term, the fear of breast cancer returning or spreading […] can cause considerable stress for both the patients and their loved ones"

"One potential disadvantage [of pertuzumab is] its method of administration […] Patients may need to spend longer in hospital to receive this treatment as pertuzumab and trastuzumab will be delivered intravenously where given together. However, the reduced risk of recurrence may outweigh the potential inconvenience to patients of spending longer in hospital"

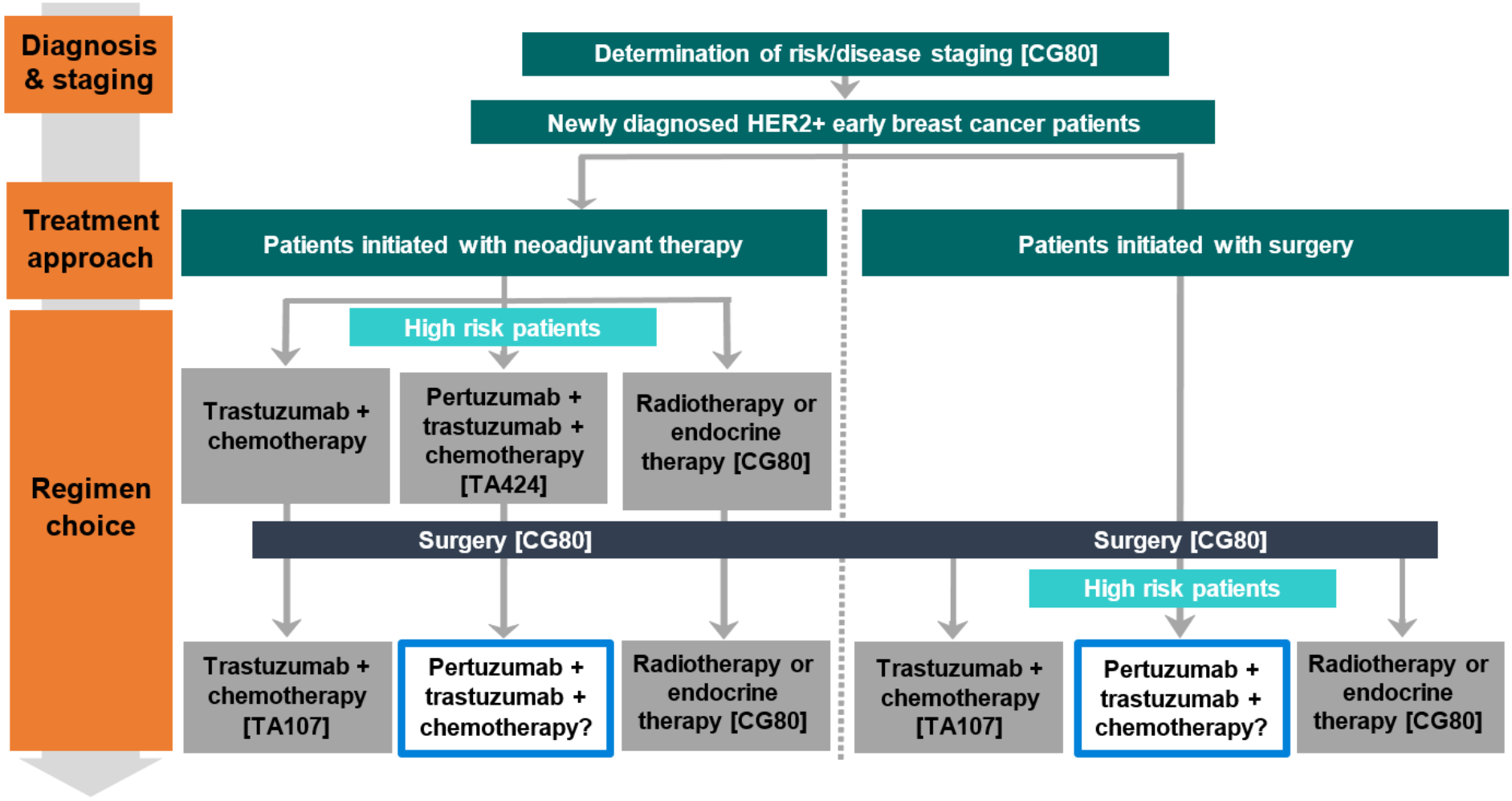
"Any treatment that improves outcomes is a welcome step forward"

Pertuzumab (Perjeta)

Mechanism of action	Pertuzumab is a recombinant monoclonal antibody which targets HER2-positive breast tumours. The antibody binds to HER2 receptor proteins on breast cancer cells. In doing so it prevents the HER2 receptors from binding to growth factor proteins which can cause the cancer cells to divide and grow
Positive CHMP opinion received on 26th April 2018	In combination with trastuzumab and docetaxel as adjuvant treatment of patients with HER2-positive early breast cancer at high risk of disease recurrence
Administration	Intravenous (IV) in combination with trastuzumab and docetaxel for a total of one year (maximum of 18 cycles) regardless of the timing of surgery.
Dose	840 mg loading dose, then 420 mg every three weeks
Cost (list price)	£2,395 per 420 mg vial
Patient access scheme	Commercial access agreement approved by Department of Health which provides a simple discount to list price

How is HER2-positive breast cancer treated?

Summary of the clinical care pathway and proposed placement of adjuvant pertuzumab (adapted from figure 1 in section B.1.3.3 of company submission)



Decision problem – NICE vs. Company

Population in company's decision problem is in line with marketing authorisation

Population	
NICE scope	Company submission
People with early or locally advanced HER2-positive breast cancer who have undergone surgery	People with early or locally advanced HER2-positive breast cancer who have undergone surgery *and are at **high risk of recurrence***

Company submission argues that lymph node-positive and hormone (oestrogen or progesterone) receptor-negative patients are at higher risk of recurrence

Decision problem – NICE vs. Company

Company's decision problem reflects APHINITY trial outcomes

Outcomes	
NICE scope	Company submission
• Overall survival (OS) • Disease-free survival (DFS) • Recurrence-free interval (RFI) • Adverse effects of treatment • Health-related quality of life (HRQoL)	• OS • Disease Free Survival • Recurrence-free interval (RFI) • Adverse effects of treatment • HRQoL • Invasive Disease-Free Survival (IDFS) *excluding* second primary non-breast cancer events *[this was the primary endpoint in the APHINITY trial and company submission]* • IDFS (including second primary non-breast cancer events [STEEP definition]) • Distant recurrence-free interval (DRFI)

The company's primary IDFS endpoint was defined as *"time from randomization until the date of the first occurrence of one of the following events: recurrence of ipsilateral invasive breast tumour, recurrence of ipsilateral locoregional invasive disease, a distant disease recurrence, contralateral invasive breast cancer, or death from any cause"*

Clinical effectiveness evidence

Company submission, section B2

Key trial: APHINITY study

Design	Phase III, randomised, double-blind placebo-controlled trial
Population	Patients **newly diagnosed** with primary invasive HER2-positive breast cancer (N=4,805)
Intervention	Pertuzumab + trastuzumab + standard chemotherapy
Comparator	Placebo + trastuzumab + standard chemotherapy
Primary outcomes	IDFS excluding second primary non-breast cancer events
Secondary outcomes	IDFS including second primary non-breast cancer (STEEP definition); DFS; OS; RFI; DRFI; cardiac safety; overall safety; HRQoL
Follow-up	3-years
Stratification groups	**Nodal status**, chemotherapy regimen, **hormone receptor status**, geographic region, and **protocol version (A or B)**

The company's submission includes clinical evidence for the ITT population but the main economic model is specific patients with lymph node-positive disease. They also present cost effectiveness data for patients with hormone (oestrogen or progesterone) receptor-negative disease:

- These subgroups were named in the NICE scope
- The APHINITY study was not powered for subgroups
- The company stated that after 3,655 patients, the protocol was amended to prevent further enrolment of patients with node-negative disease; an additional 1,000 node-positive patients were then included

Patient characteristics – ITT population

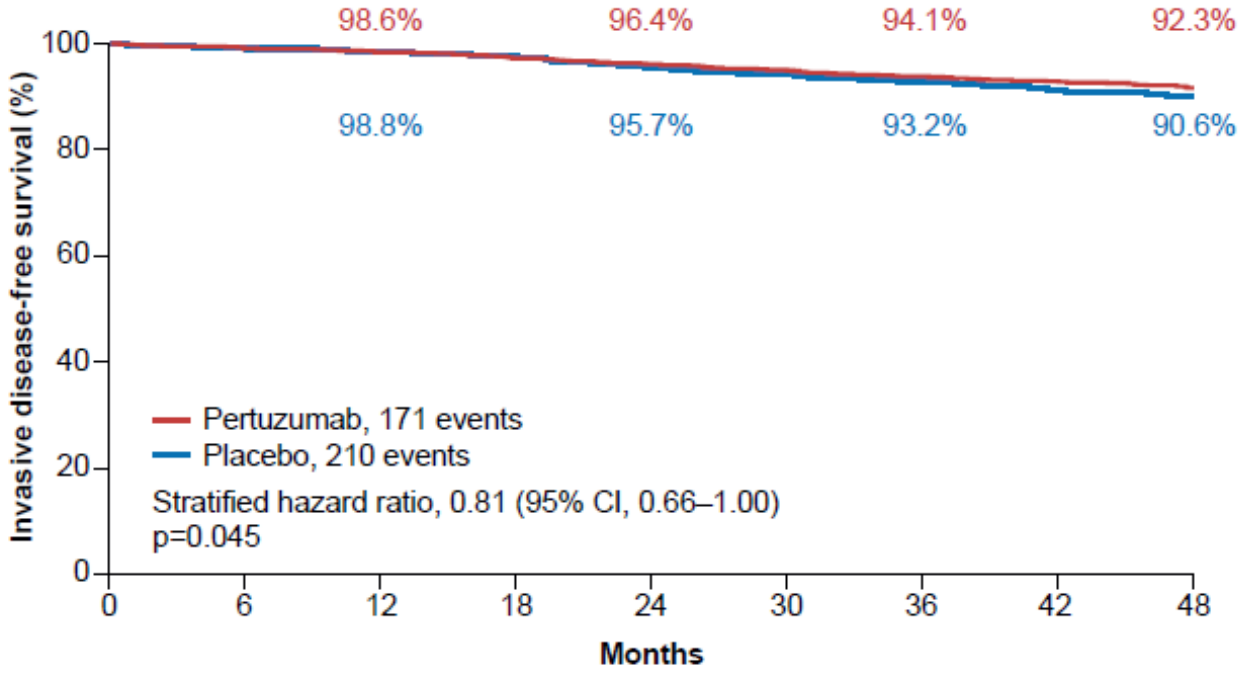
Characteristic	Pertuzumab	Placebo
Age, median, range (years)	51.0 (22–86)	51.0 (18–85)
<65 years ≥65 years	86.9% 13.1%	87.8% 12.2%
Race, white / Asian / Other	71.2 / 24.7 / 4.1%	70.5 / 24.9 / 4.6%
USA	12.3%	12.2%
Canada/Western Europe/ Australia-New Zealand/South Africa	53.9%	53.6%
Eastern Europe	8.3%	8.3%
Asia-Pacific / Latin America	22.9 / 2.5%	23.2 / 2.7%
Type of primary surgery		
Mastectomy / Breast conserving surgery	53.3 / 46.7%	55.2 / 44.8%
Adjuvant radiotherapy		
Yes / no	72.2 / 27.8	72.8 / 27.2

Differences across ITT treatment groups were not tested for statistical significance but appeared well balanced

Question for committee: is this evidence generalizable to English population?

Primary outcome: IDFS excluding second primary non-breast cancer events

Marginal benefit in ITT population



No. at Risk									
Pertuzumab	2400	2309	2275	2236	2199	2153	2101	1687	879
Placebo	2404	2335	2312	2274	2215	2168	2108	1674	866

The pre-specified primary analysis was conducted after 379 IDFS events (19th December 2016) in the ITT population. The 3-year event-free rates were derived from Kaplan-Meier estimates. Hazard ratio (95% CIs) was estimated by Cox-regression. One patient was excluded from ITT population due to falsification of personal information

- Treatment benefit demonstrated in ITT population but borderline statistical significance - ERG note company assumption that effect was maintained until year 7 not well substantiated. ERG tested impact of shorter treatment duration in their revised model
- ERG noted that curves only begin to diverge around 20 months – treatment effect appears delayed

IDFS in ITT population cont.

Results for primary and secondary IDFS outcomes are similar

Outcome definition	Pertuzumab (n=2,400)	Placebo (n=2,404)	HR (95% CI; P value)
Primary outcome: IDFS excluding second primary non-breast cancer events	94.1	93.2	0.81 (0.66, 1.00; 0.045)
Secondary outcome: IDFS including second primary non-breast cancer events	93.5	92.5	0.82 (0.68, 0.99; 0.043)

- In the ITT population findings are very similar for both IDFS definitions
- Primary outcome was associated with the more conservative of the two estimates of effect. The use of this IDFS *excluding* second primary non-breast cancer events is unlikely to result in overestimation of treatment benefit compared to the secondary outcome definition
- However, as already noted, the treatment effect is of borderline statistical significance and the ITT population data was not used in the company's economic analysis (no evidence to determine if the findings were the same in the key subgroups)

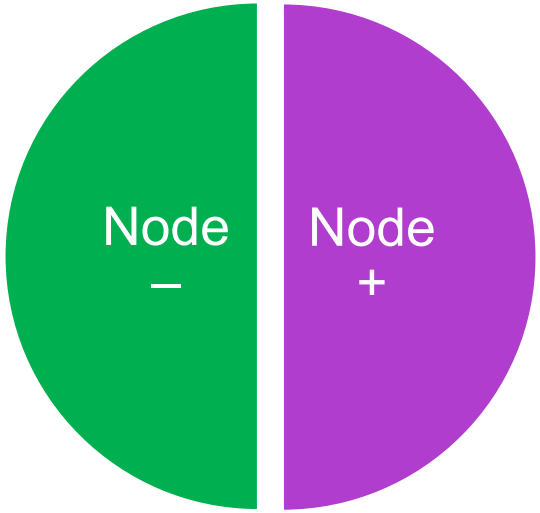
Secondary efficacy outcomes for ITT population
Marginal benefit in DFS and RFS

Outcome	Pertuzumab (n=2,400)	Placebo (n=2,404)	HR (95% CI); P value
Overall survival (OS)	97.7	97.7	0.89 (0.66, 1.21; 0.467)
Disease-free survival (DFS)	93.4	92.3	0.81 (0.67, 0.98; 0.033)
Recurrence-free interval (RFS)	95.2	94.3	0.79 (0.63, 0.99; 0.043)
Distant recurrence-free interval (DRFI)	95.7	95.1	0.82 (0.64, 1.04; 0.101)

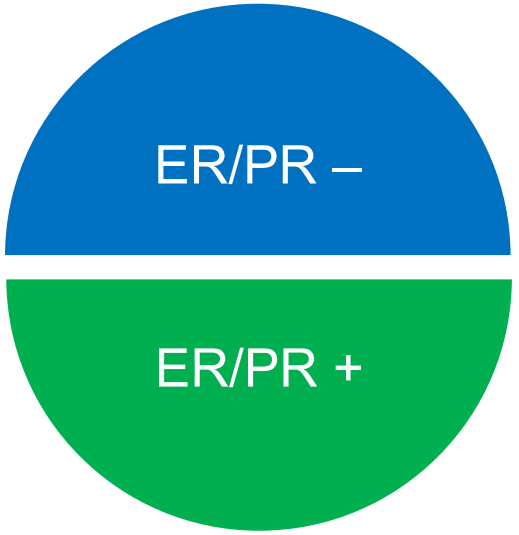
- Findings for DFS and RFI show borderline statistically significant treatment benefit
- No survival benefit – however data are immature (only 26% of the events required for the final analysis of OS having occurred (i.e. 169 deaths of the 640 deaths planned at the final OS analysis))
- ERG noted that Kaplan-Meier plots were not presented for the secondary outcomes

Subgroups prioritised by company

ITT population HER2+ N=4,805; Pertuzumab n=2,400 vs. Placebo n=2,404
(Safety population N=4,769; Pertuzumab n=2,364 vs. Placebo n=2,405)



Prioritised Node-positive subgroup n=3,005; Pertuzumab n=1,503 vs. Placebo n=1,502



Also considered Hormone receptor-negative subgroup n=1722; pertuzumab n=864 vs. placebo n=858

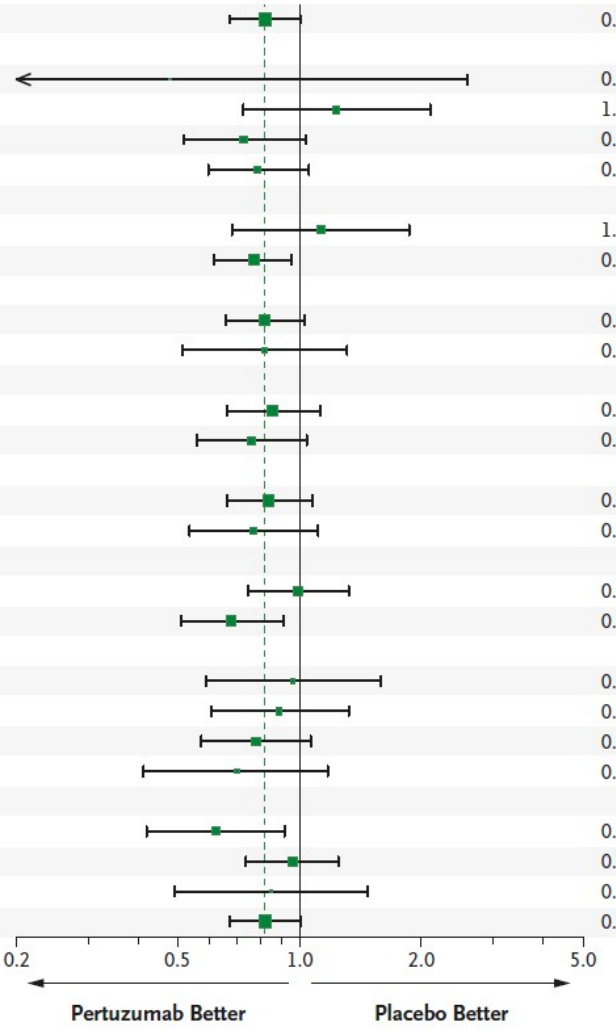
The ERG noted that baseline characteristics were well balanced across the treatment arms of the nodal status and hormone-receptor subgroups

Patients with node-negative tumours between 0.5 and 1.0 cm were initially eligible if they met one of three additional criteria: tumour grade 3, age <35 years, or hormone-receptor (ER/PgR) positive. However, enrollment of patients with node-negative tumors ≤1 cm was limited to <10% of the total number of randomised patients and **following the protocol amendment patients with node-negative disease were excluded completely**

Subgroup results – IDFS

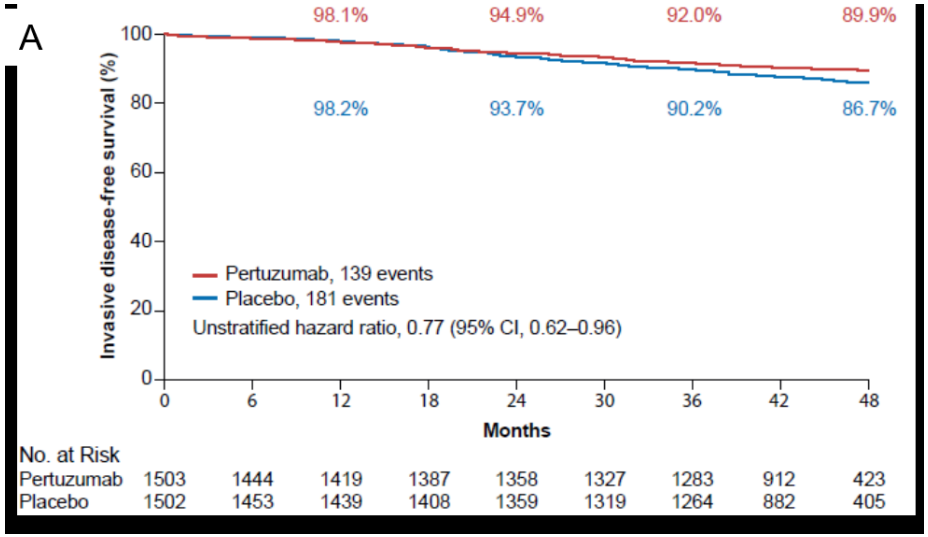
Forest plot for different subgroups in the ITT population (primary analysis, clinical cut-off date 19th December 2016)

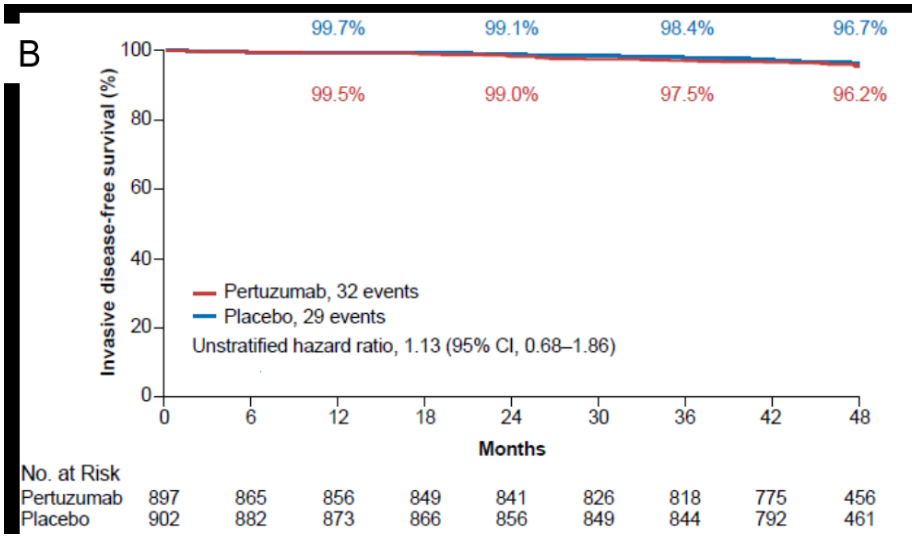
Subgroup	Pertuzumab	Placebo	Unstratified Hazard Ratio for Invasive-Disease Event (95% CI)	3-Yr Invasive Disease–free Survival Rate		P Value for Interaction
				Pertuzumab	Placebo	
	no. of patients with an invasive-disease event/total no.			%		
All patients	171/2400	210/2404	0.82 (0.67–1.00)	94.1	93.2	NA
No. of positive nodes						0.37
0 Positive nodes, tumor ≤1 cm	2/90	4/84	0.48 (0.09–2.60)	97.7	97.5	
0 Positive nodes, tumor >1 cm	30/807	25/818	1.23 (0.72–2.10)	97.5	98.5	
1–3 Positive nodes	55/907	75/900	0.73 (0.52–1.04)	94.9	93.8	
≥4 Positive nodes	84/596	106/602	0.79 (0.59–1.05)	87.5	84.7	
Nodal status						0.17
Node-negative	32/897	29/902	1.13 (0.68–1.86)	97.5	98.4	
Node-positive	139/1503	181/1502	0.77 (0.62–0.96)	92.0	90.2	
Adjuvant chemotherapy regimen						1.00
Anthracycline	139/1865	171/1877	0.82 (0.66–1.03)	93.8	93.0	
Nonanthracycline	32/535	39/527	0.82 (0.51–1.31)	94.9	94.0	
Hormone-receptor status						0.54
Positive	100/1536	119/1546	0.86 (0.66–1.13)	94.8	94.4	
Negative	71/864	91/858	0.76 (0.56–1.04)	92.8	91.2	
Protocol version						0.69
Protocol A	120/1828	143/1827	0.84 (0.66–1.08)	94.7	94.1	
Protocol B	51/572	67/577	0.77 (0.53–1.11)	91.9	90.6	
Menopausal status at screening						0.07
Before menopause	93/1152	96/1173	0.99 (0.75–1.32)	93.5	93.7	
After menopause	78/1242	113/1220	0.68 (0.51–0.91)	94.5	92.7	
Age group						0.78
<40 yr	30/326	32/327	0.96 (0.59–1.59)	93.4	93.1	
40–49 yr	48/708	53/702	0.89 (0.60–1.32)	94.5	94.3	
50–64 yr	69/1051	91/1082	0.78 (0.57–1.07)	94.3	93.3	
≥65 yr	24/315	34/293	0.70 (0.41–1.17)	92.9	90.6	
Tumor size						0.20
<2 cm	41/977	64/944	0.62 (0.42–0.92)	97.0	94.6	
2 to <5 cm	108/1273	115/1283	0.96 (0.74–1.24)	92.5	93.0	
≥5 cm	22/147	31/174	0.85 (0.49–1.47)	87.5	87.5	
Female sex	171/2397	209/2396	0.82 (0.67–1.01)	94.1	93.2	NA



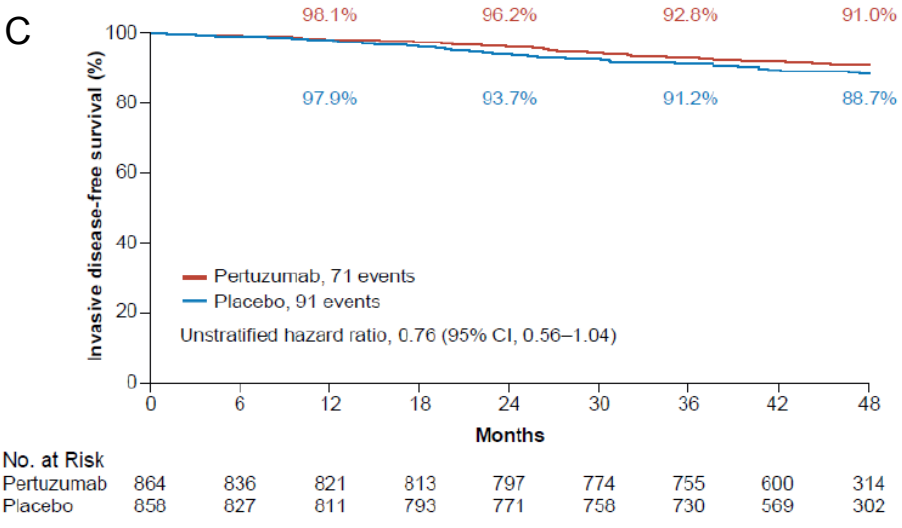
IDFS in subgroups prioritised by company

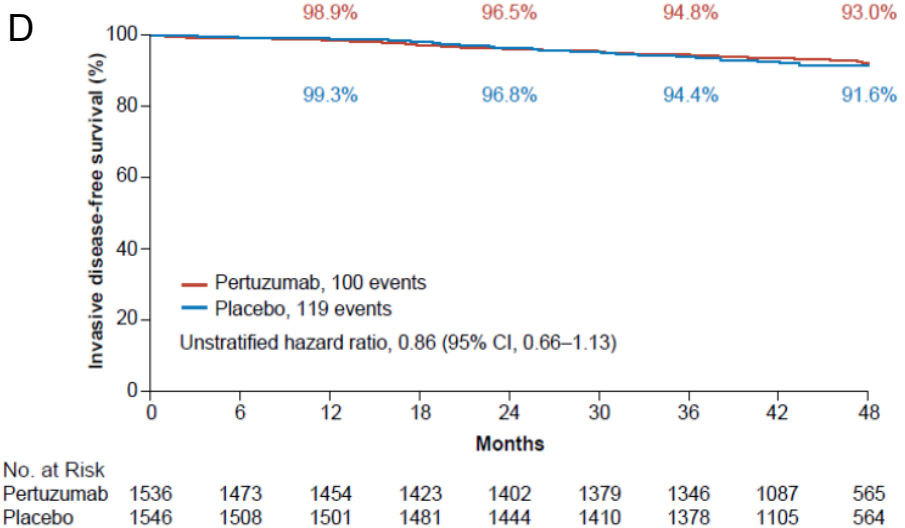
IDFS improved in lymph node-positive subgroup (figure A); no benefit in lymph node-negative subgroup (figure B); P value for interaction: 0.17





No statistically significant benefit in either the hormone receptor-negative (figure C) or hormone receptor positive subgroup (figure D); P value for interaction: 0.54





IDFS in ITT vs. subgroup populations

Population	F/U	Pertuzumab	Placebo	HR (95% CI)
ITT population (N=4,804)		n=2,400	n=2,404	
Median f/u: 45.4 mo	3 years	94.1	93.2	0.81 (0.66, 1.00)
	4 years	93.2	90.6	
Lymph node-positive patients (n=3,005)		n=1,503	n=1,502	
Median f/u: 44.5 mo	3 years	92.0	90.2	0.77 (0.62, 0.96)
	4 years	89.9	86.7	
Hormone receptor negative patients (n=1,722)		n=864	n=856	
Median f/u: NR	3 years	92.8	91.2	0.76 (0.56, 1.04)
	4 years	91.0	88.7	

- IDFS is only efficacy outcome reported for both ITT and subgroups
  - Node positive population – clearer evidence of benefit compared to ITT
  - Hormone receptor negative – lower point estimate than ITT but results are not statistically significant
  - Trend in event rates continues at 4 years
- Committee to consider
  - Generalisability – does the evidence show meaningful benefit in the population outlined in the MA (patients at high risk of recurrence)
  - Uncertainty regarding true effect size; upper bound of confidence interval in node-positive population = 0.96

Treatment discontinuation in ITT population vs. lymph-node positive subgroup

	Pertuzumab N=2,400	Placebo N=2,404
ITT population		
Discontinued treatment	15.5%	12.6%
Discontinued for safety reasons	7.8%	6.4%
Adverse events	7.3%	6.2%
Death	0.4%	0.2%
Pregnancy	<0.1%	0.0%
Lymph-node positive subgroup		
Discontinued treatment	15.6%	13.3%
Discontinued for safety reasons	8.0%	6.8%
Adverse events	7.5%	6.5%
Death	0.4%	0.3%
Pregnancy	<0.1%	0.0%

ERG found difference in discontinuations between pertuzumab and placebo to be statistically significant (p=0.005)

Adverse events – Safety population

- Over 99% of patients in both arms experienced at least one adverse event during the treatment period (pertuzumab: 99.9%; placebo: 99.5%)
- Statistical significance of differences between treatment arms was not reported in company submission but was investigated by ERG – see below

Most frequently reported AEs for pertuzumab	Pertuzumab (N=2,364)	Placebo (N=2,405)	ERG P values
Nausea	69.0%	65.5%	0.009
Diarrhoea	71.2%	45.2%	<0.0001
Fatigue	48.8%	44.3%	0.002
Stomatitis	28.4%	23.8%	0.0003
Anaemia	27.7%	23.2%	0.0003
Dysgeusia	26.0%	21.5%	0.0003
Rash	25.8%	20.3%	<0.0001
Decreased appetite	23.9%	19.9%	0.0008
Mucosal inflammation	23.4%	18.6%	<0.0001
Epistaxis	18.2%	13.6%	<0.0001

15 other adverse events also reported with ≥15% incidence in at least one arm but differences were not statistically significant: alopecia, arthralgia, constipation, myalgia, vomiting, neutropenia, headache, asthenia, hot flush, pyrexia, oedema peripheral, peripheral sensory neuropathy, insomnia, neuropathy peripheral, cough

Adverse events in safety population cont.

Fatal and serious adverse events

- Higher incidence of grade ≥3 AEs in the pertuzumab arm – company note mainly driven by diarrhoea but ERG found anaemia was also statistically worse

Cardiac safety events

- Almost double the number of patients in the pertuzumab arm had primary cardiac event (n=17 versus n=8 in the placebo arm) but overall percentage of patients in either arm experiencing this type of event was very low (0.7% and 0.3% respectively). Secondary cardiac event rates similar across groups: pertuzumab group n=64 (2.7%); placebo group n=67 (2.8%)
- NYHA class III or IV heart failure and substantial decrease in LVEF only cardiac event to be found statistically significant by ERG

Event	Pertuzumab N=2,364	Placebo N=2,405	ERG Relative risk (95% CI)	ERG P value
Deaths (total)	73 (3.1%)	95 (4.0%)	-	-
Fatal AE	18 (0.8%)	20 0.8%	0.92 (0.49 to 1.73)	0.787
Grade ≥3 AE	1,518 (64.2%)	1,379 (57.3%)	1.12 (1.07 to 1.17)	<0.0001
Diarrhoea	232 (9.8%)	90 (3.7%)	2.62 (2.07 to 3.32)	<0.0001
Anaemia	163 (6.9%)	113 (4.7%)	1.47 (1.16 to 1.85)	0.001
NYHA class III/IV heart failure and substantial decrease in LVEF	15 (0.6)	6 (0.2)	2.54 (1.00 to 6.54)	0.044

Health-related quality of life (HRQoL) – ITT population

- HRQoL was measured in APHINITY ITT population using three validated tools (see below)
- The ERG noted
  - patients completed questionnaires at baseline, end of anthracycline treatment period (if applicable), end of taxane therapy, week 25, at the end of study treatment and at 18, 24 and 36 months post randomisation
  - completion rates were satisfactory (consistently above 85%)
- Only the evidence from the EQ-5D was incorporated into the company's economic analyses - ERG note that the EQ-5D administration schedule was not designed to identify differences between treatment arms

EuroQol 5-Dimension (EQ-5D):	Generic, non-disease specific QoL questionnaire
European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30)	General cancer QoL measure
EORTC QLQ-BR23	Breast cancer-specific QoL measure

HRQoL in ITT population cont.

EQ-5D results vs. other PRO measures

EQ-5D	• No differences (≥5%) between treatment arms in the EQ-5D domains
EORTC QLQ-C30	ERG note: • Whilst no MCID was observed between the treatments, average scores consistently lower (worse) for pertuzumab arm • Changes from baseline at week 13 greater than MCID were observed for physical functioning scale in both arms, but not for other functional scales (role, emotional, cognitive and social) • Changes in physical function from baseline were similar between arms (-10.7 vs -10.6, pertuzumab vs placebo) • Mean (SD) change from baseline at 1 year for diarrhoea symptoms exceeded MCID in the pertuzumab arm (22.3 (29.8) vs. 9.2 (23.9))
EORTC QLQ-C30	ERG note: • Decrease (exceeding the MCID) in scores from baseline to end of taxane treatment for both body image and sexual enjoyment in both arms • Decrease in sexual enjoyment sustained until HER2 treatment end in pertuzumab arm but not placebo arm • Other findings not clearly reported

EORTC QLQ-C30 / QLQ-C30 more sensitive to the impact of AEs – statistical differences NR

ERG's critique – clinical evidence

Evidence of treatment efficacy is not robust

1. The ERG considered the outcomes of the trial to be appropriate
2. The observed **treatment effect measured by IDFS in the ITT population was marginal**
   - ERG note that, in contrast to stratified HR of 0.81 (95% CI: 0.66, 1.00; p=0.045), unstratified log-rank test yielded a HR of 0.82 (p=0.0549) which was not statistically significant at 0.05 threshold
   - ERG considers that **none of the primary or secondary outcomes would have been statistically significant had the significance level been adjusted for multiplicity**
3. The **results of the trial may not be a reliable estimate of the true treatment effect**
   - hazard ratios produced from the comparison of KM data using stratified Cox models unlikely to be reliable because test assumes proportional hazards were maintained throughout treatment
   - the 0.05 significance threshold for p values may not be appropriate
4. Although there was a small statistically significant benefit in IDFS in the ITT population there was no consistent difference in effect until roughly 20 months

ERG's critique – clinical evidence

Evidence of HRQoL unlikely to have captured real impact of adverse events.

HRQoL outcomes

5. The **patient reported outcome measures (PROMs) data reported in the APHINITY trial may underrepresent the true HRQoL impact of the treatments** due to the methods and timings of data capture in this study
   - the infrequency of the collection of the PROMs during the APHINITY trial means that they potentially failed to capture the effects of adverse events
   - the evidence of increased frequency of adverse events provides some evidence that pertuzumab may be associated with a slightly worse HRQoL
     - this is not represented in the summaries of the PROMs
     - it can be seen in the difference in mean diarrhoea score from the QLQ-C30

ERG's critique - clinical evidence

Adverse events

Adverse events

6. The ERG believe **the results of the safety analysis may be subject to bias**
7. Only **events that occurred in at least 15% of patients in either arm were reported. The ERG considers this threshold to be rather high**, but were unable to compare it against pre-existing thresholds due to the lack of previous technology appraisals evaluating adjuvant early breast cancer treatments
8. Evidence suggests **pertuzumab has a worse safety profile** than placebo
   - **Incidence** grade ≥3 adverse events higher in pertuzumab arm p<0.0001
   - **6% higher rate of grade 3/4 diarrhoea in the pertuzumab arm**
     - in line with data from other trials (CLEOPATRA/PHEREXA)
     - may be an underestimate as recurrence of episodes were NR in company submission
   - Significantly higher rates of grade ≥3 anaemia in the pertuzumab arm (p=0.001)
   - Incidence of **NYHA class III of IV heart failure with a substantial decrease in LVEF**) **statistically worse in pertuzumab arm (0.6% vs. 0.2%, p=0.04)**
   - Association between pertuzumab and heart disease (clinical adviser)
   - Moderately **higher discontinuation rates for pertuzumab** compared to placebo, while this difference was not significant at the 0.05 threshold, it is consistent with the view that adjuvant pertuzumab+trastuzumab combination has a worse safety profile

ERG's critique – clinical evidence cont.

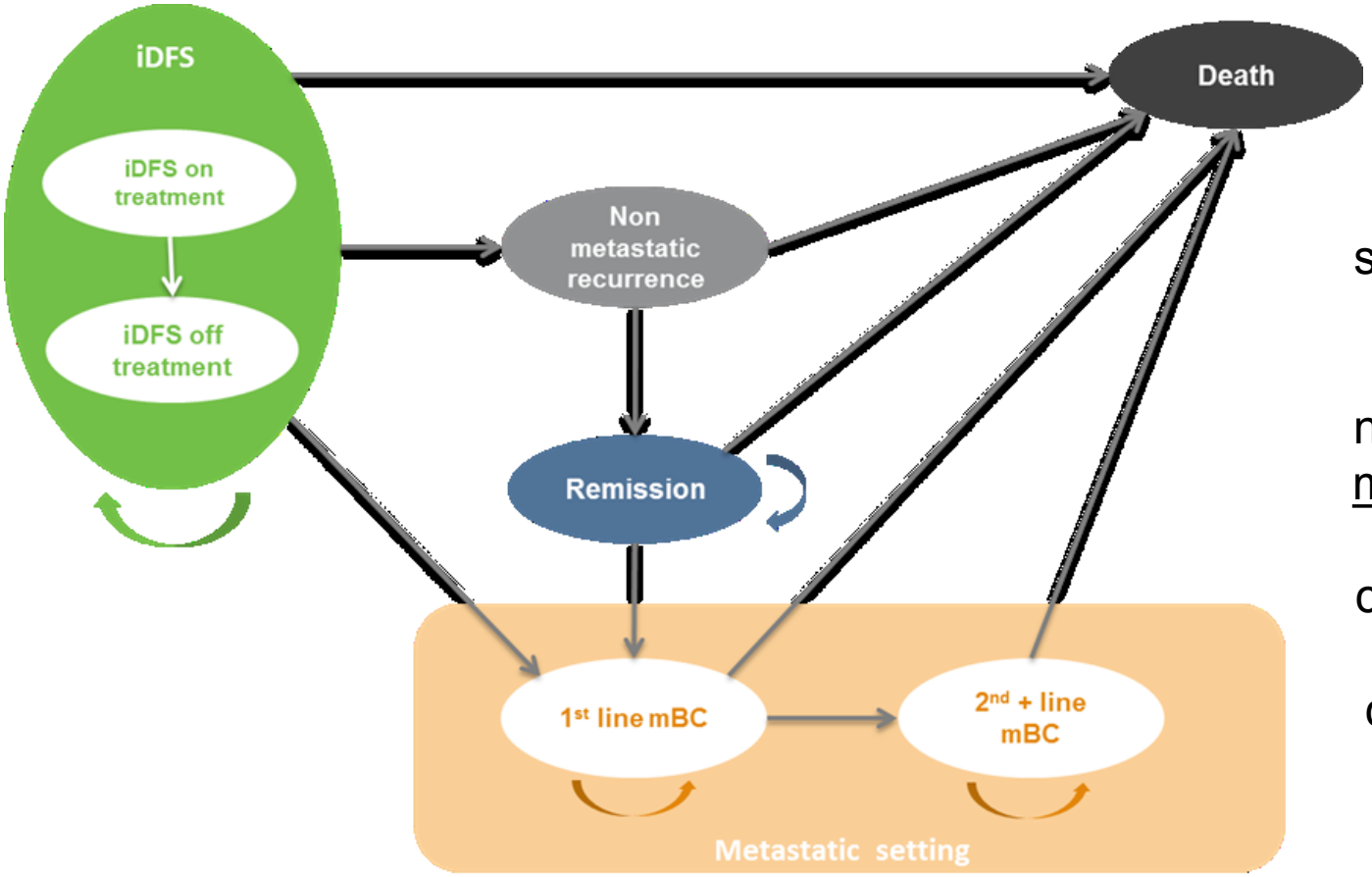
Company's consideration of clinically relevant subgroups

9. The APHINITY trial was not powered to detect subgroup differences; lack of clarity in the supporting documentation regarding the point at which nodal status was prioritised for subgroup analysis
10. ERG unconvinced of pertuzumab efficacy for the hormone receptor-negative population
11. ERG concerned lack of evidence of efficacy in the node-negative population is being treated as evidence that the drug is ineffective in this subgroup

Cost effectiveness evidence

Company submission, section B3

Company's economic model – structure

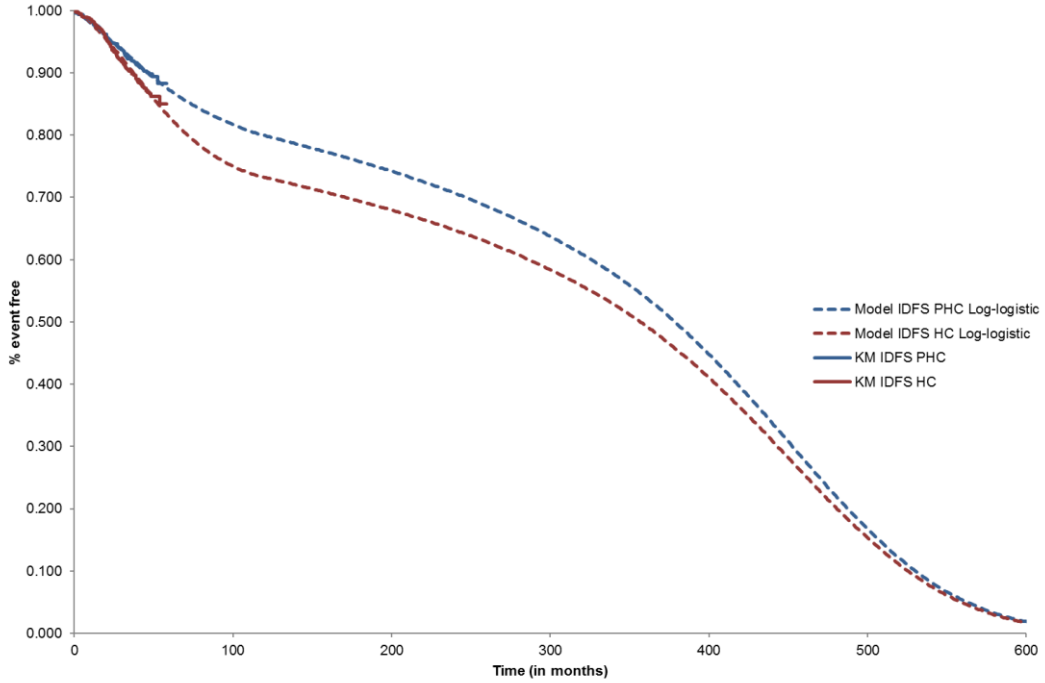


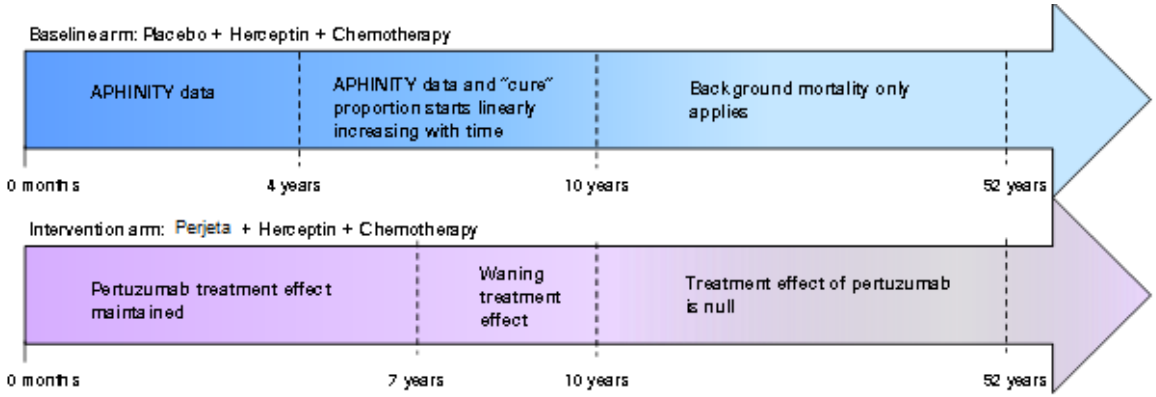
The company examined the cost effectiveness of pertuzumab in two subgroups: lymph node-positive patients and hormone receptor-negative patients. Same model structure used for both analyses. ERG considered the type and structure of the company's model to be appropriate and in line with NICE reference case

Type	Markov model with n=7 health states
Time horizon	Lifetime (52 years) (discounted at 3.5% per annum)
Cycle length	1 month, with the proportion of patients in each health state calculated every 30.4 days. A half cycle correction has been applied in the model

Company's economic model: node-positive population

Treatment effectiveness (modelled using IDFS)





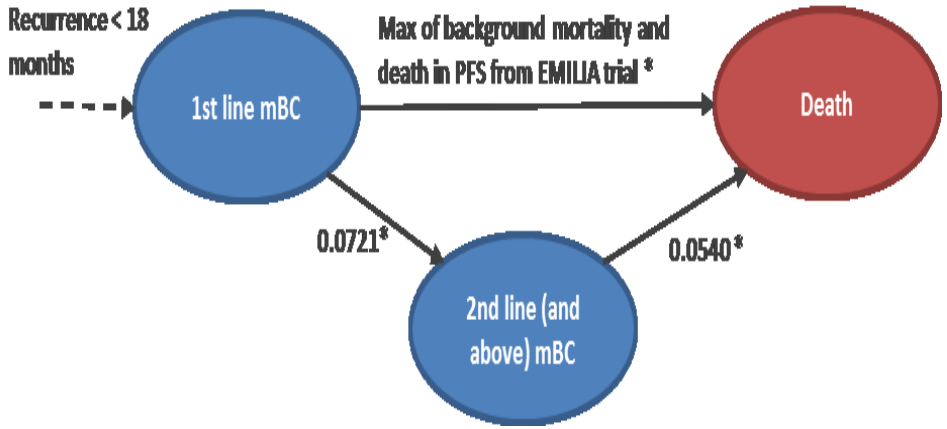
Long term treatment effect on IDFS using parametric curve (log-logistic distribution) used as a surrogate for OS benefit. The curve was initially fitted to the observed Kaplan Meier data from APHINITY then adjusted at two time points to reflect data from other studies. The time points at which adjustments were made varied by treatment arm. The ERG agree with the choice of log-logistic distribution and the overall rationale for the adjustments but have queried some of the specific parameters

Company's economic model: node-positive population

Transition probabilities

- APHINITY trial data (pooled across treatment arms) used to model the proportion of initial recurrences that were metastatic (81.07%) vs. non-metastatic (18.93%) – ERG considered approach was reasonable and determined through their own sensitivity analysis that using un-pooled data resulted in only a modest change to the ICER
- Recurrence within 18 months of treatment initiation assumed to be metastatic, survival estimates for these patients derived from the EMILIA study - ERG considered approach reasonable but concluded proportion of metastatic events after 18 months required re-calculation
- Following initial recurrence, patients were at risk of further relapse and death; probabilities taken from the fast relapse sub-population of the EMILIA study

Summary of monthly transition probability sources in the metastatic setting following early relapse (within 18 months)



Company's economic model: node-positive population Transition probabilities cont.

Starting state	Destination state	Value	Source
IDFS	Non-metastatic recurrence	Adjusted Exponential extrapolation	APHINITY
	Metastatic recurrence		
	Death	Maximum of BGM or IDFS death rate	UK life tables, APHINITY
Non-metastatic recurrence	Remission	1.00	Assumption
	Death	Max of BGM or IDFS death rate	UK life tables, APHINITY
Remission	First-line mBC	0.0076	Hamilton et al.
	Death	Max of BGM or IDFS death rate	UK life tables, APHINITY
First-line mBC	2nd + line mBC	Pertuzumab = 0.032; Trastuzumab = 0.069	CLEOPATRA or M77001
	Death	Max of BGM or PFS in relevant trial	UK life tables, CLEOPATRA, or M77001
Second+ line mBC	Death	Pertuzumab = 0.027; Trastuzumab = 0.060	CLEOPATRA or M77001

Company's economic model: node-positive population

Health utility values

- HRQoL data collected using the EQ-5D-3L tool during the APHINITY study was used to generate the health state utility values. Specifically, utilities derived from the EQ-5D responses of the node-positive population
- The company's model assumed that any disutility resulting from treatment-related adverse effect was reflected in the EQ-5D responses from the APHINITY study
- EQ-5D responses from both treatment arms were pooled and the resulting utility values were applied across both arms of the model – ERG took the view this was acceptable

State		Utility (SE)	Source
Non-metastatic	IDFS - On chemotherapy	0.756 (0.004)	EQ-5D from APHINITY (pooled)
	IDFS - On treatment/off chemotherapy	0.785 (0.004)	
	IDFS - Off treatment	0.822 (0.004)	
	Locoregional recurrence	0.756 (0.004)	Assumption
	Remission	0.822 (0.004)	
Metastatic	First-line metastatic breast cancer	0.773 (0.004)	Lloyd et al. 2006
	Second+ line metastatic breast cancer	0.520 (0.004)	

Company's economic model: node-positive population

Drug acquisition costs – targeted therapies

Drug (preparation)	Dose/Mode of administration	List price	CAA
Pertuzumab (intravenous [IV])	Initial loading dose: 840 mg (60-minute infusion) Maintenance dose: 420 mg (30 to 60 minute infusion) every 3 weeks	£2,395.00 (420 mg vial)	XXX
Trastuzumab (subcutaneous [SC])	Fixed dose: 600 mg (subcutaneously every 3 weeks)	£1,222.20 (600 mg vial)	XXXXX
Trastuzumab (IV)	Initial loading dose: 8 mg/kg body weight Maintenance dose: 6 mg/kg body weight every 3 weeks	£407.40 (150 mg vial)	XXXXX

Trastuzumab biosimilar administered as an IV infusion is not currently available in the UK (the dosing is likely to be similar but the price is unknown)

Company's economic model: node-positive population

Drug acquisition costs – chemotherapy

Drug	Concentration	List price	Quantity used
5-fluorouracil	2,500 mg/50 ml	£2.06	31,697
	5,000 mg/100 ml	£3.12	25,287
Epirubicin	10 mg/5 ml	£2.57	6,208
	50 mg/25 ml	£5.62	23,762
Cyclophosphamide	500 mg	£8.62	4,316
	1,000 mg	£15.89	27,906
Doxorubicin	10 mg/5 ml	£1.34	10,776
	50 mg/25 ml	£3.63	36,439
Docetaxel	20 mg/1 ml	£3.85	28,367
	80 mg/4 ml	£14.74	44,259
Carboplatin	150 mg/15 ml	£6.35	28,300
	450 mg/45 ml	£18.73	38,286
Paclitaxel	30 mg/5 ml	£3.44	27,320
	100 mg/16.7 ml	£9.85	46,299

In the company's base case 18.40% of patients received paclitaxel (in combination with carboplatin) which is not recommended by NICE. All other patients received docetaxel-based regimens

Company's economic model: node-positive population

Drug administration costs

Costs	First cycle	Subsequent cycles
IV treatment: - chemotherapy + trastuzumab + pertuzumab OR - chemotherapy + trastuzumab	£386.00	£310.00
SC treatment: - chemotherapy + trastuzumab	N/A[c]	£260.00
Pharmacy cost	£8.60	£8.60

Trastuzumab usage in the company's base case

Treatment arm	Form of trastuzumab	Proportion of patients	Reference
Intervention (chemotherapy + trastuzumab + pertuzumab)	IV	100%	Pertuzumab license
Comparator (chemotherapy + trastuzumab)	IV SC	XX XXX	Market research

Company's economic model: node-positive population

Health state costs

ERG note

- Health state costs were applied to both treatment arms over the duration of the analysis
- For IDFS health states
  - Was assumed resource use differed according to the length of time a patient spent in an IDFS state (specific supportive care costs were calculated and applied to year 1, years 2–5 and years ≥5)
  - IDFS supportive care regimen included oncologist and GP visits, regular mammograms and cardiac monitoring – ERG clinical expert confirmed representative of UK clinical practice
- For non-metastatic recurrence state: patients were modelled to undergo 12 months of adjuvant therapy
- For metastatic health states: resource use related to assessing response to treatment (outpatient visits, CT scans, cardiac monitoring, and health care practitioner time; ERG confirmed company's approach to estimating resource use associated with CT scans was reasonable)

C

Company's economic model: node-positive population

Adverse event costs

Adverse events	Frequency		Event cost
	Pertuzumab (n=1,503)	Placebo (n=1,502)	
Diarrhoea	67 (4.46%)	17 (1.13%)	£334.00
Neutropenia	37 (2.46%)	45 (3.00%)	£79.00
Neutrophil count decreased	36 (2.40%)	35 (2.33%)	£0.00

- Only treatment-related grade ≥3 adverse events with ≥2% prevalence (shown in table above) were included in company's base case
- The ERG requested that the company adjusted the model so that the impact of also modelling the cardiac and anaemia adverse events (which were found to occur more often in the pertuzumab arm) could be explored – adding in these costs resulted in a very small increase in the cost-effectiveness results by £130

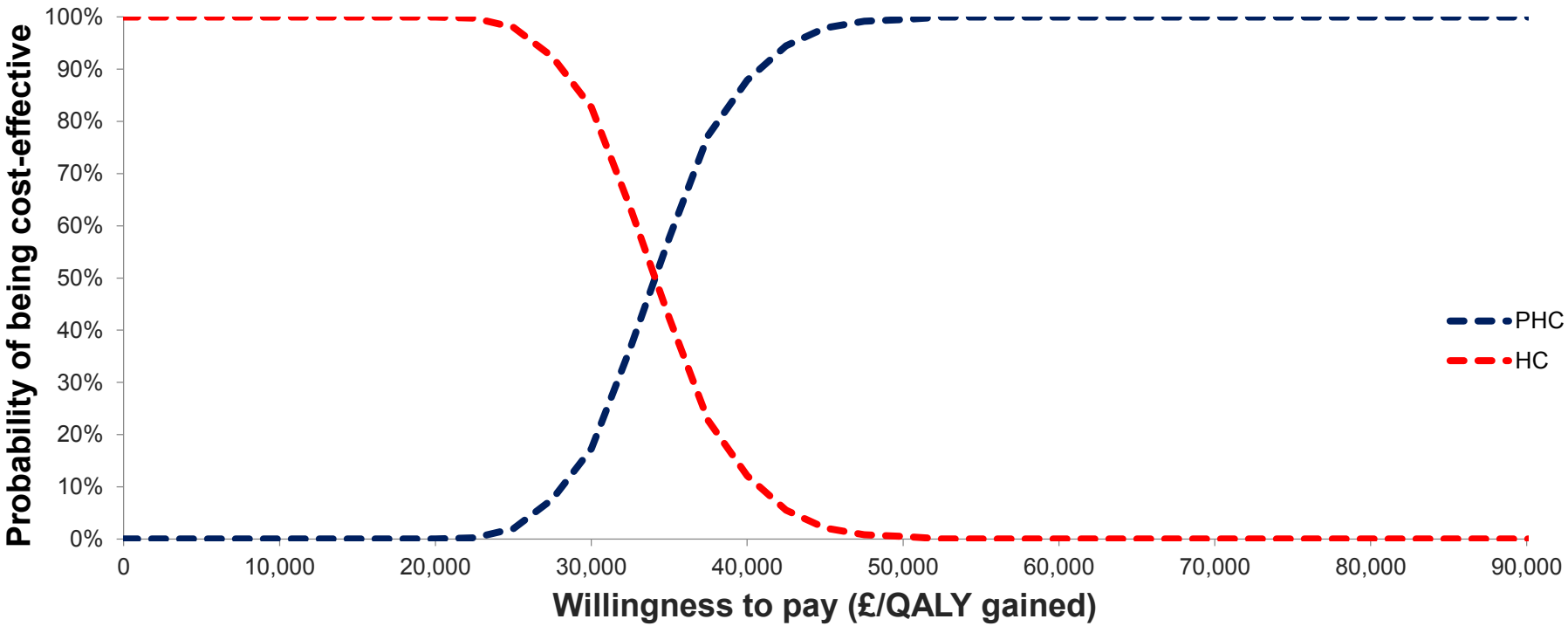
Company's economic model: node-positive population

Cost effectiveness results with CAA

Technologies	Total		Incremental		ICER
	Costs	QALYs	Costs	QALYs	
Trastuzumab + chemotherapy	XXXXXX	XXXX			
Pertuzumab + trastuzumab + chemotherapy	XXXXXX	XXXX	XXXXXX	XXXX	£34,087

Company's economic model: node-positive population

Probabilistic sensitivity analysis (PSA) results



Adapted from figure 24 of company submission (axes re-scaled only – no changes to data)

- PSA ICER = £33,621
- Probability of cost effectiveness at £30,000/QALY is 17.3%

Company's economic model: node-positive population

Deterministic sensitivity analysis results

The company also undertook a deterministic sensitivity analysis; for each parameter, the lower and upper values used in the univariate analysis were the 10th and 90th percentiles of the values used in the simulations of the PSA

- ERG noted that company's DSA (summarised in tornado diagram) gives an indication of the impact of a single parameter on the results but the range of parameters investigated was limited

The company also undertook several 'scenario analyses' designed to assess uncertainty around model structure and parameters (including the model settings, clinical inputs, health state utilities, costs and resource use)

- ERG noted this was more comprehensive and ICERs generated through these analyses ranged from £14,929 per QALY gained for early breast cancer health state utilities drawn by Hedden et al. to £63,456 per QALY gained when the percentage of metastatic recurrences was set to zero

ERG's critique of the company's model – node positive population

Impact of 3 changes on the node-positive model

The ERG did not agree with the following clinical parameters:

- duration of treatment effect chosen by the company was not well justified
- the 'cure' adjustment to the parametric extrapolation appropriate in principle - starting point and maximum cure proportion was considered implausible
- the proportion of patients estimated to experience metastatic vs. non-metastatic recurrences was miscalculated by the company

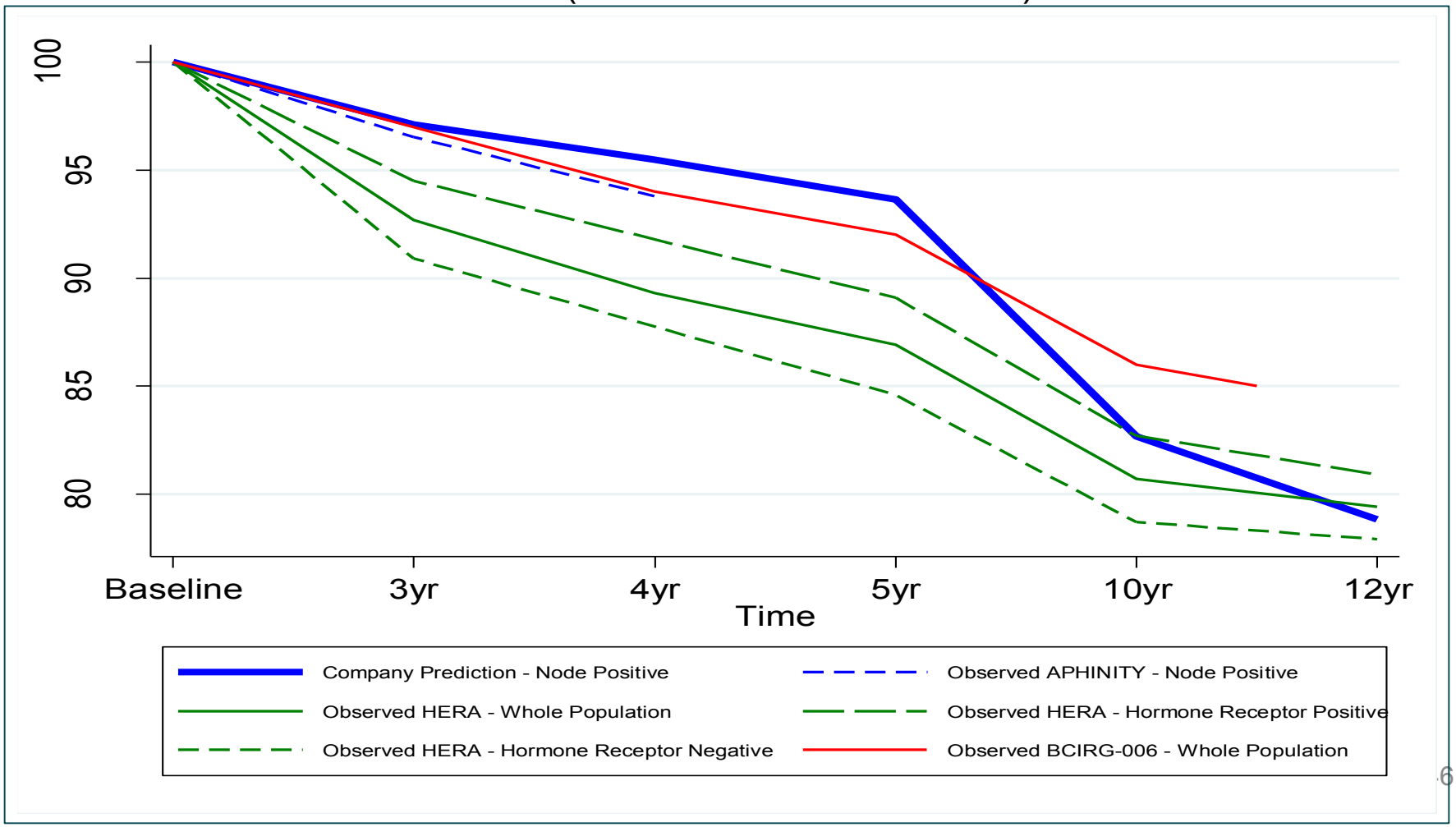
Parameter	Company's base case	ERG's preferred value	ERG's ICER
Time point when incremental treatment effect begins to wane	Year 7	Year 4	£54,901
Time point when incremental treatment effect ceases	Year 10	Year 7	
Time point when 'cure' adjustment is introduced in the analysis	Year 4	Year 3	£37,686
Time point when maximum 'cure' is reached	Year 10	Year 10	
Maximum "cure" proportion	90.00%	95.00%	
% patients with metastatic recurrence	81.07%	72.40%	£35,933
% patients with non-metastatic recurrence	18.93%	27.60%	

ERG's ICER for the node+ population: £60,679 (vs. company £34,087)

ERG's critique of the company's model – node positive population cont.

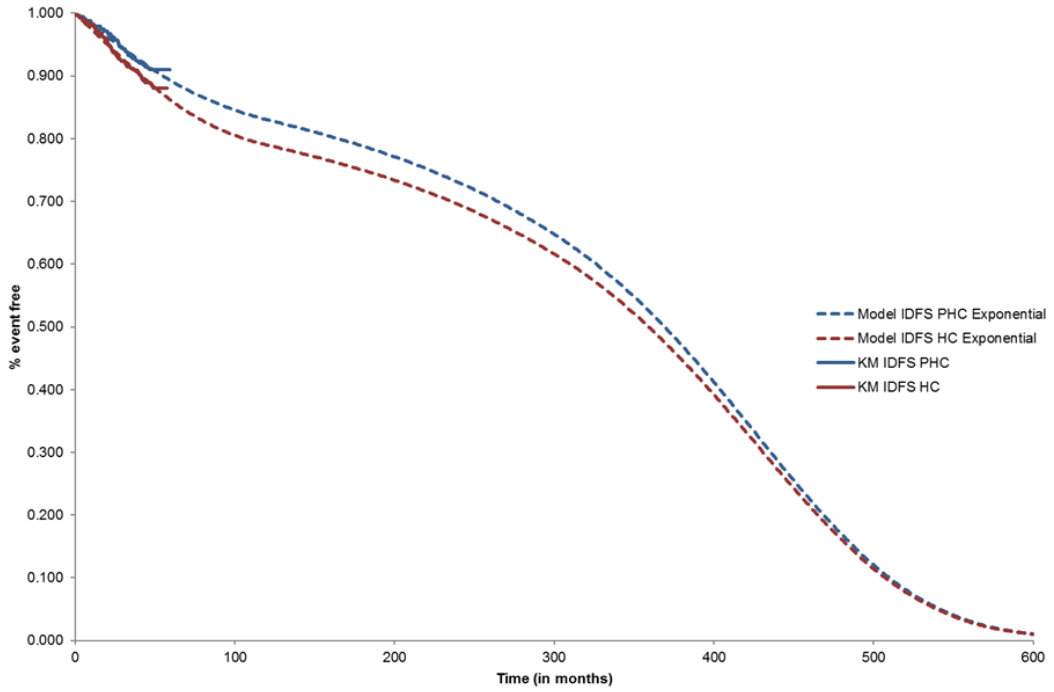
Other issues raised by ERG

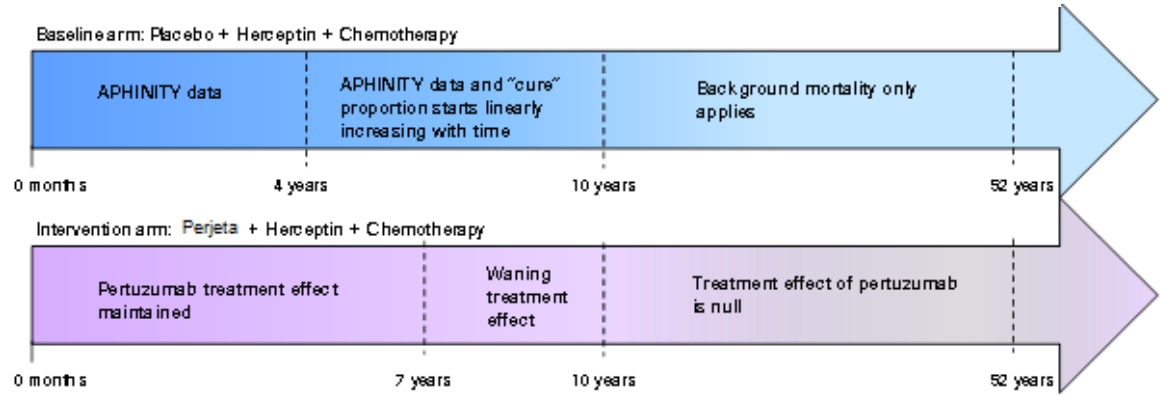
OS predictions (shown in solid blue line) appear to be overly optimistic and do not fit the observed APHINITY data (shown in broken blue line) well



Company's economic model: hormone receptor-negative population

Treatment effectiveness (modelled using IDFS)





IDFS used as a surrogate for OS benefit as per the node-positive population. For the hormone receptor-negative population company chose exponential distribution for extrapolation to long term. Again the curve was initially fitted to the observed Kaplan Meier data from APHINITY then adjusted at two time points - assumptions pertaining to the 2nd and 3rd time periods were identical to those in the node-positive analysis and subject to the same issues identified by the ERG

Company's economic model: hormone receptor-negative population

Other model inputs

- **Modelling of recurrence states:** same overall approach as for node-positive analysis but using IDFS events (excluding death) observed in the hormone receptor-negative population of the APHINITY study
- **Non-metastatic recurrence pathway:** as per the node-positive analysis
- **Measurement and valuation of health effects:** EQ-5D responses in the hormone receptor-negative population of the APHINITY study were used to derive the health state utilities
- **Cost and healthcare resource use identification, measurement and valuation:** as per the node-positive analysis

Company's economic model: hormone receptor-negative population

Cost effectiveness results with CAA

	Technologies	Total		Incremental		ICER
		Costs	QALYs	Costs	QALYs	
Company	Trastuzumab + chemotherapy	XXXXXX	XXXX	XXXXXX	XXXX	£65,699
	Pertuzumab + trastuzumab + chemotherapy	XXXXXX	XXXX			

- PSA ICER = £66,158
- Probability of cost effectiveness at £30,000/QALY is 0%

ERG's critique of the company's model – hormone-receptor negative population

Impact of 3 changes on the hormone receptor-negative model

ERG did not subject company's model for the hormone receptor-negative subgroup to the same level of scrutiny as the analysis for node-positive patients (e.g. selection of survival curve and survival specifications for the hormone receptor-negative model were not examined in detail). The ERG's amendments to hormone receptor-negative model were the same as those implemented in ERG's analysis for the node-positive population

Parameter	Company's base case	ERG's preferred value	ERG's ICER
Time point when incremental treatment effect begins to wane	Year 7	Year 4	£84,291
Time point when incremental treatment effect ceases	Year 10	Year 7	
Time point when 'cure' adjustment is introduced in the analysis	Year 4	Year 3	£69,808
Time point when maximum 'cure' is reached	Year 10	Year 10	
Maximum "cure" proportion	90.00%	95.00%	
% patients with metastatic recurrence	76.87%	65.60%	£70,378
% patients with non-metastatic recurrence	23.13%	34.40%	

ERG's ICER for the node-positive population: £92,778 (vs. company £65,699)

ERG's cost effectiveness results for ITT population

The ERG presented cost-effectiveness results for the ITT population derived from the submitted in the economic model but again did not scrutinise the details of the company's analysis (e.g. selection of survival curve and survival specifications) in detail

ICER for ITT population (with CAA): £66,238

Summary of company and ERG ICERs by population group

Population	Source	Technologies	Total		Incremental		ICER
			Costs	QALYs	Costs	QALYs	
Node-positive	Company	HC	XXXXXX	XXXX	XXXXXX	XXXX	£34,087
		PHC	XXXXXX	XXXX			
	ERG	HC	XXXXXX	XXXXX	XXXXXX	XXXX	£60,679
		PHC	XXXXXX	XXXXX			
Hormone receptor-negative	Company	HC	XXXXXX	XXXX	XXXXXX	XXXX	£65,699
		PHC	XXXXXX	XXXX			
	ERG	HC	XXXXXX	XXXXX	XXXXXX	XXXX	£92,778
		PHC	XXXXXX	XXXXX			
ITT		HC	XXXXXX	XXXX	XXXXXX	XXXX	£66,238
		PHC	XXXXXX	XXXX			

Innovation

As per the company:
“When pertuzumab was first approved in Europe in 2013 for the treatment of HER2-positive mBC, it was the first-in-class HER2 dimerisation inhibitor and was considered a step-change in the treatment of BC. Pertuzumab in combination with trastuzumab offers a comprehensive HER2 blockade that inhibits the signaling pathways essential for tumour growth”

Wider context:

- One targeted therapy (trastuzumab) is already recommended for patients with HER2+ early breast cancer in the adjunctive setting
- Pertuzumab is being considered as additional add-on adjunctive therapy for patients who are at high risk of disease recurrence (continuation of the neoadjuvant therapy)
- There is not a clear case for innovative nature of adjuvant pertuzumab given that it is an extension of neoadjuvant therapy

Equalities

No equalities issues were raised during scoping or in any of the submission (company, patient submission or expert statement)

Authors

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- with input from the Lead Team (Iain Squire, John McMurray and Stephen Sharp)

Common abbreviations

CAA	Commercial access agreement
CG	Clinical guideline
CI	Confidence interval
DRFI	Distant recurrence-free interval
EQ-5D	EuroQol 5-Dimension
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EORTC QLQ-BR23	EORTC QOL Module for Breast Cancer
ERG	Evidence review group
ER/PR	oestrogen-receptor/progesterone receptor
HER2	Human epidermal growth factor receptor
HR	Hazard ratio
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IDFS	Invasive disease-free survival
ITT	Intention-to-treat

Common abbreviations cont.

MA	Marketing authorisation
MCID	Minimally clinically important difference
NICE	National Institute for Health and Care Excellence
OS	Overall survival
PROM	Patient reported outcome measure
PSA	Probabilistic sensitivity analysis
RFI	Recurrence-free interval
SD	Standard deviation
STEEP	Standardised efficacy endpoints
TA	Technology appraisal

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Pertuzumab for adjuvant treatment of HER2-positive early breast cancer (ID1192)

Document B

Company evidence submission

February, 2018

File name	Version	Contains confidential information	Date
ID1192_ Pertuzumab Company Submission Document B_09-February 2018 - ACIC	**1.0**	**Yes**	**9th February 2018**

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 150 pages, excluding appendices and the pages covered by this template. If it is too long it will not be accepted.

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.

In this template any information that should be provided in an appendix is listed in a box.

Highlighting in the template (excluding the contents list)

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

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Grey highlighted text in the footer does not work as an automatic form field, but serves the same purpose – as prompt text to show where you need to fill in relevant details. Replace the text highlighted in [grey] in the header and footer with appropriate text. (To change the header and footer, double click over the header or footer text. Double click back in the main body text when you have finished.)

Contents

Tables and figures

Abbreviations

A	Doxorubicin
ABACUS	Awareness and Beliefs about Cancer
ADCC	Antibody-dependent cell-mediated cytotoxicity
AC	Doxorubicin + cyclophosphamide
AE	Adverse event
AIC	Akaike Information Criterion
AUC	Area under the curve
BC	Breast cancer
BCIRG	Breast Cancer International Research Group
BIC	Bayesian Information Criterion
BNF	British National Formulary
C	Cyclophosphamide
CAA	Commercial access agreement
CAB	Cardiac advisory board
CC	Casemix companion
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CISH	Chromogenic in situ hybridisation
CMU	Commercial Medicines Unit
CNS	Central nervous system
CSR	Clinical study report
CT	Computerised tomography
DCIS	Ductal carcinoma *in situ*
DDFS	Distant disease-free survival
DFS	Disease-free survival
DRFI	Distant recurrence-free interval
E	Epirubicin
eBC	Early breast cancer
EC	Epirubicin + cyclophosphamide
ECHO	Echocardiogram
eCRF	Electronic case report form
EFS	Event-free survival

EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
eMIT	Electronic market information tool
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D	EuroQol 5-Dimensions Questionnaire
ER	Oestrogen receptor/early relapser
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
F	5-fluororacil
FAC	5-fluorouracil + doxorubicin + cyclophosphamide
FDA	Food and Drug Administration
FEC	5-fluorouracil + epirubicin + cyclophosphamide
FISH	Fluorescence *in situ* hybridisation
FU	Follow-up
G-CSF	Granulocyte colony-stimulating factor
GnRH	Gonadotropin releasing hormone
GP	General practitioner
H	Trastuzumab
HER2	Human epidermal growth factor receptor 2
HER3	Human epidermal growth factor receptor 3
HER4	Human epidermal growth factor receptor 4
HR	Hazard ratio
HRQoL	Health-related quality of life
HSUV	Health state utility value
HT	Trastuzumab + chemotherapy
H_0	Null hypothesis

H_1	Alternative hypothesis
ICER	Incremental cost-effectiveness ratio
IDFS	Invasive disease-free survival
IHC	Immunohistochemistry
ITT	Intent-to-treat
IV	Intravenous
K	Trastuzumab emtansine
KM	Kaplan-Meier
LHRH	Luteinising-hormone-releasing hormone
LVEF	Left ventricular ejection fraction
LYG	Life years gained
MAP	Mitogen-activated protein
mBC	Metastatic breast cancer
MDT	Multidisciplinary team
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
ml	Millilitre
MTA	Multiple Technology Assessment
MUGA	Multigated acquisition
NA	Not applicable
NCCN	National Comprehensive Cancer Network
NCRI	National Cancer Research Institute
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMR	Non-metastatic recurrence
NYHA	New York Heart Association
OS	Overall survival
PAS	Patient access scheme
pCR	Pathological complete response
PFS	Progression-free survival
PHT	Pertuzumab + trastuzumab + chemotherapy
PgR	Progesterone receptor
PI3K	Phosphoinositide 3-kinase

PRS	Post-recurrence survival
PSA	Probabilistic sensitivity analysis
PSS	Personal and Social Services
PSSRU	Personal and Social Services Research Unit
QALY	Quality-adjusted life year
QLQ-BR23	EORTC breast cancer-specific quality of life questionnaire
QLQ-C30	EORTC core 30 questionnaire
QoL	Quality of life
Q1W	Every week
Q3W	Every three weeks
RFI	Recurrence-free interval
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
SoC	Standard of care
STEEP	Standardised efficacy endpoints
T	Taxane
TA	Technology appraisal
TC	Docetaxel + carboplatin
TCH	Docetaxel + carboplatin + trastuzumab
TE	Trastuzumab emtansine
TH	Taxane + trastuzumab
TTOT	Time-to-off-treatment
tx	Treatment
UK	United Kingdom
US	United States of America
WPAI	Work Productivity and Activity Impairment
1L	First-line
2L	Second-line
5-FU	5-fluororacil
Δ	Difference

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 *Decision problem*

The patient population described under the final scope of this appraisal is "people with early or locally advanced HER2-positive breast cancer (BC) who have undergone surgery". Following recent regulatory discussions with the Committee for Medicinal Products for Human Use (CHMP), the company does not expect to receive marketing authorisation in the intent-to-treat (ITT) population. The anticipated label for pertuzumab is expected to read as follows:

"Perjeta is indicated for use in combination with trastuzumab and chemotherapy in:

- 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)
- the adjuvant treatment of adult patients with HER2-positive early breast cancer at high risk of recurrence (see section 5.1)."

Linked to this change, the following text in section 5.1 of the summary of product characteristics (SmPC) will be included:

- "In the adjuvant setting, based on data from the APHINITY study, HER2-positive early breast cancer patients at high risk of recurrence are defined as those with lymph node-positive disease or hormone receptor-negative disease."

In the APHINITY study, patients with HER2-positive early BC (eBC) received treatment with pertuzumab or placebo, in combination with Herceptin (trastuzumab) + chemotherapy. Although the APHINITY study met its primary objective, with a statistically significant improvement in invasive disease-free survival (IDFS) in the ITT population (supporting the original proposed indication statement), Roche proposed a revised indication because:

- Nodal status and hormone receptor status are routinely assessed in all patients with BC undergoing adjuvant therapy, and node-positivity and hormone receptor-negativity indicate well-established high-risk subgroups. In the APHINITY study, patients in these pre-specified subgroups derived the greatest benefit from the addition of pertuzumab to standard adjuvant therapy, with hazard ratios (HRs) of 0.77 (95% confidence interval [CI], 0.62–0.96) and 0.76 (95% CI, 0.56–1.04]), respectively (compared to 0.81 [95% CI, 0.66–1.00] for the ITT population).
- This is the recommendation that appears in the latest St Gallen guidelines.[1]

The EMA provided feedback that the proposed revised indication for adjuvant pertuzumab treatment (i.e. in patients at high risk of disease recurrence) was seen positively by the CHMP, but will be submitted formally on 23rd February 2018 with responses to the requested supplementary information. The economic analysis will focus on patients who are diagnosed as being at high risk of recurrence (node-positive subgroup as the base case, hormone receptor-negative subgroup as an additional scenario). This population is narrower than the final scope of this appraisal but will be aligned with the expected marketing authorisation in the UK.

Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with early or locally advanced HER2-positive BC who have undergone surgery.	People with HER2-positive eBC at high risk of recurrence (N.B. node-positive population submitted as base case, and hormone receptor-negative population as an additional scenario).	The anticipated market authorisation for the adjuvant use of pertuzumab is in patients with HER2-positive eBC at high risk of recurrence (i.e. node-positive or hormone receptor-negative). The APHINITY study met its primary objective in the ITT population. An assessment of key pre-specified, stratified subgroups showed that patients with a high risk of recurrence (i.e. node-positive or hormone receptor-negative) appear to derive the most benefit from pertuzumab + trastuzumab with an almost 25% risk reduction in recurrence or death when compared to the control arm.[2] Node-positivity and hormone receptor-negativity are known prognostic factors and have not been discovered in the APHINITY study; patients with node-positive or hormone receptor-negative eBC have a higher risk of relapsing than patients with node-negative or hormone receptor-positive disease. The subgroup analyses confirm that these subgroups are at high-risk of recurrence and the importance of underlying tumour biology when considering treatment options. The economic analyses included in this submission are the node-positive subgroup as the base case and the hormone receptor-negative subgroup as an additional scenario.
Intervention	Adjuvant pertuzumab in combination with trastuzumab and chemotherapy	Adjuvant pertuzumab in combination with trastuzumab and chemotherapy	Not applicable

Comparator(s)	Standard adjuvant therapy without pertuzumab for HER2-positive BC: trastuzumab in combination with chemotherapy	Standard adjuvant therapy without pertuzumab for HER2-positive BC: trastuzumab in combination with chemotherapy	Not applicable
Outcomes	The outcome measures to be considered include: • Overall survival (OS) • Disease-free survival (DFS) • Recurrence-free interval (RFI) • Adverse effects of treatment • Health-related quality of life (HRQoL)	The outcome measures to be considered include: • IDFS • IDFS including second primary non-breast cancer • DFS • OS • RFI • Distant recurrence-free interval (DRFI) • Adverse effects of treatment • HRQoL	IDFS was the primary endpoint of the pivotal phase III study for adjuvant pertuzumab in HER2-positive eBC (the APHINITY study). DRFI was a secondary outcome of the APHINITY study.
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 (QALY). 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 (PSS) perspective. The availability of any patient access schemes for the intervention or comparator technologies will be taken into account.	• Cost per QALY • Time horizon suitably long to reflect differences • NHS PSS perspective • Commercial access agreement (CAA) to be taken into account	Not applicable

Subgroups to be considered	If evidence allows, subgroups with higher risk of recurrence, such as people with lymph node-positive disease or people with hormone receptor-negative disease, will be considered.	People with HER2-postive eBC that is hormone receptor-negative (note: this is a subgroup of the ITT population, NOT a subgroup of the node-positive population).	This subgroup of the ITT population has been included in the submission because hormone receptor-negativity is a clinically relevant prognostic factor for BC recurrence. Patients with hormone receptor-negative disease are considered a high-risk subgroup because, unlike patients with hormone receptor-positive disease, they cannot be treated with hormone therapy. Furthermore, this patient population is likely to be included in the label for adjuvant pertuzumab. In the economic analyses of this submission the node-positive subgroup is the base case and the hormone receptor-negative subgroup is an additional scenario.
Special considerations including issues related to equity or equality	None specified.	None identified.	Not applicable

Abbreviations: BC, breast cancer; DFS, disease-free survival; DRFI, distant recurrence-free interval; eBC, early breast cancer; HER2, human epidermal growth factor receptor 2; HRQoL, health-related quality of life; IDFS, invasive disease-free survival; ITT, intention-to-treat; NHS, National Health Service; OS, overall survival; PAS, patient access scheme; PSS, personal social services; QALY, quality adjusted life year; RFI, recurrence-free interval.
Source: NICE. Pertuzumab for the adjuvant treatment of HER2-positive breast cancer - Final scope[3]

B.1.2 *Description of the technology being appraised*

Table 2. Technology being appraised

UK approved name and brand name	Perjeta® (pertuzumab)
Mechanism of action	Pertuzumab is a recombinant humanised monoclonal antibody that specifically targets the extracellular dimerisation domain (subdomain II) of the HER2 protein, and thereby blocks ligand-dependent heterodimerisation of HER2 with other HER family members, including EGFR, HER3 and HER4.[4-6] As a result, pertuzumab 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, pertuzumab mediates antibody-dependent cell-mediated cytotoxicity (ADCC).[4] Pertuzumab and trastuzumab 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.[7, 8]
Marketing authorisation/CE mark status	• **2013**: A European marketing authorisation was granted for pertuzumab in patients with metastatic HER2-positive BC.[4] • **2013**: pertuzumab was granted accelerated approval for use with trastuzumab and docetaxel for neoadjuvant treatment of HER2-positive BC (US Food and Drug Administration [FDA]).[9, 10] • **2015**: A European marketing authorisation was granted for pertuzumab for the neoadjuvant treatment of patients with HER2-positive eBC.[4] • **2017**: The US FDA approved pertuzumab for the adjuvant treatment of patients with HER2-positive eBC at high risk of recurrence in December 2017 and states “up to 18 cycles” and “as part of a complete regimen for eBC”.[10] • **2018**: A European marketing authorisation application to extend the use of pertuzumab to include adjuvant treatment of patients with HER2-positive eBC was filed in 2017 and EMA approval is expected to be granted in July 2018 (see Section B.1.1).

Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Current indications: • Pertuzumab is indicated for use in combination with trastuzumab and docetaxel in adult patients with HER2-positive metastatic or locally recurrent unresectable BC, who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease.[4] • Pertuzumab 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 BC at high risk of recurrence.[4] Contraindications include hypersensitivity to pertuzumab or to glacial acetic acid, L-histidine, sucrose, polysorbate 20 and water for injections.[4] For full details of the, warnings and precautions for use of pertuzumab, please see Appendix C.
Method of administration and dosage	Pertuzumab should be administered as an intravenous (IV) 840 mg loading dose, then 420 mg every three weeks (Q3W). Pertuzumab should be administered in combination with trastuzumab for a total of one year (maximum 18 cycles) for high-risk patients regardless of the timing of surgery.
Additional tests or investigations	It is standard clinical practice to test the HER2 status of tumours at the point of diagnosis.[11-13] No additional tests are required prior to the administration of pertuzumab.
List price and average cost of a course of treatment	The list price of pertuzumab is £2,395 per 420 mg vial and the list price of trastuzumab is £407.4 per 150 mg vial. The average cost of a course of treatment is £62,733.
Patient access scheme (if applicable)	A commercial access agreement is in place for pertuzumab of [redacted]

Abbreviations: ADCC, antibody-dependent cell-mediated cytotoxicity; BC, breast cancer; eBC, early breast cancer; EGFR, epidermal growth factor receptor; EMA, European Medicines Agency; EU, European Union; FDA, US Food and Drugs Administration; HER2, human epidermal growth factor receptor 2; IV, intravenous; MA, marketing authorisation; MAP, mitogen-activated protein; mg, milligram; PI3K, phosphoinositide 3-kinase; Q3W, every three weeks.

B.1.3 *Health condition and position of the technology in the treatment pathway*

Summary of health condition and position of the technology

- BC is the most common cancer type in the UK, accounting for 15% of all new cancer cases and representing the third most common cause of cancer death in 2014.[14]
- Approximately 14% of patients with eBC in the UK have tumours that overexpress HER2, and are classified as HER2-positive.[15] HER2-positivity is associated with increased tumour aggressiveness, high rates of recurrence and increased mortality vs HER2-negative disease.[16-23] Furthermore, the median age of patients presenting with HER2-positive BC is mid-50s, around five years younger than the general BC population.[24, 25] HER2-positive eBC therefore frequently impacts women in the prime of their careers and whilst they still have responsibilities at home and in their families.
- Within patients with HER2-positive eBC, node-positive or hormone receptor-negative disease represent particularly high-risk subgroups:
    - The five-year survival rate of women with HER2-positive, node-positive eBC is approximately 20% less than for those with HER2-negative, node-negative eBC.[18]
    - Patients with HER2-positive, hormone receptor-negative eBC have a significantly higher hazard of recurrence in years 1 to 5 compared to patients with HER2-positive hormone receptor-positive disease, with a mean risk of recurrence of 9%/year for hormone receptor-negative disease vs 5%/year for hormone receptor-positive disease (HR=0.59; p=0.002 for years 1–5).[26]
- The treatment goal in eBC is cure, whilst the treatment goal in metastatic BC (mBC) is to delay progression and is of palliative intent. Since mBC is currently incurable, improving the results of eBC treatment, whilst the disease is still localised to the breast and regional lymph nodes but without distant metastases, offers patients the best chance of cure.
- HER2-targeted treatment has already transformed the treatment and prognosis of patients with HER2-positive eBC. Trastuzumab has become the backbone therapy in UK practice for the treatment of HER2-positive eBC; when started in the neoadjuvant (i.e. pre-surgery) setting, patients normally continue trastuzumab treatment in the adjuvant (i.e. post-surgery) setting to complete up to one year (18 cycles) of treatment (with chemotherapy also administered in the neoadjuvant period). However, despite the advances achieved with one year of trastuzumab treatment (irrespective of whether initiated neoadjuvantly or adjuvantly) up to one in four patients experience disease recurrence within 10–11 years of diagnosis.[27-29]
- Patients with high-risk eBC are most likely to receive neoadjuvant pertuzumab + trastuzumab + chemotherapy to improve surgical outcomes. However, patients who receive neoadjuvant pertuzumab + trastuzumab + chemotherapy followed by adjuvant trastuzumab may still relapse, irrespective of achieving a pathological complete response (pCR) at the time of surgery.[30] BC disease risk is determined at diagnosis, and staging and baseline risk are used to determine the overall treatment plan.
- The safety and efficacy of dual-HER2 blockade with pertuzumab + trastuzumab has been previously demonstrated in the neoadjuvant eBC[30, 31] and mBC[32] settings. pertuzumab + trastuzumab is now standard of care in the neoadjuvant setting for patients with high risk of

recurrence. Patients at high risk of disease relapse are the population that require dual-HER2 blockade for 18 cycles, irrespective of the time of surgery.

B.1.3.1 Early breast cancer overview

BC is a malignant cancer that forms in tissues of the breast, usually the ducts or lobules. It is classified as eBC if it has not spread beyond the breast or lymph nodes. In the UK, BC is the most common type of cancer, accounting for 15% of all new cancer cases, and was the third most common cause of cancer death in 2014.[14]

Approximately 14% of eBC patients have HER2-positive disease,[15] meaning that approximately 7,900 patients in the UK are diagnosed with this eBC sub-type each year.[14] The HER2 cell surface protein is a member of the epidermal growth factor receptor (EGFR) family that regulate normal cell growth, development and survival processes, and HER2 signalling may be driving the growth of HER2-positive BCs. Importantly, overexpression of HER2 is associated with an aggressive disease course and poor prognosis.[16, 17] BCs that overexpress HER2 are also associated with increased tumour size, increased risk of disease recurrence and poorer clinical outcomes.[16-21] Patients diagnosed with HER2-positive BC are on average around five years younger than the average BC population,[24, 25] and therefore are more likely than patients in the general BC population to still be in work, and/or have dependent children or relatives.

As well as classifying BC by HER2 status, BC is also classified based on presence of cancer cells in the lymph nodes (i.e. nodal status). BC cells can break away from the tumour and can spread to the axillary lymph nodes via the lymphatic system.[33] To determine if the lymph nodes contain cancer, ultrasound imaging may be performed prior to surgery, and a (sentinel) node biopsy performed prior to and/or during surgery to confirm nodal status.[34] If the lymph nodes contain cancer, the disease is termed “node-positive” and if the nodes do not contain cancer, the disease is termed “node-negative”.[33] Patients with node-positive disease are a subgroup at higher risk of recurrence compared to patients with node-negative disease,[26, 27, 35] as the disease has begun to spread beyond the primary breast tumour and may have metastasised elsewhere in the body.

In a UK report of BCs diagnosed in 2007, younger patients were more likely to have a positive nodal status, indicating that their breast tumours tended to be more aggressive: 54% of patients aged <40 years were lymph node-positive compared to 30% of patients aged 60–69 years and 48% of patient aged >80 years. A higher proportion of patients with symptomatic invasive BC were found to have node-positive disease compared to patients with screen-detected invasive disease (50% vs 22.5%).[36] Prior NICE appraisals (TA108 and TA109), have assessed therapies in BC patient subgroups as classified by nodal status, highlighting the importance of this factor for treatment decisions.[37, 38]

BC can be classified according to the presence of the hormone receptors (i.e. oestrogen receptor [ER] and progesterone receptors [PgR]) on the BC cells. All BCs are tested for the overexpression of ER at diagnosis, and tests may also be done for PgR. ER-negative BCs contain very low levels of, or no, ER.[39] Patients with hormone receptor-negative disease (i.e. ER-negative AND PgR-negative) are not eligible to receive hormone therapy and because of this, are known to be a subgroup at higher risk of recurrence than patients with hormone receptor-positive disease.[26, 40]

The treatment goal in eBC patients is cure, which entails giving the most effective treatment options available to prevent the development of mBC (which is currently incurable). Despite advances in treatment of HER2-positive eBC, there are still patients that go on to develop mBC (also called advanced or secondary BC): for HER2-positive mBC in the UK specifically, an interim analysis of the ESTHER non-interventional study found that 71.2% of the mBC patients had a recurrence following eBC (rather than *de novo* mBC), and the median duration from eBC to mBC diagnosis was four years.[41] In the Phase III CLEOPATRA study in patients with mBC, treatment with pertuzumab + trastuzumab + chemotherapy produced a median OS of 4.7 years (95% CI, 4.1–not reached) vs 3.4 years (95% CI, 3.0–4.0) with trastuzumab + chemotherapy.[32] The patients included in CLEOPATRA study had a median age of 54 years at enrolment.[42] Combined with an estimated life expectancy of 4.7 years, this shows that many patients with HER2-positive mBC die at a relatively young age. Accordingly, it is of the utmost importance to patients diagnosed with HER2-positive eBC in the UK, and their families, to utilise the best possible treatment options. Improving the results of initial therapy, when the disease is at an early stage and localised to the breast and regional lymph nodes, offers patients the best chance of cure.

Social and economic burden of BC

Regardless of clinical stage, BC has significant negative personal, social and economic effects on patients, their families, friends and wider society. Chemotherapy can reduce a patient's quality of life (QoL) during and after treatment through adverse physical and psychological effects. These effects also extend to cancer survivors, who are at higher risk of disease recurrence and cardiovascular complications, infertility and neurocognitive problems, and may face a financial burden and employment discrimination even after their disease.[43]

In addition to the impact on patients and caregivers, BC has an overarching impact on the UK economy. A National Cancer Research Institute (NCRI) report from 2012 showed that BC of all subtypes and stages accounts for an annual economic cost of £1.5 billion in the UK (including both direct and indirect costs).[44] The same study showed that 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.[44] These values demonstrate the significance of the indirect costs of BC when considering the overall cost of the disease.

Burden of eBC

Patients with eBC report lower HRQoL compared to the general population. In one Swedish study, patients with eBC of any subtype had a mean EQ-5D index value of 0.696 (95% confidence interval [CI], 0.634–0.747), with 71% of patients reporting moderate to severe problems with pain and 65% of patients reporting moderate to severe problems with anxiety/depression.[45] Another study found that nearly 50% of women with eBC of any subtype had depression, anxiety or both in the year after diagnosis.[46] QoL in eBC patients is related to the treatment phase, with patients reporting a decrease in QoL during chemotherapy owing to symptoms such as diarrhoea, systemic therapy symptoms, hair loss, sexual dysfunction and fatigue. Although many symptoms affecting QoL in eBC patients can decline or disappear following completion of treatment, some of them, such as anticipatory nausea, weight gain, endocrine effects, disturbed sleep and sexual dysfunction, may persist following treatment cessation, indicating that the effects on QoL of eBC patients can be long-lasting.[47, 48]

Caregiver QoL is negatively affected by the life-threatening nature of BC and the distressing treatment side effects that patients experience, resulting in a strain on the caregiver themselves and their families.[48-50] For example, husbands of women with BC of any stage (80.3% non-metastatic) who were receiving active BC treatment were shown by Wagner (2006) to score significantly lower on general health, vitality, role-emotional and mental health MOS SF-36 subscales compared with spouses of healthy women.[51] An adverse impact on ability to work for the caregiver has also been reported

Burden of mBC

Treating patients with eBC with the most effective treatment regimen in the first instance may result in a reduced societal burden and healthcare costs later down the line, as the burden associated with progression and developing mBC may be avoided in some patients.[41, 52]

Patients with mBC of any subtype tend to have a diminished QoL compared to the general population, which can be seen through higher rates of psychiatric and psychological disturbance,[53] and worsening of sexual functioning.[48] mBC patients also score lower than reference populations on multiple HRQoL questionnaires, including the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30, for which the mean of the five functional scales for mBC patients was 24.5 points lower (i.e. indicating poorer HRQoL) than a reference group of 50–59 year old women.[54] Patients with HER2-positive mBC in the UK have poorer health utility scores than eBC patients receiving HER2 therapy + chemotherapy.[52]

The socio-economic impacts of mBC are substantial. The gross national cost of incident mBC cases of any subtype in the UK has been estimated at $22 million annually (2002 GBP).[55] UK studies have found that a higher proportion of HER2-positive mBC patients are unable to work and report significantly higher levels of activity impairment compared to HER2-positive eBC patients.[52, 56] BC progression contributes directly to lower rates of employment among affected individuals, and patients with mBC experience a substantial loss of productivity compared to patients living with non-metastatic disease.[57] mBC patients also report practical service needs including help with daily living, housework, transportation and financial assistance.[58]

The recent PURPOSE non-interventional study, conducted at 14 UK secondary care centres, compared work productivity in three patient groups with HER2-positive BC: eBC during adjuvant treatment (n=89, 50.6% employed), eBC post-treatment (n=108, 50.9% employed) and mBC (n=102, 27.5% employed).[52] The study found that patients who completed the Work Productivity and Activity Impairment (WPAI) measure reported:

- Activity impairment. Mean WPAI scores for activity impairment were 30.4% in patients receiving treatment after surgery, 27.6% in patients who had completed adjuvant treatment and 48.1% in patients receiving treatment for mBC.[52]
- HRQoL as measured by generic EQ-5D and disease-specific FACT-B, was similar in eBC patients (regardless of being on or off adjuvant treatment), and was better compared to those in mBC group.[56]
- Significantly fewer mBC patients were employed, and more reported being unable to work vs eBC patients, reflecting the impact of advanced disease.[56]
- Work impairment (employed patients only). Mean overall work impairment was 48.7% in patients receiving treatment after surgery, 26.4% in patients who had completed adjuvant treatment and 44.8% in patients receiving treatment for mBC.[52]

- Absenteeism (employed patients only). Mean absenteeism was 38.1% in patients receiving treatment after surgery, 9.2% in patients who had completed adjuvant treatment and 30.6% in patients receiving treatment for mBC.[52]
    - The estimated yearly total cost of absenteeism per patient (in employed patients and those reporting being unable to work) was £8,528 in patients receiving treatment after surgery, £3,068 in patients who had completed adjuvant treatment and £10,556 in patients receiving treatment for mBC.[52]

These results show that the impact on work productivity in the HER2-positive mBC setting is higher than in the eBC setting, reinforcing the need to treat with the most effective treatments in the eBC setting whilst the goal is of curative intent.[52]

An interim analysis of the ESTHER non-interventional study (which follows UK patients from diagnosis of HER2-positive mBC or unresectable locally advanced BC) found that the anti-cancer resource use in the initial management of advanced HER2-positive BC was high. In the 205 patients analysed, 93.2% received systemic HER2-targeted therapies, 41% received bone-modifying agents, 22.9% received radiotherapy and 6.3% received metastatic ressection.[41] These data demonstrate that mBC has substantial long-term cost and resource implications for the NHS.

The premature death of patients with mBC has particularly severe social and economic implications due to the relatively young average age at diagnosis of HER2-positive mBC (approximately 55 years).[42, 59] The unknown future can bring considerable emotional burden on the patient themselves and on their children, other dependents and caregivers. A Canadian study of financial and family burden 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.[50] Furthermore, the impact on the work productivity of caregivers for patients with BC would be expected to be even more severe for patients with mBC compared to those with earlier stages of the disease, due to the severity of the mBC symptoms and treatment side-effects.

The substantial burden of BC and poor prognosis of mBC highlights the importance of providing the most comprehensive treatment option for eBC, to prevent or slow progression to mBC and reduce the potentially avoidable morbidity and mortality associated with mBC.

B.1.3.2 Treatment aims, guidelines and current treatment options

Since mBC is currently incurable, improving the results of treatment whilst the disease is still localised to the breast and regional lymph nodes (i.e. at the eBC stage) offers patients the best possible chance of cure. The goal of systemic treatment for eBC is to reduce the risk of micrometastases. The benefits of starting systemic treatment for HER2-positive eBC prior to surgery is to reduce the burden of the tumour prior to surgery and potentially de-escalate the surgical procedure, allowing for breast-conservation surgery rather than mastectomy in high-risk patients.[60, 61] Following surgery, HER2-targeted systemic treatment is continued to prevent micrometastases and the development of distant metastases.[12, 62] Patients, especially those with high-risk disease (e.g. node-positive or hormone receptor-negative at diagnosis), may still relapse irrespective of their response to neoadjuvant treatment.[30] As such, the most comprehensive systemic treatment is imperative to reduce the risk of BC recurrence.

Relevant guidelines for the systemic treatment of HER2-positive eBC are listed below in Table 3.

Table 3. Relevant guidelines for the systemic treatment of HER2-positive eBC

Organisation	Date of issue/most recent update	Summary of recommendations
NICE (CG80)[12]	2017	In the adjuvant setting, trastuzumab, given at three-week intervals for one year or until disease recurrence (whichever is the shorter period), is recommended as a treatment option for women with early-stage HER2-positive BC following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable).
ESMO[63]	2015	Systemic adjuvant therapy with trastuzumab combined with chemotherapy is recommended in patients with HER2-positive BC who are node-positive or node-negative with tumours >1 cm. It should also be considered for patients who are node-negative with tumours <1 cm, particularly if they have ER-negative tumours. In selected high-risk cases, pertuzumab can be considered an acceptable option as neoadjuvant therapy.
St Gallen[1, 64]	2017	The St Gallen Consensus Conference took place prior to the availability of APHINITY data. The authors added key points relating to the APHINITY data released after the Consensus Conference, to include recommendations on the adjuvant systemic treatment for HER2-positive eBC. The Panel recommended dual blockade with pertuzumab + trastuzumab in the adjuvant setting in patients who are at higher risk for relapse because of lymph node involvement or hormone receptor negativity.
NCCN[65]	2017[a]	The NCCN guidelines support the continuation of HER2-targed therapy with pertuzumab + trastuzumab to complete one year of therapy in patients with node-positive, HER2-positive BC post-surgery.

Footnotes: Pertuzumab was approved for the neoadjuvant treatment of eBC in the US in September 2013 and in the EU in July 2015. Pertuzumab use in the US in the adjuvant setting is based on the NCCN guidelines. Pertuzumab is not yet approved in the adjuvant setting. [a]On 10th November 2017, the NCCN guidelines were partially updated. It should be noted that only the algorithm(s) have been updated and that the supporting discussion parts of the guidelines are still in development.
Abbreviations: BC, breast cancer; eBC, early breast cancer; ER, oestrogen receptor; ESMO, European Society for Medical Oncology; HER2, human epidermal growth factor receptor 2; NCCN, National Comprehensive Cancer Network; NICE, National Institute for Health and Care Excellence.

Current treatment for patients with HER2-positive eBC in England usually involves a combination of HER2-targeted therapy, chemotherapy, surgery, radiotherapy and hormone therapy, depending on the characteristics of the tumour. Systemic therapy can be given neoadjuvantly and adjuvantly as part of a complete eBC treatment regimen, with the goal being to reduce the risk of both local and systemic recurrence.[60, 61]

The goal of systemic treatment for eBC is to reduce the risk of micrometastases. Most patients with high-risk disease in the UK now receive neoadjuvant treatment, and UK clinical experts have stated there is a trend towards treating patients with pertuzumab + trastuzumab earlier because earlier treatment is linked to achieving better pCR outcomes (with pCR a significant predictor of longer-term event-free survival [EFS] and distant disease-free survival (DDFS) across all BC treatments and regardless of BC subtype),[66] and since access to pertuzumab in eBC is currently

only possible via neoadjuvant treatment.[67] Initiating pertuzumab treatment in the neoadjuvant setting means that patients may be able to have a de-escalated surgical procedure (i.e. from mastectomy to breast-conservation) and potentially improve their longer-term disease outcomes, but it does not mean neoadjuvant treatment is enough.

In England, systemic trastuzumab is the backbone therapy for patients with HER2-positive BC across all stages of the disease, eBC to mBC.[68-70] Dual-HER2 blockade (pertuzumab + trastuzumab) with chemotherapy is commonly used in the neoadjuvant setting in patients with high-risk disease and in patients with mBC.[4] Current evidence suggests that long-term clinical outcomes are not influenced by the timing of initiation of systemic treatment (before or after surgery),[71] and NICE CG80 was published in 2006 to allow adjuvant trastuzumab treatment for up to one year (18 cycles) for eBC patients following surgery.[12] In clinical practice, initiation with neoadjuvant HER2-targeted treatment is common for patients with eBC with high-risk factors, and typically these patients would continue trastuzumab treatment in the adjuvant setting to complete one year of therapy. This treatment approach is also reflected in the recent NCCN Guidelines (updated 10th November 2017), which recommend that patients with node-positive, HER2-positive BC treated with neoadjuvant systemic therapy and surgery can complete up to one year of HER2-targeted therapy with pertuzumab + trastuzumab.[1, 65]

B.1.3.3 Proposed use and positioning of adjuvant pertuzumab

Current unmet need in the treatment of eBC

Despite substantial advances in the treatment of patients with HER2-positive eBC in recent years with the introduction of trastuzumab and neoadjuvant pertuzumab, there remains room for improvement in the treatment of this disease:

- pCR has been shown to be a very strong surrogate for improved EFS and DDFS.[66] However, even if patients achieve a pCR there is still a risk of relapse and mortality, and this risk is correlated with the extent of residual disease.[35] Disease risk is determined at the time of diagnosis and staging and the risk does not alter as a result of neoadjuvant intervention.
- Approximately one in four eBC patients will relapse despite being treated with one year of adjuvant trastuzumab experience disease relapse.[72]

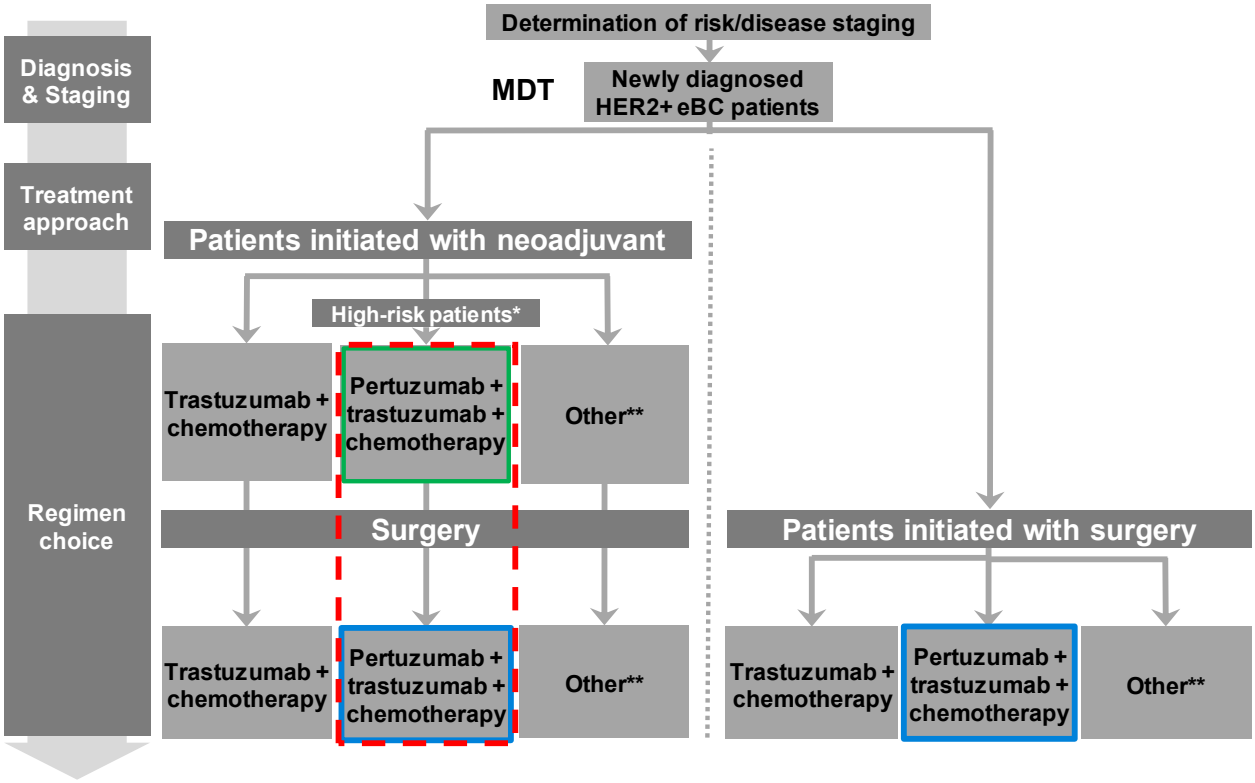
As such, there is a need to further improve systemic therapy for eBC, with the aim of preventing progression to incurable mBC. Systemic therapy improvements could ultimately reduce the incidence of mBC, and alleviate the burden that this disease places on patients, their families, wider society, the economy and healthcare systems.

Positioning of pertuzumab in treatment of eBC in the adjuvant setting

BC disease risk is determined at the time of diagnosis and staging, and this risk does not change as a result of neoadjuvant treatment. There is strong biological rationale for the combination of pertuzumab + trastuzumab in the treatment of HER2-positive eBC, and this was recognised by the CHMP when assessing pertuzumab preceding its recommendation in neoadjuvant treatment.[73] The positive efficacy results from the APHINITY study provides justification for the use of 18 cycles of pertuzumab + trastuzumab for patients with HER2-positive eBC, particularly those with a high risk of recurrence (i.e. patients with node-positive or hormone receptor-negative disease).

The suggested positioning of pertuzumab in the treatment pathway for patients with HER2-positive eBC at high risk of recurrence is shown in Figure 1. These high-risk patients may have been treated with pertuzumab + trastuzumab + chemotherapy in the neoadjuvant setting to improve the outcomes of surgery, and a positive recommendation for adjuvant pertuzumab would allow them to continue this treatment into the adjuvant setting, to complete up to one year (18 cycles) of treatment to increase the likelihood of reaching their treatment goals in this curative setting. This is similar to the manner in which trastuzumab is currently used in clinical practice and reflective of how clinicians in the UK would use pertuzumab in the eBC setting.

Figure 1. Summary of the clinical care pathway and proposed placement of adjuvant pertuzumab



Footnotes: *High-risk patients: Patients with node-positive or hormone receptor-negative eBC; **Other: Patients who receive chemotherapy only or hormonal therapy only.
Key: Blue border = proposed use of adjuvant pertuzumab as discussed in this submission; Green border = currently approved use of neoadjuvant pertuzumab; Red border = proposed use of pertuzumab treatment for a total of 18 cycles through from neoadjuvant to adjuvant treatment in patients with high-risk (i.e. node-positive or hormone receptor-negative) eBC.
Abbreviations: eBC, early breast cancer; HER2+, human epidermal growth factor receptor 2-positive; MDT, multidisciplinary team.

B.1.4 *Equality considerations*

No equality issues have been identified in relation to the use of pertuzumab for the adjuvant treatment of adults with HER2-positive eBC.

B.2 Clinical effectiveness

Summary of clinical effectiveness

- One study was identified in a systematic literature review to find studies relevant to the decision problem: the Phase III APHINITY study, which evaluated the efficacy and safety of adjuvant pertuzumab + trastuzumab + chemotherapy (n=2,400) vs placebo + trastuzumab + chemotherapy (n=2,405) in patients with HER2-positive eBC.[2]
    - Mean patient age was 51.7 years in the pertuzumab arm, and 51.4 years in the placebo arm. Disease was classified as node-positive in 63% of patients and hormone receptor-negative in 36% of patients.[2]
- The pre-specified primary analysis was conducted after 379 IDFS events (19th December 2016), at which point the median follow-up duration in the ITT population was 45.4 months. The primary endpoint of the study showed the clinical benefit of the addition of pertuzumab to trastuzumab + chemotherapy:
    - The addition of pertuzumab reduced the risk of an IDFS event by 19% compared with the placebo arm (HR=0.81; 95% CI, 0.66–1.00; p=0.045).[2]
    - Estimates of IDFS at three years were 94.1% in the pertuzumab arm vs 93.2% in the placebo arm.[2]
    - Estimates of IDFS at four years were 92.3% in the pertuzumab arm vs 90.6% in the placebo arm (p=0.045).[2]
- Results from key secondary endpoints were supportive of the benefit seen in the primary IDFS analysis: significant between-group differences in favour of pertuzumab in IDFS including second primary non-breast cancers, DFS and RFI were observed.[2]
- Assessment of mean global health status scores using EORTC QLQ-C30 indicated that the addition of pertuzumab to trastuzumab + chemotherapy did not adversely affect patients' global health status.[2]
- A pre-specified subgroup analysis by nodal status was conducted, because of the known importance of nodal status in disease prognosis and outcomes. In patients with node-positive disease there was a 23% reduction in the risk of recurrence or death in the pertuzumab arm vs the placebo arm (HR=0.77; 95% CI, 0.62–0.96; p=0.02).[2] Estimates of IDFS at three years were 92.0% in the pertuzumab arm and 90.2% in the placebo arm. Estimates of IDFS at four years were 89.9% in the pertuzumab arm and 86.7% in the placebo arm.[2]
- A pre-specified subgroup analysis by hormone receptor status was conducted, because of the known importance of hormone receptor status in disease prognosis and outcomes. In patients with hormone receptor-negative disease there was a 24% reduction in the risk of recurrence or death in the pertuzumab arm vs the placebo arm (HR=0.76; 95% CI, 0.56–1.04; p=0.08).[2] Estimates of IDFS at three years were 92.8% in the pertuzumab arm and 91.2% in the placebo arm. Estimates of IDFS at four years were 91.0% in the pertuzumab arm and 88.7% in the placebo arm.[2]
- No new safety signals for pertuzumab were observed in the APHINITY trial. The adverse event (AE) profile during the treatment period was generally balanced between the two treatment arms, although diarrhoea was more common in the pertuzumab than in the placebo arm. Heart failure, cardiac death and cardiac dysfunction were infrequent in both.[2]

B.2.1 *Identification and selection of relevant studies*

To provide support for the use of pertuzumab in combination with trastuzumab + chemotherapy in the adjuvant treatment of patients with HER2-positive eBC, a systematic literature review (SLR) of published clinical evidence was undertaken to identify and summarise all eligible publications pertaining to all licensed and investigational pharmacological treatments in patients with newly diagnosed, non-metastatic, operable, primary invasive HER2-positive BC. The SLR also aimed to identify and summarise previously published SLRs and meta-analyses of interventions used for the adjuvant treatment of patients with HER2-positive eBC. The process and methods used to identify and select the relevant clinical evidence in this submission are described in Appendix D.

This SLR identified one relevant study for pertuzumab in the adjuvant treatment of patients with HER2-positive eBC: the APHINITY study, as described in Section B.2.2.

B.2.2 *List of relevant clinical effectiveness evidence*

A summary of the APHINITY study is presented in Table 4 below. One ongoing study (BERENICE; NCT02132949) is expected to provide some additional relevant safety evidence in the next 12 months (Section B.2.11).

Table 4. Clinical effectiveness evidence

Study	APHINITY (von Minckwitz *et al*. 2017)[2]
Study design	Phase III, randomised, prospective, double-blind, multicentre, multinational, placebo-controlled study[2]
Population	Patients newly diagnosed with primary invasive HER2-positive BC (N=4,805) with baseline LVEF ≥55% and either:[2] • Node-positive BC of any tumour size except T0 (no evidence of primary tumour), OR • Node-negative BC for which one of the following conditions had to be met: o Tumour size >1 cm o Tumour size >0.5 cm and ≤1 cm, and at least one of the following three features: • Histologic/nuclear Grade 3, OR • Negative for ER or PgR, OR • Age <35 years o Enrolment of patients with node-negative tumours ≤1 cm was limited to <10% of the total number of randomised patients
Intervention(s)	**Arm 1:** pertuzumab + trastuzumab + standard chemotherapy* *Standard chemotherapy included anthracycline-based regimens ([3–4 FEC (or FAC) → 3–4 TH] or [4 x AC (or EC) → 4 x TH]) and non-anthracycline-based regimens (6 x TCH). See Section B.2.3.1 for details.[2, 74]
Comparator(s)	**Arm 2:** Placebo + trastuzumab + standard chemotherapy* *Standard chemotherapy included anthracycline-based regimens ([3–4 FEC (or FAC) → 3–4 TH] or [4 x AC (or EC) → 4 x TH]) and non-

	anthracycline-based regimens (6 x TCH). See Section B.2.3.1 for details.[2, 74]				
Indicate if trial supports application for marketing authorisation	Yes	*X*	**Indicate if trial used in the economic model**	Yes	*X*
	No			No	
Rationale for use/non-use in the model	The APHINITY study was used in the economic model as it was the pivotal study submitted for the marketing authorisation of pertuzumab in this indication and provides directly relevant evidence for treatment effect of pertuzumab on outcomes important to the model. The APHINITY study is the only study to assess the use of adjuvant pertuzumab treatment in HER2-positive eBC patients that has results available at this time.				
Reported outcomes specified in the decision problem	• OS • DFS • RFI • **Adverse effects of treatment** • **HRQoL**				
All other reported outcomes	• **IDFS** • IDFS including second primary non-breast cancer • DRFI				
Pre-planned subgroups	Subgroup analyses were performed for the randomisation stratification factors (underlined below) as well as for other disease or patient-related prognostic or predictive factors for the primary endpoint and secondary endpoints OS and DRFI. • Nodal status[a] (categorised as zero positive nodes vs ≥1 positive nodes) and tumour size • Adjuvant chemotherapy regimen (anthracycline-containing regimen; non-anthracycline containing regimen) • Centrally assessed hormone receptor status (ER-positive PgR-positive; ER-positive PgR-negative; ER-negative PgR-positive; ER-negative PgR-negative) • Geographical region (USA; Canada/Western Europe/Australia-New Zealand/South Africa; Eastern Europe; Asia-Pacific; Latin America) • Menopausal status at screening (pre-menopausal; post-menopausal) • Age (<40, 40–49, 50–64, <65, ≥65 years) • Histological grade (Grade 1; Grade 2; Grade 3) • Type of surgery for primary tumour (breast-conserving surgery; non-conserving breast surgery) • Tumour size (0–<2 cm; ≥2–5 cm; ≥5 cm) • Loco-regional radiotherapy (Yes; No) • Race (White; Black; Asian; Other) • Sex (female patients; the number of male patients is considered insufficient to warrant meaningful subgroup analysis) • Protocol version[b] (patients enrolled to either of the two node-positive strata[a] during Protocol A vs Protocol Amendment B) • HER2 subgroups (these analyses were not described in the protocol or the SAP but were defined prior to database lock)				

Footnotes: [a]Nodal status is a key prognostic factor in HER2-positive eBC and this subgroup was a key high-risk subgroup in relation to the decision problem presented in this submission. Following the implementation of Protocol Amendment B, the stratification factor "nodal status and tumour size" only included the two categories with positive nodes; [b]Protocol version was introduced as a stratification factor at the time Protocol Amendment B was issued.
Abbreviations: AC, doxorubicin and cyclophosphamide; BC, breast cancer; CISH, chromogenic *in situ* hybridisation; DFS, disease-free survival; DRFI, distant recurrence-free interval; eBC, early breast cancer; EC, epirubicin and cyclophosphamide; ER, oestrogen receptor; FAC, 5-fluorouracil, doxorubicin and cyclophosphamide; FEC, 5-fluorouracil, epirubicin and cyclophosphamide; FISH, fluorescence *in situ* hybridisation; HER2, human epidermal growth factor receptor 2; HRQoL, health-related quality of life; IDFS, invasive disease-free survival; IHC, immunohistochemistry; IV, intravenous; LVEF, left ventricular ejection fraction; OS, overall survival; PgR, progesterone receptor; RFI, recurrence-free interval; SAP, statistical analysis plan; T, taxane; TCH, docetaxel, carboplatin + trastuzumab; TH, taxane + trastuzumab.
Source: Clinicaltrials.gov. APHINITY (NCT01358877) study record[74]; von Minckwitz *et al*. 2017[2]; APHINITY study CSR[75]

B.2.3 *Summary of methodology of the relevant clinical effectiveness evidence*

B.2.3.1 Summary of trial methodology

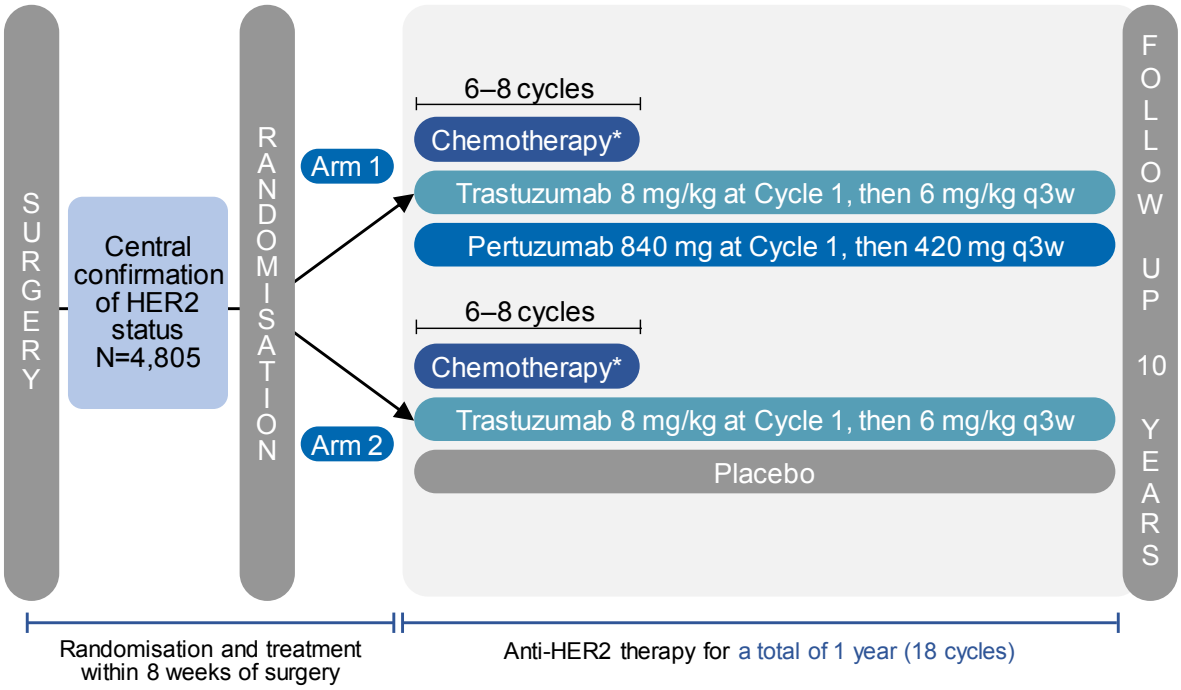
The APHINITY study[2, 75]

Study design: The APHINITY study is an ongoing, Phase III, randomised, prospective, double-blind, multicentre, multinational, placebo-controlled study to assess the efficacy and safety of adjuvant pertuzumab + trastuzumab + chemotherapy (n=2,400) compared with placebo + trastuzumab + chemotherapy (n=2,405) in 4,805 patients with operable HER2-positive eBC.

Patients were randomised 1:1 to treatment with either adjuvant pertuzumab + trastuzumab + chemotherapy (Arm 1) or placebo + trastuzumab + chemotherapy (Arm 2). Adjuvant chemotherapy was the investigator's choice of anthracycline-based or non-anthracycline-based regimens. Randomisation and treatment occurred within eight weeks of surgery. Patients were stratified by nodal status, chemotherapy regimen, hormone receptor status, geographic region, and protocol version (A or B). Anti-HER2 treatment was administered for a total of one year (up to 18 cycles). Radiotherapy was given as clinically indicated at the end of chemotherapy and concomitantly with anti-HER2 treatment, and patients with hormone receptor-positive disease received standard hormone therapy for at least five years, starting at the end of chemotherapy.

The primary objective of the APHINITY study was to compare IDFS (excluding second primary non-breast cancers) in patients between the pertuzumab + trastuzumab + chemotherapy and placebo + trastuzumab + chemotherapy treatment arms. Secondary objectives were to compare IDFS including second primary non-breast cancers, DFS, OS, RFI, DRFI, cardiac safety, overall safety, and HRQoL in patients in the two treatment arms. An overview of the APHINITY study design and endpoints is presented in Figure 2.

Figure 2. Overview of the APHINITY study design



Primary endpoint: IDFS
Secondary endpoints: IDFS with second primary non-breast cancers included, DFS, OS, RFI, DRFI, safety, HRQoL
Stratification factors: Chemotherapy regimen, hormone receptor status, nodal status, geographic region, protocol version (A vs B)

Footnote: *A number of standard anthracycline-taxane sequences or non-anthracycline regimens were allowed – please refer to Table 4 and B.2.3.1 for these.
Abbreviations: DFRI, distant recurrence-free interval; DFS, disease-free survival; HER2, human epidermal growth factor receptor 2; HRQoL, health-related quality of life; IDFS, invasive disease-free survival; OS, overall survival; q3w, every three weeks; RFI, recurrence-free interval.
Source: von Minckwitz G *et al*. ASCO 2017. LBA500[76]

Pertuzumab or placebo was administered on Day 1 of the first taxane-containing cycle as an 840 mg loading dose, followed by 420 mg q3w for all subsequent cycles. Trastuzumab was administered as an 8 mg/kg loading dose, followed by 6 mg/kg q3w for all subsequent cycles. Anti-HER2 therapy was administered for a total of one year (up to 18 cycles). The following chemotherapy regimens were options given in combination with anti-HER2 therapy:

Anthracycline-based chemotherapy: FEC (or FAC) → T^2

- Three or four cycles of 5-fluorouracil (500–600 mg/m^2) + epirubicin (90–120 mg/m^2) or doxorubicin (50 mg/m^2) administered IV q3w + cyclophosphamide (500–600 mg/m^2).
- Followed by three or four cycles of docetaxel (100 mg/m^2) IV q3w or 75 mg/m^2 IV at the first docetaxel cycle escalating to 100 mg/m^2 for subsequent cycles as per local practice or 75 mg/m^2 IV, q3w, for four cycles.
- Paclitaxel was acceptable instead of docetaxel, and was given at doses of 80 mg/m^2 once weekly for 12 cycles.

Anthracycline-based chemotherapy: AC (or EC) → T[2]

- Four cycles of AC (or EC) administered q3w or dose-dense, q2w, with granulocyte colony-stimulating factor (G-CSF) support.
  - Doxorubicin 60 mg/m^2 (or epirubicin 90–120 mg/m^2)
  - Cyclophosphamide 500–600 mg/m^2
- Followed by four cycles of T:
  - Docetaxel 100mg/m^2 IV, q3w or 75 mg/m^2 IV at the first docetaxel cycle escalating to 100 mg/m^2 for subsequent cycles as per local practice or 75 mg/m^2 IV q3w for four cycles.
  - Paclitaxel was acceptable instead of docetaxel and was given at doses of 80 mg/m^2, qw, for 12 weekly cycles.

Non-anthracycline-based chemotherapy: TC[2]

- TCH administered IV, q3w, for six cycles of docetaxel (75 mg/m^2, no escalation) plus carboplatin area under the curve of six (maximum dose 900 mg).

Patients were followed from the first day of treatment through to Week 52 of targeted treatment. After completion of study treatment and a 28-day safety follow-up visit, patients were followed at approximately two-monthly intervals for two years, then every six months for three to five years, and annually thereafter, even if the assigned treatment was discontinued prematurely.[2]

Key eligibility criteria: Key inclusion and exclusion criteria for patients entering the APHINITY trial are listed in Table 5.

Table 5. Key eligibility criteria from the APHINITY trial[a]

Inclusion Criteria	Exclusion Criteria

• HER2-positivity of the BC had to be confirmed by a central laboratory
• Node-positive disease (any tumour size except T0) or node-negative disease (only under Protocol Version A) were allowed to enroll. For patients with node-negative disease, one of the following conditions had to be met:
  ○ Tumour size >1 cm
  ○ Tumour size >0.5 cm and ≤1 cm, and at least one of the following three features:
  ▪ Histologic/nuclear Grade 3, OR
  ▪ Negative for oestrogen-receptor or progesterone receptor, OR
  ▪ Age <35 years
Enrollment of patients with node-negative tumors ≤1 cm was limited to <10% of the total number of randomised patients
• Baseline LVEF ≥55%
	• History of any prior invasive breast carcinoma
	• Non-operable breast cancer
	• History of non-breast malignancies within five years prior to study entry (except for the following: carcinoma in situ of the cervix, carcinoma in situ of the colon, melanoma in situ, and basal cell and squamous cell carcinomas of the skin)
	• Metastatic disease (stage IV)
	• Previous or current anti-cancer therapy or previous radiotherapy for any malignancy
	• Cardiac dysfunction or serious medical conditions

Footnotes: [a]A complete list of inclusion and exclusion criteria are available for the APHINITY study online at Clinicaltrials.gov.
Abbreviations: BC, breast cancer; HER2, human epidermal growth factor receptor 2.
Source: Clinicaltrials.gov. APHINITY (NCT01358877) study record[74]

Study settings and locations: From 8th November 2011 to 31st August 2013, patients were enrolled across 43 countries in Europe, North, Central and South America, Australasia, Asia, the Middle East and Africa. Of the 549 centres involved, 25 were from the UK.[2, 74]

Concomitant medications and treatments: All medications taken by the patient for concomitant diseases were continued during the study treatment period, unless they were not permitted (see Table 6).[77]

Table 6. Permitted and excluded concomitant medications

Permitted concomitant medications/treatments	Excluded concomitant medications/treatments
• Acceptable methods of contraception (when the patient is not surgically sterilised or does not meet the study definition of post-menopausal) • H1 and H2 antagonists • Cardiovascular medications • Analgesics/anti-inflammatories • Short term use of corticosteroids to treat or prevent allergic or infusion reactions • Anti-emetics • Medication to treat diarrhoea • Colony-stimulating factors • Oestrogen receptor antagonists or aromatase inhibitors after completion of post-operative chemotherapy as per local practice • LHRH/GnRH analogues • Vitamin and mineral supplements • Bisphosphonates • Adjuvant radiotherapy	• Anti-cancer therapies other than those administered in the study • Any targeted anti-cancer therapy • Regular treatment with steroids • Any investigational agent, except for those used for the study • Initiation of herbal remedies • Any systemically active oral, injected or implanted hormonal method of contraception • Oestrogen-replacement therapy

Abbreviations: LHRH, luteinising-hormone-releasing hormone; GnRH, gonadotropin releasing hormone.
Source: APHINITY study protocol[77]

Study endpoints:

Primary efficacy endpoint

- **IDFS, excluding second primary non-breast cancer events:** defined as the time from randomisation until the date of first occurrence of one of the following: recurrence of ipsilateral invasive breast tumour, recurrence of ipsilateral locoregional invasive disease, a distant disease recurrence, contralateral invasive BC or death from any cause.[74] Second primary non-breast cancers, *in situ* carcinomas (ductal carcinoma *in situ* [DCIS] and lobular carcinoma *in situ* [LCIS]) and non-melanoma skin cancer were excluded as events.[75]
    - The APHINITY definition of IDFS excludes second primary non-breast cancer tumours. This definition was based on the US FDA's recommended definition for a trial intended to support a regulatory filing. Inclusion of second primary non-breast cancer events in the IDFS definition has the disadvantage of including events not related to the cancer or the treatment under study, thereby potentially diluting any treatment effect.[78]

Secondary endpoints[75]

- **IDFS, including second primary non-breast cancer events:** defined as time from randomisation until the date of first occurrence of one of: recurrence of ipsilateral invasive breast tumour, recurrence of ipsilateral locoregional invasive disease, a distant disease recurrence, contralateral invasive BC, second primary non-breast cancers or death from any cause.[74]
- **Disease-free survival (DFS):** defined as time between randomisation and the date of the first occurrence of an IDFS event including second primary non-breast cancer event or contralateral or ipsilateral DCIS.
- **Overall survival (OS):** defined as the time from randomisation to death attributable to any cause.
- **RFI:** defined as the time between randomisation and the date of local, regional or distant BC recurrence.
- **DRFI:** defined as the time between randomisation and the date of distant BC recurrence.
- **HRQoL:** defined as symptoms of therapy, patient functioning and global health status as assessed by the EORTC QLQ-C30, QLQ-BR23 and EQ-5D questionnaires.
- **Overall safety outcomes, and cardiac safety outcomes specifically.**

B.2.3.2 Baseline patient characteristics

Key patient demographics and pre-specified randomisation and stratification factors are presented in Table 7.[2] Baseline characteristics of the patients were balanced between the two treatment arms: median age was 51 years, approximately one third had hormone receptor-negative disease and nearly two thirds had node-positive disease,[2] which is considered representative of the HER2-positive eBC patient population in the UK.

