NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Premeeting briefing

Bevacizumab in combination with oxaliplatin and either 5-fluorouracil or capecitabine for the treatment of metastatic colorectal cancer

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

The manufacturer was asked to provide:

The statistical rationale for presenting pooled data from the two-arm study and the 2 x 2 factorial design, and to use data from the 2 x 2 factorial design only (as per the statistical protocol) to calculate survival.

Tabulated results (intention-to-treat analysis) for each of the six treatment groups separately for progression-free survival, overall survival and tumour response, adverse events, rate of and reasons for treatment discontinuation, compliance with treatment and number of patients treated until disease progression.

Data on the number of patients for whom treatment with bevacizumab continued after chemotherapy was stopped, and to clarify whether all treatment was stopped at the same time.

Reasons why survival was reported to be better in the capecitabine in combination with oxaliplatin (XELOX) plus placebo and 5-fluorouracil (5-FU) in combination with folinic acid and oxaliplatin (FOLFOX)

plus placebo arms compared with the XELOX/FOLFOX arms in the initial two-arm part of the study.

The rationale for not including data after median follow-up and the use of the whole data set to fit the curve in the base-case analysis, and to present a graph comparing the entire Kaplan–Meier curve to the fitted parametric curve.

The rationale for using an exponential distribution for progression-free survival rather than a Weibull distribution as used for overall survival, and to fit a Weibull curve to the progression-free survival data from month 6 onwards and use it in the base-case analysis.

Evaluation of the cost effectiveness of bevacizumab in combination with oxaliplatin regimens in patients with liver metastases.

Details on whether bevacizumab will be offered as a continuous or intermittent treatment in the real clinical practice.

References for the sources of the utility values used in the economic model.

Additional sensitivity analyses for utilities using data from Sharp et al.

Results (incremental cost-effectiveness ratios (ICERs), incremental quality-adjusted life years (QALYs), incremental life-years gained (LYG)) without the patient access scheme for all scenarios.

Licensed indication

Bevacizumab (Avastin, Roche Products), in combination with fluoropyrimidine-based chemotherapy, has a UK marketing authorisation for the treatment of metastatic carcinoma of the colon or rectum.

Key issues for consideration

- What is the Committee's view on the pooling of the clinical evidence from the initial two-arm part and the 2 x 2 factorial part of the NO16966 trial without weighting for uncertainty, given the European Medicines Agency's

(EMEA) concerns about combining the two parts of the study and the potential imbalance in prognostic factors between the two parts of the study?

- What is the Committee's view on excluding patients with prior adjuvant treatment from the analysis?
- What is the Committee's view on the approach that was used to select utility values? Does the Committee have any concerns with regard to the utility values used in the economic analysis and the assumptions made around them?
- What is the Committee's view on the place of bevacizumab in the treatment pathway, given that NICE has recommended irinotecan-based regimens and cetuximab (for people with specific genetic mutation and liver-only, unresectable metastases) as first-line treatment options for metastatic colorectal cancer?
- Current care in England is often intermittent treatment with chemotherapy. However, both the NO16966 study and the economic analysis presented continuous treatment. What is the Committee's view on this?
- In clinical practice, treatment with non-oxaliplatin chemotherapy regimens may continue after oxaliplatin-alone chemotherapy regimens have stopped, until disease progression. However, in the NO16966 study treatment was stopped early. What is the Committee's view on this and its potential impact on ICERs?
- What is the Committee's view on the fact that FOLFOX-4 was used in the pivotal trial of bevacizumab, but in the economic modelling this was adjusted to FOLFOX-6 by assuming similar efficacy with reduced costs?
- What is the Committee's view on not accounting for bevacizumab and oxaliplatin wastage in the cost-effectiveness analyses?
- What is the Committee's view on the patient access scheme and the assumptions made surrounding its administration costs?

1 Decision problem

1.1 Decision problem approach in the manufacturer's submission

Population	People with metastatic colorectal cancer for whom oxaliplatin-including chemotherapy regimens are suitable. The marketing authorisation for bevacizumab (Avastin) permits its use with oxaliplatin-based chemotherapy for any line of treatment. However, Roche will be seeking recommendation for these combinations for first-line treatment only.
Intervention	Bevacizumab in combination with oxaliplatin and either 5-FU or capecitabine.
Comparators	Primary analysis: oxaliplatin-based chemotherapy regimens without bevacizumab. Secondary analyses: irinotecan-based regimens are considered of limited clinical relevance. However, for completeness an economic comparison has been performed against irinotecan-based chemotherapy, because there may be a small number of patients for whom this comparison is relevant.
Outcomes	The outcome measures considered included: overall survival; progression-free survival; response rate; adverse effects of treatment; health-related quality of life.
Economic evaluation	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of quality-adjusted life years. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.
Other considerations	Consideration will be given to the activity of bevacizumab in patients with isolated liver metastases because 'Cetuximab for the first-line treatment of metastatic colorectal cancer' (NICE technology appraisal guidance 176) has defined this as a group for whom different approaches to drug therapy may be required.

1.2 Evidence Review Group comments

1.2.1 Population

The population considered by the manufacturer was people with metastatic colorectal cancer for whom oxaliplatin-based chemotherapy regimens were suitable. This population matched the marketing authorisation for bevacizumab and was in line with the NICE scope. However, the term

'suitable' was not defined in the NICE scope; the manufacturer suggested that this includes people who are not resistant to oxaliplatin treatment.

Although the summary of product characteristics (SPC) does not specify a line of treatment for bevacizumab, the manufacturer is seeking approval only for the first-line setting as the cost-effectiveness for the second-line setting could not be demonstrated

1.2.2 Intervention

The intervention, bevacizumab in combination with oxaliplatin and either 5-FU or capecitabine, was in accordance with the scope and marketing authorisation. The licensed dose of bevacizumab is either 5 mg/kg or 10 mg/kg of body weight given once every 2 weeks or 7.5 mg/kg or 15 mg/kg of body weight given once every 3 weeks. The ERG observed that the clinical efficacy of the 15 mg/kg dose has not been demonstrated in a randomised controlled trial that recruited people with metastatic colorectal cancer.

1.2.3 Comparators

The ERG noted that the main comparators considered by the manufacturer were oxaliplatin-regimens without bevacizumab. This differed from the main comparators in the scope, which also included irinotecan-including chemotherapy regimens without bevacizumab. The manufacturer stated that this approach was based on market research analysis, which indicated that oxaliplatin chemotherapy regimens are the most commonly used regimens in UK clinical practice. The ERG noted that the findings of the market research appeared to be representative of the UK clinical setting. For completeness, the manufacturer also undertook an economic evaluation using irinotecan chemotherapy regimens as a comparator. However, the ERG suggested that irinotecan chemotherapy regimens without bevacizumab were potential main comparators because 'Irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer' (NICE technology appraisal guidance 93) recommended irinotecan in combination with folinic acid and 5-FU (FOLFIRI) as a first-line treatment option for people with metastatic colorectal cancer.

