NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Premeeting briefing

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

This briefing presents the key issues arising from the manufacturer's submission, Evidence Review Group (ERG) report and statements made by consultees and their nominated clinical specialists and patient experts. Please note that this briefing is a summary of the information available and should be read with the full supporting documents.

The manufacturer was asked to:

- provide additional background information regarding which regimens are currently used in UK clinical practice
- provide information on patients not accounted for in the consort flow chart for study E2100
- provide further justification for including studies with more than 50% HER2-negative patients in the indirect comparison, given that this criterion is more than 90% in the direct comparison
- provide full intervention details for the E2100 study as well as more recent follow-up data
- provide comprehensive details and data for the AVADO study and complete data for the subgroup of relevant patients from the RIBBON-1 trial
- provide justification of the selection criteria for the indirect comparisons: that is, excluding trials where more than 60% of patients received second or later line treatment; including studies that did not meet the selection criteria that more than 50% of study participants must be HER2-negative and for combining the included trials in the indirect comparison, given the observed variation in baseline characteristics
- provide tabulated data on treatment efficacy for each arm in all trials included in the indirect comparison
- provide further justification for imputing FACT-B values of zero for patients who had disease progression as well as reasons for censoring/missing data at various time points in the quality-of-life data

- consider approaches to formally incorporate 3-weekly paclitaxel and bevacizumab plus docetaxel into the existing economic analysis and present the results of these analyses
- provide estimated coefficients, standard errors and variance-covariance matrices for all parametric functions
- report the mean duration of progression-free survival for the regimens bevacizumab plus paclitaxel and paclitaxel alone based on both the Kaplan-Meier curves and to provide details of the parametric functions considered
- model overall survival using a similar approach to progression-free survival
- model time from progression to death separately for each arm and to conduct an additional scenario of the cost-effectiveness model using this approach
- report the mean overall survival assumed for bevacizumab plus paclitaxel and paclitaxel alone derived from the economic model, the separate Kaplan-Meier curves reported in figure 14 and based on the alternative parametric functions (either assuming proportional hazards or based on fitting individual survival curves).

The manufacturer was also asked to provide further information on the following key issues, but further data were not provided.

- The manufacturer did not incorporate bevacizumab plus docetaxel in the model either as an intervention or as a comparator.
- More recent follow-up data from the E2100 trial (since 2005–06) were not provided.
- The manufacturer did not provide comprehensive details and data for the AVADO study or complete data for the subgroup of relevant patients from the RIBBON-1 trial.

Licensed indication

Bevacizumab (Avastin, Roche Products) in combination with paclitaxel or docetaxel is indicated for the first-line treatment of patients with metastatic breast cancer.

Key issues for consideration

Decision problem

- Does the Committee consider that sufficient and appropriate comparisons have been made given that:
  - Bevacizumab plus docetaxel was not addressed in the submission?
  - The licensed regimen for paclitaxel monotherapy is once every 3 weeks; however, weekly paclitaxel plus bevacizumab and weekly paclitaxel as monotherapy were modelled in the base case (the manufacturer did provide a comparison of bevacizumab plus weekly paclitaxel compared with 3-weekly paclitaxel monotherapy in response to clarification).

Clinical effectiveness

- Does the Committee consider the evidence from the direct comparison (the open-label E2100 trial) to be sufficiently robust?
- Does the Committee consider the selection of clinical effectiveness and safety evidence to be sufficiently robust?
  - Should the following trials have been included in the direct and the indirect comparisons?
    - ◊ AVADO (3-weekly 100-mg docetaxel versus docetaxel plus bevacizumab)
    - ◊ RIBBON-1 (subgroup of 180 patients received bevacizumab in combination with docetaxel)
    - ◊ Will Weekly Win (weekly versus 3-weekly paclitaxel).
- Does the Committee believe that studies included in the indirect comparison are relevant to the decision problem?
  - Studies with at least 50% unknown HER2 status were included.
  - Studies with up to 60% previously treated patients were included.
  - The study by Jones et al. was included (this study used a 3-weekly 100-mg docetaxel regimen).

- Does the Committee consider the indirect comparison based on the Bucher method to be a robust demonstration of clinical effectiveness?
- What is the Committees overall view on the estimates of clinical effectiveness derived from the key trial (median progression-free survival improved by 5.5 months and overall survival improved by 1.7 months in the bevacizumab plus paclitaxel arm compared with the paclitaxel arm) and those derived from the indirect comparisons?

Cost effectiveness

- What is the Committee's view on the assumptions made by the manufacturer in the economic model and their impact, individually and overall, on estimates of cost effectiveness?
  - Does the Committee accept the assumption that mortality after disease progression is independent of initial treatment?
  - Does the Committee accept the assumption that all comparators are equally effective (measured by both progression-free survival and overall survival)?
  - Which prices (that is, 'British national formulary' [BNF] list prices, Purchasing and Supplies Agency (PASA) mean prices, future possible generic prices) does the Committee consider to be most appropriate to the evaluation of cost effectiveness?
- Does the Committee consider it is appropriate to include the treatment effects of the comparators derived from the indirect treatment comparison in the consideration of cost effectiveness?
- Does the Committee consider the utility values used in the manufacturer's model to be robust estimates?
- What is the Committee's overall view on the estimates of cost effectiveness? What is the most plausible incremental cost-effectiveness ratio (ICER)?

1 Decision problem

Related NICE guidance

NICE clinical guideline 81 recommends single-agent docetaxel as a first-line treatment for HER2-negative metastatic breast cancer.

NICE technology appraisal guidance 116 recommends gemcitabine in combination with paclitaxel as an option for the treatment of metastatic breast cancer only when docetaxel monotherapy or docetaxel plus capecitabine are also considered appropriate.

NICE technology appraisal guidance 147 was unable to recommend the use in the NHS of bevacizumab in combination with paclitaxel for the first-line treatment of metastatic breast cancer because no evidence submission was received from the manufacturer or sponsor of the technology.

