

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

Technology appraisal guidance
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This guidance replaces TA147.

1 Guidance

During the course of this appraisal the European Medicines Agency conducted a review of the use of bevacizumab in combination with taxanes for the treatment of metastatic breast cancer. Following that review, the EMA's Committee for Medicinal Products for Human Use (CHMP) recommended that bevacizumab, when used to treat metastatic breast cancer, should be used only in combination with the taxane paclitaxel.

This guidance updates and replaces terminated technology appraisal 147, Bevacizumab in combination with paclitaxel for the first-line treatment of metastatic breast cancer, issued June 2008.

- 1.1 Bevacizumab in combination with a taxane is not recommended for the first-line treatment of metastatic breast cancer.
- 1.2 Patients currently receiving bevacizumab in combination with a taxane for the first-line treatment of metastatic breast cancer should have the option to continue therapy until they and their clinicians consider it appropriate to stop.

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 paclitaxel or docetaxel has a marketing authorisation for 'first-line treatment of patients with metastatic breast cancer'.
- 2.2 The summary of product characteristics (SPC) 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 SPC.
- 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 59). The acquisition cost of bevacizumab (excluding VAT and assuming wastage) for a patient weighing 70 kg is £1652.38 at a dosage of 10 mg/kg every 2 weeks and £2576.78 at a dosage of 15 mg/kg every 3 weeks. This amounts to an average monthly cost of £3304.76 at a dosage of 10 mg/kg every 2 weeks and £3435.70 at a dosage of 15 mg/kg every 3 weeks. Costs may vary in different settings because of negotiated procurement discounts.

3 The manufacturer's submission

The Appraisal Committee ([appendix A](#)) considered evidence submitted by the manufacturer of bevacizumab and a review of its submission by the Evidence Review Group (ERG; [appendix B](#)). This appraisal will replace the terminated technology appraisal number 147, June 2008, 'Bevacizumab in combination with paclitaxel for the first-line treatment of metastatic breast cancer'.

The manufacturer's original submission focused on the combination of bevacizumab plus paclitaxel. The manufacturer did not submit evidence on the clinical or cost effectiveness of bevacizumab plus docetaxel in its original submission. The evidence from this submission is outlined from paragraphs 3.1 to 3.12. Following consultation on the appraisal consultation document, the manufacturer provided additional subgroup data on prior taxane-treated groups and groups with triple negative disease, as well as additional data from the AVADO and RIBBON-1 studies. The evidence from this additional submission is outlined from sections 3.21 to 3.33.

Clinical effectiveness

3.1 The manufacturer's original submission presented clinical-effectiveness data from one randomised, open-label, controlled trial (E2100). A total of 722 patients were randomised to either bevacizumab plus weekly paclitaxel (n = 368) or weekly paclitaxel alone (n = 354). The randomisation was stratified by disease-free interval (less than or equal to 24 months; greater than 24 months), number of metastatic sites (less than 3; greater than or equal to 3), prior receipt of adjuvant chemotherapy (yes; no) and oestrogen receptor status (positive; negative; and unknown). All patients were given intravenous weekly paclitaxel (90 mg/m² over 1 hour) once a week for 3 weeks, with no treatment given at week 4. Patients in the bevacizumab plus weekly paclitaxel arm also 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. The patients in the trial had locally recurrent or metastatic breast cancer and over 90% had HER2-negative breast cancer. 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 measuring quality of life among breast cancer patients.

- 3.2 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. The interim analyses consisted of a stratified log rank test where the stratification factors were disease-free interval and prior adjuvant chemotherapy. There was a statistically significant increase in median progression-free survival of 5.5 months, from 5.8 months in the paclitaxel alone arm to 11.3 months in the bevacizumab plus paclitaxel arm. The stratified hazard ratio for progression was 0.48 (95% confidence interval [CI] 0.39 to 0.61; $p < 0.0001$). The stratified hazard ratio for death was 0.87 (95% CI 0.72 to 1.05; $p = 0.14$), indicating a non-statistically significant improvement in median overall survival of 1.7 months, from 24.8 months with paclitaxel alone to 26.5 months with bevacizumab plus paclitaxel.
- 3.3 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. At week 33, 163 patients in the paclitaxel arm and 205 patients in the bevacizumab plus paclitaxel arm completed the questionnaire. If scores were missing at week 17 or week 33, 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). When imputed values were used, the difference in total FACT-B score between the two treatment arms was statistically significant ($p = 0.0046$) in favour of the bevacizumab plus paclitaxel arm at week 33. There were no statistically significant differences between treatment arms at week 17, or at week 33 if imputed values were not used. The manufacturer stated that, taken together, these results demonstrated that the addition of bevacizumab to paclitaxel led to a

relative improvement in health-related quality of life.

- 3.4 The safety analyses from the E2100 trial reported that the addition of bevacizumab to paclitaxel resulted in a 20% overall increase in the incidence of grade 3–5 adverse events. These included neuropathy (25.3%), hypertension (16%), arterial thromboembolic events (3.6%), proteinuria (3%), bleeding (2.2%) and congestive heart failure (2.2%). In addition, adverse event data from a non-randomised single-arm, open-label study (ATHENA, n = 2251) were presented. The most frequent serious adverse events (grade 3–5) were febrile neutropenia (5.1%), neutropenia (3.6%) and pyrexia (1.5%).
- 3.5 The manufacturer carried out indirect comparisons for bevacizumab plus weekly paclitaxel compared with docetaxel alone and gemcitabine plus 3-weekly paclitaxel. The comparisons were carried out by an indirect method using two comparators to link three trials. The manufacturer noted that studies conducted only in patients having first-line treatment for metastatic breast cancer were not always available, so the exclusion criteria specified that trials in which more than 60% of patients were receiving second or later lines of treatment would be excluded. The manufacturer noted that one study used a higher docetaxel dosage (100 mg/m² 3-weekly) and a longer duration of treatment (maximum 32 cycles) compared with standard UK practice (considered by the manufacturer to be 75 mg/m² 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.
- 3.6 The hazard ratio for progression with bevacizumab plus weekly paclitaxel compared with docetaxel alone was estimated to be 0.56 (95% CI 0.39 to 0.78) and 0.46 (95% CI 0.34 to 0.64) compared with gemcitabine plus 3-weekly paclitaxel. For weekly paclitaxel compared with 3-weekly docetaxel the hazard ratio for progression was 1.15 (95% CI 0.89 to 1.48) and for weekly paclitaxel compared with gemcitabine plus 3-weekly paclitaxel the hazard ratio for progression was 0.96 (95% CI 0.76 to 1.21).

Cost effectiveness

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

- weekly paclitaxel or
- docetaxel or
- gemcitabine plus 3-weekly paclitaxel.

Although bevacizumab plus docetaxel was included in the scope it was not formally evaluated in the manufacturer's economic analysis.

3.8 Patients were assumed to be in one of three possible discrete health states at any given time: 'progression-free survival', 'progressed' or 'death'. It was assumed that patients would have the same risk of dying after disease progression regardless of the first-line treatment they had received. In addition, the model assumed that patients would have the same sequence of further treatment and resource use after disease progression, regardless of their initial treatment. The number of patients who died while in the 'progression-free survival' state was determined either by the maximum of background mortality or the monthly rate at which patients died (from any cause) while progression-free in the E2100 trial. In the base-case model, the progression-free mortality rates for weekly paclitaxel alone were used as a proxy for the mortality rates for docetaxel and gemcitabine plus paclitaxel.

3.9 The manufacturer provided two base-case analyses, both incorporating a 10-year time horizon:

- The first used the list prices in accordance with the NICE reference case. The prices for bevacizumab (total average cost per patient, £25,929) and paclitaxel (total average cost per patient, £7720) were taken from the BNF, edition 58. Drug costs were calculated according to the recommended adult dose and duration of treatment was estimated from the E2100 trial. Dose reductions were not modelled.

