NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Premeeting briefing

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

This premeeting briefing is a summary of:

- the evidence and views submitted by the manufacturer, the consultees and their nominated clinical specialists and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal. Please note that this document is a summary of the information available before the manufacturer has checked the ERG report for factual inaccuracies.

Key issues for consideration

- The population in the manufacturer's clinical evidence submission is the patient population in the capecitabine cohort of the RIBBON-1 trial and represents the population specified in the licensed indication. In its economic submission, the manufacturer restricted the population to a subgroup of patients who had previously received a taxane. Does the Committee consider the population modelled by the manufacturer to be appropriate, given the ERG's concerns that this is a more restricted population than the one specified in the licensed indication and the final scope issued by NICE?
- Does the Committee consider the subgroup previously treated with a taxane to be sufficiently robust, given that 'prior taxane' was not a stratification factor for randomisation and the subgroup was specified after the trial had begun but before the analysis was completed?
- What is the Committee's view on the reasons why 60% of patients in the capecitabine cohort of the RIBBON-1 trial with no previous taxane therapy but still of good performance status were not considered to be suitable for

standard taxane treatment and were thus entered into the capecitabine cohort of RIBBON-1?

- The ERG noted that the RIBBON-1 trial used a dose of 1000 mg/m^2 for capecitabine, rather than the licensed dose of 1250 mg/m^2? What is the Committee's view on the generalisability of the trial to UK practice?
- What is the Committee's view on the robustness of the overall survival results for the population in the capecitabine cohort of the RIBBON-1 trial given that patients from both the capecitabine plus placebo arm and the bevacizumab plus capecitabine arm were able to receive subsequent bevacizumab?
- What is the Committee's view on the subgroup analyses conducted by the manufacturer, given that no statistical adjustments were performed to control for multiple testing in all subgroups and of all outcomes?
- Patient-reported quality of life data were not collected in the RIBBON-1 trial. What is the Committee's view on the appropriateness of the literature-derived quality of life values used by the manufacturer in the economic analysis?
- What is the Committee's view on the impact of not including any second-line treatment in the manufacturer's model following disease progression after treatment with either bevacizumab plus capecitabine or capecitabine plus placebo?
- The ERG commented that the rank preserving structural failure time (RPSFT) approach was unsuitable when a large proportion of patients cross over from the control arm, or when patients in both arms cross over. Does the Committee consider that the RPSFT modelling approach used by the manufacturer to estimate progressed disease, using 'uncrossed' post-taxane RIBBON-1 trial data for the first 12 months and a fitted exponential curve thereafter, was credible?
- Does the Committee consider that the costs of terminal care and second-line treatment should be included in the model?

1 Background: Clinical need and practice

1.1 There were over 42,000 women and around 300 men newly diagnosed with breast cancer in England and Wales in 2008. There were around 12,000 deaths from breast cancer in the UK in 2008; an average rate of 38.6 deaths per 100,000 women and 0.2 deaths per 100,000 men. Approximately 5% of women presenting with breast cancer have advanced disease with distant metastases (where cancer cells have spread to other parts of the body), and approximately 35% of women presenting with early or localised breast cancer will develop metastatic breast cancer in the 10 years after diagnosis.

1.2 Current treatments for metastatic breast cancer aim to relieve symptoms, prolong survival and maintain a good quality of life with minimal adverse events. The type of treatment used depends on previous therapy, oestrogen receptor status, human epidermal growth factor receptor 2 (HER2) status, extent of the disease and performance status.

1.3 'Advanced breast cancer: diagnosis and treatment' (NICE clinical guideline 81) recommends first-line treatment with an anthracycline-based chemotherapy regimen. Where an anthracycline is unsuitable (for example, if the person has previously received anthracycline-based adjuvant therapy or has a contraindication to anthracyclines) the guideline recommends docetaxel monotherapy as a first-line treatment for advanced HER2-negative breast cancer. The guideline states that combination chemotherapy may be considered to treat patients with advanced breast cancer for whom a greater probability of response is important and who understand and are likely to tolerate the additional toxicity. 'Gemcitabine for the treatment of metastatic

breast cancer' (NICE technology appraisal guidance 116) recommends gemcitabine in combination with paclitaxel as an option for metastatic breast cancer only when docetaxel monotherapy or docetaxel plus capecitabine are also considered appropriate. Vinorelbine or capecitabine monotherapy should then be considered for subsequent treatment.

2 The technology

2.1 Bevacizumab (Avastin, Roche) is a humanised anti-vascular endothelial growth factor (VEGF) monoclonal antibody that inhibits VEGF-induced signalling and inhibits VEGF-driven angiogenesis. This reduces vascularisation of tumours, thereby inhibiting tumour growth. Bevacizumab is administered by intravenous infusion. The recommended dose is 10 mg/kg body weight given once every 2 weeks or 15 mg/kg body weight given once every 3 weeks. Bevacizumab in combination with capecitabine has a marketing authorisation for 'first-line treatment of patients with metastatic breast cancer in whom treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate. 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'. Capecitabine monotherapy has a marketing authorisation for 'the treatment of patients with locally advanced or metastatic breast cancer after failure of taxanes and an anthracycline-containing chemotherapy regimen or for whom further anthracycline therapy is not indicated'.

2.2 The summary of product characteristics lists the following adverse effects that may be associated with bevacizumab treatment: gastrointestinal perforations, fistulae, wound healing complications,

hypertension, proteinuria, arterial and venous thromboembolism, haemorrhage, pulmonary haemorrhage/haemoptysis, congestive heart failure, reversible posterior leucoencephalopathy syndrome and neutropenia. For full details of side effects and contraindications, see the summary of product characteristics.

2.3 Bevacizumab is available in 100-mg and 400-mg vials at net prices of £242.66 and £924.40, respectively (excluding VAT; 'British national formulary' [BNF] edition 62). The acquisition cost of bevacizumab (excluding VAT and assuming wastage) for a patient weighing 72.1 kg is £2576.78 at a dosage of 15 mg/kg every 3 weeks. This amounts to an average monthly cost of £3689.12 at a dosage of 15 mg/kg every 3 weeks. Costs may vary in different settings because of negotiated procurement discounts.

3 Remit and decision problem(s)

3.1 The remit from the Department of Health for this appraisal was: to appraise the clinical and cost effectiveness of bevacizumab in combination with capecitabine within its licensed indication for the first-line treatment of metastatic breast cancer.

	Final scope issued by NICE	**Decision problem addressed in the submission**
Population	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	

In the economic model, the manufacturer restricted its population to a subgroup of patients who had previously received a taxane. See the section on economic evaluation below for details.

