

Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine for the treatment of metastatic colorectal cancer

Technology appraisal guidance

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Your responsibility

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1 Guidance

- 1.1 Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine is not recommended for the treatment of metastatic colorectal cancer.
- 1.2 People currently receiving bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine for the treatment of metastatic colorectal cancer should have the option to continue treatment until they and their clinicians consider it appropriate to stop.

2 The technology

- 2.1 Bevacizumab (Avastin, Roche Products) is a recombinant humanised monoclonal IgG1 antibody that inhibits the formation of blood vessels (angiogenesis inhibitor). It targets the biological activity of human vascular endothelial growth factor (VEGF), which stimulates new blood vessel formation in the tumour. Bevacizumab in combination with fluoropyrimidine-based chemotherapy has a UK marketing authorisation for the treatment of patients with metastatic carcinoma of the colon or the rectum.
- 2.2 The summary of product characteristics (SPC) lists the following conditions 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 and neutropenia. For full details of side effects and contraindications, see the SPC.
- 2.3 Bevacizumab is administered as an intravenous infusion. Bevacizumab treatment is given in combination with chemotherapy and is licensed for use until progression of the underlying disease. The recommended dosage for metastatic carcinoma of the colon or rectum is 5 mg/kg or 10 mg/kg of body weight once every 2 weeks when given with oxaliplatin and fluorouracil plus folinic acid (FOLFOX) or 7.5 mg/kg or 15 mg/kg of body weight given once every 3 weeks when given with oxaliplatin and capecitabine (XELOX). 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 58). For first-line treatment with bevacizumab, the manufacturer's economic model assumed a dosage of 5 mg/kg of body weight once every 2 weeks when given with FOLFOX and 7.5 mg/kg of body weight given once every 3 weeks XELOX, in line with the NO16966 trial. The acquisition cost of bevacizumab (excluding VAT and assuming wastage) for a patient weighing 70 kg is £924.40 at a dosage of 5 mg/kg every 2 weeks and £1409.72 at a dosage of 7.5 mg/kg every 3 weeks. The manufacturer of bevacizumab (Roche Products) proposed a patient access scheme to the Department of Health for the

use of bevacizumab in metastatic colorectal cancer. The Department of Health was content for NICE to consider the patient access scheme proposed by Roche. However, it had concerns about the scheme's complexity and believed that the administrative burden of the scheme was greater than that originally set out by the manufacturer.

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](#)).

- 3.1 The manufacturer's approach to the decision problem compared bevacizumab plus FOLFOX (B-FOLFOX) or bevacizumab plus XELOX (B-XELOX) with FOLFOX and XELOX without bevacizumab as a first-line treatment. The manufacturer stated that the use of irinotecan in combination with folinic acid and fluorouracil (FOLFIRI) is decreasing and that it is mainly used in the small minority of patients in whom oxaliplatin is contraindicated or who cannot tolerate oxaliplatin. This was based on market research analysis, which indicated that combination chemotherapy regimens including oxaliplatin are the most commonly used in UK clinical practice. However, for completeness, the manufacturer performed an economic evaluation comparing B-FOLFOX or B-XELOX with FOLFIRI. The manufacturer stated that the cost effectiveness of bevacizumab as a second-line treatment could not be demonstrated.
- 3.2 The manufacturer undertook a systematic review of the literature and identified two randomised controlled trials: one assessed bevacizumab as a first-line therapy (NO16966) and one assessed bevacizumab as a second-line therapy (E3200). No evidence of bevacizumab used in lines of treatment beyond second-line therapy was provided by the manufacturer.
- 3.3 The NO16966 study started as a phase III, multinational, two-arm, randomised, open-label study. This study was originally designed to demonstrate the non-inferiority of XELOX compared with FOLFOX-4 (that is, the FOLFOX regimen given every 2 weeks, with two long infusions in the first 48 hours) in adult patients with histologically confirmed metastatic colorectal cancer who had not been treated before with chemotherapy. After randomisation of 634 patients to XELOX or FOLFOX-4, the original protocol design was amended to include a 2 x 2 factorial randomised study in which patients were subsequently

randomised to either XELOX or FOLFOX plus either bevacizumab or placebo. A further 1401 patients were then recruited (blinded to the allocation of bevacizumab or placebo), and a final total of 2035 patients were randomised in the NO16966 study. The study amendment included an additional objective of demonstrating superiority of bevacizumab in combination with chemotherapy (B-XELOX or B-FOLFOX-4) over placebo in combination with chemotherapy (P-XELOX or P FOLFOX-4). The dosage of bevacizumab was 5 mg/kg every 2 weeks (B-FOLFOX-4) or 7.5 mg/kg every 3 weeks (B-XELOX). Treatment was planned to continue until disease progression, unacceptable toxicity, resection of metastatic disease or for 48 weeks, whichever came first (this being at the discretion of the investigator). Patients who completed the 48-week study treatment phase without progressive disease were eligible to enter the post-study treatment phase and continue their allocated treatment until their disease progressed. Patients whose disease became operable, and underwent resection, were eligible to enter the post-study treatment phase. The NO16966 protocol also allowed continuation of allocated treatment (bevacizumab or placebo) until disease progression (in line with the bevacizumab SPC, which was produced after the NO16966 study) if oxaliplatin treatment was terminated because of adverse events.

- 3.4 All patients in the study had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. The study was stratified to ensure that study arms were balanced with regards to ECOG performance status (0 versus 1), number of organs with metastases at baseline (one versus more than one), alkaline phosphatase level at baseline (within normal range versus above normal range), liver as a site of metastasis (yes versus no) and geographic region. The median follow-up was 28 months. The manufacturer acknowledged that patients in the study were slightly younger and fitter than patients with metastatic colorectal cancer in the UK who are, on average, over 60 years of age.
- 3.5 The primary pooled analysis of non-inferiority of the NO16966 study (that is, pooling of all XELOX arms compared with pooling of all FOLFOX-4 arms) showed that the XELOX and FOLFOX-4 regimens were equivalent for overall and progression-free survival. The primary pooled analysis of superiority for the NO16966 study (that is, pooling of the

initial two-arm study and the 2 x 2 factorial part of the study) showed that the addition of bevacizumab to chemotherapy (B-XELOX and B-FOLFOX-4) significantly improved progression-free survival compared with chemotherapy alone (P XELOX and P-FOLFOX-4 and XELOX and FOLFOX-4 combined). The median progression-free survival was 7.7 months in the placebo plus chemotherapy group and 9.4 months in the bevacizumab plus chemotherapy group (intention-to-treat analysis, hazard ratio [HR] 0.79; 95% confidence interval [CI] 0.72 to 0.87, $p = 0.0001$). The median overall survival was 18.9 months in the placebo plus chemotherapy group compared with 21.2 months in the bevacizumab plus chemotherapy group (HR 0.83; 95% CI 0.74 to 0.93, $p = 0.0019$).