1.2.4 Outcomes

The ERG noted that the outcomes included in the manufacturer's submission were in accordance with the NICE scope.

1.2.5 Economic evaluation

The time horizon of 8 years in the manufacturer's economic evaluation was considered equivalent to the life expectancy of people with metastatic colorectal cancer and therefore appropriate.

Treatment pathway

'Irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer' (NICE technology appraisal guidance 93) recommends FOLFOX or FOLFIRI as first-line treatment options for advanced colorectal cancer. FOLFOX or irinotecan alone were also recommended as subsequent therapies. 'Guidance on the use of capecitabine and tegafur with uracil for metastatic colorectal cancer' (NICE technology appraisal guidance 61) recommends either capecitabine or tegafur with uracil (in combination with folinic acid) as first-line treatment options for metastatic colorectal cancer. 'Cetuximab for the first-line treatment of metastatic colorectal cancer' (NICE technology appraisal guidance 176) recommends cetuximab in combination with FOLFOX or FOLFIRI as first-line treatment options in metastatic colorectal cancer. This guidance only applies if a patient has unresectable metastases being confined to the liver, the primary colorectal tumour having been resected or being potentially operable and the patient being fit enough to undergo surgery. In addition patients have to have Kirsten rat sarcoma (KRAS) wild type tumour.

Following the recommendations of the guidance on cetuximab for metastatic colorectal cancer (NICE technology appraisal guidance 176), the manufacturer of bevacizumab provided a post-hoc subgroup analysis for the subgroup with unresectable liver metastases.

2 Clinical effectiveness evidence

2.1 Clinical effectiveness in the manufacturer's submission

The manufacturer undertook a systematic literature review and identified two randomised controlled trials; one study assessed bevacizumab as first-line therapy (NO16966) and one as second-line therapy (E3200).

The NO16966 study was a phase III, multicentre, multinational, two-arm, randomised, open-label study. This study was originally designed to demonstrate the non-inferiority of XELOX compared with FOLFOX-4 in adult patients with histologically confirmed metastatic colorectal cancer who had not been treated before. During the course of this study, additional phase II and III studies were published that demonstrated the benefit of adding bevacizumab to irinotecan, 5-FU and folinic acid. Based on these results the original protocol design of the NO16966 study was amended to include a 2 x 2 factorial randomised study, after randomisation of the first 634 patients to XELOX or FOLFOX. A further 1401 patients were then recruited (partially blinded for bevacizumab). This study amendment included a co-primary objective of demonstrating superiority of bevacizumab in combination with chemotherapy (B-XELOX or B-FOLFOX-4) compared with placebo (P-XELOX or P-FOLFOX-4). Therefore, a total of 2035 people were randomised in the NO16966 study, all of whom had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 with mean age of 59.7 years. The dose of bevacizumab was 5 mg/kg every 2 weeks (B-FOLFOX-4) or 7.5 mg/kg every 3 weeks (B-XELOX).

Throughout the randomisation process the study was stratified to ensure that study arms were balanced with regard to the following factors:

- ECOG performance status (0 versus 1)
- number of metastatic sites (organs) at baseline (1 versus > 1)

- alkaline phosphatise level at baseline (within normal ranges versus above normal range)
- liver as a site of metastasis (yes versus no)
- geographic region.

The manufacturer assessed the validity and methodological quality of this study. The manufacturer acknowledged that patients in this study were slightly younger and fitter than people diagnosed with metastatic colorectal cancer in the UK who are, on average, over 60 years. The manufacturer concluded that the demographic characteristics of the patients were generally representative of the UK population.

In general, the manufacturer stated that the demographic characteristics and prognostic factors were well balanced between the initial two-arm part and the 2 x 2 factorial part of the study. All treatment regimens were administered for at least 48 weeks and were continued until disease progression or unacceptable toxicity, at the discretion of the investigator. The median follow-up period was 28 months.

The primary pooled analysis of superiority of the NO16966 study (that is, pooling of the initial two-arm study and the 2x2 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). In the intention-to-treat analysis, the hazard ratio for progression-free survival was 0.79 (97.5% confidence interval [CI] 0.72 to 0.87, p = 0.0001) at a median follow-up of 28 months. 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.

The primary pooled analysis of superiority of 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 significantly

improved overall survival compared with chemotherapy alone. In the intention-to-treat analysis the hazard ratio for overall survival was 0.83 (97.5% CI 0.74 to 0.93, p = 0.0019) at a median follow-up period of 28 months. 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.

After an ERG request, the manufacturer provided a secondary pooled analysis of superiority based only on the 2 x 2 factorial design (as per the original statistical trial plan, that is B-XELOX and B-FOLFOX-4 combined compared with P-XELOX and P-FOLFOX-4 combined). This analysis showed that the addition of bevacizumab to chemotherapy significantly improved progression-free survival compared with chemotherapy alone. In the intention-to-treat analysis the hazard ratio for progression-free survival was 0.83 (97.5% CI 0.72 to 0.95, p = 0.0023) at a median follow-up of 28 months. 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. However, the manufacturer reported that analysis by chemotherapy showed that progression-free survival was statistically significant only for the XELOX groups (hazard ratio 0.80, 97.5% CI 0.66 to 0.96, p = 0.0059) and not for the FOLFOX groups (hazard ratio 0.89, 97.5% CI 0.74 to 1.06, p = 0.1312).

The secondary pooled analysis of superiority (based only on the 2 x 2 factorial design) that was conducted after a request from the ERG showed that in the intention-to-treat analysis the hazard ratio for overall survival was 0.89 (97.5% CI 0.76 to 1.03, p = 0.0769) at a median follow-up of 28 months. The median overall survival was 19.9 months in the placebo plus chemotherapy group and 21.3 months in the bevacizumab plus chemotherapy group.

The primary pooled analysis of non-inferiority of the NO16966 study (that is, pooling of all XELOX arms compared with pooling of all FOLFOX arms) showed that the XELOX and FOLFOX-4 regimens were equivalent for overall survival. This was demonstrated in both the intention-to-treat analysis, in

which the hazard ratio for overall survival was 0.99 (97.5% CI 0.88 to 1.12, p-value not reported) and in the eligible patient population analysis, in which the hazard ratio for overall survival was 1.00 (97.5% CI 0.88 to 1.13, p-value not reported).

