NICE National Institute for Health and Care Excellence

Slides for Projector and Public– no ACIC

Pertuzumab for adjuvant treatment of early HER2-positive breast cancer

Chair's presentation

2nd 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
19 July 2018

Key issues for consideration

- Does the committee stand by it's original interpretation of the clinical evidence, specifically, is it still of the view that:
  - A statistically significant treatment effect was seen in the ITT population but the clinical benefit in this population is likely to be marginal and there is considerable uncertainty in the effect size
  - Although patients at high-risk of recurrence are in theory likely to benefit most from pertuzumab as adjuvant therapy in absolute terms, data from the APHINITY trial do not demonstrate evidence of heterogeneity between subgroups in the relative treatment effect
- 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 £30,560 which is premised on
  - revised parameters for the cure adjustment and metastatic recurrence
  - unchanged parameters treatment effect duration
  - an improved CAA offer
- Does the committee stand by it's original conclusion that the economic model is likely to overestimate OS

[redacted]

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Key issues for consideration cont.

- How should the committee take into account the availability of biosimilar trastuzumab?
- Is there any plausible potential for adjuvant pertuzumab to be cost effective in all patients covered the marketing authorisation (patients at high risk of disease recurrence)?
- Other issues to be considered if adjuvant pertuzumab is not recommended for routine commissioning
  - 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 estimate?

[redacted]

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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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APHINITY study

Design	Phase III, randomised, double-blind placebo-controlled trial
Population	
Intervention	Pertuzumab + trastuzumab + standard chemotherapy
Comparator	
Primary outcomes	IDFS excluding second primary non-breast cancer events
Secondary outcomes	
Follow-up	3-years
Stratification groups	

Company submission included clinical evidence for the intention to treat population and 2 high risk subgroups (node positive and hormone receptor negative).

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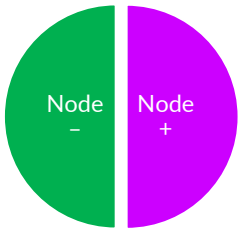
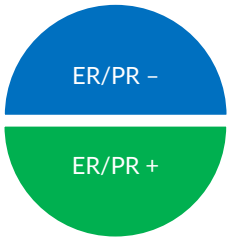
Subgroups prioritised by company

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

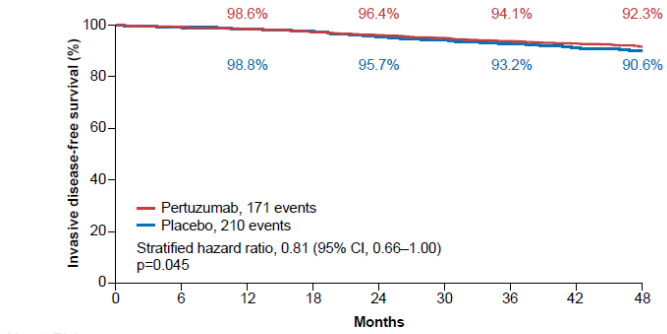


Also considered Hormone receptor-negative subgroup n=1722; pertuzumab n=864 vs. placebo n=858

The ERG noted baseline characteristics were well balanced across the treatment arms within the 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**

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



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.

ERG noted:

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

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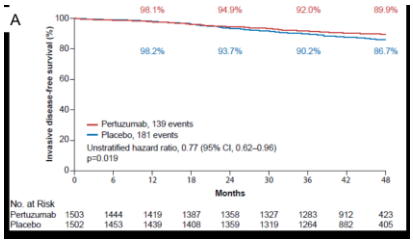
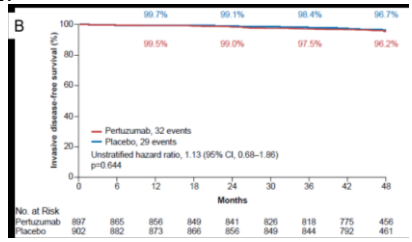
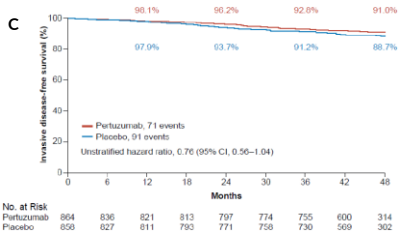
IDFS in subgroups prioritised by company

