NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

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

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Comments received from consultees

Consultee	Comment	Response
Roche	**1. Has all of the relevant evidence been taken into account?** ***1.1. The relevance of capecitabine dose to UK clinical practice*** *"The Committee noted that the dose of capecitabine in the trial was 1000 mg/m^2 rather than the licensed dose of 1250 mg/m^2. The Committee was aware that the dose of capecitabine used in UK practice was often lower in older patients and those with poor performance status, but observed that all patients in the RIBBON-1 trial were of ECOG performance status 0 or 1 and the median age was 56 years. It therefore considered the licensed dose of 1250 mg/m^2 capecitabine would be more appropriate. The Committee concluded that the trial may have limited relevance to clinical practice in the UK." (section 4.3)* **COMMENT:** More than 40 UK patients entered the capecitabine arm of the RIBBON-1 study, at 4 sites in England and Wales, to be randomised between placebo or bevacizumab. The full study protocol was submitted to both main and local ethics committees and was approved by all 5 committees. This approval would never have been granted unless the ethics committees were convinced by their local clinicians that all the patients randomised to 1000mg/m^2 capecitabine plus placebo would receive the UK standard of care therapy for their disease. This further reinforces the acceptability of the 1000 mg/m^2 bd dose in UK clinical practice.	Comment noted. The generalisability of the trial to UK clinical practice was discussed at the second committee meeting. Section 4.4 of the FAD has been amended in line with comments from the clinical specialists and committee discussions.
	1.2. The presentation of probabilistic sensitivity analysis results *"The Committee noted that an ICER based on probabilistic sensitivity analysis had not been reported and so the deterministic ICERs presented should be treated with caution."(section 4.8)* **COMMENT:** Our submission included the results of a PSA in the form of a cost-effectiveness plane and cost-effectiveness acceptability curve in Section 6.6.8 (Figures 21 and 22 on pages 134 and 135). For information, the mean ICER of 1000 iterations of the PSA was £80,073 (mean incremental costs = £40,161 (95% CI, £36,703- £45,079), mean incremental QALYs = 0.502 (95% CI, 0.33-0.66)). This is compared to the deterministic base case ICER of £77,318 per QALY (incremental costs = £38,856, incremental QALYs = 0.5034).	Comment noted. This result has been included in section 3.26 of the FAD.

Consultee	Comment	Response
	1.3. The calculation of overall survival in the economic model *"The Committee concluded that the manufacturer's modelled overall survival results could not be considered to be robust."(section 4.10)* **COMMENT:** The decision problem under assessment is for bevacizumab in combination with capecitabine in HER2-negative metastatic breast cancer patients previously untreated in the metastatic setting – thereby covering only the use of bevacizumab in the first-line setting. In the only relevant RCT, there was no control over the therapies available to patients following progression of the disease and since a large number of these patients received bevacizumab in this setting (for which it is unlicensed), we feel it is appropriate to make an adjustment to account for this. However, whilst we remain unconvinced of the arguments put forward concerning the limitations of the method used in the base case model compared to alternatives, we have used the unadjusted survival data from the trial in an alternative scenario analysis provided below. We believe that this alternative economic model provides a robust estimate of the cost-effectiveness of the addition of bevacizumab to capecitabine in mBC as observed in the RIBBON-1 trial. Our original model included information on the therapies received by patients (as well as the treatment durations) in the trial after progression (Table 1), although this information was not used to extrapolate post-progression therapy costs in either treatment arm as they were considered likely to cancel each other out. This assumption is justified somewhat by the observation that the expected difference in costs of therapies received in the PD state is between approximately £130 and £490 per patient in the 2 arms of the trial (Table 2). However, we accept the Committee's concern that the costs of these treatments had not been modelled and provide estimates of the cost-effectiveness of a number of scenarios using survival curves adjusted and un-adjusted for post-progression bevacizumab where the cost of these treatments are included according to observations in RIBBON-1 and likely use in clinical practice in the NHS (Table 3). These changes have been implemented in a revised model which incorporates both the correction to the calculation of utility in the CAPE arm identified by the ERG and the inclusion of terminal care costs as described on p64 of ERG Report Erratum. Although the ERG also described one further alteration to the model, concerning the use of UK-specific patient characteristics to calculate drug costs, this is the subject of a separate comment (2.2 below) and was not included in the revised model.	Comment noted. Section 3.5.34 of the **Guide to the single technology appraisal process** states; *'At the ACD consultation stage, the Centre Director must agree to accept any new evidence before it is submitted. New evidence will only be accepted if it is likely to affect the provisional recommendations in the ACD. The new evidence must be presented as a separate appendix to the comments on the ACD. NICE may need to extend timelines to allow for new evidence to be considered.'* This additional evidence was not verified by the evidence review group (ERG) and was not formally considered at the second appraisal committee meeting as the above conditions for acceptance of new evidence were not met. The committee felt that there was no evidence to alter its conclusion on the most plausible ICER for the appraisal (see FAD section 4.13).