	Final scope issued by NICE	Decision problem addressed in the submission
Intervention	Bevacizumab in combination with capecitabine	
Comparators	• Capecitabine monotherapy • Vinorelbine monotherapy	Capecitabine monotherapy

The manufacturer stated that vinorelbine was not a common therapy used in this setting, and only presented it as a comparator as part of a scenario analysis. The ERG noted that its own clinical advisers agreed that capecitabine is usually preferred to vinorelbine because it is believed to have a more favourable safety profile. The ERG stated that in the absence of any studies comparing bevacizumab plus capecitabine with vinorelbine and in the absence of evidence to suggest that vinorelbine was superior to capecitabine, it was satisfied that capecitabine should be considered the main comparator.

	Final scope issued by NICE	Decision problem addressed in the submission
Outcomes	• Overall survival • Progression-free survival • Response rate • Adverse effects of treatment • Health-related quality of life	

The ERG stated that progression-free survival and overall survival were used as proxy outcomes for health-related quality of life and that progression-free survival and overall survival were presented for selected subgroups of patients.

	Final scope issued by NICE	Decision problem addressed in the submission
Economic evaluation	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and personal social services perspective.	

The manufacturer noted that the capecitabine marketing authorisation states that it is indicated for the treatment of metastatic breast cancer after the failure of taxanes and an anthracycline-containing regimen. The manufacturer interpreted this as indicating a subgroup of patients from the RIBBON-1 capecitabine cohort who have previously received an adjuvant taxane (and probably an anthracycline as well). While first-line taxanes and anthracyclines were considered unsuitable for all patients in the RIBBON-1 capecitabine cohort, the manufacturer stated that it was not possible to identify the patients in the intention to treat (ITT) population in the capecitabine cohort who were previously given taxanes and anthracyclines. Therefore for the economic model the manufacturer restricted its population to a subgroup of patients who had previously received a taxane.

The ERG agreed that most patients in the subgroup from the RIBBON-1 capecitabine cohort would probably have previously received an anthracycline and a taxane. However, the ERG questioned whether these patients were considered to have disease for which further taxanes were inappropriate, since the RIBBON-1 trial excluded patients who had received an adjuvant taxane or anthracycline within the last 12 months. The ERG highlighted that because most clinicians would consider a disease-free interval of greater than 12 months long enough to consider another anthracycline or taxane, it was debatable whether such treatments should be considered to be inappropriate. Further, the ERG noted that while capecitabine is only licensed for patients in whom taxane and anthracycline treatment has failed, in clinical practice it is

also given (off-label) to patients for whom anthracyclines and taxanes are not considered appropriate, regardless of whether these treatment regimens have failed in the past.

The ERG emphasised that the subgroup identified by the manufacturer was a more restricted population than bevacizumab plus capecitabine is licensed for, and that the ITT population from the capecitabine cohort of the RIBBON-1 trial was the most appropriate population in whom to consider this treatment.

	Final scope issued by NICE	Decision problem addressed in the submission
Other considerations	Potential subgroups such as by histology and hormone receptor status will be considered if evidence allows. Guidance will be issued in accordance with the marketing authorisation.	

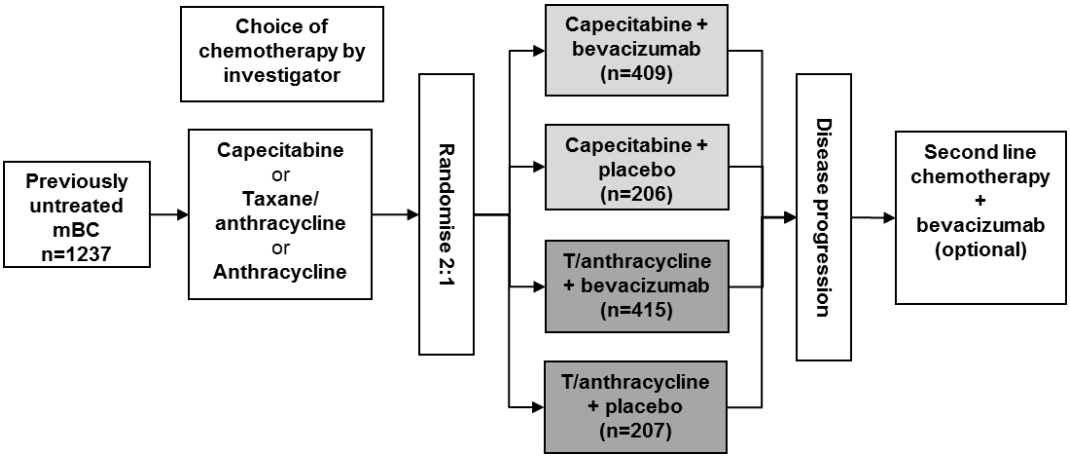
4 Clinical-effectiveness evidence

4.1 The manufacturer conducted a literature search and identified two randomised control trials that investigated the effect of first-line bevacizumab plus capecitabine in adults with metastatic breast cancer. Of these, the TURANDOT trial was excluded because it was ongoing and no efficacy data were available. The review of clinical effectiveness was consequently based on a single trial: the RIBBON-1 trial. This was an international, multicentre, double-blind, phase III, randomised, placebo-controlled trial comparing bevacizumab plus chemotherapy with chemotherapy alone for the first-line treatment of HER2-negative, locally recurrent or metastatic breast cancer.

4.2 The RIBBON-1 trial enrolled 1237 people to receive bevacizumab plus chemotherapy or chemotherapy alone. Investigators were able to select their choice of chemotherapy before randomisation, and

this could be either an anthracycline and/or a taxane, or capecitabine, reflecting the choice of first-line therapy for these patients in routine clinical practice. Patients were therefore enrolled into the two different cohorts: the anthracycline and/or taxane cohort or the capecitabine cohort. The randomisation process then allocated patients to bevacizumab plus the chosen chemotherapy or to chemotherapy alone.