1.1 Decision problem approach in the manufacturer's submission

Population	People with first-line metastatic HER2-negative breast cancer for whom anthracyclines are not appropriate. However, the economic analysis is based on the intention-to-treat population for the pivotal trial to maintain randomisation.
Intervention	Bevacizumab in combination with a taxane.
Comparators	Bevacizumab in combination with paclitaxel and bevacizumab in combination with docetaxel should be compared with each other. In addition, the interventions should be compared with the following: • docetaxel monotherapy • paclitaxel monotherapy • paclitaxel plus gemcitabine. Indirect comparisons were necessary because head-to-head trials were not available for all comparisons requested.
Outcomes	• Overall survival. • Progression-free survival. • Response rates. • Adverse effects of treatment. • Health-related quality of life.
Economic evaluation	The NICE reference case is followed. The reference case stipulates that cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year and 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 are considered from an NHS and Personal Social Services perspective. A second base case is provided that deviates from this (by using the PASA price for paclitaxel and a 10-g cap for bevacizumab).

1.2 Evidence Review Group comments

1.2.1 Population

The ERG stated that the key trial used in the direct efficacy comparison (that is, the E2100 study; bevacizumab plus paclitaxel compared with paclitaxel

monotherapy) and an additional uncontrolled safety study (ATHENA) were relevant to the decision problem. Both of these studies included patients with previously untreated metastatic breast cancer and were mainly HER2-negative, as specified in the scope. However, the ERG noted that the indirect comparisons included trials with populations other than those described in the decision problem, such as people who had received previous treatment or who did not have HER2 status recorded.

1.2.2 Intervention

Bevacizumab is licensed in combination with paclitaxel or docetaxel for the first-line treatment of metastatic breast cancer and the final scope issued by NICE defines the intervention as bevacizumab in combination with a taxane. However, the manufacturer's evaluation of clinical efficacy and cost-effectiveness included only evidence relating to bevacizumab in combination with weekly paclitaxel (that is, paclitaxel given once a week for 3 weeks, followed by a week of rest).

The ERG noted that the submission focused on weekly paclitaxel and that the 'Summary of product characteristics' for paclitaxel specifies the regimen is 3-weekly (that is, paclitaxel given once every 3 weeks). The manufacturer provided a comparison with 3-weekly paclitaxel in response to clarification.

Evidence on bevacizumab in combination with docetaxel was excluded from the submission.

1.2.3 Comparators

The decision problem specified that bevacizumab in combination with paclitaxel and bevacizumab in combination with docetaxel should be compared with each other. No head-to-head trials were available for this comparison, and the manufacturer did not address this in its indirect comparison and cost-effectiveness analysis. The ERG noted that docetaxel is

the taxane currently recommended for first-line treatment of patients with advanced breast cancer in existing NICE guidelines.

The remaining comparators specified in the decision problem were: docetaxel monotherapy, paclitaxel monotherapy and paclitaxel in combination with gemcitabine. One included trial directly evaluated bevacizumab in combination with paclitaxel (E2100) compared with weekly paclitaxel monotherapy; the remaining comparators were addressed using indirect comparisons.

1.2.4 Outcomes

The ERG noted that each of the outcomes specified in the decision problem were addressed in the evaluation of bevacizumab in combination with paclitaxel versus paclitaxel monotherapy, with a focus on progression-free survival. However, for all other comparisons, progression-free survival was the only efficacy outcome reported. Data on progression-free survival were combined with assumptions on overall survival to estimate mean survival times in the cost-effectiveness analysis.

1.2.5 Time frame

Patients were followed until disease progression then death, or for 5 years after randomisation in the trial evaluating bevacizumab in combination with paclitaxel compared with paclitaxel monotherapy (E2100). The manufacturer conducted interim analyses and the analysis of progression-free survival and objective response presented in this submission is based on data collected before 9 February 2005. The analysis for overall survival is based on data collected before 21 October 2006. The ERG stated that the length of follow-up appeared to be adequate for a metastatic breast cancer population. However, the median length of follow-up was not reported.

1.3 Statements from professional/patient groups and nominated experts

The clinical specialists noted that HER2-negative metastatic breast cancer represented a population with a variety of different symptoms, performance status and life expectancy. They noted that patients with visceral metastases, poor performance status and comorbidities have a poorer prognosis, while those with indolent soft-tissue disease that is hormone-receptor positive have a better outcome irrespective of treatment received. Accordingly, they noted that bevacizumab plus paclitaxel should be used within the groups that were included in the clinical trials. The clinical specialists highlighted that it would not be appropriate to offer bevacizumab plus paclitaxel to patients with uncontrolled hypertension and other cardiac disease.

2 Clinical effectiveness evidence

2.1 Clinical effectiveness in the manufacturer's submission

2.1.1 Direct efficacy comparison

The manufacturer's submission presented clinical-effectiveness data from one randomised controlled trial. E2100 was a multicentre, randomised, open-label trial that evaluated the efficacy and safety of bevacizumab plus weekly paclitaxel compared with weekly paclitaxel monotherapy. The patients in the trial had locally recurrent or metastatic breast cancer and over 95% had HER2-negative breast cancer. Over 90% of patients were enrolled in study centres in the USA; there were no UK centres. The primary endpoint of the trial was duration of progression-free survival. Secondary endpoints were overall survival, objective response (complete response and partial response) rate, duration of response and health-related quality of life. Health-related quality of life was measured by the Functional Assessment of Cancer Therapy

[Fact-B] questionnaire, which is a scale for measurement of quality of life amongst breast cancer patients.

A total of 722 patients were randomised to either bevacizumab plus weekly paclitaxel (n = 368) or weekly paclitaxel monotherapy (n = 354). All patients were given intravenous weekly paclitaxel (90 mg/m^2 over 1 hour) once a week for 3 weeks, with no treatment given at week 4. Patients in the bevacizumab plus weekly paclitaxel arm received intravenous bevacizumab (10 mg/kg) every 2 weeks, until progression of disease or unacceptable toxicity occurred. There was no limit to the number of cycles of therapy allowed. Patients were followed for response until progressive disease, whether or not study therapy was discontinued prior to disease progression, and for survival for 5 years from the date of randomisation. At the time of the manufacturer's interim analysis most patients had discontinued randomised therapy; for 360 patients (50%) this was because of disease progression, and 131 patients (18%) withdrew from the study because of unacceptable toxicity. For further details of the study design and analysis plan see the manufacturer's submission pages 82–95.