Consultee	Comment	Response
	We believe these results are more robust than those proposed by the ERG and more representative of the cost-effectiveness of the RIBBON-1 trial as observed (Scenario 6, ICER = £92,658), as well as for patients receiving bevacizumab in addition to capecitabine in 1L treatment of mBC in the NHS (Scenario 3, ICER = £76,061). In addition, we provide supplementary cost-effectiveness estimates based on the assumption that all patients in the model receive vinorelbine as a second-line therapy until death in agreement with recent clinical guidelines (NICE CG81 2009). This assumption has the effect of increasing monthly supportive care costs in PD from £804 to £1077.38 (£804 + [monthly cost of generic vinorelbine (£77.29) + IV administration (196.09)] from Table 29 on p118 of original submission) and results in an increase in the ICER of approximately £3000 - £4000 for the 2 scenarios considered here (Scenario 4 and 8 in Table 3). *(Tables not included; see manufacturer's original comments)*	
Roche	**2. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** ***2.1. The robustness of the results from the prior taxane subgroup*** *"… However, the Committee noted that previous taxane therapy was not a stratification factor at randomisation and that this subgroup was specified after the trial had begun but before the analysis was completed. The Committee also noted that the overall survival results were based on very small numbers of events: 70 patients in the bevacizumab plus capecitabine arm and 44 patients in the capecitabine plus placebo arm. In addition, the Committee was aware that no statistical adjustments were made to control for multiple testing, thus increasing the risk of chance findings. The Committee noted the ERG's statement that the patients in this subgroup appeared to be younger and healthier than the ITT population. The Committee concluded that the results from the subgroup of patients who were previously treated with a taxane were not robust."(section 4.7)* **COMMENT:** Data from RIBBON-1 demonstrates that patients who had received a prior taxane have extended progression free and overall survival with capecitabine in combination with bevacizumab. The addition of bevacizumab to capecitabine in this large subgroup of patients (n=245) raised their overall survival and PFS above a level found in the ITT population with bevacizumab and capecitabine, thus counteracting the poor prognosis of these patients (Table 1).	Comment noted.

Consultee	Comment	Response
	Whilst the ERG correctly identified that the age and prognostic factors of the prior-taxane subgroup would suggest that they should have a better prognosis than the ITT population, median PFS and OS figures in the control arm of RIBBON-1 highlight that these patients actually experienced worse outcomes. Whilst the prior-taxane subgroup was not pre-stratified, thereby suggesting the possibility that the results are a consequence of data dredging, two additional phase III studies (Gray et al. 2009;Miles et al. 2010; Miller et al. 2007) have demonstrated a similar PFS increase in prior taxane treated patients who have received bevacizumab and chemotherapy compared to chemotherapy alone thereby supporting the convergent validity of a treatment effect of bevacizumab specifically in prior-taxane treatment patients. The AVADO study (Miles et al. 2010) compared placebo plus docetaxel (DOC) against bevacizumab plus docetaxel (BEV+DOC) in first-line therapy of metastatic breast cancer and prior-taxane use was a stratification factor for randomisation. In contrast, the E2100 study (Gray et al. 2009) compared placebo plus paclitaxel (PAC) against bevacizumab plus paclitaxel (BEV+PAC) in first-line therapy of metastatic breast cancer and prior-adjuvant therapy was pre-stratified, as in the RIBBON-1 (Robert et al. 2011) trial. However, despite the lack of this specific stratification for prior-taxane use, the patients previously treated with taxanes in the latter 2 studies were well balanced between the placebo- and bevacizumab-containing arms. The results (Table) demonstrate that incremental PFS and OS in prior taxane treated patients are notably and consistently increased across all three trials, compared to the ITT population, strongly suggesting that these patients, with a particularly poor prognosis and few treatment options, benefit especially from bevacizumab treatment. For example, median OS in prior taxane treated patients not given bevacizumab is between 2 and 9 months worse than the ITT population, whilst survival in prior taxane treated patients receiving bevacizumab is at least as good as that in the ITT. Furthermore, meta-analyses of the hazard ratios for PFS and OS from the 3 studies above are shown in Figure 1 and Figure 2, respectively. These clearly demonstrate the significant improvement in both PFS and OS seen with bevacizumab in such patients, while the improvement in outcomes for patients in the ITT population is considerably less and is non-significant for OS.	The committee considered the observation of beneficial progression free survival from AVADO, E2100 and Ribbon-1, (see section 4.8 of the FAD).