Table 7. Baseline characteristics of patients included in the APHINITY study[2]

		Pertuzumab + trastuzumab + chemotherapy N=2,400	Placebo + trastuzumab + chemotherapy N=2,404[a]
Demographics	Age, median, range (years)	51.0 (22–86)	51.0 (18–85)
	<65 years	2,085 (86.9%)	2,111 (87.8%)
	≥65 years	315 (13.1%)	293 (12.2%)
	Weight, median, range (kg)	65 (37–154)	65 (37–162)
	Sex, female / male	99.9 / 0.1%	99.7 / 0.3%
	Race, White / Asian / Other	71.2 / 24.7 / 4.1%	70.5 / 24.9 / 4.6%
Baseline BC characteristics	Histologic grade of primary tumour[b]		
	Grade 1	53 (2.2%)	42 (1.7%)
	Grade 2	770 (32.0%)	764 (31.7%)
	Grade 3	1,493 (62.1%)	1,506 (62.5%)
	Unevaluable	87 (3.6%)	94 (3.9%)
	Unknown	0	2 (<0.1%)
	HER2 status by central laboratory (IHC result)[b, c]		
	0	6 (0.3%)	2 (<0.1%)
	1+	16 (0.7%)	9 (0.4%)

		Pertuzumab + trastuzumab + chemotherapy N=2,400	Placebo + trastuzumab + chemotherapy N=2,404[a]
	2+	193 (8.0%)	200 (8.3%)
	3+	2,184 (91.0%)	2,190 (91.2%)
	Type of primary surgery[d]		
	Mastectomy	1,280 (53.3%)	1,327 (55.2%)
	Breast conserving surgery	1,118 (46.7%)	1,076 (44.8%)
Randomisation stratification factors	Nodal status		
	0 positive nodes and tumour ≤1 cm[e]	90 (3.8%)	84 (3.5%)
	0 positive nodes and tumour >1 cm[e]	807 (33.6%)	818 (34.0%)
	1-3 positive nodes	907 (37.8%)	900 (37.4%)
	≥4 positive nodes	596 (24.8%)	602 (25.0%)
	Standard adjuvant chemotherapy regimen (randomised)		
	Anthracycline containing regimen	1865 (77.7%)	1877 (78.1%)
	Non-anthracycline containing regimen	535 (22.3%)	527 (21.9%)
	Hormone receptor status (central)		
	Negative (ER and PgR-negative)	864 (36.0%)	858 (35.7%)
	Positive (ER and/or PgR-positive)	1,536 (64.0%)	1,546 (64.3%)
	Geographic Region		
	USA	296 (12.3%)	294 (12.2%)
	Canada/Western Europe/Australia-New Zealand/South Africa	1,294 (53.9%)	1,289 (53.6%)
	Eastern Europe	200 (8.3%)	200 (8.3%)
	Asia-Pacific	550 (22.9%)	557 (23.2%)
	Latin America	60 (2.5%)	64 (2.7%)
	Protocol Version		
	Protocol A	1,828 (76.2%)	1,827 (76.0%)
	Protocol Amendment B	572 (23.8%)	577 (24.0%)

Footnotes: [a]One patient excluded from ITT population due to falsification of personal information; [b]For patients with bilateral tumours, the grade and HER2 status for each tumour was counted separately; [c]For cases that were anything other than IHC3+, patients needed to be positive according to FISH; [d]Mastectomy included radical mastectomy, modified radical mastectomy and simple mastectomy. Breast conserving surgery included partial mastectomy and breast lumpectomy and others that did not meet the criteria for mastectomy. Information on type of surgery is not available for three patients (two in pertuzumab + trastuzumab + chemotherapy arm and one in placebo + trastuzumab + chemotherapy arm); [e]Randomised under Protocol Version A only.
Abbreviations: BC, breast cancer; ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; PgR, progesterone receptor.
Sources: von Minckwitz *et al*. 2017[2]; Clinicaltrials.gov. APHINITY (NCT01358877) study record[74]; von Minckwitz G *et al*. ASCO 2017. LBA500[76]; APHINITY study CSR[75]

B.2.4 *Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence*

B.2.4.1 Statistical analysis and study populations

A summary of the analysis populations for efficacy and safety outcomes for the APHINITY study is presented in Table 8, while a summary of statistical analyses for the primary efficacy analysis in the study is presented in Table 9. Details of the participant flow for the APHINITY trial are presented in Appendix D.

After 3,655 patients had been randomised, Protocol amendment B was put into place to prevent further enrolment of patients with node-negative disease and to allow for enrolment for an additional 1,000 node-positive patients, in order reflect the nodal status ratio originally planned and powered (based on data from the BCIRG 006 study[79]). The protocol amendment is explained in Appendix L.

Table 8. Summary of analysis populations

	APHINITY
Primary efficacy analysis	The ITT population receiving treatment with either pertuzumab or placebo, as defined by the protocol (n=4,804)[a]
Secondary analyses	The ITT population (including patients with second primary non-breast cancers) receiving treatment with either pertuzumab or placebo, as defined by the protocol (n=4,804)[a]
Safety analyses	Patients who received at least one dose of pertuzumab or study medication (including chemotherapy or trastuzumab) (n=4,769)

Footnotes: [a]One patient excluded from ITT population due to falsification of personal information.
Abbreviations: BC, breast cancer; ITT, intention-to-treat.
Source: von Minckwitz *et al*. 2017[2].

Table 9. Summary of statistical analyses for the primary efficacy analysis in APHINITY

	APHINITY
Hypothesis objective	• The primary objective of APHINITY was to compare IDFS in patients with HER2-positive BC. • The null hypothesis for the primary endpoint was that the survival distributions of IDFS in the two treatment arms were the same. The alternative hypothesis was that the survival distributions of IDFS in the treatment and the control arm were different: ○ H_0: $S_{pertuzumab} = S_{placebo}$ ○ H_1: $S_{pertuzumab} \neq S_{placebo}$
Statistical analysis[a]	• The stratified log-rank test was used to compare the rates of IDFS between the two treatment arms. Unstratified log-rank test results were provided as a sensitivity analysis. • The Kaplan-Meier approach was used to estimate 3-year IDFS rates for each treatment arm. • The stratified Cox proportional hazards model was used to estimate the HR between the two treatment arms (i.e. the magnitude of treatment effect) and its 95% confidence interval. • An expanded analysis for IDFS was performed using Cox proportional hazards regression models to determine if adjustment for covariates would modify the conclusions from the primary analysis. Variables considered were the stratification factors as well as other disease or patient-related prognostic or predictive factors (e.g. menopausal status, race, loco-regional radiotherapy, type of surgery, tumour size and histological grade). • The final (event-driven) OS analysis is planned to be conducted when 640 deaths have occurred. Three interim OS analyses are planned, with the first reported in the primary manuscript at an adjusted two-sided significance level of 0.00001 to control the overall alpha level at 0.05.

	APHINITY
Sample size/power calculation	• ~379 events and 4,800 patients were required for 80% power to test the null hypothesis of no true difference in risk of an IDFS event (HR=1) vs the alternative hypothesis of a difference (HR=0.75) in HRs with an alpha of 5%. • The smallest estimated difference detectable at a 5%, 2-sided significance level would be HR=0.818, under which the magnitude of treatment effect would be 1.9%. • A 3-year rate of IDFS of 89.2% was assumed for the placebo arm, on the basis of the results of the BCIRG 006 trial[79], and a 3-year IDFS of 91.8% was assumed for the pertuzumab arm – assuming a 35%/65% node-negative/node-positive split.
Data management/ patient withdrawals	• A patient was allowed to withdraw from the study or study specific procedures at any time during the entire duration of the study for any reason and without prejudicing future medical treatment. • The investigator had the responsibility to establish that the patient's decision was an informed choice and to ascertain to what extent the patient might be willing to continue limited participation in the trial, (e.g. willing to continue being contacted or seen to providing follow-up information). • Discussion outcomes were documented in both the patient's medical records and the eCRF. Patient withdrawal was defined within three different scenarios that have a different impact on the study analysis and data collection: o Withdrawal from study treatment: the decision to withdraw from treatment could be made by the patient or by the investigator. Patients were to be kept on the study and followed up according to the protocol schedule of assessments until study completion. The reason for treatment discontinuation had to be recorded on the eCRF. o Withdrawal from the entire study: if a patient decided to withdraw from the study, all efforts were made to complete and report the observations as thoroughly as possible. No further data were collected after the date of withdrawal from study. o Partial withdrawal from the study, with consent to allow collection of information regarding disease recurrence, survival status, and reportable toxicity: The patient had to accept to be contacted for further information on recurrence as per the primary study endpoint and survival status. Documented in both the medical records and in the eCRF that the patient accepted to be contacted for survival despite withdrawal from the study consent. • In the case of patients who failed to attend scheduled visits, several attempts had to be made by the site to contact these patients for follow up information, at least three attempts within a reasonable extent of time. If contact was unsuccessful, after sufficient attempts, the patient was declared "Lost to follow-up". • Data from patients without documented events were censored at the date the patient was last known to be event-free.

Footnotes: [a]Statistical analyses were performed in demographic subgroups of interest as appropriate.[77]

Abbreviations: BC, breast cancer; BCIRG, Breast Cancer International Research Group; CI, confidence interval; eCRF, electronic case report form; HR, hazard ratio; H_0, null hypothesis; H_1, alternative hypothesis; IDFS, invasive disease-free survival; OS, overall survival; $S_{pertuzumab}$, the survival distributions of IDFS in the pertuzumab arm; $S_{placebo}$, the survival distributions of IDFS in the placebo arm.
Source: von Minckwitz *et al*. 2017[2, 77]

B.2.4.2 Analysis data cut-offs

The primary analysis of efficacy took place after 379 IDFS events had occurred, in line with the pre-specified statistical analysis plan. The clinical cut-off date for this analysis was 19th December 2016, at which point the median follow-up duration in the ITT population was 45.4 months. The first interim analysis of OS was conducted at the same time, along with other analyses of safety and efficacy.[2] The results from this first cut-off date are presented in this submission.

Two further interim analyses of OS will be performed approximately 2.5 years and five years after the primary analysis of IDFS. The final event-driven OS analysis is planned to take place when 640 deaths have occurred (estimated to be around 9–10 years after the last patient was randomised [31st August 2013]). The study will formally end approximately ten years from the date the last patient was randomised.[75]

B.2.5 *Quality assessment of the relevant clinical effectiveness evidence*

Quality (risk of bias) assessment of the APHINITY RCT was conducted using the seven-criteria checklist provided in section 2.5 of the NICE single technology appraisal user guide.[80] An overview of the quality assessment is provided in Table 10 below. The full quality assessment is provided in Appendix D, Table 12.

Table 10. Quality assessment results for parallel group RCTs[a]

	APHINITY
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes
Were there any unexpected imbalances in drop-outs between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes

Footnotes: [a]Adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination)[81]

B.2.6 *Clinical effectiveness results of the relevant trials*

Summary of clinical effectiveness results

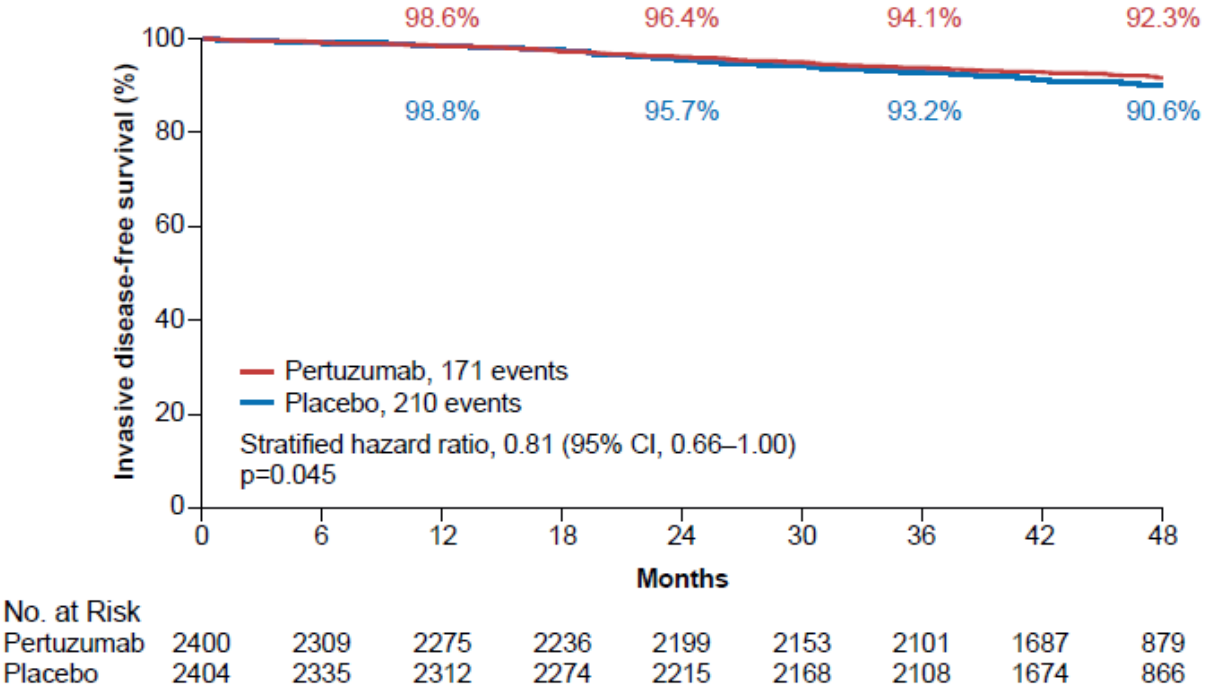
- The APHINITY study met its primary endpoint; the addition of pertuzumab to trastuzumab + chemotherapy reduced the risk of an IDFS event by 19% compared with the placebo arm (HR=0.81; 95% CI, 0.66–1.00; p=0.045) at a median follow up of 45.4 months.[2]
- Estimates of IDFS at three years were 94.1% in the pertuzumab arm vs 93.2% in the placebo arm, and at four years were 92.3% in the pertuzumab arm vs 90.6% in the placebo arm (p=0.045).[2]
- Subgroup analyses in high-risk subgroups of node-positive patients and hormone receptor-negative patients found that:
    - In patients with node-positive disease, there was a 23% reduction in the risk on an IDFS event (HR=0.77; 95% CI, 0.62–0.96; p=0.02).[2] Estimates of IDFS at three years in patients with node-positive disease were 92.0% in the pertuzumab arm and 90.2% in the placebo arm.[2] Estimates of 4-year IDFS event-free rates were 89.9% in the pertuzumab arm and 86.7% in the placebo arm.[2]
    - In patients with hormone receptor-negative disease, there was a 24% reduction in the risk on an IDFS event (HR=0.76; 95% CI, 0.56–1.04; p=0.08).[2] In the hormone receptor-negative patient subgroup, estimates of IDFS at three years were 92.8% in the pertuzumab arm and 91.2% in the placebo arm.[2] Estimates of IDFS at four years were 91.0% in the pertuzumab arm and 88.7% in the placebo arm.[2]
- The addition of pertuzumab to standard adjuvant trastuzumab + chemotherapy has been deemed clinically meaningful (a Group B intervention) when assessed using the Magnitude of Clinical Benefit Scale developed by the European Society for Medical Oncology (ESMO) for solid cancers. This means that this anti-cancer treatment derives a high level of clinically meaningful benefit, and substantial improvement over the standard of care, suggesting that this treatment should be emphasised for accelerated assessment of value and cost-effectiveness.[82]

B.2.6.1 Primary endpoint

The APHINITY study met its primary endpoint. In the ITT population, pertuzumab + trastuzumab + chemotherapy significantly reduced the risk of an IDFS event by 19% vs placebo + trastuzumab + chemotherapy (HR=0.81; 95% CI, 0.66–1.00; p=0.045; Figure 3) with a median follow-up of 45.4 months. This length of follow-up is relatively early in the context of this disease, so the current results may underestimate the whole extent of the treatment effect of adjuvant pertuzumab. The estimates of IDFS at three years were 94.1% in the pertuzumab arm vs 92.3% in the placebo arm. At four years the IDFS estimates were 93.2% in the pertuzumab arm vs 90.6% in the placebo arm.

The data indicate that the treatment effect difference between the pertuzumab and placebo arms may continue to increase over time (i.e. the IDFS curves are still diverging).[2]

Figure 3. ITT primary endpoint analysis of IDFS (primary analysis, clinical cut-off date 19th December 2016)



Abbreviations: CI, confidence interval.
Source: von Minckwitz *et al*. 2017[2]

The site of first occurrence of an invasive-disease event is summarised in Table 11.

Table 11. Site of first occurrence of an IDFS (primary analysis, clinical cut-off date 19th December 2016)

	Pertuzumab + trastuzumab + chemotherapy n=2,400	Placebo + trastuzumab + chemotherapy n=2,404[a]
Total patients with IDFS event, n (%)	171 (7.1)	210 (8.7)
Category of first IDFS event, n (%)		
Distant recurrence	112 (4.7)	139 (5.8)
Locoregional recurrence	26 (1.1)	34 (1.4)
Contralateral BC	5 (0.2)	11 (0.5)
Death without prior event	28 (1.2)	26 (1.1)
Site of first distant recurrence, n (%)		
Lung/liver/pleural effusion	43 (1.8)	61 (2.5)
CNS	46 (1.9)	45 (1.9)
Bone	9 (0.4)	9 (0.4)
Other	21 (0.9)	30 (1.2)

Footnotes: [a]One patient excluded from ITT population due to falsification of personal information.
Abbreviations: IDFS, invasive disease-free survival.
Source: von Minckwitz G *et al.* ASCO 2017. LBA500[76]

B.2.6.2 Secondary endpoints

Secondary efficacy endpoints

Overall, results of the secondary efficacy outcomes were consistent with and supportive of the clinical benefit of dual-blockade with pertuzumab + trastuzumab + chemotherapy on the primary endpoint, IDFS. At the primary analysis, there were significant between-arm differences in IDFS (including second primary non-breast cancer events – i.e. the standardised efficacy endpoints [STEEP] definition[78]), DFS and RFI, and the proportion of patients with DRFI was numerically higher in the pertuzumab than the placebo treatment arm (Table 12).[76]

The OS data were immature at the clinical cut-off date, with only 26% of the events required for the final analysis of OS having occurred (i.e. 169 deaths of the 640 deaths planned at the final OS analysis). Therefore, any differences in OS may become apparent in later analyses. The clinical cut-off for the next (second) interim OS analysis is planned to take place approximately 2.5 years after the primary analysis.[75]

Table 12. Summary of primary and secondary efficacy endpoint results for the ITT population

Endpoints	Hazard ratio[b] (95% CI)	Pertuzumab + trastuzumab + chemotherapy n=2,400	Placebo + trastuzumab + chemotherapy n=2,404[c]	p-value
IDFS (primary efficacy parameter)[a] estimated 3-year event-free rate, %	0.81 (0.66, 1.00)	94.1	93.2	0.045
Secondary efficacy endpoints, %				
IDFS including second non-primary breast cancer events (STEEP definition)[78]	0.82 (0.68, 0.99)	93.5	92.5	0.043
DFS	0.81 (0.67, 0.98)	93.4	92.3	0.033
RFI	0.79 (0.63, 0.99)	95.2	94.3	0.043
DRFI	0.82 (0.64, 1.04)	95.7	95.1	0.101
OS[d]	0.89 (0.66, 1.21)	97.7	97.7	0.467

Footnotes: [a]The pre-specified primary analysis was conducted after 379 IDFS events, the 3-year event-free rate was derived from Kaplan-Meier estimates; [b]Estimated by Cox-regression; [c]One patient excluded from ITT population due to falsification of personal information; [d]First interim analysis at 26% of the target events for the final OS analysis.
Abbreviations: CI, confidence interval; DFS, disease-free survival; DRFI, distant recurrence-free interval; IDFS: invasive disease-free survival; OS, overall survival; RFI, recurrence-free interval; STEEP, standardised efficacy endpoints.
Source: von Minckwitz *et al*. 2017[2]; von Minckwitz G *et al.* ASCO 2017. LBA500[76]

HRQoL

Patient-reported HRQoL was a secondary endpoint, and was defined as symptoms of therapy, patient functioning, and global health status. Specific scales assessing symptoms of therapy, patient functioning, and global health status were evaluated in both treatment arms with the validated European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30), the EORTC BC-specific quality of life questionnaire (QLQ-BR23), and the EuroQol 5-Dimension (EQ-5D) questionnaire. Patients were required to complete the patient-reported outcome (PRO) measures until recurrence or until 36 months after

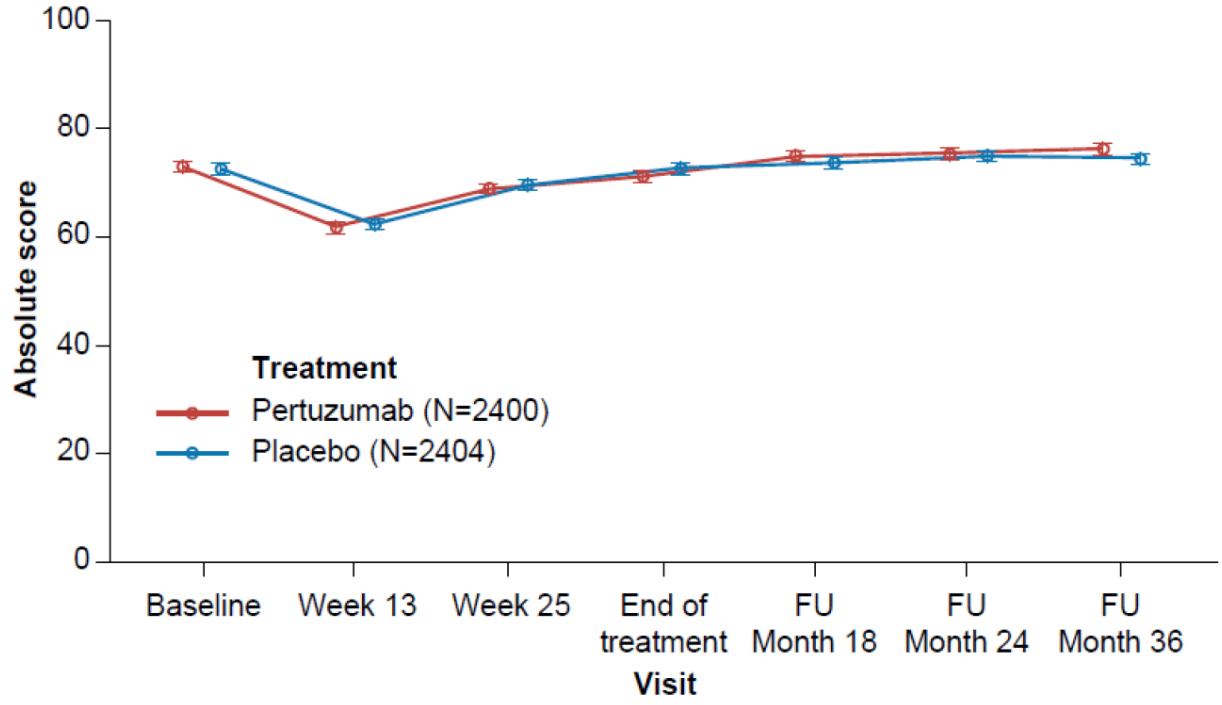
randomisation, regardless of whether the patient completed study treatment or not. At 36 months after randomisation, 2,094 and 2,097 patients were evaluable in the pertuzumab and placebo arms, respectively. Completion rates for all questionnaires were consistently high throughout the study (>85.0%).[75]

For the analyses of treatment-related symptoms, patient functioning, and global health status, as assessed by the scales of the validated EORTC QLQ-C30 and the QLQ-BR23 questionnaires, a difference of ≥10 points from the baseline score within a treatment arm was considered a clinically meaningful change.[83]

The mean global health status scores as measured using the EORTC QLQ-C30 showed a clinically meaningful worsening from the baseline mean score (72.9 in the pertuzumab arm vs 72.5 in the placebo arm) at the end of taxane treatment (Week 13) and returned to baseline thereafter in both arms. The results suggest that the addition of pertuzumab to trastuzumab + chemotherapy did not have an adverse effect on patients' global health status (Figure 4). The same pattern was seen for EORTC QLQ C30 physical functioning scores. There were no clinically meaningful changes from baseline observed in the four other functional scales of the EORTC QLQ-C30: role functioning, social functioning and cognitive functioning.[75]

Diarrhoea symptoms scores as measured by EORTC QLQ-C30 were highest (i.e., worst) at the end of taxane treatment (Week 13) in both arms. The scores in both arms remained elevated during the HER2-targeted treatment period, but the difference from baseline was clinically meaningful (≥10 points) only for the pertuzumab arm during this period, consistent with the diarrhoea adverse events (AEs) observed in the pertuzumab arm (see Section B.2.10). Scores in both arms returned to baseline after the end of HER2-targeted treatment.

Figure 4. APHINITY mean EORTC QLQ-C30 global health status in the ITT population (primary analysis, clinical cut-off date 19th December 2016)



Abbreviations: FU, follow-up.
Source: von Minckwitz *et al*. 2017[2]

In terms of EORTC QLQ-BR23 results, body image and sexual enjoyment scores were lowest at the end of taxane treatment (Week 13) with clinically meaningful worsening in these parameters at that time. The mean (SD) changes from Baseline at Week 13 were -12.9 (24.7) vs -13.9 (25.2) for body image and -16.5 (28.4) vs -13.1 (27.2) for sexual enjoyment in the pertuzumab arm vs the placebo arm, respectively. After that, the scores for both of these symptom scales improved. The scores for sexual enjoyment were also clinically meaningfully decreased during the remainder of the HER2-targeted treatment period in the pertuzumab arm only (pertuzumab arm vs placebo arm: Week 25: -11.9 [26.8] vs -7.9 [26.5] and "Final Treatment Value": -10.7 [27.5] vs -8.0 [27.7]). Of note, the number of patients contributing to the analysis of the sexual enjoyment score was relatively low, since this question was only applicable if the patient was sexually active. Scores for sexual functioning showed a similar temporal pattern as sexual enjoyment, but the changes were not clinically meaningful.[75]

The mean scores for future perspective (reporting patients' perspective on future health; higher scores mean improvement) increased during the observation period and were meaningfully improved from baseline when compared to follow-up Month 18 and onwards in both arms.[75]

No clinically meaningful differences in patient-reported treatment-related symptoms, all function scales, or global health status were observed in either arm after cessation of HER2-targeted treatment. All returned to or remained at baseline levels during the follow-up period (Months 18, 24, and 36).[75]

There were no major differences (≥5%) between treatment arms in the five EQ-5D domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression).[75]

B.2.7 *Subgroup analysis*

As the APHINITY study met the primary endpoint in the ITT population, assessment of key pre-specified subgroups was appropriate to investigate drivers behind the overall ITT effect. Subgroup analyses were performed for the primary endpoint IDFS and were intended to assess consistency of the overall result in the ITT population. The p-value associated with the subgroups was taken as a measure of strength of evidence of a treatment effect and the CI to indicate the variability around the estimate. These values are not the only evidence used to make an assessment: the p-value and CIs are coupled with the overall ITT positive treatment effect and clinical and biological rationale of these known subgroups.

Pre-defined subgroups of interest were the randomisation stratification factors using the following categories: nodal status, adjuvant chemotherapy regimen, hormone receptor status, geographical region and protocol version; as well as disease- or patient-related prognostic or predictive factors.[75] A list of pre-planned subgroup analyses is provided in Table 4. Node-positive and hormone receptor-negative status are known prognostic factors for poorer long-term disease outcomes, and patients with these subtypes of disease are known to be at high-risk of disease recurrence, therefore these subgroups are of particular relevance to this submission. Treatment effect (as determined by HR and 3-year IDFS rate) was estimated separately for the defined subgroups. Exploratory tests of interaction between treatment effect and subgroup (at a 10% significance level) were reported using Cox proportional hazards models.

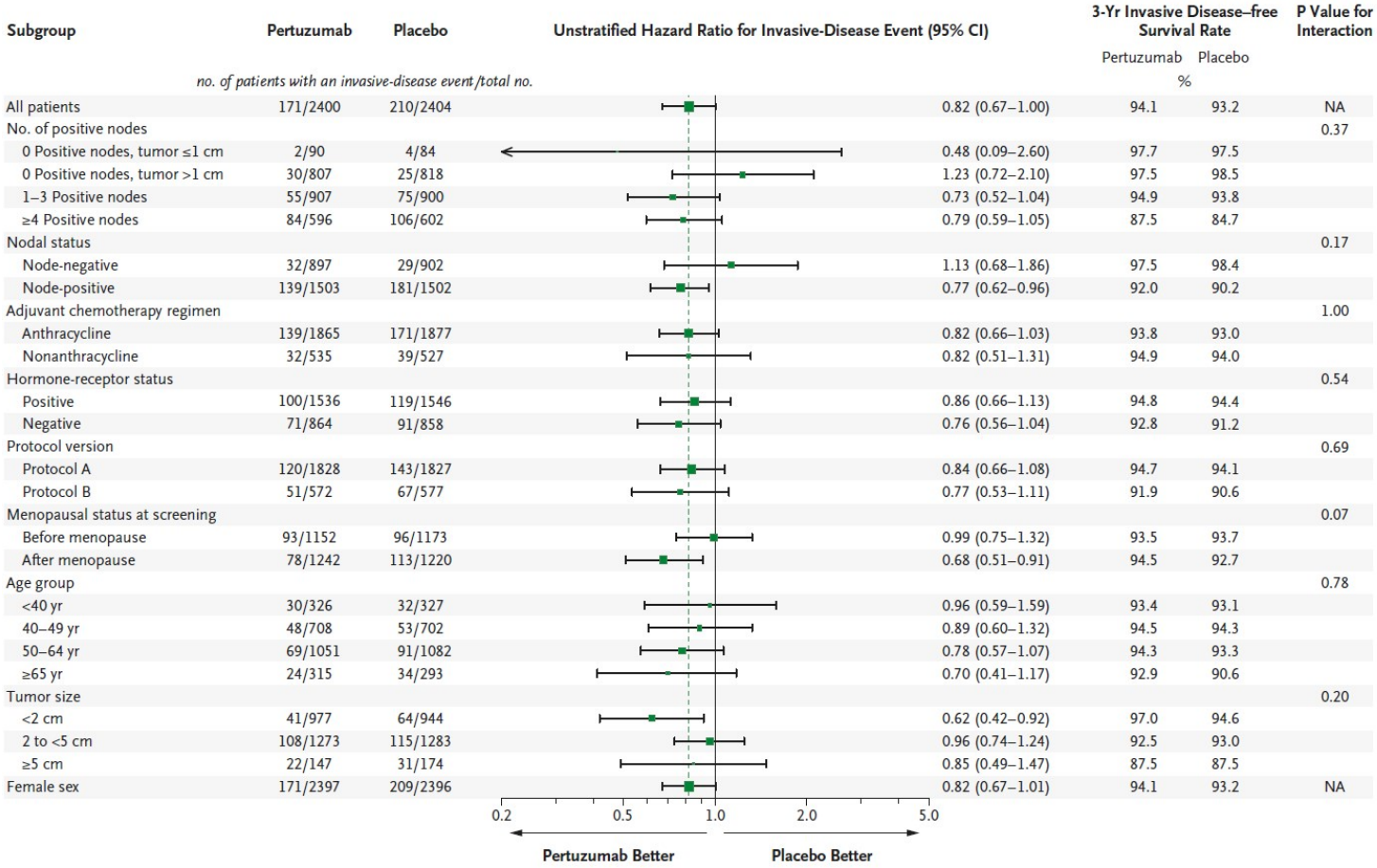
Overall, the IDFS improvements were seen in the great majority of clinically relevant subgroups analysed, providing evidence of internal consistency of the primary endpoint across pre-specified patient subpopulations, and further demonstrating the robustness of the primary result (Figure 5).

Importantly, marked benefits were seen in the node-positive and hormone receptor-negative patient subgroups (Sections B.2.7.1 and B.2.7.2) – patient populations known to have particularly high levels of disease recurrence.

The following points provide confidence in the results of the APHINITY study subgroup analyses:

- The overall ITT result is positive, providing strong evidence that there is an increase in IDFS between patients that received treatment with pertuzumab over those that received placebo. APHINITY is a randomised, double-blind and placebo-controlled trial, meaning that the only difference between the two treatment arms is the treatment received. The increase in IDFS can therefore be attributed to pertuzumab, and subgroup analyses are appropriate to assess the drivers of the pertuzumab treatment effect.
- Lymph node-positivity and hormone receptor-negativity (subgroup analyses for which are described in in B.2.7.1 and B.2.7.2) are well-known prognostic factors for poor disease prognosis, with supporting clinical rationale for why these characteristics identify higher risk disease. The APHINITY trial has not discovered these subgroups but further confirms them.

Figure 5. Forest plot of IDFS for different subgroups in the ITT population (primary analysis, clinical cut-off date 19th December 2016)



Footnotes: Hormone-receptor status was based on the test results determined by a central laboratory, which repeated the testing that was performed locally at each participating centre. For hormone receptor status, negative denotes oestrogen receptor-negative and progesterone receptor-negative; positive denotes oestrogen receptor-positive, progesterone receptor-positive, or both. Under the original protocol (protocol A), patients with node-negative tumours were initially eligible for participation in the trial if at least one of the following high-risk features was present: histologic or nuclear grade 3, negativity for oestrogen and progesterone receptors, or age younger than 35 years. Under protocol B, which included an amendment that was added after 3,655 patients had undergone randomisation, patients with node-negative disease were no longer eligible for enrolment. NA denotes not applicable.

Abbreviations: CI, confidence interval; NA, not applicable.

Source: von Minckwitz *et al*. 2017[2]

B.2.7.1 Subgroup analysis by nodal status

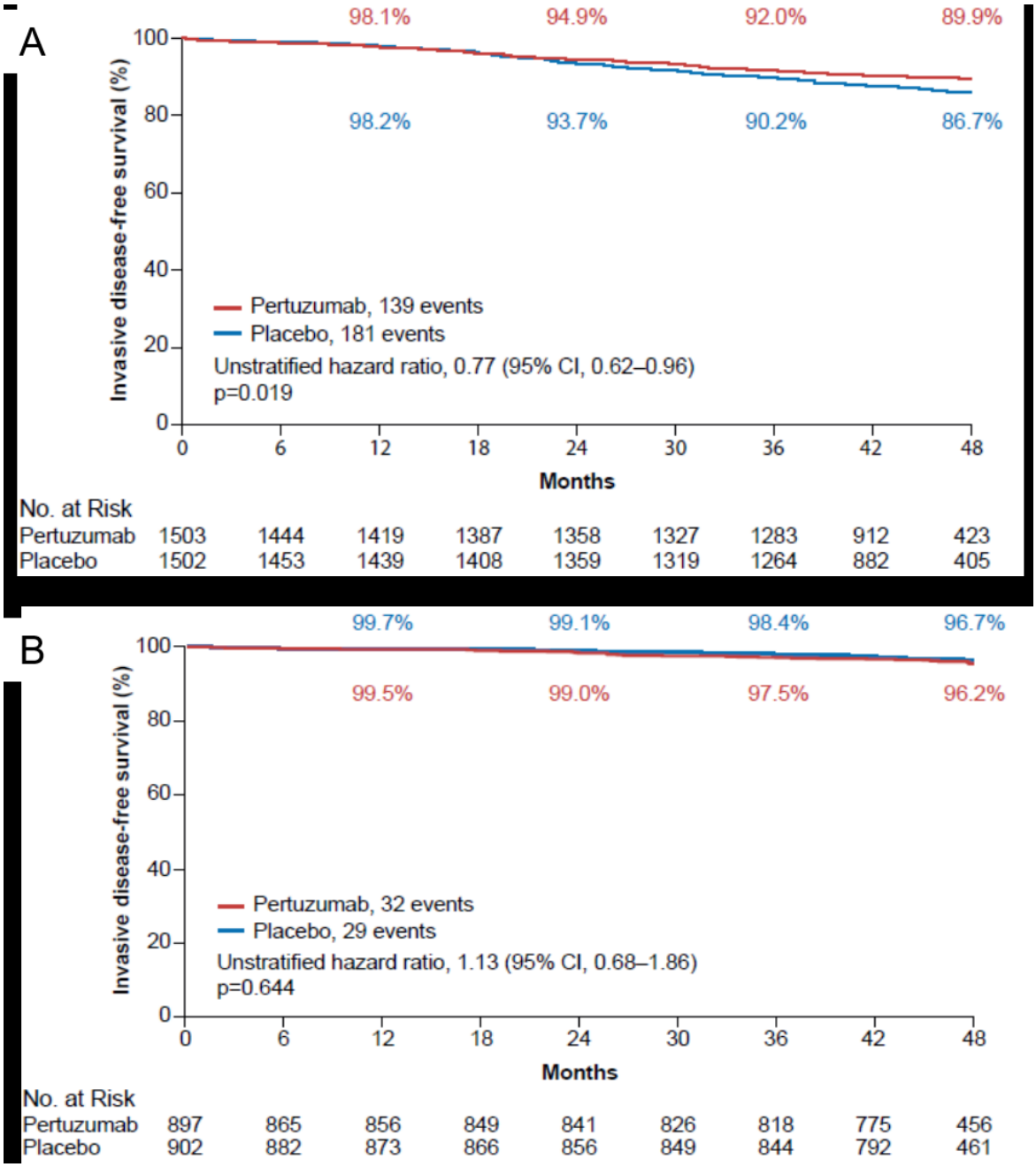
A pre-planned subgroup analysis of IDFS in node-positive patients showed improvement in IDFS, corresponding to a 23% reduction in risk of recurrence or death in the pertuzumab arm vs placebo arm (HR=0.77; 95% CI, 0.62–0.96; p=0.02), as shown in Figure 6A.[2] Node-positivity is a well-known prognostic factor associated with a high risk of recurrence.[18]

The median follow-up period at the time of the primary analysis was 44.5 months in the node-positive subgroup and 48.3 months in the node-negative subgroup. The estimates of 3-year IDFS event-free rates were 92.0% in the pertuzumab arm (n=1,503) and 90.2% in the placebo arm (n=1,502). The estimates of 4-year IDFS event-free rates were 89.9% in the pertuzumab arm and 86.7% in the placebo arm.[2]

The number of invasive-disease events was low among patients with node-negative disease (32 patients [3.6%] in the pertuzumab arm and 29 patients [3.2%] in the placebo arm), and no treatment effect was detectable (HR=1.13; 95% CI, 0.68–1.86; p=0.64), as shown in Figure 6B. However, at the time of clinical cut-off, less than 4% of patients in the node-negative subgroup had had an IDFS event,[2] meaning that a treatment effect would be difficult to detect in this population.

The APHINITY study confirms that node-positivity in eBC is an important prognostic factor and that these patients are at high-risk of recurrence.

Figure 6. Kaplan-Meier plots of IDFS for ITT population with node-positive (A) and node-negative (B) disease (primary analysis, clinical cut-off date 19th December 2016)



Abbreviations: CI, confidence interval.
Source: von Minckwitz *et al.* 2017[2]

B.2.7.2 Subgroup analysis by hormone receptor status

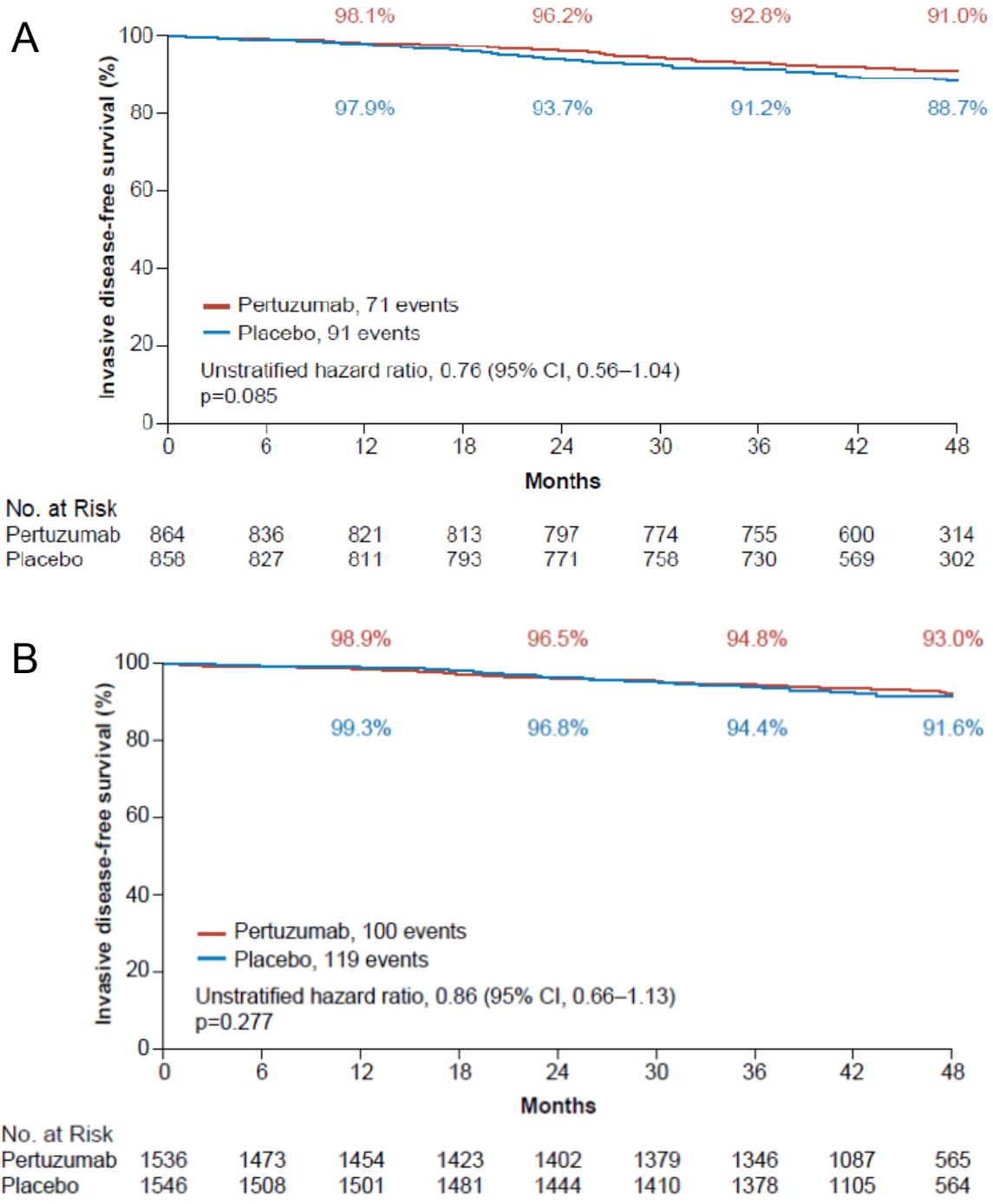
In pre-planned subgroup analyses, pertuzumab demonstrated numerical improvements in IDFS vs the placebo arm in both hormone receptor subgroups (i.e. hormone receptor-positive and hormone receptor-negative).

Patients with hormone receptor-negative disease are not eligible to receive hormone therapy (which is normally used to treat patients with hormone receptor-positive disease), hence it is a patient subgroup with unmet need and known to have a particularly high risk of recurrence. Patients with hormone receptor-negative disease had a 24% reduction in risk of recurrence in the pertuzumab arm vs placebo arm (HR=0.76; 95% CI, 0.56–1.04; p=0.08; Figure 7A). In the cohort of patients with hormone receptor-negative disease at three years, estimates of IDFS event-free rates were 92.8% and 91.2% in the pertuzumab arm and placebo arm, respectively. Estimates of IDFS at four years were 91.0% in the pertuzumab arm and 88.7% in the placebo arm.[75]

The benefit of pertuzumab was apparent for the cohort of patients with hormone receptor-positive BC (HR=0.86; 95% CI, 0.66–1.13; p=0.28), although to a lesser extent than those with hormone receptor-negative disease. In patients with hormone receptor-positive BC, estimates of IDFS event-free rates at three years were 94.8% and 94.4% in the pertuzumab arm and placebo arm, respectively (Figure 7B). Estimates of IDFS at four years were 93.0% in the pertuzumab arm and 91.6% in the placebo arm.[2]

The APHINITY confirms that hormone receptor-negative status is an important prognostic factor in eBC, and that these patients are at a particularly high risk of recurrence.

Figure 7. Kaplan-Meier plots of IDFS for ITT population with hormone receptor-negative (A) and hormone receptor-positive (B) disease (primary analysis, clinical cut-off date 19th December 2016)



Abbreviations: CI, confidence interval.
Source: von Minckwitz *et al*. 2017[2]

B.2.8 *Meta-analysis*

As no further RCTs comparing the efficacy and safety of pertuzumab + trastuzumab + chemotherapy as adjuvant treatment of HER2-positive BC were found, no meta-analysis was conducted.

B.2.9 *Indirect and mixed treatment comparisons*

Trastuzumab is the SoC in the adjuvant treatment of HER2-positive eBC and an appropriate comparator to adjuvant pertuzumab, as per the NICE scope. As the APHINITY study provided a head-to-head comparison of pertuzumab vs trastuzumab it was not necessary to perform an indirect treatment comparison/network meta-analysis and as such none were conducted.

B.2.10 *Adverse reactions*

Summary of adverse reactions

- No new safety signals were identified in the APHINITY trial.[2] The addition of pertuzumab to trastuzumab + chemotherapy was well tolerated and adverse reactions were as expected from previous studies investigating the safety and efficacy of dual-HER2 blockade with pertuzumab + trastuzumab in eBC[30, 31] and mBC[32] settings.[2]
- In the pertuzumab arm, 99.9% of patients experienced at least one AE during the treatment period vs 99.5% of patients in the placebo arm.[75] The largest differences between treatment arms for all AE Grades were for diarrhoea (71.2% for pertuzumab vs 45.2% for placebo) and rash (25.8% for pertuzumab vs 20.3% for placebo).[2] Gastrointestinal Disorders system organ class (SOC) AEs were most frequently reported.[2]
- Neutropenia, diarrhoea and anaemia were the most common Grade ≥3 AEs reported in both arms in the trial.[2] Diarrhoea Grade ≥3 was observed in 9.8% and 3.7% of patients in the pertuzumab and placebo arms, respectively, and was most common when a non-anthracycline chemotherapy regimen was used.[84] During targeted therapy alone the incidence of Grade ≥3 diarrhoea was 0.5% in the pertuzumab arm and 0.2% in the placebo arm.[2]
- Primary cardiac events occurred in 17 patients (0.7%) in the pertuzumab arm and in eight patients (0.3%) in the placebo arm (95% CI of the treatment difference, 0.0–0.8%); secondary cardiac events occurred in 64 patients (2.7%) in the pertuzumab arm and 67 patients (2.8%) in the placebo arm (95% CI of the treatment difference, −1.0–0.9%).[2]
- Deaths due to AEs, including all fatal AEs reported at any time in the study period, occurred 0.8% of patients in each arm.[2]

B.2.10.1 Introduction

Patients who received at least one dose of study treatment (pertuzumab or placebo) were included in safety analyses. The safety analysis population included 2,364 patients who were treated with at least one dose of pertuzumab and 2,405 patients who received study medication (including chemotherapy or trastuzumab) but no pertuzumab (placebo arm).[2]

B.2.10.2 General safety

Almost all patients in the APHINITY study safety population experienced at least one AE during the treatment period (99.9% of patients in the pertuzumab + trastuzumab + chemotherapy arm vs 99.5% of patients in the placebo + trastuzumab + chemotherapy arm). As shown in Table 13, which presents the most common AEs (≥15% incidence in at least one arm), AEs were most frequently reported in the Gastrointestinal Disorders SOC.[2]

Table 13. Most common adverse events (≥15% incidence in at least one arm) by treatment arm (safety analysis population; primary analysis, clinical cut-off date 19th December 2016)

MedDRA Preferred Term	Pertuzumab + trastuzumab + chemotherapy (N=2,364)	Placebo + trastuzumab + chemotherapy (N=2,405)
Nausea	1,632 (69.0%)	1,575 (65.5%)
Alopecia	1,577 (66.7%)	1,610 (66.9%)
Diarrhoea	1,683 (71.2%)	1,086 (45.2%)
Fatigue	1,154 (48.8%)	1,065 (44.3%)
Vomiting	768 (32.5%)	733 (30.5%)
Arthralgia	678 (28.7%)	782 (32.5%)
Constipation	684 (28.9%)	759 (31.6%)
Myalgia	615 (26.0%)	710 (29.5%)
Stomatitis	671 (28.4%)	573 (23.8%)
Anaemia	655 (27.7%)	557 (23.2%)
Neutropenia	587 (24.8%)	562 (23.4%)
Dysgeusia	614 (26.0%)	518 (21.5%)
Rash	609 (25.8%)	488 (20.3%)
Headache	531 (22.5%)	563 (23.4%)
Decreased appetite	565 (23.9%)	478 (19.9%)
Asthenia	505 (21.4%)	500 (20.8%)
Mucosal inflammation	552 (23.4%)	448 (18.6%)
Hot flush	482 (20.4%)	509 (21.2%)
Pyrexia	473 (20.0%)	469 (19.5%)
Oedema peripheral	405 (17.1%)	483 (20.1%)
Peripheral sensory neuropathy	427 (18.1%)	422 (17.5%)
Insomnia	404 (17.1%)	400 (16.6%)
Epistaxis	430 (18.2%)	326 (13.6%)
Neuropathy peripheral	366 (15.5%)	369 (15.3%)
Cough	374 (15.8%)	351 (14.6%)

Footnotes: Investigator text for AEs encoded using MedDRA v19.1. Percentages are based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. Table includes AEs with onset from first dose of any study treatment through 28 days after last dose of study treatment.
Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities.
Source: APHINITY study CSR[75]

Treatment was discontinued for safety reasons by 7.8% and 6.4% of patients in the pertuzumab and placebo arms, respectively.[2]

There was a higher incidence of Grade ≥3 AEs in the pertuzumab than the placebo arm, and this was mainly driven by diarrhoea (Table 14). Neutropenia, diarrhoea and anaemia were the most common (in >5% of patients) Grade ≥3 AEs reported in both treatment arms in the trial.

Table 14. Summary of AEs (safety analysis population; primary analysis, clinical cut-off date 19th December 2016)

Event	Pertuzumab + trastuzumab + chemotherapy N=2,364[d]	Placebo + trastuzumab + chemotherapy N=2,405[d]
	No. of patients (%)	
Grade ≥3 AE[a]	1,518 (64.2)	1,379 (57.3)
Neutropenia	385 (16.3)	377 (15.7)
Febrile neutropenia	287 (12.1)	266 (11.1)
Neutrophil count decreased	228 (9.6)	230 (9.6)
Diarrhoea	232 (9.8)	90 (3.7)
Anaemia	163 (6.9)	113 (4.7)
Fatal AE	18 (0.8)	20 (0.8)
Primary cardiac event[b]	17 (0.7)	8 (0.3)
NYHA class III of IV heart failure and substantial decrease in LVEF	15 (0.6)	6 (0.2)
Definite or probably cardiac death	2 (<0.1)	2 (<0.1)
Secondary cardiac event[c]	64 (2.7)	67 (2.8)
Identified automatically from LVEF assessments	50 (2.1)	47 (2.0)
Identified by cardiac advisory board	14 (0.6)	20 (0.8)

Footnotes: [a]The summary of Grade ≥3 AEs includes AEs with onset from first dose of any study treatment through 28 days after the final dose of study treatment. The incidence of all other Grade ≥3 AEs was lower than 5% in both safety and analysis population groups; [b]Primary cardiac events were counted over the whole trial period, including post-treatment follow-up. The 95% CI (with Hauck–Anderson correction) for the between-arm difference was 0.0 to 0.8%; [c]Secondary cardiac events were counted up to the date of recurrence or the end of post treatment follow-up, whichever occurs earlier, and are counted only for patients who have not had a primary cardiac event. The 95% CI (with Hauck-Anderson correction) for the between-arm difference was -1.0–0.9 percentage points; [d]The safety population included patients who received any amount of study medication (chemotherapy, pertuzumab/placebo, or trastuzumab). A total of 4,769 patients were included (2,364 patients in the pertuzumab + trastuzumab + chemotherapy arm and 2,405 in the placebo + trastuzumab + chemotherapy arm). Thirty-eight patients randomised to the pertuzumab + trastuzumab + chemotherapy arm received study treatment but did not receive pertuzumab, and were therefore included in the placebo + trastuzumab + chemotherapy arm for safety analyses (none of these 38 patients went on to receive trastuzumab or taxane therapy as part of 'study treatment', although 3 received 'non-study' adjuvant treatment with trastuzumab and a taxane). Conversely, 24 patients randomised to the placebo + trastuzumab + chemotherapy arm received at least one dose of pertuzumab and, therefore, were included in the pertuzumab + trastuzumab + chemotherapy arm for safety analyses.
Abbreviations: AE, adverse event; CI, confidence interval; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.
Source: von Minckwitz *et al*. 2017[2]

B.2.10.3 Safety by chemotherapy regimen

Table 15 presents a summary of AEs by treatment arm and chemotherapy regimen. AEs were similar between the pertuzumab and placebo arms, except for diarrhoea, which was higher in the pertuzumab arm and in particular when given with a non-anthracycline chemotherapy regimen. In the pertuzumab arm, a primary cardiac event occurred in 15 patients (0.8%) in the anthracycline cohort and 2 patients (0.4%) in the non-anthracycline cohort.

Table 15. Summary of AEs by chemotherapy regimen (safety analysis population; primary analysis, clinical cut-off date 19th December 2016)

Event	Pertuzumab + trastuzumab + anthracycline N=1,834	Placebo + trastuzumab + anthracycline N=1,894	Pertuzumab + trastuzumab + non-anthracycline N=528*	Placebo + trastuzumab + non-anthracycline N=510
At least one Grade ≥3 AE	1,133 (61.8%)	1,080 (57.0%)	384 (72.7%)	299 (58.6%)
Neutropenia	301 (16.4%)	304 (16.1%)	84 (15.9%)	73 (14.3%)
Febrile neutropenia	235 (12.8%)	204 (10.8%)	51 (9.7%)	62 (12.2%)
Neutrophil count decreased	193 (10.5%)	197 (10.4%)	35 (6.6%)	33 (6.5%)
Diarrhoea	137 (7.5%)	59 (3.1%)	95 (18.0%)	31 (6.1%)
Anaemia	74 (4.0%)	56 (3.0%)	89 (16.9%)	57 (11.2%)
Fatal AE	12 (0.7%)	16 (0.8%)	6 (1.1%)	4 (0.8%)
Primary cardiac event	15 (0.8%)	7 (0.4%)	2 (0.4%)	1 (0.2%)
Treatment difference (pertuzumab – placebo 95% CI[a])	0.4 (-0.1, 1.0)		0.2 (-0.6, 0.9)	
Heart failure (NYHA III or IV) and significant LVEF decline	13 (0.7%)	5 (0.3%)	2 (0.4%)	1 (0.2%)
Cardiac death (definite or probable)	2 (0.1%)	2 (0.1%)	0	0
Secondary Cardiac Event	55 (3.0%)	60 (3.2%)	9 (1.7%)	7 (1.4%)
Treatment difference (pertuzumab – placebo 95% CI[a])	-0.2 (-1.3, 1.0)		0.3 (-1.3, 1.9)	
Identified automatically from LVEF assessments	46 (2.5%)	44 (2.3%)	4 (0.8%)	3 (0.6%)
Identified by CAB	9 (0.5%)	16 (0.8%)	5 (0.9%)	4 (0.8%)

Footnotes: Percentages are based on N in the column heading. The summary of Grade ≥3 AEs includes AEs with onset from first dose of any study treatment through 28 days after last dose of study treatment. The incidence of all other Grade ≥3 AEs was <5% in both safety analysis population arms. Primary cardiac events are counted over the whole study period, including post-treatment follow-up. Secondary cardiac events are counted to the date of recurrence or end of post-treatment follow-up, whichever occurs earlier. Secondary cardiac events are only counted for patients who have not experienced a primary cardiac event. Significant LVEF decline defined as a decline of ≥10% points to a value <50%. [a]95% CI with Hauck-Anderson correction.
* Three patients included in the safety population were excluded from the outputs of safety by chemotherapy since they did not receive any carboplatin
Abbreviations: AE, adverse event; CAB, cardiac advisory board; CI, confidence interval; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.
Source: von Minckwitz *et al.* 2017[2]

B.2.10.4 Cardiac safety

The primary cardiac endpoint was defined as heart failure of New York Heart Association (NYHA) class III or IV and a substantial decrease in left ventricular ejection fraction (LVEF) (defined as a decrease of at least 10% from baseline and to below 50% or cardiac death). Cardiac death was identified by the cardiac advisory board (CAB) for the APHINITY trial in accordance with a prospective definition. A secondary cardiac endpoint was an asymptomatic or mildly symptomatic (NYHA class II) substantial decrease in LVEF, assessed by multiple-gated acquisition scanning or echocardiography, confirmed by a second LVEF assessment conducted within approximately three weeks also showing a substantial decrease or as confirmed by the CAB.[77]

Primary cardiac events occurred in 17 patients (0.7%) in the pertuzumab arm and in eight patients (0.3%) in the placebo arm (95% CI of the treatment difference, 0.0–0.8%); 15 patients in the pertuzumab arm and six patients in the placebo arm had NYHA class III or IV heart failure and a substantial decrease in LVEF, and two patients in each arm died from cardiac causes (Table 14). In the pertuzumab arm, a primary cardiac event occurred in 15 patients (0.8%) in the anthracycline cohort and two patients (0.4%) in the non-anthracycline cohort (Table 15). At the time of the clinical cut-off, seven events in the pertuzumab arm and four events in the placebo arm had resolved, per investigator assessment and data on LVEF (details not shown). Secondary cardiac events occurred in 64 patients (2.7%) in the pertuzumab arm and 67 patients (2.8%) in the placebo arm (95% CI of the treatment difference, −1.0 to 0.9%; Table 14).[2]

In agreement with results from previous trials investigating the safety and efficacy of dual-HER2 blockade with pertuzumab + trastuzumab in eBC[30, 31] and mBC[32] settings, there was no increase in cardiac-related AEs in the pertuzumab-based arm of the APHINITY trial compared to the control arm.[30-32]

B.2.10.5 Diarrhoea

The largest difference between the treatment arms for all grades of AEs was found for diarrhoea (71.2% with pertuzumab vs 45.2% with placebo).[2] Diarrhoea Grade ≥3 was observed in 9.8% and 3.7% in the pertuzumab and placebo arms, respectively.[84] The highest incidence was reported during administration of HER2 targeted therapy + taxane chemotherapy (61.4% in the pertuzumab arm vs 33.8% in the placebo arm) and this decreased markedly with cessation of chemotherapy (to 18.1% in the pertuzumab arm vs 9.2% in the placebo arm in the post chemotherapy treatment period).[84] During targeted therapy alone, after cessation of chemotherapy, the incidence of Grade ≥3 diarrhoea was 0.5% in the pertuzumab arm and 0.2% in the placebo arm (Table 16). The frequency of Grade ≥3 diarrhoea was lower in the anthracycline cohort (with anti-HER2 treatment started after anthracycline) than in the non-anthracycline cohort (Table 15).

The median time from first targeted treatment to onset of diarrhoea during the chemotherapy phase was shorter in the pertuzumab vs placebo arm (seven and ten days, respectively) and diarrhoea events lasted longer on average with pertuzumab than with placebo (median eight vs six days). Diarrhoea was generally manageable with anti-diarrhoeals and rarely led to changes in dosage or discontinuation.[84] Events were more frequent with docetaxel + carboplatin + targeted agents, irrespective of severity.[84]

Table 16. Summary of incidence of Grade ≥3 diarrhoea (safety analysis population; primary analysis, clinical cut-off date 19th December 2016)

Number (%)	Pertuzumab + trastuzumab + anthracycline N=2,364	Placebo + trastuzumab + anthracycline N=2,405
Study treatment period[a]	232 (9.8)	90 (3.7)
Targeted therapy (post-chemotherapy period)[b]	12 (0.5)	4 (0.2)

Footnotes: [a]Includes Grade ≥3 AEs with onset from first dose of any study treatment through 28 days after last dose of study treatment; [b]Includes Grade ≥3 AEs with onset during the targeted therapy post-chemotherapy treatment period.
Source: von Minckwitz *et al.* 2017[2]

B.2.10.6 Deaths

At the time of the clinical cut-off, a total of 73 patients (3.1%) in the pertuzumab arm and 95 patients (4.0%) in the placebo arm had died during the study (Table 17). Recurrence of disease was the most common cause of death in each treatment arm (pertuzumab + trastuzumab + chemotherapy arm: 48 patients [2.0%]); placebo + trastuzumab + chemotherapy arm: 63 patients [2.6%], Table 17), and was higher in the placebo arm vs the pertuzumab arm.[75]

Deaths due to AEs, including all fatal AEs reported at any time in the study period, occurred 0.8% of patients in each arm (18 deaths due to AEs in the pertuzumab arm, and 20 deaths due to AEs in the Placebo arm, Table 17). Fatal AEs according to body system were neoplasms (benign, malignant and unspecified – nine patients in the pertuzumab arm and eight in the placebo arm); cardiac disorders (two and three); infections and infestations (one and three); respiratory, thoracic, and mediastinal disorders (two and two); gastrointestinal disorders (zero and three); injury, poisoning, and procedural complications (two and zero); blood and lymphatic system disorders (one and zero); metabolism and nutrition disorders (one and zero); nervous system disorders (one and zero); and psychiatric disorders (zero and one). One patient in the pertuzumab arm had a fatal AE that was reported in both the nervous system disorders and the injury, poisoning, and procedural complications body-system categories.

Table 17. Summary of deaths (safety population; primary analysis, clinical cut-off date 19th December 2016)

	Pertuzumab + trastuzumab + chemotherapy N=2,364	Placebo + trastuzumab + chemotherapy N=2,405
Total number of deaths	73 (3.1%)	95 (4.0%)
Primary cause of death		
Recurrence of disease	48 (2.0%)	63 (2.6%)
AE	18 (0.8%)	20 (0.8%)
Other[a]	7 (0.3%)	12 (0.5%)

Footnote: [a]'Other' primary cause of death includes deaths due to accident, suicide, or other medical condition, or unknown cause.
Abbreviations: AE, adverse event.
Source: APHINITY study CSR[75]

B.2.11 *Ongoing studies*

Patients in the APHINITY study will be followed for approximately ten years from the date of randomisation of the last patient (31st August 2013). More mature data for all study outcomes are anticipated over the coming years. The next interim analysis of OS is expected in 2020, and the study is expected to complete in 2023.[74, 75]

Furthermore, one other study that includes a pertuzumab + trastuzumab + chemotherapy arm in the adjuvant treatment of eBC is currently ongoing and will provide additional safety evidence for this indication in the next 12 months. This study is described in the following section.

B.2.11.1 BERENICE (NCT02132949)[85, 86]

The BERENICE study is a non-randomised, open-label, multicentre, multinational, Phase II study to evaluate the safety of pertuzumab + trastuzumab + standard neoadjuvant anthracycline-based

chemotherapy in 401 patients with HER2-positive, locally advanced, inflammatory, or eBC (with primary tumours >2 cm in diameter or node-positive disease).

In this study, patients are treated neoadjuvantly (i.e. pre-surgery) with:

- Dose-dense doxorubicin and cyclophosphamide, followed by paclitaxel, with pertuzumab + trastuzumab given from the start of paclitaxel (Cohort A), or
- FEC, followed by docetaxel, with pertuzumab + trastuzumab given from the start of docetaxel (Cohort B).

Following surgery, patients resumed treatment with pertuzumab + trastuzumab to receive up to 18 cycles of pertuzumab + trastuzumab.

The BERENICE trial, which began in 2014, is primarily a safety study. The primary endpoint measures are the percentage of participants with NYHA Class III and IV heart failure during the neoadjuvant treatment period and the percentage of participants with a drop in LVEF of at least 10% from baseline and to below 50% during the neoadjuvant treatment period. Secondary outcome measures look at treatment efficacy, such as EFS determined by the investigator according to the Response Evaluation Criteria in Solid Tumours (RECIST), IDFS and OS (all assessed until ~6.5 years). The safety results available for the BERENICE study to date are summarised in Appendix F.

The efficacy results for BERENICE will be reported after the estimated overall study completion date in 2020, although it is important to note that BERENICE is primarily a safety study, thus this efficacy evidence will be of limited value to this submission.

B.2.12 *Innovation*

When pertuzumab was first approved in Europe in 2013 for the treatment of HER2-positive mBC, it was the first-in-class HER2 dimerisation inhibitor and was considered a step-change in the treatment of BC. Pertuzumab in combination with trastuzumab offers a comprehensive HER2 blockade that inhibits the signaling pathways essential for tumour growth.[87]

Following from this, pertuzumab was licensed for the neoadjuvant treatment of HER2-positive eBC in 2015, based on evidence from the Phase II NeoSphere study and the Phase II TRYPHAENA cardiac safety study.[30, 31] These trials provided the rationale for the further exploration of dual-HER2 blockade with pertuzumab + trastuzumab in adjuvant treatment trials. Following the American Society of Clinical Oncology (ASCO) 2017 annual meeting where the primary results of the APHINITY study were presented, the 2017 St Gallen International Breast Cancer Guidelines were updated to state “Dual blockade with pertuzumab and trastuzumab improves outcomes among patients who are at high risk for relapse because of lymph-node involvement or hormone receptor negativity”.[1]

The APHINITY study showed that adjuvant pertuzumab treatment significantly improved IDFS in the HER2-positive eBC population, with a 19% reduction in risk of relapse or death (HR=0.81; 95% CI, 0.66–1.00; p=0.045) compared with the control arm. Subgroup analyses at the current cut-off indicate that the treatment effect of pertuzumab is especially pronounced in patients with baseline characteristics associated with a high risk of BC relapse (i.e. node-positive or hormone receptor-negative disease).

Since the onset of HER2-positive BC is relatively early compared to other BC types (approximately 55 years compared to approximately 65 years for all subtypes of BC[42, 59, 88]) patients diagnosed with this disease will often be income earners for their family and play pivotal roles in the care of children and other family members. By improving the IDFS and reducing the risk of recurrence or death, pertuzumab can provide patients with high-risk HER2-positive eBC more time with their families and friends, thus the social and psychological benefit of treatment would reach beyond the patients themselves.

B.2.13 *Interpretation of clinical effectiveness and safety evidence*

Despite the advances achieved with the addition of one year of trastuzumab to standard chemotherapy in the treatment of patients with HER2-positive BC, up to one in four patients experience BC recurrence within 10–11 years of diagnosis.[27-29] Metastatic BC is currently incurable and causes greater social and economic pressures than early disease.[52] Therefore, improving the results of treatment whilst the disease is still localised to the breast and regional lymph nodes is crucial in maximising the chance of cure. The benefits of 18 cycles of pertuzumab + trastuzumab + chemotherapy in patients with HER2-positive eBC was shown through the APHINITY trial: 18 cycles of pertuzumab + trastuzumab + chemotherapy treatment in patients with HER2-positive eBC significantly increased IDFS, resulting in a 19% risk reduction of recurrence or death (HR=0.81; 95% CI, 0.66–1.00; p=0.045) when compared to placebo + trastuzumab + chemotherapy.[2]

Lymph node status is a well-known prognostic factor in eBC and has been shown to be among the most important risk factors in patients with HER2-positive eBC.[89] Treatment effect of 18 cycles of pertuzumab + trastuzumab + chemotherapy was seen in the majority of pre-specified patient subgroups in the APHINITY study, with a marked benefit seen in patients at high risk of recurrence. In the node-positive subgroup, the addition of pertuzumab to trastuzumab + chemotherapy resulted in a 23% relative risk reduction in an IDFS event vs the placebo arm (HR=0.77; 95% CI, 0.62–0.96; p=0.02), whilst in the hormone receptor-negative subgroup the addition of pertuzumab to trastuzumab + chemotherapy resulted in a 24% relative risk reduction in an IDFS event vs the placebo arm (HR=0.76; 95% CI, 0.56–1.04; p=0.08).[2] At the time of primary analysis, the clinically meaningful benefit in the ITT population appears to be driven by stratified subgroups of patients with high risk of recurrence (i.e. node-positive or hormone receptor-negative).

The results of the secondary endpoints of the APHINITY study were in line with and supportive of the primary endpoint of IDFS. Although there was no statistical difference in terms of OS at this first data cut, this may be due to the relatively short-term follow-up of the study so far; i.e. because the data were immature (only 26% of the target events required for the final planned OS analysis had occurred). Nonetheless, the addition of pertuzumab to trastuzumab + chemotherapy reduced the incidence of invasive disease recurrence, which represents the most life-threatening type of IDFS events. The estimates of IDFS at three years were 94.1% in the pertuzumab arm vs 93.2% in the placebo arm, and the estimates at four years were 92.3% in the pertuzumab arm and 90.6% in the placebo arm.[2] Since the majority of patients in both treatment arms who relapsed had distant recurrences (mostly visceral metastases) future OS analyses to ten years are anticipated to demonstrate an improvement with adjuvant pertuzumab treatment.

A recent meta-analysis has shown that four surrogate endpoints (IDFS, DFS, RFS and distant DFS) have high, individual-level associations with OS in adjuvant BC[90] suggesting that the significant results in terms of HR and three-year IDFS rate from the APHINITY study could be

indicative of OS benefits in the long-term. Furthermore, the results of another recent meta-analysis (manuscript in preparation), which evaluated DFS and other time-to-event endpoints as surrogates for OS in the systemic therapy of HER2-positive eBC, suggested there [redacted] between DFS and OS. The patient level association was [redacted] over all analyses with typical values of Spearman's rho of [redacted] and Kendall's tau of [redacted]. At trial level association, the R^2 was [redacted] for the ITT. Subgroups had [redacted] R^2, [redacted], than the ITT population: [redacted] for node-positive and [redacted] for hormone receptor-negative. In addition, when the lower limit of the CI of both individual and trial level exceeds 0.7, this is an acceptable limit to claim surrogacy (suggestion by Piedbois and Buyse [2008][91]), [redacted][92]

The median period of follow-up for this primary analysis was 45.4 months, which might be too early for a full assessment of the effect size, especially in the cohorts of patients with lower-risk eBC (e.g. with hormone receptor-positive or node-negative disease), who tend to experience disease relapse at a later timepoint than patients with higher-risk eBC (e.g. hormone receptor-negative and node-positive patients). However, at the current data-cut, a marked benefit is seen in patients at high risk of disease recurrence (i.e. the node positive or hormone receptor-negative patient subgroups). Subsequent analyses are planned in accordance with the trial protocol, with up to ten years of minimum follow-up and the next analysis 2.5 years after this primary analysis.[2] It is important to note however, that the present results from APHINITY have been deemed clinically meaningful in the ITT population when assessed using the ESMO-magnitude of clinical benefit scale: the addition of pertuzumab to standard adjuvant trastuzumab + chemotherapy is categorised as a Group B intervention, indicating a high level of clinical benefit in the curative setting.[82] This benefit is characterised by an improvement in primary endpoint, with a 95% CI for the hazard ratio in the range 0.65–0.8, without mature survival data, and indicates a high level of clinical benefit in the curative setting and substantial improvement over the current standard of care.[82] By reducing the risk of disease relapse and development of mBC, adjuvant pertuzumab treatment can therefore reduce the high economic and resource burden associated with metastatic disease,[41, 93] particularly for those patients with high risk of disease recurrence (e.g. due to node-positive or hormone receptor-negative disease at diagnosis).

Treatment recommendations for adjuvant eBC therapy are based on improvements in risk of recurrence and OS and, depending on the type of treatment, the expected benefit to patients will differ. Introduction of new treatment principles, such as new chemotherapy, endocrine or anti-HER2 therapies, can be expected to provide larger benefits (relative risk reductions ranging from 30–50% risk of recurrence and 15–34% for risk of death historically),[94-97] while optimisation of current treatment principles can be expected to provide smaller benefits (relative risk reductions ranging from 11–30% risk of recurrence and 10–19% for risk of death historically).[95, 98, 99] The addition of adjuvant pertuzumab to standard eBC therapy would provide an important optimisation of the current treatment principle and improved outcomes for patients with HER2-positive eBC in the UK, especially those with high-risk (e.g. node-positive or hormone receptor-negative) disease. The positive APHINITY study data build on the results of the NEOSPHERE[30], TRYPHAENA[31] and CLEOPATRA[32] studies. The totality of data now available indicate that pertuzumab provides benefit for patients with a wide spectrum of HER2-positive BC, and additional relevant data will become available in the future from the BERENICE (NCT02132949)[85, 86] and KRISTINE (NCT02131064)[100] trials.

Patients with node-positive HER2-positive eBC are at high risk of disease recurrence. Some patients in this subgroup may have operable disease, similar to the patients of the APHINITY study, and could receive primary surgery. These patients would be eligible for 18 cycles of

pertuzumab + trastuzumab therapy after surgery. Other patients in this subgroup may have inoperable disease and would receive neoadjuvant dual-HER2-targeted therapy to enable de-escalation of breast surgery from mastectomy to breast-conserving surgery, and ultimately to reduce the risk of both local and systemic recurrence. These patients would also be eligible for 18 cycles of pertuzumab + trastuzumab treatment. Despite neoadjuvant treatment with pertuzumab + trastuzumab and adjuvant continuation with trastuzumab up to one year, 12% of those that achieved pCR at the time of surgery still relapse,[30] therefore emphasising the need to further improve treatment for patients at high risk of recurrence.

The determination of a patient's risk of relapse is made at the time the disease is diagnosed and staged, and interventions to improve outcomes are then planned accordingly. As such, starting treatment neoadjuvantly is an important option to improve surgical and potentially survival outcomes for patients with a high risk of BC relapse. However, BC risk is determined at the time of diagnosis and staging, and this risk does not change because of neoadjuvant treatment. As part of a complete regimen for eBC, HER2-targeted treatment is continued post-surgery to prevent micrometastases and development of distant disease recurrence. The APHINITY study confirms that dual-blockade with 18 cycles of pertuzumab + trastuzumab in patients with node-positive eBC provides an improvement over placebo + trastuzumab in terms of IDFS (HR=0.77; 95% CI: 0.62–0.96; p=0.02). This treatment approach has been reflected in the recently updated NCCN Guidelines (updated 10th November 2017), which state that: patients with node-positive, HER2-positive eBC treated with preoperative (i.e. neoadjuvant) systemic therapy, who then go on to receive surgical treatment, can complete up to one year of HER2-targeted pertuzumab + trastuzumab adjuvant therapy.[65]

The AE profiles observed in the two treatment arms during the APHINITY study treatment period was generally balanced between the two arms and no new safety signals were observed (Section B.2.10).[2] This finding is supported by the results of the BERENICE safety study discussed in Appendix F.[85, 86]

The APHINITY study is robust, as it is a large, double-blind, placebo-controlled, Phase III trial that used a choice of chemotherapy regimens that is generalisable to UK clinical practice, as confirmed by UK clinical experts.[101] A major strength of the APHINITY study is that the comparator arm of the study represents the SoC combination therapy used in UK clinical practice: trastuzumab + chemotherapy. As such, the APHINITY study provides direct, head-to-head, randomised evidence for pertuzumab vs the relevant UK comparator.

It should be noted that the APHINITY study protocol was amended to limit the number of patients with node-negative disease and increase the sample size during the recruitment phase, to ensure that the patient population enrolled in the study had a nodal status distribution as anticipated when the study was designed. The reasons for the higher-than-initially-foreseen enrollment of patients with node-negative disease remain unclear, but may be in part due to breast screening programmes, which are likely to find BC at an early (i.e. node-negative) stage of the disease.

The APHINITY study confirms the dual-HER2 blockade of 18 cycles of pertuzumab + trastuzumab in the eBC setting, and will provide an option for those at high risk of recurrence to continue treatment in the adjuvant setting to complete up to one year (18 cycles) of treatment.

B.3 Cost effectiveness

B.3.1 *Published cost-effectiveness studies*

No published studies were found that assessed the cost-effectiveness of adjuvant treatment with pertuzumab in patients with HER2-positive eBC. Please see Appendix G for a full description of the cost-effectiveness SLR and results.

B.3.2 *Economic analysis*

The economic analysis described below evaluates the use of pertuzumab in the adjuvant setting. The model upon which the analysis is predicated is believed to accurately reflect the disease pathway in this therapeutic area. Furthermore, the structure is in line with previous HTA submissions and published cost-effectiveness analyses of pertuzumab in patients with eBC.[67, 102, 103]

Patient population

The ITT population in the pivotal APHINITY study is aligned with the patient population described in the final scope of this appraisal. Following recent regulatory discussions with the CHMP, the company does not expect to receive marketing authorisation in the ITT population. The anticipated label for pertuzumab in eBC is expected to read as follows:

Perjeta is indicated for use in combination with trastuzumab and chemotherapy in:

- *The neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence.*
- *The adjuvant treatment of adult patients with HER2-positive early breast cancer at high risk of recurrence.*

The updated label is expected to define "high risk of recurrence" as follows: "*based on data from the APHINITY study, HER2-positive early breast cancer patients at high risk of recurrence are defined as those with lymph node-positive disease or hormone receptor-negative disease*". The economic analysis centres on patients who are diagnosed as being at high risk of recurrence. This population differs from the APHINITY ITT population and the final scope of this appraisal. However, it is aligned with the expected marketing authorisation in the UK.

Patients with node-positive or hormone receptor-negative eBC are at a greater risk of disease recurrence vs patients with node-negative or hormone receptor-positive eBC respectively, and have higher unmet medical need. The wider medical community expects patients with node-positive disease to receive the most benefit from pertuzumab therapy in this setting. As a result, the node-positive population comprises the base case analysis in this appraisal. In addition to the node-positive analysis, an analysis in patients with hormone receptor-negative disease has also been included in Appendix M. This submission will report cost-effectiveness results of pertuzumab in patients with eBC in two distinct subgroups of the ITT population:

- **Node-positive disease** (base case – below)
- **Hormone receptor-negative disease** (scenario analysis – Appendix M)

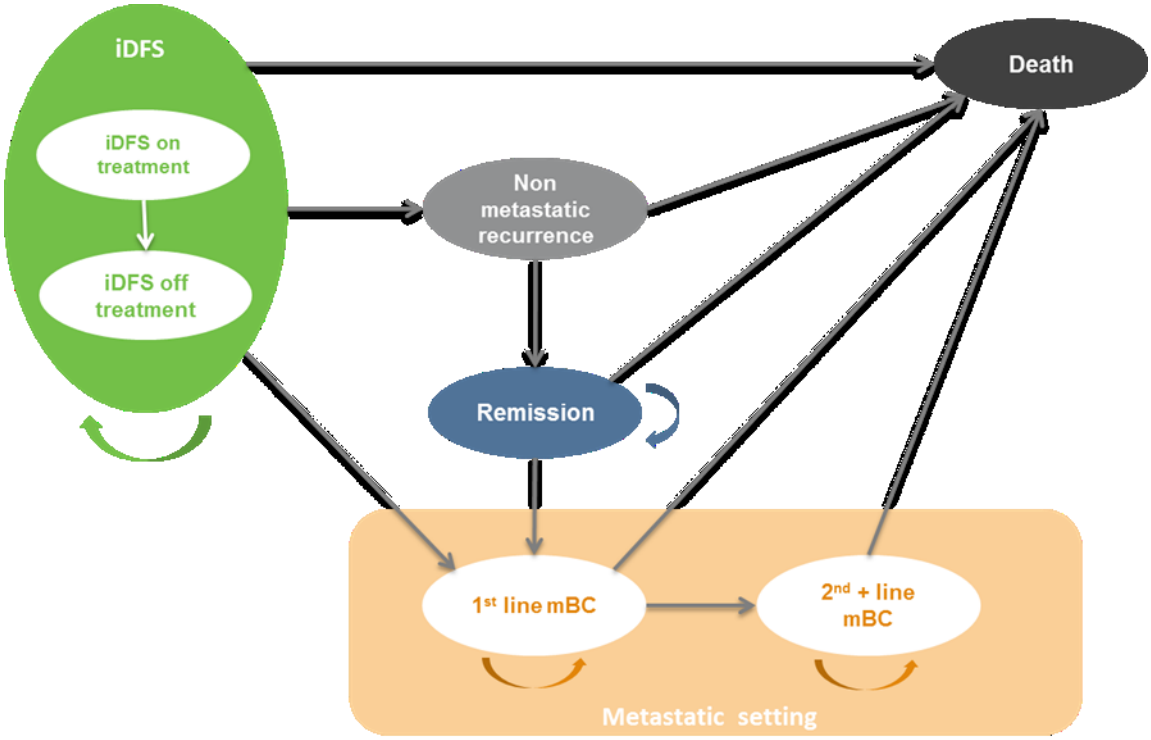
Clinical parameters of the model for the node-positive and hormone receptor-negative analyses were primarily populated using data from the pivotal APHINITY trial. Section B.3.3 describes the sourcing and implementation of clinical data in the model. Full details of the APHINITY study characteristics are described in Section B.2 of this submission.

Model structure

A Markov model was developed in Microsoft Excel® with the following seven health states: 'IDFS – on treatment', 'IDFS – off treatment', 'Non-metastatic recurrence', 'Remission', 'First-line treatment for mBC (First-line mBC)', 'Subsequent treatment lines for mBC (Second+ line mBC)', and 'Death', see Figure 8.

The cycle length of the model is one month, with the proportion of patients in each health state calculated every 30.4 days. A half cycle correction has been applied in the model. Costs and quality-adjusted life-years (QALYs) have been discounted at a rate of 3.5% per annum, as is recommended in the NICE Reference Case, 2013.[104]

Figure 8. Model structure schematic for HER2-positive breast cancer



Abbreviations: iDFS, invasive disease-free survival; mBC, metastatic breast cancer.

Transition between health states

Patients enter the model in the IDFS health state and remain there until recurrence (non-metastatic or metastatic) or death. The non-metastatic recurrence health state includes various types of non-distant recurrence, including locoregional and contralateral recurrences. This classification is consistent with the definition of the primary endpoint (IDFS) in the APHINITY study. No distinction was made in terms of the type of non-metastatic recurrence in this analysis. All types of non-metastatic recurrence were believed to be similar in terms of the associated resource use, QoL and mortality.

The possible transitions between each of the health states are described briefly below. Please see Section B.3.3 for full details of how the probabilities of these transitions were derived.

Non-metastatic recurrence pathway

- **IDFS on-treatment to off-treatment health state:** Patients receive a maximum of 18 cycles of pertuzumab + trastuzumab + chemotherapy in the intervention arm or a maximum of 18 cycles of trastuzumab + chemotherapy in the comparator arm (IDFS – on-treatment). Once patients discontinue their eBC assigned regimen they transition to the IDFS off-treatment state.
- **IDFS to non-metastatic recurrence health state:** Patients who experience a non-distant recurrence transition to the non-metastatic recurrence health state. Patients entering this health state will be subject to 12 months of additional adjuvant therapy. In this context, the non-metastatic recurrence health state is a one year "tunnel state". Upon completion of the additional adjuvant treatment, all patients are assumed to be in remission.
- **Remission to first-line mBC health state:** Once in remission, if a patient's disease returns, it is assumed they would progress to the (first-line mBC) health state (i.e. the event is assumed to be metastatic).

Metastatic recurrence pathway

- **IDFS to first-line mBC health state:** Patients who experience a distant recurrence when in the IDFS health state transition to the first-line mBC state. In this state, first-line treatment for mBC is administered.
- **First-line mBC to subsequent lines for mBC health state:** Once in the first-line mBC health state, patients are at risk of disease progression and transitioning to the metastatic – progressed health state (second+ line mBC). In this state patients are administered subsequent lines of treatment for their progressed mBC.
- **Transition to death:** Death is an absorbing state. Patients can transition to death from any health state in the model.

This type of model was considered appropriate for the decision problem. Both the structure and health states are in-line with the clinical pathway outlined in Section B.1. The chosen approach is consistent with previous NICE technology appraisals in this disease area (TA107 and TA424)[11, 67] as well as the economic studies identified in the SLR (Section B.3.1). Furthermore, the model structure was discussed and validated by an independent UK advisory board held in September 2017, see Section B.3.10.[105]

Table 18. Features of the economic analysis

	Previous appraisals		Current appraisal	
	TA107 – Trastuzumab for the adjuvant treatment of early-stage HER2-positive breast cancer[11]	**TA424** – pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer[67]	**Chosen values**	**Justification**
Time horizon	45 years (lifetime)	50 years (lifetime)	52 years (lifetime)	In accordance with NICE Reference Case[104]
Treatment waning effect	Effect maintained for ten years. Two-thirds of this benefit is seen until year 45	No waning. Treatment effect set equal after seven years	Effect maintained for seven years before waning to null at ten years	Modification of the assumption used in TA424. Full justification explained in Section B.3.3.1
Source of utilities	Published literature	Published literature: - *Lloyd, 2004* - *Lidgren, 2007*	EQ-5D data collected during the APHINITY trial	In accordance with NICE Reference Case[104]
Source of costs	MEDTAP study, ABACUS study, HERA database, and MIMS	NHS reference costs, BNF, published literature, and expert opinion	Published literature and expert opinion	In accordance with NICE Reference case[104]

Abbreviations: ABACUS, Awareness and Beliefs about Cancer; BNF, British National Formulary; EQ-5D, EuroQol 5-Dimension; HER2, human epidermal growth factor receptor 2; NHS, National Health Service; NICE, National Institute for Health and Care Excellence.

Intervention technology and comparators

This analysis evaluates the cost-effectiveness of pertuzumab + trastuzumab + chemotherapy (intervention arm) vs trastuzumab + chemotherapy (comparator arm) in the adjuvant treatment of patients with HER2-positive eBC. The intervention and comparators are in line with the decision problem set out in the final scope of this appraisal.

The remainder of this subsection outlines the basic dosing schedules of the primary treatment options in the APHINITY study. Further details around the acquisition costs, administration schedule, and real-world usage applied in the cost-effectiveness model are available in Section B.3.5.1.

Pertuzumab: Pertuzumab was administered for a total of 52 weeks plus a window of three days (i.e. maximum of 18 cycles. In the APHINITY study, pertuzumab was administered on Day 1 of the first taxane-containing cycle at the required loading dose of 840 mg as an IV infusion, followed every 3 weeks thereafter by a maintenance dose of 420 mg.[4]

Trastuzumab: trastuzumab was administered for a total of 52 weeks, plus a window of three days (i.e. maximum of 18 cycles within one year).

In the APHINITY study, trastuzumab was administered on Day 1 of the first taxane-containing cycle at the required loading dose of 8 mg/kg, as an IV infusion, followed every three weeks thereafter by a maintenance dose of 6 mg/kg as an IV infusion.[106]

Please note that whilst branded trastuzumab IV was the comparator in the APHINITY trial, subcutaneous (SC) trastuzumab and trastuzumab biosimilar have also been included in this economic analysis – see Section B.3.5.1 for more details.

Adjuvant chemotherapy: The choice of standard adjuvant chemotherapy given to each individual patient was determined by the Investigator with the patient, prior to randomisation. The Investigator could choose to treat the patient with either an anthracycline-based chemotherapy or a non-anthracycline-based chemotherapy. Table 19 summarises the regimens.

Table 19. Protocol approved chemotherapy regimens (Investigators' choice)[77]

Regimen	Dose	Frequency
Anthracycline therapy: FEC (or FAC) → T		
Three/four cycles x FEC (or FAC) → Three/four cycles x docetaxel	F: 500 to 600 mg/m^2 E: 90 to 120 mg/m2 OR A: 50 mg/m^2 C: 500 to 600 mg/m^2	q3w
	Followed by: Docetaxel: 100 mg/m^2 OR docetaxel: 75 mg/m^2 for four cycles[a] OR docetaxel: 75 mg/m^2 in the first cycle, escalating to 100 mg/m^2 in subsequent cycles	q3w
Three/four cycles x FEC (or FAC) → 12 weekly cycles of paclitaxel	F: 500 to 600 mg/m^2 E: 90 to 120 mg/m^2 OR A: 50 mg/m^2 C: 500 to 600 mg/m^2	q3w
	Followed by: paclitaxel: 80 mg/m^2	q1w
Anthracycline therapy: AC (or EC) → T		
Four cycles x AC[b] (or EC) → four cycles x docetaxel	A: 60 mg/m^2 OR E: 90 to 120 mg/m^2 C: 500 to 600 mg/m^2	q3w OR dose-dense q2w with G-CSF support
	Followed by: Docetaxel: 100 mg/m^2 OR docetaxel: 75 mg/m^2 for four cycles[a] OR docetaxel: 75 mg/m^2 in the first cycles, escalating to 100 mg/m^2 in subsequent cycles	q3w
Four cycles x AC[b] (or EC) → 12 weekly cycles of paclitaxel	A: 60 mg/m^2 OR E: 90 to 120mg/m^2 C: 500 to 600 mg/m^2	q3w
	Followed by: paclitaxel: 80 mg/m^2	q1w
Non-anthracycline therapy: docetaxel/carboplatin		
Six cycles x docetaxel + carboplatin	Docetaxel: 75 mg/m^2	q3w

	Carboplatin: AUC 6 (900 mg maximum dose)	

Footnotes: [a]If docetaxel 75 mg/m^2 was used and not escalated to 100mg/m^2 then four cycles had to be given; [b]EC or AC could be given at the same dose (A: 60mg/m^2 or E: 90 to 120mg/m^2) every two weeks (dose-dense) with G-CSF support, for a total of four cycles; [c]Phase III randomised trastuzumab (H) trial comparing AC → T with AC → TH and with TCH in the adjuvant treatment of node-positive and high-risk node-negative patients with operable breast cancer containing the HER2neu alteration.
Abbreviations: A, doxorubicin; AUC, area under the curve; C, cyclophosphamide; E, epirubicin; F, 5-fluororacil; G-CSF, granulocyte colony-stimulating factor; mg, milligram; q1w, every week; q3w, every three weeks; T, taxane.

Please refer to Section B.3.5.1 for further information on the intervention and comparators in this analysis.

B.3.3 *Clinical parameters and variables*

The primary data source used to populate the clinical elements of the cost-effectiveness model was the pivotal APHINITY trial. APHINITY was a Phase III study evaluating pertuzumab + trastuzumab + chemotherapy compared to placebo + trastuzumab + chemotherapy.[2] In situations where the APHINITY data were insufficient, additional evidence from various sources was utilised. These sources included published literature, expert advice and assumptions.

It is believed that the node-positive trial population observed in APHINITY is representative of node-positive patients who would receive pertuzumab + trastuzumab + chemotherapy in the UK (see Section B.2.3.2). As a result, responses and outcomes seen in this study are assumed to be reflective of UK clinical practice.

The main body of the submission outlines the analysis and implementation of the node-positive subgroup data. Other analyses of the ITT population, including those in the hormone receptor-negative population, are documented in the appendices of this submission.

B.3.3.1 Modelling of IDFS

Patients remain in the IDFS health state as long as they remain disease-free, as defined by the study protocol (see Section B.2.3.1), and alive. The probability of remaining in the IDFS health state is derived from patient-level data in the APHINITY study. The median follow-up period in the node-positive population was 44.5 months, with only 9.2% and 12.1% of IDFS events occurred in the pertuzumab + trastuzumab + chemotherapy and placebo + trastuzumab + chemotherapy arms, respectively. Given the truncated follow-up period in APHINITY, extrapolation techniques were essential to model IDFS over a lifetime time horizon (52 years).

Modelling of IDFS was informed using data from the APHINITY study. Parametric functions were applied to the observed data to facilitate extrapolation beyond the follow-up period. The selected parametric function was subsequently adjusted to produce a more clinically accurate and robust extrapolation. Empirical evidence was used to help inform this adjustment and create IDFS curves that are reflective of longer-term outcomes in this indication.

Since pertuzumab is not yet licensed in the adjuvant eBC setting, empirical data only exist for the comparator arm (trastuzumab + chemotherapy). Therefore, data from long-term studies of trastuzumab (HERA and BCIRG 006 trials)[27, 29] were used to inform the adjustment of the extrapolations.

The modelling of IDFS over the time horizon of the model can be broken down into three discrete periods:

- **Time period 1** – Zero to four years
- **Time period 2** – From year four to year ten
- **Time period 3** – From year ten until the end of the time horizon (year 52)

For each of these time periods, different data and assumptions were incorporated to produce accurate extrapolations. The methodology involved in generating the IDFS curves is detailed in the following subsections.

Time period 1 (zero to four years) – the APHINITY study

In accordance with standard practice, a parametric extrapolation function was fitted to the Kaplan-Meier data from the APHINITY study. Several candidate distributions were fitted to the IDFS data and assessed for "goodness of fit". The selected distribution provided the basis of the extrapolation beyond the observed period of the trial. Additional adjustment of this distribution, using empirical data, dictated the final shape of the IDFS curves used in the model (see subsection relating to "Time period 2"). The following parametric functions were fitted to the trial-data: Exponential, Weibull, Log-logistic, Log-normal, Gamma and Gompertz.

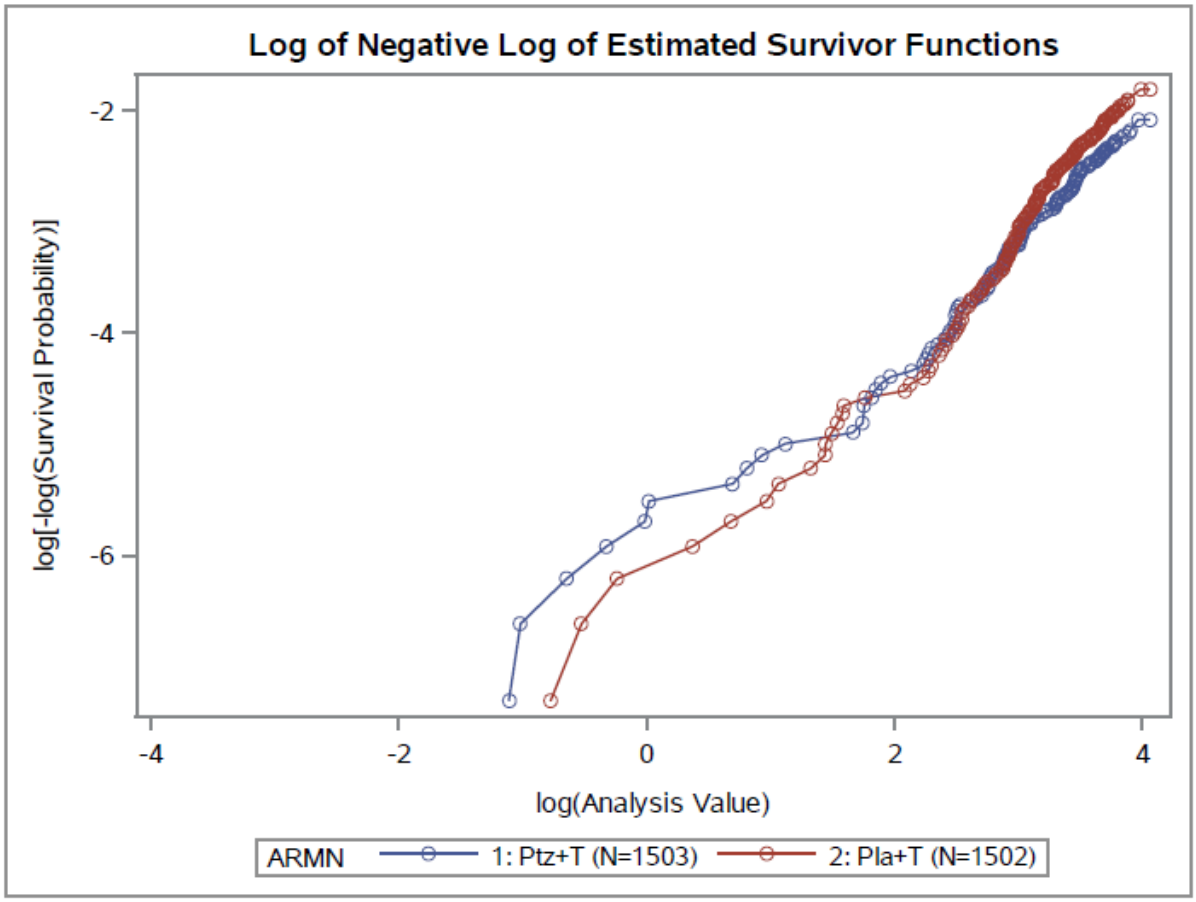
The selection process of the most appropriate distribution is outlined below. A criterion-based guide was used to facilitate the accurate extrapolation and justification of survival estimates. Methodology employed during this selection process is in accordance with the NICE Decision Support Unit Technical Report.[107]

Proportional hazard assumption

Prior to deciding on the most appropriate parametric distribution, it was important to check the existence of proportional hazards (PH). The PH assumption states that the hazard in one group (arm A) is a constant proportion of the hazard in the other group (arm B). This proportion is the hazard ratio. That is, although the hazard may vary with time, the ratio of the hazard rates is constant.

The PH assumption can be tested graphically, using log-cumulative hazard plots. These graphs plot log(time) on the x-axis vs log(–log(S(time)) on the y-axis, where S(time) is the survival time. The PH assumption can be assumed to hold if the gradient of the two curves is found to be reasonably constant (i.e. they do not obviously diverge, converge or intersect). The log of the survival probabilities plotted with the log of time for APHINITY arms are shown in Figure 9.

Figure 9. Log of negative log of estimated survivor functions – IDFS endpoint from the APHINITY study (node-positive population)



Abbreviations: Pla+T, Placebo + trastuzumab + chemotherapy; Ptz+T, pertuzumab + trastuzumab + chemotherapy.

As shown in Figure 9, the two curves cross at several time points, signaling that the PH assumption may not hold.

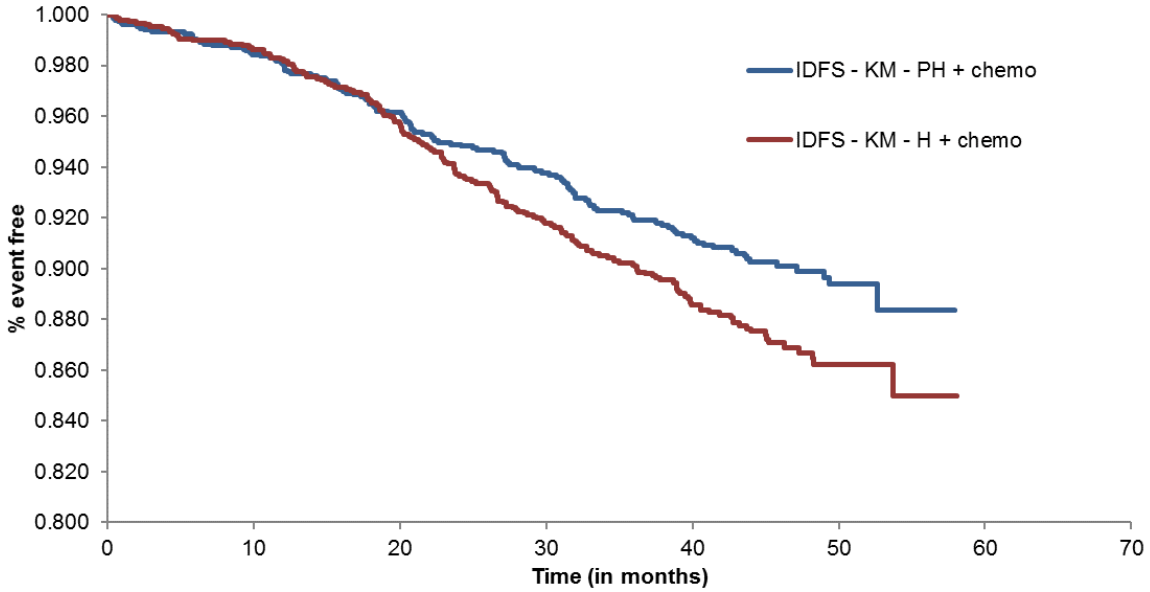
An alternative method of testing the PH assumption is by analysing whether the annualised hazard ratio remains constant over time. As can be seen in Table 20, the hazard ratio does not remain constant over time, thus indicating that the PH assumption is violated. In addition, the Kaplan-Meier plots from APHINITY show that the IDFS curves overlap for the first 20 months of follow-up and diverge thereafter (Figure 10). A PH model cannot properly model this behaviour, and consequently, the parametric models for each treatment arm were modelled independently (i.e. treatment effect was not included as a covariate).

Table 20. Annualised IDFS hazard ratio over time (APHINITY Kaplan-Meier data, node-positive population)

Time period	Pertuzumab + trastuzumab + chemotherapy arm hazard rate	Placebo + trastuzumab + chemotherapy arm hazard rate	Annualised hazard ratio
0–1 year	0.01661	0.01621	1.025
1–2 years	0.03140	0.03971	0.791

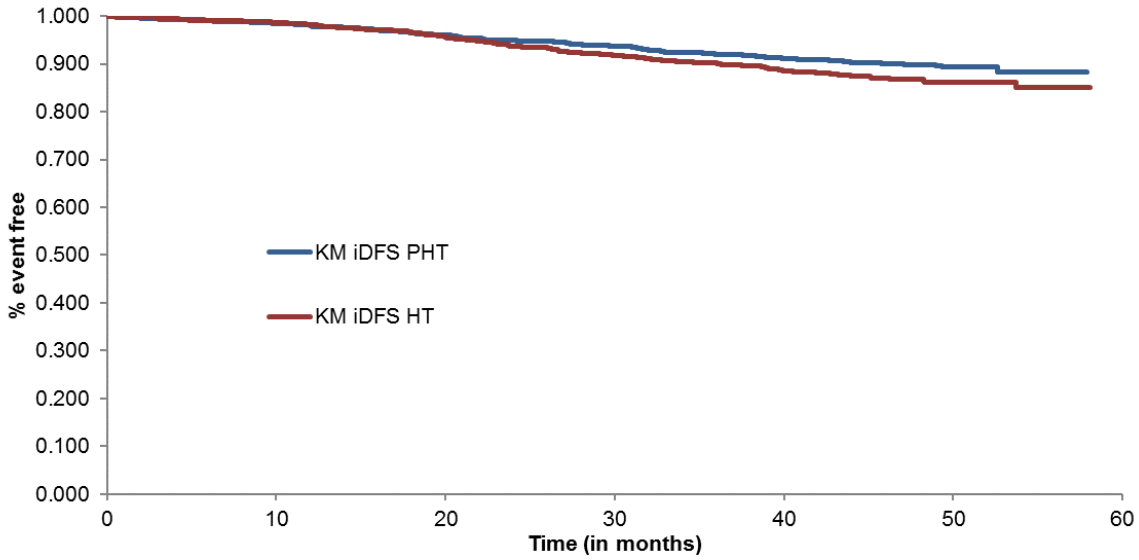
2–3 years	0.02754	0.03644	0.756
3–4 years	0.02126	0.03600	0.591

Figure 10. IDFS Kaplan-Meier curves from the APHINITY study[a] (node-positive population)



Footnotes: [a]y-axis has been adjusted to magnify the curves. Unadjusted Kaplan-Meier APHINITY data are available in Figure 11.
Abbreviations: H, trastuzumab; IDFS, invasive disease-free survival; KM, Kaplan-Meier, PH, pertuzumab + trastuzumab.

Figure 11. IDFS Kaplan-Meier curves from the APHINITY study (node-positive population)



Abbreviations: HT, placebo + trastuzumab + chemotherapy; iDFS, invasive disease-free survival; KM, Kaplan-Meier; PHT, pertuzumab + trastuzumab + chemotherapy.

In addition to what the data suggest, clinical experts also highlighted that patients have different patterns of relapse according to the hormone receptor status of their disease.[105] Patients with hormone receptor-negative disease are thought to experience recurrences earlier in the disease pathway, whereas those with hormone receptor-positive disease tend to experience later events. Based on this rationale, more events in the hormone receptor-positive population are anticipated at a later timepoint, i.e. beyond the current observed data period. As a result, the curves are expected to separate further over time.

This behaviour suggests that the hazard rate does not remain constant across the node-positive population, thus indicating that modelling a constant treatment effect is not appropriate.

Akaike Information Criterion (AIC) / Bayesian Information Criterion (BIC) Goodness of fit

Parametric distributions were assessed for their goodness of fit to the observed data using the AIC. Lower values for AIC indicate a better mathematical assessment of the fit to the actual data. BIC values have also been calculated and reported in this submission. As the approach taken here is Frequentist, as opposed to Bayesian, the BIC values do not factor into the decision-making process when selecting a distribution, and have instead been included for completeness.

Table 21 presents the AIC and BIC values for the extrapolation of IDFS data. The relative ranking of goodness of fit is shown in brackets, with one indicating the best fit and six the worst, i.e. lowest and highest AIC values, respectively.

Table 21. IDFS extrapolation – AIC and BIC values (relative ranking of goodness of fit shown in brackets) (node-positive population)

	AIC		BIC	
	Pertuzumab + trastuzumab + chemotherapy arm	**Placebo + trastuzumab + chemotherapy arm**	**Pertuzumab + trastuzumab + chemotherapy arm**	**Placebo + trastuzumab + chemotherapy arm**
Exponential	1,175.6 (1)	1,384.9 (6)	1,180.9 (1)	1,390.2 (4)
Weibull	1,176.3 (3)	1,374.8 (2)	1,186.9 (3)	1,385.5 (2)
Log-normal	1,182.0 (6)	1,379.5 (4)	1,192.6 (5)	1,390.1 (3)
Gamma	1,178.3 (5)	1,376.4 (3)	1,194.2 (6)	1,392.4 (6)
Log-logistic	**1,176.2 (2)**	**1,374.2 (1)**	**1,186.8 (2)**	**1,384.8 (1)**
Gompertz	1,176.7 (4)	1,380.1 (5)	1,187.4 (4)	1,390.7 (5)

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

According to the AIC values, the Exponential and Log-logistic functions provide the best fit to the data in the pertuzumab + trastuzumab + chemotherapy and the placebo + trastuzumab + chemotherapy arms, respectively. Despite the Exponential having the lowest figure in the pertuzumab + trastuzumab + chemotherapy arm, all other functions report AIC values that are within close proximity (range 2.70) with the exception of the Log-normal. In the placebo + trastuzumab + chemotherapy arm, the three best-fitting functions (Log-logistic, Weibull, and Gamma) report negligible differences in AIC values.

The technical support document, developed by Latimer *et al.,* states that the same parametric function should be used across both treatment arms (where feasible).[107] Using the same type of

function ensures consistency and limits potential problems such as the crossing of the curves. When considering the fit across the two arms jointly, the best fitting extrapolation is produced by the Log-logistic function.

Mathematical measures such as the AIC and BIC are designed to show how well a parametric function fits to the Kaplan-Meier data, relative to the other functions in question. In other words, the AIC (BIC) values say nothing of the appropriateness of the extrapolation beyond the Kaplan-Meier data. As the degree of immaturity and censoring are high in the APHINITY data, the AIC and BIC values quoted here should be interpreted with caution.

Visual inspection

The AIC and BIC statistics serve to illustrate the relative fit of a parametric function. When selecting an appropriate extrapolation, it is also important to take the absolute fit to the Kaplan-Meier data into consideration. To quantify this, a simple comparison of IDFS events at different timepoints was undertaken. Table 22 presents the proportion of patients who did not experience an IDFS event at three and four years according to the parametric extrapolations and Kaplan-Meier data.

Table 22. IDFS events at 36 and 48 months (node-positive population)

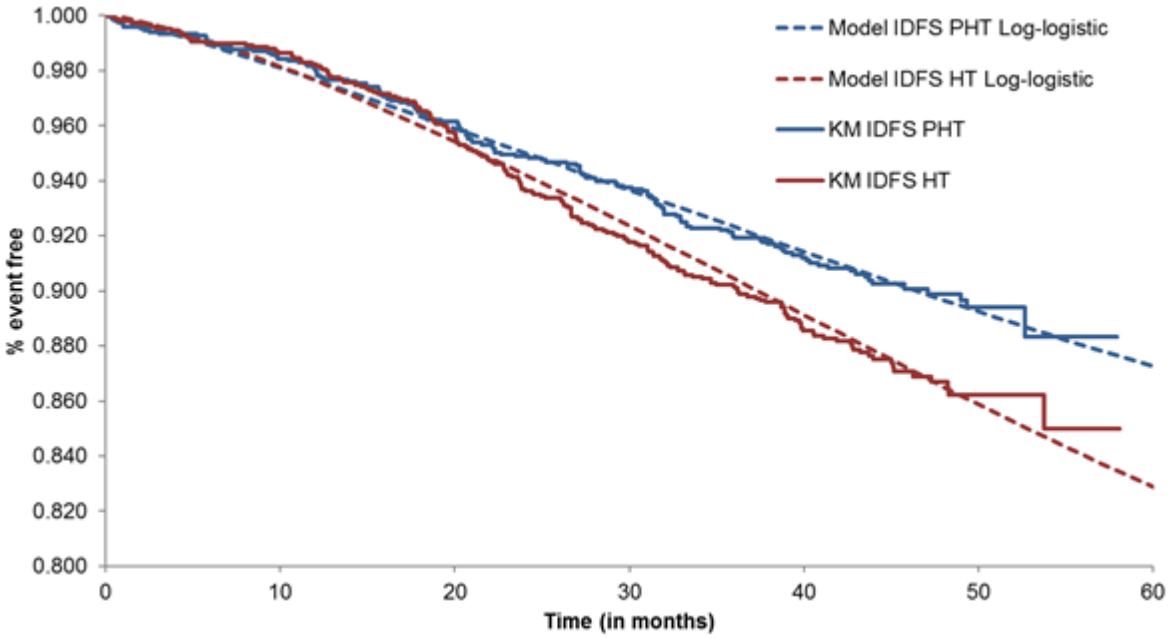
Timepoint	Parametric function	Pertuzumab + trastuzumab + chemotherapy	Placebo + trastuzumab + chemotherapy	Pertuzumab + trastuzumab + chemotherapy vs Placebo + trastuzumab + chemotherapy	Δ vs KM data	
					Pertuzumab + trastuzumab + chemotherapy	Placebo + trastuzumab + chemotherapy
36 months	KM data	91.88%	89.91%	1.97%	-	-
	Exponential	92.10%	89.85%	2.26%	0.22%	-0.06%
	Weibull	92.24%	90.34%	1.90%	0.36%	0.43%
	Log-normal	92.03%	90.01%	2.02%	0.15%	0.10%
	Gamma	92.25%	90.26%	1.98%	0.37%	0.35%
	Log-logistic	**92.21%**	**90.27%**	**1.94%**	**0.33%**	**0.36%**
	Gompertz	92.29%	90.43%	1.86%	0.41%	0.52%
48 months	KM data	89.65%	86.46%	3.19%	-	-
	Exponential	89.65%	86.74%	2.91%	0.00%	0.28%
	Weibull	89.54%	86.34%	3.20%	-0.11%	-0.12%
	Log-normal	89.79%	86.67%	3.12%	0.14%	0.21%
	Gamma	89.54%	86.39%	3.15%	-0.11%	-0.07%
	Log-logistic	**89.56%**	**86.35%**	**3.21%**	**-0.09%**	**-0.11%**
	Gompertz	89.53%	86.34%	3.19%	-0.12%	-0.12%

Abbreviations: KM, Kaplan-Meier; Δ, difference.

Overall, all functions across both treatment arms, proved to be a good absolute fit to the Kaplan-Meier IDFS data. At both 36 and 48 months, incremental differences between the extrapolations and the Kaplan-Meier data were always below 1%. It can be reasonably assumed that differences in the absolute fit of the parametric function extrapolations are negligible.

Based on the assessment and selection process described above, the Log-logistic distribution has been used for the IDFS extrapolation in years zero to four (time period 1) in both treatment arms (Figure 12). This distribution also provides the basis for the adjusted curves from year four onwards.

Figure 12. IDFS Kaplan-Meier curves from the APHINITY study and corresponding parametric extrapolation (node-positive population)[a]



Footnotes: [a]y-axis has been adjusted to magnify the curves.
Abbreviations: HT, trastuzumab + chemotherapy; IDFS, invasive disease-free survival; KM, Kaplan-Meier; PHT, pertuzumab + trastuzumab + chemotherapy.

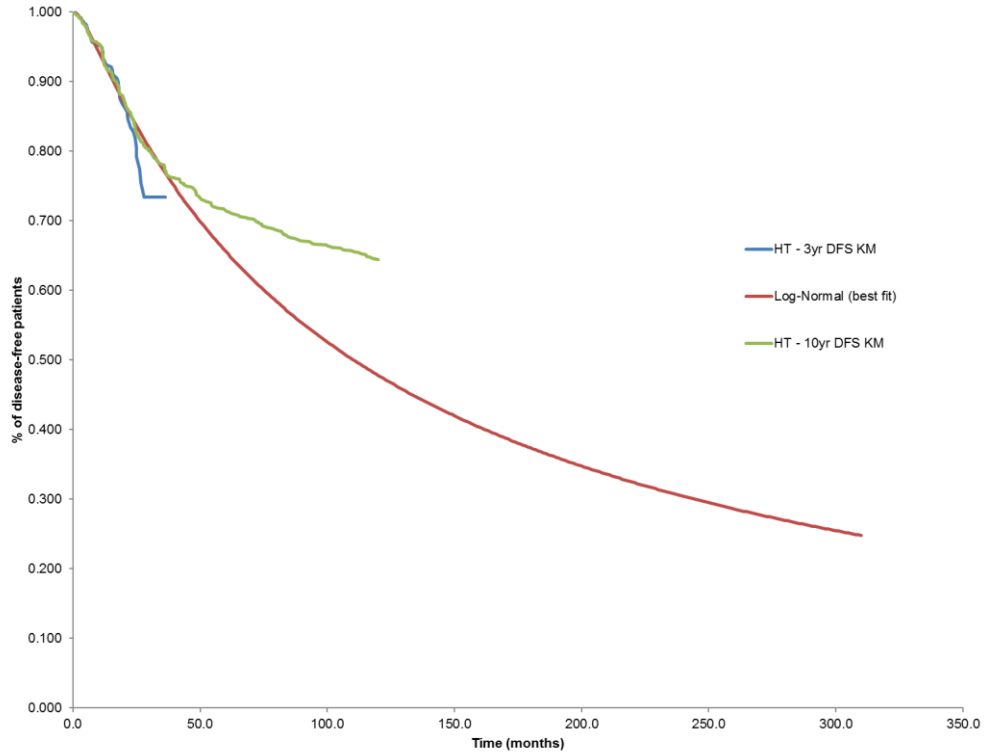
Time period 2 (year four to year ten) – empirical data

At the time of this submission, the APHINITY trial has a follow-up period of approximately four years. Published literature shows that the underlying risk of recurrence in the first four years for a patient with eBC is not representative of the risk of recurrence at a later date.[108] Patients in the IDFS state are exposed to a far greater risk of recurrence in the first four to five years, although this risk eventually decreases over time. Ultimately, the extrapolation parameter estimates that have been calculated based on APHINITY data correspond to a time period with a high recurrence rate. This results in the extrapolation overestimating the rate of recurrence at later timepoints. These conclusions are reflected in the evidence reported in both the BCIRG-006 and HERA trials, which are long-term studies of trastuzumab therapy.[27, 29]

Figure 13 shows the extrapolation of DFS based on the three-year data cut of the HERA trial and the actual Kaplan-Meier curve seen at year 11 of the same trial.[27] It is apparent that the extrapolation based on the three-year data-cut vastly underestimates the actual DFS estimates seen at year ten.

A similar situation is expected to be observed in the APHINITY data, thus indicating that an adjustment of the underlying risk (i.e. IDFS curve) is required.

Figure 13. Comparison of 3-year HERA data extrapolation and latest HERA data cut (ten-year) (node-positive population)



Abbreviations: DFS, disease-free survival; HT, trastuzumab + chemotherapy; KM, Kaplan-Meier.

A three-year DFS data cut was not available for the BCIRG-006 trial, therefore only the HERA study has been included in Figure 13. Though it may have been possible to construct an extrapolation based on BCIRG-006 Kaplan-Meier data at year three, this was deemed inappropriate from a methodological point of view.

Adjustment of the extrapolation based on external data

Two external long-term studies have been used to examine the relationship between time in IDFS/DFS and the underlying risk of recurrence.

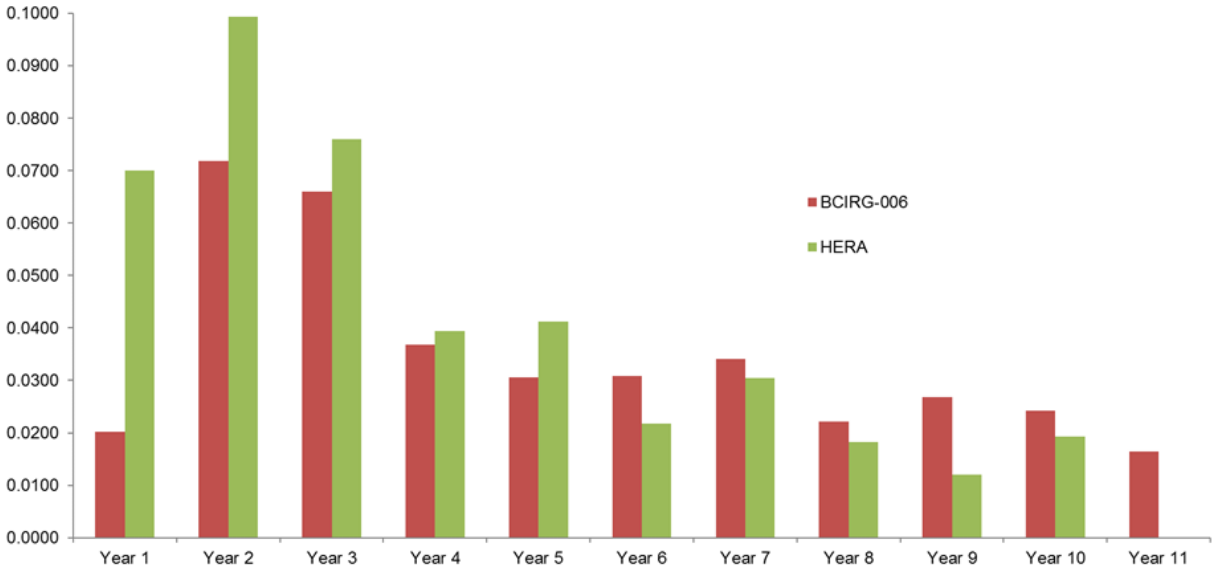
The first study, HERA, is a randomised, open-label, multi-centre, Phase III trial investigating the efficacy of trastuzumab therapy over one and two years after standard neoadjuvant chemotherapy, adjuvant chemotherapy, or both, in patients with HER2-positive eBC.[27] The HERA trial provides longer term follow-up data on DFS in patients with eBC. These data can be used as an additional source to inform the long-term extrapolation of IDFS in the APHINITY study. It should be noted that the primary outcome in HERA was DFS, as compared to IDFS in the APHINITY study.

The second study, BCIRG 006, was also a randomised Phase III trial of patients with node-positive or high-risk node-negative eBC, and compared doxorubicin + cyclophosphamide followed by docetaxel (AC-T); AC-T + trastuzumab (AC-TH); and a non-anthracycline-containing arm, docetaxel + carboplatin + trastuzumab (TCH).[29] The final ten-year analyses of the BCIRG 006 were also recently published.[29] The APHINITY study was expected to enrol a similar population to the BCIRG 006 study and thus statistical assumptions for the trastuzumab arm

performance were based on the data from the BCIRG 006 study. The APHINITY study is thought to more closely resemble the BCIRG 006 study rather than the HERA study.[75]

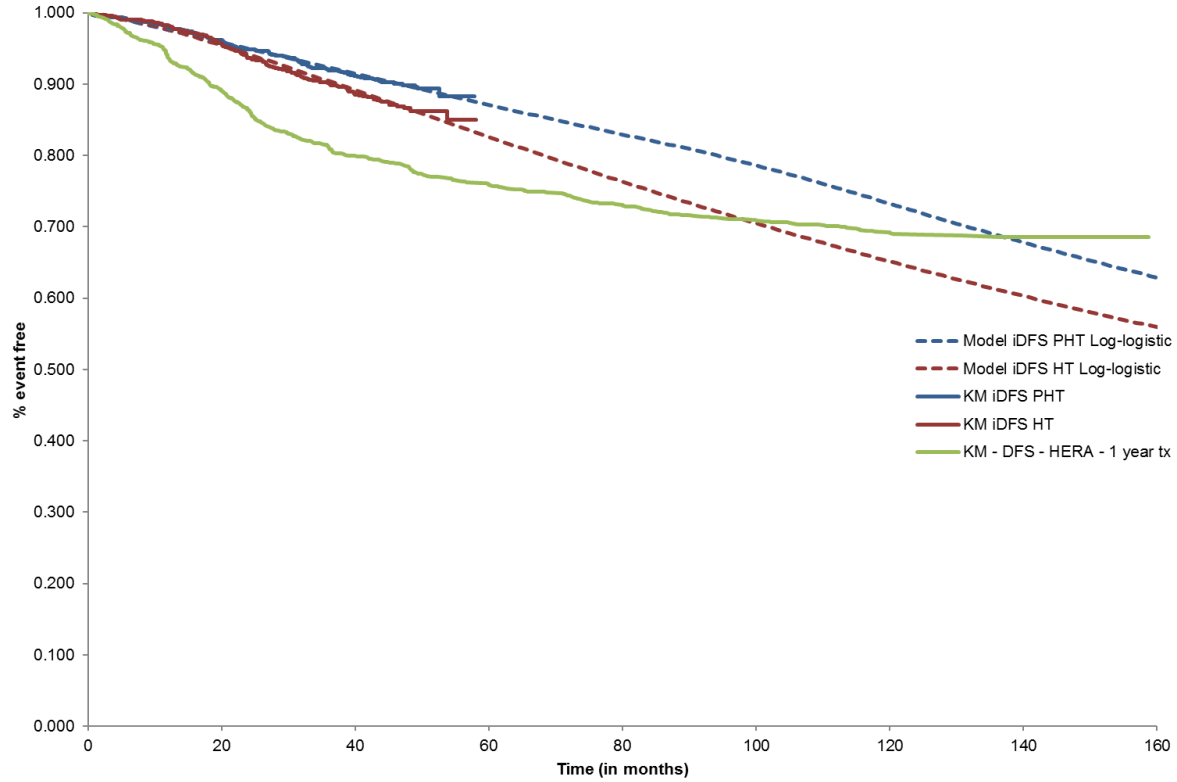
Analyses of the long-term data from the HERA and BCIRG 006 studies show that recurrence rate starts off relatively high before sharply decreasing and finally stabilising (at approximately 120 months). A clear change in the incidence of events is observed between 36 and 48 months of follow-up (Figure 14). Following randomisation up until 36 months, the recurrence rate is maintained at a high level in both trials. After 36 months, the recurrence rate begins to decrease with time. In essence, the follow-up data from these trials illustrates that the number of additional DFS events decreased with time from 36 months onwards. This trend is assumed to also be evident in the APHINITY data.

Figure 14. Annual recurrence rate (DFS endpoint) from HERA and BCIRG 006 clinical trials (node-positive population)



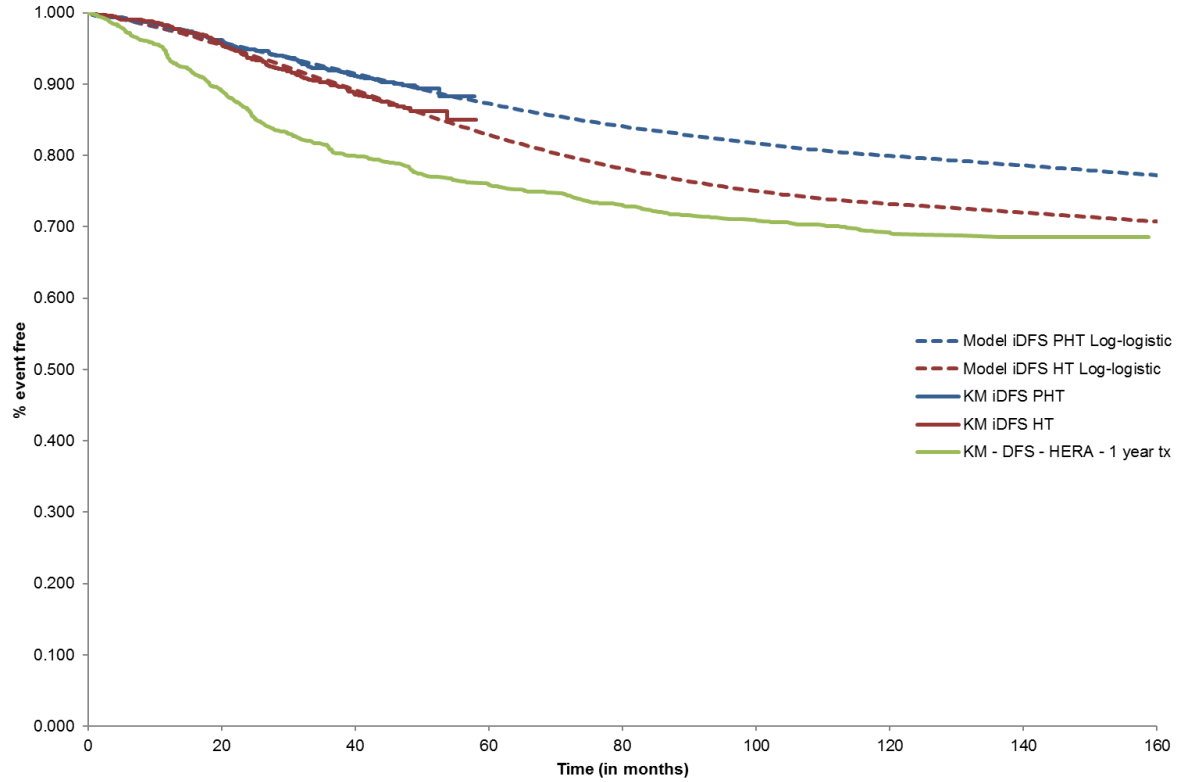
The trend seen in Figure 14 and described above has been replicated in the economic analysis by assuming that from 48 months onwards, the proportion of patients being “cured” (no longer at risk of recurrence and only subject to background mortality) linearly increases with time from 0% at 48 months to 90% at 120 months (a complete [100%] cure rate has been assumed to be clinically implausible). Forty-eight months was selected in the base case as opposed to 36 months, as APHINITY data are available up until this timepoint (48 months). This adjustment results in IDFS curves that are broadly reflective of the long-term trend in recurrence rate in the HERA trial – See Figure 15 and Figure 16.

Figure 15. Unadjusted APHINITY IDFS extrapolations vs HERA DFS Kaplan-Meier (0% "cure" proportion) (node-positive population)



Abbreviations: DFS, disease-free survival; HT, placebo + trastuzumab + chemotherapy; iDFS, invasive disease-free survival; KM, Kaplan-Meier, PHT, pertuzumab + trastuzumab + chemotherapy.

Figure 16. Adjusted APHINITY IDFS extrapolations vs HERA DFS Kaplan-Meier (90% "cure" proportion) (node-positive population)

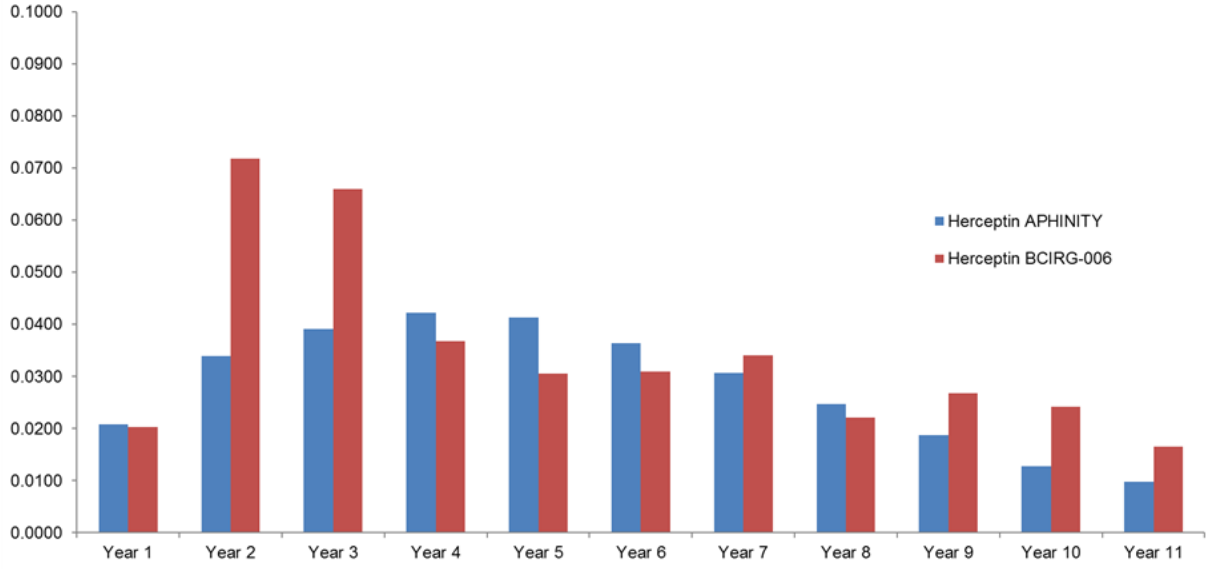


Abbreviations: DFS, disease-free survival; HT, placebo + trastuzumab + chemotherapy; iDFS, invasive disease-free survival; KM, Kaplan-Meier; PHT, pertuzumab + trastuzumab + chemotherapy.

Validation of the trastuzumab + chemotherapy extrapolation

Following the aforementioned adjustments, it is important to validate the final extrapolations with the longer-term data. Given that the patient population included in the APHINITY study was very similar to that of the BCIRG 006 study, it was deemed most appropriate to use this source when validating the extrapolation of the APHINITY IDFS data. Figure 17 shows the recurrence rate in the trastuzumab + chemotherapy arm of the model, and the pooled observed recurrence rate of both trastuzumab arms in the BCIRG 006 study.

Figure 17. Annual recurrence rate observed in the BCIRG 006 trial compared to the modelled IDFS rate



The difference in recurrence rate seen in the first four years is driven by the results from the respective trials. From year four to year ten the recurrence rates observed in BCIRG 006 are broadly similar to the modelled recurrence rate in the economic analysis. This similarity confirms that the adjustments are reasonable and appropriately reflect the long-term risk of eBC patients.

It is important to note here that the APHINITY trial used a different primary endpoint (IDFS) to the BCIRG 006 study (DFS). The IDFS and DFS endpoints are similar in terms of their definitions and hence results across the two measures are assumed comparable.

Duration of incremental treatment effect

In the base case analyses, it is assumed that the treatment effect of pertuzumab will be maintained for seven years and then slowly decrease to be null at ten years. The assumption of maintenance of treatment effect beyond the APHINITY follow-up period is based on observations from long-term studies of trastuzumab.

In HERA, after a median follow-up of 11 years, one year of trastuzumab treatment significantly reduced the risk of a disease-free survival event (HR=0.76; 95% CI, 0.68–0.86) and death (HR=0.74; 95% CI, 0.64–0.86) compared with the observation group. In addition, 52% of patients assigned to the observation group selectively crossed over to receive trastuzumab. The estimates provided above are not adjusted for patient cross-over.[27]

In BCIRG 006, at a median follow-up of 10.3 years, a significant DFS benefit was also seen in both trastuzumab-containing arms compared to chemotherapy (AC-TH: HR=0.70; 95% CI, 0.60–0.83; p<0.001 and TCH: HR=0.76; 95% CI, 0.65–0.90; p<0.001). An OS benefit was observed in both AC-TH (HR=0.64; 95% CI, 0.52–0.79; p<0.001) and TCH (HR=0.76; 95% CI, 0.62–0.93; p=0.0081).[29]

The addition of pertuzumab to trastuzumab should only serve to strengthen the assumption that treatment effect is maintained over time. The biological evidence in support of the synergistic

action of pertuzumab and trastuzumab is fairly robust.[7, 8] The dual-blockade mechanism (pertuzumab + trastuzumab) has been shown to improve long-term survival outcomes in the eBC and mBC settings. In first-line mBC, the CLEOPATRA study demonstrated a large survival benefit resulting from the addition of pertuzumab to the standard docetaxel-trastuzumab regimen. In the neoadjuvant setting, in addition to chemotherapy, dual-HER2 blockade by trastuzumab and pertuzumab nearly doubled the proportion of patients achieving a pCR).[30] With longer follow-up, pertuzumab demonstrated a survival outcome benefit in the neoadjuvant setting, which seemed to be maintained at five years despite only four 21-day cycles of neoadjuvant treatment.[109]

It is important to note here that no assumption is made on the duration of treatment effect of trastuzumab in the placebo arm. In this treatment arm it is assumed that a treatment effect exists until the patients reach cure (i.e. patients will never revert to the original recurrence risk seen with chemotherapy treatment). There is no biological rationale or evidence to suggest a shorter duration of treatment effect for pertuzumab + trastuzumab compared to trastuzumab alone.