- The second used an average NHS cost for paclitaxel (total average cost per patient, £649) based on the average price paid by NHS trusts over a 4-month period, and a patient access scheme for bevacizumab whereby the NHS covers the cost of the first 10 g bevacizumab needed for each patient. Sensitivity analyses were only provided for this case. The patient access scheme (10-g cap) for bevacizumab was not approved by the Department of Health and was not considered by the Committee.
- 3.10 The base-case utility values were taken from one study that derived proxy 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, and -0.21 for disutility from febrile neutropenia and peripheral sensory neuropathy (both applied only in month 1 of experiencing the event). It was assumed that the remaining adverse events (hypersensitivity, infection and hypertension) would not have a notable impact on health-related quality of life.
- 3.11 The results based on the NHS list prices indicated incremental costs of £30,469, £31,416 and £27,358 and incremental quality-adjusted life years (QALYs) of 0.259, 0.273 and 0.259 for bevacizumab plus weekly paclitaxel therapy relative to weekly paclitaxel, docetaxel and gemcitabine plus paclitaxel therapy respectively. The cost per QALY was £117,803, £115,059 and £105,777 for bevacizumab plus weekly paclitaxel therapy relative to weekly paclitaxel, docetaxel and gemcitabine plus paclitaxel therapy respectively. The results based on average prices paid by NHS trusts over a 4-month period for paclitaxel and the patient access scheme (not approved by the Department of Health) for bevacizumab were provided and indicated a lower cost per QALY for bevacizumab plus weekly paclitaxel therapy relative to weekly paclitaxel, docetaxel and gemcitabine plus paclitaxel therapy respectively, though remaining above £57,000 per QALY gained. The manufacturer stated that it can be inferred from the high incremental cost-effectiveness ratios (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 of bevacizumab plus docetaxel was not presented. The manufacturer carried out sensitivity analyses only on the second base-case scenario, in which the average price of paclitaxel paid by NHS

trusts over a 4-month period and the patient access scheme for bevacizumab were used, and it was observed that using different parametric functions for time to progression and alternative assumptions on treatment duration had the largest impact on the ICERs.

- 3.12 The manufacturer conducted further analyses in response to points of clarification requested by the ERG, incorporating into the model a comparison of bevacizumab plus weekly paclitaxel with 3-weekly paclitaxel alone. The ICER for bevacizumab plus weekly paclitaxel compared with 3-weekly paclitaxel was £59,339 per QALY gained using average prices paid by NHS trusts for paclitaxel and incorporating the patient access scheme for bevacizumab. 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 was also based on the average price of paclitaxel paid by NHS trusts and the patient access scheme for bevacizumab. 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.

ERG comments on the original manufacturer's submission

- 3.13 The ERG had several concerns about the selection and quality of the evidence presented in the manufacturer's original submission. The evaluation of the clinical effectiveness of bevacizumab was based primarily on a single trial 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 about treatments given after disease progression. The ERG noted concerns that, as the conclusions about health-related quality of life were based primarily on the analyses using extreme imputed values for patients who had died or whose disease had progressed, 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 suggested that more recent follow-up data would be

valuable, particularly for survival outcomes. The ERG also noted that the E2100 trial suggested that overall survival was not statistically significantly different between the treatment arms. However, the ERG was unable to establish whether or not the lack of difference in overall survival was due to crossover between treatment groups or any other post-progression events, because these data were not collected in the trial.

- 3.14 The ERG noted that the manufacturer had not presented any data on the clinical effectiveness of bevacizumab plus docetaxel in its submission. The ERG noted that a trial of bevacizumab plus docetaxel compared with docetaxel plus placebo (the AVADO trial) had been excluded. In addition, the ERG also considered that data from the RIBBON-1 trial could potentially have been included. The RIBBON-1 trial was excluded by the manufacturer because of insufficient statistical power for the relevant docetaxel comparison. Data from both these studies were provided by the manufacturer in response to consultation on the appraisal consultation document (see sections 3.23 and 3.24).
- 3.15 The ERG also highlighted a number of concerns about the indirect comparison conducted by the manufacturer. The ERG noted that an additional study (the Will Weekly Win study comparing weekly paclitaxel with 3-weekly paclitaxel, for which there were some data reported in an abstract) had not been included by the manufacturer. The ERG noted that the inclusion criteria specified that studies could be included as long as fewer than 60% (rather than a strict majority of 50%) of patients were receiving second-line treatments for metastatic breast cancer. The ERG highlighted that the validity of the studies included in the indirect comparison had not been adequately assessed. The ERG also reported concerns about the methods of the indirect comparison, noting differences between patient populations and potentially important methodological limitations among the trials included in this comparison. Given these methodological limitations, the ERG did not consider the findings of the indirect comparison to be reliable.
- 3.16 The ERG had a number of concerns about the economic model submitted by the manufacturer. The ERG considered that the series of pair wise comparisons for bevacizumab plus paclitaxel relative to each separate

comparator regimen were inappropriate. It stated that, to establish the correct estimate of the ICER for bevacizumab plus paclitaxel, a fully incremental analysis should have been conducted, comparing all the regimens simultaneously. In addition, 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.

- 3.17 The ERG highlighted that the base-case model did not include the results from the indirect comparison and that the model made the assumption that all included comparators (docetaxel alone, paclitaxel alone and gemcitabine plus paclitaxel) were equally effective in terms of progression-free survival and overall survival. Additionally, in the second base case, the cost of bevacizumab was based on the NHS paying for a maximum dose of 10 g per patient, and this patient access scheme had not been agreed with the Department of Health. The cost of paclitaxel used in the second base case was based on the average price paid by NHS trusts over a 4-month period, whereas other proprietary prices were taken from the BNF 58. The ERG also reported that the utility values were taken from a non-systematic review of the literature. In addition, the ERG 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 a preference-based measure or collate alternative values.
- 3.18 The ERG conducted two sets of exploratory incremental analyses, both including 3-weekly paclitaxel as a comparator. One was based on the revised results, that incorporated the indirect comparison undertaken by the manufacturer rather than assuming that all comparators were equally effective. The second analysis was based on the original approach employed by the manufacturer where all comparators were assumed to be equally effective. These analyses used the following drug acquisition costs:

- Case 1 (ERG re-analysis) – NHS list prices from BNF 58 excluding the patient access scheme for bevacizumab.
- Case 2 (manufacturer re-analysis) – average prices paid by NHS trusts over a 4-month period for paclitaxel including the patient access scheme for bevacizumab.
- Case 3 (ERG re-analysis) – average prices paid by NHS trusts for paclitaxel over a 4-month period excluding the patient access scheme for bevacizumab.

In both analyses, for Case 1 and Case 3 (excluding the patient access scheme), the ICER for bevacizumab plus paclitaxel versus the next best treatment exceeded £100,000 per QALY gained. .

- 3.19 The ERG agreed with the manufacturer's conclusion that bevacizumab plus paclitaxel and bevacizumab plus docetaxel would be expected to be of similar effectiveness. Therefore, the inclusion and exclusion of studies in the indirect comparison would not have a major effect. The analyses by the ERG found that the acquisition cost of docetaxel had very little effect on the ICER of bevacizumab plus paclitaxel compared with docetaxel.
- 3.20 The ERG conducted further exploratory analyses and calibrated the model to the E2100 trial results for overall survival. This was considered important to test the internal validity of the model by comparing the median progression-free survival and overall survival found by the E2100 trial with the model predictions. The pair wise ICER of bevacizumab plus paclitaxel versus weekly paclitaxel was £259,267 per QALY gained (incremental cost of £29,675 and incremental QALY of 0.114) in the exploratory analyses.

Extra analyses provided by the manufacturer

- 3.21 After consultation on the appraisal consultation document, the manufacturer provided summaries of the results from the AVADO and RIBBON-1 trials. In addition, new evidence for two subgroups was provided:
- Patients who had previously received treatment with a taxane, and

- Patients with disease that was triple negative (that is, oestrogen and progesterone receptor negative, and HER2 negative).

