NICE National Institute for Health and Care Excellence

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Pertuzumab for adjuvant treatment of early HER2-positive breast cancer

Chair's presentation

3rd appraisal committee meeting
Committee A
Lead team: John McMurray, Pamela Rees, Stephen Sharp
ERG: Warwick Evidence
NICE technical team: Eleanor Donegan, Juliet Kenny
Company: Roche
16 October 2018

Key issues for consideration (1)

- Is invasive disease free survival a reliable surrogate for overall survival?
- Is the observed benefit in invasive disease free survival with pertuzumab clinically meaningful?
- How much uncertainty is there in the modelled QALY gain ?
- Although lymph node-positive is a relevant subgroup is the efficacy of pertuzumab better than in the intention to treat population?
  - Unreasonable weight been placed on the test for statistical interaction?
  - Consistency with subgroup recommendations in other appraisals?
- How should biosimilar and administration costs be incorporated in the economic model?

Key issues for consideration (2)

- Is a 7 year pertuzumab treatment effect then waning and ceasing at 10 years assumed by the company plausible (vs 4 year effect waning and ceasing at 7 years)?
- The company model has maximum separation of the survival curves at 109 months (9.5 years) while the ERG estimate is at 78 months (6.5 years). Which is more plausible ?
- Does the committee accept the company's revised base-case analysis (lymph-node positive population only) which is premised on:
  - unchanged parameters treatment effect duration
  - an improved CAA offer
- If pertuzumab is not cost effective for routine commissioning is it suitable for the CDF?
- Clinical uncertainty? Plausible potential for being cost effective? More precise ICER?

[redacted]

3

Pertuzumab (Perjeta)

Marketing authorisation	In combination with trastuzumab and docetaxel as adjuvant treatment of patients with HER2-positive early breast cancer at **high risk of disease recurrence**
Mechanism of action	The antibody binds to HER2 receptor proteins on breast cancer cells, prevents the receptors from binding to growth factor proteins which can cause the cancer cells to divide and grow
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
Patient access scheme	Commercial access agreement approved by Department of Health which provides a simple discount to list price

ACD: preliminary recommendations:
Pertuzumab is not recommended, within its marketing authorisation, for the adjuvant treatment of early stage human epidermal growth factor receptor 2 (HER2)-positive breast cancer in adults with high risk of disease recurrence.

[redacted]

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History of the appraisal

- 1st committee meeting 17 April 2018
  - Pertuzumab was not recommended
  - Uncertainty in the clinical effectiveness of pertuzumab as adjuvant treatment (small benefit) and little evidence that pertuzumab is more effective for high risk subgroups.
  - The company's cost effectiveness estimates are implausible and the model seems to overestimate overall survival.
- 2nd committee meeting 19 June 2018
  - Pertuzumab was not recommended
  - Continued uncertainty in the improved clinical efficacy in the high risk subgroups vs. the intention to treat population.
  - Company's cost effectiveness estimates are implausible and the ERGs estimates do not represent a cost effective use of NHS resources. Therefore it was also not recommended within the CDF

[redacted]

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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)**

Company submission prioritised 2 high risk subgroups (node positive and hormone receptor negative).

[redacted]

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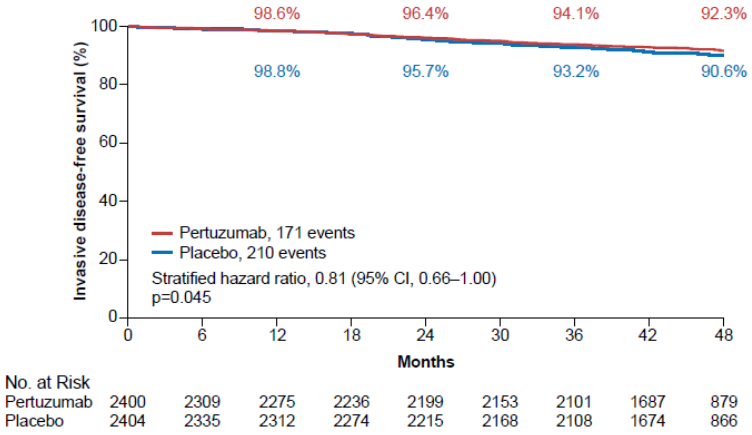
Primary outcome: IDFS excluding second primary non-breast cancer events



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.