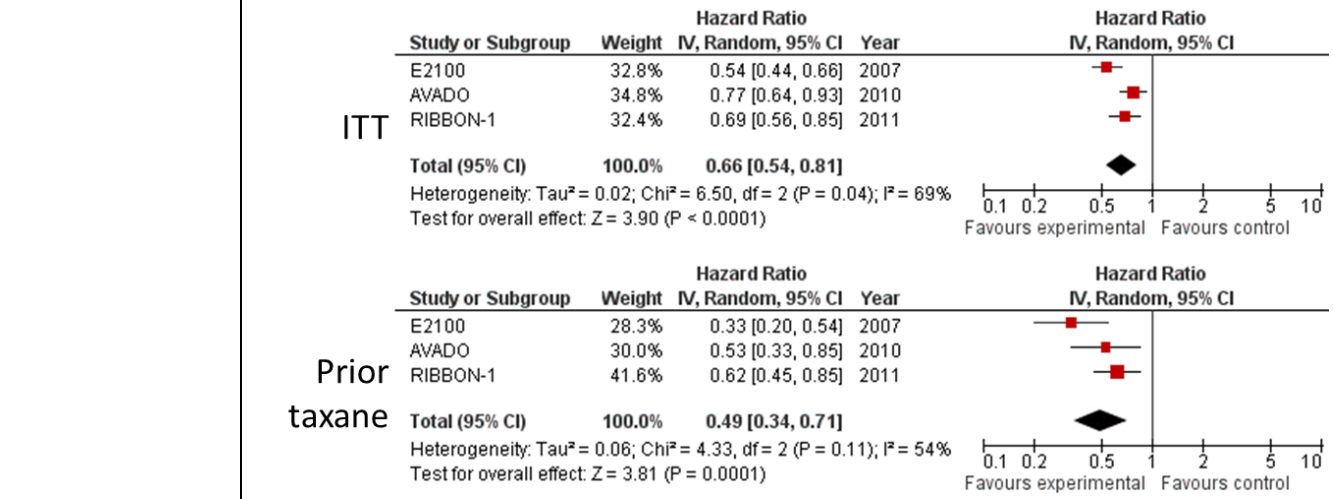
Consultee	Comment	Response

Table 1: ITT and sub group data from 3 trials of bevacizumab in mBC

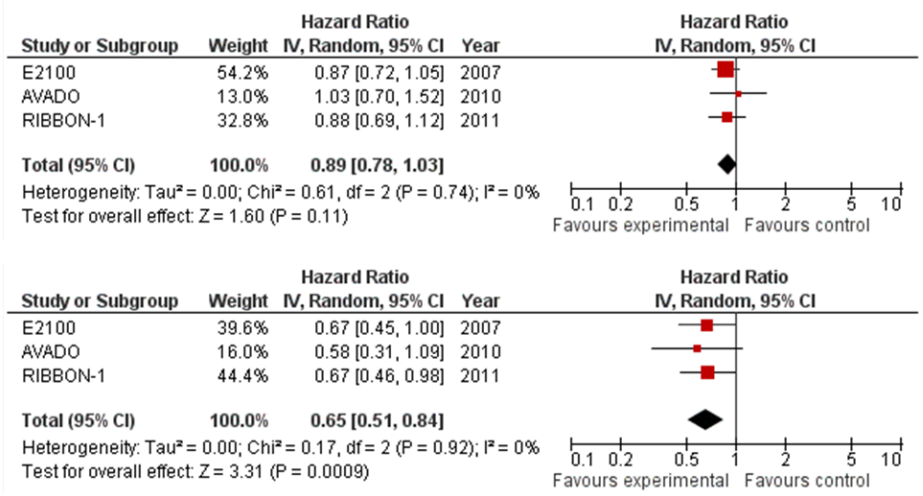
		PFS					
		ITT			Prior Taxane		
		N	Median	Benefit	N	Median	Benefit
E2100	PAC vs BEV+PAC	354/368	5.8 vs 11.3	5.5	68/74	5.8 vs 13.1	7.3
AVADO	DOC vs BEV+DOC	247/241	8.2 vs 10.1	1.9	42/35	6.7 vs 10.3	3.6
RIBBON-1	CAPE vs BEV+CAPE	206/409	5.7 vs 8.6	2.9	84/161	4.2 vs 8.7	4.5

