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The use of bevacizumab and cetuximab for the treatment of metastatic colorectal cancer

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Responsibility for the report

The views expressed in this report are those of the authors and not necessarily those of the NHS R&D HTA Programme. Any errors are the responsibility of the authors.

Contributions of authors

Suzy Paisley and Chris Carroll undertook the systematic searches. Roy Jones screened the results of the systematic searches. Roy Jones undertook the systematic reviews of clinical effectiveness for bevacizumab and cetuximab. Paul Tappenden critically reviewed the cost-effectiveness models submitted to NICE by the sponsor companies, and undertook the health economic assessments of bevacizumab and cetuximab.

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1. DEFINITION OF TERMS AND LIST OF ABBREVIATIONS

Definition of terms

Metastatic colorectal cancer: Cancer originally located in the colon or rectum that has spread, or metastasised, through either the bloodstream or the lymph node system, to other organs within the body.

Monoclonal antibodies: Monoclonal antibodies are used to try to destroy some types of cancer cells while causing little harm to normal cells. They are designed to recognise certain proteins (receptors) that are found on the surface of particular cancer cells.

Chemotherapy: The use of special anti-cancer (cytotoxic) drugs to destroy cancer cells.

Abbreviations

5-FU	5-fluorouracil
5-FU/FA	5-fluorouracil plus folinic acid, also know as 5-FU/LV
ACRC	Advanced Colorectal Cancer
AIC	Academic In Confidence
ASCO	American Society of Clinical Oncology
BNF	British National Formulary
BSC	Best supportive care
CI	Confidence interval
CIC	Commercial In Confidence
CNS	Central Nervous System
CRC	Colorectal cancer
CRF	Case Report Form
CT	Computerised Tomography
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
EQ-5D	Euroqol 5D
FA	Folinic acid
FAP	Familial adenomatous polyposis
FOLFIRI	Irinotecan + FU
HNPCC	Hereditary non-polyposis colorectal cancer
HRQoL	Health-related quality of life

HUI3	Health Utilities Index (Mark 3)
i.v.	Intravenous
IFL	Irinotecan, fluorouracil, and leucovorin
ITT	Intention to treat
LV	Leucovorin
LYG	Life years gained
MRC	Medical Research Council
NICE	National Institute for Health and Clinical Excellence
OS	Overall survival
PFS	Progression-free survival
PS	Performance status
PSSRU	Personal Social Services Research Unit
QALY	Quality adjusted life year
Q-TWIST	Quality Adjusted Time Without Symptoms of Disease or Toxicity of Treatment
RCT	Randomised Controlled Trial
RECIST	Response Evaluation in Solid Tumours
SEER	Surveillance Epidemiology and End Results
TTO	Time Trade Off
UFT	Tegafur with uracil

2. EXECUTIVE SUMMARY

2.1 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, 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 per 100,000 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 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) and cetuximab (Erbitux) 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 carcinoma of the colon or rectum. Cetuximab, used in combination with irinotecan, is indicated for the second- and subsequent-line treatment of EGFR-expressing metastatic colorectal carcinoma in patients who are refractory to irinotecan-based chemotherapy. Within this subset of patients, there are typically no further active treatment options available.

2.2 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 health-related quality of life (HRQoL) compared with current standard treatments;
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.

2.3 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 Epidermal growth-factor receptor (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 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.

2.4 Results

2.4.1 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 5mg/kg bevacizumab to irinotecan in combination with 5-FU/FA irinotecan, fluorouracil and leucovorin (IFL) resulted in a statistically significant increase in median overall survival of 4.7 months ($p<0.001$, primary endpoint). The addition of 5mg/kg bevacizumab to 5-FU/FA resulted in a non-significant increase in median overall survival of 3.7 ($p=0.16$, primary endpoint) within one study, and an increase in median overall survival of 7.7 months within another study (p-value not reported).

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

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

The addition of bevacizumab to IFL or 5-FU/FA was observed to result in an increase of grade 3/4 adverse events, however these were generally manageable. None of the studies reported the impact of bevacizumab treatment on health-related quality of life.

The manufacturer of bevacizumab submitted models relating to the cost-effectiveness and cost-utility of bevacizumab plus IFL versus IFL alone, and bevacizumab plus 5-FU/FA versus 5-FU/FA alone, based upon two of the three RCTs of bevacizumab. Critical appraisal of these models identified problems in the methodology used to estimate overall survival. The Assessment Group developed health economic models using overall survival 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 LYG; the cost-utility of bevacizumab plus IFL versus IFL is unlikely to be better than £62,857 per 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 £84,396 per LYG; the cost-utility of bevacizumab plus 5-FU/FA versus 5-FU/FA is unlikely to be better than £88,436 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.

2.4.2 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 overall survival 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 overall survival duration of 8.6 months for patients receiving cetuximab plus irinotecan. The single arm study of cetuximab plus irinotecan reported a median overall survival 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 endpoint) 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 grade 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 ***(CIC data removed)*** outcomes from the MABEL trial. ***(CIC data removed)***

The manufacturer of cetuximab submitted a cost-effectiveness model to the National Institute for Health and Clinical Excellence (NICE) based upon 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 life year gained, 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 suggest that this magnitude of incremental benefit is unlikely, although there are clear biases in drawing evidence from these sources.

2.5 Conclusions

The trials indicate that bevacizumab in combination with 5-FU/FA, and bevacizumab in combination with IFL, is clinically effective in comparison to 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 £88,436 per QALY gained.

There is no direct evidence to demonstrate whether cetuximab in combination with irinotecan improves health-related quality of life or overall survival in comparison to 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. Whilst 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.

2.6 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 overall survival in patients with metastatic CRC who are representative of the typical population of CRC patients in the 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/FA 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 health-related quality of life is warranted. This may 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 to active/best supportive care in terms of overall survival 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 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 health-related quality of life.
- 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.

3. BACKGROUND

3.1 Description of underlying health problem

3.1.1 Epidemiology

Colorectal cancer (CRC) is the third most commonly diagnosed cancer in the UK, with around 34,900 new cases registered in the UK in 2002.[1] Approximately 30,000 of these were registered in England and Wales. In the UK, cancer of the large bowel accounts for around 12% of all cancers diagnosed in women, making it the second most common cancer, after breast cancer. In men, CRC the third most commonly diagnosed cancer after prostate and lung cancer, accounting for around 14% of all cancers.

Table 1 shows the estimated number of new cases of CRC in England and Wales.

Table 1 Colorectal cancer: new cases (2002)

Number of new cases	Age bands (years)				All cases
	0-44	45-64	65-74	75+	
England					
Colon cancer	410	3625	4937	8392	17364
Rectal cancer	256	2848	3060	4105	10269
Colorectal cancer	666	6473	7997	12497	27633
Wales					
Colon cancer	27	252	333	567	1179
Rectal cancer	24	210	219	282	735
Colorectal cancer	51	462	552	849	1914
England and Wales					
Colon cancer	437	3877	5270	8959	18543
Rectal cancer	280	3058	3279	4387	11004
Colorectal cancer	717	6935	8549	13346	29547

Source: Office for National Statistics[2] and Welsh Cancer Intelligence and Surveillance Unit[3]

The incidence of CRC is gradually increasing: as with most forms of cancer, the probability of developing CRC rises sharply with age and the UK population is ageing. In the younger population, the risk of developing CRC is very low; between the ages of 45 and 49, the incidence rate for CRC is approximately 20 per 100,000 for both males and females.[4] Amongst those over 75 years of age, the incidence rate for CRC is over 300 per 100,000 and over 200 per 100,000 per year for males and females respectively.[4] The median age of patients at diagnosis is over 70 years.[4]

The Office for National Statistics Longitudinal Study[5] examined patterns of stomach, colorectal and pancreatic cancer across socio-economic groups, i.e. differences for men and women, aged 30 years and over according to their housing tenure and occupational social class. Whilst large socio-economic differences were found for stomach cancer, the pattern of CRC was less clear, with women in more advantaged social groups experiencing higher incidence whilst for men there was no significant association. Between 1986 and 1990, CRC incidence was highest in social class IV/V for women and in social class IIIN and IIIM for men when a recent measure of social class was used. Continued monitoring would be required to observe whether incidence patterns for CRC are changing.

3.1.2 Aetiology

Hereditary, experimental, and epidemiological studies[6,7,8] suggest that CRC results from complex interactions between inherited susceptibility and environmental factors. The two main inherited CRC syndromes are familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer (HNPCC). FAP accounts for less than 1% of all CRC, and is caused by a mutation in the adenomatous polyposis coli (APC) gene. Patients develop multiple adenomatous polyps in the bowel between the ages of 10 to 30 years. These polyps are histologically identical to those in sporadic CRC, however, the large numbers of polyps found in the large bowel amount to almost 100% chance of developing CRC by the age of 40.

HNPCC accounts for 5-10% of all CRC, and is caused by a dominantly inherited alteration in the DNA mismatch repair genes. Tumours tend to develop in the proximal colon and patients with HNPCC are also associated with both synchronous and metachronous tumours. The diagnosis of HNPCC is set out by the 'Amsterdam' criteria.[9†] In general, the risk of developing CRC is greater for people with a family history of the disease,[10] even when no specific genetic syndrome is found. The risk of developing CRC is also raised for patients with a personal history of chronic bowel inflammation or one or more adenomatous polyps as occur in familial adenomatous polyposis and other hereditary conditions.

A diet that is high in red meat and fat and low in vegetables, folate and fibre may increase the risk of CRC.[11] A high intake of animal fat in the diet is linked with an increase in faecal bile acids and neutral steroids, which are degraded by certain anaerobic bacteria to produce carcinogens. Other risk factors associated with colon cancer are lack of physical activity and

† Patients must have at least three family members with colorectal cancer, must have at least two generations affected, one person must have been under 50 years of age at the time of diagnosis, and FAP has been excluded.

family history of the disease. There is some evidence that colon cancer in women may be related to sex hormones or reproductive history.[4]

Sporadic cancers account for around 90% of all CRC. Unless there is a high risk of having an inherited CRC syndrome, the likelihood of developing CRC at a young age is typically very low. It is now a commonly accepted concept that most CRCs develop from pre-existing adenomatous polyps located in the bowel wall.[12,13] Adenomas are particularly common in older age groups, and around one third of people will develop at least one adenoma by the age of 60.[14] Most adenomatous polyps are asymptomatic and remain undiagnosed, and most do not develop into cancer. Indirect evidence suggests the adenoma-carcinoma sequence is typically slow; adenomas may be present for 10 years or more before malignancy develops.[15] The size, histological type, presence of epithelial dysplasia, and the number of adenomas can affect the risk associated with the development to carcinoma. Converse to the slow progression of adenomatous polyps to invasive cancer, small flat adenomas which develop in the muscosa are thought to progress more rapidly.

3.1.3 Pathology

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. A pathology report, made on the basis of tissue taken from a biopsy or surgery, will describe the cell type and grade of the cancer.

Cancer staging systems describe how far cancer has spread through the layers of the intestine, from the innermost lining to outside the intestinal wall and beyond, and attempt to put patients with a similar prognosis and treatment in the same staging group. Staging information is discussed in more detail in Section 3.1.4.

3.1.4 Prognosis

Historically, the most commonly used staging system for CRC has been the Dukes' staging classification, which is useful in defining the extent of and prognosis of CRC. More recently, the Dukes' staging system has been superseded by the more precise TNM (tumour, node, metastasis) staging system.[16] The TNM staging system is useful for surgical purposes, such as providing guidelines on the extent of resection. These two staging systems are described in more detail below.

The Dukes' staging system is a pathological staging based on resection of the tumour and measures the depth of invasion through the mucosa and bowel wall. It does not take into account the level of nodal involvement or the grade of the tumour. The modified Dukes' staging system has four stages, from small and localised (stage A), to spread into surrounding structures (stages B and C) or other parts of the body (stage D).

The TNM staging system is based on the anatomical extent of spread, where, T refers to the extent of the primary tumour, N refers to the extent of nodal metastases and M refers to the presence or absence of distant metastases. Each of these three factors is assigned a number; T indicates the size of the tumour; N indicates which lymph nodes have cancer cells in them and M indicates whether the cancer has spread outside the colon or rectum (see Appendix 1). Table 2 demonstrates how the Dukes' and TNM staging classifications relate to one another, together with estimates of 5-year survival.[17]

Table 2 Staging of colorectal cancer with five-year survival[17]

TNM staging system			Dukes staging system	Five-year overall survival[a]
TIS	N0	M0	-	
T1	N0	M0	A	75%
T2	N0	M0	-	
T3	N0	M0	B	57%
T4	N0	M0	-	
Any T	N1	M0	C	35%
Any T	N2, N3	M0	-	
Any T	Any N	M >= 1	D	12%

[a] Survival estimates taken from Wessex Colorectal Cancer audit, 1999.

The treatment and outlook for CRC depends, to a large extent, on the stage of the cancer. For early cancer, treatment may consist of surgery alone. For more advanced cancers, other treatments such as chemotherapy or radiation therapy may also be required.

The stage of disease is a central determinant of survival duration.[18] The overall 5-year survival rate for individuals with CRC in England is approximately 35%; however, there is evidence of wide variations in treatment and outcomes in Britain.[19] On average patients survive for approximately 3 years following diagnosis.[20]

Individuals with CRC may develop a variety of physical and psychological symptoms which detract from their quality of life; the management of these symptoms typically requires hospital admission.[21] The proportion of patients who present with metastatic CRC (stage D) is uncertain; current estimates range from 20%[22] to 55%.[19] Where surgical removal of the primary tumour is an option, accurate staging remains essential for the appropriate choice of treatment.

Approximately 80% of patients diagnosed with CRC undergo surgical resection.[19] Many have potentially good survival outcomes following surgery (with adjuvant chemotherapy in some cases), but over 50% of those who have undergone surgery with apparently complete macroscopic clearance of their disease will develop recurrence.[23] Without treatment, the median survival of patients with metastatic disease is six to nine months following diagnosis.

The most frequent site of metastases is the liver. In as many as 50% of patients with advanced disease, the liver may be the only site of spread,[22] and for these patients surgery provides the only chance of a cure. Reported 5-year survival rates for resection of liver metastases range from 16% to 48%,[20] which is considerably better than those for systemic chemotherapy. However, reported operative mortality rates range from 0% to 14%, and postoperative complications are common and often serious.[20]

3.1.5 Significance in terms of ill-health (burden of disease)

CRC is a significant cause of morbidity. When treating patients with metastatic CRC, the main aims of treatment are to relieve symptoms, and to improve health-related quality of life (HRQoL) and survival. In 2003, bowel cancer caused around 16,000 deaths in the UK, approximately 14,000 of which were in England and Wales. CRC is a significant cause of premature death (Table 3), with almost half of all cancer-related deaths occurring in the under-75 age group.[24]

Table 3 Mortality due to colorectal cancer 2003

Mortality (2003)		England	Wales
Number of deaths	Males	6,961	512
	Females	6,118	440
	Persons	13,079	952
Age Standardised Rates per 100,000	Males	23.3	27.0
	Females	14.3	15.9
	Persons	18.3	20.8

Statistics: colorectal cancer. *Cancer Research UK* 2005; Available: http://www.cancerresearchuk.org/aboutcancer/statistics/factsheets/

The technologies assessed within this report may confer palliative benefits yet offer no real chance of long-term survival. Since chemotherapy can cause disabling adverse events, the assessment of quality of life outcomes is essential. For this reason, information regarding HRQoL and its relationship with treatment-related toxicity will be given careful consideration.

3.2 Current service provision

3.2.1 National guidelines

In 2000, the NHS Executive published guidelines for the management of CRC in England and Wales, *Improving Outcomes in Colorectal Cancer.* The guidelines summarised contemporary service provision for the diagnosis, treatment and follow-up of patients with advanced CRC.[20]

The National Institute for Health and Clinical Excellence (NICE) has issued guidance on the use of 5-fluorouracil (5FU) with folinic acid (FA), irinotecan, oxaliplatin, raltitrexed, capecitabine and tegafur with uracil (UFT) for the treatment of metastatic CRC.[25,26] In August 2005, NICE extended the recommendations for the use of irinotecan and oxaliplatin from the original guidance.[27] A brief timeline of NICE guidance on the use of cytotoxic treatments for advanced/metastatic CRC is given below.

- March 2002 – Colorectal cancer (advanced) – irinotecan, oxaliplatin and raltitrexed (No. 33)[25]
- May 2003 – Colorectal cancer – capecitabine and tegafur uracil (No. 61)[26]
- August 2005 – Colorectal cancer - irinotecan, oxaliplatin and raltitrexed (update of previous guidance) (No. 93)[27]

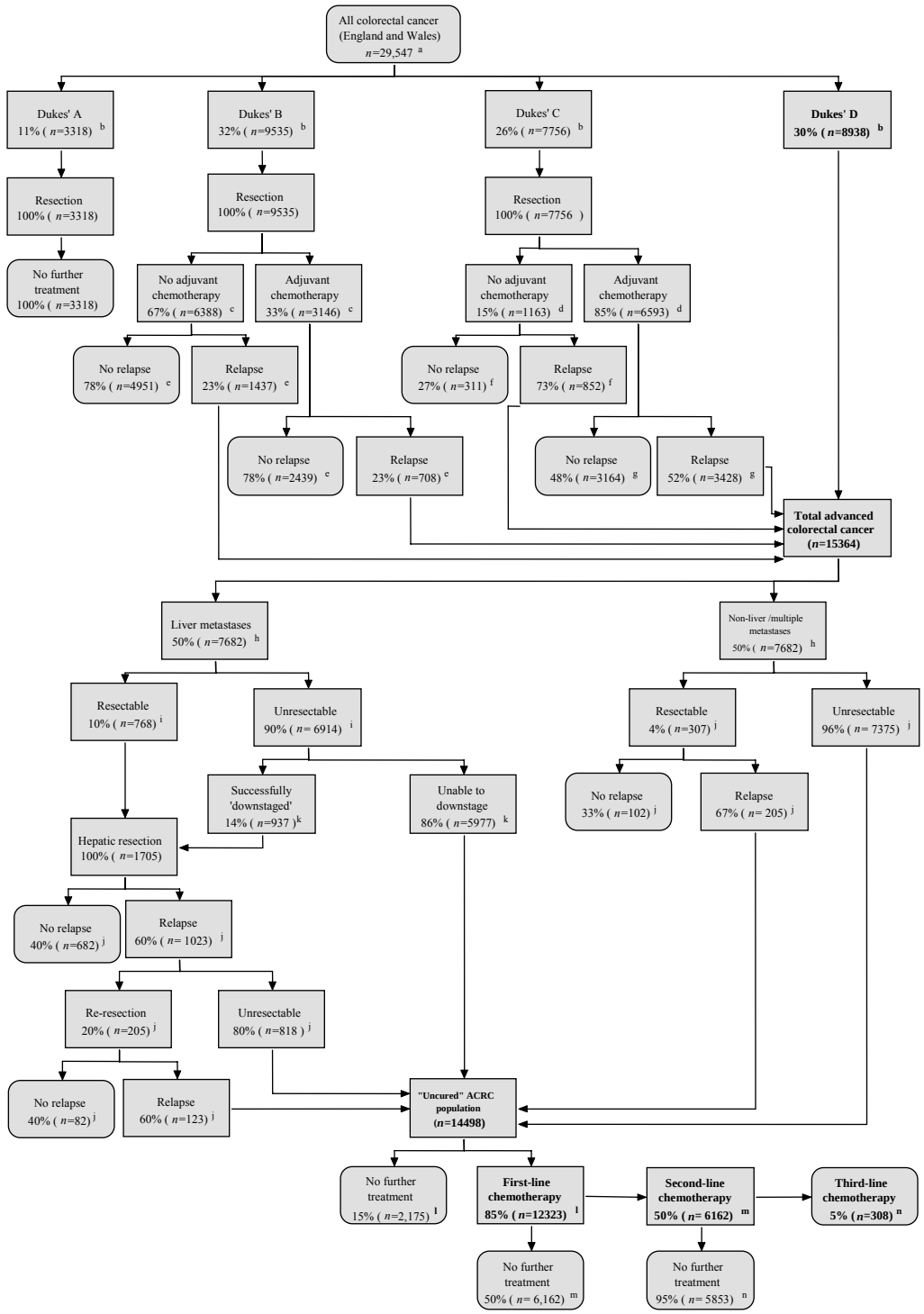
The extended NICE guidance recommended irinotecan and oxaliplatin as treatment options for people with advanced CRC within the following indications: irinotecan in combination with 5-FU and FA as first-line therapy, or irinotecan alone in subsequent therapy, oxaliplatin in combination with 5-FU and FA as first-line or subsequent therapy.

In 2003, NICE recommended oral therapy using either capecitabine or tegafur with uracil (in combination with FA) as an option for the first-line treatment of metastatic CRC.[26] The choice of the regimen (5-FU/FA or oral treatment) should be made jointly by the individual and the clinician(s) responsible for treatment.

