

# **Systematic review and economic evaluation of bevacizumab and cetuximab for the treatment of metastatic colorectal cancer**

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## ***Executive summary***

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## Executive summary

### Background

Colorectal cancer (CRC) is the third most commonly diagnosed cancer in the UK. In 2002, there were approximately 30,000 new cases of CRC registered in England and Wales. The probability of developing CRC rises sharply with age. In the younger population, the risk of developing CRC is very low; between the ages of 45 and 49 years, the incidence rate for CRC is approximately 20 per 100,000 for both males and females. Amongst those over 75 years of age, the incidence rate for CRC is over 300 and over 200 per 100,000 per year for males and females, respectively. The median age of patients at diagnosis is over 70 years.

CRC includes cancerous growths in the colon, rectum and appendix. Cancer cells eventually spread to nearby lymph nodes (local metastases) and subsequently to more remote lymph nodes and other organs in the body. The liver and the lungs are common metastatic sites of CRC. CRC is a significant cause of morbidity. The main aims of treatment are to relieve symptoms and to improve health-related quality of life (HRQoL) and survival. In 2003, CRC caused around 14,000 deaths in England and Wales.

The most widely used chemotherapeutic agent for the treatment of CRC is 5-fluorouracil (5-FU) in combination with folinic acid (FA). Within the last decade there have been numerous developments in the treatment of CRC, with the introduction of newer agents such as oxaliplatin, irinotecan and oral fluoropyrimidines. This assessment report evaluates evidence concerning the use of bevacizumab (Avastin<sup>®</sup>) and cetuximab (Erbix<sup>®</sup>) for the treatment of metastatic CRC. Bevacizumab is currently licensed in combination with intravenous 5-FU/FA or irinotecan plus intravenous 5-FU/FA in the first-line treatment of patients with metastatic cancer of the colon or rectum. Cetuximab, used in combination with irinotecan, is indicated for the second- and subsequent-line treatment of epidermal growth factor receptor (EGFR)-expressing metastatic colorectal cancer in patients who are refractory to irinotecan-based chemotherapy. For many of these patients, there are typically no further active treatment options available.

### Objectives

The main aim of this review is to assess the clinical effectiveness and cost-effectiveness of bevacizumab and cetuximab in the treatment of individuals with metastatic CRC.

More specifically, the objectives of the review are:

1. to evaluate the relative clinical effectiveness of bevacizumab and cetuximab in terms of progression-free survival, overall survival, tumour response rates, time to treatment failure and HRQoL compared with current standard therapies
2. to evaluate the adverse effect profiles of bevacizumab and cetuximab
3. to estimate the incremental cost-effectiveness of bevacizumab and cetuximab compared with current standard therapies
4. to estimate the annual cost to the NHS in England and Wales.

### Methods

Searches in nine electronic bibliographic databases identified existing studies relating to the clinical effectiveness of bevacizumab and cetuximab. For the assessment of bevacizumab, trials were included if they recruited participants with untreated metastatic CRC for first-line treatment with bevacizumab. Only trials which compared bevacizumab in combination with irinotecan and/or established fluorouracil-containing or releasing regimens given as first-line therapy were included in this review. For the assessment of cetuximab, trials were included if they recruited participants with EGFR-expressing metastatic CRC who had previously failed irinotecan-including therapy. All identified studies which included cetuximab as a second- or subsequent-line therapy for patients with metastatic CRC who were refractory to irinotecan were included in the review.

The systematic searches did not identify any existing economic evaluations of bevacizumab or cetuximab in the treatment of metastatic CRC; mathematical models were submitted to the National Institute for Health and Clinical



Excellence (NICE) by the manufacturers of bevacizumab and cetuximab. Independent health economic models to assess the cost-effectiveness of bevacizumab and cetuximab were developed by the Assessment Group using survival modelling methods.

## Results

### Results for bevacizumab

Three RCTs were included in the assessment of bevacizumab. All of the trials included within the review of bevacizumab appear to have been reasonably well designed and conducted and, with the exception of one study, appear to have included balanced populations. The main issue of concern is that the population of the Phase III trial is relatively younger than the UK NHS population of CRC patients. One of the Phase II trials, however, included older patients who had a comparatively poorer prognosis, which may better reflect the UK NHS population of CRC patients.

The addition of 5 mg/kg bevacizumab to irinotecan, fluorouracil and leucovorin (IFL) resulted in a statistically significant increase in median overall survival (OS) of 4.7 months ( $p < 0.001$ , primary end-point). The addition of 5 mg/kg bevacizumab to 5-FU/FA resulted in a non-significant increase in median OS of 3.7 ( $p = 0.16$ , primary end-point) within one study and an increase in median OS of 7.7 months within another study ( $p$ -value not reported).