Data from two additional randomised controlled trials, the AVADO and the RIBBON-1 studies, were not presented in the manufacturer's submission because the manufacturer considered that they had limited relevance. In the AVADO study all patients were given docetaxel at a dose of 100 mg/m^2 3-weekly (that is, once every 3 weeks) for up to nine cycles. The manufacturer stated that this dosing regimen was not considered representative of routine NHS clinical practice, because clinicians generally treat first-line metastatic breast cancer patients with docetaxel 75 mg/m^2 3-weekly for a maximum of six, or in exceptional cases, eight cycles. In the RIBBON-1 study, patients were randomised to receive treatment with capecitabine, a taxane or anthracyclines in combination with bevacizumab or placebo. The manufacturer stated that this study was excluded because it was not powered

to provide any individual outcome data for the 180 patients treated with bevacizumab plus docetaxel.

2.1.2 Results of E2100 study

An intention-to-treat stratified analysis of the primary endpoint of progression-free survival for all randomised patients demonstrated a statistically significant increase in median progression-free survival of 5.5 months, from 5.8 months in the paclitaxel monotherapy arm to 11.3 months in the bevacizumab plus paclitaxel arm. The stratified hazard ratio for progression-free survival was 0.48 (95% confidence interval [CI] 0.39, 0.61; $p < 0.0001$). This suggested that the addition of bevacizumab to paclitaxel halved the relative risk of progression compared with paclitaxel monotherapy. The manufacturer stated that patients derived progression-free survival benefit with the addition of bevacizumab irrespective of prior therapy (anthracyclines or taxanes), disease-free interval, disease sites or tumour burden quantified by size of target lesions in patients with measurable disease. Full details of the analyses of progression-free survival in subgroups of the E2100 study are presented on page 92 of the manufacturer's submission.

The median overall survival was improved by 1.7 months, from 24.8 months with paclitaxel alone to 26.5 months with bevacizumab plus paclitaxel. The stratified hazard ratio for overall survival was 0.87 (95% CI 0.72, 1.05; $p = 0.14$), indicating a non-statistically significant 13% improvement in overall survival with the combination therapy. The manufacturer stated that no information was collected regarding subsequent therapy after disease progression for any patient. Thus, the effect of post-progression therapy (including bevacizumab) on overall survival could not be analysed. In addition, the manufacturer stated that the number of patients originally randomised to paclitaxel monotherapy and subsequently switched over to receive bevacizumab plus paclitaxel was not recorded.

In the intention-to-treat population, the median time to treatment failure was 4.9 months with paclitaxel alone and 8.3 months with bevacizumab plus paclitaxel (hazard ratio 0.52, 95% CI 0.43–0.63). The overall response rate was more than twice as high in the bevacizumab plus paclitaxel arm (49.8%) compared with the paclitaxel alone arm (22.2%) ($p < 0.0001$), indicating that half of the patients in the bevacizumab plus paclitaxel arm had an objective response.

At baseline, 302 (87.3%) patients in the paclitaxel alone arm and 317 (88.8%) patients in the bevacizumab plus paclitaxel arm completed the FACT-B questionnaire, which measured health-related quality of life. At week 33, 205 people in the bevacizumab plus paclitaxel arm and 163 people in the paclitaxel arm completed the questionnaire. If scores were missing at week 17 or week 33, then the patient was not included in the analysis for that respective time point; except when disease progression or death was recorded earlier. For those patients who died or had disease progression, a value of zero (that is, the worst score) for each of the five subscales in the FACT-B questionnaire was imputed (rather than the patient being excluded from the analysis).

The manufacturer stated that, with imputed values, the difference in total FACT-B score between the two treatment arms was statistically significantly different ($p = 0.0046$) in favour of the bevacizumab plus paclitaxel arm at week 33. The manufacturer stated that the score for each of the five subscales showed a similar pattern. There were no statistically significant differences between treatment arms at week 17 or 33 if imputed values were not used. See tables 17 and 18 in the manufacturer's submission for further details. The manufacturer stated that, taken together, these results demonstrate that the addition of bevacizumab to paclitaxel led to a relative improvement in health-related quality of life.

The safety analyses reported that the addition of bevacizumab to paclitaxel resulted in a 20% overall increase in the incidence of grade 3–5 adverse

events, driven mainly by an increase in grade 3 hypertension and sensory neuropathy. Grade 3–5 adverse events associated with bevacizumab included hypertension (15.7% incidence with the addition of bevacizumab), proteinuria (3% incidence with the addition of bevacizumab), arterial thromboembolic events (3.6% incidence with the addition of bevacizumab), bleeding (2.2% incidence with the addition of bevacizumab) and congestive heart failure (2.2% incidence with the addition of bevacizumab).

2.1.3 Non-randomised studies

Clinical effectiveness data were presented from one non-randomised trial (ATHENA). It was a multicentre, single-arm, open-label study evaluating the safety and efficacy of bevacizumab when combined with a taxane as a first-line treatment of patients with HER2-negative locally recurrent or metastatic breast cancer. The manufacturer stated that the large number of patients (n = 2251) was considered appropriate to evaluate the occurrence of rare adverse events. Serious adverse events (grade 3–5) were reported in 655 patients (29%), the most frequent of which were febrile neutropenia (5.1%), neutropenia (3.6%) and pyrexia (1.5%). At the time of data cut-off, disease had progressed in 58% of patients and the median time to progression was 9.5 months (95% CI 9.1–9.9). The overall response rate ('best response') was 52% in the intent-to-treat population and a further 33% achieved stable disease.