3.2.2 Current service cost

A treatment algorithm developed by researchers at the School of Health and Related Research, University of Sheffield, as shown in Figure 1, puts forward the various treatment pathways for patients with all stages of CRC. This algorithm should be considered as illustrative of scale of the service. The treatment pathways model suggests that approximately 12,300 patients with metastatic disease undergo first-line treatment with one or more cytotoxic agents (excluding chemotherapy for down-staging). Currently, fewer patients with metastatic disease are thought to undergo second-line and third-line chemotherapy treatment (around 6,200 patients and 300 patients respectively). It has been estimated that the total cost to the NHS for surgical, adjuvant and palliative treatment is in excess of £300 million per year for all CRC.[28,27]

Figure 1 Treatment algorithm for people with colorectal cancer in England and Wales



[a] Office for National Statistics,[29] Welsh Cancer Intelligence and Surveillance Unit;[30] [b] South West Cancer Intelligence Service;[31] [c] personal communication, Dr Matt Seymour, Leeds Teaching Hospitals NHS Trust: between 33% and 60% of people with Dukes' B cancer receive adjuvant chemotherapy (we have assumed the lower estimate); [d] personal communication, Dr Seymour: more than 85% receive adjuvant chemotherapy; [e] personal communication, Dr Seymour: 20-25% of patients with Duke's B will relapse; [f] Relative risk increase applied to five-year disease-free survival estimates from X-ACT study;[32] [g] five-year disease-free survival estimates

from X-ACT study;[32] [h] personal communication, Professor Tim Maughan, Velindre Hospital, Cardiff; [i] data from case series[33] suggest up to 20% may be resectable, although this is an aggressive stance; a maximum of 15% of patients are suitable (personal communication, Professor Maughan); [j] personal communication, Mr Graeme Poston, Royal Liverpool University Hospital; [k] data from case series;[33] [l] personal communication, Dr Seymour: 85-90% of advanced patients receive chemotherapy; [m] preliminary data from FOCUS trial;[34] [n] personal communication, Dr Rob Glynne Jones, Watford and Barnet General Hospitals, London: only 3-5% patients would receive third-line therapy.

3.3 Summary of interventions

The most widely used chemotherapeutic agent for the treatment of CRC is the antimetabolite fluorouracil (5-FU). This fluoridated pyrimidine was synthesised in the late 1950s and has been the cornerstone of medical treatment for CRC for the last four decades. Current standard practice is to use 5-FU in combination with calcium folinate (calcium leucovorin - LV/folinic acid - FA).

Within the last decade there have been developments in the treatment of CRC, with the introduction of newer agents such as oxaliplatin, irinotecan and the oral fluoropyrimidines. Recently, novel chemotherapeutic agents which target specific abnormalities in the pathway of carcinogenesis such as cetuximab and bevacizumab have demonstrated potential benefit. This section provides a brief overview of some of the current chemotherapy options for the treatment of metastatic CRC. The key overall survival outcomes and progression-free survival outcomes from the earlier assessment of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced CRC[27] are presented in Appendix 2.

3.3.1 Best Supportive Care (BSC)

Supportive care has traditionally been given to improve the comfort of patients and their ability to function, as well as to lessen the adverse effects of anti-cancer treatments. However, the scope of modern comprehensive supportive care is broadening and can cover not only specific palliative treatment but non-tumour specific treatment such as social, psychological and spiritual support. In oncology, best supportive care (BSC) has been used as a comparator arm for several randomised controlled trials of chemotherapy. However the BSC arm is usually not well defined and its evaluation is difficult due to the heterogeneity between definitions.

BSC can be defined as the best palliative care available, as judged appropriate by the investigator, and could include antibiotics, analgesics, radiation therapy for pain control (limited to bone metastases), corticosteroids, transfusions, psychotherapy, growth factors, palliative surgery, or any other symptomatic therapy as clinically indicated.[35]

3.3.2 5-FU

5-FU works by stopping cancer cells from duplicating their DNA, which means the cells cannot grow and are eventually killed. 5-FU is usually administered by intravenous injection or infusion, and is licensed for use in monotherapy or combination therapy in the first- or second-line management of advanced CRC. The most commonly used bolus and infusional 5-FU regimens are detailed in Table 4.[27]

5-FU is licensed for use as monotherapy or combination therapy in the first- or second-line treatment of advanced CRC. Patients with a WHO performance status greater than 2 (confined to bed, see Appendix 3) would usually be deemed unsuitable for chemotherapy; these patients may instead receive BSC.[36] 5-FU does not have a cumulative dose limit, and in some countries it is standard practice to continue treatment until disease progression.[21] Approximately 60% of patients with advanced CRC have either a tumour response or a period of stable disease with first-line 5-FU-based therapy, but in all cases this is temporary as patients develop resistance to the drug. The remaining 40% of patients have disease which is refractory to 5-FU. Both groups have a very poor prognosis. Second-line therapy is considered both for those patients who do not respond to first-line 5-FU-based therapy ("primary non-responders") and for those who initially respond to therapy when the disease eventually but inevitably progresses. In some cases, patients who are disease resistant to bolus 5-FU may respond to infusional 5-FU; this has led to the use of infusional 5-FU regimens as second-line therapy, but tumour response rates are usually low.[37] In most studies, median overall survival for people with advanced CRC treated with 5-FU is consistently between ten and twelve months.[38]

Table 4 Comparison of key 5-FU regimens[27]

Regimens	Description
Bolus schedules	
Mayo Clinic[39]	Monthly for 5 days with low-dose FA (5-FU 425 mg/m^2; FA 20 mg/m^2)
Machover[40]	Monthly for 5 days with high-dose FA (5-FU 400 mg/m^2; FA 200 mg/m^2 over 2 h by infusion)
Roswell Park[41]	Weekly (5-FU 500 mg/m^2; FA 500 mg/m^2 over 2 h by infusion)
Infusional schedules	
Lokich[42]	Protracted infusion (5-FU 300 mg/m^2)
De Gramont[43]	48-h both bolus and continuous infusion bimonthly (5-FU 400 mg/m^2 bolus, 600 mg/m^2 c.i. over 22 h, FA 200 mg/m^2 over a 2-h infusion day 1 and 2 before 5-FU)
Modified de Gramont[44](MdG)	48-h both bolus and continuous infusion bimonthly (5-FU 400 mg/m^2 bolus, 2800 mg/m^2 c.i. over 46 h, FA 175 mg/m^2 over a 2-h infusion day 1 before 5-FU)
Grupo Espanol para el Tratamiento de Tumores Digestivos (TTD)[45]	48-h infusion weekly (5-FU; 3000 mg/m^2)
Arbeitsgemeinschaft Internistische Onkologie (AIO)[46]	24-h infusion weekly (5-FU 2600mg/m^2; FA 500mg/m^2)
Chronomodulated delivery[47]	5-FU 700 mg/m^2; FA 300 mg/m^2/day, peak delivery rate at 04:00 a.m. for 5 days

3.3.3 Irinotecan

Irinotecan is a camptothecin analogue; it is an inhibitor of topoisomerase I (an enzyme responsible for the unwinding of DNA during DNA replication, thus essential for cell division). It is currently indicated for, *"the treatment of patients with advanced colorectal cancer: in combination with 5-FU/FA in patients without prior chemotherapy for advanced disease; as a single agent in patients who have failed an established 5-FU containing treatment regimen."*[48]

At the time of writing, NICE guidance recommends as an option, the use of irinotecan in combination with 5-FU and FA as first-line therapy, or irinotecan alone in subsequent therapy for patients with advanced CRC.[27]

Irinotecan hydrochloride may result in a raised plasma-bilirubin concentration. Patients receiving irinotecan should be monitored closely for neutropenia if their plasma-bilirubin concentration is up to 1.5 times the upper limit of the normal range.[49] Irinotecan is contraindicated in those with chronic inflammatory bowel disease, bowel obstruction, or a plasma bilirubin concentration more than 1.5 times the upper limit of reference range. It is also contraindicated in pregnant women. Women should avoid conception for at least 3

months after cessation of treatment and breast-feeding should be discontinued. In addition to dose-limiting myelosuppression, adverse effects of irinotecan include acute cholinergic syndrome (with early diarrhoea), gastro-intestinal effects (delayed diarrhoea requiring prompt treatment may follow irinotecan treatment), asthenia, alopecia, and anorexia.[49]

The recommended dose in first-line combination therapy is 180mg/m^2 administered as an intravenous (i.v.) infusion every two weeks over 30-90 minutes, followed by 5-FU infusion, and in second-line monotherapy is 350mg/m^2 as an i.v. infusion over 30-90 minutes every three weeks.[50]

3.3.4 Oxaliplatin

Oxaliplatin is a third generation platinum cytotoxic compound. It is licensed in the UK, *"in combination with 5-fluorouracil (5-FU) and folinic acid (FA) and is indicated for: adjuvant treatment of stage III (Duke's C) colon cancer after complete resection of primary tumour; treatment of metastatic colorectal cancer."*[51]

The guidance issued by NICE in March 2002 recommended that oxaliplatin, in combination with 5-FU/FA, may be considered as an option for the first-line treatment of advanced CRC only in patients with metastases which are confined to the liver and which could be resected following a response to treatment. The review of the March 2002 guidance recommended the use of oxaliplatin in combination with 5-FU and FA as an option for first-line or subsequent therapy.[27]

Clinicians are cautioned that oxaliplatin can lead to renal failure: the manufacturer recommends avoiding its use if cretanine clearance is less than 30 ml/minute. It is contraindicated in peripheral neuropathy with functional impairment. The manufacturer recommends that oxaliplatin is not used in pregnant women and that breast-feeding be discontinued. Neurotoxic adverse effects (including sensory peripheral neuropathy) are dose-limiting. Other adverse events include gastro-intestinal disturbances, ototoxicity, and myelosuppression. Manufacturers advise renal function monitoring in moderate impairment. The approved dose is 85mg/m2 every two weeks by i.v. infusion over 2-6 hours prior to the administration of 5-FU.

3.3.5 Tegafur with uracil (UFT)

Tegafur/uracil is a combination of tegafur (an oral form of 5-FU) and uracil (a competitive inhibitor which inhibits the degradation of 5-FU, resulting in sustained higher levels of 5-FU

in tumour cells) in a 1:4 molar ratio.[52] Tegafur is a 5-FU prodrug, meaning that after administration it is metabolised into the pharmacologically active compound 5-FU. When tegafur is given in combination with uracil, FA is usually added to the tegafur and uracil (UFT) combination to act as a modulator. These drugs can be taken orally. The side effects of UFT are similar to those with 5-FU, including myelosuppression, asthenia, diarrhoea, mucositis, asthenia and rash. UFT is indicated as first-line treatment of metastatic CRC, in combination with calcium folinate in adults.

In 2003 NICE recommended that oral therapy with UFT (in combination with FA) may be used in the first-line treatment of metastatic bowel cancer, as an alternative to intravenous 5-FU/FA regimens.[26] The recommended dose of UFT is tegafur 300 mg/m^2 (with uracil 672 mg/m^2) daily, combined with oral FA 90 mg/day, given in three divided doses (preferably every 8 hours) for 28 days. Subsequent courses are repeated at 7-day intervals, giving a treatment cycle of 35 days.

3.3.6 Capecitabine

Capecitabine, another 5-FU pro-drug, is absorbed intact through gastrointestinal mucosa and is metabolised in the liver to 5-deoxy-5-fluorocytosine and in turn to doxifluridine. Doxifluridine is then converted by the enzyme thymidine phosphorylase, which is found in high concentration in tumour tissue, to 5-FU.[53] Adverse effects include diarrhoea, abdominal pain, nausea, stomatitis and hand-foot syndrome. Capecitabine is indicated for first-line monotherapy of metastatic CRC.

In 2003, NICE recommended capecitabine as an option for first-line monotherapy of metastatic CRC.[26] The recommended dose of capecitabine is 1250 mg/m^2 twice daily for 14 days, followed by a 7-day rest period before another cycle of treatment.

3.3.7 Raltitrexed

Raltitrexed inhibits the enzyme thymidylate synthase, which is involved in DNA synthesis; this is the same enzyme that 5-FU targets. Raltitrexed is licensed in the UK for the palliative treatment of advanced CRC where 5-FU/FA based regimens are either not tolerated or inappropriate.

Current NICE guidance states that raltitrexed is not recommended for the treatment of patients with advanced CRC. The use of raltitrexed within this patient group should be

confined to appropriately designed clinical studies.[27] The recommended dose of raltitrexed is 3 mg/m2 given intravenously as an intravenous infusion over 15 minutes every 3 weeks.

3.3.8 Mitomycin C

Mitomycin is an antineoplastic medication. Mitomycin interferes with the growth of cancer cells and slows their growth and spread in the body. Mitomycin is one of the older chemotherapy drugs, and has been in use for decades. It is an active medicine against many cancers. Mitomycin is a purple colour powder, or liquid, and is given by intravenous route only.

There are numerous dosing schedules which depend on disease, tumour response and concomitant therapy. Dosage may be reduced and/or delayed in patients with bone marrow depression due to cytotoxic/radiation therapy. Examples for adults are show below.
Intravenous: q4-8w: 10-20 mg/m2 q6-8w: 2 mg/m2/day x 5 days, stop x 2 days, repeat x 1
Intravesical: q1w: 20-40 mg in 30-60 ml SWI x 8 weeks.

3.4 Description of new interventions

3.4.1 Bevacizumab (Avastin®, Roche)

Bevacizumab (Avastin) is a recombinant humanised monoclonal antibody that targets vascular endothelial growth factor (VEGF). It is thought that bevacizumab inhibits angiogenesis (the formation of new blood vessels) by binding to VEGF. Bevacizumab is thought to improve survival when used in combination with chemotherapy for the first-line treatment of metastatic CRC. Bevacizumab is used to treat cancer of the colon or rectum that has spread to other parts of the body. Bevacizumab is currently licensed in combination with intravenous 5-fluorouracil/folinic acid or intravenous 5-fluorouracil/folinic acid/irinotecan in the first -line treatment of patients with metastatic carcinoma of the colon or rectum. Bevacizumab is subject to the following contraindications:[54]

- Hypersensitivity to the active substance or to any of the excipients.
- Hypersensitivity to Chinese hamster ovary (CHO) cell products or other recombinant human or humanised antibodies.
- Pregnancy.
- Avastin is contraindicated in patients with untreated CNS metastases

Special warnings and precautions for use include: gastrointestinal perforations, wound healing complications, hypertension, proteinuria, arterial thromboembolism, haemorrhage, congestive heart failure (CHF)/cardiomyopathy.[54] Further information on contraindications, special

warnings and precautions for use are available from http://www.emea.eu.int/. Bevacizumab must be administered under the supervision of a clinician experienced in the use of antineoplastic medicinal products.[49] It is recommended that bevacizumab treatment is continued until progression of the underlying disease. The recommended dose of bevacizumab is 5 mg/kg of body weight given once every 14 days as an intravenous infusion. Dose reduction of bevacizumab for adverse events is not recommended. Bevacizumab should not be administered as an intravenous push or bolus.

3.4.2 Cetuximab (Erbitux®, Merck Pharmaceuticals)

Cetuximab (Erbitux) is a monoclonal antibody that targets a protein called the epidermal growth factor receptor (EGFR). EGFR is found on the surface of some cells, and plays a role in regulating cell growth. Erbitux is believed to interfere with the growth of cancer cells by binding to EGFR so that the normal epidermal growth factors cannot bind and stimulate the cells to grow. Over-expression of EGFR is common in many solid tumours, such as colorectal and lung carcinomas as well as cancers of the head and neck. It correlates with increased metastasis, decreased survival and a poor prognosis. EGFR protects malignant tumour cells from the cytotoxic effects of chemotherapy and radiotherapy, making these treatments less effective.

There is no universal method for evaluating EGFR expression, and the relationship between expression level and prognosis is unclear. It is of particular interest in the clinical setting whether EGFR expression levels can predict the response to therapy. Receptor expression cannot be assumed to predict response because the EGFR signaling network is comprised of a complex series of interconnecting pathways and each component is likely to affect the level of EGFR signaling output.[55]

Cetuximab, used in combination with irinotecan is indicated for the treatment of EGFR-expressing metastatic colorectal carcinoma in patients who are refractory to irinotecan-based chemotherapy. Within this subset of patients, there are typically no further active treatment options available. Guidance from the British National Formulary[50] states that resuscitation facilities should be available and a specialist should initiate treatment. Erbitux is contraindicated in patients with known severe (grade 3 or 4) hypersensitivity reactions to cetuximab.[54] Special warnings and precautions for use include: hypersensitivity reactions, dyspnoea, and skin reactions.[54] Only patients with adequate renal and hepatic function have been investigated to date (serum creatinine $\leq$ 1.5fold, transaminases $\leq$ 5fold and bilirubin $\leq$ 1.5fold the upper limit of normal). Cetuximab has not been studied in patients presenting with one or more of the following laboratory parameters:[54]

- haemoglobin < 9 g/dl
- leukocyte count < 3000/mm³
- absolute neutrophil count < 1500/mm³
- platelet count < 100000/mm³

The safety and effectiveness of cetuximab in paediatric patients have not been established.

There is limited experience in the use of cetuximab in combination with radiotherapy in colorectal cancer.[54] Further information on contraindications, special warnings and precautions for use are available from http://www.emea.eu.int/.

4. DEFINITITION OF THE DECISION PROBLEM

4.1 Decision problem

The assessment addresses the question *"What is the clinical effectiveness and cost-effectiveness of bevacizumab and cetuximab for the treatment of metastatic colorectal cancer?"* The clinical effectiveness and cost-effectiveness of bevacizumab (Avastin) in combination with 5-FU/FA or irinotecan plus 5-FU/FA are assessed in comparison to 5-FU/FA and irinotecan plus 5-FU/FA respectively. The clinical effectiveness and cost-effectiveness of cetuximab (Erbitux) in combination with irinotecan are assessed in comparison to oxaliplatin in combination with infusional 5-FU/FA, or active/best supportive care alone.

Whilst the clinical effectiveness and cost-effectiveness of bevacizumab and cetuximab are both assessed within this report, these are not competing therapies and are indicated for different lines of treatment and different patient populations. Therefore, bevacizumab and cetuximab are not compared against each other; instead the assessment focuses on differences between these therapies and their current relevant comparators in terms of overall survival, progression-free survival, tumour response rates, time to treatment failure, adverse events and toxicity, as well as any significant impacts that such treatments may have on health-related quality of life (HRQoL).

4.1.1 Interventions to be assessed

Two interventions are assessed within the review in accordance with their licensed indications. These are:

(1) First-line therapy using bevacizumab in combination with 5-FU/FA or 5-FU/FA plus irinotecan
(2) Second- or subsequent-line therapy using cetuximab in combination with irinotecan

4.1.2 Populations

The relevant population for the assessment of bevacizumab is people with untreated metastatic CRC. The relevant population for the assessment of cetuximab is people with EGFR-expressing metastatic CRC who have previously failed on irinotecan-including therapy.

4.1.3 Relevant comparators

The relevant comparators for bevacizumab are established fluorouracil-containing or releasing regimens given as first-line therapy. The relevant comparators for cetuximab are oxaliplatin in combination with infusional 5-FU/FA, or active/best supportive care alone given as second- or subsequent-line therapy.

4.1.4 Key outcomes

Bevacizumab and cetuximab are assessed in terms of the following outcomes:

- Overall survival
- Progression-free survival
- Tumour response rates
- Time to treatment failure
- Adverse events/ toxicity
- Health-related quality of life
- Cost-effectiveness and cost-utility

4.2 Aims and objectives of the review

The main aim of this review is to assess the clinical effectiveness and cost-effectiveness of bevacizumab (Avastin) and cetuximab (Erbitux) in the treatment of individuals with metastatic colorectal cancer.

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 health-related quality of life (HRQoL) compared with current standard treatments;
(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 overall cost to the NHS in England and Wales.

This assessment does not include evidence concerning the use of bevacizumab or cetuximab in the adjuvant treatment of CRC.

5. CLINICAL EFFECTIVENESS

5.1 Methods for reviewing effectiveness

This systematic review of clinical effectiveness were undertaken according to the recommendations of the Quality of Reporting of Meta-analyses (QUOROM) statement.[56]

5.1.1 Search strategy

The searches aimed to identify all literature relating to the clinical effectiveness and cost-effectiveness of bevacizumab and cetuximab in the treatment of metastatic CRC (Appendix 4). The main searches were conducted in April and May 2005. No language, study/publication, or date restrictions were applied to the main searches. Searches were performed in Medline, Embase, CINAHL, BIOSIS, the Cochrane Database of Systematic Reviews (CDSR), the Cochrane Controlled Trials Register (CCTR), the Science Citation Index and the NHS Centre for Reviews and Dissemination databases (DARE, NHS, EED, HTA) and OHE HEED.

5.1.2 Inclusion and exclusion criteria

Phase III and Phase II randomised controlled trials (RCT) were included if they compared any of the proposed interventions with existing recommended comparators. Primary outcomes were identified as overall survival and/or progression-free survival. Secondary outcomes were identified as health-related quality of life, tumour response rates and adverse events. The use of data from Phase II studies and non-randomised studies was considered only where there was insufficient evidence from good quality Phase III trials, the former being studies appropriately powered to assess efficacy outcomes, rather than those directly associated with clinical effectiveness, and both being subject to selection bias.

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. The scope of this assessment was to compare treatment with cetuximab plus irinotecan as second- or subsequent-line therapy against oxaliplatin in combination with 5-FU/FA or active/best supportive care**. It should be noted from the outset that no randomised or non-**

randomised studies of cetuximab met the inclusion criteria for this review. Therefore, all 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 review of cetuximab is not a typical systematic review of clinical effectiveness, but rather represents a comprehensive and wide review of the current state of knowledge on the clinical effectiveness of cetuximab in the second- and subsequent-line treatment of patients with metastatic CRC.

Only trials which reported at least one of the primary outcomes, overall survival (OS) or progression-free survival (PFS) were included in the review. Survival duration was defined as the interval from randomisation to death. PFS was defined as the interval from randomisation to disease progression or death during the study. Disease progression was defined according to the Response Evaluation Criteria in Solid Tumors (RECIST).[57] For patients alive and without disease progression at the time of analysis, PFS was censored at the time of analysis. Secondary outcomes, tumour response rates, toxicities and health-related quality of life, were extracted where reported. Tumour response rates were defined as the number of patients in each group who achieved a partial or complete response, however defined. Toxicities and quality of life data were abstracted as reported, however defined.