		OS					
		ITT			Prior Taxane		
		N	Median	Benefit	N	Median	Benefit
E2100	PAC vs BEV+PAC	354/368	24.8 vs 26.5	1.7	68/74	17.6 vs 26.3	8.7
AVADO	DOC vs BEV+DOC	247/241	31.9 vs 30.2	-1.7	42/35	22.3 vs 31.6	9.3
RIBBON-1	CAPE vs BEV+CAPE	206/409	22.8 vs 25.7	2.9	84/161	20.5 vs 28.4	7.9

Figure 1: Meta-analysis of PFS hazard ratios from 3 trials of bevacizumab in mBC



Consultee	Comment	Response
	Figure 2: Meta-analysis of OS hazard ratios from 3 trials of bevacizumab in mBC	



An article in the Lancet in 2005 which explored the importance, indications and interpretation of subgroup analysis in randomised controlled trials (Rothwell 2005), states that the best test of the validity of subgroup analyses is not significance, but replication. For example, although an early RCT of coronary artery bypass grafting, suggesting that survival benefit was mainly confined to patients with left main coronary artery disease or three-vessel disease, had only a few hundred patients (Takaro et al. 1976), the observation was biologically plausible and was reproduced in a subsequent trial (European Coronary Surgery Study Group 1982). However, it was not until 20 years later that a pooled analysis of seven RCTs had sufficient power to demonstrate a significant interaction (Yusuf et al. 1994). Similarly, in the metastatic breast cancer indication three phase III RCTs have all demonstrated that patients who have received a taxane in the adjuvant setting gain greater benefit from bevacizumab in combination with chemotherapy for 1st line metastatic treatment than the ITT population. There are a number of possible biological explanations for this observation, including adaptive resistance to earlier taxane therapy and the increased level of angiogenesis which is seen in more aggressive breast tumours. Importantly, in the context of the management of metastatic breast cancer, this greater efficacy of bevacizumab in prior-taxane treated patients enables a subgroup of HER2 negative breast cancer patients to realize the same incremental survival gains as observed following the introduction of trastuzumab in HER2+ positive metastatic breast cancer patients (Marty et al. 2005;Slamon et al. 2001).

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<tr><th>Consultee</th><th>Comment</th><th>Response</th></tr>
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2.2. The re-calculation of drug costs in the economic model

“The Committee noted the adjustments made by the ERG to the economic model:
• <u>basing costs on the distribution of patient body weight and body surface area in a UK-specific cohort of patients rather than using a simple average based on trial data</u>

The Committee concluded that these adjustments were appropriate.” (section 4.9)
COMMENT:
We wish to draw the Committee’s attention to the fact that the reference supplied by the ERG in relation to the “UK-specific cohort of patients” used in this calculation (Sacco et al. 2010) only provides data on the body surface area of cancer patients and can therefore only be used to recalculate the estimated capecitabine dose. This lack of data means that it has not been possible to verify the increase in drug costs in patients receiving bevacizumab (which required information on weight in kg) in combination with capecitabine (reported to be £2,966). The relevant data from that paper and our submission (based on the RIBBON-1 trial) are summarised in Table 2.

