# NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

## Final appraisal determination

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

This guidance was developed using the single technology appraisal (STA) process

## 1 Guidance

1.1 Bevacizumab in combination with capecitabine is not recommended within its marketing authorisation for the first-line treatment of metastatic breast cancer, that is, when treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate, or when taxanes or anthracyclines have been used as part of adjuvant treatment within the past 12 months.

1.2 People currently receiving bevacizumab in combination with capecitabine that is not recommended according to 1.1 should have the option to continue treatment until they and their clinician 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. Bevacizumab in combination with capecitabine has a marketing

authorisation for ‘first-line treatment of patients with metastatic breast cancer in whom treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate. Patients who have received taxane and anthracycline-containing regimens in the adjuvant setting within the last 12 months should be excluded from treatment with bevacizumab in combination with capecitabine’.

2.2 The summary of product characteristics lists the following adverse reactions 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, hypersensitivity/infusion reactions, osteonecrosis of the jaw, ovarian failure and neutropenia. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 Bevacizumab is available in 100 mg and 400 mg vials at net prices of £242.66 and £924.40, respectively (excluding VAT; ‘British national formulary’ [BNF] edition 63). 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. The manufacturer estimated the price of bevacizumab (excluding VAT and assuming wastage) to be £2577 for a patient weighing 72.1 kg at a dosage of 15 mg/kg every 3 weeks, amounting to an average monthly cost of £3689. 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 this submission by the Evidence Review Group (ERG; appendix B).

## *Clinical effectiveness*

3.1 The manufacturer conducted a literature search and identified two randomised controlled trials (TURANDOT and RIBBON-1) that investigate the effect of first-line bevacizumab plus capecitabine in adults with metastatic breast cancer. The TURANDOT trial was excluded because it is ongoing and no efficacy data are available. The RIBBON-1 trial was an international, multicentre, double-blind, phase III, randomised, placebo-controlled trial comparing bevacizumab plus chemotherapy with chemotherapy alone for the first-line treatment of HER2-negative, locally recurrent or metastatic breast cancer.

3.2 The RIBBON-1 trial enrolled 1237 patients to receive bevacizumab plus chemotherapy or chemotherapy plus placebo. Investigators were able to select their choice of chemotherapy before randomisation. Patients were enrolled into two different cohorts; in one cohort patients received either an anthracycline or a taxane, and in the other cohort patients received capecitabine, reflecting the choice of first-line therapy for these patients in routine clinical practice. Patients were then randomised to bevacizumab plus the chosen chemotherapy or to the chosen chemotherapy plus placebo. The manufacturer stated that only the results from the capecitabine cohort provided evidence on the use of bevacizumab in its licensed indication, in combination with capecitabine for the first-line treatment of metastatic breast cancer. The manufacturer highlighted that anthracyclines and taxanes were not considered

appropriate as first-line treatment for all patients in the capecitabine cohort; about 40% of the patients had previously received taxanes and around 63% had received anthracycline therapy for early breast cancer.

3.3 In the capecitabine cohort of the RIBBON-1 trial 615 patients were randomised in a 2:1 ratio to the bevacizumab plus capecitabine arm (n=409) and the capecitabine plus placebo arm (n=206). Randomisation was stratified by the following criteria: disease-free interval (12 months or less, more than 12 months since completion of adjuvant chemotherapy or surgery if no adjuvant chemotherapy); previous adjuvant chemotherapy; and number of metastatic sites (fewer than three, three or more). The dosage of bevacizumab was 15 mg/kg by intravenous infusion every 3 weeks, and the dosage of capecitabine was 1000 mg/m$^2$ orally twice daily for 2 weeks of a 3-week cycle. Treatment was continued until disease progression, unacceptable toxicity, investigator or patient decision to stop treatment, or death. Patients continued to receive capecitabine if bevacizumab was discontinued before disease progression. After disease progression, patients in either arm could move to an open-label phase consisting of treatment including bevacizumab and chemotherapy at the investigator's discretion. Patients who chose not to enter the post-progression phase and patients who discontinued treatment during the post-progression phase were followed up in a survival follow-up phase.

3.4 The primary endpoint in the trial was investigator-assessed progression-free survival according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria. It was defined as the time from randomisation to first disease progression or death from any cause. Progression-free survival based on an Independent Review Committee (IRC) review of the data was considered a secondary

endpoint and presented as a sensitivity analysis to support the investigator-assessed primary endpoint. Other secondary endpoints included objective response rates, defined as the percentage of patients with a complete or partial response determined on two consecutive assessments more than 4 weeks apart; duration of objective response, defined as the time from the first tumour assessment that supported an objective response to the time of disease progression, or death from any cause; overall survival, defined as the time from randomisation until death from any cause; and the 1-year survival rate, defined as the percentage of patients still alive one year after randomisation. In addition, progression-free survival and overall survival were calculated for a number of pre-specified subgroups, post hoc exploratory subgroups, and subgroups specified after the trial had begun but before the analysis was completed (for example, the subgroup of patients previously treated with a taxane, which was included in the manufacturer's economic model).

3.5 There was a statistically significant increase in the investigator assessed median progression-free survival of 2.9 months, from 5.7 months in the capecitabine plus placebo arm to 8.6 months in the bevacizumab plus capecitabine arm. The stratified hazard ratio for progression was 0.69 (95% confidence interval [CI] 0.564 to 0.840, p=0.0002). Median overall survival improved by 2.9 months, from 22.8 months with capecitabine plus placebo to 25.7 months with bevacizumab plus capecitabine. The stratified hazard ratio for death was 0.88 (95% CI 0.69 to 1.13, p=0.33), indicating a 12% improvement in overall survival with bevacizumab plus capecitabine compared with capecitabine plus placebo. However this improvement was not statistically significant. The manufacturer acknowledged that the results from the patients who crossed over to bevacizumab in the open-label post-progression phase of the

trial (44.7% in the bevacizumab/capecitabine arm and 52.4% in the capecitabine/placebo arm) may have confounded overall survival results. This was because the trial was not designed to evaluate the effect of subsequent therapies.

3.6 A number of subgroup analyses for progression-free survival (16 in total) and for overall survival (24 in total) with no correction for multiple testing were presented in the manufacturer's submission. The manufacturer highlighted that bevacizumab plus capecitabine gave a progression-free survival benefit over capecitabine plus placebo in all of the pre-specified subgroups defined by stratification variables, although not all were statistically significant. The manufacturer investigated a number of additional planned and post hoc subgroups and showed that some subgroups (for example, the group previously treated with a taxane) had a greater overall survival benefit than the intention-to-treat (ITT) population of the capecitabine cohort.