- 3.6 The manufacturer provided a secondary pooled analysis of superiority based only on the 2 x 2 factorial design (according to the original statistical plan, that is B-XELOX and B-FOLFOX-4 combined compared with P-XELOX and P-FOLFOX-4 combined). The median progression-free survival was 8.0 months in the placebo plus chemotherapy group and 9.4 months in the bevacizumab plus chemotherapy group (HR 0.83; 95% CI 0.72 to 0.95, $p = 0.0023$). The median overall survival was 19.9 months in the placebo plus chemotherapy group and 21.3 months in the bevacizumab plus chemotherapy group (HR 0.89; 95% CI 0.76 to 1.03, $p = 0.0769$).
- 3.7 The manufacturer reported that the difference in progression-free survival was statistically significant for bevacizumab versus placebo in the XELOX subgroup (HR 0.80; 97.5% CI 0.66 to 0.96, $p = 0.0059$) but not in the FOLFOX-4 subgroup (HR 0.89; 97.5% CI 0.74 to 1.06, $p = 0.1312$). An exploratory analysis submitted by the manufacturer suggested that bevacizumab did not deliver a benefit to patients in the FOLFOX-4 group who had received prior adjuvant treatment (HR 1.75; 97.5% CI 1.15 to 2.65, p value not reported), whereas it did give a benefit to patients in the FOLFOX-4 group who had not had adjuvant therapy (HR 0.72; 97.5% CI 0.58 to 0.90, p value not reported). The manufacturer stated that this difference could be because the patients in the P-FOLFOX-4 group had a greater time between adjuvant treatment and development of metastatic disease than all of the other groups. This suggested that there was an imbalance in the data due to the better prognosis in the P-FOLFOX-4 group because the cancers in this group were growing more slowly than

in the other groups. Additional exploratory analyses showed that when the data for all patients who had received adjuvant treatment were removed from all treatment groups (and thereby including the removal of the subgroup of patients that may have had slower tumour progression), the hazard ratios for overall survival and for progression-free survival ranged from 0.83 to 0.85 (all p values < 0.03) and from 0.74 to 0.77 (all p values < 0.0001).

- 3.8 The manufacturer also conducted a post-hoc subgroup analysis of the impact of bevacizumab treatment on liver resection rates. This analysis suggested that bevacizumab improved liver resection rates, although this was not statistically significant. No analyses of KRAS or other mutations were submitted.
- 3.9 The rates of discontinuation in the NO16966 study were higher in the bevacizumab plus chemotherapy groups than in the placebo plus chemotherapy groups. In the 2 x 2 factorial part of the study, 29% (203/699) of patients receiving bevacizumab plus chemotherapy and 47% (329/701) of patients receiving chemotherapy alone were treated until progression (despite the protocol allowing treatment to be continued until disease progression, in line with the SPC of bevacizumab).
- 3.10 In the NO16966 study, the most common adverse events of bevacizumab treatment were thromboembolic (7.8% venous thromboembolic events compared with 5.1% in the placebo plus chemotherapy groups and 1.7% arterial thromboembolic events compared with 0.9% in the placebo plus chemotherapy groups). Grade 3 or 4 hypertension, proteinuria and bleeding were more common in the bevacizumab groups than in the placebo plus chemotherapy groups (4% versus 0.8%, 3.5% versus 0.9% and 1.9% versus 1.5% respectively). The incidence of serious and life-threatening (grade 3 and 4) adverse events was higher in the bevacizumab plus chemotherapy groups (79.9%) than the placebo plus chemotherapy groups (74.8%) and higher with FOLFOX-4 regimens than XELOX regimens (although FOLFOX-4 was associated with different adverse events than XELOX). The manufacturer stated that most adverse events were associated with cytotoxic chemotherapy, and the higher incidence in the bevacizumab groups was likely to be a consequence of a longer duration of chemotherapy for

patients receiving bevacizumab. No health-related quality-of-life data were collected in the NO16966 study.

- 3.11 The E3200 study was a phase III, multicentre, three-arm, randomised, open-label study. It compared B-FOLFOX-4 (n = 293), FOLFOX-4 (n = 292), and bevacizumab alone (n = 244) in adult patients with advanced or metastatic colorectal cancer previously treated with a fluoropyrimidine and irinotecan, either separately or in combination. Following a data monitoring review 18 months after the start of the trial, the bevacizumab-alone arm was terminated because of poorer efficacy. Patients were stratified by ECOG performance status (0 versus 1 or more) and prior radiation therapy (yes versus no). The dosage of bevacizumab was 10 mg/kg every 2 weeks. Median overall survival was 10.8 months in the FOLFOX 4 group and 13 months in the B-FOLFOX-4 group (intention-to-treat analysis, HR 0.751; 95% CI 0.332 to 0.893, p = 0.0012). Median progression-free survival increased from 4.5 months with FOLFOX-4 to 7.5 months with B-FOLFOX-4 (HR 0.518; 97.5% CI 0.416 to 0.646, p < 0.0001).
- 3.12 The manufacturer produced a Markov model to estimate the cost effectiveness of bevacizumab plus FOLFOX and XELOX compared with FOLFOX and XELOX alone. The model had four distinct health states: first-line treatment, after first-line treatment without progression, progressed disease and death. It was assumed that all patients start in the first health state (first-line treatment) in accordance with the NO16966 study. The model had a cycle length of 1 month and the time horizon was 8 years (equivalent to life expectancy in the population of interest). A half-cycle correction was applied to the model. An NHS and personal social services (PSS) perspective was taken.
- 3.13 Costs were mainly derived from 2007–2008 national reference costs, BNF 57 and PSSRU (Personal Social Services Research Unit) 2008. FOLFOX-4 was used in the pivotal trial of bevacizumab but the manufacturer stated that FOLFOX-6 (that is, the FOLFOX regimen delivered over 2 weeks but with only one long infusion in the first 48 hours) is more commonly used in UK clinical practice. Therefore, the economic model was adjusted to include FOLFOX-6 by assuming similar efficacy to FOLFOX-4 but with reduced costs.

- 3.14 Treatment duration and dose intensity were based on the NO16966 study. Mean and median treatment durations (6 and 7 months respectively) were shorter in the NO16966 study than progression-free survival. Duration of treatment varied between treatment arms and was longer with the addition of bevacizumab and longer in the FOLFOX than in the XELOX arms. Treatment duration was estimated and applied in the model for each arm of the NO16966 study. However, for simplicity it was assumed that oxaliplatin treatment duration was the same as bevacizumab treatment duration in the B-FOLFOX and B-XELOX arms. It was also assumed that treatment was given continuously, as in the NO16966 study, rather than intermittently. Kaplan–Meier estimates from the NO16966 study were used for progression-free and overall survival up to a median survival of 28 months. After this point, a Weibull probability distribution for overall survival and an exponential probability distribution of progression-free survival (based on average hazard for months 13–28) were used to model the tails. For overall survival, treatment effect was assumed to continue after the median follow-up period and this was further explored in the sensitivity analysis.
- 3.15 The manufacturer used utility values from 'Cetuximab for the first-line treatment of metastatic colorectal cancer' (NICE technology appraisal guidance 176). These utility values were taken from a randomised controlled trial comparing cetuximab plus FOLFIRI with FOLFIRI alone in first-line treatment of metastatic colorectal cancer and represented mean utility values from 42 patients using the EQ 5D questionnaire; however, only 37 patients fully completed the questionnaire. A utility value of 0.77 was assigned to the first-line treatment health state, the average of all the EQ-5D completed responses over the study period (this assumption was used in NICE technology appraisal guidance 176). A utility value of 0.79 was assigned to the health state after first-line treatment (that is, without disease progression). This was based on expert opinion that patients in this state will experience a higher quality of life than patients receiving first-line treatment, because of fewer adverse events, and their utility value will be similar to a person aged 55–64 years in the UK general population. A utility value of 0.68 was assigned to the progressed disease state, taken from a trial of cetuximab for the third-line treatment of metastatic colorectal cancer and using the Health Utility Index questionnaire (this assumption was used in NICE

technology appraisal guidance 176).