Figure 1. RIBBON-1 trial design (manufacturer's submission, page 32)

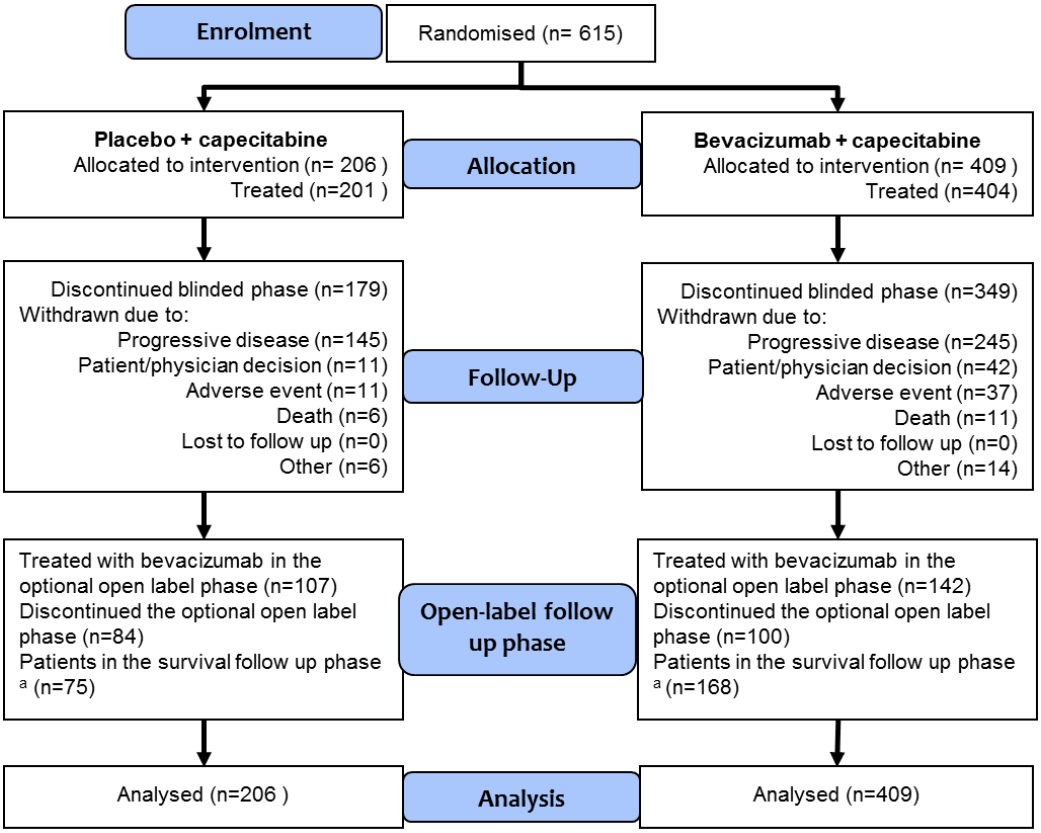


4.3 The manufacturer stated that only the results from the capecitabine cohort provided evidence on the use of bevacizumab in its licensed indication for the first-line treatment of metastatic breast cancer. The manufacturer highlighted that anthracycline and taxane therapy were considered unsuitable for all patients in the capecitabine cohort, although about 40% of the patients had previously received taxane and/or anthracycline therapy for early breast cancer. The manufacturer therefore only presented analyses based on this one cohort.

4.4 The capecitabine cohort of the RIBBON-1 trial randomised 615 patients in a 2:1 randomisation ratio to the bevacizumab plus capecitabine arm (n = 409) and the capecitabine plus placebo arm

(n = 206). Randomisation was stratified by the following criteria: disease-free interval (less than or equal to 12 months, greater than 12 months since completion of adjuvant chemotherapy or surgery if no adjuvant chemotherapy); previous adjuvant chemotherapy; number of metastatic sites (less than 3, greater than or equal to 3); and choice of chemotherapy (taxane, anthracycline, capecitabine). The dosage of bevacizumab was 15 mg/kg^2 by intravenous infusion every 3 weeks until disease progression. The dosage of capecitabine was 1000 mg/m^2 given orally twice daily for two weeks of a three week cycle until disease progression, unacceptable toxicity, investigator/patient decision, or death. Patients continued to receive capecitabine if the trial drug was discontinued before disease progression. Following progression, patients were permitted to move to an open-label post-progression phase consisting of treatment including bevacizumab and chemotherapy at the investigator's discretion. Patients who chose not to enter into the post-progression phase and patients who discontinued from the post-progression phase were followed up in a survival follow-up phase.

Figure 2. Capecitabine cohort in the RIBBON-1 trial (manufacturer's submission, page 49)



[a] = includes all patients who discontinued from either the blinded treatment phase or the optional open label post-progression phase

4.5 The primary endpoint in the trial was investigator-assessed progression-free survival according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria, and it was defined as the time from randomisation to first disease progression or death because of any cause. Progression-free survival based on the Independent Review Committee (IRC) reviewed data was considered a secondary efficacy endpoint and presented as a sensitivity analysis to support the investigator-determined assessment. Secondary endpoints included objective response rates, defined as the percentage of patients with a complete or partial response determined on two consecutive assessments more than 4 weeks

apart; duration of objective response, defined as the time from the first tumour assessment that supported an objective response to the time of disease progression, or death because of any cause; overall survival, defined as the time from randomisation until death from any cause; and the 1-year survival rate, defined as the percentage of patients still alive one year after the randomisation. In addition, progression-free survival and overall survival were calculated for a number of pre-specified subgroups, post-hoc exploratory subgroups, as well as subgroups specified after the trial had begun but before the analysis was completed, such as the post-taxane subgroup used by the manufacturer in the economic model.

4.6 Results for the capecitabine cohort in the RIBBON-1 trial are presented in table 1.

Table 1 Capecitabine cohort results

Endpoint	**Bevacizumab plus capecitabine arm**	**Capecitabine plus placebo arm**	**Absolute difference, Hazard ratio (95% confidence interval [CI]) p-value**
Median PFS (investigator-assessed)	8.6 months (291/409)	5.7 months (162/206)	2.9 months Stratified analysis: 0.69 (95% CI 0.564 to 0.840) p = 0.0002 Unstratified analysis: 0.67 (95% CI 0.55 to 0.82) p < 0.0001
Median PFS (IRC-assessed) – stratified analysis	9.8 months (219/409)	6.2 months (119/206)	3.6 months 0.68 (95% CI 0.54 to 0.86) p = 0.0011
Median PFS (investigator-assessed, not	8.8 months (309/409)	5.5 months (168/206)	3.3 months 0.66 (95% CI 0.55 to

censored for NPT) – stratified analysis			0.81) p < 0.0001
Overall survival – stratified analysis (number of patients who died – updated analysis)	25.7 months (186/409)	22.8 months (99/206)	2.9 months 0.88 (95% CI 0.69 to 1.13) p = 0.33
One-year survival rate – updated analysis	81%	74.8%	6.2% (95%CI 1.0% to 13.4%) p = 0.092
Objective response rate	35.4% (115/409)	23.6% (38/206)	11.8% (95% CI 3.4% to 20.2%) p = 00097
Median duration of objective response	9.2 months (115/325)	7.2 months (38/161)	2 months

IRC, Independent Review Committee; PFS, progression-free survival; NPT, non-protocol specified antineoplastic therapies

The manufacturer acknowledged that the two thirds of patients who crossed over to bevacizumab in the open-label post-progression phase of the trial may have confounded overall survival results. This is because the trial was not designed to evaluate the effect of subsequent therapies.