The pooled analysis of non-inferiority showed that XELOX and FOLFOX-4 were also equivalent for progression-free survival. This was both in the intention-to-treat analysis with a hazard ratio for progression-free survival of 1.01 (97.5% CI 0.91 to 1.12, p-value not reported) and in the eligible patient population analysis with a hazard ratio for progression-free survival of 1.02 (97.5% CI 0.92 to 1.14, p-value not reported).

An additional analysis conducted by the manufacturer reported that bevacizumab delivered no benefit to all people in the FOLFOX groups who had received prior adjuvant treatment (hazard ratio 1.75, 97.5% CI 1.15 to 2.65, p-value not reported), but delivered a benefit to people in the FOLFOX groups with no adjuvant therapy (hazard ratio 0.72, 97.5% CI 0.58 to 0.90, p-value not reported). The manufacturer stated that a possible explanation for this difference is that in the P-FOLFOX-4 group the time between the end of adjuvant treatment and relapse was longer than in the other groups (FOLFOX, 517 days; XELOX, 511 days [initial two-arm study]; B-FOLFOX, 623 days; B-XELOX, 597 days, P-FOLFOX, 769 days; P-XELOX, 660 days [2 x 2 factorial study]). When people who had received prior adjuvant treatment were excluded (from all four treatment arms of the factorial study, or from FOLFOX groups only or from the P-FOLFOX group only) the hazard ratios for overall survival and for progression-free survival ranged from 0.83 to 0.85 ($p < 0.03$) and from 0.74 to 0.77 ($p < 0.0001$).

The manufacturer also submitted details of a post-hoc subgroup of the impact on R0 hepatic resection rates (that is, removal of metastasis or metastases with a margin of healthy tissue) in NO16966. Analysis of this small subgroup suggested that bevacizumab plus chemotherapy compared with placebo plus chemotherapy improved R0 hepatic resection rates (6.3% versus 4.9%),

although the difference was not statistically significant. The 2-year survival was 82.3% (95% CI 69.4 to 95.1) in the placebo plus chemotherapy group and 90.0% (95% CI 82.4 to 99.4) in the bevacizumab plus chemotherapy group (no p-values were reported). No analysis by KRAS wild-type was provided by the manufacturer.

The rates of discontinuation in the NO16966 study were higher in the bevacizumab plus chemotherapy groups than in the placebo plus chemotherapy groups. The analyses based on the 2 x 2 factorial design, as requested by the ERG, produced similar results. Discontinuation of treatment was mainly associated with chemotherapy-related events rather than with bevacizumab-related events (for example, neurotoxicity, gastrointestinal events, and hematologic events). In the 2 x 2 factorial part of the study only 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, as per the SPC of bevacizumab). The manufacturer stated that a greater therapeutic benefit of bevacizumab might have been observed if these patients had remained on treatment. In general, the rates of discontinuation were similar between both the FOLFOX-4 and XELOX regimens. The analyses based on the 2 x 2 factorial design, as requested by the ERG, produced similar results.

The overall incidence of the most common adverse events was similar between the bevacizumab plus chemotherapy group compared with the placebo plus chemotherapy group. However, the incidence of stomatitis, hand-foot syndrome, bleeding problems and hypertension was at least 5% higher in the bevacizumab plus chemotherapy group than the placebo plus chemotherapy group. Adverse events of special interest with regard to bevacizumab included hypertension, proteinuria, bleeding, gastrointestinal perforation, thromboembolic events and wound healing complications. The most common of these in the NO16966 study was thromboembolic events; 7.8% of patients experienced venous thromboembolic events and 1.7% of

patients experienced arterial thromboembolic events. The occurrence of grade 3 and 4 hypertension, proteinuria and bleeding was 1.9–4% in the bevacizumab arms. Similar results were reported in the 2 x 2 factorial design analyses.

The manufacturer stated that the majority of these adverse events were generally associated with cytotoxic chemotherapy and that the increased incidence was likely to be a consequence of longer chemotherapy treatment duration for people receiving bevacizumab.

The incidence of serious and life-threatening adverse events was higher in the bevacizumab plus chemotherapy group compared with the placebo plus chemotherapy group. Similar results were reported in the 2 x 2 factorial design analyses. The overall incidence of the serious and life-threatening adverse events was reported to be higher in the FOLFOX-4 regimens compared with XELOX regimens. In the 2 x 2 factorial design analysis similar results were reported. For further details of safety associated with all treatment regimens, see pages 42–46 of the ERG report.

The E3200 study was a phase III, multicentre, three-arm, randomised, open-label study that compared the safety and efficacy of B-FOLFOX-4 (n = 293) versus FOLFOX-4 (n = 292) versus bevacizumab alone (n = 244) in adult patients with advanced or metastatic colorectal cancer previously treated with a fluoropyrimidine-based and irinotecan-based chemotherapy regimen in the USA. Patients were stratified by ECOG performance status (0 versus more than or equal to 1) and prior radiation therapy (yes versus no). The dosage of bevacizumab was 10 mg/kg every 2 weeks.

Following a review of efficacy by the data monitoring committee, 18 months after the start of the trial, the bevacizumab-alone arm was terminated. The E3200 trial showed that bevacizumab plus FOLFOX-4 significantly improved overall survival compared with FOLFOX-4 at median follow-up of 28 months (intention-to-treat analysis, hazard ratio 0.751, 95% CI 0.332 to 0.893,

p = 0.0012). The median overall survival was 10.8 months in the FOLFOX-4 group and 13 months in the FOLFOX-4 plus bevacizumab group. Similar results were reported for progression-free survival with a hazard ratio at a follow-up of 28 months of 0.518 (97.5% CI 0.416 to 0.646, p < 0.0001). Median progression-free survival increased from 4.5 months with FOLFOX-4 to 7.5 months with FOLFOX-4 plus bevacizumab.

The manufacturer also identified additional observational studies, namely the TREE study, the BRITE study and the BEAT study. In the TREE study the addition of bevacizumab to each of the regimens used significantly improved partial and complete response rates, time to disease progression and overall survival and added little to the toxicity of chemotherapy. The BRITE observational study reported similar efficacy outcomes and tolerability in people receiving first-line chemotherapy plus bevacizumab for metastatic colorectal cancer as those in the B-FOLFOX and B-XELOX arms in the NO16966 study. The BEAT study reported similar results of safety and efficacy of bevacizumab as reported in other studies and that bevacizumab plus oxaliplatin increased resection rates. Further details of these studies can be found in pages 84–95 of the manufacturer's submission.