3.7 The manufacturer focused on the subgroup of patients who had a previous adjuvant or neo-adjuvant taxane. This subgroup of 245 patients had an increase in median progression-free survival of 4.5 months, from 4.2 months in the capecitabine plus placebo arm to 8.7 months in the bevacizumab plus capecitabine arm. The hazard ratio for progression was 0.62 (95% CI 0.45 to 0.84). This benefit also translated into an overall survival benefit, with an increase in median overall survival of 7.9 months, from 20.5 months in the capecitabine plus placebo arm to 28.4 months in the bevacizumab plus capecitabine arm. The hazard ratio for death was 0.67 (95% CI 0.46 to 0.98). These overall survival results were based on 70 deaths in the bevacizumab plus capecitabine arm and 44 deaths in the capecitabine plus placebo arm. The manufacturer stated that patients previously treated with

a taxane had worse outcomes than the patients in the ITT population, and the addition of bevacizumab increased their progression-free survival and overall survival to levels similar to or above those of the ITT population. The manufacturer presented the results of two similar metastatic breast cancer trials (the AVADO and E2100 trials) which demonstrated the same pattern of progression-free and overall survival gains from bevacizumab in patients who have previously received a taxane. The AVADO trial compared bevacizumab plus docetaxel with docetaxel plus placebo, and the E2100 trial compared bevacizumab plus paclitaxel with paclitaxel alone.

3.8 The primary safety analyses were based on all patients who received any trial treatment, defined as at least one full or partial dose of either trial treatment during the blinded phase of the trial. This population was referred to by the manufacturer as the safety population. The manufacturer stated that adding bevacizumab to capecitabine resulted in adverse events that were predictable based on previous use of bevacizumab, and generally manageable. Grade 3–5 adverse events were higher with bevacizumab plus capecitabine (36.6%) compared with capecitabine plus placebo (22.9%). In addition, the following adverse events were higher with bevacizumab plus capecitabine compared with capecitabine plus placebo: hypertension (10.6% compared with 1%), proteinuria (2.2% compared with 0%), sensory neuropathy (3% compared with 0.5%) and venous thromboembolic events (5% compared with 3.5%).

3.9 Health-related quality of life data were not collected in the RIBBON-1 trial. The manufacturer stated that the most important factor causing distress among cancer patients was the fear of disease progression. Therefore a major objective of each

successive line of therapy, in addition to extending overall survival, was to maintain progression-free survival for as long as possible.

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

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

3.12 The ERG noted the subgroup analyses conducted by the manufacturer, and commented that most increases in progression-free survival with bevacizumab plus capecitabine compared with capecitabine plus placebo were statistically significant in these subgroups. However, the only overall survival results that were statistically significant were for subgroups of patients younger than 50 years and subgroups of patients previously treated with a taxane or anthracycline as neoadjuvant or adjuvant chemotherapy. The ERG stated that the results of the subgroup analyses should be considered with caution because no statistical adjustments were performed to control for multiple testing in any of the 40 subgroups and of all outcomes, thus increasing the likelihood of significant results emerging by chance when using the usual level of significance of 5%.

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

3.14 Regarding the safety of bevacizumab plus capecitabine compared with capecitabine plus placebo in the subgroup of people who had previously received a taxane, the ERG stated that it was not possible to compare the proportions of patients who experienced any adverse events, any grade 3–5 adverse events, any serious adverse events or any adverse events leading to discontinuation of

bevacizumab or placebo because the manufacturer did not present these data. The ERG extracted some data from the economic model, and stated that adverse events of special interest mostly appeared to be similar in frequency in the subgroup and in the overall trial population. A slightly greater proportion of patients in the subgroup reported grade 3 or higher cardiac disorders (4.4%) than in the overall safety population (2.1%). However, the ERG stated that these findings must be viewed with caution because of the small numbers of patients in this subgroup.

### *Cost effectiveness*

3.15 In a systematic review of the literature the manufacturer found no cost-effectiveness studies comparing bevacizumab plus capecitabine with capecitabine plus placebo as first-line treatments for metastatic breast cancer. No relevant cost-effectiveness analyses were identified. The economic evaluation was based on the subgroup of patients from the RIBBON-1 trial who had previously received a taxane, and all efficacy and treatment duration parameters were derived from this subgroup. The manufacturer assumed that patients in this subgroup would probably have received an anthracycline as well. The manufacturer stated that this subgroup reflected the marketing authorisation for capecitabine. Capecitabine monotherapy has a marketing authorisation for 'the treatment of patients with locally advanced or metastatic breast cancer after failure of taxanes and an anthracycline-containing chemotherapy regimen or for whom further anthracycline therapy is not indicated'. The manufacturer acknowledged that this post hoc subgroup analysis of patients previously treated with a taxane was the main weakness of the economic evaluation.

3.16 The manufacturer developed a three-state model. All patients enter the model in the progression-free survival health state and in each month can either progress to a 'worse' health state (that is, from progression-free survival to progressed disease or from either state to death) or remain in the same health state. The manufacturer stated that these health states were consistent with previous modelling of metastatic cancer. The progression-free survival health state is designed to capture a patient's relatively high quality of life before disease progression and the progressed disease state is designed to capture the relatively poor quality of life after disease progression. Survival data from the capecitabine plus placebo arm of the subgroup previously treated with a taxane from the RIBBON-1 trial were used to inform disease progression in the comparator arm. The treatment duration in the trial was used to determine the expected cost of treatment with each regimen in the base case. The model has a one-month cycle length, includes a half-cycle correction and both costs and benefits are discounted at 3.5%. The time horizon was 15 years.

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

3.18 A number of tunnel states, health states which can only be passed through in a certain order, were generated for patients with

progressed disease according to the time spent in this state. The tunnel states were arranged so that each state had a progression only to death or the next temporary state. Patients who entered the progressed disease state had a probability of dying that increased each month based on an extrapolation of the survival data for patients with progressed disease. Mean overall survival was the sum of mean duration of progression-free survival and mean duration of progressed disease.

3.19 During the progressed disease phase, patients in the capecitabine cohort of the RIBBON-1 trial received a variety of different therapies. The manufacturer modelled survival in progressed disease based on adjusted analyses that aimed to 'uncross' the survival curves by excluding survival gains from patients who crossed over to bevacizumab in the open-label phase of the trial. An exponential survival distribution was assumed thereafter. The data were 'uncrossed' using a rank preserving structural failure time model to take account of the bias that may have been introduced by allowing patients from both treatment arms to receive bevacizumab after progression, potentially distorting overall survival rates in the control arm.