Clinical effectiveness

- 3.22 The manufacturer stated that these groups are likely to have poorer prognosis and may gain greater benefit from bevacizumab therapy than the full licensed population. In addition to the data from the E2100 trial the manufacturer also included data from the AVADO and RIBBON-1 trials as evidence to support the subgroups identified.
- 3.23 The AVADO trial (n = 736) was a randomised double blind trial that investigated the combination of bevacizumab with docetaxel in women with HER2 negative disease who had not previously received chemotherapy for metastatic disease. Patients were assigned to receive either docetaxel plus bevacizumab at 7.5mg/kg every 3 weeks, docetaxel plus bevacizumab at 15 mg/kg every 3 weeks or docetaxel plus placebo. Docetaxel was given at 100 mg/m² on day 1 of each 3 week cycle for a maximum of 9 cycles. The primary endpoint was progression-free survival. The manufacturer presented results for the licensed dose of bevacizumab at 15 mg/kg every 3 weeks. Median progression-free survival for the intention-to-treat population was 8.2 months in the docetaxel plus placebo arm and 10.1 months in the docetaxel plus bevacizumab arm (unstratified HR 0.77, 95% CI 0.64 to 0.93). Median overall survival was 31.9 months in the placebo arm and 30.2 months in the bevacizumab arm (HR 1.03, 95% CI: 0.70, 1.33).
- 3.24 The RIBBON-1 trial (n = 1237) was a randomised double-blind placebo controlled trial of standard chemotherapy with or without bevacizumab. Three hundred and seven patients received taxane chemotherapy with or without bevacizumab. Results for progression-free survival were provided for the group of patients receiving either anthracycline or taxane chemotherapy (n = 622). Median progression-free survival increased from 8 months in the chemotherapy arm to 9.2 months in the bevacizumab plus chemotherapy arm (HR 0.66, 95% CI 0.54 to 0.81).
- 3.25 For the triple negative subgroup, results from the E2100 study (n = 232) indicated a statistically significant increase in median progression-free

survival of 5.3 months, from 5.3 months in the paclitaxel alone arm to 10.6 months in the bevacizumab plus paclitaxel arm. The unstratified hazard ratio for progression was 0.49 (95% CI 0.34 to 0.70). The hazard ratio for death was 0.89 (95% CI 0.66 to 1.19), indicating a non-statistically significant improvement in median overall survival of 4.2 months, from 16.3 months in the paclitaxel alone arm to 20.5 months in the bevacizumab plus paclitaxel arm. Results from the AVADO study (n = 111) indicated that the unstratified hazard ratio for progression with bevacizumab plus docetaxel compared with docetaxel alone was estimated to be 0.68 (95% CI 0.46 to 0.99). The hazard ratio for death with bevacizumab plus docetaxel compared with docetaxel alone was estimated to be 0.82 (95% CI 0.51 to 1.32).

- 3.26 For the prior taxane-treated subgroup, results from the E2100 study (n = 140) indicated a statistically significant increase in median progression-free survival of 7.3 months, from 5.8 months in the paclitaxel alone arm to 13.1 months in the bevacizumab plus paclitaxel arm. The unstratified hazard ratio for progression was 0.33 (95% CI 0.20 to 0.54). There was a statistically significant increase in median overall survival of 8.7 months, from 17.6 months in the paclitaxel alone arm to 26.3 months in the bevacizumab plus paclitaxel arm. The hazard ratio for death was 0.67 (95% CI 0.45 to 0.99). Results from the AVADO study (n = 78) indicated a statistically significant increase in median progression-free survival of 3.6 months, from 6.7 months in the docetaxel alone arm to 10.3 months in the bevacizumab plus docetaxel arm. The unstratified hazard ratio for progression with bevacizumab plus docetaxel compared with docetaxel alone was estimated to be 0.53 (95% CI 0.33 to 0.85). There was a 9.3-month increase in median overall survival, from 22.3 months in the docetaxel alone arm to 31.6 months in the bevacizumab plus docetaxel arm. The hazard ratio for death was 0.58 (95% CI 0.31 to 1.08).
- 3.27 The manufacturer also provided meta-analyses based on individual patient data. One was a meta-analysis of progression-free survival and overall survival in 2447 patients from the E2100, AVADO and RIBBON-1 trials. In this pooled intention-to-treat analysis, there was a statistically significant increase in median progression-free survival of 2.5 months, from 6.7 months in the chemotherapy alone arm to 9.2 months in the

bevacizumab plus chemotherapy arm. The hazard ratio for progression with bevacizumab plus chemotherapy compared with chemotherapy alone was estimated to be 0.64 (95% CI 0.58 to 0.71). The hazard ratio for death was 0.97 (95% CI 0.86 to 1.08), indicating a non-statistically significant difference in median overall survival of 0.3 months from 26.4 months in the chemotherapy alone arm to 26.7 months in the bevacizumab plus chemotherapy arm. The pooled dataset also included 621 patients with triple negative disease who were meta-analysed separately. Results were similar in this triple negative subgroup to the results from the overall population, with a hazard ratio for progression with bevacizumab plus chemotherapy compared with chemotherapy alone estimated to be 0.63 (95% CI 0.52 to 0.76). The hazard ratio for death with bevacizumab plus chemotherapy compared with chemotherapy alone was estimated to be 0.96 (95% CI 0.79 to 1.16). Median length of progression-free and overall survival for the triple negative subgroup were not provided. No data were provided for the group (n = 1826) that did not have triple negative disease.

- 3.28 Another meta-analysis was described as exploratory and focused on the prior taxane-treated subgroup. This analysis was restricted to the 1765 patients treated with taxanes, with or without bevacizumab, in the E2100, AVADO and RIBBON-1 trials. No data for the entire group of 1765 patients were provided. For the prior taxane-treated subgroup (n = 311), results indicated a statistically significant increase in median progression-free survival of 4.5 months, from 6.2 months in the taxane alone arm to 10.7 months in the bevacizumab plus taxane arm. The hazard ratio for progression was 0.47 (95% CI 0.35 to 0.62). There was a statistically significant increase in median overall survival of 5.6 months, from 21.3 months in the taxane alone arm to 26.9 months in the bevacizumab plus taxane arm. The hazard ratio for death was 0.73 (95% CI 0.55 to 0.97). No data were provided for the group (n = 1454) that had not received prior taxanes.

Cost-effectiveness

- 3.29 The manufacturer provided cost-effectiveness estimates for the two subgroups. The model that was used in the original submission was adapted to reflect the progression-free survival, overall survival, time to

stopping treatment and adverse event rates of the subgroups. Overall survival curves for the relevant subgroups from the E2100 study were fitted with parametric functions. The analysis focused on the cost effectiveness of bevacizumab plus paclitaxel and did not consider the comparator of gemcitabine plus paclitaxel. The analysis assumed equal efficacy for weekly paclitaxel and 3-weekly docetaxel.

- 3.30 For both subgroups, a log-logistic model was selected as the best fit for progression-free survival and overall survival and the Weibull function was used for both treatments to reflect time to stopping treatment for each treatment arm. The base-case results were presented using both the average price of paclitaxel paid by NHS trusts and the list price. The patient access scheme for bevacizumab was excluded from the base case, although it was included in sensitivity analysis.
- 3.31 For the triple negative subgroup, the cost per QALY for bevacizumab plus paclitaxel compared with paclitaxel alone was £87,865 (with an incremental cost of £27,387 and an incremental QALY of 0.312) based on list prices for paclitaxel and £82,469 (with an incremental cost of £25,705 and an incremental QALY of 0.312) based on the average price paid by NHS trusts for paclitaxel. The cost per QALY for bevacizumab plus paclitaxel compared with docetaxel alone was £84,740 (with an incremental cost of £26,540 and an incremental QALY of 0.313) based on list prices for paclitaxel and £64,092 (with an incremental cost of £20,073 and an incremental QALY of 0.313) based on the average price paid by NHS trusts for paclitaxel.
- 3.32 For the prior taxane-treated subgroup, the cost per QALY for bevacizumab plus paclitaxel compared with paclitaxel alone was £74,640 (with an incremental cost of £37,358 and an incremental QALY of 0.501) based on list prices for paclitaxel and £67,714 (with an incremental cost of £33,892 and an incremental QALY of 0.501) based on the average price paid by NHS trusts for paclitaxel. The cost per QALY for bevacizumab plus paclitaxel compared with docetaxel alone was £73,605 (with an incremental cost of £36,951 and an incremental QALY of 0.502) based on list prices for paclitaxel and £57,416 (with an incremental cost of £28,824 and an incremental QALY of 0.502) based on the average price paid by NHS trusts for paclitaxel.

- 3.33 Sensitivity analysis was conducted on the prior taxane-treated subgroup assuming that variations in ICERs would be similarly reflected in the triple negative subgroup. The analysis indicated that there was considerable variation in the estimate of cost effectiveness depending on the function adopted. Probabilistic sensitivity analyses produced similar estimates of cost effectiveness, and the probability of bevacizumab being cost effective at £30,000 per QALY gained was 0% against both weekly paclitaxel and 3-weekly docetaxel.