2.1.4 Indirect comparison

The manufacturer carried out indirect comparisons with bevacizumab plus paclitaxel compared with docetaxel monotherapy and gemcitabine plus paclitaxel. The comparisons were carried out using a common comparator (that is, 3-weekly paclitaxel) based on the Bucher method. A systematic review was conducted and a summary of trials used in the comparison is presented in table 1. The manufacturer noted that studies conducted only in first-line metastatic breast cancer patients were not always available, so the

exclusion criteria specified that trials in which the majority of patients (more than 60%) were receiving second or later lines of treatment would be excluded.

Table 1 Summary of trials used to conduct indirect comparison (manufacturer's submission page 123)

Trial	Intervention	Comparator	Study population
E2100 2005	Bevacizumab +paclitaxel (weekly) n = 368	Paclitaxel (weekly) n = 354	First-line LR/mBC
Albain 2008	Gemcitabine +paclitaxel (3-weekly) n = 266	Paclitaxel (3-weekly) n = 263	First-line LR/mBC
Seidman 2008 (CALGB 9840)	Paclitaxel (weekly) n = 350	Paclitaxel (3-weekly) n = 385	mBC, predominantly first-line (19% second-line)
Jones 2005	Docetaxel n = 225	Paclitaxel (3-weekly) n = 224	Locally advanced/mBC, first-line (45%) and second-line (55%)
LR: locally recurrent; mBC: metastatic breast cancer; weekly: once a week for 3 weeks, followed by a week of rest; 3-weekly: once every three weeks			

The manufacturer noted that the studies were associated with some limitations in terms of their relevance and subsequent inclusion in the indirect comparison. In particular, the Seidman study (weekly paclitaxel compared with 3-weekly paclitaxel) allowed for an imbalance of trastuzumab-treated patients in the two arms and therefore the possibility of biased results. Also, the Jones study used a higher docetaxel dose (100 mg/m^2 3-weekly) and a longer duration of treatment (maximum 32 cycles) compared with standard UK practice (75 mg/m^2 3-weekly; maximum 6–8 cycles). However, based on the

similar populations, baseline characteristics and exclusion/inclusion criteria, the manufacturer assumed that heterogeneity would not be significant.

The progression-free survival hazard ratio for bevacizumab plus weekly paclitaxel compared with docetaxel monotherapy was estimated to be 0.555 (95% CI 0.39–0.78) and 0.464 (95% CI 0.34–0.64) compared with gemcitabine plus 3-weekly paclitaxel. The progression-free survival hazard ratio for weekly paclitaxel compared with 3-weekly docetaxel was 1.147 (95% CI 0.89–1.48) and the hazard ratio for weekly paclitaxel compared with gemcitabine plus 3-weekly paclitaxel was 0.958 (95% CI 0.76–1.2). The manufacturer's submission notes that both of these latter comparisons were not statistically significant.

2.2 Evidence Review Group comments

The ERG considered that the manufacturer's search strategies were appropriate and likely to have identified all the evidence relevant to the decision problem. However, the ERG had several concerns about the selection and quality of the evidence presented in the manufacturer's submission.

The evaluation of the clinical effectiveness of bevacizumab was primarily based on a single RCT (E2100) comparing bevacizumab plus weekly paclitaxel with weekly paclitaxel alone. The ERG highlighted limitations in the methodological quality of the study (for example, lack of blinding and lack of data collection regarding treatments given after disease progression). However, the ERG considered that reasonable attempts were made to minimise the potential for bias in data collection and analysis. In addition, the ERG noted concerns about the reliability of the health-related quality-of-life data. The conclusions were primarily based on the analyses using extreme imputed values for people who had died or whose disease had progressed, and therefore the significant improvement in the FACT-B score stated by the manufacturer may not be reliable. The ERG noted that the results reported in

the manufacturer's submission were derived from interim analyses and that more recent follow-up data would be valuable, particularly for survival outcomes. The manufacturer clarified that more recent analyses were not available. The ERG also noted the trial suggested that overall survival was not statistically significantly different between treatment arms. However, the ERG was unable to establish whether or not the lack of overall survival difference was due to crossover between treatment groups or any other post-progression events, because these data were not collected in the trial.

The ERG was concerned that the manufacturer excluded evidence from both the direct and indirect efficacy comparison that was relevant to the decision problem. In particular, evidence that could have provided information on the efficacy of adding bevacizumab to docetaxel (the taxane monotherapy currently recommended by NICE for the first-line treatment of HER2-negative metastatic breast cancer) was excluded from the submission. The ERG noted that the manufacturer had excluded a trial of bevacizumab plus docetaxel compared with docetaxel plus placebo (the AVADO trial) because the dose was considered inappropriate compared with routine clinical practice. However, clinical advice to the ERG indicated that the dose of docetaxel used in AVADO is used in routine clinical practice. The ERG also noted that the Jones trial, which was included in the indirect comparison, also used the same dose of docetaxel as in the AVADO trial. Because of the lack of other data for comparison of effectiveness of bevacizumab plus docetaxel, the ERG also considered that data from the RIBBON-1 trial (which had been excluded by the manufacturer due to insufficient statistical power for the relevant docetaxel comparison) could have been included. The ERG noted that an additional study (the Will Weekly Win study comparing weekly paclitaxel with 3-weekly paclitaxel), for which there were limited data available, had also not been included by the manufacturer.

The ERG identified several other limitations and inconsistencies relating specifically to study selection for the indirect efficacy comparison. The ERG

noted that the inclusion criteria specified that studies could be included as long as less than 60% (rather than a strict majority of 50%) of people were receiving second-line treatments for metastatic breast cancer. The ERG noted that the Jones (2005) study was included as a result of this broader criterion. The ERG also noted that studies were included even if the proportion of the study population who were HER2-negative was not reported, although they did not consider this alone to be a major limitation. The ERG also noted that the validity of the studies included in the indirect comparison had not been adequately assessed.