3.20 The manufacturer carried out a literature review to identify relevant health-related quality of life data to use in the economic evaluation. Three studies that measured utility values directly were identified and, of these, the manufacturer calculated utility values for progression-free survival and progressed disease from the results of the mixed model analysis presented by Lloyd et al. (2006). The manufacturer stated that it was most appropriate to use a base-case progression-free survival utility value that was derived from a large population, and then to adjust that base-case utility by response rate. In addition, the utility values from Lloyd et al. have

been used in previous health technology appraisals for metastatic breast cancer. For patients in the progressed disease state, a health state utility value of 0.496 was incorporated in both treatment arms. For patients in the progression-free survival state a treatment-specific weighted average of the values for stable disease and treatment response, based on the reported overall response rate, was calculated: 0.784 in the bevacizumab plus capecitabine arm and 0.774 in the capecitabine plus placebo arm. The manufacturer acknowledged that the utility values reported by Lloyd et al. were not derived from patient experience, and presented a sensitivity analysis using data from Peasgood et al. (2010) to derive estimated utilities from patients valuing their own health.

3.21 The drug costs incorporated in the model for bevacizumab plus capecitabine and capecitabine were from BNF 62 (£4001.53 per month and £312.41 per month respectively). No vial sharing was assumed for bevacizumab. The manufacturer's submission assumed administration and pharmacy costs of £348.82 in the first month and £205.97 per month for subsequent months of treatment with bevacizumab and capecitabine. Administration and pharmacy costs for capecitabine alone were assumed to be £255.32 per month. The manufacturer stated that in clinical practice some patients stop treatment before disease progression, and therefore it is essential to consider the distinction between disease progression and treatment discontinuation when evaluating the real incremental cost. In order to account for this difference, patient data on treatment duration were used to produce 'time to off treatment' Kaplan-Meier curves that could be used to determine the proportion of patients still receiving bevacizumab and/or capecitabine each month.

3.22 Progression-free survival health state costs were based on 'Advanced breast cancer: diagnosis and treatment' (NICE clinical guideline 81) 'package 1' with the addition of an outpatient consultation with an oncologist and a computed tomography (CT) scan assumed to occur every 3 months, and were estimated to be £263.55 per month. Progressed disease health state costs were based on NICE clinical guideline 81 'package 2' and estimated to be £804.00 per month. The same costs and utilities were assumed regardless of first-line treatment. Adverse events of grade 3 or 4 severity occurring in greater than 2% of patients were incorporated into the analysis. When clinical advice indicated that the usual response to the adverse event was discontinuation of treatment (for peripheral sensory neuropathy, hand-foot syndrome and proteinuria), it was assumed this had been accounted for elsewhere in the model and no additional costs were accrued. In addition, treatment of diarrhoea was considered to have negligible contribution to costs. Therefore only costs associated with deep vein thrombosis and hypertension were included in the model. All adverse events were assumed to occur in month 1 for both treatment arms and were therefore not discounted.

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

3.24 The base-case results indicated incremental costs of £38,924 and incremental QALYs of 0.5034 for bevacizumab plus capecitabine compared with capecitabine alone. The cost per QALY gained was £77,318 for bevacizumab plus capecitabine compared with capecitabine alone. The manufacturer conducted deterministic sensitivity analyses for a range of parameters. The manufacturer stated that the cost-effectiveness results were most sensitive to the costs and utilities associated with progressed disease.

3.25 The manufacturer conducted a scenario analysis using utility values from Peasgood et al. but this had little impact on the ICER and did not result in it increasing above £79,991 per QALY gained. A second scenario analysis was conducted including different formulations of vinorelbine as the comparator. It was assumed that vinorelbine had an equivalent efficacy and safety profile to capecitabine, with different list prices and costs of administration. The ICER was £58,972 per QALY gained for bevacizumab plus capecitabine compared with oral vinorelbine, £76,198 per QALY gained compared with branded intravenous vinorelbine, and £80,260 per QALY gained compared with generic intravenous vinorelbine.

3.26 The manufacturer conducted a probabilistic sensitivity analysis and concluded that bevacizumab plus capecitabine compared with capecitabine alone had a 0% probability of being cost effective if the maximum acceptable ICER was £30,000 to £50,000 per QALY gained. In response to consultation, the manufacturer provided the ICER based on the probabilistic sensitivity analysis, which was £80,073 per QALY gained for bevacizumab plus capecitabine compared with capecitabine alone (mean incremental costs were £40,161 [95% CI 36,703 to 45,079], mean incremental QALYs were 0.502 [95% CI 0.33 to 0.66]).

3.27 The manufacturer acknowledged that its economic evaluation was only relevant to patients with similar characteristics to those randomised to the capecitabine cohort of the RIBBON-1 trial who had previously been treated with a taxane. The ERG requested additional cost-effectiveness data for the ITT population of the capecitabine cohort for clarification. However, the manufacturer stated that because the submitted analysis calculated an ICER of £77,318 per QALY gained for the subgroup previously treated with a taxane, analysis of the ITT population would result in a larger ICER and therefore would not be considered a cost-effective use of NHS resources.

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

bevacizumab. In addition, the ERG identified that there appeared to be baseline differences between the subgroup of patients who had previously received a taxane and the ITT population. In particular, the ERG noted from differences in the mean and median age and Eastern Cooperative Oncology Group (ECOG) performance status that the population of patients who had previously received a taxane appeared to be younger and healthier. The ERG also noted that the differences in progression-free and overall survival between the bevacizumab plus capecitabine and capecitabine plus placebo arms appeared to be greater in the subgroup of patients previously treated with a taxane than in the ITT population, as well as being statistically significant. However, the ERG reiterated that because no statistical adjustments were made to control for multiple testing in all subgroups and of all outcomes, these findings may have occurred by chance, and must be interpreted with caution.

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

3.30 The ERG was satisfied that the modelling approach used by the manufacturer to estimate progression-free survival from the RIBBON-1 trial using Kaplan-Meier methods for the first 12 months and assuming an exponential distribution thereafter was credible. The ERG noted that the approach was similar for progressed disease, however the manufacturer had 'uncrossed' the data using the rank preserving structural failure time model to minimise bias. The ERG stated that this approach was unsuitable when a large proportion of patients from both arms cross over. The ERG noted that 44.7% of patients in the bevacizumab plus capecitabine arm and 52.4% of patients in the capecitabine plus placebo arm received bevacizumab after disease progression. Further, patients in the modelled subgroup who previously received a taxane also received other therapies after progression. The ERG stated that given the limitations of the rank preserving structural failure time model and without any other estimate to adjust for crossover, they were unable to confirm the likely effect of the crossover and post-progression therapies on overall survival in this subgroup and caution should be exercised when interpreting the manufacturer's overall survival results.

