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

Response to consultee and commentator comments on the draft remit and draft scope

Comment 1: the draft scope

Section	Consultees	Comments	Action
Background information	Breakthrough Breast Cancer	The draft scope states that "there were over 45,000 women and around 300 men newly diagnosed with breast cancer in England and Wales during 2008." This figure apparently includes cases of ductal carcinoma in situ (DCIS). As the usual figure cited for England and Wales[1] is "over 42,000" and does not include DCIS it should be made clear that this number includes cases of DCIS to avoid confusion. The sentence on the number of breast cancer patients who will eventually develop metastatic breast cancer should be slightly changed to improve accuracy: "…it is estimated that around 35% of those presenting with early or localised breast cancer will develop metastatic breast cancer in the 10 years following diagnosis. [Secondary Breast Cancer Taskforce (2007). Stand up and be counted: the need for the collection of data on incidence of secondary breast cancer and survival. Breast Cancer Care.] [1] e.g. on the Cancer Research UK "Breast cancer: UK incidence statistics" website at http://info.cancerresearchuk.org/cancerstats/types/breast/incidence/	Comment noted. The scope has been amended to state that: "there were over 42,000 women and around 300 men newly diagnosed with breast cancer in England and Wales during 2008." The sentence on the number of breast cancer patients who will eventually develop metastatic breast cancer has been changed to: "…it is estimated that around 35% of those presenting with early or localised breast cancer will develop metastatic breast cancer in the 10 years following diagnosis."

Section	Consultees	Comments	Action
	NCRI/RCP/RCR /ACP/JCCO	No comment.	Comment noted.
	Roche Products Ltd	No comment.	Comment noted.
The technology/ intervention	Breakthrough Breast Cancer	The description of the technology appears to be accurate.	Comment noted.
	NCRI/RCP/RCR /ACP/JCCO	No comments.	Comment noted.
	Roche Products Ltd	Yes	Comment noted.
Population	Breakthrough Breast Cancer	The population appears to be appropriately defined. The mode of action for bevacizumab, unlike many other treatments, is not specific to a particular type of tumour. This may be of particular benefit in patients with forms of breast cancer that have more limited treatment options, such as those with triple negative breast cancer as they have no other biological therapies available to them.	Comment noted. Bevacizumab will be appraised within its licensed indication. The marketing authorisation for bevacizumab is for the first-line treatment of metastatic breast cancer. The population within the scope reflects the population within the pivotal trial (RIBBON 1). The 'Other considerations' section of the scope specifies that potential subgroups such as by hormone receptor status will be considered if the available evidence allows.

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	NCRI/RCP/RCR /ACP/JCCO	No comments.	Comment noted.

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	Roche Products Ltd	Yes. We believe the population under consideration would be best represented by those patients in the RIBBON-1 trial previously treated with a taxane in an adjuvant setting (according to NICE CG80, this criteria would also require that an anthracycline has already been considered and is not appropriate in the 1st line metastatic setting).	Comment noted. The summary of product characteristics specifies that: "Patients who have received taxane and anthracycline-containing regimens in the adjuvant setting within the last 12 months should be excluded from treatment with bevacizumab in combination with capecitabine." The description of the population under consideration in the scope has been amended for further clarity to: Adults with HER2-negative metastatic breast cancer previously untreated in the metastatic setting: - for whom treatment with other chemotherapy options, including taxanes or anthracyclines, is not considered appropriate and - who have not received taxane or anthracycline-containing regimens in the adjuvant setting within the last 12 months

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Comparators	Breakthrough Breast Cancer	The comparators appear to be appropriate.	Comment noted.
	NCRI/RCP/RCR /ACP/JCCO	Appropriate comparators of capecitabine or vinorlebine, and this will be an increasing group of patients who relapse after adjuvant anthracyclines+taxanes. We note that as the treatment is indicated more than a year after completing adjuvant taxanes and/or anthracyclines, re-treatment with a taxane is often considered. For those who haven't had a taxane in the adjuvant setting then it is unlikely that a taxane will be contraindicated. For the scope to say that it is when taxanes not appropriate gives a very small potential population of patients.	Comment noted. The comparators listed in the scope reflect the marketing authorisation, which states that bevacizumab in combination with capecitabine only as first-line treatment of patients with metastatic breast cancer in whom treatment with other chemotherapy options, including taxanes or anthracyclines, is not considered appropriate.
	Roche Products Ltd	Market research data (IMS Patient Chart Audit, 2011) shows that vinorelbine monotherapy is rarely used in this setting (1% of all first line HER2 negative patients) and therefore is not considered a standard of care.	Comment noted. The NICE clinical guideline for advanced breast cancer (CG81) currently recommends vinorelbine (or capecitabine) as a second or third-line monotherapy for patients with advanced breast cancer who are not suitable for anthracyclines.