The ERG also reported concerns relating to the methods of the indirect comparison, noting differences between patient populations and potentially important methodological limitations among the trials included in this comparison. In addition the ERG considered that the statistical method used had been applied beyond its intended use in the submitted indirect comparison network. Given these methodological limitations, the ERG did not consider the findings of the indirect comparison to be reliable.

2.3 Statements from professional/patient groups and nominated experts

The clinical specialists noted that a randomised placebo-controlled trial of docetaxel with or without bevacizumab (AVADO) has recently completed. They noted that, like E2100, it met its primary endpoint and suggested that there was a benefit in terms of progression-free survival in favour of the bevacizumab plus docetaxel combination. It was also noted that the patient population studied in the E2100 trial does reflect the circumstances under which patients are treated in current everyday UK clinical practice, so the trial results can be extrapolated to the UK setting. Clinical specialists highlighted that bevacizumab is considered a useful addition to the current first-line treatment options available for patients with metastatic breast cancer. In particular, the magnitude of the progression-free survival benefit seen in the

E2100 trial and the tolerability of the bevacizumab plus paclitaxel regimen are similar to those seen in other combination chemotherapy trials.

However, some clinical specialists noted that there are important clinical questions relevant to UK everyday practice, such as the optimal duration of therapy, that have not been addressed in the manufacturer's submission.

Patient and professional groups noted that 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. Because metastatic breast cancer is not curable, treatments that can effectively delay progression and improve survival are vital for this patient group.

Experts representing primary care trusts noted that it is important to determine the quality of life during the time of delayed disease progression, because the E2100 and AVADO studies did not report a significant improvement in overall survival. In addition, these experts noted that the AVADO study has not yet been published in a peer-reviewed journal.

3 Cost effectiveness

3.1 Cost effectiveness in the manufacturer's submission

No publications evaluating the cost effectiveness, or examining the health economics, of bevacizumab for the first-line treatment of metastatic breast cancer from a UK perspective were identified. Therefore, the manufacturer developed a new economic model for this submission.

The manufacturer's model was a 3-state Markov model with a cycle length of 1 month. Patients in the original model received treatment with either bevacizumab plus weekly paclitaxel or the comparator treatment, that is,

- weekly paclitaxel
- docetaxel

- gemcitabine plus 3-weekly paclitaxel.

Bevacizumab plus docetaxel was not included as a comparator in the model. The manufacturer stated that the combination is not recommended and is not used in the NHS. The cost effectiveness of bevacizumab plus docetaxel was discussed briefly, but not formally evaluated by the manufacturer.

Patients were assumed to be in one of three possible discrete health states at any given time; 'progression-free survival', 'progressed' or 'death'. The 'progressed' health state represented the time period from first treatment relapse until death and included the possibility of remission and relapse following second and subsequent lines of treatments. It was assumed that patients would have the same risk of dying after disease progression regardless of the first-line therapy received. For this, the progression to death from both arms of the E2100 trial was combined and treated as a single population; the mean time to death was converted to a constant hazard of dying regardless of treatment arm. In addition, the model assumed that patients would have the same sequence of further health-care resource after disease progression, regardless of initial treatment.

The number of patients who died while in progression-free survival was determined either by background mortality or by the monthly rate at which patients died (from any cause) while in progression-free survival in the E2100 trial. The progression-free survival mortality rates for weekly paclitaxel monotherapy were used as a proxy for the mortality rates for docetaxel and gemcitabine plus paclitaxel. Progression-free survival was modelled parametrically using a Gompertz function and the impact on ICERs of using alternative parametric curves was explored in the sensitivity analysis.

The 'time to off treatment' was calculated from the E2100 trial for both paclitaxel and bevacizumab. Weibull functions were used in the economic model to reflect time on treatment, which was subsequently used to estimate treatment costs. Alternative fits and non-parametric modelling using Kaplan-

Meier methods were also explored. In addition, the assumption of proportional hazards was assumed for paclitaxel because it was administered in both arms.

See manufacturer's submission page 169 for more information on the structure of the economic model.

The manufacturer provided two base-case analyses:

- The first used the list prices in accordance with the NICE reference case. The prices for bevacizumab (total average per patient cost over 10 years, £25,929) and paclitaxel (total average per patient cost over 10 years, £7720) were taken from the BNF, edition 58.
- The second used the paclitaxel PASA price (total average per patient cost over 10 years, £649) and a 10-g cap for bevacizumab. Sensitivity analyses were only provided for this case. The 10-g cap for bevacizumab has not been approved by the Department of Health.

Dosing was modelled using Kaplan-Meier methods and parametric extrapolation based upon the dosing curves from the E2100 trial. The cost of febrile neutropenia (1%), hypersensitivity (3%), hypertension (4%) and infection (6%) were £3803, £274, £367, £243 respectively. See manufacturer's submission pages 163–165 for more information on the costs used in the economic model.

Although quality of life was measured in the E2100 trial, the use of the FACT-B instrument was not considered adequate for informing the requisite generic measure of health or subsequent utility scores. Therefore, the manufacturer identified utility values from the literature.

The economic analysis considered the utility of individuals with metastatic breast cancer associated with the model health states and also included disutility associated with febrile neutropenia and peripheral sensory

neuropathy. The manufacturer assumed that the remaining adverse events (hypersensitivity, infection, hypertension) would not have a notable impact on health-related quality-of-life. It was assumed that the docetaxel adverse events would be equivalent to those for paclitaxel, with the exception of the increased incidence of febrile neutropenia which was incorporated as an additional adverse event in the docetaxel arm.

The base-case utility scores were taken from one study that derived utility values from oncology nurses using the standard gamble technique. The values were 0.73 for progression-free survival (this was an average of values of 0.81 for response and 0.65 for stable disease), 0.45 for progressive disease, −0.21 for disutility from febrile neutropenia and for peripheral sensory neuropathy (both applied only in month 1 of experiencing the event).

The results based on the NHS list prices indicated a cost per quality-adjusted life year (QALY) of £117,803, £115,059 and £105,777 for bevacizumab plus weekly paclitaxel therapy relative to weekly paclitaxel, docetaxel and gemcitabine plus paclitaxel therapy (table 2).

