Lead team presentation

Pertuzumab for the adjuvant treatment of HER2-positive breast cancer

For projector and public

1st Appraisal Committee meeting

Cost effectiveness

Committee A

Lead team: Stephen Sharp

Assessment Group: Warwick Evidence

NICE technical team: Juliet Kenny, Eleanor Donegan

22 May 2018

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Preview: Cost-effectiveness issues

- Does the committee accept the company's general approach to modelling the cost effectiveness of pertuzumab i.e. using IDFS outcome data from the APHINITY study to estimate treatment benefit?
- Does the committee feel confident that the modelling techniques employed by the company (the use of a parametric curve adjusted to reflect the duration of treatment effect, expected rates of disease recurrence and background mortality rates) give a reliable estimate of the cost effectiveness of pertuzumab treatment over the lifetime (52 year) time horizon?
- Does the committee consider the company or ERG treatment effect assumptions to be most plausible? Specifically,
- Is a cure adjustment appropriate and
  - should it be introduced from year 4 (company) or year 3 (ERG)?
  - should the maximum cure proportion be 90% (company) or 95% (ERG)?
- Should a waning treatment effect start at year 7 (company) or year 4 (ERG)?
- Should the treatment benefits cease at year 10 (company) or year 7 (ERG)?
- Should the percentages of patients likely to experience metastatic vs. non-metastatic disease be estimated as 81.07% vs. 18.93% (company) or 72.40% vs. 27.60% (ERG)?

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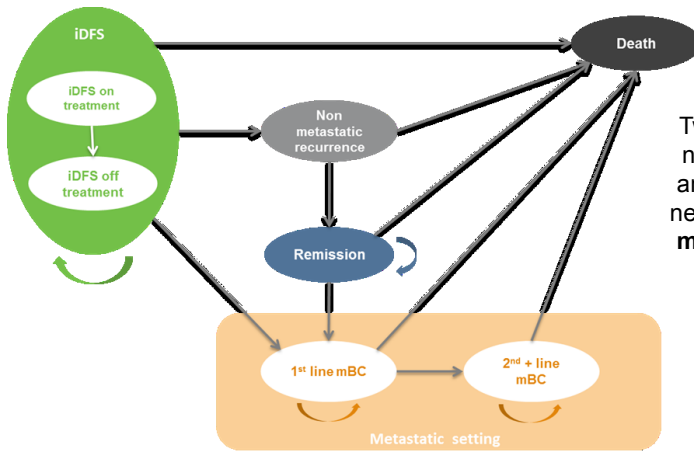
Company's economic model – structure

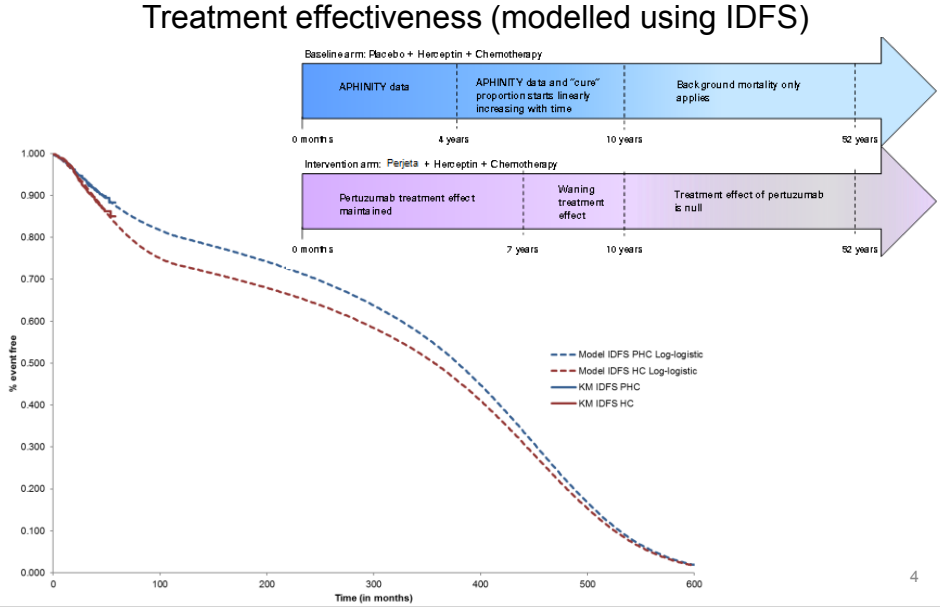


Two subgroups: lymph node-positive patients and hormone receptor-negative patients. **Same model structure used for both analyses.**

Type	Markov model with n=7 health states
Time horizon	Lifetime (52 years) (discounted at 3.5% per annum)
Cycle length	1 month, half cycle correction.