ERG noted:

- Treatment benefit borderline statistically significant
- 7yr treatment effect not well substantiated

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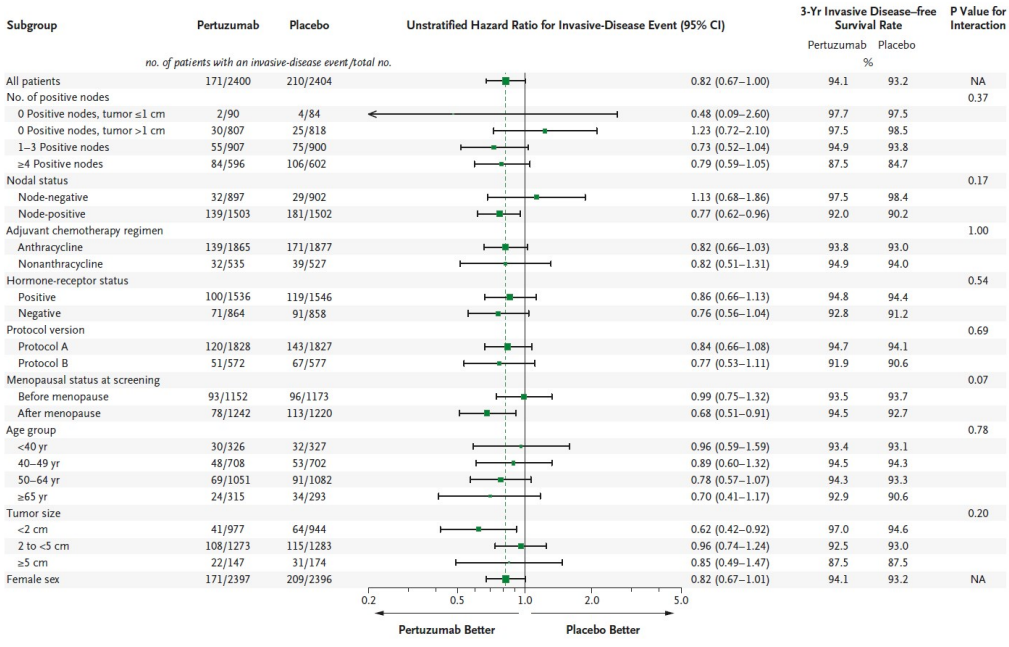
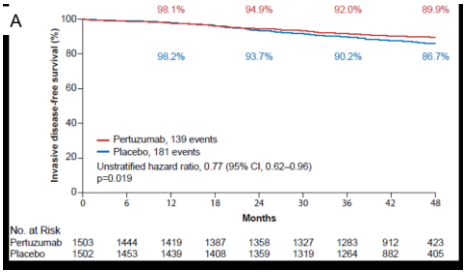
Forest plot for different subgroups in the ITT population (primary analysis, clinical cut-off date 19th December 2016)

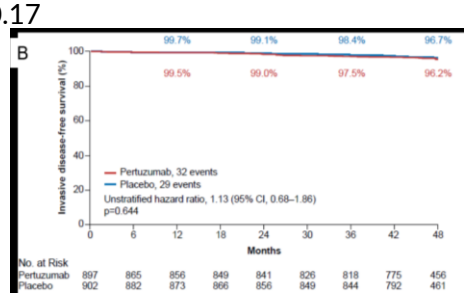


Subgroup	Pertuzumab	Placebo	Unstratified Hazard Ratio for Invasive-Disease Event (95% CI)	3-Yr Invasive Disease–free Survival Rate		P Value for Interaction
				Pertuzumab	Placebo	
	no. of patients with an invasive-disease event/total no.			%		
All patients	171/2400	210/2404	0.82 (0.67–1.00)	94.1	93.2	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

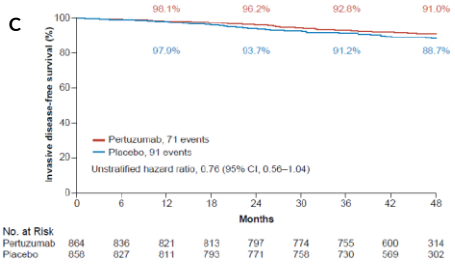
IDFS in subgroups prioritised by company

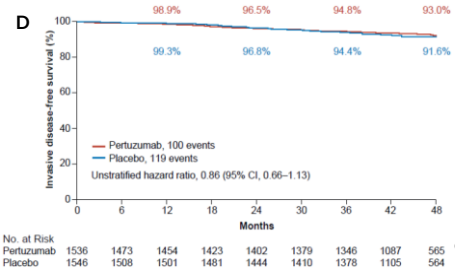
IDFS in lymph node-positive subgroup (figure A) and in lymph node-negative subgroup (figure B); P value for interaction: 0.17