ERG comments on the extra subgroup analysis

- 3.34 The ERG noted that 25% (615/2447) of all patients included in the intention-to-treat meta-analysis that was used to address the triple negative subgroup received bevacizumab plus capecitabine, a combination that is outside the scope of this appraisal. The ERG highlighted that the progression-free survival and overall survival hazard ratios for the intention-to-treat population and the triple negative subgroup were almost identical. Furthermore, the median progression-free survival, overall survival and 1-year survival data were not reported for this subgroup. It was noted that these data were not provided for the RIBBON-1 study.
- 3.35 The ERG noted that the meta-analysis addressing the prior taxane-treated subgroup was described as an exploratory meta-analysis. It stated that it included only a small number of patients from trials that individually were insufficiently powered to detect a difference in overall survival. Only one trial (AVADO) appeared to stratify for taxane pre-treatment and no interaction tests were conducted. Therefore, although the hazard ratios did show a trend towards being more favourable towards bevacizumab than in the intention-to-treat meta-analysis for both progression-free survival and overall survival, the ERG stated that the analysis cannot be considered as convincing evidence of a subgroup effect.
- 3.36 The ERG had a number of concerns about the economic modelling. The ERG highlighted that rather than using estimates from these subgroup meta-analyses in the subsequent economic model, only the subgroup data from the E2100 trial were used. The ERG noted that this approach

may have yielded more favourable ICER estimates because the progression-free survival and overall survival values for E2100 were more favourable than those from the meta-analyses.

- 3.37 The ERG commented that, although the manufacturer selected the log-logistic model as the best fit, the difference in goodness of fit statistics was small, suggesting that the choice between different functions was marginal. However, there was subsequent variation in the ICER estimates based on the different survival functions. At the extreme ends, for the prior taxane-treated subgroup, the ICER using the log-logistic function (the manufacturer's base case), and incorporating the average price for paclitaxel paid by NHS trusts, was £67,714 per QALY gained, whereas if the Weibull function had been used this figure would have risen to £86,854 per QALY gained. When the NHS list prices for paclitaxel were incorporated, the ICERs ranged from £74,640 per QALY gained with the log-logistic function to £95,807 per QALY gained with the Weibull function. The ERG concluded that there was considerable uncertainty surrounding the choice of statistical function used in the cost-effectiveness analysis for the prior taxane-treated subgroup. Equivalent goodness of fit statistics were not reported for the triple negative subgroup so the ERG could not undertake a similar assessment for this subgroup.
- 3.38 The ERG undertook an exploratory analysis in the prior taxane-treated subgroup using the hazard ratio estimated from the individual patient data meta-analysis of the prior taxane-treated group presented by the manufacturer (HR = 0.738) and the Weibull function. The results demonstrated an increase in the ICER from £95,807 to £109,242 per QALY gained using the list prices for paclitaxel and from £86,854 to £98,834 per QALY gained using the average price for paclitaxel paid by NHS trusts.
- 3.39 The ERG noted that all the parametric functions investigated by the manufacturer assumed long-term sustained treatment effects for overall survival with bevacizumab plus paclitaxel. Consequently, the ERG undertook an exploratory analysis for both subgroups using the manufacturer's model. This analysis used the Kaplan-Meier survival estimates from the E2100 study up to about 3.2 years, assuming no

difference in survival after that point, since the curves suggested that the difference in overall survival may not be sustained over a longer time horizon. For the prior taxane-treated subgroup, the ICERs increased from £74,640 per QALY gained when using the log-logistic function to £129,794 per QALY gained when using the Kaplan-Meier function, both incorporating the list prices for paclitaxel, and from £67,714 per QALY gained when using the log-logistic function to £117,587 per QALY gained when using the Kaplan-Meier function, both incorporating the average price for paclitaxel paid by NHS trusts. For the triple negative subgroup, the ICERs increased from £87,865 per QALY gained when using the log-logistic function to £187,339 per QALY gained when using the Kaplan-Meier function, incorporating the list prices for paclitaxel, and from £82,469 per QALY gained when using the log-logistic function to £175,575 per QALY gained when using the Kaplan-Meier function, incorporating the average price for paclitaxel paid by NHS trusts.

- 3.40 Full details of all the evidence are in the [manufacturer's submission and the ERG report](#).

4 Consideration of the evidence

- 4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of bevacizumab in combination with a taxane, having considered evidence on the nature of metastatic breast cancer and the value placed on the benefits of bevacizumab in combination with a taxane by people with metastatic breast cancer, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

Clinical effectiveness

- 4.2 The Committee considered current clinical practice for the treatment of metastatic breast cancer. The Committee noted the manufacturer's clarification response, which stated that approximately 30% of patients receive a taxane in the adjuvant setting, particularly in node positive disease at diagnosis. The clinical specialist stated that in current practice, if metastatic disease subsequently develops, taxanes (that is, weekly paclitaxel or 3-weekly docetaxel) are then offered as first-line treatment for the majority of people in England and Wales. The Committee also heard from the clinical specialist that 3-weekly paclitaxel is no longer routinely used in clinical practice, having been largely replaced by weekly dosing schedules. The Committee heard that the choice between the two taxanes is made locally and that weekly paclitaxel and 3-weekly docetaxel are considered to have comparable efficacy. The Committee concluded that the relevant comparators for bevacizumab in combination with a taxane for the first-line treatment of metastatic breast cancer are weekly paclitaxel and 3-weekly docetaxel.
- 4.3 The Committee discussed the clinical effectiveness of bevacizumab in combination with a taxane. It heard that bevacizumab is the first VEGF-targeted therapy for this indication. The Committee discussed the E2100 trial which compared bevacizumab plus paclitaxel with weekly paclitaxel. The Committee heard from the ERG that the trial had several limitations, such as the lack of blinding. The trial demonstrated a statistically significant increase in median progression-free survival of 5.5 months,

from 5.8 months in the paclitaxel alone arm to 11.3 months in the bevacizumab plus paclitaxel arm. The Committee explored the value of an increase in progression-free survival with the clinical specialist and patient expert. It heard about the importance and significance of progression-free survival for patients in terms of being able to carry out normal daily activities, as well as being a therapeutic aim of treatment for clinicians.

4.4 The Committee then discussed the overall survival results of the E2100 trial and noted a non-statistically significant increase in median survival of 1.7 months, from 24.8 months with paclitaxel alone to 26.5 months with bevacizumab plus paclitaxel. The Committee discussed the possible reasons for the increase in progression-free survival not being reflected in overall survival in the trial. It acknowledged that although it was possible that the relative treatment effect may have been confounded by crossover or other treatments received after disease progression, no data on this had been collected. The Committee heard from the clinical specialist that the response in E2100 to paclitaxel alone was lower than demonstrated in previous studies. The Committee concluded that it was likely that bevacizumab plus paclitaxel improved progression-free survival relative to weekly paclitaxel, but that there was no robust evidence that bevacizumab plus paclitaxel improved overall survival compared with weekly paclitaxel alone.

4.5 The Committee discussed the health-related quality of life data for bevacizumab plus paclitaxel compared with weekly paclitaxel. The Committee heard from the primary care trust expert that robust data on the magnitude of quality of life improvements were important. The Committee noted concerns about the data presented by the manufacturer. It was aware that a statistically significant improvement in health-related quality of life at 33 weeks was only demonstrated when extreme values were imputed. The Committee also heard from the clinical specialist that the scores for psychological and emotional wellbeing were not explicitly addressed by the manufacturer. The Committee concluded that the magnitude of health-related quality of life benefits with bevacizumab plus paclitaxel compared with paclitaxel alone was uncertain.