The results based on average PASA prices for paclitaxel and a 10-g cap for bevacizumab indicated a cost per QALY of £77,314, £57,753 and £60,101 for bevacizumab plus weekly paclitaxel therapy relative to weekly paclitaxel, docetaxel and gemcitabine plus paclitaxel therapy (table 3).

Table 2 Cost per life year/cost per QALY gained ratios for bevacizumab plus paclitaxel over a lifetime period of 10 years (deterministic analysis) – NHS list price

Cost-utility results	Bev-Pac	Pac	Doc	Gem-Pac
Mean life years (yrs)	2.682	2.330	2.330	2.330
Mean QALYs	1.498	1.239	1.225	1.239
Mean total cost	£56,473	£26,004	£25,057	£29,115
Incremental life years		0.352	0.352	0.352
Incremental QALYs		0.259	0.273	0.259
Incremental cost		£30,469	£31,416	£27,358
Cost per life year gained		£86,572	£89,263	£77,734
Cost per QALY gained		£117,803	£115,059	£105,777

Table 3 Cost per life year/cost per QALY gained ratios for bevacizumab plus paclitaxel over a lifetime period of 10 years (deterministic analysis) – PASA price for paclitaxel and a 10-g cap for bevacizumab

Cost-utility results	Bev-Pac	Pac	Doc	Gem-Pac
Mean life years (yrs)	2.682	2.330	2.330	2.330
Mean QALYs	1.498	1.239	1.225	1.239
Mean total cost	£40,826	£20,829	£25,057	£25,281
Incremental life years		0.352	0.352	0.352
Incremental QALYs		0.259	0.273	0.259
Incremental cost		£19,997	£15,769	£15,545
Cost per life year gained		£56,818	£44,805	£44,168
Cost per QALY gained		£77,314	£57,753	£60,101

The manufacturer stated that it can be inferred from the high ICERs in the model that bevacizumab plus docetaxel (the more expensive taxane) is unlikely to provide a more cost-effective outcome than the analysis presented in the submission and, hence, a full economic analysis was not presented.

The manufacturer conducted further analyses in response to points of clarification from the ERG. The manufacturer incorporated a comparison of bevacizumab plus weekly paclitaxel with 3-weekly paclitaxel monotherapy into the model. For this, the economic model for the comparison against

gemcitabine plus 3-weekly paclitaxel was used with certain adjustments. The treatment benefit of bevacizumab plus weekly paclitaxel relative to 3-weekly paclitaxel was derived using the indirect comparison network (which included gemcitabine plus 3-weekly paclitaxel). The drug and administration cost of gemcitabine was removed from the model inputs. The ICER of bevacizumab plus paclitaxel compared with 3-weekly paclitaxel was £59,339 per QALY gained using PASA prices and incorporating the capping scheme for bevacizumab (table 7, page 39 of clarification response). Bevacizumab plus docetaxel was not included.

The manufacturer also incorporated the results of the evidence synthesis into the economic model as opposed to assuming that all comparators were equally effective. This resulted in an ICER for bevacizumab plus weekly paclitaxel compared with docetaxel and gemcitabine plus 3-weekly paclitaxel of £59,310 and £51,795 per QALY gained respectively.

Sensitivity analyses were performed only on the second base-case scenario in which the PASA price of paclitaxel and the 10-g bevacizumab cap were used. One-way sensitivity analyses were presented as tornado diagrams and probabilistic sensitivity analyses were presented as scatter plots and cost-effectiveness acceptability curves (see pages 211–219 of the manufacturer's submission). Using different parametric functions for survival extrapolation and alternative assumptions on treatment duration had the largest impact on the ICERs. When parametric assumptions were varied, ICERs ranged between £53,492 and £70,662, £40,448 and £52,128, £41,660 and £54,951 for bevacizumab plus paclitaxel therapy relative to weekly paclitaxel, docetaxel and gemcitabine plus paclitaxel therapy respectively. Supportive care costs and different assumptions to utility scores had a smaller impact on the ICERs. The cost-effectiveness acceptability curve suggested that, at a willingness to pay of £30,000 per QALY gained, bevacizumab plus paclitaxel had a 0% probability of being cost effective against all comparators.

3.2 Evidence Review Group comments

The ERG considered that the submission of a de novo economic evaluation was appropriate. However, the ERG considered that one published economic evaluation from the perspective of the Swiss Health Service may have been a potentially important omission considering the lack of publications from a UK perspective. This study used a similar model structure to the manufacturer in their submission to NICE. Parameters were estimated from the E2100 trial but used the results for overall survival and progression-free survival published in Miller et al. (2007), which differ from those presented in the manufacturer's submission. The base-case ICER for bevacizumab plus paclitaxel versus paclitaxel alone was 189,427 euro per QALY gained (2008 prices).

The ERG considered the series of pairwise comparisons for bevacizumab and paclitaxel relative to each separate comparator regimen were inappropriate. They stated that, to establish the correct estimate of the ICER for bevacizumab plus paclitaxel, a fully incremental analysis comparing all the regimens simultaneously should have been conducted.

The ERG highlighted uncertainties and issues relating to the modelling undertaken by the manufacturer, which may have reduced the validity of the cost-effectiveness estimates. The uncertainties and issues with potentially major consequences included:

- Exclusion of relevant interventions/comparators.
- Rate of death after disease progression was assumed to be the same for all treatments in the model.
- Drug acquisition costs used in the model and 10-g cap on the cost of bevacizumab.

The ERG considered that the assumptions in the base case were not necessarily inappropriate individually, but that alternative assumptions were not adequately explored and that, taken together, the assumptions in the base

case tended to be optimistic towards the estimated cost effectiveness of bevacizumab. These assumptions are summarised in table 23, pages 81–82, of the ERG report.