TA424 (appraisal of pertuzumab in the neoadjuvant treatment of HER2-positive BC) adopted an incremental treatment effect duration of seven years.[67] This assumption was validated by a clinical advisory board and subsequently accepted by the Evidence Review Group (ERG). In this adjuvant submission, Roche has also assumed an incremental treatment effect duration of seven years, before decreasing linearly and then ceasing completely at ten years. This increased duration is assumed because patients will receive a total of 18 cycles of pertuzumab + trastuzumab + chemotherapy in the adjuvant setting, as opposed to only four to six in the neoadjuvant setting.

Time period 3 (year 10 to year 52)

The hazard rate observed in the eleventh year of the HERA trial appears similar to that of the UK mortality table, when assuming the patient is 65 years old.[110] It has therefore been reasonably assumed that 90% of patients are no longer at risk of recurrence beyond 120 months and are only exposed to death thereafter. This assumption will be tested in a scenario analysis.

The model assumes the following for each treatment arm:

- **Trastuzumab + chemotherapy:** Only 10% of patients are assumed to be at risk of recurrence. For this 10% of patients, the risk of recurrence is derived from the APHINITY data. The remaining 90% of patients are subject to the background mortality rate of the age-adjusted UK population only.
- **Pertuzumab + trastuzumab + chemotherapy:** No more treatment effect is assumed beyond the ten years, which means that the hazard rate of recurrence from the trastuzumab + chemotherapy arm is applied to the pertuzumab + trastuzumab + chemotherapy arm.

Empirical data pertaining to this time-period does not exist in this indication. This makes it difficult to validate the IDFS curves beyond the ten-year time point.

Modelling of death in the IDFS health state

Whilst in the IDFS state, patients are at risk of both recurrence and death. The risk of death applied here is the superior value between the risk of dying without recurrence (as observed in the APHINITY study) and background mortality in the age-adjusted UK population.

The risk of dying without recurrence is derived from the APHINITY trial. In the node-positive population, there were a total of 40 deaths without prior events (20 in each treatment arm). A constant probability was calculated and applied in both treatment arms until UK background mortality rates were superior (90 months). This parameter was assumed to be constant due to limitations in the data. Too few death events (40/3,005 = 1%) were observed to accurately and robustly extrapolate this parameter over time.

Summary of IDFS curve construction

A summary of the methodology involved in extrapolating the APHINITY IDFS curves is given below. Figure 18 displays the data sources used to construct the IDFS curves in each of the time periods. Figure 19 shows IDFS extrapolation as per model base case (node-positive, Log-logistic).

- **Time period 1 (0–4 years)** – APHINITY data are used to estimate the recurrence rate.
- **Time period 2 (4–10 years)** – Extrapolated recurrence rate is adjusted to more accurately reflect the trend in the recurrence rate observed in the trastuzumab studies.
- **Time period 3 (10–52 years)** – 90% of patients are assumed to be "cured" and are no longer at risk of recurrence, only background mortality applies.

Figure 18. Summary of the method use to extrapolate IDFS over the model time horizon

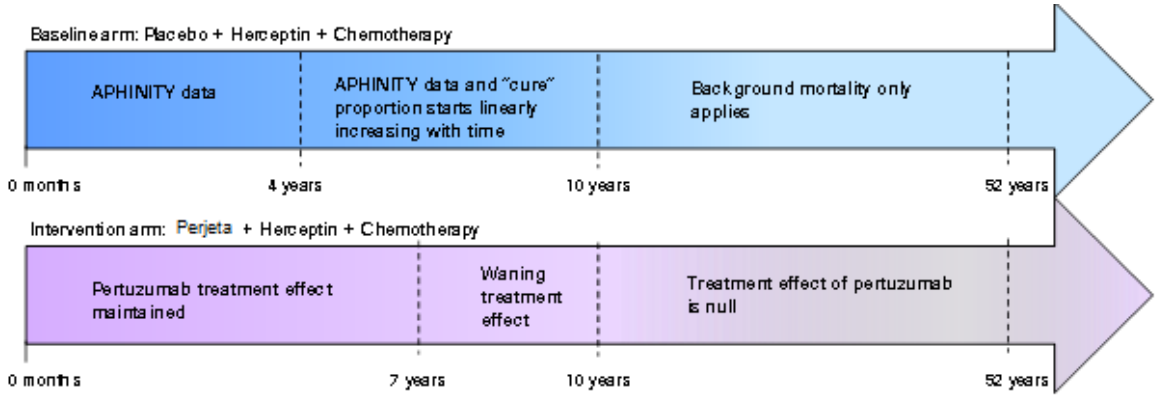
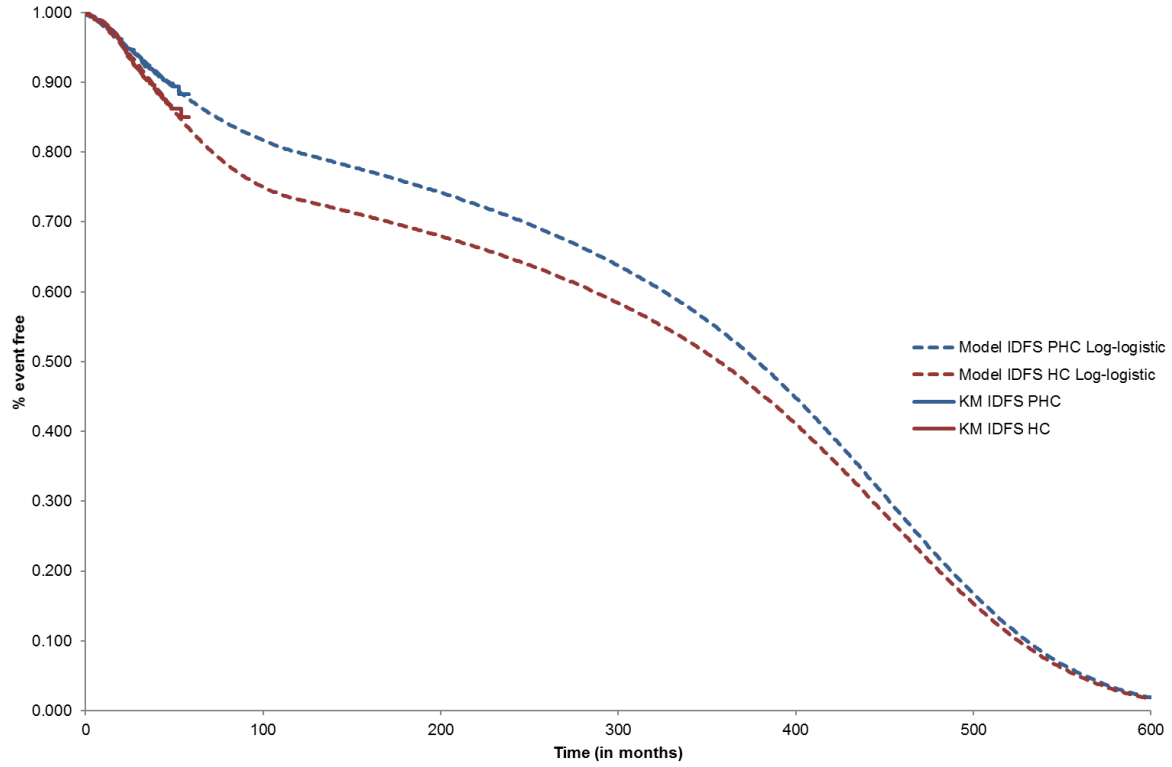


Figure 19. IDFS extrapolation as per model base case (node-positive population, Log-logistic)



Abbreviations: HT, placebo + trastuzumab + chemotherapy; IDFS, invasive disease-free survival; KM, Kaplan-Meier; PHT, pertuzumab + trastuzumab + chemotherapy.

B.3.3.2 Modelling of recurrences

As per Figure 8, patients in the IDFS health state can transition to either first-line mBC (a metastatic recurrence) or non-metastatic recurrence health states. These transition probabilities are derived from clinical data observed in the APHINITY study.

No meaningful differences were observed in the proportion of each IDFS events across the two treatment arms (i.e. the proportions of metastatic recurrence, non-metastatic recurrence, and deaths were broadly similar across the two treatment arms of the APHINITY study). As a result, the pooled proportion of metastatic vs. non-metastatic recurrences were applied to both arms in the model. Table 23 provides a breakdown of IDFS events observed in each treatment arm of the node-positive population.

It should be noted that deaths were not included as an IDFS event when calculating the proportion of metastatic and non-metastatic recurrences. Deaths in the IDFS health state are accounted for separately in the model.

Table 23. Types of IDFS event observed within the APHINITY study (node-positive population)

	Pertuzumab + trastuzumab + chemotherapy	Placebo + trastuzumab + chemotherapy	Both arms
IDFS event, n	139	181	320

	Pertuzumab + trastuzumab + chemotherapy	Placebo + trastuzumab + chemotherapy	Both arms
Deaths without prior event, n (%)	20 (14.39%)	20 (11.05%)	40 (12.50%)
IDFS event excluding deaths, n	119	161	280
Distant recurrence, n (%)	99 (83.19%)	128 (79.50%)	227 (81.07%)
Other types of recurrence, n (%)	20 (16.81%)	33 (20.50%)	53 (18.93%)

Abbreviations: IDFS, invasive disease-free survival.

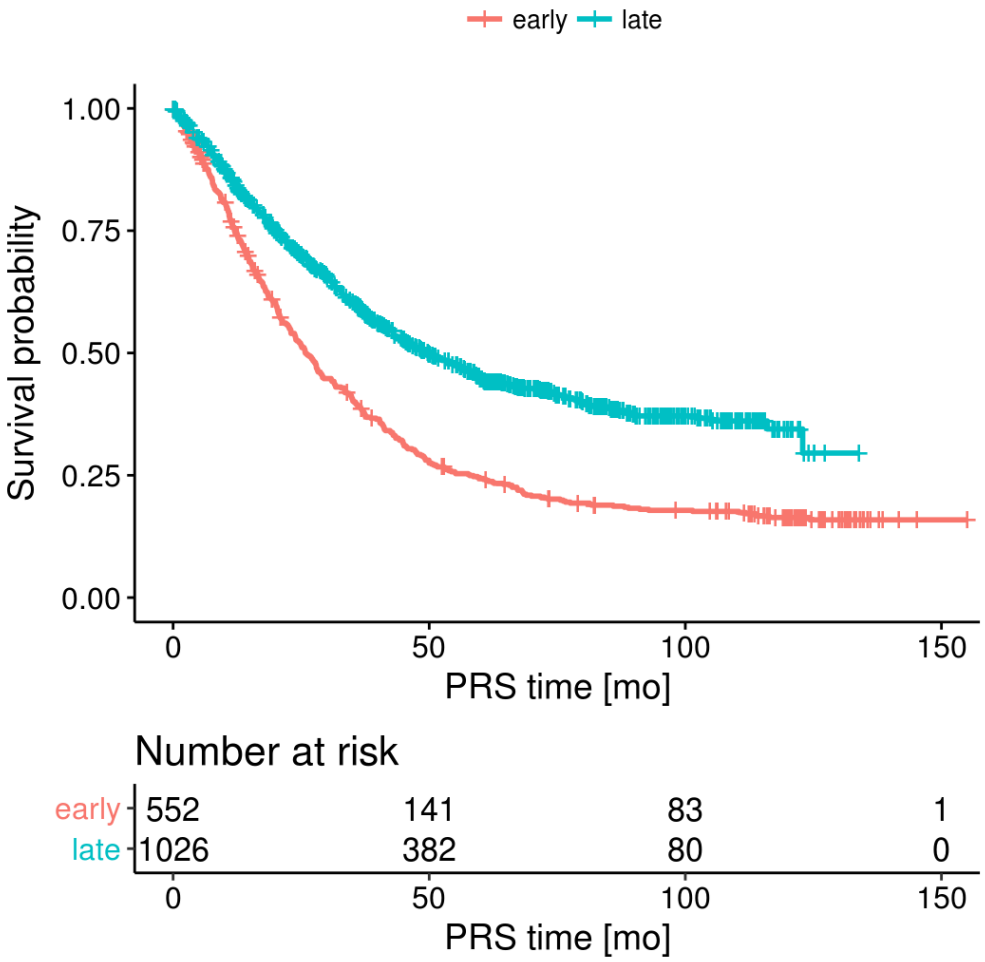
As reported in Table 23, of the IDFS events (excluding death) observed in the node-positive population of APHINITY, 81.07% were metastatic and 18.93% were non-metastatic. These proportions remained constant for the duration of the model time horizon.

Definition and modelling of disease recurrence

Incorporating the timing of relapse into the model was recommended by clinical experts. These experts explained that patients who relapse early tend to have more aggressive disease which does not respond well to treatment, and so are on later lines of therapy for a relatively short duration. However, patients who relapse later tend to have less aggressive disease which is more amenable to treatment, so are on later lines of treatment for a longer amount of time, therefore have much higher total treatment costs.[105] It was decided that early vs late relapses should be considered in the model because of the impact that the timing of relapse has on treatment outcomes and costs.

Figure 20 displays the survival of patients who experienced a disease recurrence in the HERA study. The “early” curve represents the survival of those patients who experienced a metastatic event within 18 months of adjuvant treatment initiation. The “late” curve represents the same information but for those patients who experienced a metastatic event after 18 months of adjuvant treatment initiation. There is a clear difference in post-progression survival between these two populations. Patients who progress on adjuvant therapy, or shortly after completion (within six months), clearly have a worse prognosis than those who progress after 18 months.

Figure 20. Post-progression survival of patients with disease recurrence in the HERA study ("early" vs "late" relapsers)

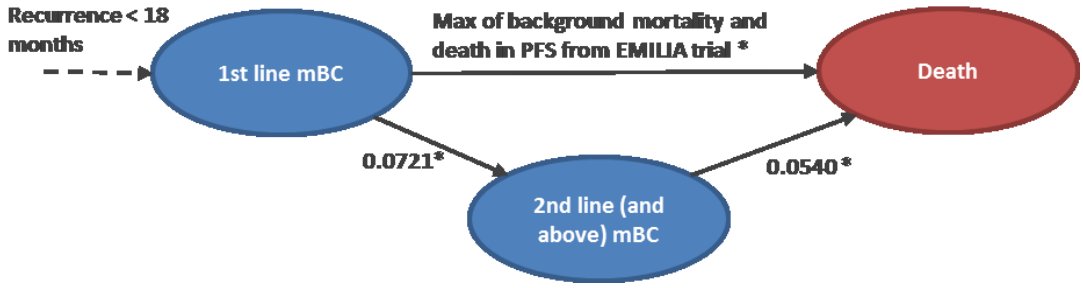


Abbreviations: PRS, post-recurrence survival.

In addition, patients in the UK may be eligible for differing treatments depending on when their disease progresses. For example, patients who experience a metastatic disease recurrence within 18 months of beginning adjuvant initiation ("early" relapsers) can be treated with trastuzumab emtansine (Kadcyla®▼).

In the model, it is assumed that every disease recurrence observed within 18 months after initiation of adjuvant therapy is a metastatic recurrence. These patients are expected to have a worse prognosis and will therefore receive a more aggressive treatment. Survival estimates derived from the EMILIA study (study of trastuzumab emtansine in second-line mBC)[111] are used to model the survival of patients who experience a metastatic recurrence within the first 18 months after adjuvant treatment initiation. In the EMILIA study, the corresponding population was selected to estimate the risk of disease progression (PFS) and the risk of death following progression. EQ-5D results from both treatment arms were pooled (i.e. analysed as a single treatment group) to generate more robust survival estimates (Figure 21).

Figure 21. Summary of monthly transition probability sources in the metastatic setting following early relapse (within 18 months)



Footnotes: *All data derived from the EMILIA study are based on the fast relapsers sub-population.

Non-metastatic recurrence pathway

Patients in the IDFS state can experience either a non-metastatic recurrence or a metastatic recurrence. The non-metastatic recurrence pathway consists of two health states: “Non-metastatic recurrence” and “Remission”. The transitions and associated probabilities to and from these states are described below.

Non-metastatic recurrence

Patients transition from the IDFS state to the non-metastatic recurrence health state based on the percentage observed in the APHINITY study (23.13%). The model assumes that all patients who experience a non-metastatic recurrence would undergo one year of additional adjuvant therapy. Following this treatment, all patients would then enter the remission health state. In this context, the non-metastatic recurrence health state acts as a “tunnel-state”. The assumption that all patients transition to remission following additional adjuvant therapy is perhaps not realistic. Roche acknowledges that, in reality, some patients may incur a metastasis during this 12-month treatment period. However, clinical experts consulted by Roche suggested that very few patients would progress or die during the first 12 months following a non-metastatic recurrence. Thus, this assumption is unlikely to significantly impact on the overall cost-effectiveness results.

Patients are also at risk of death during their year in the non-metastatic recurrence health state. This risk of death applied here is the superior value between the risk of dying without recurrence (as observed in the APHINITY study) and background mortality in the age-adjusted UK population. When background mortality is applied, the risk of breast cancer-related death is zero. This methodology is applied for the following transitions:

- IDFS to death
- Non-metastatic recurrence to death
- Remission to death

The number of deaths without disease recurrence in the APHINITY study is low. As a result, the general population mortality risk exceeds the risk of death (without recurrence) in the APHINITY study by the time the patients reach approximately 56 years of age (five years into the model time horizon).

Remission

Following the adjuvant therapy received during the non-metastatic recurrence state, patients who are still alive automatically transition to the remission state. When in remission, patients can either die or experience another recurrence.

Risk of death in the remission health state is assumed to be the same as in IDFS. Once background mortality exceeds this value, the patients observe the death risk of the age-adjusted UK population. This is the same methodology used for the transition to death from the IDFS state and the non-metastatic recurrence health state (see above).

A patient in remission will have already experienced a non-metastatic recurrence; this analysis assumes that any additional recurrence would be metastatic in nature. In other words, a patient would transition directly from the remission state to the metastatic – first-line mBC state. The probability of this transition has been sourced from a study by Hamilton *et al*.[112] This study included a cohort of 12,836 patients with eBC and reported the estimated risk of incurring a second malignancy following adjuvant therapy.

Recurrence rate from the remission health state was assumed to remain constant over time. Therefore, an exponential distribution was used to derive a constant transition probability. The Hamilton study reports a mean time until progression of 7.6 years (91.2 months);[112] this value was converted into a monthly transition probability of 0.00760 using Equation 1. There are several differences between the populations being evaluated in this analysis and the one in the Hamilton *et al*. publication, as described below.

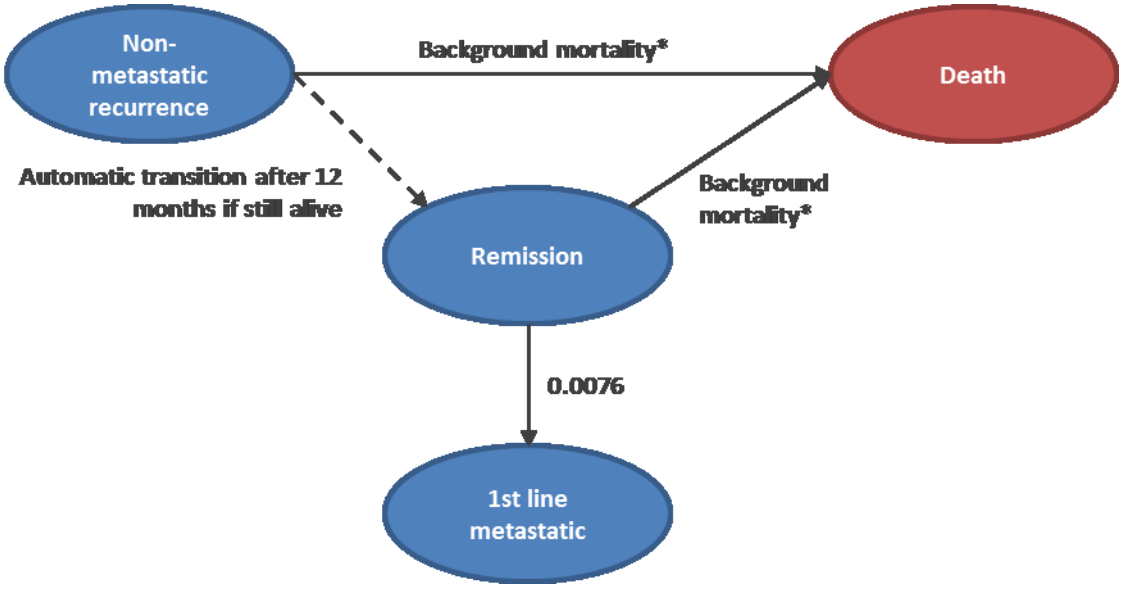
Equation 1: Calculation of remission to first line mBC transition probability

$$S(t) = e^{-\varphi t}$$

The population in the Hamilton *et al*. study was heterogeneous, as it included stage I/II female patients with BC (HER2-positive, negative or unknown status), ranging between 20 to 79 years of age, diagnosed between 1989 and 2005. Furthermore, all patients were treated with adjuvant chest-wall radiation and were from one institution in Canada. This concern was originally raised by the ERG in the appraisal of pertuzumab in the neoadjuvant setting. Nevertheless, the committee accepted the use of this source as it was believed to be the best available evidence at the time of writing, a fact which is also believed to be true here. This parameter was manipulated extensively during sensitivity analysis (please see Section B.3.8.3) as a result of the associated uncertainty.

Transition probabilities in the non-metastatic recurrence pathway are summarised in Figure 22.

Figure 22. Summary of monthly transition probability sources in the non-metastatic recurrence pathway



Footnotes: *This risk of death applied here is the superior value between the risk of dying without recurrence (as observed in APHINITY) and background mortality in the age-adjusted UK population. The number of deaths without disease recurrence in APHINITY is low. As a result, the general population mortality risk exceeds the risk of death (without recurrence) in APHINITY by the time the patients reach approximately 56 years old (5 years into the model time horizon).

Metastatic recurrence pathway

The metastatic recurrence pathway is comprised of two health states: i) 1L mBC treatment and ii) subsequent treatment lines for mBC (2L+ mBC).

1L mBC treatment

Patients can arrive in this health state from the IDFS or remission health states (see above). Once in this state, patients can either die or their metastatic recurrence can progress.

The risk of progression in the mBC setting has evolved substantially over the past five years. The advent of certain transformative therapies means that, on average, patients are remaining progression-free for longer than ever before. Consequently, it has been assumed that the patients in the mBC setting today would experience different progression rates than those seen in the APHINITY trial.

In the first line metastatic setting, three treatment regimens are available to patients in the UK: pertuzumab + trastuzumab + chemotherapy, trastuzumab + chemotherapy, and chemotherapy. The probability of metastatic progression has therefore been derived from available evidence relating to these treatment regimens.

- **Pertuzumab + trastuzumab + chemotherapy and trastuzumab + chemotherapy** – risk of disease progression derived from the CLEOPATRA trial data.[32]
- **Chemotherapy** – risk of disease progression derived from the M77001 trial.[113]

The rate of metastatic progression would be expected to vary over time. This would ordinarily warrant the use of time-dependent transition probabilities. However, one of the flaws of a Markov model is its “memoryless” feature. There is no easy way of tracking when a patient enters a health state or knowing how long they remain there for (unless they enter the model in said health state). This limitation makes the introduction of time-dependent transition probabilities in the 1L metastatic health state problematic. To avoid the use of time-dependent transition probabilities and thus a vastly more complex modelling approach, the Kaplan-Meier data from the trials above have been extrapolated using an exponential distribution. An exponential extrapolation assumes constant hazards over time and therefore produces transition probabilities that are independent of time.

The final transition probability associated with metastatic progression is a weighted average of the probabilities from the three possible metastatic treatment regimens (see Table 24). Treatment usage data presented in Table 24 has been taken from an interim analysis of the ESTHER study, a study of resource use in patients with advanced HER2-positive BC in the UK, due for publication in Q1 2018.

Table 24. Summary of monthly metastatic progression transition probabilities

Transition	Treatment regimen	Treatment usage	Monthly probability	Data source
First line mBC to 2+ line mBC	Pertuzumab + trastuzumab + chemotherapy	71.2%	0.03172	CLEOPATRA
	Trastuzumab + chemotherapy	22.9%	0.04696	CLEOPATRA
	Chemotherapy	5.9%	0.06936	M77001
	Metastatic prog.	**100%**	**0.03810**	**Weighted avg.**

Abbreviations: mBC, metastatic breast cancer.

The transition to death from the first-line mBC state is modelled using the number of deaths (without progression events) observed in the studies mentioned above. In practice, the general population mortality is higher because patients usually progress before dying from the disease. Therefore, background mortality is used as the transition probability once it exceeds the number of deaths (without progression events) observed in the trials.

Subsequent lines for mBC treatment

Following metastatic progression, only one further transition is possible (subsequent lines for mBC treatment to death). The risk of death in the 2L+ metastatic setting has been estimated according to the therapies a UK mBC patient can receive today (see above). Post-progression (post first-line) survival probabilities have been derived using the same methodology as the metastatic progression probabilities.

Pertuzumab + trastuzumab + chemotherapy and trastuzumab + chemotherapy – Post-progression survival probabilities have been derived from the CLEOPATRA trial data.

Chemotherapy – Post-progression survival probabilities have been derived from the M77001 trial.

Once again, the Kaplan-Meier data from these trials have been extrapolated using an exponential distribution to circumvent the use of complex time-dependent transition probabilities. Similarly, to the metastatic progression probability, this value is also an average weighted by the treatment usage percentages seen in Table 24.

As shown by the figures reported in Table 25, the average progression-free (1L mBC) and post-progression (2L+ mBC) survival predicted by the exponential extrapolations are similar to the estimates seen in the CLEOPATRA and M77001 trials.

Table 25. Metastatic recurrence pathway – Comparison of Kaplan Meier and extrapolated (exponential) estimates

Transition	Kaplan-Meier estimates (months)	Exponential (months)	Data source
PFS – pertuzumab	28.0	28.4	CLEOPATRA
PFS – trastuzumab	20.8	21.1	CLEOPATRA
PFS – chemotherapy	14.9	15.6	M77001
PPS – pertuzumab	29.9	30.7	CLEOPATRA
PPS – trastuzumab	19.4	18.6	CLEOPATRA
PPS – chemotherapy	13.9	15.3	M77001

Abbreviations: PFS, progression-free survival; PPS, post-progression survival.

In reality, the treatment option chosen in the second line mBC setting would impact on a patient's survival (i.e. patients receiving trastuzumab emtansine could expect greater survival than patients receiving lapatinib + capecitabine, according to results of the EMILIA study). The following rationale justifies why the analysis described here does not account for the survival impact imposed by treatment choi ce in the 2L mBC setting.

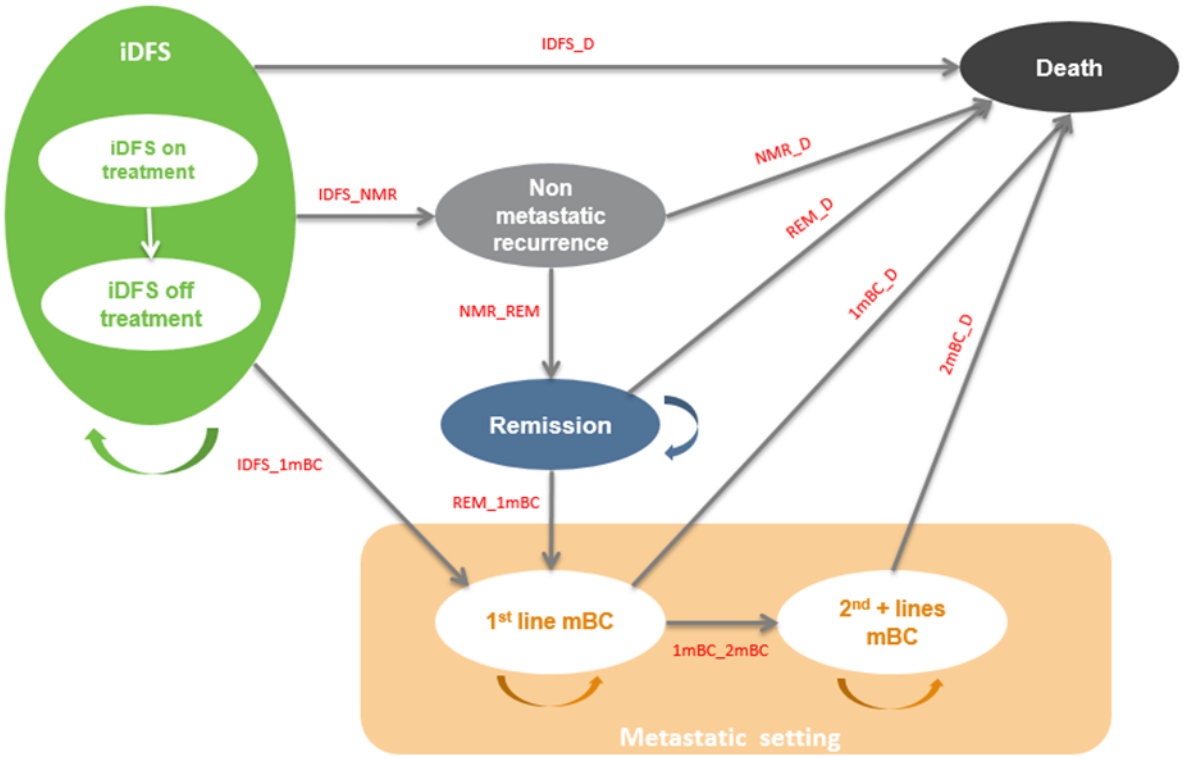
- **First-line treatment choice has a greater impact on OS than second-line treatment choice –** Receiving pertuzumab + trastuzumab + chemotherapy as opposed to trastuzumab + chemotherapy in first-line mBC offers a 15.7-month OS benefit, whereas trastuzumab emtansine instead of lapatinib + capecitabine in the second-line mBC setting provides a OS benefit of five months.
- **Data limitations –** No data are currently available on the sequential use of pertuzumab + trastuzumab + chemotherapy and trastuzumab emtansine in mBC. To reduce the uncertainty, second-line options impact only costs and not survival.

Because of these limitations, it was preferred to derive survival data in mBC for pertuzumab and trastuzumab from a single trial. Using a single data source helped to avoid various issues with population comparability across trials.

Summary of transition probabilities

Figure 23 displays an updated model diagram which includes labels of the various possible transitions. Table 26 lists these transitions along with their values, sources, and the subsection in which they are fully described.

Figure 23. Summary of transition probabilities



Abbreviations: BC, breast cancer; iDFS, invasive disease-free survival; mBC, metastatic breast cancer. Transition probabilities defined in Table 26.

Table 26. Summary of transition probabilities (node-positive population)

Starting state	Destination state	Transition name	Value	Source	Subsection
IDFS	Non-metastatic recurrence	IDFS_NMR	Adjusted Exponential extrapolation	APHINITY	B.3.3.1
	Metastatic recurrence	IDFS_1mBC	Adjusted Exponential extrapolation	APHINITY	
	Death	IDFS_D	Maximum of BGM or IDFS death rate	UK life tables, APHINITY	
Non-metastatic recurrence	Remission	NMR_REM	1.00	Assumption	B.3.3.2
	Death	NMR_D	Max of BGM or IDFS death rate	UK life tables, APHINITY	
Remission	First-line mBC	REM_1mBC	0.0076	Hamilton *et al.*	B.3.3.2
	Death	REM_D	Max of BGM or IDFS death rate	UK life tables, APHINITY	
First-line mBC	2nd + line mBC	1mBC_2mBC	Pertuzumab + trastuzumab + chemotherapy = 0.032 Trastuzumab + chemotherapy = 0.047 Chemotherapy = 0.069	CLEOPATRA or M77001	B.3.3.2
	Death	1mBC_D	Max of BGM or PFS in relevant trial	UK life tables, CLEOPATRA, or M77001	
Second+ line mBC	Death	2mBC_D	Pertuzumab + trastuzumab + chemotherapy = 0.027 Trastuzumab + chemotherapy = 0.032 Chemotherapy = 0.060	CLEOPATRA or M77001	B.3.3.2

Abbreviations: BGM, background mortality; IDFS, invasive disease-free survival; mBC, metastatic breast cancer; PFS, progression-free survival

B.3.3.3 Treatment duration

In the APHINITY study, patients were expected to receive treatment for a maximum of 18 cycles. It was possible for treatment to be discontinued because of unacceptable toxicity or disease progression. Treatment duration in the model was derived from time-to-off-treatment (TTOT) data observed in the APHINITY trial.

In the APHINITY study, most patients in the node-positive population (84.4% in the pertuzumab + trastuzumab + chemotherapy arm and 86.7% in the placebo + trastuzumab + chemotherapy arm) completed the full therapy regimen, as per the study protocol (i.e. they did not discontinue due to toxicity or progression – Table 27). Therefore, the APHINITY study can be seen as an accurate and mature data source for treatment duration. Consequently, extrapolation beyond the observation period was not required.

Table 27. Treatment discontinuation in the APHINITY study node-positive population

	Pertuzumab + trastuzumab + chemotherapy (n=1,503)	**Placebo + trastuzumab + chemotherapy (n=1,502)**
Completed treatment, n (%)	1,269 (84.4)	1,302 (86.7)
Discontinued treatment, n (%)	234 (15.6)	200 (13.3)
Safety, n (%)	120 (8.0)	102 (6.8)
Adverse events	113 (7.5)	98 (6.5)
Death	6 (0.4)	4 (0.3)
Pregnancy	1 (<0.1)	0 (0.0)

The model incorporates two options for modelling treatment duration. The first option, and Roche's base case, is the actual treatment duration as seen in the APHINITY study. When this option is selected, the treatment duration is calculated by using the actual proportion of patients that receive the drug at each treatment cycle in the APHINITY study.

The second option allows treatment duration to be modelled as per the APHINITY protocol or the SmPC label. This option essentially sets TTOT equal to IDFS until the maximum of 18 treatment cycles have elapsed. When treatment duration is modelled using this option, it is assumed that patients only discontinue treatment due to progression. In other words, discontinuations due to toxicity are assumed not to occur. This assumption is obviously clinically implausible and therefore this option is only included as part of the scenario analyses.

B.3.4 *Measurement and valuation of health effects*

B.3.4.1 HRQoL data from clinical trials

Patients in the APHINITY trial reported HRQoL, eBC symptoms and health status using the EORTC QLQ-C30, EORTC QLQ-BR23 and EQ-5D-3L.

EORTC QLQ-C30 and EORTC QLQ-BR23

The EORTC QLQ-C30 is a 30-item questionnaire which includes five functional scales (physical, role, emotional, cognitive and social), three symptom scales (fatigue, nausea & vomiting and pain) and a global health status/QoL scale. Furthermore, it contains six single items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties).[114] The EORTC QLQ-BR23 is a breast-specific supplementary to the EORTC QLQ-C30 that comprises 23 questions to assess body image, sexual functioning, sexual enjoyment, future perspective, systemic therapy side effects, breast symptoms, arm symptoms and being upset by hair loss.[115]

Both the EORTC QLQ-C30 and the BR23 supplement were completed at the following timepoints of the APHINITY study: baseline, end of the anthracycline treatment period, week 13, week 25, end of study treatment, and 18 months, 24 months and 36 months after randomisation.

Given that EQ-5D-3L measurements were also taken during the trial, it was decided that the EORTC data would not be incorporated into the cost-effectiveness analysis.

EQ-5D-3L

Patients provided data on eBC symptoms and functioning using the EQ-5D-3L. The EQ-5D-3L was administered on the same schedule as the EORTC QLQ-C30 and the BR23 supplement. Responses were collected at: baseline, end of the anthracycline treatment period, week 13, week 25, end of study treatment, and 18 months, 24 months and 36 months after randomisation.

The EQ-5D is NICE's preferred instrument for the measurement of HRQoL in adults. This data was therefore used to derive the health state utility values (HSUVs) in the cost-effectiveness analysis. This methodology is consistent with the guidance given in the NICE Reference Case.[104]

B.3.4.2 Mapping

According to the NICE reference case, EQ-5D is the preferred measure of HRQoL in adults.[104] Given that EQ-5D data were collected during the pivotal APHINITY study, no mapping techniques were required.

B.3.4.3 HRQoL studies

An SLR was conducted to identify HRQoL evidence in patients treated adjuvantly for HER2-positive eBC. Detailed descriptions of the search strategy and extraction methods are provided in Appendix H.

Summary of identified studies and results

The SLR identified a total of 21 studies, all reporting HRQoL data; no studies were identified that reported utility values that could directly inform the cost-effectiveness model. Given this, and the availability of EQ-5D data from the APHINITY trial to directly inform model utilities for eBC health states, none of the HRQoL studies identified by the SLR were considered further for the submission. A summary of the 21 identified HRQoL studies is provided in Appendix H.

B.3.4.4 Adverse reactions[75]

Almost all patients experienced at least one AE during the treatment period (99.9% of patients in the pertuzumab arm vs 99.5% of patients in the placebo arm) in the APHINITY study. More than 90% of the AEs in both treatment arms were Grade 1 or 2 in severity.

The most frequently reported AEs (occurring in ≥30% of patients in either arm) were as follows: (expressed in the pertuzumab vs placebo arm): diarrhoea (71.2% vs 45.2%), nausea (69.0% vs 65.5%), alopecia (66.7% vs 66.9%), fatigue (48.8% vs 44.3%), vomiting (32.5% vs 30.5%), arthralgia (28.7% vs 32.5%) and constipation (28.9% vs 31.6%). The incidence of most of the common AEs was similar between treatment arms except for diarrhoea, nausea and fatigue, which were higher in the pertuzumab arm, and arthralgia, which was higher in the placebo arm.

Adverse event data used in the model were taken directly from the APHINITY study. There were two approaches that could have been adopted when quantifying AE impacts on HRQoL:

- **"Double-counting"** – Any disutility resulting from AEs will have been captured in the trial-collected HRQoL data. These data were used to derive the health state utilities in the base case economic analysis. It can therefore be assumed that incorporating an additional disutility can be considered double-counting.
- **Underestimation** – It can be assumed that trial derived utilities typically underestimate disutility associated with AEs. It is therefore reasonable to apply an additional disutility in the model.

In this analysis, it is assumed that any disutility resulting from treatment-related AEs is reflected in the EQ-5D responses from the APHINITY study. It is possible that this approach underestimates the disutility associated with the AEs. Despite this, the incremental difference between treatment arms is thought to be negligible. Ultimately, this omission is not expected to significantly impact the overall cost-effectiveness results.

B.3.4.5 HRQoL data used in the cost-effectiveness analysis

Utility has been applied cyclically in the model. The differing levels of utility across health states meant that HRQoL is not assumed constant over time. The section below outlines the utility sources used both in the base case setting and in the accompanying scenario analyses.

Base case analysis

In the base case analysis, model health states have been categorised into "eBC" and "mBC" states. Table 28 shows the classification of health states. A different combination of data sources has been used to derive utilities for the eBC and mBC groups.

Table 28. Classification of eBC and mBC health states

eBC	mBC
• IDFS • Non-metastatic recurrence • Remission	• 1st line mBC • ≥2nd line mBC

Abbreviations: eBC, early breast cancer; IDFS, invasive disease-free survival; mBC, metastatic breast cancer.

eBC health state utilities

In accordance with the NICE reference case, utility estimates in the IDFS health state were derived from EQ-5D responses of the node-positive population in the APHINITY study. Values for the non-metastatic recurrence and remission health states are predicated on assumptions, which are fully explained below.

No statistically significant difference was found in the EQ-5D results of the two treatment arms in the APHINITY study. This was because the schedule of EQ-5D administration was designed to capture differences in QoL across the various stages of disease, not between treatment arms. The lack of a statistically significant difference meant that EQ-5D responses from both treatment arms could be pooled. Pooling the responses increased the number of observations and consequently produced more robust utility estimates. These estimates were then applied across both arms of the model, regardless of whether a patient initially received pertuzumab or placebo. For the sake of completeness, cost-effectiveness results have also been generated using utilities derived from the treatment-specific EQ-5D responses. This analysis is described in greater detail below and the results are available in Section B.3.8.3 of this submission.

Treatment-related AEs mean that QoL can be expected to vary depending on whether or not a patient is receiving treatment. The differing side-effect profiles of anti-HER2 treatments and chemotherapy can also impact on a patients HRQoL. To account for these differences, the IDFS health state has been stratified as follows:

- **IDFS – On chemotherapy**
- **IDFS – On treatment/off chemotherapy**
- **IDFS – Off treatment**

The EQ-5D questionnaire was not administered to patients who had progressed in the APHINITY study. As a result, no EQ-5D data were available to derive utility estimates for the non-metastatic recurrence and remission health states. In the base case analysis, non-metastatic recurrence and remission utilities were assumed equal to “IDFS – on chemotherapy” and “IDFS – off treatment”, respectively. Similar equivalencies were also assumed in the neoadjuvant pertuzumab appraisal.[67] These assumptions have been examined during the sensitivity/scenario analysis process. Results of these analyses are available in Section B.3.8.3.

The base case utilities for the eBC health states are reported in Table 34.

mBC health state utilities

As mentioned above, EQ-5D was not administered to patients who had progressed in the APHINITY study. It was therefore not possible to use APHINITY-derived utility estimates for the mBC health states in the model. Base case utilities in the mBC health states have therefore been taken from a publication by Lloyd *et al*.[116]

Lloyd *et al.* report the results of 100 participants asked to value various health states and side-effects associated with mBC using the Standard Gamble technique. An overall value for PFS 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 various NICE Technology Appraisals in mBC.[117]

The utilities used in the base case analysis for both the early and metastatic health states are reported in Table 34.

Scenario analyses

Health state utility estimates in patients with HER2-positive BC are available from a range of published sources. To present a more complete evaluation, utilities from these sources have also been included here as scenario analyses. A brief description of these sources is given below, along with an overview of how the estimates were incorporated into the model.

eBC – the APHINITY study EQ-5D (per treatment arm)

Pooled EQ-5D data were used to derive eBC utilities in the base case analysis. As mentioned above, no statistically significant difference was detected between the EQ-5D results of the two treatment arms. Nevertheless, a scenario analysis using treatment-specific EQ-5D data is included for completeness. The utility estimates used in this scenario are reported in Table 34.

eBC – Hedden *et al.*[118]

The publication by Hedden *et al.* is a cost-effectiveness analysis of the real-world effectiveness of adjuvant trastuzumab in Canada. The analysis centres on a HER2-positive population. This population is broadly in line with the population being evaluated in this appraisal. No estimates were reported according to lymph node involvement or hormone receptor status.

Health states in the Hedden *et al.* model differ slightly from the *de novo* analysis in this submission. Despite the differences, the health state definitions between the two analyses were deemed similar enough not to require any further adjustment of the utilities. Table 29 illustrates how the Hedden values have been applied in this analysis.

Table 29. eBC health state utilities used in the Hedden *et al.* analysis and *de novo* analysis[118]

Health state in *de novo* analysis	Health state in Hedden *et al.*	Utility reported
IDFS – On chemotherapy	Post-surgical with adjuvant treatment	0.970
IDFS – On treatment/off chemotherapy	Post-surgical with adjuvant treatment	0.970
IDFS – Off treatment	Relapse-free survival	0.990
Locoregional recurrence	Local relapse	0.750
Remission	Relapse-free survival	0.990

Abbreviations: IDFS, invasive disease-free survival.

eBC – Lidgren *et al.*[45]

The aim of this study was to describe HRQoL in different BC disease states using preference-based measures. A total of 361 consecutive patients with BC attending the BC outpatient clinic at Karolinska University Hospital, Solna, Sweden for outpatient visits between April and May 2005

were included in the study. The EQ-5D self-classifier and a direct TTO question were used to estimate the HRQoL in different BC disease states.

The resultant EQ-5D values from this study are reported below, along with how they were assigned to the health states used in this analysis. Once again, no further adjustment was deemed necessary.

Table 30. eBC health state utilities used in the Lidgren *et al*. analysis and *de novo* analysis[45]

Health state in *de novo* analysis	Health state in Lidgren *et al.*	Utility reported
IDFS – On chemotherapy	First year after primary breast cancer	0.696
IDFS – On treatment/off chemotherapy	First year after primary breast cancer	0.696
IDFS – Off treatment	Second and following years after primary breast cancer/recurrence	0.779
Locoregional recurrence	Second and following years after primary breast cancer/recurrence	0.779
Remission	Second and following years after primary breast cancer / recurrence	0.779

Abbreviations: IDFS, invasive disease-free survival.

mBC – Hedden *et al.*[118]

The Hedden *et al.* publication (cited above) also includes utility estimates for metastatic health states. As can be seen in Table 31, the mBC health states included here and in the Hedden *et al.* publication are almost equivalent.

Table 31. mBC health state utilities used in the Hedden *et al.* analysis and *de novo* analysis[118]

Health state in *de novo* analysis	Health state in Hedden *et al.*	Utility reported
First-line mBC	Non-progressive metastatic disease with or without trastuzumab	0.650
Second+ line mBC	Progressive metastatic disease	0.290

Abbreviations: mBC, metastatic breast cancer.

mBC – Lidgren *et al.*[45]

Much like the Hedden publication, the Lidgren study also reported utilities in both the eBC and mBC setting – see Table 32.

A single value has been reported for metastatic disease. In essence, the Lidgren study does not distinguish between first and second-line (non-progressed/progressed) metastatic disease. When this source is selected during scenario analysis, the utility associated with 2+ line mBC is assumed equal to the utility associated with first-line mBC.

Table 32. mBC health state utilities used in the Lidgren *et al.* analysis and *de novo* analysis[45]

Health state in *de novo* analysis	Health state in Lidgren *et al.*	Utility reported
First-line mBC	Metastatic disease	0.650
Second+ line mBC		0.290

Abbreviations: mBC, metastatic breast cancer.

mBC – Paracha *et al.*[119]

This study analysed data from a large (n=906), repeated measure (11,451 observations), EQ-5D-3L dataset from the MARIANNE trial to estimate HSUVs. Patient responses to the EQ-5D-3L were used to derive utility values using the UK tariff. At the time of the analysis, 336 patients had experienced disease progression; whereas 354 deaths were observed in the trial. Two mixed models (random-coefficient) using an unstructured covariance structure were fitted to predict utility values according to baseline patient characteristics and key clinical outcomes. Time was included as a random effect. Key sets of variables considered for the multivariable mixed regression models were included. Table 33 reports the utilities quoted in this study and how they are applied to the health states in this analysis.

Table 33. mBC health state utilities used in the Paracha *et al.* analysis and *de novo* analysis[119]

Health state in *de novo* analysis	Health state in Paracha *et al.*	Utility reported
First-line mBC	mBC - Stable disease with no toxicity	0.806
Second-line mBC	mBC progression	0.536

Abbreviations: mBC, metastatic breast cancer.

Age adjustment

As the population ages, HRQoL and utility are expected to decline because of an increased number of comorbidities. To reflect this trend, all health state utilities (base case and scenario analyses) have been adjusted over the time horizon to reflect the modelled patient's age. This adjustment prevents the health state utilities exceeding those of the age-matched UK population. The data used to perform this adjustment was taken from Ara *et al.*[120] Table 34 shows how the utilities have been assigned in the respective health state in the model.

Table 34. Summary of utility values used in the cost-effectiveness analysis

State	Utility (SE)	95% CI	Source	Reference in submission	Justification
Health state utilities – base case					
IDFS - On chemotherapy	0.756 (0.004)	N/A	EQ-5D from APHINITY (pooled)[75]	Section B.3.4.5	Derived from APHINITY EQ-5D data. In-line with NICE reference case
IDFS - On treatment/off chemotherapy	0.785 (0.004)	N/A			
IDFS - Off treatment	0.822 (0.004)	N/A			
Locoregional recurrence	0.756 (0.004)	N/A	Assumption		
Remission	0.822 (0.004)	N/A			
First-line mBC	0.773 (0.004)	N/A	Lloyd *et al.*[116]		Well-established source of utilities. Used in previous TAs in this disease area
Second+ line mBC	0.520 (0.004)	N/A			
eBC health state utilities – Scenario analysis					
IDFS - On chemotherapy	PH+C = 0.763 H+C = 0.750	N/A	EQ-5D from APHINITY (per treatment arm)[75]	Section B.3.4.5	Utilities derived from APHINITY EQ-5D data. In-line with NICE reference case
IDFS - On treatment/off chemotherapy	PH+C = 0.787 H+C = 0.784	N/A			
IDFS - Off treatment	PH+C = 0.827 H+C = 0.817	N/A			
Locoregional recurrence	PH+C = 0.763 H+C = 0.750	N/A	Assumption		
Remission	PH+C = 0.827 H+C = 0.817	N/A			
eBC health state utilities – Scenario analysis					
IDFS - On chemo	0.97 (0.026)	0.94-0.99	Hedden *et al.*[118]	Section B.3.4.5	Well-established source of utilities. Used in previous TAs in this disease area
IDFS - On treatment/off chemotherapy	0.97 (0.026)	0.94-0.99			
IDFS - Off treatment	0.99 (0.010)	0.98-1.00			
Locoregional recurrence	0.75 (0.194)	0.56-0.94			
Remission	0.99 (0.010)	0.98-1.00			
eBC health state utilities – Scenario analysis					
IDFS - On chemo	0.696	0.63-0.75	Lidgren *et al.*[45]	Section B.3.4.5	Well-established

State	Utility (SE)	95% CI	Source	Reference in submission	Justification
IDFS - On treatment/off chemotherapy	0.696	0.63-0.75			source of utilities. Used in previous TAs in this disease area
IDFS - Off treatment	0.779	0.75-0.81			
Locoregional recurrence	0.779	0.75-0.81			
Remission	0.779	0.75-0.81			
mBC health state utilities – Scenario analysis					
First-line mBC	0.65	0.50-0.80	Hedden *et al.*[118]	Section B.3.4.5	Well-established source of utilities. Used in previous TAs in this disease area
Second+ line mBC	0.29	0.16-0.41			
mBC health state utilities – Scenario analysis					
First-line mBC	0.685	0.620-0.735	Lidgren *et al.*[45]	Section B.3.4.5	Well-established source of utilities. Used in previous TAs in this disease area
Second+ line mBC	0.685	0.620-0.735			
mBC health state utilities – Scenario analysis					
First-line mBC	0.806	0.645-0.967	Paracha *et al.*[119]	Section B.3.4.5	Well-established source of utilities. Used in previous TAs in this disease area
Second+ line mBC	0.536	0.423-0.643			

Abbreviations: CI, confidence interval; eBC, early breast cancer; EQ-5D, EuroQol 5-Dimension questionnaire; H+C, trastuzumab + chemotherapy; IDFS, invasive disease-free survival; mBC, metastatic breast cancer; NICE, National Institute for Health and Care Excellence; PH+C, pertuzumab + trastuzumab + chemotherapy; SE, standard error; TA, Technology Assessment.

B.3.5 *Cost and healthcare resource use identification, measurement and valuation*

B.3.5.1 Intervention and comparators' costs and resource use

Drug acquisition costs – Intervention and comparator

Pertuzumab

Pertuzumab is available as a 420 mg vial at a list price of £2,395.00. The recommended initial loading dose of pertuzumab is 840 mg administered as a 60-minute IV infusion, followed q3w thereafter by a maintenance dose of 420 mg administered over a period of 30 to 60 minutes.

Pertuzumab, [redacted] is subject to a confidential commercial access agreement (CAA) between Roche Products Ltd. and NHS England. Pertuzumab (list price = £2,395.00) is offered at a discount of [redacted].

Trastuzumab

Three different forms of trastuzumab are included in the economic analysis:

- Trastuzumab IV: branded trastuzumab (Herceptin) administered as an IV infusion
- Trastuzumab SC: branded trastuzumab (Herceptin) administered as an SC injection
- Trastuzumab Biosimilar: trastuzumab biosimilar administered as an IV infusion

Trastuzumab IV

The list price of trastuzumab IV is £407.40 for a 150 mg vial. The recommended initial loading dose of trastuzumab is 8 mg/kg, followed every three weeks thereafter by a maintenance dose of 6 mg/kg body weight.

Trastuzumab SC

Trastuzumab SC is available as a 600 mg vial for a list price of £1,222.20. The SC form of trastuzumab is given as a fixed dose of 600 mg, no loading dose is necessary.

[redacted]

Trastuzumab biosimilar

Trastuzumab biosimilars are expected to become available in the UK in the near future.[121] The biosimilars will be administered intravenously. It has therefore been assumed that the dosing and treatment schedule will be equal to that of trastuzumab IV (see above).

The UK list price and market share of trastuzumab biosimilars are unknown at the time of writing. This submission contains economic results in which both of these parameters are varied. It should be noted, however, that the base case settings of this analysis reflect the current UK

market at the time of submission (February 2018) i.e. trastuzumab biosimilars will not have yet entered the UK market and their market share is therefore set to 0%.

The assumptions surrounding biosimilar usage have the potential to significantly impact overall cost-effectiveness, therefore this aspect of the submission is discussed in more detail in Section B.3.7.2.

Trastuzumab usage in the cost-effectiveness model

The form of trastuzumab used in each arm of the model is dependent on both licensing and UK market shares.

Pertuzumab is not licensed for use in combination with trastuzumab SC. As a result, the entirety of trastuzumab received in combination with pertuzumab is assumed to be trastuzumab IV. The comparator arm of the model includes both SC and IV forms of trastuzumab. The proportion of patients who receive trastuzumab intravenously and subcutaneously is dependent upon UK market shares. These proportions have been ascertained through market intelligence research conducted by Roche.[122] As previously stated, trastuzumab biosimilars are assumed to have not yet entered the UK market in the base case analysis, hence usage in the model is set to 0% in both arms.

The trastuzumab usage assumed in both arms of the economic model are reported below in Table 35.

Table 35. Trastuzumab usage in the base case setting of the economic model

Treatment arm	Form of trastuzumab	Proportion of patients	Reference
Intervention	Trastuzumab IV	100%	Pertuzumab license
Comparator	Trastuzumab IV	[redacted]	Market research[122]
	Trastuzumab SC	[redacted]	

Abbreviations: IV, intravenous; SC, subcutaneous.

Chemotherapy

During the APHINITY study, patients could receive either “sequential chemotherapy” (four cycles of anthracycline chemotherapy followed by taxane in combination with targeted treatment), or “concurrent chemotherapy” (docetaxel plus carboplatin in combination with targeted treatment). This set-up was mirrored in the economic analysis as it is believed to be representative of UK clinical practice. Please see Section B.2.3.1 for further details on the chemotherapy regimens in the APHINITY study.

List prices of chemotherapy medications are given below in Table 36. Two vial sizes have been included in the model to account for optimised dosing and costs per cycle, i.e. minimise wastage. The vial sizes included in the economic analysis were those that have been most frequently used in UK practice from June 2016 to June 2017. Medication list prices and the quantities sold were taken from the drugs and pharmaceutical electronic market information tool (eMIT).

Table 36. Chemotherapy acquisition costs

Drug	Concentration	Quantity used	List price	Source
5-fluorouracil	2,500 mg/50 ml	31,697	£2.06	CMU eMIT - NPS: DHA102
	5,000 mg/100 ml	25,287	£3.12	CMU eMIT - NPS: DHA137
Epirubicin	10 mg/5 ml	6,208	£2.57	CMU eMIT - NPS: DHA084
	50 mg/25 ml	23,762	£5.62	CMU eMIT - NPS: DHA086
Cyclophosphamide	500 mg	4,316	£8.62	CMU eMIT - NPS: DHA016
	1,000 mg	27,906	£15.89	CMU eMIT - NPS: DHA014
Doxorubicin	10 mg/5 ml	10,776	£1.34	CMU eMIT - NPS: DHB015
	50 mg/25 ml	36,439	£3.63	CMU eMIT - NPS: DHB010
Docetaxel	20 mg/1 ml	28,367	£3.85	CMU eMIT - NPS: DHC025
	80 mg/4 ml	44,259	£14.74	CMU eMIT - NPS: DHC029
Carboplatin	150 mg/15 ml	28,300	£6.35	CMU eMIT - NPS: DHE001
	450 mg/45 ml	38,286	£18.73	CMU eMIT - NPS: DHE002
Paclitaxel	30 mg/5 ml	27,320	£3.44	CMU eMIT - NPS: DHA144
	100 mg/16.7 ml	46,299	£9.85	CMU eMIT - NPS: DHA145

Abbreviations: CMU, Commercial Medicines Unit; eMIT, electronic market information tool; mg, milligram; ml, millilitre.

The included chemotherapy regimens and the proportion of patients who received them are outlined in Table 37. These regimens and proportions were taken directly from the APHINITY study and were applied equally across both treatment arms in the model. Please note, the split across taxanes was not captured in the anthracycline regimens in the APHINITY study. All anthracycline-based regimens were assumed to include docetaxel, as opposed to paclitaxel.

Table 37. Chemotherapy regimens and usage (node-positive patient population in the APHINITY study)

	Chemotherapy regimen	Proportion of patients (%)	Duration of treatment (cycles)
Anthracycline-based chemotherapy	FEC → docetaxel	35.10%	8
	FAC → docetaxel	1.30%	8
	EC → docetaxel	21.30%	8

	AC → docetaxel	23.90%	8
	TOTAL	**81.60%**	-
Non-anthracycline-based chemotherapy	Paclitaxel + carboplatin	18.40%	6
	TOTAL	**18.40%**	-

Abbreviations: AC, doxorubicin and cyclophosphamide; EC, epirubicin and cyclophosphamide; FAC, 5-fluorouracil, doxorubicin and cyclophosphamide; FEC, 5-fluorouracil, epirubicin and cyclophosphamide.

Drug acquisition costs – Subsequent treatments

Upon experiencing a recurrence, patients are assumed to receive additional treatment. A variety of different therapies are available to UK patients, and which treatment they receive depends on the disease setting (i.e. non-metastatic recurrence, first-line mBC, or second + line mBC).

The acquisition costs of subsequent therapies included in the model are detailed below in Table 38. As mentioned above, pertuzumab, [redacted]. Roche also offers a CAA on trastuzumab emtansine, which equates to a [redacted] discount on list price.

Table 38. Drug acquisition costs (subsequent treatments)

Drug	Concentration/amount	Cost per pack/vial	Source
Pertuzumab – mBC	420 mg/14 ml	[redacted]	BNF – 2017
Trastuzumab IV	150 mg	[redacted]	BNF – 2017
Trastuzumab SC	600 mg / 5 ml	[redacted]	BNF – 2017
Trastuzumab emtansine	100 mg	[redacted]	BNF – 2017
	160 mg	[redacted]	
Docetaxel	20 mg/1 ml	£3.85	eMIT
	80 mg/4 ml	£14.74	
Paclitaxel	30 mg/5 ml	£3.44	eMIT
	100 mg/16.7 ml	£9.85	
Lapatinib	250 mg (105 tablets)	£1,206.45	BNF – 2017
Capecitabine	150 mg (60 tablets)	£10.40	BNF – 2017

Abbreviations: BNF, British National Formulary; eMIT, electronic market information tool; IV, intravenous; mBC, metastatic breast cancer; mg, milligram; ml, millilitre; SC, subcutaneous.

The total costs of these subsequent lines of treatment are calculated as a weighted average based on current market shares in the UK. Table 39 details the market shares, and the average treatment duration in each health state. The quoted market shares have been primarily ascertained through internal market research conducted by Roche Products Ltd. In situations where market share data were not available, assumptions have been utilised. In terms of the duration of treatment data, these have been primarily taken from economic models in previous NICE appraisals.

Please note that Table 39 details subsequent treatment regimens in the base case setting. Therefore, biosimilar market share is assumed to be zero and is not included here.

Table 39. Subsequent therapy treatment durations and market shares

Health state	Treatment regimen	# cycles	Source	Market share	Source
Non-metastatic recurrence	Trastuzumab IV + docetaxel	18	Assumption	[redacted]	Market research
	Trastuzumab SC + docetaxel	18	Assumption	[redacted]	NHSE
First-line mBC – Early recurrence	Trastuzumab IV + docetaxel	23.65	ID523 – P in mBC	[redacted]	Market research
	Trastuzumab SC + docetaxel	23.65	ID523 – P in mBC	[redacted]	
	Trastuzumab emtansine	19.3	Assumed equal to TA371 – K in 2L mBC	[redacted]	
First-line mBC	Trastuzumab IV + docetaxel	23.65	ID523 – P in mBC	[redacted]	Market research
	Pertuzumab + trastuzumab IV + docetaxel	37.39	ID523 – P in mBC	[redacted]	
	Trastuzumab SC + docetaxel	23.65	ID523 – P in mBC	[redacted]	
	Chemotherapy	6.00	Assumption	[redacted]	Assumption
Second + line mBC – Early recurrence	Trastuzumab IV + capecitabine	9.36	TA371 – K in 2L mBC	[redacted]	Market research
	Trastuzumab SC + capecitabine	9.36	TA371 – K in 2L mBC	[redacted]	
	Trastuzumab emtansine	19.33	TA371 – K in 2L mBC	[redacted]	
	Chemotherapy	6.00	Assumption	[redacted]	Assumption
Second + line mBC	Trastuzumab IV + capecitabine	9.36	TA371 – K in 2L mBC	[redacted]	Market research
	Trastuzumab SC + capecitabine	9.36	TA371 – K in 2L mBC	[redacted]	
	Trastuzumab emtansine	19.33	TA371 – K in 2L mBC	[redacted]	
	Lapatinib + capecitabine	12.29	TA371 – K in 2L mBC	[redacted]	

Abbreviations: IV, intravenous; K, trastuzumab emtansine; mBC, metastatic breast cancer; NHSE, National Health Service England; P, pertuzumab; SC, subcutaneous.

Administration and Pharmacy costs

Administration costs associated with each technology have been sourced using the National Tariff for Chemotherapy Regimens list 2017–2018, the NHS reference costs schedule 2016/17, and the Personal Social Services Research Unit (PSSRU) costs 2017 document.[123-125] TA424 was used as a guide when calculating the administration costs in the adjuvant setting.[67] Costs

and assumptions used in the neoadjuvant appraisal were judged to be reasonable by both the ERG and the appraisal committee.

According to the National Tariff of chemotherapy regimens, the administration of the initial dose of pertuzumab, trastuzumab IV and chemotherapy should be costed using code SB14Z in the NHS reference costs schedule 2016/17 (Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance (chemotherapy delivery: day case) whereas the administration cost for subsequent (maintenance) cycles should equate to SB13Z of the reference schedule (Deliver more Complex Parenteral Chemotherapy at First Attendance (chemotherapy delivery: day case)).[125]

The administration costs quoted in the preceding paragraph are applied to all treatments that are administered via IV infusion. The cost of a subcutaneous administration of trastuzumab should be equivalent to SB12Z (Deliver Simple Parenteral Chemotherapy at First Attendance (chemotherapy delivery: day case)) according to the National Tariff of chemotherapy regimens.

An additional administration cost has been included in the model to account for the pharmacist's time during the prescription and preparation of treatments. It has been assumed that each administration will require 12 minutes of a pharmacist's time, as per Millar *et al.*[126] This cost is applied to every administration, regardless of treatment or treatment arm. When a medication is administered orally, the pharmacy cost is the only administration cost applied. A full breakdown of administration costs applied in the model is given in Table 40.

Table 40. Drug administration costs

Drug	First cycle			Subsequent cycles		
	NHS reference code	Cost per admin.	Source	NHS reference code	Cost per admin.	Source
Chemotherapy delivery – IV	SB14Z	£386.00	NHS ref. costs 2016/17	SB13Z	£310.00	NHS ref. costs 2016/17
Chemotherapy delivery - SC	N/A[a]	N/A[a]	N/A[a]	SB12Z	£260.00	NHS ref. costs 2016/17
Pharmacy cost	N/A	£8.60	PSSRU 2017	N/A	£8.60	PSSRU 2017

Footnotes: [a]No loading dose is required for subcutaneous trastuzumab.
Abbreviations: admin, administration; IV, intravenous; N/A, not applicable; NHS, National Health Service; PSSRU, Personal and Social Services Research Unit; ref., reference; SC, subcutaneous.

B.3.5.2 Health-state unit costs and resource use

Health state costs have been applied cyclically and irrespective of treatment arm throughout the duration of the model time horizon. The cost and resource use required in each health state is outlined below.

The supportive care regimens and assumptions used here are highly similar to those used in the pertuzumab neoadjuvant appraisal. These regimens and assumptions have been validated by numerous clinical experts, and have consequently been accepted by the ERG and appraisal committee.

IDFS health state

Resource use and supportive care regimens are expected to differ depending on how long a patient has remained in the IDFS health state. Specific supportive care costs have been derived and applied in the following time periods:

- Year 1
- Years 2–5
- Years ≥5

Patients can remain on adjuvant treatment in the IDFS health state for a maximum of 12 months. Typically, not all patients will complete the full 12 months of therapy, a proportion may discontinue treatment due to, for example, safety concerns. As a result, the IDFS health state in the first year of the model time horizon will contain two different subpopulations: i) IDFS – on treatment and ii) IDFS – off treatment. Although resource use and supportive care is expected to be minimal in this health state, the supportive care provided would be expected to differ between these two populations. This difference in supportive care regimens has not been reflected in the model. The company acknowledges that theoretically this approach would be more accurate. However, the incremental difference in discontinuation of IDFS patients between the two arms is considered minimal. This would ultimately translate into a negligible impact on overall cost-effectiveness results.

The supportive care regimen of patients in the IDFS health state is considered to comprise oncologist and GP visits, as well as regular mammograms, and cardiac monitoring. The frequency of mammograms was based on NICE CG80 that includes recommendations with respect to the diagnosis and treatment of early and locally advanced breast cancer.[12] In terms of the cardiac assessment costs, these are applied every three months and used in a weighted average of 30% multigated acquisition (MUGA) scan and 70% echocardiogram (ECHO). Resource use and supportive care costs for patients in the IDFS health state are shown in Table 41.

The resource use assumed here is in line with the “EFS” health state of the neoadjuvant pertuzumab appraisal, although slight alterations have been made because of expert advice received during the development of this submission. Despite these alterations, the cyclical costs applied in the EFS and IDFS states are still very much comparable.

Table 41. IDFS health state – resource use and supportive care costs

Resource	Unit cost	Source	% of patients	Frequency per year		
				Year 1	Years 2–5	Years ≥5
Oncologist visit	£130.00	NHS ref. 2016/17 - 800	100%	2	0	0
GP visit	£37.00	PSSRU 2017 - page 162	100%	0	1	1
Mammogram	£11.34	TA767 - NHS BSP (inflated)	100%	1	1	0
ECHO scan	£70.36	NHS ref. 2016/17 – RD51A	70%	4	0	0
MUGA scan	£249.00	NHS ref. 2016/17 – RN22Z	30%			

Total base case cost per (four-week) cycle:	£63.93	£7.11	£3.08

Abbreviations: ECHO, echocardiogram; GP, general practitioner; MUGA, multigated acquisition; NHS, National Health Service; PSSRU, Personal and Social Services Research Unit.

Non-metastatic recurrence

Patients who experience a non-metastatic recurrence undergo an additional 12 months of adjuvant therapy. The supportive care regimen in this state is assumed equal to that of year one in IDFS (on treatment). In addition, it has also been assumed that 75% of patients will receive a CT scan to facilitate the monitoring of the recurrence (Table 42). This assumption has been validated by expert clinicians at a Roche advisory board. Assumed resource use in this health state is also aligned with the neoadjuvant pertuzumab submission.[102]

Table 42. Non-metastatic recurrence state – resource use and supportive care costs

Resource	Unit cost	Source	Proportion of patients (%)	Frequency per year	Cost per cycle
Oncologist visit	£130.00	NHS ref. 2016/17 - 800	100%	2	£21.67
Mammogram	£11.34	TA767 - NHS BSP (inflated)	100%	1	£0.95
ECHO scan	£70.36	NHS ref. 2016/17 – RD51A	70%	4	£41.32
MUGA scan	£249.00	NHS ref. 2016/17 – RN22Z	30%		
CT scan	£103.00	NHS ref. schedule - 2016/17 - RD20A	75%	2	£12.88
Total base case cost per (4-week) cycle: £76.80					

Abbreviations: CT, computerised tomography; ECHO, echocardiogram; GP, general practitioner; MUGA, multigated acquisition; NHS, National Health Service.

Remission

In the NICE appraisal of pertuzumab in the neoadjuvant setting it was assumed that patients in remission would incur the same health state costs as those in year 1–2 of EFS. Patients in remission in this model receive an identical supportive care regimen to those patients who are in year 2–5 of IDFS (see Table 41).

Metastatic (first-line mBC and 2nd + line mBC)

In the metastatic health states, response to treatment is assessed using outpatient visits, CT scans, cardiac monitoring, and health care practitioner time. 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 vary depending on treatment centre. In light of this, and the assumptions made in previous NICE MTAs and SMC submissions, the model applies a conservative estimate of one CT scan per year in the first-line mBC health state.

Costs and assumptions described here are in line with those used in the appraisal of pertuzumab in the neoadjuvant setting. A full breakdown of the supportive care costs for the mBC health states are summarised in Table 43 and Table 44. Please note that mBC resource use is not assumed to vary according to the timing of recurrence. The costs quoted in the tables below have been applied equally to both “early” and “late” relapsers.

Table 43. First-line mBC state – resource use and supportive care costs

Items	Frequency (yearly)	Unit cost per contact	Proportion of patients	Cost sources	Resource use sources
Cycle costs					
GP visit	12	£37.00	100%	PSSRU 2017 - page 162	Assumption
ECHO Scan	2	£70.36	70%	NHS ref. 2016/17 – RD51A	CG81
MUGA Scan	2	£249.00	30%	NHS ref. 2016/17 – RN22Z	CG81
Clinical nurse specialist	12	£69.85	100%	NHS ref. - 2016/17 – N09AF	CG81
District Nurse (home visit)	22	£37.00	100%	NHS ref. - 2016/17 - N02AF	CG81
CT Scan	One off cost	£103.00	75%	NHS ref. 2016/17 - RD20A	Ad. board (03/2013); CG81
Social worker	One off cost	£82.00	100%	PSSRU 2017 - 11.2 - page 174	CG81
Total base case cost per (4-week) cycle = £214.78					

Abbreviations: CT, computerised tomography; ECHO, echocardiogram; GP, general practitioner; MUGA, multigated acquisition; NHS, National Health Service; PSSRU, Personal and Social Services Research Unit.

Table 44. Second + line mBC state – resource use and supportive care costs

Items	Frequency (yearly)	Unit cost per contact	Proportion of patients	Cost sources	Resource use sources
GP visit	12	£37.00	100%	PSSRU 2017 - page 162	Assumption
Clinical nurse specialist	12	£69.85	100%	NHS ref. - 2016/17 – N09AF	CG81
District Nurse (home visit)	24	£37.00	100%	NHS ref. - 2016/17 - N02AF	CG81
Average monthly supportive care cost = £180.85					

Abbreviations: GP, general practitioner; NHS, National Health Service; PSSRU, Personal and Social Services Research Unit.

Validation of health state costs and resource use

Given the model structures used, similar health state costs have been included in both the adjuvant and neoadjuvant appraisals of pertuzumab. Cyclical supportive care costs used in both models are reported in Table 45.

Table 45. Comparison of health state costs in the neoadjuvant and adjuvant appraisals

TA424 – pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer		ID1192 – pertuzumab for the adjuvant treatment of HER2-positive breast cancer	
Health state	**Cycle cost**	**Health state**	**Cycle cost**
EFS	Year 1–2 = £67.85 Year 3–5 = £15.11 ≥5 years = £3.83	IDFS	Year 1 (on treatment) = £63.93 Year 2–5 = £7.11 ≥5 years = £3.08
Locoregional recurrence	£73.97	Non-metastatic recurrence	£76.80
Remission	£67.85	Remission	£7.11
mBC – non-progressed	£232.00	First-line mBC	£214.78
mBC – progressed	£185.00	Second+ line mBC	£180.85

Abbreviations: EFS, event-free survival; HER2, human epidermal growth factor receptor 2; IDFS, invasive disease-free survival; mBC, metastatic breast cancer.

Table 45 illustrates that the cyclical costs reported in this appraisal are in close proximity to those used in the neoadjuvant submission. Any differences stem primarily from the fact that the IDFS year one cost has been separated into on-treatment and off-treatment in the adjuvant setting.

The biggest disparity between the two sets of costs is in the “remission” health state. In the neoadjuvant appraisal, remission health state costs have been assumed equal to year 1–2 of the EFS health state; this cost makes no distinction between those patients who are on- or off-treatment. In other words, certain costs are included for patients in remission that are not clinically accurate (e.g. patients are assumed to undergo frequent cardiac monitoring despite no longer receiving treatment). This inclusion results in a remission health state cost that is overestimated. In the adjuvant analysis, patients in remission are assumed to receive a supportive care regimen equal to that of patients in year 2–5 of IDFS. This regimen is believed to be more akin to what a patient could expect to receive in UK clinical practice.

B.3.5.3 Adverse reaction unit costs and resource use

IDFS

Following the guidance received in recent technology appraisals in this disease area, the criteria used for the inclusion/exclusion of an AE in the model are outlined below:

- **Only AEs of Grade ≥3:** Typically, clinicians will only intervene and treat an AE if it is severe enough to be classified as grade 3 or above. The costs and HRQoL effects associated with grade 1 and 2 events are therefore assumed to be negligible and hence omitted from this analysis.
- **Occur in ≥2% of patients:** A reasonable assumption was made that an AE must have occurred in at least 2% of the study population to be included in the model.

The data used to inform this aspect of the analysis were taken directly from the APHINITY trial. The frequency and cost of treating these AEs are reported in Table 46. The principal source of cost information were the NHS reference costs 2016–2017.

Table 46. List of adverse events and costs included in the economic model

Adverse events	Frequency		Treatment	Event cost	Source
	Pertuzumab + trastuzumab + chemotherapy	Placebo + trastuzumab + chemotherapy			
Diarrhoea	67 (4.46%)	17 (1.13%)	Malignant Breast Disorders with Interventions, with CC Score 3-6 - Day case	£334.00	NHS Reference costs schedule - 2016/17 - JA12E
Neutropenia	37 (2.46%)	45 (3.00%)	Neutropenia Drugs, Band 1 - outpatient	£79.00	NHS Reference costs schedule - 2016/17 - XD25Z
Neutrophil count decreased	36 (2.40%)	35 (2.33%)	No treatment available	£0.00	Not applicable

Abbreviations: CC, Casemix companion; NHS, National Health Service.

The adverse event profile seen in the APHINITY study was similar to that of the NEOSPHERE trial. This similarity meant that the AEs included in this analysis were very much in line with those included in the appraisal of pertuzumab in the neoadjuvant setting (TA424).[67]

For ease of implementation, these costs have been applied to patients in cycle one of the model. In reality, AEs can occur at any point while a patient receives treatment. The application of the costs at this timepoint in the analysis is expected to result in an overestimation of AE costs in both treatment arms. Nevertheless, both side-effect profiles appear to be relatively mild and the costs associated with AEs is thought to have a negligible impact on the overall cost-effectiveness results.

Subsequent therapies

The details of post-progression AEs were not captured in the APHINITY study. The total AE management cost associated with each subsequent treatment was taken from other economic analyses. Table 47 details the costs applied to each subsequent treatment regimen.

Table 47. Adverse event management costs in subsequent therapies

Setting	Subsequent therapy	Management cost	Source
Non-metastatic recurrence	Trastuzumab + docetaxel	£13.51	ID523 – pertuzumab in mBC
First-line metastatic breast cancer	Trastuzumab + docetaxel	£13.51	ID523 – pertuzumab in mBC
	Trastuzumab emtansine	£2.12	TA458 – TE in advanced HER2+ BC
	Pertuzumab + trastuzumab + docetaxel	£13.51	ID523 – pertuzumab in mBC
	Chemotherapy	£1.28	TA458 – TE in advanced HER2+ BC
Second + line metastatic breast cancer	Trastuzumab + docetaxel	£13.51	ID523 – pertuzumab in mBC
	Trastuzumab emtansine	£2.12	TA458 – TE in advanced HER2+ BC
	Chemotherapy	£1.28	TA458 – TE in advanced HER2+ BC
	Pertuzumab + trastuzumab + docetaxel	£13.51	ID523 – pertuzumab in mBC
	Lapatinib + capecitabine	£7.21	TA458 – TE in advanced HER2+ BC

Abbreviations: BC, breast cancer; HER2+, human epidermal growth factor receptor 2-positive; mBC, metastatic breast cancer; TE, trastuzumab emtansine.

B.3.5.4 Miscellaneous unit costs and resource use

No other costs and resource use have been identified as suitable for inclusion in this analysis. All relevant inputs have been described and justified in the preceding sections.

B.3.6 *Summary of base case analysis inputs and assumptions*

B.3.6.1 Summary of base case analysis inputs

Table 48 summarises all key variables applied in the base case of the economic model.

Table 48. Summary of variables applied in the base case setting of the economic model (node-positive population)

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
General model parameters			
Time horizon	52 years	Fixed	Section B.3.2
Discount rate - efficacy	3.5%	Fixed	
Discount rate - costs	3.5%	Fixed	
Population parameters			

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Age	55.10 years	Fixed	Section B.2.3.2
Body weight	67.40 kg	Fixed	
Height	161.70 cm	Fixed	
Body surface area	1.72 m^2	Fixed	
Average serum creatinine	0.85	Fixed	
Clinical parameters			
Treatment duration	Trial-observed	Fixed	Section B.3.3
IDFS parametric distribution	Log-logistic	Fixed	
% of metastatic recurrences	81.07%	Fixed	
% of non-metastatic recurrences	18.93%	Fixed	
Incremental treatment effect begins to wane	7 years	Fixed	
Incremental treatment effect ceases	10 years	Fixed	
“Cure” proportion is applied	4 years	Fixed	
Maximum cure is reached	10 years	Fixed	
Maximum “cure” proportion	90%	Fixed	
Definition of “early relapser” (ER)	18 months	Fixed	
Transition probabilities	Section B.3.3.2	Multivariate normal	
Treatment share in first-line metastatic setting			
Pertuzumab + trastuzumab + chemotherapy	71.2%	Fixed	
Trastuzumab + chemotherapy	22.9%	Fixed	
Chemotherapy	6.9%	Fixed	
Treatment share in second-line metastatic setting			
Trastuzumab emtansine	67%	Fixed	
Trastuzumab SC	11%	Fixed	
Lapatinib	5%	Fixed	
Trastuzumab IV	5%	Fixed	
Utilities – base case			
IDFS – on chemo	0.756 (0.004)	Gamma	Section B.3.4.5
IDFS – on treatment, off chemo	0.785 (0.004)	Gamma	
IDFS – off treatment	0.822 (0.004)	Gamma	
Non-metastatic recurrence	0.756 (0.004)	Gamma	
Remission	0.822 (0.004)	Gamma	
First-line metastatic recurrence	0.773	Gamma	
Second + line metastatic recurrence	0.520	Gamma	

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Technology acquisition costs (unit costs)			
Pertuzumab – eBC	[redacted]	Fixed	Section B.3.5
Pertuzumab – mBC	[redacted]	Fixed	
Trastuzumab IV	[redacted]	Fixed	
Trastuzumab SC	[redacted]	Fixed	
Trastuzumab emtansine (100 mg)	[redacted]	Fixed	
Trastuzumab emtansine (160 mg)	[redacted]	Fixed	
Docetaxel (20 mg / 1 ml)	£3.85	Fixed	
Docetaxel (80 mg / 4 ml)	£14.74	Fixed	
Doxorubicin (10 mg / 5 ml)	£1.34	Fixed	
Doxorubicin (50 mg / 25 ml)	£3.63	Fixed	
Paclitaxel (30 mg / 5 ml)	£3.44	Fixed	
Paclitaxel (100 mg / 16.7 ml)	£9.85	Fixed	
Epirubicin (10 mg / 5 ml)	£2.57	Fixed	
Epirubicin (50 mg / 25 ml)	£5.62	Fixed	
Cyclophosphamide (500 mg)	£8.62	Fixed	
Cyclophosphamide (1 g)	£15.89	Fixed	
5-FU (2.5 g / 50 ml)	£2.06	Fixed	
5-FU (5 g / 100 ml)	£3.12	Fixed	
Carboplatin (150 mg / 15 ml)	£6.35	Fixed	
Carboplatin (450 mg / 45 ml)	£18.73	Fixed	
Trastuzumab usage			
Trastuzumab IV market share (pertuzumab + trastuzumab + chemotherapy arm)	100%	Fixed	Section B.3.5
Trastuzumab SC market share (trastuzumab + chemotherapy arm)	[redacted]	Fixed	
Trastuzumab IV share (trastuzumab + chemotherapy arm)	[redacted]	Fixed	
Biosimilar market share (both arms)	[redacted]	Fixed	
Chemotherapy usage			
Anthracycline chemotherapy	78.30%	Fixed	Section B.3.5
Non-anthracycline chemotherapy	21.70%	Fixed	
Administration costs			

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
IV administration cost – loading	£394.60	£315.12 – £490.81 (Gamma)	Section B.3.5
IV administration cost – maintenance	£310.00	£197.00 – £428.00 (Gamma)	
SC administration cost – all cycles	£260.00	£189.00 – £219.00 (Gamma)	
Pharmacy preparation	£43.00	£33.60 – £50.40 (Gamma)	
Health state costs (cyclical costs only)			
IDFS – year 1	£63.93 (0.13)	Log Normal	Section B.3.5
IDFS – year 2-5	£4.03 (0.13)	Log Normal	
IDFS – ≥5 years	£3.08 (0.13)	Log Normal	
Non-metastatic recurrence	£76.80 (0.13)	Log Normal	
Remission	£7.11 (0.13)	Log Normal	
First-line metastatic recurrence	£214.78 (0.13)	Log Normal	
Second + line metastatic recurrence	£180.85 (0.13)	Log Normal	
Adverse event management costs (per event) - IDFS			
Diarrhoea	£489.00	£390.00 – £504.00 (Gamma)	Section B.3.5
Neutropenia	£137.00	£69.00 – £163.00 (Gamma)	
Neutrophil count decreased	N/A	N/A	
Adverse event management costs (per event) – Subsequent therapies			
Trastuzumab + docetaxel	£13.51	Fixed	Section B.3.5
Trastuzumab emtansine	£2.12	Fixed	
Pertuzumab + trastuzumab + docetaxel	£13.51	Fixed	
Chemotherapy	£1.28	Fixed	
Lapatinib + capecitabine	£7.21	Fixed	

Abbreviations: CI, confidence interval; eBC, early breast cancer; ER, early relapser; IDFS, invasive disease-free survival; IV, intravenous; mBC, metastatic breast cancer; SC, subcutaneous; 5-FU, 5-fluororacil.

B.3.6.2 Assumptions

The key assumptions applied in the base case of the economic model are specified in Table 49.

Table 49. Key assumptions used in the economic model (base case)

Area	Assumption	Justification
Time horizon	52 years	Fifty-two years is believed to be long enough to reflect all important differences in costs or

Area	Assumption	Justification
		outcomes between the technologies being compared. This value is also in line with previous appraisals in this disease area.
Clinical inputs	Treatment duration as observed in APHINITY	Treatment duration in the model has been derived from the TTOT data that were collected during the APHINITY trial. This is considered to reflect the actual use of pertuzumab + trastuzumab + chemotherapy and trastuzumab + chemotherapy in UK clinical practice, when the combination becomes commercially available.
	Incremental treatment effect duration	The incremental treatment effect will be applied for seven years before waning and ceasing completely at ten years. Long-term follow-up in trastuzumab studies have shown maintenance of treatment effect. The complementary mechanism of action of pertuzumab is expected to further enhance this. See B.3.3.1 for full details on this assumption In addition, a seven year treatment effect duration has been assumed in a previous appraisal of the combination of pertuzumab + trastuzumab + chemotherapy in the neoadjuvant breast cancer setting, where the treatment duration is even shorter (4–6 cycles).[67]
	"Cure" proportion assumptions	1. "Cured" patients are assumed to be at risk of death from other causes ("background mortality") and no longer at risk of disease recurrence or breast cancer-related death 2. The point at which a proportion of patients start to be "cured" is 48 months. The selection of this time point is predicated on data available from APHINITY. Please see Section B.3.3.1 for a full explanation of this assumption. 3. Maximum "cured" proportion is reached at ten years. Much like 2), this assumption is based on observations from long term historical studies of trastuzumab. Further details are provided in Section B.3.3.1. 4. Maximum "cured" proportion is 90% (i.e. 10% of patients would never be "cured"). 90% of the IDFS population remain cured for the duration of the time horizon. It was deemed clinically implausible to assume a 100% "cure" rate. 5. "Cured" proportion between starting point (48 months) and maximum (120 months) is assumed to linearly increase with time.

Area	Assumption	Justification
		Assumption that everyone will be "cured" after a time point is less appropriate, therefore a linear relationship between time and "cured" proportion seems more reasonable, i.e. the more patients stay on IDFS the more likely are to be "cured".
	Fast or early relapse vs late relapser	1. Patients who experience a recurrence in under 18 months from commencing adjuvant therapy are classed as "Fast relapsers". Fast relapsers are assumed to have a worse prognosis. This assumption is based on data from the HERA trial (See Figure 20). 2. It is assumed that a disease recurrence observed within 18 months after initiation of adjuvant therapy is metastatic. This is justified by the fact that a patient having a recurrence during or soon after receiving adjuvant therapy will have a worse prognosis and may therefore receive a more aggressive treatment. 3. Fast relapser survival estimates were derived from the EMILIA study. Transitions from first-line mBC to second+ line mBC and death probabilities from first-line and second-line mBC follow an exponential rate (Markov property). See Section B.3.3.2.
	Probability from remission to first-line mBC	Monthly probability of subsequent metastatic recurrence has been derived from Hamilton *et al*. There are several differences between the populations evaluated in the model and the one described in the publication. Nevertheless, the same probability has been used in previous appraisals in eBC.[67]
	Late relapse probabilities	Slow relapsers are assumed to receive the three most commonly used therapies in the UK: • pertuzumab + trastuzumab + taxane, • trastuzumab + taxane, • Chemotherapy For pertuzumab + trastuzumab + taxane, and trastuzumab + taxane, adjustment to the survival curve was based on the CLEOPATRA study, while for chemotherapy adjustment was based on M77001 study. These were used to model three transitions: from first-line mBC to second-line mBC, first-line mBC to death and second-line mBC to death. A weighted average probability (probabilities weighted by their market shares) was used for

Area	Assumption	Justification
		each transition. CLEOPTRA and M77001 studies did not include patients with adjuvant pertuzumab + trastuzumab + chemotherapy, as the combination was not available at that time. Prior adjuvant therapy with chemotherapy, anthracyclines, hormone therapy and radiotherapy was used in most of patients in M77001, and in CLEOPATRA adjuvant or neoadjuvant trastuzumab was allowed.
HRQoL	Pooled utilities across treatment arms	No statistically significant difference was detected in EQ-5D results between the two treatment arms. Therefore, EQ-5D results were pooled and health state utilities have been applied across both treatment arms in the model.
	Utilities for the "non-metastatic recurrence" and "remission" health states have been assumed equal to "IDFS – on chemotherapy" and "IDFS – off treatment", respectively	EQ-5D was not collected following recurrence in the APHINITY study. As a result, it was not possible to estimate utilities for post-recurrence health states. A variety of published utilities have been included as scenario analyses. This assumption was also made in the NICE appraisal of pertuzumab in the neoadjuvant setting.[67]
	AE disutilities are not applied in the model	The disutility associated with AEs was assumed to have been captured in the EQ-5D responses in APHINITY. See Section B.3.4.4
Costs and resource use	Post-recurrence treatments	In the APHINITY study, post-recurrence treatments do not reflect UK practice. The majority of patients who progressed to first-line mBC received chemotherapy (64.7%), trastuzumab + chemotherapy (17%) and pertuzumab + trastuzumab + chemotherapy (18.4%). However, recent data on first-line metastatic breast cancer demonstrated that the majority of patients in the UK receive pertuzumab + trastuzumab + chemotherapy (71.2%), trastuzumab + chemotherapy (22.9% (includes 3.4% patients on trastuzumab emtansine) and chemotherapy or hormone therapy (no HER2 agent): 6.9%.[41] Data from second-line mBC could not be obtained from the APHINITY study, as patients were not followed up until that point. Patient record data showed that 67% of patients receive trastuzumab emtansine, 11% trastuzumab SC, trastuzumab IV 5%, lapatinib + capecitabine 5%, and capecitabine alone 12%. These estimates are then used to calculate costs in second-line mBC.
	Remission health state costs	Clinically plausible and in line with the

Area	Assumption	Justification
	are assumed equal to IDFS – year one (off-treatment)	methodology used in TA424.[67]

Abbreviations: AE, adverse event; eBC, early breast cancer; EQ-5D, EuroQol 5-dimension questionnaire; HER2, human epidermal growth factor receptor 2; IDFS, invasive disease-free survival; IV, intravenous; mBC, metastatic breast cancer; SC, subcutaneous; TTOT, time-to-off-treatment; UK, United Kingdom.

B.3.7 *Base case results*

B.3.7.1 Base case incremental cost-effectiveness analysis results

Base case results of the economic model are presented below. Only results pertaining to the node-positive population are featured here. Please see the supplementary Appendix M for the results specific to the hormone receptor-negative analysis.

Pertuzumab + trastuzumab + chemotherapy provided a QALY gain of [redacted] and a life-year gain of 17.31, at a total overall cost of £[redacted]. In contrast, trastuzumab + chemotherapy provides a QALY gain of [redacted] and a life-year gain of 16.57, at a total cost of £[redacted]. The resulting base case incremental cost-effectiveness ratio (ICER) when comparing pertuzumab + trastuzumab + chemotherapy to trastuzumab + chemotherapy is £34,087/QALY gained.

See Table 50 for a top-line summary of the base case cost-effectiveness results.

Table 50. Base case cost-effectiveness results (node-positive population)

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Trastuzumab + chemotherapy	[redacted]	16.57	[redacted]	[redacted]	0.742	[redacted]	£34,087
Pertuzumab + trastuzumab + chemotherapy	[redacted]	17.31	[redacted]				

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.

B.3.7.2 Modified base case results

The introduction of trastuzumab biosimilars to the UK market is expected to have a sizable impact on the cost-effectiveness of pertuzumab + trastuzumab + chemotherapy vs trastuzumab + chemotherapy. The base case results presented in Table 50 have been generated assuming that trastuzumab biosimilars are not yet available in the UK. Therefore, the results presented above are reflective of the UK market at the time of submission.

Trastuzumab biosimilars are expected to become available in the UK in the near future.[121] Consequently, the assumption surrounding no biosimilar usage is expected to be outdated shortly after the submission of this analysis. To mitigate this situation, Roche has proactively provided some additional results to illustrate the effect of biosimilar entry on the ICER of pertuzumab + trastuzumab + chemotherapy vs trastuzumab + chemotherapy – see below.

At the time of writing, both the price and market share of trastuzumab biosimilars are unknown. The two-way table below (Table 51) shows the corresponding ICERs when assuming various biosimilar price and market share combinations.

At the time of the appraisal guidance publication (within 90 days following the EMA approval of pertuzumab in the adjuvant setting), trastuzumab biosimilars are expected to have a market share between 40%–60% and a net price that is in between a 50% and 70% discount on the branded trastuzumab list price. These estimated ranges have been derived through a composite of competitive intelligence, previous technology appraisals in which Roche has been involved and engagement with NHS England.

Roche appreciates that these parameters are currently associated with a high amount of uncertainty and are expected to evolve over time. Nevertheless, it is believed important to present the potential impact that these assumptions will have on the cost-effectiveness of pertuzumab in the adjuvant eBC setting.

Table 51. Biosimilar price and market share impact on base case cost-effectiveness results (node-positive population)

		Trastuzumab biosimilar discount compared to branded trastuzumab list price										
		0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
Trastuzumab biosimilar market share (%)	0%	£34,087	£34,087	£34,087	£34,087	£34,087	£34,087	£34,087	£34,087	£34,087	£34,087	£34,087
	10%	£35,031	£34,714	£34,398	£34,081	£33,764	£33,447	£33,130	£32,814	£32,497	£32,180	£31,863
	20%	£35,976	£35,342	£34,709	£34,075	£33,441	£32,808	£32,174	£31,540	£30,907	£30,273	£29,640
	30%	£36,921	£35,970	£35,020	£34,069	£33,119	£32,168	£31,218	£30,267	£29,317	£28,367	£27,416
	40%	£37,865	£36,598	£35,331	£34,063	£32,796	£31,529	£30,262	£28,994	£27,727	£26,460	£25,193
	50%	£38,810	£37,226	£35,642	£34,058	£32,474	£30,890	£29,305	£27,721	£26,137	£24,553	£22,969
	60%	£39,755	£37,854	£35,953	£34,052	£32,151	£30,250	£28,349	£26,448	£24,547	£22,646	£20,746
	70%	£40,699	£38,482	£36,264	£34,046	£31,828	£29,611	£27,393	£25,175	£22,957	£20,740	£18,522
	80%	£41,644	£39,109	£36,575	£34,040	£31,506	£28,971	£26,437	£23,902	£21,368	£18,833	£16,299
	90%	£42,589	£39,737	£36,886	£34,035	£31,183	£28,332	£25,480	£22,629	£19,778	£16,926	£14,075
	100%	£43,533	£40,365	£37,197	£34,029	£30,861	£27,692	£24,524	£21,356	£18,188	£15,020	£11,852

Footnote: Blue shaded area represents the expected market share and discount of trastuzumab biosimilars, derived from competitive intelligence from Roche.

B.3.8 *Sensitivity analyses*

B.3.8.1 Probabilistic sensitivity analysis

To assess the uncertainty surrounding the variables included in the cost-effectiveness model, a probabilistic sensitivity analysis (PSA) was undertaken using 1,000 samples. The mean values, distributions around the means, and sources used to estimate the parameters are detailed in Section B.3.6.1.

The PSA results produced a mean ICER of £33,621/QALY gained when pertuzumab + trastuzumab + chemotherapy was compared with trastuzumab + chemotherapy. Results of the PSA compared to the base case analysis are presented in Table 52. Figure 24 and Figure 25 show the cost-effectiveness plane and acceptability curve, respectively.

The analyses below have been conducted using medication prices with confidential discounts applied.

Table 52. PSA results compared to base case (node-positive population)

	Costs		QALYs		ICERs (£/QALY)	
	Base case	**PSA**	**Base case**	**PSA**	**Base case**	**PSA**
Trastuzumab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£34,087	£33,621
Pertuzumab + trastuzumab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]		

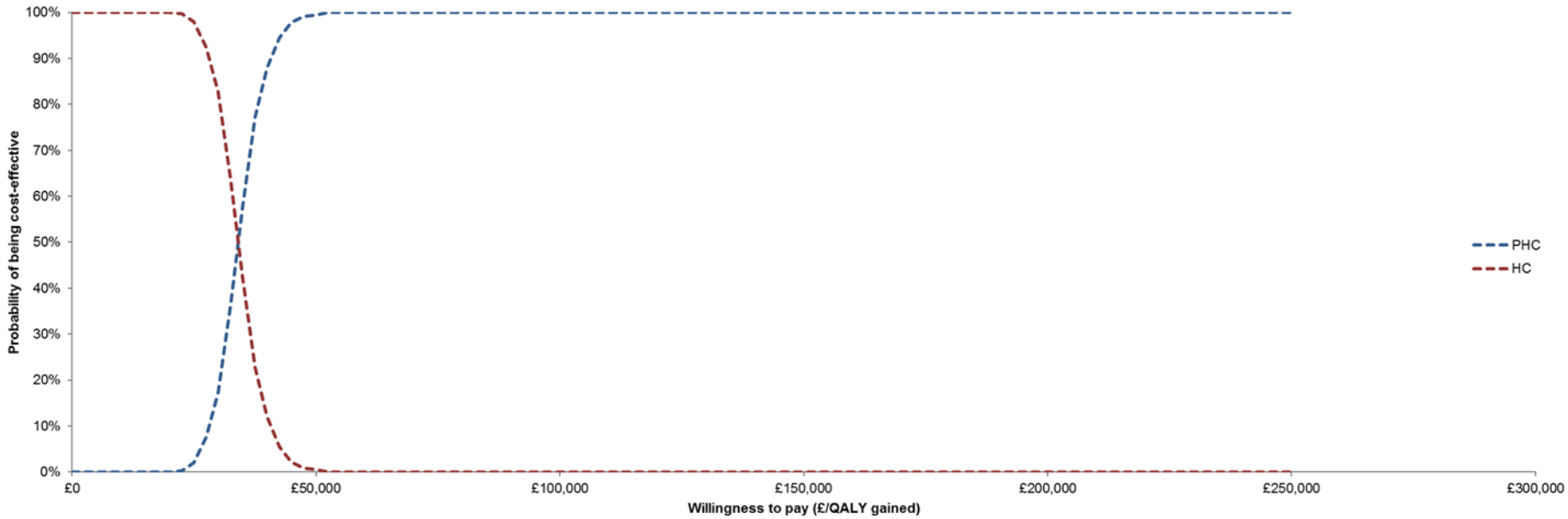
Abbreviations: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.

Figure 24. Cost-effectiveness plane (node-positive population)

REDACTED

Abbreviations: Inc, incremental; QALYs, quality-adjusted life years.

Figure 25. Cost-effectiveness acceptability curve (node-positive population)



Abbreviations: HT, trastuzumab + chemotherapy; PHT, pertuzumab + trastuzumab + chemotherapy; QALYs, quality-adjusted life years.

B.3.8.2 Deterministic sensitivity analysis

The choice of parameters to include in the univariate analysis was considered *a priori*, and was further informed by the results in Section B.3.7. For each parameter, the lower and upper values used in the univariate analysis were the 10th and 90th percentiles of the values used in the simulations of the PSA.

The parameters, distributions used in the PSA, and the values featured in the univariate analysis are given in Table 53. For presentation purposes, only the most sensitive of analyses have been included in the Tornado diagram (Figure 26).

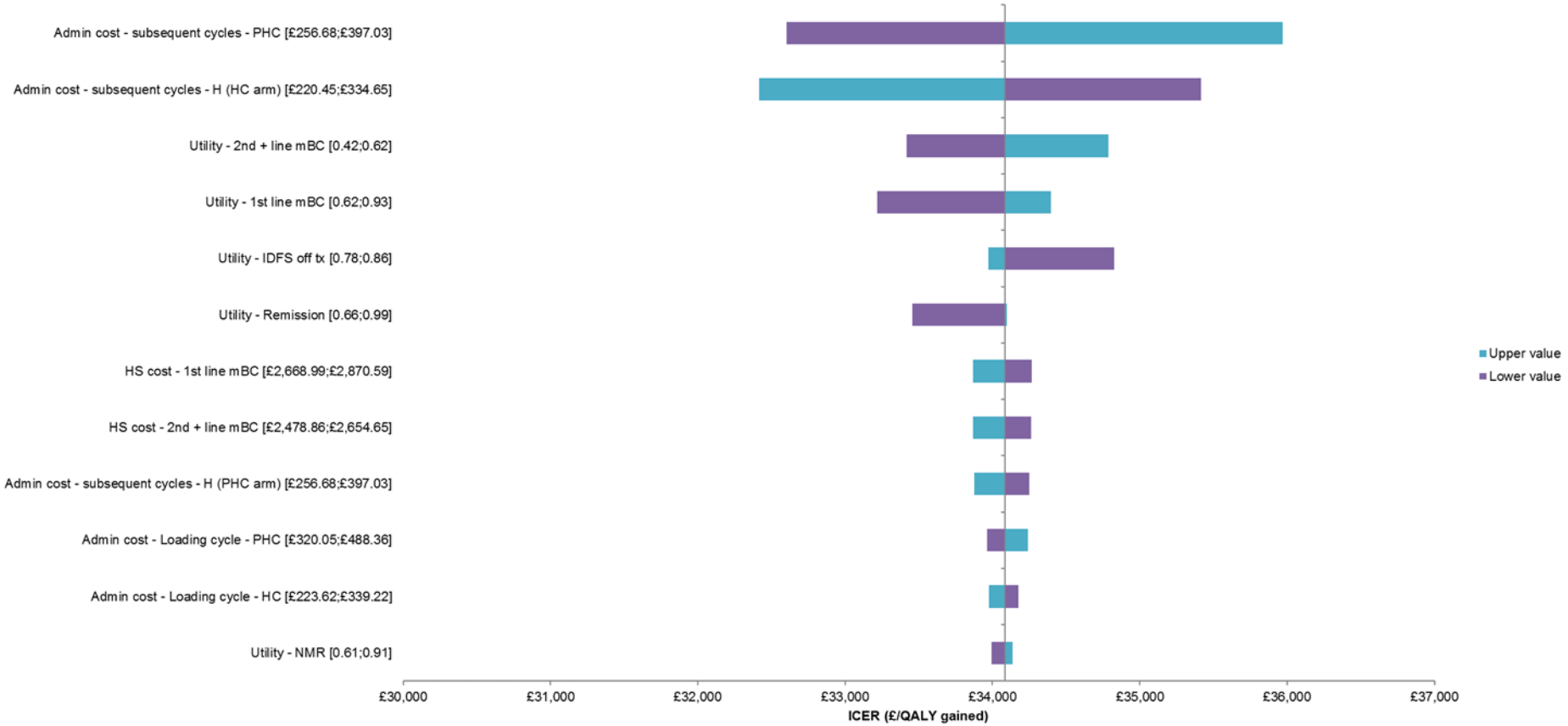
Table 53. Parameter values for univariate sensitivity analysis (node-positive population)

Parameter	Base case value	Distribution	Lower value	Upper value
Total AE management cost – Pertuzumab + trastuzumab + chemotherapy	£17.18	Gamma	£12.93	£23.53
Total AE management cost – trastuzumab + chemotherapy	£6.12	Gamma	£5.05	£7.75
Administration cost – Loading cycle – pertuzumab + trastuzumab + chemotherapy	£394.60	Gamma	£320.05	£488.36
Administration cost – Loading cycle – trastuzumab + chemotherapy	£274.90	Gamma	£223.62	£339.22
Administration cost – Loading cycle – AC	£394.60	Gamma	£320.05	£488.36
Administration cost – subsequent cycles – pertuzumab + trastuzumab + chemotherapy	£318.60	Gamma	£256.68	£397.03
Administration cost – subsequent cycles – trastuzumab (pertuzumab + trastuzumab + chemotherapy arm)	£318.60	Gamma	£256.68	£397.03
Administration cost – subsequent cycles – trastuzumab (trastuzumab + chemotherapy arm)	£271.10	Gamma	£220.45	£334.65
Administration cost – subsequent cycles – AC	£318.60	Gamma	£256.68	£397.03
Health state cost – IDFS – Year 1	£63.93	Log normal	£54.33	£75.80
Health state cost – IDFS – Year 2 to 5	£7.11	Log normal	£6.04	£8.43
Health state cost – IDFS – Year 6 onwards	£3.08	Log normal	£2.62	£3.66
Health state cost – Remission	£7.11	Log normal	£6.04	£8.43
Health state cost – NMR	£2,022.40	Log normal	£1,945.85	£2,116.38
Health state cost – First-line mBC	£2,571.18	Log normal	£2,478.60	£2,685.51

Parameter	Base case value	Distribution	Lower value	Upper value
– early relapsers				
Health state cost – Second+ line mBC – early relapsers	£2,749.33	Log normal	£2,654.28	£2,864.85
Health state cost – First line mBC	£2,759.39	Log normal	£2,668.99	£2,870.59
Health state cost – Second+ line mBC	£2,557.41	Log normal	£2,478.86	£2,654.65
Utility – IDFS – on chemo	0.76	Gamma	0.61	0.91
Utility – IDFS – on treatment/off chemo	0.79	Gamma	0.63	0.94
Utility – IDFS off treatment	0.82	Gamma	0.78	0.86
Utility – NMR	0.76	Gamma	0.61	0.91
Utility – Remission	0.82	Gamma	0.66	0.99
Utility – First line mBC	0.77	Gamma	0.62	0.93
Utility – Second+ line mBC	0.52	Gamma	0.42	0.62

Abbreviations: AC, doxorubicin and cyclophosphamide; AE, adverse event; IDFS, invasive disease-free survival; mBC, metastatic breast cancer; NMR, non-metastatic recurrence.

Figure 26. Univariate sensitivity analysis – Tornado diagram (node-positive population)



Abbreviations: H, trastuzumab; HC, trastuzumab + chemotherapy; HS, health state; ICER, incremental cost-effectiveness ratio; IDFS, invasive disease-free survival; mBC, metastatic breast cancer; NMR, non-metastatic recurrence; PHC, pertuzumab + trastuzumab + chemotherapy; QALY, quality-adjusted life year; tx, treatment.

B.3.8.3 Scenario analysis

Scenario analyses were conducted to assess uncertainty around model structure and parameters. The list below outlines the areas of the model that were evaluated. Key results are shown in Table 54 and Table 55; entire results of the scenario analysis are reported in Appendix N.

- Model settings
    - Time horizon
    - Patient weight
- Clinical inputs
    - IDFS parametric distribution
    - Duration of treatment effect
    - Proportion of recurrences that are metastatic
    - Definition of “early” relapsers
- Health state utilities
    - Age adjustment of utilities
    - Source of eBC health state utilities
    - Source of mBC health state utilities
- Costs and resource use
    - Drug dosing assumptions
    - Trastuzumab SC market share (Biosimilar market share = 0%)
    - AE treatment costs (per episode)
    - Selected health state costs

Table 54. Results from scenario analyses – costs and utilities (node-positive population)

Parameter	Value	Pertuzumab + trastuzumab + chemotherapy			Trastuzumab + chemotherapy			Pertuzumab + trastuzumab + chemotherapy vs trastuzumab + chemotherapy			
		Life Years	QALYs	Costs	Life Years	QALYs	Costs	Life Years	QALYs	Costs	ICER (£/QALY)
Utility in eBC	EQ-5D (per treatment arm)	17.31	[redacted]	[redacted]	16.57	[redacted]	[redacted]	0.74	[redacted]	[redacted]	£30,673
	EQ-5D (pooled)	17.31	[redacted]	[redacted]	16.57	[redacted]	[redacted]	0.74	[redacted]	[redacted]	£34,087
	Hedden *et al.*	17.31	[redacted]	[redacted]	16.57	[redacted]	[redacted]	0.74	[redacted]	[redacted]	£14,929
	Lidgren *et al.*	17.31	[redacted]	[redacted]	16.57	[redacted]	[redacted]	0.74	[redacted]	[redacted]	£25,189
Utility in mBC	Hedden *et al.*	17.31	[redacted]	[redacted]	16.57	[redacted]	[redacted]	0.74	[redacted]	[redacted]	£31,998
	Lidgren *et al.*	17.31	[redacted]	[redacted]	16.57	[redacted]	[redacted]	0.74	[redacted]	[redacted]	£34,673
	Lloyd *et al.*	17.31	[redacted]	[redacted]	16.57	[redacted]	[redacted]	0.74	[redacted]	[redacted]	£34,087
	Paracha *et al.*	17.31	[redacted]	[redacted]	16.57	[redacted]	[redacted]	0.74	[redacted]	[redacted]	£34,376
Trastuzumab SC market share (0% biosimilar)	70%	17.31	[redacted]	[redacted]	16.57	[redacted]	[redacted]	0.74	[redacted]	[redacted]	£34,652
	75%	17.31	[redacted]	[redacted]	16.57	[redacted]	[redacted]	0.74	[redacted]	[redacted]	£34,539
	80%	17.31	[redacted]	[redacted]	16.57	[redacted]	[redacted]	0.74	[redacted]	[redacted]	£34,426
	85%	17.31	[redacted]	[redacted]	16.57	[redacted]	[redacted]	0.74	[redacted]	[redacted]	£34,313
	90%	17.31	[redacted]	[redacted]	16.57	[redacted]	[redacted]	0.74	[redacted]	[redacted]	£34,200
	95%	17.31	[redacted]	[redacted]	16.57	[redacted]	[redacted]	0.74	[redacted]	[redacted]	£34,087
	100%	17.31	[redacted]	[redacted]	16.57	[redacted]	[redacted]	0.74	[redacted]	[redacted]	£33,973
Health state cost – IDFS – year 1	£43.81	17.31	[redacted]	[redacted]	16.57	[redacted]	[redacted]	0.74	[redacted]	[redacted]	£34,086
	£58.41	17.31	[redacted]	[redacted]	16.57	[redacted]	[redacted]	0.74	[redacted]	[redacted]	£34,086
	£73.01	17.31	[redacted]	[redacted]	16.57	[redacted]	[redacted]	0.74	[redacted]	[redacted]	£34,087
Health state cost – non-	£1,314.00	17.31	[redacted]	[redacted]	16.57	[redacted]	[redacted]	0.74	[redacted]	[redacted]	£34,240
	£1,752.00	17.31	[redacted]	[redacted]	16.57	[redacted]	[redacted]	0.74	[redacted]	[redacted]	£34,145

Parameter	Value	Pertuzumab + trastuzumab + chemotherapy			Trastuzumab + chemotherapy			Pertuzumab + trastuzumab + chemotherapy vs trastuzumab + chemotherapy			
		Life Years	QALYs	Costs	Life Years	QALYs	Costs	Life Years	QALYs	Costs	ICER (£/QALY)
metastatic recurrence	£2,189.99	17.31	[redacted]	[redacted]	16.57	[redacted]	[redacted]	0.74	[redacted]	[redacted]	£34,050
Health state cost – first-line mBC – early relapsers	£1,643.38	17.31	[redacted]	[redacted]	16.57	[redacted]	[redacted]	0.74	[redacted]	[redacted]	£34,141
	£2,191.17	17.31	[redacted]	[redacted]	16.57	[redacted]	[redacted]	0.74	[redacted]	[redacted]	£34,109
	£2,738.97	17.31	[redacted]	[redacted]	16.57	[redacted]	[redacted]	0.74	[redacted]	[redacted]	£34,077
Health state cost – second+ line mBC – early relapsers	£1,932.61	17.31	[redacted]	[redacted]	16.57	[redacted]	[redacted]	0.74	[redacted]	[redacted]	£34,147
	£2,576.82	17.31	[redacted]	[redacted]	16.57	[redacted]	[redacted]	0.74	[redacted]	[redacted]	£34,099
	£3,221.02	17.31	[redacted]	[redacted]	16.57	[redacted]	[redacted]	0.74	[redacted]	[redacted]	£34,052
Health state cost – first-line mBC	£1,921.12	17.31	[redacted]	[redacted]	16.57	[redacted]	[redacted]	0.74	[redacted]	[redacted]	£35,746
	£2,561.49	17.31	[redacted]	[redacted]	16.57	[redacted]	[redacted]	0.74	[redacted]	[redacted]	£34,478
	£3,201.86	17.31	[redacted]	[redacted]	16.57	[redacted]	[redacted]	0.74	[redacted]	[redacted]	£33,211
Health state cost – second+ line mBC	£1,809.43	17.31	[redacted]	[redacted]	16.57	[redacted]	[redacted]	0.74	[redacted]	[redacted]	£35,764
	£2,412.57	17.31	[redacted]	[redacted]	16.57	[redacted]	[redacted]	0.74	[redacted]	[redacted]	£34,411
	£3,015.71	17.31	[redacted]	[redacted]	16.57	[redacted]	[redacted]	0.74	[redacted]	[redacted]	£33,059
Diarrhoea event cost	£366.75	17.31	[redacted]	[redacted]	16.57	[redacted]	[redacted]	0.74	[redacted]	[redacted]	£34,088
	£489.00	17.31	[redacted]	[redacted]	16.57	[redacted]	[redacted]	0.74	[redacted]	[redacted]	£34,095
	£611.25	17.31	[redacted]	[redacted]	16.57	[redacted]	[redacted]	0.74	[redacted]	[redacted]	£34,102
Neutropenia event cost	£102.75	17.31	[redacted]	[redacted]	16.57	[redacted]	[redacted]	0.74	[redacted]	[redacted]	£34,086
	£137.00	17.31	[redacted]	[redacted]	16.57	[redacted]	[redacted]	0.74	[redacted]	[redacted]	£34,086
	£171.25	17.31	[redacted]	[redacted]	16.57	[redacted]	[redacted]	0.74	[redacted]	[redacted]	£34,086

Parameter	Value	Pertuzumab + trastuzumab + chemotherapy			Trastuzumab + chemotherapy			Pertuzumab + trastuzumab + chemotherapy vs trastuzumab + chemotherapy			
		Life Years	QALYs	Costs	Life Years	QALYs	Costs	Life Years	QALYs	Costs	ICER (£/QALY)
Neutrophil decrease event cost	£0.00	17.31	[redacted]	[redacted]	16.57	[redacted]	[redacted]	0.74	[redacted]	[redacted]	£34,087
	£150.00	17.31	[redacted]	[redacted]	16.57	[redacted]	[redacted]	0.74	[redacted]	[redacted]	£34,087
	£300.00	17.31	[redacted]	[redacted]	16.57	[redacted]	[redacted]	0.74	[redacted]	[redacted]	£34,087

Abbreviations: eBC, early breast cancer; IDFS, invasive disease-free survival; mBC, metastatic breast cancer; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life year; SC, subcutaneous.

Table 55. Results from scenario analyses – clinical parameters and efficacy (node-positive population)

Parameter	Value	Pertuzumab + trastuzumab + chemotherapy			Trastuzumab + chemotherapy			Pertuzumab + trastuzumab + chemotherapy vs trastuzumab + chemotherapy			
		Life Years	QALYs	Costs	Life Years	QALYs	Costs	Life Years	QALYs	Costs	ICER (£/QALY)
IDFS parametric distribution	Exponential	17.42	[redacted]	[redacted]	16.89	[redacted]	[redacted]	0.54	[redacted]	[redacted]	£53,236
	Weibull	17.08	[redacted]	[redacted]	16.30	[redacted]	[redacted]	0.78	[redacted]	[redacted]	£31,873
	Log-normal	17.64	[redacted]	[redacted]	16.99	[redacted]	[redacted]	0.65	[redacted]	[redacted]	£40,555
	Gen. Gamma	17.21	[redacted]	[redacted]	16.53	[redacted]	[redacted]	0.68	[redacted]	[redacted]	£38,136
	Log-logistic	17.31	[redacted]	[redacted]	16.57	[redacted]	[redacted]	0.74	[redacted]	[redacted]	£34,087
	Gompertz	15.22	[redacted]	[redacted]	14.42	[redacted]	[redacted]	0.80	[redacted]	[redacted]	£33,542
Proportion of metastatic recurrences	0%	18.21	[redacted]	[redacted]	17.79	[redacted]	[redacted]	0.42	[redacted]	[redacted]	£63,456
	25%	17.93	[redacted]	[redacted]	17.41	[redacted]	[redacted]	0.52	[redacted]	[redacted]	£50,441
	50%	17.65	[redacted]	[redacted]	17.04	[redacted]	[redacted]	0.62	[redacted]	[redacted]	£41,672
	75%	17.38	[redacted]	[redacted]	16.66	[redacted]	[redacted]	0.72	[redacted]	[redacted]	£35,361

Parameter	Value	Pertuzumab + trastuzumab + chemotherapy			Trastuzumab + chemotherapy			Pertuzumab + trastuzumab + chemotherapy vs trastuzumab + chemotherapy			
		Life Years	QALYs	Costs	Life Years	QALYs	Costs	Life Years	QALYs	Costs	ICER (£/QALY)
	100%	17.10	[redacted]	[redacted]	16.29	[redacted]	[redacted]	0.82	[redacted]	[redacted]	£30,602
Definition of "Early" relapsers (months)	6	17.34	[redacted]	[redacted]	16.60	[redacted]	[redacted]	0.74	[redacted]	[redacted]	£33,994
	12	17.33	[redacted]	[redacted]	16.59	[redacted]	[redacted]	0.74	[redacted]	[redacted]	£34,025
	18	17.31	[redacted]	[redacted]	16.57	[redacted]	[redacted]	0.74	[redacted]	[redacted]	£34,087
	24	17.30	[redacted]	[redacted]	16.55	[redacted]	[redacted]	0.75	[redacted]	[redacted]	£34,169
Incremental treatment effect begins to decrease	48	17.20	[redacted]	[redacted]	16.57	[redacted]	[redacted]	0.63	[redacted]	[redacted]	£42,682
	60	17.24	[redacted]	[redacted]	16.57	[redacted]	[redacted]	0.67	[redacted]	[redacted]	£38,891
	72	17.28	[redacted]	[redacted]	16.57	[redacted]	[redacted]	0.71	[redacted]	[redacted]	£36,103
	84	17.31	[redacted]	[redacted]	16.57	[redacted]	[redacted]	0.74	[redacted]	[redacted]	£34,087
	96	17.34	[redacted]	[redacted]	16.57	[redacted]	[redacted]	0.76	[redacted]	[redacted]	£32,680
	108	17.35	[redacted]	[redacted]	16.57	[redacted]	[redacted]	0.78	[redacted]	[redacted]	£31,765
	120	17.36	[redacted]	[redacted]	16.57	[redacted]	[redacted]	0.79	[redacted]	[redacted]	£31,286
Maximum "cure" proportion	0%	15.61	[redacted]	[redacted]	14.86	[redacted]	[redacted]	0.75	[redacted]	[redacted]	£34,210
	20%	15.94	[redacted]	[redacted]	15.19	[redacted]	[redacted]	0.75	[redacted]	[redacted]	£34,015
	40%	16.29	[redacted]	[redacted]	15.54	[redacted]	[redacted]	0.75	[redacted]	[redacted]	£33,899
	60%	16.68	[redacted]	[redacted]	15.93	[redacted]	[redacted]	0.75	[redacted]	[redacted]	£33,881
	80%	17.09	[redacted]	[redacted]	16.35	[redacted]	[redacted]	0.74	[redacted]	[redacted]	£33,982
	100%	17.54	[redacted]	[redacted]	16.80	[redacted]	[redacted]	0.74	[redacted]	[redacted]	£34,232
"Cure" proportion begins to increase	48	17.31	[redacted]	[redacted]	16.57	[redacted]	[redacted]	0.74	[redacted]	[redacted]	£34,087
	60	17.22	[redacted]	[redacted]	16.43	[redacted]	[redacted]	0.79	[redacted]	[redacted]	£31,409
	72	17.13	[redacted]	[redacted]	16.30	[redacted]	[redacted]	0.83	[redacted]	[redacted]	£29,277
	84	17.04	[redacted]	[redacted]	16.19	[redacted]	[redacted]	0.86	[redacted]	[redacted]	£27,722

Parameter	Value	Pertuzumab + trastuzumab + chemotherapy			Trastuzumab + chemotherapy			Pertuzumab + trastuzumab + chemotherapy vs trastuzumab + chemotherapy			
		Life Years	QALYs	Costs	Life Years	QALYs	Costs	Life Years	QALYs	Costs	ICER (£/QALY)
	96	16.95	[redacted]	[redacted]	16.07	[redacted]	[redacted]	0.88	[redacted]	[redacted]	£26,864
	108	16.85	[redacted]	[redacted]	15.97	[redacted]	[redacted]	0.88	[redacted]	[redacted]	£26,628
	120	16.76	[redacted]	[redacted]	15.89	[redacted]	[redacted]	0.88	[redacted]	[redacted]	£26,871

Abbreviations: ICER, incremental cost-effectiveness ratio; IDFS, invasive disease-free survival; QALYs, quality-adjusted life year.

B.3.8.4 Summary of sensitivity analyses results

PSA results are compared to the base case in Table 52. The PSA simulations produced a mean ICER of £33,621/QALY gained. This value is close to the base case value of £34,087/QALY gained. Furthermore, the cost-effectiveness acceptability curve showed that the pertuzumab + trastuzumab + chemotherapy arm had a ~17% probability of being the most cost-effective treatment at the £30,000 willingness-to pay-threshold.

The results of the univariate sensitivity analysis show that the model drivers were the administration costs associated with maintenance doses and utilities in the first- and second-line mBC health states. The lowest ICER produced was £32,418/QALY gained. This result was generated using the upper value (£334.65) for the administration cost in the loading cycles of the trastuzumab + chemotherapy arm. When using the upper value for the administration cost in the loading cycles of the pertuzumab + trastuzumab + chemotherapy arm, the highest ICER was generated (£35,968/QALY gained). The analysis around administration cost in the loading cycles of the pertuzumab + trastuzumab + chemotherapy arm also produced the largest range in ICERs (£32,601–£35,968/QALY gained).

Many scenario analyses were conducted as part of this submission. The parameters varied included those pertaining to the model settings, clinical parameters, health state utilities, and cost and resource use. ICERs produced by the scenario analysis ranged from £14,929/QALY gained (Hedden *et al*.[118] as the source of eBC health state utilities) to £63,456/QALY gained (proportion of metastatic recurrences set to 0%).

This analysis was limited by the availability of relevant data. To compensate for the shortfall in data, assumptions and expert opinion were utilised. These factors introduced a degree of uncertainty into the analysis. The company is aware of this uncertainty, hence the extensive sensitivity analysis that has been documented in this section.

B.3.9 *Subgroup analysis*

The analysis and results described above pertain to the node-positive population, a subgroup of the APHINITY ITT cohort. As stated in Section B.3.2, an analysis in a second subgroup of the ITT population (patients with hormone receptor-negative disease) has also been conducted as part of this appraisal. The methodology and results associated with this analysis are available in Appendix M.

B.3.10 *Validation*

The modelling approach and structure described here is consistent with various other oncology models and previous submissions to NICE in the BC therapy area. The methodology described above has broadly adhered to the guidelines stipulated in the NICE reference case. Instances in which Roche has deviated from this guide have been highlighted and justified.

The general modelling approach and inputs were cross referenced with previous technology appraisals and subsequently validated by external health economists and UK clinical experts. The purpose of this validation was to ensure the model was both theoretically sound and reflective of clinical practice.

Clinical data have been incorporated into the model from the APHINITY study and long-term clinical trial data. This methodology is described fully in Section B.3.3. Clinical outcomes in both arms of the model have been extensively compared and validated against relevant evidence to assess the accuracy of modelled survival (see Appendix J). Furthermore, the relationship of DFS (and IDFS) to OS has also been described in detail in Appendix J.

This analysis took the perspective of the UK NHS. The health states included in this evaluation are similar to those of the neoadjuvant pertuzumab appraisal.[67] Consequently, health state cost and resource use used here mirrors that of the neoadjuvant submission. A comparison of the two sets of health state costs can be found in Table 45.

A formal quality assessment and validation of model outcomes was conducted by an independent assessor prior to submission. A technical cell by cell verification of formulas, functions and coding was performed as part of this process. In addition, a number of 'pressure tests' were conducted, often using extreme values. The results of the model using these values were then compared to expected outputs to assess functional accuracy.

B.3.11 *Interpretation and conclusions of economic evidence*

This economic evaluation focused on assessing the cost-effectiveness of pertuzumab for the adjuvant treatment of patients with HER2-positive eBC from a UK health system perspective.

The model draws upon clinical data from the APHINITY study: an ongoing, Phase III, randomised, placebo-controlled study in patients with operable HER2-positive eBC. The focus of the economic analysis was the node-positive population of APHINITY, justification of this approach has been provided in Section B.3.2. The baseline characteristics of the node-positive patients in APHINITY have been validated by clinical experts and can be considered broadly representative of the corresponding population in the UK.[105] This evaluation can therefore be considered relevant to clinical practice in England and Wales.

The EQ-5D questionnaire was administered as part of the APHINITY trial. No clinically significant difference was observed between responses of the two treatment arms. Therefore, EQ-5D data was pooled and health state utilities, irrespective of treatment arm, were derived and applied as such in the model. This methodology is in-line with the guidance stipulated in the NICE Reference Case.

A UK NHS perspective was taken with respect to the costs and resource use quantified in the model. All costs were taken from published UK sources or previous NICE technology appraisals in this disease area. Once again, this methodology is in accordance with that of the NICE Reference Case.

As reported in Table 50, the pertuzumab + trastuzumab + chemotherapy arm was associated with a gain of 17.31 life-years, an increase of 0.742 compared to the trastuzumab + chemotherapy arm. Pertuzumab + trastuzumab + chemotherapy is also associated with an incremental QALY gain of [redacted]. Given the modelling approach, this differential is driven solely by the time to recurrence benefit seen in the pertuzumab arm. As a result of a surrogate endpoint validation study, this incremental gain in IDFS has been shown to correlate with an OS gain– please see Appendix J for further details.

The base case ICER when comparing pertuzumab + trastuzumab + chemotherapy to trastuzumab + chemotherapy in the node-positive population is £34,087/QALY gained. Please note that this ICER has been generated when incorporating confidential discounts on the list prices of pertuzumab, trastuzumab IV and trastuzumab SC.

The situation regarding trastuzumab biosimilars has been iterated in full in Section B.3.7.2. Briefly, trastuzumab biosimilars are not currently available in the UK yet they will become available before the first appraisal committee meeting. When available, biosimilars are expected to have a sizable impact on the cost-effectiveness of pertuzumab in this setting. Base case results presented in this analysis reflect the market at the time of submission, however results of a “modified base case” have also been presented in Section B.3.7.2. These modified results are believed to be a more accurate representation of the cost-effectiveness of pertuzumab in eBC. Roche is cognizant of the fact that assumptions regarding biosimilar price and market share are uncertain and are expected to change over time.

Extensive sensitivity and scenario analyses have been conducted to test the robustness of model results when parameter values were manipulated, alternative approaches implemented, and different data sources utilised. Complete results of these analyses can be found in Section B.3.8. Main drivers of the cost-effectiveness results were found to be the administration costs of subsequent cycles of pertuzumab + trastuzumab + chemotherapy and trastuzumab (in the trastuzumab + chemotherapy arm) and utilities in mBC.

The key strengths associated with the presented cost-effectiveness analysis surround its use of the best available evidence to inform the model:

- Clinical effectiveness data taken from a randomised placebo-controlled trial (APHINITY) which included the current standard of care in the UK as the comparator.
- Health state utilities derived directly from EQ-5D data collected in the population of interest during the APHINITY study.
- Costs and resource use data taken from well-established UK sources and previous NICE technology appraisals.
- Extensive sensitivity and scenario analyses conducted to quantify uncertainty and identify major drivers of cost-effectiveness results.
- Comprehensive external validation undertaken using TA424, ID523, and available evidence from long-term clinical studies.

Limitations associated with this analysis are analogous to those seen across recent economic evaluations in general. Major uncertainties stem from the lack of observed data pertaining to pertuzumab and the as yet unknown impact of trastuzumab biosimilars in this market.

The analysis presented here could be strengthened in two respects. First, a greater cache of clinical data documenting pertuzumab therapy in eBC. The APHINITY trial is still ongoing, therefore the uncertainty associated with extrapolations and treatment effect in the medium term is likely to be lessened somewhat with later data read-outs. Secondly, the reduction of uncertainty associated with the price and market share of trastuzumab biosimilars. It is expected that trastuzumab biosimilars will enter the UK market shortly after the submission of this dossier (April 2018). Once these drugs are readily available in the UK, it is expected that far more will become known in terms of their list prices and uptake. Roche does however understand that these parameters are likely to be dynamic in nature and are expected to evolve over time.

Ultimately, the methodology detailed in this document is believed to have produced a robust economic analysis. It should be noted however, that the base case settings of the model (0% biosimilar market share), fail to fully capture the cost-effectiveness of pertuzumab in the adjuvant treatment of eBC.

B.4 References

1. Curigliano G, Burstein HJ, E PW, et al. De-escalating and escalating treatments for early-stage breast cancer: the St. Gallen International Expert Consensus Conference on the Primary Therapy of Early Breast Cancer 2017. *Ann Oncol* 2017;28:1700-1712.
2. von Minckwitz G, Procter M, de Azambuja E, et al. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. *NEJM* 2017;377:122-131.
3. NICE. Pertuzumab for the adjuvant treatment of HER2-positive breast cancer - Final scope. Available at: www.nice.org.uk/guidance/gid-ta10184/documents/final-scope. Accessed January 2018.
4. Electronic Medicines Compendium (eMC). Perjeta 420 mg concentrate for solution for infusion. Summary of product characteristics. Available at: www.medicines.org.uk/emc/medicine/27473/. Accessed November 2017.
5. Fendly BM, Winget M, Hudziak RM, et al. Characterization of murine monoclonal antibodies reactive to either the human epidermal growth factor receptor or HER2/neu gene product. *Cancer Res* 1990;50:1550-1558.
6. Franklin MC, Carey KD, Vajdos FF, et al. Insights into ErbB signaling from the structure of the ErbB2-pertuzumab complex. *Cancer Cell* 2004;5:317-328.
7. Nahta R, Hung MC, Esteva FJ. The HER-2-targeting antibodies trastuzumab and pertuzumab synergistically inhibit the survival of breast cancer cells. *Cancer Res* 2004;64:2343-2346.
8. Scheuer W, Friess T, Burtscher H, et al. Strongly enhanced antitumor activity of trastuzumab and pertuzumab combination treatment on HER2-positive human xenograft tumor models. *Cancer Res* 2009;69:9330-9336.
9. Roche Media Release. FDA grants Roche's Perjeta accelerated approval for use before surgery in people with HER2-positive early stage breast cancer. 1 October 2013. Available at: www.roche.com/dam/jcr:a7067ac5-4e90-4414-a433-0ec8b1b13d05/en/med-cor-2013-10-01-e.pdf. Accessed January 2018.
10. FDA. Perjeta Highlights of Prescribing Information. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2017/125409s113s118lbl.pdf. Accessed January 2018.
11. NICE. TA107: Trastuzumab for the adjuvant treatment of early-stage HER2-positive breast cancer. Available at: www.nice.org.uk/Guidance/TA107. Accessed September 2017.
12. NICE. CG80: Early and locally advanced breast cancer: diagnosis and treatment. Available at: www.nice.org.uk/Guidance/CG80. Accessed September 2017.
13. Wolff A, Hammond M, Hicks D, et al. Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Update. *J Clin Oncol* 2013;31:3997-4013.
14. Cancer Research UK. Breast Cancer Statistics. Available at: www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer#heading-Zero. Accessed September 2017.
15. Rakha E, Pinder S, Bartlett J, et al. Updated UK Recommendations for HER2 assessment in breast cancer. *J Clin Pathol* 2015;68:93-99.
16. Borg A, Tandon AK, Sigurdsson H, et al. HER-2/neu amplification predicts poor survival in node-positive breast cancer. *Cancer Res* 1990;50:4332-4337.
17. Ross JS, Fletcher JA. The HER-2/neu Oncogene in Breast Cancer: Prognostic Factor, Predictive Factor, and Target for Therapy. *Oncologist* 1998;3:237-252.
18. Menard S, Fortis S, Castiglioni F, et al. HER2 as a prognostic factor in breast cancer. *Oncology* 2001;61 Suppl 2:67-72.
19. Brown M, Tsodikov A, Bauer KR, et al. The role of human epidermal growth factor receptor 2 in the survival of women with estrogen and progesterone receptor-negative, invasive breast cancer: the California Cancer Registry, 1999-2004. *Cancer* 2008;112:737-747.