3.31 The ERG undertook an analysis of the original progressed disease trial data (rather than the 'uncrossed' data) to explore survival during this phase. This analysis separated the bevacizumab plus capecitabine and capecitabine plus placebo arms according to whether patients had crossed over to a different treatment or not. A comparison of survival times during the progressed disease phase indicated that survival is similar in each group and overall, the four groups in the RIBBON-1 trial did not show strong evidence of heterogeneity. However, the capecitabine plus placebo group with no crossover appeared to differ when tested pairwise against the other three groups. Therefore, the ERG explored two different

scenarios. The first scenario grouped all patients together and modelled a scenario in which survival after progression was equivalent irrespective of first-line therapy or crossover (common projection scenario). This method resulted in an ICER of £171,411 per QALY gained for bevacizumab plus capecitabine compared with capecitabine alone. The second scenario grouped together all the bevacizumab plus capecitabine patients and the capecitabine plus placebo patients who crossed over, and considered the capecitabine plus placebo patients who did not cross over separately (different projections scenario). This method resulted in an ICER of £92,060 per QALY gained for bevacizumab plus capecitabine compared with capecitabine alone. The ERG stated that the second scenario allowed a clear comparison between patients who did and did not receive bevacizumab during the trial and gives a representation of the effect of crossover. The ERG highlighted that each analysis portrayed an extreme, allowing consideration of a best and worst case scenario for the effect of crossover on post-progression survival.

3.32 The ERG conducted a sensitivity analysis to study the impact of including the licensed dose of capecitabine (1250 mg/$m^2$) rather than the dose widely used in clinical practice (1000 mg/$m^2$). It found that changing the dose of capecitabine to 1250 mg/$m^2$ results in an overall incremental increase in drug costs of £3782 and an accompanying increase of £7512 per QALY gained in the ICER estimate. The ERG re-estimated the costs of therapy based on the distribution of patient body weight and body surface area in a UK-specific cohort of patients rather than using a simple average based on trial data. The ERG found that this resulted in an increase in drug costs of £2966 per patient in the bevacizumab plus capecitabine arm and an increase of £50 per patient in the capecitabine alone arm. The adjustment resulted in a revised ICER

that was £5793 higher per QALY gained than the manufacturer's base-case ICER. The ERG also added in the costs of terminal care during the last two weeks of life, as specified in the guideline on advanced breast cancer (NICE Clinical Guideline 81), and these adjustments resulted in a revised ICER that was £105 lower per QALY gained than the manufacturer's base-case ICER.

3.33 The ERG noted that the utility values used in the manufacturer's model were estimated using the statistical model detailed in a study by Lloyd et al. The ERG noted that there is a lack of consensus among economists in relation to the most appropriate value for age in the Lloyd et al. model, that is, whether it should be the age of the population surveyed in the study or the age of the population taking part in the original health state valuation exercise carried out by Kind et al. (1999). The ERG noted that the manufacturer used 47 years, the mean age of the population taking part in the original Kind et al. study, with the advantage that it was consistent with standard UK EQ-5D tariff scores. However, the ERG stated that the lack of consensus relating to the most appropriate age to use introduces a degree of uncertainty to the utility values used in the model. The ERG also corrected for a typing mistake in the formula used in the manufacturer's model in the capecitabine alone arm and this resulted in a revised ICER that was £786 lower per QALY gained than the manufacturer's base-case ICER.

3.34 The combined impact of the ERG's revisions to the drug costs, terminal care costs and utility estimates in the manufacturer's base case resulted in an ICER of £82,162 per QALY gained for bevacizumab plus capecitabine compared with capecitabine alone. In addition, combining these revisions with the revised progressed disease estimates resulted in an ICER of £181,648 per QALY gained when using the common projection scenario and £97,963

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

3.35 Full details of all the evidence are in the manufacturer's submission and the ERG report, which are available from www.nice.org.uk/guidance/TAXXX

# 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 capecitabine, having considered evidence on the nature of metastatic breast cancer and the value placed on the benefits of bevacizumab in combination with capecitabine by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

4.2 The Committee considered the clinical need for treatment in patients with metastatic breast cancer for whom treatment with other chemotherapy options, including taxanes or anthracyclines, is not considered appropriate. The Committee heard from the clinical specialist that there was broad agreement among breast cancer specialists that the case for incorporating bevacizumab into first-line treatment was stronger for patients with triple negative breast cancer (breast cancer that is oestrogen-, progesterone- and HER2-receptor negative) with aggressive visceral disease, for whom there were limited treatment options. The Committee heard from the patient expert and clinical specialist that prolonging progression-free survival was very important for patients with advanced breast cancer, but this had to be coupled with maximising quality of life at

the same time. The adverse events associated with treatment were therefore also of significance, as was the method of administration and convenience of therapy. The Committee concluded that bevacizumab plus capecitabine represented an option for patients with limited treatment options, and that an improvement in progression-free survival combined with a quality of life benefit, and the adverse event profile were key considerations.

## *Clinical effectiveness*

4.3 The Committee considered the generalisability of the RIBBON-1 trial to UK clinical practice. The Committee was aware of NICE clinical guideline 81 for advanced breast cancer in which capecitabine follows both anthracycline and taxane therapy in the care pathway. It noted the design of the RIBBON-1 trial, which had two cohorts of patients; those to be treated with anthracyclines or a taxane and those to be treated with capecitabine. The Committee noted that 63% of the capecitabine cohort had received prior anthracycline therapy and 40% had received prior taxane therapy. Because there was likely to have been considerable overlap between these two groups (and perhaps total overlap, as assumed by the manufacturer), a significant percentage of patients (up to 37%) could have received capecitabine for first-line treatment of their metastatic breast cancer as their first ever chemotherapy. The Committee considered that this meant that this group of patients were not representative of the typical UK metastatic breast cancer population. The Committee also noted that the 60% of patients in the capecitabine cohort of the RIBBON-1 trial who had not received prior taxane therapy had good performance status and yet taxane treatment was not considered appropriate for them. In addition, the Committee observed that 30% of the patients in the prior taxane subgroup for whom taxanes were not considered appropriate (as

indicated by the entry criteria for the capecitabine arm of the RIBBON-1 trial) subsequently received taxanes after disease progression. However, the Committee was aware that the decision to treat with capecitabine or a taxane could also be based on other factors which may be important to patients, such as the lack of hair loss with capecitabine. The Committee concluded that there were still some issues about the generalisability of the RIBBON-1 trial to clinical practice in the UK. This was because a significant proportion of patients in the trial had not received previous chemotherapy, and taxanes had not been considered for a significant proportion despite their young age and good performance status.

4.4 The Committee also noted that the dose of capecitabine in the trial was 1000 mg/m$^2$ rather than the licensed dose of 1250 mg/m$^2$. The Committee was aware that the dose of capecitabine used in UK practice was often lower in older patients and those with poor performance status, but observed that all patients in the RIBBON-1 trial were of ECOG performance status 0 or 1 and the median age was 56 years. However, it noted the comments during consultation that some clinicians in the UK start at a dose lower than the licensed dose (often 1000 mg/m$^2$) even in fitter patients. The Committee therefore concluded that the dose of capecitabine used in the trial may have some relevance to clinical practice in the UK.