A flow chart describing the process of identifying relevant literature can be found in Appendix 5.

5.1.3 Validity assessment

Published papers were assessed according to the accepted hierarchy of evidence, whereby meta-analyses of RCTs are considered to be the most authoritative forms of evidence, and expert opinion is considered to be the least authoritative. Two researchers assessed papers, in order to give a narrative assessment of the potential for bias in the studies and, in the event that statistical synthesis (meta-analysis) was appropriate, to inform sensitivity analysis. A table summarising data on quality assessment can be found in Appendix 6.

5.1.4 Data abstraction

All abstracts were read and those studies which met the inclusion criteria were identified. Data from identified studies, reviews and other evidence were extracted by the reviewer using a standardised data extraction form. The data extraction form used within this review is presented in Appendix 7.

5.1.5 Analysis

Results of eligible studies were to be statistically synthesised (meta-analysed) for trials with similar populations, interventions and outcomes. However, meta-analysis was not undertaken within the systematic review of bevacizumab as the populations and control treatments used within the included trials differed. Owing to the paucity of evidence on the effectiveness of cetuximab in combination with irinotecan in the treatment of patients with EGFR-expressing CRC who are refractory to irinotecan, meta-analysis was not undertaken. It was stated prospectively, that sub-group analyses would be performed on the basis of whether 5-FU/FA was delivered by bolus injection or continuous infusion. This is because it is widely believed that there is a systematic difference in treatment effect based on the mode of delivery which is likely to interact in different ways with the new interventions under evaluation.

5.2 Results: The clinical effectiveness of bevacizumab in the first-line treatment of patients with metastatic CRC

5.2.1 Quantity and quality of research available

5.2.1.1 Number of studies identified

The search retrieved seven citations for studies of bevacizumab as first-line therapy for people with metastatic CRC.

5.2.1.2 Number and type of studies included

Of the seven citations identified, three were RCTs,[58,59,60] one was a combined study of efficacy data from these three RCTs,[61] and three were abstracts[62,63,64] presented at the American Society of Clinical Oncology (ASCO) general meetings. Only the three RCTs identified were included in the assessment of clinical effectiveness. The combined analysis of efficacy data and the three additional abstracts were used to present a more complete overview of bevacizumab as first-line therapy for metastatic CRC. Study information is reported in Section 5.2.1.3.

5.2.1.3 Number and type of studies excluded, with reasons for specific exclusions

A flow chart which details the number of studies included in the review is presented in Appendix 5, as recommended by the QUOROM statement.[56] Justification of all studies which were identified as full papers but subsequently excluded from the review are detailed in Appendix 8.

5.2.1.4 Quality and characteristics of identified studies of bevacizumab in the first-line treatment of metastatic CRC

Of the seven citations identified, the three RCTs were included in the assessment of the clinical effectiveness of bevacizumab in the first-line treatment of metastatic CRC, whilst the three abstracts and the combined efficacy analysis were used to present a comprehensive overview of the effectiveness of bevacizumab. Table 5 displays summary information of all seven citations.

Table 5 First-line bevacizumab: summary information of included studies

Study	Year	Study type	Publication	Intervention	Comparator
Hurwitz et al AVF2107g[58]	2004	Phase III RCT	Journal article	IFL plus Bevacizumab 5-FU/FA plus bevacizumab (for safety evaluation)	IFL
Kabbinavar et al AVF0780g[59]	2003	Phase II RCT	Journal article	5-FU/FA plus bevacizumab	5-FU/FA
Kabbinavar et al AVF2192g[60]	2005	Phase II RCT	Journal article	5-FU/FA plus bevacizumab	5-FU/FA plus placebo
Giantonio et al E2200[63]	2003	Phase II trial	Abstract	IFL plus bevacizumab	None
Giantonio et al E2200[62]	2004	Phase II trial	Abstract	IFL plus bevacizumab	None
Mass et al[64]	2004	Combined analysis	Abstract	5-FU/FA plus bevacizumab	5-FU/FA or IFL
Kabbinavar et al[61]	2005	Combined analysis	Journal article	5-FU/FA plus bevacizumab	5-FU/FA or IFL

One multicentre, international (United States, Australia and New Zealand) Phase III RCT was retrieved which compared first-line bevacizumab plus irinotecan, fluorouracil and leucovorin (IFL) compared with IFL and placebo; this was study AVF2107g.[58] Within this study, patients could also be allocated to a third treatment arm of bevacizumab plus 5-FU/FA; recruitment to this treatment group was discontinued after the safety of adding bevacizumab to irinotecan plus 5-FU/FA was confirmed within a pre-planned interim analysis.

Two multicentre Phase II RCTs were retrieved which compared first-line bevacizumab in combination with 5-FU/LV against 5-FU/LV alone[59] or with 5-FU/LV plus placebo.[60] Both studies were reported by Kabbinavar and colleagues. In order to avoid confusion, these trials are hereafter referenced using the study identification numbers. The earlier study reported by Kabbinavar et al in 2003 was study AVF0780g.[59] The later study reported by Kabbinavar et al in 2005 was study AVF2192.[60]

Within all three studies, chemotherapy was delivered by bolus injection.[58,59,60] The Phase III trial AVF2107g[58] was a large multicentre study whilst the Phase II trials AVF0780g[59] and AVF2192g[59,60] were small multicentre studies. Mature results from all three of these trials have been reported in peer-reviewed journal articles.[58,59,60]

The Phase III trial[58] and two Phase II trials[59,60] met the inclusion criteria to address relevant comparisons, established fluorouracil-containing or releasing regimens given as first-line therapy. The inclusion criteria employed within two of the studies included in this review of clinical effectiveness, AVF2107g [58] and study AVF0780g,[59] stated that patients must be at least 18 years old. Within study AVF2192g,[60] patients had to be aged 65 years or above, or have an ECOG performance status of 1 or 2, or serum albumin ≤3.5g/dL, or have had prior abdominal/pelvic radiotherapy (see Table 6). Where reported, the mean age of the bevacizumab treatment arms across the studies was 59.2 years for the AVF2107g study[58] and 71.3 years for the study AVF2192g.[60] This suggests that study AVF2192g[60] presents a substantially older population than the AVF2107g trial.[58] However this study is a closer representation of the NHS population of patients with CRC, whereby the median age is over 70 (see Section 3.1.1). It should also be noted that patients enrolled in study AVF2192g were deemed by their treating physician to be sub-optimal candidates for first-line irinotecan-containing therapy, either because of a low likelihood of benefit or a high likelihood of treatment-associated toxicities.[60]

Two abstracts presented at ASCO general meetings by Giantonio[62,63] reported results from the Eastern Cooperative Oncology Group (ECOG) study E2200. The E2200 study was a single arm Phase II study of bevacizumab added to IFL in previously untreated patients with measurable advanced CRC. The study recruited 92 patients over a 12-month period. Data from study E2200 is limited; at the time of writing, the study had only been reported in abstract form. Patient characteristics, as reported within an abstract presented by Giantonio et al,[62] gave a median age of 58.7 years and a gender split of 58.7% (54) males and 41.3% (38) females.

Mass,[64] and subsequently Kabbinavar et al,[61] presented the results of a combined analysis of patient-level data from studies AVF2107g,[58] AVF2192g[60] and AVF0780g.[59]

Table 6 First-line bevacizumab: study characteristics

Study	Participants	Interventions	Study objectives	Outcomes	Comments
AVF2107g[58]	**Inclusion criteria** Histologically confirmed metastatic CRC with bidimensionally measurable disease, aged >18 (no upper age limit), ECOG performance status 0-2, life expectancy of more than 3 months, adequate hematologic, hepatic and renal function, informed consent. **Exclusion criteria** Prior chemotherapy or biologic therapy for metastatic disease (adjuvant or radiosensitising use of fluoropyrimidines with or without leucovorin or levamisole more than 12 months before study entry was permitted), receipt of radiotherapy within 14 days before the initiation of study treatment, major surgery within 28 days before the initiation of study treatment, clinically significant cardiovascular disease, clinically detectable ascites, pregnancy or lactation, regular use of aspirin (more than 325mg per day) or other nonsteroidal anti-inflammatory agents, pre-existing bleeding diatheses or coagulopathy or the need for full-dose anticoagulation, and known CNS metastases.	Arm 1: placebo plus bolus- IFL ('Saltz') regimen consisting of 125 mg/m^2 irinotecan, 500 mg/m^2 5-FU by IV bolus injection, 20 mg/m^2 FA by IV bolus, administered in repeating 6-week cycles of weekly treatments for 4 weeks followed by 2 weeks of rest. n=411] Arm 2: bevacizumab 5 mg/kg IV infusion (90 →¨30 min) once every 2 weeks (regardless of possible chemotherapy delays) plus bolus-IFL regimen as in arm 1. [n=402] Arm 3: bevacizumab as in arm 2 plus bolus 5-FU/FA ('Roswell Park') regimen (5-FU 500 mg/m^2+FA 20 mg/m^2) weekly for 6 weeks of every 8- week cycle. Arm 3 was added since the safety of the IFL combination was not sufficiently known. After 313 patients had been randomly assigned to one of the three groups (100 to IFL plus placebo, 103 to IFL plus bevacizumab, and 110 to fluorouracil, leucovorin, and bevacizumab), and the safety of bevacizumab plus IFL had been determined, assignment to the group given fluorouracil, leucovorin, and bevacizumab was halted. Enrolment into arms 1 and 2 was continued until 400 patients per arm had been included.	This Phase III trial was designed to determine whether the addition of bevacizumab to a combination of irinotecan, fluorouracil, and leucovorin (IFL) improves survival among patients with metastatic CRC more than does a regimen of IFL plus placebo.	**Primary:** Overall survival **Secondary:** Progression-free survival; Response rate; Health-related quality of life. Overall survival and progression-free survival measured using Kaplan-Meier estimates	Efficacy analysis performed by intention-to-treat. To detect a hazard ratio of 0.75 for death in the group given IFL/ bevacizumab as compared with the control group, approximately 385 deaths were required. All calculations were performed with the log-rank test and involved two-sided p-values, with an alpha value of 0.05, a statistical power of 80% and one interim analysis of efficacy.
AVF0780g[59]	**Inclusion criteria** Patients with histologically confirmed colorectal carcinoma and evidence of bi-dimensionally measurable disease with metastases more than 1 cm^2, and patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and a life expectancy of more than 3 months were eligible. Patients had to be at least 18 years of age. **Exclusion criteria** Exclusion criteria included prior chemotherapy (other than adjuvant fluoropyrimidines in combination with FU/LV and/or levamisole > 12 months before day 0) and radiotherapy or major surgery within 28 days before day 0. Patients with serious nonhealing wounds, ulcers, or bone fractures or with clinically significant cardiovascular or peripheral vascular disease were excluded, as were those who had undergone a major surgical procedure within 28 days before day 0. Recent or current use of oral and parenteral anticoagulants (except for the maintenance of central lines) or aspirin was not allowed. Adequate hematologic, hepatic, and renal function was required. Pregnant or lactating women were excluded.	Arm 1: FU (500 mg/m^2)/LV (500 mg/m^2) Alone [n=36] Arm 2: FU/LV plus low-dose bevacizumab (5 mg/kg every 2 weeks), [n=35] Arm 3: FU/LV plus high-dose bevacizumab (10 mg/kg every 2 weeks**)** [n=33] All patients received FU/LV weekly for the first 6 weeks of an 8-week cycle according to the Roswell Park regimen (LV, 500 mg/m2, by 2-hour intravenous infusion, once weekly for 6 weeks per cycle; FU, 500 mg/m2 by IV bolus [slow push] 1 hour after initiation of the LV infusion). Patients continued FU/LV in subsequent cycles until disease progression or for a total of six cycles, whichever occurred first. In addition to FU/LV, patients in the two experimental arms received bevacizumab (5 or 10 mg/kg) as a continuous 90-minute IV infusion every 2 weeks until disease progression or for up to 48 weeks, whichever occurred first.	The objective of this Phase II trial was to investigate the safety, efficacy, and pharmacokinetics of bevacizumab plus FU/LV as first-line therapy for metastatic CRC.	**Primary:** Time to disease progression and best (confirmed) tumor response rate (complete or partial response). **Secondary:** Overall survival and duration of response Time to disease progression, duration of response, and survival were evaluated using survival analysis techniques. The Kaplan-Meier method, log-rank test, and Cox proportional hazards model were	To increase the power for detecting a treatment effect, a retrospective efficacy analysis was conducted using data pooled from both bevacizumab arms.

Study	Participants	Interventions	Study objectives	Outcomes	Comments
				used.	
AVF2192g[60]	**Inclusion criteria** Patients with histologically confirmed, previously untreated, measurable metastatic CRC were eligible if, in the judgment of the investigator, they were not optimal candidates for first-line irinotecan-containing therapy. In addition, they were required to have at least one of the following characteristics: age ≥ 65 years, ECOG PS of 1 or 2, serum albumin ≤ 3.5 g/dL, or prior radiotherapy to abdomen or pelvis. **Exclusion criteria** Patients were excluded if they had undergone major surgical procedures or open biopsy, or had experienced significant traumatic injury, within 28 days before study entry; had an anticipated need for major surgery during the course of the study; were currently using or had recently used therapeutic anticoagulants (except as required for catheter patency), thrombolytic therapy, or chronic, daily treatment with aspirin (> 325 mg/d) or nonsteroidal anti-inflammatory medications; had a serious, nonhealing wound, ulcer, or bone fracture; had a history or evidence of CNS metastases; were pregnant or lactating; or had proteinuria or clinically significant impairment of renal function at baseline.	Arm 1: FU/LV plus placebo [n=105] Arm 2: FU/LV plus bevacizumab [n=104] The FU/LV treatment, comprising LV 500 mg/m2 over 2 hours and FU 500 mg/m2 as a bolus midway through the LV infusion (Roswell Park regimen), was administered weekly for the first 6 weeks of each 8-week cycle. Chemotherapy was continued until study completion (96 weeks) or disease progression. Bevacizumab 5 mg/kg or placebo was administered every 2 weeks.	This Phase II trial was designed to evaluate the safety and efficacy of bevacizumab in combination with FU/LV delivered on a weekly, high-dose schedule.	**Primary:** Overall survival **Secondary:** Progression-free survival, objective response rate, response duration and change in FACT-C QOL Kaplan-Meier methodology was applied to estimate the median survival, progression-free survival, and duration of response time for each treatment group.	Efficacy analyses were performed on the intent-to-treat population, defined as all randomly assigned patients. Safety analyses included all patients who received at least one dose of study drug. To detect a hazard ratio of 0.61 for death in the FU/LV/bevacizumab group relative to the FU/LV/placebo group, approximately 133 deaths were required. A two-tailed log-rank test at the 5% level of significance with 80% power and two interim analyses were assumed in the calculations.

Where reported, baseline performance status was generally well-balanced apart from study AVF2192g,[60] whereby the percentage of ECOG performance score patients differed from the other two studies (see Table 7). In two trials, the site of primary tumour was the colon for the majority of participants in both arms.[58,60] One trial did not report the site of primary tumour in the baseline characteristics.[59]

Table 7 First-line bevacizumab: population characteristics

Patient characteristic	Study		
	AVF2107g[58]	AVF0780g[59]	AVF2192g[60]
Median age years, (range)	Arm 1: 60 (21-83) Arm 2: 60 (23-86) Arm 3: 61.5 (29-88)	64 (Arm 1 and Arm 2)[54]	72 (Arm 1 and Arm 2)[54]
Mean age years	Arm 1: 59.2 Arm 2: 59.5 Arm 3: -	Not reported	Arm 1: 70.7 Arm 2: 71.3
Male (%)	Arm 1: 60 Arm 2: 59 Arm 3: 63	Arm 1: 75 Arm 2: 49 Arm 3: 46	Arm 1: 51 Arm 2: 56
ECOG PS*	Arm 1: 0 (55%) 1 (44%) 2 (<1%) Arm 2: 0 (58%) 1 (41%) 2 (<1%) Arm 3: -	Arm 1: 0 (61%) 1 (39%) 2 (0%) Arm 2: 0 (60%) 1 (40%) 2 (0%) Arm 3: 0 (54%) 1 (40%) 2 (1%)	Arm 1: 0 (28%) 1 (67%) 2 (6%) Arm 2: 0 (29%) 1 (64%) 2 (8%)
Site of primary tumour	Arm 1: Colon 81%; Rectum 19% Arm 2: Colon 77%; Rectum 23% Arm 3: -	Not reported	Arm 1: Colon 80%; Rectum 20% Arm 2: Colon 82%; Rectum 18%
Number of metastatic sites	Arm 1: 1, 39%; >1 61% Arm 2: 1, 37%; >1 63% Arm 3: -	Not reported	Arm 1: 1, 31%; >1 70% Arm 2: 1, 39%; >1 62%
Site(s) of metastases	Not reported	Arm 1: Liver 69%, Lung 22%, Both 11% Arm 2: Liver 83%, Lung 40%, Both 26% Arm 3: Liver 82%, Lung 36%, Both 24%	Not reported

*Eastern Cooperative Oncology Group Performance Status

Two trials (studies AVF2192g and AVF2107g) reported an adequate method of randomisation (a dynamic randomisation algorithm).[58,60] The method of randomisation employed within study AVF0780g[59] was unclear.

Information concerning the assessment of the quality of the three included RCTs is reported in Table 8. Two of the three trials included within the review indicated that blinding was

undertaken,[58,60] although specific details were not reported. The principal investigator of the study AVF2107g[58] informed the Assessment Group that this study was double-blinded (*Personal communication: Dr H Hurwitz, M.D., Duke University Medical Center*).

As far as can be determined from the published studies, all of the trials included within the review of bevacizumab were reasonably well-designed and conducted, and, with the exception of study AVF0780g,[59] 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. However, it should be noted that the mean age of patients enrolled within study AVF2192g[60] was 71.3 for the intervention group and 70.7 for the comparator group, hence these patients may be more likely to reflect the typical NHS CRC population.

Table 8 First-line bevacizumab: Quality assessment

Study	Allocation Concealment	Randomisation	Blinding	Withdrawals	Comments
AVF2107g[58]	Adequate	Adequate	Adequate	Adequate	Randomisation: based on a minimisation algorithm; Blinding: patients in arms 1 and 2 received the study drugs in a double-blind fashion.
AVF0780g[59]	Unclear	Unclear	Adequate	Adequate	Method of randomisation not reported.
AVF2192g[60]	Unclear	Adequate	Adequate	Adequate	An interactive voice response system was used to randomly assign eligible patients to one of two treatment groups.

5.2.2 Outcomes: overall and progression-free survival

5.2.2.1Outcomes: overall survival

Survival outcomes for those studies which assessed bevacizumab given alongside first-line chemotherapy are presented in Table 9. All three trials[58,59,60] reported median overall survival (OS) durations. Whilst the use of the median is the accepted reporting method for survival outcomes within cancer trials, it is commonly a weak measure of OS as it ignores the distribution of survival times. Where survival distributions are skewed, the median may give a biased estimate of OS. Mean OS would be more appropriate, calculated as the area under the

curve, although the extent of right-censoring has an important bearing on the estimated mean OS duration. Where Kaplan-Meier curves have been presented, TechDig® software (shareware, http://home.xnet.com/~ronjones/) has also been used to estimate the mean of the area under the empirical survival curve, using the trapezium rule. The information presented on OS has been taken from articles available in the public domain; this information is used in the clinical effectiveness assessment presented within this report. Differences between results reported within the sponsor submission to NICE and the published articles are highlighted in the text. The differences are due to the submission being prepared directly from the Avastin Clinical Database which has been subject to data revisions after the corresponding investigator had written publications.

Overall survival was used as the primary endpoint for studies AVF2107g[58] and AVF2192g.[60] Within study AVF2107g, bevacizumab plus IFL, compared with IFL plus placebo, significantly improved median OS by 4.7 months ($p<0.001$).[58] In study AVF2192g,[60] the addition of 5mg/kg bevacizumab to 5-FU/FA increased OS by 3.7 months (16.6 months compared to 12.9 months), although this was not statistically significant at the 5% level ($p=0.16$). Within the sponsor's submission, the median OS for study AVF2192 was reported to be 16.6 months for the bevacizumab arm and 13.2 months for the control arm ($p=0.09$).[65]

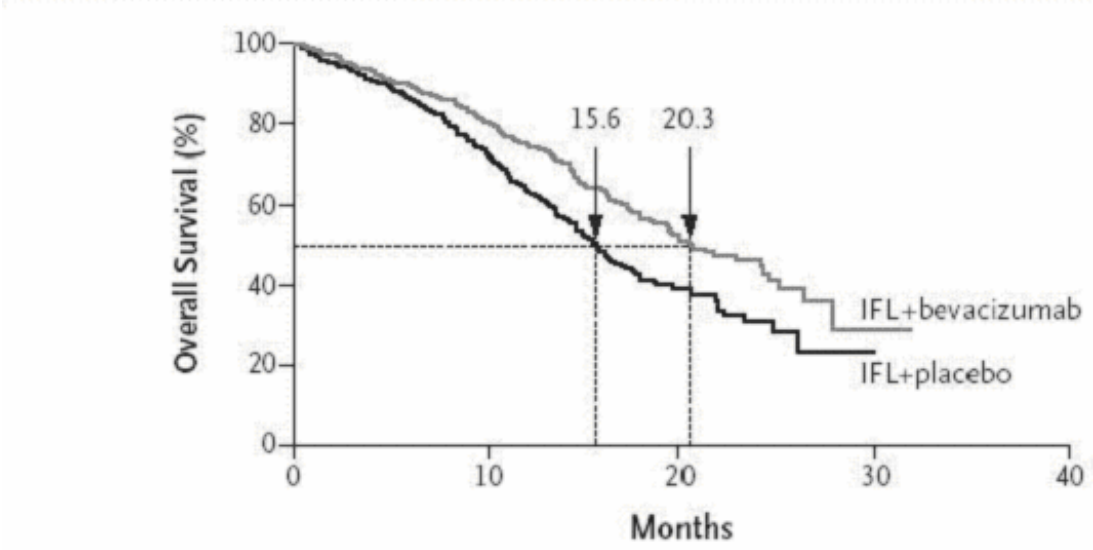
Study AVF0780g[59] was not powered to detect a difference in overall survival. Within this trial, the addition of 5mg/kg bevacizumab to 5-FU/FA increased OS by 7.7, (21.5 months compared to 13.8 months); the authors did not report whether this result was statistically significant. In the sponsor's submission, the median OS values were 17.7 months for the 5mg/kg bevacizumab group and 13.6 months for the control group, which led to a difference of 4.1 months ($p=0.07$).[65] Within study AVF0780g,[59] the addition of bevacizumab at 5 mg/kg was more effective than at 10 mg/kg, although the reason for this is unclear. At 5 mg/kg there was an increase of 7.7 months in OS, while at 10 mg/kg there was an increase of 2.3 months.[59] Notably, there were imbalances in the randomisation, and more women were assigned to the bevacizumab arms than the control arm. The authors stated that the survival rate for women with CRC is higher than that for men. The causes of these imbalances were not explained by the authors.