20. Curigliano G, Viale G, Bagnardi V, et al. Clinical relevance of HER2 overexpression/amplification in patients with small tumor size and node-negative breast cancer. *J Clin Oncol* 2009;27:5693-5699.
21. Ross JS, Slodkowska EA, Symmans WF, et al. The HER-2 receptor and breast cancer: ten years of targeted anti-HER-2 therapy and personalized medicine. *Oncologist* 2009;14:320-368.
22. Slamon D, Clark G, Wong S, et al. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science* 1987;235:177-182.
23. Subbiah IM, Gonzalez-Angulo AM. Advances and future directions in the targeting of HER2-positive breast cancer: implications for the future. *Curr Treat Options Oncol* 2014;15:41-54.
24. Kwan ML, Kushi LH, Weltzien E, et al. Epidemiology of breast cancer subtypes in two prospective cohort studies of breast cancer survivors. *Breast Cancer Res* 2009;11:R31.
25. Neven P, Van Calster B, Van den Bempt I, et al. Age interacts with the expression of steroid and HER-2 receptors in operable invasive breast cancer. *Breast Cancer Res Tr* 2008;110:153-159.
26. Strasser-Weippl K, Horick N, Smith IE, et al. Long-term hazard of recurrence in HER2+ breast cancer patients untreated with anti-HER2 therapy. *Breast Cancer Research: BCR* 2015;17:56.
27. Cameron D, Piccart-Gebhart MJ, Gelber RD, et al. 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. *Lancet* 2017;389:1195-1205.
28. 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* 2014;32:3744-3752.
29. Slamon DJ, Eiermann W, Robert NJ, et al. S5-04: Ten year follow-up of BCIRG 006 comparing doxorubicin plus cyclophosphamide followed by docetaxel (AC→T) with doxorubicin plus cyclophosphamide followed by docetaxel and trastuzumab (AC→TH) with docetaxel, carboplatin and trastuzumab (TCH) in HER2+ early breast cancer. Presented at SABCS 2015.
30. Gianni L, Pienkowski T, Im Y-H, et al. 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. *The Lancet Oncology* 2012;13:25-32.
31. Schneeweiss A, Chia S, Hickish T, et al. 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). *Ann Oncol* 2013;24:2278-2284.
32. Swain SM, Baselga J, Kim SB, et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. *NEJM* 2015;372:724-734.
33. BreastCancer.org. Lymph Node Involvement. Available at: www.breastcancer.org/symptoms/diagnosis/lymph_nodes. Accessed September 2017.
34. Cancer Research UK. Lymph node ultrasound and biopsy. Available at: www.cancerresearchuk.org/about-cancer/breast-cancer/getting-diagnosed/tests-stage/lymph-node-ultrasound-biopsy. Accessed January 2018.
35. Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. *Lancet* 2014;384:164-172.
36. National Cancer Intelligence Network. The Second All Breast Cancer Report: Focussing on Inequalities: Variation in breast cancer outcomes with age and deprivation. Available at: www.ncin.org.uk/publications. Accessed November 2017.
37. NICE. TA108: Paclitaxel for the adjuvant treatment of early node-positive breast cancer. Available at: www.nice.org.uk/guidance/ta108. Accessed September 2017.
38. NICE. TA109: Docetaxel for the adjuvant treatment of early node-positive breast cancer. Available at: www.nice.org.uk/guidance/ta109. Accessed September 2017.

39. BreastCancer.org. Hormone Receptor Status. Available at: www.breastcancer.org/symptoms/diagnosis/hormone_status. Accessed January 2018.
40. Untch M, Gelber RD, Jackisch C, et al. Estimating the magnitude of trastuzumab effects within patient subgroups in the HERA trial. *Ann Oncol* 2008;19:1090-1096.
41. Wardley A, Fredriksson J, Leslie I, et al. Anti-cancer resource use in the initial management of advanced HER2+ breast cancer: an interim analysis of the UK ESTHER study. Submitted abstract EBCC-0377 2018.
42. Baselga J, Cortes J, Kim SB, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *N Engl J Med* 2012;366:109-119.
43. Kim P. Cost of cancer care: the patient perspective. *J Clin Oncol* 2007;25:228-232.
44. NCRI. Press Release: Lung Cancer UK Price Tag Eclipses The Cost Of Any Other Cancer. National Cancer Research Institute Press Release. Wednesday 7th November 2012.
45. Lidgren M, Wilking N, Jonsson B, et al. Health related quality of life in different states of breast cancer. *Qual Life Res* 2007;16:1073-1081.
46. Burgess C, Cornelius V, Love S, et al. Depression and anxiety in women with early breast cancer: five year observational cohort study. *BMJ* 2005;330:702.
47. Groenvold M. Health-related quality of life in early breast cancer. *Dan Med Bull* 2010;57:B4184.
48. Bukovic D, Fajdic J, Hrgovic Z, et al. Sexual dysfunction in breast cancer survivors. *Onkologie* 2005;28:29-34.
49. Mayer M, Huñis A, Oratz R, et al. Living with metastatic breast cancer: a global patient survey. *Community Oncology* 2010;7:406-412.
50. Longo CJ, Fitch M, Deber RB, et al. Financial and family burden associated with cancer treatment in Ontario, Canada. *Support Care Cancer* 2006;14:1077-1085.
51. Wagner CD, Bigatti SM, Storniolo AM. Quality of life of husbands of women with breast cancer. *Psychooncology* 2006;15:109-120.
52. Verrill M, Schmid P, Retzler J, et al. PCN234: Work productivity in HER2 positive breast cancer: a comparison of patients across stages of early and metastatic disease. Presented at ISPOR Annual European Conference 2017.
53. Grabsch B, Clarke DM, Love A, et al. Psychological morbidity and quality of life in women with advanced breast cancer: a cross-sectional survey. *Palliat Support Care* 2006;4:47-56.
54. Wallwiener M, Simoes E, Sokolov AN, et al. Health-related Quality of Life in Metastatic and Adjuvant Breast Cancer Patients. *Geburtshilfe und Frauenheilkunde* 2016;76:1065-1073.
55. Foster T, Miller J, Boye M, et al. The Economic Burden of Metastatic Breast Cancer: A Systematic Review of Literature from Developed Countries. *Cancer Treatment Reviews* 2011;37:405-415.
56. Verrill M, Wardley A, Retzler J, et al. P6-12-14: Quality of life and ability to work in patients at different disease stages of HER2+ breast cancer. Presented at SABCS 2017.
57. Yin W, Horblyuk R, Perkins JJ, et al. Breast cancer progression and workplace productivity. *J Clin Oncol* 2015;33:6586-6586.
58. Aranda S, Schofield P, Weih L, et al. Mapping the quality of life and unmet needs of urban women with breast cancer, 2005.
59. Marty M, Cognetti F, Maraninchi D, et al. Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: the M77001 study group. *J Clin Oncol* 2005;23:4265-4274.
60. Haddad TC, Goetz MP. Landscape of neoadjuvant therapy for breast cancer. *Ann Surg Oncol* 2015;22:1408-1415.
61. Chatterjee A, Erban JK. Neoadjuvant therapy for treatment of breast cancer: the way forward, or simply a convenient option for patients? *Gland surgery* 2017;6:119.
62. NICE Pathways. Adjuvant therapy for early and locally advanced breast cancer. Available at: https://pathways.nice.org.uk/pathways/early-and-locally-advanced-breast-cancer#path=view%3A/pathways/early-and-locally-advanced-breast-cancer/adjuvant-

therapy-for-early-and-locally-advanced-breast-cancer.xml&content=view-index. Accessed September 2017.
63. Senkus E, Kyriakides S, Ohno S, et al. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. *Ann Oncol* 2015;26:v8-v30.
64. Gnant M, Thomssen C, Harbeck N. St. Gallen/Vienna 2017: A Brief Summary of the Consensus Discussion about Escalation and De-Escalation of Primary Breast Cancer Treatment. *Breast Care* 2017;12:102-107.
65. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®), Breast Cancer - Version 3.2017 - November 10, 2017. Available at: www.nccn.org/professionals/physician_gls/default.aspx. Accessed November 2017.
66. Yee D, DeMichele A, Isaacs C, et al. GS3-08: Pathological complete response predicts event-free and distant disease-free survival in the I-SPY2 TRIAL. Presented at SABCS 2017.
67. NICE. TA424: Pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer. Available at: www.nice.org.uk/guidance/ta424. Accessed August 2017.
68. Aebi S, Davidson T, Gruber G, et al. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2011;22 Suppl 6:vi12-24.
69. Cardoso F, Costa A, Norton L, et al. 1st International consensus guidelines for advanced breast cancer (ABC 1). *The Breast* 2012;21:242-252.
70. Carlson RW, Allred DC, Anderson BO, et al. Breast cancer. Clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 2009;7:122-192.
71. Mauri D, Pavlidis N, Ioannidis JP. Neoadjuvant versus adjuvant systemic treatment in breast cancer: a meta-analysis. *J Natl Cancer Inst* 2005;97:188-194.
72. Jackisch C, Piccart MJ, Gelber RD, et al. Poster PD5-01: HERA trial: 10 year follow up of trastuzumab after adjuvant chemotherapy in HER2 positive early breast cancer – Final analysis. 2015.
73. Committee for Medicinal Products for Human Use. Assessment Report - Perjeta EMA/CHMP/285991/2015. 25 June 2015. Available at: www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/002547/WC500191986.pdf. Accessed January 2018.
74. Clinicaltrials.gov. APHINITY study record (NCT01358877). Available at: https://clinicaltrials.gov/ct2/show/NCT01358877. Accessed September 2017.
75. Roche Products Ltd. APHINITY (BO25126) Primary Clinical Study Report No. 1075429, July 2017.
76. von Minckwitz G, Procter M, de Azambuja E, et al. LBA005: The APHINITY Study. Adjuvant Pertuzumab and Herceptin in Initial Therapy. . Presented at the American Society of Clinical Oncology (ASCO) Annual Meeting. 2-6th June 2017. Chicago, IL, USA.
77. F. Hoffmann-La Roche Ltd. Clinical Study Protocol BIG 4-11/BO25126/TOC4939G Amendment D. 2015.
78. Hudis CA, Barlow WE, Costantino JP, et al. Proposal for standardized definitions for efficacy end points in adjuvant breast cancer trials: the STEEP system. *J Clin Oncol* 2007;25:2127-2132.
79. Slamon D, Eiermann W, Robert N, et al. Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med* 2011;365:1273-1283.
80. NICE. Single technology appraisal: User guide for company evidence submission template. Available at: www.nice.org.uk/process/pmg24/chapter/instructions-for-companies. Accessed December 2017.
81. University of York. Centre for Reviews Dissemination. Systematic reviews: CRD's guidance for undertaking reviews in health care. 2009. Available at: www.york.ac.uk/media/crd/Systematic_Reviews.pdf. Accessed February 2018:
82. Cherny NI, Sullivan R, Dafni U, et al. A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). *Ann Oncol* 2015;26:1547-1573.

83. Osoba D, Rodrigues G, Myles J, et al. Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol* 1998;16:139-144.
84. Bines J, de Azambuja E, Zardavas D, et al. P1-13-07: Incidence and management of diarrhea with adjuvant pertuzumab and trastuzumab in HER2-Positive breast cancer. Presented at SABCS 2017.
85. Clinicaltrials.gov. BERENICE Study Record (NCT02132949). Available at: https://clinicaltrials.gov/ct2/show/NCT02132949. Accessed August 2017.
86. Swain SM, Ewer MS, Viale G, et al. Pertuzumab, trastuzumab, and standard anthracycline- and taxane-based chemotherapy for the neoadjuvant treatment of patients with HER2-positive localized breast cancer (BERENICE): a phase II, open-label, multicenter, multinational cardiac safety study. *Ann Oncol* 2017.
87. Agus DB, Akita RW, Fox WD, et al. Targeting ligand-activated ErbB2 signaling inhibits breast and prostate tumor growth. *Cancer Cell* 2002;2:127-137.
88. Cancer Research UK. Breast Cancer Incidence (Invasive) Statistics. Available at: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer/incidence-invasive#heading-Zero. Accessed February 2018.
89. Cianfrocca M, Goldstein LJ. Prognostic and predictive factors in early-stage breast cancer. *Oncologist* 2004;9:606-616.
90. Savina M, Jacot W, Mathoulin-Pe´lissier S, et al. 161PD: Surrogate endpoints for overall survival in randomized controlled trials evaluating adjuvant treatment for breast cancer: A meta-analysis. Presented at ESMO 2017.
91. Piedbois P, Buyse M. Endpoints and surrogate endpoints in colorectal cancer: a review of recent developments. *Current opinion in oncology* 2008;20:466-471.
92. Roche Data on File. Burzykowski T, Buyse M, Quinaux E et al. Evaluation of disease-free survival and other time-to-event endpoints as surrogates for overall survival in the systemic therapy of HER-2-positive early breast cancer. Progress Report 2. 19th December 2017.
93. Clinicaltrials.gov. PURPOSE Study Record (NCT03099200). Available at: https://clinicaltrials.gov/ct2/show/NCT03099200. Accessed September 2017.
94. Dahabreh IJ, Linardou H, Siannis F, et al. Trastuzumab in the adjuvant treatment of early-stage breast cancer: a systematic review and meta-analysis of randomized controlled trials. *Oncologist* 2008;13:620-630.
95. Early Breast Cancer Trialists' Collaborative G. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. *The Lancet* 2012;379:432-444.
96. Yin W, Jiang Y, Shen Z, et al. Trastuzumab in the Adjuvant Treatment of HER2-Positive Early Breast Cancer Patients: A Meta-Analysis of Published Randomized Controlled Trials. *PLOS ONE* 2011;6:e21030.
97. Möbus V, Hell S, Schmidt M. Assessing the clinical benefit of systemic adjuvant therapies for early breast cancer. *Geburtshilfe und Frauenheilkunde* 2017;77:1079-1087.
98. Early Breast Cancer Trialists' Collaborative G. Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. *Lancet* 2015;386:1341-1352.
99. Petrelli F, Cabiddu M, Coinu A, et al. Adjuvant dose-dense chemotherapy in breast cancer: a systematic review and meta-analysis of randomized trials. *Breast Cancer Res Treat* 2015;151:251-259.
100. Clinicaltrials.gov. KRISTINE Study Record (NCT02131064). Available at: https://clinicaltrials.gov/ct2/show/NCT02131064. Accessed August 2017.
101. Roche Products Ltd. Advisory board report: Understanding the treatment landscape for adjuvant treatment in HER2-postitive early breast cancer with the APHINITY Study. Available on request. 2017.
102. Squires H, Pandor A, Thokala P, et al. Pertuzumab for the Neoadjuvant Treatment of Early-Stage HER2-Positive Breast Cancer: An Evidence Review Group Perspective of a NICE Single Technology Appraisal. *Pharmacoeconomics* 2017;36:29-38.

103. Ward S, Pilgrim H, Hind D. Trastuzumab for the treatment of primary breast cancer in HER2-positive women: a single technology appraisal. *Health Technol Assess* 2006;13:1-6.
104. NICE. Guide to the methods of technology appraisal 2013: The reference case. Available at: www.nice.org.uk/process/pmg9/chapter/the-reference-case. Accessed January 2018.
105. Roche Products Ltd. Advisory board report: Health Technology Assessment (HTA) Advisory Board: Perjeta® (pertuzumab) for the Adjuvant Treatment of Human Epidermal Growth Factor Receptor 2-Positive (HER2+) Early Breast Cancer. Available on request. 2017.
106. Electronic Medicines Compendium (eMC). Herceptin 150 mg powder for concentrate for solution for infusion. Summary of product characteristics. Available at: www.medicines.org.uk/emc/medicine/3567/. Accessed November 2017.
107. Latimer N. NICE DSU Technical Support Document 14: Survival Analysis for Economic Evaluations Alongside Clinical Trials - Extrapolation with Patient-level Data. 2013. Available at: http://scharr.dept.shef.ac.uk/nicedsu/wp-content/uploads/sites/7/2016/03/NICE-DSU-TSD-Survival-analysis.updated-March-2013.v2.pdf.
108. Kristeleit H, Parton M, Beresford M, et al. Long-term follow-up data from pivotal studies of adjuvant trastuzumab in early breast cancer. *Targeted oncology* 2016;11:579-591.
109. Gianni L, Pienkowski T, Im YH, et al. 5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial. *Lancet Oncol* 2016;17:791-800.
110. Office for National Statistics. National life tables: United Kingdom. Available at: www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables. Accessed January 2018.
111. Dieras V, Miles D, Verma S, et al. Trastuzumab emtansine versus capecitabine plus lapatinib in patients with previously treated HER2-positive advanced breast cancer (EMILIA): a descriptive analysis of final overall survival results from a randomised, open-label, phase 3 trial. *Lancet Oncol* 2017;18:732-742.
112. Hamilton SN, Tyldesley S, Li D, et al. Second malignancies after adjuvant radiation therapy for early stage breast cancer: is there increased risk with addition of regional radiation to local radiation? *Int J Radiat Oncol Biol Phys* 2015;91:977-985.
113. Marty M, Cognetti F, Maraninchi D, et al. Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2–positive metastatic breast cancer administered as first-line treatment: the M77001 study group. *Journal of clinical oncology* 2005;23:4265-4274.
114. EORTC. EORTC Quality of Life: Glossary. Available at: http://groups.eortc.be/qol/glossary. Accessed January 2018.
115. Tan ML, Idris DB, Teo LW, et al. Validation of EORTC QLQ-C30 and QLQ-BR23 questionnaires in the measurement of quality of life of breast cancer patients in Singapore. *Asia Pac J Oncol Nurs* 2014;1:22-32.
116. Lloyd A, Nafees B, Narewska J, et al. Health state utilities for metastatic breast cancer. *Br J Cancer* 2006;95:683-690.
117. Fleeman N, Bagust A, Beale S, et al. Pertuzumab in combination with trastuzumab and docetaxel for the treatment of HER2-positive metastatic or locally recurrent unresectable breast cancer. *Pharmacoeconomics* 2015;33:13-23.
118. Hedden L, O'Reilly S, Lohrisch C, et al. Assessing the real-world cost-effectiveness of adjuvant trastuzumab in HER-2/neu positive breast cancer. *Oncologist* 2012;17:164-171.
119. Paracha N. Assessing the contribution of patients' proximity to death in economic evaluations in patients with HER2+ metastatic breast cancer: an event based analysis. SMDM 16th Biennial European Conference. *London, UK*, 2016.
120. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. *Value Health* 2010;13:509-518.

121. EMA. Ontruzant Product Information. Available at: www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/004323/human_med_002188.jsp&mid=WC0b01ac058001d124. Accessed February 2018.
122. Roche Market Research. Available on request.
123. Department of Health and Social Care. NHS reference costs 2016 to 2017. Available at: https://improvement.nhs.uk/resources/reference-costs/. Accessed January 2018.
124. Personal Social Services Research Unit. Unit Costs of Health and Social Care 2017. Available at: www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2017/.
125. NHS National Tariff. Annex A: The national process and national tariff workbook. Available at: https://improvement.nhs.uk/resources/national-tariff-1719/. Accessed February 2018.
126. Millar D, Corrie P, Hill M, et al. PCN74 A service evaluation to compare secondary care resource use between Xelox and Folfox-6 regimens in the treatment of metastatic colorectal cancer (MCRC) from a UK National Health Service (NHS) perspective. *Value in Health* 2008;11:A483.

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Single technology appraisal

Pertuzumab for adjuvant treatment of early HER2-positive breast cancer [ID1192]

Dear Company,

The Evidence Review Group, Warwick Evidence, and the technical team at NICE have looked at the submission received on 9 February 2018 from Roche. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on **Tuesday 20 March 2018**. Your response and any supporting documents should be uploaded to NICE Docs.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Boglarka Mikudina, Technical Lead (Boglarka.Mikudina@nice.org.uk). Any procedural questions should be addressed to Thomas Feist, Project Manager (Thomas.Feist@nice.org.uk).

Yours sincerely

Eleanor Donegan
Technical Adviser – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for confidential information

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Clarifications for the Company

Literature searching

1. For Company Submission (CS), Appendix G, Tables 15 and 16, please supply an additional column with numbers retrieved for each line. This will aid the ERG in critiquing the MEDLINE, MEDLINE In-Process and Embase search strategies.

2. Please provide the following four missing references from the reference pack:

   92. Roche Data on File. Burzykowski T, Buyse M, Quinaux E et al. Evaluation of disease-free survival and other time-to-event endpoints as surrogates for overall survival in the systemic therapy of HER-2-positive early breast cancer. Progress Report 2. 19th December 2017. Cited on page 54 of CS.

   101. Roche Products Ltd. Advisory board report: Understanding the treatment landscape for adjuvant treatment in HER2-postitive early breast cancer with the APHINITY Study. Available on request. 2017. Cited on page 55 of CS.

   105. Roche Products Ltd. Advisory board report: Health Technology Assessment (HTA) Advisory Board: Perjeta® (pertuzumab) for the Adjuvant Treatment of Human Epidermal Growth Factor Receptor 2-Positive (HER2+) Early Breast Cancer. Available on request. 2017. Cited on pages 58, 65, 76, 127 of CS.

   122. Roche Market Research. Available on request. Cited on page 95 of CS.

Section A: Clarification on effectiveness data

A1. **Priority question: Credibility of selection of subgroups:** On pages 8 and 33 of CS, Document A, the company states that node-positive and hormone receptor-negative patients were “pre-specified” subgroups in the trial.

   a. Please clarify how these subgroups (nodal status and hormone receptor status) were pre-specified.

   b. Please justify the rationale for not including in the decision problem the other specified subgroups in the APHINITY trial protocol (section 8.1.2.4).

A2. **Priority question:** Please provide APHINTY Protocol version A and B and details of when the protocol was amended (month and year), and the BCIRG-006 trial protocol.

A3. **Priority question:** Please explain the mechanism(s) for the delayed effect of pertuzumab as shown in the survival curves (see CS, Document B, Figure 3 and Document A Figure 4)?

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A4. In the CS, Document B, on page 47 it was stated that: "Treatment was discontinued for safety reasons by 7.8% and 6.4% of patients in the pertuzumab and placebo arms, respectively". Please clarify what were the 'safety reasons' listed for each discontinuation?

Section B: Clarification on cost-effectiveness data

B1. **Priority question:** In the CS, Document B, on page 77 it was stated that: *"In the model, it is assumed that every disease recurrence observed within 18 months after initiation of adjuvant therapy is a metastatic recurrence. These patients are expected to have a worse prognosis and will therefore receive a more aggressive treatment. Survival estimates derived from the EMILIA study (study of trastuzumab emtansine in second-line mBC)[111] are used to model the survival of patients who experience a metastatic recurrence within the first 18 months after adjuvant treatment initiation. In the EMILIA study, the corresponding population was selected to estimate the risk of disease progression (PFS) and the risk of death following progression."*

Please clarify whether APHINITY data were available to inform the survival of patients who experienced a metastatic recurrence, and if so, please explain the rationale for using estimates from EMILIA and report how the employed data from EMILIA compare to the respective survival estimates from APHINITY.

B2. **Priority question:** In the CS, Document B, on page 87 it was stated that: *"In this analysis, it is assumed that any disutility resulting from treatment-related AEs is reflected in the EQ-5D responses from the APHINITY study. It is possible that this approach underestimates the disutility associated with the AEs. Despite this, the incremental difference between treatment arms is thought to be negligible. Ultimately, this omission is not expected to significantly impact the overall cost-effectiveness results."*

The expectation that disutility due to AEs is reflected in EQ-5D responses is contentious; unless by design, it is unlikely that EQ-5D data were collected exactly on days that AEs were experienced. In addition, the company uses pooled utility values in their base case analysis. Given this, we feel it is important to account for AEs separately. Please present an analysis where the disutility of adverse events is taken into account.

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B3. **Priority question.** In the CS, Document B, on pages 103-104 it was stated that: *"Following the guidance received in recent technology appraisals in this disease area, the criteria used for the inclusion/exclusion of an AE in the model are outlined below:*

> *- Only AEs of Grade ≥3: Typically, clinicians will only intervene and treat an AE if it is severe enough to be classified as grade 3 or above. The costs and HRQoL effects associated with grade 1 and 2 events are therefore assumed to be negligible and hence omitted from this analysis.*
>
> *- Occur in ≥2% of patients: A reasonable assumption was made that an AE must have occurred in at least 2% of the study population to be included in the model."*

Please explain the rationale for inclusion of AEs only if they have occurred in at least 2% of the study population.

The assessment of AEs reported in the APHINITY trial shows that primary cardiac events occurred in 17 patients (0.7%) in the pertuzumab group and in 8 patients (0.3%) in the placebo group, with 15 (0.6%) patients in the pertuzumab group and 6 (0.2%) patients in the placebo group presenting NYHA class III or IV heart failure and a substantial decrease in left ventricular ejection fraction. The analysis of AEs also shows a substantial imbalance in proportions of patients with anaemia in the pertuzumab arm (n = 163, 6.9%) versus placebo (n = 113, 4.7%) Given this imbalance in primary cardiac events and anaemic events across groups and the fact that such events are expected to be detrimental for patients' HRQL and costly to resolve, please present total costs, total QALY and ICER values that take into account these events.

B4. In relation to the proportion of patients who experienced metastatic recurrence, non-metastatic recurrence and died, the CS, Document B, on page 75 suggests that: *"No meaningful differences were observed in the proportion of each Invasive disease-free survival (IDFS) events across the two treatment arms (i.e. the proportions of metastatic recurrence, non-metastatic recurrence, and deaths were broadly similar across the two treatment arms of the APHINITY study)."* Owing to this, *"the pooled proportion of metastatic vs. non-metastatic recurrences were applied to both arms in the model.* ***Error! Reference source not found.*** *provides a breakdown of IDFS events observed in each treatment arm of the node-positive population."*

Given the availability of data from the APHINITY trial, please explain the rationale for pooling the proportions of IDFS events across the two treatment arms and using this pooled value. Please adjust the economic model to allow for unpooled values for the proportion of IDFS events and provide further analyses where IDFS events for each arm correspond to APHINITY trial data for the particular arm.

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B5. In the CS, Document B, on pages 65-66 it was stated that: "*According to the AIC values, the exponential and log-logistic functions provide the best fit to the data in the pertuzumab + trastuzumab + chemotherapy and the placebo + trastuzumab + chemotherapy arms, respectively*" […] *"The technical support document, developed by Latimer et al., states that the same parametric function should be used across both treatment arms (where feasible).[107] Using the same type of function ensures consistency and limits potential problems such as the crossing of the curves. When considering the fit across the two arms jointly, the best fitting extrapolation is produced by the Log-logistic function."*

While the ERG agrees that using different distributions across treatment arms is not always feasible, please explain whether this is actually (rather than potentially) problematic in this particular case. Given the fact that different functions (exponential and log-logistic) provide the best fit to each of the two arms, the ERG would like the economic model to allow for different distribution types to be fitted to each arm.

B6. In the CS, Document B, on page 78 it was stated that: "*Patients are also at risk of death during their year in the non-metastatic recurrence health state. This risk of death applied here is the superior value between the risk of dying without recurrence (as observed in the APHINITY study) and background mortality in the age-adjusted UK population".*

Please justify using the risk of dying without recurrence to reflect the probability of a patient dying after they have experience a non-metastatic recurrence.

B7. In the CS, Document B, on pages 88-90 concerning metastatic health state utilities, in the absence of utility values for metastatic health states from APHINITY, utilities for such states have been taken from the literature (base case values from Lloyd et al; alternative values from Hedden et al; Lindgren et al and Paracha et al).

Please clarify the process that led to the identification and selection of these studies from which values were obtained for metastatic health states. If these studies were not identified and selected through a systematic process, please provide assurance that other relevant studies reporting utility values for metastatic states have not been missed?

B8. In the CS, Document B, on page 89 it was stated that: *"Health state utility estimates in patients with HER2-positive BC are available from a range of published sources. To present a more complete evaluation, utilities from these sources have also been included here as scenario analyses. A brief description of these sources is given below, along with an overview of how the estimates were incorporated into the model."*

Please clarify how 'utilities from other published sources' were identified and selected.

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B9. In the CS, Document B, Table 34, concerning the base case values for utilities of state IDFS (on treatment, on treatment/off chemotherapy and off treatment), Locoregional recurrence, Remission, First-line mBC and Second line mBC. Please clarify where the standard error values (0.004) were obtained from.

B10. With regards to the CS, Document B, Table 34, please provide additional information related to the base case utility values for health states '*IDFS - On treatment/off chemotherapy'* and '*IDFS - On chemotherapy'*. Please provide details on the calculations of utility values obtained from APHINITY, outlined as in the table below, for each population (ITT, Node+, HR). Please also confirm how the utility scores were calculated (whether they were averaged across all responses within a health state, or averaged within patients, and then within health state).

Health State	Pertuzumab Arm	Placebo Arm	Pooled
IDFS - On chemotherapy	Average Value: SD of Value: No. of responses: No. of patients who provided response: No. of patients in health state:	Average Value: SD of Value: No. of responses: No. of patients who provided response: No. of patients in health state:	Average Value: SD of Value: No. of responses: No. of patients who provided response: No. of patients in health state:
IDFS - On treatment / off chemotherapy	Average Value: SD of Value: No. of responses: No. of patients who provided response: No. of patients in health state:	Average Value: SD of Value: No. of responses: No. of patients who provided response: No. of patients in health state:	Average Value: SD of Value: No. of responses: No. of patients who provided response: No. of patients in health state:
IDFS - Off treatment	Average Value: SD of Value: No. of responses: No. of patients who provided response: No. of patients in health state:	Average Value: SD of Value: No. of responses: No. of patients who provided response: No. of patients in health state:	Average Value: SD of Value: No. of responses: No. of patients who provided response: No. of patients in health state:
Non-metastatic recurrence	Average Value: SD of Value: No. of responses: No. of patients who provided response: No. of patients in health state:	Average Value: SD of Value: No. of responses: No. of patients who provided response: No. of patients in health state:	Average Value: SD of Value: No. of responses: No. of patients who provided response: No. of patients in health state:
Remission	Average Value:	Average Value:	Average Value:

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	SD of Value: No. of responses: No. of patients who provided response: No. of patients in health state:	SD of Value: No. of responses: No. of patients who provided response: No. of patients in health state:	SD of Value: No. of responses: No. of patients who provided response: No. of patients in health state:

B11. Please provide standard errors for eBC health state utility values – scenario analysis' (utility values for all three IDFS states, locoregional recurrence, remission) in the CS, Document B, Table 34.

B12. The prevalence of AE in the economic model, as reported in CS, Document B, Table 46, do not appear to match those reported in B.2.10 for APHINITY trial, not even for the ITT population. Please could the company confirm the reported prevalence are correct and inform why they are different to section B.2.10.

B13. For clarity, please provide an additional table detailing the parameters that were subjected to probabilistic sensitivity analysis, together with the assigned distributions, their distribution parameters and the source of this information.

Section C: Clarification on statistics and survival analysis

C1. **Priority question:** Please provide a table with patient numbers in the different subgroups of the APHINITY trial as follows:

	Hormone Positive	**Hormone Negative**
Node Negative	Cell A	Cell B
Node Positive	Cell C	Cell D

Please provide summary of patient baseline statistics and Clinical Evidence comparing the trial arms (KM plots, hazard ratios for primary and secondary outcomes [stratified and un-stratified]) for the following sub groups:
Cell B only – Hormone Negative and Node Negative
Cell C only – Hormone Positive and Node Positive
Cell D only – Hormone Negative and Node Positive
Cell B + C + D combined – Node Positive or Hormone Negative

C2. **Priority question:** Please provide

- goodness of fit statistics,
- smoothed hazard vs time plots and
- cumulative hazard vs time plots

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for each of the parametric functions and overlaid with the observed data, where the parametric fit begins at 22 months for both arms and KM data used before this point, and also for the company base case (parametric fit from 0 months).

C3. **Priority question:** The ERG notes that the clinical data used in the submission for the APHINITY study is from December 2016. The ERG kindly request that the clinical and cost effectiveness analyses are updated with the most up-to-date data (e.g., December 2017). If this is not possible, then ERG request the summary data by treatment arm (numbers/percentages) for the main outcomes (IDFS, overall survival) for as recently as possible (e.g., December 2017).

C4. **Priority question:** Please present full results (hazard ratios and confidence intervals) of the stratified cox model fitted to the APHINITY trial data, for the primary outcome (IDFS). This could be in the form of a forest plot. Please present, as above, but also including the interaction of nodal status and hormone receptor status with treatment, if they are not already included in the model.

C5. Please provide a table with patient numbers in the different subgroups of the APHINITY trial as follows:

	Pre-Menopausal	**Post-Menopausal**
Node Negative	Cell A	Cell B
Node Positive	Cell C	Cell D

Please provide a summary of patient baseline statistics and clinical evidence (KM plots, hazard ratios for primary and secondary outcomes [stratified and un-stratified]) comparing the trial arms for the following subgroups:
Cell A – Pre Menopausal and Node Negative
Cell B – Post Menopausal and Node Negative
Cell C – Pre Menopausal and Node Positive
Cell D – Post Menopausal and Node Positive

C6. Please provide forest plots as in the CS, Document B, Figure 5, for the following factors:
Size of Tumour: <1cm, 1-5cm, 5+ cm
Grade of Tumour: Grade 1, Grade 2, Grade 3
Node Positive Status: 0, 1-3, 4-10, 10+
Adjuvant Radiotherapy Status: Yes, No

C7. Please explain how does the higher than expected recruitment of node-negative patients in the APHINITY trial affects the generalisability of the trial results to the UK population?

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C8. The ERG estimates that the change in node status inclusion criteria occurred around June 2013 based on information from Appendix L, the APHINITY study results and the study protocol. Is that correct? If yes, please explain the reason for the delay in implementing the changes, when the problem with Nodal distribution was noticed in September 2012, as reported in Appendix L.

C9. Please reproduce CS, Document B, Figure 13, using 4 years of observed data from the HERA trial, and divided by treatment arm, as it is currently observed in the APHINITY trial.

C10. Please reproduce CS, Document B, Figure 13 (ideally both 3- and 4-year data from the HERA trial), based on extrapolations fitted to data from 30 months and beyond, divided by treatment arm.

C11. Due to the ill-fitting of the current parametric model to observed overall survival (OS), please update the economic model to allow parametric models to be fitted to the OS data. If this is not feasible, then please provide comment on the ill fit and suggest and implement alternative methods of improving the fit to the OS data.

C12. Please reproduce CS, Document B, Figure 14, for the node positive patients in the 1-year trastuzumab arm of the HERA trial, as these are the most relevant to the APHINTY population under consideration.

C13. Please provide more detail about how the trend seen in CS, Document B, Figure 14, has resulted in the decision to model the proportion of patients being “cured”, and why other methods such as hazard ratio adjustment or time varying covariates were not explored?

C14. With regards to the CS, Document B, Figure 20, please provide a definition of ‘event’ for this KM plot.

ID 1192 – Pertuzumab for adjuvant treatment of early HER2-positive breast cancer

Company response to the ERG's clarification questions

27th March, 2018

Literature searching

1. For Company Submission (CS), Appendix G, Tables 15 and 16, please supply an additional column with numbers retrieved for each line. This will aid the ERG in critiquing the MEDLINE, MEDLINE In-Process and Embase search strategies.

Please see Table 1 and 2 of the Appendix that has been provided as part of this response.

2. Please provide the following four missing references from the reference pack:

- **92.** Roche Data on File. Burzykowski T, Buyse M, Quinaux E *et al.* Evaluation of disease-free survival and other time-to-event endpoints as surrogates for overall survival in the systemic therapy of HER-2-positive early breast cancer. Progress Report 2. 19th December 2017. Cited on page 54 of CS.
- **101.** Roche Products Ltd. Advisory board report: Understanding the treatment landscape for adjuvant treatment in HER2-postitive early breast cancer with the APHINITY Study. Available on request. 2017. Cited on page 55 of CS.
- **105.** Roche Products Ltd. Advisory board report: Health Technology Assessment (HTA) Advisory Board: Perjeta® (pertuzumab) for the Adjuvant Treatment of Human Epidermal Growth Factor Receptor 2-Positive (HER2+) Early Breast Cancer. Available on request. 2017. Cited on pages 58, 65, 76, 127 of CS.
- **122.** Roche Market Research. Available on request. Cited on page 95 of CS.

These references have been provided as part of this response, with the exception of reference 122 (cited on page 95 of CS). This market share figure was ascertained during correspondence (teleconference) with officials from NHS England regarding anticipated market share of trastuzumab intravenous (IV) versus subcutaneous (SC), January, 2018.

A Clarification on effectiveness data

A.1 Priority question: Credibility of selection of subgroups: On pages 8 and 33 of CS, Document A, the company states that node-positive and hormone receptor-negative patients were “pre-specified” subgroups in the trial.

a) Please clarify how these subgroups (nodal status and hormone receptor status) were pre-specified.

Nodal status and hormone receptor status are the most influential prognostic factors in early breast cancer (eBC).[1-3] For this reason, they were included as randomisation stratification factors for the APHINITY study and were pre-specified in the protocol and statistical analysis plan (SAP) for subgroup analyses.

b) Please justify the rationale for not including in the decision problem the other specified subgroups in the APHINITY trial protocol (section 8.1.2.4).

The subgroup analyses were intended to assess consistency of the overall result in the intention-to-treat (ITT) population. Subgroup analyses were performed for a set of randomisation stratification factors (nodal status, adjuvant chemotherapy regimen, hormone receptor status, geographical region, and protocol version). These factors (excluding protocol version) are considered the most clinically important prognostic or predictive factors in eBC, and were selected as stratification factors to ensure balance between the treatment arms. The inclusion of protocol version reflects the actual study design, and as with all stratification variables is included to allow a valid and robust statistical analysis taking into account the protocol version randomised under.

Particular focus was given to nodal status and hormone receptor status subgroups in this submission, as these are clinically accepted as the most influential prognostic factors in eBC.[1-3] The APHINITY trial further confirmed patients with node-positive or hormone receptor-negative disease to be at higher risk of disease recurrence compared to patients with node-negative or hormone receptor-positive disease. Survival estimates in the placebo arm were lower for patients with node-positive or

hormone receptor-negative disease, compared to the placebo arms in the node-negative and hormone receptor-positive subgroups: estimates of invasive disease-free survival (IDFS) at three years in the placebo arm were 90.2% and 91.2% for patients with node-positive and hormone receptor-negative disease, respectively, compared to 98.4% and 94.4% for the placebo arm in the node-negative and hormone receptor-positive population, respectively. Thereby, confirming that patients with node-positive or hormone receptor-negative disease are at higher risk of recurrence and that these are clinically relevant prognostic factors. These two subgroups are aligned to where the clinical community see the value of pertuzumab in the eBC setting,[4] and are [redacted]

Further subgroup analyses were performed for other disease or patient-related factors, including age, race, sex, histological grade, tumour size and menopausal status. Pre-planned subgroup analyses were generally consistent with the benefits seen in the ITT population (CS Document B, Figure 5). Other pre-defined subgroups were not included in the decision problem as they are not as influential as nodal status and hormone receptor status in affecting prognosis in eBC and [redacted]

A.2 **Priority question:** Please provide APHINTY Protocol Version A and B and details of when the protocol was amended (month and year), and the BCIRG-006 trial protocol.

APHINITY protocol versions A and B, and the BCIRG 006 trial protocol have been provided as part of this response.

Protocol amendment B was released in November 2012.

A.3 **Priority question:** Please explain the mechanism(s) for the delayed effect of pertuzumab as shown in the survival curves (see CS, Document B, Figure 3 and Document A Figure 4)?

The divergence of the Kaplan-Meier (KM) curves in Document B, Figure 3 (ITT population) and Document A, Figure 4 (node-positive population) does not indicate that pertuzumab itself has a delayed effect. The APHINITY primary analysis was

event-driven, and conducted after 379 IDFS events. The benefit of pertuzumab + trastuzumab + chemotherapy can be seen in KM curves of IDFS over the median follow-up period of 45.4 months. Pertuzumab + trastuzumab + chemotherapy reduced the risk of an IDFS event by 19% compared to placebo + trastuzumab + chemotherapy in the ITT population (hazard ratio [HR]=0.81; 95% confidence interval [CI], 0.66–1.00; p=0.0446).

In Document B, Figure 3 (ITT population), the efficacy in the placebo arm (i.e. placebo + trastuzumab + chemotherapy) is higher than seen in historical trials. The statistical assumptions used in the design of the APHINITY study were based on BCIRG 006 data; an estimated disease-free survival (DFS) at three years of 89.2% was assumed for the placebo arm (based on DFS rates of 87% and 88% achieved in the placebo arms [i.e. trastuzumab + chemotherapy] of BCIRG 006). Several reasons may explain the better-than-expected performance observed in the placebo arm, including changes in standard practice:[5-8]

- Improvements in imaging over time, providing more accurate diagnosis and reducing the number of patients with advanced disease incorrectly enrolled in APHINITY versus historical studies in patients with HER2-positive eBC.
- Improvements in the management of local and systemic therapy increasing patients' ability to complete treatment regimens.
- Advances in standard of care, e.g. aromatase inhibitors are now standard of care for patients with hormone receptor-positive disease.
- An increase in the use of neoadjuvant therapy in patients with high-risk breast cancer. Since patients could not be included in the APHINITY study if they had received any previous chemotherapy or radiotherapy for cancer or any previous anti-HER2 therapy, it could be that only patients with lower-risk eBC were available for recruitment into the APHINITY study.

Elements of the APHINITY study design may have further contributed to this over-performance of the placebo arm:[9-13]

- The APHINITY study allowed enrolment of lower-risk patients than earlier eBC trials (i.e. 0.5 cm with a high-risk feature or 1 cm node-negative; lower rate of patients with four or more positive lymph nodes).

- More patients with hormone receptor-positive breast cancer were enrolled (64%) than expected, which was likely due to ASCO guidelines for the definition of hormone receptor-positive disease. Changes in the definition of hormone receptor-positive disease could also have led to additional patients receiving endocrine therapy.
- In the APHINITY study, pertuzumab + trastuzumab were administered concomitantly with taxane, which may not have been the case in previous studies.

Despite this, an increased delta can be seen in the node-positive patient population, with a 23% reduction in risk of breast cancer recurrence or death in pertuzumab + trastuzumab + chemotherapy arm versus placebo + trastuzumab + chemotherapy (HR=0.77; 95% CI, 0.62–0.96; p=0.019) (Document A, Figure 4). Patients with node-positive disease are known to be at high risk of recurrence, and it is expected that these patients will experience recurrences earlier than patients with node-negative disease. The divergence in the KM curves is aligned to what we would expect for patients with node-positive disease in comparison to patients with node-negative disease, and confirms that this subgroup is at a high risk of recurrence.

A.4 In the CS, Document B, on page 47 it was stated that: "Treatment was discontinued for safety reasons by 7.8% and 6.4% of patients in the pertuzumab and placebo arms, respectively". Please clarify what were the 'safety reasons' listed for each discontinuation?

The reasons for discontinuation referred to in the CS are detailed in Table S5 of the Supplementary Appendix to the von Minckwitz manuscript.[14] This table has been provided below (Table 1).

Table 1. Discontinuations due to safety reasons in APHINITY[14]

	Pertuzumab + trastuzumab + chemotherapy N=2,400	**Placebo + trastuzumab + chemotherapy N=2,404**
Discontinuations due to safety, n (%)	186 (7.8%)	155 (6.4%)

Adverse events	176 (7.3%)	149 (6.2%)
Death	9 (0.4%)	6 (0.2%)
Pregnancy	1 (<0.1%)	0

B Clarification on cost-effectiveness data

B.1 **Priority question:** In the CS, Document B, on page 77 it was stated that: "In the model, it is assumed that every disease recurrence observed within 18 months after initiation of adjuvant therapy is a metastatic recurrence. These patients are expected to have a worse prognosis and will therefore receive a more aggressive treatment. Survival estimates derived from the EMILIA study (study of trastuzumab emtansine in second-line mBC)[111] are used to model the survival of patients who experience a metastatic recurrence within the first 18 months after adjuvant treatment initiation. In the EMILIA study, the corresponding population was selected to estimate the risk of disease progression (PFS) and the risk of death following progression."

Please clarify whether APHINITY data were available to inform the survival of patients who experienced a metastatic recurrence, and if so, please explain the rationale for using estimates from EMILIA and report how the employed data from EMILIA compare to the respective survival estimates from APHINITY.

In the node-positive population, a total of 227 distant recurrence events occurred across both treatment arms (99 and 128 in the pertuzumab + trastuzumab + chemotherapy and placebo + trastuzumab + chemotherapy arms, respectively). This equates to approximately 7% of the node-positive population experiencing a metastatic event. Such a proportionately low number of metastatic events was believed to be insufficient to support a robust analysis of survival in the metastatic breast cancer (mBC) health states, hence the use of alternative data sources.

B.2 **Priority question:** In the CS, Document B, on page 87 it was stated that: "In this analysis, it is assumed that any disutility resulting from treatment-related AEs is reflected in the EQ-5D responses from the APHINITY study. It is possible that this approach underestimates the disutility associated with the AEs. Despite this, the incremental difference between treatment arms is thought to be negligible. Ultimately, this omission is not expected to significantly impact the overall cost-effectiveness results."

The expectation that disutility due to AEs is reflected in EQ-5D responses is contentious; unless by design, it is unlikely that EQ-5D data were collected exactly on days that AEs were experienced. In addition, the company uses pooled utility values in their base case analysis. Given this, we feel it is important to account for AEs separately. Please present an analysis where the disutility of adverse events is taken into account.

Please see the response to question B3.

B.3 **Priority question.** In the CS, Document B, on pages 103-104 it was stated that: "Following the guidance received in recent technology appraisals in this disease area, the criteria used for the inclusion/exclusion of an AE in the model are outlined below:

- Only AEs of Grade ≥3: Typically, clinicians will only intervene and treat an AE if it is severe enough to be classified as grade 3 or above. The costs and HRQoL effects associated with grade 1 and 2 events are therefore assumed to be negligible and hence omitted from this analysis.
- Occur in ≥2% of patients: A reasonable assumption was made that an AE must have occurred in at least 2% of the study population to be included in the model."

Please explain the rationale for inclusion of AEs only if they have occurred in at least 2% of the study population.

The assessment of AEs reported in the APHINITY trial shows that primary cardiac events occurred in 17 patients (0.7%) in the pertuzumab group and in 8 patients (0.3%) in the placebo group, with 15 (0.6%) patients in the pertuzumab group and 6 (0.2%) patients in the placebo group presenting NYHA class III or IV heart failure and a substantial decrease in left ventricular ejection fraction. The analysis of AEs also shows a substantial imbalance in proportions of patients with anaemia in the pertuzumab arm (n = 163, 6.9%) versus placebo (n = 113, 4.7%) Given this imbalance in primary cardiac events and anaemic events across groups and the fact that such events are expected to be detrimental for patients' HRQL and costly to resolve, please present total costs, total QALY and ICER values that take into account these events.

The use of an "occurrence threshold" is common across cost-effectiveness analyses. A lack of a threshold would result in all grade ≥3 treatment-related adverse events (AEs) that occurred in the pivotal trial being quantified in the model.[9] This would require disutilities and costs to be sourced for a multitude of different events, thus making the model highly data intensive and potentially impractical. In addition, the use of a 2% threshold could be considered conservative. Many analyses use a value of 5% which increases the impact of AEs. If a 5% threshold was used here, then the marginally favourable safety profile of the comparator arm would ensure the incremental cost-effectiveness ratio (ICER) decreased.

The company agrees with the ERG's assessment that anaemia and primary cardiac events will be costly and detrimental to a patient's health-related quality of life (HRQoL). Despite this, the inclusion of these events in the analysis is unlikely to have a significant impact on the overall cost-effectiveness results. Treatment-related AEs are only likely to occur during the treatment period i.e. the first 13 months of the time horizon. The costs and disutilities accrued here are likely to be negligible in the context of the total costs and quality-adjusted life years (QALYs) accrued over the entire 52-year time horizon. Irrespective of these objections, the company has provided some analyses in which the ERG's requested AEs have been included.

Table 2 below reports an updated list of costs that have been added into the model.

Table 2. Updated list of adverse events and costs included in the model – node-positive population

Adverse events	Frequency		Treatment	Event cost	Source
	Pertuzumab + trastuzumab + chemotherapy	Placebo + trastuzumab + chemotherapy			
Diarrhoea	67 (4.46%)	17 (1.13%)	Malignant Breast Disorders with Interventions, with CC Score 3-6 - Day case	£334.00	NHS Reference costs - 2016/17 - JA12E
Neutropenia	37 (2.46%)	45 (3.00%)	Neutropenia Drugs, Band 1 - outpatient	£79.00	NHS Reference costs - 2016/17 - XD25Z
Neutrophil count decreased	36 (2.40%)	35 (2.33%)	No treatment available	£0.00	Not applicable
Anaemia	23 (1.56%)	14 (0.93%)	Iron Deficiency Anaemia with CC Score 6-9	£978.83	NHS Reference costs - 2016/17 – SA04J
Cardiac failure	15 (1.02%)	7 (0.46%)	Heart Failure or Shock, with CC Score 8-10	£1,865.56	NHS Reference costs - 2016/17 – EB03C

Abbreviations: CC, Casemix companion; NHS, National Health Service.

Unfortunately, disutilities were not readily available for the adverse events included in Table 2, the values used had to be estimated by the company in order to conduct this scenario analysis. The company assumed a disutility of -0.5 for all events. This value is extreme and believed to be far in excess of the actual disutility a patient could expect from any of these events. Such a conservative value was chosen to illustrate the limited impact this analysis would have on the overall cost-effectiveness results originally presented in the company submission.

Table 3. Adverse event disutilities included in the model – node-positive population

Adverse events	Frequency		Duration of adverse event	Disutility
	Pertuzumab + trastuzumab + chemotherapy	Placebo + trastuzumab + chemotherapy		
Anaemia	23 (1.56%)	14 (0.93%)	13 months*	-0.5
Cardiac failure	15 (1.02%)	7 (0.46%)	13 months*	-0.5
Diarrhoea	67 (4.55%)	17 (1.13%)	13 months*	-0.5
Neutropenia	37 (2.51%)	45 (2.98%)	13 months*	-0.5
Neutrophil count decrease	6 (2.44%)	35 (2.32%)	13 months*	-0.5

*13 months is the safety duration (12-month episode of care + 28 days)

The results of this analysis (incorporating the updated costs and disutilities) are presented alongside the results presented in the original submission below. As seen in the tables, a modest increase in the ICER was observed.

Table 4. Results when incorporating the updated adverse event costs and disutilities – node-positive population

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
No anaemia and cardiac failure costs or disutilities							
Placebo + trastuzumab + chemotherapy	[redacted]	16.57	[redacted]	[redacted]	0.742	[redacted]	£34,087
Pertuzumab + trastuzumab + chemotherapy	[redacted]	17.31	[redacted]				
Results incorporating anaemia and cardiac failure costs and disutilities							
Placebo + trastuzumab + chemotherapy	[redacted]	16.57	[redacted]	[redacted]	0.742	[redacted]	£34,212
Pertuzumab + trastuzumab + chemotherapy	[redacted]	17.31	[redacted]				

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.

B.4 In relation to the proportion of patients who experienced metastatic recurrence, non-metastatic recurrence and died, the CS, Document B, on page 75 suggests that: "No meaningful differences were observed in the proportion of each Invasive disease-free survival (IDFS) events across the two treatment arms (i.e. the proportions of metastatic recurrence, non-metastatic recurrence, and deaths were broadly similar across the two treatment arms of the APHINITY study)." Owing to this, "the pooled proportion of metastatic vs. non-metastatic recurrences were applied to both arms in the model. Table 23 provides a breakdown of IDFS events observed in each treatment arm of the node-positive population."

Given the availability of data from the APHINITY trial, please explain the rationale for pooling the proportions of IDFS events across the two treatment arms and using this pooled value. Please adjust the economic model to allow for unpooled values for the proportion of IDFS events and provide further analyses where

IDFS events for each arm correspond to APHINITY trial data for the particular arm.

In line with the ERG's request, the economic model has been adjusted to allow for the use of unpooled values for the "proportion of metastatic IDFS events" parameter. The updated model has been provided as part of this response and the results of these additional analyses are presented below.

Table 5. Base case cost-effectiveness results (node-positive population)

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Pooled values							
Placebo + trastuzumab + chemotherapy	[redacted]	16.57	[redacted]	[redacted]	0.742	[redacted]	£34,087
Pertuzumab + trastuzumab + chemotherapy	[redacted]	17.31	[redacted]				
Treatment arm-specific estimates							
Placebo + trastuzumab + chemotherapy	[redacted]	16.59	[redacted]	[redacted]	0.69	[redacted]	£36,563
Pertuzumab + trastuzumab + chemotherapy	[redacted]	17.29	[redacted]				

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.

Table 6. Base case cost-effectiveness results (hormone receptor-negative population)

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Pooled values							
Placebo + trastuzumab + chemotherapy	[redacted]	16.88	[redacted]	[redacted]	0.46	[redacted]	£65,699
Pertuzumab + trastuzumab + chemotherapy	[redacted]	17.34	[redacted]				
Treatment arm-specific estimates							
Placebo + trastuzumab + chemotherapy	[redacted]	16.86	[redacted]	[redacted]	0.51	[redacted]	£59,268
Pertuzumab + trastuzumab + chemotherapy	[redacted]	17.36	[redacted]				

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.

The APHINITY data show that patients receiving pertuzumab + trastuzumab + chemotherapy have a slightly higher proportion of metastatic recurrences (in relation to all disease recurrences) than those in the placebo + trastuzumab + chemotherapy arm. This is believed to be an artefact of the data.

Distant recurrence means that the cancer has metastasised to another part of the body (i.e. liver, lungs, or bone). Whereas, the other disease recurrences defined in IDFS are where the cancer has come back to where it started or within the region of the breast. The most common type of recurrence event in women with breast cancer is distant recurrence and is reflective in the proportion of distant versus local recurrences in both treatment arms in the APHINITY study.[15] Advances in imaging, surgical and radiotherapy techniques have reduced the problem of missing extensive or multifocal sites of cancer in the breast at the time of surgery, and resulted in a decrease in the rate of local recurrence risk, leaving distant risk the primary target of systemic adjuvant

therapy. Roche are aware of no clinical rationale that suggests pertuzumab modifies the risk of a disease recurrence being metastatic.

In addition, these findings are shown to be inconsistent across the APHINITY study – the conclusion drawn from the hormone receptor-negative data is the reversal of that seen in the node-positive population. Furthermore, distant recurrence-free interval (DRFI) was investigated in the APHINITY study as a secondary endpoint. Pertuzumab + trastuzumab + chemotherapy treatment was found to improve the DRFI rates (from 95.1% to 95.7%) and reduce the risk of distant recurrence by 18% (HR=0.82; 95% CI, 0.64–1.04) in the ITT population - though this endpoint was not included in the hierarchical testing procedure and is not statistically significant.[16]

Ultimately, the "proportion of metastatic recurrences" is a parameter predicated on a small number of events. As a result, a small change in the actual number of metastatic recurrences can have a relatively large effect on the parameter used in the model.

It is also worth noting that the preferred modelling approach used in this analysis was to not differentiate between treatment arms unless a clear clinical rationale exists. For example, in terms of utility values, pertuzumab + trastuzumab + chemotherapy patients have a slightly higher EuroQol 5-Dimension questionnaire (EQ-5D) value compared to placebo + trastuzumab + chemotherapy patients (see Table 7). Given that no clinical explanation for this finding exists, it was assumed that the difference seen was not meaningful. Consequently, utility estimates were pooled across treatment arms in the base case analysis. It is the view of the company that in order to remain consistent, in terms of modelling approach, the proportion of metastatic recurrences used in the model should also be independent of treatment arm.

B.5 In the CS, Document B, on pages 65-66 it was stated that: "According to the AIC values, the exponential and log-logistic functions provide the best fit to the data in the pertuzumab + trastuzumab + chemotherapy and the placebo + trastuzumab + chemotherapy arms, respectively" […] "The technical support document, developed by Latimer et al., states that the same parametric function should be used across both treatment arms (where feasible).107 Using the same type of function ensures consistency and limits potential problems such as the crossing of the curves. When considering the fit across the two arms jointly, the best fitting extrapolation is produced by the Log-logistic function."

While the ERG agrees that using different distributions across treatment arms is not always feasible, please explain whether this is actually (rather than potentially) problematic in this particular case. Given the fact that different functions (exponential and log-logistic) provide the best fit to each of the two arms, the ERG would like the economic model to allow for different distribution types to be fitted to each arm.

The economic model has been modified and this updated version has been submitted as part of this response.

In the node-positive population, the best fit for the pertuzumab + trastuzumab + chemotherapy arm and the placebo + trastuzumab + chemotherapy arm were the Exponential and Log-logistic distributions, respectively. Applying treatment-specific functions to the IDFS survival curves reduces the ICER from £34,087 to £31,086 per QALY gained. No changes were required in the hormone receptor-negative analysis because the Exponential function was found to be the best fit for both treatment arms.

B.6 In the CS, Document B, on page 78 it was stated that: "Patients are also at risk of death during their year in the non-metastatic recurrence health state. This risk of death applied here is the superior value between the risk of dying without recurrence (as observed in the APHINITY study) and background mortality in the age-adjusted UK population".

Please justify using the risk of dying without recurrence to reflect the probability of a patient dying after they have experience a non-metastatic recurrence.

The mortality rate in patients who experienced a non-metastatic recurrence was not available from the APHINITY data set. In HER2-positive breast cancer, the majority of recurrences are metastatic, consequently there were only 53 non-metastatic events across the entirety of the node-positive population of APHINITY. Given that patients are unlikely to die following a non-metastatic recurrence, there were insufficient events to robustly calculate this probability. These issues were also found to be consistent across previous trastuzumab studies (HERA and BCIRG 006).[2, 10]

In clinical practice, patients rarely die following a non-metastatic recurrence. The expectation is that a patient's disease would progress (i.e. become metastatic) before resulting in death. On this basis, a reasonable structural assumption was made in the model.

Ultimately, the risk of death for these patients is broadly similar to patients in the IDFS state (in both health states, patients are treated for non-metastatic cancer). Therefore, the mortality rate for a patient following a non-metastatic recurrence is assumed equal to that of the mortality rate of an IDFS patient.

B.7 In the CS, Document B, on pages 88-90 concerning metastatic health state utilities, in the absence of utility values for metastatic health states from APHINITY, utilities for such states have been taken from the literature (base case values from Lloyd et al; alternative values from Hedden et al; Lindgren et al and Paracha et al).

Please clarify the process that led to the identification and selection of these studies from which values were obtained for metastatic health states. If these studies were not identified and selected through a systematic process, please provide assurance that other relevant studies reporting utility values for metastatic states have not been missed.

The list of sources included as scenario analyses for mBC health state utilities is extensive. This list was compiled by cross-referencing with published cost-effectiveness analyses and the analyses conducted in both the pertuzumab mBC and neoadjuvant NICE appraisals.[17, 18] Although the sources were identified in a non-systematic way, it is believed that the best available evidence, pertaining to these parameters, has been incorporated here.

B.8 In the CS, Document B, on page 89 it was stated that: "Health state utility estimates in patients with HER2-positive BC are available from a range of published sources. To present a more complete evaluation, utilities from these sources have also been included here as scenario analyses. A brief description of these sources is given below, along with an overview of how the estimates were incorporated into the model."

Please clarify how 'utilities from other published sources' were identified and selected.

The list of sources included as scenario analyses for health state utilities is extensive. This list was compiled by cross-referencing against published cost-effectiveness analyses and the analyses conducted in both the pertuzumab mBC and neoadjuvant NICE appraisals.[17, 18] Although the sources were identified in a non-systematic way, it is believed that the best available evidence, pertaining to these parameters, has been incorporated here.

B.9 In the CS, Document B, Table 34, concerning the base case values for utilities of state IDFS (on treatment, on treatment/off chemotherapy and off treatment), Locoregional recurrence, Remission, First-line mBC and Second line mBC. Please clarify where the standard error values (0.004) were obtained from.

The values referred to in Table 34 of the CS are in fact variances and not standard errors (SE). These variances were calculated as part of the derivation of the health state utilities. Please see the response to Question B.11 for further clarification on the SEs of the eBC utilities.

The first and second (+) line mBC health state utilities were actually taken from the Lloyd *et al.* publication.[19] The study does not present SE values pertaining to final health state utilities. Instead, Lloyd *et al.* present the SEs for the variables included in their mixed model, which is eventually used to calculate utilities. It is not possible for the company to report the SEs of the final mBC utilities used in the model. However, the SEs reported by Lloyd *et al.* have been used to vary the variables of the mixed model, and consequently the mBC utilities, during the probabilistic sensitivity analysis. Please see the "Utilities" tab of the cost-effectiveness model for more details.

B.10 Please provide standard errors for eBC health state utility values – scenario analysis' (utility values for all three IDFS states, locoregional recurrence, remission) in the CS, Document B, Table 34.

Table 7 below presents the EQ-5D-3L values for each visit in the node-positive population of the APHINITY study. The responses for the ITT and hormone receptor-negative populations are available as an Appendix to this response.

Please note that the visit referred to as "Week 13" in the tables represents the visit at the end of chemotherapy treatment. Patients can finish chemotherapy at different time points, depending on whether they received a concurrent or sequential regimen, therefore the visit may not have necessarily occurred at Week 13 from randomisation. For each patient visit, utilities were calculated using the Dolan *et al.* algorithm.[20] The utility values were then averaged across patients for the same visit. In order to derive the final utilities used in the model, the following assumptions were made:

- The utility for the "IDFS on chemotherapy" health state is the weighted average of the Week 13 and End of anthracycline visit values.
- The utility for the "IDFS off chemotherapy / on treatment" health state is the weighted average of the Baseline, Week 25, and End of treatment visit values.
- The utility for the "IDFS on treatment" health state is the weighted average of the Follow Up month 18, Follow Up month 24, and Follow Up month 36 visit values

- The “Non-metastatic recurrence” health state utility is assumed equal to the “IDFS on chemotherapy” value.
- The “Remission” health state utility is assumed equal to the “IDFS off treatment” value.

Table 7. EQ-5D-3L values in node-positive population of APHINITY

Assessment	Pertuzumab + trastuzumab + chemotherapy arm	Placebo + trastuzumab + chemotherapy arm	Pooled
Baseline	- Avg value: 0.7753 - SD of value: 0.1947 - Std Err: 0.0052 - No. of patients. 1,503 - No. of patients who provided responses: 1,428 - No. of responses: 1,428	- Avg value: 0.7679 - SD of value: 0.2022 - Std Err: 0.0053 - No. of patients. 1,502 - No. of patients who provided responses: 1,437 - No. of responses: 1,437	- Avg value: 0.7716 - SD of value: 0.1985 - Std Err: 0.0037 - No. of patients. 3,005 - No. of patients who provided responses: 2,865 - No. of responses: 2,865
End of anthracycline	- Avg value: 0.7800 - SD of value: 0.2072 - Std Err: 0.0062 - No. of patients. 1,209 - No. of patients who provided responses: 1,106 - No. of responses: 1,106	- Avg value: 0.7743 - SD of value: 0.1980 - Std Err: 0.0059 - No. of patients. 1,217 - No. of patients who provided responses: 1,123 - No. of responses: 1,123	- Avg value: 0.7771 - SD of value: 0.2026 - Std Err: 0.0043 - No. of patients. 2,426 - No. of patients who provided responses: 2,229 - No. of responses: 2,229
Week 13	- Avg value: 0.7634 - SD of value: 0.2162 - Std Err: 0.0060 - No. of patients. 1,394 - No. of patients who provided responses: 1,301 - No. of responses: 1,301	- Avg value: 0.7497 - SD of value: 0.2255 - Std Err: 0.0062 - No. of patients. 1,422 - No. of patients who provided responses: 1,317 - No. of responses: 1,317	- Avg value: 0.7564 - SD of value: 0.2210 - Std Err: 0.0043 - No. of patients. 2,816 - No. of patients who provided responses: 2,618 - No. of responses: 2,618
Week 25	- Avg value: 0.7860 - SD of value: 0.1972 - Std Err: 0.0055 - No. of patients. 1,358 - No. of patients who provided responses: 1,279 - No. of responses: 1,279	- Avg value: 0.7845 - SD of value: 0.1968 - Std Err: 0.0055 - No. of patients. 1,394 - No. of patients who provided responses: 1,283 - No. of responses: 1,283	- Avg value: 0.7853 - SD of value: 0.1970 - Std Err: 0.0040 - No. of patients. 2,752 - No. of patients who provided responses: 2,562 - No. of responses: 2,562
End of treatment	- Avg value: 0.8019 - SD of value: 0.2040 - Std Err: 0.0057 - No. of patients. 1,489 - No. of patients who provided responses: 1,272	- Avg value: 0.8000 - SD of value: 0.2036 - Std Err: 0.0056 - No. of patients. 1,493 - No. of patients who provided responses: 1,310	- Avg value: 0.8009 - SD of value: 0.2038 - Std Err: 0.0040 - No. of patients. 2,982 - No. of patients who provided responses: 2,582

	- No. of responses: 1,272	- No. of responses: 1,310	- No. of responses: 2,582
FU month 18	- Avg value: 0.8194 - SD of value: 0.1936 - Std Err: 0.005611 - No. of patients. 1,371 - No. of patients who provided responses: 1,190 - No. of responses: 1,190	- Avg value: 0.8126 - SD of value: 0.2055 - Std Err: 0.0060 - No. of patients. 1,390 - No. of patients who provided responses: 1,172 - No. of responses: 1,172	- Avg value: 0.8160 - SD of value: 0.1996 - Std Err: 0.0041 - No. of patients. 2,761 - No. of patients who provided responses: 2,362 - No. of responses: 2,362
FU month 24	- Avg value: 0.8272 - SD of value: 0.2035 - Std Err: 0.0060 - No. of patients. 1,343 - No. of patients who provided responses: 1,155 - No. of responses: 1,155	- Avg value: 0.8174 - SD of value: 0.2127 - Std Err: 0.0063 - No. of patients. 1,343 - No. of patients who provided responses: 1,144 - No. of responses: 1,144	- Avg value: 0.8223 - SD of value: 0.2081 - Std Err: 0.0043 - No. of patients. 2,554 - No. of patients who provided responses: 2,155 - No. of responses: 2,155
FU month 36	- Avg value: 0.8361 - SD of value: 0.1952 - Std Err: 0.0059 - No. of patients. 1,288 - No. of patients who provided responses: 1,094 - No. of responses: 1,094	- Avg value: 0.8209 - SD of value: 0.2058 - Std Err: 0.0063 - No. of patients. 1,266 - No. of patients who provided responses: 1,061 - No. of responses: 1,061	- Avg value: 0.8287 - SD of value: 0.2006 - Std Err: 0.0043 - No. of patients. 2,554 - No. of patients who provided responses: 2,155 - No. of responses: 2,155

Abbreviations: Avg, average; FU, follow-up; No., number; SD, standard deviation; Std. Err., standard error.

B.11 Please provide standard errors for eBC health state utility values – scenario analysis' (utility values for all three IDFS states, locoregional recurrence, remission) in the CS, Document B, Table 34.

As stated in the response to Question B.10, the utilities used in the model were weighted averages of EQ-5D values across multiple visits. This makes the calculation of the standard errors for the final utilities rather complicated. The standard errors for the EQ-5D values have been reported above in Table 7.

B.12 The prevalence of AE in the economic model, as reported in CS, Document B, Table 46, do not appear to match those reported in B.2.10 for APHINITY trial, not even for the ITT population. Please could the company confirm the reported prevalence are correct and inform why they are different to section B.2.10.

The AE data reported in Section B.2.10 of the CS pertain to any AE reported during the APHINITY study. In the model, and Table 46 of Document B, only AEs that have been classified as "treatment-related" were included.

B.13 For clarity, please provide an additional table detailing the parameters that were subjected to probabilistic sensitivity analysis, together with the assigned distributions, their distribution parameters and the source of this information.

Table 8 below contains a list of the parameters varied during the probabilistic sensitivity analysis. It is impractical to provide some of the information requested by ERG in tabular form, therefore this table has been provided as a guide to be used in conjunction with the cost-effectiveness model.

Table 8. Probabilistic sensitivity analysis variables

Variable	Value	Measurement of uncertainty and distribution	Source
Utilities			
IDFS – on chemo	0.756	See "Utilities" tab of CEM-(Gamma)	Variances derived from APHINITY EQ-5D responses
IDFS – on treatment, off chemo	0.785		
IDFS – off treatment	0.822		
Non-metastatic recurrence	0.756		
Remission	0.822		
First-line metastatic recurrence	0.773		Lloyd *et al.*[19]*
Second+ line metastatic recurrence	0.520		

Variable	Value	Measurement of uncertainty and distribution	Source
Administration costs			
IV administration cost – loading	£394.60	£315.12 – £490.81 (Log normal)	Upper and lower estimates taken from NHS ref. costs 2016/17[21]
IV administration cost – maintenance	£310.00	£197.00 – £428.00 (Log normal)	
SC administration cost – all cycles	£260.00	£189.00 – £219.00 (Log normal)	
Pharmacy preparation	£43.00	£33.60 – £50.40 (Log normal)	PSSRU 2017[22]
Health state costs (cyclical costs only)			
IDFS – year 1	£63.93	£47.95 - £79.91 (Log normal)	Assumption - ± 25% of base case value
IDFS – year 2-5	£7.11	£5.33 - £8.89 (Log normal)	
IDFS – ≥5 years	£3.08	£2.31 - £3.85 (Log normal)	
Non-metastatic recurrence	£76.80	£57.60 - £96.01 (Log normal)	
Remission	£7.11	£5.33 - £8.89 (Log normal)	
First-line metastatic recurrence	£214.78	£161.08 - £268.47 (Log normal)	
Second+ line metastatic recurrence	£180.85	£135.64 - £226.06 (Log normal)	
Adverse event management costs (per event) - IDFS			
Diarrhoea	£489.00	£390.00 – £504.00 (Gamma)	Upper and lower estimates taken from NHS ref. costs 2016/17[21]
Neutropenia	£137.00	£69.00 – £163.00 (Gamma)	
Monthly probability - "Early recurrence"			
Monthly probability of disease progression in first-line mBC	0.0721	See "Early rec. data" tab in CEM (Log normal)	Covariances are results of survival analysis
Monthly probability of death in second+ line mBC	0.0540		
Monthly probability of disease progression in first-line mBC			
Pertuzumab + trastuzumab + chemotherapy	0.0317	See "1st line data" tab in CEM	Covariances are results of survival

Variable	Value	Measurement of uncertainty and distribution	Source
Trastuzumab + chemotherapy	0.0470	(Log normal)	analysis
Chemotherapy	0.0694		
Monthly probability of death in second+ line mBC			
Pertuzumab + trastuzumab + chemotherapy	0.0273	See "2nd line data" tab in CEM (Log normal)	Covariances are results of survival analysis
Trastuzumab + chemotherapy	0.0315		
Chemotherapy	0.0598		

Abbreviations: CEM, cost-effectiveness model; EQ-5D, EuroQol 5-Dimension questionnaire; IDFS, invasive disease-free survival; IV, intravenous; mBC, metastatic breast cancer; NHS, National Health Service; rec., recurrence; ref, reference; SC, subcutaneous.

*Lloyd *et al.* reported the standard errors for the mixed model inputs. It was these SEs that were used to vary the mBC utilities used in the base case of the CEM – please see the "utilities" tab of the CEM for more details.

C Clarification on statistics and survival analysis

C.1 Priority question: Please provide a table with patient numbers in the different subgroups of the APHINITY trial as follows:

	Hormone Positive	**Hormone Negative**
Node Negative	Cell A	Cell B
Node Positive	Cell C	Cell D

Please provide summary of patient baseline statistics and Clinical Evidence comparing the trial arms (KM plots, hazard ratios for primary and secondary outcomes [stratified and un-stratified]) for the following sub groups:

Cell B only – Hormone Negative and Node Negative

Cell C only – Hormone Positive and Node Positive

Cell D only – Hormone Negative and Node Positive

Cell B + C + D combined – Node Positive or Hormone Negative

The data requested here has been provided in a supplementary zip folder entitled "ID1192_Pertuzumab_Roche response to CQs_C1_27-03-2018_AIC". Despite providing this data, Roche has major reservations with respect to the validity of these additional analyses.

Assessing treatment effect in subgroups of subgroups raises major statistical concerns. It is important to note that this analysis was not pre-specified before data were unblinded and the trial was not powered to detect a significant difference between treatment arms within subgroups of subgroups. Furthermore, when multiple subgroup analyses are performed, the probability of a false positive finding can be substantial.[23]

Splitting the data, and thus the already limited number of events, into smaller groups increases the variability associated with these estimates. A fact illustrated by the wide confidence intervals. Considering these limitations, it is impossible to draw reliable conclusions from these analyses.

C.2 Priority question: Please provide

- goodness of fit statistics,
- smoothed hazard vs time plots and
- cumulative hazard vs time plots

for each of the parametric functions and overlaid with the observed data, where the parametric fit begins at 22 months for both arms and KM data used before this point, and also for the company base case (parametric fit from 0 months).

The goodness of fit statistics requested by the ERG have been provided below in Table 9. The company has major concerns around the methodology used to derive these figures and consequently the wider implication of the ERG's request for these data.

Table 9 Goodness of fit statistics - from 22 months onwards

	AIC		BIC	
	PHT arm	**HT arm**	**PHT arm**	**HT arm**
Node positive population				
Exponential	705.286	970.335	710.505	975.562
Weibull	707.173	970.899	717.612	981.353
Log-logistic	707.158	970.728	717.597	981.182
Log-normal	709.706	969.998	720.145	980.452
Gamma	709.173	971.107	724.832	981.561
Gompertz	707.286	972.335	717.725	982.789
HR- population				
Exponential	442.912	473.812	447.602	478.470
Weibull	442.793	473.319	452.173	482.635
Log-logistic	442.639	473.324	452.018	482.640
Log-normal	441.801	473.537	451.180	482.853
Gamma	443.794	475.323	457.863	489.297
Gompertz	444.912	475.812	454.291	485.128

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion.

The request to generate AIC/BIC values from 22-months onwards, has necessitated the use of unconventional methodology. The company strongly urges caution in the interpretation of these values. The use of these values in the decision-making process, regarding modelling approach and best fitting parametric model, is inappropriate.

It is the company's belief that parametric extrapolations should be informed using the totality of observed data available (i.e. from trial randomisation up to the end of follow-up). To generate the goodness of fit statistics quoted in Table 9, the data had to be cut at 22-months. Therefore, all patients who have had events or have been censored prior to this time point have been excluded from the calculation of the AIC/BIC values. Given that the majority of censoring in APHINITY occurs after 22 months, the parametric extrapolations are based on fewer events, thus substantially increasing the level of uncertainty associated with both the parametric extrapolations and any decision on goodness of fit based on the AIC/BIC figures.

It should be noted here, that the values reported in Table 9 are not applicable to the model that has been submitted as part of this response. In the company's model, all parametric functions (irrespective of the timepoint at which they are implemented) have been calculated based on all the observed data available from the APHINITY trial. To properly model parametric functions predicated on only 22 months of the observed data would require a re-running of all survival analyses and a major update of the current model.

Please see the supplementary appendix that has been provided as part of this response for the other figures requested in this question.

n.b. In response to the ERG's additional clarification questions, the company can confirm that Figures 7-12 of the appendix are based on models with parametric fits beginning at 22 months, however the parameter estimates used to model these curves have been derived using the totality of observed data.

C.3 **Priority question:** The ERG notes that the clinical data used in the submission for the APHINITY study is from December 2016. The ERG kindly request that the clinical and cost effectiveness analyses are updated with the most up-to-date data (e.g., December 2017). If this is not possible, then ERG request the summary data by treatment arm (numbers/percentages) for the main outcomes (IDFS, overall survival) for as recently as possible (e.g., December 2017).

The data used in the clinical and cost-effectiveness analyses are based on the primary analysis data-cut, conducted after 379 events as per protocol. The poster presented at the San Antonio Breast Cancer Symposium in December 2017 focused on diarrhoea adverse events and is also based on the primary analysis data-cut.[24] We have no updated efficacy data since the primary analysis. Updated efficacy data will be available following the next overall survival (OS) interim analyses, which are scheduled for approximately 2.5 and 5 years after the first analysis, and then 10 years, according to the pre-defined SAP. Although further analyses are likely to provide additional insight into the benefit of pertuzumab and trastuzumab in the adjuvant setting, they will be of an exploratory nature.

C.4 **Priority question:** Please present full results (hazard ratios and confidence intervals) of the stratified cox model fitted to the APHINITY trial data, for the primary outcome (IDFS). This could be in the form of a forest plot. Please present, as above, but also including the interaction of nodal status and hormone receptor status with treatment, if they are not already included in the model.

Please see Table 10 for results of the stratified Cox model and Table 11 for information on the interaction test. These tables are also available on pages 125 and 4103 of the APHINITY CSR respectively.

Table 10. Summary of Time to First IDFS Event by Treatment Regimen, Stratified Analysis, ITT Population

	Pertuzumab + trastuzumab + chemotherapy (N=2400)	Placebo + trastuzumab + chemotherapy (N=2404)
Patients with event (%)	171 (7.1%)	210 (8.7%)
Patients without event (%)	2,229 (92.9%)	2,194 (91.3%)
Stratified Analysis		
p-value (log-rank)	0.0446	
Hazard Ratio	0.81	
95% CI	(0.66, 1.00)	
3-year duration		
Patients remaining at risk	2101	2108
Event Free Rate (%)	94.06	93.24
95% CI	(93.09, 95.03)	(92.21, 94.26)

Abbreviations: CI, confidence interval.

Table 11. Likelihood Ratio Test of Treatment by Subgroup Interaction for IDFS, ITT Population

Interaction of Treatment Effect With	p-value*
Nodal status (strata)	0.3739
Nodal status (0 vs >=1) 0.1692	0.1692
Adjuvant chemotherapy regimen	0.9962
Central hormone receptor status	0.5429
Protocol version	0.6864
Region	0.6198
Central ER/PgR status	0.4802
Menopausal status at screening	0.0689
Age group	0.7807
Histological grade	0.5158
Surgery type for primary tumor	0.5027
Tumor size	0.2029
Loco-regional radiotherapy	0.5459
Race	0.7992
Protocol version, node positive	0.6834

Abbreviations: CI, confidence interval; ER, oestrogen receptor; PgR, progesterone receptor.
*Likelihood ratio test, each covariate tested separately.

C.5 Please provide a table with patient numbers in the different subgroups of the APHINITY trial as follows:

	Pre-Menopausal	**Post-Menopausal**
Node Negative	Cell A	Cell B
Node Positive	Cell C	Cell D

Please provide a summary of patient baseline statistics and clinical evidence (KM plots, hazard ratios for primary and secondary outcomes [stratified and un-stratified]) comparing the trial arms for the following subgroups:

Cell A – Pre Menopausal and Node Negative

Cell B – Post Menopausal and Node Negative

Cell C – Pre Menopausal and Node Positive

Cell D – Post Menopausal and Node Positive

The data requested here has been provided in a supplementary zip folder entitled "ID1192_Pertuzumab_Roche response to CQs_C5_27-03-2018_AIC". Despite providing this data, Roche has major reservations with respect to the validity of these additional analyses.

There is little evidence to suggest that menopausal status is an important prognostic factor for OS or IDFS in eBC patients.[25-27] In clinical practice, menopausal status is useful in guiding treatment decisions regarding endocrine therapy (if the patient is hormone receptor-positive). Post-menopausal patients can have access to aromatase inhibitors, which is considered more efficacious than previous endocrine therapy. Naturally, post-menopausal patients tend to be older than pre-menopausal patients, yet menopausal status should not be considered a relevant prognostic indicator when making decisions on the efficacy of pertuzumab + trastuzumab + chemotherapy. Consequently, Roche does not consider these subgroups to be relevant to the overall submission. Instead, the submission focuses on nodal and HR status, which were pre-specified as key stratification factors in APHINITY based on biological and clinical characteristics.

In addition to the clinical rationale outlined above, Roche believes that the statistical caveats stated in the responses to C1 are also pertinent here. As noted above, the APHINITY trial was not powered to detect a significant difference in treatment effect across treatment arms in these subgroups. Similarly, multiplicity issues should also be considered in these analyses i.e. conducting multiple subgroup analyses greatly increases the risk of seeing a false-positive.[23]

In summary, Roche believes that the results of these requested analyses should be interpreted with caution. Concerns regarding the robustness of these analyses are further compounded by the fact that menopausal status is not documented to be a known prognostic indicator. Thus, the company also has concerns regarding the relevance of these analyses.

C.6 Please provide forest plots as in the CS, Document B, Figure 5, for the following factors:

Size of Tumour: <1cm, 1-5cm, 5+ cm

Grade of Tumour: Grade 1, Grade 2, Grade 3

Node Positive Status: 0, 1-3, 4-10, 10+

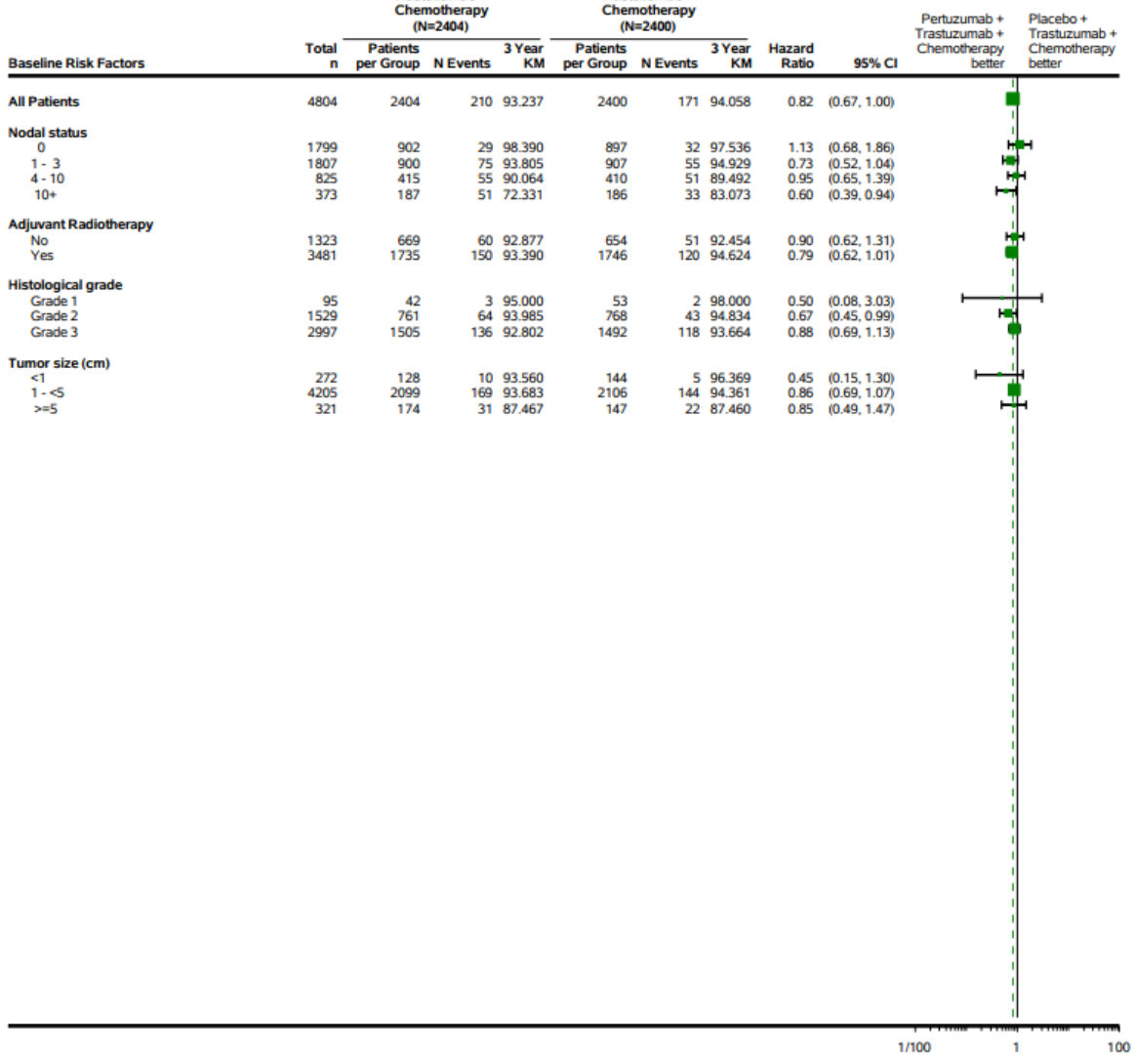
Adjuvant Radiotherapy Status: Yes, No

Please see the requested forest plot below.

Figure 1. IDFS forest plot in the ITT population of APHINITY

POPULATION: ITT
ENDPOINT: IDFS (Invasive Disease-Free Survival)
STUDY: j25126a

Baseline Risk Factors	Total n	Placebo + Trastuzumab + Chemotherapy (N=2404) Patients per Group	N Events	3 Year KM	Pertuzumab + Trastuzumab + Chemotherapy (N=2400) Patients per Group	N Events	3 Year KM	Hazard Ratio	95% CI
All Patients	4804	2404	210	93.237	2400	171	94.058	0.82	(0.67, 1.00)
Nodal status									
0	1799	902	29	98.390	897	32	97.536	1.13	(0.68, 1.86)
1 - 3	1807	900	75	93.805	907	55	94.929	0.73	(0.52, 1.04)
4 - 10	825	415	55	90.064	410	51	89.492	0.95	(0.65, 1.39)
10+	373	187	51	72.331	186	33	83.073	0.60	(0.39, 0.94)
Adjuvant Radiotherapy									
No	1323	669	60	92.877	654	51	92.454	0.90	(0.62, 1.31)
Yes	3481	1735	150	93.390	1746	120	94.624	0.79	(0.62, 1.01)
Histological grade									
Grade 1	95	42	3	95.000	53	2	98.000	0.50	(0.08, 3.03)
Grade 2	1529	761	64	93.985	768	43	94.834	0.67	(0.45, 0.99)
Grade 3	2997	1505	136	92.802	1492	118	93.664	0.88	(0.69, 1.13)
Tumor size (cm)									
<1	272	128	10	93.560	144	5	96.369	0.45	(0.15, 1.30)
1 - <5	4205	2099	169	93.683	2106	144	94.361	0.86	(0.69, 1.07)
>=5	321	174	31	87.467	147	22	87.460	0.85	(0.49, 1.47)



Clinical cut-off: 19Dec2016
Program: /opt/BIOSTAT/prod/cdp11450.pbe/r25126a.pbe/g_ef_tte_sub_uk.sas
Output: /opt/BIOSTAT/prod/cd11450g.pbe/j25126a.pbe/reports/g_ef_tte_sub_uk_26a_IDFS_IT.pdf 19MAR2018 16:23

Abbreviations: CI, confidence interval; KM, Kaplan-Meier.

C.7 Please explain how does the higher than expected recruitment of node-negative patients in the APHINITY trial affects the generalisability of the trial results to the UK population?

By the end of September 2012 (about ten months after the first patient entered the study), approximately 1,900 patients had been enrolled in the APHINITY trial and the monthly recruitment rate was more than 50% higher than foreseen. Furthermore, it was observed that the proportion of patients with node-negative disease was nearly twice that expected (based on the original assumptions for the study).

In December 2011, positive and clinically relevant results from the CLEOPATRA and NeoSPHERE pivotal studies with pertuzumab and trastuzumab, respectively for the first-line metastatic and neoadjuvant treatment of HER2-positive breast cancer, were presented.[28] These data contributed to establish the role of dual blockade of HER2 for the treatment of HER2-positive breast cancer, potentially supporting a faster enrollment than expected in APHINITY.

The reason for the higher-than-foreseen recruitment of node-negative patients in the first ten months of recruitment is unclear. It is important to note that at the time the recruitment in APHINITY started (First Patient In [FPI] in November 2011):

- Neoadjuvant treatment was a common option for high risk (including node-positive) HER2-positive breast cancer.[29] Notably, previous neoadjuvant therapy was not permitted in APHINITY.
- International guidelines recommended the use of adjuvant Herceptin also for the treatment of HER2-positive, node-negative patients with small tumors (e.g. <1 cm) differently than the past.[29]

As such, it is possible that in some countries this could have resulted in a relatively higher proportion of patients with node-negative disease eligible for the APHINITY trial in the early phase of recruitment.

Ultimately, the implementation of protocol amendment B ensured that the number of node-negative/node-positive patients recruited into the APHINITY study reflected the ITT population originally defined in the SAP.

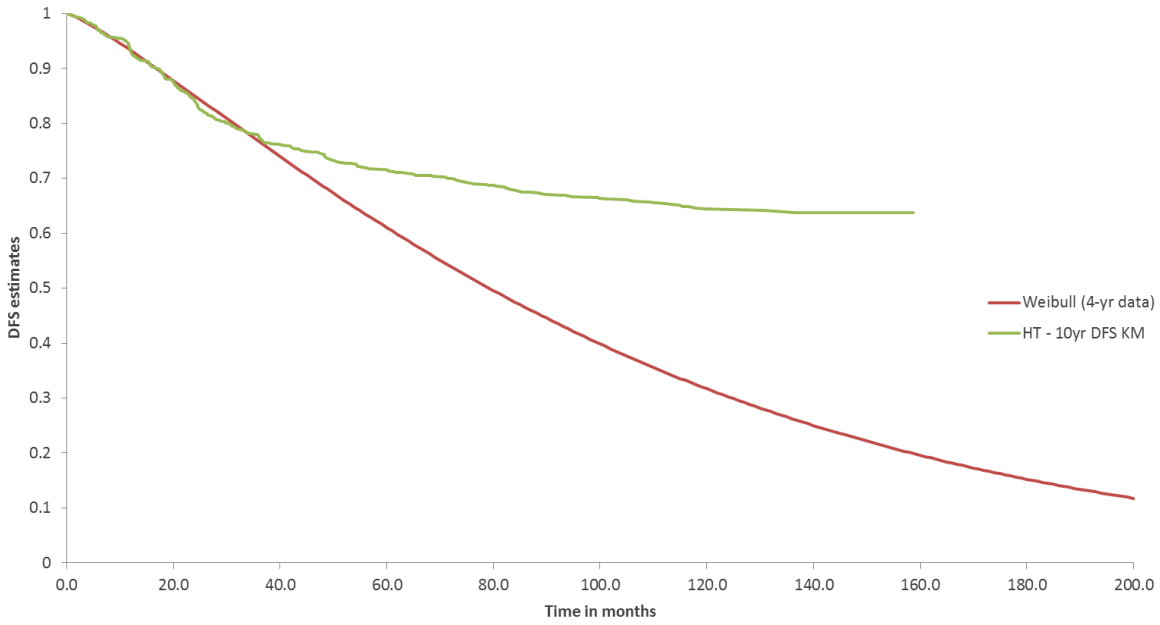
C.8 The ERG estimates that the change in node status inclusion criteria occurred around June 2013 based on information from Appendix L, the APHINITY study results and the study protocol. Is that correct? If yes, please explain the reason for the delay in implementing the changes, when the problem with Nodal distribution was noticed in September 2012, as reported in Appendix L.

Protocol amendment B was released in November 2012, approximately one year after the first patient was recruited into the study, as stated in Appendix L. However, due to Ethics Committee approval processes in respective countries, this meant that it took time for this amendment to be fully implemented in all sites. The first site approval for protocol amendment B was gained in December 2012, with >90% of sites gaining approval within four months.

C.9 Please reproduce CS, Document B, Figure 13, using 4 years of observed data from the HERA trial, and divided by treatment arm, as it is currently observed in the APHINITY trial.

No four-year data cut is available in the HERA trial.[2] In order to reproduce the figure requested by the ERG, the ten-year data cut had to be truncated. Following this truncation, a Weibull function was fit to the four-year data and extrapolated. As seen in Figure 2, the extrapolation based on four years of data still dramatically underestimates the observed DFS in the ten-year data cut.

Figure 2. Comparison of four-year HERA data extrapolation and the ten-year HERA data cut (node-positive population of the one-year trastuzumab therapy arm)[2]



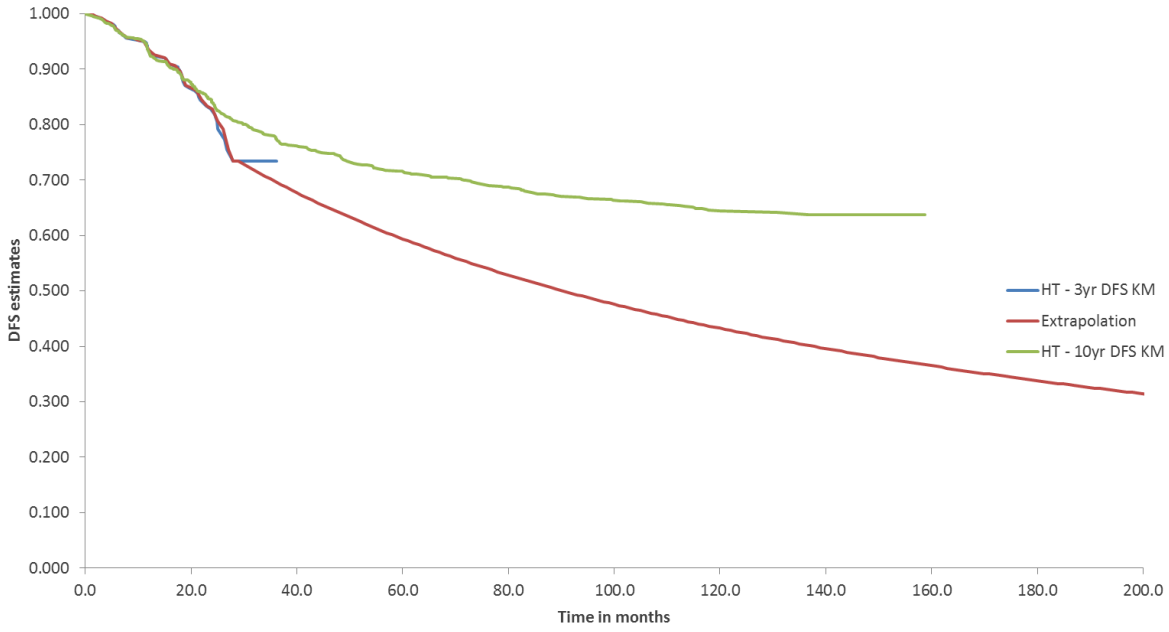
Abbreviations: DFS, Disease-free survival; HT, Trastuzumab + chemotherapy; yr., year.

It is worth noting here that in both APHINITY and HERA, the primary analysis was event-driven. In the HERA trial, events occurred fairly quickly and therefore the primary analysis was conducted at three years. In contrast, the events occurred more slowly in APHINITY and therefore the primary analysis was not triggered until four years. This difference in the speed of event occurrence helps to explain why three-year and four-year data cuts are available for HERA and APHINITY respectively.[2, 9]

C.10 Please reproduce CS, Document B, Figure 13 (ideally both 3- and 4-year data from the HERA trial), based on extrapolations fitted to data from 30 months and beyond, divided by treatment arm.

Figure 3 and Figure 4 report the extrapolations based on the three-year and four-year data cuts, respectively. Once again, both extrapolations comfortably underestimate the observed DFS rates in the ten-year data cut.

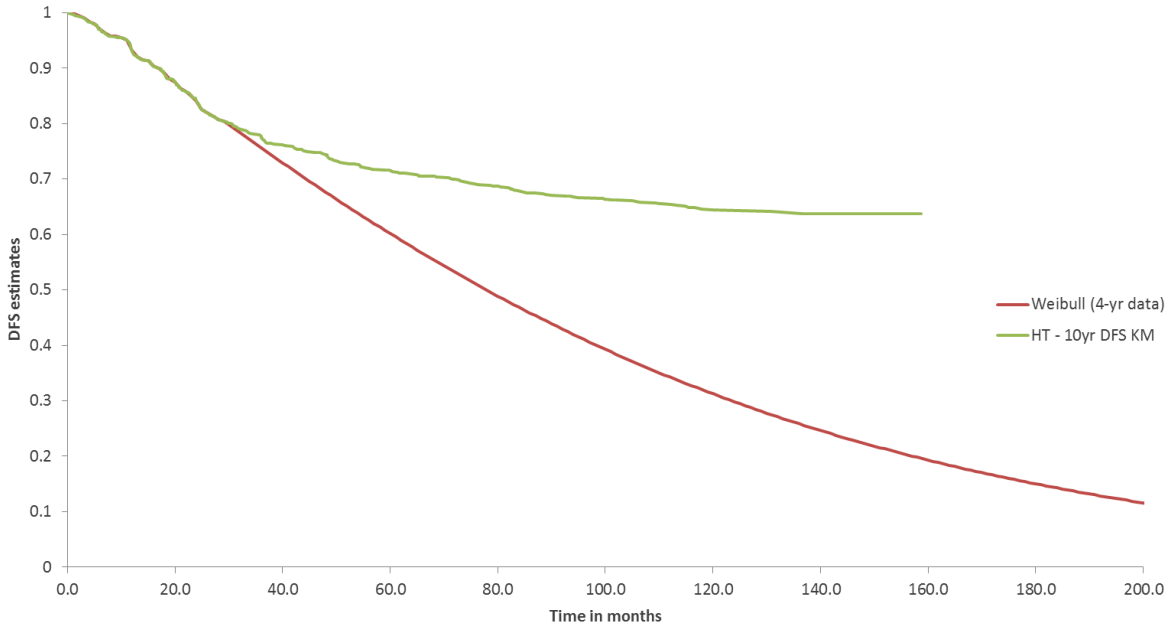
Figure 3. Comparison of three-year HERA data extrapolation and the ten-year HERA data cut (node-positive population of the one-year trastuzumab therapy arm)



Abbreviations: DFS, Disease-free survival; HT, Trastuzumab + chemotherapy; yr., year.

N.B.: Extrapolation was based on the Log-logistic function, as it proved to be the best fit to the data.

Figure 4. Comparison of four-year HERA data extrapolation and the ten-year HERA data cut (node-positive population of the one-year trastuzumab therapy arm)



Abbreviations: DFS, Disease-free survival; HT, Trastuzumab + chemotherapy; yr., year.

N.B.: Extrapolation was based on the Weibull function, as it proved to be the best fit to the data.

C.11 Due to the ill-fitting of the current parametric model to observed overall survival (OS), please update the economic model to allow parametric models to be fitted to the OS data. If this is not feasible, then please provide comment on the ill fit and suggest and implement alternative methods of improving the fit to the OS data.

The submitted cost-effectiveness model (CEM) is a seven-state Markov model. When adopting this approach, it is difficult to explicitly model overall survival (OS). A notable flaw in the Markov approach is that although death events can be accounted for, the origin of the patient who died is difficult to ascertain (i.e. a patient may die, but it is difficult to tell which health state the patient was in at the time of death).

In theory, it is possible to conduct survival analysis on the APHINITY OS data and subsequently fit parametric functions to the KM curves. However, the immaturity of the OS data means that a substantial amount of uncertainty would be introduced to the model. Only 144 deaths occurred across both treatment arms in the node-positive population of APHINITY, which means approximately 95% of the population are still alive at the end of follow-up. This number of events was judged to be insufficient to robustly model OS parametrically.

Currently, OS is modelled by accounting for the risk of death in each individual health state. Background mortality applies in all health states and is the main reason for death in the IDFS, non-metastatic recurrence, and remission states. The risk of death is significantly higher in the mBC health states. For mBC patients, the risk of death is modelled according to trial data on therapies available to current UK patients. In the UK, the proportion of mBC patients receiving pertuzumab + trastuzumab + chemotherapy or trastuzumab + chemotherapy as first-line options (other options exists but have smaller market shares) is higher than in the APHINITY trial.[30] These medicines are transformative and have a direct impact on survival outcomes in patients who receive them. In other words, the mBC patients in the model can expect better survival outcomes than those patients in APHINITY. This difference in access

helps to explain the ill-fit of the modelled OS data compared to the observed curves from APHINITY.

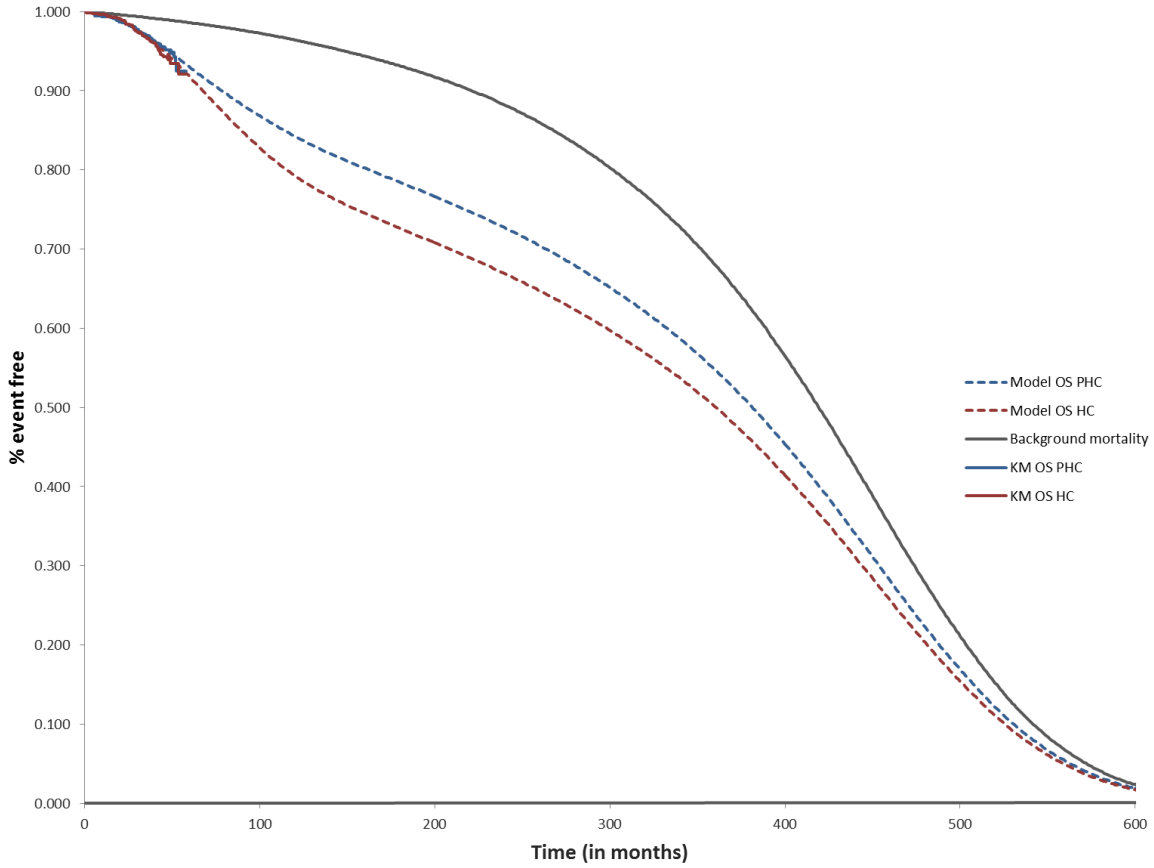
Once the proportion of patients receiving pertuzumab + trastuzumab + chemotherapy and trastuzumab + chemotherapy in the mBC states of the model is set equal to the proportions seen in APHINITY (see Table 12), the modelled OS fit to the OS KM curves is much improved (Figure 5).

Table 12. Proportion of treatment options on each treatment option in first-line mBC

Treatment option received after distant recurrence	APHINITY trial	ESTHER study[30]
Pertuzumab + trastuzumab + chemotherapy	18.4%*	71.2%
Placebo + trastuzumab + chemotherapy	17.0%*	22.9%
Chemotherapy alone	64.7%*	5.9%

*Please note: The treatment used in each line of therapy is not captured in the study database, therefore these numbers are an approximation.

Figure 5. OS modelling fit using the mBC treatment options as per APHINITY – node-positive population

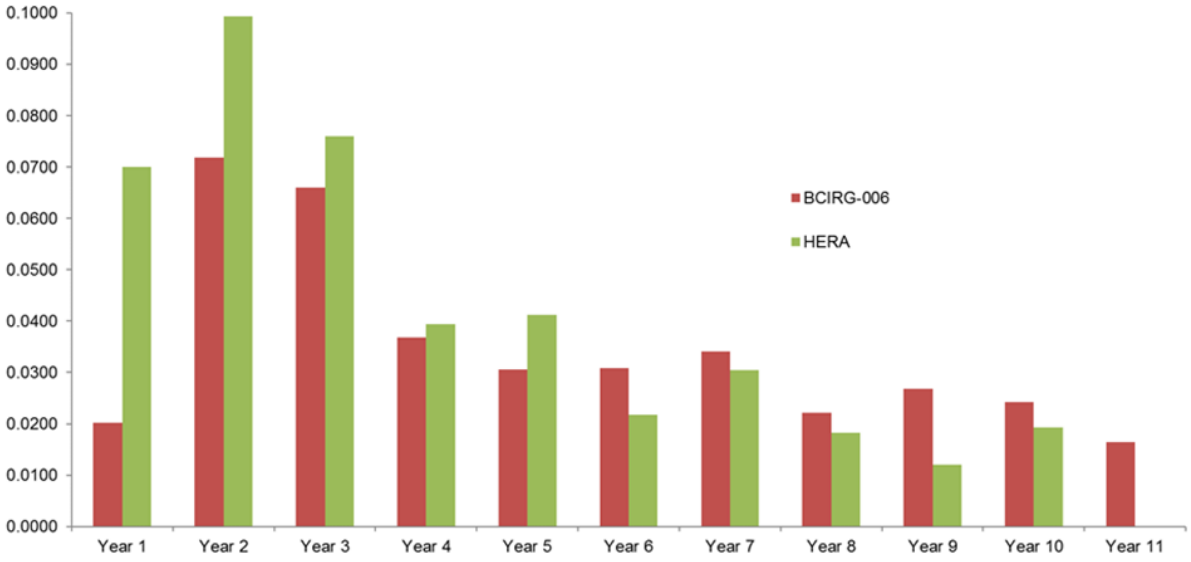


Abbreviations: HC, Placebo + trastuzumab + chemotherapy; KM, Kaplan-Meier; OS, Overall survival; PHC, Pertuzumab + trastuzumab + chemotherapy.

C.12 Please reproduce CS, Document B, Figure 14, for the node positive patients in the 1-year trastuzumab arm of the HERA trial, as these are the most relevant to the APHINTY population under consideration.

Figure 14 in the CS currently already refers to the node-positive patient in the "1-year trastuzumab therapy" arm of the HERA trial and therefore no response to this question is required. The figure has also been reported below for convenience.

Figure 6. Annual recurrence rate (DFS endpoint) in the node-positive populations of the HERA (one-year trastuzumab therapy arm) and BCIRG 006 clinical trials[2, 10]



C.13 Please provide more detail about how the trend seen in CS, Document B, Figure 14, has resulted in the decision to model the proportion of patients being "cured", and why other methods such as hazard ratio adjustment or time varying covariates were not explored?

The trend seen in the CS, Document B, Figure 14 shows that the DFS event rate (event being defined as a disease recurrence or death) is decreasing over time. These patients are disease-free therefore the death rate is expected to remain stable and eventually increase over time, as patients age. Ultimately, the disease recurrence rate (excluding death) decreases over time.

It is not possible to accurately extrapolate IDFS based on APHINITY data alone. Parametric survival analysis supports the extrapolation of the trial-observed recurrence rate, however if the reduction in recurrence rate is not observed in the trial (as per APHINITY), then it cannot be properly modelled. Consequently, neither standard parametric extrapolations nor covariate adjustments can be used to properly reflect this reduction in recurrence rate over time. Furthermore, the possibility of hazard ratio adjustment was excluded on the grounds that the proportional hazard assumption is violated.

The method currently in place in the model was considered the most appropriate, as it is both flexible (no need to run complex statistical analyses to adjust the assumptions or run sensitivity analyses), and fairly simple to implement.

C.14 With regards to the CS, Document B, Figure 20, please provide a definition of 'event' for this KM plot.

This KM plot was taken from the HERA study, therefore the primary endpoint was DFS, defined as time from randomisation to the first occurrence of any of the following disease-free–survival events: recurrence of breast cancer at any site; the development of ipsilateral or contralateral breast cancer, including ductal carcinoma in situ but not lobular carcinoma in situ; second non-breast malignant disease other than basal-cell or squamous-cell carcinoma of the skin or carcinoma in situ of the cervix; or death from any cause without documentation of a cancer-related event.[10]

References

1. Strasser-Weippl K, Horick N, Smith IE, et al. Long-term hazard of recurrence in HER2+ breast cancer patients untreated with anti-HER2 therapy. Breast Cancer Res 2015;17:56.
2. Cameron D, Piccart-Gebhart MJ, Gelber RD, et al. 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. Lancet 2017;389:1195-1205.
3. Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 2014;384:164-72.
4. Roche Products Ltd. Advisory board report: Health Technology Assessment (HTA) Advisory Board: Perjeta® (pertuzumab) for the Adjuvant Treatment of Human Epidermal Growth Factor Receptor 2-Positive (HER2+) Early Breast Cancer. Available on request., 2017.
5. Hammond ME, Hayes DF, Dowsett M, et al. American Society of Clinical Oncology/College Of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. J Clin Oncol 2010;28:2784-95.
6. Holloway CM, Easson A, Escallon J, et al. Technology as a force for improved diagnosis and treatment of breast disease. Can J Surg 2010;53:268-77.
7. Linder JM, Schiska AD. Progress in diagnosis of breast cancer: Advances in radiology technology. Asia Pac J Oncol Nurs 2015;2:186-191.
8. NCCN. NCCN Clinical Practice Guidelines in Oncology. Breast Cancer. Version V2., 2017.
9. von Minckwitz G, Procter M, de Azambuja E, et al. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. N Engl J Med 2017;377:122-131.
10. Slamon D, Eiermann W, Robert N, et al. Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med 2011;365:1273-83.
11. Perez EA, Romond EH, Suman VJ, et al. Four-year follow-up of trastuzumab plus adjuvant chemotherapy for operable human epidermal growth factor receptor 2-positive breast cancer: joint analysis of data from NCCTG N9831 and NSABP B-31. J Clin Oncol 2011;29:3366-73.
12. Slamon D, Swain S, Buse M, et al. Primary results from BETH, a phase 3 controlled study of adjuvant chemotherapy and trastuzumab +/- bevacizumab in patients with HER2-positive, node-positive or high risk node-negative breast cancer. San Antonio Breast Cancer Symposium (SABCS), 2013.
13. Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med 2005;353:1673-84.
14. von Minckwitz G, Procter M, de Azambuja E, et al. Adjuvant Pertuzumab and Trastuzumab in Early HER2-positive breast cancer: Supplementary Appendix. N Engl J Med 2017;377:122-131.
15. Rugo HS. The Risk of Early Recurrence and Distant Metastases - Lessons from the Monotherapy Adjuvant Aromatase Inhibitor Trials with a Focus on BIG I-98. European Oncological Disease 2006;1:24-27.
16. Roche Products Ltd. APHINITY (BO25126) Primary Clinical Study Report No. 1075429. 2017.

17. NICE. TA107: Trastuzumab for the adjuvant treatment of early-stage HER2-positive breast cancer, 2006.
18. NICE. TA424: Pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer, 2016.
19. Lloyd A, Nafees B, Narewska J, et al. Health state utilities for metastatic breast cancer. Br J Cancer 2006;95:683-90.
20. Dolan P. Modeling valuations for EuroQol health states. Med Care 1997;35:1095-108.
21. Department of Health and Social Care. NHS reference costs 2016 to 2017, 2017.
22. Personal Social Services Research Unit. Unit Costs of Health and Social Care 2017.
23. Lagakos SW. The challenge of subgroup analyses--reporting without distorting. N Engl J Med 2006;354:1667-9.
24. Bines J, de Azambuja E, Zardavas D, et al. Incidence and management of diarrhea with adjuvant pertuzumab and trastuzumab in HER2-Positive breast cancer, In SABCS, 2017.
25. Cianfrocca M, Goldstein LJ. Prognostic and predictive factors in early-stage breast cancer. Oncologist 2004;9:606-16.
26. Kim KJ, Huh SJ, Yang JH, et al. Treatment results and prognostic factors of early breast cancer treated with a breast conserving operation and radiotherapy. Jpn J Clin Oncol 2005;35:126-33.
27. Pistelli M, Pagliacci A, Battelli N, et al. Prognostic factors in early-stage triple-negative breast cancer: lessons and limits from clinical practice. Anticancer Res 2013;33:2737-42.
28. Baselga J, Cortes J, Kim SB, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med 2012;366:109-19.
29. Aebi S, Davidson T, Gruber G, et al. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2010;21 Suppl 5:v9-14.
30. Wardley A, Fredrikkson J, Leslie I, et al. Anti-cancer resource use in the initial management of advanced HER2+ breast cancer: an interim analysis of the UK ESTHER study. Submitted abstract EBCC-0377 2018.

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Company response to the ERG's clarification questions - Appendix

27th March, 2018

1. For Company Submission (CS), Appendix G, Tables 15 and 16, please supply an additional column with numbers retrieved for each line. This will aid the ERG in critiquing the MEDLINE, MEDLINE In-Process and Embase search strategies.

Search terms and numbers retrieved are provided in Table 1 and Table 2 for the original search, and Table 3 and Table 4 for the updated search.

Table 1 Search terms for MEDLINE and MEDLINE In-Process, original search (November 20th, 2014)

Database: **(1) Ovid MEDLINE(R)** **(2) Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations**			**Results**
Category	**#**	**Search terms**	
Disease	1	cancer[MeSH] OR cancer[TIAB] OR malignancy[TIAB] OR tumor[TIAB] OR tumour[TIAB] OR carcinoma[TIAB] OR neoplasm*[TIAB]	3,108,931
	2	((((breast[Title/Abstract]) OR mammary[Title/Abstract]) AND cancer[Title/Abstract]) OR tumour[Title/Abstract]) OR neoplasm[Title/Abstract]	397,137
	3	Breast Neoplasms[Mesh]	218,768
	4	#1 AND (#2 OR #3)	465,689
Interventions	5	((Neoadjuvant Therapy[Mesh]) OR Chemotherapy, Adjuvant[Mesh]) OR Radiotherapy, Adjuvant[Mesh]	46,928
	6	(((((adjuvant therapy[Title/Abstract]) OR neoadjuvant therapy[Title/Abstract]) OR adjuvant chemotherapy[Title/Abstract]) OR adjuvant radiotherapy[Title/Abstract])) OR ((adjuvant[Title/Abstract]) OR neoadjuvant[Title/Abstract])	107,597
	7	#5 OR #6	129,296
Disease & intervention	8	#4 AND #7	30,843
Economic evaluations	9	"Technology Assessment, Biomedical"[MeSH]	9,186
	10	((health technology assessment[Title/Abstract]) OR health technology assessments[Title/Abstract]) OR health technologies assessment[Title/Abstract]	2,232
	11	economic[TIAB] AND (evaluation[TIAB] OR evaluations[TIAB])	14,399
	12	pharmacoeconomic*[TIAB]	2,900
	13	"cost-effectiveness"[TIAB] OR "cost effectiveness"[TIAB] OR "cost-effective"[TIAB] OR "cost effective"[TIAB] OR "cost-benefit"[TIAB] OR "cost benefit"[TIAB] OR "cost-benefits"[TIAB] OR "cost benefits"[TIAB] OR "cost-utility"[TIAB] OR "cost utility"[TIAB] OR "cost-utilities"[TIAB] OR "cost utilities"[TIAB] OR "cost-minimisation"[TIAB] OR "cost	88,477

		minimisation"[TIAB] OR "cost-minimization"[TIAB] OR "cost minimization"[TIAB]	
Quality of life	14	#9 OR #10 OR #11 OR #12 OR #13	108,519
	15	("Quality of Life"[MeSH]) OR "Quality-Adjusted Life Years"[MeSH]	125,288
	16	("quality of life"[TIAB] OR "quality of lives"[TIAB])) OR QoL[TIAB] OR HRQoL[TIAB] OR HRQL[TIAB] OR QALY[TIAB] OR QALYs[TIAB] OR ((("health year equivalent"[TIAB] OR "healthy year equivalent"[TIAB]) OR HYE[TIAB] OR ("utility value"[TIAB] OR "utility weight"[TIAB] OR "utility values"[TIAB] OR "utility weights"[TIAB])	159,455
	17	generic[TIAB] AND (instrument*[TIAB] OR measurement*[TIAB])	4,008
	18	(disease-specific[TIAB] OR "disease specific"[TIAB] OR "condition-specific"[TIAB] OR "condition specific"[TIAB]) AND (instrument*[TIAB] OR measurement*[TIAB])	2,762
	19	"short form"[TIAB] OR "sf-36"[TIAB] OR "sf 36"[TIAB] OR "sf36"[TIAB] OR "sf-12"[TIAB] OR "sf 12"[TIAB] OR "sf12"[TIAB] OR "sf-6d"[TIAB] OR "sf 6d"[TIAB] OR "sf6d"[TIAB] OR "euroqol"[TIAB] OR "eq-5d"[TIAB] OR "eq 5d"[TIAB] OR "eq5d"[TIAB] OR "eq-15d"[TIAB] OR "eq 15d"[TIAB] OR "eq15d"[TIAB] OR "quality and well being"[TIAB] OR "quality and wellbeing"[TIAB] OR "quality and well-being"[TIAB] OR "qwb"[TIAB] OR "health utilities index"[TIAB] OR "hui"[TIAB] OR "qlq-c30"[TIAB] OR "qlq-br23"[TIAB] OR "qlq br23"[TIAB] OR "eortc"[TIAB] OR "vignette"[TIAB] OR "vignettes"[TIAB]	43,772
	20	"time tradeoff"[TIAB] OR "time trade off"[TIAB] OR "time trade-off"[TIAB] OR TTO[TIAB] OR "standard gamble"[TIAB] OR "rating scale"[TIAB] OR "rating scales"[TIAB] OR "visual analog scale"[TIAB] OR "visual analogue scale"[TIAB] OR "visual analog scales"[TIAB] OR "visual analogue scales"[TIAB] OR "willingness to pay"[TIAB] OR "willingness-to-pay"[TIAB] OR WTP[TIAB]	69,954
	21	#15 OR #16 AND (#17 OR #18 OR #19 OR #20)	30,478
Disease & intervention combined	22	#8 AND (#14 OR #21)	612
Irrelevant publication restriction	23	#22 NOT review[TI] OR review[PT] or editorial[PT] or guideline[PT] or letter[PT] or "meta-analysis"[PT] or "case reports"[PT] or comment[PT] or news[PT]	453
Subject restriction	24	#23 NOT ((animal[mesh] not human[mesh]))	452
Language filter	25	#24 AND Filters: English	421

Table 2 Search terms for EMBASE, original search (November 20th, 2014)

	Database: EMBASE		Results
Category	**#**	**Search terms**	
Disease	1	cancer/EXP OR cancer:TI,AB OR malignancy:TI,AB OR tumor:TI,AB OR tumour:TI,AB OR carcinoma:TI,AB OR neoplasm*:TI,AB	4,047,545
	2	((((breast:TI,AB) OR mammary:TI,AB) AND cancer:TI,AB) OR tumour:TI,AB) OR neoplasm:TI,AB	557,174
	3	Breast Neoplasms/EXP	698,963
	4	#1 AND (#2 OR #3)	418,430
Interventions	5	((Neoadjuvant Therapy/EXP) OR Chemotherapy, Adjuvant/EXP) OR Radiotherapy, Adjuvant/EXP	10,335
	6	(((((adjuvant therapy:TI,AB) OR neoadjuvant therapy:TI,AB) OR adjuvant chemotherapy:TI,AB) OR adjuvant radiotherapy:TI,AB)) OR ((adjuvant:TI,AB) OR neoadjuvant:TI,AB)	156,137
	7	#5 OR #6	157,356
Disease & intervention	8	#4 AND #7	41,125
Economic evaluations	9	'Biomedical technology assessment'/EXP	11,309
	10	'Economic evaluation'/EXP	217,773
	11	('health technology assessment' OR 'health technologies assessment' OR 'health technology assessments' OR 'health technologies assessments'):TI,AB	2844
	12	(economic NEXT/1 evaluation$):TI,AB	7,349
	13	(pharmacoeconomic OR pharmacoeconomics OR 'pharmaco-economic' OR 'pharmaco-economics' OR 'pharmaco economic' OR 'pharmaco economics'):TI,AB	6,337
	14	('cost-effectiveness' OR 'cost effectiveness' OR costeffectiveness OR 'cost-effective' OR 'cost effective' OR costeffective OR 'cost-benefit' OR 'cost benefit' OR costbenefit OR 'cost-benefits' OR 'cost benefits' OR costbenefits OR 'cost-utility' OR 'cost utility' OR costutility OR 'cost-utilities' OR 'cost utilities' or costutilities OR 'cost-minimisation' OR 'cost minimisation' OR costminimisation OR 'cost-minimization' OR 'cost minimization' OR costminimization):TI,AB	117,034
	15	#9 OR #10 OR #11 OR #12 OR #13 OR #14	278,961
Quality of life	16	'quality adjusted life year'/exp OR 'Quality-Adjusted Life Years'/exp	12,978
	17	("quality of life":TI,AB OR "quality of lives":TI,AB)) OR QoL:TI,AB OR HRQoL:TI,AB OR HRQL:TI,AB OR QALY:TI,AB OR QALYs:TI,AB OR ((("health year equivalent":TI,AB OR "healthy year equivalent":TI,AB) OR HYE:TI,AB OR ("utility value":TI,AB OR "utility weight":TI,AB OR "utility values":TI,AB OR "utility weights":TI,AB)	271,311
	18	generic:TI,AB AND (instrument*:TI,AB OR measurement*:TI,AB)	4,903

	19	(disease-specific:TI,AB OR "disease specific":TI,AB OR "condition-specific":TI,AB OR "condition specific":TI,AB) AND (instrument*:TI,AB OR measurement*:TI,AB)	3,700
	20	short form':ab,ti OR 'sf-36':ab,ti OR 'sf 36':ab,ti OR sf36:ab,ti OR 'sf-12':ab,ti OR 'sf 12':ab,ti OR sf12:ab,ti OR 'sf-6d':ab,ti OR 'sf 6d':ab,ti OR sf6d:ab,ti OR euroqol:ab,ti OR 'eq-5d':ab,ti OR 'eq 5d':ab,ti OR eq5d:ab,ti OR 'eq-15d':ab,ti OR 'eq 15d':ab,ti OR eq15d:ab,ti OR 'quality and well being':ab,ti OR 'quality and wellbeing':ab,ti OR 'quality and well-being':ab,ti OR 'qwb':ab,ti OR 'health utilities index':ab,ti OR hui:ab,ti OR 'qlq-c30':ab,ti OR 'qlq-br23':ab,ti OR 'qlq br23':ab,ti OR 'eortc':ab,ti OR 'vignette':ab,ti OR 'vignettes':ab,ti	63,682
	21	"time tradeoff":TI,AB OR "time trade off":TI,AB OR "time trade-off":TI,AB OR TTO:TI,AB OR "standard gamble":TI,AB OR "rating scale":TI,AB OR "rating scales":TI,AB OR "visual analog scale":TI,AB OR "visual analogue scale":TI,AB OR "visual analog scales":TI,AB OR "visual analogue scales":TI,AB OR "willingness to pay":TI,AB OR "willingness-to-pay":TI,AB OR WTP:TI,AB	94,876
	22	#16 OR #17 AND (#18 OR #19 OR #20 OR #21)	43,062
Disease & intervention combined & (economic evaluations or quality of life)	23	#8 AND (#15 OR #22)	1,195
Irrelevant publication restriction	24	review:TI OR review:it or editorial:it or guideline:it or letter:it or "meta-analysis":it or "case reports":it or comment:it or news:it	3,457,895
	25	#23 NOT #24	932
	26	#25 NOT ('case report'/exp OR 'case study'/exp OR 'case control' OR 'longitudinal study'/exp)	896
Subject restriction	27	#26 NOT ('animal'/EXP not 'human'/EXP)	894
Language restriction	28	#27 AND Filters: English	845

Table 3 Search terms for MEDLINE and MEDLINE In-Process, updated search (November 20th, 2017)

Database: **(1) Ovid MEDLINE(R)** **(2) Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations**			**Results**
Category	**#**	**Search terms**	
Disease	1	cancer[MeSH] OR cancer[TIAB] OR malignancy[TIAB] OR tumor[TIAB] OR tumour[TIAB] OR carcinoma[TIAB] OR neoplasm*[TIAB])	3,641,715
	2	breast[TIAB]) OR mammary[TIAB] AND cancer[TIAB] OR tumour[TIAB] OR neoplasm[TIAB]	499,101
	3	Breast Neoplasms[Mesh]	256,099
	4	(#1 AND (#2 OR #3))	572,112
Interventions	5	(((Neoadjuvant Therapy[Mesh]) OR Chemotherapy, Adjuvant[Mesh]) OR Radiotherapy, Adjuvant[Mesh])	57,347
	6	((((((adjuvant therapy[TIAB]) OR neoadjuvant therapy[TIAB]) OR adjuvant chemotherapy[TIAB]) OR adjuvant radiotherapy[TIAB])) OR ((adjuvant[TIAB]) OR neoadjuvant[TIAB]))	135,165
	7	(#5 OR #6)	160,113
Disease & intervention	8	(#4 AND #7)	38,512
Economic evaluations	9	"Technology Assessment, Biomedical"[MeSH]	10,157
	10	(((health technology assessment[TIAB]) OR health technology assessments[TIAB]) OR health technologies assessment[TIAB])	3,735
	11	(economic[TIAB] AND (evaluation[TIAB] OR evaluations[TIAB]))	21,496
	12	pharmacoeconomic*[TIAB]	3,502
	13	("cost-effectiveness"[TIAB] OR "cost effectiveness"[TIAB] OR "cost-effective"[TIAB] OR "cost effective"[TIAB] OR "cost-benefit"[TIAB] OR "cost benefit"[TIAB] OR "cost-benefits"[TIAB] OR "cost benefits"[TIAB] OR "cost-utility"[TIAB] OR "cost utility"[TIAB] OR "cost-utilities"[TIAB] OR "cost utilities"[TIAB] OR "cost-minimisation"[TIAB] OR "cost minimisation"[TIAB] OR "cost-minimization"[TIAB] OR "cost minimization"[TIAB])	117,164
Quality of life	14	(#9 OR #10 OR #11 OR #12 OR #13)	143,748
	15	(("Quality of Life"[MeSH]) OR "Quality-Adjusted Life Years"[MeSH])	161,785
	16	(("quality of life"[TIAB] OR "quality of lives"[TIAB])) OR QoL[TIAB] OR HRQoL[TIAB] OR HRQL[TIAB] OR QALY[TIAB] OR QALYs[TIAB] OR ((("health year	218,623

		equivalent"[TIAB] OR "healthy year equivalent"[TIAB]) OR HYE[TIAB] OR ("utility value"[TIAB] OR "utility weight"[TIAB] OR "utility values"[TIAB] OR "utility weights"[TIAB]))	
	17	(generic[TIAB] AND (instrument*[TIAB] OR measurement*[TIAB]))	5,009
	18	((disease-specific[TIAB] OR "disease specific"[TIAB] OR "condition-specific"[TIAB] OR "condition specific"[TIAB]) AND (instrument*[TIAB] OR measurement*[TIAB]))	3,471
	19	("short form"[TIAB] OR "sf-36"[TIAB] OR "sf 36"[TIAB] OR "sf36"[TIAB] OR "sf-12"[TIAB] OR "sf 12"[TIAB] OR "sf12"[TIAB] OR "sf-6d"[TIAB] OR "sf 6d"[TIAB] OR "sf6d"[TIAB] OR "euroqol"[TIAB] OR "eq-5d"[TIAB] OR "eq 5d"[TIAB] OR "eq5d"[TIAB] OR "eq-15d"[TIAB] OR "eq 15d"[TIAB] OR "eq15d"[TIAB] OR "quality and well being"[TIAB] OR "quality and wellbeing"[TIAB] OR "quality and well-being"[TIAB] OR "qwb"[TIAB] OR "health utilities index"[TIAB] OR "hui"[TIAB] OR "qlq-c30"[TIAB] OR "qlq-br23"[TIAB] OR "qlq br23"[TIAB] OR "eortc"[TIAB] OR "vignette"[TIAB] OR "vignettes"[TIAB])	59,138
	20	("time tradeoff"[TIAB] OR "time trade off"[TIAB] OR "time trade-off"[TIAB] OR TTO[TIAB] OR "standard gamble"[TIAB] OR "rating scale"[TIAB] OR "rating scales"[TIAB] OR "visual analog scale"[TIAB] OR "visual analogue scale"[TIAB] OR "visual analog scales"[TIAB] OR "visual analogue scales"[TIAB] OR "willingness to pay"[TIAB] OR "willingness-to-pay"[TIAB] OR WTP[TIAB])	93,303
	21	(#15 OR #16 AND (#17 OR #18 OR #19 OR #20))	42,264
Disease & intervention combined	22	(#8 AND (#14 OR #21))	773
Irrelevant publication restriction	23	(review[TI] OR review[PT] or editorial[PT] or guideline[PT] or letter[PT] or "meta-analysis"[PT] or "case reports"[PT] or comment[PT] or news[PT])	5,752,408
	24	(#22 NOT #23)	578
Subject restriction	25	(#24 NOT ((animal[mesh] not human[mesh])))	577
Language filter	26	(#25) AND English[Filter]	546
Time restriction	27	(#25) AND English[Filter] Filters: Publication date from 2014/11/20	122

Table 4 Search terms for EMBASE, updated search (November 20th, 2017)

Database: EMBASE			Results
Category	**#**	**Search terms**	
Disease	1	'cancer'/exp OR cancer:ti,ab OR malignancy:ti,ab OR tumor:ti,ab OR tumour:ti,ab OR carcinoma:ti,ab OR neoplasm*:ti,ab	4,214,081
	2	(breast:ti,ab OR mammary:ti,ab) AND cancer:ti,ab OR tumour:ti,ab OR neoplasm:ti,ab	657,301
	3	breast neoplasms/exp	516,425
	4	#1 AND (#2 OR #3)	799,271
Interventions	5	((Neoadjuvant therapy/exp OR chemotherapy,) AND 'adjuvant'/exp OR radiotherapy,) AND 'adjuvant'/exp	15,856
	6	(((adjuvant AND therapy:ti,ab OR neoadjuvant) AND therapy:ti,ab OR adjuvant) AND chemotherapy:ti,ab OR adjuvant) AND radiotherapy:ti,ab OR adjuvant:ti,ab OR neoadjuvant:ti,ab	204,783
	7	#5 OR #6	206,101
Disease & intervention	8	#4 AND #7	56,050
Economic evaluations	9	'biomedical technology assessment'/exp	12,546
	10	'economic evaluation'/exp	264,061
	11	'health technology assessment':ti,ab OR 'health technologies assessment':ti,ab OR 'health technology assessments':ti,ab OR 'health technologies assessments':ti,ab	4,627
	12	(economic NEXT/1 evaluation$):ti,ab	12,979
	13	pharmacoeconomic:ti,ab OR pharmacoeconomics:ti,ab OR 'pharmaco-economic':ti,ab OR 'pharmaco-economics':ti,ab OR 'pharmaco economic':ti,ab OR 'pharmaco economics':ti,ab	7,515
	14	'cost-effectiveness':ti,ab OR 'cost effectiveness':ti,ab OR costeffectiveness:ti,ab OR 'cost-effective':ti,ab OR 'cost effective':ti,ab OR costeffective:ti,ab OR 'cost-benefit':ti,ab OR 'cost benefit':ti,ab OR costbenefit:ti,ab OR 'cost-benefits':ti,ab OR 'cost benefits':ti,ab OR costbenefits:ti,ab OR 'cost-utility':ti,ab OR 'cost utility':ti,ab OR costutility:ti,ab OR 'cost-utilities':ti,ab OR 'cost utilities':ti,ab OR costutilities:ti,ab OR 'cost-minimisation':ti,ab OR 'cost minimisation':ti,ab OR costminimisation:ti,ab OR 'cost-minimization':ti,ab OR 'cost minimization':ti,ab OR costminimization:ti,ab	158,018
	15	#9 OR #10 OR #11 OR #12 OR #13 OR #14	347,611

Quality of life	16	'quality adjusted life year'/exp OR 'quality-adjusted life years'/exp	19,803
	17	'quality of life':ti,ab OR 'quality of lives':ti,ab OR qol:ti,ab OR hrqol:ti,ab OR hrql:ti,ab OR qaly:ti,ab OR qalys:ti,ab OR 'health year equivalent':ti,ab OR 'healthy year equivalent':ti,ab OR hye:ti,ab OR 'utility value':ti,ab OR 'utility weight':ti,ab OR 'utility values':ti,ab OR 'utility weights':ti,ab	336,445
	18	generic:ti,ab AND (instrument*:ti,ab OR measurement*:ti,ab)	6,362
	19	('disease specific':ti,ab OR 'condition-specific':ti,ab OR 'condition specific':ti,ab) AND (instrument*:ti,ab OR measurement*:ti,ab)	5,002
	20	'short form':ab,ti OR 'sf-36':ab,ti OR 'sf 36':ab,ti OR sf36:ab,ti OR 'sf-12':ab,ti OR 'sf 12':ab,ti OR sf12:ab,ti OR 'sf-6d':ab,ti OR 'sf 6d':ab,ti OR sf6d:ab,ti OR euroqol:ab,ti OR 'eq-5d':ab,ti OR 'eq 5d':ab,ti OR eq5d:ab,ti OR 'eq-15d':ab,ti OR 'eq 15d':ab,ti OR eq15d:ab,ti OR 'quality and well being':ab,ti OR 'quality and wellbeing':ab,ti OR 'quality and well-being':ab,ti OR 'qwb':ab,ti OR 'health utilities index':ab,ti OR hui:ab,ti OR 'qlq-c30':ab,ti OR 'qlq-br23':ab,ti OR 'qlq br23':ab,ti OR 'eortc':ab,ti OR 'vignette':ab,ti OR 'vignettes':ab,ti	91,194
	21	'time tradeoff':ti,ab OR 'time trade off':ti,ab OR 'time trade-off':ti,ab OR tto:ti,ab OR 'standard gamble':ti,ab OR 'rating scale':ti,ab OR 'rating scales':ti,ab OR 'visual analog scale':ti,ab OR 'visual analogue scale':ti,ab OR 'visual analog scales':ti,ab OR 'visual analogue scales':ti,ab OR 'willingness to pay':ti,ab OR 'willingness-to-pay':ti,ab OR wtp:ti,ab	132,193
	22	(#16 OR #17) AND (#18 OR #19 OR #20 OR #21)	64,803
Disease & intervention combined & (economic evaluations or quality of life)	23	#8 AND (#15 OR #22)	1,646
Irrelevant publication restriction	24	review:ti OR review:it OR editorial:it OR guideline:it OR letter:it OR 'meta-analysis':it OR 'case reports':it OR comment:it OR news:it	4,062,821
	25	#23 NOT #24	1,341
	26	#25 NOT ('case report'/exp OR 'case study'/exp OR 'case control' OR 'longitudinal study'/exp)	1,293
Subject restriction	27	#26 NOT ('animal'/exp NOT 'human'/exp)	1,291
Language restriction	28	#27 AND [english]/lim	1,240

Time restriction	29	#28 AND [20-11-2014]/sd NOT [20-11-2017]/sd AND [2014-2017]/py	364

C2. Priority question: Please provide

- goodness of fit statistics,
- smoothed hazard vs time plots and
- cumulative hazard vs time plots

for each of the parametric functions and overlaid with the observed data, where the parametric fit begins at 22 months for both arms and KM data used before this point, and also for the company base case (parametric fit from 0 months).