4.5 The Committee considered the clinical-effectiveness data from the capecitabine cohort of the RIBBON-1 trial for the comparison of bevacizumab plus capecitabine with capecitabine plus placebo. The Committee noted that the results from the ITT population demonstrated a statistically significant median investigator-assessed progression-free survival benefit of 2.9 months for bevacizumab plus capecitabine compared with capecitabine plus

placebo. However, the Committee noted this improvement in progression-free survival did not translate into a statistically significant improvement in overall survival. The Committee was aware that patients from both arms of the trial could receive treatment with bevacizumab after disease progression as well as other subsequent treatments and that all these subsequent therapies could have confounded the relative treatment effect in terms of overall survival. The Committee also noted that no quality of life data had been collected in the trial. The Committee considered quality of life to be an important outcome measure in advanced cancer and that this was an omission from the trial. Without quality of life data and a statistically significant improvement in overall survival, the Committee explored the value of an increase in progression-free survival. The Committee was aware of a statement from the clinical specialist that the most important outcome for patients with metastatic breast cancer is prolonging disease-free survival. However, the Committee heard from the patient expert that patients would value an increase in progression-free survival when it is accompanied by an improvement in quality of life that would allow them to carry out normal daily activities. The Committee concluded that bevacizumab plus capecitabine improved progression-free survival relative to capecitabine plus placebo, but that there was no robust evidence that it improved overall survival and that its effects on health-related quality of life had not been captured.

4.6 The Committee discussed the adverse event profile associated with bevacizumab plus capecitabine compared with capecitabine plus placebo. The Committee noted that grade 3–5 adverse events were higher with bevacizumab plus capecitabine (36.6%) compared with capecitabine plus placebo (22.9%). In addition, the number of patients with hypertension, proteinuria, sensory neuropathy and

venous thromboembolic events was higher with bevacizumab plus capecitabine compared with capecitabine plus placebo. The Committee considered that the adverse event profile of bevacizumab plus capecitabine was particularly important because if people opt for capecitabine instead of taxane-based treatment it may be an indication that a better adverse event profile was important to them. The Committee concluded that bevacizumab plus capecitabine had a less favourable adverse event profile than capecitabine plus placebo.

4.7 The Committee noted that no clinical evidence of the effectiveness of bevacizumab plus capecitabine compared with vinorelbine was presented by the manufacturer as specified in the final scope issued by NICE. The Committee noted the manufacturer's statement that capecitabine is generally preferred to vinorelbine in in UK clinical practice and that vinorelbine had been included as a comparator as part of the scenario analysis in the economic modelling. The Committee concluded that, without studies that would allow for an indirect comparison of bevacizumab plus capecitabine with vinorelbine, and without evidence to suggest that vinorelbine was superior to capecitabine, it was appropriate for capecitabine to be presented as the main comparator.

4.8 The Committee examined the subgroup analysis conducted by the manufacturer comparing bevacizumab plus capecitabine with capecitabine plus placebo in patients who had previously received a taxane. The Committee was aware that the differences in progression-free and overall survival between the bevacizumab plus capecitabine and capecitabine plus placebo arms were statistically significantly greater in this subgroup of patients. However, the Committee noted that previous taxane therapy was not a stratification factor at randomisation and that this subgroup

was specified after the trial had begun but before the analysis was completed. The Committee also noted that the overall survival results were based on small numbers of events: 70 deaths in the bevacizumab plus capecitabine arm and 44 deaths in the capecitabine plus placebo arm. In addition, the Committee was aware that no statistical adjustments were made to control for multiple testing, thus increasing the risk of chance findings. The Committee considered the manufacturer's original submission and their consultation comments about an increased benefit observed in the prior taxane subgroup compared with the ITT population in other metastatic breast cancer trials of bevacizumab as part of first-line chemotherapy (the AVADO and E2100 trials). The Committee noted that although the prior taxane subgroups showed significant benefits with bevacizumab in the AVADO and E2100 trials, the benefits were not replicated in the prior taxane subgroup in the anthracycline/taxane cohort of RIBBON-1. The Committee heard from the clinical specialist that the prior taxane subgroup was a clinically relevant subgroup given the current treatment pathway of metastatic breast cancer. The Committee also noted the comment from the consultees and clinical specialist that women with triple negative breast cancer for whom there are limited treatment options are the most clinically relevant subgroup, with a realistic chance of benefitting from bevacizumab plus capecitabine treatment. However, the Committee was aware that the RIBBON-1 trial results did not show an advantage for bevacizumab plus capecitabine in this triple negative subgroup. The Committee was concerned about the robustness of the data from the AVADO and E2100 trials because of the small patient numbers in the prior taxane subgroups in the AVADO and E2100 trials and the unblinding and non-stratification for prior taxane use in the E2100 trial. It noted that although the progression-free survival and overall

survival benefits were higher in the prior taxane subgroups in the E2100, AVADO and the capecitabine cohort of the RIBBON-1 trials, there was no biologically plausible reason why bevacizumab plus capecitabine would be more effective in this subgroup than in the ITT population. The Committee therefore considered that a formal study would be needed to confirm these benefits, as had been recognised by the manufacturer. The Committee concluded that the results from the prior taxane subgroup of the RIBBON-1 trial were not sufficiently robust to use for the development of guidance.

### *Cost effectiveness*

4.9 The Committee considered the manufacturer's economic model and the ERG's critique of this model. The Committee was aware that the manufacturer had based the economic evaluation on the subgroup of patients who had previously received a taxane rather than the Committee's preferred choice of the whole capecitabine cohort (the ITT population). The Committee noted the manufacturer's and ERG's statements that an analysis of the ITT population would result in a larger ICER than the £77,000 per QALY gained for the subgroup included in the manufacturer's base-case analysis. The Committee agreed with this assessment. The Committee considered the ERG critique and explorations of the manufacturer's model to determine the most plausible ICER for the subgroup previously treated with a taxane. The aim was to establish a benchmark for the incremental cost per QALY gained for the ITT population.

4.10 The Committee noted the explorations made by the ERG to the economic model:

- basing costs on the distribution of patient body weight and body surface area in a UK-specific cohort of patients rather than using a simple average based on trial data
- including costs of terminal care during the last two weeks of life
- correcting a typing mistake in the calculation of utilities.

The Committee noted that these changes resulted in the ERG's estimated ICER of £82,000 per QALY gained for bevacizumab plus capecitabine compared with capecitabine alone. The Committee concluded that these explorations were appropriate.