IDFS in hormone receptor-negative subgroup (figure C) or hormone receptor positive subgroup (figure D); P value for interaction: 0.54





ACD2 model assumptions – lymph node-positive disease

Parameter	Value used in company's revised estimates	Value used in ERG's revised estimates
Time point cure model begins	36 months	36 months
Maximum cure rate	95%	95%
Time point cure model ends	120 months	120 months
Metastatic recurrence – Pre 18 months	75.58%	75.58%
Non-metastatic recurrence – Pre 18 months	24.42%	24.42%
Metastatic recurrence – Post 18 months	79.38%	79.38%
Non-metastatic recurrence – Post 18 months	20.62%	20.62%
Assumptions regarding treatment effect	Runs for 7 years before waning and ceasing completely at 10 years	Runs for 4 years before waning and ceasing completely at 7 years

Model assumptions for the revised model received during consultation on ACD1. This formed the basis of the ICERs in ACD2

[redacted] Company and ERG revised estimates also take account of improved CAA discount

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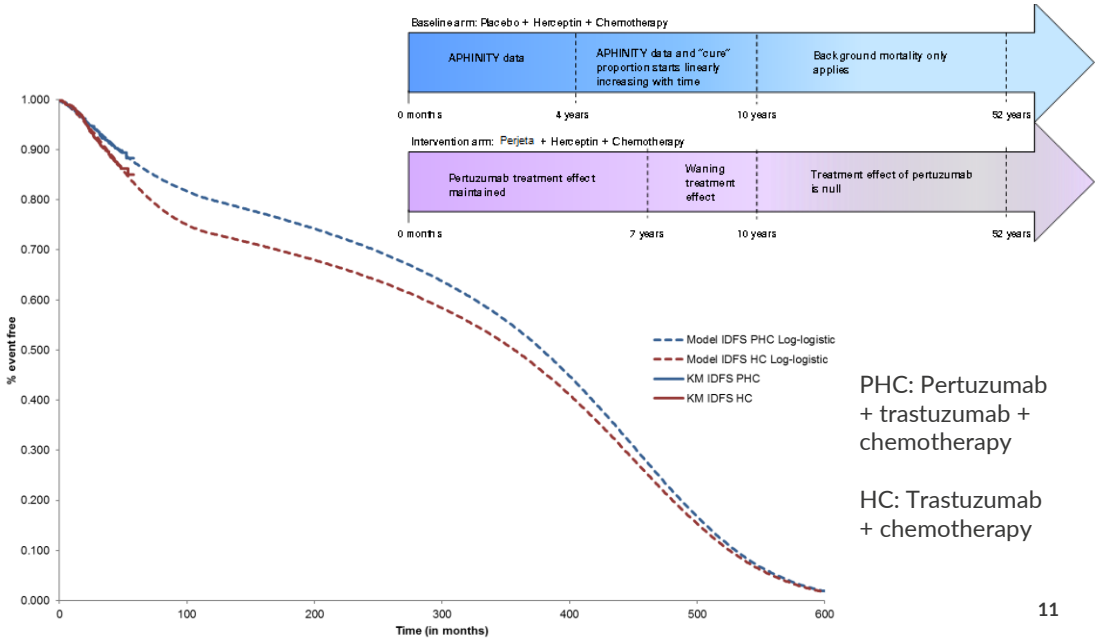
Company's model: node-positive population

Treatment effectiveness (modelled using IDFS)