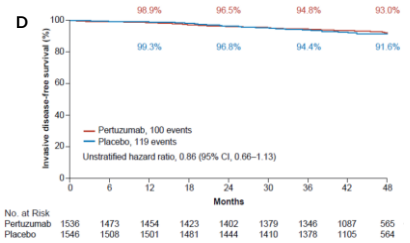
IDFS in lymph node-positive subgroup (figure A) and in lymph node-negative subgroup (figure B); P value for interaction: 0.17





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





IDFS results: ITT and high risk groups

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	
Lymph node-negative patients (n=1,799)		n=897	n=902	
Median f/u: 48.3 mo	3 years	97.5	98.4	1.13 (0.68-1.86)
	4 years	96.2	96.2	
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	
Hormone receptor-positive patients (n=3,082)		n=1,536	n=1,546	
Median f/u:	3 years	94.8	94.4	0.86 (0.66, 1.13)
	4 years	93.0	91.6	

[redacted]

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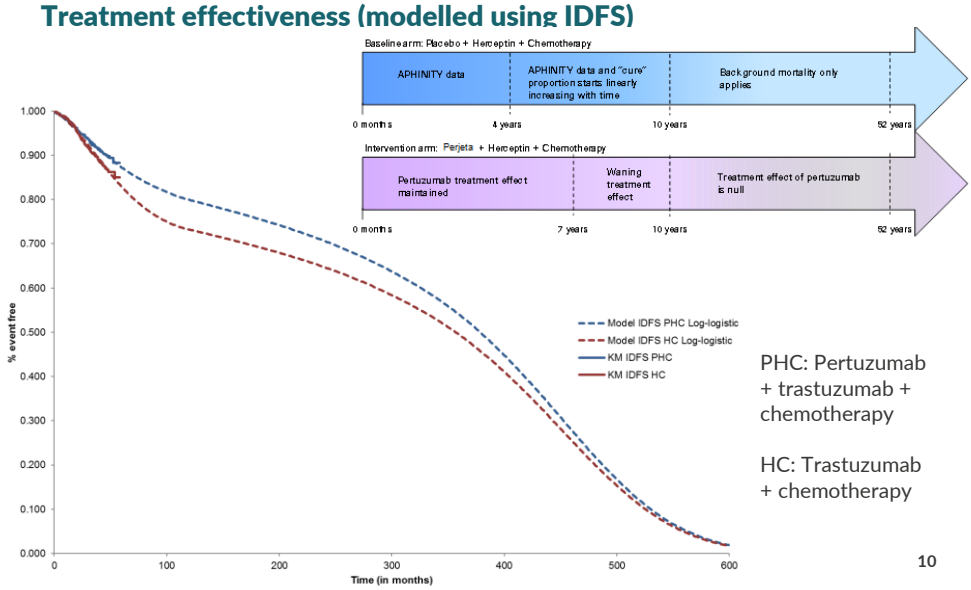
Company's model: node-positive population

Treatment effectiveness (modelled using IDFS)



PHC: Pertuzumab + trastuzumab + chemotherapy

HC: Trastuzumab + chemotherapy

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Company's original cost effectiveness (original commercial access agreement [CAA])

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

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

Committee noted all ICERs above threshold for what is considered cost effective.
Committee did not accept greater benefit in the above subgroups vs. ITT.
The ICER in the ITT population could therefore be higher therefore pertuzumab could not be recommended

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Company and ERG ICERs (original CAA)

ERG preferred different duration of treatment effect (waning at 4 vs. 7 yr), effect cease (7yr vs. 10 yr), time point of the cure adjustment (3yr vs. 4yr), maximum cure proportion (95% vs 90%) and % patients with metastatic recurrence

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

[redacted] PHC: Pertuzumab + trastuzumab + chemotherapy, HC: Trastuzumab + chemotherapy

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Committee's considerations

- Statistical tests for interaction for the node positive and HR negative subgroup showed that neither nodal nor hormone receptor status were associated with a statistically significant difference in treatment effect
- Committee concluded on the basis of the patient and clinical expert testimony that pertuzumab is generally a well-tolerated treatment
- Cost-effectiveness estimates are implausible, a small IDFS benefit translates into 0.6 QALY gain for the node positive group (overestimates overall survival)
- None of the ICERs were cost effective (range of £34,087 to £60,679 per QALY gained for node-positive and £65,669 to £92778 per QALY gained for hormone receptor-negative). ERG ICERs were not preferred but showed how uncertainty in the model affected the ICER. ITT results could give substantially higher ICERs
- More mature OS would reduce the uncertainty in the cost effectiveness estimates (final analysis due in 2023)

[redacted]

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ACD consultation responses

- Consultee comments from:
  - Breast Cancer Now
  - UK Breast Cancer Group
  - Breast Cancer Care
  - Roche Products Limited
- No comments were received from commentators
- Web comments from:
  - 9 NHS Professionals

[redacted]

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What did patient organisations say?

