

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

2nd Appraisal Committee meeting
21 June 2016

Issues for committee (1)

- Is the clinical evidence sufficient to allow committee to make a decision for pertuzumab for this indication?
- What is the committee's view of the outcome 'pathological complete response' and its validity to predict overall survival/clinical benefit?
- Is there a way to reduce the clinical uncertainty?
- What are the clinical risks of making a positive recommendation for this technology?
 - Patients could receive the side effects of pertuzumab with no long term health benefit
- What are the clinical risks of a negative recommendation for this technology?
 - Could lose opportunity to potentially cure disease
 - Patients may not get the psychological benefit associated with early response of disease to treatment
 - Could reduce opportunities for breast conserving surgery

Issues for committee (2)

- The economic model is based on uncertain long term clinical effectiveness – therefore the clinical uncertainty translates into uncertainty in the cost effectiveness.
- What are the financial risks to the NHS of a positive recommendation?
 - If ineffective, costs of £12,000 per patient at the beginning of treatment, with no health benefit
 - ICERs are dependent on the CDF, which has uncertainty
 - Recommending a treatment which may not be cost effective
- What are the financial risks to the NHS of a negative recommendation?
 - Possible loss of opportunities to provide breast conserving surgery rather more costly mastectomy and reconstructive surgery
 - NHS may be missing out on a cost-effective treatment
- Does the committee understand the differences between the company's submission to NICE and SMC?

ACD preliminary recommendation

- 1.1 Pertuzumab, in combination with trastuzumab and chemotherapy, is not recommended within its marketing authorisation for the neoadjuvant treatment of human epidermal growth factor receptor 2 (HER2) positive breast cancer; that is, in patients with HER2-positive, locally advanced, inflammatory or early-stage breast cancer at high risk of recurrence.

Pertuzumab

- Licensed “in combination with trastuzumab and chemotherapy for the neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory or early stage breast cancer at high risk of recurrence”
- Recombinant monoclonal antibody
- Targets extracellular dimerization HER2 domain (subdomain II) and interrupts signalling that causes cell growth and division; first monoclonal antibody to target this receptor (trastuzumab targets subdomain IV)
- Administered intravenously, 840mg initially then 420mg every 3 weeks for 3-6 cycles

Pathological complete response

3 definitions of pathological complete response considered in appraisal:

- pathological complete response in the breast (bpCR): breast tissue has no invasive cancer but can have disease in lymph nodes or ductal carcinoma in situ still in the breast (rate of progression of in situ to invasive disease not certain)
 - Primary outcome in NeoSphere trial
- total pathological complete response (tpCR): no invasive cancer in breast tissue or lymph nodes but can still have ductal carcinoma in situ
 - Collected retrospectively in NeoSphere, used in model
- German Breast Group pathological complete response (GBG pCR): No invasive or in situ carcinoma in breast or lymph nodes

