Bevacizumab in combination with fluoropyrimidine-based chemotherapy for the first-line treatment of metastatic colorectal cancer

S Whyte,* A Pandor, M Stevenson and A Rees

ScHARR Technology Assessment Group, The University of Sheffield, Sheffield, UK

*Corresponding author

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Abstract

This paper presents a summary of the evidence review group (ERG) report into the clinical effectiveness and cost-effectiveness of bevacizumab in combination with fluoropyrimidine-based chemotherapy for the first-line treatment of metastatic colorectal cancer based on the manufacturer's submission to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal (STA) process. Evidence was available in the form of one phase III, multicentre, multinational, randomised, open-label study (NO16966 trial). This two-arm study was originally designed to demonstrate the non-inferiority of oral capecitabine plus oxaliplatin (XELOX) compared with 5-fluorouracil plus folinic acid plus oxaliplatin (FOLFOX)-4 in adult patients with histologically confirmed metastatic colorectal cancer who had not previously been treated. Following randomisation of 634 patients, the open-label study was amended to include a 2×2 factorial randomised (partially blinded for bevacizumab) phase III trial with the coprimary objective of demonstrating superiority of bevacizumab in combination with chemotherapy compared with chemotherapy alone. Measured outcomes included overall survival, progression-free survival, response rate, adverse effects of treatment and health-related quality of life. The manufacturer's primary pooled analysis of superiority (using the intention-to-treat population) showed that after a median follow-up of 28 months, the addition of bevacizumab to chemotherapy significantly improved progression-free survival and overall survival compared

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List of authors:
S Whyte, A Pandor, M Stevenson and A Rees

Contact details:
Sophie Whyte, Research Associate, ScHARR, University of Sheffield, Regent Court, 30 Regent Street, Sheffield S1 4DA, UK

E-mail: sophie.whyte@shef.ac.uk

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with chemotherapy alone in adult patients with histologically confirmed metastatic colorectal cancer who were not previously treated [median progression-free survival 9.4 vs 7.7 months (absolute difference 1.7 months); hazard ratio (HR) 0.79, 97.5% confidence interval (CI) 0.72 to 0.87; $p = 0.0001$; median overall survival 21.2 vs 18.9 months (absolute difference 2.3 months); HR 0.83, 97.5% CI 0.74 to 0.93; $p = 0.0019$]. The NO16966 trial was of reasonable methodological quality and demonstrated a significant improvement in both progression-free survival and overall survival when bevacizumab was added to XELOX or FOLFOX. However, the size of the actual treatment effect of bevacizumab is uncertain. The ERG believed that the modelling structure employed was appropriate, but highlighted several key issues and areas of uncertainty. At the time of writing, NICE was yet to issue the guidance for this appraisal.

Introduction

The National Institute for Health and Clinical Excellence (NICE) is an independent organisation within the NHS that is responsible for providing national guidance on the treatment and care of people using the NHS in England and Wales. One of the responsibilities of NICE is to provide guidance to the NHS on the use of selected new and established health technologies, based on an appraisal of those technologies.

NICE's single technology appraisal (STA) process is specifically designed for the appraisal of a single product, device or other technology, with a single indication, where most of the relevant evidence lies with one manufacturer or sponsor.[1] Typically, it is used for new pharmaceutical products close to launch. The principal evidence for an STA is derived from a submission by the manufacturer/sponsor of the technology. In addition, a report reviewing the evidence submission is submitted by the evidence review group (ERG), an external organisation independent of the Institute. This paper presents a summary of the ERG report for the STA entitled '*Bevacizumab in combination with fluoropyrimidine-based chemotherapy for the first-line treatment of metastatic colorectal cancer*'.

Description of the underlying health problem

Colorectal cancer is the third most common cancer in the UK, with 36,766 new cases diagnosed in England and Wales in 2005.[2] Metastatic disease is, in the majority of cases, incurable and treatment is palliative in nature. Although local radiotherapy and, less commonly, surgery both have a role, metastatic disease is essentially a systemic disease requiring systemic treatment. Traditionally this has meant cytotoxic chemotherapy although, in recent years, passive immunotherapy in the form of monoclonal antibody treatment has been added to chemotherapy regimens. Commonly used regimens include oral capecitabine monotherapy, oral capecitabine + intravenous (IV) oxaliplatin (XELOX), IV 5-fluorouracil + folinic acid + oxaliplatin (FOLFOX), IV 5-fluorouracil + folinic acid + irinotecan (FOLFIRI), IV 5-fluorouracil ± folinic acid, and oral capecitabine + IV irinotecan (XELIRI). With current standard first-line chemotherapy, median survival is around 15–20 months.[3–5]

Scope of the evidence review group report

The objective of the appraisal was to evaluate the clinical effectiveness and cost-effectiveness of bevacizumab, within its licensed indications, in combination with oxaliplatin and either 5-fluorouracil or capecitabine for the treatment of metastatic colorectal cancer. The comparator was oxaliplatin or irinotecan, including chemotherapy regimens without bevacizumab. Measured outcomes included overall survival, progression-free survival, response rate, adverse effects of treatment and health-related quality of life.