Giantonio[62] presented updated results from the Eastern Cooperative Oncology Group (ECOG) study E2200 at the 2004 ASCO general meeting. The E2200 study was a Phase II trial of bevacizumab added to IFL in previously untreated patients with measurable advanced CRC. Although median OS had not been reached and outcomes data were not mature, the one-year OS was 85% (± 4%).[62]

Figures 2 and 3 present empirical Kaplan-Meier survival curves for bevacizumab plus IFL and IFL plus placebo from study AVF2107g,[58] and for bevacizumab plus 5-FU/FA and 5-FU/FA plus placebo from study AVF2192g[60] respectively. Kaplan Meier survival curves were not reported for study AVF0780.[59]

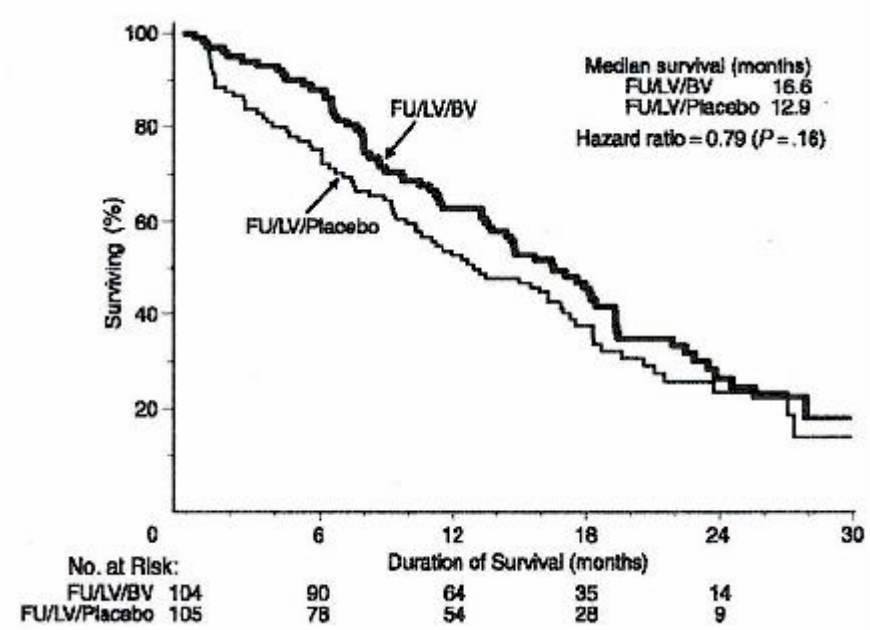
For study AVF2107g,[58] the OS duration estimated using TechDig software gave a mean of 19.9 months of IFL plus bevacizumab and 16.5 months for IFL plus placebo. For study AVF2192g,[60] the OS duration estimated using TechDig software gave a mean of 17.3 months of FU/LV plus bevacizumab and 15.2 months for FU/LV plus placebo.

Figure 2 Kaplan-Meier estimates of OS study AVF2107g[58]



No. at Risk								
IFL+bevacizumab	402	362	320	178	73	20	1	0
IFL+placebo	411	363	292	139	51	12	0	0

Figure 3 Kaplan-Meier estimates of OS study AVF2192g[60]



The reader should be aware of two considerations in the interpretation of these results. Firstly, the data presented in these Kaplan-Meier survival curves are censored where patient outcomes are unknown. The censoring of patient outcomes reduces the sample size of patients at risk after the time of censoring; reducing this sample size always reduces reliability, hence the greater the degree of censoring, the lesser degree of reliability of the curve. Secondly, the estimation of mean survival in the presence of censoring leads to downwardly biased estimate of the mean; this is an important problem where the degree of censoring is large.

Hazard ratios (HR) estimated using OS data observed within the three included RCTs[58,59,60] are presented in Table 9. A HR which is below 1.0 indicates that the hazard of death is lower in the intervention arm (bevacizumab arm) than in the comparator arm. In all three included RCTs of bevacizumab,[58,59,60] the hazard of death was lower in the intervention arm for bevacizumab at a dose of 5mg/kg.

Within study AVF0780g[59] a hazard ratio of 0.63 was reported in the published article; the sponsor's submission reported this HR to be 0.52.[65] For study AVF2192g,[60] a hazard ratio of 0.79 (95% CI 0.56 – 1.10) was reported in the published article; the sponsor's submission reported this HR to be 0.77 (95% CI 0.56 – 1.05).

Table 9 First-line bevacizumab: Overall survival hazard ratios

Study	Median overall survival (months)			Difference (months) for 5 mg/kg BV group	P-value
AVF2107g[58]	**IFL + BV (5 mg/kg)**		**IFL**		
	20.3 HR 0.66		15.6	+4.7	<0.001
AVF0780g[59]	**FU/LV + BV (5 mg/kg)**	**FU/LV + BV (10 mg/kg)**	**FU/LV**		
	21.5 HR 0.63	16.1 HR 1.17	13.8	+7.7	Not reported
AVF2192g[60]	**FU/LV + BV (5 mg/kg)**		**FU/LV**		
	16..6 HR 0.79		12.9	+3.7	0.16

5.2.2.2 Outcomes: progression-free survival (PFS)

PFS, which is defined as the time from randomisation until objective tumour progression or death, for studies assessing first-line bevacizumab are presented in Table 10. Bevacizumab plus IFL, compared with IFL plus placebo, improved median PFS by 4.4 months (p<0.001) in the AVF2107g trial,[58] whilst for study AVF2192g,[60] an increase in PFS of 3.7 months was reported for bevacizumab plus 5-FU/FA compared to 5-FU/FA plus placebo. HRs are also presented in Table 10.

Table 10 First-line bevacizumab: progression-free survival

Study	Median progression-free survival (months)			Difference (months) for BV 5 mg/kg	P-value
AVF2107g[58]	**IFL + BV (5 mg/kg)**		**IFL**		
	10.6 HR 0.54		6.2	+4.4	<0.001
AVF0780g[59]	**FU/LV + BV (5 mg/kg)**	**FU/LV + BV (10 mg/kg)**	**FU/LV**		
	Not reported				
AVF2192g[60]	**FU/LV + BV (5 mg/kg)**		**FU/LV**		
	9.2 HR 0.50		5.5	+3.7	0.0002

Figures 4 and 5 present Kaplan-Meier PFS curves for studies AVF2107g[58] and AVF2192g.[60] An estimation of the mean progression-free survival using TechDig software gave a mean of 10.9 months of IFL plus bevacizumab and 7.8 months for IFL plus placebo. An estimation of the mean progression-free survival using TechDig software gave a mean of 11.4 months of FU/LV plus bevacizumab and 6.7 months for FU/LV plus placebo.

Figure 4 Kaplan-Meier estimates of PFS study AVF2107g[58]

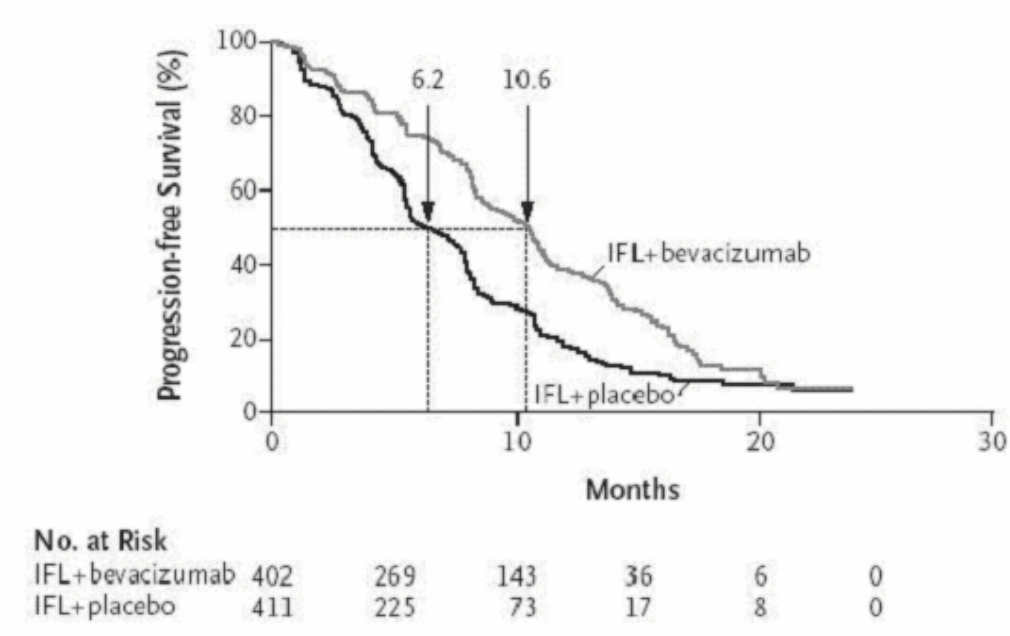
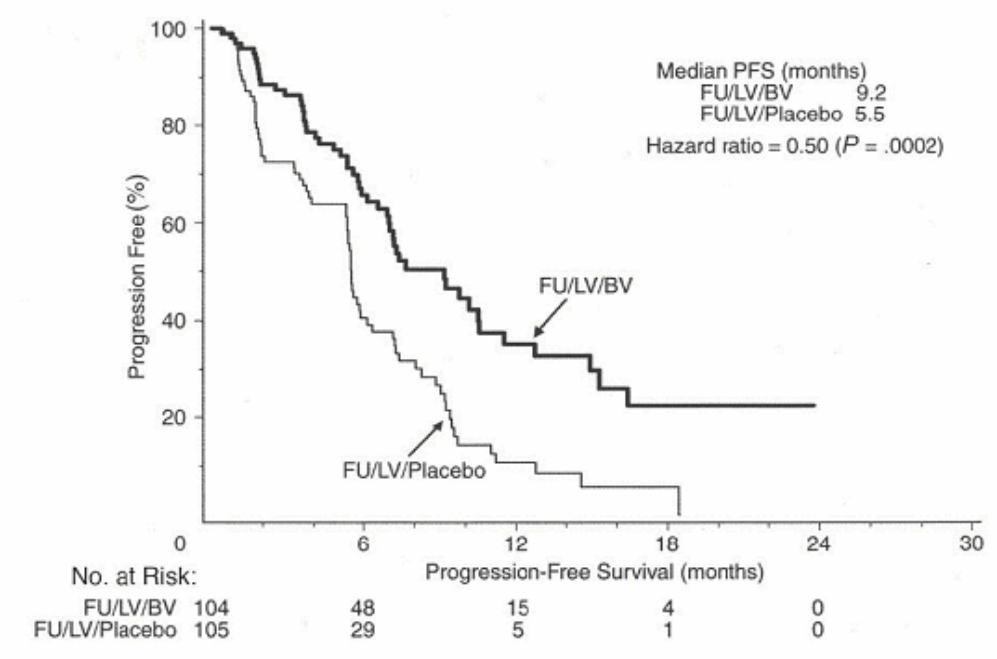


Figure 5 Kaplan-Meier estimates of PFS study AVF2192g[60]



Study AVF0780g[59] did not report progression-free survival but reported time to progression, where time to progression is defined as the time from randomisation until objective tumour progression. Time to progression was used as the primary endpoint within this trial.[59] The results of this study showed that the addition of bevacizumab at 5 mg/kg resulted in an increase of 3.8 months in time to disease progression compared to FU/LV alone (9.0 months compared to 5.2 months, p=0.005).[59] The addition of bevacizumab at 10mg/kg resulted in an

increase of 2.0 months in time to progression compared to FU/LV alone (7.2 months compared to 5.2 months, p=0.217).[59]

5.2.2.5 Outcomes: combined analysis of overall survival and progression-free survival

Whilst it was envisioned that a meta-analysis of the three included RCTs[58,59,60] of bevacizumab would be undertaken, this review has revealed heterogeneities in the study populations and comparator arms. These heterogeneities suggest that the meta-analysis of these published data would be inappropriate. However, Kabbinavar et al[61] used the statistical rationale that a pooled analysis of raw data was possible as all trials[58,59,60] used the same definitions and procedures for collecting data on baseline characteristics, primary and secondary efficacy end points, and safety assessments as well as identical regimens of 5-FU/FA. However, Kabbinavar et al state that study AVF2192g was designed to include a poor-prognosis study population.[60] Furthermore, the comparator arm of the combined analysis is composed of two chemotherapy treatments, rather than one chemotherapy treatment.

Mass[64] presented a combined analysis of patient data from the three main trials at the 2004 ASCO annual meeting. In the Phase III AVF2107g study,[58] a third treatment arm of bevacizumab plus FU/LV was included until the safety of bevacizumab plus IFL had been demonstrated in a pre-specified analysis. The two Phase II studies[59,60] compared bevacizumab plus FU/LV to FU/LV alone or with a placebo. This combined analysis of patient data was undertaken in an attempt to allow a more robust evaluation of the efficacy and safety of bevacizumab. The combined control group consisted of patients with metastatic CRC who had been randomised to receive FU/LV or IFL within these studies. The combined comparator group consisted of patients who received bevacizumab at a dosage of 5 mg/kg every two weeks. The results from this combined analysis are displayed in Table 11. Mass,[64] reports a 26% reduction in daily risk of death with bevacizumab plus FU/LV, compared to FU/LV or IFL alone, with a hazard ratio of 0.742 (95% CI: 0.59-0.93, p=0.0081).

The subsequent paper by Kabbinavar et al[61] provided further details of the combined analysis. The baseline characteristics of the patient groups in the combined analysis were similar, with a median age of 67 years for both groups, a similar proportion of males (59.8% in the combined control group and 57.8% in the combined comparator group). Kabbinavar et al[61] reported a significant benefit to the median duration of PFS in patients who received FU/LV plus bevacizumab compared to FU/LV or IFL (8.77 months versus 5.55 months, see Table 11).

Table 11 Combined analysis of bevacizumab + FU/LV vs. FU/LV or IFL alone

Study	Number of patients		
	IFL	**FU/LV**	**FU/LV + bevacizumab**
AVF2107g.[58]	100	0	110
AVF0780g[59]	0	36	35
AVF2192g[60]	0	105	104
Combined analysis	FU/LV and IFL	FU/LV + bevacizumab	P value
Total N	241 (100 IFL)	249	
Median survival, months (95% CI)	14.6 (12.0-16.3)	17.9 (16.4-19.4)	0.0081
Progression free survival, months (95% CI)	5.55 (5.4-6.3)	8.77 (9.3-9.8)	0.0001

Owing to the heterogeneity between the studies included within this combined analysis, the reader should interpret these results with caution.

5.2.2.6 Outcomes: tumour response rates

Table 12 reports the observed tumour response rates within the three trials which met the inclusion criteria for this review.[58,59,60] Tumour response rate was a primary endpoint within study AVF0780g,[59] and as a secondary endpoint within studies AVF2107g[58] and AVF2192g.[60] In the two Phase II trials[59,60] which compared FU/LV plus bevacizumab with FU/LV alone or with placebo, tumour response rates were between 10 and 23 percent higher in the bevacizumab arm than in the control arm. In study AVF0780g[59] there was a statistically significant difference between bevacizumab administered at 5 mg/kg dose with FU/LV compared to FU/LV (p=0.029), but not when the bevacizumab was administered at 10 mg/kg (p=0.434). Within the larger study AVF2192g,[60] a statistically significant difference in overall tumour response rates between bevacizumab plus FU/LV and FU/LV plus placebo was not found (p=0.055). Study AVF2192g[60] reported a median duration of tumour response of 9.2 months for bevacizumab plus FU/LV and 6.8 months for FU/LV plus placebo; the hazard ratio was reported to be 0.42 (p=0.088).

In the Phase III AVF2107g study,[58] an overall tumour response rate of 44.8% was reported for bevacizumab plus IFL compared to 34.8% for IFL plus placebo (p=0.004). A median duration of tumour response of 10.4 months was reported for bevacizumab plus IFL and 7.1 months for IFL plus placebo (p=0.001).

Table 12 First line bevacizumab: overall tumour response rates

Study	Tumour response rate (%)			Difference at BV 5 mg/kg	P-value
AVF2107g[58]	**IFL + BV (5 mg/kg)**		**IFL**		
	44.8 (3.7 CR, 41.0 PR)		34.8 (2.2 CR, 32.6 PR)	10.0	0.004
AVF0780g[59]	**FU/LV + BV (5 mg/kg)**	**FU/LV + BV (10 mg/kg)**	**FU/LV**		
	40	24	17	23	0.029
AVF2192g[60]	**FU/LV + BV (5 mg/kg)**		**FU/LV**		
	26.0 (0 CR, 26.0 PR)		15.2 (0 CR, 15.2 PR)	10.8	0.055

5.2.2.7 Outcomes: toxicities

Any grade 3 or 4 adverse event, gastrointestinal, haematological and other toxicities observed within studies AVF2107g,[58] AVF0780g,[59] and AVF2192g[60] are reported in Tables 13-16 respectively. For bevacizumab plus IFL, study AVF2107g[58] reported that clinical benefit was accompanied by a relatively modest increase in adverse events of treatment, which were easily managed. Only the incidence of hypertension was significantly increased in the bevacizumab plus IFL group ($p<0.01$), with all episodes of hypertension being manageable with standard oral antihypertension agents.

Study AVF0780g[59] reported that more patients in the bevacizumab treatment groups experienced at least one National Cancer Institute (NCI) common toxicity criteria grade 3 or 4 adverse event. The authors related this increase in incidence of grade 3 and 4 events seen in the bevacizumab arms compared with the control arm as a possible result of patients in these arms being on the study intervention for a longer duration (see Table 13).

Within the smaller Phase II AVF0780g trial,[59] in which bevacizumab was given with FU/LV at a dosage of 5mg/kg, it was stated that a number of safety concerns were identified, although bevacizumab was generally well tolerated. In the larger Phase II AVF2192g trial,[60] it was stated that the results should be viewed in the context of the study population (i.e. specifically selected patients who were deemed by the treating physician to be sub-optimal candidates for first-line irinotecan-containing therapy), and that despite this higher risk study population, the regimen of bevacizumab plus FU/LV seemed to have been well tolerated.

Table 13 First-line bevacizumab: Adverse event grade 3 or 4

Study	Any grade 3 or 4 adverse event (%)			
	IFL	IFL BV (5 mg/kg)		P-value
AVF2107g[58]	74.0	84.9		<0.01
	FU/LV	**FU/LV + BV (5 mg/kg)**	**FU/LV + BV (10 mg/kg)**	
AVF0780g[59]	54.3	74.3	-	Not reported
	54.3	-	78.1	Not reported
AVF2192g[60]	71	87	-	Not reported

Giantonio et al[62] reported grade 3 diarrhoea occurring in 16% of patients in study E2200, and no patients reporting grade 4 diarrhoea. Study AVF2107g[58] reported a small increase in the incidence of diarrhoea in patients receiving IFL plus bevacizumab compared to patients receiving IFL plus placebo (see Table 14). The combined analysis of the three main bevacizumab trials[58,59,60] by Kabbinavar et al[61] reported occurrence of grade 3 or 4 diarrhoea in 34% of those patients receiving IFL plus placebo or FU/LV alone/with placebo compared to 37% of patients receiving FU/LV plus bevacizumab at 5mg/kg.

Table 14 First-line bevacizumab: gastrointestinal toxicity

Study	Toxicity (Grade 3-4)					
	Diarrhoea (%)			Gastrointestinal perforation (%)		
AVF2107g[58]	IFL	IFL + BV (5 mg/kg)		IFL	IFL + BV (5 mg/kg)	
	24.7	32.4		0.0	1.5	
AVF0780g[59]	FU/LV	FU/LV+BV (5 mg/kg)	FU/LV+BV (10 mg/kg)	FU/LV	FU/LV+BV (5 mg/kg)	FU/LV+BV (10 mg/kg)
	37.1	28.6	31.3	-	-	-
AVF2192g[60]	FU/LV	FU/LV+BV (5 mg/kg)		FU/LV	FU/LV+BV (5 mg/kg)	
	40	39		0	2	

Giantonio[62] reported that 10% patients (9 of 92 patients) experienced a grade 3 or grade 4 thrombotic event. Study AVF2107g[58] reported a non-significant increase (p=0.26) in the incidence of thrombotic events in the IFL plus bevacizumab group compared to the IFL plus placebo group (see Table 15). Within study AVF0780g,[59] it was reported that thrombosis occurred more frequently with bevacizumab than with chemotherapy alone, was fatal in one patient, and resulted in bevacizumab discontinuation in three additional patients. Study AVF2192g[60] reported no increases in grade 3 or grade 4 thrombosis. The combined analysis of the three main bevacizumab trials[58,59,60] by Kabbinavar[61] also reported no increase of thrombotic events (any grade) with 17% of thrombotic events (any grade) occurring in patients receiving IFL plus placebo or FU/LV alone/with placebo and patients receiving FU/LV plus bevacizumab at 5mg/kg.