4.11 The Committee noted the ERG's concerns around the rank preserving structural failure time method used by the manufacturer to account for the effect of crossover to open-label bevacizumab in the modelling of survival in the progressed disease state. The Committee discussed the ways in which the analyses were adjusted for crossover by the manufacturer and the ERG. The Committee was unclear as to whether these were appropriate (or whether any other method would be appropriate) or would introduce potential bias because about half the patients in both arms of the trial crossed over to have open-label bevacizumab after disease progression. The Committee also noted that the subsequent treatments received had not been modelled, which in combination with the impact of crossover, could have led to confounding of the overall survival results. The ERG confirmed that it had not been possible to estimate the effect of these factors on overall survival. The Committee noted that 60% of the manufacturer's base-case QALY gain was from the progressed disease phase and it was unsure of the impact of crossover on this finding. The Committee concluded that given these uncertainties, the manufacturer's modelled overall survival results could not be considered robust.

4.12 The Committee noted that in the manufacturer's model, the costs of administration and pharmacy time from the second cycle onwards was £255 in the capecitabine alone arm and £206 in the bevacizumab plus capecitabine arm. The Committee discussed that it was unexpected that the costs associated with bevacizumab plus capecitabine would be lower than the costs for capecitabine alone. The Committee accepted that although these costs were based on NHS reference costs, it would have been possible to generate more plausible values. The Committee concluded that despite the incorporation of NHS tariffs, the discrepancy in the costs of administration and pharmacy time contributed to the uncertainty associated with the results of the manufacturer's economic model.

4.13 The Committee noted that the ERG had carried out an exploratory analysis of the progressed disease trial data to explore survival during this phase, assuming equal survival in each arm of the model (common projection scenario) as well as assuming different survival in each arm of the model depending on what the first treatment was (different projections scenario). The Committee noted that this analysis, in combination with the rest of the ERG changes, resulted in an ICER of £182,000 per QALY gained for the common projection model and £98,000 per QALY gained for the different projections model for bevacizumab plus capecitabine compared with capecitabine alone. In addition, the Committee was also aware that a disutility for adverse events had not been applied in the manufacturer's model, despite utility estimates being available in the literature to account for adverse events, and it was likely that this could have resulted in underestimated ICERs. The Committee concluded that given all of the uncertainties, it was not possible to determine the most plausible ICER for bevacizumab plus capecitabine compared with capecitabine alone for the

subgroup of patients who were previously treated with a taxane. However, it was convinced that the ICER would be higher than the most optimistic ICER of £82,000 per QALY gained resulting from the ERG explorations. The Committee considered that the ICER for bevacizumab plus capecitabine compared with capecitabine alone in the ITT population would be even higher (see section 4.9). The Committee noted the comments received during consultation, but considered that there was no evidence to alter its conclusion that the ICER for bevacizumab plus capecitabine compared with capecitabine alone would be higher than £82,000 per QALY gained. The Committee concluded that given the lack of robust evidence of survival benefit supplemented by the high ICER, bevacizumab plus capecitabine as a first-line treatment for metastatic breast cancer was not a cost-effective use of NHS resources.

4.14 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 of the economic modelling are plausible, objective and robust.

4.15 The Committee discussed whether bevacizumab plus capecitabine for the first-line treatment of metastatic breast cancer fulfilled the criteria for a life-extending, end-of-life treatment. The Committee noted that bevacizumab is licensed for a relatively large population across a range of indications in the treatment of breast, colorectal, renal and non-small-cell lung cancers. Therefore, it does not meet the criterion of the supplementary advice that the treatment should be licensed for small populations. Having established that bevacizumab did not meet the population criterion, the Committee decided it was not necessary to make a decision about the life expectancy or extension to life criteria. The Committee concluded on this basis that bevacizumab plus capecitabine did not fulfil the criteria for being a life-extending, end-of-life treatment.

4.16 The Committee recognised the novel mode of action of bevacizumab, which may benefit breast cancer patients whose treatment options are limited. However, it considered that there were no additional gains in health-related quality of life over those already included in the QALY calculations. The Committee therefore concluded that the innovative aspects of bevacizumab were already incorporated in the economic model and it did not alter its decision on the cost effectiveness of bevacizumab in combination with capecitabine.

## *Summary of Appraisal Committee's key conclusions*

| TAXXX (STA) | Appraisal title: Bevacizumab in combination with capecitabine for the first-line treatment of metastatic breast cancer | Section |
|---|---|---|
| **Key conclusion** | | |
| Bevacizumab in combination with capecitabine is not recommended within its marketing authorisation for the first-line treatment of metastatic breast cancer, that is, when treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate, or when taxanes or anthracyclines have been used as part of adjuvant treatment within the past 12 months. | | 1.1 |
| The Committee considered that the results from the manufacturer's economic analysis, based on a subgroup of patients who were previously treated with a taxane, were not robust. The Committee was not able to determine the most plausible ICER for this subgroup but was convinced it would be higher than the ICER of £82,000 per QALY gained resulting from the ERG explorations. The Committee considered that the ICER for the ITT population would be even higher. | | 4.9, 4.13 |
| **Current practice** | | |
| Clinical need of patients, including the availability of alternative treatments | The Committee heard from the patient expert and clinical specialist that prolonging progression-free survival was very important for patients with advanced breast cancer, but this had to be coupled with maximising quality of life at the same time. The Committee concluded that bevacizumab plus capecitabine represented an option for patients with limited treatment options, and that an improvement in quality of life benefit, and the adverse event profile were key considerations. | 4.2 |

| TAXXX (STA) | Appraisal title: Bevacizumab in combination with capecitabine for the first-line treatment of metastatic breast cancer | Section |
|---|---|---|
| **The technology** | | |
| Proposed benefits of the technology | The Committee concluded that bevacizumab plus capecitabine improved progression-free survival relative to capecitabine plus placebo, but that there was no robust evidence that it improved overall survival and that its effects on health-related quality of life had not been captured. | 4.5 |
| How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits? | The Committee concluded that the innovative aspects of bevacizumab were already incorporated in the economic model and that there were no additional gains in health-related quality of life over those already included in the QALY calculations. | 4.16 |
| What is the position of the treatment in the pathway of care for the condition? | Bevacizumab in combination with capecitabine has a marketing authorisation for 'first-line treatment of patients with metastatic breast cancer in whom treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate. Patients who have received taxane and anthracycline-containing regimens in the adjuvant setting within the last 12 months should be excluded from treatment with bevacizumab in combination with capecitabine'. | 2.1 |
| Adverse reactions | The Committee noted that grade 3–5 adverse events were higher with bevacizumab plus capecitabine (36.6%) compared with capecitabine plus placebo (22.9%). In addition, the number of patients with hypertension, proteinuria, sensory neuropathy and venous thromboembolic events was higher with bevacizumab plus capecitabine compared with capecitabine plus placebo. The Committee concluded that bevacizumab plus capecitabine had a less favourable adverse event profile than capecitabine plus placebo. | 4.6 |