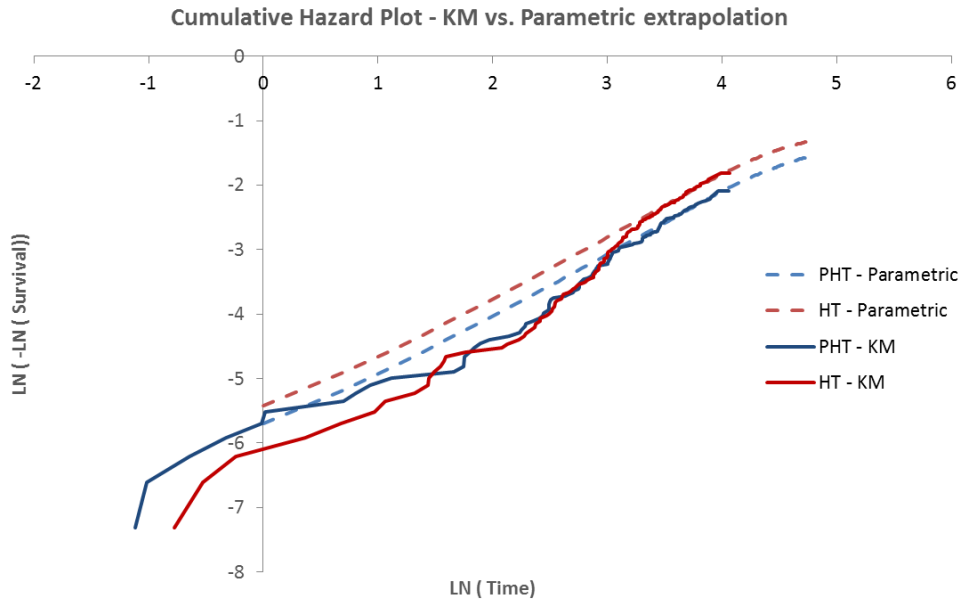
The following charts (Figure 1 to Figure 12) display the cumulative hazard and smoothed hazard plotted against all parametric distributions available:

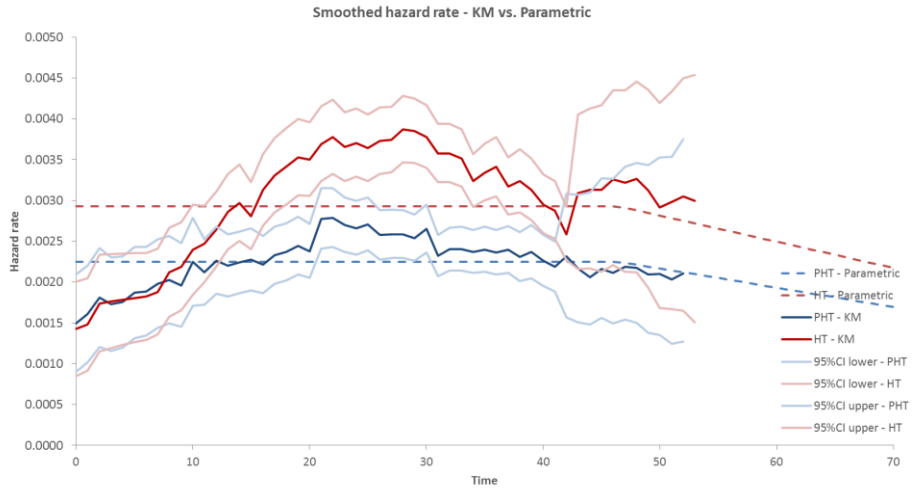
- Figures 1 to 6 display parametric extrapolation for the entire follow-up.
- Figures 7 to 12 display KM curves up to 22 months followed by parametric tail. *

** As explained in response to C2 of the main response document., these figures have been generated using parametric estimates that were calculated from all of the observed data available.*

Please note that a small difference remains when considering KM curves and KM curves followed by parametric tail. This is explained by the fact that the model is using a monthly cycle length whereas the KM data doesn't always report a value for each month (by definition, KM only present a value when there is an event). Therefore, Excel interpolates IDFS estimates between observed KM values.
To improve the readability, the charts only display the first 70 months. In addition, the hazard rate has been smoothed for the plot presenting KM curves up to 22 months followed by parametric tail (to improve readability).

Figure 1 Exponential distribution – Cumulative hazard and smoothed hazard





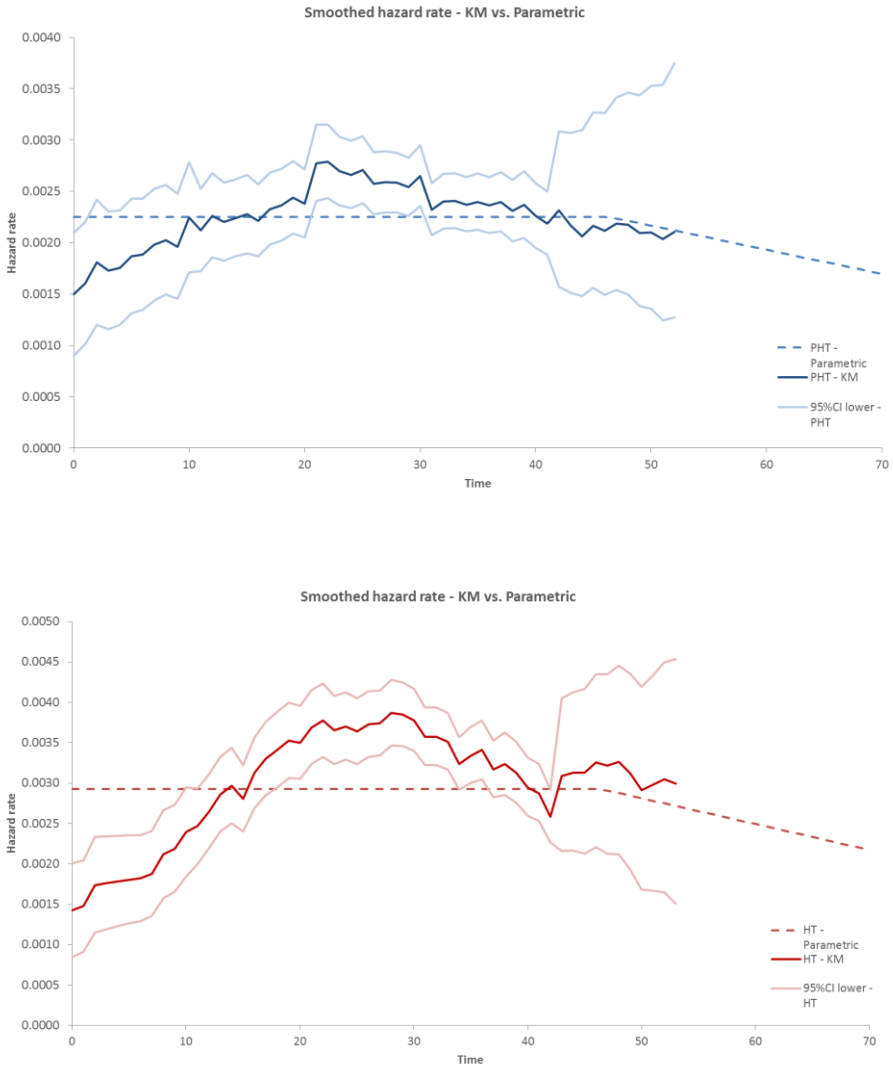
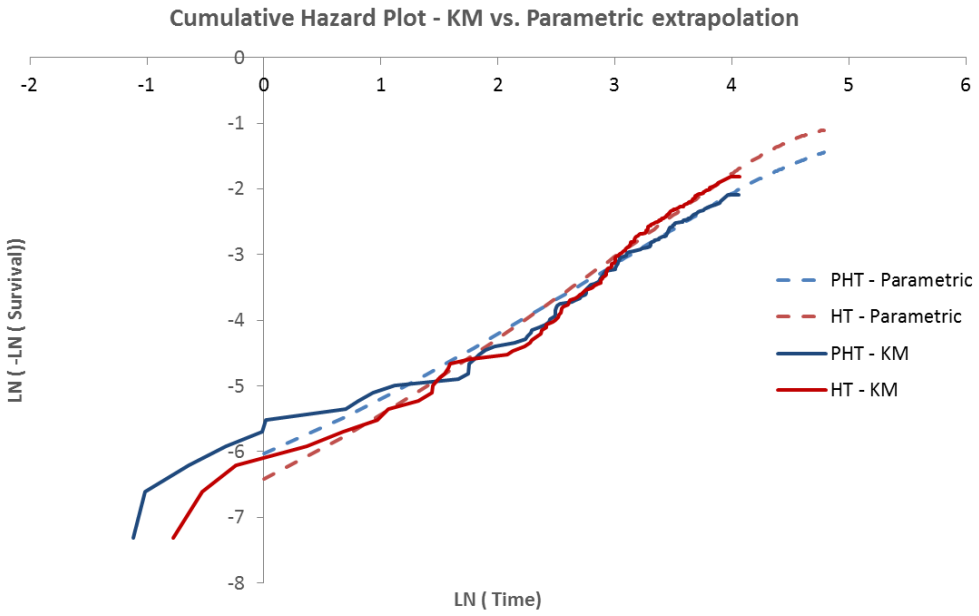
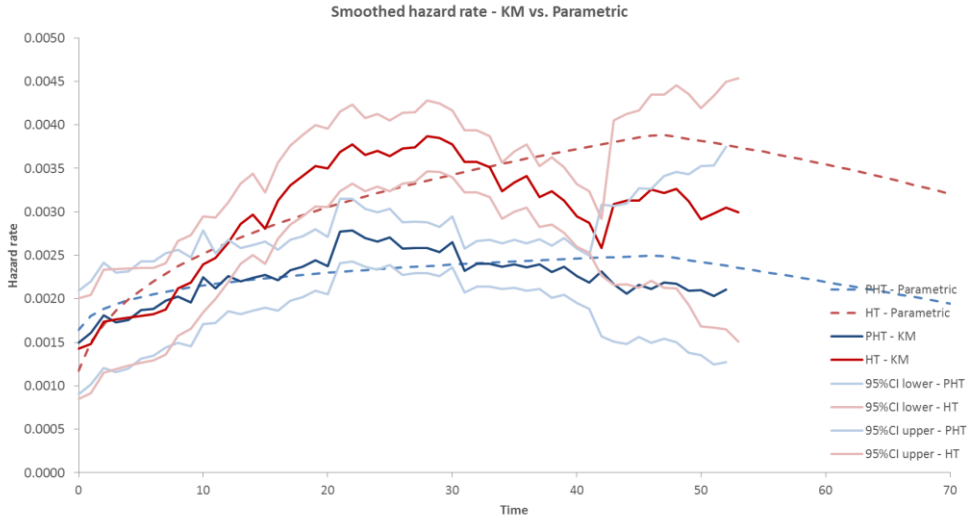
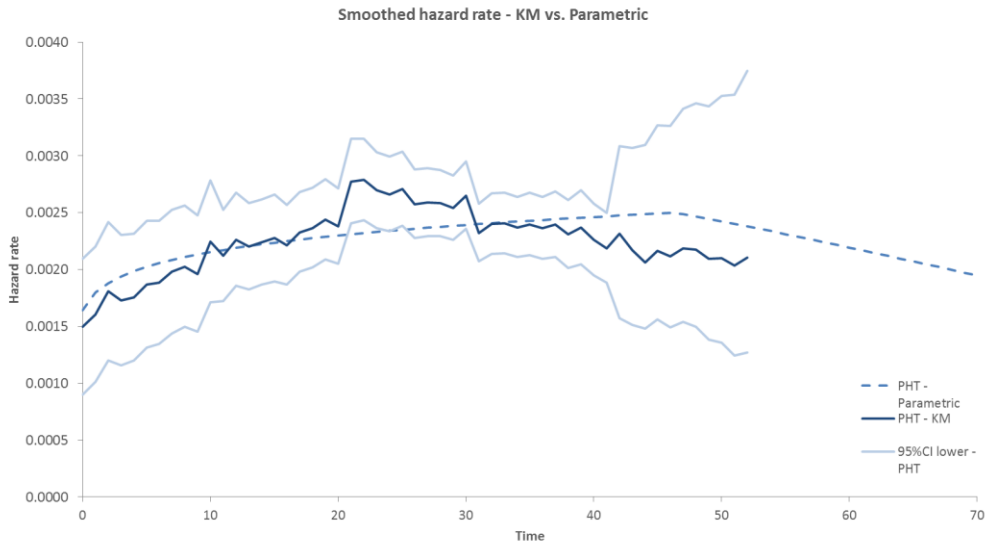


Figure 2: Weibull distribution – Cumulative hazard and smoothed hazard


Cumulative Hazard Plot - KM vs. Parametric extrapolation
LN (-LN (Survival))
LN (Time)
PHT - Parametric
HT - Parametric
PHT - KM
HT - KM


Smoothed hazard rate - KM vs. Parametric
Hazard rate
Time
PHT - Parametric
HT - Parametric
PHT - KM
HT - KM
95%CI lower - PHT
95%CI lower - HT
95%CI upper - PHT
95%CI upper - HT



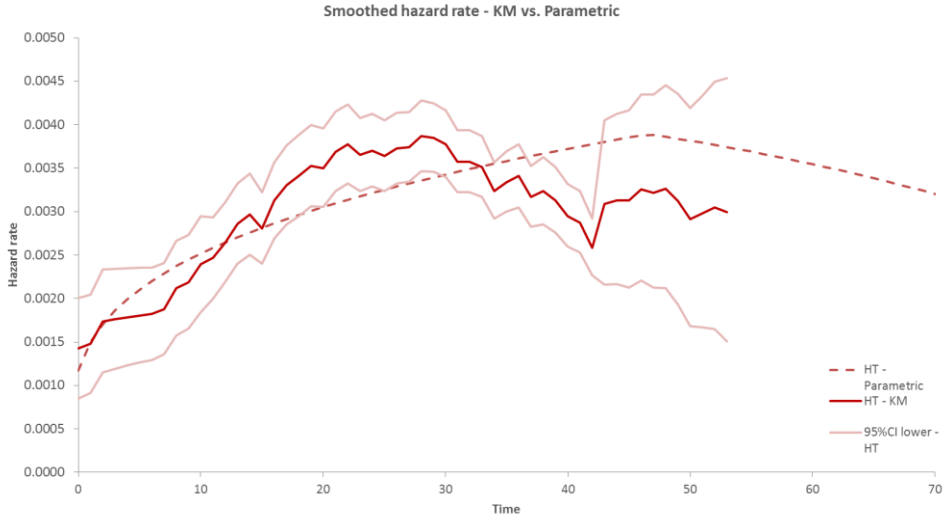
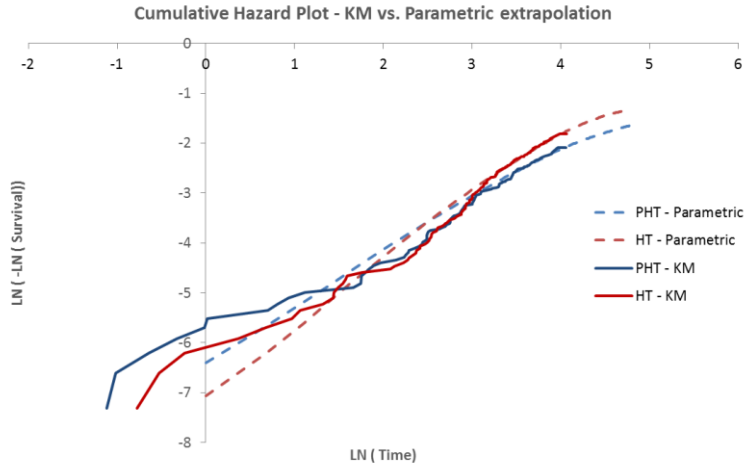
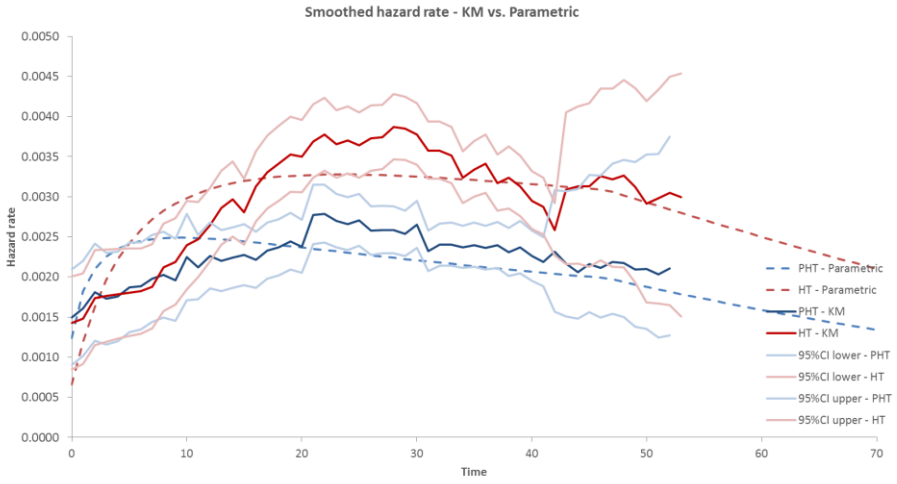
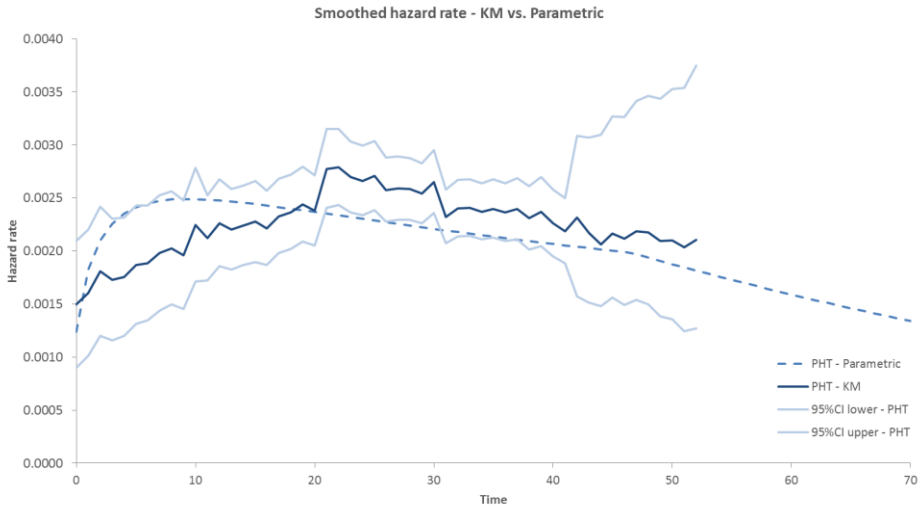


Figure 3: Log-normal distribution – Cumulative hazard and smoothed hazard




Smoothed hazard rate - KM vs. Parametric
Hazard rate
Time
PHT - Parametric
HT - Parametric
PHT - KM
HT - KM
95%CI lower - PHT
95%CI lower - HT
95%CI upper - PHT
95%CI upper - HT


Smoothed hazard rate - KM vs. Parametric
Hazard rate
Time
PHT - Parametric
PHT - KM
95%CI lower - PHT
95%CI upper - PHT

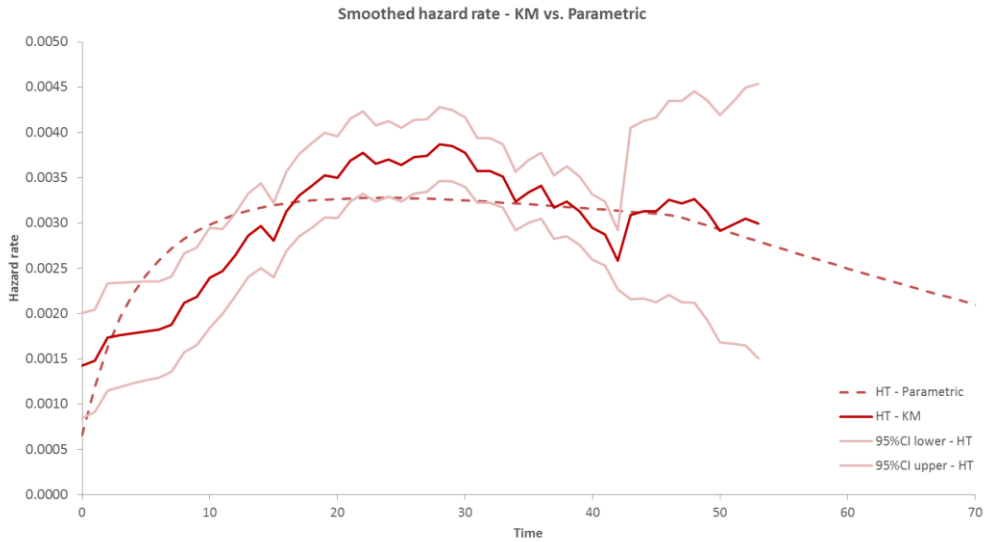
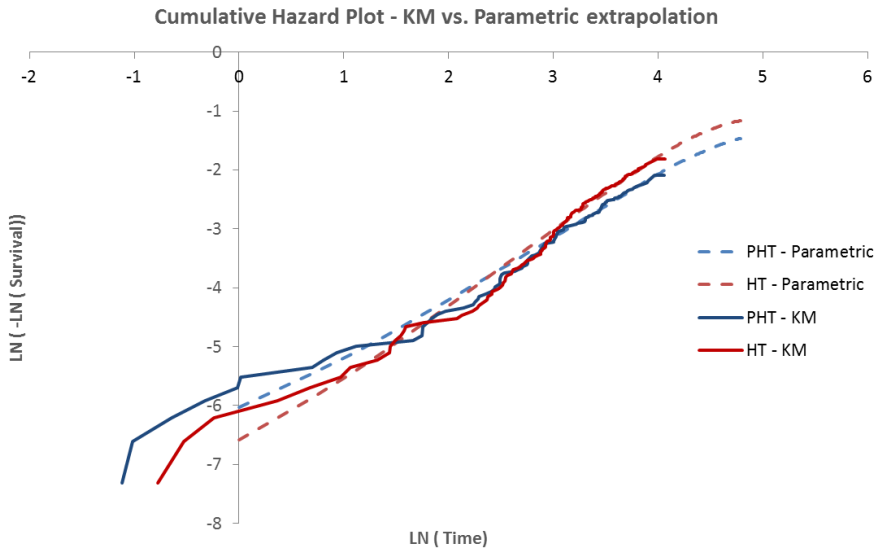
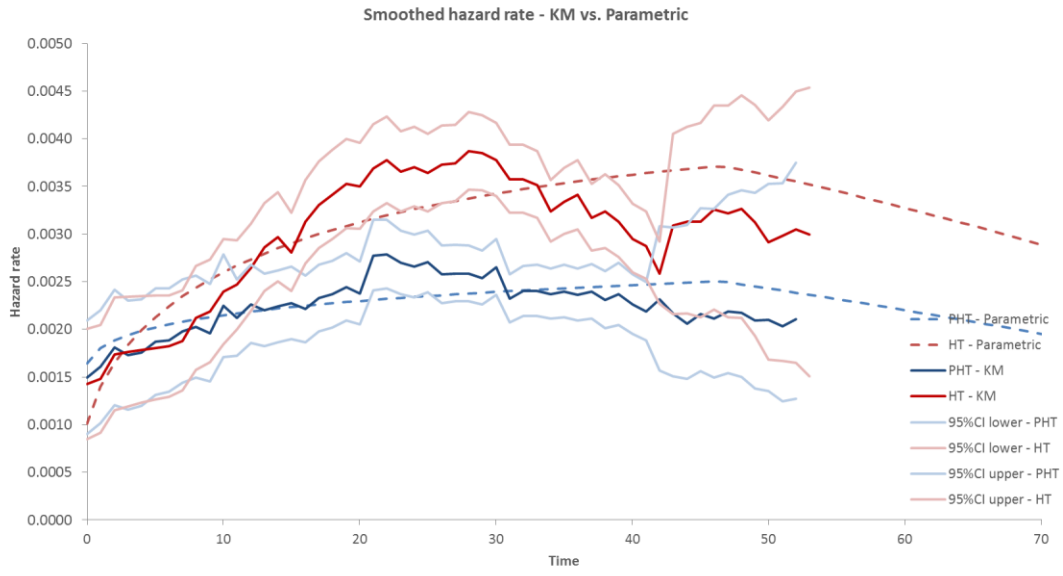
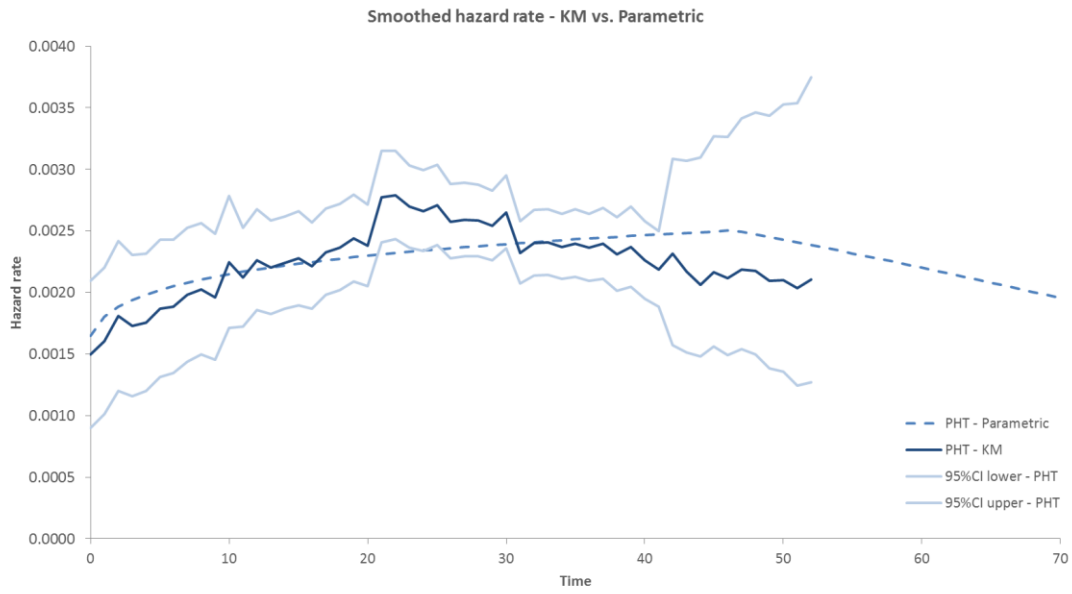

Smoothed hazard rate - KM vs. Parametric
Hazard rate
Time
HT - Parametric
HT - KM
95%CI lower - HT
95%CI upper - HT

Figure 4: Generalized Gamma distribution – Cumulative hazard and smoothed hazard







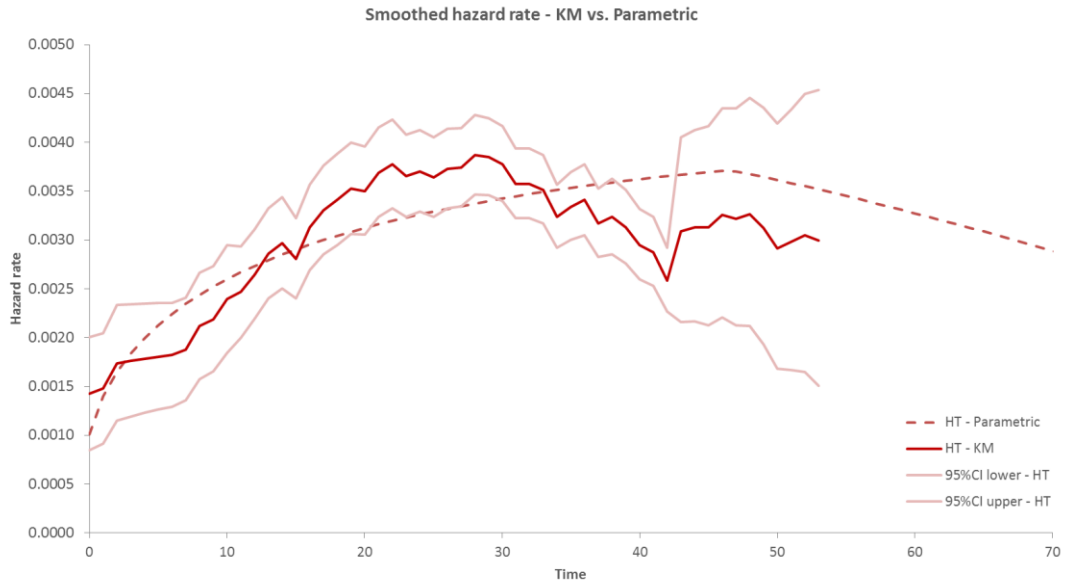
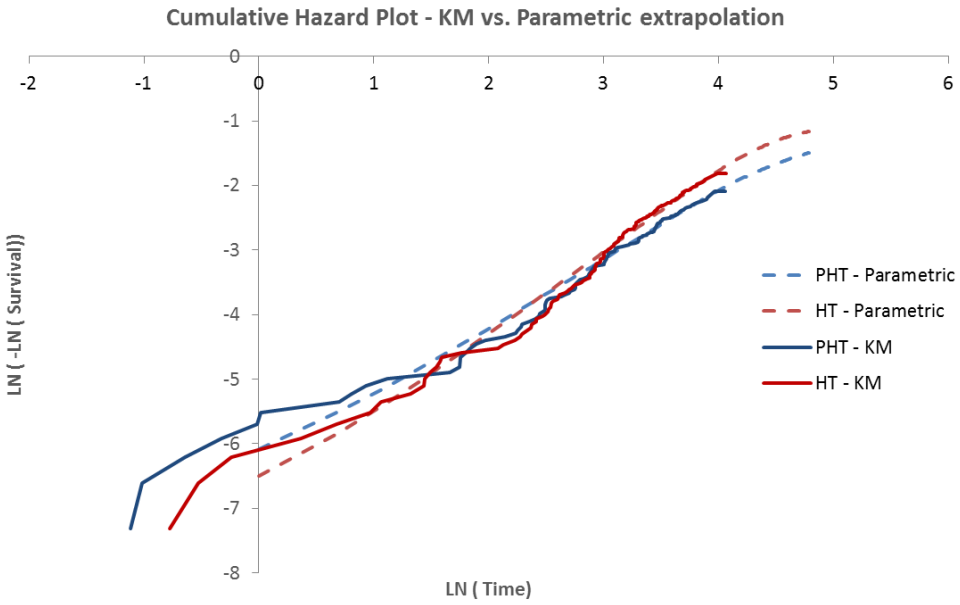
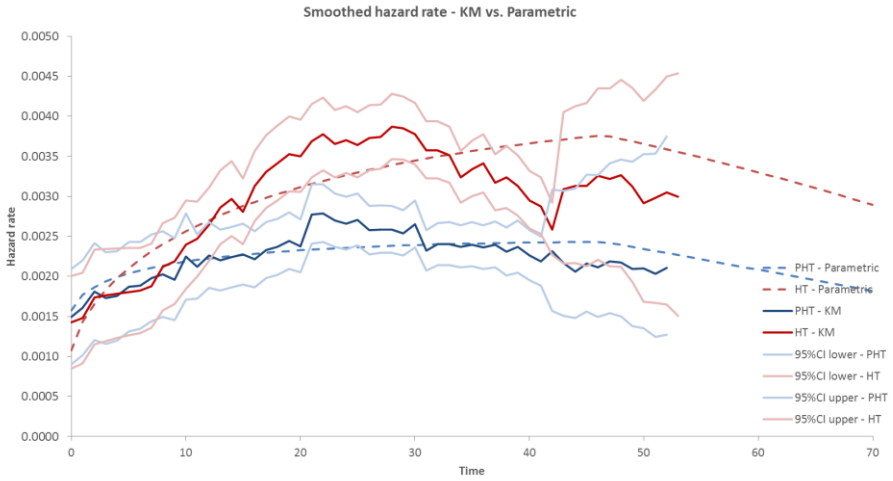


Figure 5: Log-logistic distribution – Cumulative hazard and smoothed hazard


Cumulative Hazard Plot - KM vs. Parametric extrapolation
LN (-LN (Survival))
LN (Time)
PHT - Parametric
HT - Parametric
PHT - KM
HT - KM


Smoothed hazard rate - KM vs. Parametric
Hazard rate
Time
PHT - Parametric
HT - Parametric
PHT - KM
HT - KM
95%CI lower - PHT
95%CI lower - HT
95%CI upper - PHT
95%CI upper - HT

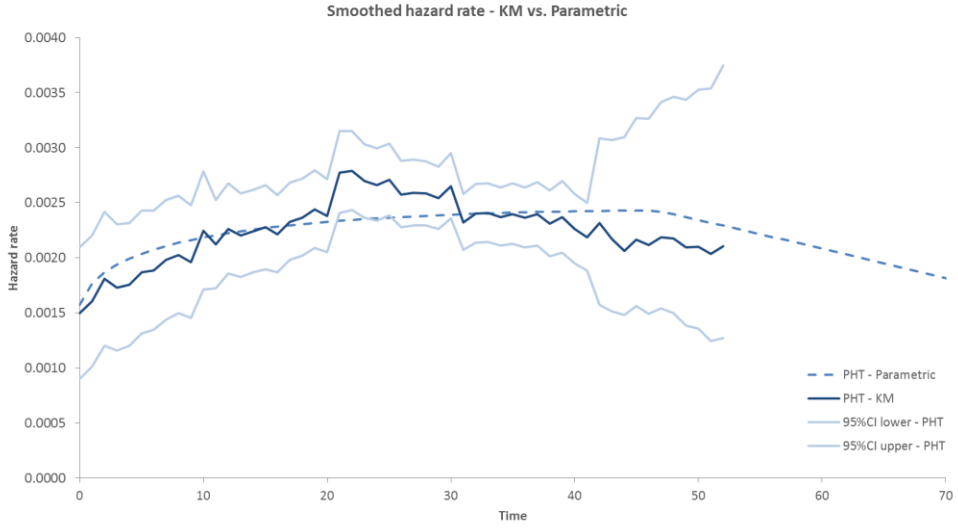
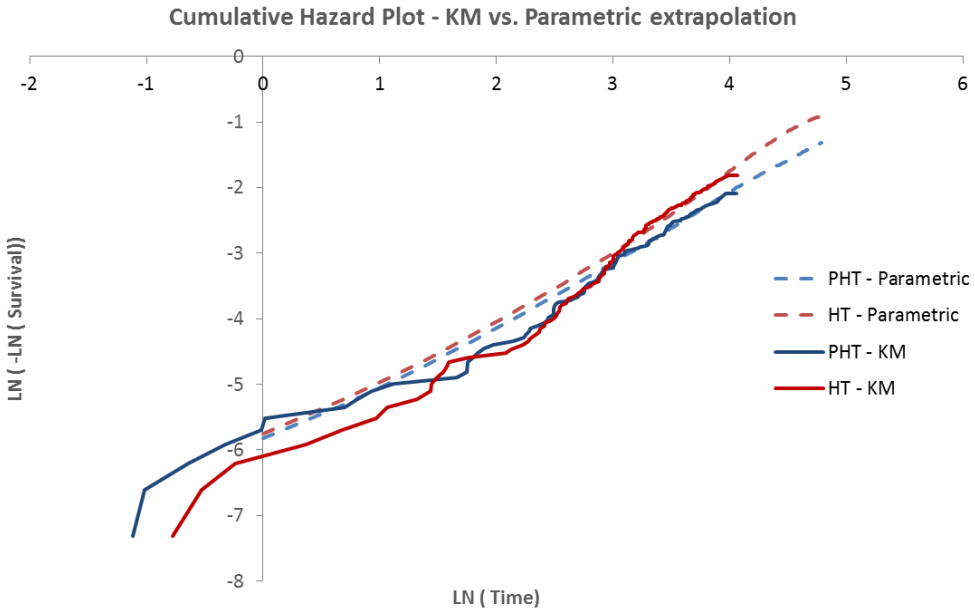
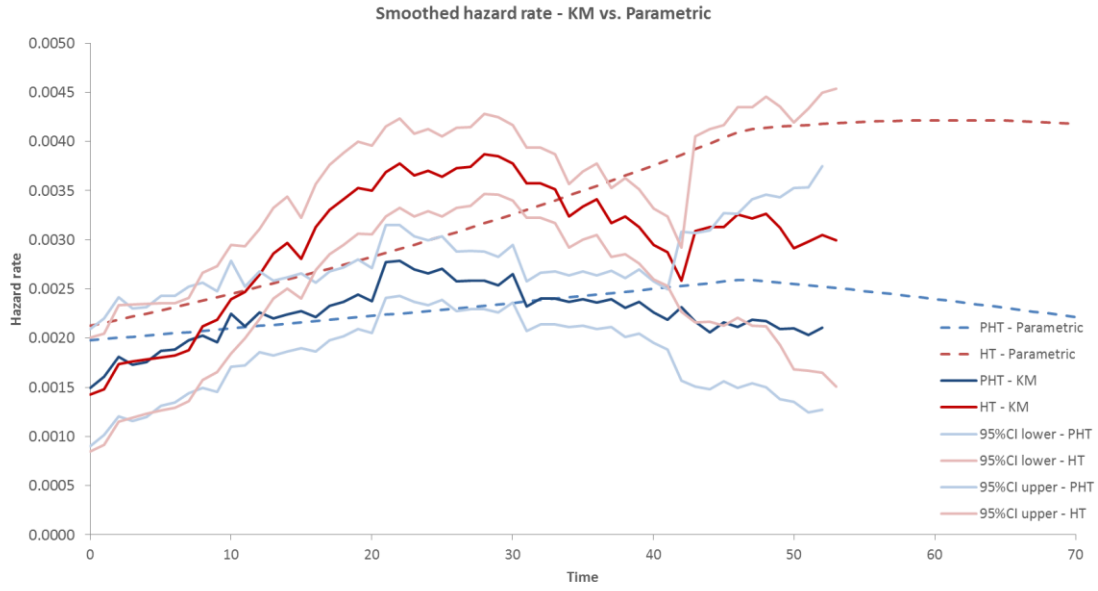

Smoothed hazard rate - KM vs. Parametric
Hazard rate
Time
PHT - Parametric
PHT - KM
95%CI lower - PHT
95%CI upper - PHT

Figure 6: Gompertz distribution – Cumulative hazard and smoothed hazard




Smoothed hazard rate - KM vs. Parametric
Hazard rate
0.0050
0.0045
0.0040
0.0035
0.0030
0.0025
0.0020
0.0015
0.0010
0.0005
0.0000
0
10
20
30
40
50
60
70
Time
PHT - Parametric
HT - Parametric
PHT - KM
HT - KM
95%CI lower - PHT
95%CI lower - HT
95%CI upper - PHT
95%CI upper - HT

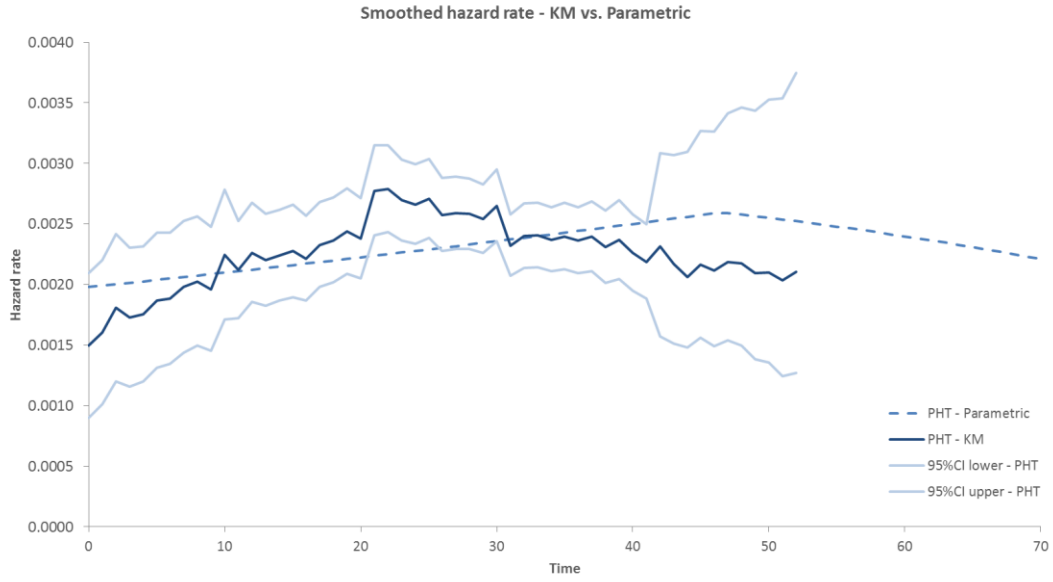
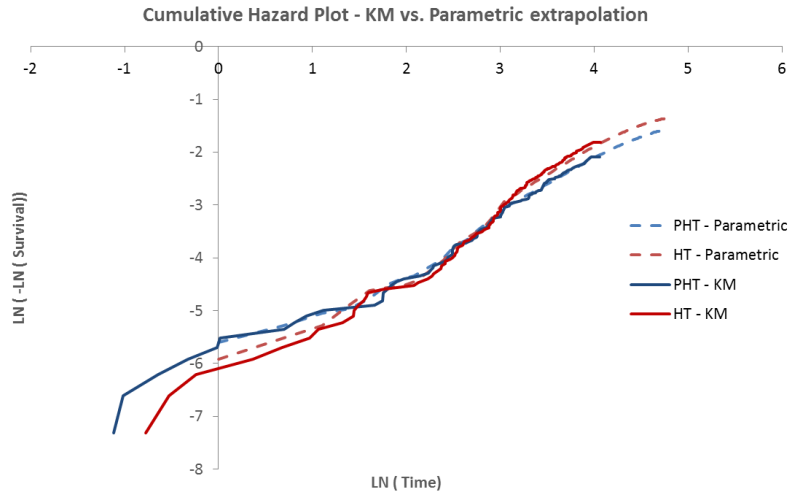
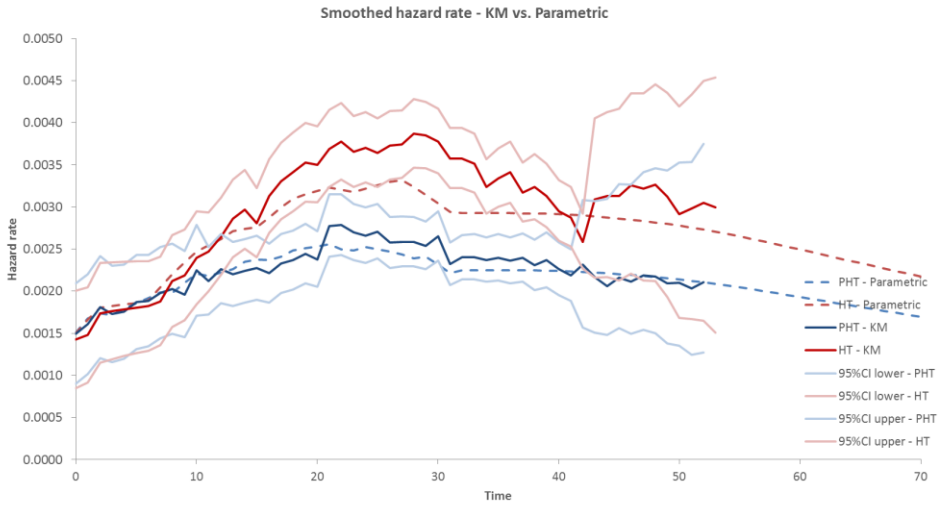
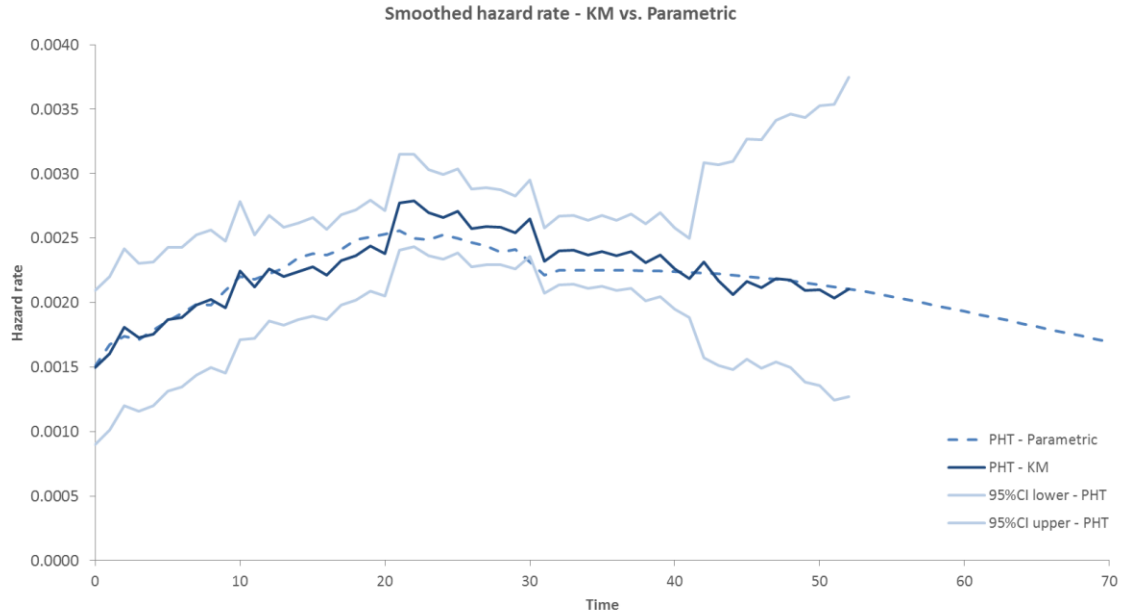

Smoothed hazard rate - KM vs. Parametric
Hazard rate
0.0040
0.0035
0.0030
0.0025
0.0020
0.0015
0.0010
0.0005
0.0000
0
10
20
30
40
50
60
70
Time
PHT - Parametric
PHT - KM
95%CI lower - PHT
95%CI upper - PHT

Figure 7: KM until 22 months followed by exponential distribution – Cumulative hazard and smoothed hazard




Smoothed hazard rate - KM vs. Parametric
Hazard rate
0.0050
0.0045
0.0040
0.0035
0.0030
0.0025
0.0020
0.0015
0.0010
0.0005
0.0000
0
10
20
30
40
50
60
70
Time
PHT - Parametric
HT - Parametric
PHT - KM
HT - KM
95%CI lower - PHT
95%CI lower - HT
95%CI upper - PHT
95%CI upper - HT


Smoothed hazard rate - KM vs. Parametric
Hazard rate
0.0040
0.0035
0.0030
0.0025
0.0020
0.0015
0.0010
0.0005
0.0000
0
10
20
30
40
50
60
70
Time
PHT - Parametric
PHT - KM
95%CI lower - PHT
95%CI upper - PHT

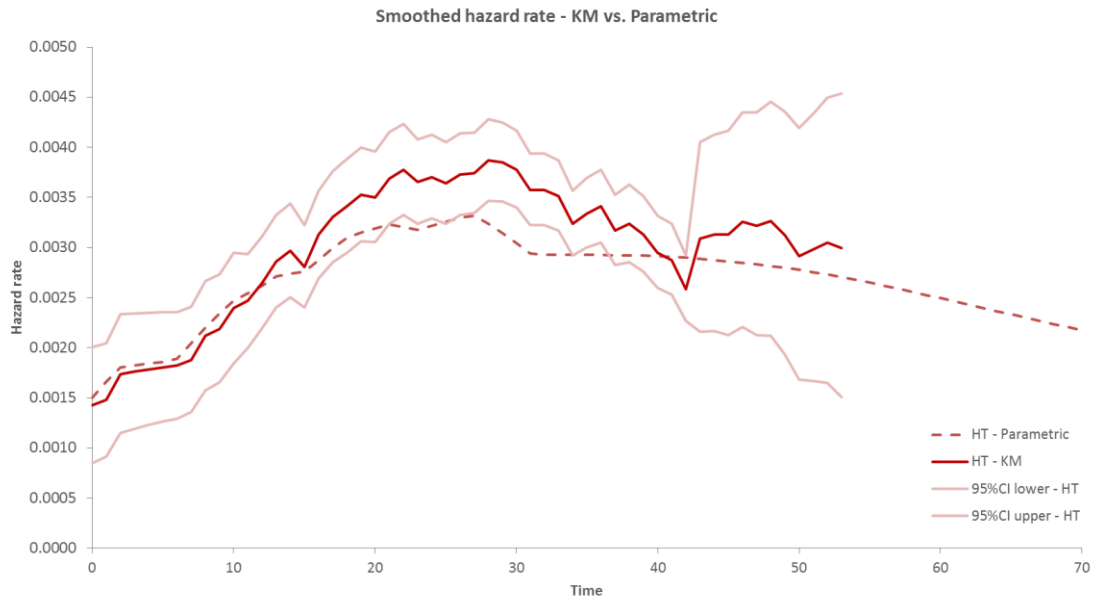
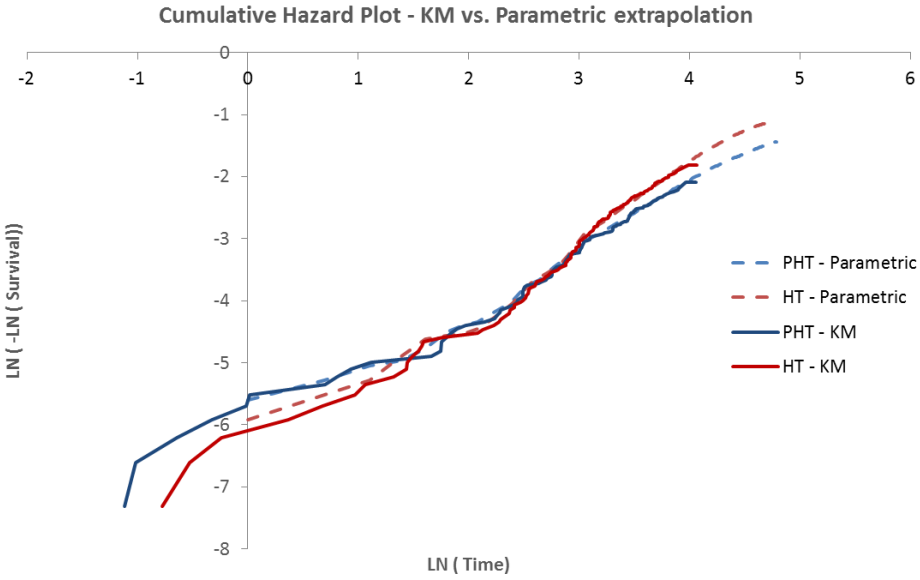
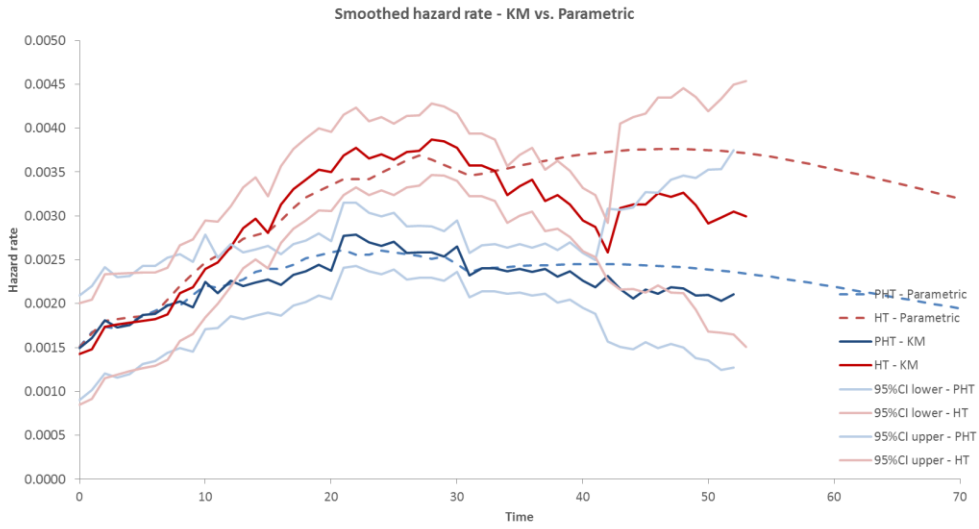


Figure 8: KM until 22 months followed by Weibull distribution – Cumulative hazard and smoothed hazard




Smoothed hazard rate - KM vs. Parametric
Hazard rate
0.0050
0.0045
0.0040
0.0035
0.0030
0.0025
0.0020
0.0015
0.0010
0.0005
0.0000
0
10
20
30
40
50
60
70
Time
PHT - Parametric
HT - Parametric
PHT - KM
HT - KM
95%CI lower - PHT
95%CI lower - HT
95%CI upper - PHT
95%CI upper - HT

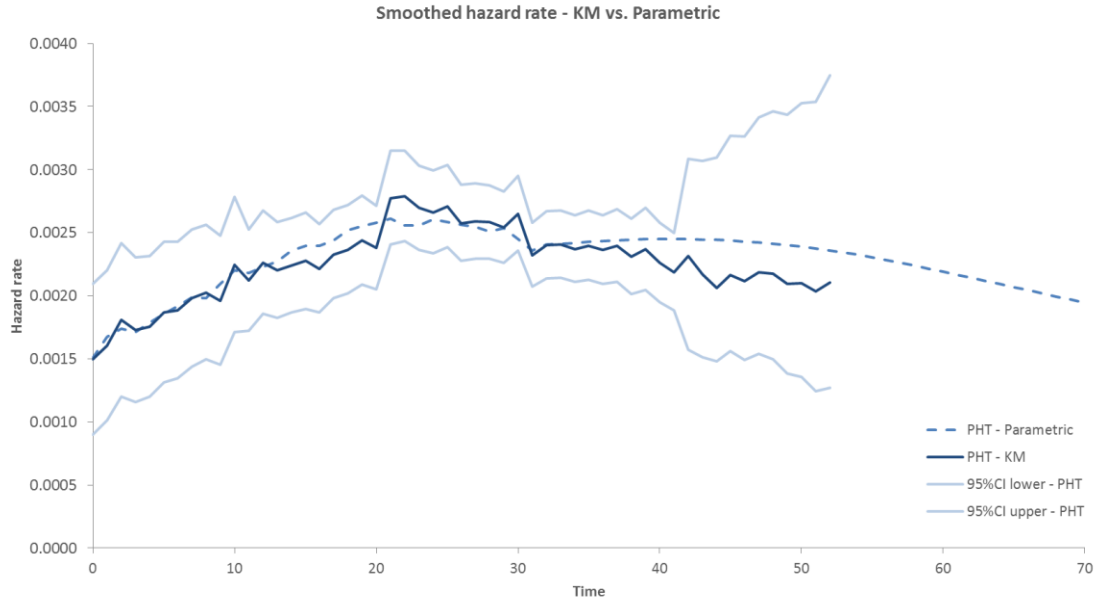
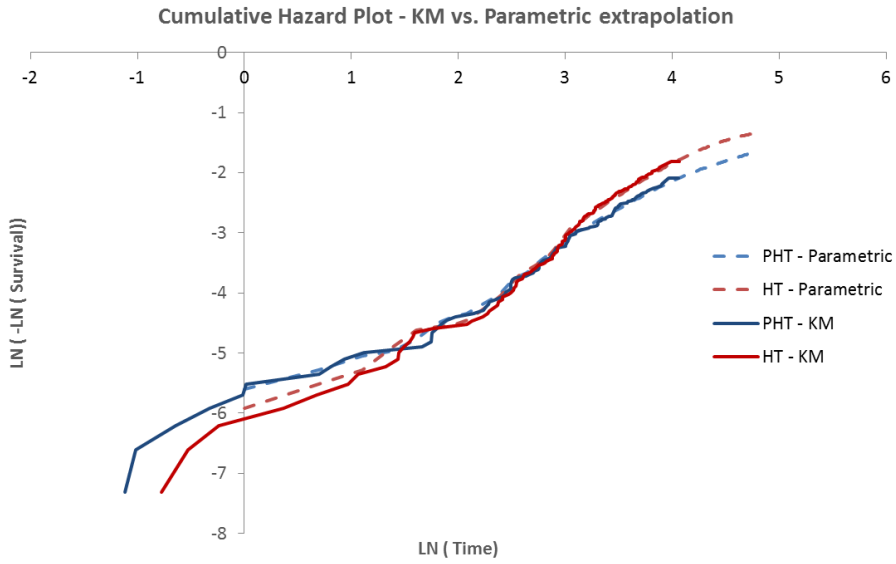
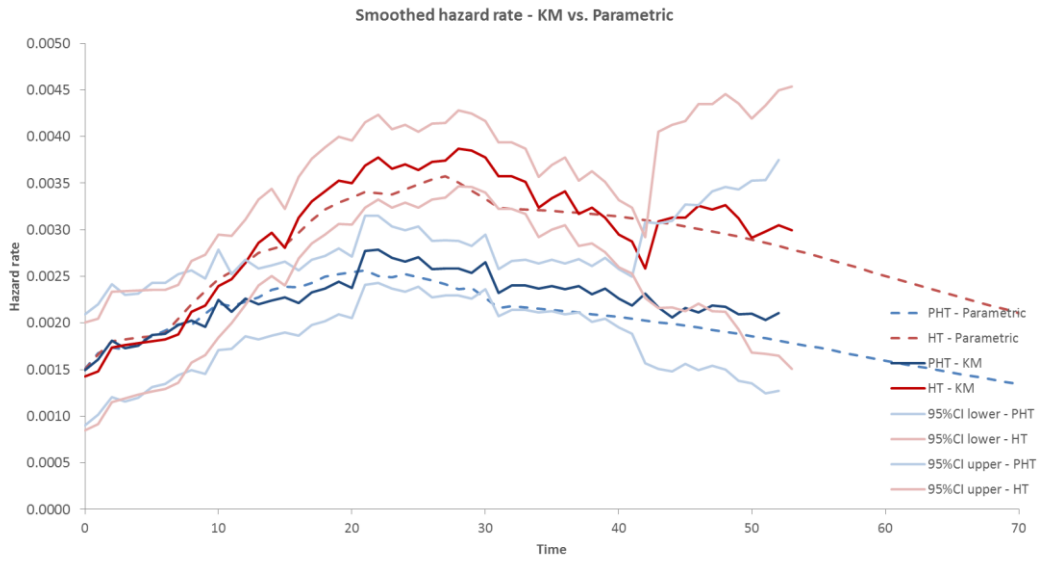

Smoothed hazard rate - KM vs. Parametric
Hazard rate
0.0040
0.0035
0.0030
0.0025
0.0020
0.0015
0.0010
0.0005
0.0000
0
10
20
30
40
50
60
70
Time
PHT - Parametric
PHT - KM
95%CI lower - PHT
95%CI upper - PHT

Figure 9: KM until 22 months followed by Log-normal distribution – Cumulative hazard and smoothed hazard




Smoothed hazard rate - KM vs. Parametric
Hazard rate
0.0050
0.0045
0.0040
0.0035
0.0030
0.0025
0.0020
0.0015
0.0010
0.0005
0.0000
0
10
20
30
40
50
60
70
Time
PHT - Parametric
HT - Parametric
PHT - KM
HT - KM
95%CI lower - PHT
95%CI lower - HT
95%CI upper - PHT
95%CI upper - HT

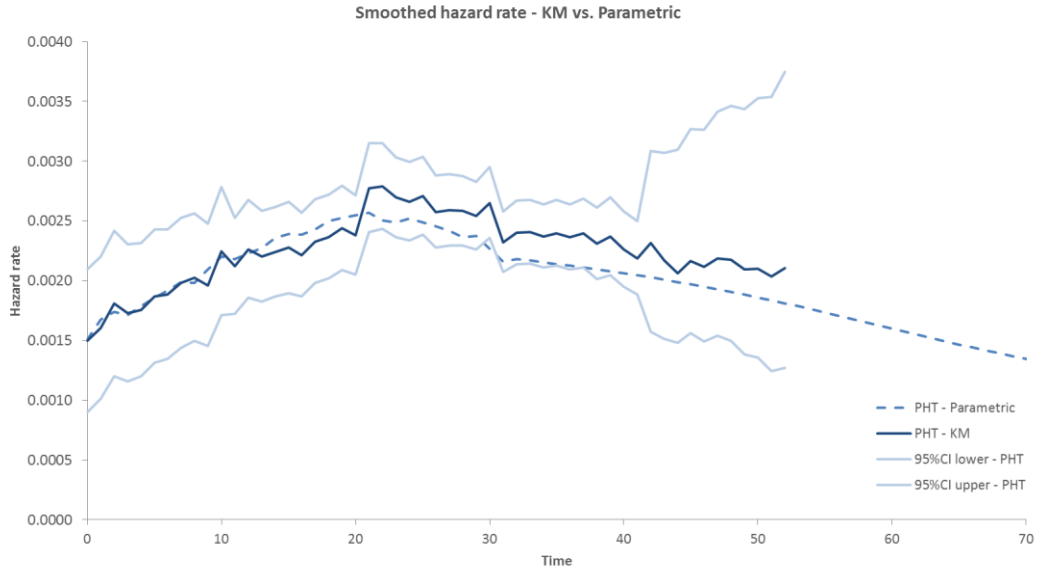
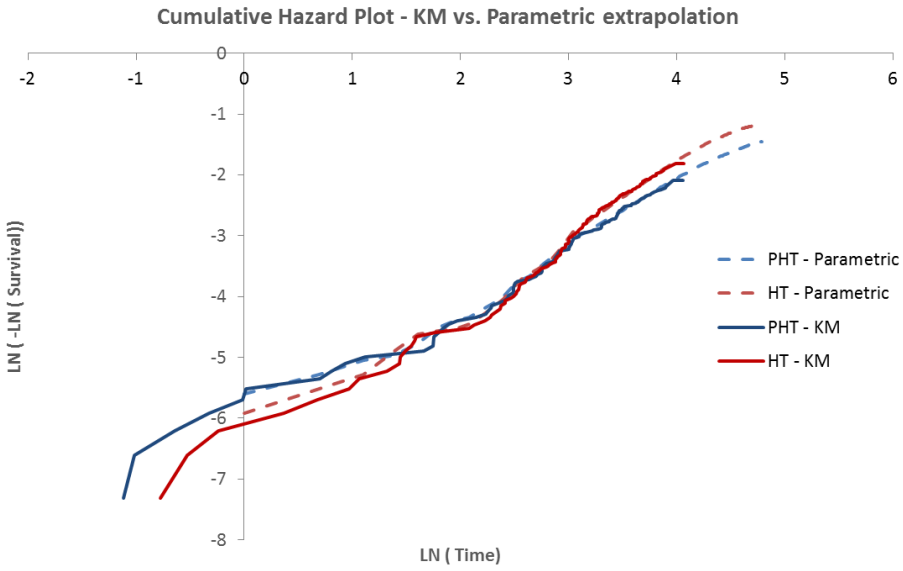
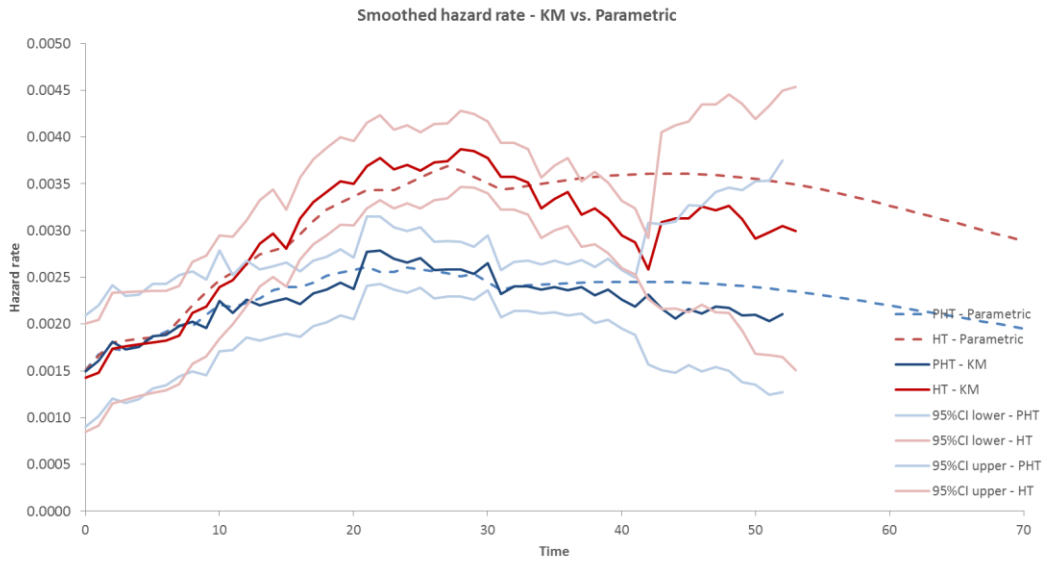

Smoothed hazard rate - KM vs. Parametric
Hazard rate
0.0040
0.0035
0.0030
0.0025
0.0020
0.0015
0.0010
0.0005
0.0000
0
10
20
30
40
50
60
70
Time
PHT - Parametric
PHT - KM
95%CI lower - PHT
95%CI upper - PHT

Figure 10: KM until 22 months followed by Generalized Gamma distribution – Cumulative hazard and smoothed hazard




Smoothed hazard rate - KM vs. Parametric
Hazard rate
0.0050
0.0045
0.0040
0.0035
0.0030
0.0025
0.0020
0.0015
0.0010
0.0005
0.0000
0
10
20
30
40
50
60
70
Time
PHT - Parametric
HT - Parametric
PHT - KM
HT - KM
95%CI lower - PHT
95%CI lower - HT
95%CI upper - PHT
95%CI upper - HT

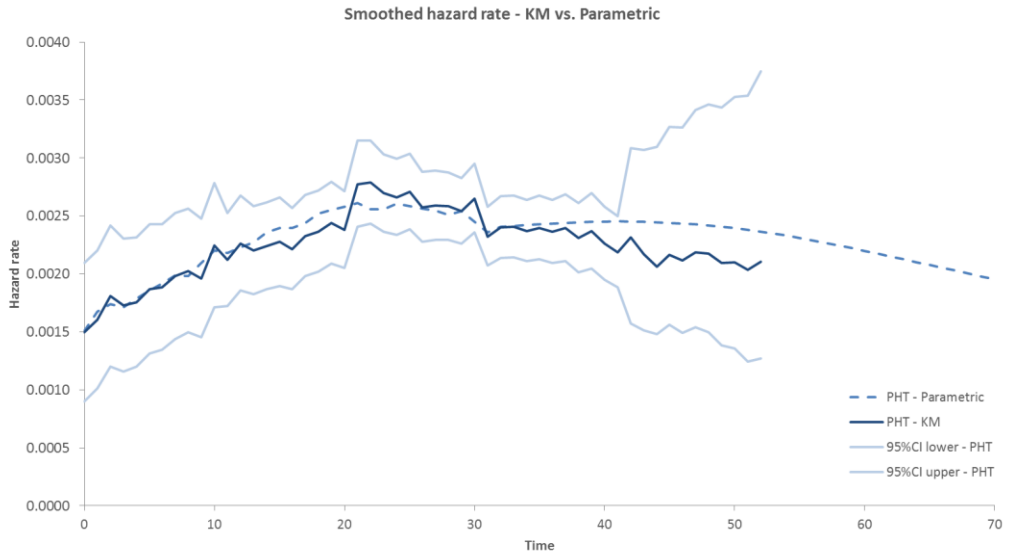
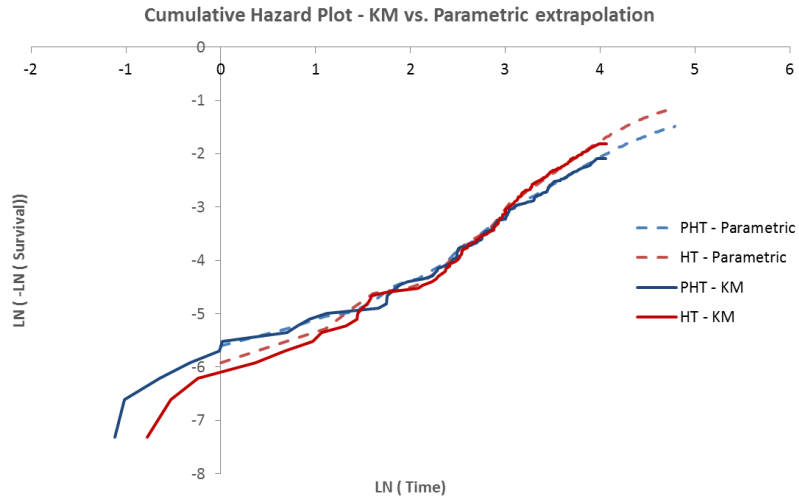
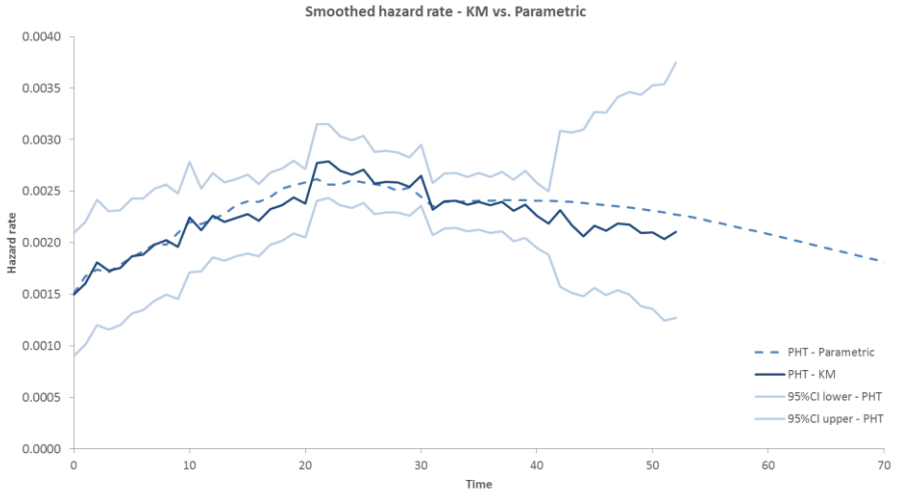

Smoothed hazard rate - KM vs. Parametric
Hazard rate
0.0040
0.0035
0.0030
0.0025
0.0020
0.0015
0.0010
0.0005
0.0000
0
10
20
30
40
50
60
70
Time
PHT - Parametric
PHT - KM
95%CI lower - PHT
95%CI upper - PHT

Figure 11: KM until 22 months followed by Log-logistic distribution – Cumulative hazard and smoothed hazard




Smoothed hazard rate - KM vs. Parametric
Hazard rate
0.0050
0.0045
0.0040
0.0035
0.0030
0.0025
0.0020
0.0015
0.0010
0.0005
0.0000
0
10
20
30
40
50
60
70
Time
PHT - Parametric
HT - Parametric
PHT - KM
HT - KM
95%CI lower - PHT
95%CI lower - HT
95%CI upper - PHT
95%CI upper - HT


Smoothed hazard rate - KM vs. Parametric
Hazard rate
0.0040
0.0035
0.0030
0.0025
0.0020
0.0015
0.0010
0.0005
0.0000
0
10
20
30
40
50
60
70
Time
PHT - Parametric
PHT - KM
95%CI lower - PHT
95%CI upper - PHT

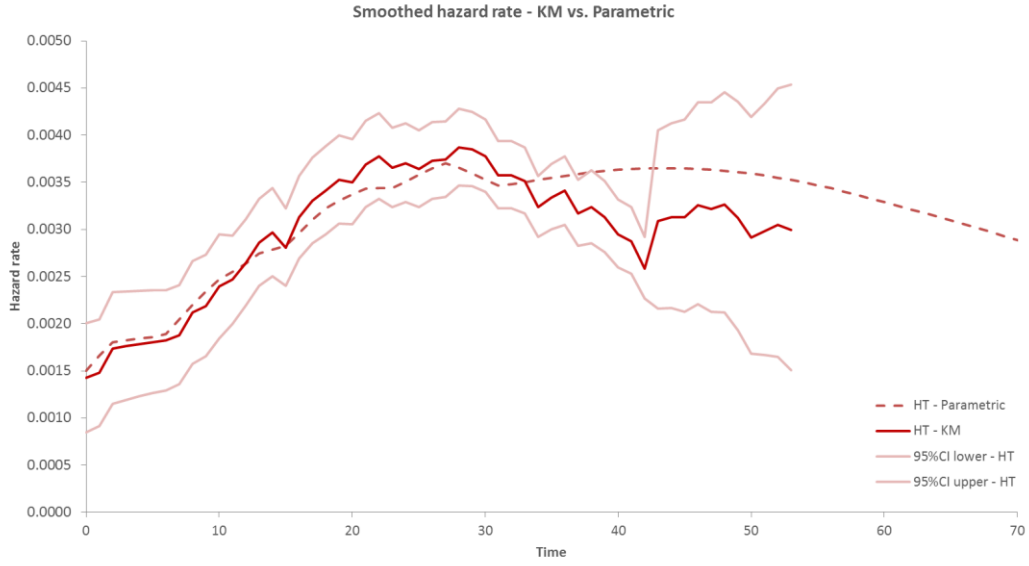
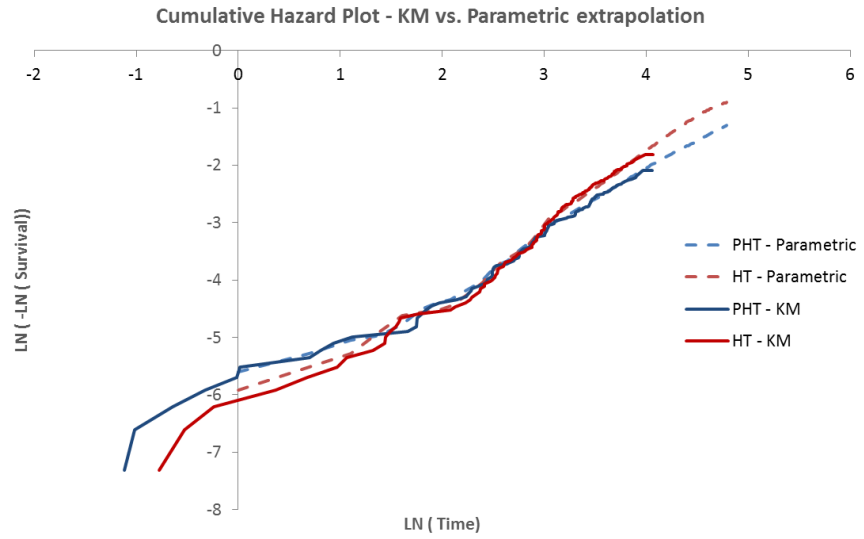
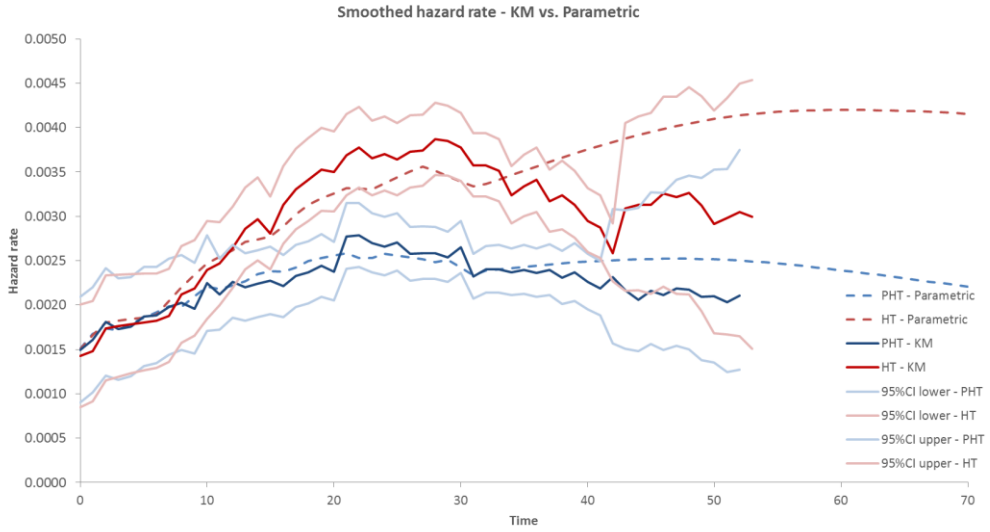
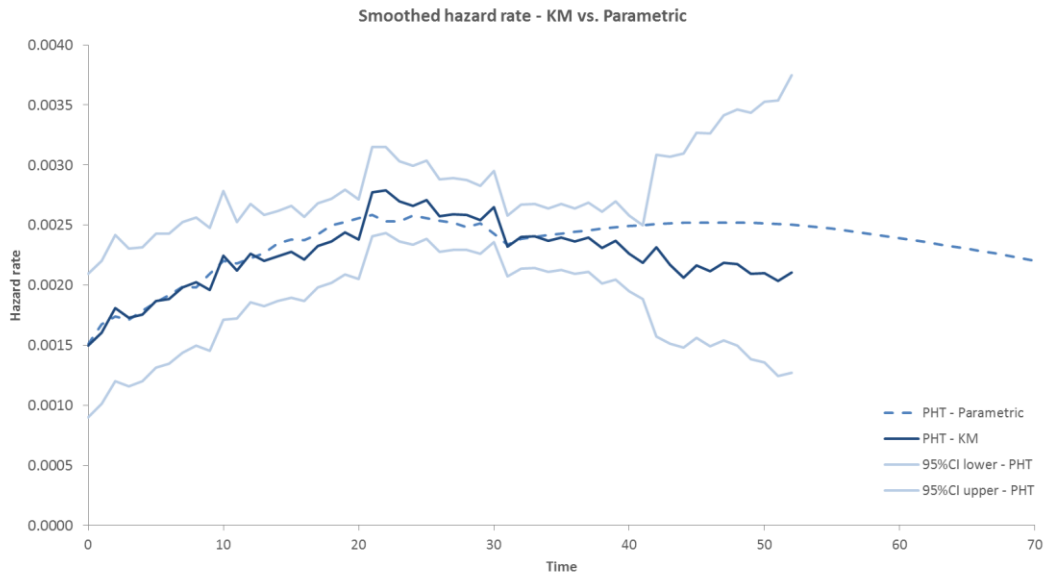

Smoothed hazard rate - KM vs. Parametric
Hazard rate
0.0050
0.0045
0.0040
0.0035
0.0030
0.0025
0.0020
0.0015
0.0010
0.0005
0.0000
0
10
20
30
40
50
60
70
Time
HT - Parametric
HT - KM
95%CI lower - HT
95%CI upper - HT

Figure 12: KM until 22 months followed by Gompertz distribution – Cumulative hazard and smoothed hazard






Smoothed hazard rate - KM vs. Parametric
Hazard rate
0.0040
0.0035
0.0030
0.0025
0.0020
0.0015
0.0010
0.0005
0.0000
0
10
20
30
40
50
60
70
Time
PHT - Parametric
PHT - KM
95%CI lower - PHT
95%CI upper - PHT


Smoothed hazard rate - KM vs. Parametric
Hazard rate
0.0050
0.0045
0.0040
0.0035
0.0030
0.0025
0.0020
0.0015
0.0010
0.0005
0.0000
0
10
20
30
40
50
60
70
Time
HT - Parametric
HT - KM
95%CI lower - HT
95%CI upper - HT

NICE National Institute for Health and Care Excellence

Patient organisation submission

Pertuzumab for the adjuvant treatment of HER2-positive breast cancer ID1192

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Breast Cancer Now
3. Job title or position	Policy Manager
4a. Brief description of the organisation (including who funds it). How many members does it have?	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. Our main sources of income are individual giving and corporate partnerships. In particular in 2016/17 we received £2.7 million of income from Pfizer for our Catalyst programme, which provides grants for research. Further details about our income are set out in our annual report, which is available on our website at http://breastcancernow.org/about-us/what-we-do/annual-report-and-accounts Our work on access to drugs is independent of any funding we may receive from the pharmaceutical industry and is based on the evidence of the clinical effectiveness of drugs.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No.
5. How did you gather information about the experiences of patients and	Breast Cancer Now utilises its various networks of supporters to gather information about patient experience.

carers to include in your submission?	
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	A diagnosis of breast cancer will cause considerable anxiety to the patient as well as their family and friends. The initial diagnosis can be shocking and in the longer-term, the fear of breast cancer returning or spreading to other parts of the body (typically the bone, lungs, liver and brain) where it becomes incurable can cause considerable stress for both the patients and their loved ones.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Surgery is usually the first option for women with primary or early breast cancer, although in some cases neoadjuvant treatment will be used to reduce the size of the tumour prior to surgery. Surgery may be followed by radiotherapy and systemic treatment such as chemotherapy, targeted therapy or hormone therapy, depending on the type of breast cancer and the balance of risks and benefits. All treatments have side effects. Treatment with chemotherapy usually has a number of unpleasant side effects which can have a significant impact on everyday activities, ability to work, social life and relationships. Hormone therapy can also have unpleasant menopausal side effects that can make it difficult for women to complete the recommended course of therapy. Targeted therapies for HER2 breast cancer tend to be better tolerated.
8. Is there an unmet need for patients with this condition?	Adjuvant drug treatment for patients with HER2 positive breast cancer are already available. However, any treatment that improves outcomes is a welcome step forward for patients.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	The advantages of adding pertuzumab to adjuvant trastuzumab and chemotherapy include: • Improved rates of invasive disease free survival. In the APHINITY trial at three years, invasive disease free survival was 94.1% in patients taking pertuzumab compared to 93.2% in those taking placebo. • Reduced rates of the first recurrence of invasive breast cancer being elsewhere in the body, where it is incurable. In the APHINITY trial 4.7% of first recurrences were elsewhere in the body in patients taking pertuzumab, compared to 5.8% in patients taking placebo. • Pertuzumab is generally well tolerated. There is already experience of pertuzumab in metastatic patients, who generally report that side effects are minimal and that they 'feel good on them [the drugs]'. The APHINITY trial raised no new safety issues. Of the most common grade 3 or higher adverse effects (diarrhoea, anaemia and neutropenia) the adverse effect more likely to be experienced by those in the pertuzumab group was diarrhoea (9.8% to 3.7%) although incidence fell in both groups after chemotherapy had been completed and treatment was with trastuzumab and pertuzumab alone.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	One potential disadvantage of adding pertuzumab to adjuvant trastuzumab and chemotherapy arises from its method of administration. In the adjuvant setting we understand that trastuzumab is largely administered subcutaneously. Patients tell us that this is quicker and more convenient for them, and they are better able to fit it around other commitments such as work, and it is also less invasive. However, pertuzumab is administered intravenously and trastuzumab would also be administered intravenously alongside it. This may mean that beyond the initial period of chemotherapy, patients would need to spend longer in hospital to receive treatment. However, the reduced risk of the recurrence of invasive breast cancer may outweigh for patients the potential inconvenience of spending longer in hospital to receive treatment.

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	The APHINITY trial shows that patients with HER2 positive early breast cancer at higher risk of recurrence (those with node positive breast cancer or hormone receptor negative breast cancer) benefitted more from adding pertuzumab to trastuzumab and chemotherapy: • At three years, the difference in the percentage of patients with invasive disease free survival between those taking pertuzumab and placebo with node positive disease was 1.8% (92.0% compared to 90.2%). In those with node negative disease the difference was 0.9% (97.5% compared to 98.4%) but with a greater percentage of patients taking pertuzumab experiencing invasive disease events. • At three years, the difference in the percentage of patients with invasive disease free survival between those taking pertuzumab and placebo with hormone receptor negative breast cancer was 1.6% (92.8% compared to 91.2%). In those with hormone receptor positive disease the difference was 0.4% (94.8% compared to 94.4%). We note that the US Food and Drug Administration has approved pertuzumab with trastuzumab and chemotherapy for adjuvant treatment of early breast cancer in those at higher risk of recurrence.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues	
13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- A diagnosis of breast cancer can cause considerable anxiety to the patient as well as their family and friends, including the fear of it recurring or spreading to other parts of the body where it becomes incurable.
- Adding pertuzumab to trastuzumab and chemotherapy as an adjuvant treatment for early breast cancer improves the rate of invasive disease free survival, in particular in those at higher risk of recurrence (those with node positive disease and with hormone receptor negative breast cancer), and also reduces the rate of the first recurrence being elsewhere in the body, where it is incurable.
- Patients may need to spend longer in hospital to receive this treatment as pertuzumab and trastuzumab will be delivered intravenously where given together. However, the reduced risk of recurrence may outweigh the potential inconvenience to patients of spending longer in hospital.
- Pertuzumab is generally well tolerated by patients, often with minimal side effects.

Thank you for your time.

NICE National Institute for Health and Care Excellence

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Clinical expert statement

Pertuzumab for the adjuvant treatment of HER2-positive breast cancer [ID1192]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	Dr Alistair Ring

2. Name of organisation	Royal Marsden Hospital NHS Foundation Trust
3. Job title or position	Consultant in Medical Oncology, Honorary Reader Institute of Cancer Research
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? **X** a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it **X** other (they didn't submit one, I don't know if they submitted one etc.) I have not been given access to the submission at this stage.
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the	☐ yes Not applicable.

rest of this form will be deleted after submission.)	
The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To reduce the risks of relapse.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	An adjuvant therapy that reduces the risks of (distant) relapse by 2% or more at 3 years is of interest, particularly as with longer follow-up the absolute benefits of treatment may increase and the benefit may be greater in high risk sub-groups. This clearly has to be balanced against side-effects (both short and long-term) and cost.
9. In your view, is there an unmet need for patients and	Yes, in the sense that when one looks at the long term relapse rates for patients with HER2 positive breast cancer: the 10 year disease-free survival was 69% (in the HERA trial 1 year of Trastuzumab arm). (Jackisch C, *et al.* SABCS 2015 (Abstract PD5-01); Cameron D, *et al. Lancet* 2017;389:1195–1205.). Therefore whilst there have been significant improvements in outcome for these patients over the last few years, there are many patients who relapse and die.

healthcare professionals in this condition?	
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Standard treatment approach for women in the APHINITY trial control arm with HER2 positive breast cancer in the adjuvant setting is: adjuvant chemotherapy (usually a combination of anthracycline and taxane) and 12 months of trastuzumab (18 doses given subcutaneously 3 weekly). But there are a number of scenarios for women in this setting (see below).
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Patients with HER2 positive early breast cancer can be treated in a number of ways: (i) Patients with tumours more than 2cm and many of those with axillary node involvement may be treated in the neoadjuvant setting (chemotherapy before surgery). In which case they will receive either: a neoadjuvant anthacyline (usually 4 cycles) followed by 4 cycles of docetaxel/pertuzumab and trastuzumab, or 6 cycles of trastuzumab/pertuzumab/docetaxel/carboplatin. This is followed by surgery and then complete a year of trastuzumab post-operatively (18 cycles trastuzumab in total). (ii) Patients with smaller tumours, or those whom neoadjuvant treatment is not indicated will have primary surgery. Then: a) If a very small tumour (<5mm) may receive no systemic therapy (beyond endocrine therapy if ER positive) b) If small node negative (or less fit) may receive weekly paclitaxel for 12 weeks and 1 year of subcutaneous trastuzumab.

	c) If larger/node positive: anthracyline-taxane and 12 months of trastuzumab (18 doses given subcutaneously 3 weekly) as above (and as the control arm of APHINITY).
• What impact would the technology have on the current pathway of care?	May lead to some patients having adjuvant rather than neoadjuvant treatment as I sense (no data) that more patients are being treated neoadjuvantly in order to access pertuzumab (currently only available/licensed/funded in neoadjuvant setting). This will depend on how clinicians interpret the results of the APHINITY trial. If pertuzumab is introduced in adjuvant setting will mean patients need to have IV trastuzumab (rather than existing subcutaneous form).
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	The key issue is the move to IV treatments from subcutaneous for 1 years. This has big implications for day unit capacity, need for indwelling lines and patient convenience.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care: DGH and academic/teaching hospitals. However, some administration of adjuvant trastuzumab occurs in community in mobile units (significant geographic variation in this).

• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	The technology is not complex to deliver, but will require upscaling of capacity due to change in route of delivery. The combination of pertuzumab and trastuzumab is already widely used around the country in patients with metastatic breast cancer.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	I expect the technology to reduce the risk of relapse, and increase the rate of cure in patients with high risk HER2 positive breast cancer.
• Do you expect the technology to increase health-related quality of life more than current care?	No. This is radical treatment to increase cure rates, not palliative treatment.
13. Are there any groups of people for whom the technology would be more or	The subgroup analyses of the APHINITY study: suggest greatest benefit likely in those with axillaty lymph node positive and oestrogen receptor negative breast cancer.

less effective (or appropriate) than the general population?	
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	More difficult (see point 11 above). This is not so much because of increased toxicity: which is limited, but route of delivery.
15. Will any rules (informal or formal) be used to start or stop treatment with the technology?	No. There is a standard treatment course/duration.

Do these include any additional testing?	
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No.
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	

• Is the technology a 'step-change' in the management of the condition?	Yes: it is a fundamental change. However absolute benefits relatively small: therefore likely restricted to higher risk groups where this will be a step change.
• Does the use of the technology address any particular unmet need of the patient population?	No: other than the high risks of recurrence in all women with HER2 positive breast cancer.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	There is minimal increased toxicity from the addition of pertuzumab to trastuzumab.
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, broadly. See my comments in section 10.
• If not, how could the results be extrapolated to the UK setting?	

• What, in your view, are the most important outcomes, and were they measured in the trials?	These are covered in the APHINITY trial.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Not applicable. Invasive disease-free survival is a standard endpoint in this setting.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No.
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No.
21. Are you aware of any new evidence for the comparator treatment(s) since the	A number of studies have been published in this area since 2006. Including long—term follow up of the pivotal adjuvant Trastuzumab studies (HERA, NSABP B31/N9831 and BCIRG006). In addition recognition of benefits for anthracycline-free regimens (Tolaney S, et al. NEJM 2015; 372: 134-141).

publication of NICE technology appraisal guidance [TA107]?	
22. How do data on real-world experience compare with the trial data?	Comparable.
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
23b. Consider whether these issues are different from issues with current care and why.	No
Topic-specific questions	
24.	I suspect there is enthusiasm for patients with highest risk disease.

a) Is there any enthusiasm in the clinical community for adding pertuzumab to standard adjuvant treatment with trastuzumab and chemotherapy? b) The primary outcome in the APHINITY trial was 'Invasive Disease-Free Survival (IDFS) excluding primary non-breast cancer events' (not the standard STEEP definition of IDFS which includes primary non-breast cancer events). Is there any reason for not using the standard STEEP definition of IDFS and what is the impact of this?	The group of patients with node positive/ER negative disease is the most relevant group: so agree review this group specifically. The proportion of patients (with HER2 positive disease) receiving neoadjuvant treatment varies considerably around the country. The company will have data on this. In my practice (a centre with relatively high rates of neoadjuvant treatment use) approximately 60-70% of patients with HER2 positive disease receive neoadjuvant chemotherapy. However a significant proportion of these patients will be having neoadjuvant chemotherapy to access pertuzumab (the only setting in which currently available) rather than for downstaging.

c) The company would like the committee to consider node positive (base case) and hormone receptor negative subgroups. Are these clinically relevant? Are there any other subgroups that have a similar risk profile which would also be appropriate to consider? d) In clinical practice what proportion of people will have had neoadjuvant therapy (biologic or chemotherapy). As the APHINITY trial did not include people who had prior neoadjuvant therapy how generalizable are the results of the trial?	

Key messages

25. In up to 5 bullet points, please summarise the key messages of your statement.

- This is a new indication for the technology
- Relevant improvements in iDFS in high risk groups
- No significant increase in toxicity
- Take into account switch from subcutaneous to IV delivery
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

Appendix D – patient expert statement declaration form

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Breast cancer (early, HER2-positive) - pertuzumab (adjuvant) Appraisal [ID1192]

Please sign and return via NICE Docs/Appraisals.

I confirm that:

- I agree with the content of the statement submitted by Breast Cancer Now and consequently I will not be submitting a personal statement.

Name: Melanie Sturtevant

Signed:

Date: 11/05/2018

Title: Single technology appraisal pertuzumab for adjuvant treatment of HER2-positive early breast cancer (ID1192)

Produced by: Warwick Evidence

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Declared competing interests of the authors
None.

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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.

This report should be referenced as follows
Grove, A., Andronis, L., Gallacher, D., Nduka, C., Court, R., Vepa, A., Sutcliffe, P. Single technology appraisal pertuzumab for adjuvant treatment of HER2-positive early breast cancer (ID1192): A Single Technology Appraisal. Warwick Evidence, 2018.

Contributions of authors
Paul Sutcliffe (Associate Professor) co-ordinated the project. Amy Grove (Assistant Professor) co-ordinated and conducted the critique of clinical effectiveness evidence. Chidozie Nduka (Researcher Fellow) conducted the critique of clinical effectiveness evidence. Daniel Gallacher (Research Associate) conducted the critique of statistics and survival analysis. Lazaros Andronis (Senior Research Fellow) co-ordinated, conducted, reviewed and critiqued the cost-effectiveness evidence. Rachel Court (Information Specialist) conducted the critique of the company searches and conducted ERG searches. Abhinav Vepa (Academic F2 Doctor) supported the writing of the background section.

Please note that: Sections highlighted in yellow and underlined are [redacted] Sections highlighted in aqua and underlined are [redacted] Figures that are CIC have been bordered with blue.

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DEFINITION OF TERMS AND LIST OF ABBREVIATIONS

AC-T	Anthracycline
AC-TH	Anthracycline plus Trastuzumab
AE	Adverse Event
AIC	Akaike Information Criterion
APHINITY	Adjuvant Pertuzumab and Herceptin IN Initial TherapY in Breast Cancer
BC	Breast Cancer
BCIRG	Breast Cancer International Research Group
BIC	Bayesian Information Criterion
BNF	British National Formulary
CAA	Commercial Access Agreement
CE plane	Cost-Effectiveness plane
CEAC	Cost-Effectiveness Acceptability Curve
CHMP	Committee for Medicinal Products for Human Use
CS	Company Submission
CSR	Clinical Study Report
CT	Computerised Tomography
DCIS	Ductal Carcinoma in Situ
DFS	Disease-Free Survival
DRFI	Distant Recurrence-free Interval
DSU	Decision Support Unit
eBC	Early Breast Cancer
ECHO	Echocardiogram
EMA	European Medicines Agency
eMC	Electronic Medicines Compendium
eMIT	Electronic Market Information Tool
EORTC QLQ-BR23	European Organisation for Research and Treatment of Cancer breast cancer-specific Quality of Life questionnaire
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer core 30 questionnaire
EPAR	European Public Assessment Reports
EQ-5D	EuroQol 5-Dimensions Questionnaire
EQ-5D-3L	EuroQol 5-Dimensions Questionnaire Three Level
ER	Oestrogen Receptor
ERG	Evidence Review Group

ESMO	European Society for Medical Oncology
GP	General Practitioner
HC	Trastuzumab in Combination with Chemotherapy
HERA	Herceptin Adjuvant Trial
HER2	Human Epidermal growth factor Receptor 2
HR	Hazard Ratio
HRQoL	Health-Related Quality of Life
HTA	Health Technology Assessment
ICER	Incremental Cost-effectiveness Ratio
IDFS	Invasive Disease-free Survival
ITT	Intent-To-Treat
IV	Intravenous
K	Trastuzumab Emtansine
KM	Kaplan-Meier
LCIS	Lobular Carcinoma in Situ
LVEF	Left Ventricular Ejection Fraction
LYG	Life Years Gained
MCID	Minimally clinically important difference
mBC	Metastatic Breast Cancer
MedDRA	Medical Dictionary for Regulatory Activities
MUGA	Multigated acquisition
NA	Not Applicable
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHS	National Health Service
NHSE	National Health Service England
NICE	National Institute for Health and Care Excellence
NMR	Non-Metastatic Recurrence
NYHA	New York Heart Association
OS	Overall Survival
P	Pertuzumab
PAS	Patient Access Scheme
PFS	Progression-Free Survival
PHC	Pertuzumab in combination with Trastuzumab and Chemotherapy

PgR	Progesterone Receptor
PLA	Placebo
PPS	Post-progression survival
PROMs	Patient Reported Outcome Measures
PSA	Probabilistic sensitivity analysis
PSS	Personal and Social Services
PSSRU	Personal and Social Services Research Unit
QALY	Quality-Adjusted Life Year
QoL	Quality of Life
RCT	Randomized Controlled Trial
RFI	Recurrence-Free Interval
RR	Risk Ratio
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard Deviation
SLR	Systematic Literature Review
SmPC	Summary of Product Characteristics
STEEP	Standardised Efficacy Endpoints
TTOT	Time-To-Off-Treatment
UK	United Kingdom
WTP	Willingness-To-Pay

1 SUMMARY

1.1 Critique of the decision problem in the company's submission

The company submission (CS) decision problem partially matches the final NICE scope (see Table 1). There were differences in the population and outcomes. The Evidence Review Group (ERG) considers the difference in outcomes reasonable, however the difference in population is uncertain.

Table 1. The decision problem

	Final scope issued by NICE	CS decision problem	CS rational for difference
Population	People with early or locally advanced HER2-positive breast cancer (BC) who have undergone surgery.	People with HER2-positive early breast cancer (eBC) at high risk of recurrence (N.B. node-positive population submitted as base case, and hormone receptor-negative population as an additional scenario).	The anticipated market authorisation for the adjuvant use of pertuzumab is in patients with HER2-positive eBC at high risk of recurrence (i.e., node-positive or hormone receptor-negative). The APHINITY study met its primary objective in the ITT population. An assessment of key prespecified, stratified subgroups showed that patients with a high risk of recurrence (i.e. node-positive or hormone receptor-negative) appear to derive the most benefit from pertuzumab + trastuzumab with an almost 25% risk reduction in recurrence or death when compared to the control arm.[1] Node-positivity and hormone receptor-negativity are known prognostic factors and have not been discovered in the APHINITY study; patients with node-positive or hormone receptor-negative eBC have a higher risk of relapsing than patients with node-negative or hormone receptor-positive disease. The subgroup analyses confirm that these subgroups are at high-risk of recurrence and the importance of underlying tumour biology when considering treatment options. The economic analyses include node-positive subgroup as the base case and the hormone receptor-negative subgroup as an additional scenario.
Intervention	Adjuvant pertuzumab in combination with trastuzumab and chemotherapy	Adjuvant pertuzumab in combination with trastuzumab and chemotherapy	Not applicable
Comparator	Standard adjuvant therapy without	Standard adjuvant therapy without	Not applicable

	pertuzumab for HER2-positive BC: trastuzumab in combination with chemotherapy	pertuzumab for HER2-positive BC: trastuzumab in combination with chemotherapy	
Outcomes	The outcome measures to be considered: • Overall survival (OS) • Disease-free survival (DFS) • Recurrence-free interval (RFI) • Adverse effects of treatment • Health-related quality of life (HRQoL)	The outcome measures to be considered: • IDFS (Invasive Disease-Free Survival) • IDFS including second primary non-breast cancer • DFS • OS • RFI • Distant recurrence-free interval (DRFI) • Adverse effects of treatment • HRQoL	IDFS was the primary endpoint of the pivotal phase III study for adjuvant pertuzumab in HER2-positive eBC. DRFI was a secondary outcome of the pivotal phase III study.
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 (QALY). 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 (PSS) perspective. The availability of any patient access schemes for the intervention or comparator technologies will be taken into account.	• Cost per QALY • Time horizon suitably long to reflect differences • NHS PSS perspective • Commercial access agreement (CAA) to be taken into account	Not applicable
Subgroups to be considered	If evidence allows, subgroups with higher risk of recurrence, such as people with lymph node-positive	People with HER2-postive eBC that is hormone receptor-negative (note: this is a subgroup of the ITT population, NOT a	This subgroup of the ITT population has been included in the submission because hormone receptor-negativity is a clinically relevant prognostic factor for BC recurrence. Patients with hormone

	disease or people with hormone receptor-negative disease, will be considered.	subgroup of the node-positive population).	receptor-negative disease are considered a high-risk subgroup because, unlike patients with hormone receptor-positive disease, they cannot be treated with hormone therapy. Furthermore, this patient population is likely to be included in the label for adjuvant pertuzumab. In the economic analyses of this submission the node-positive subgroup is the base case and the hormone receptor-negative subgroup is an additional scenario.

The intervention, adjuvant pertuzumab, is indicated for treatment of HER2-positive BC when used in combination with trastuzumab and chemotherapy. The company have yet to receive marketing authorisation from the European Medicines Agency. The recommended dose is 840mg of intravenous pertuzumab as a loading does, then 420mg given every three weeks in combination with trastuzumab for a total of one year (maximum 18 cycles).

The comparator in the decision problem is standard adjuvant therapy without pertuzumab (trastuzumab in combination with chemotherapy). No additional comparators were listed in the NICE scope. The CS decision problem complies with the intervention and comparator provided by NICE.

The population in the decision problem differs from the final scope based on the introduction of subgroups with high-risk of recurrence. These are defined in the CS as people with HER2-positive eBC with node-positive or hormone receptor-negative status. The justification for inclusion of this subgroup of the population provided by the company, is that patients with a high-risk of recurrence derive the most benefit from pertuzumab. This aligns with the findings of the pivotal trial evidence submitted by the company and the anticipated market authorisation. The ERG is uncertain about the selection of these high-risk subgroups, as the subgroups were only acknowledged in an amendment to the pivotal trial protocol which took place after approximately 75% of the study population had been randomised. The ERG clinical advisor notes that life time 'high-risk' status cannot be assumed to remain constant.

The company included IDFS excluding (primary outcome) and including (secondary outcome) second primary non-breast cancer and DRFI as additional outcomes. The CS states that these outcomes were primary and secondary endpoints in the submitted pivotal trial evidence. The remaining outcomes listed in the decision problem were included in the NICE scope. The ERG clinical advisor considers IDFS and DFRI to be appropriate outcomes.

1.2 Summary of clinical effectiveness evidence submitted by the company

The CS undertook a systematic review to search for evidence to meet their decision problem. The ERG considers the systematic review to be of reasonable quality. The CS systematic review included data from an interim analysis of a phase III randomised controlled trial (RCT) investigating adjuvant pertuzumab+trastuzumab+chemotherapy (n=2,400) compared with placebo+trastuzumab+chemotherapy (n=2,405) (APHINITY). The trial is sponsored by Hoffmann-La Roche/Genentech.

The RCT was described in detail in the CS. The ERG summarise the results from the RCT, the key outcomes were as follows:

- The primary outcome of the APHINITY trial was IDFS excluding second primary non-breast cancer events [non STEEP definition]. This was a statistically significant outcome at the existing data cut off on the ITT population (19th December 2016). The rate of IDFS events in the pertuzumab arm was 19% lower than the rate of events in the control arm. No consistent difference between the arms was found until approximately 20 months, at which point a small but sustained difference in favour of pertuzumab was observed. The ERG considers that the delay in observed benefit suggests that the assumption of proportional hazards was violated. Beyond 20 months, the magnitude of the difference is less than 1% difference observed at 24 months and 36 months. At 48 months, the IDFS rate was 1.7% higher in the pertuzumab-based arm compared to placebo
- Secondary outcomes include: IDFS including second primary non-breast cancer events [STEEP definition] (IDFS criteria with contralateral and ipsilateral DCIS), overall survival (OS; time to death from any cause), recurrence-free interval (RFI; time until local, regional or distant breast cancer recurrence), distant RFI (DRFI; time until distant breast cancer recurrence), health related quality of life (HRQoL; assessed based on three patient-reported outcome measures) and adverse events. With the exception of OS, the hazard ratios of the secondary outcomes are broadly consistent with IDFS. No assessment of proportionality of hazard was presented in the CS, so the validity of the hazard ratios is unclear. Kaplan-Meier plots for the secondary outcomes were not presented
- The ERG considers that none of the primary or secondary outcomes would have been statistically significant had the significance level been adjusted for multiplicity (e.g. using a Bonferroni calculation) demonstrating that pertuzumab is only marginally efficacious
- Limited data for the effects of pertuzumab on HRQoL were presented. Brief and selected results from three HRQoL measures were presented. Overall, there is sufficient evidence to

support the view that pertuzumab is associated with a worse HRQoL. This is evidenced most strongly by the difference in mean diarrhoea score from the QLQ-C30

- Overall, adverse event rates were higher in those treated with pertuzumab, with more adverse events which are treatment-related. The most frequently reported adverse event in the pertuzumab arm was severe (grade 3/4) diarrhoea, which was significantly higher than diarrhoeal incidence in the placebo arm (RR=2.62 CI: 2.07 to 3.32, p=0.000). The ERG also notes significantly higher incidence rates of anaemia in the pertuzumab arm (6.9%) compared to placebo (4.7%) (RR=1.47 CI:1.16 to 1.85, p=0.001). At the end of post treatment follow up, the incidence of NYHA class III or IV heart failure with substantial decrease in left ventricular ejection fraction (LVEF) was three times higher among patients in the pertuzumab-based arm compared to the placebo-based arm (0.6% vs. 0.2%, p=0.04). The ERG found higher discontinuation rates for pertuzumab compared to placebo, although this difference was not significant at the 0.05 threshold.

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

The ERG appraisal of APHINITY substantially agreed with the CS appraisal of the trial, with the trial being of generally good quality. One exception is the lack of reporting of allocation concealment. The patient characteristics were balanced across stratification factors. The analytical approach used in the trial appears reasonable. However, there were concerns regarding the protocol amendment that was performed in order to achieve the distribution of lymph node involvement between intervention and control populations. The initial sample size calculation was deemed to be suitably powered, however, it is unclear whether the protocol variation adjustments to the sample size allowed it to remain suitably powered.

All time-to-event outcomes were analysed on the intent-to-treat (ITT) population. Stratified Cox models and log-rank tests were used where appropriate. Nodal status, protocol version, hormone receptor status and adjuvant chemotherapy regimen were the stratification factors. Unstratified analyses were reportedly performed as a sensitivity analysis but were not presented within the CS. Kaplan-Meier plots are only presented for the primary outcome. Hazard ratios (HR), p-values and observed proportion of event-free patients at 3 years are presented for each time-to-event outcome. However, the ERG notes that no adjustment had been made for multiple testing. With the large number of hypotheses and subgroups being investigated, it is important to consider the possibility of false positive results. Proportionality of hazards were not investigated within the clinical effectiveness section for any of the outcomes. The ERG notes that if this assumption was violated, the company could have presented restricted mean survival times.

The primary outcome measure in the APHINITY trial is IDFS and demonstrated a statistically significant outcome at the existing data cut off on the ITT population. A stratified HR of 0.81 (95% CI: 0.66 to 1.00; p=0.045) was calculated by the company. The ERG considers this result to be marginally significant and this is supported by the ERG clinical advisor. The rate of IDFS events among node-positive patients was 23% lower in the pertuzumab arm compared to the placebo arm (HR 0.77, 95% CI: 0.62 to 0.96), whereas no statistically significant difference was observed in node-negative patients (HR 1.13, 95% CI: 0.68 to 1.86). The rate of IDFS events among hormone receptor-negative patients was 24% lower in the pertuzumab arm compared to the placebo arm (HR 0.76, 95% CI: 0.56 to 1.04, p=0.08), and 14% lower than the rate of events in the placebo based arm among hormone receptor-positive patients (HR 0.86, 95% CI: 0.66 to 1.33, p=0.28). The ERG notes that these treatment effects are not statistically significant. The ERG had concerns over the legitimacy of the subgroups focused on by the company, as it was unclear whether these were pre-specified. As a result, the ERG believe the increased efficacy observed in the node-positive population may have occurred by chance.

As only one trial was identified, no indirect comparison or multiple treatment comparisons were performed.

Strengths

The ERG consider the CS had several strengths:

- The quality of the systematic review was reasonable (e.g., relevant inclusion/exclusion criteria were reported, the validity of included studies was adequately assessed and the primary studies were summarised in detail)
- The assessment of study quality was appropriate
- The quality of the included trial (APHINITY) was generally good. However, allocation concealment was not reported
- Results for the trial were accurately presented and demonstrated the risks and benefits from including adjuvant pertuzumab to standard care.

Weaknesses and areas of uncertainty

However, the ERG noted that the CS had some weaknesses and areas of uncertainty:

- There is uncertainty regarding analyses related to high-risk of recurrence subgroups in the company decision problem

    - The subgroups were only acknowledged in an amendment to the pivotal trial protocol which took place after approximately 75% of the study population had been randomised
- The lack of consistent difference between the trial arms in IDFS (primary outcome) until 20 months could be due to the violation of the assumption of proportional hazards. Beyond 20 months, the magnitude of the difference was less than 1%. At 48 months, IDFS rate was 1.7% higher in the pertuzumab-based arm compared to placebo
- For the secondary outcomes, no assessment proportionality of hazard was presented in the CS, so the validity of the hazard ratios is unclear
- There are concerns regarding the lack of adjustment for the multiple hypotheses being tested. The majority of presented p-values are only just below the 0.05 threshold, emphasising that pertuzumab is only marginally efficacious
- There is uncertainty about adverse events. There were significantly higher incidence rates of anaemia in the pertuzumab arm compared to placebo (RR=1.47 CI:1.16 to 1.85, p=0.001). The incidence of NYHA class III or IV heart failure with substantial decrease in LVEF was three times higher among patients in the pertuzumab arm compared to the placebo (0.6% vs. 0.2%, p=0.04).

1.4 Summary of cost effectiveness submitted evidence by the company

Two analyses were contained in the CS. The main analysis compared pertuzumab + trastuzumab +chemotherapy (PHC) against trastuzumab + chemotherapy (HC) in patients with node-positive eBC within the HER2-positive population. An additional analysis relating to HER2-positive patients with hormone receptor-negative disease was included in appendix M. The focus in the CS is on the main analysis (for the node-positive population).

The company undertook a systematic literature review to identify cost effectiveness evidence relevant to this decision problem and reported that no economic evaluations relevant to the decision problem were found. As a result, the company developed and submitted a state transition model consisting of seven health states: (i) 'IDFS – on treatment', (ii) 'IDFS – off treatment', (iii) 'Non-metastatic recurrence', (iv) 'Remission', (v) 'First-line treatment for metastatic disease (First-line mBC)', (vi) 'Subsequent treatment lines for mBC (Second+ line mBC)', and (vii) 'Death'. The model evaluates costs and outcomes (quality-adjusted life years) using monthly cycles over a lifetime (52 years) time horizon, by the end of which less than 1% of the patients in the model remain alive. Transitions between states are guided by probabilities calculated according to parametric extrapolation functions fitted to Kaplan-Meier data from the APHINITY study and other trial evidence in the published

literature. Assumptions were made about the duration of pertuzumab's incremental effect and the proportion of patients who are 'cured' (i.e. no longer at risk of recurrence) at different points in time.

Preference-based health related quality of life (utility) values for states i – iv were derived from EQ-5D data collected in the APHINITY trial, while utility values for states v and vi were taken from the literature. These values were used in calculating quality-adjusted life years (QALYs), which was the main outcome of the economic analysis. Costs were calculated using data and unit cost estimates from various sources, including a previous appraisal of neoadjuvant pertuzumab (TA424). Key cost categories included were (i) treatment acquisition costs; (ii) treatments administration costs; (iii) the cost of treating selected adverse events (of severity grade 3 and above, and observed in more than 2% of the APHINITY trial participants); (iv) supportive care costs; and (v) costs of treatment associated with progressed disease. Future costs and outcomes were discounted at a rate of 3.5% per year.

The company reported a deterministic ICER of £34,084 per QALY gained for PHC compared to HC. At a willingness-to-pay value of £30,000 per additional QALY, the probability of PHC being more cost-effective than PC was 17.3%.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG considers the type and structure of the submitted model to be appropriate for representing the disease pathway and therapeutic options for the population specified in the NICE final scope. Key characteristics of the analysis (such as the selected perspective, time horizon and discount rates), were in line with recommendations set out in the NICE Reference Case. The ERG felt that the company took reasonable steps to ascertain that data used in the model were of sound quality and suitable for the particular decision problem. Face validity checks carried out by ERG did not identify any major issues. The ERG's critique raised the following points:

- In relation to the duration of pertuzumab's effect, the ERG believes that the choice of a relatively long duration is optimistic and is not justified adequately in the CS. An alternative specification is proposed, which the ERG believes to be better aligned with existing evidence. These specifications were incorporated in the ERG preferred base case.
- While the ERG agrees that a 'cure' adjustment is beneficial, it proposes an alternative specifications of the starting point and maximum 'cure' proportion, which better represents the observed behaviour of hazard rates and late recurrence events.
- Revisions were needed in the calculations of the proportion of patients estimated to experience metastatic and non-metastatic recurrences. The ERG re-calculated the

proportion of metastatic (and non-metastatic) events applicable to post-18 month relapses and updated the ERG base case analysis accordingly.

These amendments were reflected in the ERG proposed base case analysis. Incorporating these changes resulted in the ERG base case ICER of £60,679 per QALY gained. A further uncertain parameter, which the ERG consider to be relevant to the decision problem in question, relates to the proportion of patients who are likely to receive pertuzumab with trastuzumab SC or trastuzumab IV in medium and long-term, should pertuzumab be recommended. Additional analyses have been carried out to present the effect of this parameter on the cost effectiveness results. On the basis of currently available treatment options (i.e., no trastuzumab biosimilars), greater shares of trastuzumab SC are associated with higher ICER values.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

Strengths of the evidence submitted by the company include:

- appropriate model type and structure for the decision problem;
- evidence on treatment effectiveness for key health states drawn from the pivotal APHINITY trial;
- costs and resource use data derived from well-established sources and calculations in agreement with NICE technology appraisal of pertuzumab in the neoadjuvant setting (TA424);
- extensive and appropriate checks implemented to ascertain the validity of the economic model.

1.6.2 Weaknesses and areas of uncertainty

Key weaknesses include:

- uncertainty around key elements of clinical effectiveness and extrapolation, importantly the duration of pertuzumab's effect, largely due to immaturity of data derived from APHINITY;
- limited sensitivity analyses to explore the impact of pertuzumab's incremental treatment effect specifications (e.g., time point when the effect ceases) and 'cure' adjustments on the ICER;
- limited exploration of different eventualities with respect to future trastuzumab IV and SC use in combination with pertuzumab and its effect on ICER.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

Based on the critique of the submitted economic model, the ERG suggested an amended base case, which takes into account: i) the ERG's specifications related to the duration of pertuzumab's incremental effect; ii) the ERG's amendments in the specifications of the 'cure' adjustment; and iii) the ERG's revisions in the calculations of the proportion of patients estimated to experience metastatic and non-metastatic recurrences. Carrying out all the above changes simultaneously, that is, implementing the ERG's suggested base case analysis, resulted in a considerable increase in the ICER, by approximately £26,600. The ERG's base case ICER for the node-positive population was calculated to be £60,679 per QALY gained.

Further parameters and assumptions were explored in sensitivity analyses. Parameters of interest were the proportion of patients who were likely to receive pertuzumab with trastuzumab intravenous (IV) or subcutaneous (SC), and the acquisition cost of pertuzumab. A greater use of trastuzumab SC with pertuzumab in the future, which the ERG considers to be a likely eventuality should pertuzumab be recommended, would lead to an increase in the ICER. Lowering the acquisition cost of pertuzumab is shown to result in markedly lower ICER values.

2 BACKGROUND

2.1 Critique of company's description of underlying health problem

The company submission (CS) adequately describes the health condition and the position of the technology in the treatment pathway on pages 15-21. On CS page 16 the company states that breast cancer (BC) is the most common cancer type across the whole population in the United Kingdom (UK), accounting for 15% of all new cancer cases in men and women representing the third most common cause of cancer death overall in 2014.[2, 3] The Office for National Statistics reported 45,960 breast cancer registrations in England during 2016.[4]

The company goes on to provide an overview of early breast cancer (eBC) (CS section B.1.3.1). The definition of eBC in the CS is a malignant cancer that forms in the breast which has *"not spread beyond the breast or the lymph nodes"* (pg. 16). This is not consistent with the definition found in the final scope issued by National Institute of Health and Care Excellence (NICE), which states that eBC can be of clinical stage 1 which is restricted to the breast, or also stage 2, which can additionally involve spread to *"nearby lymph nodes"*.[5] The definition provided in the NICE scope is consistent with the literature.[6]

Both the final scope issued by NICE, and the CS identify HER2-positive eBC as a high-risk subgroup. However, the suggested percentage of eBC that is HER2-positive differs slightly in value in the CS from the final scope (15-25%).[5] The CS states that approximately 14% of patients with eBC in the UK have tumours that overexpress HER2, and are therefore classified as HER2-positive.[7] This equates to 7,900 patients in the UK who are diagnosed with this eBC sub-type each year.[2] Literature reviewed by the ERG suggests a prevalence of 15%.[7] The ERG clinical advisor agrees with this estimate. The CS state that overexpression of HER2 is associated with an aggressive disease course and poor prognosis,[8, 9] and that this sub-type is also associated with increased tumour size, increased risk of disease recurrence and poorer clinical outcomes.[8-13] However, the ERG clinical advisor suggests that current treatment regimens with trastuzumab improve the prognosis of HER2-positive BC.

The CS highlights two subgroups in the trial population which were deemed to be high-risk of recurrence, these are node-positive and hormone receptor-negative patients (see section 4.2.5 for further discussion). These subgroups were not outlined in the final scope issued by NICE, but where listed as subgroups to be considered. Node-positive BC patients have some lymph nodes with cancer cells in them, whereas node negative BC are free from cancer. Hormone receptor status indicates whether or not BC cells have receptors for the hormones oestrogen (ER) and progesterone (PgR).[14] Oestrogen-receptor-positive BC has cancer cells which may receive signals from oestrogen which could promote their growth, whereas PgR-positive indicates that cancer cells may receive signals from progesterone that could promote their growth. The pathophysiological reasons for the conferred high-risk is explained for both node-positivity and hormone-receptor-negativity on CS page 16. The CS describes the epidemiology of node-positive, but not hormone receptor-negative eBC. The ERG clinical advisor agrees that node-positive and hormone receptor-negative eBC are higher-risk subgroups.

Life expectancy

Life expectancy can be influenced by HER2 status. The CS describes on page 15 that HER2-positivity is associated with increased tumour aggressiveness, high rates of recurrence and increased mortality when compared to HER2-negative disease.[8-13, 15, 16] A review of this literature conducted by the ERG confirms these associations, but consider the research articles cited outdated. The ERG clinical advisor noted the improvement in prognosis of HER2-positive breast cancer following the introduction of trastuzumab to the treatment pathway. According to the CS page 17 the *"treatment goal in eBC patients is cure",* coupled with the prevention of development of metastatic BC (mBC) (also called advanced or secondary BC) which is currently incurable.

The CS states that for HER2-positive mBC in the UK, *"71.2% of the mBC patients had a recurrence following eBC (rather than de novo mBC), and the median duration from eBC to mBC diagnosis was four years".* The ERG note that this statement was derived from an interim analysis (data extracted 22 February 2017) of the ESTHER [NCT02393924] non-interventional study.[17] The CS cites this abstract reporting 205 UK patients followed up (10.8 months) from diagnosis of HER2-postive metastatic/unresectable locally advanced breast cancer. Median age was 57 (29-96) years and 71% had ER/PgR positive disease.[17] The abstract states that 191 of 205 patients treated, received a HER2-targeted agent commonly pertuzumab with trastuzumab (n=144; 70.2%). The ERG confirmed that recurrence following eBC was reported to be 71.2%, and the median time from eBC to mBC diagnosis was 4 (0-27) years. The ERG clinical advisor agrees with these estimates regarding mortality and disease progression of patients with HER2 positive BC. The ESTHER trial was also used to estimate market share in the company economic model due because it was more representative of the UK context (see overall survival section 5.2.6.1).

2.2 Critique of company's overview of current service provision

The CS provides an overview of the treatment aims, guidelines and current treatment options for patients with eBC (pg.19-21). This was considered appropriate by the ERG. The CS makes reference to diagnosis and management of HER2-positve eBC as described in four published guidelines (NICE (CG80),[18] European Society for Medical Oncology (ESMO),[19] St Gallen Consensus Conference,[20, 21] and the National Comprehensive Cancer Network (NCCN) Guideline[22]). Key recommendations from these guidelines are summarised in CS Table 3 page 20.

The CS (pg. 20) describes the current treatment for patients with HER2-positive eBC in England. It suggests treatment usually involves a *"combination of HER2-targeted therapy, chemotherapy, surgery, radiotherapy and hormone therapy, depending on the characteristics of the tumour"*. The CS notes that systemic therapy can be given neoadjuvantly and adjuvantly as part of a complete eBC treatment regimen.[23, 24] The ERG agrees that systemic therapy can include chemotherapy, hormonal therapy and targeted therapies, such as those targeted at HER2.[25]

On page 19, the CS describes the aim of systemic treatment in eBC is to reduce the risk of micrometastases. The diagnosis of micrometastases may provide additional prognostic information and therefore can be treated to reduce the risk of recurrence in eBC patients.[26] The CS continues that, systemic treatment for HER2-positive eBC can be started before surgery to *"reduce the burden of the tumour prior to surgery and potentially de-escalate the surgical procedure, allowing for breast-conservation surgery rather than mastectomy in high-risk patients"* and continue after surgery.[18, 23, 24, 27] The ERG clinical advisor agrees with these statements regarding the aims of treatment for eBC.

The ERG consulted NICE guidelines (CG80), which state that trastuzumab is recommended as an adjuvant treatment for eBC in England.[18] The guideline says: "*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.*"[18] The ERG note that a license extension for trastuzumab for HER2-positive eBC patients was granted in 2012 to include neoadjuvant use in combination with chemotherapy followed by adjuvant trastuzumab.[28] The CS echoes these statements on page 21 and declares that systemic trastuzumab is the *"backbone therapy"* for HER2-positive BC patients across all stages of the disease in England.[29-31] On page 21 of the CS, the company states that dual-HER2 blockade (pertuzumab+trastuzumab) with chemotherapy is *"commonly used in the neoadjuvant setting in patients with high-risk disease and in patients with mBC"*. Citing evidence from Electronic Medicines Compendium (eMC) SmPC document for Perjeta (420mg concentrate for solution for infusion).[32] However, the ERG notes that NICE technology appraisal guidance (TA424) only recommends, "*Pertuzumab, in combination with trastuzumab and chemotherapy, as an option for the neoadjuvant treatment of adults with HER2-positive breast cancer; that is, in patients with HER2-positive, locally advanced, inflammatory or early-stage breast cancer at high risk of recurrence*."

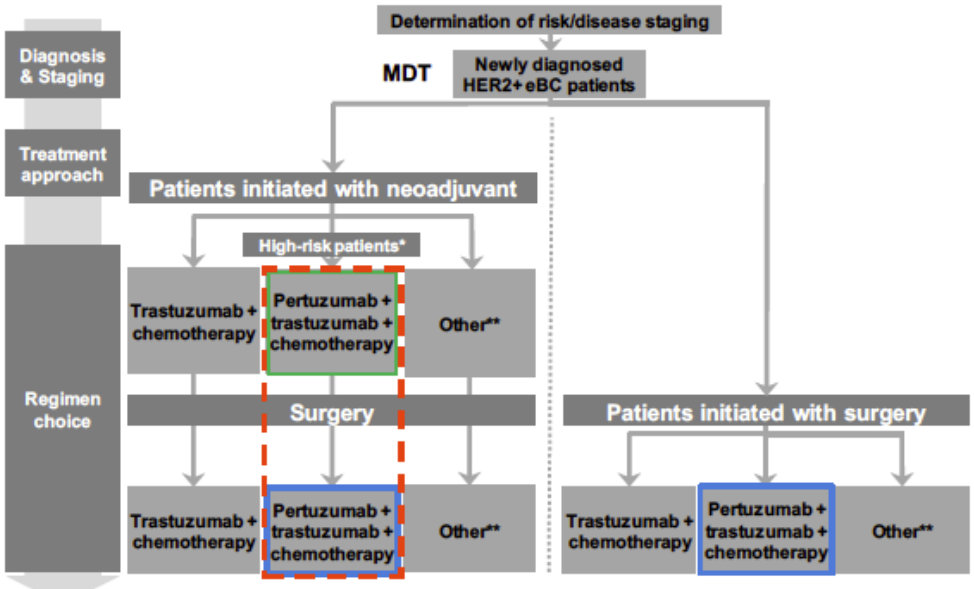
The ERG confirms that trastuzumab is currently recommended for treatment of early (TA107) and advanced HER2-positive BC (TA34). The ERG clinical advisor confirmed that the majority of NHS trusts deliver trastuzumab subcutaneously in the adjuvant and metastatic (neoadjuvant) setting. The ERG note that there are differences in treatment acquisition costs between trastuzumab administered as an intravenous infusion and trastuzumab administered as a subcutaneous injection (see section 5.2.8.1 and 6.3 for further discussion regarding impact of treatment acquisition costs on cost-effectiveness analysis). The ERG clinical advisor suggested that there are variations in the treatments options across the NHS, for example underweight patients may receive trastuzumab intravenously due to their higher risk of cardiac toxicity.

The CS (pg. 21) state that long-term clinical outcomes are not influenced by the timing of initiation of systemic treatment (before or after surgery).[33] The meta-analysis of randomized trials cited by the company compared neoadjuvant therapy with adjuvant therapy, regardless of what additional surgery and/or radiation treatment was used. The ERG note that the study did not include pertuzumab or trastuzumab in the analysis.[33] The authors concluded that there were no statistically or clinically significant differences between neoadjuvant therapy and adjuvant therapy arms in mortality (summary risk ratio (RR) = 1.00, 95% CI: 0.90 to 1.12), disease progression (summary RR = 0.99, 95% CI: 0.91 to 1.07), or distant disease recurrence (summary RR = 0.94, 95% CI: 0.83 to 1.06). The ERG notes the

cited article reports a statistically significant association of neoadjuvant therapy with increased risk of loco-regional disease recurrences (RR = 1.22, 95% CI: 1.04 to 1.43), compared with adjuvant therapy, when radiotherapy without surgery was adopted.[33]

Treatment pathway

The company propose that pertuzumab will be considered as an additional adjuvant treatment for use in combination with trastuzumab plus chemotherapy (for high-risk patients, defined as patients with node-positive or hormone receptor-negative HER2-postive eBC). This will be an addition to the current recommended treatment pathway. The CS states (pg. 22) that the proposed positioning "*is similar to the manner in which trastuzumab is currently used in clinical practice*". The proposed use and positioning of adjuvant pertuzumab is described in detail on CS page 21 and replicated in Figure 1. The ERG clinical advisor believes this to be an appropriate representation of the proposed treatment pathway. However, the ERG clinical advisor has concerns about the company's assumption that patients maintain a high-risk status throughout their lifetime. The ERG clinical advisors note that patients' risk can be deescalated following treatment, and therefore would no longer be considered high-risk.



Footnotes: *High-risk patients: Patients with node-positive or hormone receptor-negative eBC; **Other: Patients who receive chemotherapy only or hormonal therapy only.
Key: Blue border = proposed use of adjuvant pertuzumab as discussed in this submission; Green border = currently approved use of neoadjuvant pertuzumab; Red border = proposed use of pertuzumab treatment for a total of 18 cycles through from neoadjuvant to adjuvant treatment in patients with high-risk (i.e. node-positive or hormone receptor-negative) eBC.
Abbreviations: eBC, early breast cancer; HER2+, human epidermal growth factor receptor 2-positive; MDT, multidisciplinary team.

Figure 1. Summary of the clinical care pathway and proposed placement of adjuvant pertuzumab (CS document B pg. 22)

2.3 Unmet need

Sections B.1.3.1 (pg. 16-19) and B.2.12 (pg. 52-52) of the CS consider the extent of unmet treatment need and discuss how this need is met by adjuvant pertuzumab for eBC. The ERG notes that the European Medicines Agency (EMA) recommends pertuzumab for the neoadjuvant use in eBC.[34] The company propose an extension to include the adjuvant setting for high-risk patients (see section 4.2.5 for ERG discussion of high-risk subgroups). The CS (pg. 53) suggests that HER2-positive BC has an earlier onset compared to other BC types. The CS reports that HER2-postive BC occurs in women aged *"approximately 55 years compared to approximately 65 years for all [other] subtypes of BC"*.[3, 35, 36]

The company suggest that adjuvant pertuzumab in combination with trastuzumab and chemotherapy will improve invasive disease-free survival (IDFS) and reduce the risk of recurrence or death, therefore, providing patients with high-risk HER2-positive eBC with "*more time with their families and friends, [and] thus the social and psychological benefit of treatment would reach beyond the patients themselves*" (pg. 53). The ERG clinical advisor suggests that current treatment regimens with trastuzumab improve the prognosis of patients with HER2-positive BC, highlighting the out-datedness of the evidence in the CS. Therefore, there may not be any difference in the risk of BC recurrence between HER2-positive and HER2-negative BC.

2.4 Marketing authorisation

The ERG notes that pertuzumab does not currently have marketing authorization for the decision problem listed in Table 1 of the CS, page 10-11. The CS appendix C states that at the time of this submission, they are waiting for marketing authorisation for the use of pertuzumab as an adjuvant treatment for use in HER2-positive eBC. The summary of product characteristics (SmPC) and the European public assessment reports (EPAR) for pertuzumab do not include the adjuvant indication. The company anticipates that the EMA licence approval to extend the use of pertuzumab to include adjuvant treatment of patients with HER2-positive eBC will be issued in July 2018 (CS pg. 13).

The CS page 9 states, that following regulatory discussions with the Committee for Medicinal Products for Human Use (CHMP),

[redacted] (of the pivotal trial[1]). The company suggest that the anticipated label for pertuzumab is expected to read as follows:

"Perjeta is indicated for use in combination with trastuzumab and chemotherapy in:

- the neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer at high-risk of recurrence
- the adjuvant treatment of adult patients with HER2-positive early breast cancer at high-risk of recurrence."

The company go on to state that linked to this change, the following text in section 5.1 of the SmPC will be included:

- "In the adjuvant setting, based on data from the APHINITY study, HER2-positive early breast cancer patients at high-risk of recurrence are defined as those with lymph node-positive disease or hormone receptor-negative disease."

On page 9, the CS states that the EMA provided feedback that the proposed revised indication for adjuvant pertuzumab treatment [redacted].

Difference from the NICE scope

As discussed further in section 3.1 and section 4.2.5 of the ERG report, the population outlined in the proposed marketing authorization differs from the final NICE scope for the appraisal.[5] On page 9 of the CS, the company suggests that the narrower population will be aligned with the expected marketing authorisation in the UK.