Clinical trial evidence

2 x phase II randomised controlled trials

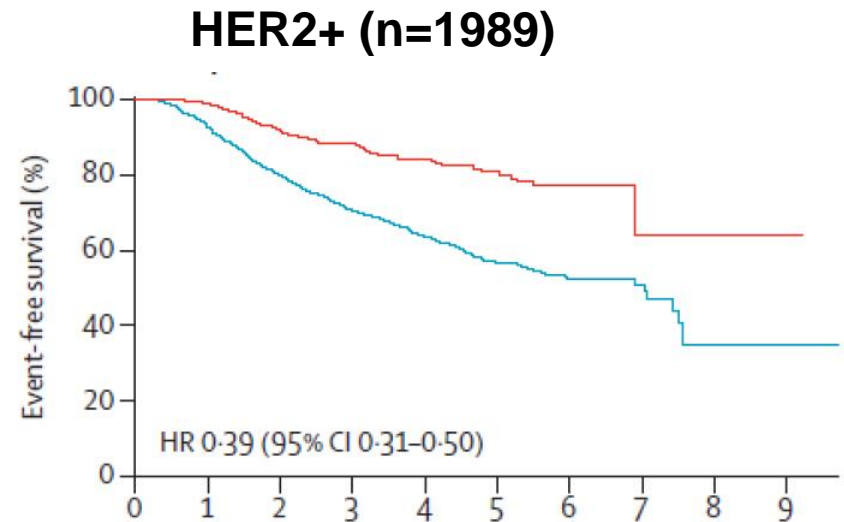
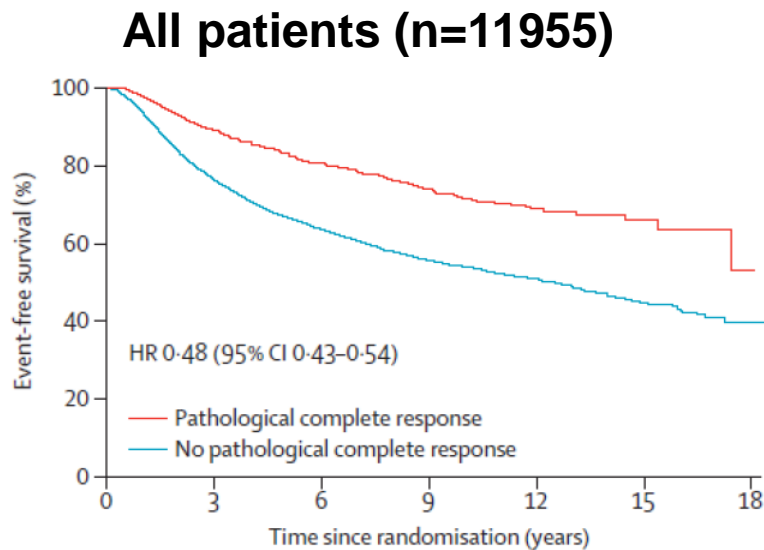
- NeoSphere (n=417): **efficacy** trial
 - Arm A (n=107, trastuzumab and docetaxel)
 - Arm B (n=107, pertuzumab, trastuzumab and docetaxel)
 - Pertuzumab arm had higher pCR responses bpCR 45.8 vs 29% (16.8% to 20.6% higher than trastuzumab arm for for all 3 definitions of pCR)
 - Similar breast conserving surgery rates (where mastectomy planned) in both arms 23.2 vs. 22.6%
- TRYPHAENA (n=225): cardiac **safety** trial
 - 3 arms, all containing pertuzumab
 - “Low” rates of left ventricular: systolic dysfunction /ejection fraction
 - tpCR rates ranged from 54.7% to 63.6% across all 3 arms

pCR and survival

- CTNeoBC Evaluated the association between pCR and survival outcomes; 12 trials, n=11,955, of whom 1,989 had HER2 disease.
 - *CTNeoBC conclusion*: Patients with GBG pCR or tpCR have improved survival (see next slide), with prognostic value greatest in aggressive subtypes. But could not validate pCR as surrogate for EFS and OS
- *ERG*: Wider evidence generally consistent. At patient-level, pCR associated with EFS and OS. But evidence pCR translates into positive effect on OS is not convincing.
- *EPAR*: “in the context of the totality of the data” (including strong biological rationale for the combination, the “compelling” efficacy in metastatic setting, acceptable toxicity and observed pCR) “it is reasonably likely that neoadjuvant treatment with pertuzumab is associated with a benefit in terms of DFS and OS.”
- *Committee*: “considerable uncertainty” about whether pCR “was a meaningful indicator of long-term survival outcomes, such that it could be viewed as a surrogate marker of long-term benefit”.

CTNeoBC: Patient level

- CTNeoBC meta-analysis published EFS curves for those with and without pathological complete response (tpCR), irrespective of treatment:



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

n at risk										
tpCR	586	527	454	371	212	120	37	4	2	1
no tpCR	1403	1157	918	713	436	269	106	33	3	1

Model inputs

Clinical effectiveness (event free survival)

- Not directly taken from NeoSphere because of small number of events
- Instead company extrapolated data from CTNeoBC for those with and without tpCR irrespective of treatment, and adjusted it using tpCR rates from the relevant arm (pertuzumab or trastuzumab) in NeoSphere.
- Company originally used inconsistent approach (used EFS curves for *whole population* in CTNeoBC, but used numbers at risk from *HER2+ subgroup*).
- The company resubmitted its base case using HER2+ subgroup only – resulted in large decrease in base case ICER

Utility values

- Taken from literature (Lidgren et al. and Lloyd et al.) or assumptions used

Costs

- 4 cycles of neoadjuvant pertuzumab (costing £11,975)
- Other costs included metastatic treatments funded by Cancer Drugs Fund