The addition of 5 mg/kg bevacizumab to IFL resulted in a statistically significant increase in median progression-free survival (PFS) of 4.4 months ( $p < 0.001$ ). The addition of 5 mg/kg bevacizumab to 5-FU/FA resulted in a statistically significant increase in median PFS of 3.7 months ( $p = 0.0002$ ) and a statistically significant increase of 3.8 months in time to disease progression compared with FU/FA alone ( $p = 0.005$ , primary end-point).

An overall tumour response rate of 44.8% was reported for 5 mg/kg bevacizumab plus IFL compared with 34.8% for IFL plus placebo ( $p = 0.004$ ) within one study. The addition of 5 mg/kg bevacizumab to 5-FU/FA resulted in a significant difference in tumour response rate within one study ( $p = 0.029$ , primary end-point), but not another ( $p = 0.055$ ).

The addition of bevacizumab to IFL or 5-FU/FA was observed to result in an increase in grade 3/4

adverse events; however, these were generally manageable. None of the studies reported the impact of bevacizumab treatment on HRQoL.

The manufacturer of bevacizumab submitted models relating to the cost-effectiveness and cost-utility of bevacizumab plus IFL versus IFL alone and of bevacizumab plus 5-FU/FA versus 5-FU/FA alone, based on two of the three randomised controlled trials (RCTs) of bevacizumab. Critical appraisal of these models identified problems in the methodology used to estimate OS. The Assessment Group developed health economic models using OS outcomes reported within the publications of the bevacizumab trials. The independent health economic assessment suggests that the cost-effectiveness of bevacizumab plus IFL versus IFL is unlikely to be better than £46,853 per life-year gained (LYG); the cost-utility of bevacizumab plus IFL versus IFL is unlikely to be better than £62,857 per quality-adjusted life-year (QALY) gained. The probability that bevacizumab plus IFL has a marginal cost-utility that is better than £30,000 is close to zero. The cost-effectiveness of bevacizumab plus 5-FU/FA versus 5-FU/FA is unlikely to be better than £84,607 per LYG; the cost-utility of bevacizumab plus 5-FU/FA versus 5-FU/FA is unlikely to be better than £88,658 per QALY gained. The probability that bevacizumab plus 5-FU/FA has a marginal cost-utility that is better than £30,000 is also close to zero.

### Results for cetuximab

No trials met the inclusion criteria for this systematic review. There is no direct evidence to demonstrate whether cetuximab plus irinotecan improves either health-related symptoms or OS in patients with EGFR-expressing metastatic CRC who have previously failed on irinotecan-containing therapy. One Phase II trial and three single-arm studies included cetuximab as a second- or subsequent-line therapy in the treatment of EGFR-expressing patients with metastatic CRC who have previously failed on irinotecan-including cytotoxic therapy. Only one of the three identified single-arm studies evaluated outcomes for patients receiving cetuximab in combination with irinotecan.

The Phase II trial reported median OS duration of 8.6 months for patients receiving cetuximab plus irinotecan. The single-arm study of cetuximab plus irinotecan reported a median OS duration of 8.4 months.

The Phase II trial reported a median time to progression of 4.1 months for patients receiving ►

cetuximab plus irinotecan. The single-arm study of cetuximab plus irinotecan reported a median time to progression of 2.9 months.

The Phase II trial reported a tumour response rate of 22.9% (17.5–29.1%, primary end-point) for patients receiving cetuximab plus irinotecan. The single-arm study of cetuximab plus irinotecan reported a tumour response rate of 15.2% (9.7–22.3%).

The Phase II trial suggested that treatment with cetuximab in combination with irinotecan is associated with significantly more adverse events (any grade 3 or 4 adverse event) than cetuximab monotherapy. Key toxicities include the presence of an acne-like rash, diarrhoea, nausea and vomiting, neutropenia, anaemia and asthenia.

Merck provided an addendum to their full submission to NICE outlining early HRQoL outcomes from the MABEL study. At baseline, the EuroQol 5D instrument (EQ-5D)-assessed utility was 0.73; this level of utility was seen to remain fairly constant while patients receive cetuximab plus irinotecan over the evaluable period. These data suggest that treatment with cetuximab plus irinotecan does not detract from a patient's baseline level of HRQoL as measured by the EQ-5D.