- 4.6 The Committee noted the adverse events and the side-effect profile from the E2100 trial as well as from a large uncontrolled study (ATHENA). The Committee noted that the frequency of grade 3–5 adverse events was slightly higher with the addition of bevacizumab to paclitaxel. However, the Committee heard from the clinical specialist that many of the adverse events were those expected in cytotoxic regimens, and could be attributed to the taxane. Increased treatment duration would also lead to an increase in the incidence of adverse events. The Committee understood that most adverse events could be satisfactorily managed (for example with dose reductions). Specific adverse events associated with bevacizumab, notably hypertension, were also readily treatable. The Committee concluded that the addition of bevacizumab did not lead to unacceptable toxicity compared with paclitaxel alone, and that adverse effects were manageable.
- 4.7 The Committee noted that evidence from the AVADO study for the clinical effectiveness of bevacizumab plus docetaxel had been provided by the manufacturer after consultation on the appraisal consultation document. The Committee noted the manufacturer's comment that the AVADO dosing regimen of 9 cycles of 100 mg/m² docetaxel was not routine UK clinical practice as 3-weekly docetaxel was usually given for 6 cycles. The Committee heard from the clinical specialist that 100 mg/m² was the standard dose used in the absence of contraindications, and that therefore he considered that the trial data were relevant to UK clinical practice. The clinical specialist also highlighted the high methodological quality of the AVADO trial and its placebo-controlled design. The Committee noted that the results from this study demonstrated an approximate 2-month, statistically significant improvement in progression-free survival for bevacizumab at a dose of 15 mg/m² plus docetaxel. However, the Committee also noted the hazard ratio for death which was 1.03 (95% CI 0.70 to 1.33), indicating a non-statistically significant reduction in median overall survival of 1.7 months from 31.9 months in the docetaxel alone arm to 30.2 months in the bevacizumab plus docetaxel arm. The Committee concluded that bevacizumab plus docetaxel was modestly clinically effective compared with docetaxel alone in terms of progression-free survival. However, its effect on overall survival was uncertain.

- 4.8 The Committee discussed the indirect treatment comparison presented by the manufacturer for bevacizumab plus weekly paclitaxel compared with docetaxel alone and gemcitabine plus 3-weekly paclitaxel. The Committee noted the ERG's comments related to the reliability of the indirect treatment comparison. The quality of the included studies was variable, and the trials included variable numbers of patients receiving second-line treatment, where the prognosis may be worse than for first-line chemotherapy. Also, it was not clear that the selection criteria for included studies had been consistently applied, with the AVADO trial being excluded on the grounds of the docetaxel dose used, while another study using the same dose of docetaxel was included. The Committee concluded that the indirect treatment comparison was not robust and that the results were not considered reliable.
- 4.9 The Committee discussed the additional data presented by the manufacturer for the triple negative subgroup in response to consultation on the appraisal consultation document. The Committee explored whether bevacizumab might be more clinically effective in this subgroup. The Committee heard from the clinical specialist that for the subgroup of women with triple negative cancers (that is, cancers that do not have receptors for oestrogen, progesterone or HER2) there may be worse outcomes. The Committee noted, however, that while it was plausible that bevacizumab could be more effective in some tumour types than others, there was no proposal of a biologically plausible specific mechanism of effect for bevacizumab having an increased benefit for this subgroup. The Committee discussed the results of the manufacturer's meta-analysis that demonstrated that the progression-free survival and overall survival hazard ratios for the triple negative subgroup (0.63 and 0.96) were indistinguishable from those of the intention-to-treat population (0.64 and 0.97). Moreover, the results for the overall survival difference were not statistically significant (95% CI 0.79 to 1.16). The Committee concluded that there was no evidence of any greater clinical benefit in the triple negative subgroup than in the intention-to-treat population.
- 4.10 The Committee then discussed the additional data provided by the manufacturer for the prior taxane-treated subgroup. It heard from the clinical specialist that this was an area of clinical need as 30% to 40% of

patients, usually those with lymph node involvement, would have received taxanes in the adjuvant setting. These patients would generally have a worse prognosis and might need different treatment options if the disease progressed after treatment. The Committee noted that although there could be taxane resistance in this subgroup, there were no specific biological markers or other hypotheses to suggest why VEGF agents would work more effectively in this subgroup compared with the intention-to-treat population. The Committee discussed the results provided for this subgroup, noting that these were based on post hoc analyses. The Committee noted that the hazard ratio for death in the E2100 trial for the prior taxane-treated subgroup was 0.67 (95% CI 0.45 to 0.99), indicating a statistically significant increase from 17.6 months in the paclitaxel alone arm to 26.3 months in the bevacizumab plus paclitaxel arm, and that the hazard ratio for death in the meta-analysis for the prior taxane-treated subgroup was 0.73 (95% CI 0.55 to 0.97), indicating a statistically significant increase from 21.3 in the taxane only arm to 26.9 months in the bevacizumab plus taxane arm. However, the Committee identified a number of concerns that questioned the robustness of the data. It noted that the E2100 trial was unblinded and did not stratify for prior taxane-treated patients, and the AVADO study, though stratified, had a very small number of patients (n = 78). Further, although the results for this subgroup were statistically significant for both progression-free survival and overall survival, there was no indication of the hazard ratios for the group who did not receive prior taxane treatment in the adjuvant setting and there were no statistical tests for interaction. The clinical specialist, while expressing interest in the findings, agreed on their exploratory nature. The Committee also noted the manufacturer's comment in its submission that although in the meta-analysis these differences appear to be statistically significant, it should be noted that this analysis is exploratory only.

- 4.11 Consequently, the Committee considered that although the results of the prior taxane-treated subgroup analyses were interesting in terms of possible clinical benefit, they were not sufficiently robust to use for the development of guidance. The Committee concluded that the results needed to be confirmed in larger, well designed studies, and that the estimates of effectiveness could not be considered suitable as the basis of a cost-effectiveness analysis. The Committee discussed whether

there were any subgroups other than those presented by the manufacturer that may have an increased benefit from bevacizumab treatment. It heard from the clinical specialist that the groups identified by the manufacturer were key subgroups. The Committee noted the clinical specialist's comment that further research into whether there are any clinical or biological subgroups (such as subgroups by biological markers) for whom bevacizumab is particularly beneficial would be useful. The Committee concluded that no robust evidence on subgroups was currently available and that the data that were available were not reliable and could not be carried forward as the basis for a cost-effectiveness analysis.

Cost effectiveness

- 4.12 The Committee discussed the pair wise cost-effectiveness estimates of bevacizumab plus paclitaxel as presented by the manufacturer. The Committee noted that the manufacturer had provided two base cases, one of which was based on average prices paid by NHS trusts for paclitaxel over a 4-month period and a patient access scheme for bevacizumab. The Committee was aware that no patient access scheme had been approved by the Department of Health and that therefore the scheme could not be taken into account in the consideration of cost effectiveness. The Committee was also aware that it was not in accordance with the NICE methods guide for the manufacturer to use average prices paid by NHS trusts for paclitaxel over a 4-month period rather than a nationally agreed discounted price that is consistently available to the NHS. However, the Committee noted the confirmation from the Department of Health Commercial Medicines Unit that discounts for paclitaxel are in a range greater than 95% from the BNF list price of the branded presentation and that prices within these ranges are available to all NHS hospital trusts in England. The Committee concluded that it would consider the range of the ICERs based both on the list prices and the average prices paid by NHS trusts for paclitaxel.
- 4.13 The Committee was aware that the manufacturer's analysis used a series of pair wise comparisons for bevacizumab plus paclitaxel relative to each separate comparator regimen. The Committee accepted comments from the ERG that the correct methodological approach would have been a

fully incremental analysis. The Committee noted that the incremental analysis carried out by the ERG resulted in ICERs that were similar to the pair wise ICERs. The Committee therefore concluded that, taking this into account, together with the fact that the ERG's exploratory analyses had been conducted using the pair wise ICERs, these were appropriate for consideration in this instance.