| TAXXX (STA) | Appraisal title: Bevacizumab in combination with capecitabine for the first-line treatment of metastatic breast cancer | Section |
|---|---|---|
| **Evidence for clinical effectiveness** | | |
| Availability, nature and quality of evidence | Data from the capecitabine cohort of the RIBBON-1 trial formed the clinical-effectiveness evidence in the manufacturer's submission.<br><br>The Committee noted that no quality of life data had been collected in the trial. The Committee considered quality of life to be an important outcome measure in advanced cancer and that this was an omission from the trial. | 4.5 |
| Relevance to general clinical practice in the NHS | The Committee noted that 60% of patients in the capecitabine cohort of the RIBBON-1 trial had not received prior taxane therapy, had good performance status and yet taxane treatment was not considered appropriate for them.<br><br>The Committee also noted that the dose of capecitabine in the trial was 1000 mg/m$^2$ rather than the licensed dose of 1250 mg/m$^2$. The Committee was aware that the dose of capecitabine used in UK practice was often lower in older patients and those with poor performance status, but observed that all patients in the RIBBON-1 trial were of ECOG performance status 0 or 1 and the median age was 56 years. However, the Committee considered the comments during consultation that some clinicians in the UK start at a dose lower than the licensed dose (often 1000 mg/m$^2$) even in fitter patients. The Committee concluded that the dose of capecitabine used in the trial may have some relevance to clinical practice in the UK. | 4.3, 4.4 |
| Uncertainties generated by the evidence | The Committee was aware that patients from both arms of the trial could receive treatment with bevacizumab after disease progression as well as other subsequent treatments and that all these subsequent therapies could have confounded the relative treatment effect in terms of overall | 4.5 |

| TAXXX (STA) | Appraisal title: Bevacizumab in combination with capecitabine for the first-line treatment of metastatic breast cancer | Section |
|---|---|---|
| | survival. The Committee also noted that no quality of life data had been collected in the trial. The Committee concluded that bevacizumab plus capecitabine improved progression-free survival relative to capecitabine plus placebo, but that there was no robust evidence that it improved overall survival and that its effects on health-related quality of life had not been captured. | |
| Are there any clinically relevant subgroups for which there is evidence of differential effectiveness? | The Committee examined the subgroup analysis conducted by the manufacturer comparing bevacizumab plus capecitabine with capecitabine plus placebo in patients who had previously received a taxane. However, the Committee noted that previous taxane therapy was not a stratification factor at randomisation and that this subgroup was specified after the trial had begun but before the analysis was completed. The Committee also heard that the overall survival results were based on small numbers of events and that no statistical adjustments were made to control for multiple testing, thus increasing the risk of chance findings. The Committee considered that there was no biologically plausible reason why bevacizumab plus capecitabine would be more effective in this subgroup than in the ITT population. The Committee concluded that the results from the prior taxane subgroup of the RIBBON-1 trial were not sufficiently robust to use for the development of guidance. | 4.8 |
| Estimate of the size of the clinical effectiveness including strength of supporting evidence | The Committee noted that the results from the ITT population demonstrated a statistically significant median investigator-assessed progression-free survival benefit of 2.9 months for bevacizumab plus capecitabine compared with capecitabine plus placebo. | 4.5 |
| **Evidence for cost effectiveness** | | |
| Availability and nature of evidence | The Committee considered the cost effectiveness of bevacizumab and capecitabine compared with capecitabine alone based on the manufacturer's model and critique by the ERG.<br>The Committee was aware that the manufacturer had based the economic evaluation on the subgroup of patients who | 4.9 |

| TAXXX (STA) | Appraisal title: Bevacizumab in combination with capecitabine for the first-line treatment of metastatic breast cancer | Section |
|---|---|---|
| | had previously received a taxane rather than the Committee's preferred choice of the whole capecitabine cohort (the ITT population). The Committee noted the manufacturer's and ERG's statements that an analysis of the ITT population would result in a larger ICER than for the subgroup included in the base-case analysis. The Committee agreed with this assessment. | |
| Uncertainties around and plausibility of assumptions and inputs in the economic model | The Committee noted the explorations made by the ERG to the costs of therapy and concluded that these adjustments were appropriate. | 4.10 |
| | The Committee noted the ERG's concerns around the rank preserving structural failure time method used by the manufacturer to account for the effect of crossover to open-label bevacizumab in the modelling of survival in the progressed disease state. The Committee discussed the ways in which the analyses were adjusted for crossover but was unclear as to the most appropriate method without introducing bias. The Committee also noted that the subsequent treatments had not been modelled, which in combination with the impact of crossover, could have led to confounding of the overall survival results. | 4.11 |
| | The Committee discussed that it was unexpected that the costs of administration and pharmacy time associated with bevacizumab plus capecitabine would be lower than the costs for capecitabine alone. The Committee concluded that despite the incorporation of NHS tariffs, this discrepancy contributed to the uncertainty associated with the results of the manufacturer's economic model. | 4.12 |
| | The Committee was also aware that that a disutility from adverse events had not been applied in the manufacturer's model, despite utility estimates being available in the literature to account for adverse events, and it was likely that this could have resulted in underestimated ICERs. | 4.13 |

| TAXXX (STA) | Appraisal title: Bevacizumab in combination with capecitabine for the first-line treatment of metastatic breast cancer | Section |
|---|---|---|
| Incorporation of health-related quality of life benefits and utility values | The Committee noted that no quality of life data had been collected in the trial and that the economic analysis included utility values from a literature review. The Committee was also aware that a disutility for adverse events had not been applied in the manufacturer's model, despite utility estimates being available in the literature to account for adverse events, and it was likely that this could have resulted in underestimated ICERs. | 4.5, 4.13 |
| 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? | The Committee recognised the novel mode of action of bevacizumab, which may benefit breast cancer patients whose treatment options are limited. However, it considered that there were no additional gains in health-related quality of life over those already included in the QALY calculations. | 4.16 |
| Are there specific groups of people for whom the technology is particularly cost effective? | The Committee concluded that the results from the prior taxane subgroup of the RIBBON-1 trial were not sufficiently robust to use for the development of guidance. The Committee only considered the economic analysis based on this subgroup to establish a benchmark for the incremental cost per QALY gained for the ITT population. | 4.8, 4.9 |
| What are the key drivers of cost effectiveness? | The costs of therapy adopted in the manufacturer's model, the impact of crossover and lack of modelling of subsequent treatments were key drivers of uncertainty around cost effectiveness. | 4.10, 4.11, 4.13 |
| Most likely cost-effectiveness estimate (given as an ICER) | The Committee concluded that given all of the uncertainties, it was not possible to determine the most plausible ICER for bevacizumab plus capecitabine compared with capecitabine alone for the subgroup of patients who were previously treated with a taxane. However, it was convinced that the ICER would be higher than the ICER of £82,000 per QALY gained resulting from the ERG explorations. The Committee considered that the ICER for bevacizumab plus capecitabine compared with capecitabine alone in the ITT population would be even higher. | 4.13 |