Table 15 First-line bevacizumab: haematological toxicity

Study	Toxicity (Grade 3-4)					
	Leucopenia (%)			Any thrombolic event (%)		
AVF2107g [58]	IFL	IFL + BV (5 mg/kg)		IFL	IFL + BV (5 mg/kg)	
	-	-		16.2	19.4	
AVF0780g[59]	FU/LV	FU/LV+BV (5 mg/kg)	FU/LV+BV (10 mg/kg)	FU/LV	FU/LV+BV (5 mg/kg)	FU/LV+BV (10 mg/kg)
	2.9	5.7	3.1	2.9	14.3	6.3
AVF2192g[60]	FU/LV	FU/LV+BV (5 mg/kg)		FU/LV	FU/LV+BV (5 mg/kg)	
	7	4		18	18	

Study AVF2107g[58] reported a statistically significant increase ($p<0.01$) in hypertension in patients receiving IFL plus bevacizumab compared to patients receiving IFL plus placebo, but no statistical significant difference in adverse events leading to death in the two groups (see Table 16).

Study AVF0780g[59] reported occurrences of hypertension in both bevacizumab arms, with a higher percentage being reported in the higher dose arm. The authors reported that these occurrences were manageable. Study AVF2192g[60] reported grade 3 hypertension occurring in a higher percentage of the FU/LV bevacizumab group than the FU/LV placebo group. No grade 4 hypertension was reported.

All three trials[58,59,60] stated that other clinical trials of bevacizumab had identified haemorrhage, thromboembolism, proteinuria and hypertension as possible adverse events associated with the use of bevacizumab. Possible adverse events may include mucocutaneous bleeding, gastro-intestinal perforation, impaired wound healing, arterial thromboembolism, hypertension or proteinuria.

Table 16 First-line bevacizumab: other toxicity

Study	Toxicity (Grade 3-4)					
	Hypertension (%)			Adverse event leading to death (%)		
AVF2107g[58]	IFL	IFL + BV (5 mg/kg)		IFL	IFL + BV (5 mg/kg)	
	2.3	11.0		2.8	2.6	
AVF0780g[59]	FU/LV	FU/LV+BV (5 mg/kg)	FU/LV+BV (10 mg/kg)	FU/LV	FU/LV+BV (5 mg/kg)	FU/LV+BV (10 mg/kg)
	0	8.6	25.0	-	-	-
AVF2192[60]	FU/LV	FU/LV+BV (5 mg/kg)		FU/LV	FU/LV+BV (5 mg/kg)	
	3	16		7	4	

5.2.2.8 Outcomes: health related quality of life

Only one of the studies included within this review (study AVF2192g[60]) set out to evaluate quality of life; this assessment was undertaken using the FACT-C quality of life instrument (See Appendix 9). The FACT-C combines specific concerns or problems related to quality of life in CRC patients with concerns that are common to all cancer patients. Ward[66] recommends the use of the entire FACT-C (general and specific questions with 36 items in all) to give a comprehensive assessment of the patients quality of life. Yoo et al[67] reported on a study that found the FACT-C (version 4) to be a valid assessment tool for the measurement of CRC patients quality of life changes over time.

Study AVF2192g[60] analysed change in quality of life (QOL) as time to deterioration in QOL, defined as the length of time from random assignment to the earliest of a >3-point decrease from base-line in colon-cancer specific FACT-C subscale score, disease progression, or death on study, but did not present any quality of life information.

5.2.3 Discussion of results

5.2.3.1 The strength of the evidence (internal validity)

All three RCTs[58,59,60] included in the review reported the use of blinding. Two trials[60,58] clearly reported the generic components of clinical trial design used to minimise the chance of systematic bias. Study AVF0780g[59] acknowledged that there were randomisation imbalances in demographic and baseline characteristics across the three treatment groups. More females were randomly assigned to the bevacizumab arms compared to the control arm; this is a relevant potential bias as the survival rate for women with CRC is higher in women than men.[68,69] A greater proportion of patients in the arm receiving the higher dose of bevacizumab had poor baseline performance status compared to the control arm.

5.2.3.2 The applicability of the results (external validity)

It has been noted that the study arm populations had, where recorded, median/mean ages of between 5 and 10 years younger than the UK population of people with CRC. Thus, the extent to which the results of included trials can provide a reasonable basis for generalisation to the UK NHS population of CRC patients is unclear. This is a recurrent problem in relating the findings of trials of therapies for CRC to the UK population.[27] As reported in Section 3.1.1, the incidence of CRC rises with age. Hutchins,[70] expressed concern that elderly people with advanced colorectal cancer are excluded or under-represented in clinical studies. However, it is commonly accepted that the choice of treatment should be guided by overall fitness rather than the age of the patient.[36]

One of the RCTs included in this review, study AVF2192g,[60] enrolled patients aged 65 years or older as specified by the trial inclusion criteria. However, patients could be recruited into the trial if they fulfilled at least one of the other inclusion criteria (see Table 5); it is therefore possible that patients younger may have been recruited. The age range within this trial was not reported, although a mean age of 70 or 71 was given for the population groups. The author also stated that the study population were specifically selected patients that had a high likelihood of treatment-associated toxicities or were deemed to be sub-optimal candidates for first-line irinotecan-containing therapy. However, the trial was designed to evaluate the safety and efficacy of bevacizumab plus FU/LV in a poor-prognosis study population. The study reported that bevacizumab was well tolerated within a higher risk population.

5.2.3.3 Assessment of clinical effectiveness

Overall survival was used as the primary endpoint within studies AVF2107g[58] and AVF2192g;[60] time to progression and tumour response rate was used as the primary endpoint within study AVF0780g.[59]

The systematic review of suggests the following:
Study AVF2107g[58] presented evidence that the addition of bevacizumab to first-line IFL significantly improved median OS by 4.7 months ($p<0.001$). The addition of bevacizumab to first-line FU/LV resulted in a non-significant improvement in OS of 3.7 months within study AVF2192g.[60] Study AVF0780g[59] reported that the addition of bevacizumab to first-line FU/LV improved OS by 7.7 months (p-value not reported).

The Phase III AVF2107g trial[58] reported that the addition of bevacizumab to IFL significantly improved median PFS by 4.4 months ($p<0.001$). Study AVF2192g suggested that the addition of bevacizumab to first-line FU/LV significantly improved PFS by 3.7 months ($p=0.0002$).[60] Study AVF0780g[59] demonstrated that the addition of bevacizumab at 5 mg/kg to FU/LV resulted in a significant increase in median time to progression of 3.8 months compared with FU/LV alone ($p =0.005$). The addition of bevacizumab at 10 mg/kg to FU/LV resulted in a non-significant increase in time to progression of 2.0 months against FU/LV alone ($p=0.217$).

Study AVF2107g[58] showed that the addition of bevacizumab to IFL significantly improved tumour response rates ($p=0.004$). Whilst the smallest Phase II trial, study AVF0780g,[59] demonstrated that the addition of bevacizumab at 5 mg/kg to FU/LV resulted in a significant increase in tumour response rate ($p=0.029$), the addition of bevacizumab at 10 mg/kg did not significantly improve tumour response rate ($p=0.434$). The larger Phase II AVF2192g[60] trial

demonstrated an improvement in tumour response rates for FU/LV plus bevacizumab, however this did not quite achieve statistical significance at the 5% level (p=0.055).

Combination therapy with bevacizumab is associated with more grade 3 or 4 toxicities than FU/LV alone and IFL therapy. There is currently no evidence available to demonstrate a significant difference in health-related quality of life between patients receiving bevacizumab plus first-line chemotherapy or first-line chemotherapy alone.

5.3. Results: The clinical effectiveness of cetuximab plus irinotecan in the second- and subsequent-line treatment of patients with EGFR-expressing metastatic CRC who are refractory to irinotecan

5.3.1 Quantity and quality of research available

5.3.1.1 Number of studies identified

The search retrieved six citations for studies of cetuximab as second- or subsequent-line therapy for people with metastatic CRC, however, none of these met the inclusion criteria for this systematic review. In addition, Merck provided an addendum to their full submission to NICE[71] outlining early ***(CIC data removed)*** results from the MABEL trial.[72] ***(CIC data removed)*** however the MABEL trial has not been subjected to a methodologically rigorous assessment of validity.

5.3.1.2 Number and type of studies included

Of the six citations identified, one was a RCT,[73] one was a single arm study of cetuximab monotherapy[74] and four were abstracts[75,76,77,78] presented at ASCO general meetings. With the exception of data from the MABEL study,[72] all trial data were derived from sources in the public domain.

5.3.1.3 Number and type of studies excluded, with reasons for specific exclusions

A flow chart detailing studies identified for inclusion in the systematic review is provided in Appendix 5, as recommended by the QUOROM statement,[56] and reasons for all trial exclusions are given in Appendix 8.

5.3.1.4 Quality and characteristics of cetuximab studies

One Phase II trial,[73] three single arm studies[74,76,77,75] and a pooled analysis[78] were the only studies which included cetuximab as a second- or subsequent-line therapy. Crucially, no trials met the inclusion criteria for this systematic review, as no studies compared the effectiveness

of cetuximab plus irinotecan against oxaliplatin plus 5-FU/FA or active/best supportive care. In an endeavour to present a comprehensive review of the use of cetuximab in the second- and subsequent-line treatment of metastatic CRC, this review reports on all clinical studies which have included cetuximab in the second- and subsequent-line treatment of metastatic CRC. Table 17 displays summary information relating to all six identified citations.

Table 17 Second- and subsequent-line cetuximab: summary information of included studies

Study	Year	Study type	Publication	Intervention	Comparator
Cunningham et al BOND[73]	2004	Phase II RCT	Journal article	Cetuximab plus irinotecan	Cetuximab monotherapy
Saltz et al IMCL CP02-0141[74]	2004	Phase II single arm open-label study	Journal article	Cetuximab monotherapy	none
Lenz et al IMCL CP02-0144[76]	2004	Phase II single arm open-label study	Abstract	Cetuximab monotherapy	none
Lenz et al* IMCL CP02-0144[77]	2005	Phase II single arm open-label study	Abstract	Cetuximab monotherapy	none
Saltz et al IMCL CP02-9923[75]	2001	Phase II single arm open-label study	Abstract	Cetuximab plus irinotecan	none
Mirtsching et al[78]	2005	Pooled analysis	Abstract	Cetuximab monotherapy	none

* Subsequent analysis of study IMCL CP02-0144

The Phase II trial[73] was an open-label, randomised trial conducted in 56 centres in 11 European countries. This trial compared cetuximab monotherapy with cetuximab plus irinotecan in 329 patients who had metastatic CRC that was refractory to fluorouracil and irinotecan. This was study EMR 62 2002-007, and is referred to hereafter as the BOND study.[73]

The single arm study was a non-randomised open-label study of 57 patients who had EGFR-expressing CRC, had previously received irinotecan (either alone or in a combination regimen) and had demonstrated clinical failure on such treatment. Within this study, all patients received cetuximab monotherapy. This was study IMCL CP02-0141.[74]

Four abstracts were also retrieved, Saltz et al presented at ASCO in 2001[75] (study IMCL CP02-9923), Lenz et al presented in 2004[76] and 2005[77] (IMCL CP02-0144), and Mirtsching et al[78] presented in 2005 (pooled analysis).

The study reported by Lenz et al[76,77] was a large open label Phase II study designed to explore the activity of cetuximab in CRC patients who had progression following treatment of fluoropyrimidine, irinotecan and oxaliplatin, and had no clear treatment alternative. This study is on-going and interim results are presented. The study presented by Lenz et al will be referred to as study IMCL CP02-0144.

Saltz[75] presented an abstract detailing the results of a single arm study of cetuximab plus irinotecan in 121 patients with CRC refractory to both fluorouracil and irinotecan. This is referred to as study IMCL CP02-9923.[75]

The study reported by Mirtsching et al[78] was a pooled analysis of CRC patients who were refractory to oxaliplatin and irinotecan regimens, and were treated with cetuximab monotherapy in two research studies: a Phase II trial[73] and access program patients.

The BOND trial[73] was a large multicentre study, whilst the single arm cetuximab monotherapy study, IMCL CP02-0141[74] was based only in the US. In both cases, study results have been published in peer-reviewed journal articles. The paper reported by Lenz, study IMCL CP02-0144,[77] was a large Phase II study. The abstract presented by Saltz, study IMCL CP02-9923,[75] reported only limited information concerning study design, inclusion/exclusion criteria or patients characteristics.

The inclusion criteria within the BOND trial[73] indicated that patients were at least 18 years old whilst the cetuximab monotherapy study. Study IMCL CP02-0141[74] did not specify age restrictions (Table 18). The median ages reported within these studies were 59 years (range 26-84),[73] 59 years (range 29-85)[77] and 56 years (range 28-80).[74] All studies recruited a population younger than the NHS population of CRC patients, where the median age of patients with CRC is over 70 years (see Section 3.1.1).

Table 18 Second and subsequent-line cetuximab: study characteristics

Study	Participants	Interventions	Study objectives	Outcomes	Comments
BOND [73]	**Inclusion criteria** Patients were eligible if they were more than 18 years of age and had stage IV, histologically confirmed colorectal adenocarcinoma. Other criteria for eligibility were a Karnofsky performance-status score of 60 or more, adequate hematologic function (hemoglobin, at least 9 g per deciliter [5.6 mmol per liter]; neutrophil count, at least 1500 per cubic millimeter; and platelet count, at least 100,000 per cubic millimeter), renal function (serum creatinine, less than 1.5 times the upper limit of normal), and liver function (bilirubin, not more than 1.5 times the upper limit of normal; aspartate aminotransferase and alanine aminotransferase, not more than 5 times the upper limit of normal). Patients must also have received one of several qualifying, prestudy irinotecan regimens for at least six weeks and must have had documented progression of disease during receipt of this regimen or within three months thereafter. These regimens were irinotecan at a dose of 125 mg per square meter of body-surface area given weekly for four consecutive weeks, followed by two weeks' rest, as a single agent or in combination with fluorouracil and leucovorin; irinotecan at a dose of 180 mg per square metre given every two weeks in combination with fluorouracil and leucovorin; and irinotecan at a dose of 350 mg per square metre given every three weeks as a single agent. At least one unidimensionally measurable lesion was required, as was immunohistochemical evidence of EGFR expression, either in the primary tumor or in at least one metastatic lesion. **Exclusion criteria** None stated	Arm 1: Cetuximab was given at an initial dose of 400 mg per square meter, followed by weekly infusions of 250 mg per square meter. A histamine-receptor antagonist was given as premedication before at least the first infusion. [n=111] Arm 2: Patients assigned to the combination-therapy group were given cetuximab (as above) and also received irinotecan at the same dose as that given during their most recent prestudy therapy. [n=218]	The objective of this study was to compare the efficacy of cetuximab in combination with irinotecan with that of cetuximab alone in metastatic CRC that was refractory to treatment with irinotecan**.**	**Primary:** The primary endpoint was the rate of confirmed radiologic tumor response **Secondary:** The time to progression, the duration of response, overall survival time, and the incidence of adverse effects	The planned sample size for the study was based on power calculations related to the estimation of the confidence interval expected for the combination-therapy group.
IMCL CP02-0141 [74]	**Inclusion criteria** Patients had to have histologically or pathologically documented CRC and measurable metastatic disease. In addition, immunohistochemical evidence of EGFR expression measured semiquantitatively >_0 on a scale of 0, 1+, 2+, or 3+) in a single reference laboratory was required. **Exclusion criteria** None stated	Patients were scheduled to receive cetuximab once weekly. On day 1 of treatment, an initial dose of 400 mg/m^2 was given by a 2-hour intravenous infusion. This loading dose was preceded by a 20-mg test dose to observe for evidence of allergic reactions. All patients were to be premedicated with diphenhydramine 50 mg intravenously. No routine antiemetic medications were given. Cetuximab infusions were then continued weekly at a dose of 250 mg/m^2 unless toxicity necessitated interruptions. [n=57]	The objective was to assess the safety and efficacy of single agent cetuximab in patients with chemotherapy-refractory metastatic CRCs that express EGFR.	**Primary:** The primary end point was response rate **Secondary:** The duration of response, survival duration and toxicity	The study utilised a modified Gehan two-stage design to allow for early stopping in the event of lack of efficacy.

Study	Participants	Interventions	Study objectives	Outcomes	Comments
IMCL CP02-0144[77]	**Inclusion criteria** Histopathologically confirmed metastatic CRC. Documented failure after receiving either, at least 2 chemotherapy regimens for metastatic disease or adjuvant therapy plus 1 chemotherapy regimen for metastatic disease providing that the patient progressed within 6 months of completing adjuvant therapy. Failed chemotherapy regimens must have included irinotecan, oxaliplatin and a fluoropyrimidine. Immunohistochemical evidence of EGFR expression. ECOG performance status of 0 to 1 at study entry. No prior cetuximab or other EGFR-directed therapy or anti-cancer murine or chimeric monoclonal antibody therapy.	Treatment consisted of cetuximab monotherapy at an initial dose of 400 mg/m^2, followed by weekly doses at 250 mg/m^2, until either disease progression or unacceptable toxicity. [n=346]	To determine response rate, disease control rate, duration of response, time to progression and survival. To evaluate the safety and toxicity of cetuximab administered weekly. To assess the impact of cetuximab on quality of life.		Study to determine response rate, disease control rate, duration of response, time to progression and survival. To evaluate the safety and toxicity of cetuximab administered weekly. To assess the impact of cetuximab on quality of life.
IMCL CP02-9923[75]	**Inclusion criteria** Radiological evidence of lack of objective response on irinotecan-containing regimen. KPS ≥ 60	Treatment consisted of Cetuximab 400 mg/m^2 initial dose then 250 mg/m^2 weekly **plus**irinotecan 125 mg/m^2 weekly (for 4 weeks) then 2 weeks rest **or** 350 mg/m^2 every 3 weeks. [n=121]	Primary study objective unclear from publication.	**Primary:** Primary endpoint was overall response rate	

In the BOND trial,[73] baseline performance status was generally well-balanced, although, the age range of the cetuximab monotherapy group (39 to 84 years) was more skewed than the cetuximab combination group (26 to 82 years). For patients enrolled in the single-arm studies of cetuximab monotherapy, the median age ranged from 56 to 59 years (see Table 19).

Table 19 Second and subsequent-line cetuximab: population characteristics

Study	Median age years (range)		Male (%)		ECOG PS		Tumour site
	cetuximab monotherapy	cetuximab+ irinotecan	cetuximab monotherapy	cetuximab+ irinotecan	cetuximab monotherapy	cetuximab+ irinotecan	
BOND[73]	58 (39-84)	59 (26-82)	57		Not reported		
IMCL CP02-0141[74]	56 (26-80)	-	61	-	Range 0-2	-	Colon: 77% Rectum: 23%
IMCL CP02-0144[77]	59 (29-85)	-	53		Range0-1		
IMCL CP029923[75]	-	56 (26-83)	-		Not reported		

The BOND trial[73] reported an adequate method of randomisation (a minimization technique, with stratification according to Karnofsky performance status [see Appendix 3], previous treatment with or without prior use of oxaliplatin, and treatment centre.) This is shown in Table 20.

Table 20 Second and subsequent-line cetuximab: **Quality assessment**

Study	Allocation Concealment	Randomisation	Blinding	Withdrawals	Comments
BOND[73]	Adequate	Adequate	Adequate	Adequate	Independent randomisation service used

Again, an important issue of concern is that the population of the main trial[73] is relatively younger than the UK NHS population of CRC patients.

5.3.2 Outcomes: overall survival and time to progression

5.3.2.1 Outcomes: overall survival

Survival outcomes and hazard ratios for studies assessing second and subsequent-line cetuximab are summarised in Table 21. A HR which is less than one indicates a lower hazard of death in the intervention arm (cetuximab plus irinotecan arm) compared to the comparator arm. Within the BOND trial [73] the hazard of death was lower in the cetuximab plus irinotecan group than the cetuximab monotherapy group.

Table 21 Second and subsequent-line cetuximab: overall survival

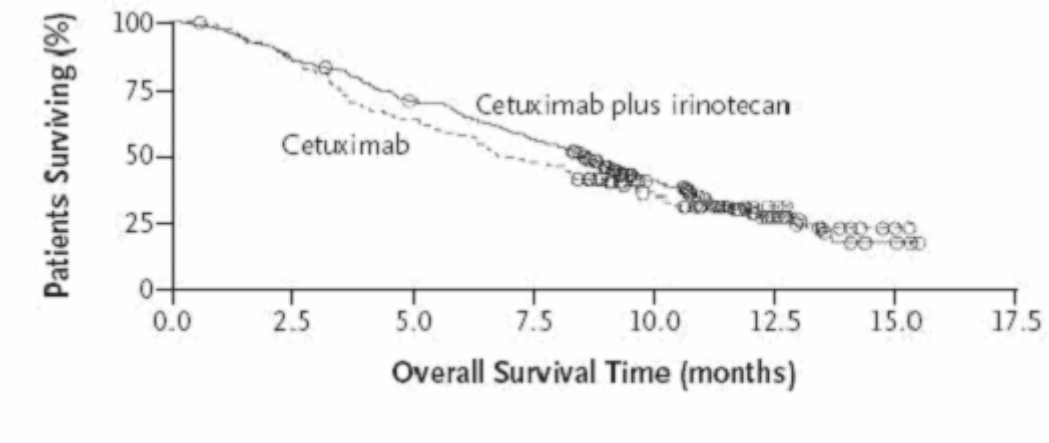
Study	Median Overall Survival (months)		Difference (months)	P-value
	Cetuximab monotherapy	Cetuximab+ irinotecan		
BOND[73]	6.9	8.6 HR 0.91	+1.7	0.48
IMCL CP02-0141[74]	6.4	-	-	-
IMCL CP02-0144[77]	6.6	-	-	-
IMCL CP02-9923[75]	-	8.4	-	-

Study IMCL CP02-0141[74] measured OS for patients receiving cetuximab monotherapy; the median survival duration was 6.4 months. Study IMCL CP02-0144[77] reported a median survival duration of 6.6 months for cetuximab monotherapy. The BOND study[73] observed a similar median OS duration for the cetuximab monotherapy arm (6.9 months). The median survival duration observed for the cetuximab plus irinotecan group was 8.6 months which leads to a difference of approximately 1.7 months. The difference in OS for the cetuximab plus irinotecan group versus the cetuximab monotherapy group was not statistically significant (p=0.48). The reader should note that this study considered two potentially active arms, and was not powered to detect a survival difference (OS was a secondary endpoint within this study).