Company base cases

3 base cases submitted

- Original base case: £17,297 per QALY gained
- Base case A: £19,939 per QALY gained
 - original base case + xx% IV & xx% subcutaneous neoadjuvant trastuzumab (comparator arm only).
- Base case B: £8,215 per QALY gained
 - base case A + EFS curves from HER2+ subgroup of CTNeoBC
- Deterministic sensitivity analyses only conducted for original base case and base case A
 - only ICERs >£30,000 were changing pCR rates (max ICER £72,673)

ERG exploratory analyses

- ERG presented alternative base case, based on company base case A and assuming:
 - EFS based on extrapolation of HER2+ subgroup of CTNeoBC, using lognormal distribution
 - Hazard of recurrence: ERG extrapolated EFS for whole 50 year time horizon (company base case assumed zero hazard of recurrence beyond 7 years; ERG stated this is not clinically valid)
- Increased ICER to £23,467
- ERG ICER sensitive to pCR rates, distribution assumed for EFS, and number of cycles of pertuzumab

ERG exploratory analyses (4): Selected results, univariate sensitivity analyses

ERG base case ICER: £23,467 /QALY (deterministic) & £23,962 (probabilistic)

Modification	Base case	(1)	(2)	ICER (1)	ICER (2)
Distribution for EFS	Lognormal	Gen. gamma	Gompertz	£8,816	£50,462
PHD pCR rate	39.25%	49.2%	30.0%	£5,959	£76,515
HD pCR rate	21.5%	30.5%	14.1%	£73,605	£9,139
No. cycles of pertuzumab (pCR rates as in NeoSphere)	4	6	3	£42,995	£14,353
No further treatment effect	7 years	6 years	5 years	£27,010	£32,241
Cost of metastatic progressed health state	£5,923	£6,689	£2,223	£21,336	£33,755
Disutility due to AEs for pertuzumab (1 year)	0	-0.083	-0.0415	£33,996	£27,767
EFS data	Modelled	From NeoSphere		£3,792	

EFS: event free survival; HD: trastuzumab + docetaxel; PHD: pertuzumab, trastuzumab + docetaxel; pCR: pathological complete response

Discrepancy with SMC submission

- Company submitted to Scottish Medicines Consortium (SMC) at similar time to NICE, but with discrepancies between submissions:
 - Incremental costs: NICE £4,557, SMC £10,370
 - Incremental QALYs: NICE 0.261, SMC 0.31
 - ICER: NICE £17,297, SMC £34,078
 - Utility metastatic progressed health state: NICE 0.452, SMC 0.5
- This difference was not stated or explained in the company submission
- NICE requested an explanation from Roche. Its response:
 - SMC submission included error identified by ERG for NICE submission (mixed population incorrectly used to extrapolate EFS rather than HER2+ subpop); Correction of this error reduces SMC ICER by approx. £10,000.
 - Trastuzumab emtansine and pertuzumab are not regularly used to treat metastatic breast cancer in Scotland but are in England (via CDF).
 - Differences in general population mortality values.
 - Other minor corrections and updates made to NICE submission.

Committee conclusions ACD (1)

- “some evidence” that pertuzumab could improve pCR however “severely limited”:
 - Phase II, small patient numbers, open label, not powered for survival outcomes, comparators omitted.
- “considerable uncertainty” about whether pCR was a meaningful indicator of long-term survival outcomes
- Uncertainty about generalisability
 - Most patients had operable disease and have best prognosis, few UK patients

Committee conclusions ACD (2)

- Concerns about discrepancy between NICE and SMC submissions
- Model clinical data based on EFS from CTNeoBC adjusted using pCR rates from NeoSphere, however:
 - CTNeoBC could not confirm pCR as a valid surrogate for survival
 - Limited NeoSphere trial data available to adjust with
 - Highly uncertain; concerning as model very sensitive to pCR
- Company used costs of metastatic treatments funded by CDF, using list prices. But CDF currently in transition and NHS not likely to be paying list price.
- Model assumed 4 cycles but licence is for 3 to 6 cycles. ERG model was sensitive to number of cycles of pertuzumab
- Too much uncertainty to determine a most plausible ICER

Consultation comments

The following organisations responded:

- Roche
- Breast Cancer Now

Breast Cancer Now

Neoadjuvant medicines:

- Disadvantaged because overall survival data takes >15 years to collect; patients miss out on treatments, patent expiry for companies, reduces incentives for innovation
- Unclear what companies need to do to mitigate uncertainty in these circumstances /what level of evidence NICE needs (DSU advice is needed)