The licensed indication permits the use of bevacizumab in combination with fluoropyrimidine-based chemotherapy for the treatment of patients with metastatic colorectal cancer but does not specify a line of treatment. The NICE scope included the use of bevacizumab in combination with oxaliplatin-based chemotherapy in individuals with histologically confirmed metastatic colorectal cancer as first-line therapy (for patients not previously treated for metastatic disease), and as second-line therapy. The manufacturer's submission (MS), however, focuses on first-line use only.

The main evidence presented in support of the clinical effectiveness of bevacizumab was based on one phase III, multicentre, multinational, randomised, open-label study (NO16966 trial).[6] This two-arm 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 previously been treated. Following randomisation of 634 patients, the open-label study was amended (additional phase II and III studies that were published demonstrated the benefit of adding bevacizumab to irinotecan, 5-fluorouracil and folinic acid)[7,8] to include a 2×2 factorial randomised (partially blinded for bevacizumab) phase III trial ($n = 1401$) with the coprimary objective of demonstrating superiority of bevacizumab in combination with chemotherapy (B-XELOX or B-FOLFOX-4) compared with chemotherapy alone (P-XELOX or P-FOLFOX-4). The dose of bevacizumab was 5 mg/kg every 2 weeks (B-FOLFOX-4) or 7.5 mg/kg every 3 weeks (B-XELOX).

The scope of the manufacturer's cost-effectiveness submission focused on a comparison with regimens containing oxaliplatin which was considered to be the most relevant comparator. A comparison with irinotecan-based chemotherapy was also included for completeness. The manufacturer submitted additional analyses in response to the ERG clarification questions. Further data and analyses were also submitted following the first committee meeting. These included further data on the patient access scheme's (PAS's) operating costs as well as pharmacy and preparation costs for bevacizumab.

Methods

The ERG report comprised a critical review of the evidence for the clinical evidence and cost-effectiveness of the technology based upon the manufacturer's/sponsor's submission to NICE as part of the STA process.

The manufacturer's literature searches were repeated and a narrative critique of the submitted evidence was undertaken. The economic model submitted by the manufacturer was considered structurally adequate to assess the decision problem, but not all of the model inputs were considered satisfactory. Additional work carried out by the ERG focused on conducting sensitivity analyses relating to areas of uncertainty.

Results

Summary of submitted clinical evidence

The manufacturer's main analysis pooled data from the initial two arms and the 2 × 2 factorial part of the NO16966 trial and compared the addition of bevacizumab to chemotherapy with chemotherapy alone. The manufacturer's primary pooled analysis of superiority (using the intention-to-treat population) showed that after a median follow-up of 28 months, the addition of bevacizumab to chemotherapy (B-XELOX/B-FOLFOX-4 combined) significantly improved progression-free survival and overall survival compared with chemotherapy alone (P-XELOX/P-FOLFOX-4/XELOX/FOLFOX-4 combined) in adult patients with histologically confirmed metastatic colorectal cancer who were not previously treated [median progression-free survival 9.4 vs 7.7 months (absolute difference 1.7 months); hazard ratio (HR) 0.79, 97.5% confidence interval (CI) 0.72 to 0.87; $p = 0.0001$; median overall survival 21.2 vs 18.9 months (absolute difference 2.3 months); HR 0.83, 97.5% CI 0.74 to 0.93; $p = 0.0019$].

A secondary pooled analysis of superiority (requested by the ERG as it was believed to be more appropriate) restricted to patients in the second 2×2 factorial part of the NO16966 study as per the original statistical trial plan (B-XELOX/B-FOLFOX-4 combined vs P-XELOX/P-FOLFOX-4 combined) found similar results [median progression-free survival 9.4 vs 8.0 months (absolute difference 1.4 months); HR 0.83, 97.5% CI 0.72 to 0.95; $p = 0.0023$; median overall survival 21.3 versus 19.9 months (absolute difference 1.4 months); HR 0.89, 97.5% CI 0.76 to 1.03; $p = 0.0769$].