A number of subgroup analyses for progression-free survival were presented in the manufacturer's submission. The manufacturer highlighted that bevacizumab plus capecitabine gave a progression-free survival benefit over capecitabine plus placebo in all of the pre-specified subgroups defined by stratification variables, and that some subgroups (for example, the group previously treated with a taxane) had a greater overall survival benefit than the ITT population of the capecitabine cohort. The subgroup of patients previously treated with a taxane was the subgroup of patients used by the manufacturer in the economic model. The subgroup of 245 patients who had a previous adjuvant or neo-adjuvant taxane had an increase in median progression-free survival of 4.5 months, from 4.2 months in the capecitabine plus placebo arm to 8.7 months in

the bevacizumab plus capecitabine arm. The hazard ratio for progression was 0.62 (95% confidence interval [CI] 0.45 to 0.84). This benefit also translated into an overall survival benefit, with an increase in median overall survival of 7.9 months, from 20.5 months in the capecitabine plus placebo arm to 28.4 months in the bevacizumab plus capecitabine arm. The hazard ratio for death was 0.67 (95% confidence interval [CI] 0.46 to 0.98). The manufacturer stated that this group of patients in the capecitabine plus placebo arm had worse outcomes than the patients in the ITT analysis, and the addition of bevacizumab raised their progression-free survival and overall survival to levels similar to or above the ITT population.

4.7 The primary safety analyses were based on all patients who received any trial treatment, defined as at least one full or partial dose of either trial treatment. This population was referred to by the manufacturer as the safety population and it differed from the ITT population in the capecitabine cohort in that patients were analysed based on their initial treatment. Adverse events from the capecitabine cohort of the RIBBON-1 trial are presented in table 2. The manufacturer stated that adding bevacizumab to capecitabine resulted in adverse events that were predictable based on previous use of bevacizumab, and generally manageable. The incidence of adverse events was low, with the exception of grade 3/4 hypertension, which was 10.1% in the bevacizumab plus capecitabine arm compared with 1.0% in the capecitabine plus placebo arm.

Table 2 Adverse events

Parameter	Capecitabine plus placebo (n = 201)	Capecitabine plus bevacizumab (n = 404)
Number (%) of patients with at least one:		
Adverse event[a]	54 (26.9%)	162 (40.1%)
Grade 3–5 adverse event	46 (22.9%)	148 (36.6%)
Serious adverse event	41 (20.4%)	102 (25.2%)
Adverse event leading to bevacizumab or placebo discontinuation	24 (11.9%)	51 (12.6%)
Adverse event of special interest	18 (9.0%)	92 (22.8%)
All deaths (including disease progression)	97 (48.3%)	185 (45.8%)
Deaths unrelated to disease progression[b]	5 (2.5%)	6 (1.5%)
Adverse events leading to death	7 (3.5%)	10 (2.5%)
Number (%) of patients with at least one[c]:		
Arterial thromboembolic event	3 (1.5%)	8 (2.0%)
Bleeding	1 (0.5%)	1 (0.2%)
Fistula	1 (0.5%)	1 (0.2%)
Hypertension	2 (1.0%)	43 (10.6%)
Left ventricular systolic dysfunction	1 (0.5%)	6 (1.5%)
Neutropenia	2 (1.0%)	5 (1.2%)
Proteinuria	0 (0.0%)	9 (2.2%)
Sensory neuropathy	1 (0.5%)	12 (3.0%)
Venous thromboembolic event	7 (3.5%)	20 (5.0%)
Wound dehiscence	0 (0.0%)	3 (0.7%)

a, adverse events collected as per study protocol (adverse events of special interest, adverse events resulting in treatment discontinuation, serious adverse events); b, deaths occurring within 30 days of the last dose of study drug due to a reason other than disease progression; c, adverse events of special interest identified through clinical review.

4.8 EQ-5D data was not collected in the RIBBON-1 trial and health-related quality of life data were not presented or discussed in the clinical evidence section of the manufacturer's submission. The manufacturer stated that the most important distress factor among cancer patients was the fear of disease progression. Therefore a major objective of each successive line of therapy, in addition to extending overall survival, was to maintain progression-free survival for as long as possible.

4.9 The ERG stated that the literature search conducted by the manufacturer was appropriate, that all relevant studies had been identified, and that the RIBBON-1 trial on which the manufacturer's submission was based was relevant to the decision problem in its analysis. The ERG stated that the patient population in the trial was in line with the marketing authorisation for bevacizumab. The ERG was satisfied that the trial was well conducted, the baseline characteristics appeared to be balanced across the treatment groups, and the stratification factors were appropriate. The ERG noted that the dose for capecitabine in the trial was 1000 mg/m^2 rather than the licensed dose of 1250 mg/m^2. However, this was considered appropriate and in line with clinical practice. The ERG stated that the results from the trial could be generalised to patients in the UK.

4.10 The ERG noted that the hazard ratios for investigator- and IRC-assessed progression-free survival were almost identical, indicating that this evidence of a benefit to progression-free survival with bevacizumab plus capecitabine was robust. The ERG was aware that the progression-free survival benefit did not translate into a statistically significant overall survival benefit, but stated that interpreting differences in overall survival was difficult because patients from both the capecitabine plus placebo arm and the bevacizumab plus capecitabine arm were able to cross over to receive subsequent bevacizumab. Other anticancer therapies were also available on progression, and in a minority of instances before progression, so bias may have been introduced.

4.11 The ERG noted the subgroup analysis conducted by the manufacturer. The ERG commented that while most differences in progression-free survival were statistically significant by subgroup, the only overall survival results that were statistically significant

were for subgroups of patients aged less than 50 years and subgroups of patients previously treated with a taxane, anthracycline or neoadjuvant/adjuvant chemotherapy. The ERG stated that the subgroup analyses results should be considered with caution because no statistical adjustments were performed to control for multiple testing in all subgroups and of all outcomes, thus increasing the likelihood of significant results emerging by chance.

4.12 The ERG agreed that there were a greater proportion of adverse events in the bevacizumab plus capecitabine arm, but that no new safety concerns were identified. The ERG also agreed that bevacizumab plus capecitabine did not lead to a clinically relevant increase in adverse events typically associated with other chemotherapy regimens, such as febrile neutropenia, neutropenia, and sensory neuropathy. The ERG stated that the difference in adverse events between the two arms could largely be attributed to differences in grade 3 adverse events (27% in the bevacizumab plus capecitabine arm versus 14% in the capecitabine plus placebo arm).

4.13 Regarding the safety of bevacizumab plus capecitabine compared with capecitabine plus placebo in the prior taxane subgroup, the ERG stated that it was not possible to compare the proportions of patients who experienced any adverse events, any grade 3–5 adverse events, any serious adverse events or any adverse events leading to discontinuation of bevacizumab or placebo because the manufacturer did not present these data. The ERG did manage to extract some data from the economic model, and stated that adverse events of special interest mostly appeared to be similar in frequency in the subgroup and in the overall trial population. A slightly greater proportion of patients in the subgroup reported

grade 3 or higher cardiac disorders (4.4%) than in the overall trial population (2.1%). However, the ERG stated that these findings must be viewed with caution because of the small numbers of patients, and therefore smaller number of adverse events, in this subgroup.