- 4.14 The Committee noted that the manufacturer's base case assumed that the clinical effectiveness of all the comparators (that is, 3-weekly docetaxel, gemcitabine plus paclitaxel and 3-weekly paclitaxel) were the same as weekly paclitaxel. The manufacturer subsequently conducted revised analyses substituting the clinical effectiveness results from the indirect comparison. The Committee noted its earlier conclusions that the results of the indirect comparison were not reliable and that there were only two relevant comparators. In addition, the Committee heard from the clinical specialist that weekly paclitaxel and 3-weekly docetaxel were not considered to demonstrate clinically meaningful differences in effectiveness. The Committee concluded that the cost-effectiveness estimates derived from assuming comparators had equivalent effectiveness to weekly paclitaxel were acceptable.
- 4.15 The Committee discussed the way in which the manufacturer had modelled overall survival in the economic model provided in the original submission. It noted that a key assumption made by the manufacturer was that patients would have the same risk of dying per unit time once disease progressed, regardless of the first-line treatment they had received. This resulted in improvements in observed progression-free survival being carried over to projected improvements in overall survival. The Committee was aware that there are various ways of modelling that would result in different estimates of overall survival. The Committee noted that the manufacturer's model (whereby overall survival was independent of previous treatments received) resulted in mean life years of 2.68 years in the bevacizumab plus paclitaxel arm and 2.33 years in the paclitaxel alone arm (an incremental benefit of 0.35 years) and a pair wise ICER of £118,000 per QALY gained, using the list price for paclitaxel. The manufacturer indicated that this represented an optimistic scenario compared with the trial data. The manufacturer did not provide results for a scenario including the average price for paclitaxel paid by NHS

trusts without the patient access scheme; however, an analysis of this by the ERG indicated an ICER of £110,500 per QALY gained. The Committee also examined the exploratory analyses carried out by the ERG that attempted to calibrate overall survival in the model with that directly observed in the E2100 trial by using an area under the curve method. These analyses resulted in mean life years of 2.16 years in the bevacizumab plus paclitaxel arm and 2.13 years in the paclitaxel alone arm (an incremental benefit of 0.03 years) and a pair wise ICER of £259,000 per QALY gained, based on the list price for paclitaxel. Using the average price for paclitaxel paid by NHS trusts, the ERG reported that the ICER remained over £200,000 per QALY gained. The ERG acknowledged that this represented a pessimistic scenario. The Committee therefore concluded that the true ICER for bevacizumab plus paclitaxel compared with weekly paclitaxel probably lay between £110,000 and £259,000 per QALY gained.

- 4.16 The Committee noted that the ICER for bevacizumab plus paclitaxel versus docetaxel alone presented by the manufacturer was £115,000 per QALY gained, based on list prices for paclitaxel. Although the ERG did not conduct a further exploratory analysis for this comparison, the Committee considered that it would also have resulted in a substantially higher ICER. The Committee concluded that the true pair wise ICER for bevacizumab plus paclitaxel compared with 3-weekly docetaxel was over £115,000 per QALY gained.
- 4.17 The Committee noted that the manufacturer did not provide any clinical or cost-effectiveness data related to bevacizumab plus docetaxel, even though it was specified in the scope. The Committee considered the manufacturer's statement 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 of bevacizumab plus docetaxel was not warranted. The Committee agreed that the ICER for bevacizumab plus docetaxel would be higher than the ICER for bevacizumab plus paclitaxel compared with weekly paclitaxel and 3-weekly docetaxel.
- 4.18 The Committee discussed the estimates of the ICERs given by the

manufacturer using subgroup data from the E2100 study. For the triple negative subgroup, the cost per QALY for bevacizumab plus paclitaxel ranged from £64,100 to £87,900 per QALY gained depending on the comparator and whether the list price for paclitaxel was used or the average price for paclitaxel paid by NHS trusts was used. For the prior taxane-treated subgroup, the corresponding range was £57,400 to £74,600 per QALY gained. The Committee noted that these estimates remained above the conventional levels normally considered cost effective, and would be further increased if alternative techniques were used to model overall survival. The Committee considered that because of the uncertainty around the subgroup clinical effectiveness estimates, those estimates could not be carried forward to form the basis of a cost-effectiveness analysis and guidance to the NHS. The Committee concluded that the estimates of cost effectiveness for the intention-to-treat population represented the most plausible estimate of cost effectiveness for bevacizumab.

4.19 The Committee discussed whether there were any equality issues relating to population groups protected by equality legislation. It noted information from the manufacturer's submission relating to the potential for worse outcomes in lower socioeconomic groups or by ethnicity. The Committee heard from the clinical specialist that there may be differences in overall treatment outcomes between these groups, but that they are likely to result from factors such as lower uptake of screening or later presentation of disease rather than differences in treatment. The Committee noted that the triple negative subgroup may be over-represented in some ethnic groups. The Committee concluded that there was no evidence of differences in access to treatment or response to treatment by socioeconomic status or ethnicity in patients with disease at the metastatic stage.

4.20 The Committee considered supplementary advice from NICE that should be taken into account when appraising treatments that may extend the life of people with a short life expectancy and that are licensed for indications that affect small numbers of people with incurable illnesses. For this advice to be applied, all the following criteria must be met:

- The treatment is indicated for patients with a short life expectancy, normally

less than 24 months.

- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment.
- The treatment is licensed or otherwise indicated for small patient populations.

In addition, when taking these criteria into account the Committee must be persuaded that the estimates of the extension to life are robust and the assumptions used in the reference case economic modelling are plausible, objective and robust.

4.21 The Committee discussed whether bevacizumab in combination with a taxane for the first-line treatment of metastatic breast cancer fulfilled the criteria for a life-extending, end-of-life treatment. The Committee noted that the E2100 trial data indicated that median overall survival in the paclitaxel alone arm was 24.8 months. The Committee considered the fact that this was just above the defined limit of life expectancy of less than 24 months in the end-of-life criteria. The Committee also noted that the change in median overall survival was an increase of 1.7 months with bevacizumab plus paclitaxel compared with paclitaxel alone. The Committee accepted that, although it was possible that this increase had been underestimated (because of the possibility of crossover or additional treatments), there was no robust evidence that bevacizumab plus paclitaxel offers an extension to life of an additional 3 months, compared with paclitaxel alone. The Committee agreed that the robustness of evidence for the subgroups was not convincing; therefore, the Committee did not discuss whether the subgroups presented fulfilled the criteria for consideration as a life-extending, end-of-life treatment. The Committee also noted that bevacizumab is licensed for a relatively large population across a range of indications, such as colorectal cancer, non-small-cell lung cancer and renal cell carcinoma, and hence does not meet the third criterion that the treatment should be licensed for small populations. The Committee concluded that bevacizumab in combination with a taxane did not fulfil the criteria for special consideration as a life-extending, end-of-life treatment.

4.22 In summary, the Committee concluded that the most plausible ICER for

bevacizumab plus paclitaxel versus weekly paclitaxel was between £110,000 and £259,000 per QALY gained and that the ICER for bevacizumab plus paclitaxel versus docetaxel would be greater than £115,000 per QALY gained. The Committee accepted the manufacturer's statement that the ICER for bevacizumab plus docetaxel would be higher than that for bevacizumab plus paclitaxel since docetaxel is the more expensive taxane. The Committee considered that although the subgroup results were promising in terms of potential clinical benefit, they were not sufficiently robust to develop guidance and could not be carried forward as the basis for a cost-effectiveness analysis. The Committee concluded that bevacizumab in combination with a taxane as a first-line treatment for metastatic breast cancer was not a cost-effective use of NHS resources.

Summary of Appraisal Committee's key conclusions

TA214 (STA)	Appraisal title: Bevacizumab in combination with a taxane for the first-line treatment of metastatic breast cancer	FAD section
Key conclusion		
Bevacizumab in combination with a taxane is not recommended for the first-line treatment of metastatic breast cancer. Patients currently receiving bevacizumab in combination with a taxane for the first-line treatment of metastatic breast cancer should have the option to continue therapy until they and their clinicians consider it appropriate to stop. The Committee concluded that bevacizumab in combination with a taxane as a first-line treatment for metastatic breast cancer was not a cost-effective use of NHS resources.		1.1, 1.2 4.22
Current practice		