The manufacturer's pooled analysis of non-inferiority (using the eligible patient population and the intention-to-treat population) showed that the XELOX (XELOX/P-XELOX/B-XELOX combined) and FOLFOX-4 (FOLFOX-4/P-FOLFOX-4/B-FOLFOX-4 combined) based regimens were equivalent for both progression-free survival and overall survival (*p*-values were stated as not significant, but these values were not reported). No analysis was undertaken for the factorial design (P-XELOX/B-XELOX combined versus P-FOLFOX-4/B-FOLFOX-4 combined).

A pre-defined subgroup analysis on progression-free survival found that the statistical superiority of bevacizumab plus chemotherapy was evident in the XELOX subgroups (B-XELOX vs P-XELOX; HR 0.80, 97.5% CI 0.66 to 0.96; *p*-value not reported) but did not reach the significance level in the FOLFOX-4 subgroups (B-FOLFOX-4 vs P-FOLFOX-4; HR 0.89, 97.5% CI 0.74 to 1.06; *p*-value not reported). Additional post hoc

exploratory analyses, following the results from the Adjuvant Colon Cancer End Points (ACCENT) study,[9] found that there was a significant and direct correlation between time to recurrence after surgery and survival after recurrence in patients whose disease recurred after surgery and adjuvant treatment. Removing the subgroup of patients that may have slower tumour progression after adjuvant treatment (an imbalance between treatment groups with regard to an important prognostic factor that was not recognised at the start of the NO16966 trial) significantly improved (i.e. lowered) the HRs for adding bevacizumab to chemotherapy compared with chemotherapy alone for both overall survival and progression-free survival. Depending on the analyses conducted (e.g. exclusion of patients with prior adjuvant chemotherapy from all four treatment arms of the factorial study, from FOLFOX groups only or from P-FOLFOX group only) the HRs for overall survival ranged from 0.83 to 0.85 ($p < 0.03$) and the HRs for progression-free survival ranged from 0.74 to 0.77 ($p < 0.0001$). Although this may be plausible, the ERG notes that caution should be exercised as this is a post hoc exploratory analysis.

The majority of adverse events were generally associated with cytotoxic chemotherapy. FOLFOX-4-based regimens were generally associated with increased neutropenia/granulocytopenia, and XELOX-based regimens were generally associated with increased diarrhoea and hand and foot syndrome. Adverse events that could be potentially related to bevacizumab included increased frequencies of high blood pressure, proteinuria, bleeding, gastrointestinal perforation, thromboembolic events and wound healing complications. Serious (grade 3) or life threatening (grade 4) adverse events that occurred more commonly in patients receiving bevacizumab plus chemotherapy (B-XELOX/B-FOLFOX-4 combined) than those receiving chemotherapy alone (P-XELOX/P-FOLFOX-4/XELOX/FOLFOX-4 combined) were thromboembolic events (7.8% vs 5.1%, respectively), hypertension (4.0% vs 0.8%, respectively), proteinuria (3.5% vs 0.9%, respectively) and bleeding problems (1.9% vs 1.5%, respectively). Grade 3 and 4 gastrointestinal perforations and wound healing complications were rare (< 1%). Similar results were observed when data were restricted to the factorial analyses.

The rates of discontinuation were higher in the bevacizumab containing groups (B-XELOX/B-FOLFOX-4 combined, 30.8%) than in the no bevacizumab containing groups (P-XELOX/P-FOLFOX-4/XELOX/FOLFOX-4 combined, 25.3%), Corresponding data, restricted to the 2×2 factorial analyses, yielded similar results (B-XELOX/B-FOLFOX-4 combined, 30.8% vs P-XELOX/P-FOLFOX-4 combined, 20.8%). The statistical analysis comparing the rates of discontinuation between treatment groups was not reported in the MS or in the manufacturer's supplementary evidence.