Study IMCL CP02-9923,[75] which evaluated OS in patients receiving cetuximab plus irinotecan, reported a median OS of 8.4 months.[35]

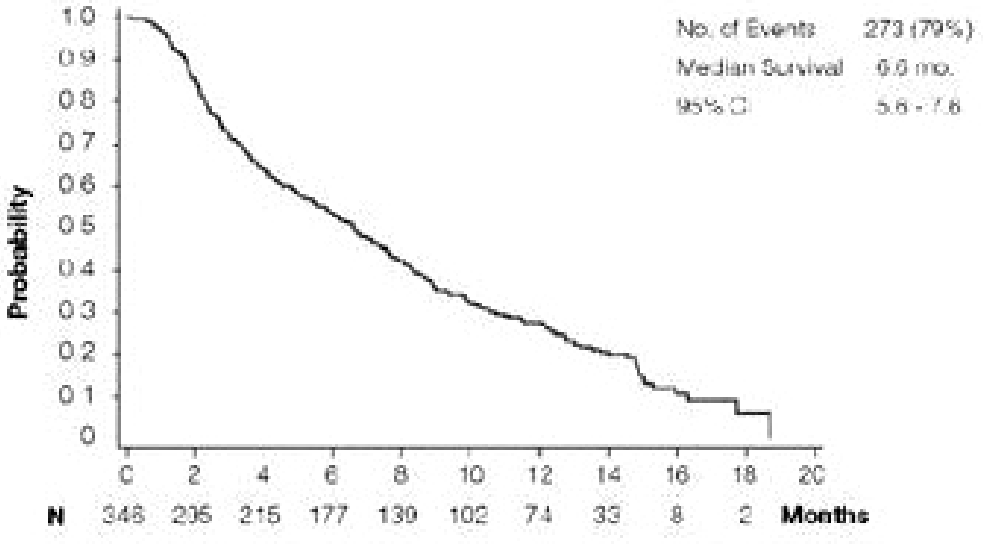
The Kaplan-Meier estimate of OS for the two treatment groups evaluated within the BOND trial[73] is shown in Figure 6. An estimation of the mean OS using TechDig software gave a mean of 8.6 months for cetuximab plus irinotecan and 8.1 months for cetuximab alone.

Figure 6 Kaplan-Meier estimates of OS BOND trial[73]



The Kaplan-Meier estimate of OS for study IMCL CP02-0144[77] is displayed in Figure 7. An estimation of the mean OS using TechDig software gave a mean of 7.7 months.

Figure 7 Kaplan-Meier estimates of OS study IMCL CP02-0144[77]



5.3.2.2 Outcomes: time to progression

Time to progression outcomes, and where appropriate hazard ratios are displayed in Table 22. The reader should note that patients enrolled within these studies had chemotherapy-resistant disease and would therefore be expected to have immediate disease progression.

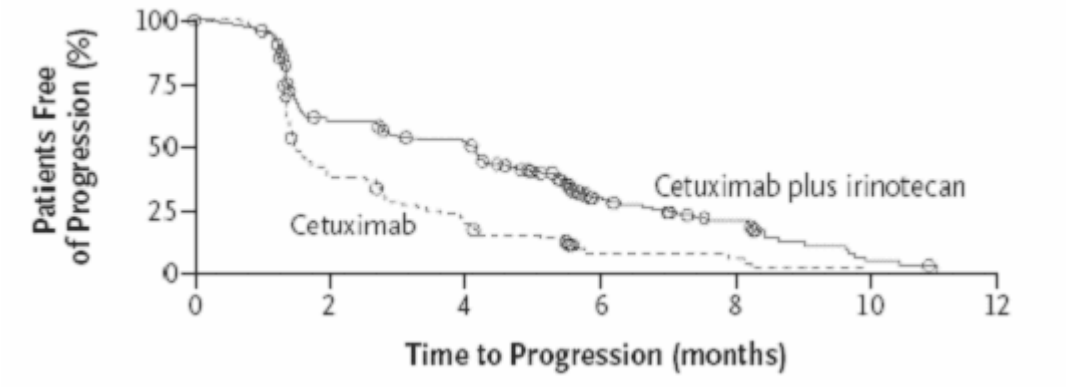
Table 22 Second- and subsequent-line cetuximab: time to progression

Study	Median time to progression (months)		Difference (months)	P-value
	Cetuximab monotherapy	Cetuximab+ irinotecan		
BOND[73]	1.5	4.1 HR 0.54	+2.6	<0.001
IMCL CP02-0141[74]	1.4	-	-	-
IMCL CP02-0144[77]	Not reported			
IMCL CP02-9923[75]	-	2.9	-	-

There was a significant difference in time to tumour progression in the BOND trial[73], with the cetuximab plus irinotecan therapy having a median time to progression of 4.1 months compared to 1.5 months in the cetuximab monotherapy group ($p<0.001$). Figure 8 shows the Kaplan-Meier curves for time to progression for the BOND study.[73]

The reader should note that the Kaplan Meier curves describing PFS are heavily skewed which leads to a bias in the median estimate of PFS. An estimate of the mean time to progression using TechDig software gave a mean of 4.5 months of cetuximab combination therapy plus bevacizumab and 2.8 months for cetuximab alone (a difference of 1.7 months).

Figure 8 Kaplan-Meier estimates of time to progression BOND study[73]



In study IMCL CP02-0141,[74] the median time to progression on cetuximab monotherapy was 1.4 months. In study IMCL CP02-9923,[75] the median time to progression on cetuximab plus irinotecan was 2.9 months.

5.3.2.3 Outcomes: tumour response rates

Tumour response rates are reported in Table 23. The rate of confirmed radiologic tumour response was used as the primary endpoint for the BOND trial.[73] Within the BOND trial[73] there was a statistically significant difference in the rate of tumour response between the cetuximab monotherapy group and the cetuximab combination therapy group. The tumour response rate was 22.9% in the cetuximab combination group compared to 10.8% in the cetuximab monotherapy group (p=0.007). Without further active treatment, one would have expected a tumour response rate of close to zero within the selected population.

A tumour response rate of 8.8% was reported for the cetuximab monotherapy study, IMCL CP02-0141.[74] For study IMCL CP02-0144,[77] an overall tumour response rate of 12.0% was reported. For the single arm study of cetuximab plus irinotecan (study IMCL CP02-9923[75]) an overall tumour response rate of 15.2% was reported.

Table 23 Second and subsequent-line cetuximab: overall tumour response rates

Study	Tumour response rate % (95% CI)†		
	Cetuximab monotherapy	Cetuximab+ irinotecan	P-value
BOND[73]	10.8% (5.7% - 18.1%)	22.9% (17.5% - 29.1%)	0.007
IMCL CP02-0141[74]	8.8% (3% - 19%)	-	-
IMCL CP02-0144[77]	12.0% (8.4%-15.4%)	-	-
IMCL CP02-9923[75]	-	15.2% (9.7%-22.3%)*	

*Taken from sponsor submission[71]

† All partial rather than complete responses

5.3.2.4 Outcomes: toxicities

Any grade 3 or 4 adverse event, gastrointestinal, haematological and other toxicities observed within studies IMCL CP02-0141[74] and BOND[73] are reported in Tables 24, 25, 26 and 27 respectively. Toxicity data from the other studies were not available.

For cetuximab monotherapy, study IMCL CP02-0141[74] reported that cetuximab given as a once-weekly cycle was well tolerated as a single agent. Cunningham et al[73] reported that cetuximab monotherapy had only mild toxic effects, therefore it may be a possible option for patients not considered as candidates for further treatment with irinotecan-based chemotherapy. Cetuximab in combination with irinotecan, had significantly more adverse events (any grade 3 or grade 4 adverse event) than cetuximab monotherapy, 65.1% compared to 43.5% ($p<0.001$) in the BOND trial[73] (see Table 24).

Table 24 Second- and subsequent-line cetuximab: Adverse event grade 3 or 4

Study	Any grade 3 or 4 adverse event (%)		
	Cetuximab monotherapy	Cetuximab+ Irinotecan	P-value
BOND[73]	43.5%	65.1%	<0.001
IMCL CP02-0141[74]	Not reported		

In the BOND trial,[73] diarrhoea was significantly more frequent amongst patients in the combination therapy arm than patients in the cetuximab monotherapy arm ($p<0.001$), as shown in Table 25. For cetuximab monotherapy, the BOND trial[73] and the IMCL CP02-0141 study[74] reported similar occurrences of diarrhoea.

There was no significant difference between cetuximab combination therapy and cetuximab monotherapy in terms of occurrences of nausea and vomiting ($p=0.47$), as shown by Table 25. Cunningham et al[73] reported a higher frequency of nausea and vomiting for cetuximab

monotherapy than the IMCL CP02-0141 study[74] in which only grade 3 or grade 4 vomiting were reported.

Table 25 Second- and subsequent-line cetuximab: gastrointestinal toxicity

Study	Toxicity (Grade 3-4)			
	Diarrhoea (%)		Nausea and vomiting (%)	
	Cetuximab monotherapy	Cetuximab+ irinotecan	Cetuximab monotherapy	Cetuximab+ irinotecan
BOND[73]	1.7%	21.2%	4.3%	7.1%
IMCL CP02-0141[74]	2%	-	2%*	-

* vomiting only recorded

Within the BOND trial,[73] neutropenia was significantly more frequent amongst patients in the combination therapy arm than patients in the cetuximab monotherapy arm ($p<0.001$), as shown in Table 26. The BOND trial[73] also reported higher occurrences of anaemia in the cetuximab combination therapy arm compared to patients in the cetuximab monotherapy arm, although this difference was not statistically significant ($p=0.55$).

Table 26 Second- and subsequent-line cetuximab: haematological toxicity

Study	Toxicity (Grade 3-4)			
	Anaemia		Neutropenia	
	Cetuximab monotherapy	Cetuximab+ irinotecan	Cetuximab monotherapy	Cetuximab+ irinotecan
BOND[73]	2.6%	4.7%	0%	9.4%
IMCL CP02-0141[74]	Not reported			

Table 27 shows that within the BOND trial,[73] higher occurrences of asthenia in the cetuximab combination therapy group were reported compared to patients in the cetuximab monotherapy group; this difference was not statistically significant ($p=0.49$). However, the number of occurrences of asthenia in the cetuximab monotherapy therapy arm of the BOND trial[73] was higher that those reported for cetuximab monotherapy in the IMCL CP02-0141 study.[74]

The BOND trial[73] reported higher occurrences of an acne-like rash adverse effect in the cetuximab combination therapy arm compared to patients in the cetuximab monotherapy arm (See Table 27), although the difference between the two groups was not statistically significant ($p=0.20$). The occurrences of a rash in the cetuximab monotherapy therapy arm in the BOND trial[73] was higher that that reported for cetuximab monotherapy in the IMCL CP02-0141 study.[74]

The authors of the BOND trial[73] reported that tumour response rates in patients with skin reactions after cetuximab treatment were higher than in those patients without skin reactions (25.8% vs. 6.3% in combination therapy group [$p=0.005$] and 13.0% vs. 0% in the

monotherapy group). The median survival times of patients with skin reactions and those without were 9.1 months and 3.0 months respectively in the combination therapy group and 8.1 months and 2.5 months respectively in the monotherapy group. Whilst this would imply a relationship between the presence of the rash and survival benefit, this sub-group analysis was not specified prospectively within the BOND trial.[73]

Table 27 Second- and subsequent-line cetuximab: other toxicity

Study	Toxicity (Grade 3-4)			
	Asthenia		Rash	
	Cetuximab monotherapy	Cetuximab+ irinotecan	Cetuximab monotherapy	Cetuximab+ irinotecan
BOND[73]	10.4%	13.7%	5.2%	9.4%
IMCL CP02-0141[74]	4%	-	2%	-

(CIC data removed)

(CIC data removed) Merck provided an addendum to their full submission to NICE[71] outlining early ***(CIC data removed)*** results from the MABEL trial.[72] This trial is an open-label, uncontrolled, multicentre, Phase II study of cetuximab in combination with irinotecan in EGFR-expressing metastatic CRC patients who have failed a previous irinotecan regimen.[72] ***(CIC data removed).***

Figure 9 Results from the Mabel study *(CIC data removed)*

(CIC data removed)

Due to the timing of the submission of the addendum[71] the MABEL trial has not been subjected to a methodologically rigorous assessment of validity.

5.3.3 Discussion of results

5.3.3.1 The strength of the evidence (internal validity)

The BOND trial[73] reported the use of blinding, and there were no major imbalances evident between the baseline characteristics of the two groups. Both the BOND study and the study reported by Saltz et al[74] reported median OS, although both studies were designed with a primary endpoint of tumour response.

5.3.3.2 The applicability of the results (external validity)

The study arm populations had median ages of between 5 and 10 years younger than the UK population of people with CRC. The extent to which the results of included trials can provide an appropriate basis for generalisation to the UK NHS population of patients with metastatic CRC is unclear.

5.3.3.3 Assessment of clinical effectiveness

There is a significant difference between cetuximab plus irinotecan and cetuximab monotherapy in terms of tumour response rate (22.9% versus 10.8%, p=0.007). Without active therapy, a response rate of close to zero would be expected. There is no direct evidence to suggest that cetuximab improves OS or PFS in comparison to oxaliplatin plus 5-FU/FA or active/best supportive care. The relationship between tumour response, overall survival and HRQoL is unclear ***(CIC data removed)***.

5.3.4 Other considerations concerning treatment with cetuximab

5.3.4.1 EGFR expression and detection

The BOND trial[73] along with studies IMCL CP02-0141[74] and IMCL CP02-9923[75] recruited patients with metastatic CRC who were irinotecan-refractory and who were EGFR-positive. This was because cetuximab was developed as a monoclonal antibody that targets EGFR. Cetuximab is believed to interfere with the growth of cancer cells by binding to EGFR so that the normal epidermal growth factors cannot bind and stimulate the cells to grow. All three trials used a commercially available testing kit (DakoCytomation EGFR pharmDx, Dako

Corporation) to test patients for EGFR positive tumours. The FDA summary of safety and effectiveness data[79] in 2004, describes the DakoCytomation EGFR pharmDx kit as a standard IHC kit that specifically detects the EGFR gene product expressed on the cell surface of normal tissues and tumours. The kit was developed due to the absence of other *in vitro* diagnostic devices indicated for assessment of patients suffering from CRC considered for EGFR targeted therapy.

In the BOND trial,[73] 577 patients were tested for EGFR positivity; of these, 82.1% (474 patients) were classed as having EGRF-positive tumours. 329 of these patients were enrolled within the trial. In study IMCL CP02-0141,[74] 140 patients were tested and 75% (105) were classed as having EGFR-positive tumours (at least 1+ expression of EGFR). Of these 105 patients, 61 patients were entered into the study. In study IMCL CP02-9923,[75] approximately 72% of CRC patients were classified as having EGFR-positive tumours. Based upon these studies, a substantial proportion (over three-quarters) of patients with metastatic CRC appear to have EGFR-positive tumours; however, no information is available concerning the sensitivity of the testing kit.

A recent study by Chung et al[80] suggested that cetuximab is also active in patients who have EGFR-negative tumours. Chung et al[80] identified 53 metastatic CRC who were patients treated with cetuximab and who had experienced prior treatment with fluorouracil and irinotecan from computer pharmacy records. Of these 53 patients, 70% (37 patients) had EGFR-positive tumours. The remaining 16 patients (30%), for whom EGFR was not detected, were evaluated in the efficacy analysis. The criteria for this small retrospective review[80] were: received cetuximab, not in a research study, with CRC, with prior irinotecan treatment, and a negative immunohistochemistry (IHC) stain for EGFR. Pharmacy computer records were reviewed to identify all patients who received cetuximab at a single institution in a non-study setting during the first 3 months of the commercial availability of cetuximab. Medical records of these patients were then reviewed to identify CRC patients who had experienced failure with a prior irinotecan-based regimen and who had a pathology report indicating an EGFR-negative tumor by IHC. Pathology slides from these patients were reviewed by a reference pathologist to confirm EGFR negativity, and CT scans during cetuximab-based therapy were reviewed by a reference radiologist.

The antibody used at the study center was a mouse monoclonal anti-EGFR antibody (clone 31G7; Ventana Medical Systems, Inc, Tucson, AZ), which was used for all specimens. Both clone 31G7 and Dako (clone 2-18C9; Dako, Carpinteria, CA) antibodies are excellent for IHC studies, as demonstrated by their interchangeable use in IHC determinations in the published

Phase I and pharmacologic study of an EGFR antagonist.[81] Whilst the DakoCytomation EGFR kit was not used within the study reported by Chung et al[80] due to cost considerations, the concordance of the clone 31G7 antibody with the DakoCytomation EGFR kit was retrospectively confirmed.

Of the sixteen subjects identified for inclusion in the study, four major objective tumour responses were observed; the tumour response rate was 25% (95% C.I. 4% to 46%). Two additional patients had a minor response, with 39% and 32% reduction in the size of measurable lesions.[80] The authors of this study[80] suggested that the current routine practice of EGFR testing for the purpose of selecting cetuximab therapy is inappropriate because patients who could potentially benefit from cetuximab may be excluded from treatment. The authors concluded that CRC patients with EGFR-negative tumors have the potential to respond to cetuximab-based therapies.[80] EGFR analysis by current IHC techniques does not seem to have predictive value, therefore the exclusion of patients for cetuximab therapy on the basis of currently available EGFR IHC does not appear to be fully justified. In addition, Nygen et al[82] suggests that there is no evidence to support that use of cetuximab should rely on IHC detection of EGFR expression. Indeed, the principal investigator of the IMCL CP02-0141 study[74] stated that the lack of correlation between the degree of EGFR expression and tumour response raises the question of whether non-EGFR expressing tumors might also be potentially sensitive to cetuximab-based therapy.

The principal investigator of study IMCL CP02-0141[74] and study IMCL CP02-9923 stated that on the basis of the lack of correlation between the degree of EGFR expression and tumour response rate, it would appear that IHC for EGFR expression is a poor indicator of which tumors are most treatable with cetuximab, that the IHC EGFR test has *"no predictive value"*,[83] and that *"there is no medical basis for ordering the test, since the test does not predict who is or is not likely to respond."*[83]

5.3.4.2 Relationship between cetuximab rash and survival benefit

Both study IMCL CP02-0141[74] and the BOND trial[73] reported a correlation between the presence and severity of an acne like rash and OS. Mirtsching[78] presented results from a pooled analysis and concluded that rash intensity did not correlate with EGFR staining intensity but that PFS and OS were significantly longer in patients with greater rash intensity and smaller number (1 or 2) of metastatic sites. In study IMCL CPO2-0141[74] it was reported that there was a correlation between the presence and severity of an acne-like rash and OS. The BOND trial[73] confirmed this correlation, based on a subgroup analysis of the trial

population and reported on correlation between skin rash and tumour response rate. This subgroup analysis was not however specified prospectively.

Study IMCL CP02-0141[74] reported that a correlation exists between the presence and severity of an acne-like rash and OS. In the single arm study, patients with skin rash of any severity had a statistically significant (p=0.02) superior median survival (6.4 months grade 1 and 2, 9.5 months grade 3) than patients with no skin rash (1.9 months grade 0).

In a review of studies that reported a rash as an adverse effect in trials of HER1/EGFR-targeted agents, Perez-Soler et al[84] concluded that current evidence suggests that the rash may be a valuable tool that could help evaluate and monitor the efficacy of HER1/EGFR-targeted inhibitors, but that further research is required in order to reach any recommendations or conclusions. Within the study reported by Chung et al,[80] no strong correlation was found between the presence of rash and OS, although the dataset was small.

6. ASSESSMENT OF COST-EFFECTIVENESS

6.1 Systematic review of existing cost-effectiveness evidence

Section 6.1 presents the methods and results of the systematic review of cost-effectiveness of bevacizumab and cetuximab for the treatment of metastatic CRC. The cost-effectiveness of first-line treatment with bevacizumab (Avastin,® Roche) in combination with 5-FU/FA or irinotecan plus 5-FU/FA is assessed in comparison to 5-FU/FA or irinotecan plus 5-FU/FA; a critical appraisal of the bevacizumab models is presented in Section 6.1.3. The cost-effectiveness of second- and subsequent-line treatment with cetuximab (Erbitux,® Merck) in combination with irinotecan is assessed in comparison to active/best supportive care alone. A critical appraisal of the cetuximab model is presented in Section 6.1.4.