Value patients put on the outcome of IDFS

Breast Cancer Now: "The impact of a diagnosis of metastatic breast cancer – which has an average life expectancy of 2 to 3 years - is devastating, as the Committee is aware from its work on breast cancer drug appraisals in this setting […] Whilst improvements in IDFS are incremental to the current standard of care, 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. As noted in the ACD, the risk of breast cancer recurring or spreading to other parts of the body, where it becomes incurable, can be a cause of stress and anxiety.
Breast cancer care "at Breast Cancer Care we know that fear of recurrence is a common concern for many people being treated for breast cancer. This fear can be a cause of great anxiety, having a significant impact on a person's wellbeing and ability to move forward after breast cancer. Additional treatment options, such as pertuzumab, that reduce the risk of breast cancer returning, are therefore highly valuable to patients"

Burden of IV treatment

Breast Cancer Now: "most, rather than some, patients would consider a reduced risk of recurrence worth the inconvenience of spending longer in hospital to receive treatment"

Price of biosimilar trastuzumab

Breast Cancer Now: "Since this appraisal began, several biosimilars of intravenous trastuzumab have become available, and several more are expected to be launched in the coming months. The list price of these biosimilars is cheaper than that for Herceptin, and we understand that confidential discounts have also been agreed for some of them. This may make a positive difference to the cost-effectiveness of pertuzumab in this setting"

What did patient organisations say? (cont.)

Possibility of CDF recommendation

Breast cancer now "Whilst the final analysis of OS data from the APHINITY trial is due in 2023, we understand that the next analysis of data is due next year. This may help provide greater certainty for the Committee in relation to the data on IDFS and OS, if any improvement in the cost-effectiveness of pertuzumab in this setting […] made it a candidate for the CDF"
UKBCG "In view of the ongoing high event rate in the trials of adjuvant trastuzumab it is likely that a larger absolute difference and a greater confidence in the difference consequent on pertuzumab treatment will emerge with time. In view of this we would support inclusion on the CDF"

How the committee interpreted the evidence presented in the original submission

UKBCG: "The hazard ratios for node-positive and hormone receptor negative sub-groups indicate a greater magnitude of benefit than the overall trial result. It is likely that the confidence intervals will reduce with time as this is seen in all other data sets"
Breast Cancer Now: "the ACD highlights the small number of events in the node negative subgroup. Although the Committee felt it was not reasonable to conclude that pertuzumab did not benefit node negative patients on this basis, we wonder whether node negative patients would generally be considered at higher risk of recurrence, and therefore fall within the marketing authorisation for adjuvant pertuzumab"

What did the company say?

The wider context in which the recommendations are being made

- Suggested that the 'curative intent' of adjuvant treatment has not been acknowledged
- Noted inconsistency between the committee's recommendation and advice issued by other bodies

How the evidence included in the company submission has been summarised in the ACD

- Requested that hazard ratios for the ITT population are presented in the ACD
- Suggested there is some ambiguity in the wording regarding the results of the tests for interaction

How the committee interpreted the evidence presented in the original submission

- Contested the committee's interpretation of the evidence for the subgroups prioritised by the company (node positive and hormone receptor negative patients)
- Contested the committee's conclusion that overestimation of OS is an issue

Price of biosimilar trastuzumab

- Suggested that the ACD should have included more information on the impact of biosimilar trastuzumab on the cost effectiveness estimates

Supplied updated cost effectiveness estimates for the lymph node positive subgroup *but did not update the analysis for the hormone receptor negative patients*

- Agreed with ERG's revised parameters regarding the cure adjustment and cure rate, provided updated data for recurrence rates, did not accept the ERGs estimates for treatment duration

Commercial access arrangements

- Noted that an improved discount for adjuvant pertuzumab has been agreed with NHSE

What did the public say?