No meta-analysis was undertaken by the manufacturer. The manufacturer stated that this was because only recommendations for first-line treatment were being sought and only one randomised controlled trial (NO16966) addressed this line of treatment. In addition, the manufacturer highlighted that there was heterogeneity between the study populations (demographic and baseline disease characteristics, dosages) of the NO16966 and E3200 studies that did not allow a meta-analysis to be performed. However, a meta-analysis of randomised controlled trials by Cao and a mixed treatment comparison by Golfinopoulos were identified by the manufacturer; for further details of these studies, see pages 73–76 of the manufacturer's submission. The meta-analysis and mixed treatment comparison suggested that the addition of bevacizumab to chemotherapy and oxaliplatin or fluoropyrimidine

combinations in general improved overall survival, progression-free survival and response rates. No ongoing studies were identified by the manufacturer.

2.2 Evidence Review Group comments

In general, the ERG considered that the search strategy was appropriate and that the most relevant randomised controlled trials were identified and included in the manufacturer's submission. The ERG stated that the method of screening and indentifying studies was inappropriate because it was performed only by one reviewer. However, no relevant studies were excluded from the review. The ERG noted that irinotecan chemotherapy regimens were not considered in the systematic review although an economic evaluation was performed. The ERG stated that since bevacizumab as a first-line treatment was the subject of this submission, then the systematic review of clinical effectiveness should have been a clearly defined focused review on first-line treatment with additional evidence to support other lines to be presented for reasons of completeness.

The ERG agreed that the NO16966 study was of reasonable methodological quality. However, the ERG noted that the reporting of the study results was not performed in a transparent way and outcomes results were not fully tabulated. The ERG acknowledged that the validity of the assessment tool used by the manufacturer was appropriate. The ERG noted that adequate methods of randomisation and allocation concealment were reported in the NO16966 and E3200 studies. Both studies had an open-label design with the exception of the bevacizumab arms, which were double-blinded in the NO16966 study.

The ERG noted that the NO16966 study used FOLFOX-4 and that FOLFOX-6 is more commonly used in UK clinical practice. However, the ERG noted that it is generally accepted that the FOLFOX-4 regimen delivers similar clinical outcomes to the FOLFOX-6 regimen.

The main areas of concern and uncertainty highlighted by the ERG on the clinical effectiveness included the following:

- Limitations with the NO16966 study design. This was a two-part study (with an initial two-arm study followed by a 2 x 2 factorial design) with an open-label design and there was an imbalance of known prognostic factors. The ERG noted that both the number of Caucasian participants and the percentages of people with ECOG performance status of 0 were reported to be 10% greater in the 2 x 2 factorial part of the study. The ERG noted that different results were reported in terms of the overall survival benefit delivered by bevacizumab in the primary pooled analysis (overall survival significantly improved) and in the pooled analysis based on the 2 x 2 factorial design (overall survival not significantly improved). The ERG suggested that this difference might be because of the imbalance of people who have slower rate of progression and the lack of statistical power to assess overall survival. Also, the ERG noted that it is difficult to assess or quantify the benefit of bevacizumab in overall survival because of its short treatment duration in the first-line setting and the additional benefits attributed to post-treatment regimens. The ERG also noted that the comparisons of some adverse events produced slightly different results, depending on the pooling techniques applied (for further information see page 47 of the ERG report). The ERG cautioned that the method of pooling data from the initial two-arm part and the 2 x 2 factorial part of the study was inappropriate because of the different designs of the two parts of the study. Unweighted pooling of results from different studies cannot account for between-study variability and might result in biased estimates of effects. The manufacturer stated that in the analysis plan for regulatory approval to the EMEA this method of pooling was included in case there were borderline results for progression-free survival in the primary analysis of superiority of bevacizumab in combination with chemotherapy versus chemotherapy alone. The appropriateness of this method was also

questioned by the EMEA in their assessment for bevacizumab as the results were not borderline for the superiority analysis.

- Progression-free survival was only statistically significant for the XELOX groups and not for the FOLFOX groups. The manufacturer stated that this difference might be because the median time from end of adjuvant treatment to randomisation in the initial two-arm part of the study was shorter than in the 2 x 2 factorial part of the study. In particular, in the P-FOLFOX group, time to the end of adjuvant treatment and relapse was longer than in the other groups. The manufacturer conducted an exploratory analysis in the FOLFOX groups that showed bevacizumab delivered no benefit to people who had prior adjuvant treatment but delivered a benefit to people with no adjuvant treatment. The ERG stated that although this is plausible it should be treated with caution as it is a post-hoc exploratory analysis.
- The ERG noted that the duration of chemotherapy treatment was relatively short (6 months), despite the protocol allowing treatment until disease progression or unacceptable toxicity. This was also contrary to treatment recommendations of the SPC.

2.3 Statements from professional/patient groups and nominated experts

Clinical experts stated that around 6530 people per year are eligible for first-line treatment of metastatic colorectal cancer with bevacizumab in England and Wales. This figure accounts for 20% of the 31,000 people diagnosed with colorectal cancer in England and Wales. Clinical experts stated that there is significant variation in the approval rates between primary care trusts regarding the addition of bevacizumab to irinotecan-based chemotherapy and the use of cetuximab for the treatment of metastatic colorectal cancer. Clinical experts noted that bevacizumab is less toxic than chemotherapy and has fewer side effects. Therefore people receiving bevacizumab may experience an improvement both in their quality and length of life. However, the potential adverse events with bevacizumab, such as hypertension, thromboembolism

and proteinuria, were highlighted and it was noted that NHS staff might need to receive additional guidance on diagnosing and treating such events. Clinical experts considered that monitoring blood pressure, testing urine for protein and early diagnosis of thromboembolism should be mandatory but that any additional costs would not be high.

3 Cost effectiveness

3.1 Cost effectiveness in the manufacturer's submission

The manufacturer identified two relevant economic analyses. The first was a study by Lewis et al. (2008) based on the manufacturer's submission of bevacizumab to the Scottish Medicines Consortium which used data from the NO16966 trial. This study compared B-XELOX with FOLFOX-4 and produced an ICER of £25,806 per QALY gained. Fewer comparators were considered in this study than in the current submission. The second was a study by Shiroiwa et al. (2009) that assessed the cost effectiveness of bevacizumab with chemotherapy for the treatment of metastatic colorectal cancer in Japan. The overall conclusion of this study was that it was difficult to estimate the cost effectiveness of bevacizumab for the first-line treatment of people with metastatic colorectal cancer before the publication of findings from the NO16966 study.