Summary of submitted cost-effectiveness evidence

Cost-effectiveness was estimated using a Microsoft EXCEL model with four states: pre-progression on treatment, pre-progression and post treatment, progressive disease and dead. An area under the curve approach was used to estimate the disease progression of metastatic colorectal cancer patients. The distribution of patients between health states was used to calculate total direct costs and quality-adjusted life-years (QALYs) for each intervention. Costs were considered from an NHS and Personal Social Services perspective. Cost-effectiveness was expressed in terms of incremental cost per QALY with a time horizon of 8 years, which is equivalent to a lifetime horizon in the population of interest. The analysis focused on the interventions B-XELOX and B-FOLFOX. The model was populated with efficacy data from the N016966 trial but as discussed in the clinical effectiveness section these trial data have been analysed in several different ways. Data on treatment duration and dose intensity were also based on the N016966 trial. Survival data were modelled using Kaplan–Meier data up to median survival of 28 months and a Weibull distribution after this point. The ERG requested several changes to the model inputs and modelling assumptions (including additional analyses).

A summary of the key incremental cost-effectiveness ratios (ICERs) included in the submission are presented in *Table 1*. Of the several analyses presented by the manufacturer, the ERG considered the analysis using the 2×2 part of the N016966 trial, with the XELOX and FOLFOX arms pooled, with patients with prior adjuvant treatment excluded to be the most appropriate. This analysis produced ICERs of £36,006 and £31,174 for B-XELOX versus XELOX and B-FOLFOX versus FOLFOX, respectively. The inclusion of patients with prior adjuvant chemotherapy resulted in higher ICERs. Unpooling the XELOX and FOLFOX arms affected the individual XELOX and

TABLE 1 *A summary of ICERs included in the manufacturer's submission (MS)*

Scenario		ICERs (£ per QALY saved)	
		B-XELOX vs XELOX	**B-FOLFOX vs FOLFOX**
MS original analysis			
Without PAS	Analysis using data from all six arms of N016966, XELOX and FOLFOX–4 arms pooled	£82,098	£94,989
With PAS	Analysis using data from all six arms of N016966, XELOX and FOLFOX–4 arms pooled	£34,170	£41,388
MS supplementary data, requested by ERG			
With PAS	Analysis using data from all six arms of N016966, XELOX and FOLFOX–4 arms pooled	£35,912	£36,569
With PAS	Analysis using the 2×2 part of N016966, XELOX and FOLFOX–4 arms pooled	£48,111	£39,771
With PAS	Analysis using 2×2 part of N016966, XELOX and FOLFOX–4 arms unpooled	£35,662	£62,714
With PAS	Analysis using the 2×2 part of N016966, XELOX and FOLFOX–4 arms pooled, without prior adjuvant treatment	£36,006	£31,174
Without PAS	Analysis using data from all six arms of N016966, XELOX and FOLFOX–4 arms pooled, including bevacizumab wastage	£90,945	£98,436
Without PAS	Analysis using the 2×2 part of N016966, XELOX and FOLFOX–4 arms pooled, without prior adjuvant treatment	£92,698	£96,687
Without PAS	Analysis using 2×2 part of N016966, XELOX and FOLFOX–4 arms unpooled	£90,779	£240,324
Without PAS	Analysis using the 2×2 part of N016966, XELOX and FOLFOX–4 arms pooled	£129,911	£134,309
MS additional submission (post first committee meeting)			
With PAS	Analysis using the 2×2 part of N016966, XELOX and FOLFOX–4 arms pooled, without prior adjuvant treatment	£36,494	£31,122

ERG, evidence review group; B-FOLFOX–4, bevacizumab in combination with FOLFOX–4; B-XELOX, bevacizumab in combination with XELOX; FOLFOX–4, intravenous 5-fluorouracil plus folinic acid plus oxaliplatin; ICERs, incremental cost-effectiveness ratios; MS, manufacturer's submission; PAS, patient access scheme; QALY, quality-adjusted life-year; XELOX, oral capecitabine plus intravenous oxaliplatin.

FOLFOX ICERs in different directions. While no systematic review was undertaken with irinotecan as a comparator, a cost-effectiveness analysis was undertaken (data not presented here).

Commentary on the robustness of submitted evidence

Strengths

The NO16966 trial was of reasonable methodological quality (with some limitations) and measured a range of outcomes that were as appropriate and clinically relevant as possible.

The ERG believed that the modelling structure employed was appropriate.

Weaknesses

Despite no evidence to suggest that the statistical validity of the factorial approach was methodologically inappropriate, the validity of simply pooling data from essentially two different study designs (i.e. a two-arm design and a 2×2 factorial design) without accounting for between-study variability is inappropriate. Unweighted (for uncertainty) pooling of results from different studies is not advisable as there are almost certainly differences between trials that, if not accounted

for, are likely to lead to biased estimates of effect. The appropriateness of combining data from the two parts of the study was also questioned by the European Medicines Agency.[10] The resulting pooled data (manufacturer's primary pooled analysis of superiority and non-inferiority) should therefore be treated with caution. Additionally it is unclear whether patients with prior adjuvant chemotherapy should be excluded from the analysis.