The model did not include bevacizumab plus 3-weekly paclitaxel or bevacizumab plus docetaxel (in line with the decision problem). Moreover, the base-case model did not include the results from the indirect comparison and assumed that all included comparators (docetaxel monotherapy, paclitaxel monotherapy and gemcitabine plus paclitaxel) were equally effective in terms of progression-free survival and overall survival. The ERG noted that the manufacturer did not explore including any differences between treatments that may have influenced the ICERs.

The ERG noted that the model assumed that mortality after disease progression was independent of initial treatment. It assumed that the rate of death after progression was constant over time and the same for all initial treatments. This meant that the differences in mean progression-free survival between treatments were maintained in the estimates of mean overall survival. The ERG stated that this was likely to have led to overestimates of overall survival for bevacizumab plus paclitaxel versus paclitaxel alone compared with the results of the E2100 trial.

The ERG also highlighted concerns relating to the drug acquisition costs used in the model. The cost of bevacizumab was based on the NHS paying for a maximum dose of 10-g per patient. However, the ERG noted that this payment scheme had not been agreed with the Department of Health and should not have been included in the base-case analyses. The cost of paclitaxel used in the model was based on the average PASA price, whereas other proprietary prices were taken from the BNF 58. The manufacturer assumed that docetaxel was available to the NHS at its proprietary price and did not consider the expected price reduction following patent expiry in

November 2010. The ERG also noted that the impact of potential dose reductions had not been explored.

The ERG also reported that the utility values were taken from a non-systematic review of the literature and that the reasoning for the choice of the study used to inform the utility values was not explained. In addition, they noted that the manufacturer had not attempted to map health-related quality-of-life data from the E2100 study (measured by the FACT-B instrument) to preference-based measure or to collate alternative values.

The ERG commented on the further analyses that were conducted by the manufacturer in response to points of clarification. First, the ERG noted that to model the acquisition and monitoring costs of the 3-weekly paclitaxel regimen, the manufacturer simply removed the drug and administration cost associated with gemcitabine from the model. Second, the ERG noted that use of the estimates of effectiveness derived from the indirect treatment comparison in the revised analysis did not appear to significantly alter the ICERs. However, the ERG noted that the ICERs for bevacizumab plus paclitaxel were marginally higher (that is, less favourable) versus docetaxel than when assuming equal effects with weekly paclitaxel and marginally lower (that is, more favourable) versus gemcitabine plus paclitaxel.

3.2.1 Exploratory analyses

The ERG noted that the manufacturer's revised analyses were based on the PASA prices for paclitaxel and the capping scheme for bevacizumab and treatment effects for comparators derived from the indirect treatment comparison. The ERG thus conducted fully incremental analyses using:

- Case 1 (ERG re-analysis) – NHS list prices from BNF 58 excluding capping scheme for bevacizumab
- Case 2 (manufacturer re-analysis) – PASA prices for paclitaxel including capping scheme for bevacizumab

- Case 3 (ERG re-analysis) – PASA prices for paclitaxel excluding capping scheme for bevacizumab.

The ICERs for each of these cases is presented in table 4.

Table 4 Full incremental analysis of the revised results regarding the cost effectiveness of alternative chemotherapy regimens for mBC – case 1 (NHS list price for all treatments), case 2 (PASA price for paclitaxel and capping scheme for bevacizumab) and case 3 (PASA price for paclitaxel).

			Mean costs	Mean QALYs	Incremental cost, next best	Incremental QALYs, next best	ICER (£/QALY), next best
Case 1— NHS list prices	PAC q3w (ITC)	Revised	£22,350	1.122	–	–	–
	DOC (ITC)	Revised	£25,111	1.233	£2,761	0.111	£24,874
	PAC qw (E2100)	Base case	£26,004	1.239			Extendedly dominated
	GEM+PAC (ITC)	Revised	£29,104	1.197			Dominated
	BEV+PAC (E2100)	Base case	£56,473	1.498	£31,362	0.265	£118,362
Case 2 — PASA price and BEV cap	PAC q3w (ITC)	Revised	£18,516	1.122	–	–	–
	PAC qw (E2100)	Base case	£20,829	1.239	£2,313	0.117	£19,769
	DOC (ITC)	Revised	£25,111	1.233			Dominated
	GEM+PAC (ITC)	Revised	£25,271	1.197			Dominated
	BEV+PAC (E2100)	Base case	£40,826	1.498	£19,997	0.259	£77,314
Case 3 — PASA price	PAC q3w (ITC)	Revised	£18,516	1.122	–	–	–
	PAC qw (E2100)	Base case	£20,829	1.239	£2,313	0.117	£19,769
	DOC (ITC)	Revised	£25,111	1.233			Dominated
	GEM+PAC (ITC)	Revised	£25,271	1.197			Dominated
	BEV+PAC (E2100)	Base case	£49,403	1.498	£28,574	0.259	£110,475

In summary, in Case 1, the ICER for bevacizumab plus paclitaxel versus docetaxel was £118,362 per QALY gained. In Case 2, the ICER for bevacizumab plus paclitaxel versus weekly paclitaxel was £77,314 per QALY

gained. In Case 3, the ICER for bevacizumab plus paclitaxel versus weekly paclitaxel was £110,475 per QALY gained. Gemcitabine plus paclitaxel was dominated throughout the three sets of analyses by weekly paclitaxel.

The ERG also conducted a second fully incremental analysis based on the original approach employed by the manufacturer in which the effects on progression-free survival of docetaxel and gemcitabine plus paclitaxel were assumed equal to those of paclitaxel. The results are presented in table 5.

Table 5 Full incremental analysis of the non-revised (original MS) results regarding the cost effectiveness of alternative chemotherapy regimens for mBC – case 1 (NHS list price for all treatments), case 2 (PASA price for paclitaxel and capping scheme for bevacizumab) and case 3 (PASA price for paclitaxel).