6.1.1 Search methods

Systematic literature searches were undertaken to identify all relevant studies relating to the cost-effectiveness of:

(1) First-line treatment with bevacizumab in combination with 5-FU/FA or irinotecan plus 5-FU/FA as compared to 5-FU/FA or irinotecan plus 5-FU/FA in patients with metastatic CRC;

(2) Second- and subsequent-line treatment with cetuximab in combination with irinotecan in comparison to active/best supportive care or oxaliplatin plus 5-FU/FA in the treatment of patients with EGFR-expressing metastatic CRC who have previously failed on irinotecan-including cytotoxic therapy.

Details of the search strategies are reported in Section 5.1.1. Medline search strategies for the cost-effectiveness review are presented in Appendix 4. Handsearching of sponsor submissions to NICE was also undertaken in order to identify any further studies which were not identified by the electronic searches.

6.1.2 Studies included in the review of cost-effectiveness

The systematic searches did not identify any published studies relating to the cost-effectiveness of either bevacizumab or cetuximab in the treatment of metastatic CRC. The Roche submission to NICE[65] included details of two mathematical models used to estimate the cost-effectiveness of bevacizumab in combination with irinotecan plus 5-FU/FA versus irinotecan plus 5-FU/FA alone, and bevacizumab in combination with 5-FU/FA versus 5-FU/FA alone. The Merck submission to NICE[35] reported details of a mathematical model used to estimate the cost-effectiveness of second- and subsequent-line treatment using

cetuximab plus irinotecan versus active/best supportive care. Appendix 5 details the studies identified for inclusion in the review of cost-effectiveness.

6.1.3 Achieving clinical excellence in the treatment of metastatic colorectal cancer: Roche submission to the National Institute for Health and Clinical Excellence (2005)[65]

6.1.3.1 Overview of Roche cost-effectiveness models

The two models submitted to NICE by Roche estimate the marginal cost-effectiveness of first-line bevacizumab in combination with IFL (irinotecan plus 5-FU/FA) in comparison to IFL alone, and first-line bevacizumab in combination with 5-FU/FA in comparison to 5-FU/FA alone in the treatment of patients with metastatic CRC. The two cost-effectiveness models are based upon effectiveness evidence and resource use data collected within studies AVF2107g[58] and AVF2192g[60] respectively. The choice of comparators within the models is relevant, as the analysis compares the marginal costs and health effects resulting from adding bevacizumab to the first-line treatment option recommended by NICE at the time of submission (5-FU/FA), as well as the marginal costs and health effects of adding bevacizumab to the first-line treatment option which is currently considered to be an effective treatment option (5-FU/FA plus irinotecan).[85]

The cost-effectiveness models based upon studies AVF2107g[58] and AVF2192g[60] use the same structural assumptions, economic perspective and many of the parameter values are the same. The health economic analysis was undertaken from the perspective of the NHS, and therefore includes only direct costs and health effects. Cost per quality adjusted life year (QALY) gained is reported as the primary health economic outcome within the analysis, although cost-effectiveness results are also presented in terms of cost per life year gained (LYG). Whilst bevacizumab is currently indicated only for the first-line treatment of patients with metastatic CRC, the analysis includes additional long-term costs and health outcomes associated with unspecified subsequent-line therapies and other palliative treatments received beyond disease progression. Appropriately, the time horizon used within the health economic models relates to the time from randomisation until death.

The Roche models use a simple state transition approach based on three health states using a monthly cycle length:

(1) Pre-progression (alive and without disease progression)

(2) Post-progression (alive following disease progression)

(3) Dead

6.1.3.2 Modelling the effectiveness of bevacizumab

Evidence relating to the additional survival benefits resulting from the use of bevacizumab in combination with first-line IFL and 5-FU/FA compared to chemotherapy alone was derived from trials AVF2107g[58] and AVF2192g.[60] Cost-effectiveness estimates were not presented using data from trial AVF0780g.[59] Within studies AVF2107g[58] and AVF2192g,[60] patients who were randomised to receive bevacizumab as a first-line treatment were also subsequently allowed to receive bevacizumab as a subsequent-line therapy following disease progression. This is currently outside of the current licensed indications for bevacizumab. In an attempt to avoid this potential confounding, which could result in additional survival benefits for the bevacizumab-including treatment groups of studies AVF2107g[58] and AVF2192g,[60] the Roche models assigned the same risk of death following disease progression on first-line treatment to all patients irrespective of treatment group. This was modelled as the risk of death following disease progression over the entire clinical trial population.[65]

Second-line therapies were controlled for as a covariate in estimating survival beyond disease progression. The assumption implied by this approach is that all of the benefit attributable to bevacizumab is derived whilst the patient is on treatment, and that post-progression chemotherapy does not include bevacizumab. As the same post-progression survival curve is applied to all treatment groups, the models assume that the additional benefit of bevacizumab on overall survival is exactly equivalent to the additional benefit of bevacizumab on progression-free survival. Regression analysis was used to estimate Weibull coefficients describing progression-free survival time and post-progression survival time, using evidence from the trial datasets. Pre-progression mortality was assumed to be zero (i.e. patients must progress before they die), although within the clinical trials[58,60] 4-9.5% patients died prior to documented disease progression; this represents a bias in all modelled treatment groups. The submission states that this assumption was tested within the sensitivity analysis, however, no results for this particular analysis were presented.

The parametric progression-free survival curves were used to estimate the probability of transiting to the post-progression health state during any given cycle for each treatment arm. The proportion of patients who make this transition are then weighted by time in order to estimate the contribution of patients in the progression-free health state to overall survival within that treatment arm. This provides an estimate of the area under the curve. Within the Roche cost-effectiveness models, the contribution to overall survival of patients in the post-progression health state is estimated by multiplying the proportion of patients who progress during each month by post-progression survival probabilities.

The Roche submission[58] notes that bevacizumab has been shown to confer a survival advantage when administered alongside second-line chemotherapy in bevacizumab-naïve patients.[86] Whilst adjusting the survival benefits observed within the intervention trial arms due to patients receiving bevacizumab following disease progression appears intuitively appropriate, the Roche submission presents *post-hoc* analyses from AVF2107g[58] which suggests that the survival of patients beyond disease progression was unaffected by the use of bevacizumab in subsequent lines of therapy. Table 28 shows the results of the analysis undertaken by Roche.[58]

Table 28 Impact of treatment with bevacizumab beyond disease progression in study AF2107g[58]

Allocated treatment group	IFL	IFL plus bevacizumab		5-FU/FA plus bevacizumab	
Treatment received following first-progression	Chemotherapy alone	Chemotherapy alone	Chemotherapy plus bevacizumab	Chemotherapy alone	Chemotherapy plus bevacizumab
Subjects	170	52	94	11	50
Survival duration in months [95% CI.]	10.09 [8.97, 12.02]	9.40 [8.28, 14.65]	9.99 [7.85, 12.09]	NR [5.78, -]	10.97 [9.4, 14.26]

The similar mean survival durations and overlapping confidence intervals between treatment groups suggests that treatment with bevacizumab alongside second-line chemotherapy in patients who have previously received bevacizumab alongside first-line chemotherapy does not confer additional survival benefits over and above other available chemotherapies. In addition, the Roche submission notes that adjusting for second-line therapy within the regression analysis made little difference to the post-progression Weibull model coefficients.

In the light of this evidence, the justification for adjusting the observed overall survival estimates for the bevacizumab-including treatment groups within the AVF2107g[58] and AVF2192g[60] trials for use in the model is unclear, and may have been unnecessary. The underlying implication of Roche's approach is that the only difference in costs and effects between bevacizumab-containing therapy and non-bevacizumab-containing therapy are observed during the progression-free survival period. As the post-progression survival duration and associated monthly costs are assumed to be the same for each treatment group, the costs and effects accrued during this period have no bearing upon the estimated cost-effectiveness of bevacizumab, except for the minor impact of discounting. This approach was intended to represent a conservative cost-effectiveness analysis (*Personal communication, Paul Catchpole, Roche Pharmaceuticals*); consideration of differences in mean progression-

free survival and mean overall survival (See Sections 5.2.2.1 and 5.2.2.2) suggests that this may be reasonable for the economic analysis of study AVF2107g.[58] However, the impact of censoring on progression-free survival outcomes for study AVF2192g[60] resulted in a notably larger difference in mean progression-free survival than mean overall survival between the treatment groups (See Sections 5.2.2.1 and 5.2.2.2); for this study, the use of progression-free survival is likely to result in cost-effectiveness estimates that are biased in favour of the bevacizumab-including treatment group.

6.1.3.3 Modelling HRQoL

Additional HRQoL benefits attributable to treatment with bevacizumab were not demonstrated within the clinical trials (see Section 5.2.2.8).[58,60] Therefore the health economic models submitted by Roche assume equivalent utility scores for both intervention and control groups within the AVF2107g[58] and AVF2192g[60] trials. Utility scores describing HRQoL in the pre-progression and post-progression health states were derived from the literature. In the base case analysis, a utility score of 0.80 was assigned to the pre-progression health state. This utility estimate was derived from a time trade off (TTO) study reported by Smith et al.[87] Within this study, health state descriptions were devised based upon a qualitative survey using patients who had recently undergone surgery for Duke's C colon cancer but were ineligible for chemotherapy, or who were yet to receive chemotherapy. The questionnaire was administered to 16 study subjects. The rationale for using this utility estimate over alternatives available within the literature is not clear.

An estimate of utility following disease-progression was obtained from a study reported by Brown et al (utility post-progression= 0.50).[88] However, Brown et al undertook a Q-TWIST (Quality Adjusted Time Without Symptoms of Disease or Toxicity of Treatment) analysis to assess the quality of life impact of adjuvant therapy for stage III colon cancer, whilst the bevacizumab models relate to patients with metastatic disease. Utility decrements associated with adverse events resulting from the use of alternative chemotherapies were not included in the cost-effectiveness models. Alternative assumptions concerning the utility associated with these two health states were explored within the sensitivity analysis.

6.1.3.4 Modelling the resource use and costs of bevacizumab

6.1.3.4.1 Pre-progression costs

Resource utilisation estimates were derived from data collected within studies AVF2107g[58] and AVF2192g.[60] These were supplemented with evidence available in the literature. Unit costs were obtained from published sources and the Chartered Institute of Public Finance and

Accountancy (CIPFA). The costs associated with the pre-progression health state include the costs of drug acquisition, hospitalisation, consultations and other services.

Monthly acquisition costs for chemotherapy were estimated using relative dose intensity data collected within the two clinical trials[58,60] multiplied by the protocol dose and the unit cost for each chemotherapy component.[89] The mean cost per dose received was multiplied by the mean number of doses of each drug received within the trials to estimate the total drug acquisition costs within each arm of the two trials.

Appropriately, the model takes account of the differential costs of administration between the intervention and comparator arms. For example, within study AVF2107g,[58] bevacizumab was administered every 2 weeks and IFL was administered weekly for four of every six weeks. Consequently, patients receiving bevacizumab plus IFL are assumed to incur the cost of one additional day of administration for each six week cycle. The Roche submission notes that in clinical practice it is likely that bevacizumab will be administered every 3 weeks, thus suggesting that the model may overestimate the costs of administration for the bevacizumab treatment groups.[65] However, the clinical effectiveness and toxicity of three-weekly rather than two-weekly administration of bevacizumab is currently unknown.

Resource requirements associated with hospitalisations, consultations and other services for patients in the comparator arms of the models were derived from resource use studies of the first-line treatment of metastatic CRC with 5-FU/FA or irinotecan reported by Schmitt et al[90] and Iveson et al.[37] The equivalent resource use requirements for patients receiving bevacizumab were modelled by applying a relative risk of 1.13 to the comparator arm resource use; this relative risk was estimated from the AVF2107g trial.[58] The equivalent relative risk for the AVF2192g trial[60] was not available. Both the models of bevacizumab plus IFL and bevacizumab plus 5-FU/FA use this same relative risk. Additional costs associated with the use of drugs to manage adverse events resulting from the use of bevacizumab were modelled using this relative risk. The total cost of resource utilisation for each treatment group was estimated by multiplying the estimated resource use in each arm by unit costs obtained from CIPFA. Unit costs for internal medical, oncology, surgical, ICU, outpatient and other types of hospital stay were taken from CIPFA (2002-2003). Monthly pharmacy costs for simple and complex infusions, monthly costs associated with treatments used to manage chemotherapy-related adverse events, and monthly primary care costs were taken from Hind et al.[27] Monthly costs associated with clinician consultations were taken from Iveson et al.[37] A formal cost year for the analysis was not reported within the submission, and costs were not uplifted within the model.

6.1.3.4.2 Post-progression costs

The Roche model assumes a fixed monthly cost of £2,000 for each month following disease progression in order to take account of subsequent-line therapies and end of life costs.[65] The value of this parameter is an assumption and is not supported by evidence (*Personal communication, Carole Cohen, Roche Pharmaceuticals*).

6.1.3.5 Discounting

Within the base case analyses, both costs and health gains were discounted at 3.5%. At the time of the appraisal, NICE recommended that costs should be discounted at 6% and health outcomes should be discounted at 1.5%. The impact of alternative discount rates on marginal cost-effectiveness was explored within the sensitivity analysis.

6.1.3.6 Sensitivity analysis

The Roche submission reports the results of a number of sensitivity analyses. One-way sensitivity analysis was undertaken using alternative assumptions concerning discount rates for costs and outcomes, the relative risk of hospitalisation and drug resource use for bevacizumab, utility scores, and post-progression costs. As noted earlier, the submission states that pre-progression mortality was tested within the sensitivity analysis, however, no results are reported. The ranges of parameter values used within the one-way sensitivity analysis were not justified within the submission. Further analysis was undertaken using an exponential distribution to estimate progression-free survival durations instead of the Weibull curve used in the base case analyses. However, as the exponential distribution is a special form of the Weibull distribution which is restricted to a single parameter and constant hazard rate, the justification for this particular sensitivity analysis is unclear. Probabilistic sensitivity analysis was undertaken to explore decision uncertainty; the results of this analysis were presented as cost-effectiveness acceptability curves (CEAccs).

6.1.3.7 Results

The marginal cost-effectiveness results reported by Roche are presented in Table 29.

Table 29 Central estimates of cost-effectiveness and cost-utility presented within the Roche submission to NICE[65]

	Study AVF2107g[58]			Study AVF2192g[60]		
Treatment arm	Bevacizumab+IFL	IFL	Marginal versus IFL	Bevacizumab plus 5-FU/FA	5-FU/FA	Marginal versus 5-FU/FA
Life years	1.938	1.666	0.272	1.92	1.57	0.35
QALYs	1.259	1.039	0.2221	1.26	0.95	0.30
Costs	£57,530	£36,995	£20,535	£51,465	£33,409	£18,056
Cost per LYG			**£75,506**			**£50,961**
Cost per QALY gained			**£93,128**			**£59,894**

Within the base case analysis, first-line treatment with bevacizumab plus IFL versus IFL is estimated to cost £75,506 per LYG and £93,128 per QALY gained (See Table 29). When compared to 5-FU/FA alone, bevacizumab plus 5-FU/FA is estimated to cost £50,961 per LYG and £59,894 per QALY gained. These results assume discount rates of 3.5% for costs and health outcomes. When costs are discounted at 6% and health outcomes are discounted at 1.5%, bevacizumab plus IFL versus IFL is estimated to cost £71,101 per LYG and £88,364 per QALY gained, whilst bevacizumab plus 5-FU/FA versus 5-FU/FA is estimated to cost £47,792 per LYG and £56,628 per QALY gained.

When alternative utility estimates derived from Petrou et al[91] were assumed within the model (pre-progression utility = 0.95, post-progression utility =0.58), bevacizumab plus IFL versus IFL was estimated to cost £78,383 per QALY gained, whilst bevacizumab plus 5-FU/FA versus 5-FU/FA was estimated to cost £50,321 per QALY gained.[65] The results of the one-way sensitivity analysis suggest that the model is not sensitive to changes in the assumptions concerning the relative risk for hospitalisation, discount rates, utility values or post-progression costs. For bevacizumab plus IFL versus IFL alone, the one-way sensitivity analysis resulted in estimates of cost-utility ranging from £82,577-£106,770 per QALY gained. For bevacizumab plus 5-FU/FA versus 5-FU/FA versus 5-FU/FA alone, the corresponding range for cost-utility was from £39,136-£69,439.[65]

The Roche submission to NICE notes that the Weibull distribution does not provide a close fit to the empirical progression-free survival data observed within the AVF2192g trial.[58] The use of an exponential distribution to estimate progression-free survival duration within the base case analysis for bevacizumab plus 5-FU/FA results in a marginal cost of £37,318 per LYG and £44,268 per QALY gained when compared to 5-FU/FA alone. As noted in Section 6.1.3.6, this particular analysis is inappropriate.

The Roche submission to NICE reported the results of the probabilistic sensitivity analysis using CEAccs, although these initial analyses were flawed as the sum of the probabilities that each intervention was optimal did not always equal 1.0 over the range of willingness-to-pay thresholds. By request, Roche subsequently re-submitted two amended CEAccs which are presented in Figures 10 and 11.

Figure 10 Study AVF2107g- Probabilistic sensitivity analysis results

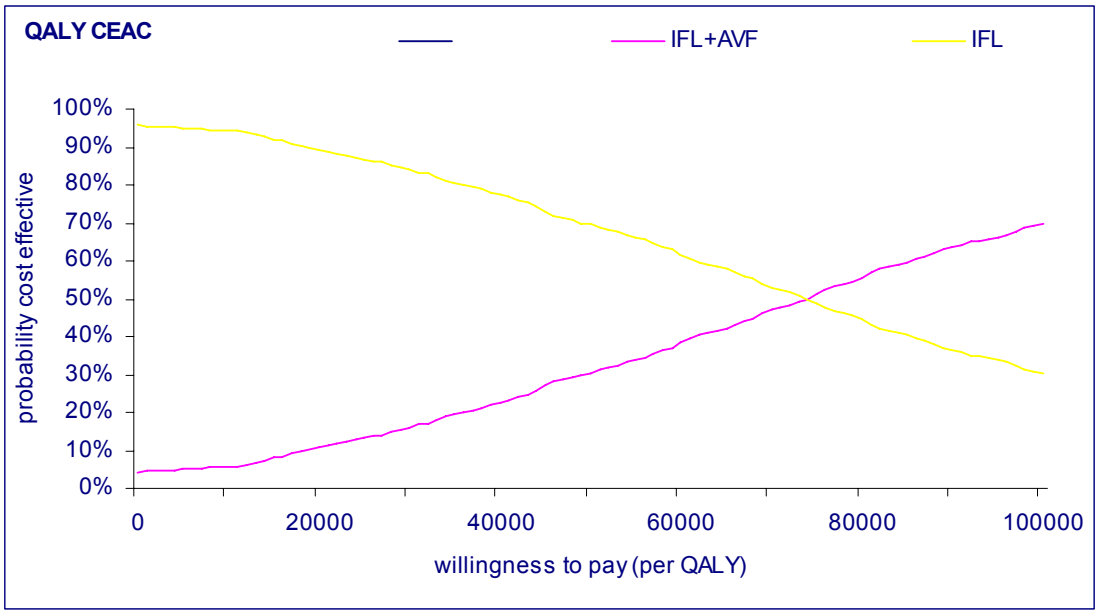
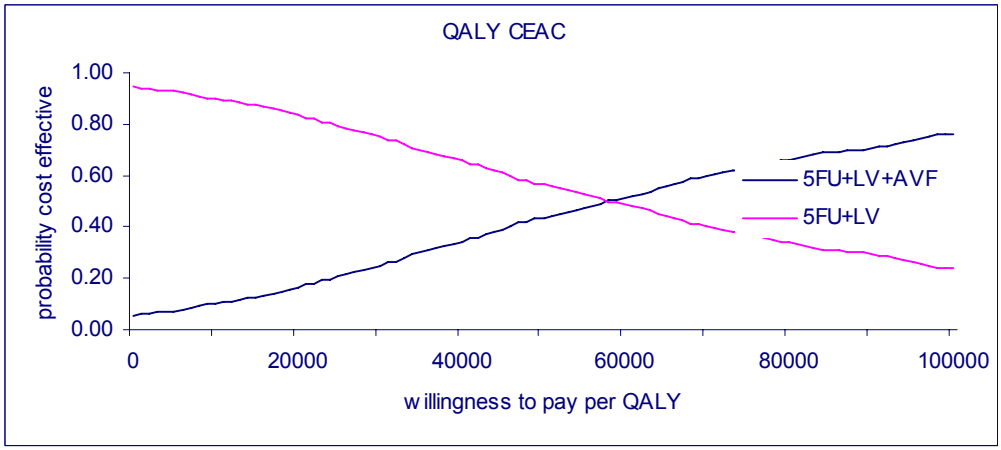


Figure 11 Study AVF2192g- Probabilistic sensitivity analysis results



The re-analysis of the probabilistic sensitivity analysis results suggests that the probability that bevacizumab plus IFL results in a greater level of net benefit than IFL alone (assuming a willingness to pay threshold of £30,000 per QALY gained) is approximately 0.16. The corresponding probability for bevacizumab plus 5-FU/FA versus 5-FU/FA is around 0.24.

6.1.3.8 Summary of Roche cost-effectiveness models

The health economic models presented by Roche appear to employ a generally appropriate methodology and most of the parameters included within the model appear to be reasonable. However, the implicit use of progression-free survival as the measure of clinical benefit means that the estimates of cost-effectiveness and cost-utility presented within the base case analysis appear to be conservative for study AVF2107g,[58] and optimistic for study AVF2192g.[60] The assumption surrounding post-progression disease management costs is not supported by existing evidence, and no explicit assumption is made concerning the drug regimen used following disease progression on first-line treatment. However, as post-progression survival is assumed to be identical for all modelled treatment options, these costs have very little impact upon the resulting estimates of cost-effectiveness and cost-utility. The sensitivity analysis suggests that the cost-effectiveness of bevacizumab is largely insensitive to the assumptions employed within the model.