Patient subset:

- Pertuzumab can increase likelihood of response and chances of curative treatment. Particularly important when advanced/aggressive disease

Cancer Drugs Fund (CDF):

- Pertuzumab should be considered for CDF, despite many years needed to collect survival data. Pertuzumab has impressive results, is for small population, and 'new' CDF is for use when high uncertainty.
- NICE unclear how submissions should include CDF funded drugs
- Delays to CDF process: company could not properly consider CDF option

Roche (1): Evidence base

- There are limitations to data e.g. open label however:
 - blinding is usually absent from oncology trials because of cytotoxic drugs
 - pertuzumab met EMA criteria
 - mismatch between regulatory and HTA processes, bringing drugs to market as soon as possible vs data limitations for positive HTA recommendation
- Wider HER2 evidence base supports pertuzumab safety and efficacy
 - TRYPHAENA: cardiac safety trial, also shows high tpCR rates for pertuzumab
 - CLEOPATRA (n=808): phase III metastatic setting, pertuzumab/trastuzumab/docetaxel vs trastuzumab/docetaxel. Provided safety data, plus pertuzumab had improved survival vs placebo
 - APHINITY (n=4,805): phase III, adjuvant pertuzumab vs placebo (both with trastuzumab and chemotherapy), for operable HER2+ breast cancer that is “adequately excised”

Roche (2): Evidence base

Pathological complete response (pCR)

- ICER sensitive to pCR, but direction uncertain (could increase or decrease ICER), and company explored uncertainty from wide pCR confidence intervals in probabilistic sensitivity analyses
- Several studies in HER2+ early breast cancer demonstrated association of pCR and long-term outcomes, including:
 - NOAH: pCR for neoadjuvant trastuzumab strongly associated with improved EFS vs patients who did not receive trastuzumab
 - HannaH: Patients with tpCR had >60% reduction in risk of an EFS event vs those who did not (hazard ratio 0.38, 95% confidence interval [CI] 0.22-0.65) in the subcutaneous arm and 0.32 (95% CI 0.18-0.60) in the intravenous arm.
 - Broglio: Meta-analysis (n=5,768) for patients with HER2-positive early breast cancer; provides further evidence of the association of pCR with improved long-term outcomes e.g. EFS in patients with early disease.

Roche (3): SMC

- Company submission to NICE did not mention SMC because company considers any submission to different jurisdiction to be confidential until published, also had taken similar approach in previous appraisal
- Incremental cost difference is £5,831, mostly due to costs incurred in metastatic health state
 - Metastatic costs differ due to different treatments available for metastatic disease in England because of CDF
 - CDF treatments also affect transition probabilities because CDF treatments are more effective than Scottish alternatives
 - Net impact of applying both costs and transition probabilities from NICE base case to the SMC reduces incremental cost difference by £5,788, and ICER by £18,640.
- Other minor impacts on costs include different assumptions for body surface area and population mortality

Roche (4): SMC

	SMC	NICE	Impact on SMC ICER	Rationale
Utility metastatic progressed	0.5	0.452	-£331	NICE: used patient age from Lloyd; SMC: CLEOPATRA
Body surface area	1.73	1.79	£4	NICE: average UK women aged 45-54; SMC: NeoSphere
Population mortality	Scot.	English	-£1,420	Jurisdiction mortality
Capping utility values	No	Yes	£6,351	To stop value being higher than general population
Impact of metastatic treatments				
Metastatic 1 st line cost	£2,295	£3,824	-£2,739	Mortality treatments appropriate to each region were applied
Metastatic 2 nd line cost	£2,295	£5,923	-£13,860	
Transition: met non prog. to progressed	4.70%	4.02%	-£130	
Transition from met progressed to death	3.15%	2.81%	£310	

Roche (5): Scenario analyses

Company presented alternative analyses for:

- CDF: CDF funded treatments excluded, and threshold analysis for % discount CDF costs required to increase ICER <£30,000
 - Important to explore: metastatic treatments are inherent part of pathway, and ongoing changes in CDF process, outside of company control
 - Inappropriate to predetermine outcome of CDF changes
- CTNeoBC: analysis using total population rather than HER2 subpopulation from CTNeoBC when extrapolating EFS
 - company noted that it, clinical advisors and ERG consider HER2 subpopulation to be most relevant