3 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

The company summarised the decision problem in Table 1 of the submission (pg. 10-12 of document B).

3.1 Population

The ERG considers that the population in the CS decision problem partially matches the population described in the final scope. However, the population described in the pivotal trial evidence submitted (Table 4 of document B) meets the NICE scope. Although the decision problem does not describe patients with locally advanced breast cancer (defined in the NICE final scope as tumour size greater than 5cm or stage III breast cancer) as part of the target population in the decision problem, the ERG note that the published report includes these patients (n=321).[1]

The target population specified in the NICE scope is people with early or locally advanced HER2-positive BC who have undergone surgery. By contrast, on page 10 of the CS the company restricted the decision problem population to HER2-positive BC patients with a high-risk of cancer recurrence, notably patients with breast cancer cells in one or more loco-regional lymph nodes (node-positive population) as the base case, and patients with few or no hormone receptors in breast cancer cells (hormone receptor-negative population) as an additional scenario. According to the company (pg. 10), patients with a high-risk of recurrence *"derive the most benefit from pertuzumab"*, and that this has therefore, informed their decision to change the decision problem and final scope populations (see section 4.2.5 for further discussion).

The ERG clinical advisor affirmed that node-positive and hormone receptor-negative HER2-positive BC patients have a higher risk of recurrence compared to patients with node-negative and hormone receptor-positive HER2-positive breast cancers, and that the most benefit from pertuzumab treatment is expected to be gained statistically in patients with node-positive disease. Nonetheless, the ERG is uncertain about the selection of these high-risk groups, given that patient subgroups were only acknowledged in an amendment to the trial protocol, which took place after approximately 75% of the study population had been randomised (pg. 32 of document B; CS appendix L) (discussed in section 4.2.5). A clarification request was made by the ERG to justify the exclusion of other high-risk patient groups from the decision problem population, including patients with high grade tumours (nuclear grade 3) and large tumours (tumour size > 5cm). In response to a clarification request the company reiterates that nodal status and hormone receptor status were the *"most influential prognostic factors for eBC"*, citing evidence to support the modifying effects of these variables on the outcomes of anti-

HER2 treatment (clarification response A1-a).[37-39] The ERG reviewed the citations and note that the clarification response was acceptable.

3.2 Intervention

The CS intervention matches that in the NICE scope: adjuvant pertuzumab in combination with trastuzumab and chemotherapy. The company anticipates that the EMA licence will be issued in July 2018.

3.3 Comparators

The CS comparator matches that in the NICE scope and is consistent with the trial evidence[1] submitted: adjuvant trastuzumab in combination with chemotherapy.

3.4 Outcomes

In addition to the outcome measures considered in the NICE scope, the company included IDFS including and excluding second primary non-breast cancer events, and DRFI as additional outcomes. IDFS excluding second primary non-breast cancer events was the primary endpoint in the trial evidence submitted, whereas DRFI and IDFS including second primary non-breast cancer events were among the secondary endpoints in the trial.[1] The CS states that the primary IDFS outcome definition *"was based on the US FDA's recommended definition for a trial intended to support a regulatory filing. Inclusion of second primary non-breast cancer events in the IDFS definition has the disadvantage of including events not related to the cancer or the treatment under study, thereby potentially diluting any treatment effect.[40]"* The ERG notes that the primary IDFS outcome definition does not align to the standardised efficacy endpoints [STEEP] definition proposed by Hudis and colleagues (2007).[40] However, the secondary IDFS outcome including second primary non-breast cancer events does align to the STEEP definition.[40]

The ERG recognise the drawbacks of selecting substitute outcomes for mortality.[41] However, the overall survival data in the trial evidence was deemed immature, and BC survival rates in the UK are improving (i.e., low levels of mortality).[42] The ERG clinical advisor judges IDFS and DRFI to be appropriate outcomes.

3.5 Other relevant factors

Subgroups with a higher risk of recurrence, such as patients with node-positive disease and patients with hormone receptor-negative disease were included in the submission as the decision problem population. The ERG clinical advisor agreed that hormone receptor status has an impact on the effect

of HER2 inhibitors in patients with early HER2-positive breast cancer. This supports hormone receptor status as an appropriate subgroup. However, the ERG notes that the submitted trial evidence also included other subgroups as defined by age (<40y vs. 40 – 49y vs. ≥65y), adjuvant chemotherapy regimen (anthracycline-based versus non-anthracycline-based), menopausal status at screening (pre-menopausal versus post-menopausal), tumour size (<2cm vs. 2 -<5cm versus ≥5cm) and protocol version (original vs. amended).[1] Although the company justify the inclusion of node-positive and hormone receptor-negative patients in their decision problem (section 3.1 and section 4.2.5), the ERG suggest that these additional subgroups could have been considered in the decision problem.

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review

The company undertook a systematic review to identify evidence of clinical effectiveness for all pharmacological interventions used for treating early-stage HER2-positive BC in the adjuvant setting. The ERG appraisal of the systematic literature review of cost effectiveness studies is described in section 5.1. The ERG had concerns about including interventions and comparators which are not licensed for the adjuvant treatment of HER2-positive eBC, including trastuzumab emtansine, lapatinib, neratinib (still ongoing) and afatinib as part of the search strategy. However, the literature searches (CS appendix D, Tables 1-9) were comprehensive and were updated to yield 16 trials. One trial (APHINITY[1]) was considered relevant to the decision problem. Study selection and data extraction were conducted appropriately. Sufficient details of all 16 trials were presented in Table 11 of appendix D. The ERG's quality assessment of the APHINITY trial is summarised in Table 2. Overall the ERG considers that the quality of the company's systematic review was reasonable and that the chance of systematic error in the systematic review was low. Following clarification, the company provided three out of four references which were missing from the CS reference pack (clarification response 2).

Table 2. Quality assessment of the CS systematic review of clinical effectiveness

CRD Quality Item	Yes/No/Uncertain with comments
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Yes
2. Is there evidence of a substantial effort to search for all relevant research?	Yes
3. Is the validity of included studies adequately assessed?	Yes (Table 12 of appendix D). Although issues pertaining to external validity (e.g. study setting, duration of follow-up) were not addressed during quality assessment, the ERG deemed the included trial generalizable to 'real world' population.
4. Is sufficient detail of the individual studies presented?	Yes
5. Are the primary studies summarised appropriately?	Yes

4.1.1 Searches (Description of company's search strategy)

Comprehensive searches in an appropriate set of bibliographic databases were undertaken on 8th November 2016 and were fully updated on 11th September 2017. The inclusion of more than one concept per line (i.e., type of breast cancer and tests and treatments) in some of the first lines of each database search would have resulted in a broader search than necessary and found, for example, literature related to other interventions for early or locally advanced HER2-positive BC. In addition, searches of trials registers, relevant conferences and Health Technology Assessment (HTA) agencies

were undertaken and are well reported. The ERG updated the searches post 11th September 2017, and identified no additional studies relevant to the decision problem.

4.1.2 Inclusion criteria (Statement of the inclusion/exclusion criteria used in the study selection)

Eligibility criteria for the CS systematic review are summarised in Table 10 of CS appendix D. The population inclusion criteria do not meet the decision problem as studies of HER2-positive eBC patients were eligible for inclusion irrespective of nodal, hormone receptor or menopausal status of these patients. The company also included studies of mixed HER2-positive/HER2-negative and early-stage/late-stage BC populations, if outcome data were retrievable for the relevant subgroup (early-stage HER2-positive breast cancer patients). The ERG considers this strategy reasonable.

Both licensed and investigational pharmacological interventions used for managing BC in the adjuvant setting were included in the eligibility criteria for interventions and/or comparators. Among the listed HER2-inhibitors were trastuzumab emtansine, lapatinib, neratinib (still ongoing) and afatinib. The ERG queries the inclusion of these drugs in the search strategy because they have not been licensed for the adjuvant treatment of newly diagnosed early-stage HER2-positive BC. For instance, trastuzumab emtansine [TA458] is recommended as an option for patients who do not meet the inclusion criteria for the systematic review, namely those with locally advanced or mBC who have received prior adjuvant trastuzumab treatment.[43] Afatinib [TA310] is recommended as an option for patients with early-stage or metastatic HER2-positive lung cancer.[44]

The outcomes selection criteria for the systematic review entailed comprehensive lists of efficacy and safety measures that meet the decision problem of the CS. Although a few of these criteria, (including IDFS with and without second primary non-breast cancer and DRFI), fall outside the NICE scope, the ERG deems these outcomes to be clinically relevant, as discussed in section 3.4.

Phase II-IV RCTs of all designs were eligible for inclusion irrespective of the sample size. Systematic reviews and meta-analyses of trials were also included in the search strategy. There were no restrictions to methodological quality, language, date of publication, or country of origin. A PRISMA flow diagram describing the original and updated search strategy and another describing the updated search strategy alone are presented respectively in figures 1 and 2 of CS appendix D (pg. 15-16). The ERG notes that the number of trials presented in the PRISMA diagram matches the number of trials in CS Table 11. However, only 20 of these references were provided in the reference pack, whereas figure 1 states that 47 references were identified. Details of the 19 systematic literature reviews/network meta-analysis were not provided.

4.1.3 Critique of data extraction

The ERG considers that study selection (two independent reviewers with third reviewer/strategic advisor resolving discrepancies) and data extraction (two independent reviewers with third reviewer/strategic advisor resolving discrepancies) were conducted appropriately. The data were extracted using a pre-approved data extraction table.

4.1.4 Quality assessment

The company provided a quality assessment of the included trial evidence (APHINITY[1]) using the minimum criteria for assessing risk of bias in RCTs as set out in the CRD guidance for undertaking reviews in health care[45] and the NICE single technology appraisal user guide.[46] The ERG conclude that this is sufficient. Results of the quality appraisal are presented in Document B (Table 10, pg. 34) and the appendix document (appendix D, table 12, pg. 19).

The ERG performed an independent quality assessment of the included trial which is reported in Table 3. As indicated, the ERG agreed with all but one aspect of the company's assessment of study quality which was that it is unclear what measures were implemented to prevent foreknowledge of forthcoming treatment allocations as "allocation concealment" was not described in the CS documents or trial protocol or report.[1]

Table 14 of CS appendix D summarises patient disposition towards the study treatment, including discontinuation rates. Although the ERG found a statistically significant difference in pertuzumab/placebo discontinuations between pertuzumab and placebo at the clinical cut-off date (p=0.005), there were no significant differences in losses to follow-up and self-withdrawals (discussed further in section 4.2).

The ERG notes that after having achieved 75% (n=3655) of the original target sample size, the company considered node-negative BC patients' ineligible for the trial. This amendment was in order to recruit more node-positive patients (n=1149). This was described in an amendment to the protocol (protocol B, appendix L), and was suggested to be in line with the distribution of patients by nodal involvement in the Breast Cancer International Research Group (BCIRG) 006 trial.[47] During clarification the ERG requested earlier versions of the APHINITY protocol but were unable to determine whether the distribution of, and proportions of women with nodal involvement informed the sample size calculation (clarification response A2, discussed in more detail in section 4.2).

While a more conservative alpha-level (i.e., <0.05) may have been more appropriate for the sample size calculation given the protocol amendment, the ERG effectively deems protocol B effectively a

second trial, in which node-positive patients were randomised to pertuzumab or placebo. Viewed in this way there is less concern of bias.

Overall, the ERG considers the quality and assessment of the company's inclusion of the trial evidence to be reasonable.

Table 3. Quality assessment of the APHINITY trial[1]

Question	CS response	ERG response	Rationale for ERG response	ERG rationale for discrepancy
Was randomisation carried out appropriately?	Yes	Yes	Participants were randomised 1:1 using a web-based randomisation system	N/A
Was the concealment of treatment allocation adequate?	Yes	Unclear	Allocation concealment was not reported in the submission or APHINITY protocol	Allocation concealment was not reported in the submission or APHINITY protocol or report[1]
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Intervention and control group baseline characteristics were balanced	N/A
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes	The study was double-blinded. All parties involved in the trial were unaware of the treatment assignments	N/A
Were there any unexpected imbalances in drop-outs between groups?	No	No	Losses to follow-up and self-withdrawals were comparable across treatment arms	N/A
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	All outcomes reported in the results were pre-specified in the protocol.	N/A
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes	Efficacy analysis performed using intention-to-treat	N/A

4.1.5 Evidence Synthesis

In the systematic review of clinical effectiveness, one RCT (Adjuvant Pertuzumab and Herceptin IN Initial TherapY in Breast Cancer, NCT01358877/ BO25126/ BIG 4-11

[APHINITY][1]) is presented in tabular and narrative form. As only one trial was identified, no meta-analysis was conducted in the CS. Where possible the ERG has checked key data presented in the CS against those in the clinical study report (CSR) provided by the company, and has determined that the data in the CS do not conflict with the CSR.

In summary, the ERG considers the quality of the company's systematic review to be reasonable.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

The only trial identified by the company and confirmed by the ERG was the APHINITY trial, which is described in detail in CS Section B.2.3.1 (pg. 26-34).[1] APHINITY is an ongoing, Phase III, randomised, prospective, double blind, multicentre (549 centres), multinational (43 countries), placebo-controlled study to assess the efficacy and safety of adjuvant pertuzumab+ trastuzumab+chemotherapy (n=2,400) compared with placebo+trastuzumab+chemotherapy (n=2,405) in 4,805 patients with operable HER2-positive eBC.[1] The estimated completion date is 1st December 2023.[48]

The intervention was pertuzumab, given on day 1 of the first taxane-containing cycle as an 840mg loading dose, followed by 420mg dose every three weeks for all subsequent cycles (up to 18 cycles). The primary study outcome was IDFS (excluding second primary non-breast cancers). The secondary outcome was IDFS including second primary non-breast cancers, disease free survival (DFS), overall survival (OS), recurrence-free interval (RFI), distance recurrence-free interval (DRFI), cardiac safety, overall safety, and health-related quality of life (HRQoL). The ERG can confirm that details on statistical methods and patient flow were clearly reported (for more discussion see section 4.2). A diagram illustrating patient flow was included in CS figure 2 (pg. 27) and CS appendix figure 3 (pg. 30).

The publication[1] and CSR of the APHINITY trial were provided in the reference pack along with the CS. Randomisation was performed using a web-based permuted block procedure. Whilst the block sizes are not reported, the ERG considers the approach is likely to be satisfactory when considering the number of stratification factors (nodal status, adjuvant chemotherapy regimen, hormone receptor status and geographical region).

The APHINITY trial was relevant to the company's decision problem in terms of population, intervention, comparator and outcomes (see section 3 for comparison to the NICE decision problem).

Outcomes reported were summarised clearly in CS Table 11 (pg. 36) and CS Table 12 (pg. 37). For discussion regarding appropriateness of outcome selection see section 3.4 and section 4.2.1. Statistical analyses were summarised in CS Table 9 (pg. 32-33), including details of participants excluded from the analyses. As per the company decision problem, the study recruited participants with node-positive disease (any tumour size except T0) or node-negative disease (only under protocol version A only) where the following conditions were met; tumour size >1 cm or tumour size >0.5 cm and ≤1 cm with at least one of the following three features: histologic/nuclear Grade 3, negative for oestrogen/progesterone receptor, or age <35 years.

The protocol was later amended by only allowing recruitment of node-positive patients only (protocol version B), apparently in order to achieve a population with a distribution of nodal involvement status similar to the BCIRG-006 trial.[47] The ERG can confirm that the APHINITY trial recruited a higher proportion of node-negative patients than the BCIRG-006 trial, however protocol A did not specifically state that the company set out to replicate the BCIRG-006 population. This aim only appeared in protocol B for the first time (trial protocols received as part of clarification response A2). The ERG has not been presented with any evidence that the APHINITY trial was designed to recruit a similar patient population to BCIRG-006. The ERG compared hormone receptor status between the two trials. There were more hormone receptor-negative patients in the APHINITY trial than in BCIRG-006 (36% vs. 46%). As the company did not lay out any criteria about what an acceptable deviation from the BCIRG-006 trial population was, it is difficult to ascertain whether the company achieved their aim of replicating the BCRG-006 trial. The ERG is surprised that no adjustment was made to the trial protocol to address this difference in hormone-receptor status distributions between the two trials, to be consistent with the aforementioned difference in nodal status.

The inclusion/exclusion criteria of APHINITY and BCIRG-006 were broadly similar, and it is unclear why the APHINITY trial experienced unexpectedly high recruitment rates of node-negative patients, as discussed above. Following clarification, the company suggest that neoadjuvant therapy is now "*a common option for high risk HER2-positive breast cancer"* and that *"international guidelines recommended the use of adjuvant Herceptin also for the treatment of HER2-positive, node-negative patients with small tumors (e.g., <1 cm) differently than the past"*, which together may have resulted in a *"higher proportion of node-negative patients being eligible for APHINITY"* (clarification response C7). The ERG agrees this is plausible but remains uncertain whether this can be responsible for the magnitude of the unexpected recruitment rate observed during protocol A.

The ERG noted inconsistency over when the protocol was reportedly amended, which was queried in clarification question C8. The company reports in section B.2.4.1 (pg. 32) that the amendment was

"*put into place"* after 3655 patients were randomised. The ERG has checked the Von Minckwitz 2017 article which states that this is the point at which the amendment was *"added"*.[1] The company also reports in CS appendix L (pg. 93) that the amendment was *"implemented"* in November 2012, supported by clarification response A2 *"amendment B was released in November 2012"* and C8, which also states this is when it was *"released"*. However, approximately 1900 patients had been enrolled into APHINITY at the end of September 2012 (protocol version D, section 8.3, pg. 132), suggesting that over 1700 patients were enrolled within a two-month period. The ERG finds the different responses confusing and conclude that, given that the initial 1900 participants took ten months to recruit, it would be surprising if over 1700 patients could be enrolled within a two-month period.

In summary, it remains unclear to the ERG to what extent the APHINITY trial aimed to match the patient population of BCIRG-006, and at what stage of the APHINITY trial this aim originated. There is an additional lack of clarity over precisely when the amendment was amended and implemented.

The initial sample size calculation of 3806 was deemed by the ERG to give the study suitable power. However, it is unclear whether the protocol variation adjustments (which increased the sample size to 4800) were suitably powered. The company report 1856 node-positive patients were recruited into the study at the point of protocol change. Whereas, based on ERG calculation using the 71.4% node-positive proportion observed in BCIRG-006, it was expected by the company that approximately 2600 node-positive patients would be recruited. This estimated shortfall of approximately 750 patients resulted in an extended recruitment of 1000 patients, which transpired to an actual recruitment of 1149 patients. The sample size appears to be appropriate to the ERG based on the numbers of node-positive patients reported above. However, it is not clear what method or assumptions were used by the company when moving to protocol B.

Baseline demographic characteristics of patients

It is also unclear to the ERG why the populations of Canada, New Zealand, Australia, South Africa and Western Europe are pooled together within a stratification factor as they have very different native populations. No detailed patient breakdown was provided in the CS. Therefore, the ERG were unable to ascertain how many patients were from the UK, or even Western Europe in the APHINITY trial. However, the ERG considers that the baseline demographic characteristics of patients recruited into the APHINITY trial are comparable to BC patients in the UK. For instance, the ERG clinical expert stated the average age of patients eligible for pertuzumab under this current indication is 45, which is reasonably consistent with the average age (51 years) of participants in the APHINITY trial. The ERG notes that most patients in the trial were of European descent (71%), which is similar to the

ethnic distribution of patient with BC in the UK.[49] In addition, the distribution of certain clinical characteristics in the trial, including nodal status (node-positive > node-negative) and hormone receptor status (hormone receptor-positive > hormone receptor-negative) are consistent with previous studies HER2 inhibitors.[47, 50]

Patient withdrawals

Details of participants excluded from the primary efficacy analysis in the APHINITY trial were reported in table 9 of the CS (pg. 33). Patients were allowed to withdraw at any time during the duration of the study for any reason. In the trial, withdrawal was defined was defined in three ways, withdrawal from study treatment, withdrawal from the entire study, and partial withdrawal from the study. Patients were declared "Lost to follow-up" when contact was unsuccessful, after sufficient attempts. The CS states that "*data from patients without documented events were censored at the date the patient was last known to be event-free*" (pg. 33). The ERG concludes that there were were no significant differences between loss to follow-up and self-withdrawals across the treatment arms (see table 14 CS appendix D). However, the ERG found a statistically significant difference in pertuzumab/placebo discontinuations between pertuzumab and placebo at the clinical cut-off date (p=0.005).

4.2.1 Description and critique of the approach to trial statistics and outcomes selection

The primary outcome of the APHINITY trial was IDFS (excluding second primary non-breast cancer events), defined as the time from randomisation to the date of first occurrence of one of the following: recurrence of ipsilateral invasive breast tumour, recurrence of ipsilateral loco-regional invasive disease, distant disease recurrence, contralateral invasive BC or death from any cause, respectively.[1] Second primary non-breast cancers, in situ carcinomas (ductal carcinoma in situ [DCIS] lobular carcinoma in situ [LCIS]) and non-melanoma skin cancer were excluded as primary events (CS B.2.3.1). Although the BCIRG-006 trial does not report IDFS as the primary endpoint, the ERG clinical advisor agrees that IDFS (excluding second primary non-breast cancer events) and IDFS (including second primary non-breast cancer) were appropriately described as primary and secondary outcomes, respectively. In addition, the ERG notes that the secondary IDFS endpoint match the Standardized Definitions for Efficacy End Points in Adjuvant Breast Cancer Trials (STEEP).[40]

Other secondary outcomes, which are consistent with the NICE final scope and decision problem include: invasive disease free survival (IDFS criteria with contralateral and ipsilateral DCIS), OS (time to death from any cause), RFI (time until local, regional or distant breast cancer recurrence), DRFI (time until distant breast cancer recurrence), HRQoL (assessed based on three patient-reported outcome measures) and adverse events. Of note, the company excluded LCIS events from the DFS

definition. While the rationale for this exclusion was not described in the CS, the ERG considers that LCIS events, unlike DCIS, are not true pre-malignant lesions.[51]

The CS reports that all time-to-event outcomes were analysed on the ITT population based on a data cut-off of 19th December 2016. Stratified Cox models and log-rank tests were used where appropriate, with nodal status, protocol version, hormone receptor status and adjuvant chemotherapy regimen used as stratification factors. Unstratified analyses were reportedly performed as a sensitivity analysis, but were not presented within the company submission. The ERG checked and found these analyses in the CSR. The ERG notes that Kaplan-Meier (KM) plots are only presented for the primary outcome. Hazard ratios, p-values and observed proportions of event-free patients at three years are presented for each time-to-event outcome, however the ERG note that there is no adjustment made for multiple testing. With the large number of hypotheses and subgroups investigated, it is important to consider the possibility of false positive results. The risk can be reduced by performing an adjustment such as those suggested by Bonferroni or Šidàk, which lower the significance threshold based on the number of hypotheses being tested.[52]

Proportional hazards (an assumption when fitting a Cox model and performing a log-rank test) were not investigated within the clinical effectiveness section for any of the outcomes. The ERG notes that if this assumption was violated, the company could have presented restricted mean survival times[53] (i.e., use an alternative method to demonstrated treatment effect).

HRQoL was collected using three different questionnaires; the European Organisation for Research and Treatment of Cancer core 30 questionnaire (EORTC QLQ-C30), European Organisation for Research and Treatment of Cancer breast cancer-specific quality of life questionnaire (EORTC QLQ-BR23) and EuroQol 5-Dimensions Questionnaire (EQ-5D) with average scores calculated at relevant points in time (see section 4.2.4 for ERG discussion of appropriateness).

Patient characteristics from the APHINITY trial are presented in CS B.2.3.2. The ERG has examined these and suggest that the patient characteristics demonstrate that the trial is balanced across arms and across stratification factors.

4.2.2 Invasive disease-free survival

The primary outcome measure in the APHINITY trial is IDFS. IDFS was found to be demonstrate a statistically significant difference for the data cut off in the ITT population.[1] A stratified HR of 0.81 (95% CI: 0.66, 1.00; p=0.045) was calculated by the company (CS B.2.6, pg.35). The ERG interprets from this that the likelihood of experiencing invasive disease in the pertuzumab arm was 19% lower

than the rate of events in the control arm. The unstratified log-rank test yielded a HR of 0.82 (p=0.0549) which was not statistically significant at the 0.05 threshold. The KM plot is displayed in Figure 2, and was produced using the company's economic model. The ERG note that the y-axis is scaled to make it easier to distinguish between the treatment arms. The ERG also notes that it is clear there is no consistent difference between the arms until roughly 20 months, at which point a small but sustained difference is observed in favour of pertuzumab. This is relevant because the duration of pertuzumab treatment effect is an uncertain parameter in the cost effectiveness model (see section 6.3). The ERG clinical advisor confirmed, that no clinical justification can be provided for the 20 month delay following treatment.

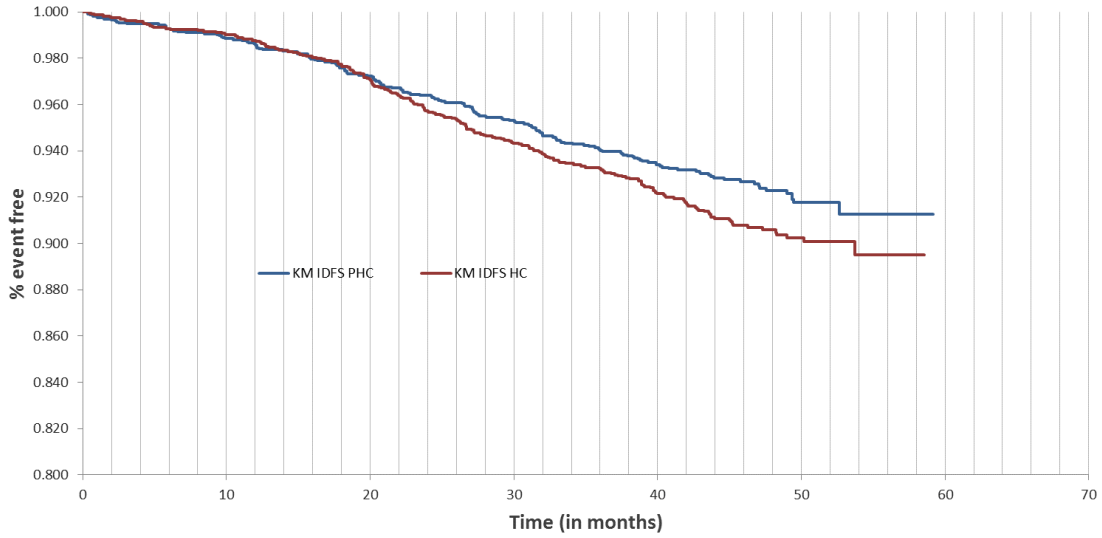


Figure 2. Kaplan Meier plot for IDFS observed in ITT population of APHINITY trial (produced using company economic model)

The ERG requested clarification regarding the reason behind the observed delayed treatment benefit. The company responded with comments describing how patients in the placebo arm performed better than expected, for example stating that *"the efficacy in the placebo arm (i.e. placebo+trastuzumab+chemotherapy) is higher than seen in historical trials"* (clarification response A3) see Box 1 for additional company explanation. The ERG consider that the company failed to justify, in their response to the clarification questions asked by the ERG, why no benefit from the intervention was observed within the first 20 months of follow-up.

- *"Improvements in imaging over time, providing more accurate diagnosis and reducing the number of patients with advanced disease incorrectly enrolled in APHINITY versus historical studies in patients with HER2-positive eBC.*
- *Improvements in the management of local and systemic therapy increasing patients' ability to complete treatment regimens.*
- *Advances in standard of care, e.g. aromatase inhibitors are now standard of care for patients with hormone receptor-positive disease.*
- *An increase in the use of neoadjuvant therapy in patients with high-risk breast cancer. Since patients could not be included in the APHINITY study if they had received any previous chemotherapy or radiotherapy for cancer or any previous anti-HER2 therapy, it could be that only patients with lower-risk eBC were available for recruitment into the APHINITY study."*

Box 1. Reasons provided by the company to explain the better-than-expected performance observed in the placebo arm (clarification response A3)

The ERG considers that the observed delay in benefit suggests that the assumption of proportional hazards may be violated. The violation was confirmed by the ERG when the company provided log-cumulative-hazard plots in the appendix to their clarification response. As shown in Figure 3, the cumulative hazards for both arms are not parallel and cross multiple times. Therefore, the ERG recommend that all HRs and associated p-values should be interpreted with caution.

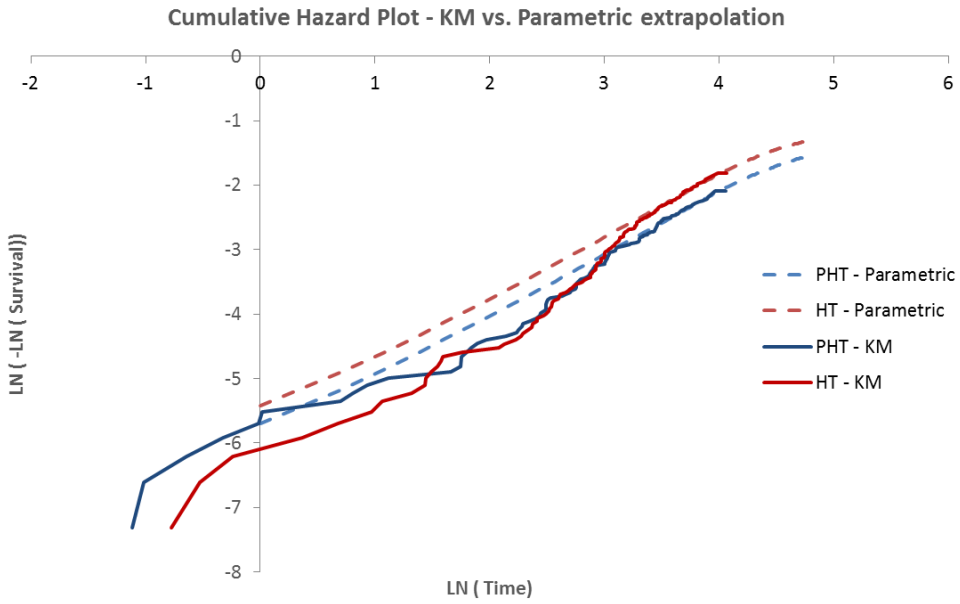


Figure 3. Cumulative hazard plot – KM versus Parametric extrapolation

The ERG notes that beyond 20 months, the magnitude of the difference between IDFS rates for pertuzumab and placebo is very slight, with less than 1% difference observed at 24 months and 36

months. At 48 months, IDFS rate was only 1.7% higher in the pertuzumab-based arm compared to placebo (Table 4). The ERG's clinical advisor considers this difference to be of marginal, not major clinical significance.

The company presented a table (Table 11, Document B) showing the distribution of types of IDFS event and of the site of distant recurrence events. The ERG noticed that there appears to be a higher combined frequency of the different sites of distant recurrence than there were total number of patients with distant recurrence, however this is suspected to be due to multiple site occurrence rather than an error. No large differences were observed between the arms for both IDFS event type and site of distant recurrence.

Table 4. Summary of Efficacy Endpoints for ITT population

Endpoints	Pertuzumab + trastuzumab + chemotherapy	Placebo + trastuzumab + chemotherapy	Difference in percentage points	Hazard ratio[b] (95% CI) [stratified]	p-value [stratified]
IDFS (primary outcome observed 2-year event-free rate, %	96.4*	95.7*	0.7*		
IDFS (primary outcome) estimated 3-year event-free rate, %	94.1*	93.2*	0.9*	0.81 (0.66, 1.00)	0.045
IDFS (primary outcome) observed 4-year event-free rate, %	92.3*	90.6*	1.7*		
Secondary efficacy endpoints					
IDFS (STEEP definition) observed 3 year, %	93.5	92.5		0.82 (0.68, 0.99)	0.043
DFS observed 3 year, %	93.4	92.3		0.81 (0.67, 0.98)	0.033
RFI observed 3 year, %	95.2	94.3		0.79 (0.63, 0.99)	0.043
DRFI observed 3 year, %	95.7	95.1		0.82 (0.64, 1.04)	0.101
OS observed 2 year, %	98.8*	98.9*	-0.1*		
OS observed 3 year, %	97.6*	97.7*	-0.1*	0.89 (0.66, 1.21)	0.467
OS observed 4 year, %	96.4*	95.8*	0.6*		
* Indicates extracted by ERG from economic model.					

4.2.3 Additional outcomes

The company presented HR, associated p-values and 3-year observations for all of the planned secondary time-to-event outcomes, shown above in Table 4. The ERG notes that with the exception of OS, the HRs of the secondary outcomes are broadly consistent with IDFS. The ERG notes that IDFS as a secondary outcome did not offer any additional information when compared to IDFS as a primary

outcome. Table 4 demonstrates fairly comparable IDFS rates between primary and secondary IDFS endpoints, hence secondary primary non BC events appear to be not very common.

However, the company emphasises that the OS data were part of an interim-analysis with only 169 (26%) of 640 planned events having occurred to detect an expected HR of 0.80 (protocol version D). The CS did not present KM plots for the secondary outcomes. According to the company's log-rank test, DRFI was not statistically significant at the 0.05 threshold, however secondary IDFS (HR 0.82), DFS (0.81), and RFI (0.79) were all significantly ($p < 0.05$) higher in the pertuzumab-based arm compared to placebo (see CS table 12). The ERG considers that none of the primary or secondary outcomes would have been statistically significant had the significance level been adjusted for multiplicity (as mentioned earlier). Pertuzumab appears to be only marginally efficacious. The unstratified analyses can be found in Table 5, which are taken from the CSR. In Table 5 only DFS is statistically significant.

Table 5. Summary of unstratified results for ITT population of APHINITY

Endpoints	Hazard ratio[b] (95% CI) (unstratified	p-value (unstratified)
IDFS (primary outcome) estimated 3-year event-free rate, %	0.82 (0.67, 1.00)	0.0549
Secondary efficacy endpoints		
IDFS (STEEP definition) 3 year	0.83 (0.68, 1.00)	0.0544
DFS 3 year	0.82 (0.68, 0.99)	0.0403
RFI 3 year	0.80 (0.64, 1.01)	0.0561
DRFI 3 year	0.83 (0.65, 1.06)	0.1275
OS 3 year	0.91 (0.67, 1.23)	0.5428
Values taken from CSR section 4.2.3		

4.2.4 HRQoL

The company presents brief and selected results from three HRQoL measures used in the APHINITY trial (pg. 37-39 CS document B). These are EORTC QLQ-C30 which is a general cancer quality of life questionnaire, EORTC QLQ-BR23 which is a BC specific quality of life questionnaire and EQ-5D-3L which is a non-disease specific quality of life questionnaire. The ERG considers the selection of these HRQoL measures to be appropriate, and comparable to previous appraisals for BC.[54] The HRQoL inputs used in the cost effectiveness analysis are described in section 5.2.7. The ERG notes that HRQoL inputs for the company model were taken from the APHINITY trial and from other and published literature sources.

The CS reports that patients completed questionnaires at baseline, end of anthracycline treatment period (if applicable), end of taxane therapy, week 25, at the end of study treatment and at 18, 24 and 36 months' post randomisation. Completion rates were consistently above 85%. The ERG considers this a satisfactory completion rate.

The company chose a minimally clinically important difference (MCID) of 10 points for the QLQ-C30 and QLQ-BR23 questionnaires. The ERG notes that this MCID was not predefined in the APHINITY protocol and is not well justified in the CS. The citation provided to support this definition is not specific to breast cancer.[55] Upon further investigation by the ERG the article suggests a difference of 5-10 points is 'a small change', 10-20 points 'moderate' and greater than 20 'a large change', rather than declaring a specific MCID.[55] The ERG would prefer the selection of a MCID to be performed via disease-specific investigation and expert clinical opinion, with additional interpretation of differences using the aforementioned scale.

QLQ-C30

In the CS findings page 38, the company report that the addition of pertuzumab did not have a detrimental effect on patients' global health. Whilst no MCID was observed in the APHINITY trial between the treatments (see Figure 4, reproduced from CS [figure 4, pg. 38]) average scores were consistently lower (worse) for the pertuzumab arm across the three measurements of QLQ-C30 taken during the year of treatment. The ERG notes that the majority of other results which were presented and discussed by the company are only done so in the context of comparing scores across time points, and not between treatment arms. Changes from baseline at week 13 greater than MCID were observed for the physical functioning scale in both arms, but not for the other functional scales (role, emotional, cognitive and social). The changes in physical function from baseline were similar between arms (-10.7 vs. -10.6, pertuzumab vs placebo, CSR). The ERG note that no other results were reported for the other scales.

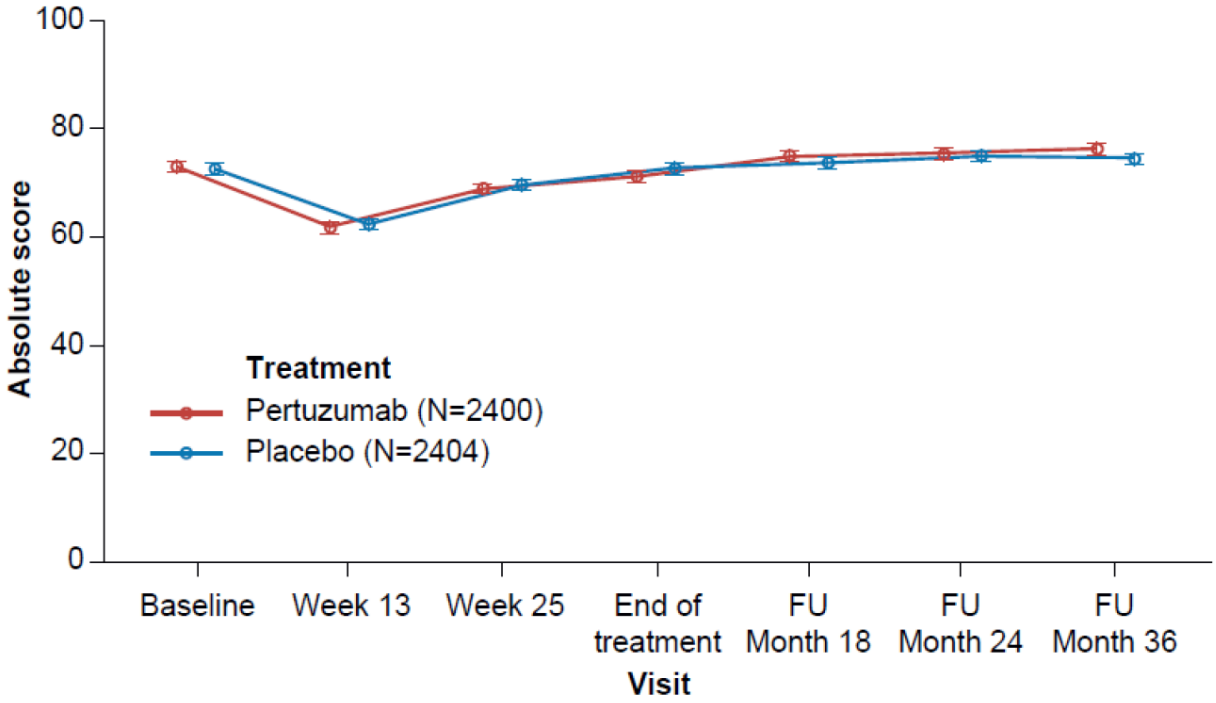


Figure 1. APHINITY mean EORTC QLQ-C30 global health status in the ITT population (primary analysis, clinical cut-off date 19th December 2016). (CS Figure 4, pg. 38)

The company states in the CSR, that only in the pertuzumab arm was there a greater than MCID difference from baseline observed for the one-year treatment period for diarrhoea symptoms (w13, w25 and treatment end). Mean (SD) changes from baseline of QLQ-C30 diarrhoea across the 1 year of treatment were 22.3 (29.8) and 9.2 (23.9) in the pertuzumab and placebo arms, respectively see Figure 5 (CS figure 15, CSR). The ERG judges this change demonstrates a sustained difference in diarrhoea occurrence between the two arms. For completeness, the ERG would have liked to have seen the data for diarrhoea and the other symptom scales of the QLQ-C30 presented within the company submission.

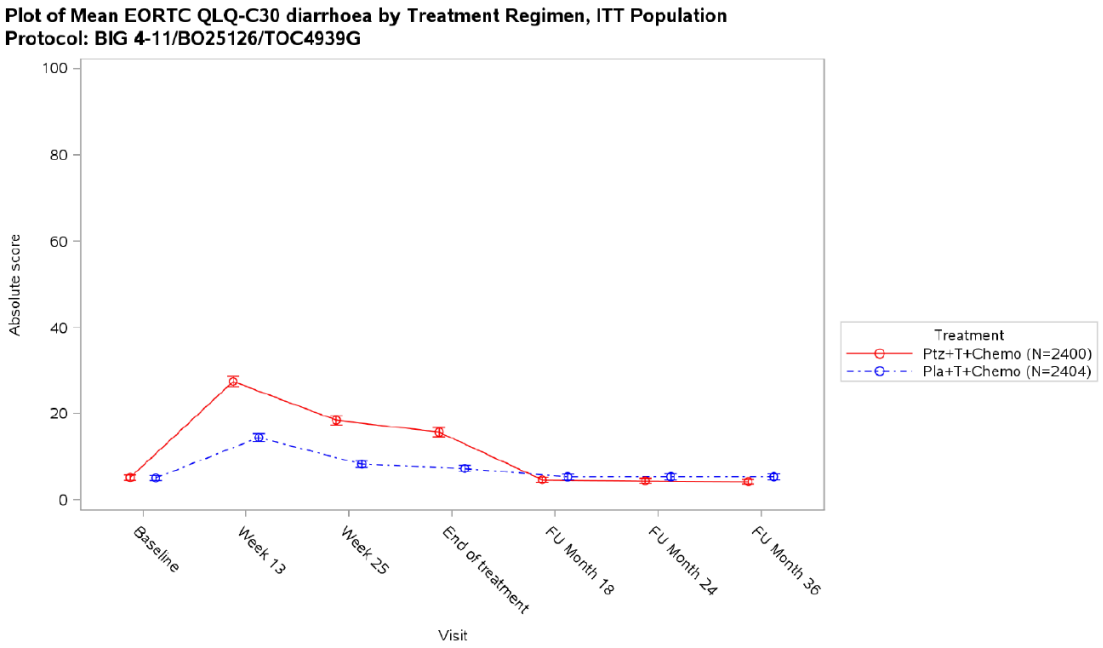


Figure 5. Mean Scores of EORTC QLQ-C30 Diarrhea (ITT Population) CSR

QLQ-BR23

On CS page 39, the company presents brief results for the QLQ-BR23 in their submission. The ERG notes a similar decrease (exceeding the MCID) in scores from baseline to end of taxane treatment for both body image and sexual enjoyment in both arms. However, only in the pertuzumab arm is the decrease in sexual enjoyment sustained until HER2 treatment end. The company reports that there were no clinically meaningful differences in other components of QLQ-BR23 in either arm, however, the ERG are unable to verify this claim due to lack of supporting evidence.

EQ-5D

On CS page 39, the company states that no major differences were observed between treatment arms in the five EQ-5D domains. However, the ERG note that it is unclear whether this referred to individual time points or a combined average across all time points individually. Examination of the EQ-5D-3L results presented in the CSR suggested that there were no major differences between pertuzumab and placebo arms. This was confirmed by the ERG when inspecting the utility values from the economic model where values were very similar between arms.

The ERG has concerns over the quality and usefulness of the HRQoL data presented in the CS. The company state in the cost-effectiveness section (B.3.4.5 page 88) that "*the schedule of EQ-5D administration was designed to capture differences in [Quality of Life] QoL across the various stages*

of disease, not between treatment arms". This same schedule was used for all HRQoL measures in the APHINITY trial.[1] The rationale for this approach is unclear to the ERG.

The ERG is concerned about the infrequency of the collection of the patient reported outcome measures (PROMs) during the APHINITY trial. This is due to the potential failure of this approach to capture the effects of adverse events. Both of the EORTC questionnaires included in the appendix of the study protocol (CS appendix 8-9) requested that the patients only consider the previous week in their response. Similarly, EQ-5D-3L (CS appendix 10) only represents the patients' health on the day the questionnaire is completed. The ERG notes that excluding baseline, the patients in the APHINITY trial completed questionnaires a maximum of three times whilst on treatment. This represents only three weeks of treatment duration despite patients receiving treatment for up to a year. The ERG considers it likely that the impact of adverse events was not accurately captured in these QoL measures.

In summary, the ERG considers that due to the increased frequency of adverse events, there is evidence that pertuzumab may be associated with a slightly worse HRQoL, although this is not represented in the summaries of the PROMs. This is evidenced most strongly by the difference in mean diarrhoea score from the QLQ-C30. The differences observed from the PROMs in the APHINITY trial data may underrepresent the true differences due to the methods and timings of data capture in this study.

4.2.5 Subgroups

The subgroup analyses methods are presented in the CS section B.2.7 (pg. 39). The company states that subgroup analyses were performed to "*assess consistency of the overall result*" from the ITT analysis across the different sub-populations in the trial. This justification of subgroup analysis contradicts the emphasis on high-risk eBC patients as the target population in the decision problem (described in section 3.1). The ERG considers that the achievement of comparable treatment effects between subgroups, would be important to demonstrate that pertuzumab is effective across all HER2 positive eBC patients, irrespective of the different baseline characteristics. However, the CS focuses on two main stratification criteria: nodal status and hormone receptor status.

The ERG noted that in the original APHINITY protocol (version A) the following subgroups were mentioned specifically: menopausal status, type of surgery for tumour, tumour size, histological grade of tumour, race, loco-regional radiotherapy and hormone receptor status. Nodal status appeared only in later versions of the trial protocol (protocol versions B and D). The forest plot of results of the subgroup analysis are displayed in Figure 6. The ERG's clinical advisor suggested that both size and

grade of tumour are predictors of risk of recurrence, alongside nodal status and hormone receptor status. On clarification, the company suggest that subgroups such as histological grade of tumour, size of tumour and menopausal status "*were not included in the decision problem as they are not as influential as nodal status and hormone receptor status in affecting prognosis in eBC*" (clarification response A1-b).

On clarification, the company reported that the subgroups had been *"pre-specified as part of the statistical analysis plan (SAP)"* (clarification response A1-a). The ERG did locate the specification of the nodal and hormone receptor status subgroups in the SAP provided by the company (version 3.0), however the SAP mentions these subgroups are based on protocol version B and so the ERG remain uncertain regarding the credibility of the subgroup selection. It is unclear why the company do not focus on other risk factors of BC recurrence, such as tumour size and histological grade.

The ERG considers that nodal status and hormone receptor status should have informed the hypothesis testing as well as power/sample size calculations, however, this is not the case in earlier versions of the protocol (protocol version A, Section 8.2.2, pg. 109).

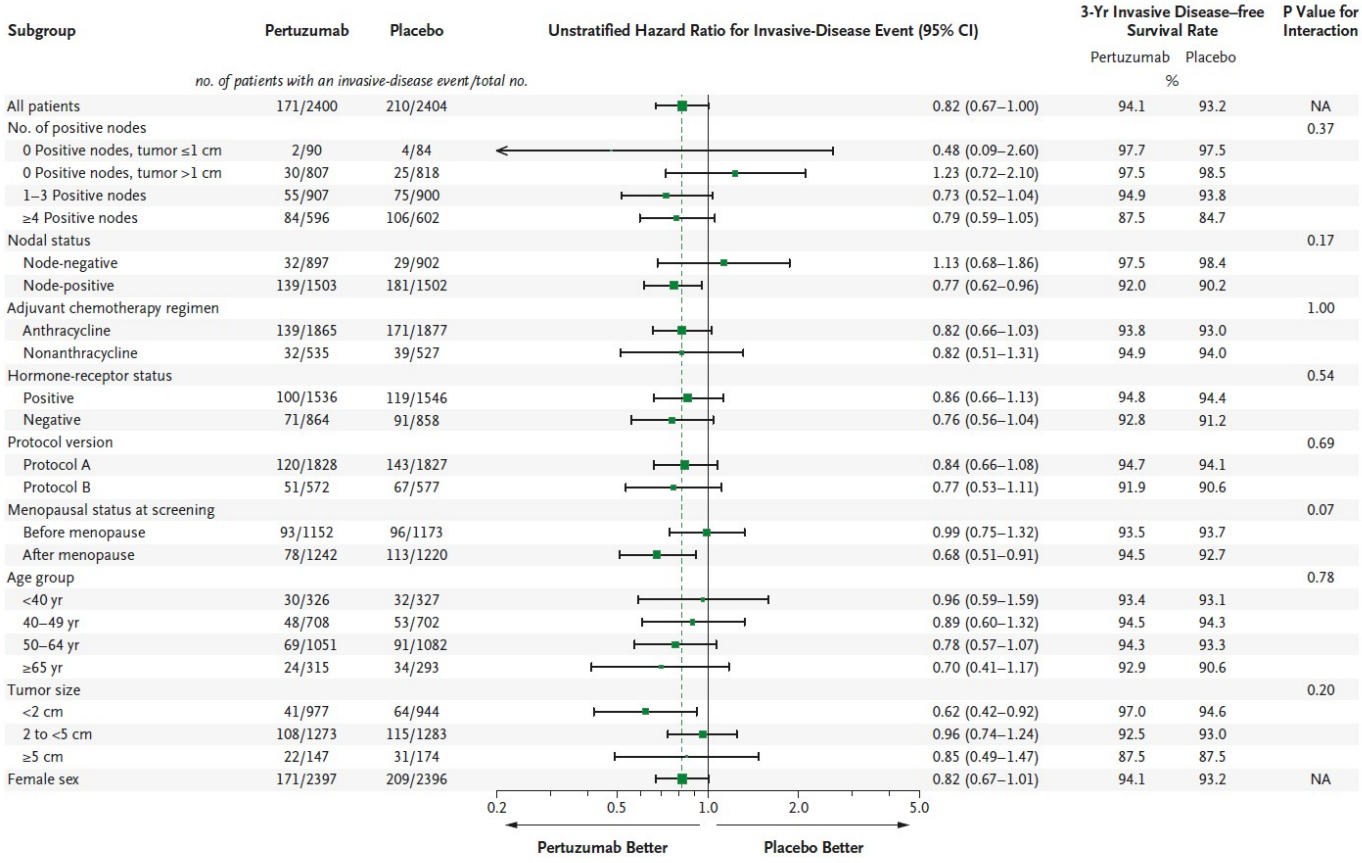


Figure 2. Forest plot of treatment efficacy among subgroups using IDFS of the OTT population of APHINITY trial[1]

Nodal status

Three hundred and twenty (320) of 3005 node-positive patients and 611 of 1799 node-negative patients developed invasive breast cancer or died by the clinical cut-off date of the APHINITY trial.[1] The rate of IDFS events among node-positive patients was 23% lower in the pertuzumab arm compared to the placebo arm (unstratified HR 0.77, 95% CI 0.62 to 0.96), whereas no significant difference was observed in node-negative patients (unstratified HR 1.13, 95% CI 0.68 to 1.86). However, the ERG notes that median IDFS had not been reached at clinical cut-off in node-positive and node-negative patients (see Figure 7, A and B).

The ERG also notes that the effect of pertuzumab was stronger in node-positive patients than the ITT population. Following the ERGs clarification request, the company provided subgroup analyses based on further stratification of node-positive patients (clarification response C6, see clarification figure 1). However, these additional analyses showed no clear pattern of a direct association between treatment effect and number of node-positive BC cells.

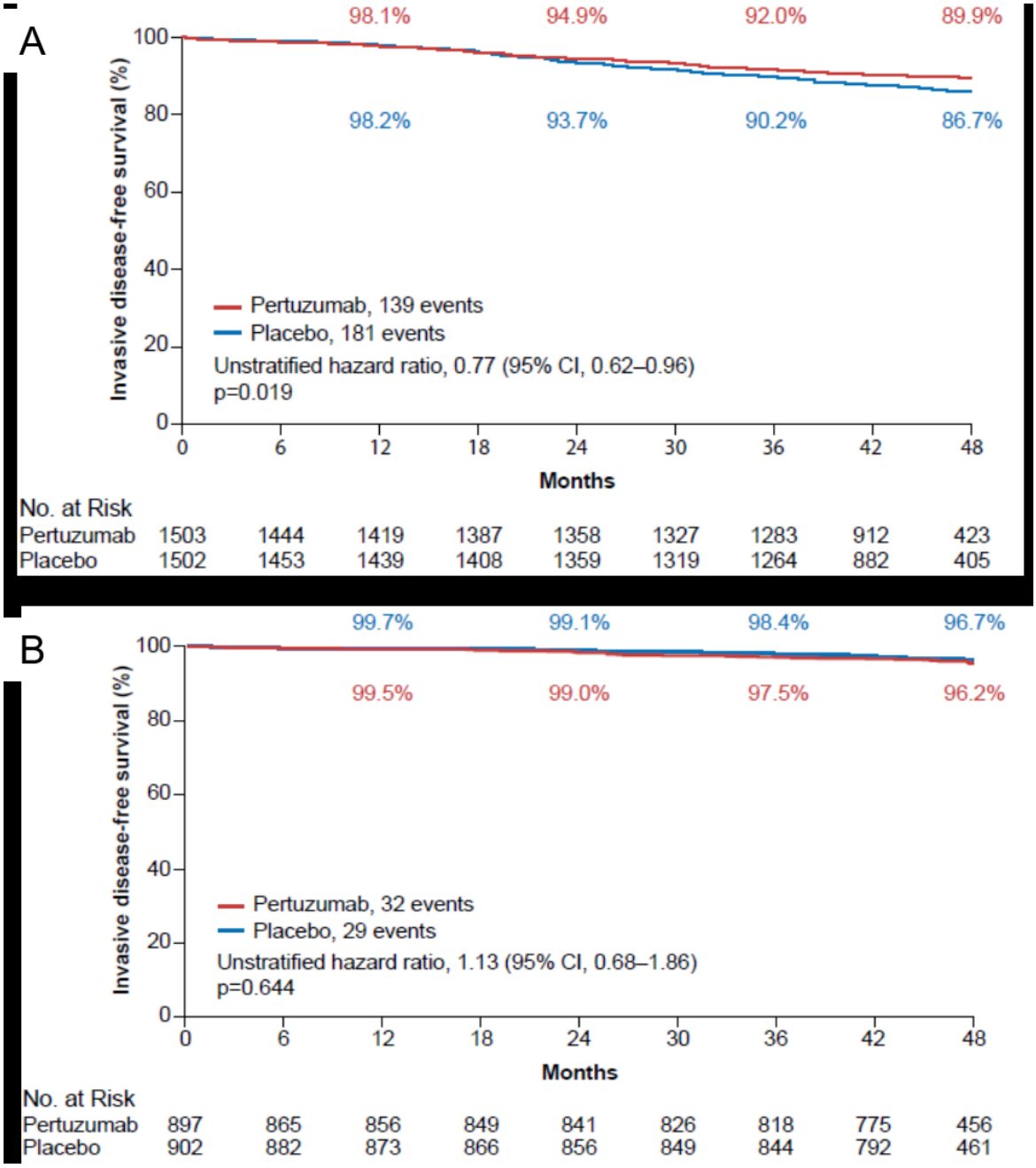


Figure 3. Kaplan-Meier plots of IDFS for ITT population with node-negative (A) and node-positive (B) disease (CS figure 6)

The ERG suggests that the effect of pertuzumab was only statistically significant for patients with 10 positive nodes (HR 0.60, 95% CI 0.39 to 0.94), but not among patients with less than 10 positive nodes: HR=0.73 (95% CI 0.52 to 1.04) and 0.95 (95% CI 0.65 to 1.39) for patients with 1-3 and 4-10 node-positive nodes respectively, though the trial was not powered to detect treatment effect in these subgroups. Regardless of power, the ERG would have expected to observe a linear trend (dose response) of treatment effect estimates if the performance of pertuzumab had been associated with disease severity, however, the observed effect was lowest in the 4-10 node group among the node positive groups.

Hormone receptor status

One hundred and sixty two (162) of 1722 hormone receptor-negative patients and 219 of 3082 hormone receptor-positive patients developed invasive BC or died by the clinical cut-off date of the APHINITY trial.[1] The rate of IDFS events in the pertuzumab arm is 24% lower than the rate of events in the placebo-based arm among hormone receptor-negative patients (HR=0.76, 95% CI 0.56 to 1.04, p=0.08), and 14% lower than the rate of events in the placebo-based arm among hormone receptor-positive patients (HR=0.86, 95% CI 0.66 to 1.33, p=0.28). The median IDFS had not been reached by clinical cut-off (see A and B). However, the ERG note that these treatment effects are not statistically significant, and do not differ significantly between hormone receptor-negative and hormone receptor-positive populations (p=0.54 for interaction) (see Figure 8, A and B). The ERG clinical advisor notes that the 10% difference in IDFS event rates between hormone receptor-positive and hormone receptor-negative patients was not statistically different and would be concerned using it as a clinical indication.

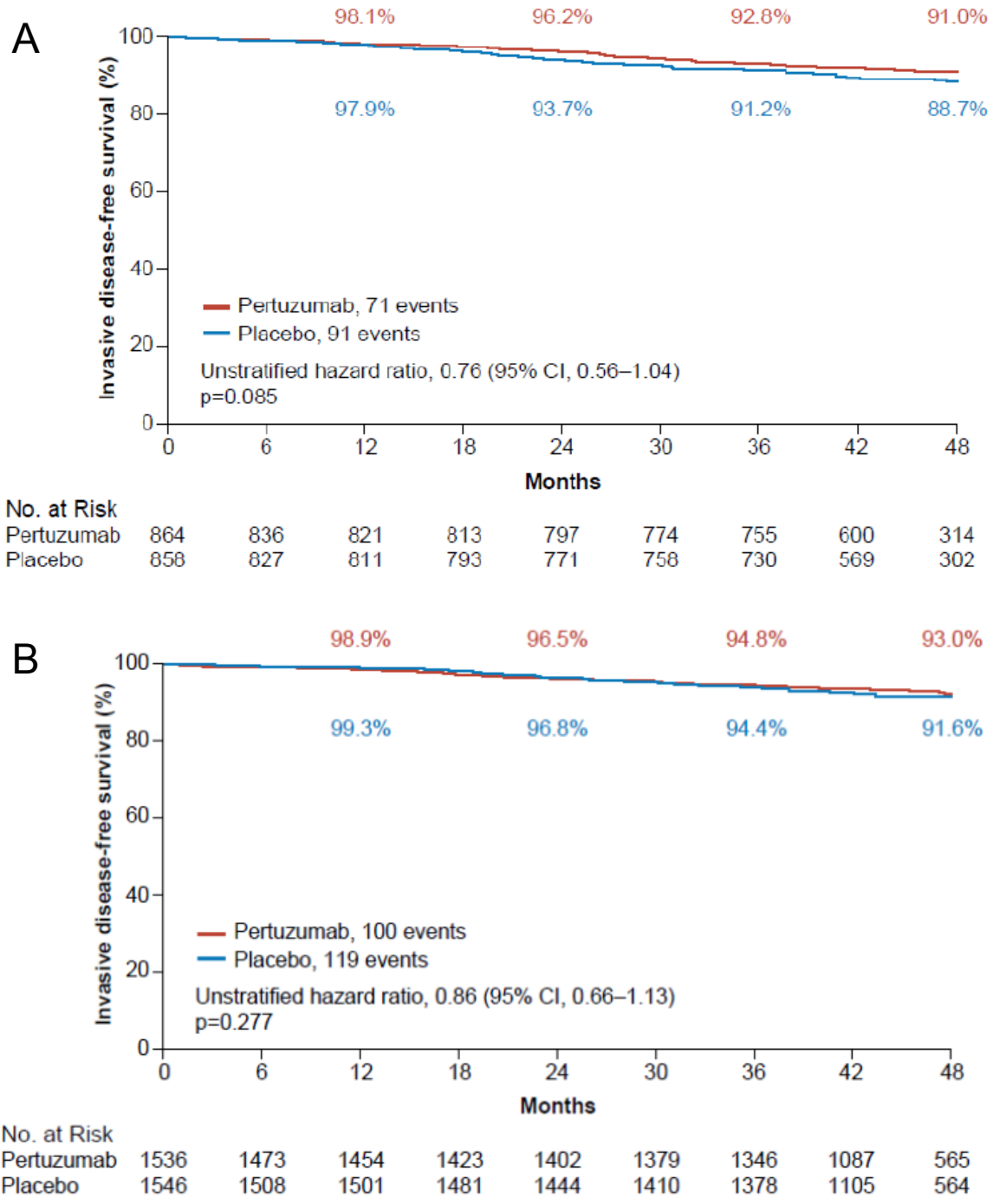


Figure 4. Kaplan-Meier plots of IDFS for ITT population with hormone receptor-negative (A) and hormone receptor-positive (B) disease (CS figure 7)

Additional subgroups

The ERG wanted to ensure the observed efficacy of pertuzumab in node-positive patients was not the result of a spurious interaction with other subgroup variables, in particular hormone receptor status. Therefore, the ERG requested additional analyses of the subgroups of patients of the node-positive

AND hormone receptor-positive ([redacted]), node-negative AND hormone-receptor negative ([redacted]), node-positive AND hormone receptor-negative ([redacted]), and also node-positive OR hormone receptor-negative ([redacted]) (data supplied in clarification response C1). The hormone receptor-positive AND node-negative subgroups was not requested during clarification, as these patients were not included in the economic analyses presented by the company.

Among the subgroups containing node-positive patients ([redacted]), there was some observed [redacted], though only group [redacted] yielded a significant result at the 0.05 threshold when stratified log-rank tests were performed. P-values were [redacted].

Investigation of the hormone receptor-negative AND node-negative subgroup ([redacted]) was of particular interest to the ERG. This is because the ERG were concerned about the possibility that the treatment interaction observed within the hormone receptor subgroups might have resulted from the interaction between node status. The KM plot for this subgroup is displayed in Figure 9. Here, there is [redacted], with a stratified analyses performed by the company producing a HR of [redacted] although only [redacted]. Given the lack of evidence, the ERG remains unconvinced of pertuzumab efficacy for the hormone receptor-negative population.

[redacted]

Figure 9. IDFS KM plot of node-negative, hormone receptor-negative ITT population of APHINITY trial

In the APHINITY trial, subgroup analysis by menopausal status at screening revealed a [redacted] for post-menopausal patients ([redacted]) not observed in pre-menopausal patients ([redacted]).[1] However, the ERG considers that these results may have no biological basis. According to the ERG clinical advisor, pre-menopausal women may have a higher risk of recurrence given their younger age as well as a higher vascular intensity of the tumour,[56-60] which together with the observed difference in efficacy of the subgroups, seems contrary to the company's preference to target 'high-risk' patients.

The ERG also requested analyses of the subgroups of the combinations of node status and menopausal status (data supplied in clarification response C5), as these were the subgroups which showed the strongest signs of treatment interaction (see Figure 6). The subgroups considered were pre-menopausal node negative ([redacted]), post-menopausal node negative ([redacted]), pre-menopausal node positive ([redacted]) and post-menopausal node positive ([redacted]). As already discussed, the ERG's clinical adviser suggested that pre-menopausal women may have a higher risk of disease recurrence than post-menopausal women. The

[redacted] The ERG suggests that the apparent effectiveness of the pertuzumab in the post-menopausal group of women (see Figure 6) could be due to the correlation with nodal status.

Table 6. IDFS treatment efficacy for subgroups of APHINITY trial

	Pre-Menopausal	Post-Menopausal
Node Negative	[redacted]	[redacted]
Node Positive	[redacted]	[redacted]

*P pertuzumab, pla placebo, HR hazard ratio, unstrat unstratified, strat stratified

The ERG is concerned that the lack of evidence of drug efficacy in the node-negative population is being treated as evidence that the drug is ineffective in this subgroup.

[redacted]

Other subgroups

To investigate all potentially relevant subgroups which were outlined in the APHINITY protocol, the ERG requested additional subgroup analyses by adjuvant radiotherapy status, tumour grade and tumour size (clarification response C6, see clarification figure 1). Approximately three-quarters (72.5%, n=3481) of patients received adjuvant radiotherapy during the trial as clinically indicated. In these patients, the rate of IDFS events was 21% lower (95% CI 0.62 to 1.01) in the pertuzumab-based arm compared to the placebo-based arm. The rate of IDFS events among patients who were not administered adjuvant radiotherapy was 10% lower in the pertuzumab arm compared to placebo (95% CI 0.62 to 1.31).

It is not clear to the ERG how many node-positive and node-negative patients received adjuvant radiotherapy during the trial. Hence, the ERG are also uncertain as to whether there could be possible interaction between nodal status and adjuvant radiotherapy status. This is pertinent as effect estimates of pertuzumab in node-positive patients and patients who received adjuvant radiotherapy were comparable. The ERG considers that the slight superior efficacy of adjuvant pertuzumab+trastuzumab+chemotherapy over placebo+trastuzumab+chemotherapy (HR=0.82, 95% CI 0.67-1.00, p=0.045) could be attributable to a potential synergism between adjuvant pertuzumab and radiotherapy.

The CS subgroup analysis by histological grade revealed an inverse association between treatment benefit and histological grade (clarification response C6, see clarification figure 1). The ERG notes that a direct association, as with tumour size, would be consistent with the anticipated market authorisation (see section 2.4).

In summary, the ERG notes that in the original APHINITY protocol (version A) seven subgroups were mentioned specifically (menopausal status, type of surgery for tumour, tumour size, histological grade of tumour, race, loco-regional radiotherapy and hormone receptor status). Only hormone receptor and nodal status have been included in the CS decision problem. Nodal status appeared only in later versions of the trial protocol after approximately 75% of the study population had been randomised (protocol versions B and D). The ERG's clinical advisor suggested that both size and grade of tumour are predictors of risk of recurrence, alongside nodal status and hormone receptor status.

4.2.6 Summary of adverse events

General safety

The CS presents safety analyses data consistent with the published report[1] and CSR, for patients who received one or more doses of pertuzumab (n=2364) or placebo (n=2405). A total of 168 participants

in the safety population died during the study. This represents 73 patients in the pertuzumab-based arm and 95 in the placebo-based arm. However, the number of deaths secondary to adverse events were comparable between pertuzumab and placebo-based arms (CS document B, table 17, pg. 51). Thirty-eight patients in the pertuzumab arm who did not receive pertuzumab were included in the placebo safety population. Twenty-four patients who were randomised to the placebo arm but who received pertuzumab were included in the pertuzumab safety population. The ERG were unable to determine why these patients did not receive their allocated treatment, or why the analysis on adverse events was not done on the ITT population.

The CS did not provide evidence to check whether there were any systematic baseline differences between these patient groups. Six more deaths than were originally reported in the placebo ITT population (n=89) occurred in the placebo-based safety arm. The ERG considers that these deaths may have come from the 38 patients in the pertuzumab ITT population who were moved to the placebo safety population. This coincides with six fewer deaths reported in the pertuzumab-based safety population compared to the pertuzumab-based ITT population. Miller (2017)[61] says in an accompanying editorial to the original NEJM paper[1]that this appears to be *"a biased analysis"* because of the failure to use an ITT based analysis and the ERG agreed that this is of concern.

Approximately all patients who received pertuzumab (99.9%) or placebo (99.5%) experienced one or more adverse events during the study treatment period. Adverse events were followed and reported if they were ongoing 28 days after the last dose of pertuzumab or placebo, or if they occurred anew at any time during or after the study treatment period. Table 13 of CS document B describes the most common adverse events experienced during the study. Only events that occurred in at least 15% of patients in either arm are reported. The ERG considers this threshold to be rather high, but were unable to compare it against pre-existing thresholds due to the lack of previous technology appraisals evaluating adjuvant eBC treatments. Of note, the CSR does not present incidence rates of adverse events not reported in CS document B (CSR Table 44).

The most frequently reported adverse event in the pertuzumab arm was diarrhoea. This was significantly higher than diarrhoeal incidence in the placebo arm (71.2% vs. 45.2%, $p < 0.001$). Other notable differences between treatment arms are summarised in Table 7.

Table 7. Most common adverse events (≥15% incidence in at least one arm) by treatment arm (safety analysis population; primary analysis, clinical cut-off date 19th December 2016)

MedDRA Preferred Term	Pertuzumab + trastuzumab + chemotherapy (N=2,364)	Placebo + trastuzumab + chemotherapy (N=2,405)	P-values
Nausea$^{\nabla}$	1,632 (69.0%)	1,575 (65.5%)	0.009$^{\nabla}$
Alopecia	1,577 (66.7%)	1,610 (66.9%)	0.865
Diarrhoea$^{\nabla}$	1,683 (71.2%)	1,086 (45.2%)	0$^{\nabla}$
Fatigue$^{\nabla}$	1,154 (48.8%)	1,065 (44.3%)	0.002$^{\nabla}$
Vomiting	768 (32.5%)	733 (30.5%)	0.134
Arthralgia	678 (28.7%)	782 (32.5%)	0.004
Constipation	684 (28.9%)	759 (31.6%)	0.049
Myalgia	615 (26.0%)	710 (29.5%)	0.002
Stomatitis$^{\nabla}$	671 (28.4%)	573 (23.8%)	0.0003$^{\nabla}$
Anaemia$^{\nabla}$	655 (27.7%)	557 (23.2%)	0.0003$^{\nabla}$
Neutropenia	587 (24.8%)	562 (23.4%)	0.238
Dysgeusia$^{\nabla}$	614 (26.0%)	518 (21.5%)	0.0003$^{\nabla}$
Rash$^{\nabla}$	609 (25.8%)	488 (20.3%)	0$^{\nabla}$
Headache	531 (22.5%)	563 (23.4%)	0.441
Decreased appetite$^{\nabla}$	565 (23.9%)	478 (19.9%)	0.0008$^{\nabla}$
Asthenia	505 (21.4%)	500 (20.8%)	0.631
Mucosal inflammation$^{\nabla}$	552 (23.4%)	448 (18.6%)	0$^{\nabla}$
Hot flush	482 (20.4%)	509 (21.2%)	0.662
Pyrexia	473 (20.0%)	469 (19.5%)	0.660
Oedema peripheral	405 (17.1%)	483 (20.1%)	0.009
Peripheral sensory neuropathy	427 (18.1%)	422 (17.5%)	0.638
Insomnia	404 (17.1%)	400 (16.6%)	0.675
Epistaxis$^{\nabla}$	430 (18.2%)	326 (13.6%)	0$^{\nabla}$
Neuropathy peripheral	366 (15.5%)	369 (15.3%)	0.897
Cough	374 (15.8%)	351 (14.6%)	0.238

MedDRA Medical Dictionary for Regulatory Activities. Values match CSR. $^{\nabla}$ indicate significantly ($p < 0.05$) higher incidence rates in pertuzumab compared to placebo. ERG calculated p-values for the difference in proportions between treatment arms.

Discontinuation rates due to safety reasons are reported in Table 8 below (provided in response to clarification question A4).

Table 8. Discontinuations due to safety reasons in APHINITY[1] (provided in response to clarification question A4)

	Pertuzumab + trastuzumab + chemotherapy N=2,400	Placebo + trastuzumab + chemotherapy N=2,404
Discontinuations due to safety, n (%)	186 (7.8%)	155 (6.4%)
Adverse events	176 (7.3%)	149 (6.2%)
Death	9 (0.4%)	6 (0.2%)
Pregnancy	1 (<0.1%)	0

The ERG has examined these results using the safety population and found moderately higher discontinuation rates for pertuzumab compared to placebo (7.8% versus 6.4%, p = 0.056). While this

difference was not significant at the 0.05 threshold, it is consistent with the view that adjuvant pertuzumab+trastuzumab combination has a worse safety profile compared to adjuvant trastuzumab in patients with eBC. There were also more deaths due to "*injury, poisoning, and procedural complications*" (2 vs. 0), "*blood and lymphatic system disorders*", "*metabolism and nutrition disorders*" and "*nervous system disorders*" (all 1 vs. 0) in the pertuzumab arm, however these are only reported for completeness. The ERG clinical advisor noted that mucosal inflammation, peripheral sensory neuropathy and epistaxis were common (>30% incidence) in clinical practice, and suggest that these three conditions are relevant adverse events in this population.

Grade ≥3 adverse events

A summary of severe (grade ≥3) adverse events is presented in Table 14 of CS document B. The severity of adverse events was assessed appropriately according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0.[62] Patients randomised to the pertuzumab arm experienced a higher incidence of grade ≥3 adverse events than patients randomised to placebo (64.2% versus 57.3%, $p < 0.0001$). The company states that differences in grade ≥3 adverse events were driven by a higher incidence of grade 3/4 diarrhoea in the pertuzumab arm compared to placebo (CS table 14 document B). However, the ERG also notes significantly higher incidence rates of anaemia in the pertuzumab arm compared to placebo (see Table 9). Rates of grade ≥3 adverse events experienced by at least 2% of patients were included in the health economic model, consistent with previous STAs of cancer treatments (TA487).[63]

Table 9. Summary of adverse events (safety analysis population; primary analysis, clinical cut-off date 19th December 2016)

Event	Pertuzumab + trastuzumab + chemotherapy N=2,364[d]	Placebo + trastuzumab + chemotherapy N=2,405[d]	RR (95% CI)	p-value for differences in proportions
	No. of patients (%)			
Grade ≥3 AE[∇]	1,518 (64.2)	1,379 (57.3)	1.12 (1.07 to 1.17)	0[∇]
Neutropenia	385 (16.3)	377 (15.7)	1.04 (0.91 to 1.18)	0.562
Febrile neutropenia	287 (12.1)	266 (11.1)	1.10 (0.94 to 1.28)	0.246
Neutrophil count decreased	228 (9.6)	230 (9.6)	1.01 (0.85 to 1.20)	0.920
Diarrhoea[∇]	232 (9.8)	90 (3.7)	2.62 (2.07 to 3.32)	0[∇]
Anaemia[∇]	163 (6.9)	113 (4.7)	1.47 (1.16 to 1.85)	0.001[∇]
Fatal AE	18 (0.8)	20 (0.8)	0.92 (0.49 to 1.73)	0.787
Primary cardiac event	17 (0.7)	8 (0.3)	2.16 (0.94 to 5.00)	0.06
NYHA class III of IV heart failure and substantial decrease in LVEF[∇]	15 (0.6)	6 (0.2)	2.54 (1.00 to 6.54)	0.044[∇]
Definite or probably cardiac death	2 (<0.1)	2 (<0.1)	1.02 (0.14 to 7.22)	0.984
Secondary cardiac event	64 (2.7)	67 (2.8)	0.97 (0.69 to 1.36)	0.865
Identified automatically from LVEF assessments	50 (2.1)	47 (2.0)	1.08 (0.73 to 1.61)	0.697
Identified by cardiac advisory board	14 (0.6)	20 (0.8)	0.71 (0.36 to 1.41)	0.327

AE, adverse event; LVEF, left ventricular ejection fraction. Grade ≥3 adverse events are not reported if rates < 5% in both treatment arms. ERG calculated p-values for the difference in proportions between treatment arms. Values match published trial[1] and CSR. [∇] indicate significantly ($p < 0.05$) higher incidence rates in pertuzumab compared to placebo.

Grade 3/4 Diarrhoea

While there were no reported diarrhoea-related deaths in the APHINITY trial, the ERG reiterates that severe (grade 3/4) diarrhoea is potentially life-threatening and a source of significant morbidity and impaired health-related quality of life.[64] The ERG also considers that the 6% higher rate of grade 3/4 diarrhoea in the pertuzumab-based arm compared to placebo (Table 9) may potentially attenuate the marginal efficacy gains attributed to pertuzumab in the submitted evidence.

The relative risk of severe diarrhoea was 2.62 (95% CI: 2.07, 3.32). This increased risk of severe diarrhoea supports observations from other pertuzumab trials, including the CLEOPATRA (+3% incidence, RR: 1.56), and PHEREXA (+6% incidence, RR: 1.61) studies.[35, 65] The true difference in effects of diarrhoea could be even greater as duration and recurrence of episodes are not reported in the CS.

Cardiac safety

The company differentiates primary cardiac events from secondary cardiac events based on the severity of symptoms: patients with primary cardiac events had a more severe symptomatology compared to patients with secondary cardiac events. The ERG considers that the absence (primary) or presence (secondary) of a previous cardiac outcome prior to the index cardiac event during the study, including the post-treatment period, should inform the distinction between primary and secondary cardiac events (CS document B, pg. 48). More importantly, the (severe) primary cardiac events were assessed at the end of post-treatment follow-up period, whereas the (less severe) secondary cardiac events were assessed after breast cancer recurrence if recurrence occurred prior to the end of post-treatment follow-up (CS document B, pg. 48). The ERG considers that primary and secondary cardiac events, as defined by the company, should have been assessed at the same time-points.

The CS stated that there was no increase in cardiac-related adverse events such as heart failure in the pertuzumab arm compared to the placebo-based arm (CS document B, section B.2.10.4, pg. 49). This statement is supported citing evidence from three previous trials.[66-68] However, further examination by the ERG revealed no indication that heart failure was included as a study outcome in all three trials. Furthermore, as demonstrated in Table 9, the incidence of New York Heart Association (NYHA) class III or IV heart failure with substantial decrease in left ventricular ejection fraction (LVEF) was three times higher among patients in the pertuzumab-based arm compared to the placebo-based arm (0.6% vs. 0.2%, p=0.04). The ERG recognises that although these rates may be low, these are all new cases within the APHINITY trial given that patients with a history of documented heart failure or systolic dysfunction (LVEF < 50%) were excluded prior to the study (protocol version D, section 4.3, pg. 64). The ERG clinical advisor confirms that there is an association between pertuzumab and heart disease. However, the ERG clinical advisor suggests that cardiac events are not very common in clinical practice, and they are not likely to modify treatment if present.

Cardiac-related adverse events, especially NYHA class III heart failure, were not included in the ERG pre-clarification health economic model submission. Given considerable differences in incidence rates between treatment arms, the ERG considers that the company should have performed a scenario analysis to determine the impact of heart failure on the health economic model. During clarification, the ERG requested total costs, total QALY and ICER values that take cardiac-related adverse events into account (discussed in section 5.2.7.5).

Anaemia

Patients in the pertuzumab-based arm had significantly higher incidence rates of anaemia compared to patients in the placebo-based arm (p=0.001). This is not acknowledged by the company in the CS. According to the ERG clinical advisor, for this patient population anaemia has a considerable impact on health-related quality of life in patients, causing increased tiredness and breathlessness. Anaemia may also have a significant impact on the cardiovascular system as it is a known cause of heart failure. During clarification, the ERG requested total costs, total QALY and ICER values that take anaemia into account (discussed in section 5.2.7.5).

In summary, adverse event rates were slightly higher in those treated with pertuzumab, with more adverse events possibly treatment-related. The most frequently reported adverse event in the pertuzumab arm was severe (grade 3/4) diarrhoea, which was significantly higher than diarrhoeal incidence in the placebo arm. The ERG also notes significantly higher incidence rates of anaemia in the pertuzumab arm compared to placebo. The incidence of NYHA class III or IV heart failure with substantial decrease in left ventricular ejection fraction (LVEF) was three times higher among patients in the pertuzumab-based arm compared to the placebo-based arm. The ERG found moderately higher discontinuation rates for pertuzumab compared to placebo, while this difference was not significant at the 0.05 threshold, it is consistent with the view that adjuvant pertuzumab+trastuzumab combination has a worse safety profile compared to adjuvant trastuzumab in patients with BC.

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

Not applicable to this STA as no indirect comparison or multiple treatment comparison were performed.

4.4 Critique of the indirect comparison and/or multiple treatment comparison

Not applicable to this STA as no indirect comparison or multiple treatment comparison were performed.

4.5 Additional work on clinical effectiveness undertaken by the ERG

Not applicable to this STA.

4.6 Conclusions of the clinical effectiveness section

The CS presents a reasonable quality systematic review of the clinical effectiveness of adjuvant pertuzumab in combination with trastuzumab and chemotherapy. The ERG agrees with the company's

decision to include the APHINITY trial as the key evidence, and notes that the comparator and intervention reported in this trial are appropriate and consistent with the NICE final scope. IDFS and DRFI were additional outcomes in the trial which were not listed in the NICE scope, but were approved by the ERG clinical advisor. The population in this trial (n=4806) addresses the decision problem which is focussed on eBC patients with a high-risk of recurrence after surgical treatment. However, the ERG is concerned about the emphasis of node-positive (base case) and hormone receptor-negative (additional scenario) patients as the target population, whereas other high-risk subgroups (such as histological grade 3 and tumour size > 5cm) were not considered in the company decision problem.

The ERG notes an amendment to the original protocol of the APHINITY trial (protocol A) which was implemented after 3655 participants had been randomised in order to enrol only node-positive patients (protocol B). The ERG suggest that protocol B is effectively a second trial in which node-positive patients were randomised to the pertuzumab-based arm or the control arm (placebo-based), hence there is no immediate concern of bias.

The efficacy analysis of the APHINITY trial revealed that pertuzumab was just marginally better than placebo for preventing recurrence of breast cancer and/or death (HR 0.82, 95% CI 0.67 to 1.00). The ERG is concerned that this difference may not be clinically meaningful. Analyses of the nodal subgroups revealed a slightly less marginal difference in IDFS rates between pertuzumab and placebo in node-positive patients (HR 0.77, 95% CI 0.62 to 0.96), whereas no statistically significant difference was detected in node-negative patients (HR 1.13, 95% CI 0.68 to 1.86). However, following clarification request for additional stratification of the node-positive subgroup, the ERG are concerned that adjuvant pertuzumab may only be effective in eBC patients with 10 or more cancer cells in the loco-regional lymph nodes. Analyses of the hormone receptor subgroups reveal no statistically significant benefit of pertuzumab over placebo in hormone receptor-negative (HR 0.76, 95% CI 0.56 to 1.04) or hormone receptor-positive patients (HR 0.86, 95% CI 0.66 to 1.13).

The ERG questions the safety profile of pertuzumab, with significantly larger proportions of patients in the pertuzumab-based arm experiencing grade 3 or higher adverse events compared to patients in the placebo-based arm (64.2% vs. 57.3%, $p < 0.001$). Of note, patients in the pertuzumab-based arm were more likely to develop grade 3 or higher diarrhoea (9.8% vs. 3.7%, $p < 0.001$), anaemia (6.9% vs. 4.7%, $p=0.001$) and symptomatic heart failure (0.6% vs. 0.2%, $p=0.04$), compared to the placebo-based arm.

In summary, the ERG notes that the APHINITY trial was not powered to detect subgroup differences. The ERG was unable to rule out any spurious interactions between subgroup variables. Whilst there is evidence of a treatment effect among the nodal status subgroups, the ERG believes that the apparent treatment interactions with hormone receptor status and menopausal status may be artefact of the interaction with nodal status for which there is slightly stronger evidence. The ERG considers that claims of treatment benefit (marginal) should be balanced against the safety of adjuvant pertuzumab in combination with trastuzumab and chemotherapy.

5 COST EFFECTIVENESS

This chapter reviews and appraises the evidence on cost-effectiveness of pertuzumab for the adjuvant treatment patients with HER2-positive breast cancer patients. Section 5.1 offers a critique of the company's systematic review. Section 5.2 provides a summary and critique of economic aspects of the CS. Section 5.3 presents the ERG's suggested base case estimates and additional work carried out by the group. Lastly, section 5.4 provides the conclusions of the cost-effectiveness section.

The main focus of this critique is the analysis pertaining to the node-positive population. This is presented as the main analysis by the company and is given in the main body of the CS. A short critique and the summary results are also presented for the analysis relating to the hormone receptor-negative sub-population. This can be found in the appendix 3 of this report. For completeness, the ERG also presents the results of the economic analysis for the ITT population (see appendix 4), although this analysis is not described or presented in the CS.

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

The main objective of the company's review of the cost-effectiveness evidence, as stated in the CS appendices document, was to identify and consider all published economic evaluations assessing health economic endpoints in the adjuvant (and neoadjuvant) treatment of eBC. Evaluations targeted included, cost-effectiveness analyses, cost-benefit analyses, cost minimisation analyses, budget impact analyses and burden of disease analyses.

Two additional reviews were carried out by the company to identify available evidence on i) HRQoL and ii) use of health care resources and costs. The review of HRQoL aimed to identify published studies reporting and/or evaluating HRQoL evidence, with a particular focus on preference-based HRQoL (i.e., utilities). The review of resource use and costs aimed to identify studies published in the last five years presenting novel cost and resource use data relevant to the developed economic model.

The methods employed to identify evidence in all three reviews are summarised and appraised below. Results and use of evidence drawn from the reviews is also discussed in relevant parts 5.2.7 and 5.2.8 of Section 5.2 below.

5.1.1 Search strategy

Searches combining terms for cost-effectiveness/HRQoL with eBC and intervention were undertaken on 20th November 2014 and were updated (with language and publication date restrictions) on 20th November 2017 (see CS appendix G). Cost-effectiveness and HRQoL searches were undertaken

together. A range of appropriate sources was searched. For most concepts, the search appears to be reasonably comprehensive, despite the choice of terms not always being ideal or clearly reported (for example, the MeSH heading for Breast Neoplasms does not appear to have been exploded in the MEDLINE searches). However, the inclusion of intervention terms in the search would have resulted in some HRQoL studies of metastatic BC being missed. The ERG therefore undertook a targeted search for HRQoL studies of metastatic BC. This additional work is described in section 5.1.4.

A separate search for cost and resource use, restricted to studies undertaken in the UK and published in the last five years, was undertaken on 26th October 2017 (see CS appendix I). Sources and search terms were appropriate to a search for UK studies, which reflects the eligibility criteria for this systematic review. Additional searches were undertaken to improve the comprehensiveness of the search. The search was constructed appropriately to include the management of recurrence and/or metastatic disease in the longer-term.

5.1.2 Inclusion criteria

The eligibility criteria for each review, as stated in the CS (appendices G, H and I), are provided in Table 10, Table 11 and Table 12 below.

Table 10. Cost-effectiveness literature review: Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Patients with BC • Adjuvant or neoadjuvant therapies • Health economic evaluation studies • Outcome of interest such as cost per QALY gained, cost per life year gained or any other health economic endpoint	• Null entries, duplicates or abstracts that are reported elsewhere • Non-human • Not patients with BC • No outcome of interest such as costing studies where denominator could not be defined

BC, breast cancer; QALY, quality-adjusted life year.

Table 11. HRQoL literature review: Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Patients with BC • Adjuvant or neoadjuvant therapies • Health economic evaluation studies • Outcome of interest: QoL data which can be mapped to the EQ-5D • Interventional or observational studies reporting data from at least one HRQoL instrument of interest (e.g. EQ-5D)	• Null entries, duplicates or abstracts that are reported elsewhere • Non-human • Not patients with BC • No QoL outcome which can be used to estimate patient utility

BC, breast cancer; EQ-5D, EuroQoL 5-Dimensions; HRQoL, health-related quality of life; QoL, quality of life.

Table 12. Cost and resource use literature review: Inclusion and exclusion criteria

Domain	Inclusion Criteria	Exclusion Criteria
Population	• Patients with BC receiving treatment at the adjuvant stage (i.e. after initial surgery) or later in the disease pathway (i.e. for metastatic disease)	• Patients without BC • Patients with BC receiving neoadjuvant treatment
Intervention(s)	• Any or none	• -
Comparator(s)	• Any or none	• -
Outcomes	• Direct cost or resource use data collected within the last ten years • Data must be relevant to the UK NHS and PSS, and of relevance to an economic model of pertuzumab as adjuvant treatment for HER2-positive eBC	• Studies not presenting relevant cost/resource use data for the population of interest (e.g. presenting indirect costs only), or studies presenting data collected more than ten years ago
Study design/ publication type	• Any original research study published as a journal article or HTA submission in 2012 or later, or as a congress abstract in 2015 or later, including: • Randomised controlled trials • Budget impact models • Cost-of-illness studies • Comparative economic evaluations such as cost-effectiveness, cost-utility, cost-benefit, cost-consequence or cost-minimisation analyses	• Publications other than SLRs not reporting original research • Journal articles or HTAs published prior to 2012, or congress abstracts published prior to 2015 • Case reports/case series
	• Systematic reviews and meta-analyses will be included at the title/abstract screening stage and used for the identification of additional primary studies not identified through other searches. They will then be excluded during the full-text review stage.	
Geographic setting	• UK	• Regions outside of the UK or, in the case of pooled data, where data from the UK has not been presented separately
Other considerations	• Full-text or abstract in English • If the full-text is non-English, the abstract must contain enough data to be eligible for inclusion in its own right • Human subjects	• Non-English language articles • Studies not on human subjects

HTA, Health Technology Assessment; NHS, National Health Service; PSS, Personal Social Services; SLR, Systematic Literature Review; UK, United Kingdom.

The inclusion/exclusion criteria were, in general, appropriate for the purpose of the reviews. However, as mentioned below, the inclusion of the terms "adjuvant or neoadjuvant therapies" in the inclusion/exclusion criteria used in the review of HRQoL studies are likely to have led to exclusion of studies on metastatic breast cancer. This potential issue, and additional work undertaken by the ERG to alleviate it, are described in section 5.1.4 below.

5.1.3 Included studies

The systematic literature reviews (SLRs) carried out by the company included 65 studies providing information on cost-effectiveness, 21 studies related to HRQoL and five studies giving information on healthcare resource use and costs. However, only a small number of these studies was used in the presented analysis.

In relation to studies identified through the cost-effectiveness SLR, the company stated that none of the 65 included studies were relevant, therefore they are not explained further in the submission. The ERG concurs that the identified studies do not address the exact decision problem that this technology assessment is concerned with and agrees that a de novo economic analysis is necessary.

Similarly, none of the 21 included studies related to HRQoL was used in the CS as, according to the company, these studies did not report utility values that could be considered for direct use in the cost-effectiveness analysis. However, evidence from four published studies (Lloyd et al.,[69] Hedden et al.,[70] Lidgren et al.,[71] and Paracha et al.,[72]), which were not among the 21 included studies, was used in the HRQoL analysis reported in the submitted model.

The five studies identified and included through searches for health care resource use and cost evidence do not appear to have been used in the company's analysis. These studies provide some information about treatment costs (e.g., for chemotherapy and radiotherapy) and primary and secondary care resource use (e.g., general practitioner, nurse and hospital doctor appointments). Costs in the CS were calculated in a fairly robust way, using evidence on resource use accepted in previous STAs and unit cost values from national sources, hence the ERG believes that use of health care resource use and cost related evidence from the literature was not necessary.

5.1.4 Conclusions

The reviews presented in the CS identified a number of studies meeting the inclusion criteria, though most of these studies do not appear to have been used in the company's analysis. The company suggests that none of the studies on cost-effectiveness currently available in the literature provide a comprehensive answer to the decision problem concerning this appraisal. The ERG considers this statement to be valid and believes that the fact that identified cost-effectiveness studies were not used in the analysis does not impair the submitted analysis.

While 21 studies providing some evidence on HRQoL were found, much of this evidence is not available in the form of preference-based HRQoL (utility) values, which are required for the cost-effectiveness analysis. Although the availability of EuroQol 5D (EQ-5D-3L) responses collected as

part of the APHINITY trial alleviates the need for drawing HRQoL evidence for eBC from heterogeneous studies in the literature, utility values were required for subsequent (metastatic) states, for which APHINITY trial data are not available. For such states, the company has used estimates from the study by Lloyd et al.[69] in their base case analysis, and others (Hedden et al.,[70] Lidgren et al.,[71] and Paracha et al.,[72]} in scenario analyses. The studies by Lloyd et al.[69] and Paracha et al.[72] do not appear to have been identified through the SLRs, the study by Hedden et al.[70] is listed amongst the identified cost-effectiveness studies (but not amongst the included studies on HRQoL), while the study by Lidgren et al.[71] is listed amongst the studies excluded from the final set of cost-effectiveness and HRQoL studies.

The fact that the study by Lloyd et al.,[69] which focuses on metastatic BC was not identified, suggests that the inclusion of search terms such as 'adjuvant' may have impaired the ability to identify studies reporting HRQoL values for metastatic states. In addition, a number of articles were excluded by the company due to unavailability of the publications' full text. In response to these issues, the ERG:

i. undertook an additional focussed search of MEDLINE combining terms for BC, metastatic, HRQoL and HRQoL measures. A UK search filter developed by NICE was then applied and results with and then without this filter were screened.[73] This search retrieved 99 articles
ii. searched for the full text of full articles that were not found by the company by checking the availability to the ERG of each full article listed in CS appendix G table 21 that had the reason for exclusion as 'Could not find publication'. Thirty-eight publications were checked, and nine of these publications were found locally or obtained quickly via the local document supply service. Details are provided in appendix 1
iii. identified articles related to Lloyd et al. through the 'related article search' feature in PubMed. This process retrieved 76 articles.

Of the identified publications, 36 were deemed to be potentially relevant on the basis of their title and abstract. Upon examination of their full text, 32 were excluded, most frequently due to not reporting preference based HRQoL values, not relating to the population of interest or being published in a format that does not provide adequate information (typically conference abstracts). Information in the remaining four papers was used in additional analyses (see Section 5.2.7).

In relation to health care resource use and costs, as mentioned above, the company's searches resulted in five included studies. Details about these studies, their aims, reported costs and resource use and applicability of the reported information to the UK clinical practice were given in the CS appendices, though no further information was provided on whether and how this evidence has been used in the

CS. Given that the cost calculations in the CS are based on robust evidence from previous technology appraisals and widely used unit cost values, the ERG believes that not using cost-related evidence from the literature in the submission has not been detrimental for the analysis.

5.2 Summary and critique of company's submitted economic evaluation by the ERG

As part of their submission to NICE, the company made available a detailed description of their economic analysis and a cohort state transition model developed in Microsoft Excel®. A combined summary and critique of this evidence is presented below. Two updated models, based on the original cohort state transition model and submitted in response to requests for clarifications, were also made available by the company later dates.

5.2.1 NICE reference case checklist

The ERG has undertaken an evaluation of the CS in relation to the NICE Reference Case. The findings are summarised in Table 13.

Table 13. NICE Reference Case Checklist Table

Element of health technology assessment	NICE Reference Case	Does the submission adhere adequately to the Reference Case?
Defining the decision problem	As detailed in the scope developed by NICE	Yes. The anticipated market authorisation for the adjuvant use of pertuzumab is in patients with HER2-positive eBC at high risk of recurrence (i.e. node-positive or hormone receptor-negative). Evidence from the APHINITY study confirms that these subgroups are at high-risk of recurrence and the importance of underlying tumour biology when considering treatment options. The economic analyses include node-positive subgroup as the base case and the hormone receptor-negative subgroup as an additional scenario.
Comparator(s)	As listed in the scope developed by NICE	Yes
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes

Perspective on costs	NHS and PSS	Yes
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes
Synthesis of evidence on health effects	Based on systematic review	Yes. A systematic review was conducted. Key information is drawn from data collected in the APHINITY trial. Other relevant information (not collected in the APHINITY trial) is taken from other trials and the literature.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Yes
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes

5.2.2 Model structure

The economic model developed as part of the CS has a lifetime horizon and comprises of seven health states: (i) 'IDFS – on treatment', (ii) 'IDFS – off treatment', (iii) 'Non-metastatic recurrence', (iv) 'Remission', (v) 'First-line treatment for metastatic disease (First-line mBC)', (vi) 'Subsequent treatment lines for mBC (Second+ line mBC)', and (vii) 'Death'. The model's cycle length is one month. A half-cycle correction has been applied in the calculations. The company's representation of the model structure is given in Figure 10 (replicating figure 8 in the CS).

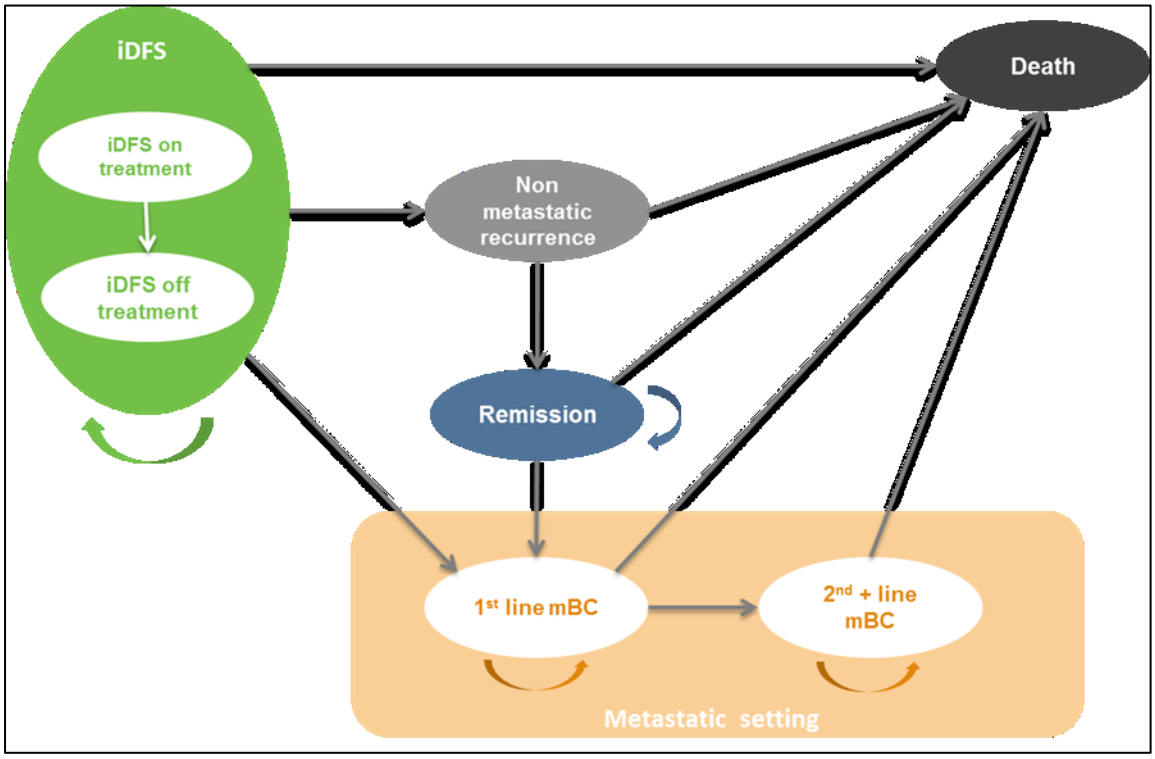


Figure 10. Model structure schematic for HER2-positive breast cancer

IDFS, invasive disease-free survival; mBC, metastatic breast cancer.

Patients enter the model in IDFS, which consists of the 'IDFS on treatment' and 'IDFS off treatment' health states. In 'IDFS on treatment', patients receive a maximum of 18 cycles of pertuzumab + trastuzumab + chemotherapy in the intervention arm or a maximum of 18 cycles of trastuzumab + chemotherapy in the comparator arm.

Once patients complete or discontinue their assigned regimen, they transition to the 'IDFS off-treatment state'. Patients can either remain in this state, die (i.e. move to state 'Death') or transition to other states. Transition to other (non-death) states occur as a result of either metastatic or non-metastatic disease recurrence. The 'Non-metastatic recurrence' state characterises any non-distant recurrence, including locoregional and contralateral recurrences. These are assumed to be similar in

terms of the associated resource use, HRQoL and mortality. Non-metastatic recurrence is a 'tunnel state', with patients entering this state scheduled to undergo 12 months of additional adjuvant therapy. As soon as they complete their therapy, all patients are assumed to be in remission and move into the 'Remission' state. Once the 'Remission' state, patients may die or experience a further recurrence. At this stage, any further recurrences are assumed to be metastatic, thus patients in the 'Remission' state experiencing recurrence would progress to the first of two metastatic health states (First-line mBC).

Entry to 'First-line mBC' (either through experiencing metastatic recurrence while in the 'IDFS' health states or through experiencing distant metastasis while in 'Remission') is followed by first-line treatment for mBC. Patients in this state may experience disease progression, which is manifested as transition to the progressed metastatic health state (Second+ line mBC), or die. Patients in Second+ line mBC can remain in this state or move to the absorbing state 'Death'. Across the model, patients can transition to death from any health state.

In general, the ERG believes that the type and structure of the developed model is appropriate for the purposes of the decision considered in this appraisal. The ERG deems the pathway represented in the model is in line with expectations about the clinical progression of the disease and believes that the structure of the model is suitable to quantify and appraise the costs and health outcomes associated with the compared treatments options. To the best of the ERG's knowledge, the company's statement that, *"the chosen approach is consistent with previous NICE technology appraisals in this disease area (TA107 and TA424)"* is valid.

5.2.3 Population

The population of interest, as stated by the company in the CS is *"people with HER2-positive eBC at high risk of recurrence"*. The economic analyses provided as part of the submission relate to two subgroups:

- Node-positive patients (presented by the company as the main analysis)
- Hormone receptor-negative subgroup (presented as an additional scenario).

The cohort of node-positive patients analysed in the economic model has a starting age of 51 years (53 years in the hormone receptor-negative subgroup). These are the median age values of participants in the corresponding subgroups in the APHINITY trial. It is worth noting that this population is narrower than that specified in the NICE final scope of this appraisal.[5]

5.2.4 Interventions and comparators

The intervention assessed in the analysis is adjuvant pertuzumab in combination with trastuzumab and chemotherapy (abbreviated as PHC). This is compared to standard adjuvant therapy without pertuzumab for HER2-positive BC (trastuzumab in combination with chemotherapy) (abbreviated as HC). This matches the intervention and comparator specified in the NICE final scope for this appraisal.

5.2.5 Perspective, time horizon and discounting

The economic analysis presented in the CS has been undertaken from the NHS and PSS perspective; this agrees with the guidelines stipulated in the NICE Reference Case.[74] The analysis is carried out over a 52 year time horizon, which effectively represents a lifetime horizon. By the end of this time horizon, less than 1% of the patients in the model remain alive. In line with the NICE Reference Case, costs and health effects are discounted at 3.5% per year.

5.2.6 Treatment effectiveness and extrapolation

In the submitted analysis, treatment effectiveness evidence and extrapolation methods were used to model transitions within and between IDFS and 'post-recurrence' states.

5.2.6.1 Modelling of IDFS states

IDFS health states capture the period of time during which patients remain disease-free and facilitate the calculation of cost-effectiveness outcomes (cost, survival and QALYs) during this period.

The company took an unusual approach to modelling IDFS states. Using a piece-wise approach, the analysis divides the 52-year period into three phases (or time periods). The first phase models IDFS events in the first four years, using a parametric curve fitted independently to both arms on the basis of the observed data from the APHINITY trial. The second phase, modelling years four to ten, adjusts the parametric curve, which was supported by external data. The final phase, from years 10 to the end of the time horizon (year 52), further adjusts the extrapolation, assuming that 90% of patients are no longer at risk of an IDFS event other than death. Each modelled phase is critiqued in turn below.

<u>Phase 1</u>

The company fitted a range of parametric models to the observed IDFS data for the node positive population of the APHINITY trial. The parametric models assessed by the company were fitted to all observed IDFS data (i.e. from month 0 until end of follow-up); however, in the economic model, an option is available to begin by using the non-parametric KM data up to a certain point in time and begin the parametric fit after this point. An assessment of proportional hazards was performed through

the comparison of the log cumulative hazards of each trial arm, shown in figure 9 of the CS. The ERG agrees with the company's conclusion of that the hazards were not proportional and that the parametric models should be fitted independently to each arm. This is further supported by the company's investigation of the HR at different years of follow-up, shown in table 20 of the CS, where the HR is not constant across the first four years of the APHINITY trial.

In the same section, the company mentions how the pattern of relapse varies according to a patient's hormone receptor status; however, it is unclear to the ERG why the company included this here. According to a confidential board report, provided by the company to the ERG, patients with a positive hormone receptor status are likely to experience events later and beyond the observed trial follow-up. The ERG agree that hormone receptor status is a risk factor in disease recurrence, however, the company posits that, as a result, the KM curves are expected to separate further over time. Since hormone receptor status was a stratification factor, and it was well balanced across the two treatment arms, this statement assumes pertuzumab to be effective in the hormone receptor positive population, which is not yet supported by strong evidence. The ERG were unsure why, if the company believe this to be true, the economic analyses submitted by the company only include node positive and hormone receptor-negative populations. The ERG were also unclear about the company's conclusion of this section, as the company referred to non-constant hazard rates in the node-positive population, rather than hazard ratios in the hormone-receptor positive population.

To assess the company's claim for further separation of the two survival curves over time, the ERG examined Figure 11, which was obtained from the node positive subpopulation of the BCIRG-006 trial. Whilst there are minor differences between the baseline populations and definitions of an event between APHINITY and BCIRG-006, the trials are broadly similar, and it is apparent that any increase in separation beyond 48 months is minimal, and certainly ceased by 72 months for the anthracycline (AC-T) and anthracycline plus trastuzumab (AC-TH) arms. The ERG also examined the hormone receptor-positive subgroup of the HERA trial (Figure 13, replicating figure 2C in Cameron et al.[38]). Here the KM curves appear to stop diverging and possibly begin to converge from approximately five years onwards. Hence, the ERG disagrees with the company's claim that the survival curves will separate further over time.

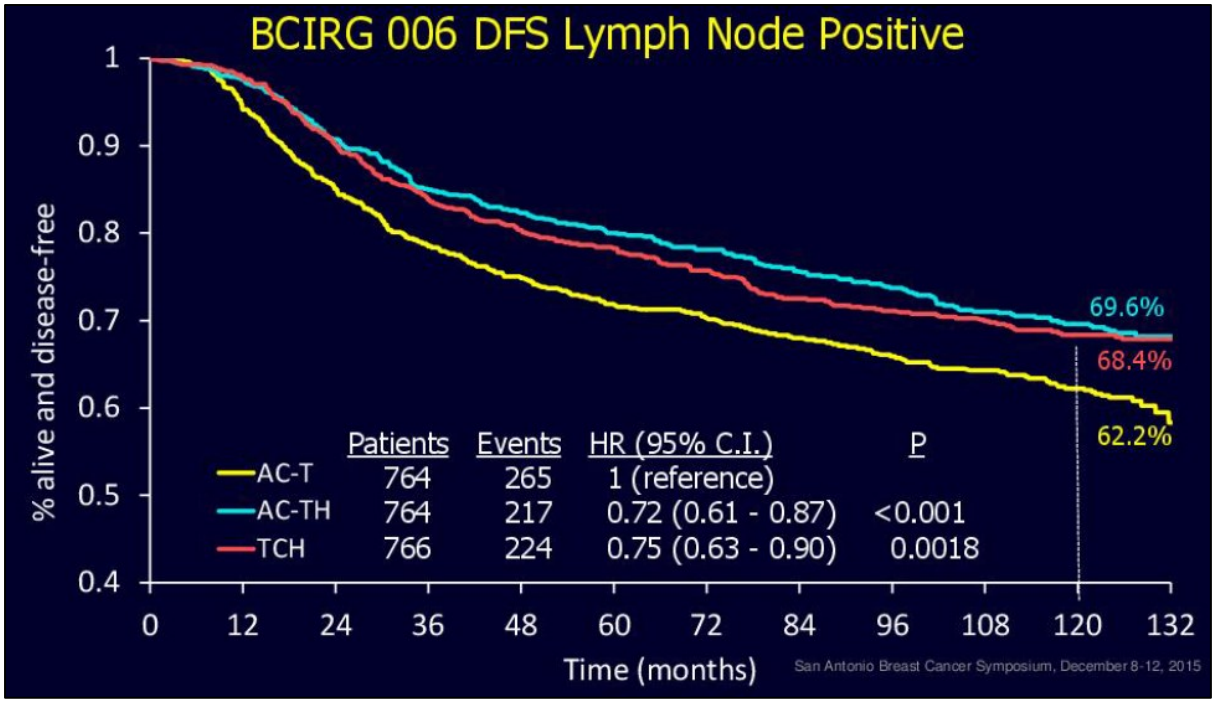


Figure 11. Survival curves from the node positive subpopulation of the BCIRG-006 trial.

Related to this is the point about the duration of pertuzumab's effect, which is brought up in the text under Phase 2 (years 4 to 10) in the CS. In their base case analyses, the company assume that the incremental treatment effect of pertuzumab will be maintained for seven years and then diminishes linearly (i.e., 'wanes'), up to the point that it completely ceases at 10 years. This was modelled by using the hazard rates from the independent parametric models fitted to each arm of the APHINITY trial for the first seven years. From year seven onwards, the hazard in the pertuzumab arm was gradually reduced to match that of the placebo arm, becoming identical at year 10 and beyond. However, the company's justification for this prolonged treatment effect duration is not adequately substantiated. The ERG is unclear how the hazard ratios presented by the company from the long term follow-up of the HERA and BCIRG-006 trials are directly relevant to the duration of treatment effect.

The company's specification of the waning effect results in the divergence of the survival curves until approximately nine years (109 months), as shown in Figure 12. The ERG have not found any evidence to support such a long effect. As already seen in Figure 11 and Figure 13, of the BCIRG-006 and HERA trials, respectively, there is no widening of the separation beyond five to six years between trastuzumab and its comparators. As the treatments considered in the APHINITY trial are both HER2 inhibitors, the ERG believes their long term effects to be similar (i.e., minimal further divergence of the KM curves beyond the observed period).

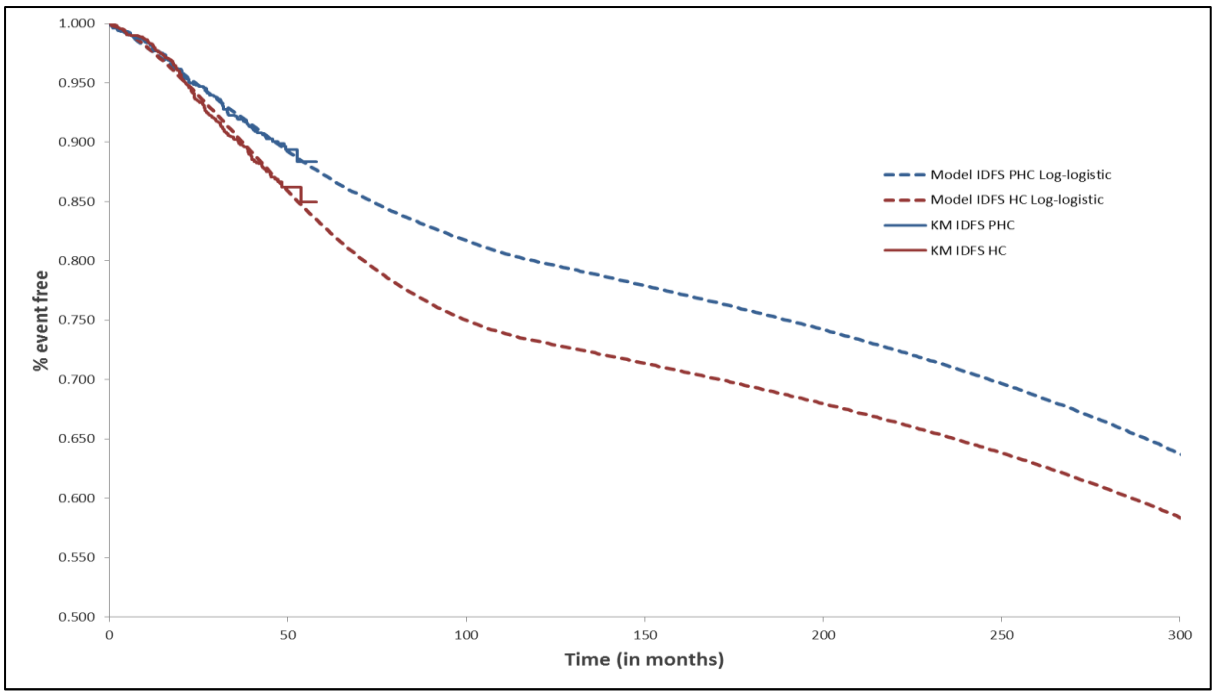


Figure 12. Company's base case predicted IDFS extrapolation

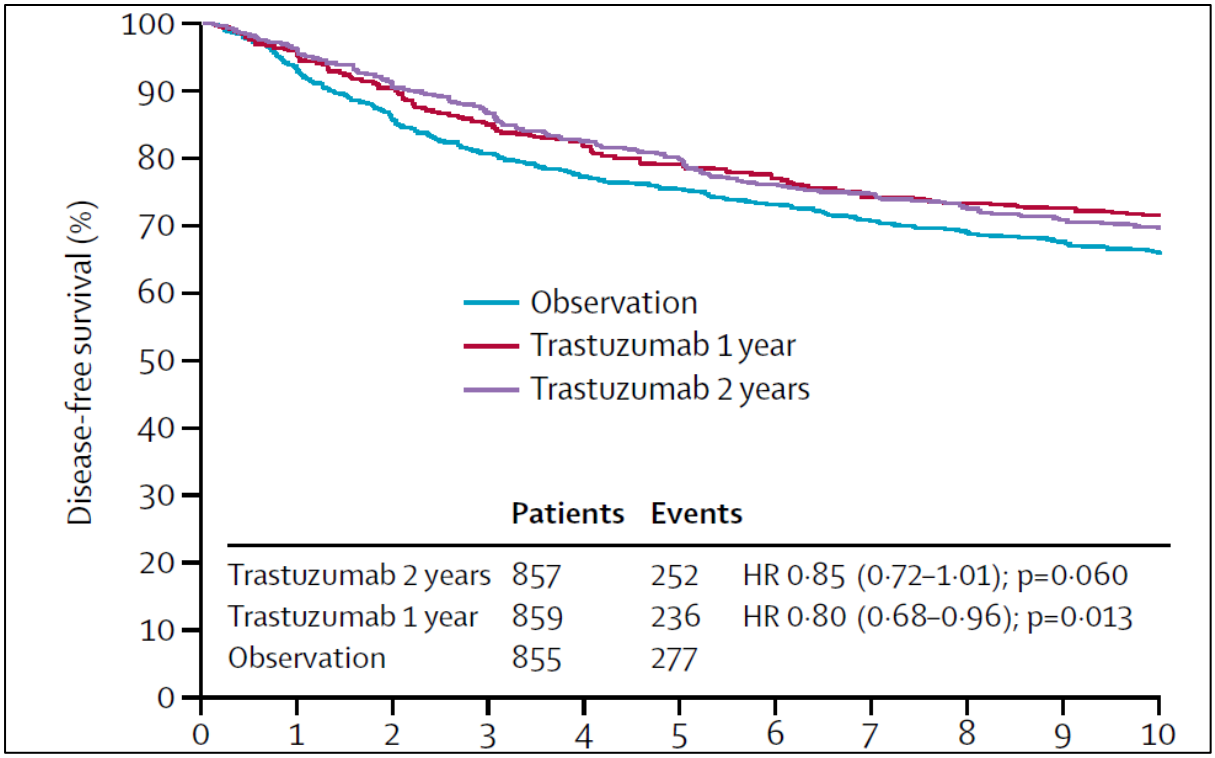


Figure 13. DFS KM Plot of hormone receptor positive population from HERA trial

The ERG also examined other pertuzumab trials to establish a plausible treatment effect duration. The PHEREXA[65] study, which assessed second-line trastuzumab and capecitabine with and without pertuzumab in patients with HER2 positive mBC, showed a widest separation of progression free survival (PFS) curves at roughly 17 months in favour of pertuzumab (Figure 14). This benefit was not sustained and the KM curves of both arms overlapped from 28 months. In the CLEOPATRA[68] study, which investigated docetaxel and trastuzumab with and without pertuzumab in HER2 positive metastatic breast cancer patients, the gap between the curves is widest at around 20-30 months, at which point they appear to slowly converge for the remainder of the follow-up period (Figure 15).

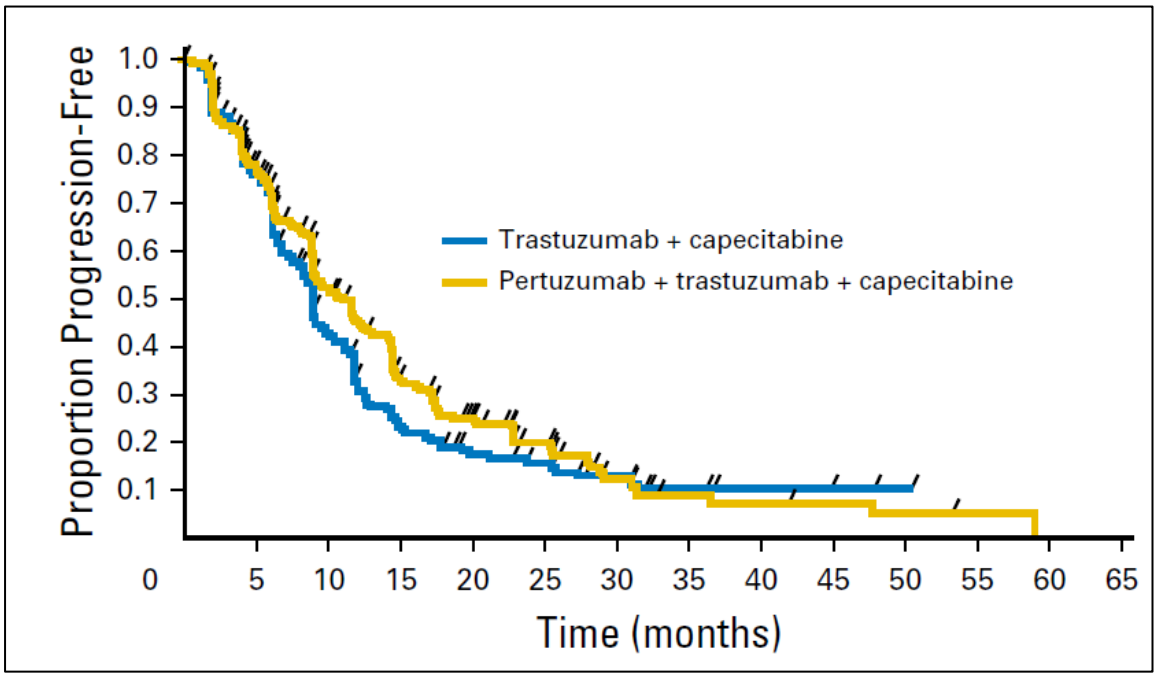


Figure 14. Progression Free Survival Kaplan Meier - PHEREXA Study

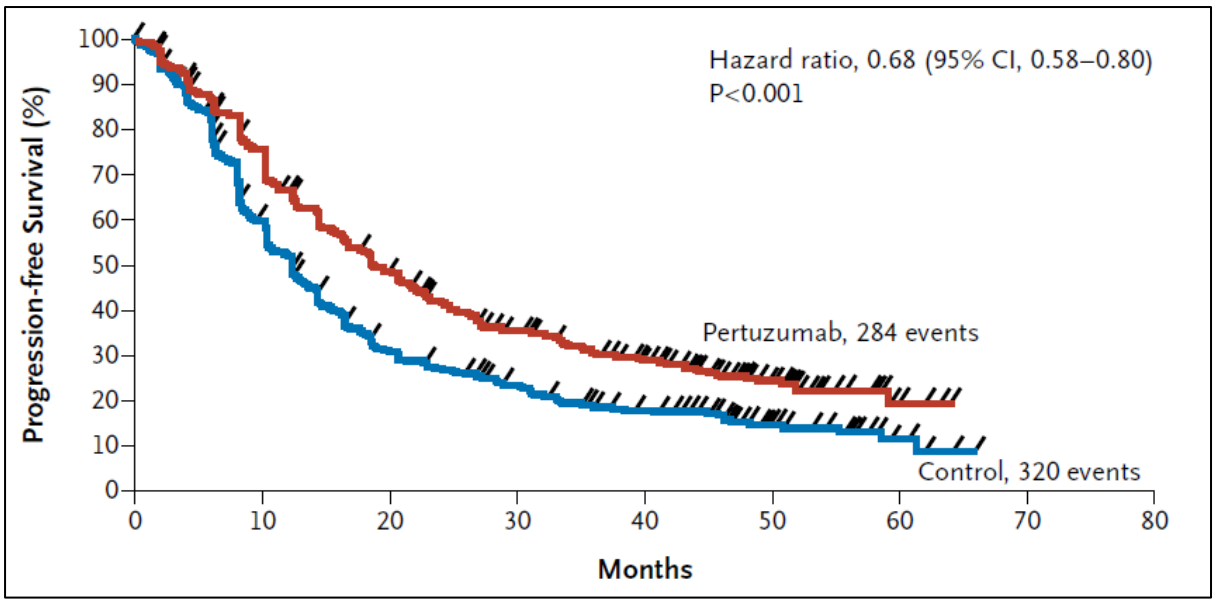
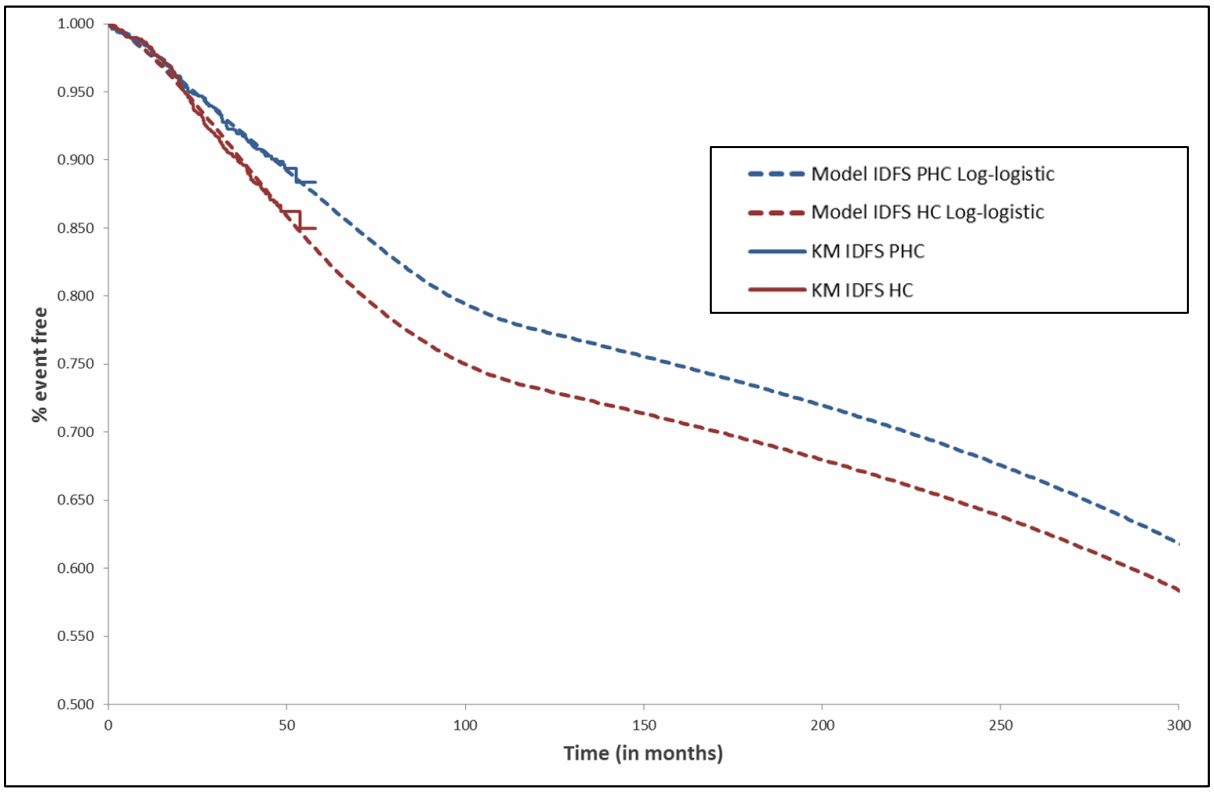


Figure 15. Progression Free Survival Kaplan Meier - CLEOPATRA study

The company also cite the neoadjuvant appraisal of pertuzumab for HER2 positive breast cancer, stating that a seven year treatment duration was used and accepted by the relevant ERG and committee (TA424).[75] The present ERG notes that, in TA424,[75] the treatment effect ceased at seven years, rather than beginning to wane at this time, as in the company's base case analysis in the present CS. Given the above, the ERG does not agree with the company's reasoning that a longer course of treatment in this adjuvant setting (one year) compared to the neoadjuvant setting) (12 weeks) justifies the gradual waning effect applied from seven to 10 years.

Based on the observed data from the trials discussed above, the ERG prefers to implement the treatment effect waning adjustment from 48 months, with all treatment effect being nullified at 84 months (shown in Figure 16). This allows limited widening of the KM curves from 48 month and 78 months, which is supported by the evidence considered. To account for the inherent uncertainty around the duration of treatment effects, the ERG undertook alternative adjustments as part of their sensitivity analyses.



Demonstrating change to IDFS of ERG preferred duration of treatment effect compared to company base case (overlaid onto Figure 12)

The company's choice of parametric curve for IDFS extrapolation is largely guided by the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC). Whilst this approach is commonly taken and is in line with DSU guidance, the company state that they did not consider the BIC values in their decision-making process due to taking a 'frequentist approach'. It must be noted that, mathematically, AIC and BIC are very similar, both helping the user to select a parsimonious model, with BIC imposing a stronger penalty for the inclusion of additional parameters when comparing models. BIC is not a Bayesian approach in the common use of the term (e.g., an approach that combines prior information with likelihoods to obtain posterior distributions) and is routinely used to appraise 'frequentist' models. The ERG agree that AIC values should be prioritised over BIC, but find the argument about not using the BIC values potentially misleading.

The AIC/BIC values are presented by the company and reproduced in Table 14 (corresponding to Table 12 in the CS). The AIC values suggest that the exponential distribution is the most parsimonious fit to the data in the pertuzumab arm, though none of the parametric models offer strong evidence of unsuitability (difference > 10).[76] The log-logistic is the best fitting model to the placebo arm, but it is apparent to the ERG that only the exponential can be classified as a significantly worse fit and so unsuitable for extrapolation.

Table 14. AIC and BIC values for parametric models fitted to full observed data from APHINITY

	AIC		BIC	
	Pertuzumab + trastuzumab + chemotherapy arm	Placebo + trastuzumab + chemotherapy arm	Pertuzumab + trastuzumab + chemotherapy arm	Placebo + trastuzumab + chemotherapy arm
Exponential	1,175.6 (1)	1,384.9 (6)	1,180.9 (1)	1,390.2 (4)
Weibull	1,176.3 (3)	1,374.8 (2)	1,186.9 (3)	1,385.5 (2)
Log-normal	1,182.0 (6)	1,379.5 (4)	1,192.6 (5)	1,390.1 (3)
Gamma	1,178.3 (5)	1,376.4 (3)	1,194.2 (6)	1,392.4 (6)
Log-logistic	1,176.2 (2)	1,374.2 (1)	1,186.8 (2)	1,384.8 (1)
Gompertz	1,176.7 (4)	1,380.1 (5)	1,187.4 (4)	1,390.7 (5)

The company conclude that the best fitting model across both arms is the log-logistic, and acknowledge that the AIC/BIC values only indicate goodness-of-fit to observed data, and do not inform on the accuracy of any predictions or extrapolations.

The ERG believes that there are a range of plausible parametric models, most notably the generalised gamma which is no worse a fit to the observed data for either arm, compared to the log-logistic model. This was confirmed through further ERG investigation of the fitted hazard and cumulative hazards (clarification C2), where there was little to distinguish between the generalised gamma and log-logistic models. Given this, the ERG explored the effect of these two distributions in sensitivity analyses. However, the ERG accepts the suitability of the log-logistic and maintains its use in their base case analysis.

The accuracy of their parametric models to the observed data was assessed on the basis on predictions at 36 and 48 months for both arms (Table 15, corresponding to table 22 in the CS). The ERG noted that the quoted KM results are not identical to the KM data appearing in the company's economic model, though the fitted parametric model results do appear identical. Furthermore, neither of these match identically to the quoted 3 and 4 year figures in the company's clinical effectiveness summary. For example, the 3 year IDFS for the node positive patients receiving pertuzumab was given as 92.0% (in page 35 of the CS), 91.88% (in table 22 in the CS), or 91.92% (in the submitted economic model). For the same patients from the placebo arm, the 'observed' IDFS were 90.2%, 89.91% or 90.08%, respectively. The ERG notes this inconsistency and the possibility of different versions of the APHINITY data being used for different analyses. The ERG was not able to assess the possible consequences of this inconsistency, however, given the fact that the differences are minimal, the ERG do not expect this to have a meaningful impact on the economic results.

Table 15. IDFS events at 36 and 48 months

Timepoint	Parametric function	Pertuzumab + trastuzumab + chemotherapy	Placebo + trastuzumab + chemotherapy	Pertuzumab + trastuzumab + chemotherapy vs Placebo + trastuzumab + chemotherapy	Δ vs KM data	
					Pertuzumab + trastuzumab + chemotherapy	Placebo + trastuzumab + chemotherapy
36 months	KM data	91.88%	89.91%	1.97%	-	-
	Exponential	92.10%	89.85%	2.26%	0.22%	-0.06%
	Weibull	92.24%	90.34%	1.90%	0.36%	0.43%
	Log-normal	92.03%	90.01%	2.02%	0.15%	0.10%
	Gamma	92.25%	90.26%	1.98%	0.37%	0.35%
	Log-logistic	92.21%	90.27%	1.94%	0.33%	0.36%
	Gompertz	92.29%	90.43%	1.86%	0.41%	0.52%
48 months	KM data	89.65%	86.46%	3.19%	-	-
	Exponential	89.65%	86.74%	2.91%	0.00%	0.28%
	Weibull	89.54%	86.34%	3.20%	-0.11%	-0.12%
	Log-normal	89.79%	86.67%	3.12%	0.14%	0.21%
	Gamma	89.54%	86.39%	3.15%	-0.11%	-0.07%
	Log-logistic	89.56%	86.35%	3.21%	-0.09%	-0.11%
	Gompertz	89.53%	86.34%	3.19%	-0.12%	-0.12%

As expected from the similar AIC values and fitted cumulative hazard plots, the models all produce very similar predictions of IDFS. All overestimate 36 month IDFS, and most underestimate 48 month IDFS. The log-normal is the best predictor of 36 month IDFS and the generalised gamma and log-logistic predict 48 month IDFS equivalently well. The ERG agree with the company's statement that the differences in absolute fit of the parametric fit function extrapolations at the 36 and 48 month timepoints are negligible. The ERG requested the updated observed rates for IDFS (clarification C3) be presented by the company to compare the predictions made by the different parametric models, however, the company declined, stating updated efficacy data would only be available at the next planned interim analysis (middle of 2019).

A careful choice of parametric model is required, as this influences the whole IDFS extrapolation and other health states. However, the assumptions behind the parametric models do not appear to have been assessed in depth. For example, fitting exponential models assumes constant hazard rates in both arms, a consequence of which is proportional hazards. Similarly, a Weibull model assumes the hazard is either monotonically increasing or monotonically decreasing. The ERG do not believe either of these are biologically plausible, thus considering these distributions appears to be unnecessary.

A comparison of IDFS estimates to external sources of data would be highly useful for validation purposes. Given that such a comparison was not available in the CS, the ERG compared the company's base case IDFS prediction with those observed in other trials in Table 16. On the whole,

the model fitted by the company appears to follow a similar pattern to that observed in the BCIRG-006 trial.

Table 16. Comparison of IDFS estimates to external sources of data

Source	Population	Time points			
		3 year	4 year	5 year	10 year
Predicted Company Extrapolation for Base Case Node Positive Placebo Arm	Base case	90.27%	86.35%	82.76%	73.19%
Obeserved APHINITY Trial – Node Positive Placebo Arm	Identical to base case population	89.91%*	86.46%*	-	-
BCIRG-006 Node Positive AC-TH arm	Comparable to base case	-	-	80%	70%
BCIRG-006 4+ nodes AC-TH arm	Unhealthier than base case	-	-	73%	63%
BCIRG-006 Node Negative AC-TH arm	Healthier than base case	-	-	93%	-
BCIRG-006 Full Trial population	Healthier than base case			84%	75%
HERA Full Trial population 1Y Trastuzumab arm	Healthier than base case	84.6%	78.6%	-	69.0%
HERA 1-3 nodes 1Y Trastuzumab arm	Slightly healthier than base case	84.7%	-	-	75%
HERA Trial 4+ Nodes Hormone Receptor Positive Population – 1Y Trastuzumab arm	Unhealthier than base case	67.8%	-	-	55%
*taken from table 22 of company submission					

Whilst the company's selection of a log-logistic model is not ill-fitting, the ERG noted that the company did not consider the possibility of delaying the implementation of the parametric model until after a certain point in time. The ERG believe this approach should have been considered by the company, and the rejection of this should have been justified, given that the two arms showed similar IDFS event rates for approximately the first 19 months of the follow-up period, and that it was beyond this point which a difference was observed and sustained. To fit models as the company has done, one must assume a difference in IDFS event rates across the whole period, which is not seen in the observed data.