The restriction to the trial data from the 2×2 part of the NO16966 study, the pooling of the XELOX and FOLFOX arms, and the restriction to the data of patients without prior adjuvant chemotherapy all had a large impact on the resulting ICERs.

The MS did not make use of the range of utility values identified from the literature review and did not explain why these values were not used. The sources of the utility values used in the MS were poorly referenced, resulting in the ERG being unable to verify them. The distributions used for the utility values in the probabilistic sensitivity analyses (PSA) reflected the uncertainty relating to the specific values used but underestimated the uncertainty relating to the selection of utility values. The ERG noted that using wider distributions for utility values would significantly increase the CIs around the mean ICERs from the PSA, and reducing the utility values by 20% markedly increased the ICERs.

Chemotherapy can be administered intermittently or continuously, but the difference in cost and effectiveness between intermittent and continuous treatment is unclear. Current care in England is often intermittent treatment with chemotherapy, but the trial and the model both represent continuous treatment chemotherapy. It is unclear how this difference may impact the ICERs but, as an example, if intermittent treatment was cheaper than continuous treatment whilst having a similar efficacy, then the ICER for continuous treatment with bevacizumab versus intermittent treatment would be greater than the ICER for continuous treatment with bevacizumab versus continuous treatment.

In clinical practice, treatment with non-oxaliplatin chemotherapy components may continue beyond oxaliplatin cessation although in the N016966 trial this was rarely seen. Because of the structure of the PAS (in which oxaliplatin is received free of charge), the incremental cost of continuing bevacizumab after oxaliplatin cessation is almost three times the incremental cost of adding bevacizumab to oxaliplatin. Hence the impact of continuing bevacizumab treatment on the ICERs could be considerable.

Under the PAS, bevacizumab has a fixed price per cycle, but for calculations without the PAS it is important that drug wastage should be included for both oxaliplatin and bevacizumab. The MS 'without PAS' ICERs did not include drug wastage within the base case although bevacizumab wastage was included within one analysis as stated in *Table 1*. The inclusion of drug wastage resulted in higher ICERs.

Conclusions

The NO16966 trial was of reasonable methodological quality and demonstrated a significant improvement in both progression-free survival and overall survival when bevacizumab was added to XELOX or FOLFOX. However, the size of the actual treatment effect of bevacizumab is uncertain due to the following:

- trial design limitations (two-part study, open-label design)
- imbalance of known prognostic factor (time between primary treatment and recurrence)
- relatively short duration of chemotherapy treatment (approximately 6 months) despite the fact that the trial protocol allowed continuation of the study therapy until progressive disease or unacceptable toxicity
- interpretation of the statistical analyses (pooled analysis of all patients versus analysis by factorial design).

In addition, there was uncertainty around whether bevacizumab treatment should be continued until progression of the underlying disease.

The ERG believed that the modelling structure employed was appropriate, but highlighted several key issues and areas of uncertainty and included the following:

- It is unclear which approach to data analysis (pooling, excluding adjuvant therapy patients, etc.) is most appropriate and the choice of approach has a significant impact on the resulting ICERs.
- Unlike the N016966 trial, in clinical practice chemotherapy may be administered intermittently rather than continuously.

This introduces considerable uncertainty as the differences in cost and efficacy between intermittent and continuous use are not known.
- At the time of writing the decision on whether the proposed PAS scheme would be accepted was unknown. The majority of the analysis presented by the manufacturer included the PAS. Running the model without the PAS resulted in much higher ICERs.
- The efficacy associated with the continuation of treatment with bevacizumab after cessation of oxaliplatin is unknown. However, with the PAS the incremental cost of continuing bevacizumab after oxaliplatin cessation is almost three times the incremental cost of adding bevacizumab to oxaliplatin. Hence bevacizumab treatment post oxaliplatin cessation has the potential to have a significant impact on the resulting ICERs.

Research recommendations

The ERG makes three recommendations for areas requiring further research:

- research into the likely duration of bevacizumab treatment in clinical practice and the survival associated with longer treatment duration
- research into the cost-effectiveness of bevacizumab for patients currently receiving intermittent XELOX or FOLFOX
- finding ways to select patients who will benefit from bevacizumab.

Summary of NICE guidance issued as a result of the STA

At the time of writing, NICE was yet to issue the guidance for this appraisal.

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