The manufacturer produced a Markov model to estimate the disease progression of metastatic colorectal cancer and the subsequent total direct costs and QALYs for each intervention. The model had four distinct health states: first-line treatment (PFS_T), after first-line treatment without progression (PFS_{PT}), progressed and death. The manufacturer stated that the progression-free survival health state was divided into the two separate states (PFS_T and PFS_{PT}) to better capture and reflect the differences in costs and utilities during treatment and after treatment while in progression-free survival. It was assumed that all patients start in PFS_T in accordance with the NO16966 study. The model had a cycle length of 1 month and the time

horizon was 8 years, which was equivalent to life expectancy in the population of interest. A half-cycle correction was applied to the model.

The model used Kaplan–Meier data from the NO16966 study for progression-free and overall survival for the first part of the curve (up to median survival of 28 months) and then used fitted parametric curves to extrapolate beyond this point. For overall survival the manufacturer extrapolated the curve by using the Weibull function and therefore treatment effect was assumed to continue after the median follow-up period; this assumption was explored in the sensitivity analysis. There were 19.7% (n = 256) and 13.7% (n = 96) patients alive after median follow-up in the XELOX/FOLFOX and B-XELOX/B-FOLFOX arms respectively. These numbers were reported incorrectly in the ERG report (see p. 57) and have been corrected in this document. The ERG asked the manufacturer to use the untruncated data to calculate Weibull estimates to fit the parametric curves to allow for the greater uncertainty at the end of the curve.

For progression-free survival the manufacturer extrapolated the curve by using the exponential function based on average hazard for months 13–28 (as the curve appeared to go through three phases from month 0 to 5, 6 to 12 and month 13 onwards). In the sensitivity analysis the impact of using alternative curves for extrapolating progression-free survival was explored. The ERG suggested fitting a Weibull distribution to the progression-free survival data from 6 months onwards and using this Weibull from month 28 onwards (rather than using exponential functions for the three different phases). The manufacturer acknowledged the ERG's suggestion, but used the Weibull curve from 6 months onwards.

A systematic literature review was undertaken by the manufacturer to obtain utility values and two sources were identified. One study reported utility values of 0.8 and 0.6 for progression-free survival and progressed disease respectively. The manufacturer stated that these utility values could not be used in the current analysis because the methods used to derive them do not

conform with the NICE reference case. The second source identified was the recent guidance on cetuximab for metastatic colorectal cancer (NICE technology appraisal guidance 176). Utility values for progression-free survival were taken from a randomised controlled trial comparing cetuximab in combination with FOLFIRI with FOLFIRI alone and represented mean utility values from 42 people using the EQ-5D questionnaire. A utility value of 0.77 was assigned to the PFS$_T$ health state; this value was an average of all the EQ-5D completed responses over the study period (assumption used in NICE technology appraisal guidance 176). A utility value of 0.79 was assigned to the PFS$_{PT}$ health state; this was based on expert opinion that people in this state will experience a higher quality of life than patients on first-line treatment, because of fewer adverse events, and their utility will be similar to an individual aged 55–64 in the UK general population. A utility value of 0.68 was assigned to the progressed state; this was taken from a trial examining the use of cetuximab for the third-line treatment of metastatic colorectal cancer, using the Health Utility Index questionnaire (assumption used in NICE technology appraisal guidance 176).

The manufacturer included only resource costs that were under the control of the NHS and personal social services (PSS). Prices were mainly derived from national reference costs 2007-2008, British National Formulary (BNF) 57 and PSSRU 2008. Kaplan–Meier survival analysis was used to calculate the mean treatment duration based on the time from first dose to the time until treatment stopped, as recorded in the NO16966 study. Although FOLFOX-4 was used in the pivotal trial of bevacizumab, the manufacturer stated that FOLFOX-6 is more commonly used in UK clinical practice. Therefore the manufacturer adjusted the economic modelling to FOLFOX-6 by assuming similar efficacy as FOLFOX-4 but with reduced costs. For each drug the mean dose per cycle as observed in the NO16966 study was used to calculate the relative dose intensity per cycle (actual dose/protocol dose per cycle) applied to the model. Dose interruptions led to longer cycle lengths and smaller numbers of cycles administered each month.

Mean and median treatment duration (6 and 7 months respectively) was shorter in the NO16966 study than time until disease progression. Duration of treatment also varied between treatment arms and was longer with the addition of bevacizumab and longer in the FOLFOX than in the XELOX arms. The manufacturer claimed that bevacizumab treatment was terminated at the same point as chemotherapy regimens. Additional analysis, requested by the ERG, showed that there was some difference between when each drug treatment was stopped. The new findings were included in the economic model and, for simplicity, it was assumed that oxaliplatin and bevacizumab treatment duration was similar on the B-FOLFOX and B-XELOX arms.

The manufacturer submitted the avastin patient access scheme (APAS) in which bevacizumab was provided at a fixed price of £1200 per 3-week cycle and £800 per 2-week cycle and free after 1 year. Oxaliplatin was free for patients receiving bevacizumab. The manufacturer stated that the APAS will only be applicable for first-line metastatic colorectal cancer patients. If a patient has progressed (by the RECIST criteria, solid evaluation criteria in solid tumours) then the APAS would no longer apply as they would no longer be considered first-line. The manufacturer stated that it will take 5 minutes per cycle of a pharmacist's time to update the registry system required for the PAS; this equated to £4 per cycle.

The manufacturer, at the ERG's request, included oxaliplatin wastage to estimate cost effectiveness with and without the APAS modifications. Under this scenario the total dose for oxaliplatin was estimated by rounding up the mean dose per cycle observed in the trial to the nearest complete 50-mg vial. The manufacturer included bevacizumab wastage to estimate cost effectiveness when the APAS scheme was not applied.

The results of the manufacturer's base-case analysis and additional analyses are presented in table 1.

Table 1 Results of the manufacturer's base-case analysis and additional analyses

Scenario	Total costs(£s) and QALYs per patient									ICERs (£ per QALY saved)	
		XELOX	FOLFOX-6	FOLFOX-4	FOLFIRI-mdG	FOLFIRI-dG	B-XELOX	B-FOLFOX-6	B-FOLFOX-4	B-XELOX versus XELOX	B-FOLFOX-6 versus FOLFOX-6
MS original analysis											
Analysis using data from all six arms of NO16966, XELOX and FOLFOX arms pooled(pooling of the initial two-arm study and the 2 x 2 factorial part of the study)	Costs (£s)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	34,170	41,388
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Probabilistic sensitivity analysis results for above analysis							95% percentiles of ICERs			£34,217 (£26,597; £52,960)	£41,519 (£31,136; £67,859)
Above analysis without APAS	Costs (£s)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	82,098	94,989
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
MS supplementary data, requested by ERG											
Analysis using data from all six arms of NO16966, XELOX and FOLFOX arms pooled(pooling of the initial two-arm study and the 2 x 2 factorial part of the study)	Costs (£s)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	35,912	36,569
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Probabilistic sensitivity analysis results for above analysis							(95% percentiles not provided)			36,205	36,907
Analysis using data from all six arms of NO16966, XELOX and FOLFOX arms pooled(pooling of the initial two-arm study and the 2 x 2 factorial part of the study)	Costs QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£84,553 without APAS	£92,634 without APAS
Probabilistic sensitivity analysis results for above analysis							95% percentiles of ICERs			84,212 (61,368, 147,392)	91,915 (65,675, 163,577)