| TAXXX (STA) | Appraisal title: Bevacizumab in combination with capecitabine for the first-line treatment of metastatic breast cancer | Section |
|---|---|---|
| **Additional factors taken into account** | | |
| Patient access schemes (PPRS) | None | -- |
| End-of-life considerations | The Committee discussed whether bevacizumab plus capecitabine for the first-line treatment of metastatic breast cancer fulfilled the criteria for a life-extending, end-of-life treatment. The Committee noted that bevacizumab is licensed for a relatively large population across a range of indications in the treatment of breast, colorectal, renal and non-small-cell lung cancers. Therefore, it does not meet the criterion of the supplementary advice from NICE that the treatment should be licensed for small populations. Having established that bevacizumab did not meet the population criterion, the Committee decided it was not necessary to make a decision about the life expectancy or extension to life criteria. The Committee concluded on this basis that bevacizumab plus capecitabine did not fulfil the criteria for being a life-extending, end-of-life treatment. | 4.15 |
| Equalities considerations and social value judgements | No equality issues were identified during the scoping process or the appraisal. | -- |

# 5 Implementation

5.1 The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the NHS in England and Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must usually 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. When there is no NICE technology appraisal guidance on a drug, treatment or other technology, decisions on funding should be made locally.

5.2 The technology in this appraisal may not be the only treatment for metastatic breast cancer. Therefore, if a NICE technology appraisal recommends use of a technology, it is as an option for the treatment of a disease or condition. This means that the technology should be available for a patient who meets the clinical criteria set out in the guidance, subject to the clinical judgement of the treating clinician. The NHS must provide funding and resources (in line with section 5.1) when the clinician concludes and the patient agrees that the recommended technology is the most appropriate to use, based on a discussion of all available treatments.

5.3 NICE has developed tools to help organisations put this guidance into practice (listed below). These are available on our website (www.nice.org.uk/guidance/TAXXX). [NICE to amend list as needed at time of publication]

- Slides highlighting key messages for local discussion.
- Costing report and costing template to estimate the savings and costs associated with implementation.

- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.

# 6 Recommendations for further research

6.1 Studies exploring the effectiveness of bevacizumab in people previously treated with a taxane and its effects on health-related quality of life.

# 7 Related NICE guidance

**Published**

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

# 8 Review of guidance

8.1 The guidance on this technology will be considered for review in June 2015. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Peter Clark

Chair, Appraisal Committee

June 2012

# 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.

**Professor Peter Clark (Chair)**

Consultant Medical Oncologist, Clatterbridge Centre for Oncology

**Professor Jonathan Michaels (Vice Chair)**

Professor of Clinical Decision Science, University of Sheffield

**Professor Kathryn Abel**

Director of Centre for Women's Mental Health, University of Manchester

**Professor Darren Ashcroft**

Professor of Pharmacoepidemiology, School of Pharmacy and Pharmaceutical Sciences, University of Manchester

**Dr Matthew Bradley**

Therapy Area Leader, Global Health Outcomes, GlaxoSmithKline

**Dr Ian Campbell**

Honorary Consultant Physician, Llandough Hospital

**Professor Usha Chakravarthy**

Professor of Ophthalmology and Vision Sciences, The Queen's University of Belfast

**Professor Simon Dixon**

Professor of Health Economics, University of Sheffield

**Gillian Ells**

Prescribing Advisor, NHS Sussex Downs and Weald

**Dr Jon Fear**

Consultant in Public Health Medicine, Head of Healthcare Effectiveness NHS Leeds

**Paula Ghaneh**

Professor of Surgery, University of Liverpool

**Dr Susan Griffin**

Research Fellow, Centre for Health Economics, University of York

**Professor Carol Haigh**

Professor in Nursing, Manchester Metropolitan University

**Professor John Hutton**

Professor of Health Economics, University of York

**Professor Peter Jones**

Emeritus Professor of Statistics, Keele University

**Dr Steven Julious**

Senior Lecturer in Medical Statistics, University of Sheffield

**Rachel Lewis**

Advanced Nurse Practitioner, Manchester Business School

**Professor Paul Little**

Professor of Primary Care Research, University of Southampton

**Professor Katherine Payne**

Professor of Health Economics, University of Manchester

**Dr John Radford**

Director of Public Health, Rotherham Primary Care Trust

**Dr Peter Selby**

Consultant Physician, Central Manchester University Hospitals NHS Foundation Trust

**Dr Brian Shine**

Consultant Chemical Pathologist, John Radcliffe Hospital, Oxford

**Dr Murray D Smith**

Associate Professor in Social Research in Medicines and Health, University of Nottingham

**Paddy Storrie**

Lay Member

**Charles Waddicor**

Chief Executive, NHS Berkshire

## *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.

**Nwamaka Umeweni, Raisa Sidhu**

Technical Leads

**Kay Nolan, Nicola Hay, Pall Jonsson**

Technical Advisers

**Rebecca Pye, Kate Moore**

Project Managers

# Appendix B: Sources of evidence considered by the Committee

A The Evidence Review Group (ERG) report for this appraisal was prepared by Liverpool Reviews and Implementation Group (LRiG):

- Fleeman N, et al, Bevacizumab in combination with capecitabine for the first-line treatment of metastatic breast cancer, February 2012

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

II Professional/specialist and patient/carer groups:

- Breakthrough Breast Cancer
- Breast Cancer Campaign
- Macmillan Cancer Support
- Cancer Research UK
- Royal College of Nursing
- Royal College of Physicians

III Other consultees:

- Department of Health
- Welsh Government

IV Commentator organisations (did not provide written evidence and without the right of appeal):

- Commissioning Support Appraisals Service
- Department of Health, Social Services, and Public Safety, Northern Ireland
- Healthcare Improvement Scotland
- Liverpool Reviews and Implementation Group (LRiG)
- National Institute for Health Research, Health Technology Assessment Programme
- National Collaborating Centre for Cancer

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 by attending the Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Dr Rachel Greig, nominated by Breakthrough Breast Cancer – patient expert (attended first Committee discussion)
- Dr Helena Earl, Consultant Medical Oncologist, nominated by Royal College of Physicians– clinical specialist (written comments submitted for first Committee discussion, attended second Committee discussion)

D 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