NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Bevacizumab in combination with capecitabine for the first-line treatment of metastatic 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:

[redacted] **submitting comments on behalf of the:**

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

Comments coordinated by [redacted], University of Cambridge Department of Oncology and Cambridge University Hospitals NHS Foundation Trust

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)?

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

How is the condition currently treated in the NHS?

Firstline treatment of metastatic breast cancer in the NHS depends on (i) the type of breast cancer (ER status and HER2 status); (ii) the extent of metastatic disease (loco-regional recurrence, bone only disease, bone / liver / and other visceral metastases); and (iii) the general medical health and age of the patient.
For ER positive patients without liver metastases, hormonal treatments would be used. For ER positive patients with liver and lung metastases who are more elderly treatment with single agent capecitabine would be the standard.
For younger women with liver metastases (ER+ / -) taxanes would be used.
For HER2 +ve patients Herceptin is used in combination with non-anthracycline-containing chemotherapy.

It is our understanding that this application concerns Bevacizumab in combination with capecitabine in first line metastatic breast cancer in younger women with aggressive breast cancer, requiring chemotherapy (liver / lung metastases), in circumstances where the patient has already received taxanes in the adjuvant setting.

Is there significant geographical variation in current practice?
Practice guidelines for metastatic breast cancer are well established, and on the whole uniform throughout the NHS. There are recently published UK Guidelines for the management of metastatic breast cancer (Coleman et al. UK Guidenace Document: Treatment of Metastatic Breast Cancer. Clin Oncol (R Coll Radiol) 2011 Nov 8. [Epub ahead of print]). There is increasing rationalisation of current practice with Cancer Network Site Specific Breast Cancer groups working in parallel up and down the country.

Are there differences of opinion between professionals as to what current practice should be?
There will always be some variation in professional opinion in this difficult area of practice. However there is broad agreement among breast cancer specialists that for patients with triple negative breast cancer, with aggressive visceral disease and limited current treatment options, the case for incorporating bevacizumab into first-line treatment is strong. Following a meta-analysis of bevacizumab trials in advanced breast cancer this case has been considerably strengthened (O'Shaughnessy J et al. A meta-analysis of overall survival data from 3 randomised trials of bevacizumab and first-line chemotherapy for patients with metastatic breast cancer. J Clin Oncol 2010; 28(15):1005.)

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What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages? Are there any subgroups of patients with the condition who have a different prognosis from the typical patient?

For the specific subgroup mentioned above there are few alternatives. For triple negative patients with visceral disease and high tumour burden, who have already received anthracyclines and taxanes in the adjuvant setting, other chemotherapy options are: weekly paclitaxel, platinum-based regimens, vinorelbine, gemcitabine and oral capecitabine alone. There is significant evidence that bevacizumab and capecitabine (where docetaxel has been used before) will improve outcomes in this subgroup.

(1. Miles DW, et al. Phase III study of bevacizumab plus docetaxel compared with placebo plus docetaxel for the first-line treatment of human epidermal growth factor receptor 2-negative metastatic breast cancer. J Clin Oncol 2010 Jul 10;28(20):3239-47. 2. Gray R. Independent review of E2100: a phase III trial of bevacizumab plus paclitaxel versus paclitaxel in women with metastatic breast cancer. J Clin Oncol 2009; 27(30): 4966-72. 3.Robert NJ, et al. RIBBON-1: randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab for first-line treatment of human epidermal growth factor receptor 2-negative, locally recurrent or metastatic breast cancer. J Clin Oncol 2011 Apr 1;29(10):1252-60.)

Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?
As discussed above the subgroup mentioned would benefit significantly and would not be put at risk by the technology.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics?
Specialist clinics.

Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?
The technology would increase the work of specialist nurses within the cancer centres and units within the UK. This would not be a substantial increase and could be absorbed within the present delivery of complex cancer treatments with marginal increase in costs for delivery.

If the technology is already available, is there variation in how it is being used in the NHS?
The technology is available through the Cancer Drug Fund in England, and it is our understanding that the majority of Networks have requested bevacizumab in this subgroup and indication.
Is it always used within its licensed indications? Yes. If not, under what circumstances does this occur? Not applicable

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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.

Coleman RE, et al. UK Guidance Document: Treatment of Metastatic Breast Cancer. Clin Oncol (R Coll Radiol) 2011 Nov 8. [Epub ahead of print]. This publication is attached to this document and we quote the relevant section below:

Three randomised trials in first-line chemotherapy for HER2-negative advanced breast cancer have been completed (E2100, AVADO and RIBBON-1). These trials have consistently shown that bevacizumab improves response rates to chemotherapy and the time to progression. Effects were consistent across a range of chemotherapy treatments, including taxanes, anthracyclines and capecitabine. To date, no significant effect on overall survival has been observed. The place of bevacizumab in breast cancer remains controversial and the agent is no longer recommended by the Food and Drugs Administration in the USA. The evaluations of cost-effectiveness of bevacizumab in advanced breast cancer result in quality adjusted life year costs that lie well above the usual threshold used by NICE in their technology assessments. However, for patients with triple negative breast cancer, with aggressive visceral disease and limited current treatment options, the case for incorporating bevacizumab into first-line treatment is stronger following a meta-analysis of bevacizumab trials in advanced breast cancer [32]. Although not NICE approved, many strategic health authorities in England have agreed to make bevacizumab and paclitaxel available for this category of patients through the Cancer Drugs Fund.

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?
Bevacizumab is already widely used in other indications, and within the context of clinical trials. The majority of cancer specialists and their teams are well used to this technology and its safe use within the NHS.

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.
The appropriate subgroup has been discussed above. The technology would be used first line in this group. At the point of starting treatment patients would have progressive disease. Stabilisation of disease, and partial response (i.e. clinical benefit0 would be indications to continue. Progressive disease would be the indication to stop, along with lack of tolerability and severe side effects.

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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.
Clinical trials reflect clinical practice in this technology. The AVADO included patients from the UK and my own centre.

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?
Yes

What, in your view, are the most important outcomes, and were they measured in the trials?
Prolongation of disease-free survival. There was a degree of cross-over, and therefore the overall survival statistic is potentially less than if cross-over was not allowed.

If surrogate measures of outcome were used, do they adequately predict long-term outcomes?
Not applicable. Prolongation of clinical benefit and disease control is the most appropriate endpoint in my opinion for these new agents introduced into the metastatic setting with cross-over allowed after initial randomisation.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?
There is now much data on the safety and toxicities of bevacizumab, from clinical trials and clinical practice internationally in a variety of solid malignancies. There are some recognised side effects (reduction in cardiac function, thrombosis and haemorrhage) which are rare and require the drug to be stopped. Close safety monitoring is part of treatment, and for the vast majority of patients bevacizumab is very well tolerated given in combination with chemotherapy.

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.
There has been a meta-analysis performed by Roche which we could not find in the recent published literature, looking at the particular subgroups and benefit. We should imagine this is in their submission.

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? **Would NHS staff need extra education and training?**
It is our impression that all Cancer Centres and Cancer Units are familiar with the use of bevacizumab. Where they are not then Roche would be able to run educational courses and visit the units for educational purposes.
Would any additional resources be required (for example, facilities or equipment)?
There would be some increase in time, facilities, day unit chemotherapy facilities use. By limiting the approval to a subgroup, this would mean that the extra resource use would be marginal.

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Equality

Are there any issues that require special attention in light of the NICE's duties to have due regard to the need to eliminate unlawful discrimination and promote equality and foster good relations between people with a characteristic protected by the equalities legislation and others?
Not to our knowledge