5 Comments from other consultees

5.1 Professional groups stated that the treatment of metastatic breast cancer depends on the type of breast cancer (ER status and HER2 status), the extent of metastatic disease and the general medical health and age of the patient, and that clinical practice was mostly uniform across the NHS and in line with previous NICE guidance. Professional groups agreed that the correct subgroup had been identified for treatment with bevacizumab, that the trial reflected UK clinical practice, and that progression-free survival was an appropriate primary outcome. It was highlighted that the degree of crossover in the trial may have affected the overall survival statistics.

5.2 Professional groups stated that there is a broad consensus that incorporating bevacizumab into first-line treatment with chemotherapy will improve outcomes more than the other chemotherapy options (such as weekly paclitaxel, platinum-based regimens, vinorelbine, gemcitabine and oral capecitabine alone) for patients with triple-negative, aggressive visceral disease who have already received adjuvant anthracyclines and taxanes. The professional groups suggested that bevacizumab should be used in specialist clinics, and that the increase to the work load of the specialist nurses would not be substantial and could be absorbed into the present delivery of complex cancer treatments. It was acknowledged that if bevacizumab is recommended for use in the

NHS, there would be an increase in treatment time, use of facilities and day unit chemotherapy facilities, but that this could be addressed by limiting approval to a subgroup of patients.

5.3 Patient experts stated that there are limited treatment options available for breast cancer patients with metastatic disease for whom anthracyclines and taxanes are not appropriate. It was emphasised that maintaining a high quality of life for as long as possible through longer progression-free survival is currently the most important outcome for patients with metastatic breast cancer. The need for a safe and effective treatment that would enable them to continue with some aspects of their normal daily activities was stressed. However, patient experts also stated that they were unaware of patient experience with this treatment outside the context of a clinical trial. It was also highlighted that adding bevacizumab to capecitabine may become a burden on patients in terms of the additional time and stress associated with administration by intravenous infusion. However, patient experts also stated that many chemotherapy treatments have these issues and bevacizumab should not be ruled out on this basis alone.

5.4 Patient experts noted that marketing authorisation for bevacizumab in combination with paclitaxel as a treatment for metastatic breast cancer had been withdrawn in the USA because of serious adverse effects, such as bleeding, heart failure, severe effects on blood pressure and development of perforations in the nose, stomach and intestines. Therefore, if bevacizumab was to be offered to patients, it must be made clear to them that their quality of life may be negatively affected by this treatment and that they must be closely monitored. Professional groups, however, stated that despite some rare side effects that usually require the drug to be stopped, such as reduction in cardiac function, thrombosis and

haemorrhage, most patients could tolerate bevacizumab plus chemotherapy.

6 Cost-effectiveness evidence

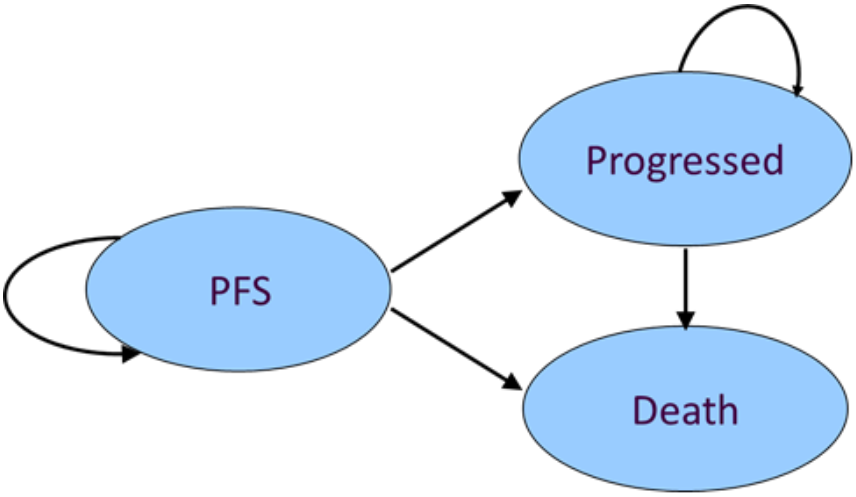
6.1 The manufacturer conducted a systematic review of the literature, but no cost-effectiveness studies were found comparing bevacizumab plus capecitabine with capecitabine plus placebo as first-line treatments for metastatic breast cancer. No relevant cost-effectiveness analyses were identified.

6.2 The economic evaluation was based on a subgroup of patients from the RIBBON-1 trial who had previously received a taxane, and all efficacy and treatment duration parameters were derived from patient-level data of this subgroup. The manufacturer assumed that patients in this subgroup would probably have received an anthracycline as well. The manufacturer stated that this subgroup reflected the marketing authorisations for capecitabine and for bevacizumab plus capecitabine. The manufacturer acknowledged that this post-hoc subgroup analysis of patients previously treated with a taxane was the main weakness of the economic evaluation.

6.3 The manufacturer developed a three-state model. All patients enter the model in the progression-free survival health state and in each month can either progress to a 'worse' health state (that is, from progression-free survival to progressed disease or from either state to death) or remain in the same health state. The manufacturer stated that these health states were consistent with previous modelling of metastatic cancer. The progression-free survival health state is designed to capture a patient's relatively high quality of life before disease progression and the progressed disease state is designed to capture the relatively poor quality of life after disease progression. The survival data from the capecitabine arm of the

subgroup previously treated with a taxane from RIBBON-1 were used to inform the disease progression of the comparator arm. The treatment duration observed in the trial was used to determine the expected cost of treatment with each regimen in the base case. The model has a one-month cycle length, includes a half-cycle correction and both costs and benefits are discounted at 3.5%. The time horizon was 15 years.

Figure 3 Model structure



PFS – progression-free survival.

6.4 The proportions of patients who are progression-free in each month were taken directly from Kaplan-Meier survival curves for either treatment arm in RIBBON-1 until the 12th month of treatment, after which the survival curve was extrapolated according to an exponential function. The number of patients in each treatment arm dying from any cause while in the progression-free survival state was used to derive a constant rate and probability of mortality. The mortality rate in the progression-free survival state was assumed to be at least as great as the underlying sex- and age-related mortality in the general population.

