Appendix C

National Institute for Health and Clinical Excellence

Bevacizumab in combination with a taxane for the first-line treatment of metastatic breast cancer

Table of responses to consultee and commentator comments on the draft scope (pre-referral)

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	Breakthrough Breast Cancer, Breast Cancer Care	It would be appropriate to refer this topic to NICE for appraisal.	Comment noted. It was agreed at the scoping workshop that an appraisal of bevacizumab in combination with a taxane was appropriate.
	Roche Products	This is an appropriate topic.	Comment noted. It was agreed at the scoping workshop that an appraisal of bevacizumab in combination with a taxane was appropriate.
	United Kingdom Oncology Nursing Society (UKONS)	I feel this is an appropriate topic	Comment noted. It was agreed at the scoping workshop that an appraisal of bevacizumab in combination with a taxane was appropriate.

Section	Consultees	Comments	Action
Wording	Breakthrough Breast Cancer, Breast Cancer Care	The wording of the remit does reflect the issues of clinical and cost effectiveness about this technology that NICE should consider.	Comment noted. It was agreed at the scoping workshop that the final remit should be to appraise the clinical and cost effectiveness of bevacizumab in combination with a taxane within its licensed indication for the first line treatment of HER-2 negative metastatic breast cancer.
	Roche Products	The wording of the remit is appropriate. However, we would like to highlight a small discrepancy: the cover letter states that "The National Institute for Health and Clinical Excellence (NICE) has been invited to carry out an appraisal of bevacizumab in combination with docetaxel for the first-line treatment of metastatic breast cancer." It would be useful to confirm that the language in the cover letter is incorrect if the remit is indeed bevacizumab in combination with any taxane.	Comment noted. It was agreed at the scoping workshop that the final remit should be to appraise the clinical and cost effectiveness of bevacizumab in combination with a taxane within its licensed indication for the first line treatment of HER-2 negative metastatic breast cancer.
	UKONS	Yes	Comment noted. It was agreed at the scoping workshop that the final remit should be to appraise the clinical and cost effectiveness of bevacizumab in combination with a taxane within its licensed indication for the first line treatment of HER-2 negative metastatic breast cancer.

Section	Consultees	Comments	Action
Timing Issues	Breakthrough Breast Cancer, Breast Cancer Care	As metastatic breast cancer is not curable it is essential that effective treatment options which could delay progression or improve survival are made available to this patient group as quickly as possible. Patients typically have limited treatment options in the metastatic setting and therefore the need for safe and effective new medicines in this patient group is relatively urgent. There needs to be a range of treatments available as not all will be suitable to individual patients. Bevacizumab is a treatment that may benefit breast cancer patients whose options have previously been limited.	Comment noted. Following the final referral from the Department of Health, the appraisal will be planned into the technology appraisal schedule to allow as timely as possible guidance to the NHS.
	UKONS	Timings appear accurate	Comment noted. No action required.

Section	Consultees	Comments	Action
Additional comments on the draft remit	National Cancer Research Institute (NCRI) Breast Clinical Studies Group (CSG), Royal College of Physicians (RCP), Royal College of Radiologists (RCR), Association of Cancer Physicians (ACP), Joint Council of Clinical Oncology (JCCO)	The remit is appropriate	Comment noted. No action required.

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	Breakthrough Breast Cancer, Breast Cancer Care	The background information is largely accurate however, the first statistic could more precisely be written as 'There were over 40,000 women newly diagnosed with breast cancer in England and Wales during 2005'. The draft scope estimates that up to 50% of women with early or localised breast cancer will eventually develop metastatic breast cancer, however this figure is not referenced or dated. This may not be an accurate figure for calculating costs as data on the incidence of advanced and metastatic breast cancer is not currently collected nationally in the UK. We would welcome clarification regarding this statistic. NICE technology appraisal guidance No. 116 also recommends the combination of docetaxel plus capecitabine.	Comment noted. The scope has been amended accordingly. This figure has been used in previous appraisals of metastatic breast cancer. No more accurate estimates have been provided. No changes to the scope made. NICE technology appraisal 116 appraised gemcitabine in combination with paclitaxel for the treatment of metastatic breast cancer. No recommendations were issued for docetaxel in combination with capecitabine. The relevant comparators are stated in the scope.
	UKONS	Appears accurate	Comment noted. No action required.