- 3.16 The manufacturer's original submission included details of a proposed patient access scheme for the first-line use of bevacizumab. The scheme involved supplying bevacizumab at a fixed price per cycle of treatment (£800 for 2-weekly cycles and £1200 for 3-weekly cycles), with bevacizumab being provided free after 12 months of treatment and with oxaliplatin being provided free of charge throughout. The manufacturer stated that it would take approximately 5 minutes per cycle for the pharmacist to update the scheme's registry system. This equated to £4 per cycle. The Department of Health stated that it has concerns around the complexity of the patient access scheme and believes that the administration costs of the scheme would probably be greater than those set out by the manufacturer.
- 3.17 The manufacturer stated that the incremental cost-effectiveness ratios (ICERs) most relevant to the decision problem were B XELOX compared with XELOX and B-FOLFOX-6 compared with FOLFOX-6. In response to a request for clarification from the ERG, the manufacturer provided a revised base-case analysis. The ERG noted that 19.7% (n = 256) and 13.7% (n = 96) of patients were alive after median follow-up in the XELOX/FOLFOX-6 and B XELOX/B-FOLFOX-6 arms respectively. The ERG asked the manufacturer to use untruncated data to calculate the estimates of the parameters of the Weibull distribution. The manufacturer used Kaplan–Meier estimates of survival up to month 6 and then a Weibull distribution fitted to untruncated data after month 6 for progression-free survival and a Weibull distribution fitted to untruncated data for overall survival. The model also accounted for oxaliplatin wastage (that is, no vial sharing was assumed). In the manufacturer's base-case analysis (that is, pooling of the initial two-arm part of the study and the 2 x 2 factorial part of the study), B-XELOX produced an ICER of £35,912 per QALY gained when compared with XELOX (£84,553 per QALY gained without the patient access scheme), and B-FOLFOX-6 produced an ICER of £36,569 per QALY gained when compared with FOLFOX-6 (£92,634 per QALY gained without the patient access scheme). In the one-way sensitivity analyses, which were only provided with the patient access scheme, the ICERs were not greatly influenced by variations in any of the parameters. In the probabilistic sensitivity

analysis, the mean ICER for the comparison of B-FOLFOX-6 with FOLFOX-6 was £36,907 per QALY gained and for the comparison of B-XELOX with XELOX the mean ICER was £36,205 per QALY gained (95% intervals not provided).

- 3.18 The manufacturer stated that currently only a minority (12%) of patients in the UK receive FOLFIRI as a first-line treatment for metastatic colorectal cancer and that in most of these patients treatment with oxaliplatin is contraindicated. For completeness, the manufacturer provided a cost-effectiveness analysis comparing bevacizumab in combination regimens containing oxaliplatin with FOLFIRI. The efficacy of FOLFIRI was derived from a mixed-treatment comparison. A constant hazard ratio was applied to the extrapolated progression-free survival and overall survival curves of FOLFOX-4 to derive the survival curves for FOLFIRI. The treatment duration and the drug administration and adverse event costs for FOLFIRI were assumed to be equivalent to those for FOLFOX-4. B-XELOX compared with FOLFIRI was associated with an ICER of £9192 per QALY gained, B-FOLFOX-6 compared with FOLFIRI was associated with an ICER of £38,835 per QALY gained, and B FOLFOX-4 compared with FOLFIRI was associated with an ICER of £58,575 per QALY gained.
- 3.19 The manufacturer provided a cost-effectiveness analysis of bevacizumab plus regimens including oxaliplatin in the second-line setting. Drug acquisition, administration and pharmacy costs per cycle were taken from the first-line analysis and multiplied by the mean number of cycles reported in the E3200 study. Costs associated with adverse events, third-line treatment and central venous access devices were not included in the second-line analysis and no discounting was applied. As a second-line treatment, B-FOLFOX-4 compared with FOLFOX-4 resulted in an ICER of £102,644 per QALY gained. The manufacturer stated that the larger ICERs reported in the second-line setting were mainly because of the higher doses of bevacizumab used and that bevacizumab could not be considered cost effective for second-line treatment.
- 3.20 The ERG stated that the manufacturer's submission generally followed the NICE reference case. It also highlighted that adequate methods of randomisation and allocation concealment were reported in the NO16966

and E3200 studies. However, the ERG noted that the manufacturer focused on a comparison of oxaliplatin chemotherapy regimens with or without bevacizumab as first-line treatment. This differed from the scope, which included irinotecan chemotherapy regimens without bevacizumab as comparators and bevacizumab plus oxaliplatin regimens as second-line treatment.

- 3.21 The ERG expressed concerns about pooling data from the initial two-arm part and the 2 x 2 factorial part of the NO16966 study. It stated that this was inappropriate because of the different designs of the two parts of the study. The European Medicines Agency (EMA) in their assessment report for bevacizumab also expressed concerns about the appropriateness of this method of pooling and it noted that this pooled analysis was specified in the protocol in case of borderline significance in progression-free survival in the 2 x 2 study. The EMA therefore questioned the validity of the results derived from the pooled analysis. The ERG also noted that the number of patients reported as Caucasian and the number of patients with ECOG performance status of 0 were 10% greater in the 2 x 2 factorial part of the study than the initial two-arm part and that both are associated with better prognosis. The ERG further highlighted that there was a difference in terms of the overall survival benefit associated with bevacizumab in the primary pooled analysis (overall survival significantly improved) and in the pooled analysis based on the 2 x 2 factorial design only (overall survival not significantly improved). The ERG suggested that this difference might be because of the imbalance of patients in the 2 x 2 part of the study who had a slower rate of disease progression (that is, patients whose disease took longer to relapse after prior adjuvant therapy) and the lack of statistical power to assess overall survival.
- 3.22 Additional analyses were provided by the manufacturer using only the 2 x 2 factorial design. For the comparison of B-XELOX with XELOX, using the 2 x 2 factorial part of the NO16966 study only (that is, the efficacies of B-XELOX and B-FOLFOX-4 combined compared with P-XELOX and P-FOLFOX-4 combined), B-XELOX produced an ICER of £48,111 per QALY gained (£129,911 per QALY gained without the patient access scheme). Removing the patients who had received prior adjuvant therapy reduced the ICER to £36,006 per QALY gained (£92,698 per QALY gained without

the patient access scheme). If the XELOX and FOLFOX arms were not pooled then the ICER was £35,662 per QALY gained (£90,779 per QALY gained without the patient access scheme). For the comparison of B-FOLFOX-6 with FOLFOX-6, using the 2 x 2 factorial part of the NO16966 study (that is, the efficacies of B XELOX and B-FOLFOX-4 combined compared with P-XELOX and P-FOLFOX-4 combined), B-FOLFOX-6 produced an ICER of £39,771 per QALY gained (£134,309 per QALY gained without the patient access scheme). Removing patients who had received prior adjuvant therapy was associated with an ICER of £31,174 per QALY gained (£96,687 per QALY gained without the patient access scheme). When the XELOX and the FOLFOX arms were not pooled, then the ICER was £62,714 per QALY gained (£240,324 per QALY gained without the patient access scheme). The manufacturer did not provide any analysis using the 2 x 2 factorial part of the study with patients who had received prior adjuvant therapy excluded and the XELOX and FOLFOX arms not pooled.