Company's model: node-positive population

Treatment effectiveness (modelled using IDFS)

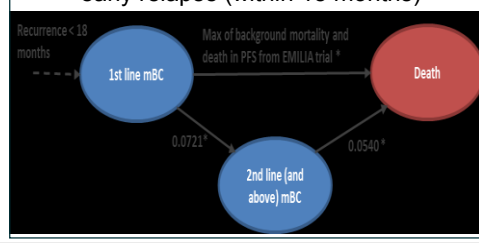


Company's model: node-positive population

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%).
- Recurrence within 18 months of treatment initiation assumed to be metastatic, survival estimates for these patients derived from the EMILIA study.
- 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 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	PHC = 0.032; HC = 0.047; C = 0.069	CLEOPATRA or M77001
	Death	Max of BGM or PFS in relevant trial	UK life tables, CLEOPATRA, or M77001
Second+ line mBC	Death	PHC = 0.027; HC = 0.032; C = 0.060	CLEOPATRA or M77001

Company's model: node-positive population

Utility values

- HRQoL data collected using the EQ-5D-3L tool in the APHINITY study node-positive population was used to generate the health state utility values.
- 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 to both arms of the model.

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

Company's model: node-positive population

Acquisition costs of 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)

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Company's 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

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Company's model: node-positive population

Cost effectiveness results with CAA

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

- PSA ICER = £33,621
- Probability of cost effectiveness at £30,000/QALY is 17.3%
- ERG noted that ICERs generated through company's scenario 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

- Duration of treatment effect chosen by the company was not well justified
- 'Cure' adjustment to the parametric extrapolation appropriate in principle -starting point and maximum cure proportion was considered implausible
- 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 (with CAA): £60,679 (vs. company £34,087)

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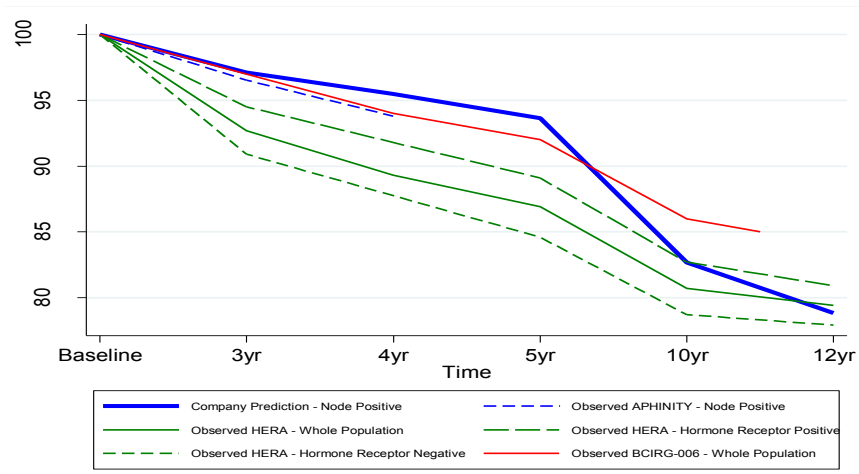
ERG's critique of the company's model – node positive population cont.

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



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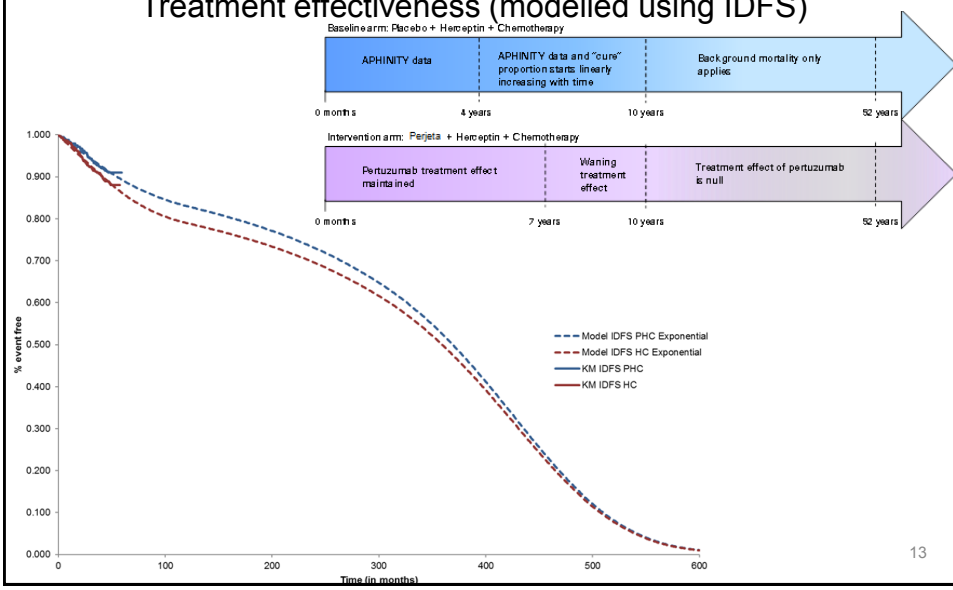
Company's economic model: hormone receptor-negative population

Treatment effectiveness (modelled using IDFS)



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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			
	Pertuzumab + trastuzumab + chemotherapy	XXXXXX	XXXX	XXXXXX	XXXX	£65,699

- 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

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 (with CAA): £92,778 (vs. company £65,699)

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Summary of company and ERG ICERs (with CAA) by population group

Population	Source	Techn-ologies	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			

Innovation

From 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

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Equalities

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

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Back up slides

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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)

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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

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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: £66,238

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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			