Table 2: Comparison of patient body mass index and weight in manufacturer submission and ERG report

<table>
<tr><th></th><th>RIBBON-1</th><th>(Sacco et al. 2010)</th></tr>
<tr><td>Mean BSA</td><td>1.761mg/m^2 (calculated)</td><td>1.75mg/m^2</td></tr>
<tr><td>Mean body weight</td><td>72.1kg</td><td>Not reported</td></tr>
</table>

It is clear that, with respect to the mean BSA of breast cancer patients, the original patient cohort in our model is actually slightly larger than the UK average. Furthermore, we have been unable to reproduce the increase in drug costs reported by the ERG for the capecitabine plus placebo arm (£50 total drug costs) and cannot confirm the validity or appropriateness of these updated calculations (our attempt to incorporate Sacco et al 2010 data in the calculation of drug cost is provided on Sheet “BSA Calculations” of the revised economic model). We would strongly recommend that the Committee treat these adjusted calculations with great caution until more details concerning the methodology and the assumptions used are available.
</td><td>Comment noted. Information on the full calculation of drug cost has been provided by the ERG.</td></tr>
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Consultee	Comment	Response
	2.3. Section 3.6 *"The overall survival results were based on 70 patients in the bevacizumab plus capecitabine arm and 44 patients in the capecitabine plus placebo arm." (section 3.6)* **COMMENT:** The use of "patients" in this sentence should be changed to "events" as the data refer to the number of deaths in a large cohort of 245 patients.	Comment noted. Section 3.7 has been updated to "deaths" rather than "patients".
	2.4. Section 4.10 *"The Committee noted that the rank preserving structural failure time method could be considered to be appropriate in situations when large numbers of patients crossed over as occurred in the RIBBON-1 trial." (section 4.10)* **COMMENT:** We believe the current wording of this sentence is confusing and should be reconsidered to avoid possible ambiguity and doubt concerning the Committee's position on RPSFT in this situation.	The sentence has been reworded in section 4.11 following clarification during the second appraisal committee meeting.
Roche	**3. Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** We are disappointed that the Committee did not accept the prior taxane cohort as a legitimate subgroup of patients (who have a worse prognosis and fewer treatment options than other patients with metastatic disease) despite the evidence we have provided and we hope further analysis presented here, as well as independent clinical advice, may be more compelling.	Comment noted. Section 4.8 of FAD details the Committee's consideration of the prior taxane subgroup.
Department of Health	The Department of Health confirmed they had no substantive comments to make, regarding this consultation.	Comment noted.

Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
Royal College of Physicians (NCRI/RCP/RCR/ACP/JCCO)	**Has all of the relevant evidence been taken into account?** There is only one directly relevant published clinical trial: RIBBON-1, and this has been discussed and analysed in detail. More data available is in the second-line setting: the RIBBON-2 trial (Brufsky et al, J Clin Oncol 29:4286-4293). Whilst not directly applicable this does provide additional information regarding efficacy and tolerability of capecitabine/bevacizumab. However the patient numbers are small and in the second line setting. **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** The summaries of clinical effectiveness appear accurate. Our experts would emphasise the challenge of the treatment of women with triple negative breast cancer for whom there are limited treatment options. In this sub-group of patients could bevacizumab/capecitabine fall within the life-extending, end-of-life treatment category? Certainly in a retrospective analysis of second-line data there was an increase in median PFS in this group of women (6 vs 2.7 months, p=0.0006), and a non-significant improvement in overall survival of 5 months (17.9 vs 12.6 months, p=0.0534) (Brufsky et al, J Clin Oncol 29: 2011 (suppl; abstr 1010)). Regarding applicability to UK clinical practice; capecitabine is not an uncommon choice as first-line treatment for metastatic (HER2 negative) breast cancer: for the reasons outlined (oral, no hair loss). This is even when a taxane has not previously been administered. Some clinicians start at a dose lower than the original licensed dose (often 1000mg/m2 bd) even in fitter patients. Therefore this combination of treatments is of relevance to UK practice. **Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** The evidence reviewed is a sound basis on which to base guidance to the NHS. Our experts wish to emphasise the value of the health state in which a patient is not-progressing as a positive one (congruent with the comments of patient expert, section 4.2). In other words the value of progression-free survival as an outcome measure, particularly give the difficulties with cross-over and interpretation of overall survival data elaborated in the document.	Comment noted. Section 4.14 details the criteria for end-of-life consideration. The committee considered this at the first meeting and concluded that bevacizumab did not fulfil the end of life criteria. The rationale is given in section 4. 15 of the FAD; "*The Committee noted that bevacizumab is licensed for a relatively large population across a range of indications in the treatment of breast, colorectal, renal and non-small-cell lung cancers. Therefore, it does not meet the third criterion of the supplementary advice from NICE that the treatment should be licensed for small populations."* Section 4.4 has been amended in line with the comments from the clinical specialists.