3.23 The ERG reviewed the additional analyses submitted by the manufacturer (as outlined in section 3.22) and suggested that the most appropriate analysis was one using the 2 x 2 factorial design of the NO16966 study with XELOX and FOLFOX not pooled and patients who had received prior adjuvant therapy excluded. However, this analysis was not provided by the manufacturer despite requests by the ERG to do so. The ERG therefore suggested that the next most appropriate analysis was the one using data from the 2 x 2 factorial design of the NO16966 study with the XELOX and FOLFOX arms pooled and patients who had received prior adjuvant therapy excluded. This analysis gave Kaplan–Meier estimates up to month 6 and then the Weibull distribution was used for extrapolating progression-free survival, and Kaplan–Meier estimates up to month 28 with the Weibull distribution then used for extrapolating overall survival. With this analysis the ERG produced an ICER for B-XELOX of £36,354 per QALY gained compared with XELOX and £31,452 per QALY gained for B-FOLFOX-6 compared with FOLFOX-6 (ICERs without the patient access scheme were not provided). The results of the one-way sensitivity analyses showed that the ICERs were not greatly influenced by any of the parameter changes.

3.24 The ERG noted that the duration of chemotherapy treatment was

relatively short (median approximately 6 months) despite the protocol allowing treatment until disease progression or unacceptable adverse events. The protocol also allowed bevacizumab/placebo treatment to continue until disease progression or unacceptable toxicity (as in the bevacizumab SPC) but the duration of therapy with bevacizumab was also relatively short (median 6.5 months). Although the ERG agreed that the manufacturer's economic model was an accurate replication of the NO16966 study, the ERG suggested that in clinical practice treatment with drugs other than oxaliplatin (fluorouracil, capecitabine, bevacizumab) might continue after oxaliplatin regimens stopped. The ERG conducted an exploratory analysis (using the 2 x 2 factorial design of the NO16966 study with the XELOX and FOLFOX arms pooled and patients who had received prior adjuvant therapy excluded) that examined the impact on ICERs of stopping oxaliplatin 1 month before the other treatment components. Under this scenario, costs in the XELOX and FOLFOX-6 arms were reduced. In the B-XELOX and B-FOLFOX arms, the cost of oxaliplatin remained the same because oxaliplatin is free for these groups. It was also assumed that no change in incremental survival occurred. In this analysis, the ICERs were increased from £36,354 to £43,511 per QALY gained when B XELOX was compared with XELOX and from £31,452 to £39,478 per QALY gained when B-FOLFOX-6 was compared with FOLFOX-6 (ICERs without the patient access scheme were not provided). The ERG also examined the impact of increasing the duration of bevacizumab treatment by 1 month on the ICERs. It was assumed that no change in survival occurred and the treatment duration of the other components remained the same. In this analysis, the ICERs increased from £36,354 to £47,312 per QALY gained when B-XELOX was compared with XELOX and from £31,452 to £41,692 per QALY gained when B-FOLFOX-6 was compared with FOLFOX-6 (ICERs without the patient access scheme were not provided).

- 3.25 The ERG stated that it was not possible to adequately check the sources considered for determining the utility values because the references were incomplete. The ERG suggested that the utility values from the guidance on 'Cetuximab for the first-line treatment of metastatic colorectal cancer' (NICE technology appraisal guidance 176) could be relevant to patients receiving bevacizumab. However, the ERG also commented that the assumption that the utility value of the health state

after first-line treatment (that is, off treatment but not yet progressed) is similar to that of people aged 55–64 years in the UK general population is unrealistic. This is because after 6 months of chemotherapy, people are often less mentally and physically fit than those of the same age in the general population. In addition, the ERG noted that the utility value for the health state first-line treatment (that is, 0.77) might be an overestimate. This is because the utility value in the UK general population of the same age group is 0.79. The ERG further noted that the model did not take into account the fact that XELOX regimens might be associated with higher health-related quality of life than FOLFOX regimens because the former are considered more convenient. The ERG performed an exploratory analysis that investigated the impact of decreasing the utility values by 20%. This decrease in utility values had a large impact on the ICERs. Using the 2 x 2 factorial part of the study with patients with prior adjuvant therapy excluded, the ICER for B-XELOX increased from £36,354 to £45,433 per QALY gained when compared with XELOX and the ICER for B-FOLFOX-6 increased from £31,452 to £39,315 per QALY gained when compared with FOLFOX-6 (ICERs without the patient access scheme were not provided).

- 3.26 In response to consultation, the manufacturer provided revised cost-effectiveness estimates. These were based on the ICERs calculated by the ERG of £36,354 per QALY gained for B-XELOX compared with XELOX and £31,452 per QALY gained for B FOLFOX-6 compared with FOLFOX-6 as detailed in section 3.23 (ICERs without the patient access scheme were not provided). The manufacturer revised the time of operating the patient access scheme, based on the number of patients expected to enrol within the first 3 years of the scheme, to 131 minutes and 152 minutes per patient for the XELOX and FOLFOX regimens respectively, based on research within the NHS. This equated to an average cost per patient over years 1 to 3 of £57 and £67 for B-XELOX and B FOLFOX respectively. This increased the ICER for B-XELOX compared with XELOX by £164 per QALY gained and the ICER for B-FOLFOX-6 compared with FOLFOX-6 by £113 per QALY gained. The manufacturer also used a utility value of 0.77 in the health state after first-line treatment (that is, without disease progression) as opposed to a value of 0.79. This increased the ICER for B XELOX compared with XELOX by £647 per QALY gained and the ICER for B-FOLFOX-6 compared with FOLFOX-6 by £560 per QALY

gained. The manufacturer also conducted a time-and-motion study of the preparation and administration of bevacizumab infusions at a private hospital. The manufacturer stated that preparation time was divided between the pharmacist and the pharmacy technician. This resulted in a reduction in the bevacizumab administration costs of £42 (as used in the original submission) to £31 per infusion. The ICER for B-XELOX compared with XELOX was reduced by £677 per QALY gained and the ICER for B-FOLFOX-6 compared with FOLFOX-6 was reduced by £1012 per QALY gained. The cumulative effect of these changes increased the ICER for B-XELOX compared with XELOX from £36,354 to £36,494 per QALY gained and decreased the ICER for B-FOLFOX-6 compared with FOLFOX-6 from £31,452 to £31,122 per QALY gained.

- 3.27 The manufacturer also confirmed that the patient access scheme would apply to bevacizumab given intermittently; that is, bevacizumab would be provided free of charge after 12 months of cumulative treatment had been given. The manufacturer did not state whether this would affect the ICERs. The manufacturer did not provide ICERs from the 2 x 2 factorial part of the study with patients who had received prior adjuvant therapy excluded and with the XELOX and FOLFOX arms not pooled.
- 3.28 The manufacturer submitted an amended patient access scheme that included all the elements of the original scheme and an additional upfront payment (designated by the manufacturer to be commercial in confidence) to the NHS for each person starting first-line treatment with bevacizumab. When the revised patient access scheme was included, the ICER for B-XELOX compared with XELOX was reduced from £36,494 to £29,975 per QALY gained and the ICER for B-FOLFOX-6 compared with FOLFOX-6 was reduced from £31,122 to £24,604 per QALY gained. Without the patient access scheme, the ICER for B-XELOX compared with XELOX was £104,870 per QALY gained and the ICER for B-FOLFOX-6 compared with FOLFOX-6 was £108,267 per QALY gained.
- 3.29 The manufacturer provided an exploration of the effect of the individual components of the revised patient access scheme on the ICERs for B-XELOX compared with XELOX and for B-FOLFOX-6 compared with FOLFOX-6. Providing bevacizumab free after 12 months slightly reduced the ICERs. Providing oxaliplatin free of charge when given with

bevacizumab led to a substantial reduction of the ICERs and was the major driver of the impact of the patient access scheme on cost effectiveness. Fixing the price of bevacizumab to £800 per 2-weekly cycle and £1200 per 3-weekly cycle and the upfront payment resulted in further but less marked reductions in the ICERs. The precise details of the effect of the individual components of the revised patient access scheme were designated by the manufacturer to be commercial in confidence.