	Roche	ERG
Base case	£8,215	£23,467
No CDF funded treatments	£23,985	£37,281
% Chance cost-effective at £30,000/QALY	62%	28%
% CDF discount to raise ICER >£30k	ICER £26,324 @100%	40%
CTNeoBC whole population	£19,939	

Roche (6): General comments

- **Cycles:** estimate 3 cycles if used with trastuzumab/FEC (based on research with UK clinicians); if 6 cycles used then would be trastuzumab/ docetaxel/ carboplatin due to concerns with cardiotoxicity
- **Breast conserving surgery:** (BCS) Advances in BCS vs mastectomy since CG80 (2009); Dutch Cancer Registry data for 37,000 patients (where 58% of patients had BCS) showed increase in 10-year survival in patients who received BCS vs mastectomy, at every tumour size and nodal status stage (although BCS group younger with smaller tumours).
- **Comparator:**
 - 25% do not receive trastuzumab containing regimens; however these patients are not relevant to this appraisal (pertuzumab licensed as addition to trastuzumab, therefore only patients who can receive trastuzumab are eligible for treatment with pertuzumab)
 - 68% of all regimens and 79% trastuzumab regimens include docetaxel
 - Alternative regimens available, but less relevant and fragmented
- **Generalisability:** Expert opinion confirms trial patient generalisability to UK

Roche (7): EMA criteria for using pCR

EMA has developed guidance on 5 key considerations for clinical trials where approval based on pCR is acceptable – pertuzumab meets all of these:

1. Well known mechanism of action
2. Add-on to an established (neo) adjuvant regimen
3. Major effect on pCR in the neoadjuvant breast cancer setting
4. Well established safety profile, minor increase in toxicity (company note pertuzumab safety profile was also demonstrated in metastatic setting in CLEOPATRA trial)
5. Confirmatory Adjuvant trial ongoing (company note ongoing APHINITY trial)

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Backup slides

- Wider evidence for pertuzumab
 - Wider clinical evidence
 - US Food and Drug Administration comments on pCR and survival outcomes

Wider clinical evidence: CLEOPATRA

- Phase III RCT (n=808), pertuzumab vs placebo, both added to trastuzumab/docetaxel, HER2 metastatic breast cancer. Median 24 cycles
- At 5 year follow-up 54.8% and 41.4% of patients in the placebo and trastuzumab arms respectively had died

CLEOPATRA adverse events (with incidence $\geq 25\%$ or a difference of $>5\%$ between arms)

Adverse event %	Pertuzumab	Placebo
Total patients with ≥ 1 AE	100	98.7
Alopecia	60.8	60.6
Diarrhoea	68.4	48.7
Neutropenia	53.4	50.0
Nausea	44.9	42.4
Fatigue	38.0	37.4
Rash	37.5	24.0
Asthenia	27.7	30.8
Decreased appetite	29.7	26.8
Peripheral oedema	24.0	28.0
Vomiting	26.0	24.5
Myalgia	24.3	25.0
Mucosal inflammation	27.2	19.9
Headache	25.7	19.2
Constipation	15.9	25.5
Upper respiratory tract infection	20.8	14.4
Pruritus	17.6	10.1
Febrile neutropenia	13.7	7.6
Dry skin	11.3	6.1
Muscle spasms	10.3	5.1

US Food and Drug Administration (FDA) comments on pCR/survival

- “Given the substantial improvements in survival for individual patients who attain pCR, a novel agent that produces a marked absolute increase in pCR rate compared with standard therapy alone in the full intent-to-treat population may be reasonably likely to result in long-term improvements in EFS or OS”
- “The FDA review team finds that the totality of data submitted, including the NEOSPHERE and TRYPHAENA study results, the overall survival improvement seen in CLEOPATRA and the tolerable safety profile, support an accelerated approval for pertuzumab in the neoadjuvant setting. The conversion to regular approval will be contingent upon the results of the fully accrued Phase 3 APHINITY trial”
- “The benefit to patients for granting accelerated approval to pertuzumab for this indication is that more patients who are at high risk for disease recurrence may be cured. The risk to patients is that they are exposed to increased toxicity without certainty that clinical benefit will ultimately be demonstrated. Given the prior data with pertuzumab in the first-line metastatic setting and the fact that the confirmatory study has already completed accrual, these risks are outweighed by the potential benefit”.