Web comments were provided by 9 NHS Professionals, 1 of whom was the clinical expert nominated by Roche who attended the first meeting

The web comments echoed the following points raised by the patient group consultees

- Reducing the risk of recurrent metastatic disease is important to patients because it is incurable

The web comments echoed the following points raised by the company

- The treatment effects observed in the trial are clinically meaningful
- The company's subgroup analysis is valid and patients with lymph node positive disease are more likely to benefit from treatment

[redacted]

Key issues arising from the comments

The remaining slides highlight issues that need to be considered by the committee in light of the feedback received during the ACD consultation

[redacted]

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Issue 1: Clinical evidence on the effectiveness of pertuzumab in the ITT population of APHINTY

Consultees have suggested that pertuzumab is an effective treatment that provides a meaningful (although numerically small) clinical benefit – does the committee agree?

Specifically, is the committee still of the view that while a statistically significant treatment effect was seen in the ITT population, the clinical benefit in this population is likely to be marginal and there is considerable uncertainty in the effect size?

[redacted]

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Issue 2: Heterogeneity in the treatment effect across subgroups in the APHITY study

Consultees have suggested that pertuzumab should be recommended for patients with lymph node-positive disease because they are at high risk of recurrence and there is a greater treatment benefit in this group – does the committee agree?

Specifically, is the committee still of the view that, although patients at high-risk of recurrence are in theory likely to benefit most from pertuzumab as adjuvant therapy in absolute terms, data from the APHINITY trial do not demonstrate evidence of heterogeneity between subgroups in the relative treatment effect?

[redacted]

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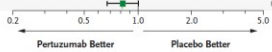
Issue 2: Heterogeneity in the treatment effect across subgroups in the APHINITY study (cont.)

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



[redacted]

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Issue 2: Heterogeneity in the treatment effect across subgroups in the APHINITY study (cont.)

The company have suggested that the wording of the ACD regarding the committee's interpretation of the P-values for interaction for the subgroup analyses in the APHINITY study is ambiguous. It is noted that there is a typo in the following paragraph – can the wording be adjusted as indicated?

ACD text:

> Finally the committee noted that statistical tests for interaction resulted in p values for invasive disease-free survival of ~~less~~ greater than 0.05 (p=0.17 for interaction between nodal status and invasive disease-free survival; p=0.54 for interaction between hormone receptor status) suggesting that neither nodal nor hormone receptor status were associated with a statistically significant difference in treatment effect

[redacted]

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Issue 3: Revised cost effectiveness estimates for patients with lymph node-positive disease (1)

The company and the ERG have each provided revised cost effectiveness estimates for patients with **lymph node-positive disease only** – does the committee consider pertuzumab to be cost effective in this patient group?

Specifically:

- does the committee accept the company's revised base case ICER for node-positive patients of £30,560 which is premised on
  - revised parameters for the cure adjustment and metastatic recurrence
  - unchanged parameters treatment effect duration
  - an improved CAA offer
- does the committee stand by it's original conclusion that the economic model is likely to overestimate OS (unrealistic QALY gain)?

[redacted]

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Issue 3: Revised cost effectiveness estimates for patients with lymph node-positive disease (2)

Parameter	Values in company's original submission	Value used in company's revised estimates	ERG's original preferred value	Value used in ERG's revised estimates
Time point cure model begins	48 months	36 months	36 months	
Maximum cure rate	90%	95%	95%	
Time point cure model ends	120 months	120 months	120 months	
Metastatic recurrence – Pre 18 months	100%	75.58%	100%	75.58%
Non-metastatic recurrence – Pre 18 months	0%	24.42%	0%	24.42%
Metastatic recurrence – Post 18 months	18.93%	79.38%	72.40%	79.38%
Non-metastatic recurrence – Post 18 months	81.07%	20.62%	27.60%	20.62%
Assumptions regarding treatment effect	Runs for 7 years before waning and ceasing completely at 10 years *(no change from original assumption)*		Runs for 4 years before waning and ceasing completely at 7 years*(no change from original assumption)*	

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

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Issue 3: Revised cost effectiveness estimates for patients with lymph node-positive disease (3)

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

During consultation the original base case ICER was updated by the company during consultation (from £34,087 to £33,857 per QALY gained due to a minor modelling error that was identified.

[redacted]

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Issue 4: Impact of biosimilar pricing on company and ERG revised ICERs for patients with lymph-node positive disease

The company has suggested that the introduction of biosimilar trastuzumab should be taken into account because similar considerations have been made in other NICE technology appraisals.