- 3.30 The ERG commented on the revised ICERs and patient access scheme submitted by the manufacturer. The ERG noted that the time-and-motion study conducted by the manufacturer to ascertain the administration costs of bevacizumab was based on information from one small private hospital and may not fully reflect the true costs to the NHS. The ERG conducted the same analyses as the manufacturer and noted slight differences in the resulting ICERs. The ICER for B-XELOX compared with XELOX was £29,956 per QALY gained and the ICER for B-FOLFOX-6 compared with FOLFOX-6 was £24,577 per QALY gained when the revised patient access scheme was incorporated. The ERG stated that the reasons for the differences between their calculations and those of the manufacturer were unclear but recognised that the differences were small. The ERG further noted that when the manufacturer used higher operating costs of the patient access scheme then the ICERs were slightly increased. The ERG conducted the same analysis as the manufacturer but it set the cost per patient of operating the patient access scheme to £100. Under this scenario analysis the ICERs were slightly increased; £30,684 per QALY gained when B-XELOX was compared with XELOX and £25,312 per QALY gained when B FOLFOX-6 was compared with FOLFOX-6.
- 3.31 The ERG performed exploratory analyses incorporating discounts on the list price of oxaliplatin. The ICER with the patient access scheme for B XELOX compared with XELOX increased from £29,975 per QALY gained to £68,140 per QALY gained assuming a 90% discount and £70,260 per QALY gained assuming a 95% discount. The ICER with the patient access scheme for B-FOLFOX-6 compared with FOLFOX-6 increased from £24,604 per QALY gained to £70,470 per QALY gained assuming a 90% discount and £73,018 per QALY gained assuming a 95% discount. The

ICERs without the patient access scheme applied were reduced slightly (by approximately 5%) when 90% and 95% discounts on the price of oxaliplatin were incorporated to all treatment arms in the model.

3.32 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, having considered evidence on the nature of metastatic colorectal cancer and the value placed on the benefits of bevacizumab 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 discussed possible comparators used in the UK for the first-line treatment of metastatic colorectal cancer in clinical practice. It noted that the manufacturer, based on a market research analysis, and the ERG considered that the standard comparators were combination chemotherapy regimens including oxaliplatin because these are most commonly used in the UK. However, the ERG commented that FOLFIRI could also be considered a relevant comparator because there is previous NICE guidance (NICE technology appraisal guidance 93 [replaced by [NICE clinical guideline 131](#)]) recommending its use. However, the Committee heard from clinical specialists that the use of FOLFIRI as a first-line treatment is decreasing in the UK. The clinical specialists highlighted that most patients with metastatic colorectal cancer who are being treated with combination chemotherapy will receive oxaliplatin-containing regimens because these regimens are associated with less marrow suppression and less diarrhoea than FOLFIRI, although there is an increased risk of significant sensory neuropathy. The clinical specialists and patient experts also stated that oxaliplatin-containing regimens are used for patients with liver metastases that are potentially resectable. In addition, they highlighted that oral capecitabine is often preferred by patients to intravenous fluorouracil. However, the risk of diarrhoea increases when irinotecan is given in combination with capecitabine; therefore if capecitabine is given, it is combined with oxaliplatin (that is, XELOX) rather than with irinotecan. The Committee understood that most of the patients who receive first-line FOLFIRI do so because of contraindications to oxaliplatin, such as a pre-existing neuropathy, or a short period elapsing between the end of adjuvant chemotherapy with oxaliplatin and the development of recurrent disease. The Committee therefore concluded that FOLFIRI should be

excluded as a comparator to bevacizumab given in combination with oxaliplatin-containing regimens.

Clinical effectiveness

- 4.3 The Committee considered the data presented by the manufacturer for the clinical effectiveness of bevacizumab as a first-line treatment for metastatic colorectal cancer. It noted that the data came from a study that included an initial two-arm part and a later 2 x 2 factorial part (six arms in total). Data from the initial two-arm part of the study and the later 2 x 2 factorial part of the study were combined in the primary analysis. The Committee noted that in the primary analysis (that is, pooling of all bevacizumab arms compared with pooling of all placebo arms) statistically significant improvements in progression-free survival of 1.7 months and in overall survival of 2.3 months were reported for bevacizumab. However, the Committee noted an imbalance in prognostic factors between the initial two-arm part of the study and the 2 x 2 factorial part of the study that could bias the results in favour of bevacizumab: the number of patients reported as Caucasian and the proportion of patients with ECOG performance status of 0 were both 10% higher in the 2 x 2 factorial part of the study. Therefore, the Committee considered that the validity of the results from the pooled analysis was not acceptable. The Committee considered the secondary analysis (of the 2 x 2 factorial part of the study only) showing a statistically significant improvement in progression-free survival of 1.4 months, but no statistically significant increase in overall survival, to be more methodologically appropriate. However, the Committee agreed with the ERG that the most appropriate method of analysis would be with the XELOX and FOLFOX arms not pooled and patients with prior adjuvant therapy excluded and noted that this was not provided. The Committee concluded that bevacizumab provided a modest increase in progression-free and overall survival when compared with regimens without bevacizumab but was mindful that there was a significant degree of uncertainty in the clinical evidence.
- 4.4 The Committee discussed the equivalence of FOLFOX-4 and XELOX regimens. It heard from clinical specialists that FOLFOX-4 regimens are considered to offer equivalent clinical benefits to XELOX regimens. It also

heard from patient experts that FOLFOX 4 regimens are associated with fewer and less serious adverse events than XELOX regimens, but XELOX regimens can be more convenient for patients. The Committee agreed that FOLFOX-4 and XELOX could be considered equivalent. The Committee discussed the imbalance observed in the study whereby the improvement in progression-free survival was only significant for the B-XELOX group and not the B-FOLFOX-4 group. The Committee understood that the P-FOLFOX-4 group (placebo and FOLFOX-4) had a greater time between adjuvant treatment and relapse than the other treatment groups and that this represented an important prognostic factor. The Committee noted that exclusion of the 25% of patients who had received prior adjuvant treatment resulted in significant improvement in progression-free survival for the B-FOLFOX-4 group. The Committee concluded that this indicated that there was an imbalance of prognostic factors within the study, but noted that at the time of the study the importance of this prognostic factor was not known.