Analysis using data from all six arms of NO16966, XELOX and FOLFOX arms pooled (pooling of the initial two-arm study and the 2 x 2 factorial part of the study) including oxaliplatin wastage	Costs (£s) QALYs	[redacted]							£86,637 without APAS	£95,357 without APAS
Probabilistic sensitivity analysis results for above analysis							95% percentiles of ICERs		86,083 (62,820, 149,013)	94,355 (67,704, 163,867)
Analysis using data from all six arms of NO16966, XELOX and FOLFOX arms pooled (pooling of the initial two-arm study and the 2 x 2 factorial part of the study) including bevacizumab wastage	Costs QALYs	[redacted]							£90,945 without APAS	£98,436 without APAS
Probabilistic sensitivity analysis results for above analysis							95% percentiles of ICERs		91,198 (67,740, 152,900)	98,488 (71,338, 163,458)
Analysis using the 2 x 2 part of NO16966, XELOX and FOLFOX arms pooled	Costs (£s)	[redacted]							48,111	39,771
	QALYs	[redacted]								
Analysis using the 2 x 2 part of NO16966, XELOX and FOLFOX arms pooled (including drug wastage)	Costs QALYs	[redacted]							129,911 without APAS	134,309 without APAS
Probabilistic sensitivity analysis results for above analysis							95% percentiles of ICERs		130,281 (-231,910, 713,057)	133,921 (63,416, 764,148)
Analysis using the 2 x 2 part of NO16966, XELOX and FOLFOX arms pooled, without prior adjuvant treatment	Costs (£s)	[redacted]							36,006	31,174
	QALYs	[redacted]								

Analysis using the 2 x 2 part of NO16966, XELOX and FOLFOX arms pooled, without prior adjuvant treatment (including drug wastage)	Costs QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£92,698 without APAS £96,687 without APAS
Probabilistic sensitivity analysis results for above analysis							95% percentiles of ICERs			92,356 (60,814, 229,158)	96,342 (59,793, 246,416)
Analysis using 2 x 2 part of NO16966, XELOX and FOLFOX arms unpooled *	Costs (£s)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	35,662	62,714
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Analysis using 2 x 2 part of NO16966, XELOX and FOLFOX arms unpooled (including drug wastage)	Costs QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£90,779 without APAS £240,324 without APAS
Probabilistic sensitivity analysis results for above analysis							95% percentiles of ICERs			90,187 (45,858, 423,809)	241,000 (-2,346,787, 2,113,555)

APAS, Avastin patient access scheme; B-XELOX, bevacizumab and oxaliplatin plus capecitabine; B-FOLFOX-6, bevacizumab and 5-FU plus folinic acid in combination with oxaliplatin; Dg, de Gramont;ERG, Evidence Review Group; FOLFOX, 5-FU plus folinic acid in combination with oxaliplatin; ICERs, incremental cost-effectiveness ratios; KM, Kaplan–Meier; mdG, modified de Gramont;MS, manufacturer's submission; PAS, patient access scheme; QALY, quality-adjusted life year; XELOX, oxaliplatin plus capecitabine.

*The MS states that this analysis "uses truncated and oxaliplatin"- the ERG are unclear of the meaning of this

The manufacturer stated that the most relevant ICERs to the decision problem are B-XELOX compared with XELOX and B-FOLFOX-6 compared with FOLFOX-6. In the base-case analysis (that is, pooling of the initial two-arm study and the 2 x 2 factorial part of the study) B-XELOX produced an ICER of £34,170 per QALY gained when compared with XELOX (£82,098 per QALY gained without the APAS). The corresponding ICER for B-FOLFOX-6 was £41,388 per QALY gained when compared with FOLFOX-6 (£94,989 per QALY gained without the APAS).

In the one-way sensitivity analyses the impact of utility values, survival analysis, clinical practice assumption and unit costs was explored. The ICERs were most sensitive to variations in the assumed treatment effect after the median follow-up period; changes to the other parameters did not greatly influence the ICER.

A probabilistic sensitivity analysis was performed to reflect the uncertainty around key clinical and cost values used in the model. The cost-effectiveness acceptability curves are shown in figure 26 of the manufacturer's submission (page 156). For the comparison of B-FOLFOX-6 with FOLFOX-6, the mean ICER was £41,519 per QALY gained (95% percentiles of ICERs: £31,136; £67,859) and for the comparison of B-XELOX with XELOX, the mean ICER was £34,217 (95% percentiles: £26,597; £52,960). No ICERs without the APAS modifications were provided.

The manufacturer also provided a revised base-case analysis (pooling of the initial two-arm study and the 2 x 2 factorial part of the study), as requested by the ERG. This analysis was based on revised modelling of treatment durations (using a Kaplan–Meier curve up to month 6 and then a Weibull function fitted to untruncated data after month 6 for progression-free survival and fitting a Weibull function fitted to untruncated data for overall survival). The revised ICER for B-XELOX was £35,912 per QALY gained (£84,553 without the APAS) when compared with XELOX and for B-FOLFOX-6 was £36,569 per QALY gained (£92,634 without the APAS) when compared with

FOLFOX-6. One-way sensitivity analyses were conducted which showed that 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 £36,205 per QALY gained (£91,915 without the APAS) and for the comparison of B-XELOX with XELOX the mean ICER was £36,907 per QALY gained (£84,212 without the APAS).

The manufacturer also included bevacizumab and oxaliplatin wastage for the revised base-case analysis (pooling of the initial two-arm study and the 2 x 2 factorial part of the study) to estimate the cost effectiveness without the APAS modifications. When bevacizumab wastage was included, the revised ICER for B-XELOX was £90,945 per QALY gained when compared to XELOX and for B-FOLFOX-6 was £98,436 per QALY gained when compared with FOLFOX-6. When oxaliplatin wastage was included the revised ICER for B-XELOX was £86,637 per QALY gained when compared with XELOX and for B-FOLFOX-6 was £95,357 per QALY gained when compared with FOLFOX-6.

In the NO16966 study bevacizumab plus chemotherapy compared with placebo plus chemotherapy appeared to increase both R0 resection rates and survival after resection. However, the manufacturer did not present an economic evaluation for the subgroup of people with liver metastases.