<p>Clinical need of patients including the availability of alternative treatments</p>	<p>The clinical specialist stated that in current practice, taxanes (that is, weekly paclitaxel or 3-weekly docetaxel) are offered as first-line treatment for the majority of people with metastatic breast cancer in England and Wales.</p> <p>The Committee heard from the clinical specialist that for women with triple negative cancers (that is, cancers that do not have receptors for oestrogen, progesterone or HER2) there may be worse outcomes.</p> <p>The Committee heard from the clinical specialist that there was an area of clinical need associated with prior taxane use as 30% to 40% of patients would have received taxanes in the adjuvant setting. These patients would generally have a worse prognosis and might need different treatment options if their disease returned following adjuvant treatment.</p>	<p>4.2, 4.9, 4.10</p>
<p>The technology</p>		
<p>Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?</p>	<p>The Committee heard that bevacizumab is the first VEGF-targeted therapy for this indication.</p> <p>The Committee heard about the importance and significance of progression-free survival for patients in terms of being able to carry out normal daily activities, as well as being a therapeutic aim of treatment for clinicians. The Committee concluded that it was likely that bevacizumab plus paclitaxel improved progression-free survival, but that there was no robust evidence that bevacizumab plus paclitaxel improved overall survival compared with weekly paclitaxel alone. The Committee concluded that the magnitude of health-related quality of life benefits with bevacizumab plus paclitaxel compared with paclitaxel alone was uncertain.</p>	<p>4.3, 4.4, 4.5</p>
<p>What is the position of the treatment in the pathway of care for the condition?</p>	<p>Bevacizumab in combination with paclitaxel or docetaxel has a marketing authorisation for 'first-line treatment of patients with metastatic breast cancer'.</p>	<p>2.1</p>

Adverse events	<p>The Committee understood that most adverse events could be satisfactorily managed (for example with dose reductions). Specific adverse events associated with bevacizumab, notably hypertension, were also readily treatable. The Committee concluded that the addition of bevacizumab did not lead to any unacceptable toxicity compared with paclitaxel alone, and that adverse effects were manageable.</p>	4.6
Evidence for clinical effectiveness		
Quality, availability and nature of evidence	<p>The Committee noted that the original submission was based on one trial (E2100) which compared bevacizumab plus paclitaxel with weekly paclitaxel.</p> <p>The Committee heard from the ERG that the E2100 trial had several limitations, such as the lack of blinding. The Committee heard from the clinical specialist that the response in E2100 to paclitaxel alone was lower than demonstrated in previous studies.</p> <p>The Committee noted that evidence from the AVADO study for the clinical effectiveness of bevacizumab plus docetaxel had been provided by the manufacturer after consultation on the appraisal consultation document.</p> <p>The Committee noted the ERG's comments related to the reliability of the indirect treatment comparison included in the manufacturer's submission and concluded that the indirect treatment comparison was not robust and that the results were not considered reliable.</p>	4.3, 4.4, 4.7, 4.8

<p>Relevance to general clinical practice in the NHS</p>	<p>The Committee concluded that the relevant comparators for bevacizumab in combination with a taxane for the first-line treatment of metastatic breast cancer are weekly paclitaxel and 3-weekly docetaxel.</p> <p>The Committee understood that the manufacturer had not considered the AVADO trial in its submission because the dose of docetaxel (100 mg/m²) was considered to be higher than that used in clinical practice. The Committee heard from the clinical specialist that the dose used in the trial was standard for 3-weekly docetaxel in the absence of contraindications and therefore the trial data were relevant to UK clinical practice. The Committee noted the manufacturer's comment in the appraisal consultation document that the AVADO dosing regimen of 9 cycles of 100mg/m² docetaxel was not routine UK clinical practice as 3-weekly docetaxel was usually given for 6 cycles.</p>	<p>4.2,</p>
<p>Uncertainties generated by the evidence</p>	<p>The Committee concluded that it was likely that bevacizumab plus paclitaxel improved progression-free survival relative to weekly paclitaxel, but that there was no robust evidence that bevacizumab plus paclitaxel improved overall survival compared with weekly paclitaxel alone.</p> <p>The Committee was aware that a statistically significant improvement in health-related quality of life at 33 weeks was only demonstrated when extreme values were imputed. The Committee also heard from the clinical specialist that the measures of psychological elements and emotional wellbeing were not provided by the manufacturer. The Committee concluded that the magnitude of health-related quality of life benefits with bevacizumab plus paclitaxel compared with paclitaxel alone was uncertain.</p> <p>The Committee considered that although the results of the subgroup analyses were promising in terms of possible clinical benefit, they were not sufficiently robust to use for the development of guidance.</p>	<p>4.4, 4.5, 4.11</p>

Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	<p>For the subgroup of women with triple negative cancers, the Committee noted that while it was plausible that bevacizumab could be more effective in some tumour types than others, there was no proposal of a biologically plausible specific mechanism of effect for bevacizumab having an increased benefit for this subgroup.</p> <p>For the prior taxane-treated subgroup, the Committee noted that although there could be taxane resistance in this subgroup, there were no specific biological markers or other hypotheses to suggest why VEGF agents would work more effectively in this subgroup compared with the intention-to-treat population.</p>	4.9, 4.10
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<p>Estimate of the size of the clinical effectiveness including strength of supporting evidence</p>	<p>The Committee discussed the E2100 trial which compared bevacizumab plus paclitaxel with weekly paclitaxel. The trial demonstrated a statistically significant increase in median progression-free survival of 5.5 months, from 5.8 months in the paclitaxel alone arm to 11.3 months in the bevacizumab plus paclitaxel arm. However, the Committee noted that the trial did not produce similar results for overall survival, with a non-statistically significant increase in median survival of 1.7 months, from 24.8 months with paclitaxel alone to 26.5 months with bevacizumab plus paclitaxel.</p> <p>The Committee noted that the results from the AVADO study demonstrated an approximate 2-month, statistically significant improvement in progression-free survival for bevacizumab at a dose of 15 mg/m² plus docetaxel. Overall survival results indicated a non-statistically significant reduction in median overall survival from 31.9 months with docetaxel alone to 30.2 months with the addition of bevacizumab (95% CI 0.7 to 1.33). The Committee concluded that bevacizumab plus docetaxel was modestly clinically effective compared with docetaxel alone in terms of progression-free survival.</p> <p>The Committee discussed the results of the manufacturer's meta-analysis that demonstrated that the progression-free survival and overall survival hazard ratios for the triple negative subgroup (0.63 and 0.96) were indistinguishable from those of the intention-to-treat population (0.64 and 0.97). Moreover, the results for the overall survival difference were not statistically significant (95% CI 0.79 to 1.16). The Committee concluded that there was no evidence of any greater clinical benefit in the triple negative subgroup than in the intention-to-treat population.</p> <p>For the prior taxane-treated subgroup, the Committee recognised that there was a statistically significant result in overall survival estimates from the E2100 trial, from 17.6 to 26.3 months with the addition of bevacizumab (95% CI 0.45 to 0.99), and in the meta-analysis for the prior taxane-treated subgroup, from 21.3 to 26.9 months with the addition of</p>	<p>4.3, 4.4, 4.7, 4.9, 4.10, 4.11</p>
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	<p>bevacizumab (95% CI 0.55 to 0.97). However, the Committee identified a number of concerns that questioned the robustness of the data. The Committee considered that although the results of the prior taxane-treated subgroup analyses were promising in terms of possible clinical benefit, they were not sufficiently robust to use for the development of guidance.</p>	
<p>Evidence for cost effectiveness</p>		
<p>Availability and nature of evidence</p>	<p>The manufacturer used a Markov model to evaluate the cost effectiveness of bevacizumab plus paclitaxel compared with weekly paclitaxel, 3-weekly docetaxel and gemcitabine plus paclitaxel, using pair wise comparison for bevacizumab plus paclitaxel with each separate comparator regimen. As an additional analysis, the manufacturer presented a comparison with 3-weekly paclitaxel.</p> <p>Bevacizumab plus docetaxel was not formally evaluated.</p> <p>The Committee considered that because of the uncertainty around the subgroup clinical effectiveness estimates those estimates could not be carried forward to form the basis of a cost-effectiveness analysis and guidance to the NHS. The Committee concluded that the estimates of cost effectiveness for the intention-to-treat population represented the most plausible estimate of cost effectiveness for bevacizumab.</p>	<p>3.7, 4.18</p>