In effect, the ERG believe the company should have investigated the use of KM data with a delayed parametric model fitted to data beyond a suitable point in time. In addition to the 19 month, the ERG

also recommends exploration using a 36 month cut-off where a clear difference in trend of hazard occurs in both the HERA and BCIRG-006 trials (Figure 14 in CS, reproduced in Figure 17 below), and explore both of these in their sensitivity analysis. The ERG requested goodness-of-fit information from the company based on a cut-off of 22 months (clarification C2), initially thought to be an optimal selection by the ERG. The response suggests all parametric models provided suitable fits to the observed data, however, the company state that "all parametric functions (irrespective of the time point at which they are implemented) have been calculated based on all the observed data available from the APHINITY trial. To properly model parametric functions predicated on only 22 months of the observed data would require a re-running of all survival analyses and a major update of the current model." Hence the ERG opted to not use a cut-off in their base-case analysis, and explore the other cut offs in scenario analyses. The ERG recommend that the company update their economic model to allow correct implementation of the delayed parametric models at key points in time (e.g., 9 months, 19 months, 36 months).

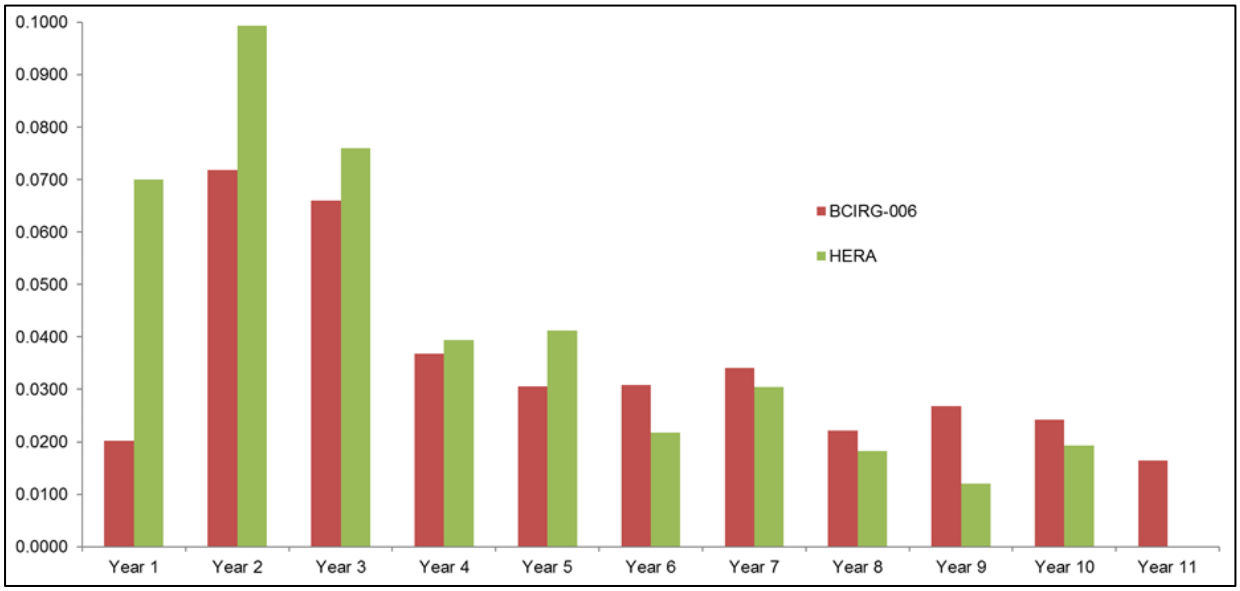


Figure 5. Annual recurrence rate (DFS endpoint) from HERA and BCIRG 006 clinical trials

Phase 2

From years four to 10, the submitted analysis adjusts the initial extrapolation for both arms using a 'cure' model where, under the company's assumptions, a steadily increasing proportion of event-free patients (from 0% to 90% from years 4 to 10) are no longer at risk of an IDFS event.

The ERG agrees that it is likely an adjustment should be performed to the parametric extrapolations of IDFS data from the APHINITY trial. In figure 13 of the CS, the company demonstrate how an unadjusted parametric fit to the observed IDFS data at three years for the HERA trial is a poor

predictor. However, the ERG requested that the graph be reproduced using four-year data, to maximise applicability to the current appraisal (clarification C9). In response, the company truncated their data and demonstrate how the unadjusted prediction remained unsuitable. The ERG noted that in the initial figure a log-normal parametric fit was used, and that this switched to a Weibull distribution in the clarification response. The ERG cannot verify if these choices of parametric models were well-justified as no supporting evidence was provided and, in this instance, it can only trust the company's decision making process. The ERG requested that similar graphs be reproduced, but with the parametric fit being fitted only after a certain time point (clarification C10). The company provided these and it was clear that any parametric models would still require adjustment to obtain accurate extrapolations. The ERG note that the company did not provide similar graphs from the BCIRG-006 study stating that they deemed it inappropriate from a methodological point of view. The ERG are concerned by the possibility that the BCIRG-006 trial may not have required such extreme adjustment to the parametric model in order to accurately extrapolate IDFS, however, the ERG is unable to verify these concerns.

Given the likelihood that an adjustment offers improvement to the extrapolation, the company justify their specification of the adjustment. They show the difference in trend in recurrence rates between years 3 and 4 of the HERA and BCIRG studies for their node positive populations (see Figure 17 above). The ERG is unsure why the recurrence rates for the first four years of APHINITY were not included in Figure 3, as the company could have demonstrated the beginnings of a similar pattern. The company demonstrated the improvement of the adjustment on the IDFS extrapolation node-positive population through a side by side comparison of Figures 15 and 16 in the CS. The ERG concurs that the adjustment is beneficial to the extrapolation, but underlines the uncertainty around the most suitable parameters of this adjustment. Given that the change in recurrence rates is observed after three years, and not four, the ERG believes that the 'cure' should be implemented from 36 months. This is supported by the smoothed hazard plots provided by the company in the clarification appendices. In Figure 18, it is clear that the parametric model fitted by the company begins to overestimate the hazard rate in both arms from roughly 36 months. The ERG were unable to reproduce updated smoothed-hazard plots with the cure being implemented from 36 months, but predict that the change currently observed at 48 months would be brought forward and that the model would more accurately represent the observed hazard.

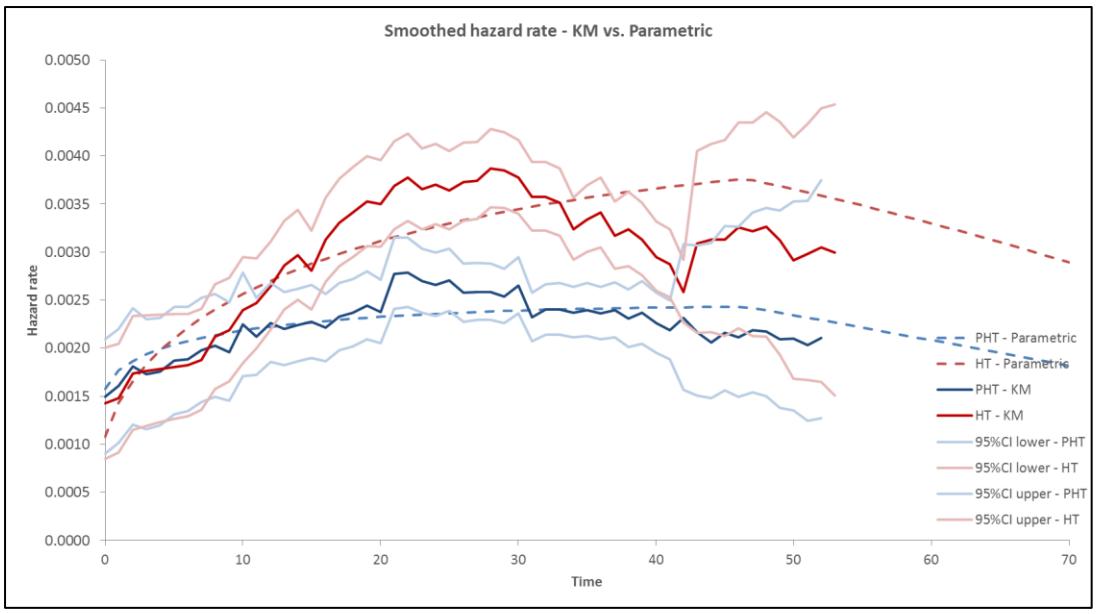


Figure 18. Smoothed hazard plot for Node Positive Population with log-logistic fitted model

Hence, the ERG disagree with the company's conclusion that the adjustment should be implemented from 48 months, and believe that it should occur from 36 months, as this is when the difference in recurrence rates is observed. The ERG agree that the use of a cure model was biologically plausible, although cure modelling was not implemented in the same manner within the trastuzumab technology appraisal (TA107), or the pertuzumab neoadjuvant appraisal (TA424). The ERG notes that the 90% cure threshold chosen by the company appeared to be chosen arbitrarily. A literature search performed by the ERG revealed that very late disease recurrence has been observed, but is very rare and it is unclear how the risk is affected by either trastuzumab or pertuzumab. In this study of late recurrence of 1114 patients with surgically treated breast carcinoma, 25.5% experienced recurrence similar to predictions made within the company's base case analysis. However, only 1.08% of patients experienced recurrence after 10 years in the Takeuchi et al study, whereas using a 90% cure rate, the company's base case model estimates 3% of patients in the control arm would experience disease recurrence in the same period which the ERG finds implausible. By changing the cure threshold to 95% and implementing the cure from 36 months, the ERG reduces this to 1.6% recurrence, which the ERG believes to be a more plausible prediction. The ERG agreed that 10 years was a suitable end point for this second phase.

The ERG queried why other options such as time-varying covariates or a simple hazard ratio adjustment were not explored as a possibility for accounting for the changing risk of recurrence (clarification C13), with the company replying that a cure model was suitable and simple to implement.

Phase 3

Beyond 10 years (120 months) it is assumed that 90% of patients are no longer at risk, and they are subject to background mortality rates. The company state that this is supported by the fact that the hazard rate observed in the 11th year of the HERA trial is similar to that of the UK mortality table for patients aged 65. The ERG are unable to verify that this claim as the hazard rate for the 11th year of the HERA trial was not reported, thus it remains unclear how similar the two rates are. The ERG note that patients in the economic model would be aged 61 after 10 years have passed, and not 65 as used in the company's comparison. However, the ERG's clinical advisor suggested it was plausible to assume that patients were no longer at an increased risk of an IDFS event compared to the general population beyond 10 years.

Overall survival

Overall survival (OS) is not modelled parametrically from the observed data, but is assessed indirectly based on patient progression through the health states comprising the economic model. As a general comment, the ERG notes that the resulting OS predictions appear to be overly optimistic and do not fit the data well. The predicted OS from the company's base case analysis is shown with the observed OS from the APHINITY trial in Figure 20, which taken from the economic model. From 29 months onwards, it is clear that OS is overestimated for both arms. When comparing survival rates from other studies (Figure 19 and Table 17) it is apparent that they are not consistent with the trend predicted by the company for the placebo arm of the node-positive APHINITY population. The observed APHINITY population appear to perform very similarly to the population of the BCIRG-006 trial. Also, across the BCIRG and HERA trial populations presented, there is a clear consistency of long term trends. Whilst the optimistic prediction for the APHINITY trial may be plausible due to differences in baseline population and improvements in healthcare, there is clear inconsistency between the 5 and 10-year OS predictions for this group. The rapid change in trajectory is not observed in any other of the trials, with the APHINITY node positive population changing from the best to the second worst percentage alive. When asked to comment on the poor fit to observed OS (clarification C11), the company stated that this was partly due to the modelled market share of therapies for first line metastatic treatment. The company stated that the model used market share taken from the ESTHER study,[17] rather than the APHINITY trial. The company also stated that when the APHINITY market share was used, the OS was modelled more accurately. The ERG presents this scenario in their exploratory analysis, but agree that the market share from ESTHER is likely to be more representative of the UK.

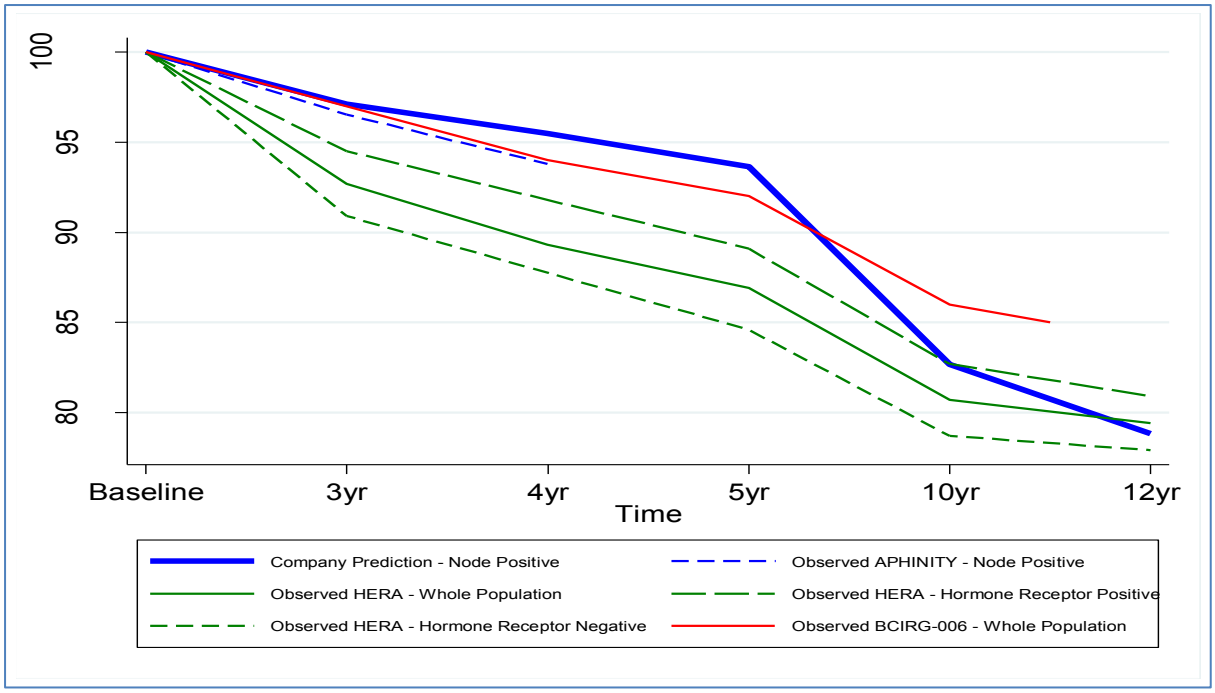


Figure 19. OS for trastuzumab from APHINITY, HERA and BCIRG-006 trials

The ERG believe that this is not in line with clinical expectations and, given that OS is not modelled parametrically, but rather as a result of a number of various assumptions within the model, the ERG has explored possible adjustments (e.g., in relation to 'cure' assumptions, other transitions) in the model with a view to achieving OS curves that provider a better reflection of clinical expectations.

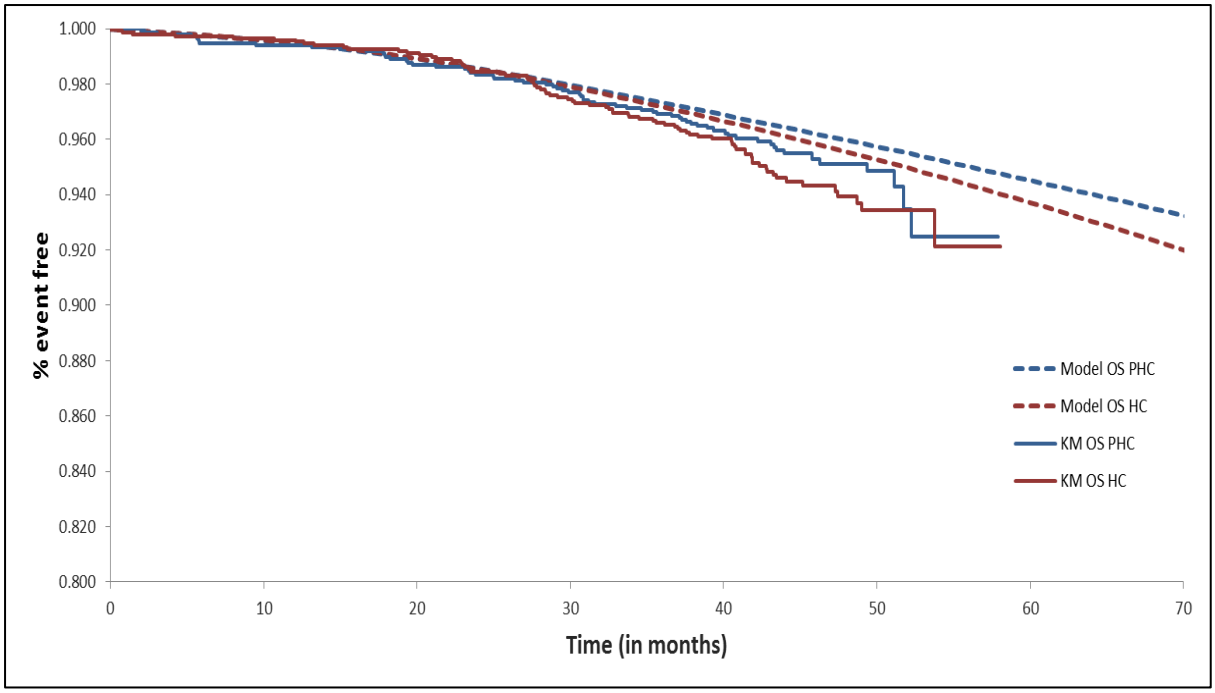


Figure 20. OS curves from the submitted decision model and observed from APHINITY trial

Table 17. Overall survival comparison

		3 year	4 year	5 year	10 year	12 year
Predicted Company Extrapolation for Base Case Node Positive Placebo Arm	Base case	97.11%	95.49%	93.63%	82.67%	78.83%
Obeserved APHINITY Trial – Node Positive Control Arm	Identical to base case population	96.54%*	93.80%*	-	-	-
HERA Trial Full Population – 1Y Trastuzumab arm	Healthier than base case	92.70%	89.30%	86.90%	80.70%	79.40%
HERA Trial Hormone Receptor Positive Population – 1Y Trastuzumab arm	Much healthier than base case	94.50%	-	89.10%	82.70%	80.90%
HERA Trial Hormone Receptor Negative Population – 1Y Trastuzumab arm	Healthier than base case	90.90%	-	84.60%	78.70%	77.90%
BCIRG-006 Full trial population, AC-TH arm	Healthier than base case	97%**	94%**	92%	85.9%	-

*approximate, extracted from economic model. **approximate, extracted from KM plot.

5.2.6.2 Modelling of recurrence

In the submitted analysis, once patients present disease recurrence, they can transition to either the first-line mBC (a metastatic recurrence) or non-metastatic recurrence health states. The analysis of pathways and events following recurrence is critique below.

Early metastatic recurrence

The proportion of patients who experienced metastatic recurrence, non-metastatic recurrence and died was guided by data from the APHINITY trial. In the CS, the company stated that no meaningful difference was observed in the distribution of the types of recurrence events between the two arms of the trial, thus the company opted to pool the proportion of metastatic and non-metastatic recurrences (81.07% and 18.93%, respectively) and apply them to both arms in the model.

Pooling the proportion of metastatic and non-metastatic recurrences across arms means that available data collected for each arm of the APHINITY trial are not used, and this can potentially hide differences in the type of recurrent events, however subtle these may be. Thus, the company's decision to pool the proportions across both arms, rather than use the proportions observed for each trial arm in APHINITY, was queried by the ERG (clarification B4). An amendment was carried out in the economic model to allow for non-pooled recurrence proportions to be used, and the results of this were presented by the company. In their response, the company defended their preference for pooled data on grounds of no clear clinical rationale that suggests pertuzumab modifies the risk of a disease recurrence being metastatic, and on the company's approach not to differentiate between treatment arms unless a clear clinical rationale exists. These justifications were deemed to be reasonable and were accepted by the ERG. However, given the availability of arm-specific data from a randomised trial, and in order to ensure that no differences in observed data are suppressed, the ERG explored the use of the available non-pooled data in sensitivity analysis.

In the CS, the company explains that the timing of relapse is expected to be suggestive of disease severity, and this has been built into the economic model. The company state that patients who relapse earlier tend to have more aggressive disease which is less likely to respond well to treatment, and assume that every recurrence event that occurs in the first 18 months is a metastatic event. This was supported by evidence from the HERA trial (figure 20 in the CS), where a clear difference in post progression survival is observed between early and late recurrence patients. The ERG's clinical advisor considered this assumption to be reasonable. The timing of the relapse is also likely to be associated with differing treatment costs due to treatment type and duration of treatment, which was also confirmed by the ERG's clinical advisor. However, the ERG noted that a consequence of the company's approach is that the proportion of metastatic events from the whole observed trial is only applied to events occurring beyond 18 months. Hence the ERG estimated more accurate proportions which represented events beyond 18 months (Table 18) and found the pooled estimate to be 72.40%.

Table 18. ERG calculations of proportion of metastatic events for the post-18 month period

	Pertuzumab	Placebo	Combined	Explanation
	Node Positive	Node Positive	Node Positive	
Total number of events	139	181	320	Obtained from the KM data in the IDFS tab of the economic model
Total number of IDFS recurrence events	119 (85.61%)	161 (88.95%)	280 (87.50%)	Provided by company (table 23 in CS)
Total number of events in the pre-18 month period	51	50	101	Obtained from the KM data in the IDFS tab of the economic model
Estimated numbers of recurrence events in the pre-18 months (assumed to be all metastatic)	44	44	88	Calculated by multiplying the total pre-18 month events by the proportion of events which were metastatic
Total number of events in the post-18 month period	88	131	219	Obtained from the KM data in the IDFS tab of the economic model
Total number of recurrence events in the post-18 month period	75	117	192	Calculated by multiplying the total post-18 month events by proportion of events which were metastatic
Total number of metastatic recurrence events	99	128	227	Provided by company (table 23 in CS)
Total number of metastatic recurrence events post-18 months	55 (73.33%)	84 (71.79%)	139 (72.40%)	Calculated by subtracting the pre 18-month metastatic recurrence from the total number of metastatic recurrence. Percentages are calculated according to post-18 month recurrence events which are metastatic

Following initial recurrence, patients were at risk at further relapse and consequently death using probabilities taken from the fast relapse sub-population of the EMILIA study[77] (shown in Figure 21, corresponding to figure 21 in the CS). This study investigated the use of trastuzumab emtansine in second line mBC. When the reasoning was queried by the ERG (clarification B1), the company stated that the APHINITY trial had insufficient data on post-recurrence deaths to obtain reliable estimates, which the ERG accepted. However, despite the ERG's request, the company did not provide any comment on the differences in population between APHINITY and EMILIA, nor verified whether the resulting model estimates matched the observed data from APHINITY.

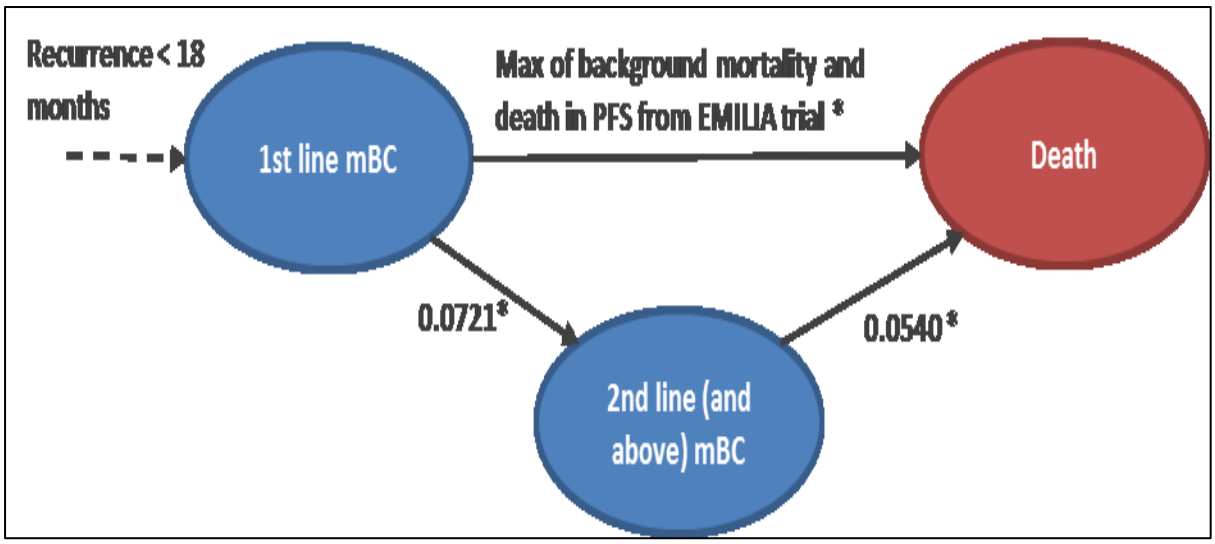


Figure 21. Summary of monthly transition probability sources in the metastatic setting following early relapse (within 18 months)

The economic model contained a demonstration of the exponential models fitted to the EMILIA trial for both PFS and post-progression survival. As the company did not compare the model predictions against the observed APHINITY data, the ERG are unable to comment about their suitability. Based on visual inspection, the ERG notes that the exponential model fitted to PFS does not present a suitable fit (Figure 22) to the EMILIA data, and believes alternative parametric models are likely to have provided a more accurate prediction. However, the ERG were not able to explore other parametric fits to the EMILIA data within the submitted economic model. The exponential model for PPS appeared more suitable, but again this could only be assessed visually by the ERG.

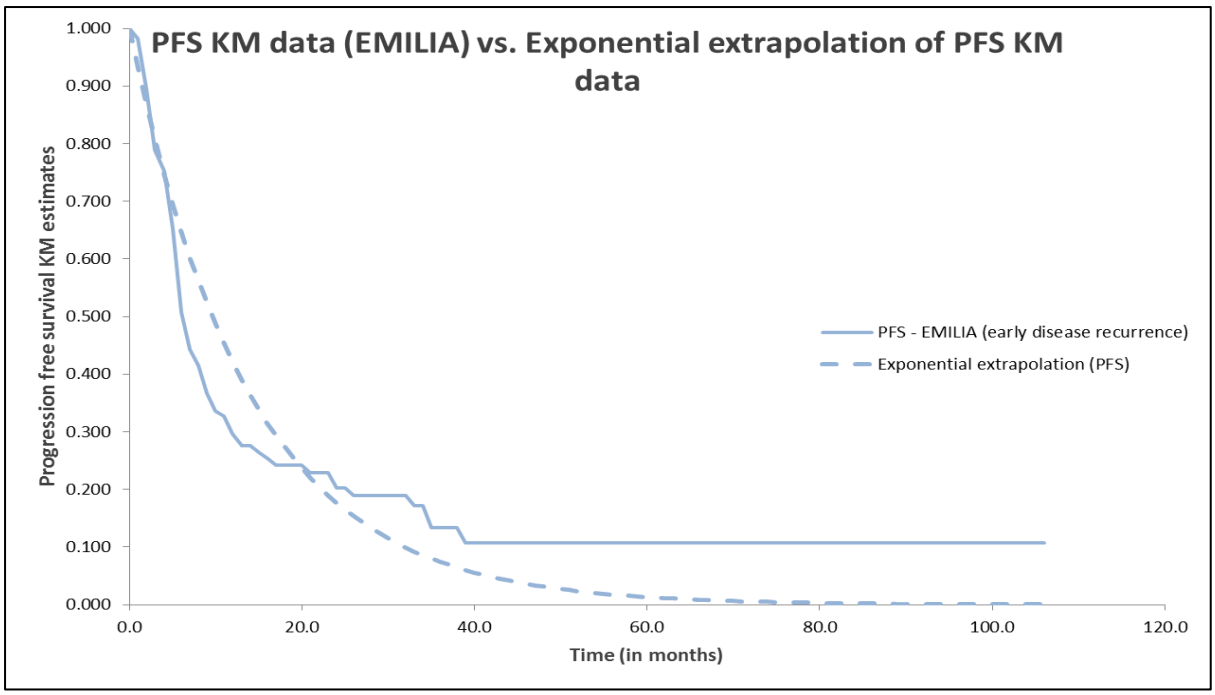


Figure 22. Exponential model fitted to progression free survival events observed in EMILIA study (reproduced from the submitted economic model)

Non-metastatic recurrence

Patients who have a non-metastatic recurrence take a different pathway in the economic model, shown in Figure 23, (corresponding to figure 22 in CS). The model assumes that all patients who experience a non-metastatic recurrence undergo one year of additional adjuvant therapy. Following this, all patients enter the remission health state. The company acknowledges that the assumption that all patients transition to remission is not realistic, but state that their clinical advisors suggested that very few patients would progress or die during this 12-month period. The company states that as a result the assumption will have little impact on the cost effectiveness results. The ERG believe any effect is likely to be similar across treatment arms and agree that this assumption is unlikely to have a prominent impact on the results.

Background mortality rates were applied during the patients' year in the non-metastatic recurrence health state. The ERG requested greater justification for this (clarification B6) and the company stated that patients rarely enter the death health state without progression. The ERG accept this explanation and believe any improvement made would not influence the cost-effectiveness analysis strongly.

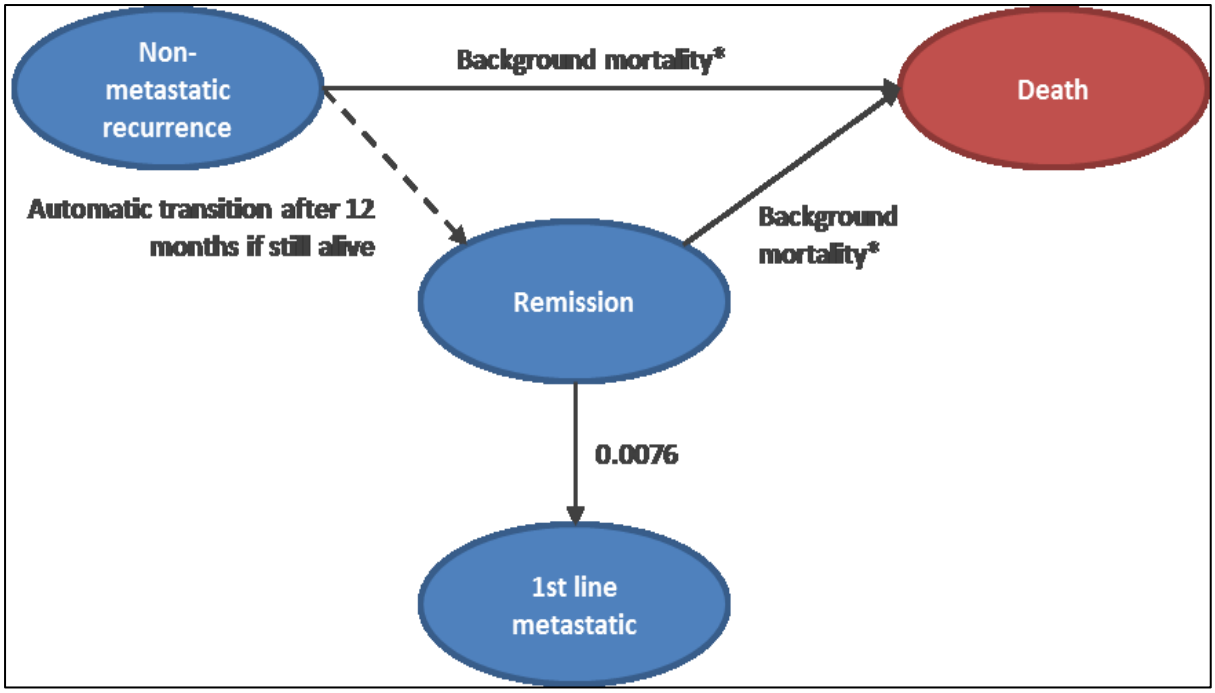


Figure 23. Summary of monthly transitions in the non-metastatic recurrence population

Remission

Following adjuvant therapy received during the non-metastatic recurrence state, patients who are still alive automatically transition to the 'Remission' state. From here, patients can transition to either the metastatic or death health states. Risk of death in the remission health state was assumed to be the same as the IDFS health state, which, given the lack of available data, the ERG accepts as plausible. The transition probability to the metastatic health state was calculated using information from the Hamilton et al.[78] study. The time to progression, as stated in the submission, is 7.6 years, but this represents the median, rather than the mean time as reported by the company. The approach taken by the company to obtain the resulting monthly transition probability of 0.0076 was not clearly reported, though upon examination, the ERG confirmed this estimate as correct. The company, and subsequently the ERG, used extreme values of this parameter to examine its impact on the results; this was found to be minimal.

Post metastatic recurrence

The metastatic recurrence pathway consists of two health states: i) first line mBC; and ii) subsequent treatment lines for mBC. Patients could arrive in the first line mBC from IDFS or remission health states. From first line mBC, patients are modelled to transition to progressive disease or death. On the company's presumption that the risk of progression has changed substantially over the past five years, and that patients now remain progression-free for longer, the analysis assumes that patients with mBC have different progression rates than those observed in APHINITY. The company assumes that

transition probability is related to treatment and takes estimates from the CLEOPATRA study[68] for patients on combinations of trastuzumab and chemotherapy with or without pertuzumab, and from the M77001 trial[36] for patients just receiving chemotherapy alone. The transition probabilities of these three groups are averaged to obtain a final probability, weighted according the treatment usage observed in the ESTHER study,[17] as shown in Table 19 (replicating table 24 in the CS). As relevant data from APHINITY are not presented, the ERG are unable to comment on how suitable the use of the data from external studies is.

It must be noted that, while the rate of metastatic progression would be expected to vary over time, the employed probabilities governing the transition between first line and progressive mBC are time-independent. The company recognises that, ideally, time dependent probabilities could be used, but this would result in a considerably more complex modelling approach. Instead, the analysis utilised probabilities obtained by modelling KM data from the CLEOPATRA and M77001 trials using an exponential distribution. The ERG deems this justification to be reasonable, and, given that the exponential curve fits the KM data reasonably well within the economic model, the ERG considers the approach used to derive time-independent probabilities as acceptable.

Table 19. Summary of monthly transition probabilities for metastatic progression

Transition	Treatment regimen	Treatment usage	Monthly probability	Data source
First line mBC to 2+ line mBC	Pertuzumab + trastuzumab + chemotherapy	71.2%	0.03172	CLEOPATRA
	Trastuzumab + chemotherapy	22.9%	0.04696	CLEOPATRA
	Chemotherapy	5.9%	0.06936	M77001
	Metastatic prog.	100%	0.03810	Weighted average

Following further progression to subsequent lines of treatment, patients can only transition to the absorbing state 'Death'. The company used the same methods and studies to obtain probabilities for this transition, however these were based on the first line treatment received by the patient, and not the second line treatment. The average survival, as predicted by exponential models compared to observations from CLEOPATRA and M77001 studies, is shown in table 25 in the CS. The ERG were not able to verify any of these reported observed and modelled survival times, but accept that the predicted values from the exponential models appear similar to the observed values.

Table 20. Metastatic recurrence pathway: comparison of KM and extrapolated (exponential) estimates

Transition	Kaplan-Meier estimates (months)	Exponential (months)	Data source
PFS – pertuzumab	28.0	28.4	CLEOPATRA
PFS – trastuzumab	20.8	21.1	CLEOPATRA
PFS – chemotherapy	14.9	15.6	M77001
PPS – pertuzumab	29.9	30.7	CLEOPATRA
PPS – trastuzumab	19.4	18.6	CLEOPATRA
PPS – chemotherapy	13.9	15.3	M77001

PFS: progression free survival, PPS: post-progression survival

The company acknowledge that patients' survival is impacted by the choice of treatment in the second line mBC setting. In explaining why the company did not account for second line treatment when calculating survival, the company cite data limitations of sequential treatments and state the first line OS benefit is more significant than the benefit of second line treatment. Although the ERG is unsure where the estimates of a 15.7-month OS benefit for first-line pertuzumab and a 5-month benefit for second-line trastuzumab emtansine over lapatinib and capecitabine came from, as neither are referenced. The ERG acknowledge the difficulty the company would have faced implemented treatment-specific second line transition probabilities, and do not believe this would have major impact on the ICER.

5.2.6.3 Treatment duration

In the company's base case analysis, the duration of treatment (i.e. the number of treatment cycles completed in each arm) was guided by the actual proportion of patients who received the compared treatments in each cycle during the APHINITY trial. This option takes into account the fact that treatment discontinuation may occurs due to progression or toxicity. An alternative approach which effectively assumes that patients discontinue only due to progression is available as an option in the economic model. The ERG concurs that the approach taken in the company's base case is preferable.

5.2.7 Health related quality of life

HRQoL inputs used in the analysis were obtained from two key sources: the APHINITY trial (for non-metastatic health states in the base case analysis) and published literature (for metastatic states and scenario analyses). These are critiqued below.

5.2.7.1 Utility estimates obtained from the literature

As explained in Section 5.1, the company undertook an SLR to identify published reporting HRQoL. The company concluded that none of the 21 studies identified through the SLR reported utility values that could be considered for direct use in the cost-effectiveness analysis. In light of this, and the availability of EQ-5D data for eBC health states from the APHINITY trial, the company stated that

none of the identified studies were considered further for the submission. However, the submission did make direct use of utility estimates drawn from published studies.[69-72] The use of values from these studies is detailed in Sections 5.2.7.3 and 5.2.7.4 below.

5.2.7.2 Utility values obtained from the APHINITY trial

HRQoL data in the APHINITY study were collected by means of the EQ-5D-3L instrument and the EORTC QLQ-C30 and BR23 disease specific questionnaires. Responses to EQ-5D-3L were collected at the following points: baseline, end of the anthracycline treatment period, week 13, week 25, end of study treatment, and 18 months, 24 months and 36 months after randomisation. EQ-5D-3L responses were converted into preference-based HRQoL (utility) values, though the CS does not report to the value set (tariff) used for this conversion. According to the CS, the EQ-5D questionnaire was not administered to patients who presented with disease progression (either non metastatic or metastatic) in the APHINITY study.

As mentioned in Section 4.2.4, although the use of patient-level EQ-5D-3L data collected from the exact population of interest within a randomised controlled trial is generally considered to be a strength, the collection of such data in the APHINITY trial raises some issues. First, as the company explains, the schedule of EQ-5D data collection was designed to capture differences in QoL across the various stages of disease, but not between treatment arms. This makes it difficult to assess the incremental impact of pertuzumab on patients' HRQoL. In addition, the infrequent and periodic (rather than event-driven) data collection schedule means that it is desirable to account for the disutility of adverse events (AE) separately. This point is elaborated in the discussion about AEs below.

5.2.7.3 Utility values used in company's base case analysis

With reference to utilities, two main types of health states were distinguished in the company submission: i) eBC states; and ii) mBC health states.

As mentioned above, utility values for eBC states ('IDFS on chemotherapy', 'IDFS on treatment/off chemotherapy', 'IDFS off treatment', 'Non-metastatic recurrence' and 'Remission') were drawn from patient-level data collected through the EQ-5D in APHINITY. While EQ-5D responses were collected for each of the trial arms, the company explained that no statistically significant difference was found in the EQ-5D results of the two treatment arms in the APHINITY study. Given this, in their base case analysis, the company pooled the responses and applied the resulting values to both comparators in the model. The ERG accepts this justification and considers the analytic approach taken to be

reasonable. Utilities derived from the treatment-specific EQ-5D responses have been used in the company's sensitivity analysis.

As the EQ-5D questionnaire was not administered to patients who experienced a non-metastatic progression (i.e., states 'non-metastatic recurrence' and 'remission'), in the base case analysis, the company assumed that the utility values for these states are equal to those of the "IDFS – on chemotherapy" and "IDFS – off treatment" states, respectively. This assumption, which clinical experts consulted by the ERG consider to be reasonable, was also employed in the assessment of pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer.[75]

HRQoL data for metastatic states (1st line mBC and 2nd + line mBC) were also not available from APHINITY. Thus, values for these health states were taken from the literature. In the base case, utility values for the 1st line mBC and 2nd + line mBC states were taken from a study by Lloyd et al.[69]

Briefly, Lloyd et al. asked 100 members of the general population in England and Wales to rate states of mBC and common toxicities with a view to deriving utility values. The study by Lloyd et al.[69] has been widely used in the literature and has been utilised in past appraisals, including the appraisal of pertuzumab in the neoadjuvant setting.[75] Utility values used in the company's base case analysis for both the early and metastatic health states are given in Table 21.

Table 21. Utility values used in company's base case analysis

State		Utility value	Source/comment
eBC	IDFS – On chemotherapy	0.756	Values obtained from the APHINITY trial. Values are pooled across treatment arms and is used for both PHC and HC.
	IDFS- On treatment/off chemotherapy	0.785	
	IDFS- Off treatment	0.822	
	Non-metastatic recurrence	0.756	Value is assumed to be equal to state 'IDFS – On chemotherapy'. The value is used for both PHC and HC.
	Remission	0.822	Value is assumed to be equal to state 'IDFS –Off treatment'. The value is used for both PHC and HC.
mBC	1st Line mBC	0.773	Value taken from Lloyd et al. [69] The value is used for both PHC and HC.
	2+ line mBC	0.520	Value taken from Lloyd et al. [69] The value is used for both PHC and HC.

5.2.7.4 Utility values used in the company's sensitivity analyses

Alternative values and assumptions were used in sensitivity (scenario) analyses. These included: (i) use of treatment arm- specific utilities from APHINITY and use of values taken from the studies from Hedden et al.,[70] Lidgren et al.,[71] and Paracha et al.,[72] (Table 22). It must be noted that, expectedly, patient populations involved and health states explored in these studies present differences to those in the present technology appraisal. For example, utility values presented in Hedden et al[70] relate to patients who were diagnosed with breast cancer irrespective of node involvement. Expert opinion sought by ERG suggested that cancer patients with and without node involvement may have different HRQoL, as the former may present more problems (e.g., arm swelling) due to more extensive surgery. While the ERG consider it reasonable to use values from these studies as alternative estimates in sensitivity analyses, this highlighted the need for ascertaining whether more suitable estimates are available in the published literature.

Table 22. Utility values used in company's scenario analyses

		Non-pooled values from APHINITY trial		Values from Hedden et al. [70]	Values from Lidgren et al. [71]	Values from Paracha et al. [72]
State		PHC	HC	PHC and HC*	PHC and HC*	PHC and HC*
eBC	IDFS – On chemotherapy	0.756	0.756	0.970	0.696	N/A
	IDFS- On treatment/off chemotherapy	0.785	0.785	0.970	0.696	N/A
	IDFS- Off treatment	0.822	0.822	0.990	0.779	N/A
	Non-metastatic recurrence	0.756	0.756	0.750	0.779	N/A
	Remission	0.822	0.822	0.990	0.779	N/A
mBC	1st Line mBC	0.773	0.773	0.650	0.685	0.806
	2+ line mBC	0.520	0.520	0.290	0.685	0.536

* The same utility values were used for both PHC and HC.
eBC: early breast cancer; mBC: metastatic breast cancer; N/A: not available;
PHC: pertuzumab + trastuzumab + chemotherapy; HC: trastuzumab + chemotherapy.

5.2.7.5 Impact of AE on HRQoL

According to APHINITY trial results, the vast majority of patients in the trial experienced at least one AE during the treatment period (99.9% in HCP and 99.5% in HC). Most of the observed AEs were of mild or moderate severity (Grade 1 or 2), with only 10% being classified as severe (i.e., Grade 3 and above). To ascertain that the impact of AE is reflected on HRQoL, one could either apply a disutility effect to collected HRQoL, or disregard any disutility resulting from AEs on the premise that this will have been reflected in the trial-collected HRQoL data. In the CS, it has been assumed that disutility resulting from treatment-related AEs is already reflected in the EQ-5D responses from the APHINITY study. However, the expectation that disutility due to AEs is reflected in EQ-5D responses is contentious; unless by design, it is unlikely that EQ-5D data were collected exactly on days that AEs were experienced.

Upon request by the ERG, the company provided an analysis where the disutility of severe AEs (anaemia, cardiac failure, diarrhoea, neutropenia and neutrophil count decrease) is taken into account by assuming that utility scores for the proportion of people who experienced such events is reduced by 0.5 over the first 13 months (treatment period). The number of AEs (and consequently, the derived probability of a patient experiencing an AE) was small, as the number of 'treatment-related' AEs in the submitted model was small. As a result, the inclusion of the disutility (and costs) of AEs had a minimal impact, which was largely proportional across treatments. This led to a very small change in the ICER of approximately £130.

5.2.7.6 Utility values used in ERG sensitivity analyses

In order to establish whether literature evidence from relevant studies and values might have been overlooked, the ERG asked for further information about the process and criteria of selecting the studies by Lloyd et al,[69] (in the company's base case analysis) Hedden et al,[70] Lidgren et al[71] and Paracha et al[72] (in the company's sensitivity analyses) (clarification question B.7). In their response, the company stated that *"although the sources were identified in a non-systematic way, it is believed that the best available evidence, pertaining to these parameters, has been incorporated here."* To ascertain that appropriate values available in the literature have not been missed out, the ERG undertook the additional searches detailed in Section 5.1. Retrieved utility values are given in Table 23. These values were used in additional analyses carried out by the ERG's.

Table 23. Utility values used in ERG's additional analyses

Source	Study/population	Non-metastatic recurrence	Remission	1st Line mBC	2+ line mBC
Ward et al. [79]	Systematic review and economic evaluation of taxanes for the adjuvant treatment of early breast cancer. Utility estimates were taken from the literature [80] Women with early and metastatic BC.	0.740	0.850	0.500	0.500
Peasgood et al. [81]	Systematic review and meta-regression of utility values in breast cancer. Various populations, including HER2-positive women.	0.637	0.710	-	0.435
Zhou et al. [82]	Study reporting on HRQoL findings of the EGF100151 trial (lapatinib plus capecitabine vs. capecitabine alone). Women with advanced or metastatic HER2 positive cancer.	-	-	0.650	-
Sherrill et al. [83]	HRQoL analysis based on findings of the EGF100151 trial (lapatinib plus capecitabine vs. capecitabine alone). Women with advanced or metastatic HER2 positive breast cancer who had progressive disease.	-	-	-	0.425

5.2.8 Resource use and costs

The following categories of resource use and costs have been included in the company's analysis: (i) treatment acquisition costs; (ii) treatments administration costs; (iii) the cost of treating selected adverse events (of severity grade 3 and above, and observed in more than 2% of the APHINITY trial participants); (iv) supportive care costs; and (v) costs of treatment associated with progressed disease.

5.2.8.1 Treatment acquisition costs

Drug acquisition costs were calculated according to list prices of commercially available vials as listed in the British National Formulary (BNF).[84] As pertuzumab is subject to a confidential commercial access agreement (CAA) between Roche Products Ltd. and NHS England, the drug is offered at a discount of [redacted].

Drug dosages for pertuzumab were fixed and in agreement with the recommended dose in the British National Formulary.[84] Trastuzumab, docetaxel and chemotherapy dosages were calculated according to patients' height, weight or body surface area. In the base case analysis of the CS, the employed weight (67.70 kg) and height (161.60 cm) were the mean values pooled across treatment arms taken from node-positive patients in the APHINITY trial. In line with good practice, the average body surface area was calculated according to the mean weight and height values using the commonly employed Dubois formula. The patient weight value, and as a result, the set body surface area, were varied in scenario analyses.

Trastuzumab is commercially available in three different forms: (i) branded trastuzumab (Herceptin) administered as an intravenous (IV) infusion; (ii) branded trastuzumab (Herceptin) administered as a subcutaneous (SC) injection and (iii) trastuzumab biosimilar administered as an IV infusion.

Herceptin IV (list price £407 for a 150 mg vial) requires an initial loading dose and subsequent maintenance doses, while Herceptin SC is given as a fixed dose of 600 mg (list price £1,222), with no loading dose being necessary.

[redacted]. Trastuzumab biosimilars were, at the time of the submission (February 2018), not available in the UK; however the expectation that this option will be available in the near future and the potential of this to have a notable impact on the cost-effectiveness results led the company to explore the use of biosimilar trastuzumab in an additional analysis (CS, document B, section B.3.7.2.). The unit costs of trastuzumab administered intravenously and subcutaneously used in the model agreed with the prices listed in the British National Formulary.[84]

On the premise that pertuzumab is not currently licensed for use in combination with trastuzumab SC, the analysis assumes that, in the PHC arm, all patients receive pertuzumab with trastuzumab IV. Conversely, in the HC arm of the model, 95% of patients receive the more expensive trastuzumab SC formulation, with the rest receiving trastuzumab IV. The proportion of patients who receive trastuzumab IV and SC was drawn from research on market shares conducted by the company. These values could not be verified by the ERG.

Should pertuzumab be approved, expert opinion sought by the ERG suggested that the treatment will, at least for the first year, be given typically offered with trastuzumab IV. Nonetheless, experts expressed their expectations that, in subsequent years, an increasing share of patients will be receiving pertuzumab (should this be recommended) with trastuzumab SC. In light of this, the ERG undertook additional analyses to account for the eventuality that, post approval, an increasing proportion of patients will receive pertuzumab with trastuzumab SC.

In the submitted analysis, chemotherapy provided in addition to targeted treatment could be "sequential" (four cycles of anthracycline chemotherapy followed by taxane in combination with targeted treatment), or "concurrent" (docetaxel plus carboplatin in combination with targeted treatment), which reflects the set up in the APHINITY study. Expert opinion sought by ERG confirmed that such arrangements are representative of UK clinical practice.

Treatment duration, and, by extension, the number of treatment cycles provided, was derived from time-to-off-treatment (TTOT) data collected during the APHINITY trial. In the base case, the company calculated treatment duration by using the proportion of patients who received the drug at each treatment cycle in the trial. In this way, the calculations account for the fact that patients can discontinue treatments, that is, receive fewer than 18 cycles of treatment, due to toxicity or disease progression. The ERG considers this approach to be reasonable.

Upon experiencing a recurrence, patients are expected to receive various additional treatment depending on the disease setting (i.e. non-metastatic recurrence, first-line mBC, or second + line mBC). In their analysis, the company calculated the total expected cost of subsequent treatments as a weighted average across available treatments based on current market shares in the UK (Table 24 below, corresponding to table 39 in CS). The source of the value for the market share of trastuzumab SC + docetaxel in the non-metastatic recurrence health state ([redacted]) could not be traced. Medication prices and quantities employed in calculating the cost of chemotherapy regimens were consistent with entries in the electronic market information tool (eMIT).

Table 24. Treatment durations and market shares for subsequent therapies

Health state	Treatment regimen	# cycles	Source	Market share	Source
Non-metastatic recurrence	Trastuzumab IV + docetaxel	18	Assumption	[redacted]	Market research
	Trastuzumab SC + docetaxel	18	Assumption	[redacted]	NHSE
First-line mBC – Early recurrence	Trastuzumab IV + docetaxel	23.65	ID523 – P in mBC	[redacted]	Market research
	Trastuzumab SC + docetaxel	23.65	ID523 – P in mBC	[redacted]	
	Trastuzumab emtansine	19.3	Assumed equal to TA371 – K in 2L mBC	[redacted]	
First-line mBC	Trastuzumab IV + docetaxel	23.65	ID523 – P in mBC	[redacted]	Market research
	Pertuzumab + trastuzumab IV + docetaxel	37.39	ID523 – P in mBC	[redacted]	
	Trastuzumab SC + docetaxel	23.65	ID523 – P in mBC	[redacted]	
	Chemotherapy	6.00	Assumption	[redacted]	Assumption
Second + line mBC – Early recurrence	Trastuzumab IV + capecitabine	9.36	TA371 – K in 2L mBC	[redacted]	Market research
	Trastuzumab SC + capecitabine	9.36	TA371 – K in 2L mBC	[redacted]	
	Trastuzumab emtansine	19.33	TA371 – K in 2L mBC	[redacted]	
	Chemotherapy	6.00	Assumption	[redacted]	Assumption
Second + line mBC	Trastuzumab IV + capecitabine	9.36	TA371 – K in 2L mBC	[redacted]	Market research
	Trastuzumab SC + capecitabine	9.36	TA371 – K in 2L mBC	[redacted]	
	Trastuzumab emtansine	19.33	TA371 – K in 2L mBC	[redacted]	
	Lapatinib + capecitabine	12.29	TA371 – K in 2L mBC	[redacted]	

IV, intravenous; K, trastuzumab emtansine; mBC, metastatic breast cancer; NHSE, National Health Service England; P, pertuzumab; SC, subcutaneous.

5.2.8.2 Administration costs

Administration costs for each treatment entry were calculated in line with the appraisal of pertuzumab for neoadjuvant use.[75] In the analysis, unit costs were drawn from appropriate national sources (National Tariff for Chemotherapy Regimens list 2017–2018,[85] the NHS reference costs schedule 2016/17,[86] and the Personal Social Services Research Unit (PSSRU) costs 2017 document[87]). An additional administration cost, which was applied to every administration in both arms and regardless of treatment, was added to account for the pharmacist's time during the prescription and preparation of treatments (12 minutes). The ERG deems the calculation of administration costs in the CS to be comprehensive and appropriate.

5.2.8.3 Costs associated with different health states

Health state costs were applied to both treatment arms over the duration of the analysis. In relation to IDFS health states, it was assumed that use of resources differs according to the length of time a patient has been in an IDFS state. Thus, specific supportive care costs were calculated and applied to: (i) Year 1, (ii) years 2–5 and (iii) years ≥5. The cohort in year 1 post-surgery is expected to comprise of patients who continue treatment and eventually complete the full 12 months of therapy and patients who discontinue treatment. Differences in supportive resource use due to differences in proportions of people who did or did not discontinue were not reflected in the analysis. The company posits that the incremental difference in discontinuation of IDFS patients between the two arms is considered minimal, thus the impact of supportive costs on overall cost-effectiveness results would be negligible. The ERG considers this statement to be reasonable.

The supportive care regimen of patients in the IDFS health state was assumed to comprise oncologist and GP visits, as well as regular mammograms and cardiac monitoring. This was confirmed as being representative of clinical practice in the UK by clinical experts consulted by the ERG. Patients who experience a non-metastatic recurrence were modelled to undergo 12 months of adjuvant therapy. In the metastatic health states, resource use related to assessing response to treatment using outpatient visits, CT scans, cardiac monitoring, and health care practitioner time. While acknowledging that the frequency of CT scans often varies across treatment centres, the model accounts for on CT scan per year in the first-line mBC health state. This assumption was considered to be reasonable and in line with clinical practice by the independent clinical expert advising the ERG.

A breakdown of the supportive care costs for the metastatic health states are summarised in Table 25 and Table 26 below (corresponding to table 43 and table 44 in the CS).

Table 25. First-line mBC state – resource use and supportive care costs

Items	Frequency (yearly)	Unit cost per contact	Proportion of patients	Cost sources	Resource use sources
Cycle costs					
GP visit	12	£37.00	100%	PSSRU 2017 - page 162	Assumption
ECHO Scan	2	£70.36	70%	NHS ref. 2016/17 – RD51A	CG81
MUGA Scan	2	£249.00	30%	NHS ref. 2016/17 – RN22Z	CG81
Clinical nurse specialist	12	£69.85	100%	NHS ref. - 2016/17 – N09AF	CG81

Items	Frequency (yearly)	Unit cost per contact	Proportion of patients	Cost sources	Resource use sources
District Nurse (home visit)	22	£37.00	100%	NHS ref. - 2016/17 - N02AF	CG81
CT Scan	One off cost	£103.00	75%	NHS ref. 2016/17 - RD20A	Ad. board (03/2013); CG81
Social worker	One off cost	£82.00	100%	PSSRU 2017 - 11.2 - page 174	CG81
Total base case cost per (4-week) cycle = £214.78					

CT, computerised tomography; ECHO, echocardiogram; GP, general practitioner; MUGA, multigated acquisition; NHS, National Health Service; PSSRU, Personal and Social Services Research Unit.

Table 26. Second + line mBC state – resource use and supportive care costs

Items	Frequency (yearly)	Unit cost per contact	Proportion of patients	Cost sources	Resource use sources
GP visit	12	£37.00	100%	PSSRU 2017 - page 162	Assumption
Clinical nurse specialist	12	£69.85	100%	NHS ref. - 2016/17 – N09AF	CG81
District Nurse (home visit)	24	£37.00	100%	NHS ref. - 2016/17 - N02AF	CG81
Average monthly supportive care cost = £180.85					

GP, general practitioner; NHS, National Health Service; PSSRU, Personal and Social Services Research Unit.

5.2.8.4 Resource use and costs associated with AEs

As mentioned in Section 5.2.7, only AEs of Grade ≥3 were accounted for in the analysis, on the reasonable premise that less severe (grade 1 and 2) events would typically not result in use of health care resources. In addition, only AEs observed in ≥2% of patients were included in the analysis. While the 2% occurrence cut-off threshold is relatively conservative, this left out severe events (primary cardiac events and anaemia) which occurred more often in the pertuzumab arm of the APHINITY trial. Given the imbalance in primary cardiac events and anaemic events across groups and the fact that such events are expected to be detrimental for patients' HRQoL and costly to resolve, the ERG requested that a revised analysis presents total costs, total QALY and incremental cost-effectiveness ratio (ICER) values that take into account cardiac events and anaemia. The frequency of these AEs was calculated according to observed events in the APHINITY trial which have been classified as 'treatment-related'. The inclusions of the costs (and disutility) associated with these severe, but infrequent, AEs in the analysis resulted in a very small increase in the cost-effectiveness results, by £130.

In the absence of post-progression AEs from the APHINITY study, the total AE management cost for subsequent treatments was taken from other appraisals. These costs were low (ranging from £1.28 to

£13.51), thus, in the ERG's opinion, they are highly unlikely to have a notable effect on the final cost-effectiveness results.

5.2.9 Cost effectiveness results

In their CS, the company presented results from: (i) a base case (deterministic) analysis; (ii) a modified base case (deterministic) analysis; and (iii) sensitivity analyses, including probabilistic, univariate deterministic and scenario analyses (section 5.2.10). Results of the company's main analysis (node positive population) were presented in the main body of the CS, while findings for the additional subgroup (HR-negative population) were given in the submitted appendices (appendix M). Additional analyses provided as part of the clarification process resulted in changes in the cost-effectiveness results, though the company did not explicitly amend the base case analysis results presented in the CS.

5.2.9.1 Base case results

The company's base case deterministic cost-effectiveness results, as presented in the CS, are reproduced in Table 27 below (corresponding to table 50 in the CS).

Table 27. Base case cost-effectiveness results (node-positive population).

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
HC (trastuzumab + chemotherapy)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£34,087
PHC (pertuzumab + trastuzumab + chemotherapy)	[redacted]	[redacted]	[redacted]				

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

Results suggest that, on average, pertuzumab led to a gain of [redacted] QALYs at an additional cost of [redacted] per person. Given this, the ICER for the comparison between PHC and HC in node positive eBC patients was estimated to be £34,087 per QALY gained.

In addition, the results of a 'modified base case analysis were presented, on the basis that introduction of trastuzumab biosimilars to the UK market in the near future is expected to have a sizeable impact on the calculated ICER. As the price and market share of biosimilars is currently (February 2018) unknown, the company presented a two-way table (Table 11, corresponding to table 51 in the CS) showing ICER values corresponding to different combinations of biosimilar price and market share.

Table 28. Biosimilar price and market share impact on base case cost-effectiveness results (node-positive population).

		Trastuzumab biosimilar discount compared to branded trastuzumab list price										
		0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
Trastuzumab biosimilar market share (%)	0%	£34,087	£34,087	£34,087	£34,087	£34,087	£34,087	£34,087	£34,087	£34,087	£34,087	£34,087
	10%	£35,031	£34,714	£34,398	£34,081	£33,764	£33,447	£33,130	£32,814	£32,497	£32,180	£31,863
	20%	£35,976	£35,342	£34,709	£34,075	£33,441	£32,808	£32,174	£31,540	£30,907	£30,273	£29,640
	30%	£36,921	£35,970	£35,020	£34,069	£33,119	£32,168	£31,218	£30,267	£29,317	£28,367	£27,416
	40%	£37,865	£36,598	£35,331	£34,063	£32,796	£31,529	£30,262	£28,994	£27,727	£26,460	£25,193
	50%	£38,810	£37,226	£35,642	£34,058	£32,474	£30,890	£29,305	£27,721	£26,137	£24,553	£22,969
	60%	£39,755	£37,854	£35,953	£34,052	£32,151	£30,250	£28,349	£26,448	£24,547	£22,646	£20,746
	70%	£40,699	£38,482	£36,264	£34,046	£31,828	£29,611	£27,393	£25,175	£22,957	£20,740	£18,522
	80%	£41,644	£39,109	£36,575	£34,040	£31,506	£28,971	£26,437	£23,902	£21,368	£18,833	£16,299
	90%	£42,589	£39,737	£36,886	£34,035	£31,183	£28,332	£25,480	£22,629	£19,778	£16,926	£14,075
	100%	£43,533	£40,365	£37,197	£34,029	£30,861	£27,692	£24,524	£21,356	£18,188	£15,020	£11,852

Blue shaded area represents the expected market share and discount of trastuzumab biosimilars, derived from competitive intelligence from Roche.

5.2.9.2 Sensitivity analyses

Three types of uncertainty analyses were undertaken by the company: probabilistic, deterministic and scenario analyses.

Probabilistic sensitivity analysis (PSA) comparing PHC against PC was based on 1000 replications. While some information about the type of distributions used was presented in tabular form in the CS (table 48), the parameter values of assigned distributions were often unclear. This led to a request for all the distributions and their parameters used in PSA, to which the company responded by providing an amended table (see Appendix 2, Table 38).

Briefly, parameters varied in PSA included utilities for all the modelled health states, treatment administration costs, additional health state costs applied to each monthly cycle, AE management costs, transition probabilities (first-line mBC to second + line mBC, second + line mBC to death) for

'early' and 'late' relapsers, and AE management costs. Wherever the submitted model permitted, probability distributions and parameter values assigned to the above variables were checked for appropriateness. In addition, checks were carried out to verify that the mean of each variable's simulated distribution (i.e., drawn from 1000 replications in the PSA) was close to the deterministic value of the variable. The ERG was satisfied that differences were minimal, in line with what would be expected due to deriving estimates from random draws. However, the ERG notes some discrepancies between the values provided in response to clarification questions and in table 48 in the CS, and those used in the submitted model. For example, the cost of managing neutropenia is reported to be £137.00 (ranging from £69.00 to £163.00 and assigned a gamma distribution in the CS), but the 'most likely value' used in the model appears to be £79 (with low and high values specified as £49 and £77, respectively). The ERG considers this to be a reporting error and accepts the values used in the model as correct. These values fed into the results reported below.

The PSA gave an ICER of £33,621 per QALY gained, which was similar to that produced by the company's base case (deterministic) analysis (see Table 12, corresponding to table 52 in CS). The cost-effectiveness plane and cost-effectiveness acceptability curve resulting from the output of the probabilistic sensitivity analysis is shown in Figure 24 (figure 24 in CS) and Figure 25 (figure 25 in CS), respectively. At a willingness-to-pay value of £30,000 per additional QALY, the probability of PHC being more cost-effective than PC was 17.3%.

Table 29. PSA results compared to base case (node-positive population)

	Costs		QALYs		ICERs (£/QALY)	
	Base case	PSA	Base case	PSA	Base case	PSA
Trastuzumab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£34,087	£33,621
Pertuzumab + trastuzumab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]		

ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.

Figure 6. Cost-effectiveness plane (node-positive population)

Inc, incremental; QALYs, quality-adjusted life years

Figure 7. Cost-effectiveness acceptability curve (node-positive population)

HT, trastuzumab + chemotherapy; PHT, pertuzumab + trastuzumab + chemotherapy; QALYs, quality-adjusted life years.

The company also undertook and reported a series of univariate sensitivity analyses, where values used in the base case analysis were replaced by the 10th and 90th percentile of the distributions used in PSA. Results generated from varying the most sensitive parameters are depicted in Figure 26 (figure 26 in CS). This analysis gives an indication of the impact of a single parameter on the results, although it is worth noting that the range of parameters used is limited. The impact of a more complete set of parameters and assumptions was assessed in the company's scenario analyses.

Figure 26. Univariate sensitivity analysis – Tornado diagram (node-positive population)

H, trastuzumab; HC, trastuzumab + chemotherapy; HS, health state; ICER, incremental cost-effectiveness ratio; IDFS, invasive disease-free survival; mBC, metastatic breast cancer; NMR, non-metastatic recurrence; PHC, pertuzumab + trastuzumab + chemotherapy; QALY, quality-adjusted life year; tx, treatment.

Scenario analyses aimed to assess the impact of various assumptions or approaches used in the model on the results. Results of these analyses, presented in terms of change in incremental costs, QALYs and ICER compared to the equivalent base line values, can be found in table 54 and table 55 in the CS. Due to their length, these tables are not reproduced here. In brief, the ICERs generated through these analyses ranged from £14,929 per QALY gained for eBC health state utilities drawn by Hedden et al.[70] to £63,456 per QALY gained when the percentage of metastatic recurrences was set to zero.

5.2.10 Model validation and face validity check

The company stated that the validity of the submitted model was assured through: i) ensuring that there is agreement between the modelling approach followed, previous submissions to NICE and other oncology models; ii) adhering to NICE guidance on methods for technology appraisal; iii) ascertaining the appropriateness of the model inputs through cross-reference with previous technology appraisals and through validation by independent experts, and iv) through carrying out 'cell by cell' checks to identify technical errors in the formulae, functions and coding consisting the submitted model. The ERG assessed the validity of the model, particularly with respect to suitability of model structure, appropriateness of data sources and inputs, and plausibility of the obtained results.[88]

The structure of the submitted model was scrutinised in order to ascertain than no meaningful health states and pathways had been omitted. The ERG was satisfied that the structure of the model is suitable for the particular decision problem, and is in line with the approach taken for the evaluation of pertuzumab as a neoadjuvant treatment[75] and work assessing similar treatments in the published literature.[89] The ERG also notes that important elements of the analysis (e.g., the adopted perspective, time horizon and discount rates) are in agreement with the NICE Reference Case.[74]

The ERG felt that the company took reasonable steps to ascertain that evidence used in the model was rigorous and suitable. Much of the data used to populate key model parameters (e.g., transitions within and from IDFS and metastatic states, proportions and types of recurrent events, utility values for eBC) were obtained from relevant randomised clinical trial. While there were instances when the choice of evidence (e.g., the choice of the Lloyd et al.[69] study as a source of utilities for mBC health states) was not adequately justified, the ERG felt that the employed evidence *per se* was largely appropriate. In cases where inappropriate use of evidence, unrealistic assumptions or errors in the calculations of input values were identified by the ERG (e.g., calculations of percentages of metastatic and non-metastatic recurrences, as described in Section 5.2.6.2) these are highlighted in this critique and are addressed in the ERG's additional work.

The economic model, which was submitted in a spreadsheet, was also scrutinised by the ERG. Wherever possible, 'extreme value' tests were performed, by replacing the base case value of influential variables with low and high estimates. Results were found to agree with expectations

about the direction and magnitude of change in model parameters and final results. Examination of macro used to perform simulations did not identify errors in the code.

In summary, the ERG believes the steps undertaken by the company to ensure the validity of the model are appropriate, and deems the model's face validity (i.e. the extent to which the model structure, employed assumptions and generated results are valid) to be, on the whole, sound.

5.3 Exploratory and sensitivity analyses undertaken by the ERG

Additional work carried out by the ERG is reported below. This work aimed to: i) reconstruct the base case analysis for this decision problem by amending elements of the company's analysis which were considered to be problematic (section 5.3.1); and ii) conduct sensitivity analyses to explore the effect of alternative values and approaches on the final cost-effectiveness results (Sections 5.3.2 and 5.3.3 below).

5.3.1 The ERG's suggested base case

On the basis of the critique of the submitted economic model, the ERG suggests an amended base case. The rationale for these amendments has been given alongside the critique provided in Section 5.2 and is briefly summarised below.

a. Changes related to the duration of the incremental treatment effect. In their base case analysis, the company assumes an incremental treatment effect associated with pertuzumab that lasts for 10 years (set to be 100% until year seven and set to diminish linearly thereafter until year ten). As explained in Section 5.2.6.1, the ERG believes that the justifications offered for this choice are not substantiated adequately and proposes an alternative specification, which is more aligned with existing evidence.
b. Amendments in the specifications of the 'cure' adjustment. As explained in Section 5.2.6.1, from years four to 10, the submitted model adjusts the initial extrapolation for both arms using a 'cure' model where, under the company's assumptions, a steadily increasing proportion of event-free patients (from 0% at year four to 90% at year 10) are no longer at risk of an IDFS event. The ERG concurs that the adjustment is beneficial to the extrapolation, but proposes an alternative specification of the cure model (starting point and maximum cure proportion), which better represents the observed behaviour of hazard rates and late recurrence events.

c. Revisions in the calculations of the proportion of patients estimated to experience metastatic and non-metastatic recurrences. As noted in Section 5.2.6.2, the proportion of metastatic events obtained from the whole observed trial is, incorrectly, applied only to events occurring beyond 18 months. The ERG re-calculated the proportion of metastatic (and non-metastatic) events applicable to post-18 month relapses (see Table 18 above) and used the revised values in the proposed ERG base case.

For each of these amendments, the values used in the company's base case analysis and the values preferred by the ERG (given in bold) can be found in Table 30 below. Results of the ERG base case analysis are presented in Section 6.1.

Table 30. Values used in the ERG's base case analysis

Parameter	Values in company's base case	ERG's preferred value	Section where justification is given
Duration of incremental treatment effect			
Time point when incremental treatment effect begins to wane	Year 7	Year 4	Section 5.2.6.1
Time point when incremental treatment effect ceases	Year 10	Year 7	
'Cure' adjustments			
Time point when 'cure' adjustment is introduced in the analysis	Year 4	Year 3	Section 5.2.6.1
Time point when maximum 'cure' is reached	Year 10	Year 10	
Maximum "cure" proportion	90.00%	95.00%	
Percentages of disease recurrence			
metastatic recurrence	76.87%	65.60%	Section 5.2.6.2
non-metastatic recurrence	23.13%	34.40%	

5.3.2 Probabilistic sensitivity analysis

The ERG re-run the PSA in order to obtain results that reflect the amendments in parameters specified in the ERG suggested base case. The revised PSA results (joint distribution of cost and QALY estimates) were generated through 1000 iterations and are depicted in the cost-effectiveness plane and cost-effectiveness acceptability curves presented in Section 6.2.

5.3.3 Additional deterministic analyses

Additional analyses were performed by the ERG, including:

i. re-running the company's scenario analyses on the basis of the ERG suggested base case
ii. undertaking additional analyses using alternative assumptions, approaches or values for key parameters
iii. carrying out further analyses on key uncertain parameters, including the duration of pertuzumab's effect, the future market share of trastuzumab SC given in combination with pertuzumab and the acquisition cost of pertuzumab.

The main findings of this additional work are presented in Section 6.3 below.

5.4 Conclusions of the cost effectiveness section

The company developed and presented a *de novo* economic analysis to evaluate the cost-effectiveness of pertuzumab + trastuzumab + chemotherapy, as compared to trastuzumab + chemotherapy in the adjuvant setting. The centrepiece of this analysis was the company's economic model, which was developed in a widely available spreadsheet application. The ERG considers the type and structure of the submitted model to be appropriate for representing the disease pathway and therapeutic options for the population specified in the NICE Final Scope for this appraisal. Key characteristics of the analysis, such as the selected perspective, time horizon, main outcome and discount rates, were in line with recommendations set out in the NICE Reference Case. The ERG felt that the company took reasonable steps to ascertain that data used in the model were of sound quality and suitable for the particular decision problem. The company's deterministic base case ICER, which is reported in the original submission, is £34,087 per QALY gained.

Model inputs and assumptions used in the model were scrutinised by the ERG. The following issues were identified and discussed in the ERG's critique:

- Uncertainties related to the duration of pertuzumab's incremental effect. The ERG believes that the choice of a relatively long duration of treatment effect is not justified adequately in the CS, and proposes alternative specifications, which the ERG believes to be better aligned with existing evidence. These specifications were incorporated in the ERG preferred base case
- Uncertainties around the specifications of the 'cure' adjustment. While the ERG agrees that the adjustment is beneficial, it proposes an alternative specification (i.e. different starting point and maximum cure proportion), which better represents available data on

the behaviour of hazard rates and late recurrence events. This amendment was reflected in the ERG's proposed base case

- Revisions in the calculations of the proportion of patients estimated to experience metastatic and non-metastatic recurrences. The ERG re-calculated the proportion of metastatic (and non-metastatic) events applicable to post-18 month relapses and used the revised values in the proposed ERG base case.

Carrying out these changes resulted in the ERG's base case ICER value of £60,679 per QALY gained.

Further uncertain parameters, which the ERG consider to be relevant to the decision problem in question, related to:

- the proportion of patients who are likely to receive pertuzumab with trastuzumab SC, should pertuzumab be recommended. Two experts consulted by the ERG felt that, should pertuzumab be available in the adjuvant setting, patients will initially (in the first one to two years after approval) receive this treatment with trastuzumab IV. However, both experts expressed the expectation that, in the medium and long term, the greatest share of patients on pertuzumab will receive the treatment with trastuzumab SC. Combinations assuming different shares of trastuzumab IV and SC are reported in ERG's additional analyses. It is noted that these results have been generated on the basis of currently available treatments and makes no assumptions about the possible availability, market share or price of biosimilar options in the future
- the acquisition cost of pertuzumab. While this is not an uncertain parameter, the fact that pertuzumab is offered as an additional treatment to trastuzumab and chemotherapy means that the acquisition cost of pertuzumab is an important cost driver. Lower and higher values of pertuzumab's price were used to illustrate the impact of this parameter on incremental costs and the resulting ICER.

To explore the impact of these parameters and facilitate the Committee's deliberations, the ERG present additional analyses undertaken using a range of alternative combinations and values.

6 IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

The impact of changes undertaken in order to implement the ERG's preferred base case analysis and additional sensitivity analyses is discussed below.

6.1 Impact of the ERG base case on ICER

The effect of the ERG's amendments on the ICER, when each change is carried out one at a time can be seen in Table 31. Revised ICERs are compared with the company's base case ICER for the node-positive population.

Using the ERG's preferred values on parameters related to the duration of treatment effect had a significant impact on the ICER, leading to an increase by approximately £20,820 (or 61%) over the company's base case ICER. After implementing this adjustment, the revised ICER was found to be £54,901 per QALY gained.

The effect of the two other amended parameters was smaller. Replacing the parameters controlling the 'cure' adjustment with values the ERG deem more appropriate resulted in an ICER of £37,686 per QALY gained, which is about £3,600 (or 10.6%) higher than the company's base case ICER. Changing the proportions for metastatic and non-metastatic disease recurrences according to the ERG's calculations led to an ICER of £35,933 per QALY gained, which is higher than the company's base case value by approximately £1,850 (5.4%).

Table 31. ICER values after implementing ERG's amendments in the company's base case

Parameter	Values in company's base case	ERG's preferred value	ERG's ICER (£ per QALY gained)
Duration of incremental treatment effect			
Time point when incremental treatment effect begins to wane	Year 7	Year 4	£54,901
Time point when incremental treatment effect ceases	Year 10	Year 7	
'Cure' adjustments			
Time point when 'cure' adjustment is introduced in the analysis	Year 4	Year 3	£37,686
Time point when maximum 'cure' is reached	Year 10	Year 10	
Maximum "cure" proportion	90.00%	95.00%	
Percentages of disease recurrence			
metastatic recurrence	76.87%	72.40%	£35,933
non-metastatic recurrence	23.13%	27.60%	

Carrying out all the above changes simultaneously, that is, implementing the ERG's suggested base case analysis, resulted in a considerable increase in the ICER, by approximately £26,600. The ERG's base case ICER in the node-positive population was calculated to be £60,679 per QALY gained (Table 32).

Table 32. Results of ERG suggested base case analysis

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£ per QALY gained)
HC (trastuzumab + chemotherapy)	[redacted]	[redacted]	[redacted]	[redacted]	£60,679
PHC (pertuzumab + trastuzumab + chemotherapy)	[redacted]	[redacted]			

6.2 Revised probabilistic sensitivity analysis based on ERG base case

PSA undertaken on the basis of the ERG amendments produced a mean ICER of £60,344 per QALY gained, which was very similar to the obtained deterministic value. The revised Cost Effectiveness (CE) plane and Cost Effectiveness Acceptability Curve (CEAC) depicting the comparison between PHC and HC are given in Figure 27 and Figure 28 below, respectively.

Figure 27. Cost-effectiveness plane depicting incremental cost and QALY pairs generated from revised PSA

Figure 28. Cost-effectiveness acceptability curves depicting the results of revised PSA

The probability of PHC being cost-effective was zero for willingness-to-pay (WTP) values up to £45,000 per QALY, it became greater than 50% for WTP values over £60,000 per QALY (i.e., the mean ICER derived from the PSA results) and it reached 100% for WTP values in excess of £90,000 per QALY. At £20,000 to £30,000 per QALY, the probability of PHC being cost-effective compared to HC at the £30,000 per QALY threshold was zero.

6.3 Additional deterministic sensitivity analyses

The ERG re-run the company's deterministic and scenario analyses on the basis of the ERG suggested base case. Results of these analyses, undertaken by keeping the ERG suggested base case values fixed and varying each of a number of parameters or assumptions, are presented below. Table 33 shows the revised variables used in the company's sensitivity analysis. For presentation purposes, only variables that lead to an increase or decrease in the ICER by more than 10% are shown. The greatest decrease in the ICER, was observed when utility values for eBC states were taken by Hedden et al.,[70] while the greatest increase resulted from limiting the model time horizon to 10 years. It must be noted that the main aim of this analysis was to test the effect of parameters on results, when these parameters assume extreme values. Thus, some of the values used are inevitably inappropriate (e.g., a 10 year time horizon) or unrealistic (all recurrent events assumed to be distant metastases).

Table 33. Revised results of company's scenario analyses based on ERG base case

Parameter	Value	PHC		HC		ICER	% change in ICER
		QALY	Costs	QALY	Costs		
Base case		[redacted]	[redacted]	[redacted]	[redacted]	£60,679	
Utility data source used in eBC	EQ-5D (per treatment arm)	[redacted]	[redacted]	[redacted]	[redacted]	£51,534	-15.07%
Utility data source used in eBC	Lidgren et al.	[redacted]	[redacted]	[redacted]	[redacted]	£34,727	-42.77%
Utility data source used in eBC	Heden et al.	[redacted]	[redacted]	[redacted]	[redacted]	£19,365	-68.09%
Proportion of metastatic recurrences	100%	[redacted]	[redacted]	[redacted]	[redacted]	£171,527	182.68%
Proportion of metastatic recurrences	0%	[redacted]	[redacted]	[redacted]	[redacted]	£21,286	-64.92%

Model time horizon	10 years	[redacted]	[redacted]	[redacted]	[redacted]	£305,682	403.77%
Model time horizon	20 years	[redacted]	[redacted]	[redacted]	[redacted]	£100,498	65.62%
Maximum "cure" proportion	0 years	[redacted]	[redacted]	[redacted]	[redacted]	£70,009	15.38%
Maximum "cure" proportion	0.2	[redacted]	[redacted]	[redacted]	[redacted]	£68,090	12.21%
Incremental tx effect begins to decrease	60	[redacted]	[redacted]	[redacted]	[redacted]	£53,853	-11.25%
Incremental tx effect begins to decrease	72	[redacted]	[redacted]	[redacted]	[redacted]	£48,901	-19.41%
Incremental tx effect begins to decrease	84	[redacted]	[redacted]	[redacted]	[redacted]	£45,562	-24.91%
Incremental tx effect begins to decrease	96	[redacted]	[redacted]	[redacted]	[redacted]	£40,775	-32.80%
Incremental tx effect begins to decrease	108	[redacted]	[redacted]	[redacted]	[redacted]	£38,162	-37.11%
Incremental tx effect begins to decrease	120	[redacted]	[redacted]	[redacted]	[redacted]	£37,071	-38.91%
IDFS parametric distribution	KM with Gompertz tail	[redacted]	[redacted]	[redacted]	[redacted]	£70,383	15.99%
IDFS parametric distribution	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	£66,836	10.15%
IDFS parametric distribution	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	£51,147	-15.71%
IDFS parametric distribution	KM with Log-normal tail	[redacted]	[redacted]	[redacted]	[redacted]	£48,227	-20.52%
Duration of treatment effect	Effect is maintained over time	[redacted]	[redacted]	[redacted]	[redacted]	£33,884	-44.16%

The ERG carried out further analyses, where each of a number of key variables were assigned alternative plausible values specified by the ERG (Table 34). The impact of these changes on the ICER was, in general, modest.

Table 34. Results of ERG additional analyses

Variable	Value	Diff. Costs (PHC vs HC)	Diff. QALYs (PHC vs HC)	ICER (£ per QALY gained)
Company's base case		[redacted]	[redacted]	£34,087
ERG's base case		[redacted]	[redacted]	£60,679
IDFS parametric distribution				
Gen Gamma fitted from 0 months	Gen Gamma fitted from 0 months	[redacted]	[redacted]	£64,050
Log-logistic fitted from 36 months	Log-logistic fitted from 36 months	[redacted]	[redacted]	£61,491
Gamma fitted from 36 months	Gamma fitted from 36 months	[redacted]	[redacted]	£65,914
Log-logistic fitted from 19 months	Log-logistic fitted from 19 months	[redacted]	[redacted]	£64,263
Gamma fitted from 19 months	Gamma fitted from 19 months	[redacted]	[redacted]	£69,067
Remission to First-line mBC				
Base case value (0.0076) halved	0.0038	[redacted]	[redacted]	£64,788
Base case value (0.0076) doubled	0.0152	[redacted]	[redacted]	£57,272
First-line mBC to 2nd + line mBC for pertuzumab + trastuzumab + chemotherapy				
Base case value (0.032) halved	0.016	[redacted]	[redacted]	£61,451
Base case value (0.032) doubled	0.064	[redacted]	[redacted]	£60,679
First-line mBC to 2nd + line mBC for trastuzumab + chemotherapy				
Base case value (0.047) halved	0.023	[redacted]	[redacted]	£60,987
Base case value (0.047) doubled	0.094	[redacted]	[redacted]	£60,261
First-line mBC to 2nd + line mBC for chemotherapy				
Base case value (0.069) halved	0.035	[redacted]	[redacted]	£60,786
Base case value (0.069) doubled	0.277	[redacted]	[redacted]	£60,495
Treatment-specific (non-pooled) percentages of recurrence calculated by the ERG				
PHC	73.33%	[redacted]	[redacted]	£63,236
HC	71.79%			
Proportion of treatment usage in 1st line metastatic disease: approximate shares based on the APHINITY trial				
Pertuzumab + trastuzumab + chemotherapy	18.40%	[redacted]	[redacted]	£59,744
Placebo + trastuzumab + chemotherapy	17.00%			
Chemotherapy alone	64.70%			
Utility values for IDFS states, non-metastatic recurrence and remission	Treatment specific (non-pooled) EQ-5D from APHINITY	[redacted]	[redacted]	£51,534
Utility values for non-metastatic recurrence				

from Ward et al.[79]	0.740	[redacted]	[redacted]	£60,652
from Peasgood et al.[81]	0.637	[redacted]	[redacted]	£60,485
Utility values for 'Remission'				
from Ward et al.[79]	0.850	[redacted]	[redacted]	£60,723
from Peasgood et al.[81]	0.710	[redacted]	[redacted]	£59,573
Utility values for 'First-line metastatic BC'				
from Ward et al.[79]	0.500	[redacted]	[redacted]	£58,053
from Zhou et al.[82]	0.650	[redacted]	[redacted]	£59,469
Utility values for 'Second + line BC'				
from Ward et al.[79]	0.500	[redacted]	[redacted]	£60,450
Peasgood et al.[81]	0.435	[redacted]	[redacted]	£59,720
from Sherill et al.[83]	0.425	[redacted]	[redacted]	£59,609
Non-pooled utility values for IDFS states.	Treatment specific EQ-5D values from APHINITY trial	[redacted]	[redacted]	£51,534
Disutility associated with adverse events (anaemia, cardiac events, diarrhoea, neutropenia, neutrophil count decrease)				
Disutility value	0.100	[redacted]	[redacted]	£60,734
Disutility value	0.500	[redacted]	[redacted]	£60,956
Disutility value	0.700	[redacted]	[redacted]	£61,068

Specific parameters which are likely to have an impact on the ICER and/or which the ERG considers to be particularly uncertain were looked at more closely. These include: i) the duration of pertuzumab's treatment effect; ii) the specifications of the 'cure' model adjustments; iii) the proportion of patients who are likely to receive pertuzumab with trastuzumab SC, should pertuzumab be recommended, and iv) the acquisition cost of pertuzumab. Further sensitivity analyses have been undertaken by using combinations of assumptions and values for each of these parameters and keeping the rest of the model parameters fixed at the ERG's preferred values. As mentioned in Section 6.1, the number of years that pertuzumab's treatment effect is expected to last is an inherently uncertain parameter, which also has a substantial impact the ICER. The ICER values associated with different specifications of this parameter can be seen in Table 35. Assuming that pertuzumab's effect starts to wane early and is null after a few years reduces the incremental effectiveness and incremental QALYs of the PHC and increases the ICER. Conversely, assuming a treatment effect that lasts for longer and, once it starts to diminish, it takes longer to disappear, leads to lower ICER values. Following the ERG's preferred specifications, a treatment effect that starts to wane at four years and disappears completely three years later, at seven years, the resulting ICER is £60,679 per QALY gained.

Table 35. Effect of different assumptions about pertuzumab's incremental treatment effect on ERG's base case ICER

	Duration of treatment waning (years)										
Effect starts to wane	0	1	2	3	4	5	6	7	8	9	10
Year 1	-£9,857,138	£938,870	£388,205	£228,726	£159,407	£122,494	£100,305	£85,911	£76,107	£69,226	£64,287
Year 2	£438,158	£241,196	£162,988	£122,337	£98,456	£83,211	£72,937	£65,771	£60,682	£57,017	-
Year 3	£168,911	£121,482	£96,576	£80,761	£70,150	£62,770	£57,529	£53,784	£51,096	-	-
Year 4	£97,526	£79,387	£68,353	£60,679	£55,226	£51,317	£48,531	£46,558	-	-	-
Year 5	£68,562	£59,631	£53,853	£49,699	£46,719	£44,622	£43,174	-	-	-	-
Year 6	£53,844	£48,901	£45,655	£43,345	£41,757	£40,706	-	-	-	-	-
Year 7	£45,562	£42,718	£40,907	£39,711	£38,969	-	-	-	-	-	-
Year 8	£40,775	£39,204	£38,319	£37,822	-	-	-	-	-	-	-
Year 9	£38,162	£37,461	£37,155	-	-	-	-	-	-	-	-
Year 10	£37,071	£36,853	-	-	-	-	-	-	-	-	-

Similarly, the time point at which the 'cure' adjustment should be introduced in the analysis, and the maximum cure proportion (i.e., the proportion of patients no longer at risk of recurrence) are subject to uncertainty. The effect of different specification can be seen in Table 36. While the ERG agrees with the company that the maximum 'cure' proportion is likely to be reached at ten years, the ERG believes that the 'cure' effect is likely to start earlier (at three years) and reach a maximum proportion of 95% of the patients.

Table 36. Effect of different assumptions about the 'cure' adjustment.

	Maximum cure (percentage of patients in IDFS states no longer in risk of recurrence)		
Start of 'cure' adjustment	95%	90%	80%
Year 1	£73,118	£72,784	£72,193
Year 2	£66,130	£66,298	£66,652
Year 3	£60,679	£61,180	£62,180
Year 4	£57,012	£57,707	£59,095
Year 5	£55,258	£56,037	£57,596
Year 6	£55,067	£55,855	£57,431
Year 7	£55,876	£56,625	£58,123
Year 8	£56,865	£57,567	£58,968
Year 9	£57,803	£58,459	£59,767
Year 10	£58,617	£59,232	£60,457

The ERG experts suggested that, should pertuzumab be recommended, they would expect an increasing share of patients to be receiving the treatment with trastuzumab SC. The company's analysis assumes that the entirety of trastuzumab received in combination with pertuzumab will be trastuzumab IV, which, according to ERG's expert advisors, it is only likely to be the case in the short term (one to two years post approval). Figure 29 shows the impact of different assumptions about plausible shares of trastuzumab IV and SC on ICER. On the basis of currently available treatment options and formulations (i.e. no biosimilars), greater shares of trastuzumab SC are associated with higher ICER values.

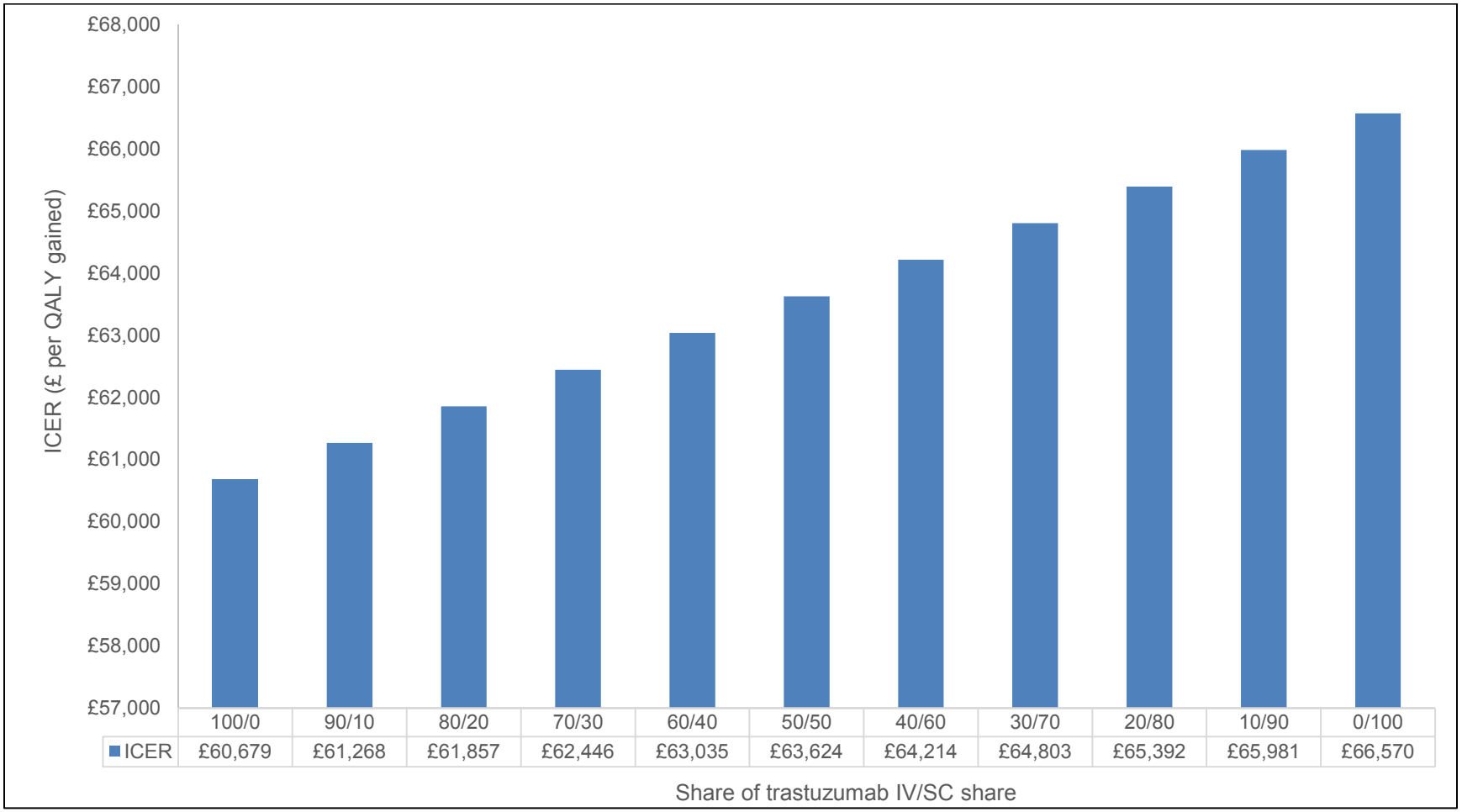


Figure 29. Effect of different assumptions about trastuzumab IV and SC administration when given in combination with pertuzumab

Pertuzumab's acquisition cost has a notable impact on the generated ICER values. Naturally, a lower price for pertuzumab would reduce the additional cost associated with PHC and lead to a lower ICER value. For illustration purposes, the effect of lower and higher prices of pertuzumab can be seen in Figure 30 below.

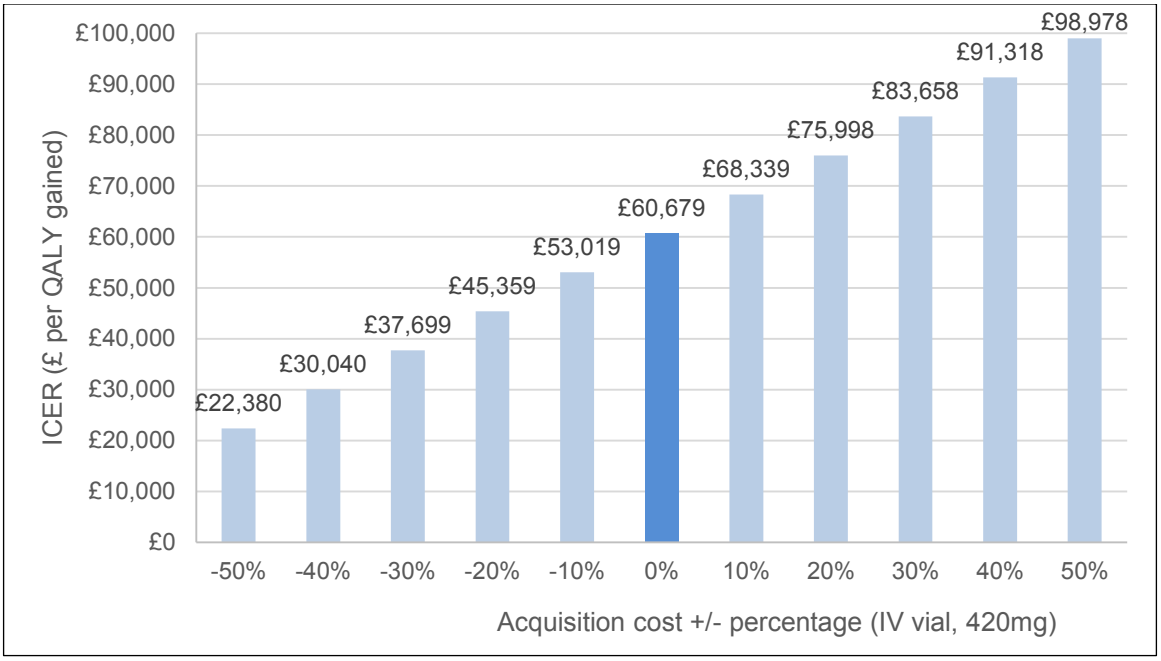


Figure 30. Effect of pertuzumab acquisition cost on ICER

7 END OF LIFE

The company has not presented a case in support of pertuzumab as an 'end of life' treatment. NICE prescribes that, for an 'end of life' case to be made, the appraised treatment needs to satisfy all of the following criteria: i) the treatment is indicated for patients with a short life expectancy, normally less than 24 months and; ii) 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; iii) the treatment is licensed or otherwise indicated, for small patient populations. The ERG considers that these criteria are not met.

8 OVERALL CONCLUSION

Clinical effectiveness conclusion

The company present a reasonable quality systematic review of the clinical effectiveness of adjuvant pertuzumab in combination with trastuzumab and chemotherapy. The APHINITY trial is the main source of evidence, and the comparator and intervention reported in this trial are appropriate and consistent with the NICE final scope. IDFS and DRFI were additional outcomes in the trial which were not listed in the NICE scope, but were considered appropriate by the ERG clinical advisor. The population in the APHINITY trial (n=4806) addresses the decision problem which focusses on eBC patients with a high-risk of recurrence after surgical treatment. The ERG is concerned about the emphasis of node-positive (base case) and hormone receptor-negative (additional scenario) patients as the target population, whereas other high-risk subgroups (such as histological grade 3 and tumour size > 5cm) lacked consideration in the company decision problem.

The ERG notes an amendment to the original protocol of the APHINITY trial (protocol A) which was implemented after 3655 participants had been randomised in order to enrol only node-positive patients (protocol B). The ERG suggest that protocol B is effectively a second trial in which node-positive patients were randomised to the pertuzumab-based arm or the control arm (placebo-based), hence, there is no immediate concern of bias.

The efficacy analysis of the APHINITY trial revealed that pertuzumab was marginally better than placebo for preventing recurrence of breast cancer and/or death (HR 0.82, 95% CI 0.67 to 1.00). The ERG is concerned that this difference may not be clinically meaningful. Analyses of the nodal subgroups revealed a less marginal difference in IDFS rates between pertuzumab and

placebo in node-positive patients (HR 0.77, 95% CI 0.62 to 0.96), whereas no statistically significant difference was detected in node-negative patients (HR 1.13, 95% CI 0.68 to 1.86). The ERG is concerned that adjuvant pertuzumab may only be effective in eBC patients with 10 or more cancer cells in the loco-regional lymph nodes. Analyses of the hormone receptor subgroups reveal no statistically significant benefit of pertuzumab over placebo in hormone receptor-negative (HR 0.76, 95% CI 0.56 to 1.04) or hormone receptor-positive patients (HR 0.86, 95% CI 0.66 to 1.13).

The ERG questions the safety profile of pertuzumab, with significantly larger proportions of patients in the pertuzumab-based arm experiencing grade 3 or higher adverse events compared to patients in the placebo-based arm (64.2% vs. 57.3%, $p < 0.001$). Of note, patients in the pertuzumab-based arm were more likely to develop grade 3 or higher diarrhoea (9.8% vs. 3.7%, $p < 0.001$), anaemia (6.9% vs. 4.7%, $p=0.001$) and symptomatic heart failure (0.6% vs. 0.2%, $p=0.04$), compared to the placebo-based arm.

In summary, the ERG notes that the APHINITY trial was not powered to detect subgroup differences. The ERG was unable to rule out any spurious interactions between subgroup variables. Whilst there is evidence of a treatment effect among the nodal status subgroups, the ERG believes that the apparent treatment interactions with hormone receptor status and menopausal status may be artefacts of the interaction with nodal status for which there is slightly stronger evidence. The ERG considers that claims of treatment benefit (marginal) should be balanced against the safety of adjuvant pertuzumab in combination with trastuzumab and chemotherapy.

Cost effectiveness conclusion

The main analysis presented in the CS relates to a population with HER2-positive, node-positive disease. An additional analysis pertaining to patients with HER2-positive hormone receptor-negative disease was included in appendix M of the CS. The ERG's critique focused on the main analysis (node-positive population); however, issues identified and points raised are also applicable to the additional analysis (hormone receptor-negative population).

The company's economic analysis was based on a decision analytic model developed in a spreadsheet application. The ERG considers the type and structure of the submitted model to be

appropriate for representing the disease pathway and therapeutic options for the particular population of breast cancer patients. The perspective, time horizon, outcomes and discount rates chosen for this analysis are in line with NICE recommendations.

The ERG felt that the company took appropriate steps to ascertain that data used in the model were of reasonable quality. When possible, clinical and HRQoL data were drawn from the APHINITY trial. Of note is the fact that the collection schedule of HRQoL (EQ-5D) data which were used in early BC states, was not designed to capture differences attributable to treatment arms. Resource use and cost inputs used in the models were in line with those in the appraisal of neoadjuvant pertuzumab. The company's deterministic base case ICER, which is reported in the original submission, is £34,087 per QALY gained.

The ERG's critique on the company's economic analyses focused on the following key uncertainties:

- Duration of the pertuzumab's treatment effect. The ERG believes that a shorter duration of treatment effect than specified in the economic model would be better aligned with existing evidence
- Specifications of the 'cure' adjustment. While the ERG agrees that the adjustment is beneficial, it proposes an alternative specification of the 'cure' model (starting point and maximum cure proportion), which better represents available data
- Revisions in the calculations of the proportion of patients estimated to experience metastatic and non-metastatic recurrences. The ERG re-calculated the proportion of metastatic (and non-metastatic) events applicable to post-18 month relapses and used the revised values in the proposed ERG base case.

Incorporating these changes in the ERG base case resulted in the ERG's base case ICER value of £60,679 per QALY gained. The ERG's amendment of the duration of treatment effect was the parameter with the greatest impact on the revised ICER.

A further point, which the ERG considers to be relevant to the decision problem in question, relates to the number of patients who are likely to receive pertuzumab with trastuzumab SC in the future, should pertuzumab be recommended. Experts consulted by the ERG felt that, should pertuzumab be available in the adjuvant setting, the vast majority of patients will initially (in the

first one to two years after approval) receive this treatment with trastuzumab IV. This is the assumption on which the company's and the ERG's base case is based on. However, experts suggested that, in the medium and long term, an increasingly larger proportion of patients on pertuzumab will receive the treatment with trastuzumab SC. This suggests that this analysis (and the decision made in light of it) may need to be revisited, when further information about the share of trastuzumab SC becomes available.

8.1 Implications for research

- Further evidence on the duration of pertuzumab's effect in the particular population and setting would be highly useful. The number of years for which this effect was assumed to last had a significant impact on the calculated ICER. Mature data from APHINITY is expected to reduce the uncertainty around this key parameter.
- Further evidence is needed on the medium and long-term split between trastuzumab IV and SC usage when combined with pertuzumab, should pertuzumab be recommended in the adjuvant setting. Additionally, further information would be useful on the market share and price of trastuzumab biosimilars, should these become available in the near future.

9 REFERENCES

1. von Minckwitz G, Procter M, de Azambuja E, Zardavas D, Benyunes M, Viale G*, et al.* Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. *NEJM* 2017;**377**:122-31. http://dx.doi.org/10.1056/NEJMoa1703643

2. Cancer Research UK. *Breast Cancer Statistics*. URL: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer (Accessed 28 March 2018).

3. Cancer Research UK. *Breast Cancer Incidence (Invasive) Statistics*. URL: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer/incidence-invasive (Accessed 28 March 2018).

4. Office for National Statistics. *Cancer registration statistics, England: first release, 2016*. 2018. URL: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/cancerregistrationstatisticsengland/2016 (Accessed 13 April 2018).

5. National Institute for Health and Care Excellence. *Pertuzumab for the adjuvant treatment of HER2-positive breast cancer - Final scope*. 2017. URL: https://www.nice.org.uk/guidance/gid-ta10184/documents/final-scope (Accessed 10 March 2018).

6. BreastCancer.org. *Breast cancer stages*. 2010. URL: http://www.breastcancer.org/symptoms/diagnosis/staging (Accessed 27 March 2018).

7. Rakha EA, Pinder SE, Bartlett JM, Ibrahim M, Starczynski J, Carder PJ*, et al.* Updated UK Recommendations for HER2 assessment in breast cancer. *J Clin Pathol* 2015;**68**:93-9.

8. Borg A, Tandon AK, Sigurdsson H, Clark GM, Ferno M, Fuqua SA*, et al.* HER-2/neu amplification predicts poor survival in node-positive breast cancer. *Cancer Res* 1990;**50**:4332-7.

9. Ross JS, Fletcher JA. The HER-2/neu Oncogene in Breast Cancer: Prognostic Factor, Predictive Factor, and Target for Therapy. *Oncologist* 1998;**3**:237-52.

10. Menard S, Fortis S, Castiglioni F, Agresti R, Balsari A. HER2 as a prognostic factor in breast cancer. *Oncology* 2001;**61 Suppl 2**:67-72. http://dx.doi.org/55404

11. Brown M, Tsodikov A, Bauer KR, Parise CA, Caggiano V. The role of human epidermal growth factor receptor 2 in the survival of women with estrogen and progesterone receptor-negative, invasive breast cancer: the California Cancer Registry, 1999-2004. *Cancer* 2008;**112**:737-47. http://dx.doi.org/10.1002/cncr.23243

12. Curigliano G, Viale G, Bagnardi V, Fumagalli L, Locatelli M, Rotmensz N*, et al.* Clinical relevance of HER2 overexpression/amplification in patients with small tumor size and node-negative breast cancer. *J Clin Oncol* 2009;**27**:5693-9. http://dx.doi.org/10.1200/JCO.2009.22.0962

13. Ross JS, Slodkowska EA, Symmans WF, Pusztai L, Ravdin PM, Hortobagyi GN. The HER-2 receptor and breast cancer: ten years of targeted anti-HER-2 therapy and personalized medicine. *Oncologist* 2009;**14**:320-68. http://dx.doi.org/10.1634/theoncologist.2008-0230

14. BreastCancer.org. *Hormone Receptor Status*. URL: http://www.breastcancer.org/symptoms/diagnosis/hormone_status (Accessed 10 March 2018).

15. Slamon D, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science* 1987;**235**:177-82.

16. Subbiah IM, Gonzalez-Angulo AM. Advances and future directions in the targeting of HER2-positive breast cancer: implications for the future. *Curr Treat Options Oncol* 2014;**15**:41-54. http://dx.doi.org/10.1007/s11864-013-0262-4

17. Wardley A, Fredriksson J, Leslie I, Batten T, Ring A. Anti-cancer resource use in the initial management of advanced HER2+ breast cancer: an interim analysis of the UK ESTHER study. Abstract EBCC-0377 2018. Paper presented at: European Breast Cancer Conference (EBCC-11); Barcelona, Spain.

18. National Institute for Health and Care Excellence. *CG80: Early and locally advanced breast cancer: diagnosis and treatment*. 2009. URL: https://www.nice.org.uk/Guidance/CG80 (Accessed 10 March 2018).

19. Senkus E, Kyriakides S, Ohno S, Penault-Llorca F, Poortmans P, Rutgers E*, et al.* Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. *Ann Oncol* 2015;**26**:v8-v30. http://dx.doi.org/10.1093/annonc/mdv298

20. Curigliano G, Burstein HJ, E PW, Gnant M, Dubsky P, Loibl S*, et al.* De-escalating and escalating treatments for early-stage breast cancer: the St. Gallen International Expert Consensus Conference on the Primary Therapy of Early Breast Cancer 2017. *Ann Oncol* 2017;**28**:1700-12. http://dx.doi.org/10.1093/annonc/mdx308

21. Gnant M, Thomssen C, Harbeck N. St. Gallen/Vienna 2017: A Brief Summary of the Consensus Discussion about Escalation and De-Escalation of Primary Breast Cancer Treatment. *Breast Care* 2017;**12**:102-7.

22. National Comprehensive Cancer Network. *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®), Breast Cancer - Version 3.2017*. 2017. URL: https://www.nccn.org/professionals/physician_gls/default.aspx (Accessed 10 March 2018).

23. Haddad TC, Goetz MP. Landscape of neoadjuvant therapy for breast cancer. *Ann Surg Oncol* 2015;**22**:1408-15.

24. Chatterjee A, Erban JK. Neoadjuvant therapy for treatment of breast cancer: the way forward, or simply a convenient option for patients? *Gland surgery* 2017;**6**:119.

25. BreastCancer.org. *Systemic Treatments for IDC: Chemotherapy, Hormonal Therapy, Targeted Therapies*. 2016. URL: http://www.breastcancer.org/symptoms/types/idc/treatment/systemic (Accessed 27 March 2018).

26. Chen SL, Hoehne FM, Giuliano AE. The prognostic significance of micrometastases in breast cancer: a SEER population-based analysis. *Ann Surg Oncol* 2007;**14**:3378-84. http://dx.doi.org/10.1245/s10434-007-9513-6

27. National Institute for Health and Care Excellence. *NICE Pathways: Adjuvant therapy for early and locally advanced breast cancer*. 2018. URL: https://pathways.nice.org.uk/pathways/early-and-locally-advanced-breast-cancer#path=view%3A/pathways/early-and-locally-advanced-breast-cancer/adjuvant-therapy-for-early-and-locally-advanced-breast-cancer.xml&content=view-index (Accessed 9 March 2018).

28. European Medicines Agency (EMA). *Herceptin: Procedural steps taken and scientific information after the authorisation*. 2018. URL: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Procedural_steps_taken_and_scientific_information_after_authorisation/human/000278/WC500049820.pdf (Accessed 5 April 2018).

29. Aebi S, Davidson T, Gruber G, Cardoso F, Esmo Guidelines Working Group. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2011;**22 Suppl 6**:vi12-24. http://dx.doi.org/10.1093/annonc/mdr371

30. Cardoso F, Costa A, Norton L, Cameron D, Cufer T, Fallowfield L*, et al.* 1st International consensus guidelines for advanced breast cancer (ABC 1). *The Breast* 2012;**21**:242-52. http://dx.doi.org/http://dx.doi.org/10.1016/j.breast.2012.03.003

31. Carlson RW, Allred DC, Anderson BO, Burstein HJ, Carter WB, Edge SB*, et al.* Breast cancer. Clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 2009;**7**:122-92.

32. Electronic Medicines Compendium (eMC). *Perjeta 420 mg concentrate for solution for infusion: Summary of product characteristics*. 2018. URL: www.medicines.org.uk/emc/medicine/27473/ (Accessed 9 March 2018).

33. Mauri D, Pavlidis N, Ioannidis JP. Neoadjuvant versus adjuvant systemic treatment in breast cancer: a meta-analysis. *J Natl Cancer Inst* 2005;**97**:188-94. http://dx.doi.org/10.1093/jnci/dji021

34. Committee for Medicinal Products for Human Use (CHMP). *Perjeta: Assessment Report - Variation*. European Medicines Agency (EMA); 2015. URL: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/002547/WC500191986.pdf (Accessed 5 April 2018).

35. Baselga J, Cortes J, Kim SB, Im SA, Hegg R, Im YH*, et al.* Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *N Engl J Med* 2012;**366**:109-19. http://dx.doi.org/10.1056/NEJMoa1113216

36. Marty M, Cognetti F, Maraninchi D, Snyder R, Mauriac L, Tubiana-Hulin M*, et al.* Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: the M77001 study group. *J Clin Oncol* 2005;**23**:4265-74. http://dx.doi.org/10.1200/JCO.2005.04.173

37. Strasser-Weippl K, Horick N, Smith IE, O'Shaughnessy J, Ejlertsen B, Boyle F*, et al.* Long-term hazard of recurrence in HER2+ breast cancer patients untreated with anti-HER2 therapy. *Breast Cancer Research: BCR* 2015;**17**:56. http://dx.doi.org/10.1186/s13058-015-0568-1

38. Cameron D, Piccart-Gebhart MJ, Gelber RD, Procter M, Goldhirsch A, de Azambuja E*, et al.* 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. *Lancet* 2017;**389**:1195-205. http://dx.doi.org/10.1016/S0140-6736(16)32616-2

39. Cortazar P, Zhang L, Untch M, Mehta K, Costantino JP, Wolmark N*, et al.* Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. *Lancet* 2014;**384**:164-72. http://dx.doi.org/10.1016/S0140-6736(13)62422-8

40. Hudis CA, Barlow WE, Costantino JP, Gray RJ, Pritchard KI, Chapman JA*, et al.* Proposal for standardized definitions for efficacy end points in adjuvant breast cancer trials: the STEEP system. *J Clin Oncol* 2007;**25**:2127-32. http://dx.doi.org/10.1200/JCO.2006.10.3523

41. Kemp R, Prasad V. Surrogate endpoints in oncology: when are they acceptable for regulatory and clinical decisions, and are they currently overused? *BMC Med* 2017;**15**:134. http://dx.doi.org/10.1186/s12916-017-0902-9

42. Cancer Research UK. *Breast cancer survival statistics*. URL: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer/survival (Accessed 13 April 2018).

43. National Institute for Health and Care Excellence. *Trastuzumab emtansine for treating HER2-positive advanced breast cancer after trastuzumab and a taxane. Technology appraisal guidance [TA458]*. 2017. URL: https://www.nice.org.uk/guidance/ta458 (Accessed 28 March 2018).

44. National Institute for Health and Care Excellence. *Afatinib for treating epidermal growth factor receptor mutation-positive locally advanced or metastatic non-small-cell lung cancer. Technology appraisal guidance [TA310]*. 2014. URL: https://www.nice.org.uk/guidance/ta310 (Accessed 28 March 2018).

45. Centre for Reviews Dissemination. *Systematic reviews: CRD's guidance for undertaking reviews in health care*. York: University of York; 2009. URL: https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf (Accessed 25 March 2018).

46. National Institute for Health and Care Excellence. *Single technology appraisal: User guide for company evidence submission template*. 2015. URL: https://www.nice.org.uk/process/pmg24/chapter/instructions-for-companies (Accessed 3 March 2018).

47. Slamon D, Eiermann W, Robert N, Pienkowski T, Martin M, Press M*, et al.* Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med* 2011;**365**:1273-83. http://dx.doi.org/10.1056/NEJMoa0910383

48. Clinicaltrials.gov. *A Study of Pertuzumab in Addition to Chemotherapy and Trastuzumab as Adjuvant Therapy in Participants With Human Epidermal Growth Receptor 2 (HER2)-Positive Primary Breast Cancer (APHINITY) [APHINITY study record (NCT01358877)]*. URL: https://clinicaltrials.gov/ct2/show/NCT01358877 (Accessed 15 March 2018).

49. National Cancer Intelligence Network. *Cancer Incidence and Survival By Major Ethnic Group, England, 2002 - 2006*. 2009. URL: http://www.ncin.org.uk/view?rid=75 (Accessed 27 March 2018).

50. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, Goldhirsch A, Untch M, Smith I*, et al.* Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *NEJM* 2005;**353**:1659-72.

51. Mastracci TL, Boulos FI, Andrulis IL, Lam WL. Genomics and premalignant breast lesions: clues to the development and progression of lobular breast cancer. *Breast Cancer Res* 2007;**9**:215. http://dx.doi.org/10.1186/bcr1785

52. Blakesley RE, Mazumdar S, Dew MA, Houck PR, Tang G, Reynolds CF, 3rd*, et al.* Comparisons of methods for multiple hypothesis testing in neuropsychological research. *Neuropsychology* 2009;**23**:255-64. http://dx.doi.org/10.1037/a0012850

53. Royston P, Parmar MK. Restricted mean survival time: an alternative to the hazard ratio for the design and analysis of randomized trials with a time-to-event outcome. *BMC Med Res Methodol* 2013;**13**:152. http://dx.doi.org/10.1186/1471-2288-13-152

54. Chilcott J, Lloyd Jones M, Wilkinson A. Docetaxel for the adjuvant treatment of early node-positive breast cancer: a single technology appraisal. *Health Technol Assess* 2009;**13**:7-13.

55. Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol* 1998;**16**:139-44. http://dx.doi.org/10.1200/jco.1998.16.1.139

56. Miliaras D, Kamas A, Kalekou H. Angiogenesis in invasive breast carcinoma: is it associated with parameters of prognostic significance? *Histopathology* 1995;**26**:165-9.

57. Marinho A, Soares R, Ferro J, Lacerda M, Schmitt FC. Angiogenesis in breast cancer is related to age but not to other prognostic parameters. *Pathol Res Pract* 1997;**193**:267-73. http://dx.doi.org/10.1016/s0344-0338(97)80003-9

58. Dabrosin C. Variability of vascular endothelial growth factor in normal human breast tissue in vivo during the menstrual cycle. *J Clin Endocrinol Metab* 2003;**88**:2695-8. http://dx.doi.org/10.1210/jc.2002-021584

59. Retsky M, Bonadonna G, Demicheli R, Folkman J, Hrushesky W, Valagussa P. Hypothesis: Induced angiogenesis after surgery in premenopausal node-positive breast cancer patients is a major underlying reason why adjuvant chemotherapy works particularly well for those patients. *Breast Cancer Res* 2004;**6**:R372-4. http://dx.doi.org/10.1186/bcr804

60. Retsky M, Demicheli R, Hrushesky W. Premenopausal status accelerates relapse in node positive breast cancer: hypothesis links angiogenesis, screening controversy. *Breast Cancer Res Treat* 2001;**65**:217-24.

61. Miller KD. Questioning Our APHINITY for More. *N Engl J Med* 2017;**377**:186-7. http://dx.doi.org/10.1056/NEJMe1706150

62. National Cancer Institute. *Common Terminology Criteria for Adverse Events (CTCAE) v5.0*. 2017. URL: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50 (Accessed 13 April 2018).

63. National Institute for Health and Care Excellence. *Venetoclax for treating chronic lymphocytic leukaemia: Technology appraisal guidance [TA487]*. 2017. URL: https://www.nice.org.uk/guidance/ta487 (Accessed 13 April 2018).

64. *Gastroenteritis: Scenario: Adult*. National Institute for Health and Care Excellence, Clinical Knowledge Summaries; 2017. URL: https://cks.nice.org.uk/gastroenteritis#!scenario:2 (Accessed 04 April 2018).

65. Urruticoechea A, Rizwanullah M, Im SA, Ruiz ACS, Lang I, Tomasello G*, et al.* Randomized Phase III Trial of Trastuzumab Plus Capecitabine With or Without Pertuzumab in Patients With Human Epidermal Growth Factor Receptor 2-Positive Metastatic Breast Cancer Who Experienced Disease Progression During or After Trastuzumab-Based Therapy. *J Clin Oncol* 2017;**35**:3030-8. http://dx.doi.org/10.1200/jco.2016.70.6267

66. Gianni L, Pienkowski T, Im Y-H, Roman L, Tseng L-M, Liu M-C*, et al.* 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. *The Lancet Oncology* 2012;**13**:25-32. http://dx.doi.org/10.1016/S1470-2045(11)70336-9

67. Schneeweiss A, Chia S, Hickish T, Harvey V, Eniu A, Hegg R*, et al.* 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). *Ann Oncol* 2013;**24**:2278-84. http://dx.doi.org/10.1093/annonc/mdt182

68. Swain SM, Baselga J, Kim SB, Ro J, Semiglazov V, Campone M*, et al.* Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. *NEJM* 2015;**372**:724-34. http://dx.doi.org/10.1056/NEJMoa1413513

69. Lloyd A, Nafees B, Narewska J, Dewilde S, Watkins J. Health state utilities for metastatic breast cancer. *Br J Cancer* 2006;**95**:683-90. http://dx.doi.org/10.1038/sj.bjc.6603326

70. Hedden L, O'Reilly S, Lohrisch C, Chia S, Speers C, Kovacic L*, et al.* Assessing the real-world cost-effectiveness of adjuvant trastuzumab in HER-2/neu positive breast cancer. *Oncologist* 2012;**17**:164-71. http://dx.doi.org/10.1634/theoncologist.2011-0379

71. Lidgren M, Wilking N, Jonsson B, Rehnberg C. Health related quality of life in different states of breast cancer. *Qual Life Res* 2007;**16**:1073-81.

72. Paracha N. *Assessing the contribution of patients' proximity to death in economic evaluations in patients with HER2+ metastatic breast cancer: an event based analysis*. London, UK; 2016. URL: https://smdm.confex.com/smdm/16BEC/webprogram/Paper9942.html (Accessed 1 March 2018).

73. Ayiku L, Levay P, Hudson T, Craven J, Barrett E, Finnegan A*, et al.* The medline UK filter: development and validation of a geographic search filter to retrieve research about the UK from OVID medline. *Health Info Libr J* 2017;**34**:200-16. http://dx.doi.org/10.1111/hir.12187

74. National Institute for Health and Care Excellence. *Guide to the methods of technology appraisal 2013: The reference case*. 2013. URL: https://www.nice.org.uk/process/pmg9/chapter/the-reference-case (Accessed 3 March 2018).

75. National Institute for Health and Care Excellence. *TA424: Pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer*. 2016. URL: https://www.nice.org.uk/guidance/ta424 (Accessed 1 March 2018).

76. Burnham KP, Anderson DR. Multimodel inference: understanding AIC and BIC in model selection. *Sociological methods & research* 2004;**33**:261-304.

77. Dieras V, Miles D, Verma S, Pegram M, Welslau M, Baselga J*, et al.* Trastuzumab emtansine versus capecitabine plus lapatinib in patients with previously treated HER2-positive advanced breast cancer (EMILIA): a descriptive analysis of final overall survival results from a randomised, open-label, phase 3 trial. *Lancet Oncol* 2017;**18**:732-42. http://dx.doi.org/10.1016/s1470-2045(17)30312-1

78. Hamilton SN, Tyldesley S, Li D, Olson R, McBride M. Second malignancies after adjuvant radiation therapy for early stage breast cancer: is there increased risk with addition of regional radiation to local radiation? *Int J Radiat Oncol Biol Phys* 2015;**91**:977-85. http://dx.doi.org/10.1016/j.ijrobp.2014.12.051

79. Ward S, Simpson E, Davis S, Hind D, Rees A, Wilkinson A. Taxanes for the adjuvant treatment of early breast cancer: systematic review and economic evaluation. *Health Technol Assess* 2007;**11**:1-144.

80. Tengs TO, Wallace A. One thousand health-related quality-of-life estimates. *Med Care* 2000;**38**:583-637.

81. Peasgood T, Ward SE, Brazier J. Health-state utility values in breast cancer. *Expert Rev Pharmacoecon Outcomes Res* 2010;**10**:553-66. http://dx.doi.org/10.1586/erp.10.65

82. Zhou X, Cella D, Cameron D, Amonkar MM, Segreti A, Stein S*, et al.* Lapatinib plus capecitabine versus capecitabine alone for HER2+ (ErbB2+) metastatic breast cancer: quality-of-life assessment. *Breast Cancer Research & Treatment* 2009;**117**:577-89. http://dx.doi.org/https://dx.doi.org/10.1007/s10549-009-0310-8

83. Sherrill B, Amonkar MM, Stein S, Walker M, Geyer C, Cameron D. Q-TWiST analysis of lapatinib combined with capecitabine for the treatment of metastatic breast cancer. *British Journal of Cancer* 2008;**99**:711-5. http://dx.doi.org/https://dx.doi.org/10.1038/sj.bjc.6604501

84. Joint Formulary Committee. *British National Formulary (online)*. London: BMJ Group and Pharmaceutical Press; 2018. URL: https://www.medicinescomplete.com/mc/bnf/current/ (Accessed 5 March 2018).

85. NHS National Tariff. *Annex A: The national process and national tariff workbook*. URL: https://improvement.nhs.uk/resources/national-tariff-1719/ (Accessed 3 March 2018).

86. Department of Health and Social Care. *NHS reference costs 2016 to 2017*. 2017. URL: https://improvement.nhs.uk/resources/reference-costs/ (Accessed 12 March 2018).

87. Curtis L, Burns A. *Unit Costs of Health and Social Care 2017*. Canterbury, UK: Personal Social Services Research Unit (PSSRU), University of Kent; 2017. URL: https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2017/ (Accessed 13 March 2018).

88. Eddy DM, Hollingworth W, Caro JJ, Tsevat J, McDonald KM, Wong JB. Model transparency and validation: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force-7. *Med Decis Making* 2012;**32**:733-43. http://dx.doi.org/10.1177/0272989x12454579

89. Hall PS, Hulme C, McCabe C, Oluboyede Y, Round J, Cameron DA. Updated cost-effectiveness analysis of trastuzumab for early breast cancer: a UK perspective considering duration of benefit, long-term toxicity and pattern of recurrence. *Pharmacoeconomics* 2011;**29**:415-32. http://dx.doi.org/https://dx.doi.org/10.2165/11588340-000000000-00000

10 APPENDICES

10.1 Appendix 1. Records excluded from company's SLR due to inability to obtain their full text

Table 37. Records excluded from the company's cost effectiveness and HRQoL SLR at full-text review stage for reason 'Could not find publication'. Extract from CS appendix G table 21 with additional column 'ERG Notes'

No.	Author(s)	Year	Article title	Reason for exclusion	ERG Notes
Original Searches					
1	-	2013	Accelerated radiotherapy after breast-conserving surgery for early stage breast cancer	Could not find publication	commercial HTA report – not obtained
6	Berger et al.	2009	Variability of patterns of fatigue and quality of life over time based on different breast cancer adjuvant chemotherapy regimens	Could not find publication	full text publication obtained
8	Bossart et al.	2011	Early breast cancer - Quality of life after switching from tamoxifen to exemestane: Results of a non-interventional study	Could not find publication	non-English journal
10	Campone et al.	2013	BOLERO-2: Efficacy, safety, and quality of life in patients with advanced breast cancer receiving first-line everolimus plus exemestane	Could not find publication	meeting abstract
13	Estalella Mendoza et al.	2013	Quality of life in women with breast cancer that receive adjuvant chemotherapy	Could not find publication	meeting abstract
20	Gozzo et al.	2011	Evaluating the quality of life of women with breast cancer during chemotherapy treatment	Could not find publication	meeting abstract
22	Groenvold	2010	Health-related quality of life in early breast cancer	Could not find publication	full text publication (preprint) obtained
24	Hall et al.	2010	Cross-sectional study of Quality of Life (QL) 6 years after start of treatment in the UK Taxotere as Adjuvant Chemotherapy Trial (TACT; CRUK01/001)	Could not find publication	meeting abstract
25	Hall et al.	2011	Updated cost-effectiveness analysis of trastuzumab for early breast cancer: a UK perspective considering duration of benefit, long-term toxicity and pattern of recurrence	Could not find publication	full text publication obtained
27	Hayman et al.	1998	Cost-effectiveness of routine radiation therapy following conservative surgery for early-stage breast cancer	Could not find publication	full text publication obtained
30	Karnon et al.	2009	A survival-based cost-effectiveness analysis of 5 years of letrozole versus tamoxifen as adjuvant therapy in postmenopausal women with early breast cancer: 76-month update of BIG-1-98	Could not find publication	meeting abstract
31	Karnon et al.	2010	Updated survival-based analysis using inverse probability of censoring weighted analysis (IPCW) to estimate the cost-	Could not find publication	meeting abstract

No.	Author(s)	Year	Article title	Reason for exclusion	ERG Notes
			effectiveness of letrozole and anastrozole versus tamoxifen as adjuvant therapy in postmenopausal women with early breast cancer		
32	Kaura et al.	2008	Cost-effectiveness of late extended adjuvant letrozole following a prolonged therapy break from tamoxifen - Updated MA-17 post-unblinding analysis	Could not find publication	Could not find, but found meeting abstract with same title (Karnon first author)
35	Larsson et al.	2010	Health-related quality of life and healthcare experiences in breast cancer patients in a study of Swedish women	Could not find publication	full text publication obtained
36	Lazzaro	2007	Cost-utility analysis of anastrozole versus tamoxifen for adjuvant treatment in postmenopausal women with early breast cancer	Could not find publication	non-English journal (Italian)
37	Lee et al.	2002	Decision-analytic model and cost-effectiveness evaluation of postmastectomy radiation therapy in high-risk premenopausal breast cancer patients	Could not find publication	full text publication obtained
40	Limwattananon et al.	2006	Cost-effectiveness analysis of sequential paclitaxel adjuvant chemotherapy for patients with node positive primary breast cancer	Could not find publication	non-English journal (Thai)
41	Lindner et al.	2013	Cost-effectiveness analysis of adjuvant therapy with trastuzumab for the treatment of early-stage breast cancer	Could not find publication	non-English journal (Spanish)
42	Lipsitz et al.	2010	Cost effectiveness of letrozole versus anastrozole in postmenopausal women with HR+ early-stage breast cancer	Could not find publication	full text publication obtained
43	Liubao et al.	2009	Cost-effectiveness analysis of adjuvant therapy for operable breast cancer from a Chinese perspective: doxorubicin plus cyclophosphamide versus docetaxel plus cyclophosphamide	Could not find publication	full text publication obtained
44	Livartowski et al.	1992	Cost-utility analysis in oncology. Application of adjuvant chemotherapy in the treatment of node positive premenopausal breast cancer	Could not find publication	non-English journal (French)
45	Lux et al.	2009	Cost-effectiveness of anastrozole versus tamoxifen as adjuvant therapy in early breast cancer (EBC) - A German health economic analysis	Could not find publication	meeting abstract
49	Mia et al.	2010	Breast cancer and quality of life: A study of the effects of hormonal treatment during concomitant tamoxifen	Could not find publication	meeting abstract
50	Mihailova et al.	2001	Evaluation of the Bulgarian version of the European Organization for the Research and Treatment of Cancer Quality-of-Life Questionnaire C30 (version 2) and breast cancer module (BR23) on the psychometric properties of breast cancer patients under adjuvant	Could not find publication	Could not find for 2001 and earlier

No.	Author(s)	Year	Article title	Reason for exclusion	ERG Notes
			chemotherapy. Prognostic value of estrogen and progesterone receptors to quality of life		
54	Moeremans et al.	2006	Cost-effectiveness of anastrozole compared to tamoxifen in hormone receptor-positive early breast cancer. Analysis based on the ATAC trial	Could not find publication	full text publication obtained
56	Mould-Quevedo et al.	2011	Economic evaluation of adjuvant hormone therapy for postmenopausal women with hormone receptor positive early stage breast cancer	Could not find publication	non-English journal (Spanish)
60	Murray	2007	Cost-utility of adjuvant hormone therapies with aromatase inhibitors in postmenopausal women with breast cancer: Upfront anastrozole, sequential tamoxifen-exemestane and tamoxifen-letrozole	Could not find publication	Could not find
74	Ramirez et al.	2012	Cost-effectiveness analysis of neoadjuvant chemotherapy with intensive dose of epirubicin and different cycles in patients with locally advanced breast cancer: 4 FE100C versus 6 FE100C	Could not find publication	meeting abstract
75	Ray et al.	2009	Projected long-term economic outcomes associated with Bevacizumab treatment in patients with adjuvant triplenegative breast cancer to inform early decision making	Could not find publication	meeting abstract
77	Reimer et al.	2009	Quality of life (QoL) in elderly patients (pts) with early-stage breast cancer treated with ibandronate (I) with or without capecitabine (X): Results of the GBG 32 ICE trial	Could not find publication	meeting abstract
83	Skedgel et al.	2011	Is adjuvant trastuzumab economically justified in Her-2/neu positive T1bNO breast cancer?	Could not find publication	meeting abstract
86	Sura et al.	2012	Cost-effectiveness analysis of aromatase inhibitors and tamoxifen as an adjuvant therapy in postmenopausal women with early-stage hormone receptor positive breast cancer	Could not find publication	meeting abstract
88	Velikova et al.	2014	Quality of life results of the UK TACT2 Trial: More intensive chemotherapy for early breast cancer has a measurable impact on patient-reported symptoms and functioning (CRUK/05/019)	Could not find publication	meeting abstract
89	Verma et al.	2009	Docetaxel plus cyclophosphamide is cost-effective compared to doxorubicin plus cyclophosphamide, based on an economic analysis of US oncology trial 9735: Additional rationale to avoid anthracyclines in the adjuvant treatment of operable breast cancer?	Could not find publication	meeting abstract
90	Volovat et al.	2011	Quality of life of women with breast cancer treated in adjuvant setting with tamoxifen or aromatase inhibitors	Could not find publication	meeting abstract

No.	Author(s)	Year	Article title	Reason for exclusion	ERG Notes
91	Von Blanckenburg et al.	2011	Illness representations, quality of life and fatigue in breast cancer patients treated with adjuvant endocrine therapy. Preliminary results of a prospective study	Could not find publication	meeting abstract
98	Younis et al.	2009	Adjuvant chemotherapy in breast cancer: Is TC a cost-effective regimen compared to AC?	Could not find publication	meeting abstract
100	Zinchuk et al.	2013	Pharmacoeconomic analysis of docetaxel in the adjuvant therapy of breast cancer	Could not find publication	meeting abstract

10.2 Appendix 2. Variables used in company's PSA

Table 38. Table with variables used in probabilistic sensitivity analysis (provided in response to clarification question B.13)

Variable	Value	Measurement of uncertainty and distribution	Source
Utilities			
IDFS – on chemo	0.756	See "Utilities" tab of CEM- (Gamma)	Variances derived from APHINITY EQ-5D responses
IDFS – on treatment, off chemo	0.785		
IDFS – off treatment	0.822		
Non-metastatic recurrence	0.756		
Remission	0.822		
First-line metastatic recurrence	0.773		Lloyd *et al.*[69]*
Second+ line metastatic recurrence	0.520		
Administration costs			
IV administration cost – loading	£394.60	£315.12 – £490.81 (Log normal)	Upper and lower estimates taken from NHS ref. costs 2016/17[86]
IV administration cost – maintenance	£310.00	£197.00 – £428.00 (Log normal)	
SC administration cost – all cycles	£260.00	£189.00 – £219.00 (Log normal)	
Pharmacy preparation	£43.00	£33.60 – £50.40 (Log normal)	PSSRU 2017[87]
Health state costs (cyclical costs only)			
IDFS – year 1	£63.93	£47.95 - £79.91 (Log normal)	Assumption - ± 25% of base case value
IDFS – year 2-5	£7.11	£5.33 - £8.89 (Log normal)	
IDFS – ≥5 years	£3.08	£2.31 - £3.85 (Log normal)	
Non-metastatic recurrence	£76.80	£57.60 - £96.01 (Log normal)	

Variable	Value	Measurement of uncertainty and distribution	Source
Remission	£7.11	£5.33 - £8.89 (Log normal)	
First-line metastatic recurrence	£214.78	£161.08 - £268.47 (Log normal)	
Second+ line metastatic recurrence	£180.85	£135.64 - £226.06 (Log normal)	
Adverse event management costs (per event) - IDFS			
Diarrhoea	£489.00	£390.00 – £504.00 (Gamma)	Upper and lower estimates taken from NHS ref. costs 2016/17[86]
Neutropenia	£137.00	£69.00 – £163.00 (Gamma)	
Monthly probability - "Early recurrence"			
Monthly probability of disease progression in first-line mBC	0.0721	See "Early rec. data" tab in CEM (Log normal)	Covariances are results of survival analysis
Monthly probability of death in second+ line mBC	0.0540		
Monthly probability of disease progression in first-line mBC			
Pertuzumab + trastuzumab + chemotherapy	0.0317	See "1st line data" tab in CEM (Log normal)	Covariances are results of survival analysis
Trastuzumab + chemotherapy	0.0470		
Chemotherapy	0.0694		
Monthly probability of death in second+ line mBC			
Pertuzumab + trastuzumab + chemotherapy	0.0273	See "2nd line data" tab in CEM (Log normal)	Covariances are results of survival analysis
Trastuzumab + chemotherapy	0.0315		
Chemotherapy	0.0598		

CEM, cost-effectiveness model; EQ-5D, EuroQol 5-Dimension questionnaire; IDFS, invasive disease-free survival; IV, intravenous; mBC, metastatic breast cancer; NHS, National Health Service; rec., recurrence; ref, reference; SC, subcutaneous.
*Lloyd *et al.* reported the standard errors for the mixed model inputs. It was these SEs that were used to vary the mBC utilities used in the base case of the CEM – please see the "utilities" tab of the CEM for more details.