- In previous NICE TAs nationally agreed discounts on the prices of biosimilar drugs have been taken into account
- The company has provided a threshold analysis based on assumptions about future prices and estimates of market share

[redacted]

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Issue 4: Impact of biosimilar pricing on company and ERG revised ICERs for patients with lymph-node positive disease

ICERs are presented for both the company's and ERG's revised base cases to show how the cost effectiveness results could change following the uptake of biosimilar trastusumab depending on the price and market share of these products.

As before, differences between the company and ERG estimates are due to the different underlying assumptions regarding duration of treatment effect:

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

Trastuzumab biosimilar		Discount compared to Herceptin list price (%)					
		70%		74%		80%	
		Company	ERG	Company	ERG	Company	ERG
Market share	90%	£18,062	£30,344	£16,817	£28,597	£14,950	£25,977
	95%	£17,367	£29,371	£16,053	£27,527	£14,082	£24,761
	100%	£16,673	£28,398	£15,290	£26,457	£13,215	£23,546

[redacted]

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Issue 5: Other patients covered by the marketing authorisation

The company have not provided any revised cost effectiveness estimates for patients with hormone receptor-negative disease who are also covered by the marketing authorisation– does the committee believe that there is any plausible potential for adjuvant pertuzumab to be cost effective in these patients?

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**

[redacted]

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Issue 6: 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
- Further IDFS and OS may not confirm the OS in the model

Does the committee wish to reconsider this conclusions in light of the 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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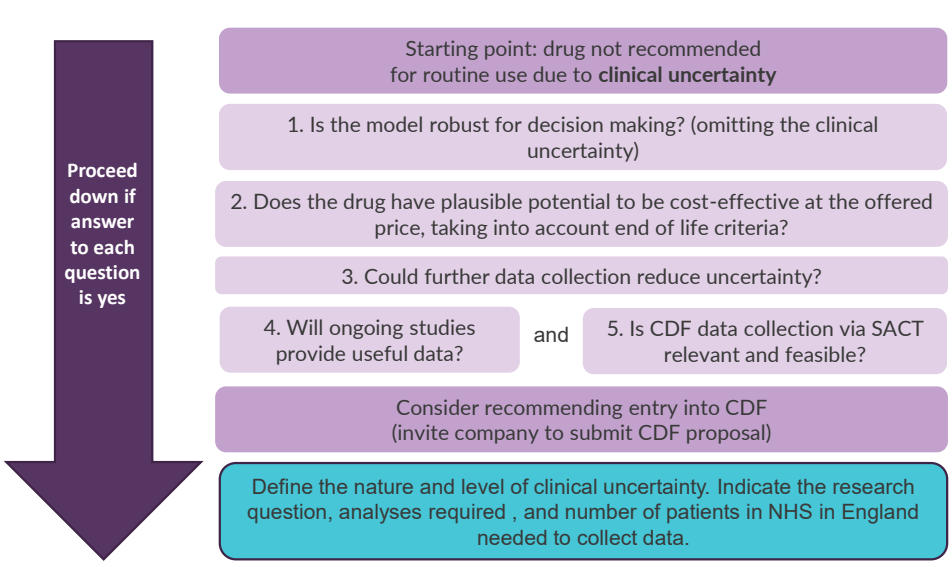
Issue 6: Use of adjuvant pertuzumab in the CDF



Key issues for consideration

- Does the committee stand by it's original interpretation of the clinical evidence, specifically, is it still of the view that:
  - A statistically significant treatment effect was seen in the ITT population but the clinical benefit in this population is likely to be marginal and there is considerable uncertainty in the effect size
  - Although patients at high-risk of recurrence are in theory likely to benefit most from pertuzumab as adjuvant therapy in absolute terms, data from the APHINITY trial do not demonstrate evidence of heterogeneity between subgroups in the relative treatment effect
- 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 £30,560 which is premised on
  - revised parameters for the cure adjustment and metastatic recurrence
  - unchanged parameters treatment effect duration
  - an improved CAA offer
- Does the committee stand by it's original conclusion that the economic model is likely to overestimate OS

[redacted]

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Key issues for consideration cont.

- How should the committee take into account the availability of biosimilar trastuzumab?
- Is there any plausible potential for adjuvant pertuzumab to be cost effective in all patients covered the marketing authorisation (patients at high risk of disease recurrence)?
- Other issues to be considered if adjuvant pertuzumab is not recommended for routine commissioning
  - 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 estimate?

[redacted]

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