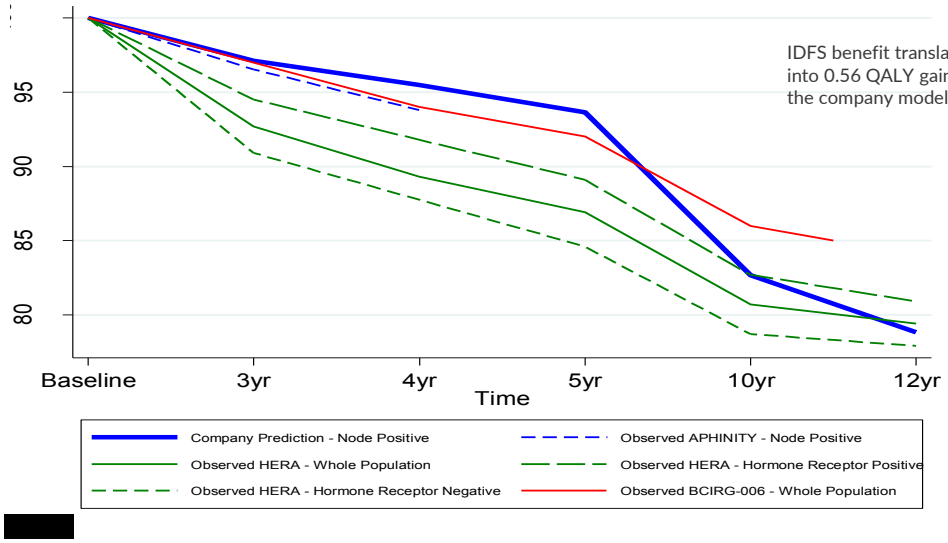


PHC: Pertuzumab + trastuzumab + chemotherapy

HC: Trastuzumab + chemotherapy

OS predictions in the model have been overestimated (ERG critique LN +ve population)

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

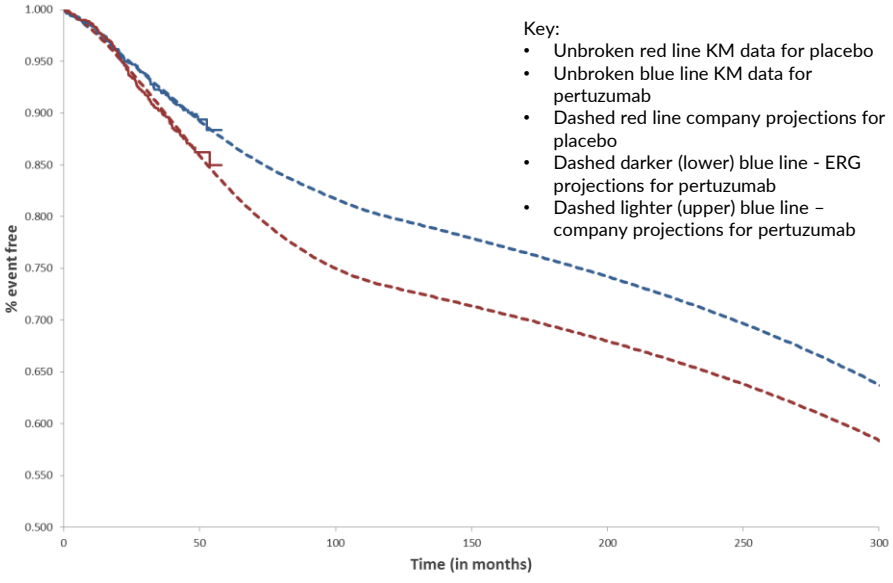


IDFS benefit translates into 0.56 QALY gain in the company model

[redacted]

Figure 16 ERG report

Demonstrating change to IDFS of ERG preferred duration of treatment effect compared to company base case



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ACD2 ICERs - lymph node-positive disease

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£ per QALY gained)
Company's original base case					
HC	XXXXXX	XXXX	XXXXXX	XXXX	£33,857
PHC	XXXXXX	XXXX			
ERG's original base case					
HC	XXXXXX	XXXX	XXXXXX	XXXX	£60,679
PHC	XXXXXX	XXXX			
Revised company estimates					
HC	XXXXXX	XXXX	XXXXXX	XXXX	£30,561
PHC	XXXXXX	XXXX			
Revised ERG estimates					
HC	XXXXXX	XXXX	XXXXXX	XXXX	£47,856
PHC	XXXXXX	XXXX			

The company updated the original base case ICER during 1st consultation (£34,087 to £33,857 /QALY gained – model error).

Committee considered **£39,939 per QALY gained to be the most plausible ICER** (ERG ICER with updated drug administration costs and the biosimilar trastuzumab discount and market share)

[redacted]

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Committee's considerations (ACD2)