10.3 Appendix 3. Critique of submitted economic analysis for the hormone receptor-negative subgroup

As a supplement to their analysis for the node positive subgroup ('main analysis'), the company provided a brief summary of the economic analysis carried out for hormone receptor-negative patients. The methodology used for this analysis is very similar to that for the main analysis. In the interest of space, the company provided only data and assumptions related to the specific subgroup, and noted that the rest of the assumptions are similar to the main case analysis. A brief description and critique of the methods and inputs employed is given below.

10.3.1 Model structure

The hormone receptor-negative analysis was conducted using the same model structure and used the same specifications (i.e., length of time horizon, cycle length, discounting) as the main analysis carried out for the node-positive subgroup. As in the case of the 'main analysis', the ERG deems the employed model and its specifications to be suitable for the economic evaluation of the technologies assessed in this appraisal.

10.3.2 Clinical parameters and variables – hormone receptor-negative subgroup

Similar to the base case analysis in the node-positive patient population, the primary data source used to populate the clinical elements of the hormone receptor-negative cost effectiveness analysis was the APHINITY trial. The clinical evidence and methods used in modelling the IDFS health states and recurrent events are described and appraised below.

10.3.2.1 Modelling of IDFS

Modelling of IDFS was informed using data from the APHINITY study. Data related to 71 patients (8.2%) in the pertuzumab + trastuzumab + chemotherapy arm and 91 patients (10.6%) in the trastuzumab + chemotherapy arm who had an invasive-disease event. As in the main analysis, modelling of IDFS states involved splitting the time horizon in three periods (period 1: zero to four years; period 2: year four to ten; period 3: year ten to 52).

In time period 1, the analysis employed a parametric function to extrapolate the available APHINITY data beyond the trial's follow-up. While there was evidence suggesting that the PH

assumption may hold, the company justified using a parametric approach on grounds of convenience, adding that this was not expected to significantly impact the cost effectiveness results. The ERG accepts the choice of a parametric approach for this extrapolation and considers the provided justification to be valid.

The choice of the exact type of parametric function was guided by comparison of generated AIC and BIC goodness of fit values (Table 39, corresponding to table 35 in the submitted CS appendices), as well as by consideration of the absolute fit of the curves to observed KM data, assessed through a simple comparison of modelled versus observed IDFS events at two time points (36 and 48 months) (Table 31, replicating table 36 in the CS appendices). These comparisons, and a visual inspection of the fitted curves (figure 9 in the company's appendices), led the company to conclude that all parametric function presented a good fit to the KM IDFS data and to select the exponential distribution as the preferable parametric function.

Table 39. AIC and BIC values for IDFS (hormone receptor-negative population) (relative ranking of goodness of fit shown in brackets) (hormone receptor-negative subgroup)

	AIC		BIC	
	Pertuzumab + trastuzumab + chemotherapy arm	Trastuzumab + chemotherapy arm	Pertuzumab + trastuzumab + chemotherapy arm	Trastuzumab + chemotherapy arm
Exponential	619.02 (1)	748.62 (1)	623.78 (1)	753.37 (1)
Weibull	620.27 (3)	749.99 (3)	629.80 (3)	759.50 (3)
Log-normal	620.19 (2)	749.71 (2)	629.71 (2)	759.21 (2)
Gamma	622.30 (6)	750.94 (5)	631.82 (5)	760.45 (5)
Log-logistic	622.26 (5)	751.67 (6)	636.55 (6)	765.93 (6)
Gompertz	620.69 (4)	750.55 (4)	630.21 (4)	760.06 (4)

AIC, Akaike information criterion; BIC, Bayesian information criterion.

Table 40. DFS events at 36 and 48 months (hormone receptor-negative subgroup)

Timepoint	Parametric function	Pertuzumab + trastuzumab + chemotherapy	Placebo + trastuzumab + chemotherapy	Pertuzumab + trastuzumab + chemotherapy vs placebo + trastuzumab + chemotherapy	Δ vs Kaplan-Meier data	
					Pertuzumab + trastuzumab + chemotherapy	Trastuzumab + chemotherapy
36 months	KM data	92.60%	90.99%	1.62%		
	Exponential	93.20%	91.18%	2.03%	0.60%	0.19%
	Weibull	93.35%	91.32%	2.03%	0.75%	0.33%
	Log-normal	93.14%	91.05%	2.09%	0.54%	0.06%

Timepoint	Parametric function	Pertuzumab + trastuzumab + chemotherapy	Placebo + trastuzumab + chemotherapy	Pertuzumab + trastuzumab + chemotherapy vs placebo + trastuzumab + chemotherapy	Δ vs Kaplan-Meier data	
					Pertuzumab + trastuzumab + chemotherapy	Trastuzumab + chemotherapy
	Gamma	93.33%	91.22%	2.12%	0.73%	0.23%
	Log-logistic	93.32%	91.26%	2.06%	0.72%	0.28%
	Gompertz	93.36%	91.25%	2.11%	0.76%	0.27%
48 months	KM data	90.59%	88.37%	2.22%		
	Exponential	91.07%	88.45%	2.62%	0.48%	0.08%
	Weibull	91.01%	88.37%	2.63%	0.41%	0.00%
	Log-normal	91.15%	88.54%	2.61%	0.56%	0.17%
	Gamma	91.01%	88.41%	2.60%	0.42%	0.04%
	Log-logistic	91.01%	88.37%	2.64%	0.42%	0.00%
	Gompertz	91.02%	88.42%	2.60%	0.42%	0.05%

IDFS, invasive disease-free survival.

Time period 2 (year four to year ten) was modelled on the basis of the same assumptions as those in the main analysis (node positive population). Here, too, is has been assumed that, from year 4 to year 10, the proportion of patients that are effectively no longer at risk of recurrence and only subject to background mortality (i.e. are being 'cured') is linearly increasing with time, from 0% to 90%. In addition, identically to the main analysis, the incremental treatment effect of pertuzumab is assumed to be maintained for seven years and 'wane' thereafter. The ERG's opinion about the 'cure' adjustment and incremental treatment effect, as expressed in the analysis for the node positive population, applies here, too: while the ERG's does not object to the use of the 'cure' and 'incremental treatment effect' adjustments, it questions the parameters used in implementing them. The assumptions employed for time period 3 (year 10 to 52) are the same as those used for the node positive population (i.e. 90% of the patients are no longer at risk of recurrence, thus the ERGs position mirrors the critique provided for the equivalent analysis in the node positive population.

10.3.3 Modelling of recurrence states

The proportion of IDFS events (excluding deaths) used in the economic analysis was derived from APHINITY data specific to the hormone receptor-negative population. The pooled (across arms) estimate suggests that 76.87% of the events in question were metastatic, while 23.13% were non-metastatic. An 'early recurrence' adjustment was also implemented based on the 18-month cut-off point, identically to the main analysis (Section 5.2.6.2). In this present analysis, too, the ERG note that the proportion of metastatic events for the whole trial has only been

applied to events occurring beyond 18 months. Thus, the ERG recalculated the proportions for events beyond 18 months (Table 41). The revised proportion of patients who experience metastatic recurrence is 65.6%, as opposed to 76.9% in the company's analysis.

Table 41. ERG calculations of proportion of metastatic events for the post-18 month period (hormone receptor-negative subgroup)

	Pertuzumab + trastuzumab + chemotherapy arm	Placebo + trastuzumab + chemotherapy arm	Total	Comment/explanation
Total Events	71	91	162	Obtained KM IDFS tab economic model
Total IDFS Recurrence Events	58 (81.7%)	76 (83.5%)	134 (82.7%)	Provided by company (appendix)
Total Events Pre 18 months	21	32	53	Obtained KM IDFS tab economic model
Estimated Recurrence Events Pre 18 months (assumed to be all metastatic)	17	27	44	Calculated multiplying total pre-18 month events by proportion of events which were metastatic.
Total Events Post 18 months	50	59	109	Obtained KM IDFS tab economic model
Total Recurrence Events Post 18 months	41	49	90	Calculated multiplying total post-18 month events by proportion of events which were metastatic.
Total Number of Metastatic Recurrence	43	60	103	Provided by company (appendix)
Total Number of Metastatic Recurrence Post 18 months	26 (63.4%)	33 (67.3%)	59 (65.6%)	Calculated subtracting pre 18-month metastatic recurrence from total metastatic recurrence. Percentages are the percentage of Post 18 month recurrence events which are metastatic

Possible pathways for patients who experience recurrence are identical to those in the main analysis. Patients with a non-metastatic recurrence can transition to the "Non-metastatic recurrence" and "Remission" states (in addition to 'Death'). Patients who suffer a metastatic recurrence pathway move to the first-line mBC) and second+ line mBC. The methods used to derive the transition probabilities for these pathways are the same as in the main analysis. Similarly, treatment duration (i.e. number of cycles completed) was calculated using the same methodology as in the main analysis; this is based in actual treatment completion and discontinuation data observed in the APHINITY study. The ERG do not have further issues over and above those expressed over and above those expressed in Sections 5.2.6.2 and 5.2.6.3 above.

10.3.4 Health related quality of life

Utility values used in the hormone receptor-negative analysis are calculated in a similar fashion to those for the node-positive population, with the difference that, for the present analysis, utility values for eBC states are derived from EQ-5D responses of the hormone receptor-negative population in APHINITY. As in the node-positive analysis, utility values for these states are pooled across arms, which the ERG consider to be acceptable.

10.3.5 Resources and costs

Health care resource use and unit cost inputs used in the hormone receptor-negative analysis were identical to those in the node-positive analysis. On the premise that pertuzumab approval is expected to result in a share of patient receiving this treatment with trastuzumab SC, the ERG's suggestions for amendments in the employed treatment shares are applicable here, too.

10.3.6 Results

In the hormone receptor-negative population, PHC resulted in a small QALY gain and a higher total overall cost compared to HC. The company's base case ICER for this patient group was calculated to be £65,699 per QALY gained (Table 14, reproducing table 42 in the CS appendices).

Table 42. Base case cost effectiveness results (HR-negative population)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Trastuzumab + chemotherapy	£[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£65,699
Pertuzumab + trastuzumab + chemotherapy	£[redacted]	[redacted]	[redacted]				

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

Similar to sensitivity analyses for the node positive population, the company undertook PSA (1000 iterations). Comparing pertuzumab + trastuzumab + chemotherapy with trastuzumab + chemotherapy in PSA gave a mean ICER of £66,158 per QALY, which is close to the ICER of £65,699 per QALY found in the base case analysis). The cost effectiveness plane and acceptability curves generated through the PSA output for the HR-negative population is reproduced in Figure 31 and Figure 32 below. (figures 12 and 13 in appendix M).

Figure 31. Cost effectiveness plane (HR-negative population)

Figure 32. Cost effectiveness acceptability curve (HR-negative population)

HT, trastuzumab + chemotherapy; PHT, pertuzumab + trastuzumab + chemotherapy; QALYs, quality-adjusted life years.

In addition, the company carried out deterministic sensitivity analyses by using the lower 10th and upper values 90th percentiles of the values used in PSA. The results of analyses which had the greatest impact on the ICER were presented in a Tornado diagram (as shown in Figure 33). The lowest ICER produced was £62,932 per QALY gained, this result was generated using the upper value (£336.32) for the administration cost in the loading cycles of the trastuzumab + chemotherapy arm. When using the upper value for the administration cost in the loading cycles of the pertuzumab + trastuzumab + chemotherapy arm, the highest ICER was generated (£68,975/QALY gained). The analysis around administration cost in the loading cycles of the pertuzumab + trastuzumab + chemotherapy arm also produced the largest range in ICERs (£63,012 to £68,975 per QALY gained).

Figure 8. Tornado diagram depicting the results of univariate s.a. (HR-negative population)

H trastuzumab; HC, trastuzumab + chemotherapy; HS, health state; ICER, incremental cost effectiveness ratio; IDFS, invasive disease-free survival; mBC, metastatic breast cancer; NMR, non-metastatic recurrence; PHC, pertuzumab + trastuzumab + chemotherapy; QALY, quality-adjusted life year; tx, treatment.

In scenario analyses, the specifications used in the hormone receptor-negative analyses were the same as those for the node-positive population. As in the node-positive population, the lowest ICER estimate produced in scenario analysis (£22,390 per QALY gained) was due to using eBC utility values from Hedden *et al.* [70]. The highest ICER value (£293,335 per QALY gained) resulted from setting the model time horizon to 10 years (as opposed to 52 years in the base case analysis).

10.3.7 ERG's suggested base case (hormone receptor-negative population)

The amendments implemented to derive the ERG's preferred base case for the node-positive population were also carried out here. The effect of each of the individual amendment on the ICER can be seen in Table 43. Revised ICERs are compared with the company's base case ICER for this sub-population.

Changing the parameters related to the duration of treatment effect (i.e. points in time at which this effect begins to wane and ceases) led to an ICER value of approximately £84,291 per QALY gained, an increase of approximately £18,600 (28%) over the company's base case ICER for this population. Changes in the rest of the parameters led to smaller increases. Replacing the parameters guiding the 'cure' adjustment with values preferred by the ERG resulted in an ICER of £69,808 per QALY gained, which is about £4,100 (6%) higher than the company's ICER. Revising the proportions for metastatic and non-metastatic disease recurrences according to the ERG's calculations led to an ICER of £70,378 per QALY gained, which is higher than the company's base case value by approximately £4,700 (7%).

Table 43. ICER values after implementing ERG's amendments in the company's base case (hormone receptor-negative population)

Parameter	Values in company's base case	ERG's preferred value	ERG's ICER (£ per QALY gained)
Duration of incremental treatment effect			
Time point when incremental treatment effect begins to wane	Year 7	Year 4	£84,291
Time point when incremental treatment effect ceases	Year 10	Year 7	
'Cure' adjustments			
Time point when 'cure' adjustment is introduced in the analysis	Year 4	Year 3	£69,808
Time point when maximum 'cure' is reached	Year 10	Year 10	
Maximum "cure" proportion	90.00%	95.00%	
Percentages of disease recurrence			
metastatic recurrence	76.87%	65.60%	£70,378
non-metastatic recurrence	23.13%	34.40%	

Carrying out all these changes simultaneously—i.e., effectively implementing the ERG's suggested base case analysis-increased the ICER by approximately £27,079 (41% higher than the

company's base case ICER) and resulted in the ERG's base case ICER of £92,778 per QALY gained for the hormone receptor-negative population.

Table 44. Results of ERG suggested base case analysis (hormone receptor-negative population)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£ per QALY gained)
HC (trastuzumab + chemotherapy)	[redacted]	[redacted]	[redacted]	[redacted]	£92,778
PHC (pertuzumab + trastuzumab + chemotherapy)	[redacted]	[redacted]			

The revised PSA, which was undertaken on the basis of the ERG amendments, produced a mean ICER of £93,559 per QALY gained, only slightly higher than the deterministic value.
The revised CE plane and CEAC depicting the comparison between PHC and HC are given in Figure 34 and Figure 35 below. The probability of PHC being cost effective compared to HC at the £30,000 per QALY threshold is zero.

Figure 34. Cost effectiveness plane (hormone receptor-negative population)

Figure 35. Cost effectiveness acceptability curves (hormone receptor-negative population)

10.4 Appendix 4. Results for the ITT population

Table 45. Base case (deterministic) results for the ITT population (derived from the submitted economic model)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£ per QALY gained)
HC (trastuzumab + chemotherapy)	[redacted]	[redacted]	[redacted]	[redacted]	£66,238
PHC (pertuzumab + trastuzumab + chemotherapy)	[redacted]	[redacted]			

Figure 36. CE plane for the ITT population (derived from the submitted economic model)

Figure 37. Cost effectiveness acceptability curves for the ITT population (derived from the submitted economic model)

	disease or people with hormone receptor-negative disease, will be considered.	subgroup of the node-positive population).	receptor-negative disease are considered a high-risk subgroup because, unlike patients with hormone receptor-positive disease, they cannot be treated with hormone therapy. Furthermore, this patient population is likely to be included in the label for adjuvant pertuzumab. In the economic analyses of this submission the node-positive subgroup is the base case and the hormone receptor negative subgroup is an additional scenario.

The intervention in the NICE scope and decision problem is adjuvant pertuzumab in combination with trastuzumab and chemotherapy. The company have yet to receive marketing authorisation from the European Medicines Agency. The recommended dose is 840mg of intravenous pertuzumab as a loading does, then 420mg given every three weeks in combination with trastuzumab for a total of one year (maximum 18 cycles).

The comparator in the decision problem is standard adjuvant therapy without pertuzumab (trastuzumab in combination with chemotherapy). No additional comparators were listed in the NICE scope. The CS decision problem complies with the intervention and comparator provided by NICE.

The population in the decision problem differs from the final scope based on the introduction of subgroups with high-risk of recurrence. These are defined in the CS as people with HER2-positive eBC with node-positive or hormone receptor-negative status. The justification for inclusion of this subgroup of the population provided by the company, is that patients with a high-risk of recurrence derive the most benefit from pertuzumab. This aligns with the findings of the pivotal trial evidence submitted by the company and the anticipated market authorisation. The ERG clinical advisor notes that life time 'high-risk' status cannot be assumed to remain constant.

The company included IDFS excluding (primary outcome) and including (secondary outcome) second primary non-breast cancer and DRFI as additional outcomes. The CS states that these outcomes were primary and secondary endpoints in the submitted pivotal trial evidence. The remaining outcomes listed in the decision problem were included in the NICE scope. The ERG clinical advisor considers IDFS and DFRI to be appropriate outcomes.

1.2 Summary of clinical effectiveness evidence submitted by the company

The CS undertook a systematic review to search for evidence to meet their decision problem. The ERG considers the systematic review to be of reasonable quality. The CS systematic review included data from an analysis of a phase III randomised controlled trial (RCT) investigating adjuvant pertuzumab+trastuzumab+chemotherapy (n=2,400) compared with placebo+trastuzumab+chemotherapy (n=2,405) (APHINITY). The trial is sponsored by Hoffmann-La Roche/Genentech.

The RCT was described in detail in the CS. The ERG summarise the results from the RCT, the key outcomes were as follows:

- The primary outcome of the APHINITY trial was IDFS excluding second primary non-breast cancer events [non STEEP definition]. This was a statistically significant outcome at the existing data cut off on the ITT population (19th December 2016). The rate of IDFS events in the pertuzumab arm was 19% lower than the rate of events in the control arm. No consistent difference between the arms was found until approximately 20 months, at which point a small but sustained difference in favour of pertuzumab was observed. The ERG considers that the delay in observed benefit suggests that the assumption of proportional hazards was violated. Beyond 20 months, the magnitude of the difference is less than 1% difference observed at 24 months and 36 months. At 48 months, the IDFS rate was 1.7% higher in the pertuzumab-based arm compared to placebo
- Secondary outcomes include: IDFS including second primary non-breast cancer events [STEEP definition] (IDFS criteria with contralateral and ipsilateral DCIS), overall survival (OS; time to death from any cause), recurrence-free interval (RFI; time until local, regional or distant breast cancer recurrence), distant RFI (DRFI; time until distant breast cancer recurrence), health related quality of life (HRQoL; assessed based on three patient-reported outcome measures) and adverse events. With the exception of OS, the hazard ratios of the secondary outcomes are broadly consistent with IDFS. No assessment of proportionality of hazard was presented in the CS, so the validity of the hazard ratios is unclear. Kaplan-Meier plots for the secondary outcomes were not presented
- The ERG considers that none of the primary or secondary outcomes would have been statistically significant had the significance level been adjusted for multiplicity (e.g. using a Bonferroni calculation) demonstrating that pertuzumab is only marginally efficacious
- Limited data for the effects of pertuzumab on HRQoL were presented. Brief and selected results from three HRQoL measures were presented. In summary, there is sufficient evidence to

- support the view that pertuzumab is associated with a worse HRQoL. This is evidenced most strongly by the difference in mean diarrhoea score from the QLQ-C30
- Overall, adverse event rates were higher in those treated with pertuzumab, with more adverse events which are treatment-related. The most frequently reported adverse event in the pertuzumab arm was severe (grade 3/4) diarrhoea, which was significantly higher than diarrhoeal incidence in the placebo arm (RR=2.62 CI: 2.07 to 3.32, p=0.000). The ERG also notes significantly higher incidence rates of Grade ≥3 anaemia in the pertuzumab arm (6.9%) compared to placebo (4.7%) (RR=1.47 CI:1.16 to 1.85, p=0.001). At the end of post treatment follow up, the incidence of NYHA class III or IV heart failure with substantial decrease in left ventricular ejection fraction (LVEF) was three times higher among patients in the pertuzumab-based arm compared to the placebo-based arm (0.6% vs. 0.2%, p=0.04). The ERG found higher discontinuation rates for pertuzumab compared to placebo, although this difference was not significant at the 0.05 threshold.

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

The ERG appraisal of APHINITY substantially agreed with the CS appraisal of the trial, with the trial being of generally good quality. One exception is the lack of reporting of allocation concealment. The patient characteristics were balanced across stratification factors. The analytical approach used in the trial appears reasonable. However, there were concerns regarding the protocol amendment that was performed in order to achieve the distribution of lymph node involvement between intervention and control populations. The initial sample size calculation was deemed to be suitably powered, however, it is unclear whether the protocol variation adjustments to the sample size allowed it to remain suitably powered.

All time-to-event outcomes were analysed on the intent-to-treat (ITT) population. Stratified Cox models and log-rank tests were used where appropriate. Nodal status, protocol version, hormone receptor status and adjuvant chemotherapy regimen were the stratification factors. Unstratified analyses were reportedly performed as a sensitivity analysis but were not presented within the CS. Kaplan-Meier plots are only presented for the primary outcome. Hazard ratios (HR), p-values and observed proportion of event-free patients at 3 years are presented for each time-to-event outcome. However, the ERG notes that no adjustment had been made for multiple testing. With the large number of hypotheses and subgroups being investigated, it is important to consider the possibility of false positive results. Proportionality of hazards were not investigated within the clinical effectiveness section for any of the outcomes. The ERG notes that if this assumption was violated, the company could have presented restricted mean survival times.

The primary outcome measure in the APHINITY trial is IDFS and demonstrated a statistically significant outcome at the existing data cut off on the ITT population. A stratified HR of 0.81 (95% CI: 0.66 to 1.00; p=0.045) was calculated by the company. The ERG considers this result to be marginally significant and this is supported by the ERG clinical advisor. The rate of IDFS events among node-positive patients was 23% lower in the pertuzumab arm compared to the placebo arm (HR 0.77, 95% CI: 0.62 to 0.96), whereas no statistically significant difference was observed in node-negative patients (HR 1.13, 95% CI: 0.68 to 1.86). The rate of IDFS events among hormone receptor-negative patients was 24% lower in the pertuzumab arm compared to the placebo arm (HR 0.76, 95% CI: 0.56 to 1.04, p=0.08), and 14% lower than the rate of events in the placebo based arm among hormone receptor-positive patients (HR 0.86, 95% CI: 0.66 to 1.13, p=0.28). The ERG notes that these treatment effects are not statistically significant. The ERG had concerns over the legitimacy of the subgroups focused on by the company. As a result, the ERG believe the increased efficacy observed in the node-positive population may have occurred by chance.

As only one trial was identified, no indirect comparison or multiple treatment comparisons were performed.

Strengths

The ERG consider the CS had several strengths:

- The quality of the systematic review was reasonable (e.g., relevant inclusion/exclusion criteria were reported, the validity of included studies was adequately assessed and the primary studies were summarised in detail)
- The assessment of study quality was appropriate
- The quality of the included trial (APHINITY) was generally good. However, allocation concealment was not reported
- Results for the trial were accurately presented and demonstrated the risks and benefits from including adjuvant pertuzumab to standard care.

Weaknesses and areas of uncertainty

However, the ERG noted that the CS had some weaknesses and areas of uncertainty:

- There is uncertainty regarding analyses related to high-risk of recurrence subgroups in the company decision problem

- The lack of consistent difference between the trial arms in IDFS (primary outcome) until 20 months could be due to the violation of the assumption of proportional hazards. Beyond 20 months, the magnitude of the difference was less than 1%. At 48 months, IDFS rate was 1.7% higher in the pertuzumab-based arm compared to placebo
- For the secondary outcomes, no assessment proportionality of hazard was presented in the CS, so the validity of the hazard ratios is unclear
- There are concerns regarding the lack of adjustment for the multiple hypotheses being tested. The majority of presented p-values are only just below the 0.05 threshold, emphasising that pertuzumab is only marginally efficacious
- There is uncertainty about adverse events. There were significantly higher incidence rates of anaemia in the pertuzumab arm compared to placebo (RR=1.47 CI:1.16 to 1.85, p=0.001). The incidence of NYHA class III or IV heart failure with substantial decrease in LVEF was three times higher among patients in the pertuzumab arm compared to the placebo (0.6% vs. 0.2%, p=0.04).

1.4 Summary of cost effectiveness submitted evidence by the company

Two analyses were contained in the CS. The main analysis compared pertuzumab + trastuzumab +chemotherapy (PHC) against trastuzumab + chemotherapy (HC) in patients with node-positive eBC within the HER2-positive population. An additional analysis relating to HER2-positive patients with hormone receptor-negative disease was included in appendix M. The focus in the CS is on the main analysis (for the node-positive population).

The company undertook a systematic literature review to identify cost effectiveness evidence relevant to this decision problem and reported that no economic evaluations relevant to the decision problem were found. As a result, the company developed and submitted a state transition model consisting of seven health states: (i) 'IDFS – on treatment', (ii) 'IDFS – off treatment', (iii) 'Non-metastatic recurrence', (iv) 'Remission', (v) 'First-line treatment for metastatic disease (First-line mBC)', (vi) 'Subsequent treatment lines for mBC (Second+ line mBC)', and (vii) 'Death'. The model evaluates costs and outcomes (quality-adjusted life years) using monthly cycles over a lifetime (52 years) time horizon, by the end of which less than 1% of the patients in the model remain alive. Transitions between states are guided by probabilities calculated according to parametric extrapolation functions fitted to Kaplan-Meier data from the APHINITY study and other trial evidence in the published

literature. Assumptions were made about the duration of pertuzumab's incremental effect and the proportion of patients who are 'cured' (i.e. no longer at risk of recurrence) at different points in time.

Preference-based health related quality of life (utility) values for states i – iv were derived from EQ-5D data collected in the APHINITY trial, while utility values for states v and vi were taken from the literature. These values were used in calculating quality-adjusted life years (QALYs), which was the main outcome of the economic analysis. Costs were calculated using data and unit cost estimates from various sources, including a previous appraisal of neoadjuvant pertuzumab (TA424). Key cost categories included were (i) treatment acquisition costs; (ii) treatments administration costs; (iii) the cost of treating selected adverse events (of severity grade 3 and above, and observed in more than 2% of the APHINITY trial participants); (iv) supportive care costs; and (v) costs of treatment associated with progressed disease. Future costs and outcomes were discounted at a rate of 3.5% per year.

The company reported a deterministic ICER of £34,087 per QALY gained (with PAS) for PHC compared to HC. At a willingness-to-pay value of £30,000 per additional QALY, the probability of PHC being more cost-effective than PC was 17.3%.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG considers the type and structure of the submitted model to be appropriate for representing the disease pathway and therapeutic options for the population specified in the NICE final scope. Key characteristics of the analysis (such as the selected perspective, time horizon and discount rates), were in line with recommendations set out in the NICE Reference Case. The ERG felt that the company took reasonable steps to ascertain that data used in the model were of sound quality and suitable for the particular decision problem. Face validity checks carried out by ERG did not identify any major issues. The ERG's critique raised the following points:

- In relation to the duration of pertuzumab's effect, the ERG believes that the choice of a relatively long duration is optimistic and is not justified adequately in the CS. An alternative specification is proposed, which the ERG believes to be better aligned with existing evidence. These specifications were incorporated in the ERG preferred base case.
- While the ERG agrees that a 'cure' adjustment is beneficial, it proposes an alternative specifications of the starting point and maximum 'cure' proportion, which better represents the observed behaviour of hazard rates and late recurrence events.
- Revisions were needed in the calculations of the proportion of patients estimated to experience metastatic and non-metastatic recurrences. The ERG re-calculated the

The ERG consulted NICE guidelines (CG80), which state that trastuzumab is recommended as an adjuvant treatment for eBC in England.[18] The guideline says: "*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.*"[18] The ERG note that a license extension for trastuzumab for HER2-positive eBC patients was granted in 2012 to include neoadjuvant use in combination with chemotherapy followed by adjuvant trastuzumab.[28] The CS echoes these statements on page 21 and declares that systemic trastuzumab is the *"backbone therapy"* for HER2-positive BC patients across all stages of the disease in England.[29-31] On page 21 of the CS, the company states that dual-HER2 blockade (pertuzumab+trastuzumab) with chemotherapy is *"commonly used in the neoadjuvant setting in patients with high-risk disease and in patients with mBC"*. Citing evidence from Electronic Medicines Compendium (eMC) SmPC document for Perjeta (420mg concentrate for solution for infusion).[32] However, the ERG notes that NICE technology appraisal guidance (TA424) only recommends, "*Pertuzumab, in combination with trastuzumab and chemotherapy, as an option for the neoadjuvant treatment of adults with HER2-positive breast cancer; that is, in patients with HER2-positive, locally advanced, inflammatory or early-stage breast cancer at high risk of recurrence*."

The ERG confirms that trastuzumab is currently recommended for treatment of early (TA107) and advanced HER2-positive BC (TA34). The ERG clinical advisor confirmed that the majority of NHS trusts deliver trastuzumab subcutaneously in the adjuvant and metastatic setting. The ERG note that there are differences in treatment acquisition costs between trastuzumab administered as an intravenous infusion and trastuzumab administered as a subcutaneous injection (see section 5.2.8.1 and 6.3 for further discussion regarding impact of treatment acquisition costs on cost-effectiveness analysis). The ERG clinical advisor suggested that there are variations in the treatments options across the NHS, for example underweight patients may receive trastuzumab intravenously due to their higher risk of cardiac toxicity.

The CS (pg. 21) state that long-term clinical outcomes are not influenced by the timing of initiation of systemic treatment (before or after surgery).[33] The meta-analysis of randomized trials cited by the company compared neoadjuvant therapy with adjuvant therapy, regardless of what additional surgery and/or radiation treatment was used. The ERG note that the study did not include pertuzumab or trastuzumab in the analysis.[33] The authors concluded that there were no statistically or clinically significant differences between neoadjuvant therapy and adjuvant therapy arms in mortality (summary risk ratio (RR) = 1.00, 95% CI: 0.90 to 1.12), disease progression (summary RR = 0.99, 95% CI: 0.91 to 1.07), or distant disease recurrence (summary RR = 0.94, 95% CI: 0.83 to 1.06). The ERG notes the

2.3 Unmet need

Sections B.1.3.1 (pg. 16-19) and B.2.12 (pg. 52-52) of the CS consider the extent of unmet treatment need and discuss how this need is met by adjuvant pertuzumab for eBC. The ERG notes that the European Medicines Agency (EMA) recommends pertuzumab for the neoadjuvant use in eBC.[34] The company propose an extension to include the adjuvant setting for high-risk patients (see section 4.2.5 for ERG discussion of high-risk subgroups). The CS (pg. 53) suggests that HER2-positive BC has an earlier onset compared to other BC types. The CS reports that HER2-postive BC occurs in women aged *"approximately 55 years compared to approximately 65 years for all [other] subtypes of BC"*.[3, 35, 36] The company suggest that adjuvant pertuzumab in combination with trastuzumab and chemotherapy will improve invasive disease-free survival (IDFS) and reduce the risk of recurrence or death, therefore, providing patients with high-risk HER2-positive eBC with "*more time with their families and friends, [and] thus the social and psychological benefit of treatment would reach beyond the patients themselves*" (pg. 53). The ERG clinical advisor suggests that current treatment regimens with trastuzumab improve the prognosis of patients with HER2-positive BC, highlighting the out-datedness of the evidence in the CS. Therefore, there may not be any difference in the risk of BC recurrence between HER2-positive and HER2-negative BC.

2.4 Marketing authorisation

The ERG notes that pertuzumab does not currently have marketing authorization for the decision problem listed in Table 1 of the CS, page 10-11. The CS appendix C states that at the time of this submission, they are waiting for marketing authorisation for the use of pertuzumab as an adjuvant treatment for use in HER2-positive eBC. The summary of product characteristics (SmPC) and the European public assessment reports (EPAR) for pertuzumab do not include the adjuvant indication. The company anticipates that the EMA licence approval to extend the use of pertuzumab to include adjuvant treatment of patients with HER2-positive eBC will be issued in July 2018 (CS pg. 13).

The CS page 9 states, that following regulatory discussions with the Committee for

Medicinal Products for Human Use (CHMP), the

[redacted]

[redacted] (of the pivotal trial[1]). The company suggest that the anticipated label for pertuzumab is expected to read as follows:

"Perjeta is indicated for use in combination with trastuzumab and chemotherapy in:

- the neoadjuvant treatment of adult patients with HER2-positive, locally advanced,

inflammatory, or early stage breast cancer at high-risk of recurrence

- the adjuvant treatment of adult patients with HER2-positive early breast cancer at high-risk of recurrence."

The company go on to state that linked to this change, the following text in section 5.1 of the SmPC will be included:

- "In the adjuvant setting, based on data from the APHINITY study, HER2-positive early breast cancer patients at high-risk of recurrence are defined as those with lymph node-positive disease or hormone receptor-negative disease."

On page 9, the CS states that the EMA provided feedback that the proposed revised indication for adjuvant pertuzumab treatment [redacted]

Difference from the NICE scope

As discussed further in section 3.1 and section 4.2.5 of the ERG report, the population outlined in the proposed marketing authorization differs from the final NICE scope for the appraisal.[5] On page 9 of the CS, the company suggests that the narrower population will be aligned with the expected marketing authorisation in the UK.

of HER2 inhibitors in patients with early HER2-positive breast cancer. This supports hormone receptor status as an appropriate subgroup. However, the ERG notes that the submitted trial evidence also included other subgroups as defined by age (<40y vs. 40, vs. 50-64, 49y vs. ≥65y), adjuvant chemotherapy regimen (anthracycline-based versus non-anthracycline-based), menopausal status at screening (pre-menopausal versus post-menopausal), tumour size (<2cm vs. 2 -<5cm versus ≥5cm) and protocol version (original vs. amended).[1] Although the company justify the inclusion of node-positive and hormone receptor-negative patients in their decision problem (section 3.1 and section 4.2.5), the ERG suggest that these additional subgroups could have been considered in the decision problem.

4.1.3 Critique of data extraction

The ERG considers that study selection (two independent reviewers with third reviewer/strategic advisor resolving discrepancies) and data extraction (two independent reviewers with third reviewer/strategic advisor resolving discrepancies) were conducted appropriately. The data were extracted using a pre-approved data extraction table.

4.1.4 Quality assessment

The company provided a quality assessment of the included trial evidence (APHINITY[1]) using the minimum criteria for assessing risk of bias in RCTs as set out in the CRD guidance for undertaking reviews in health care[45] and the NICE single technology appraisal user guide.[46] The ERG conclude that this is sufficient. Results of the quality appraisal are presented in Document B (Table 10, pg. 34) and the appendix document (appendix D, table 12, pg. 19).

The ERG performed an independent quality assessment of the included trial which is reported in Table 3. As indicated, the ERG agreed with all but one aspect of the company's assessment of study quality which was that it is unclear what measures were implemented to prevent foreknowledge of forthcoming treatment allocations as "allocation concealment" was not described in the CS documents or trial protocol or report.[1]

Table 14 of CS appendix D summarises patient disposition towards the study treatment, including discontinuation rates. Although the ERG found a statistically significant difference in pertuzumab/placebo discontinuations between pertuzumab and placebo at the clinical cut-off date (p=0.005), there were no significant differences in losses to follow-up and self-withdrawals (discussed further in section 4.2).

The ERG notes that after 3655 patients were recruited, the company considered node-negative BC patients' ineligible for the trial. This amendment was in order to recruit more node-positive patients (n=1149). This was described in an amendment to the protocol (protocol B, appendix L), and was suggested to be in line with the distribution of patients by nodal involvement in the Breast Cancer International Research Group (BCIRG) 006 trial.[47] During clarification the ERG requested earlier versions of the APHINITY protocol but were unable to determine whether the distribution of, and proportions of women with nodal involvement informed the sample size calculation (clarification response A2, discussed in more detail in section 4.2).

While a more conservative alpha-level (i.e., <0.05) may have been more appropriate for the sample size calculation given the protocol amendment, the ERG effectively deems protocol B effectively a

Outcomes reported were summarised clearly in CS Table 11 (pg. 36) and CS Table 12 (pg. 37). For discussion regarding appropriateness of outcome selection see section 3.4 and section 4.2.1. Statistical analyses were summarised in CS Table 9 (pg. 32-33), including details of participants excluded from the analyses. As per the company decision problem, the study recruited participants with node-positive disease (any tumour size except T0) or node-negative disease (only under protocol version A only) where the following conditions were met; tumour size >1 cm or tumour size >0.5 cm and ≤1 cm with at least one of the following three features: histologic/nuclear Grade 3, negative for oestrogen/progesterone receptor, or age <35 years.

The protocol was later amended by only allowing recruitment of node-positive patients only (protocol version B), apparently in order to achieve a population with a distribution of nodal involvement status similar to the BCIRG-006 trial.[47] The ERG can confirm that the APHINITY trial recruited a higher proportion of node-negative patients than the BCIRG-006 trial, however protocol A did not specifically state that the company set out to replicate the BCIRG-006 population. This aim only appeared in protocol B for the first time (trial protocols received as part of clarification response A2). The ERG has not been presented with any evidence that the APHINITY trial was designed to recruit a similar patient population to BCIRG-006. The ERG compared hormone receptor status between the two trials. There was a lower proportion of hormone receptor-negative patients in the APHINITY trial than in BCIRG-006 (36% vs. 46%). As the company did not lay out any criteria about what an acceptable deviation from the BCIRG-006 trial population was, it is difficult to ascertain whether the company achieved their aim of replicating the BCRG-006 trial. The ERG is surprised that no adjustment was made to the trial protocol to address this difference in hormone-receptor status distributions between the two trials, to be consistent with the aforementioned difference in nodal status.

The inclusion/exclusion criteria of APHINITY and BCIRG-006 were broadly similar, and it is unclear why the APHINITY trial experienced unexpectedly high recruitment rates of node-negative patients, as discussed above. Following clarification, the company suggest that neoadjuvant therapy is now "*a common option for high risk HER2-positive breast cancer"* and that *"international guidelines recommended the use of adjuvant Herceptin also for the treatment of HER2-positive, node-negative patients with small tumors (e.g., <1 cm) differently than the past"*, which together may have resulted in a *"higher proportion of node-negative patients being eligible for APHINITY"* (clarification response C7). The ERG agrees this is plausible but remains uncertain whether this can be responsible for the magnitude of the unexpected recruitment rate observed during protocol A.

The ERG noted inconsistency over when the protocol was reportedly amended, which was queried in clarification question C8. The company reports in section B.2.4.1 (pg. 32) that the amendment was

outcome. Table 4 demonstrates fairly comparable IDFS rates between primary and secondary IDFS endpoints, hence secondary primary non BC events appear to be not very common.

However, the company emphasises that the OS data were part of an interim-analysis with only 169 (26%) of 640 planned events having occurred to detect an expected HR of 0.80 (protocol version D). The CS did not present KM plots for the secondary outcomes. According to the company's log-rank test, DRFI was not statistically significant at the 0.05 threshold, however secondary IDFS (HR 0.82), DFS (0.81), and RFI (0.79) were all significantly ($p < 0.05$) higher in the pertuzumab-based arm compared to placebo (see CS table 12). The ERG considers that none of the primary or secondary outcomes would have been statistically significant had the significance level been adjusted for multiplicity (as mentioned earlier). Pertuzumab appears to be only marginally efficacious. The unstratified analyses can be found in Table 5, which are taken from the CSR. In Table 5 only DFS is statistically significant.

Table 5. Summary of unstratified results for ITT population of APHINITY

Endpoints	Hazard ratio[b] (95% CI) (unstratified	p-value (unstratified)
IDFS (primary outcome)	0.82 (0.67, 1.00)	0.0549
Secondary efficacy endpoints		
IDFS (STEEP definition)	0.83 (0.68, 1.00)	0.0544
DFS	0.82 (0.68, 0.99)	0.0403
RFI	0.80 (0.64, 1.01)	0.0561
DRFI	0.83 (0.65, 1.06)	0.1275
OS	0.91 (0.67, 1.23)	0.5428
Values taken from CSR section 4.2.3		

4.2.4 HRQoL

The company presents brief and selected results from three HRQoL measures used in the APHINITY trial (pg. 37-39 CS document B). These are EORTC QLQ-C30 which is a general cancer quality of life questionnaire, EORTC QLQ-BR23 which is a BC specific quality of life questionnaire and EQ-5D-3L which is a non-disease specific quality of life questionnaire. The ERG considers the selection of these HRQoL measures to be appropriate, and comparable to previous appraisals for BC.[54] The HRQoL inputs used in the cost effectiveness analysis are described in section 5.2.7. The ERG notes that HRQoL inputs for the company model were taken from the APHINITY trial and from other and published literature sources.

Nodal status

Three hundred and twenty (320) of 3005 node-positive patients and 61 of 1799 node-negative patients developed invasive breast cancer or died by the clinical cut-off date of the APHINITY trial.[1] The rate of IDFS events among node-positive patients was 23% lower in the pertuzumab arm compared to the placebo arm (unstratified HR 0.77, 95% CI 0.62 to 0.96), whereas no significant difference was observed in node-negative patients (unstratified HR 1.13, 95% CI 0.68 to 1.86). However, the ERG notes that median IDFS had not been reached at clinical cut-off in node-positive and node-negative patients (see Figure 7, A and B).

The ERG also notes that the effect of pertuzumab was stronger in node-positive patients than the ITT population. Following the ERGs clarification request, the company provided subgroup analyses based on further stratification of node-positive patients (clarification response C6, see clarification figure 1). However, these additional analyses showed no clear pattern of a direct association between treatment effect and number of positive lymph nodes.

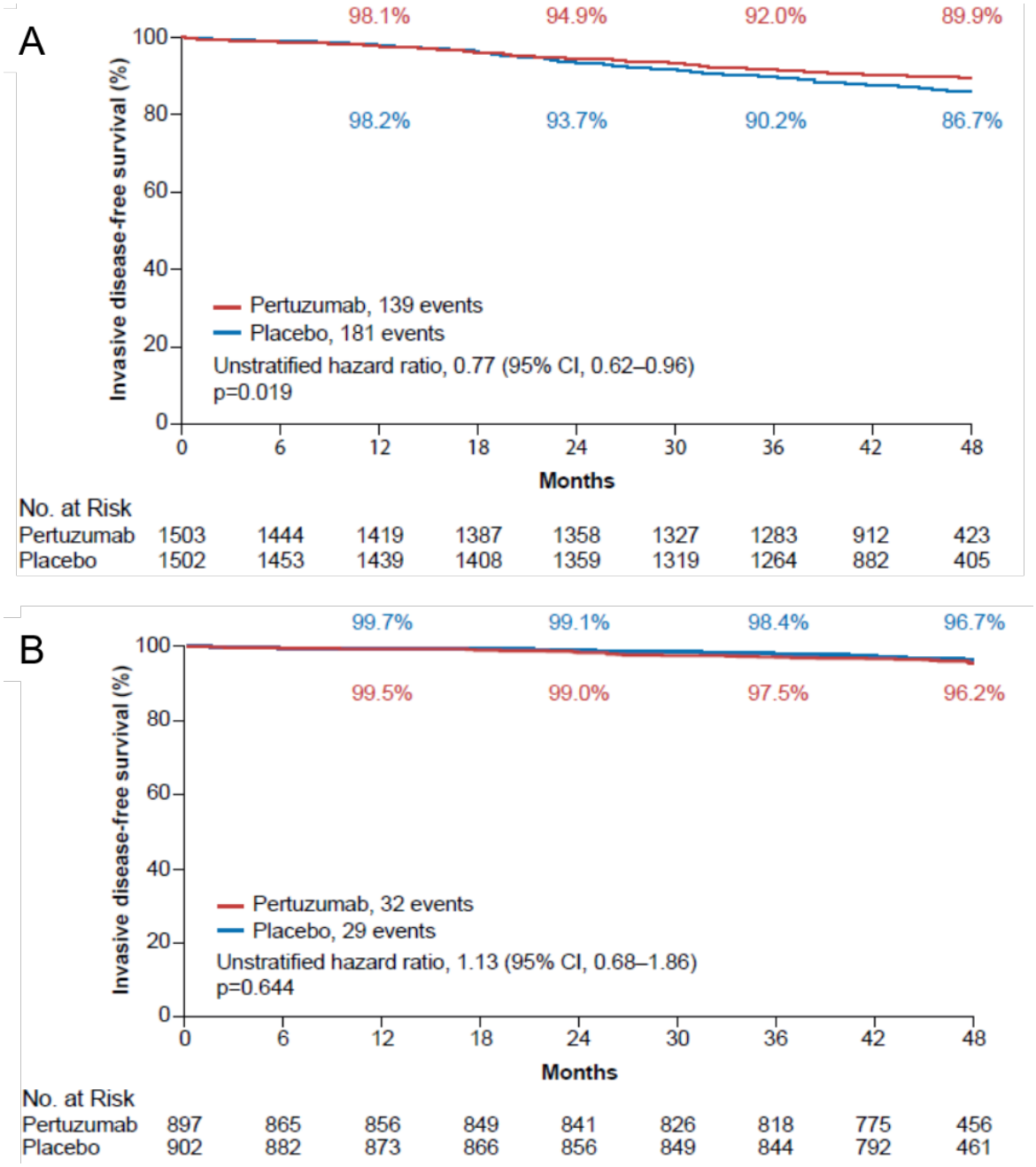


Figure 7. Kaplan-Meier plots of IDFS for ITT population with node-negative (A) and node-positive (B) disease (CS figure 6)

The ERG suggests that the effect of pertuzumab was only statistically significant for patients with 10 positive nodes (HR 0.60, 95% CI 0.39 to 0.94), but not among patients with less than 10 positive nodes: HR=0.73 (95% CI 0.52 to 1.04) and 0.95 (95% CI 0.65 to 1.39) for patients with 1-3 and 4-10 node-positive nodes respectively, though the trial was not powered to detect treatment effect in these subgroups. Regardless of power, the ERG would have expected to observe a linear trend (dose response) of treatment effect estimates if the performance of pertuzumab had been associated with disease severity, however, the observed effect was lowest in the 4-10 node group among the node positive groups.

Hormone receptor status

One hundred and sixty two (162) of 1722 hormone receptor-negative patients and 219 of 3082 hormone receptor-positive patients developed invasive BC or died by the clinical cut-off date of the APHINITY trial.[1] The rate of IDFS events in the pertuzumab arm is 24% lower than the rate of events in the placebo-based arm among hormone receptor-negative patients (HR=0.76, 95% CI 0.56 to 1.04, p=0.08), and 14% lower than the rate of events in the placebo-based arm among hormone receptor-positive patients (HR=0.86, 95% CI 0.66 to 1.13, p=0.28). The median IDFS had not been reached by clinical cut-off (see A and B). However, the ERG note that these treatment effects are not statistically significant, and do not differ significantly between hormone receptor-negative and hormone receptor-positive populations (p=0.54 for interaction) and do not differ significantly between the hormone receptor-negative and hormone receptor positive populations due to the heavily overlapping confidence intervals of the treatment effect estimates. The hypothesis of an interaction between treatment effect and HR status was not significant (p=054) (see Figure 8, A and B). The ERG clinical advisor notes that the 10% difference in IDFS event rates between hormone receptor-positive and hormone receptor-negative patients was not statistically different and would be concerned using it as a clinical indication.

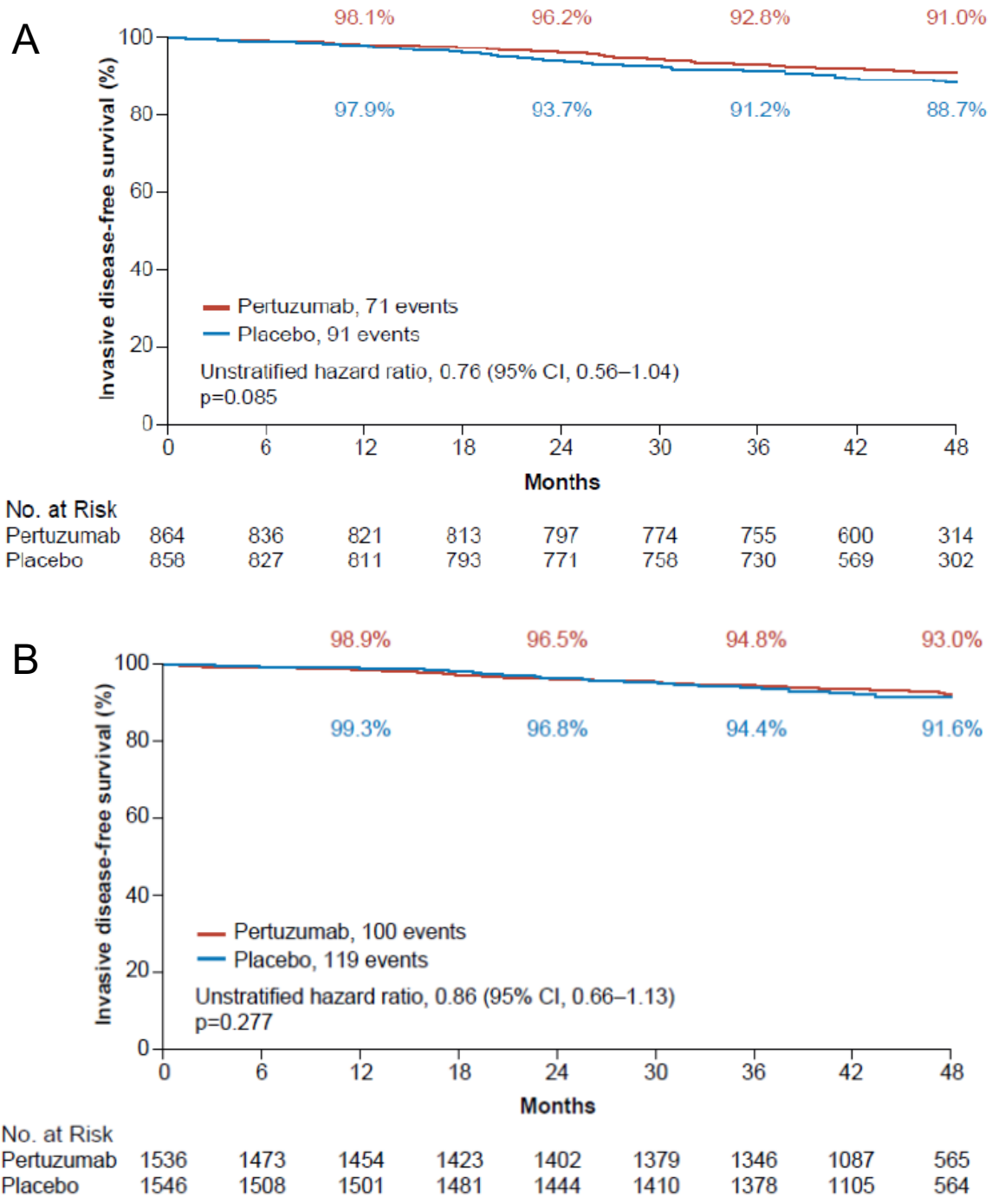


Figure 2. Kaplan-Meier plots of IDFS for ITT population with hormone receptor-negative (A) and hormone receptor-positive (B) disease (CS figure 7)

Additional subgroups

The ERG wanted to ensure the observed efficacy of pertuzumab in node-positive patients was not the result of a spurious interaction with other subgroup variables, in particular hormone receptor status. Therefore, the ERG requested additional analyses of the subgroups of patients of the node-positive

tumour size (clarification response C6, see clarification figure 1). Approximately three-quarters (72.5%, n=3481) of patients received adjuvant radiotherapy during the trial as clinically indicated. In these patients, the rate of IDFS events was 21% lower (95% CI 0.62 to 1.01) in the pertuzumab-based arm compared to the placebo-based arm. The rate of IDFS events among patients who were not administered adjuvant radiotherapy was 10% lower in the pertuzumab arm compared to placebo (95% CI 0.62 to 1.31).

It is not clear to the ERG how many node-positive and node-negative patients received adjuvant radiotherapy during the trial. Hence, the ERG are also uncertain as to whether there could be possible interaction between nodal status and adjuvant radiotherapy status. This is pertinent as effect estimates of pertuzumab in node-positive patients and patients who received adjuvant radiotherapy were comparable. The ERG considers that the slight superior efficacy of adjuvant pertuzumab+trastuzumab+chemotherapy over placebo+trastuzumab+chemotherapy (HR=0.81, 95% CI 0.66-1.00, p=0.045) could be attributable to a potential synergism between adjuvant pertuzumab and radiotherapy.

The CS subgroup analysis by histological grade revealed an inverse association between treatment benefit and histological grade (clarification response C6, see clarification figure 1). The ERG notes that a direct association, as with tumour size, would be consistent with the anticipated market authorisation (see section 2.4).

In summary, the ERG notes that in the original APHINITY protocol (version A) seven subgroups were mentioned specifically (menopausal status, type of surgery for tumour, tumour size, histological grade of tumour, race, loco-regional radiotherapy and hormone receptor status). Only hormone receptor and nodal status have been included in the CS decision problem. Nodal status appeared only in later versions of the trial protocol after approximately 75% of the study population had been randomised (protocol versions B and D). The ERG's clinical advisor suggested that both size and grade of tumour are predictors of risk of recurrence, alongside nodal status and hormone receptor status.

4.2.6 Summary of adverse events

General safety

The CS presents safety analyses data consistent with the published report[1] and CSR, for patients who received one or more doses of pertuzumab (n=2364) or placebo (n=2405). A total of 168 participants in the safety population died during the study. This represents 73 patients in the pertuzumab-based arm and 95 in the placebo-based arm. However, the number of deaths secondary to adverse events

Table 9. Summary of adverse events (safety analysis population; primary analysis, clinical cut-off date 19th December 2016)

Event	Pertuzumab + trastuzumab + chemotherapy N=2,364[d]	Placebo + trastuzumab + chemotherapy N=2,405[d]	RR (95% CI)	p-value for differences in proportions
	No. of patients (%)			
Grade ≥3 AE[∇]	1,518 (64.2)	1,379 (57.3)	1.12 (1.07 to 1.17)	0[∇]
Neutropenia	385 (16.3)	377 (15.7)	1.04 (0.91 to 1.18)	0.562
Febrile neutropenia	287 (12.1)	266 (11.1)	1.10 (0.94 to 1.28)	0.246
Neutrophil count decreased	228 (9.6)	230 (9.6)	1.01 (0.85 to 1.20)	0.920
Diarrhoea[∇]	232 (9.8)	90 (3.7)	2.62 (2.07 to 3.32)	0[∇]
Anaemia[∇]	163 (6.9)	113 (4.7)	1.47 (1.16 to 1.85)	0.001[∇]
Fatal AE	18 (0.8)	20 (0.8)	0.92 (0.49 to 1.73)	0.787
Primary cardiac event	17 (0.7)	8 (0.3)	2.16 (0.94 to 5.00)	0.06
NYHA class III of IV heart failure and substantial decrease in LVEF[∇]	15 (0.6)	6 (0.2)	2.54 (1.00 to 6.54)	0.044[∇]
Definite or probably cardiac death	2 (<0.1)	2 (<0.1)	1.02 (0.14 to 7.22)	0.984
Secondary cardiac event	64 (2.7)	67 (2.8)	0.97 (0.69 to 1.36)	0.865
Identified automatically from LVEF assessments	50 (2.1)	47 (2.0)	1.08 (0.73 to 1.61)	0.697
Identified by cardiac advisory board	14 (0.6)	20 (0.8)	0.71 (0.36 to 1.41)	0.327

AE, adverse event; LVEF, left ventricular ejection fraction. Grade ≥3 adverse events are not reported if rates < 5% in both treatment arms. ERG calculated p-values for the difference in proportions between treatment arms. Values match published trial[1] and CSR. [∇] indicate significantly ($p < 0.05$) higher incidence rates in pertuzumab compared to placebo.

Grade 3/4 Diarrhoea

While there were no reported diarrhoea-related deaths in the APHINITY trial, the ERG reiterates that severe (grade 3/4) diarrhoea is potentially life-threatening and a source of significant morbidity and impaired health-related quality of life.[64] The ERG also considers that the 6% higher rate of grade 3/4 diarrhoea in the pertuzumab-based arm compared to placebo (Table 9) may potentially attenuate the marginal efficacy gains attributed to pertuzumab in the submitted evidence.

The relative risk of severe diarrhoea was 2.62 (95% CI: 2.07, 3.32). This increased risk of severe diarrhoea supports observations from other pertuzumab trials, including the CLEOPATRA (+2.9% incidence, RR: 1.56), and PHEREXA (+6% incidence, RR: 1.61) studies.[35, 65] The true difference in effects of diarrhoea could be even greater as duration and recurrence of episodes are not reported in the CS.

Cardiac safety

The company differentiates primary cardiac events from secondary cardiac events based on the severity of symptoms: patients with primary cardiac events had a more severe symptomatology compared to patients with secondary cardiac events. The ERG considers that the absence (primary) or presence (secondary) of a previous cardiac outcome prior to the index cardiac event during the study, including the post-treatment period, should inform the distinction between primary and secondary cardiac events (CS document B, pg. 48). More importantly, the (severe) primary cardiac events were assessed at the end of post-treatment follow-up period, whereas the (less severe) secondary cardiac events were assessed after breast cancer recurrence if recurrence occurred prior to the end of post-treatment follow-up (CS document B, pg. 48). The ERG considers that primary and secondary cardiac events, as defined by the company, should have been assessed at the same time-points.

The CS stated that there was no increase in cardiac-related adverse events such as heart failure in the pertuzumab arm compared to the placebo-based arm (CS document B, section B.2.10.4, pg. 49). This statement is supported citing evidence from three previous trials.[66-68] Furthermore, as demonstrated in Table 9, the incidence of New York Heart Association (NYHA) class III or IV heart failure with substantial decrease in left ventricular ejection fraction (LVEF) was three times higher among patients in the pertuzumab-based arm compared to the placebo-based arm (0.6% vs. 0.2%, p=0.04). The ERG recognises that although these rates may be low, these are all new cases within the APHINITY trial given that patients with a history of documented heart failure or systolic dysfunction (LVEF < 50%) were excluded prior to the study (protocol version D, section 4.3, pg. 64). The ERG clinical advisor confirms that there is an association between pertuzumab and heart disease. However, the ERG clinical advisor suggests that cardiac events are not very common in clinical practice, and they are not likely to modify treatment if present.

Cardiac-related adverse events, especially NYHA class III heart failure, were not included in the ERG pre-clarification health economic model submission. Given considerable differences in incidence rates between treatment arms, the ERG considers that the company should have performed a scenario analysis to determine the impact of heart failure on the health economic model. During clarification, the ERG requested total costs, total QALY and ICER values that take cardiac-related adverse events into account (discussed in section 5.2.7.5).

Anaemia

decision to include the APHINITY trial as the key evidence, and notes that the comparator and intervention reported in this trial are appropriate and consistent with the NICE final scope. IDFS and

DRFI were additional outcomes in the trial which were not listed in the NICE scope, but were approved by the ERG clinical advisor. The population in this trial (n=4806) addresses the decision problem which is focussed on eBC patients with a high-risk of recurrence after surgical treatment. However, the ERG is concerned about the emphasis of node-positive (base case) and hormone receptor-negative (additional scenario) patients as the target population, whereas other high-risk subgroups (such as histological grade 3 and tumour size > 5cm) were not considered in the company decision problem.

The ERG notes an amendment to the original protocol of the APHINITY trial (protocol A) which was implemented after 3655 participants had been randomised in order to enrol only node-positive patients (protocol B). The ERG suggest that protocol B is effectively a second trial in which node-positive patients were randomised to the pertuzumab-based arm or the control arm (placebo-based), hence there is no immediate concern of bias.

The efficacy analysis of the APHINITY trial revealed that pertuzumab was just marginally better than placebo for preventing recurrence of breast cancer and/or death (HR 0.81, 95% CI 0.66 to 1.00). The ERG is concerned that this difference may not be clinically meaningful. Analyses of the nodal subgroups revealed a slightly less marginal difference in IDFS rates between pertuzumab and placebo in node-positive patients (HR 0.77, 95% CI 0.62 to 0.96), whereas no statistically significant difference was detected in node-negative patients (HR 1.13, 95% CI 0.68 to 1.86). However, following clarification request for additional stratification of the node-positive subgroup, the ERG are concerned that adjuvant pertuzumab may only be effective in eBC patients with 10 or more cancer cells in the loco-regional lymph nodes. Analyses of the hormone receptor subgroups reveal no statistically significant benefit of pertuzumab over placebo in hormone receptor-negative (HR 0.76, 95% CI 0.56 to 1.04) or hormone receptor-positive patients (HR 0.86, 95% CI 0.66 to 1.13).

The ERG questions the safety profile of pertuzumab, with significantly larger proportions of patients in the pertuzumab-based arm experiencing grade 3 or higher adverse events compared to patients in the placebo-based arm (64.2% vs. 57.3%, $p < 0.001$). Of note, patients in the pertuzumab-based arm were more likely to develop grade 3 or higher diarrhoea (9.8% vs. 3.7%, $p < 0.001$), anaemia (6.9% vs. 4.7%, $p=0.001$) and symptomatic heart failure (0.6% vs. 0.2%, $p=0.04$), compared to the placebo-based arm.

5.2.4 Interventions and comparators

The intervention assessed in the analysis is adjuvant pertuzumab in combination with trastuzumab and chemotherapy (abbreviated as PHC). This is compared to standard adjuvant therapy without pertuzumab (trastuzumab in combination with chemotherapy) (abbreviated as HC). This matches the intervention and comparator specified in the NICE final scope for this appraisal.

5.2.5 Perspective, time horizon and discounting

The economic analysis presented in the CS has been undertaken from the NHS and PSS perspective; this agrees with the guidelines stipulated in the NICE Reference Case.[74] The analysis is carried out over a 52 year time horizon, which effectively represents a lifetime horizon. By the end of this time horizon, less than 1% of the patients in the model remain alive. In line with the NICE Reference Case, costs and health effects are discounted at 3.5% per year.

5.2.6 Treatment effectiveness and extrapolation

In the submitted analysis, treatment effectiveness evidence and extrapolation methods were used to model transitions within and between IDFS and 'post-recurrence' states.

5.2.6.1 Modelling of IDFS states

IDFS health states capture the period of time during which patients remain disease-free and facilitate the calculation of cost-effectiveness outcomes (cost, survival and QALYs) during this period.

The company took an unusual approach to modelling IDFS states. Using a piece-wise approach, the analysis divides the 52-year period into three phases (or time periods). The first phase models IDFS events in the first four years, using a parametric curve fitted independently to both arms on the basis of the observed data from the APHINITY trial. The second phase, modelling years four to ten, adjusts the parametric curve, which was supported by external data. The final phase, from years 10 to the end of the time horizon (year 52), further adjusts the extrapolation, assuming that 90% of patients are no longer at risk of an IDFS event other than death. Each modelled phase is critiqued in turn below.

<u>Phase 1</u>

The company fitted a range of parametric models to the observed IDFS data for the node positive population of the APHINITY trial. The parametric models assessed by the company were fitted to all observed IDFS data (i.e. from month 0 until end of follow-up); however, in the economic model, an option is available to begin by using the non-parametric KM data up to a certain point in time and begin the parametric fit after this point. An assessment of proportional hazards was performed through

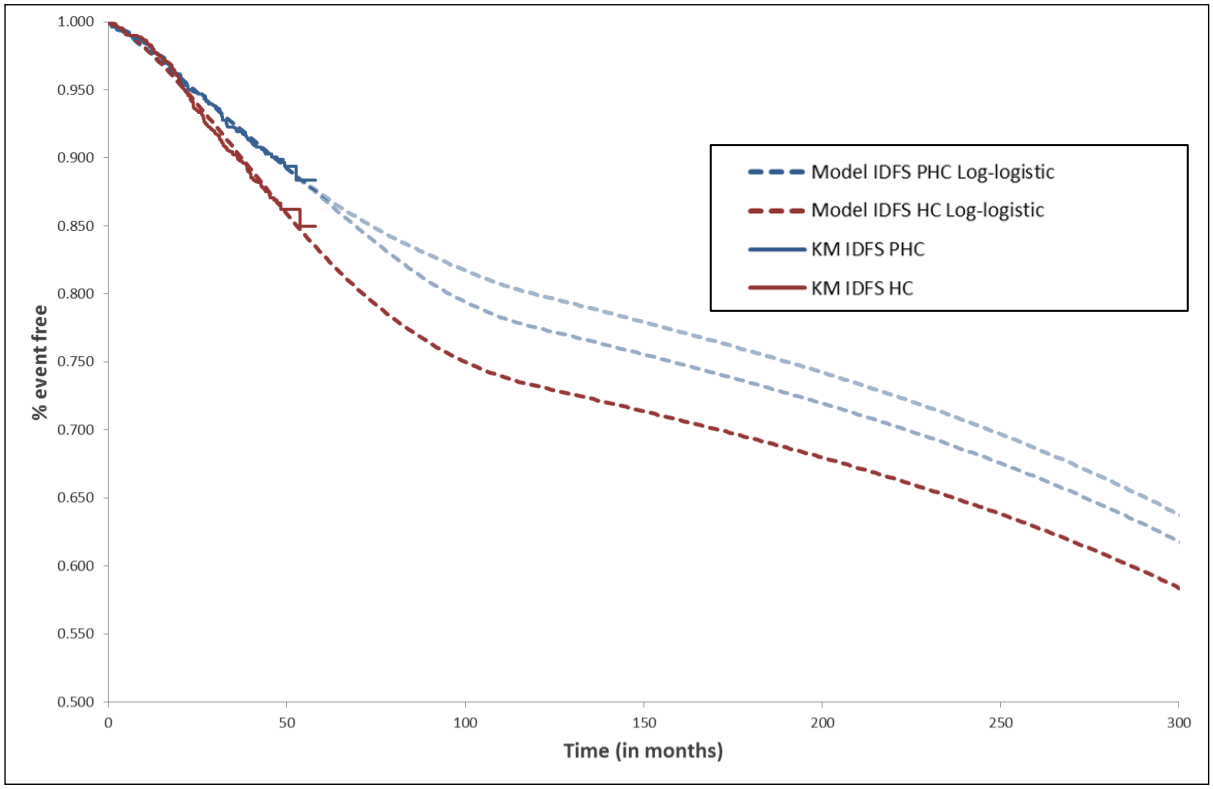


Figure 16. Demonstrating change to IDFS of ERG preferred duration of treatment effect compared to company base case (overlaid onto Error! Reference source not found.**)**

The company's choice of parametric curve for IDFS extrapolation is largely guided by the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC). Whilst this approach is commonly taken and is in line with DSU guidance, the company state that they did not consider the BIC values in their decision-making process due to taking a 'frequentist approach'. It must be noted that, mathematically, AIC and BIC are very similar, both helping the user to select a parsimonious model, with BIC imposing a stronger penalty for the inclusion of additional parameters when comparing models. BIC is not a Bayesian approach in the common use of the term (e.g., an approach that combines prior information with likelihoods to obtain posterior distributions) and is routinely used to appraise 'frequentist' models. The ERG agree that AIC values should be prioritised over BIC, but find the argument about not using the BIC values potentially misleading.

The AIC/BIC values are presented by the company and reproduced in Table 14 (corresponding to Table 21 in the CS). The AIC values suggest that the exponential distribution is the most parsimonious fit to the data in the pertuzumab arm, though none of the parametric models offer strong evidence of unsuitability (difference > 10).[76] The log-logistic is the best fitting model to the placebo arm, but it is apparent to the ERG that only the exponential can be classified as a significantly worse fit and so unsuitable for extrapolation.

Table 15. IDFS events at 36 and 48 months

Timepoint	Parametric function	Pertuzumab + trastuzumab + chemotherapy	Placebo + trastuzumab + chemotherapy	Pertuzumab + trastuzumab + chemotherapy vs Placebo + trastuzumab + chemotherapy	Δ vs KM data	
					Pertuzumab + trastuzumab + chemotherapy	Placebo + trastuzumab + chemotherapy
36 months	KM data	91.88%	89.91%	1.97%	-	-
	Exponential	92.10%	89.85%	2.26%	0.22%	-0.06%
	Weibull	92.24%	90.34%	1.90%	0.36%	0.43%
	Log-normal	92.03%	90.01%	2.02%	0.15%	0.10%
	Gamma	92.25%	90.26%	1.98%	0.37%	0.35%
	Log-logistic	92.21%	90.27%	1.94%	0.33%	0.36%
	Gompertz	92.29%	90.43%	1.86%	0.41%	0.52%
48 months	KM data	89.65%	86.46%	3.19%	-	-
	Exponential	89.65%	86.74%	2.91%	0.00%	0.28%
	Weibull	89.54%	86.34%	3.20%	-0.11%	-0.12%
	Log-normal	89.79%	86.67%	3.12%	0.14%	0.21%
	Gamma	89.54%	86.39%	3.15%	-0.11%	-0.07%
	Log-logistic	89.56%	86.35%	3.21%	-0.09%	-0.11%
	Gompertz	89.53%	86.34%	3.19%	-0.12%	-0.12%

As expected from the similar AIC values and fitted cumulative hazard plots, the models all produce very similar predictions of IDFS. All overestimate 36 month IDFS, and most underestimate 48 month IDFS. The log-normal is the best predictor of 36 month IDFS and the generalised gamma and log-logistic predict 48 month IDFS equivalently well. The ERG agree with the company's statement that the differences in absolute fit of the parametric fit function extrapolations at the 36 and 48 month timepoints are negligible. The ERG requested the updated observed rates for IDFS (clarification C3) be presented by the company to compare the predictions made by the different parametric models, however, the company declined, stating updated efficacy data would only be available at the next planned analysis of OS (estimated 2020).

A careful choice of parametric model is required, as this influences the whole IDFS extrapolation and other health states. However, the assumptions behind the parametric models do not appear to have been assessed in depth. For example, fitting exponential models assumes constant hazard rates in both arms, a consequence of which is proportional hazards. Similarly, a Weibull model assumes the hazard is either monotonically increasing or monotonically decreasing. The ERG do not believe either of these are biologically plausible, thus considering these distributions appears to be unnecessary.

A comparison of IDFS estimates to external sources of data would be highly useful for validation purposes. Given that such a comparison was not available in the CS, the ERG compared the company's base case IDFS prediction with those observed in other trials in Table 16. On the whole, Limited data for the effects of pertuzumab on HRQoL were presented. Brief and selected results from three HRQoL measures were presented. Overall, there is sufficient evidence to Phase 1

Table 22. Utility values used in company's scenario analyses

		Non-pooled values from APHINITY trial		Values from Hedden et al. [70]	Values from Lidgren et al. [71]	Values from Paracha et al. [72]
State		PHC	HC	PHC and HC*	PHC and HC*	PHC and HC*
eBC	IDFS – On chemotherapy	0.763	0.756	0.750	0.696	N/A
	IDFS- On treatment/off chemotherapy	0.787	0.785	0.784	0.696	N/A
	IDFS- Off treatment	0.827	0.822	0.817	0.779	N/A
	Non-metastatic recurrence	0.763	0.756	0.750	0.779	N/A
	Remission	0.827	0.822	0.990	0.779	N/A
mBC	1st Line mBC	0.773	0.773	0.650	0.685	0.806
	2+ line mBC	0.520	0.520	0.290	0.685	0.536

* The same utility values were used for both PHC and HC.
eBC: early breast cancer; mBC: metastatic breast cancer; N/A: not available;
PHC: pertuzumab + trastuzumab + chemotherapy; HC: trastuzumab + chemotherapy.

5.2.7.5 Impact of AE on HRQoL

According to APHINITY trial results, the vast majority of patients in the trial experienced at least one AE during the treatment period (99.9% in HCP and 99.5% in HC). Most of the observed AEs were of mild or moderate severity (Grade 1 or 2), with only 10% being classified as severe (i.e., Grade 3 and above). To ascertain that the impact of AE is reflected on HRQoL, one could either apply a disutility effect to collected HRQoL, or disregard any disutility resulting from AEs on the premise that this will have been reflected in the trial-collected HRQoL data. In the CS, it has been assumed that disutility resulting from treatment-related AEs is already reflected in the EQ-5D responses from the APHINITY study. However, the expectation that disutility due to AEs is reflected in EQ-5D responses is contentious; unless by design, it is unlikely that EQ-5D data were collected exactly on days that AEs were experienced.

Upon request by the ERG, the company provided an analysis where the disutility of severe AEs (anaemia, cardiac failure, diarrhoea, neutropenia and neutrophil count decrease) is taken into account by assuming that utility scores for the proportion of people who experienced such events is reduced by 0.5 over the first 13 months (treatment period). The number of AEs (and consequently, the derived probability of a patient experiencing an AE) was small, as the number of 'treatment-related' AEs in the submitted model was small. As a result, the inclusion of the disutility (and costs) of AEs had a minimal impact, which was largely proportional across treatments. This led to a very small change in the ICER of approximately £130.

Conversely, in the HC arm of the model, 95% of patients receive the more expensive trastuzumab SC formulation, with the rest receiving trastuzumab IV. The proportion of patients who receive trastuzumab IV and SC was drawn from research on market shares conducted by the company. These values could not be verified by the ERG.

Should pertuzumab be approved, expert opinion sought by the ERG suggested that the treatment will, at least for the first year, be given typically offered with trastuzumab IV. Nonetheless, experts expressed their expectations that, in subsequent years, an increasing share of patients will be receiving pertuzumab (should this be recommended) with trastuzumab SC. In light of this, the ERG undertook additional analyses to account for the eventuality that, post approval, an increasing proportion of patients will receive pertuzumab with trastuzumab SC.

In the submitted analysis, chemotherapy provided in addition to targeted treatment could be "sequential" (four cycles of anthracycline chemotherapy followed by taxane in combination with targeted treatment), or "concurrent" (docetaxel plus carboplatin in combination with targeted treatment), which reflects the set up in the APHINITY study. Expert opinion sought by ERG confirmed that such arrangements are representative of UK clinical practice.

Treatment duration, and, by extension, the number of treatment cycles provided, was derived from time-to-off-treatment (TTOT) data collected during the APHINITY trial. In the base case, the company calculated treatment duration by using the proportion of patients who received the drug at each treatment cycle in the trial. In this way, the calculations account for the fact that patients can discontinue treatments, that is, receive fewer than 18 cycles of treatment, due to toxicity or disease progression. The ERG considers this approach to be reasonable.

Upon experiencing a recurrence, patients are expected to receive various additional treatment depending on the disease setting (i.e. non-metastatic recurrence, first-line mBC, or second + line mBC). In their analysis, the company calculated the total expected cost of subsequent treatments as a weighted average across available treatments based on current market shares in the UK (Table 24 below, corresponding to table 39 in CS). The source of the value for the market share of trastuzumab SC + docetaxel in the non-metastatic recurrence health state ([redacted]) could not be traced. Medication prices and quantities employed in calculating the cost of chemotherapy regimens were consistent with entries in the electronic market information tool (eMIT).

£13.51), thus, in the ERG's opinion, they are highly unlikely to have a notable effect on the final cost-effectiveness results.

5.2.9 Cost effectiveness results

In their CS, the company presented results from: (i) a base case (deterministic) analysis; (ii) a modified base case (deterministic) analysis; and (iii) sensitivity analyses, including probabilistic, univariate deterministic and scenario analyses (section 5.2.10). Results of the company's main analysis (node positive population) were presented in the main body of the CS, while findings for the additional subgroup (HR-negative population) were given in the submitted appendices (appendix M). Additional analyses provided as part of the clarification process resulted in changes in the cost-effectiveness results, though the company did not explicitly amend the base case analysis results presented in the CS.

5.2.9.1 Base case results

The company's base case deterministic cost-effectiveness results, as presented in the CS, are reproduced in Table 27 below (corresponding to table 50 in the CS).

Table 27. Base case cost-effectiveness results (node-positive population).

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
HC (trastuzumab + chemotherapy)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£34,087
PHC (pertuzumab + trastuzumab + chemotherapy)	[redacted]	[redacted]	[redacted]				

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

Results suggest that, on average, pertuzumab led to an incremental gain of [redacted] QALYs at an additional cost of [redacted] per person. Given this, the ICER for the comparison between PHC and HC in node positive eBC patients was estimated to be £34,087 per QALY gained.

In addition, the results of a 'modified base case analysis were presented, on the basis that introduction of trastuzumab biosimilars to the UK market in the near future is expected to have a sizeable impact on the calculated ICER. As the price and market share of biosimilars is currently (February 2018) unknown, the company presented a two-way table (Table 11, corresponding to table 51 in the CS) showing ICER values corresponding to different combinations of biosimilar price and market share.

c. Revisions in the calculations of the proportion of patients estimated to experience metastatic and non-metastatic recurrences. As noted in Section 5.2.6.2, the proportion of metastatic events obtained from the whole observed trial is, incorrectly, applied only to events occurring beyond 18 months. The ERG re-calculated the proportion of metastatic (and non-metastatic) events applicable to post-18 month relapses (see Table 18 above) and used the revised values in the proposed ERG base case.

For each of these amendments, the values used in the company's base case analysis and the values preferred by the ERG (given in bold) can be found in Table 30 below. Results of the ERG base case analysis are presented in Section 6.1.

Table 30. Values used in the ERG's base case analysis

Parameter	Values in company's base case	ERG's preferred value	Section where justification is given
Duration of incremental treatment effect			
Time point when incremental treatment effect begins to wane	Year 7	Year 4	Section 5.2.6.1
Time point when incremental treatment effect ceases	Year 10	Year 7	
'Cure' adjustments			
Time point when 'cure' adjustment is introduced in the analysis	Year 4	Year 3	Section 5.2.6.1
Time point when maximum 'cure' is reached	Year 10	Year 10	
Maximum "cure" proportion	90.00%	95.00%	
Percentages of disease recurrence			
metastatic recurrence	81.07%	72.40%	Section 5.2.6.2
non-metastatic recurrence	18.93%	27.60%	

5.3.2 Probabilistic sensitivity analysis

The ERG re-run the PSA in order to obtain results that reflect the amendments in parameters specified in the ERG suggested base case. The revised PSA results (joint distribution of cost and QALY estimates) were generated through 1000 iterations and are depicted in the cost-effectiveness plane and cost-effectiveness acceptability curves presented in Section 6.2.

5.3.3 Additional deterministic analyses

Additional analyses were performed by the ERG, including:

i. re-running the company's scenario analyses on the basis of the ERG suggested base case
ii. undertaking additional analyses using alternative assumptions, approaches or values for key parameters
iii. carrying out further analyses on key uncertain parameters, including the duration of pertuzumab's effect, the future market share of trastuzumab SC given in combination with pertuzumab and the acquisition cost of pertuzumab.

The main findings of this additional work are presented in Section 6.3 below.

1.6 Conclusions of the cost effectiveness section

The company developed and presented a *de novo* economic analysis to evaluate the cost-effectiveness of pertuzumab + trastuzumab + chemotherapy, as compared to trastuzumab + chemotherapy in the adjuvant setting. The centrepiece of this analysis was the company's economic model, which was developed in a widely available spreadsheet application. The ERG considers the type and structure of the submitted model to be appropriate for representing the disease pathway and therapeutic options for the population specified in the NICE Final Scope for this appraisal. Key characteristics of the analysis, such as the selected perspective, time horizon, main outcome and discount rates, were in line with recommendations set out in the NICE Reference Case. The ERG felt that the company took reasonable steps to ascertain that data used in the model were of sound quality and suitable for the particular decision problem. The company's deterministic base case ICER, which is reported in the original submission, is £34,087 per QALY gained.

Model inputs and assumptions used in the model were scrutinised by the ERG. The following issues were identified and discussed in the ERG's critique:

- Uncertainties related to the duration of pertuzumab's incremental effect. The ERG believes that the choice of a relatively long duration of treatment effect is not justified adequately in the CS, and proposes alternative specifications, which the ERG believes to be better aligned with existing evidence. These specifications were incorporated in the ERG preferred base case
- Uncertainties around the specifications of the 'cure' adjustment. While the ERG agrees that the adjustment is beneficial, it proposes an alternative specification (i.e. different starting point and maximum cure proportion), which better represents available data on

Table 31. ICER values after implementing ERG's amendments in the company's base case

Parameter	Values in company's base case	ERG's preferred value	ERG's ICER (£ per QALY gained)
Duration of incremental treatment effect			
Time point when incremental treatment effect begins to wane	Year 7	Year 4	£54,901
Time point when incremental treatment effect ceases	Year 10	Year 7	
'Cure' adjustments			
Time point when 'cure' adjustment is introduced in the analysis	Year 4	Year 3	£37,686
Time point when maximum 'cure' is reached	Year 10	Year 10	
Maximum "cure" proportion	90.00%	95.00%	
Percentages of disease recurrence			
metastatic recurrence	76.87%	72.40%	£35,933
non-metastatic recurrence	23.13%	27.60%	

Carrying out all the above changes simultaneously, that is, implementing the ERG's suggested base case analysis, resulted in a considerable increase in the ICER, by approximately £26,600. The ERG's base case ICER in the node-positive population was calculated to be £60,679 per QALY gained (Table 32).

Table 32. Results of ERG suggested base case analysis

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£ per QALY gained)
HC (trastuzumab + chemotherapy)	[redacted]	[redacted]	[redacted]	[redacted]	£60,679
PHC (pertuzumab + trastuzumab + chemotherapy)	[redacted]	[redacted]			

6.2 Revised probabilistic sensitivity analysis based on ERG base case

PSA undertaken on the basis of the ERG amendments produced a mean ICER of £60,344 per QALY gained, which was very similar to the obtained deterministic value. The revised Cost Effectiveness (CE) plane and Cost Effectiveness Acceptability Curve (CEAC) depicting the comparison between PHC and HC are given in Figure 27 and Figure 28 below, respectively.

Table 34. Results of ERG additional analyses

Variable	Value	Diff. Costs (PHC vs HC)	Diff. QALYs (PHC vs HC)	ICER (£ per QALY gained)
Company's base case		[redacted]	[redacted]	£34,087
ERG's base case		[redacted]	[redacted]	£60,679
IDFS parametric distribution				
Gen Gamma fitted from 0 months	Gen Gamma fitted from 0 months	[redacted]	[redacted]	£64,050
Log-logistic fitted from 36 months	Log-logistic fitted from 36 months	[redacted]	[redacted]	£61,491
Gamma fitted from 36 months	Gamma fitted from 36 months	[redacted]	[redacted]	£65,914
Log-logistic fitted from 19 months	Log-logistic fitted from 19 months	[redacted]	[redacted]	£64,263
Gamma fitted from 19 months	Gamma fitted from 19 months	[redacted]	[redacted]	£69,067
Remission to First-line mBC				
Base case value (0.0076) halved	0.0038	[redacted]	[redacted]	£64,788
Base case value (0.0076) doubled	0.0152	[redacted]	[redacted]	£57,272
First-line mBC to 2nd + line mBC for pertuzumab + trastuzumab + chemotherapy				
Base case value (0.032) halved	0.016	[redacted]	[redacted]	£61,451
Base case value (0.032) doubled	0.064	[redacted]	[redacted]	£60,679
First-line mBC to 2nd + line mBC for trastuzumab + chemotherapy				
Base case value (0.047) halved	0.023	[redacted]	[redacted]	£60,987
Base case value (0.047) doubled	0.094	[redacted]	[redacted]	£60,261
First-line mBC to 2nd + line mBC for chemotherapy				
Base case value (0.069) halved	0.035	[redacted]	[redacted]	£60,786
Base case value (0.069) doubled	0.277	[redacted]	[redacted]	£60,495
Treatment-specific (non-pooled) percentages of recurrence calculated by the ERG				
PHC	73.33%	[redacted]	[redacted]	£63,236
HC	71.79%			
Proportion of treatment usage in 1st line metastatic disease: approximate shares based on the APHINITY trial				
Pertuzumab + trastuzumab + chemotherapy	18.40%	[redacted]	[redacted]	£59,744
Placebo + trastuzumab + chemotherapy	17.00%			
Chemotherapy alone	64.70%			
Utility values for IDFS states, non-metastatic recurrence and remission	Treatment specific (non-pooled) EQ-5D from APHINITY	[redacted]	[redacted]	£51,534
Utility values for non-metastatic recurrence				
from Ward et al.[79]	0.740	[redacted]	[redacted]	£60,652

from Peasgood et al.[81]	0.637	[redacted]	[redacted]	£60,485
Utility values for 'Remission'				
from Ward et al.[79]	0.850	[redacted]	[redacted]	£60,723
from Peasgood et al.[81]	0.710	[redacted]	[redacted]	£59,573
Utility values for 'First-line metastatic BC'				
from Ward et al.[79]	0.500	[redacted]	[redacted]	£58,053
from Zhou et al.[82]	0.650	[redacted]	[redacted]	£59,469
Utility values for 'Second + line BC'				
from Ward et al.[79]	0.500	[redacted]	[redacted]	£60,450
Peasgood et al.[81]	0.435	[redacted]	[redacted]	£59,720
from Sherill et al.[83]	0.425	[redacted]	[redacted]	£59,609
Non-pooled utility values for IDFS states.	Treatment specific EQ-5D values from APHINITY trial	[redacted]	[redacted]	£51,534
Disutility associated with adverse events (anaemia, cardiac events, diarrhoea, neutropenia, neutrophil count decrease)				
Disutility value	0.100	[redacted]	[redacted]	£60,734
Disutility value	0.500	[redacted]	[redacted]	£60,956
Disutility value	0.700	[redacted]	[redacted]	£61,068

Specific parameters which are likely to have an impact on the ICER and/or which the ERG considers to be particularly uncertain were looked at more closely. These include: i) the duration of pertuzumab's treatment effect; ii) the specifications of the 'cure' model adjustments; iii) the proportion of patients who are likely to receive pertuzumab with trastuzumab SC, should pertuzumab be recommended, and iv) the acquisition cost of pertuzumab. Further sensitivity analyses have been undertaken by using combinations of assumptions and values for each of these parameters and keeping the rest of the model parameters fixed at the ERG's preferred values. As mentioned in Section 6.1, the number of years that pertuzumab's treatment effect is expected to last is an inherently uncertain parameter, which also has a substantial impact the ICER. The ICER values associated with different specifications of this parameter can be seen in Table 35. Assuming that pertuzumab's effect starts to wane early and is null after a few years reduces the incremental effectiveness and incremental QALYs of the PHC and increases the ICER. Conversely, assuming a treatment effect that lasts for longer and, once it starts to diminish, it takes longer to disappear, leads to lower ICER values. Following the ERG's preferred specifications, a treatment effect that starts to wane at four years and disappears completely three years later, at seven years, the resulting ICER is £60,679 per QALY gained.

Table 35. Effect of different assumptions about pertuzumab's incremental treatment effect on ERG's base case ICER

	Duration of treatment waning (years)										
Effect starts to wane	0	1	2	3	4	5	6	7	8	9	10
Year 1	-£9,857,138	£938,870	£388,205	£228,726	£159,407	£122,494	£100,305	£85,911	£76,107	£69,226	£64,287
Year 2	£438,158	£241,196	£162,988	£122,337	£98,456	£83,211	£72,937	£65,771	£60,682	£57,017	-
Year 3	£168,911	£121,482	£96,576	£80,761	£70,150	£62,770	£57,529	£53,784	£51,096	-	-
Year 4	£97,526	£79,387	£68,353	£60,679	£55,226	£51,317	£48,531	£46,558	-	-	-
Year 5	£68,562	£59,631	£53,853	£49,699	£46,719	£44,622	£43,174	-	-	-	-
Year 6	£53,844	£48,901	£45,655	£43,345	£41,757	£40,706	-	-	-	-	-
Year 7	£45,562	£42,718	£40,907	£39,711	£38,969	-	-	-	-	-	-
Year 8	£40,775	£39,204	£38,319	£37,822	-	-	-	-	-	-	-
Year 9	£38,162	£37,461	£37,155	-	-	-	-	-	-	-	-
Year 10	£37,071	£36,853	-	-	-	-	-	-	-	-	-

7 END OF LIFE

The company has not presented a case in support of pertuzumab as an 'end of life' treatment. NICE prescribes that, for an 'end of life' case to be made, the appraised treatment needs to satisfy all of the following criteria: i) the treatment is indicated for patients with a short life expectancy, normally less than 24 months and; ii) 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; iii) the treatment is licensed or otherwise indicated, for small patient populations. The ERG considers that these criteria are not met.

8 OVERALL CONCLUSION

Clinical effectiveness conclusion

The company present a reasonable quality systematic review of the clinical effectiveness of adjuvant pertuzumab in combination with trastuzumab and chemotherapy. The APHINITY trial is the main source of evidence, and the comparator and intervention reported in this trial are appropriate and consistent with the NICE final scope. IDFS and DRFI were additional outcomes in the trial which were not listed in the NICE scope, but were considered appropriate by the ERG clinical advisor. The population in the APHINITY trial (n=4805) addresses the decision problem which focusses on eBC patients with a high-risk of recurrence after surgical treatment. The ERG is concerned about the emphasis of node-positive (base case) and hormone receptor-negative (additional scenario) patients as the target population, whereas other high-risk subgroups (such as histological grade 3 and tumour size > 5cm) lacked consideration in the company decision problem.

The ERG notes an amendment to the original protocol of the APHINITY trial (protocol A) which was implemented after 3655 participants had been randomised in order to enrol only node-positive patients (protocol B). The ERG suggest that protocol B is effectively a second trial in which node-positive patients were randomised to the pertuzumab-based arm or the control arm (placebo-based), hence, there is no immediate concern of bias.

The efficacy analysis of the APHINITY trial revealed that pertuzumab was marginally better than placebo for preventing recurrence of breast cancer and/or death (HR 0.81, 95% CI 0.66 to 1.00). The ERG is concerned that this difference may not be clinically meaningful. Analyses of the nodal subgroups revealed a less marginal difference in IDFS rates between pertuzumab and

placebo in node-positive patients (HR 0.77, 95% CI 0.62 to 0.96), whereas no statistically significant difference was detected in node-negative patients (HR 1.13, 95% CI 0.68 to 1.86). The ERG is concerned that adjuvant pertuzumab may only be effective in eBC patients with 10 or more positive loco-regional lymph nodes. Analyses of the hormone receptor subgroups reveal no statistically significant benefit of pertuzumab over placebo in hormone receptor-negative (HR 0.76, 95% CI 0.56 to 1.04) or hormone receptor-positive patients (HR 0.86, 95% CI 0.66 to 1.13).

The ERG questions the safety profile of pertuzumab, with significantly larger proportions of patients in the pertuzumab-based arm experiencing grade 3 or higher adverse events compared to patients in the placebo-based arm (64.2% vs. 57.3%, $p < 0.001$). Of note, patients in the pertuzumab-based arm were more likely to develop grade 3 or higher diarrhoea (9.8% vs. 3.7%, $p < 0.001$), anaemia (6.9% vs. 4.7%, $p=0.001$) and symptomatic heart failure (0.6% vs. 0.2%, $p=0.04$), compared to the placebo-based arm.

In summary, the ERG notes that the APHINITY trial was not powered to detect subgroup differences. The ERG was unable to rule out any spurious interactions between subgroup variables. Whilst there is evidence of a treatment effect among the nodal status subgroups, the ERG believes that the apparent treatment interactions with hormone receptor status and menopausal status may be artefacts of the interaction with nodal status for which there is slightly stronger evidence. The ERG considers that claims of treatment benefit (marginal) should be balanced against the safety of adjuvant pertuzumab in combination with trastuzumab and chemotherapy.

Cost effectiveness conclusion

The main analysis presented in the CS relates to a population with HER2-positive, node-positive disease. An additional analysis pertaining to patients with HER2-positive hormone receptor-negative disease was included in appendix M of the CS. The ERG's critique focused on the main analysis (node-positive population); however, issues identified and points raised are also applicable to the additional analysis (hormone receptor-negative population).

The company's economic analysis was based on a decision analytic model developed in a spreadsheet application. The ERG considers the type and structure of the submitted model to be appropriate for representing the disease pathway and therapeutic options for the particular

assumption may hold, the company justified using a parametric approach on grounds of convenience, adding that this was not expected to significantly impact the cost effectiveness results. The ERG accepts the choice of a parametric approach for this extrapolation and considers the provided justification to be valid.

The choice of the exact type of parametric function was guided by comparison of generated AIC and BIC goodness of fit values (Table 39, corresponding to table 35 in the submitted CS appendices), as well as by consideration of the absolute fit of the curves to observed KM data, assessed through a simple comparison of modelled versus observed IDFS events at two time points (36 and 48 months) (Table 31, replicating table 36 in the CS appendices). These comparisons, and a visual inspection of the fitted curves (figure 9 in the company's appendices), led the company to conclude that all parametric function presented a good fit to the KM IDFS data and to select the exponential distribution as the preferable parametric function.

Table 39. AIC and BIC values for IDFS (hormone receptor-negative population) (relative ranking of goodness of fit shown in brackets) (hormone receptor-negative subgroup)

	AIC		BIC	
	Pertuzumab + trastuzumab + chemotherapy arm	Trastuzumab + chemotherapy arm	Pertuzumab + trastuzumab + chemotherapy arm	Trastuzumab + chemotherapy arm
Exponential	619.02 (1)	748.62 (1)	623.78 (1)	753.37 (1)
Weibull	620.27 (3)	749.99 (3)	629.80 (3)	759.50 (3)
Log-normal	620.19 (2)	749.71 (2)	629.71 (2)	759.21 (2)
Gamma	622.30 (6)	750.94 (5)	631.82 (5)	760.45 (5)
Log-logistic	622.26 (5)	751.67 (6)	636.55 (6)	765.93 (6)
Gompertz	620.69 (4)	750.55 (4)	630.21 (4)	760.06 (4)

AIC, Akaike information criterion; BIC, Bayesian information criterion.

Table 40. IDFS events at 36 and 48 months (hormone receptor-negative subgroup)

Timepoint	Parametric function	Pertuzumab + trastuzumab + chemotherapy	Placebo + trastuzumab + chemotherapy	Pertuzumab + trastuzumab + chemotherapy vs placebo + trastuzumab + chemotherapy	Δ vs Kaplan-Meier data	
					Pertuzumab + trastuzumab + chemotherapy	Trastuzumab + chemotherapy
36 months	KM data	92.60%	90.99%	1.62%		
	Exponential	93.20%	91.18%	2.03%	0.60%	0.19%
	Weibull	93.35%	91.32%	2.03%	0.75%	0.33%
	Log-normal	93.14%	91.05%	2.09%	0.54%	0.06%

Changing the parameters related to the duration of treatment effect (i.e. points in time at which this effect begins to wane and ceases) led to an ICER value of approximately £84,291 per QALY gained, an increase of approximately £18,600 (28%) over the company's base case ICER for this population. Changes in the rest of the parameters led to smaller increases. Replacing the parameters guiding the 'cure' adjustment with values preferred by the ERG resulted in an ICER of £69,808 per QALY gained, which is about £4,100 (6%) higher than the company's ICER. Revising the proportions for metastatic and non-metastatic disease recurrences according to the ERG's calculations led to an ICER of £70,378 per QALY gained, which is higher than the company's base case value by approximately £4,700 (7%).

Table 43. ICER values after implementing ERG's amendments in the company's base case (hormone receptor-negative population)

Parameter	Values in company's base case	ERG's preferred value	ERG's ICER (£ per QALY gained)
Duration of incremental treatment effect			
Time point when incremental treatment effect begins to wane	Year 7	Year 4	£84,291
Time point when incremental treatment effect ceases	Year 10	Year 7	
'Cure' adjustments			
Time point when 'cure' adjustment is introduced in the analysis	Year 4	Year 3	£69,808
Time point when maximum 'cure' is reached	Year 10	Year 10	
Maximum "cure" proportion	90.00%	95.00%	
Percentages of disease recurrence			
metastatic recurrence	76.87%	65.60%	£70,378
non-metastatic recurrence	23.13%	34.40%	

Carrying out all these changes simultaneously—i.e., effectively implementing the ERG's suggested base case analysis-increased the ICER by approximately £27,079 (41% higher than the

company's base case ICER) and resulted in the ERG's base case ICER of £92,778 per QALY gained for the hormone receptor-negative population.

Table 44. Results of ERG suggested base case analysis (hormone receptor-negative population)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£ per QALY gained)
HC (trastuzumab + chemotherapy)	[redacted]	[redacted]	[redacted]	[redacted]	£92,778
PHC (pertuzumab + trastuzumab + chemotherapy)	[redacted]	[redacted]			

The revised PSA, which was undertaken on the basis of the ERG amendments, produced a mean ICER of £93,559 per QALY gained, only slightly higher than the deterministic value.
The revised CE plane and CEAC depicting the comparison between PHC and HC are given in Figure 34 and Figure 35 below. The probability of PHC being cost effective compared to HC at the £30,000 per QALY threshold is zero.

Figure 34. Cost effectiveness plane (hormone receptor-negative population)

10.4 Appendix 4. Results for the ITT population

Table 45. Base case (deterministic) results for the ITT population (derived from the submitted economic model)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£ per QALY gained)
HC (trastuzumab + chemotherapy)	[redacted]	[redacted]	[redacted]	[redacted]	£66,238
PHC (pertuzumab + trastuzumab + chemotherapy)	[redacted]	[redacted]			

Figure 36. CE plane for the ITT population (derived from the submitted economic model)

The revised CE plane and CEAC depicting the comparison between PHC and HC are given in Figure 34 and Figure 35 below. The probability of PHC being cost effective compared to HC at the £30,000 per QALY threshold is zero.

Table 1. ICER values after implementing ERG's amendments in the company's base case

Parameter	Values in company's base case	ERG's preferred value	ERG's ICER (£ per QALY gained)
Duration of incremental treatment effect			
Time point when incremental treatment effect begins to wane	Year 7	Year 4	£54,901
Time point when incremental treatment effect ceases	Year 10	Year 7	
'Cure' adjustments			
Time point when 'cure' adjustment is introduced in the analysis	Year 4	Year 3	£37,686
Time point when maximum 'cure' is reached	Year 10	Year 10	
Maximum "cure" proportion	90.00%	95.00%	
Percentages of disease recurrence			
metastatic recurrence	81.07%	72.40%	£35,933
non-metastatic recurrence	18.93%	27.60%	

Carrying out all the above changes simultaneously, that is, implementing the ERG's suggested base case analysis, resulted in a considerable increase in the ICER, by approximately £26,600. The ERG's base case ICER in the node-positive population was calculated to be £60,679 per QALY gained (Table 2).

Table 2. Results of ERG suggested base case analysis

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£ per QALY gained)
HC (trastuzumab + chemotherapy)	[redacted]	[redacted]	[redacted]	[redacted]	£60,679
PHC (pertuzumab + trastuzumab + chemotherapy)	[redacted]	[redacted]			

6.2 Revised probabilistic sensitivity analysis based on ERG base case

PSA undertaken on the basis of the ERG amendments produced a mean ICER of £60,344 per QALY gained, which was very similar to the obtained deterministic value. The revised Cost Effectiveness (CE) plane and Cost Effectiveness Acceptability Curve (CEAC) depicting the comparison between

PHC and HC are given in **Error! Reference source not found.** and **Error! Reference source not found.** below, respectively.

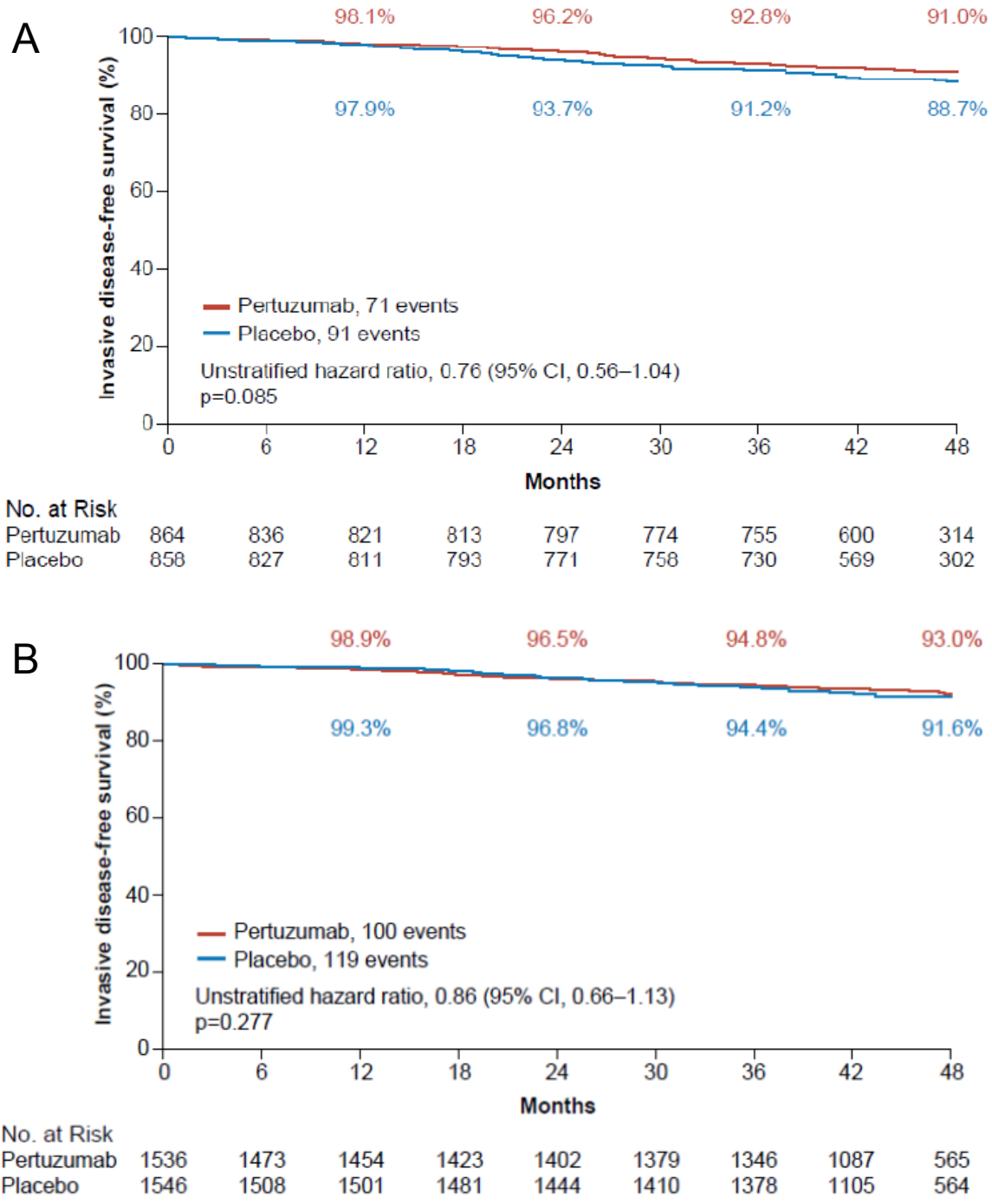


Figure 1. Kaplan-Meier plots of IDFS for ITT population with hormone receptor-negative (A) and hormone receptor-positive (B) disease (CS figure 7)

Additional subgroups

The ERG wanted to ensure the observed efficacy of pertuzumab in node-positive patients was not the result of a spurious interaction with other subgroup variables, in particular hormone receptor status. Therefore, the ERG requested additional analyses of the subgroups of patients of the node-positive

AND hormone receptor-positive ([redacted]), node-negative AND hormone-receptor negative ([redacted]), node-positive AND hormone receptor-negative ([redacted]), and also node-positive OR hormone receptor-negative ([redacted]) (data supplied in clarification response C1). The hormone receptor-positive AND node-negative subgroups was not requested during clarification, as these patients were not included in the economic analyses presented by the company.

Among the subgroups containing node-positive patients ([redacted]), there was some observed [redacted], though only group [redacted] yielded a significant result at the 0.05 threshold when stratified log-rank tests were performed. P-values were [redacted].

Investigation of the hormone receptor-negative AND node-negative subgroup ([redacted]) was of particular interest to the ERG. This is because the ERG were concerned about the possibility that the treatment interaction observed within the hormone receptor subgroups might have resulted from the interaction between node status. The KM plot for this subgroup is displayed in Figure 2. Here, there is [redacted], with a stratified analyses performed by the company producing a HR of [redacted] although only [redacted]. Given the lack of evidence, the ERG remains unconvinced of pertuzumab efficacy for the hormone receptor-negative population.

[redacted]

Figure 2. IDFS KM plot of node-negative, hormone receptor-negative ITT population of APHINITY trial

In the APHINITY trial, subgroup analysis by menopausal status at screening revealed a [redacted] for post-menopausal patients [redacted] not observed in pre-menopausal patients [redacted][1] However, the ERG considers that these results may have no biological basis. According to the ERG clinical advisor, pre-menopausal women may have a higher risk of recurrence given their younger age as well as a higher vascular intensity of the tumour,[56-60] which together with the observed difference in efficacy of the subgroups, seems contrary to the company's preference to target 'high-risk' patients.

The ERG also requested analyses of the subgroups of the combinations of node status and menopausal status (data supplied in clarification response C5), as these were the subgroups which showed the strongest signs of treatment interaction (see **Error! Reference source not found.**). The subgroups considered were pre-menopausal node negative ([redacted]), post-menopausal node negative ([redacted]), pre-menopausal node positive ([redacted]) and post-menopausal node positive ([redacted]). As already discussed, the ERG's clinical adviser suggested that pre-menopausal women may have a higher risk of disease recurrence than post-menopausal women. The results are [redacted]), with [redacted]), [redacted]). The ERG suggests that the apparent effectiveness of the pertuzumab in the post-menopausal group of women (see **Error! Reference source not found.**) could be due to the correlation with nodal status.

Table 1. IDFS treatment efficacy for subgroups of APHINITY trial

	Pre-Menopausal	Post-Menopausal
Node Negative	[redacted]	[redacted]
Node Positive	[redacted]	[redacted]

*P pertuzumab, pla placebo, HR hazard ratio, unstrat unstratified, strat stratified

The ERG is concerned that the lack of evidence of drug efficacy in the node-negative population is being treated as evidence that the drug is ineffective in this subgroup. With approximately [redacted].

Other subgroups

To investigate all potentially relevant subgroups which were outlined in the APHINITY protocol, the ERG requested additional subgroup analyses by adjuvant radiotherapy status, tumour grade and

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Pertuzumab for adjuvant treatment of early HER2-positive breast cancer [ID1192]

You are asked to check the ERG report from Warwick Evidence to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on Tuesday 8 May 2018** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Description of problem	Description of proposed amendment	Justification for amendment	Response
Page 14, 18: "The subgroups were only acknowledged in an amendment to the pivotal trial protocol which took place after approximately 75% of the study population had been randomised"	Remove statement	Inaccurate statement. The original protocol references stratification factors as subgroups of interest, which therefore includes nodal status & HR status. This should also be corrected elsewhere in the ERG report.	Sentence deleted on Pg 14+18. The ERG are incorrect as the HR negative subgroup is mentioned specifically. The protocol does also mention “stratification factors”, but hormone receptor is both a stratification factor, and is mentioned specifically

			Other pages where this is mentioned: Pg 47 – not factually incorrect no change Pg 55 – not factually incorrect no change
Page 14: "The intervention, adjuvant pertuzumab, is indicated for treatment of HER2-positive BC when used in combination with trastuzumab and chemotherapy."	This should state "early BC with a high risk of recurrence". This should also be amended anywhere else this is misquoted in the report.	The indication for pertuzumab is early BC with a "high risk" of recurrence. (http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion/human/002547/WC500247977.pdf)	Amended on Pg 14 to The intervention in the NICE scope and decision problem is adjuvant pertuzumab in combination with trastuzumab and chemotherapy. Amended on Pg 73
Page 15: "…data from an interim analysis of a phase III randomised controlled trial (RCT) investigating adjuvant pertuzumab+trastuzumab+chemotherapy (n=2,400) compared with placebo+trastuzumab+chemotherapy (n=2,405) (APHINITY)"	Remove "an interim analyses of"	Inaccurate statement. The analysis of the primary endpoint was conducted after approx. 379 events (as specified in the SAP). It is not an interim analysis of the primary endpoint. It is the interim analysis of overall survival as the number of events required has not been reached at this point in time, only 26% of the 640 events required have been reached.	Deleted "interim" Pg 15 & 81
Page 15 and 43: "The ERG considers that none of the primary or secondary outcomes would have been statistically significant had the significance level been adjusted for multiplicity (e.g. using a Bonferroni calculation) demonstrating that pertuzumab is only marginally efficacious"	Remove statement	The Sponsor implemented Type 1 error control through a pre-specified fixed-sequence (ordered) testing hierarchy as described in CSR 3.9.3.2 for the primary endpoint and secondary endpoints of IDFS-SPNBC, DFS, OS. Therefore, Type 1 error is considered controlled for these primary and secondary endpoints and in this context, apa rt from OS, are considered statistically significant at 5% level.	Upon review, the ERG consider that the fixed sequence testing is a method of accounting for multiplicity. However, it is not an adjustment on the alpha/significance level. Not a factual error. No change made
Page 15: "Overall, there is sufficient evidence to support the view that pertuzumab is associated with a worse HRQoL"	Remove the word "overall" from the beginning of this sentence	This statement is misleading, as whilst there were more diarrhoea events in the PHC arm, the overall QLQ-C30 summary score did not show any difference (except for the diarrhoea score). All PROs included showed that patients have similar QoL regardless of the treatment received. Results on individual sub-scale are likely chance-findings.	Amended to 'in summary' on Pg 15
Page 16: "significantly higher incidence rates of anaemia in the pertuzumab arm (6.9%) compared to placebo (4.7%) (RR=1.47 CI:1.16 to 1.85, p=0.001)"	Either specify "Grade ≥3" or change the %s to reflect the percentages of patients experiencing any grade of anaemia (27.7% vs 23.2%)	This statistic refers to the incidence of Grade ≥3 anaemia, not all anaemia.	Amended to Grade ≥3 anaemia on Pg 16

Page 17: "HR 0.86, 95% CI: 0.66 to 1.33, p=0.28"	Replace 1.33 with 1.13.	Incorrect number.	Amended. Pg 17
Page 17,18,43,59,62,63,129,130: "The ERG considers this result to be marginally significant and this is supported by the ERG clinical advisor"	Remove "marginally".	The term 'marginally' is subjective, so should be removed.	This phrase was used by the ERG clinical advisor. Difference of opinion not factual error. No change made
Page 17, 50, 62,130 (various):"whereas no statistically significant difference was observed in node-negative patients (HR 1.13, 95% CI: 0.68 to 1.86)"	Remove all claims of statistical significance (or lack of) from discussions of the subgroup analyses throughout the ERG report.	The subgroup analyses in APHINITY were not powered to detect statistical significance. p-values in the CS for the subgroups are provided as a measure of strength of evidence of a treatment effect, and should be viewed alongside the 95% confidence intervals to indicate the variability around the estimate.	The ERG consider this to be a difference of opinion. Not a factual error. No change made
Page 17: "as it was unclear whether these were pre-specified"	Amend statement	All subgroups in the CSR forest plot were pre-specified in the statistical analysis plan prior to database lock. In particular, the 1st version of the protocol also indicates that stratification factors will be included as subgroup variables, which therefore includes nodal status and HR status.	Amended. Sentence deleted. Pg 17
Page 17: "The ERG believe the increased efficacy observed in the node-positive population may have occurred by chance"	Remove/re-phrase statement.	This statement is conjecture and potentially misleading	Difference of opinion (e.g., "the ERG believe"). Not a factual error. No change made
Page 19, (various): Reference to "ICER of £34,084 per QALY"	Add "with PAS" and amend to £34,087.	To clarify that this ICER is with the confidential commercial access scheme applied. This should also be amended elsewhere in the submission.	Amended as requested. Pg 19
Page 24: "The ERG clinical advisor confirmed that the majority of NHS trusts deliver trastuzumab subcutaneously in the adjuvant and metastatic (neoadjuvant) setting"	Remove "(neoadjuvant)"	Metastatic does not equal neoadjuvant, so this is incorrect.	Amended. Pg 24
Page 26: [redacted]	Underline and highlight in blue	Mark as "CiC"	Amended as requested. Pg 26
Page 26: "Therefore, there may not be any difference in the risk of BC recurrence between HER2-positive and HER2-negative BC."	Remove statement	Whilst we agree that that current treatment regimens with trastuzumab have substantially improved the prognosis of patients with HER2-positive BC over time, there is no literature	This statement came directly from the ERG clinical advisor. This is a difference of opinion. Not a factual error. No change made

		comparing BC recurrence rates or survival of trastuzumab-treated HER2-positive eBC patients vs HER2-negative eBC. There are many factors that can influence recurrence rates/survival including stage, age, hormone receptor status, node positive status.	
Page 27: [redacted]	Underline and highlight in blue	Mark as “CiC”	Amended as requested. Pg 27
Page 30: "subgroups as defined by age (<40y vs. 40 – 49y vs. ≥65y)"	Add "vs. 50-64" for completeness.	Subgroup has been omitted.	Amended as requested. Pg 30
Page 33: "The ERG notes that after having achieved 75% (n=3,655) of the original target sample size, the company considered node-negative BC patients' ineligible for the trial."	Replace with "Under a protocol amendment that was added after 3,655 patients had undergone randomisation, patients with node-negative disease were no longer eligible for enrollment, in order to enroll a patient population with the nodal-status distribution that had been anticipated when the trial was designed."	Inaccurate statement. 3,655 patients represent the total number of patients enrolled under protocol A prior to implementing protocol B. It represents the lag until amendment became approved and implemented across the sites. Each country has their own Ethics Committee approval timelines, and hence implementation dates vary in respective countries. Protocol B was released in November 2012, first site gained approval with Protocol B in Dec 2012 with >90% sites gained approval within 4 months.	Amended to “after 3655 patients were recruited…” Pg 33
Page 36: "There were more hormone receptor-negative patients in the APHINITY trial than in BCIRG-006 (36% vs. 46%)"	Replace "were more" with "was a lower proportion of".	This is an incorrect statement (as shown by proportions in each trial, which were lower in the APHINITY study). Further, proportions are quoted rather than absolute numbers, so it would better reflect the statistics given to use the term "proportions".	Amended as requested. Pg 36
Page 43, Table 5: "IDFS (primary outcome) estimated 3-year event-free rate, %" and "3 year" in all the secondary endpoints	Remove "estimated 3-year event-free rate, %" and "3 year" from all the secondary endpoints	Incorrect. IDFS and secondary endpoint HRs and p-values are based on the total follow up (i.e. are not truncated at 3 years).	Amended as requested Pg 43
Page 44: "average scores were consistently lower (worse) for the pertuzumab arm across the three measurements of QLQ-C30 taken during the year of treatment"	Add in numbers to show the extent of the worsening, e.g. “The mean global health status scores showed a clinically meaningful worsening from the baseline mean score (72.9 in Ptz+H+Chemo vs. 72.5 Pla+H+Chemo) at the end of taxane treatment (Week 13) and	Misleading. One-sided statement without information on the absolute extent of the worsening, and does not mention the higher scores in the pertuzumab arm post-treatment.	This is a difference of opinion. Not a factual error. The ERG were only interested in the on treatment period. No change made

	returned to baseline thereafter in both arms; the mean (SD) changes from baseline at Week 13 were -11.2 (22.8) vs. -10.2 (22.6) in the Ptz+H+Chemo vs. Pla+H+Chemo arms, respectively." For balance, it could also be mentioned that scores in pertuzumab arm were in fact higher than the placebo arm at months 18, 24 and 36.		
Page 47: "The ERG noted that in the original APHINITY protocol (version A) the following subgroups were mentioned specifically: menopausal status, type of surgery for tumour, tumour size, histological grade of tumour, race, loco-regional radiotherapy and hormone receptor status. "	Amend paragraph	Although these subgroups were specifically listed, it was also noted that stratification factors would be included, which covers nodal status & HR status	Not a factual error. No change made
Page 49: "However, these additional analyses showed no clear pattern of a direct association between treatment effect and number of node-positive BC cells"	Amend sentence to "However, these additional analyses showed no clear pattern of a direct association between treatment effect and number of positive lymph nodes"	Inaccurate sentence.	Amended sentence deleted. NB – this sentence was on page 50 not Pg 49. Pg 50
Page 49: "611 of 1799 node-negative patients developed invasive breast cancer or died..."	Change "611" to "61" Change "developed invasive breast cancer or died" to "IDFS event"	Incorrect number. eBC is invasive breast cancer, the way it is currently worded does not make capture the primary endpoint events.	Amended as requested. Pg 49
Page 50: "of treatment effect estimates if the performance of pertuzumab had been associated with disease severity, however, the observed effect was lowest in the 4-10 node group among the node positive groups."	Add in the following caveat "… caution should be used when interpreting the results in subgroups of subgroups as small numbers of events results in greater variability".	Misleading statement. Caution should be used when interpreting subgroups within subgroups as this becomes based on small numbers of events, so more variable.	This is not a factual error. No change made
Page 50: "are not statistically significant, and do not differ significantly between hormone receptor-negative and hormone receptor-positive populations (p=0.54 for interaction)"	Remove statement	Though there is no evidence of an interaction between treatment and HR status, we can only say that there is no evidence against the hypotheses of interaction. It is not correct to say they do not differ significantly.	Amended to "… and do not differ significantly between the hormone receptor-negative and hormone receptor positive populations due to the heavily overlapping confidence intervals of the treatment effect estimates. The hypothesis of an interaction between treatment effect and HR status was not significant (p=054)." Pg 51 NB – this is page 51 not 50

Page 50: "and do not differ significantly between hormone receptor-negative and hormone receptor-positive populations (p=0.54 for interaction)"	Amend to: "and there is no evidence against the hypothesis of interaction"	The interpretation of the interaction is incorrect. Can only say that there is no evidence against the hypotheses of interaction, and not accurate to say they do not differ significantly	Amended to "… and do not differ significantly between the hormone receptor-negative and hormone receptor positive populations due to the heavily overlapping confidence intervals of the treatment effect estimates. The hypothesis of an interaction between treatment effect and HR status was not significant (p=054)." Pg 51 NB – this is page 51 not 50
Page 51: "HR=0.76, 95% CI 0.56 to 1.04, p=0.08"	Replace with "p=0.08" with "p=0.09"	Incorrect number.	No change, in the company submission B, p=0.08 is used multiple times referring to HR negative IDFS, and not 0.09.
Page 51: "HR=0.86, 95% CI 0.66 to 1.33, p=0.28"	Replace "1.33" with "1.13"	Incorrect number.	Amended as requested. Pg 51
Page 52: Data and conclusions pertaining to the "Additional subgroups" requested during the ERG's clarification (question C1 and C5)	Underline and highlight in yellow	Data and conclusions regarding the request in question C1 and C5 of clarification questions should be marked as "Academic in confidence" as this is unpublished data.	Amended as requested. Pg 52
Page 56: "Of note, the CSR does not present incidence rates of adverse events not reported in CS document B (CSR Table 44)."	Remove statement	Table 52 in the CSR reports adverse events with an incidence rate of at least 5% in either treatment arm (safety population).	The ERG refers to Table 44 of the CSR which was supposed to describe all adverse events irrespective of the 15% threshold, and not Table 52 of the CSR which describes the incidence of grade 3 or higher adverse events. Hence, this is not a factual error. No change made
Page 58: "There were also more deaths due to "injury, poisoning, and procedural complications" (2 vs. 0), "blood and lymphatic system disorders", "metabolism and nutrition disorders" and "nervous system disorders" (all 1 vs. 0) in the pertuzumab arm, however these are only reported for completeness"	Add that there were more deaths in the placebo arm than the pertuzumab arm due to other factors (e.g. cardiac disorders, gastrointestinal disorders)	This is a one-sided argument - add extra information for balance.	This is not a factual error. No change made

Page 59: "The ERG also considers that the 6% higher rate of grade 3/4 diarrhoea in the pertuzumab-based arm compared to placebo (Table 9) may potentially attenuate the marginal efficacy gains attributed to pertuzumab in the submitted evidence."	Remove statement "attenuate the marginal efficacy gains attributed to pertuzumab in the submitted evidence".	This claim is not evidence-based and potentially misleading	This is not a factual error. No change made
Page 59: "This increased risk of severe diarrhoea supports observations from other pertuzumab trials, including the CLEOPATRA (+3 %... "	Update percentage to 2.9%	2.9% is the figure stated in the Baselga citation.	Amended as requested. Pg 59
Page 59, 62, 129: "The efficacy analysis of the APHINITY trial revealed that pertuzumab was just marginally better than placebo for preventing recurrence of breast cancer and/or death (HR 0.82, 95% CI 0.67 to 1.00)."	HR and CIs should be amended to HR=0.81 (95% CI 0.66-1.00). This should also be updated in other places where misquoted throughout the report. [N.B. HR=0.82, 95% CI 0.67-1.00 is the unstratified result]	Inaccurate figures	The ERG cannot find this statement on Pg 52, however, we have amended as requested on Pg 55 Pg 62 has been amended as requested The ERG cannot find this statement on Pg 129. However, we have amended as requested on Pg 128
Page 60: "However, further examination by the ERG revealed no indication that heart failure was included as a study outcome in all three trials. "	Remove sentence or amend to reflect that heart failure was a primary endpoint in the TRYPHEANA study, and was measured in the NeoSphere and CLEOPATRA studies.	Ref 66 (the NeoSphere study) reports the incidence of congestive heart failure and left ventricular ejection fraction during neoadjuvant treatment. Ref 67 (the TRYPHAENA study) was a cardiac safety study, with primary safety endpoints of "incidence of symptomatic left ventricular systolic dysfunction (LVSD) as assessed by the investigator, and decline in LVEF of ≥10% points from baseline to <50% over the course of neoadjuvant treatment". Ref 68 (the CLEOPATRA study) reports "the rate of left ventricular dysfunction, as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3.0, and the New York Heart Association".	The ERG assumes the reference is to this sentence on Pg 60, “Further examination by the ERG revealed that heart failure was included as a study outcome in all three trials”. Amended, sentence deleted. Pg 60

Page 61: "it is consistent with the view that adjuvant pertuzumab+trastuzumab combination has a worse safety profile compared to adjuvant trastuzumab in patients with BC."	Remove statement.	This statement is misleading. The rates are not statistically significantly different between the two arms which should preclude such statements being made.	This is not a factual error. No change made
Page 62, 129: "The ERG is concerned that this difference may not be clinically meaningful."	Remove statement	The addition of pertuzumab to standard adjuvant trastuzumab + chemotherapy has been deemed clinically meaningful (a Group B intervention) when assessed using the Magnitude of Clinical Benefit Scale developed by the European Society for Medical Oncology (ESMO) for solid cancers. This means that this anti-cancer treatment provides a clinically meaningful benefit, and substantial improvement over the standard of care, suggesting that this treatment should be emphasised for accelerated assessment of value and cost-effectiveness.	This statement came directly from the ERG clinical advisor. This is a difference of opinion, not a factual error. No change made
Page 62: "The population in this trial (n=4806)"	Replace "4806" with "4804"	Incorrect number.	The ERG consider this should be 4805 as stated in the published article. Amended. Pg 62 NB. 4804 patients were included in the efficacy analyses, whereas 4805 patients were included in the safety analyses. The ERG account for this distinction in our report.
Page 62: "concerned that adjuvant pertuzumab may only be effective in eBC patients with 10 or more cancer cells in the loco-regional lymph nodes"	Replace with "concerned that adjuvant pertuzumab may only be effective in eBC patients with 10 or more positive (i.e. cancer-containing) loco-regional lymph nodes", or equivalent.	The number 10 refers to the number of positive nodes, not the number of cancer cells in the lymph nodes.	Amended as requested. Pg 62
Page 63, 130: "The ERG considers that claims of treatment benefit (marginal) should be balanced against the safety of adjuvant pertuzumab in combination with trastuzumab and chemotherapy."	Remove statement	This is a subjective statement - it is not a claim of treatment benefit; it has been proven. Also the benefit risk ratio has been established by regulatory approvals in Europe.	This is not a factual error. No change made
Page 64: "For completeness, the ERG also presents the results of the economic analysis for the ITT population (see appendix 4),	Remove this part of the analysis	This population is now irrelevant and no longer in-line with the updated label of pertuzumab in the adjuvant setting.	For completeness, the ERG prefers to keep the results for the ITT population as this population is extensively discussed in the clinical

although this analysis is not described or presented in the CS. "			effectiveness part of the ERG report. This is not a factual error. No change made
Page 74: “Here the KM curves appear to stop diverging and possibly begin to converge from approximately five years onwards”	Remove statement	Inaccurate statement. Curves do not converge	The ERG used the word “possibly”, referring to Fig 13. Curves do converge between years 5 and 6. It is difficult to be certain of behaviour beyond this point without access to data, and knowing how many patients are still at risk. Therefore, this is not a factual error. No change made
Page 79: "The AIC/BIC values are presented by the company and reproduced in Table 14 (corresponding to Table 12 in the CS)."	Change the information in brackets to "corresponding to Table 21 in the CS".	The current cross-reference to the CS is incorrect.	Amended as requested. Pg 79
Page 81: "The ERG requested the updated observed rates for IDFS (clarification C3) be presented by the company to compare the predictions made by the different parametric models, however, the company declined, stating updated efficacy data would only be available at the next planned interim analysis (middle of 2019)."	Replace "next planned interim analysis" with "next planned interim analysis of OS (estimated 2020)"	Inaccurate statement. Next interim analysis is of OS. Further IDFS data will be analysed but will be of exploratory nature. Next interim analysis is planned after approximately 2.5 years after first analysis, mid-2019 refers to the clinical cut-off date, and will take some time for data to be summarised in CSR before reporting.	Amended as requested. Pg 81
Page 99 (Table 22): "Non-pooled values from APHINITY trial"	Values reported in the table are actually the pooled values across treatment arms. Please report the treatment arm-specific figures instead	Inaccurate figures	Amended as requested. Pg 99
Page 102: "...[redacted] of patients receive the more expensive trastuzumab SC formulation..."	Add blue highlighting and underlining to "[redacted]" to denote confidentiality.	This information is CiC.	Amended as requested. Pg 102
Page 102: "The source of the value for the market share of trastuzumab SC + docetaxel in the non-metastatic recurrence health state ([redacted])"	Add underlining to "[redacted]" to denote confidentiality.	This information is CiC.	Amended as requested. Pg 102
Page 106: "Results suggest that, on average, pertuzumab led to a gain of [redacted] QALYs at an additional cost of [redacted] per person"	State "incremental gain versus placebo" and add underlining to [redacted] and [redacted] (already highlighted in turquoise).	It is unclear that this is the incremental gain versus placebo (total gain in QALYs is 13.56).	Amended as requested. Pg 106
Page 106: "estimated to be £34,087 per QALY gained"	Remove highlighting.	The ICER does not require confidential highlighting. (However, the absolute and incremental costs and QALYs do, as they would allow the back-calculation of the confidential commercial access agreements.)	Amended as requested. Pg 106

Page 115: "...the ERG estimated more accurate proportions which represented events beyond 18 months (Table 18) and found the pooled estimate to be 72.40%".	Align Table 30 to mirror Table 18 and the corresponding cost-effectiveness results	Incorrect statement	The statement quoted is from Pg 89 not Pg 115. The ERG have amended Table 30 which is on Pg 114. Pg 114
Page 115: The values relating to "Percentage of disease recurrence" in the company submission (Table 30 of the ERG report) correspond to the hormone receptor negative population.	Values for the percentages of metastatic and non-metastatic recurrences in Table 30 should be amended to 81.07% and 18.93%, respectively.	Incorrect statement	Amended as requested. Table 30 is on Pg 114, not 115. Pg 114
Page 118: Table 32	Add underlining and turquoise highlighting to all total and incremental costs and QALYs in this table.	The ICER does not require confidential highlighting. However, the absolute and incremental costs and QALYs do, as they would allow the back-calculation of the confidential commercial access agreements.	Amended as requested. Pg 118
Page 122: Table 34	Remove underlining from values in the ICER column and add underlining to all valued in the "diff costs" and "diff "QALYs" columns.	The ICER does not require confidential highlighting. However, the absolute and incremental costs and QALYs do, as they would allow the back-calculation of the confidential commerical access agreements.	Amended as requested. Table 34 spans Pg 122-123, both have been updated
Page 125: Table 35	Suggest to add key for what the shading in some cells means.	Improve ease of interpretation of this table.	Amended as requested, but table 35 is on Pg 124 not 125. Pg 124
Page 129: "The population in the APHINITY trial (n=4806)..."	Change n-value to 4,805.	As stated on pages 24 and 26 of the CS, 4,805 patients were included in the APHINITY study.	Amended as requested, but this statement is on Pg 128 not 129. Pg 128
Page 129: "Analyses of the nodal subgroups revealed a less marginal difference in IDFS rates between pertuzumab and placebo in node-positive patients"	Replace "less marginal" with greater.	Marginal is subjective - the difference was greater in the patients with node-positive disease.	Not a factual error. No change made
Page 130: "10 or more cancer cells in the loco-regional lymph nodes."	Replace with "10 or more positive loco-regional lymph nodes".	The number 10 refers to the number of positive nodes, not the number of cancer cells in the lymph nodes.	Amended as requested. This is on Pg 129 not 130. Pg 129
Page 150: "Table 40: DFS events"	Replace DFS with IDFS.	Error.	Amended as requested. Pg 150
Page 159: Table 43 (ICER values after implementing ERG's amendments in the company's base case (hormone receptor-negative population)	Remove yellow highlighting and underlining.	The ERG's ICER values do not need highlighting as AiC.	Amended as requested, the ERG note that this is Pg 158 not Pg 159. Pg 158

Page 160: Table 44 (Results of ERG suggested base case analysis (hormone receptor-negative population))	Add underlining to numbers already highlighted in turquoise.	Underlining is also needed for values that are confidential.	Amended as requested, the ERG note that this is Pg 159 not Pg 160. Pg 159
Page 162: Table 45 (Base case (deterministic) results for the ITT population (derived from the submitted economic model))	Add underlining to numbers already highlighted in turquoise.	Underlining is also needed for values that are confidential.	Amended as requested, the ERG note that this is Pg 161 not Pg 162. Pg 161