Section	Consultees	Comments	Action
	NCRI Breast CSG, RCP, RCR, ACP, JCCO	The vast majority of patients in the UK receive an anthracycline as adjuvant therapy. Very few patients presenting with metastatic disease will therefore receive an anthracycline as standard first line treatment. An increasing population also receive a taxane (prediminantly docetaxel) as adjuvant therapy. This is relevant regarding clinician choice of taxane in first line MBC treatment (see later comment re consideration for weekly paclitaxel as an appropriate comparator for this appraisal).	Comment noted. No action required.
The technology/ intervention	Breakthrough Breast Cancer, Breast Cancer Care	The description of the technology mentions studies in only HER2 -ve patients. However, clinical trials are currently ongoing in both HER2 -ve and HER2 +ve patients. An example of a trial in HER2 +ve patients is: A Study of Avastin (Bevacizumab) in Combination With Herceptin (Trastuzumab)/Docetaxel in Patients With HER2 Positive Metastatic Breast Cancer (NCT 00391092).	Comment noted. It was agreed at the scoping workshop that this appraisal would focus only on people with HER-2 negative metastatic breast cancer.
	Roche Products	We would like to clarify that no standard economic evidence was submitted by Roche in support for TA147. However Roche did provide a full clinical submission and alternative economic submission as discussed and agreed with NICE at a meeting on 21st September 2007.	Comment noted. The scope has been amended to indicate that no economic submission was received.
	UKONS	Yes	Comment noted. No action required.
	NCRI Breast CSG, RCP, RCR, ACP, JCCO	Accurate	Comment noted. No action required.

Section	Consultees	Comments	Action
Population	Breakthrough Breast Cancer, Breast Cancer Care	People with HER2 positive breast cancer will need consideration as it is necessary to determine if this group will benefit from Bevacizumab. This could be important for any patients in whom Herceptin is not considered to be an appropriate treatment because of the risk of cardiac toxicity.	Comment noted. It was agreed at the scoping workshop that the population in the appraisal should be people with untreated metastatic HER-2 negative breast cancer for whom anthracyclines are not appropriate.
	Roche Products	This should instead read: "people requiring 1st line treatment for metastatic HER-2 negative breast cancer". It should be noted that one of the bevacizumab trials did not exclude HER-2 positive patients. In addition, we would like to focus strictly on patients requiring 1st-line therapy for whom an anthracycline is unsuitable.	Comment noted. It was agreed at the scoping workshop that the population in the appraisal should be people with untreated metastatic HER-2 negative breast cancer for whom anthracyclines are not appropriate.
	UKONS	Yes	Comment noted. No action required.
	NCRI Breast CSG, RCP, RCR, ACP, JCCO	In the reported first line trials there are no clinical patient subgroups that are clearly differentiated as having particular benefit from the technology. There was a trend in favour of improved benefit for patients receiving adjuvant taxanes.	Comment noted. It was agreed at the scoping workshop that the population in the appraisal should be people with untreated metastatic HER-2 negative breast cancer for whom anthracyclines are not appropriate.

Section	Consultees	Comments	Action
Comparators	Breakthrough Breast Cancer, Breast Cancer Care	NICE Advanced breast cancer clinical guidelines (CG81) recommend hormone therapy as first line treatment for people with metastatic breast cancer. It might be useful to include hormone therapy as a comparator for economic costings. When anthracyclines are not suitable docetaxel plus capecitabine is also recommended (NICE TA 116). Bevacizumab in combination with a taxane plus trastuzumab is currently being compared against a taxane plus trastuzumab in HER2 positive patients and should be considered (NCT 00391092).	Comment noted. At the scoping workshop it was agreed that paclitaxel monotherapy should be included as a comparator and that anthracycline based regimens should be excluded as a comparator. It was agreed that hormone therapies should not be considered a comparator as these would be given in addition to other treatments. NICE technology appraisal 116 appraised gemcitabine in combination with paclitaxel for the treatment of metastatic breast cancer. No recommendations were issued for docetaxel in combination with capecitabine. The relevant comparators are stated in the scope.
	Roche Products	From comment above, focusing on 1st line therapy for patients when anthracyclines are not suitable - the comparator of anthracycline-based regimens should be removed. In addition to current list of taxane-based comparators, we would like to add paclitaxel as monotherapy (since this is an important head to head comparator for bevacizumab).	Comment noted. At the scoping workshop it was agreed that paclitaxel monotherapy should be included as a comparator and that anthracycline based regimens should be excluded as a comparator.

