NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Pertuzumab in combination with trastuzumab and docetaxel for the treatment of HER2 positive metastatic or locally recurrent unresectable breast cancer

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Dr Helena Earl

Name of your organisation: NCRI/RCP/RCR/ACP/JCCO

Are you (tick all that apply):

√ a specialist in the treatment of people with the condition for which NICE is considering this technology?

√ a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?

- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?
- other? (please specify)

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What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS?
First-line HER2+ve metastatic breast cancer at present is treated in the NHS with trastuzumab concomitantly with chemotherapy (often docetaxel). The CLEOPATRA trial ran from 2008 to 2010, and it is of interest that in the publication (Baselga J, Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. NEJM 2012;366:109-19) only 10-11% of patients had received trastuzumab in the neo/adjuvant setting. Today the percentage of patients relapsing with metastatic HER2+ve breast cancer would be much higher, and in the UK over 90% of HER2+ve patients under the age of 75yrs would receive trastuzumab in the neo/adjuvant setting. The trial eligibility criteria included a 12 month treatment free interval. Currently in the NHS, even with neo/adjuvant trastuzumab, after 12 months standard treatment would be trastuzumab and docetaxel. Therefore the treatment for this condition currently is the control / standard arm of the Cleopatra study.

Is there significant geographical variation in current practice?
No significant geographical variation.

Are there differences of opinion between professionals as to what current practice should be?
No substantial disagreements amongst professionals about current practice for firstline relapse without CNS disease.

What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?
Pertuzumab represents an addition to the current technology. There is no alternative at present.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient?
In the era before the availability of neo/adjuvant trastuzumab, the HER2 subgroup of breast cancer patients had the worse prognosis (Curtis et al. The genomic and transcriptomic architecture of 2,000 breast tumours reveals novel subgroups. Nature. 2012 Apr 18;486(7403):346-52). This work led by Caldas, shows that integrative cluster 5 which is predominantly HER2+ve, shows the fastest rate of relapse within the first 5 years. This is shown in all other trial databases in the pre-trastuzumab era. The subgroup eligible for the CLEOPATRA trial, is probably a prognostically more favourable sub group of the HER2 breast cancer population. In particular, most had <u>not</u> received neo/adjuvant trastuzumab, and 12 months had passed since the end of adjuvant treatment. Patients excluded from this trial are those who (not having received trastuzumab), relapsed within the first 12 months. The majority of the population treated in the CLEOPATRA trials is trastuzumab naïve, and therefore there is no chance of resistance to anti-HER2 treatment having developed.

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Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?
So far our experts have looked at how the patients got onto the trial, rather than examining the characteristics of those who were eligible. No particular subgroup seem more at risk from the new technology. The new technology may cause more heart damage, and therefore patients had an upper limit of previous doxorubicin exposure of 360mg/m2. This represents a quite low level of previous exposure which is usually at 450-500mg/m2. The risk of previous anthracycline cardiac damage is going to be very low in this group. Pertuzumab is possibly more active in patients with visceral rather than non-visceral (bone) metastatic disease.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics?
Pertuzumab would be prescribed in secondary care, but can be delivered either in primary or secondary care, or in the patients own home. Trastuzumab is at present successfully delivered in this way.

Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?
See above.

If the technology is already available, is there variation in how it is being used in the NHS?
The technology has been made available in 2 ways. The PERUSE trial (a phase IV trial) has made Pertuzumab available in the NHS, and the National CDF has agreed its use in first relapse (12 months post adjuvant trastuzumab) for HER2+ve breast cancer pending the NICE single technology appraisal.
The introduction of National CDF Approved lists on April 1st, should mean there is no variation in the take-up of new technology.

Is it always used within its licensed indications? If not, under what circumstances does this occur? N/A

Please tell us about any relevant clinical guidelines and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.
The National CDF has agreed its use in first relapse (12 months post adjuvant trastuzumab) for HER2+ve breast cancer pending the NICE single technology appraisal. The CDF agrees first line metastatic use with docetaxel and trastuzumab, in patients who have a 12 month treatment-free interval from all adjuvant treatment.

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The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

The technology is very similar to using trastuzumab, and will be given concomitantly with it. All the mechanisms for delivery of IV monoclonal antibodies are well worked out; the only issue will be that delivery will take longer adding at least one hour to each delivery time.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

Except for apply the same criteria as in the trial, we are not aware of the development of informal or formal starting or stopping rules.