The manufacturer provided an additional analysis for bevacizumab as a second-line treatment. This analysis resulted in an ICER of £101,048 per QALY gained for B-FOLFOX-4 compared with FOLFOX-4. The manufacturer stated that the larger ICERs reported in the second-line setting were mainly dose-driven (higher dose of bevacizumab). In this analysis bevacizumab costs were £1600 per cycle and oxaliplatin was free with bevacizumab. The ERG understood that the APAS was only applicable to first-line therapy. This analysis seemed to use the APAS but this is unclear as the cost of bevacizumab seemed to be doubled at £1600 per cycle. The reasons for these assumptions were unclear.

3.2 Evidence Review Group comments

The ERG identified a number of issues with the economic model submitted by the manufacturer of bevacizumab. In particular, the ERG suggested that the most appropriate base-case analysis was one using the 2 x 2 factorial design of the NO16966 study with XELOX and FOLFOX unpooled and people who had received prior adjuvant therapy excluded. However, the ERG stated that because this analysis was not provided by the manufacturer the next most appropriate base-case analysis was the one presented in bold in table 2. Under this analysis the ICER for B-XELOX was £36,354 per QALY gained compared with XELOX and £31,452 per QALY gained for B-FOLFOX-6 compared with FOLFOX-6. The results of the one-way sensitivity analyses showed that the ICERs were not greatly influenced by any of the parameter changes. All of the ICERs included in table 2 include the APAS proposed by the manufacturer. The corresponding ICERs without the APAS modifications were not provided.

Table 2 Exploratory analyses examining the impact of parameter changes on the ICERs

	Progression-free survival modelling	Overall survival modelling	Scenario	ICERs	
				B-XELOX versus XELOX	**B-FOLFOX-6 versus FOLFOX-6**
Manufacturer's submission	KM up to month 6 then Weibull	Weibull	–	£36,006	£31,174
ERG analysis	**KM up to month 6 then Weibull**	**KM up to month 28 then Weibull**	*****	**£36,354**	**£31,452**
ERG analysis	Weibull	Weibull	–	£35,135	£28,976
ERG analysis	KM up to month 6 then Weibull	KM up to month 6 then Weibull	As treatment arms stop crossing at month 6 this may be an appropriate point at which to start extrapolation	£36,438	£31,523
ERG analysis	KM up to month 6 then Weibull	KM up to month 28 then Weibull	−20% all utility values (0.63, 0.62, 0.54)	£45,443	£39,315
ERG analysis	KM up to month 6 then Weibull	KM up to month 28 then Weibull	Treatment duration: Oxaliplatin stopped one month earlier (assumed no change in incremental survival)	£43,511	£39,478
ERG analysis	KM up to month 6 then Weibull	KM up to month 28 then Weibull	Cycle lengths unpooled (were not pooled across trials)	£36,488	£32,900

All analyses use data from 2 x 2 part of NO16966, XELOX and FOLFOX arms pooled, patients with prior adjuvant therapy excluded, with APAS

APAS, Avastin patient access scheme; B-XELOX, bevacizumab and oxaliplatin plus capecitabine; B-FOLFOX-6, bevacizumab and 5-FU plus folinic acid in combination with oxaliplatin; ERG, Evidence Review Group; FOLFOX, 5-FU plus folinic acid in combination with oxaliplatin; ICERs, incremental cost-effectiveness ratios; KM, Kaplan–Meier; XELOX, oxaliplatin plus capecitabine.

* The ERG suggests that the results using the 2x2 part of the NO16966 trial with XELOX and FOLFOX unpooled and prior adjuvant patients excluded may be tge most appropriate base case. As this analysis was not presented in the MS and data was not available for the ERG to perform it the analysis in bold may be the most appropriate analysis available.

The main areas of concern and uncertainty about cost effectiveness highlighted by the ERG included:

- The method of pooling data from the initial two-arm part and the 2 x 2 factorial part of the study was inappropriate because of the different designs of the two parts of the study. The manufacturer provided additional analysis using only the 2 x 2 factorial design (B-XELOX and B-FOLFOX-4 combined compared with P-XELOX and P-FOLFOX-4 combined) with XELOX and FOLFOX arms pooled and unpooled, which increased the ICERs (see section 3.1 of this document).
- It was unclear why the health-related quality-of-life literature review did not to conform to the NICE reference case. The ERG stated that it was not possible to adequately check the sources of the utility values because the references were incomplete. The ERG suggested that the utility values from the guidance on cetuximab for metastatic colorectal cancer (NICE technology appraisal guidance 176) could be relevant to people receiving bevacizumab. However, the ERG also commented that the assumption that the utility value of the PFS_{PT} health state (that is, off treatment but not yet progressed) is similar to that of people aged 55–64 in the UK general population is unrealistic. This is because after 6 months of chemotherapy, people are often less mentally and physically fit than the general population. In addition, the ERG noted that the utility value for the PFS_{T} health state (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.
- All treatment was often terminated early (that is, before progression) despite the SPC recommendations that if oxaliplatin is stopped because of toxicity then bevacizumab and 5-FU should be continued until progression. Additionally, this was allowed in the NO16966 study protocol. The ERG noted that this might be a reason why no significant survival benefits were reported. 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 non-oxaliplatin

chemotherapy regimens might continue after oxaliplatin regimens stopped. The ERG conducted an exploratory analysis that examined the impact on ICERs when oxaliplatin was stopped 1 month before the other chemotherapy components. Under this scenario costs in the XELOX and FOLFOX-6 arms were reduced by [redacted] and [redacted]. In the B-XELOX and B-FOLFOX, the cost of oxaliplatin remained the same because oxaliplatin is free for these arms. It was also assumed that no change in incremental survival occurred. In this analysis the ICERs were greatly increased: B-XELOX had an ICER of £43,511 per QALY gained when compared with XELOX and B-FOLFOX-6 had an ICER of £39,478 per QALY gained when compared with FOLFOX-6. No ICERs without the APAS modifications were provided.