6.5 A number of tunnel states were generated for patients with progressed disease according to the time spent in this state. The tunnel states were arranged so that each state had a progression only to death or the next temporary state. Patients who entered the progressed disease state had a probability of dying that increased each month based on an extrapolation of the survival data for patients with progressed disease. Mean overall survival was the sum of mean duration of progression-free survival and mean duration of progressed disease. During the progressed disease phase, patients in the capecitabine cohort of the RIBBON-1 trial received a variety of different therapies. The manufacturer modelled survival in progressed disease based on 'uncrossed' data from the subgroup of patients who had previously received a taxane up to month 12, with curves extrapolated according to an exponential function thereafter. The data were 'uncrossed' using the RPSFT model to take account of the bias that may have been introduced by allowing patients from both treatment arms to receive bevacizumab post-progression, potentially distorting overall survival rates in the control arm.

6.6 The manufacturer undertook a literature review to identify relevant health-related quality of life data to use in the economic evaluation. Three studies that measured utility values directly were identified and, of these, the manufacturer calculated utility values for progression-free survival and progressed disease from the results of the mixed model analysis presented by Lloyd et al. (2006). The manufacturer stated that it was most appropriate to use a base-case progression-free survival utility value that was derived from a large population, and then to adjust that base utility by response rate. In addition, the utility values from this study have been used in previous health technology appraisals for metastatic breast cancer. For patients in the progressed disease state, a common health

state utility value of 0.496 was incorporated in both treatment arms. For patients in the progression-free survival state a treatment-specific weighted average of the values for stable disease and treatment response, based on the reported overall response rate, was calculated. The utility values incorporated in the economic modelling are presented in table 3.

Table 3 Utility values

State	Utility value
Progression-free survival – bevacizumab plus capecitabine arm	0.784
Progression-free survival –- capecitabine plus placebo arm	0.774
Progressed disease	0.496

The manufacturer acknowledged that the utility values reported by Lloyd et al. (2006) were not derived from patient experience, and presented a sensitivity analysis using data from Peasgood et al. (2010) to derive estimated utilities from patients valuing their own health.

6.7 The drug and administration costs incorporated in the model for the intervention and the comparator are summarised in table 4. No vial sharing was assumed for bevacizumab.

Table 4 Intervention and comparator costs

	Cost	Source
Bevacizumab plus capecitabine drug costs	£4001.53 per month	BNF 62
Month 1: bevacizumab plus capecitabine administration and pharmacy cost	£348.82 per month	Millar 2008 NHS reference costs 2009/10 (SB13Z: Deliver more complex parenteral chemotherapy at first attendance (day case)) PSSRU 2010
Subsequent months: bevacizumab plus capecitabine administration and pharmacy cost	£205.99 per month	Millar 2008 NHS reference costs 2009/10 (SB97Z: Same day chemotherapy admission/attendance (day case and regular day/night)) PSSRU 2010
Capecitabine drug cost	£312.41 per month	BNF 62
Capecitabine administration and pharmacy cost	£255.32 per month	Millar 2008 NHS reference costs 2009/10 (SB11Z: Deliver exclusively oral chemotherapy) PSSRU 2010

BNF, British National Formulary; PSSRU, Personal Social Services Research Unit.

The manufacturer stated that in clinical practice a proportion of patients stop treatment before disease progression, and therefore it is essential to consider the distinction between progression-free survival and treatment cessation when evaluating the real incremental cost. In order to account for this disparity, patient-level data on treatment duration were used to produce parametrically-fitted time to off treatment Kaplan-Meier curves that could be used to determine the proportion of patients still receiving bevacizumab and/or capecitabine in each month. This fitting was conducted in the same manner as for progression-free survival or progressed disease.

6.8 Progression-free survival health state costs were based on 'Advanced breast cancer: diagnosis and treatment' (NICE clinical guideline 81) 'package 1' with the addition of an outpatient consultation with an oncologist and a CT scan assumed to occur

every 3 months, and were estimated to be £263.55 per month. Progressed disease health state costs were based on NICE clinical guideline 81 'package 2' and estimated to be £804.00 per month. The same costs and utilities were assumed regardless of first-line treatment. Adverse events of grade 3/4 severity occurring in greater than 2% of patients were incorporated into the analysis. Where clinical advice indicated that the usual response to the adverse event was discontinuation of treatment (peripheral sensory neuropathy, palmar-plantar erythrodysesthesia syndrome and proteinuria), it was assumed this had been accounted for elsewhere in the model and no additional costs were accrued. In addition, treatment of diarrhoea was considered to have negligible contribution to costs. Therefore only costs associated with deep vein thrombosis and hypertension were included in the model. All adverse events were assumed to occur in month 1 for both treatment arms and were therefore not discounted.

6.9 The manufacturer did not include terminal care costs in the model, stating that these would refer to costs in the last two weeks and would therefore have a minimal impact on the ICER irrespective of the regimen received. In addition, no second-line treatment cost was included in the model as it was felt that the duration of second-line treatment would be the same for a patient receiving first-line bevacizumab plus capecitabine as for a patient receiving first-line capecitabine alone, and the second-line costs in each arm would cancel each other out.

6.10 The base-case results from the manufacturer's model are shown in table 5.

Table 5 Base-case results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Capecitabine	12,721	0.8346			
Bevacizumab plus capecitabine	51,645	1.3381	38,924	0.5034	77,318

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

6.11 The manufacturer conducted deterministic sensitivity analyses for a range of parameters. The manufacturer stated that the cost-effectiveness results were most sensitive to the costs and utilities associated with progressed disease.

6.12 The manufacturer conducted a scenario analysis using utility values from Peasgood et al. (2010), but this had little impact on the ICER and did not cause it to go above £79,991 per QALY gained. A second scenario analysis was conducted including different formulations of vinorelbine as the comparator. It was assumed that vinorelbine had an equivalent efficacy and safety profile to capecitabine, with different costs of acquisition and administration. The results from this comparison are presented in table 6.

Table 6 Cost-effectiveness results of the vinorelbine comparison

Comparator	ICER
Intravenous branded vinorelbine regimen	£76,199
Generic vinorelbine	£80,260
Oral formulation of vinorelbine	£58,198

The manufacturer conducted a probabilistic sensitivity analysis and concluded that bevacizumab plus capecitabine compared with capecitabine plus placebo had a 0% probability of being cost effective at a maximum acceptable ICER of £30,000 or £50,000 per QALY gained.

6.13 The manufacturer acknowledged that its economic evaluation was only relevant to patients with similar characteristics to those randomised to the capecitabine cohort of RIBBON-1 who had previously been treated with a taxane. The ERG requested additional cost-effectiveness data for the ITT population of the capecitabine cohort for clarification. However, the manufacturer stated that since the submitted analysis calculated an ICER of approximately £77,000 per QALY gained for the subgroup previously treated with anthracyclines and taxanes, analysis of the ITT population would result in a larger ICER and therefore would not be considered a cost-effective use of NHS resources.