- Any improvement in IDFS in the intention to treat population was small.
- Statistical tests for interaction for the node positive and HR negative subgroup showed that increased relative efficacy in these groups was not convincing.
- Pertuzumab is generally a well-tolerated treatment
- A small IDFS benefit translates into 0.56 QALY gain in the company model for the node positive group which is too optimistic. Company ICER (£30,561 per QALY gained) is therefore implausible
- Treatment costs which include the commercial biosimilar price and market share are most appropriate for decision making.
- The ERG ICER corrected for the tariff costs (for the administration of pertuzumab and standard care) and the biosimilar trastuzumab discount and market share, which is £39,939 per QALY gained.
- The committee concluded that this does not represent a cost-effective use of NHS resources for routine commissioning
- More mature IDFS and OS would reduce the uncertainty in the cost effectiveness estimates (final analysis due in 2023). However, as there is no plausible potential for cost effectiveness it cannot be recommended on the Cancer Drugs Fund

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ACD consultation responses

- Consultee comments from:
  - Breast Cancer Now
  - UK Breast Cancer Group
  - Roche Products Limited
- No comments were received from commentators
- Web comments from:
  - 4 NHS Professionals (including 1 clinical expert)

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Patient Group - Breast Cancer Now

General

Disappointed that despite Roche adopting the majority of the ERG's recommendations for cost-effectiveness modelling, a further discount on the price of pertuzumab and including the current price and market share of trastuzumab biosimilars NICE is still not able to recommend pertuzumab

Small improvements in IDFS are valued by patients and their families

"We would reiterate that … much progress has been made in breast cancer over the years through incremental improvements. **Any improvement** in outcomes is welcomed by patients and their loved ones. The risk of breast cancer recurring or spreading to other parts of the body, where it becomes incurable, can be a source of stress and anxiety… One in four patients will experience a recurrence. Metastatic breast cancer … has an average life expectancy of 2 to 3 years. "

IDFS as a surrogate for overall survival

"We understand that the immaturity of overall survival data is an issue in many technology appraisals for cancer medicines, and urge NICE to ensure that a consistent approach is taken to decision making across technology appraisals when using surrogates such as IDFS and progression free survival."

Possibility of CDF recommendation

The next analysis of data is due in 2019 (final analysis in 2013). This may help provide greater certainty for the Committee in relation to data on IDFS and OS. We would urge Roche, NICE and NHS England to work together to see if the cost-effectiveness of adjuvant pertuzumab could be improved to the extent that it could be recommended for use on the CDF.

[redacted]

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Professional- UK Breast Cancer Group (1)

Surrogate markers for overall survival in adjuvant breast cancer (Neosphere trial)

Neosphere was not powered to show any difference in progression free, event free or overall survival. However, at 5 years although overlapping, the confidence intervals for progression and disease survival supported the pathological complete response data suggesting that neoadjuvant pertuzumab is beneficial when combined with trastuzumab and docetaxel.
Total pathological complete response could be an early indicator of long-term outcome in early-stage HER2-positive breast cancer. Per patient pathological complete response (pCR) is an accepted surrogate for long-term outcomes (Cortazaar et al., 2014, Yee et al., 2017)

Lymph node positive subgroup (ACD section 3.5)

The hazard ratio's were lower in these subgroups compared with the intention to treat population HOWEVER the absolute benefit was small.

- The hazard ratio is the important factor in determining effect of treatment. The hazard ratio for IDFS for node positive group (0.77, 95% confidence interval [CI] 0.62-0.96) is consistent with what would be expected in a population of patients with micro-metastatic disease rather than a population that includes a large proportion of patients with no micro-metastatic breast cancer
- Question the conclusion that there is no difference in IDFS between lymph node positive vs negative and hormone receptor negative vs. positive given that LN+ and HR- are at high risk of recurrence.
- **Committee concluded no statistical difference had been demonstrated (not no difference)**
- "The improvement in outcomes in the node-positive patients represents a clinically meaningful benefit in the curative setting and adjuvant pertuzumab should be available as an option on the NHS for node-positive patients."

[redacted]

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Professional- UK Breast Cancer Group (2)

Consistency in the way that subgroups are considered across appraisals

NICE are being inconsistent with their approach to subgroups. NICE recommendation based on a subgroup analysis is not uncommon. There are examples where NICE have recommended a technology for use in a subgroup when the study was not statistically powered to detect a treatment effect in that subgroup.

- NICE recommendation of nivolumab in previously treated locally advanced or metastatic non-squamous non-small-cell lung cancer was based on PDL-1+ subgroup [TA484]
- NICE recommendation of cetuximab in recurrent or metastatic squamous cell cancer of the head and neck was based on a subgroup that started in oral cavity [TA473]
- NICE recommendation of cetuximab in locally advanced squamous cell cancer of the head and neck was based on a subgroup with Karnofsky performance-status score of 90% or greater [TA145]
- NICE recommendation of cetuximab in previously untreated metastatic colorectal cancer was based on a post-hoc subgroup analyses in RAS wild type subgroup [TA439]
- NICE recommendation of imatinib for adjuvant treatment of KIT (CD117)-positive gastrointestinal stromal tumours in a high risk subgroup defined by the Miettinen criteria [TA326]

[redacted]

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What did the public say?