Section	Consultees	Comments	Action
	NCRI Breast CSG, RCP, RCR, ACP, JCCO	Weekly paclitaxel is also used as first line therapy for patients who are unsuitable for treatment with anthracyclines but where the toxicity of docetaxel every three weeks at full dose is of concern, or where a patient has received docetaxel in the adjuvant setting. Therefore weekly paclitaxel should be one of the comparators used in the evaluation of the paclitaxel / bevacizumab combination'.	Comment noted. At the scoping workshop it was agreed that paclitaxel monotherapy should be included as a comparator
Outcomes	Breakthrough Breast Cancer, Breast Cancer Care	For newly diagnosed advanced or metastatic patients it will be incredibly important to have a first line treatment that is effective and tolerable.	Comment noted. No action required.
	UKONS	Yes and QOL is the most important aspect	Comment noted. Health related quality of life is included in the outcomes listed in the scope
	NCRI Breast CSG, RCP, RCR, ACP, JCCO	Survival at one year should be considered as an endpoint in the evaluation of this technology. For patients with aggressive disease, survival at one year may capture differences in treatment better than overall survival.	Comment noted. Survival is included in the outcomes listed in the scope. This does not exclude the use of survival at one year.
Economic analysis	Breakthrough Breast Cancer, Breast Cancer Care	The economic analysis appears to be appropriate.	Comment noted. No action required.

Section	Consultees	Comments	Action
	NCRI Breast CSG, RCP, RCR, ACP, JCCO	When a new treatment is added to an existing therapy and results in longer disease-free survival, the new treatment combination is administered for a longer duration, because the patients are benefitting from this. However, this creates an imbalance with regards to the total costs of the interventions favouring the less successful therapy option. This needs to be given due consideration in the economic evaluation.'	Comment noted. The appraisal will be carried out in accordance with the NICE guide to the methods of technology appraisal. No changes to the scope required.
Equality and Diversity	Breakthrough Breast Cancer, Breast Cancer Care	The scope does not appear to promote discrimination.	Comment noted. No action required
	NCRI Breast CSG, RCP, RCR, ACP, JCCO	The paclitaxel / bevacizumab combination is currently being widely used in the UK in patients with private health insurance leading to inequality of access to care based on the ability to pay for private health insurance.	Comment noted. No action required.
Other considerations	Breakthrough Breast Cancer, Breast Cancer Care	The are no additional issues for consideration.	Comment noted. No action required.
Questions for consultation	Breakthrough Breast Cancer, Breast Cancer Care	Responses to the other questions for consultations are covered in the draft scope comments.	Comment noted. No action required.

Section	Consultees	Comments	Action
Additional comments on the draft scope.	None received		

Comment 4: Regulatory issues

Section	Consultees	Comments		Action
Remit	Roche Products Limited	The wording is appropriate for the proposed marketing authorisation.		Comment noted.
Current or proposed marketing authorisation	Roche Products Limited	*What are the current indications for the technology?*	Avastin (bevacizumab) in combination with fluoropyrimidine-based chemotherapy is indicated for treatment of patients with metastatic carcinoma of the colon or rectum. Avastin in combination with paclitaxel is indicated for first-line treatment of patients with metastatic breast cancer. Avastin, in addition to platinum-based chemotherapy, is indicated for first-line treatment of patients with unresectable advanced, metastatic or recurrent non-small cell lung cancer other than predominantly squamous cell histology. Avastin in combination with interferon alfa-2a is indicated for first line treatment of patients with advanced and/or metastatic renal cell cancer.	Comment noted.
		What are the planned indications for the technology?	***CIC information removed***	

Section	Consultees	Comments		Action
		FOR EACH PLANNED INDICATION:		
		What is the target date (mm/yyyy) for regulatory submission?	***CIC information removed***	
		Which regulatory process are you following?	***CIC information removed***	
		What is the anticipated date (mm/yyyy) of CHMP positive opinion (if applicable) and regulatory approval?	***CIC information removed***	

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

1. RICE - The Research Institute for the Care of Older People
2. Sanofi-Aventis
3. Royal College of Nursing
4. Department of Health