6.14 The ERG had concerns about the population used in the manufacturer's economic model. The ERG highlighted that the manufacturer had based its economic modelling on a subgroup of patients who had previously been treated with a taxane, because the manufacturer considered this population to represent the population for whom capecitabine is licensed. That is, patients requiring treatment for metastatic breast cancer after failure of taxanes and an anthracycline-containing chemotherapy regimen or for whom further anthracycline therapy is not indicated. The ERG agreed that most patients in this subgroup would probably have previously received an anthracycline in addition to a taxane. However, the ERG questioned whether they would be considered to have 'failed' because the RIBBON-1 trial excluded patients who had received an adjuvant taxane or anthracycline in the last 12 months. The ERG did not consider the subgroup of patients who previously received a taxane to be the appropriate group of patients. The ERG considered the ITT population in the capecitabine cohort as the appropriate population because it represents the population in the final scope issued by NICE and the population specified in the marketing authorisation for

bevacizumab. In addition, the ERG identified that there appeared to be baseline differences between this subgroup and the ITT population as a whole. In particular, the ERG noted from differences in the mean and median age and Eastern Cooperative Oncology Group (ECOG) performance status that the population of patients who had previously received a taxane appeared to be younger and healthier (a comparison of baseline characteristics is presented in table 7).

Table 7 Comparison of selected baseline characteristics presented in the model for the subgroup previously treated with a taxane and the ITT population in the capecitabine cohort

Demographic variable		Previous taxane subgroup		ITT population	
		CAPE plus placebo (n = 84)	BEV plus CAPE (n = 161)	CAPE plus placebo (n = 206)	BEV plus CAPE (n = 409)
Age (years)	Mean (SD)	53.4 (11.5)	53.4 (10.2)	57.1 (12.1)	56.6 (11.5)
	Median (range)	52 (23 to 78)	52 (30 to 84)	57 (23 to 88)	56 (28 to 91)
Age category	< 40 years	9 (10.7%)	12 (7.4%)	15 (7.3%)	21 (5.1%)
	40–64 years	61 (72.6%)	126 (78.3%)	137 (66.5%)	289 (70.7%)
	≥ 65 years	14 (16.7%)	23 (14.3%)	54 (26.2%)	99 (24.2%)
Age group	<50 years	33 (39.3%)	59 (36.6%)	54 (26.2%)	119 (29.1%)
	≥ 50 years	51 (60.7%)	102 (63.4%)	152 (73.8%)	290 (70.9%)
Menopausal status	Premenopausal	35 (41.6%)	60 (37.3%)	60 (29.1%)	120 (29.3%)
	Perimenopausal	4 (4.8%)	10 (6.2%)	11 (5.3%)	26 (6.4%)
	Postmenopausal	40 (47.6%)	85 (52.8%)	125 (60.7%)	245 (59.9%)
	Not Applicable	1 (0.1%)	0 (0.0%)	1 (0.5%)	1 (0.2%)
	Unknown	5 (5.9%)	6 (3.7%)	9 (4.4%)	17 (4.2%)
Sex	Female	83 (98.8%)	161 (100%)	204 (99.0%)	408 (99.8%)
Race/ ethnicity	White	58 (69.0%)	115 (71.4%)	157 (76.2%)	308 (75.3%)
	Black	7 (8.3%)	14 (8.7%)	10 (4.9%)	21 (5.1%)
	Other	19 (22.6%)	28 (17.3%)	39 (19.0%)	80 (19.5%)
Geographical region	North America	52 (61.9%)	118 (73.3%)	104 (50.5%)	226 (55.3%)
	Latin America	9 (10.7%)	10 (6.2%)	24 (11.7%)	42 (10.3%)
	Eastern Europe	2 (2.4%)	6 (3.7%)	32 (15.5%)	53 (13.0%)
	Western Europe	7 (8.3%)	11 (6.8%)	28 (13.6%)	57 (13.9%)
	Asia	14 (16.7%)	16 (9.9%)	18 (8.7%)	31 (7.6%)
ECOG performance status	0	48 (57.2%)	94 (58.8%)	110 (53.4%)	214 (52.7%)
	1	36 (42.8%)	66 (41.2%)	96 (46.6%)	192 (47.3%)

BEV, bevacizumab; CAPE, capecitabine; ECOG, Eastern Cooperative Oncology Group; ITT, intention to treat; SD, standard deviation.

The ERG also noted that the differences in progression-free and overall survival between the bevacizumab plus capecitabine and capecitabine plus placebo arms appeared to be greater in the subgroup of patients previously treated with a taxane than in the ITT population, as well as being statistically significant. However, the ERG reiterated that as no statistical adjustments were made to control for multiple testing in all subgroups and of all outcomes these findings may have occurred by chance, and must be interpreted with caution.

6.15 The ERG raised some concerns about the structure and design of the manufacturer's economic model. The ERG noted that the manufacturer adapted a model structure previously used in NICE appraisals of cancer drugs. However, the ERG raised concerns that although the model covered a period of 15 years, no further chemotherapy was considered within the model following disease progression after treatment with bevacizumab plus capecitabine or capecitabine plus placebo. This could lead to substantial bias, because if progression-free survival differed between the arms the discounted costs and benefits of subsequent treatments would also differ. Further, if the proportion of patients able to receive subsequent lines of therapy differed between the arms then the costs and outcomes would also differ.

6.16 The ERG was satisfied that the modelling approach used by the manufacturer to estimate progression-free survival using Kaplan-Meier methods from the RIBBON-1 trial for the first 12 months and a fitted exponential curve thereafter was credible. The ERG noted that while the approach was similar for progressed disease, the manufacturer had 'uncrossed' the data using the RPSFT model to minimise bias. The ERG stated that this approach was unsuitable when a large proportion of patients from both arms cross over. The

ERG noted that 44.7% of patients in the bevacizumab plus capecitabine arm and 52.4% of patients in the capecitabine plus placebo arm received bevacizumab after disease progression. Further, patients in the modelled subgroup also received other therapies after progression. The ERG stated that given the limitations of the RPSFT model and in the absence of any other estimate to adjust for crossover, they were unable to confirm the likely effect of the crossover and post-progression therapies on overall survival in this subgroup and caution should be exercised when interpreting the manufacturer's overall survival results. A summary of different survival estimates from the trial and the model is presented in table 8.