- 4.5 The Committee discussed the use of bevacizumab in combination with oxaliplatin-containing regimens as a second-line treatment for metastatic colorectal cancer. The Committee considered the data presented by the manufacturer. It noted that the evidence suggested that both overall survival and progression-free survival were statistically significantly improved by 2 to 3 months (as detailed in section 3.11) in the second-line setting. The Committee concluded that bevacizumab was clinically effective as a second-line treatment. The Committee also noted that the manufacturer did not present any evidence of bevacizumab compared with FOLFIRI as a second-line treatment. It further noted that the manufacturer did not submit any evidence of bevacizumab in lines beyond second-line treatment.
- 4.6 The Committee noted that a significant percentage of patients withdrew early from the NO16966 study because of adverse events. It heard from clinical specialists that, in general, withdrawals often occur at an early stage for all chemotherapy regimens (including those containing bevacizumab). They further stated that if a patient is tolerant of bevacizumab at the beginning of the treatment, withdrawal is less likely at a later stage because of intolerance. For the chemotherapy agents, however, increased adverse events were likely because of increased time

on treatment. The patient experts agreed that although the adverse events experienced with bevacizumab were unpredictable and affected health-related quality of life, they could be tolerated because of the trade-off with the benefits in terms of extension to life.

- 4.7 In summary, based on the clinical-effectiveness evidence and the opinions of the clinical specialists and patient experts, the Committee concluded that, for the first-line treatment of metastatic colorectal cancer, bevacizumab in combination with oxaliplatin-containing regimens gave a modest clinical benefit compared with regimens without bevacizumab. The Committee concluded that bevacizumab was clinically effective as part of second-line treatment. Benefits from bevacizumab were achieved at the expense of small but definite increases in adverse events.

Cost effectiveness

- 4.8 The Committee reviewed the results of the economic analyses submitted by the manufacturer. The Committee noted that the manufacturer had assumed that FOLFOX-6 had similar efficacy to FOLFOX-4 but with reduced costs. The Committee heard from clinical specialists that FOLFOX-6 offers similar clinical outcomes to FOLFOX-4. In addition, it heard that FOLFOX-6 is more commonly used in UK clinical practice because it involves only one visit to hospital per therapy cycle rather than the two visits per treatment cycle on consecutive days for FOLFOX-4. The Committee agreed that the assumptions made by the manufacturer with regards to FOLFOX-6 in the economic analysis were appropriate.
- 4.9 The Committee noted that in the economic model and in the NO16966 study, treatment was continuous. It heard from clinical specialists that current practice in the UK is often intermittent treatment, with treatment restarting when there are signs of disease progression. Although intermittent chemotherapy may be associated with a small survival deficit, it involves shorter durations of treatment and this reduces adverse events such as neuropathy and other side effects of therapy. Intermittent treatment may therefore be associated with better health-related quality of life. However, the Committee noted responses from

consultation that, although intermittent treatment is commonly used in the UK, the sole evidence base for the addition of bevacizumab to first-line combination chemotherapy was reflective of a continuous treatment strategy. Therefore, the Committee concluded that the economic model reflected the clinical evidence that was available.

- 4.10 The Committee discussed the base-case cost-effectiveness estimates originally provided by the manufacturer. It noted that a revised base case was submitted after the ERG suggested that untruncated data should be used to fit alternative distributions when extrapolating the trial data. The Committee noted that the manufacturer's revised base case involved pooling of the initial two-arm part of the study and the 2 x 2 factorial part of the study. As previously noted, the Committee considered that this analysis was inappropriate because of the different designs of the study and the imbalance of demographics between the two parts of the study. Therefore, the Committee concluded that only the 2 x 2 factorial part of the study with the revised modelling of survival should be used in the cost-effectiveness analysis.
- 4.11 The Committee considered that the most plausible model assumption(s) for cost effectiveness would be to use the 2 x 2 factorial design of the NO16966 study with XELOX and FOLFOX arms not pooled and patients who had received prior adjuvant therapy excluded and noted that this had not been provided by the manufacturer. The Committee heard from the ERG that because no estimates of the effect of treatment in this scenario had been provided it was not possible to demonstrate how the ICERs would be affected. The Committee heard the manufacturer's opinion that removing patients who had received prior adjuvant treatment resulted in similar survival outcomes for XELOX and FOLFOX, and for B-XELOX and B-FOLFOX. The manufacturer stated that the basis of this view was informed by the overall results of the NO16966 study, which showed that XELOX was not inferior to FOLFOX and that there was no interaction between bevacizumab and the chemotherapy regimens used. However, the Committee noted that the analysis that used the 2 x 2 factorial part of the study, with the XELOX and FOLFOX arms pooled and patients who had received prior therapy excluded, resulted in markedly different ICERs than when the XELOX and FOLFOX arms were not pooled and patients who had received prior therapy were included.

The ICERs provided by the manufacturer without the patient access scheme for B-XELOX compared with XELOX decreased slightly from £92,700 to £90,800 per QALY gained, and the ICER for B-FOLFOX-6 compared with FOLFOX-6 increased markedly from £96,700 to £240,300 per QALY gained (as detailed in section 3.22). The Committee considered that the analysis that did not pool the XELOX and FOLFOX arms and excluded patients who had received prior adjuvant treatment should have been provided and that the effect of pooling the XELOX and FOLFOX arms was unclear. Additionally, the Committee considered that it was counter-intuitive for the analysis to pool the effects of treatment, but not to pool the duration of treatment in the XELOX and FOLFOX arms. Therefore the Committee concluded that the ICERs were associated with substantial uncertainty.

- 4.12 The Committee noted that the ICERs presented by the manufacturer represented the treatment durations observed in the trial (that is, bevacizumab was stopped at the same time as FOLFOX and XELOX and before disease progression). The Committee noted that the trial protocol and the SPC allowed bevacizumab treatment until disease progression, even if oxaliplatin was stopped early because of adverse events. The ERG and the clinical specialists stated that, if a continuous chemotherapy policy was being practised, treatment with non-oxaliplatin components (such as bevacizumab) would be likely to continue after oxaliplatin treatment had stopped. The Committee noted that stopping oxaliplatin treatment 1 month before the other treatment agents or receiving bevacizumab for 1 month after oxaliplatin treatment had stopped, increased the ICERs. It noted that both analyses assumed no increase in progression-free or overall survival. However, the Committee considered that if such increases in progression-free and overall survival were accounted for, the extra bevacizumab costs would be likely to outweigh any additional survival benefits of bevacizumab, given the previously noted modest impact on progression-free and overall survival. The Committee concluded that, although the economic model was an accurate replication of the study (in terms of treatment duration), in practice bevacizumab treatment would be expected to continue until disease progression in patients treated with a continuous therapy policy. This could potentially increase the ICERs.

- 4.13 The Committee noted the manufacturer's comments in response to consultation that it was plausible that with an increase in the treatment duration the ICERs might increase but that they might also decrease. The Committee heard from the manufacturer that this could be because patients who do not progress and continue to receive treatment are those that may receive the greatest benefit. The manufacturer thought it was possible that the additional benefits would not be outweighed by the additional costs of treatment. However, the ERG commented that ICERs were more likely to increase because the incremental cost of taking bevacizumab for 1 month after stopping oxaliplatin (that is, bevacizumab costs versus no oxaliplatin costs) is higher than the incremental cost of treatment with bevacizumab and oxaliplatin (that is, bevacizumab and oxaliplatin costs versus oxaliplatin costs). Therefore, the additional costs would outweigh any additional benefits and the ICERs would be likely to increase. The Committee agreed that there was uncertainty as to how the ICERs would be affected if bevacizumab was given until progression because of the lack of clinical evidence but noted the ERG's view that the ICERs were likely to increase. Therefore, the Committee concluded that the ICERs may not reflect the way in which bevacizumab would be used in UK clinical practice, and were therefore associated with additional uncertainty but were more likely to increase.
- 4.14 The Committee considered the utility values used in the economic model. The Committee noted that no health-related quality-of-life data were collected in the study and that the utility values were taken from 'Cetuximab for the first-line treatment of metastatic colorectal cancer' (NICE technology appraisal guidance 176). The ERG stated that the reporting of utility values in metastatic colorectal cancer was inconsistent and there is a paucity of data. The Committee noted that the manufacturer had adjusted the utility value associated with the health state after first-line treatment (that is, without disease progression) to 0.77 in the revised analyses. However, the Committee agreed that the utility value of 0.77 was still high because it was similar to the utility values of people in the UK general population rather than people with metastatic colorectal cancer. The Committee also noted that the utility values were obtained from a small study of patients with metastatic colorectal cancer receiving cetuximab and chemotherapy using the EQ-5D. In addition, the utility values in the economic model

were not regimen-specific. It further noted that decreasing the utility values by 20% increased the ICERs substantially. The Committee concluded that these issues also increased the uncertainty associated with the base-case ICERs.