Web comments were provided by 4 NHS Professionals, 1 of whom was the clinical expert who attended the first meeting. Themes raised echoed points raised by the patient group consultees

- Lymph node-positive subgroup nominated by the company is appropriate (well-recognised prognostic marker) vs. less benefit in lymph node-negative in line with the marketing authorisation
- IDFS is a well-established endpoint in early breast cancer studies, where long term impact on overall survival may be many years in maturing.
  - Small benefits in IDFS consistent with early breast cancer (also low risk in the ITT)
  - Complete pathological response (Neosphere) correlates with disease free and overall survival
- APHINITY data too early to conclude no overall survival benefit. Early positive results are likely to become more substantial with time
- Consistency of subgroup recommendations in other appraisals.
- General comments
  - effective cancer treatments earlier (cure unlikely when resistant clones have developed)

[redacted]

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Company comments (1)

NICE recommendations in subgroups are not uncommon (lymph node-positive)

ACD focuses on uncertainty in the high risk subgroups which is **inconsistent with other appraisals**

- Obinatuzumab (TA513) has a broad MA (untreated follicular lymphoma), recommended in a subgroup (FLIPI score 2 or more) although not powered to detect a difference between subgroups
- Tocilizumab (TA518) has a broad MA (giant cell arteritis), recommended in a subgroup of patients (i.e. relapsing or refractory GCA patients only).
- Other examples in oncology are NICE TA484, TA326, TA145, TA473.
- Reasonable to look at subgroups within a positive study to see what is driving the treatment effect
- Adjuvant pertuzumab provides a clinically meaningful improvement in IDFS in node-positive patients (HR=0.77, 95% CI 0.62-0.96; p=0.02, von Minckwitz et al., 2017). The clinical community are in agreement with this.
- Node-positive patients are at a higher risk of relapse and therefore have a greater need for more effective treatments. This high risk subgroup is aligned with the MA.

ERG comments

In this appraisal, the ERG believes that the company's decision to focus on the node-positive subgroup was not clearly emphasised from the beginning of APHINITY. In our opinion, the company has not presented strong evidence supporting the biological plausibility of a greater effect in the node-positive population compared to the other high-risk subgroups.

[redacted]

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Company comments (2)

Node-negative patients are not considered high risk

- Not possible to draw any conclusions in this subgroup because of the low number of events but this does not invalidate the interpretation of the results seen in the node-positive subgroup.
- The node-negative subgroup is not specifically covered by this MA
- Inconsistent to consider subgroups not covered by the MA (trastuzumab TA208 "there were no subgroups to be discussed, other than the licensed subgroup").
- The Company agree with the clinical community that adjuvant pertuzumab does not need to be offered to every early breast cancer patient with HER2-positive disease but should be offered to node-positive patients to further reduce their risk of recurrence

ERG comments

It is worth noting that the node negative patients in APHINITY have other high risk features (tumour size >1cm, or tumour size between 0.5 and 1cm with either histological grade 3, HR negative or aged under 35). Similarly, hormone-receptor negative patients are routinely referred to as "high-risk" (including the pertuzumab EMA label and the original company submission), showing inconsistency in the definition of the high-risk population.

[redacted]

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Company comments (3)

Unreasonable weight and focus on interaction test

- "The Committee have put an unjustifiable amount of weight on the test for heterogeneity …
- The rationale for proposing the node-positive and hormone-receptor negative subgroups is .. the MA …supported by the results (event rates, HR and CI).
- Statistical interaction testing was performed, in order to understand statistical evidence of heterogeneity in the treatment effect within patient subgroups of interest
- It is acknowledged that the test results do not show strong statistical evidence of heterogeneity
- In APHINITY, low power is particularly notable for nodal status as there are a very low number of events in the node-negative subgroup. Therefore the result needs to be interpreted with caution in terms of concluding homogeneity of treatment effect
- Summaries of clinical effectiveness included in the ACD around the selection of subgroups need to be re-interpreted with consideration of the multiple factors used in subgroup assessments including the totality of the observed data, clinical rationale and biological plausibility."