Table 8 Progression-free survival and overall survival estimates

Endpoint	Previous taxane subgroup		ITT population	
	CAPE plus placebo (n = 84)	BEV plus CAPE (n = 161)	CAPE plus placebo (n = 206)	BEV plus CAPE (n = 409)
PFS (median, months) – clinical results	4.2	8.7	5.7	8.6
	HR = 0.62 (95% CI 0.45 to 0.84)		HR = 0.67 (95% CI 0.55 to 0.82)	
PFS (mean, months) – from the economic model	6.59	9.69	-	-
OS (median, months) – clinical results	20.5	28.4	22.8	25.7
	HR = 0.67 (95% CI 0.48 to 0.98)		HR = 0.88 (95% CI 0.69 to 1.12)	
OS (median, months) using RPSFT model	15.0	23.0	-	-
OS (mean, months) – from the economic model	16.38	26.74	-	-

BEV, bevacizumab; CAPE, capecitabine; ITT, intention to treat; OS, overall survival; PFS, progression-free survival; RPSFT, rank preserving structural failure time.

6.17 The ERG undertook an analysis of the original progressed disease trial data to explore survival during this phase. A comparison of survival times during the progressed disease phase indicated that

although survival is similar in each group and overall the four groups in the RIBBON-1 trial did not show strong evidence of heterogeneity, the capecitabine plus placebo with no crossover group appeared to differ when tested pairwise against the other 3 groups. Therefore, the ERG developed two different models. The first grouped all patients together and modelled a scenario where survival post-progression was equivalent irrespective of first line therapy or crossover. The second grouped together all the bevacizumab plus capecitabine patients and the capecitabine plus placebo patients who crossed, and considering the capecitabine plus placebo patients who did not cross separately. The ERG stated that this second model allowed a clear comparison between patients who did and did not receive bevacizumab during the trial and gives a representation of the effect of cross over. The ERG highlighted that each analysis portrayed an extreme, allowing consideration of a best and worst case scenario for the effect of crossover on post progression survival.

6.18 The ERG conducted a sensitivity analysis to study the impact of including the licensed dose of capecitabine (1250 mg/m^2) rather than the dose widely used in clinical practice (1000 mg/m^2). The ERG found that this resulted in an increase in drug costs of £2,966 per patient in the bevacizumab plus capecitabine arm and an increase of £50 per patient in the capecitabine alone arm. These adjustments resulted in a revised ICER that was £5793 higher per QALY gained than the manufacturer's base case ICER. The ERG re-estimated the costs of therapy based 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. The ERG also added in the costs of terminal care during the last two weeks of life, as specified in NICE guidelines.

6.19 The ERG noted that the utility values used in the manufacturer's model were estimated using the statistical model detailed in a study by Lloyd et al. (2006). The ERG noted that there is a lack of consensus amongst economists in relation to the most appropriate value for the age parameter in the Lloyd et al model, that is whether it should be that of the population surveyed in the study or that relating to the age of the population taking part in the original health state valuation exercise carried out by Kind et al. The ERG noted that the manufacturer has used 47 years, the mean age of the population taking part in the original Kind et al study, with the advantage that it was consistent with standard UK EQ-5D tariff scores. However, the ERG stated that the lack of consensus relating to the most appropriate age value to use introduces a degree of uncertainty to the value of the utility scores used in the model. The ERG also corrected for a typing mistake in the formula used for some months in the manufacturer's capecitabine plus placebo arm.

6.20 The impact of the additional analyses presented by the ERG (incorporating changes to drug costs, including terminal care costs, including revised utility estimates and revised progressed disease survival estimates) are presented in table 9.

Table 9 Cost-effectiveness results following the application of ERG model amendments

Change	Bevacizumab plus capecitabine		Capecitabine plus placebo		Incremental		
	QALYs	All costs	QALYs	All costs	QALYs	Costs	ICER
Base case	**1.338**	**£51,645**	**0.835**	**£12,721**	**0.503**	**£38,924**	**£77,318**
ERG drug costs	1.338	£54,612	0.835	£12,771	0.503	£41,841	£83,111
Add terminal care costs	1.338	£53,351	0.835	£14,479	0.503	£38,871	£77,213
ERG revised utility values (formula error)	1.338	£51,645	0.829	£12,721	0.509	£38,924	£76,532
ERG revised PD survival estimates (common projection)	1.254	£50,013	1.062	£17,150	0.192	£32,862	£171,411
ERG revised PD survival estimates (different projections)	1.281	£50,542	0.880	£13,605	0.401	£36,937	£92,060
ERG changes to drug cost, terminal care & utility values	1.338	£56,317	0.829	£14,529	0.509	£41,788	£82,162
All ERG changes							
Common projection model	1.254	£54,695	1.057	£18,931	0.197	£35,764	£181,648

Different projection model	1.281	£55,221	0.875	£15,409	0.406	£39,812	£97,963

ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; PD, progressed disease.

6.21 The ERG also agreed with the manufacturer that the base-case ICER per QALY gained cannot be considered to be generalisable to the whole population covered by the marketing authorisation and that it was likely to be higher than that for the modelled subgroup.

7 Equalities issues

7.1 No equalities issues were identified during scoping consultation or in the evidence submitted.

8 Innovation

8.1 The manufacturer stated that the patients previously treated with a taxane in the capecitabine plus placebo arm did considerably worse than the patients in the ITT population, and that the addition of bevacizumab to capecitabine raised their progression-free survival to a level similar to the ITT population and their overall survival to a higher level than in the ITT population.

9 Lead team comments

9.1 The lead team noted the patient expert's statement that the marketing authorisation for bevacizumab when used in combination with paclitaxel for treating metastatic breast cancer had been withdrawn in the USA because of serious adverse effects such as bleeding, heart failure, severe effects on blood pressure and development of perforations in the nose, stomach and intestines. The lead team highlighted that the reason given for the withdrawal was reduced progression-free survival improvements noted in

studies after the first E2100 trial, and while toxicity was one of the considerations for withdrawal, it was secondary.

10 Authors

Raisa Sidhu and Nwamaka Umeweni
Technical Leads

Nicola Hay
Technical Adviser

with input from the Lead Team (Gillian Ells, John Hutton and Paddy Storrie).

Appendix A: Supporting evidence

Related NICE guidance

Published

- Bevacizumab in combination with a taxane for the first-line treatment of HER2 negative metastatic breast cancer. NICE technology appraisal 214 (2011). Available from www.nice.org.uk/guidance/TA214
- Gemcitabine for the treatment of metastatic breast cancer. NICE technology appraisal 116 (2007). Available from www.nice.org.uk/TA116
- Advanced breast cancer: diagnosis and treatment. NICE clinical guideline 81 (2009). Available from www.nice.org.uk/guidance/CG81

NICE pathways

- There is a NICE pathway on advanced breast cancer, which is available from http://pathways.nice.org.uk/pathways/advanced-breast-cancer

Appendix B: Clinical efficacy section of the draft European public assessment report

The European public assessment report for bevacizumab was published on 24 January 2006 and is available from:

www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000582/human_med_000663.jsp&mid=WC0b01ac058001d124&murl=menus/medicines/medicines.jsp&jsenabled=true