<p>Uncertainties around and plausibility of assumptions and inputs in the economic model</p>	<p>A key assumption made by the manufacturer in its base-case analysis was that patients would have the same risk of dying per unit time once disease progressed, regardless of the first-line treatment they had received. This resulted in improvements in observed progression-free survival being carried over to projected improvements in overall survival, resulting in an incremental benefit of 0.35 years for the bevacizumab plus paclitaxel arm compared with the paclitaxel alone arm and a pair wise ICER of £118,000 per QALY gained, using the list price for paclitaxel. The manufacturer indicated that this represented an optimistic scenario compared with the trial data. Including the average price for paclitaxel paid by NHS trusts, without the patient access scheme, indicated an ICER of £110,500 per QALY gained.</p> <p>The Committee also examined the exploratory analyses carried out by the ERG that attempted to calibrate overall survival in the model with that directly observed in the E2100 trial by using an area under the curve method. These analyses resulted in mean life years of 2.16 years in the bevacizumab plus paclitaxel arm and 2.13 years in the paclitaxel alone arm (an incremental benefit of 0.03 years) and a pair wise ICER of £259,000 per QALY gained, based on the list price for paclitaxel. Using the average price for paclitaxel paid by NHS trusts, the ERG reported that the ICER remained over £200,000 per QALY gained. The ERG acknowledged that this represented a pessimistic scenario.</p>	<p>4.15</p>
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<p>Incorporation of health-related quality of life benefits and utility values</p> <p>Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?</p>	<p>No health-related benefits were identified that were not included in the economic models</p>	<p>NA</p>
<p>Most likely cost-effectiveness estimate (given as an ICER)</p>	<p>The Committee concluded that the most plausible ICER for bevacizumab plus paclitaxel versus weekly paclitaxel was between £110,000 and £259,000 per QALY gained and that the ICER for bevacizumab plus paclitaxel versus docetaxel would be greater than £115,000 per QALY gained. The Committee accepted the manufacturer's statement that the ICER for bevacizumab plus docetaxel would be higher than that for bevacizumab plus paclitaxel since docetaxel is the more expensive taxane.</p>	<p>4.22</p>
<p>Additional factors taken into account</p>		

Patient access scheme	The Committee noted that the manufacturer had provided two base cases, one of which was based on average prices for paclitaxel paid by NHS trusts over a 4-month period and included a patient access scheme for bevacizumab. The Committee was aware that no patient access scheme had been approved by the Department of Health and therefore the scheme could not be taken into account in the consideration of cost effectiveness.	4.12
End-of-life considerations	The Committee concluded that bevacizumab in combination with a taxane did not fulfil the criteria for being a life-extending, end-of-life treatment.	4.21
Equalities considerations, Social value judgements	The Committee concluded that there was no evidence of differences in access to treatment or response to treatment by socioeconomic status or ethnicity in patients with disease at the metastatic stage.	4.19

5 Implementation

- 5.1 The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the NHS on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding direction, details will be available on the [NICE website](#). The NHS is not required to fund treatments that are not recommended by NICE.
- 5.2 NICE has developed [tools](#) to help organisations put this guidance into practice (listed below).
- A costing statement explaining the resource impact of this guidance.
 - Audit support for monitoring local practice.

6 Recommendations for further research

- 6.1 Further research designed to investigate differences in health-related quality of life and the clinical effectiveness of bevacizumab in subgroups, such as those with prior taxane exposure, would be particularly useful.

7 Related NICE guidance

- [Advanced breast cancer: diagnosis and treatment](#). NICE clinical guideline 81 (2009).
- [Bevacizumab for the first-line treatment of metastatic breast cancer](#) (terminated appraisal). NICE technology appraisal 147 (2008).
- [Gemcitabine for the treatment of metastatic breast cancer](#). NICE technology appraisal guidance 116 (2007).

8 Review of guidance

The guidance on this technology will be considered for review in July 2013.

Andrew Dillon
Chief Executive
February 2011

Appendix A: Appraisal Committee members, and NICE project team

A Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are four Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Jane Adam (Chair)

Department of Diagnostic Radiology, St George's Hospital

Professor Philip Home (Vice Chair)

Professor of Diabetes Medicine, Newcastle University

Professor A E Ades

Professor of Public Health Science, Department of Community Based Medicine, University of Bristol

Dr Fiona Duncan

Clinical Nurse Specialist, Anaesthetic Department, Blackpool Victoria Hospital, Blackpool

Dr Paul Ewings

Statistician, Taunton & Somerset NHS Trust, Taunton

Mr John Goulston

Chief Executive, Barking, Havering and Redbridge Hospitals NHS Trust

Mr Adrian Griffin

VP Strategic Affairs, LifeScan, Johnson & Johnson

Dr Alec Miners

Lecturer in Health Economics, London School of Hygiene and Tropical Medicine

Dr Ann Richardson

Lay Member

Mr David Thomson

Lay Member

Mr William Turner

Consultant Urologist, Addenbrooke's Hospital

Dr Luke Twelves

General Practitioner, Ramsey Health Centre, Cambridgeshire

Mr Mike Spencer

Assistant Director Patient Experience, Cardiff and Vale University Health Board

Dr James Moon

Consultant Cardiologist and Senior Lecturer, University College London Hospital (UCLH) and UCL

Dr David Newsham

Lecturer (Orthoptics), University of Liverpool

Professor Iain Squire

Consultant Physician, University Hospitals of Leicester

Dr Peter Heywood

Consultant Neurologist, Frenchay Hospital

Dr Ian Lewin

Consultant Endocrinologist, North Devon District Hospital

Dr Louise Longworth

Reader in Health Economics, HERG, Brunel University

Dr Anthony S Wierzbicki

Consultant in Metabolic Medicine/Chemical Pathology, Guy's and St Thomas' Hospitals NHS Trust

Professor Jonathan Grigg

Professor of Paediatric Respiratory and Environmental Medicine, Barts and the London School of Medicine and Dentistry, Queen Mary University London

Dr John Watkins

Clinical Senior Lecturer/Consultant in Public Health Medicine, Cardiff University and National Public Health Service Wales

Dr Olivia Wu

Reader in Health Economics, University of Glasgow

Dr Paul Robinson

Medical Director, Merck Sharp & Dohme

Mr Stephen Sharp

Senior Statistician, MRC Epidemiology Unit

B NICE project team

Each technology appraisal is assigned to a team consisting of one or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Raisa Sidhu

Technical Lead

Rebecca Trowman

Technical Adviser

Zoe Garrett

Technical Adviser

Bijal Joshi

Project Manager

Appendix B: Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this appraisal was prepared by The CRD and CHE Technology Assessment Group, University of York:

- Rodgers M, et al. Bevacizumab in combination with a taxane for the first-line treatment of HER2-negative metastatic breast cancer, May 2010

B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to give their expert views. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I) Manufacturer/sponsor:

- Roche Products

II) Professional/specialist and patient/carers groups:

- Breakthrough Breast Cancer
- Breast Cancer Care
- Royal College of Nursing
- Royal College of Physicians (NCRI Breast Clinical Studies Group/RCP/RCR/ACP/JCCO)

III) Other consultees:

- NHS Kensington and Chelsea
- NHS Milton Keynes

C. The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer/sponsor consultees and commentators. They gave their expert personal view on bevacizumab in combination with a taxane for the first-

line treatment of metastatic breast cancer by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Dr Paul Ellis, Senior Medical Oncologist, Guys Hospital, nominated by The Royal College of Physicians (NCRI/RCP/RCR/ACP/JCCO) – clinical specialist
- Ms Maria Leadbeater, nominated by Breast Cancer Care – patient expert

D. The following individuals were nominated as NHS Commissioning experts by the selected PCT allocated to this appraisal. They gave their expert/NHS commissioning personal view on bevacizumab in combination with a taxane for the first-line treatment of metastatic breast cancer by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Dr Don Sinclair, Public Health Consultant, nominated by NHS Milton Keynes – NHS Commissioning expert

E. Representatives from the following manufacturer/sponsor attended Committee Meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Roche Products

Changes after publication

February 2014: minor maintenance

March 2012: minor maintenance

About this guidance

NICE technology appraisal guidance is about the use of new and existing medicines and treatments in the NHS in England and Wales.

This guidance was developed using the NICE [single technology appraisal](#) process.

It updates and replaces terminated technology appraisal 147, Bevacizumab in combination with paclitaxel for the first-line treatment of metastatic breast cancer, issued June 2008.

The recommendations from this guideline have been incorporated into a [NICE Pathway](#). We have produced a [summary of this guidance for patients and carers](#). Tools to help you put the guidance into practice and information about the evidence it is based on are also [available](#).

Your responsibility

This guidance represents the views of NICE and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way which would be inconsistent with compliance with those duties.

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