- 4.15 The Committee noted that disutility due to adverse events was not included in the economic model. The manufacturer stated that because the utility values were obtained using the EQ-5D, then disutility due to adverse events would be included implicitly within this measure. The Committee noted that a higher incidence of grade 3 and 4 adverse events associated with bevacizumab had been reported in the trial. It considered that there would be disutility (that is, the quality-of-life estimates were likely to have been overestimated) and additional costs associated with the toxicity of bevacizumab. The Committee heard from the manufacturer that the majority of grade 3 and 4 adverse events are due to hypertension, which in most cases is readily treatable and likely to have a small impact on the health state utility of the patient. However, the Committee considered that, in some cases, the adverse effects of bevacizumab could be serious and that the disutility due to adverse events specific to bevacizumab treatment should have been incorporated into the model. The Committee further noted that the utility values used by the manufacturer could not have accounted for the adverse effects of bevacizumab because they were obtained from a study that examined cetuximab. The Committee therefore concluded that the ICERs would increase if the disutility due to adverse events related to bevacizumab treatment was included.
- 4.16 The Committee noted that in the revised analyses provided by the manufacturer in response to consultation, the treatment administration costs of B-FOLFOX and B-XELOX were stated to have been overestimated in the original submission. The Committee noted the ERG's concerns about the time-and-motion study conducted by the manufacturer; in particular, the sources of the unit costs were unclear and the study was based on data from one small private hospital. The Committee considered that the addition of a bevacizumab infusion to either XELOX or FOLFOX could incur greater additional treatment administration costs than those stated by the manufacturer. The Committee concluded that if these higher administration costs were

included, then this would result in an increase in the ICER estimates.

4.17 The Committee discussed the details of the patient access scheme and the impact of the patient access scheme on the ICERs. It noted that when the amended patient access scheme was applied the ICERs decreased from £105,000 to £30,000 per QALY gained for B-XELOX compared with XELOX, and from £108,000 to £24,600 per QALY gained for B-FOLFOX-6 compared with FOLFOX-6. The Committee noted that there was uncertainty expressed by the Department of Health around the operating costs of implementing the scheme. The Committee had concerns about the complexity of the scheme and considered that hospital trusts were likely to involve clinical staff and finance departments as well as pharmacists in its implementation. It noted the revised analyses presented by the manufacturer that incorporated higher operating costs of the patient access scheme. However, the Committee considered that the scheme was complex, with requirements for a number of financial transactions between the manufacturer, healthcare providers and commissioners. Therefore, the operating costs of the scheme were still likely to be greater than those presented by the manufacturer. The Committee noted the ERG's exploratory analysis showing that when the administration costs of the patient access scheme were increased to £100 the ICERs increased slightly. In addition, the Committee noted its earlier conclusions that all of the ICERs with and without the patient access scheme were associated with substantial uncertainty and could be underestimated.

4.18 The Committee considered how the four components of the patient access scheme contributed to the reduction in the ICERs. It noted that the provision of free oxaliplatin was the key component in reducing the ICERs. The Committee noted that the price of oxaliplatin in the economic model was based on the BNF 57 non-proprietary price of £313.50 per 100 mg. The Committee heard from the manufacturer that the list price of oxaliplatin had been used in accordance with the NICE methods guide. However, the Committee noted that the methods guide also states that when the acquisition price paid for a resource differs from the public list price then a sensitivity analysis should be conducted to assess the implications of variations from this price. The Committee acknowledged that generic versions of oxaliplatin have recently become available and

that the list price was decreasing, with the list price in BNF 60 reduced to £299.50 per 100 mg. The Committee also noted information provided by the Commercial Medicines Unit of the Department of Health which stated that oxaliplatin is widely available in the NHS through procurement contracts at a discount of more than 90% off the list price. The Committee noted the ERG's exploratory analyses, which showed that when the oxaliplatin list price was discounted by 90% the ICERs with the patient access scheme were greatly increased to £68,100 per QALY gained for B-XELOX compared with XELOX, and to £70,500 per QALY gained for B-FOLFOX compared with FOLFOX-6. The Committee considered that it was more appropriate to use the discounted cost of oxaliplatin when assessing the impact of the patient access scheme on cost effectiveness and therefore did not accept the manufacturer's estimates that ICERs of £105,000 and £108,000 per QALY gained were reduced to £30,000 and £24,600 respectively with the amended patient access scheme.

4.19 The Committee considered supplementary advice from NICE that should be taken into account when appraising treatments that may extend the life of patients with 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 that the assumptions used in the reference case of the economic modelling are plausible, objective and robust.

4.20 The Committee discussed whether bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine for the

treatment of metastatic colorectal cancer fulfilled the criteria for consideration as a life-extending, end-of-life treatment. The Committee noted that life expectancy with XELOX or FOLFOX was unlikely to be greater than 24 months and was potentially as low as 20 months and 11 months in the first-line and second-line settings respectively. In the first-line setting, the Committee noted from the 2 x 2 analysis of the clinical trial that bevacizumab increased overall survival by 1.4 months compared with XELOX and FOLFOX-4. However, the Committee considered the design of the trial was complex and that the most appropriate method of analysis (that is, with the XELOX and FOLFOX arms not pooled and patients with prior adjuvant therapy excluded) was not provided and therefore the Committee had concerns about the robustness of the evidence. The Committee further noted that bevacizumab as a second-line therapy (E3200 study) statistically significantly increased overall survival by 2.2 months compared with FOLFOX-4. The Committee was aware that the total number of patients currently presenting with metastatic colorectal cancer in England and Wales is approximately 16,000. In addition, the Committee understood that it should take into account the cumulative population for each product in considering the strength of any case, for justifying decisions which employ, in whole or part, the supplementary criteria for appraising life-extending, end-of-life treatments. It noted that bevacizumab was licensed for a number of other indications also involving large patient groups. In summary, the Committee concluded that bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine for the treatment of metastatic colorectal cancer did not meet all of the criteria for a life-extending, end-of-life treatment.