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Outcomes	Breakthrough Breast Cancer	These outcome measures will capture the most important benefits and harms of the technology. However, it is important that the emphasis is placed on patient quality of life since metastatic breast cancer is a life limiting condition. For patients with metastatic breast cancer the importance of quality of life should not be underestimated. Access to the treatments that will give them the chance of better progression free survival and improved quality of life to spend more quality time with their friends and families is very important.	Comment noted.
	NCRI/RCP/RCR /ACP/JCCO	Subgroup analysis by ER status might be helpful.	Comment noted. Potential subgroups such as by histology and hormone receptor status (which would include ER status) have been included in the 'Other considerations' section of the scope.
	Roche Products Ltd	Yes	Comment noted.
Economic analysis	Breakthrough Breast Cancer	No comment.	Comment noted.
	NCRI/RCP/RCR /ACP/JCCO	The health economics will need careful consideration as the delivery costs (introducing an intravenous therapy to a previously only oral regimen of capecitabine) as well as the drug costs will need to be considered.	Comment noted.
	Roche Products Ltd	No comment.	Comment noted.
Equality and Diversity	Breakthrough Breast Cancer	No comment.	Comment noted.

Section	Consultees	Comments	Action
	NCRI/RCP/RCR/ACP/JCCO	No comment.	Comment noted.
	Roche Products Ltd	No special equality considerations.	Comment noted.
Other considerations	Breakthrough Breast Cancer	Impacts on blood pressure and circulatory problems have been identified as two significant adverse effects of bevacizumab. Will there be criteria to identify patients with pre-existing or at high risk of developing blood pressure and/or circulatory problems? Will these patients need to be considered as a subgroup?	Comment noted. The potential impacts on blood pressure and circulatory problems will be captured under 'adverse effects of treatment' in the 'Outcomes' section of the scope.
	NCRI/RCP/RCR/ACP/JCCO	For impact/endpoints members of the CSG have of course recently commented on the area: *BMJ* 2011; 343:d4946 doi: 10.1136/bmj.d4946 (Published 3 August 2011)	Comment noted.
	Roche Products Ltd	We suggest that patients previously treated with taxanes in an adjuvant setting be considered for the reasons stated above.	Comment noted.
Questions for consultation	Breakthrough Breast Cancer	There needs to be a range of safe and effective treatments available in the metastatic setting as not all will be suitable for individual patients. Bevacizumab offers a novel mechanism of action that may benefit breast cancer patients whose options are otherwise limited (such as patients with triple negative breast cancer). For patients with metastatic breast cancer access to treatments that can offer improved progression free survival and better quality of life for longer is crucial. No further comments.	Comment noted.

Section	Consultees	Comments	Action
	NCRI/RCP/RCR /ACP/JCCO	No comment.	Comment noted.
	Roche Products Ltd	Yes, this is an innovative technology in breast cancer therapy, as it has a novel mechanism of action which provides increased efficacy in combination with cytotoxic chemotherapy, with a limited burden of side-effects and a different tolerability profile from cytotoxic chemotherapy. There are also limited treatment options for patients in whom treatment with anthracycline and taxanes are not considered appropriate.	Comment noted.
Additional comments on the draft scope.	Breakthrough Breast Cancer	No further comments.	Comment noted.
	NCRI/RCP/RCR /ACP/JCCO	As far as scope is concerned this seems reasonable. Although it would be sensible to exclude at this early stage those with a contraindication to bevacizumab (as per the RIBBON-1 trial): ie: known CNS metastases; blood pressure greater than 150/100 mmHg; unstable angina; New York Heart Association class II or greater congestive heart failure; history of myocardial infarction within 6 months; history of stroke or transient ischemic attack within 6 months; clinically significant peripheral vascular disease; evidence of bleeding diathesis or coagulopathy; history of abdominal fistula, GI perforation, or intra-abdominal abscess within 6 months.	Comment noted. These contraindications to bevacizumab are specified in the summary of product of characteristics and will be considered by clinicians when initiating treatment for an individual patient.
	Roche Products Ltd	No comment.	Comment noted.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

- Healthcare Improvement Scotland
- Marie Curie Cancer Care
- Royal College of Nursing