The manufacturer of cetuximab submitted a cost-effectiveness model to NICE based on evidence collected within the Phase II trial of cetuximab plus irinotecan versus cetuximab monotherapy. Further analysis of this model by the Assessment Group highlighted flaws in the methods used to extrapolate survival outcomes beyond the study duration. An independent model was developed by the Assessment Group using more robust survival analysis methods. The Assessment Group model suggests that the expected survival duration of patients receiving cetuximab plus irinotecan is 0.79 years (9.5 months) when the proposed continuation rule is applied. In order to obtain an incremental cost-effectiveness ratio of £30,000 per LYG, treatment with cetuximab plus irinotecan must provide an additional 0.41 life-years (4.9 months) over treatment with active/best supportive care. This implies that survival in the active/supportive care group must be 0.38 years (4.6 months) or less. In order for cetuximab plus irinotecan to achieve a cost per QALY gained of £30,000, treatment with cetuximab plus irinotecan must provide an additional 0.65 life-years (7.8 months) over treatment with active/best supportive care. This implies that survival in the

active/best supportive care group must be 0.14 life-years (1.7 months) or less. Indirect evidence concerning the survival duration of patients without treatment suggests that this magnitude of incremental benefit is unlikely, although there are clear biases in drawing evidence from these sources.

## Conclusions

The trials indicate that bevacizumab in combination with 5-FU/FA and bevacizumab in combination with IFL are clinically effective in comparison with standard chemotherapy options for the first-line treatment of metastatic CRC. The health economic analysis suggests that the marginal cost–utility of bevacizumab plus IFL versus IFL is unlikely to be better than £62,857 per QALY gained and the marginal cost–utility of bevacizumab plus 5-FU/FA versus 5-FU/FA is unlikely to be better than £88,658 per QALY gained.

There is no direct evidence to demonstrate whether cetuximab in combination with irinotecan improves HRQoL or OS in comparison with active/best supportive care or oxaliplatin plus 5-FU/FA, although the evidence on tumour response rates suggests that cetuximab plus irinotecan has some clinical activity. Although it is difficult to suggest whether cetuximab represents value for money, as its comparative efficacy remains unknown, indirect comparisons suggest that the incremental cost–utility of cetuximab plus irinotecan is unlikely to be better than £30,000 per QALY gained.

## Areas for further research

The assessment of bevacizumab and cetuximab highlights a number of areas for further research:

- Further clinical research studies may clarify the true impact of first-line bevacizumab in combination with irinotecan and/or infusional 5-FU/FA, without subsequent bevacizumab treatment following disease progression, on OS in patients with metastatic CRC who are representative of the typical population of CRC patients in England and Wales.
- Clinical evidence suggests that bevacizumab may be effective as a first-line treatment option; there is also clinical evidence outside of the remit of this assessment which suggests that bevacizumab may be an effective second-line treatment option for patients with metastatic

CRC. Further research concerning the optimal role of bevacizumab alongside sequences of oxaliplatin, irinotecan and 5-FU/EA would be valuable. The findings of the TREE-2, the NO16966C trial, the CONcePT trial and the E3200 trial may elucidate this issue.

- Further research concerning the impact of treatment with bevacizumab on HRQoL is essential. This should be undertaken as part of an RCT.
- Further evidence on the specific resource implications associated with bevacizumab would be valuable.
- Further research is required to determine the impact of cetuximab in combination with irinotecan as compared with active/best supportive care in terms of OS and disease-related symptoms. In the absence of such direct evidence, it is difficult to draw robust conclusions on either the clinical effectiveness or cost-effectiveness of cetuximab treatment. However, as there are typically no further treatment options available for many of these patients, and as the BOND study has demonstrated that cetuximab has clinically significant activity in patients with irinotecan-

refractory CRC, such research is unlikely to be considered ethically feasible.

- Further clinical research is required to determine (a) the predictive value of the EGFR testing kit and (b) the correlations between baseline and on-treatment biomarkers with tumour response and survival.
- Further research is required to establish the relationship between the presence of the cetuximab rash, treatment response and their impact upon a patient's HRQoL.
- Research concerning the optimal role of cetuximab alongside existing sequences of chemotherapy is merited. The findings of the COIN trial, the NCT00063141 trial and the BOND-2 and BOND-3 trials may elucidate this issue.

## Publication

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# NIHR Health Technology Assessment Programme

The Health Technology Assessment (HTA) Programme, now part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the costs, effectiveness and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care, rather than settings of care.

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The HTA Programme is needs-led in that it fills gaps in the evidence needed by the NHS. There are three routes to the start of projects.

First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, the public and consumer groups and professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA Programme then commissions the research by competitive tender.

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