- 4.21 The Committee concluded (on the basis of the submitted evidence) that the most appropriate cost-effectiveness estimates of bevacizumab as a first-line treatment for metastatic colorectal cancer available were those using the 2 x 2 factorial part of the study, with the XELOX and FOLFOX arms pooled and with patients who had received prior therapy excluded, giving ICERs of £105,000 per QALY gained for B-XELOX and £108,000 per QALY gained for B-FOLFOX-6 (without the patient access scheme) and £68,100 per QALY gained for B-XELOX and £70,500 per QALY gained for B-FOLFOX-6 (with the patient access scheme applied and the discounted price of oxaliplatin used). However, the Committee agreed

that these ICERs (both without and with the patient access scheme) were associated with substantial uncertainty and that plausible adjustments to the key model inputs could increase these ICERs. The Committee recognised the novel mode of action of bevacizumab but did not consider it to be a substantially innovative technology in the treatment of metastatic colorectal cancer. The Committee concluded that bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine could not be recommended as a cost-effective use of NHS resources for the first-line treatment of metastatic colorectal cancer.

4.22 The Committee reviewed the cost-effectiveness analysis of bevacizumab in combination with oxaliplatin-containing regimens as a second-line treatment for metastatic colorectal cancer. The Committee noted that the base-case ICER presented by the manufacturer was £103,000 per QALY gained. The Committee noted that this ICER was substantially higher than those normally considered an acceptable use of NHS resources. In addition, the manufacturer stated that a cost-effective case for bevacizumab as a second-line treatment could not be made. The Committee further noted that no evidence of bevacizumab given after second-line treatment was submitted by the manufacturer. Therefore, the Committee concluded that bevacizumab in combination with oxaliplatin-containing regimens could not be recommended as a cost-effective use of NHS resources for second-line or later treatment of metastatic colorectal cancer.

4.23 The Committee considered whether there were issues related to equality to be taken into account in its considerations. It noted that no equality issues had been raised during the scoping, evidence submissions or consultation stages. Therefore, it concluded that there were no specific issues relating to equality that needed to be taken into account.

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 NICE has developed [tools](#) to help organisations put this guidance into practice (listed below).
- Slides highlighting key messages for local discussion.
 - A costing statement explaining the resource impact of this guidance.
 - Audit support for monitoring local practice.

6 Related NICE guidance

- [Cetuximab for the first-line treatment of metastatic colorectal cancer](#). NICE technology appraisal guidance 176 (2009).
- Cetuximab for the treatment of metastatic colorectal cancer following failure of oxaliplatin-containing chemotherapy (terminated appraisal). NICE technology appraisal guidance 150 (2008). [replaced by [NICE technology appraisal guidance 242](#)]
- [Bevacizumab and cetuximab for the treatment of metastatic colorectal cancer](#). NICE technology appraisal guidance 118 (2007). [partially updated by [NICE technology appraisal guidance 242](#)]
- [Capecitabine and oxaliplatin in the adjuvant treatment of stage III \(Dukes' C\) colon cancer](#). NICE technology appraisal guidance 100 (2006).
- Irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer (review of technology appraisal 33). NICE technology appraisal guidance 93 (2005). [replaced by [NICE clinical guideline 131](#)]
- [Improving outcomes in colorectal cancers – manual update](#). NICE cancer service guidance (2004).
- [Guidance on the use of capecitabine and tegafur with uracil for metastatic colorectal cancer](#). NICE technology appraisal guidance 61 (2003).

7 Review of guidance

- 7.1 The guidance on this technology will be considered for review in May 2013. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Andrew Dillon
Chief Executive
December 2010

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 Darren Ashcroft

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

Dr Brian Buckley

Lay member

Mark Campbell

Director of Standards, Bury Primary Care Trust

Professor Usha Chakravarthy

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

Professor Peter Clark

Consultant Medical Oncologist, Clatterbridge Centre for Oncology, Liverpool

Dr Ian Davidson

Lecturer in Rehabilitation, University of Manchester

Dr Simon Dixon

Senior Lecturer in Health Economics, University of Sheffield

Dr Martin Duerden

Medical Director, Conwy Local Health Board

Dr Alexander Dyker

Consultant Physician, Wolfson Unit of Clinical Pharmacology, Newcastle

Dr Jon Fear

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

Miss Paula Ghaneh

Senior Lecturer and Honorary Consultant, University of Liverpool

Dr Susan Griffin

Research Fellow, Centre for Health Economics, University of York

Professor Carol Haigh

Professor in Nursing, Manchester Metropolitan University

Dr Kevin Hardy

Consultant Physician, St Helens & Knowsley Teaching Hospitals NHS Trust

Alison Hawdale

Lay member

Professor John Hutton

Professor of Health Economics, University of York

Professor Peter Jones

Pro Vice Chancellor for Research and Enterprise and Professor of Statistics, Keele University

Dr Steven Julious

Senior Lecturer in Medical Statistics, University of Sheffield

Dr Vincent Kirkbride

Consultant Neonatologist, Regional Neonatal Intensive Care Unit, Sheffield

Dr Rachel Lewis

Doctoral Researcher

Professor Jonathan Michaels

Professor of Vascular Surgery, University of Sheffield

Dr Neil Milner

General Medical Practitioner, Tramways Medical Centre

Professor Femi Oyebode

Professor of Psychiatry and Consultant Psychiatrist, The National Centre for Mental Health, Birmingham

Mike Pinkerton

Chief of Business Development – The Rotherham NHS Foundation Trust

John Radford

Director of Public Health, Rotherham Primary Care Trust

Dr Phillip Rutledge

GP and Consultant in Medicines Management, NHS Lothian

Dr Stephen Saltissi

Consultant Cardiologist, Royal Liverpool University Hospital

Dr Brian Shine

Consultant Chemical Pathologist, John Radcliffe Hospital, Oxford

Paddy Storrie

Lay member

Dr Cathryn Patricia Thomas

GP and Associate Professor, University of Birmingham

Mike Wallace

Health Economics and Reimbursement Director, Johnson & Johnson Medical Ltd

Dr Lok Yap

Consultant in Acute Medicine and Clinical Pharmacology, Whittington Hospitals NHS Trust, London

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.

Panagiota Vrouchou

Technical Lead

Rebecca Trowman

Technical Adviser

Kate Moore

Project Manager

Appendix B: Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this appraisal was prepared by School of Health and Related Research (SchHARR), University of Sheffield:

- Whyte S, Pandor A, Stevenson M, et al., Bevacizumab in combination with fluoropyrimidine-based chemotherapy for the first-line treatment of metastatic colorectal cancer, September 2009

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/carer groups:

- Association of Surgeons of Great Britain and Ireland
- Cancer Research UK
- Royal College of Nursing
- Royal College of Physicians, Medical Oncology Joint Special Committee
- Beating Bowel Cancer
- Bowel Cancer UK
- Macmillan Cancer Support

III) Other consultees:

- Department of Health
- NHS Manchester
- Welsh Assembly Government

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

- Department of Health, Social Services and Public Safety for Northern Ireland
- Medicines and Healthcare products Regulatory Agency
- NHS Quality Improvement Scotland
- Scottish Medicines Consortium
- Medac UK
- Merck Serono
- Pfizer
- Roche Products
- Sanofi-Aventis
- Institute of Cancer Research
- MRC Clinical Trials Unit
- National Institute for Health Research Health Technology Assessment Programme
- School of Health and Related Research (SchARR)
- 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 in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine for the treatment of metastatic colorectal cancer by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Professor Daniel Hochhauser, nominated by the Royal College of Physicians on behalf of NCRI/RCP/RCR/ACP/JCCO – clinical specialist
- Dr Rob Glynne-Jones, nominated by Bowel Cancer UK – clinical specialist
- Ian Beaumont (Director of Communications, Bowel Cancer UK), nominated by Bowel Cancer UK
- Barbara Moss, nominated by Bowel Cancer UK – patient expert

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 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.

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](#).

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