ERG comments

Appropriate consideration of the interaction test has been presented in ACD2. The ERG are unclear about exactly how the ACD should have interpreted "the totality of the observed data, clinical rationale and biological plausibility" as suggested by the company.

Company comment - use of surrogate markers for overall survival based on Neosphere trial

- Statements that complete pathological response is not associated with improved OS not relevant to this appraisal. DFS and IDFS have been widely adopted in adjuvant studies as a surrogate for long-term outcomes, and have been accepted by both the EMA and FDA.

[redacted]

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Company comments (4)

Overall survival data is too immature to draw conclusions

- Although the ACD claims that there are no survival benefits based on APHINITY the data is too immature - no indication of no survival benefit in the future, when more events have occurred.
  - "further OS follow up and planned statistical analyses will continue until 10 years after last patient enrolled to allow robust assessment of long-term survival effect in this population."

ERG comments

Comments on OS by the Committee in ACD2 are appropriate, as they acknowledge immaturity of data, and only make inference in reference to observed period. For example: "the impact of pertuzumab on overall survival is unknown because data for this outcome are immature."

Incorrect administration costs used in the economic analysis

- The administration costs from the CDF clinical lead are taken from the NHS Improvement Payment by Results tariff 2017 (vs. NHS Reference Costs Schedule 2016 in the company base case).
- The PbR tariff in the updated analysis is not appropriate because it represents transfer payments **within the NHS** vs. NHR Reference Costs represent the **cost to the NHS** of providing services.
- The entire cost of administration to the NHS should be accounted for – as per the guidance in the NICE Reference Case (NICE, 2013). 2016 -17 reference costs are the most up to date.
- A review of 20 appraisals (the last 10 appraisals published,5 breast cancer and 5 committee A) did not use the PbR tariff as per the NICE reference case

ERG comments

- NHS Reference Cost Schedule (2016/17) used in the Company's base case analysis and amendments following the appraisal committee meetings is preferable and the latest available version (as of 1st October 2018).

[redacted]

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Company comments (5)

Incorporation of a more accurate biosimilar trastuzumab discount in the economic analysis

- The price and the market share of biosimilars are not definitively known but a biosimilar market share of 100% and a discount of XX% (based on the budget impact test) compared to the list price of Herceptin IV was assumed (aligned with the statement from the CDF clinical lead).
- Company agrees with biosimilar market share estimate of 100% in new patients
- Company note that the XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XX)
- The committee meeting was only two weeks after the conclusion of the national tender. This is not a suitable length of time for the market to have fully calibrated following the results of the tender
- Discounts of 70% to 90% have been submitted during the tendering process and with increasing use of the least expensive increasing the weighted average discount of biosimilar trastuzumab.
- After the completion of the tender the price can further decrease outside of the tendering process so that the price paid by hospitals is lower.

ERG comments

- Neither the price nor the market share of biosimilars are definitively known. It is plausible that the market share of biosimilar trastuzumab is 100% (the Committee and Roche agree on this value). The ERG has no intelligence on manufacturers' level of discount on Herceptin IV, thus we are unable to comment on the accuracy of the discount level put forward by the Company (~XX% by the anticipated time of final guidance publication in January 2019).
- We have checked the ICER values produced on the basis of the Company's amendments following the second appraisal committee meeting (detailed in Table 4 of the submitted CE appendix) and different discount levels of biosimilar trastuzumab (reported in Tables 6-10). These appear to be correct.

[redacted]

Company comments (6)

Pertuzumab treatment effect duration

- Evidence dose not point to a specific duration of effect, ERG's assumptions are highly conservative/ implausible and are not substantiated by the annualized hazard ratios (von Minckwitz et al., 2017).

Table 1 Annualized hazard ratios in APHINITY data - Node positive population

Time periods	Annualized hazard ratio
Year 0-1	1.00
Year 1-2	0.79
Year 2-3	0.75
Year 3-4	0.59

- The decreasing hazard ratio show the treatment effect is therefore increasing over time
- Heaving censoring in the KM curve at median follow-up in the LN positive (44.5 months) leads to higher uncertainty in HR at years 3-4. The greatest separation in the KM IDFS curves at median follow up (before most censoring) suggests a continuing treatment effect.
- Evidence does not point to a specific duration of effect

ERG comments

- Unclear duration of treatment effect. With the ERG's assumptions the survival curves widen until 78 months (6.5 years) and only when the effect is fully waned (i.e., 8 years), that the hazard and transition probability for the two arms are equal, meaning some benefit of pertuzumab is maintained up until this point.
- Under company assumptions, curves are furthest apart at 109 months (9 years), with some treatment effect maintained until 10 years. Without confidence intervals around the HR's the ERG are concerned that these estimates may contain considerable uncertainty.