		Mean costs	Mean QALYs	Incremental cost, next best	Incremental QALYs, next best	ICER (£/QALY), next best
Case 1— NHS list prices	DOC (PFS equal to PAC qw)	£25,057	1.225	–	–	–
	PAC qw (E2100)	£26,004	1.239	£947	0.014	£67,643
	GEM+PAC (PFS equal to PAC qw)	£29,115	1.239			Dominated
	BEV+PAC (E2100)	£56,473	1.498	£30,469	0.259	£117,641
Case 2 — PASA price and BEV cap						
	PAC qw (E2100)	£20,829	1.239	–	–	–
	DOC (PFS equal to PAC qw)	£25,057	1.225			Dominated
	GEM+PAC (PFS equal to PAC qw)	£25,281	1.239			Dominated
	BEV+PAC (E2100)	£40,826	1.498	£19,997	0.259	£77,314
Case 3 — PASA price						
	PAC qw (E2100)	£20,829	1.239	–	–	–
	DOC (PFS equal to PAC qw)	£25,057	1.225			Dominated
	GEM+PAC (PFS equal to PAC qw)	£25,281	1.239			Dominated
	BEV+PAC (E2100)	£49,403	1.498	£28,574	0.259	£110,475

The overall results were similar to the revised analyses, except for the case in which the costs were taken from the BNF (Case 1). In this analysis, docetaxel was no longer dominated. The ICER for weekly paclitaxel versus docetaxel

was £67,643 per QALY gained and the ICER for bevacizumab plus paclitaxel versus weekly paclitaxel was £117,641 per QALY gained.

The ERG also undertook several analyses to address some of the other identified limitations and uncertainties. These analyses are presented on pages 90–99 of the ERG report. These included analyses to explore:

- the impact of a reduction in the potential price of generic docetaxel
- using alternative utility (health-related quality of life) values
- incorporating bevacizumab plus docetaxel regimen as an intervention in the economic model
- addressing some of the potential weaknesses in the indirect treatment comparison. This involved excluding studies considered inappropriate, and including relevant RCTs that were left out
- an additional analysis using an area under the curve model to check internal validity of the results for overall survival from the manufacturer's model.

The analyses by the ERG found that the acquisition cost of docetaxel had very little effect on the ICER of docetaxel versus bevacizumab plus paclitaxel. Alternative assumptions about utility values for the health states did not markedly affect the results.

The ERG evaluated bevacizumab plus docetaxel versus docetaxel based on the results of the AVADO trial. This found that the ICER was more than £250,000 per QALY gained.

The ERG also constructed an alternative model that was calibrated to the E2100 results for overall survival. This was considered important to test the internal validity of the model by comparing the median survival time for progression-free survival and overall survival found by the E2100 trial with the model predictions. These comparisons are presented in table 6:

Table 6 Comparison of model predictions with E2100 trial

		Mean PFS (months)	Median PFS (months)	Mean overall survival (months)	Median overall survival (months)
Model prediction	Paclitaxel	8.2	6.5	28.0	23
E2100 trial estimate	Paclitaxel	N/A	5.8	N/A	24.8
Model prediction	Bevacizumab plus paclitaxel	12.5	11	32.2	28
E2100 trial estimate	Bevacizumab plus paclitaxel	N/A	11.3	N/A	26.5
Model prediction	Difference	4.3	4.5	4.2	5
E2100 trial estimate	Difference	N/A	5.5	N/A	1.7

N/A: E2100 did not estimate mean survival.

PFS: progression-free survival

The ICER of bevacizumab plus paclitaxel versus paclitaxel was over £250,000 per QALY in the revised model.

Table 7 Costs and QALYs of bevacizumab plus paclitaxel versus paclitaxel (10 years) with ERG model compared with manufacturer model

	ERG model results			MS model results		
	BEV+ PAC	PAC	Incremental	BEV+ PAC	PAC	Incremental
Mean life years (yrs)	2.165	2.133	0.033	2.682	2.330	0.352
Mean life years in PFS (yrs)	1.000	0.644	0.356	1.041	0.686	0.355
Mean life years in progression (yrs)	1.165	1.489	−0.323	1.641	1.645	−0.003
Mean QALYs	1.315	1.201	0.114	1.498	1.239	0.259
Mean QALY in PFS	0.791	0.531	0.260	0.759	0.499	0.260
Mean QALY in progression	0.524	0.670	−0.145	0.739	0.740	−0.001
Mean total cost	£48,566	£18,891	£29,675	£56,473	£26,004	£30,469
Cost per QALY gained (£)		£259,267			£117,803	

PFS: progression-free survival; QALY: quality-adjusted life year

Addressing some of the limitations of the indirect treatment comparison, the revised ERG analysis reached the same conclusion as the manufacturer's submission that bevacizumab plus paclitaxel and bevacizumab plus docetaxel would be expected to be of similar effectiveness. Therefore the inclusion and exclusion of studies did not have a major effect. The ERG noted that the most cost-effective strategy between these two would then depend on the acquisition and administration cost of paclitaxel and docetaxel and noted again that docetaxel may come off patent in November 2010.

Equality and diversity

No equality and diversity issues relating to population groups protected by equality legislation were highlighted when the scope for this appraisal was developed or in any of the submissions.

4 Authors

Raisa Sidhu, Jennifer Priaulx, Rebecca Trowman, with input from the Lead Team (Jane Adam, Olivia Wu, Peter Haywood, Elizabeth Brain).

Appendix A: Sources of evidence considered in the preparation of the premeeting briefing

A The Evidence Review Group (ERG) report for this appraisal was prepared by the NHS Centre for Reviews & Dissemination (CRD) – York.

- Rogers M, Soares M, Epstein D et al. Bevacizumab in combination with a taxane for the first-line treatment of HER2-negative metastatic breast cancer, June 2010.

B Submissions or statements were received from the following organisations:

I Manufacturer/sponsor:

- Roche Products Limited

II Professional/specialist, patient/carer and other groups:

- NCRI Breast Clinical Studies Group/RCP/RCR/ACP/JCCO
- Commissioning Support Appraisals Service
- NHS Kensington and Chelsea
- Breast Cancer Care
- Breakthrough Breast Cancer