Nominating organisation	Comment	Response
Royal College of Nursing	**Has the relevant evidence been taken into account?** The evidence considered seems comprehensive. **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** We would ask that the summaries of the clinical and cost effectiveness of this appraisal should be aligned to the clinical pathway followed by patients with metastatic breast cancer. The preliminary views on resource impact and implications should be in line with established standard clinical practice. **Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** Nurses working in this area of health have reviewed the recommendations of the Appraisal Committee and do not have any other comments to add. The RCN would welcome guidance to the NHS on the use of this health technology. **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?** None that we are aware of. **Are there any equality-related issues that need special consideration that are not covered in the appraisal consultation document?** We are not aware of any specific issue at this stage. We would ask that any guidance issued should show that an equality impact analysis has been considered and that the guidance demonstrates an understanding of issues relating to all the protected characteristics where appropriate. .	Comment noted. Comment noted. Comment noted. Comment noted Comment noted. The summary table in the FAD highlights that there were no equality issues identified during the scoping and appraisal process. Additionally an equality impact assessment has been completed and will be published on the NICE website with the guidance.

Nominating organisation	Comment	Response
Breakthrough Breast Cancer	Breakthrough Breast Cancer is dedicated to improving and saving lives through breast cancer prevention, early diagnosis, more targeted treatments and better services for everyone affected by breast cancer. This submission reflects the views of Breakthrough, based on our experience of working with people with personal experience of, or who are concerned about, breast cancer. To inform our submission to this consultation, we have consulted with members of our Campaigns & Advocacy Network (Breakthrough CAN) for their views on a range of breast cancer issues. Breakthrough CAN brings together over 1,800 individuals, regional groups and national organisations to take action locally on our national campaigns to secure important improvements to breast cancer research, treatments and services. Through supporting and training members, Breakthrough CAN aims to increase the influence of breast cancer advocates on decisions regarding breast cancer issues. Breakthrough welcomes the opportunity to comment on the appraisal consultation document regarding the use of bevacizumab in combination with capecitabine for the first-line treatment of metastatic breast cancer.We are disappointed NICE were unable to approve the use of this treatment combination for breast cancer patients. However, we recognise there are significant limitations associated with this treatment and challenges associated with the appraisal. Bevacizumab is an antibody used to inhibit tumour growth and is administered by intravenous infusion. In accordance with its marketing authorisation bevacizumab can be used in combination with capecitabine as a first line treatment for patients with metastatic breast cancer. These patients may only receive this treatment combination if it is considered inappropriate for them to receive taxanes or anthracyclines or they have not received a taxane or anthracycline-containing regimen in the adjuvant setting within 12 months. The most relevant evidence that documents the effects of bevacizumab in combination with capecitabine comes from the RIBBON-1 trial which has been considered in this appraisal. The trial included two different cohorts of patients – those who received either a taxane or an anthracycline or those who received capecitabine. Patients were then randomized to receive bevacizumab or a placebo. Only results from the cohort of patients who received capecitabine (and bevacizumab or a placebo) were included in the analysis for this submission.	Comments noted, no changes required.

Nominating organisation	Comment	Response
	The data from the RIBBON-1 trial was used to calculate patients' progression free survival and overall survival. No quality of life data was collected in this trial. It was found that bevacizumab plus capecitabine improved progression free survival compared to capecitabine plus placebo. This is noteworthy because there is no cure for metastatic breast cancer so patients highly value treatments that can control their disease and stop it from progressing. Patients on the RIBBON-1 trial had the option to receive bevacizumab after disease progression as well as their subsequent treatment. However, this presented problems when calculating overall survival gains. Therefore, we recognise that the evidence included in this submission is not robust enough to demonstrate bevacizumab plus capecitabine improved overall survival over capecitabine plus placebo. Bevacizumab is associated with a number of adverse side effects and it was observed that patients on the bevacizumab plus capecitabine arm of the RIBBON-1 trial experienced more adverse events than those on the control arm. However, the manufacturer stated that when bevacizumab is added to capecitabine the adverse effects were predictable and generally manageable. Maintaining a high quality of life for as long as possible is currently the best outcome for patients with metastatic breast cancer and attractive treatments options are those which exert as few side As well as a lack of quality of life data we recognise why the Committee were unable to approve this treatment regime on the grounds of cost. However, whilst we acknowledge this regimen is expensive it is important to note that patients in the metastatic setting have limited treatment options. The availability of an increased number of safe and effective medicines is therefore highly important.	