[redacted]

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Company revised ICERs (lymph node positive disease)

- Improved CAA and corrected an error in the list price of trastuzumab emtansine
- Treatment duration (7 years, waning and ceasing at 10 years) vs. ERG (4 years and 7 years)
- **ICERs below do not include 100% market share and discounted list price of biosimilar trastuzumab:**
  - **Company ICERs** range £16,814 to £9,899 per QALY gained (for 55% to 75% biosimilar discount).
  - **ERG ICERs** range £29,645 to £19941 per QALY gained (for 55% to 75% biosimilar discount).

Technologies	Total cost	Total QALY	Incr. cost	Incr. QALY	ICER
Original base case (ACD1)					
HC	XXXXXX	XXXX	XXXXXX	XXXX	£34,087
PHC	XXXXXX	XXXX			
Updated base case (ACD2)					
HC	XXXXXX	XXXX	XXXXXX	XXXX	£30,561
PHC	XXXXXX	XXXX			
Revised base case					
HC	XXXXXX	XXXX	XXXXXX	XXXX	£25,516
PHC	XXXXXX	XXXX			

HC (trastuzumab + chemotherapy), PHC (pertuzumab + trastuzumab + chemotherapy)

[redacted]

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Impact of biosimilar discount on company and ERG ICERs

ICERs are presented for both the company's and ERG's revised base cases to show how the cost effectiveness results change following the uptake of biosimilar trastuzumab depending on the discounted price (with 100% market share).

- Company – 6 year treatment effect before waning /ceasing at 9 years
- ERG – 4 year treatment effect before waning and ceasing at 7 years

Efficacy duration	ICER (£)										
Discount (%)	55%	57%	59%	61%	63%	65%	67%	69%	71%	73%	75%
Company	£16,814	£16,123	£15,431	£14,740	£14,048	£13,356	£12,665	£11,973	£11,282	£10,590	£9,899
ERG	£29,645	£28,675	£27,704	£26,734	£25,763	£24,793	£23,822	£22,852	£21,811	£20,911	£19,941

[redacted]

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Use of adjuvant pertuzumab in the CDF

The committee was initially of the view that it did not meet the criteria for use within the CDF based on the following:

- No plausible potential for being cost effective
- IDFS and OS currently immature

Following consultation comments/updated cost effectiveness estimates provided by the company and ERG?

- Is there still a large range of plausible ICERs due to uncertainty in the clinical evidence?
- Is there any plausible potential for the ICER to be cost effective?
- Will more mature data enable the estimation of a more precise ICER?

[redacted]

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Issue 6: Use of adjuvant pertuzumab in the CDF

CDF recommendation criteria

Proceed down if answer to each question is yes

Starting point: drug not recommended for routine use due to **clinical uncertainty**

1. Is the model robust for decision making? (omitting the clinical uncertainty)

2. Does the drug have plausible potential to be cost-effective at the offered price, taking into account end of life criteria?

3. Could further data collection reduce uncertainty?

4. Will ongoing studies provide useful data? and 5. Is CDF data collection via SACT relevant and feasible?

Consider recommending entry into CDF (invite company to submit CDF proposal)

Define the nature and level of clinical uncertainty. Indicate the research question, analyses required , and number of patients in NHS in England needed to collect data.

Key issues for consideration

- Is invasive disease free survival a good surrogate for overall survival?
- Is the 'marginal' benefit with pertuzumab clinically meaningful?
- Although lymph node-positive is a relevant subgroup is the efficacy of pertuzumab better than in the intention to treat population?
  - Unreasonable weight been placed on the test for interaction?
  - Consistency with subgroup recommendations in other appraisals?
- How should biosimilar and administration costs be incorporated in the economic model?
- Is a 7 year (company) or 4 year (ERG) treatment effect most plausible?
- Does the committee accept the company's revised base-case analysis? Specifically does it accept the revised base case ICER for node-positive patients of £25,516 which is premised on:
  - unchanged parameters treatment effect duration
  - an improved CAA offer
- If pertuzumab is not cost effective for routine commissioning is it suitable for the CDF?
  - Clinical uncertainty? Plausible potential for being cost effective? More precise ICER?

[redacted]

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