- The APAS means that bevacizumab has a fixed price so adjusting for bevacizumab wastage is not necessary. Incremental costs will only be affected if oxaliplatin is associated with wastage because oxaliplatin is free with the APAS and adjusting for oxaliplatin wastage would slightly reduce the incremental cost of adding bevacizumab.
- The ERG requested analyses without the APAS modifications from the manufacturer. The ERG noted that neither bevacizumab nor oxaliplatin wastage was included any of the scenarios using the 2x2 part of the study. Bevacizumab and oxaliplatin wastage were taken into account separately in the analyses that pooled the initial two-arm part and the 2 x 2 factorial part of the study. If the APAS scheme was not approved, the ERG noted that both bevacizumab and oxaliplatin wastage combined should be taken into account.
- In the bevacizumab arms, duration of treatment was longer and cycle lengths were slightly shorter. The ERG stated that if cycle lengths were modelled separately for each treatment arm, this would result in shorter cycle lengths for the comparators and increased cycle lengths for bevacizumab. Therefore the monthly costs for the bevacizumab arms would be higher under this scenario analysis. The ERG presented an exploratory analysis where cycle lengths were not pooled across trial arms

which increased the ICERs. For B-XELOX, the ICER increased from £34,170 to £36,488 per QALY gained compared with XELOX and the ICER decreased from £41,388 to £32,900 per QALY gained for B-FOLFOX-6 compared with FOLFOX-6. No ICERs without the APAS modifications were provided.

- In the NO16966 study and in the economic model, continuous treatment was represented. However, the ERG suggested that current UK clinical practice is often intermittent treatment with chemotherapy, but it is unclear how these treatments would influence the ICERs. According to the literature, intermittent treatment reports similar efficacy benefits to continuous treatment and might result in better quality of life. Also, intermittent treatment can be less expensive than continuous. Under these circumstances the ICER for continuous treatment with bevacizumab (as in the manufacturer's submission) would be higher when compared with intermittent treatment of bevacizumab. The ERG recommended that this area should be further explored.
- Bleeding and thromboembolic events had an incidence of 2% in some arms. They were not included in the economic model. The manufacturer replied to the clarification letter that the incidence of these events was unlikely to lead to a remarkable difference in the ICERs. However, the ERG could not further comment because the costs of these events were not provided.
- The model did not take into account the fact that XELOX regimens might be associated with higher health-related quality of life compared with FOLFOX regimens because they are considered more convenient. The ERG also considered that the utility value for the progressed disease health state was quite high and that no age-specific utility values were used. The ERG performed an exploratory analysis that investigated the impact on ICERs when the utility values were decreased by 20%. This decrease in utility values had a large impact on the ICERs; the ICER for B-XELOX increased from £34,170 to £45,433 per QALY gained when compared with XELOX and the ICER for B-FOLFOX-6 decreased from £41,388 to £39,315

per QALY gained when compared with FOLFOX-6. No ICERs without the APAS modifications were provided.

Authors

Rebecca Trowman and Panagiota Vrouchou, with input from the Lead Team (Peter Jones, Philip Rutledge, Brian Buckley and Peter Clarke).

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

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

- Whyte et al, Bevacizumab in combination with fluoropyridimine-based chemotherapy for the first-lien treatment of metastatic colorectal cancer – a single technology appraisal, September 2009

B Submissions or statements were received from the following organisations:

I Manufacturer/sponsor:

- Roche Products

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

- Beating Bowel Cancer
- Bowel Cancer UK
- Royal College of Physicians on behalf of NCRI Clinical Studies Group/Royal College of Physicians/Royal College of Radiologists/Joint Collegiate Council on Oncology/Association of Cancer Physicians

Appendix B:

A. Cetuximab for the first-line treatment of metastatic colorectal cancer' (NICE technology appraisal guidance 176. Available at http://www.nice.org.uk/nicemedia/pdf/TA176Guidance.pdf

1.1 Cetuximab in combination with 5-fluorouracil (5-FU), folinic acid and oxaliplatin (FOLFOX), within its licensed indication, is recommended for the first-line treatment of metastatic colorectal cancer only when all of the following criteria are met:

- The primary colorectal tumour has been resected or is potentially operable.
- The metastatic disease is confined to the liver and is unresectable.
- The patient is fit enough to undergo surgery to resect the primary colorectal tumour and to undergo liver surgery if the metastases become resectable after treatment with cetuximab.
- The manufacturer rebates 16% of the amount of cetuximab used on a per patient basis.

1.2 Cetuximab in combination with 5-FU, folinic acid and irinotecan (FOLFIRI), within its licensed indication, is recommended for the first-line treatment of metastatic colorectal cancer only when all of the following criteria are met:

- The primary colorectal tumour has been resected or is potentially operable.
- The metastatic disease is confined to the liver and is unresectable.
- The patient is fit enough to undergo surgery to resect the primary colorectal
tumour and to undergo liver surgery if the metastases become resectable after
treatment with cetuximab.
- The patient is unable to tolerate or has contraindications to oxaliplatin.

1.3 Patients who meet the criteria in 1.1 and 1.2 should receive treatment with cetuximab for no more than 16 weeks. At 16 weeks, treatment with cetuximab should stop and the patient should be assessed for resection of liver metastases.

1.4 People with metastatic colorectal cancer with metastatic disease confined to the liver who receive cetuximab should have their treatment managed only by multidisciplinary teams that involve highly specialised liver surgical services.

B. European Medicines Agency (EMEA). Assessment Report for Avastin (page 37). Procedure Number. EMEA/H/C/000582/II/0014. Available at http://www.emea.europa.eu/humandocs/PDFs/EPAR/avastin/Avastin-H-582-II-14-AR.pdf.

A multivariable analysis adjusting for prognostic factors, stratification variables and geographic region was performed and the results confirmed the robustness of the results of the PFS primary efficacy analyses for the overall comparison and in each treatment subgroup. Sensitivity analyses were performed to investigate whether or not delays in tumour assessments had any effect on the outcome of the primary analyses for PFS, and the results confirm the primary analysis in the overall comparison
and the treatment subgroup comparisons, and thus indicate that delays in tumour assessments did not affect the outcome of the primary analysis of PFS. A superiority analysis which combined all patients in the trial (patients in 2-arm part plus patients in 2x2 factorial part of the study) was specified in the protocol in case of borderline results. This analysis was performed, and demonstrated superiority for the BV-containing arms versus the chemotherapy alone arms in the overall comparison and the XELOX treatment subgroup, and in addition significant improvement of adding bevacizumab to

FOLFOX-4 was obtained (HR=0.82, p=0.0080). However, the validity of combining the two parts of the study may be questioned, and does not alter conclusions based on the primary analysis. A clear distinction between patients who received prior adjuvant chemotherapy and those who did not was demonstrated in the subgroup analysis of the FOLFOX-4 treatment subgroup. Therefore additional exploratory analyses were performed and these analyses showed that removing the subgroup of patients that may have slower tumour progression, improved the results, and even the subgroup analysis of FOLFOX-4 became significant in favour of addition of bevacizumab. As mentioned
previously, an imbalance with regard to an important prognostic factor (the time between primary treatment and recurrence), which was not recognized when the trial was started, can explain these results. However, this is a post-hoc analysis which must be assessed with great caution.