In view of the fact that the majority of the patients in the CLEOPATRA Trial had NOT received trastuzumab or any other anti-HER2 directed therapy in adjuvant setting before relapsing and going into the trial. The 12 month treatment-free interval is likely to mean that (even in those patients who do receive trastuzumab in the adjuvant setting) patients remain sensitive to HER2 directed therapy. It is likely that patients who are *a priori* resistant to trastuzumab, and those who develop resistance during their adjuvant treatment, would relapse within the 12 months after completion of therapy, and therefore would not fulfil the criteria for Pertuzumab treatment.

The unanswered question is whether metastatic disease in patients who have received adjuvant HER2-directed therapy (mostly trastuzumab), has changed its biological nature and become HER2-ve. In the trial, since over 85% of patients had not received previous HER2-directed therapy, this is unlikely to be the case. However in the environment in which the technology will be delivered in 2013 onwards, the majority of patients will have received HER2-directed therapy as an adjuvant treatment.

The possibility of a biological change in the nature of HER2+ve breast cancer at relapse is evidenced by the change in the shape of the survival curves (progression-free and overall survival) from the 8 year FU of the HERA trial reported recently. The original HERA reports demonstrated an early and dramatic improvement in DFS and OS. This report gives longer term FU and also examines 12 versus 24 months (12 months shows no additional benefit). The survival curves for treated patients shows a small but gradual year-on-year increase in relapses. However the shape of the curve has a very gradual slope, much more similar to hormone receptor positive breast cancer.

The biological question is – Has all HER2+ve disease been eradicated leaving a more indolent breast cancer population subgroup? The effectiveness of dual HER2-directed therapy will be significantly dependent on the answer to this question.

Pertuzumab added to trastuzumab and docetaxel, as evidenced by the CLEOPATRA study, provides a significant improvement in firstline metastatic therapy for HER2+ve breast cancer, previously untreated with HER-directed therapy.

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However in 2013, the majority of our patients in this category will have received previous trastuzumab.
Should we consider biopsy of metastatic disease to confirm persisting HER2+ve status?

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice.
Yes, in broad terms. Increasingly the majority of patients will have received neo/adjuvant trastuzumab, rather than in the trial where it was the minority. Although the trial presents results broken down into the subgroup who had received previous trastuzumab, this subgroup is only 88 patients, and represents only 10-11% of the trial population.

Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting?
The eligibility criteria of a 12 month DFI should probably be maintained in clinical practice if pertuzumab use is accepted in this NICE appraisal.

What, in your view, are the most important outcomes, and were they measured in the trials?
Disease-free survival is an important outcome in metastatic breast cancer trials. In a disease for which there is available many subsequent lines of treatment, overall survival without control of crossover to active treatment, becomes a somewhat meaningless outcome measure. The primary endpoint was independently assessed disease-free survival, which we believe is the most appropriate in metastatic breast cancer.

If surrogate measures of outcome were used, do they adequately predict long-term outcomes?
This trial restricted the use of cross-over, and it was not allowed until the primary endpoint analysis had been published. In that situation when the cross-over to pertuzumab of the control arm is likely to be minimal, the disease-free survival should predict overall survival. This information is now available and a six month DFS advantage, translates into a six month overall survival advantage...

What is the relative significance of any side effects or adverse reactions?
No increase in cardiac problems was found. Some increase in non-life-threatening and temporary side effects. Relatively insignificant.

In what ways do these affect the management of the condition and the patient's quality of life?
Not significantly.

Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?
No

Any additional sources of evidence

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Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

A manuscript describing overall survival in the CLEOPATRA study has been prepared and the contents may be made available to NICE appraisals committee. The manuscript has been published – Swain SM et al. Pertzumab, trastuzumab and docetaxel for HER2-positive breast cancer (CLEOPATRA Study): overall survival results from a randomised double-blind, placebo-controlled phase 3 study Lancet Oncology 2013 May;14(6):461-71

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within
3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition?
Patients would benefit in terms of disease-free and probably overall survival from pertuzumab.

Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?
No significant increase in training. Only resources would increase pharmacy and delivery in chemotherapy day unit facilities.

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Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed; No exclusions on these grounds
- **could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;** No
- **could lead to recommendations that have any adverse impact on people with a particular disability or disabilities**. No

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.
N/A
Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

No additional information