6.1.4 Merck submission to the National Institute for Health and Clinical Excellence 2005[65]

6.1.4.1 Overview of Merck cost-effectiveness model

The health economic model reported within the Merck submission to NICE[35] estimates the incremental cost-effectiveness of cetuximab plus irinotecan as compared to active/best supportive care in patients with metastatic CRC in whom there is expression of EGFR, and in whom previous irinotecan-including cytotoxic therapy has failed. The evaluation is intended to consider the cost-effectiveness of second- and subsequent-line treatment with cetuximab plus irinotecan in comparison to active/best supportive care in patients for whom oxaliplatin plus 5-FU/FA is contraindicated and/or not tolerated, and where there are no alternative active therapies.

The model submitted by Merck[35] uses a survival modelling methodology to estimate the lifetime costs and effects of patients receiving cetuximab plus irinotecan compared to active/best supportive care. The health economic analysis was undertaken from the perspective of the NHS and PSS, and therefore includes only direct costs and health effects. Health economic outcomes are presented in terms of the incremental cost per LYG, although cost-utility estimates are also presented within the submission. Additional ***(CIC data removed)*** outcomes of the MABEL study,[72] were subsequently submitted to NICE within an addendum to the full Merck submission. [71]

6.1.4.2 Modelling health outcomes for patients receiving cetuximab plus irinotecan

The expected overall survival duration of patients receiving cetuximab plus irinotecan was estimated using patient-level data collected within the BOND trial.[73] Survival modelling techniques were used to extrapolate overall survival curves beyond the duration of the BOND study to account for censoring of patients outcomes in both arms of the trial. Parametric curves were estimated using empirical Kaplan Meier overall survival curves at the point at which the intervention and comparator curves diverged, based upon methods detailed by Gelber et al.[92] The expected overall survival time for each patient was estimated as the total survival duration up to the point at which the patient was censored *plus* the additional survival duration beyond the censored survival duration predicted by the parametric curve. The Merck submission states that this process was not undertaken for progression-free survival as almost all patients progressed during the follow-up period.[35]

For the cetuximab plus irinotecan arm of the BOND trial,[73] empirical and projected survival estimates were adjusted in order to account for those patients who continued to receive cetuximab plus irinotecan within the BOND trial, who it is anticipated would be withdrawn from treatment in usual clinical practice according to Merck's proposed continuation rule.[35] Under the continuation rule, patients would continue to receive treatment with cetuximab only if they have either a complete or partial tumour response at the 6-week CT scan, or if there is no change at the 6-week scan and there is evidence of the presence of a grade 2 or higher acne-like rash.[35] The expected survival duration for those patients who continue to receive treatment with cetuximab according to the continuation rule is calculated as the mean observed survival probability, with additional survival benefits attributed to those patients whose outcomes were censored. For those patients who have stable disease but do not have an acne-like rash, expected survival is calculated as their mean survival duration multiplied by an adjustment factor of 0.906. This adjustment factor represents the relative survival of patients with no change in CT scan at 6-weeks and without grade 2 or above acne-like rash as compared to the survival of patients who did not go on to achieve a complete or partial tumour response beyond 6-weeks in the BOND trial.[73] Following this adjustment, mean overall survival for patients receiving cetuximab plus irinotecan is estimated to be 10.76 months (undiscounted). Without this adjustment, the model estimates that the mean survival duration of these patients is 11.01 months (undiscounted). The extrapolated overall survival curve for the cetuximab plus irinotecan group estimated within the Merck model is shown in Figure 12.

Figure 12 Extrapolated overall survival curve for cetuximab plus irinotecan model estimated within the Merck model

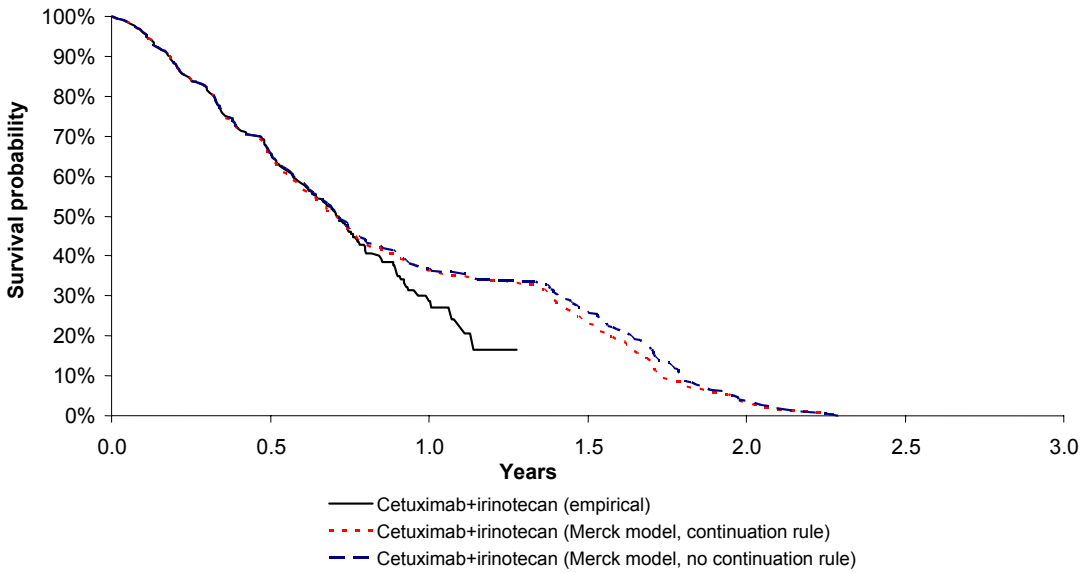


Figure 12 suggests that the validity of the extrapolation undertaken by Merck is questionable, as the modelled overall survival curves for the cetuximab plus irinotecan group diverge from the empirical overall survival curve at around 9-months following randomisation. The impact of this bias on cost-effectiveness is difficult to assess, as a similar bias is also evident in the modelled active/best supportive care treatment group.

6.1.4.3 Modelling health outcomes for patients receiving active/best supportive care

There is no comparative evidence to demonstrate either an improvement in HRQoL or overall survival duration in patients receiving cetuximab plus irinotecan compared to active/best supportive care or indeed any alternative chemotherapy except for cetuximab monotherapy (See Section 5.3). The expected survival duration of patients receiving active/best supportive care was modelled using data collected within the cetuximab monotherapy arm of the BOND trial.[73] The duration of overall survival for those patients receiving cetuximab monotherapy whose outcomes were censored was estimated using the approach reported by Gelber and colleagues.[92] Survival durations for patients receiving active/best supportive care were modelled using an assumption based upon an RCT of second-line irinotecan versus best supportive care reported by Cunningham and colleagues.[93] Within this study,[93] the hazard ratio describing the relative survival of patients receiving best supportive care as compared to those receiving irinotecan was reported to be 1.71. This hazard ratio was applied to the

observed survival duration of patients receiving cetuximab monotherapy within the BOND trial.[73]

The model therefore assumes that the relative hazard of overall survival between cetuximab monotherapy and active/best supportive care as second- and subsequent-line treatment is exactly equivalent to the relative survival hazard between irinotecan and BSC as second-line treatment. This is a crucial assumption and a key determinant of the cost-effectiveness of cetuximab plus irinotecan which cannot be justified using existing empirical evidence. Based upon the cost-effectiveness model presented by Merck, the expected overall survival duration of patients receiving active/best supportive care was estimated to be 5.64 months (undiscounted).[35]

6.1.4.4 Modelling HRQoL

The Merck model includes the use of a general utility score to describe HRQoL in patients with metastatic CRC within the sensitivity analysis, although the value of 0.95 appears to be excessively high given the nature of the disease and treatment. As the Merck cost-effectiveness model does not distinguish between the HRQoL associated with different health states (e.g. receiving treatment/not receiving treatment or progressive disease/stable disease), the use of lower valuations of HRQoL within the model results in less favourable incremental cost per QALY ratios than those presented within the base case analysis. Following their submission to NICE, Merck submitted an addendum[71] ***(CIC data removed).***

Under Merck's proposed continuation rule, one condition for continuing treatment with cetuximab is the presence of an acne-like rash. This adverse effect may have a detrimental impact upon a patient's quality of life, however, as the rash is considered to be a predictor for tumour response it could alternatively have a favourable impact. The relationship between the presence of the rash and HRQoL is unclear. A utility/disutility to represent the presence of this rash is not considered within the Merck model.

6.1.4.5 Modelling costs and resource use

The health economic model included the costs associated with drug acquisition and administration (including those receiving active cytotoxic therapy within the comparator arm), non-chemotherapy resources consumed during treatment, and supportive care costs following treatment cessation.

The acquisition costs associated with cetuximab and irinotecan were calculated according to the actual amount of the drug administered within the BOND trial.[73] The costs of continuing therapy with cetuximab plus irinotecan for those patients in the BOND trial who would be withdrawn from therapy under to the proposed continuation rule in usual clinical practice were excluded from the base case analysis. Thus, whilst 18,849 vials of 100mg cetuximab were administered within the trial (86.5 vials per patient allocated to the cetuximab plus irinotecan arm of the BOND study), the application of the continuation rule resulted in a total of 14,252 vials used in the health economic model (65.4 vials per patient allocated to the cetuximab plus irinotecan arm of the BOND study). The total acquisition cost of cetuximab per patient was estimated by multiplying the number of vials of cetuximab that would have been administered within the BOND trial according to the proposed continuation rule by the unit cost for cetuximab.[89] The total acquisition cost of irinotecan was estimated by multiplying the total number of vials of 5mL irinotecan and 2mL irinotecan administered within the BOND trial multiplied by the unit costs for irinotecan.[89]

The model includes estimates of administration costs as well as non-chemotherapy costs, including laboratory tests, imaging, hospitalisations and consultations. Costs associated with laboratory tests, imaging, hospitalisations and consultations for patients receiving cetuximab plus irinotecan were derived from Case Report Forms (CRF) from a sample of 43 patients included in the BOND trial. For patients receiving active/best supportive care, costs associated with laboratory tests, imaging, hospitalisations and consultations were estimated from a sample of CRFs for 20 patients who were eligible for, but were not included in the BOND trial. Unit costs for hospitalisation episodes were taken from NHS Reference Costs.[94]

Costs associated with other active palliative chemotherapy within the active/best supportive care treatment group of the model were estimated using data from the sample of 20 patients who were not enrolled within the BOND trial. Further chemotherapies received by these patients included oxaliplatin, irinotecan, raltitrexed, capecitabine, 5-FU and FA. The majority of these patients received oxaliplatin plus 5-FU/FA.[35] Resource utilisation associated with hospital admission was estimated from the same sample of patients, and valued using unit cost estimates obtained from NHS Reference Costs.[89] The model includes a minor error in the costing of FA, hence the costs of active supportive care are marginally underestimated.

6.1.4.6 Discounting

Both costs and health effects were discounted at an annual rate of 3.5% within the Merck cost-effectiveness model. At the time of the assessment, these discount rates were not recommended by NICE. The Assessment Group re-analysed the model using discount rates of 6% for costs and 1.5% for health outcomes.

6.1.4.7 Sensitivity analysis

Uncertainty surrounding mean estimates of resource use and overall survival was explored using bootstrapping techniques. Importantly, this approach did not account for uncertainty surrounding unit costs, utilities or hazard ratios. The exclusion of the uncertainty surrounding the hazard ratio for irinotecan versus active/best supportive care obtained from the trial reported by Cunningham et al[93] underestimates the true uncertainty surrounding the incremental costs and effects of cetuximab plus irinotecan as compared to active/best supportive care. The results of the bootstrapping analysis were presented as cost-effectiveness planes and CEAccs using LYGs as the measure of clinical benefit.

In order to account for uncertainty surrounding unit costs and hazard ratios, one-way sensitivity analyses were also undertaken by varying assumptions concerning the proposed continuation rule, the approximate proportion of patients receiving active chemotherapy within the active/best supportive group, the survival adjustment factor imposed on cetuximab/irinotecan patients who discontinue active therapy under the proposed continuation rule in the model, the survival adjustment factor imposed on cetuximab plus irinotecan patients who discontinue active therapy due to progressive disease, and discount rates for health outcomes. In addition, a number of cost parameters were tested within the sensitivity analysis; these included the cost of chemotherapy given to active/best supportive care patients, the cost of outpatient chemotherapy administration, the number of outpatient chemotherapy administrations given to those patients receiving active/best supportive care, the cost of a CT scan, and discount rates for costs.

6.1.4.8 Results

Table 30 shows the cost-effectiveness and cost-utility results obtained within the base case analysis.

Table 30 Base case model results from Merck model[35]

Treatment group	Total costs	LYGs	QALYs gained	Incremental cost per LYG	Incremental cost per QALY gained (utility=0.95)
Cetuximab/irinotecan (with continuation rule)	£17,339	0.89	0.85	**£33,263**	**£35,014 *((CIC data removed)* using MABEL [71])**
Cetuximab/irinotecan (without continuation rule)	£22,270	0.91	0.87	**£42,975**	**£45,237 *((CIC data removed)* using MABEL [71])**
Active/best supportive care	£3,368	0.47	0.45	-	-

Assuming discount rates of 3.5% for both costs and health outcomes, the base case analysis suggests that cetuximab plus irinotecan given according to the proposed continuation rule versus active/best supportive care costs an additional £33,263 per LYG and 35,014 per QALY gained.[35] Based upon the ***(CIC data removed)*** the MABEL trial,[72] cetuximab plus irinotecan given according to the continuation rule is estimated to cost an additional ***(CIC data removed)*** per QALY gained.[71] When costs and health outcomes are discounted at 6% and 1.5% respectively, cetuximab plus irinotecan given according to the proposed continuation rule is estimated to cost £32,916 per LYG and £34,648 per QALY gained. Based upon the ***(CIC data removed)*** the MABEL trial,[72] cetuximab plus irinotecan, given according to the proposed continuation rule and discounted at 6% for costs and 1.5% for health outcomes, is estimated to cost an additional ***(CIC data removed)*** per QALY gained.

When the continuation rule is not applied within the model, cetuximab plus irinotecan, discounted at 3.5% for costs and health outcomes is estimated to cost £42,975 per LYG and £45,237 per QALY gained.[35] When costs and health outcomes are discounted at 6% and 1.5% respectively, cetuximab plus irinotecan given without the proposed continuation rule is estimated to cost £42,521 per LYG and £44,759 per QALY gained. Based upon the ***(CIC data removed)*** the MABEL trial,[72] cetuximab plus irinotecan, given without the proposed continuation rule and discounted at 6% for costs and 1.5% for health outcomes, is estimated to cost an additional ***(CIC data removed)*** per QALY gained.

The results of the 2,000 bootstrap samples suggested that the incremental cost of cetuximab plus irinotecan ranged from around £10,000 to £17,000 per patient; the incremental QALYs gained ranged from approximately 0.28-0.61. The CEAccs suggest that the probability that

cetuximab plus irinotecan results in a greater level of net benefit than active/best supportive care assuming a willingness to pay threshold of £20,000 per LYG is close to zero. Assuming a willingness to pay threshold of £30,000 per LYG, the corresponding probability is around 0.10. However, it should be noted that the probabilistic sensitivity analysis does not incorporate uncertainty surrounding the hazard ratio or the unit costs, therefore the true uncertainty surrounding incremental costs and effects is underestimated.

The one-way sensitivity analysis presented in the sponsor submission resulted in incremental cost-effectiveness estimates ranging from £29,005 to £42,975 per LYG, and incremental cost-utility estimates ranging from £35,014 to £46,849 per QALY gained.[35] The least favourable cost-utility estimate was a result of applying a utility score of 0.71 based upon the study by Ko et al.[95] The sensitivity analysis suggests that the application of the proposed continuation rule has a considerable impact upon the cost-effectiveness and cost-utility of cetuximab plus irinotecan. ***(CIC data removed).***

6.1.4.9 Summary

The validity of the model developed by Merck to estimate the incremental costs and effects associated with cetuximab plus irinotecan versus active/best supportive care is questionable. Figure 12 suggests a degree of bias in the methods used to estimate overall survival for both the cetuximab plus irinotecan and the active/best supportive care treatment groups. The use of the hazard ratio for second-line active/best supportive care versus irinotecan as derived from the trial reported by Cunningham et al[93] is not intuitively sensible. Owing to the lack of direct evidence concerning the potential survival benefits conferred by cetuximab therapy over active/best supportive care, some form of indirect comparison is necessary. Given that such comparisons are required, fewer assumptions would have been required by comparing health outcomes for the cetuximab plus irinotecan treatment group against the observed survival benefits associated with active/best supportive care as reported by Cunningham et al.[93] The suitability of the adjustment in overall survival in the cetuximab monotherapy arm is highly dubious, as this assumes that the benefits conferred by cetuximab monotherapy and irinotecan are exactly equivalent. In addition, the uncertainty analysis does not account for the uncertainty surrounding this hazard ratio, therefore the CEAccs underestimate the true decision uncertainty.

Importantly, the application of the proposed continuation rule for treatment with cetuximab plus irinotecan results in favourable estimates of cost-effectiveness and cost-utility. As noted in Section 5.3.4.2, whilst the clinical studies of cetuximab plus irinotecan suggest the

existence of a relationship between the presence of the acne-like rash and overall survival, this sub-group analysis was not specified prospectively within these studies, and the validity of this relationship has not been rigorously demonstrated.

6.2 Independent economic assessment

6.2.1 Methods to estimate the cost-effectiveness and cost-utility of bevacizumab in the first-line treatment of metastatic colorectal cancer

6.2.1.1 Overview of Assessment Group models of bevacizumab

The principal aim of the health economic analysis undertaken by the Assessment Group was to estimate the marginal cost-effectiveness of two bevacizumab-containing chemotherapy regimens for the first-line treatment of metastatic CRC. The first mathematical model estimates the marginal cost-effectiveness of first-line bevacizumab in combination with irinotecan and 5-FU/FA as compared to irinotecan and 5-FU/FA. The second mathematical model estimates the marginal cost-effectiveness of first-line bevacizumab in combination with 5-FU/FA as compared to 5-FU/FA alone. As far as possible, the health economic models of bevacizumab follow the methodology for modelling chemotherapies for advanced CRC as proposed and utilised within the assessment of irinotecan, oxaliplatin and raltitrexed.[27] Notably, there are distinctions between the Roche models and the Assessment Group models in terms of the data used to inform the model parameters, the assumptions used to estimate the additional costs of chemotherapy treatment following progression on first-line treatment, and the approach used to reflect different states of HRQoL. Crucially, the Assessment Group models are based on the empirical overall survival outcomes observed within studies AVF2107g[58] and AVF2192g,[60] and do not employ the modified effectiveness estimates based on progression-free survival used within the Roche models.[65]

6.2.1.2 Health economic outcomes included in analysis

The following health economic outcomes are evaluated within the models:

- Cost per LYG
- Cost per QALY gained

6.2.1.3 Interventions included in health economic models of bevacizumab

The health economic models estimate the marginal cost-effectiveness and cost-utility of two indications of bevacizumab in comparison to standard chemotherapy treatment regimens, as shown in Table 31. The Roche model did not make explicit assumptions concerning cytotoxic therapies received following disease progression on first-line bevacizumab-containing therapy, and instead assumed a mean cost of £2,000 per month following disease progression on bevacizumab-containing therapy.[65] For the purpose of transparency, the Assessment Group models assume that patients would receive oxaliplatin in combination with 5-FU/FA following progression on first-line therapy; this is consistent with UK marketing authorisation, and current guidance issued by NICE on the use of chemotherapy for advanced CRC.[96] The Assessment Group models also assume that a small proportion of patients subsequently receive third-line treatment with Mitomycin C and protracted 5-FU.

Table 31 Interventions included within the health economic models

Treatment group	First-line therapy	Second-line therapy	Third-line therapy	Source of clinical effectiveness evidence for first-line therapy
Model 1				
Intervention	Bevacizumab + irinotecan + 5-FU/FA	Oxaliplatin + 5-FU/FA	Mitomycin-C + 5-FU	Hurwitz et al (AVF2107g)[58]
Comparator	Irinotecan + 5-FU/FA	Oxaliplatin + 5-FU/FA	Mitomycin-C + 5-FU	
Model 2				
Intervention	Bevacizumab + 5-FU/FA	Oxaliplatin + 5-FU/FA	Mitomycin-C + 5-FU	Kabbinavar et al (AVF2192g)[60]
Comparator	5-FU/FA	Oxaliplatin + 5-FU/FA	Mitomycin-C + 5-FU	

The two health economic models draw directly from clinical effectiveness evidence observed within the RCTs reported by Hurwitz and colleagues (Study AVF2107g)[58] and Kabbinavar and colleagues (Study AVF2192g).[60] This represents an important distinction from the Roche cost-effectiveness models. Study AVF2107g was designed to determine whether the addition of bevacizumab to a combination of IFL can improve overall survival in patients with metastatic CRC compared to a regimen of IFL plus placebo.[58] Study AVF2192g was designed to evaluate the safety and efficacy of bevacizumab in combination with FU/LV delivered on a weekly, high-dose schedule.[60]

Table 32 presents a description of the chemotherapy regimens included in the health economic model.

Table 32 Description of chemotherapy regimens included in the health economic models

Chemotherapy regimen	5-FU regimen	Cycle duration	Chemotherapy regimen components and protocol dose
Bevacizumab + IFL	Roswell Park (bolus)	6 weeks	*Weekly for 4 weeks, then 2 weeks rest (4 doses per cycle)* 125mg/m^2 irinotecan 500mg/m^2 5-FU 20mg/m^2 leucovorin *Once every two weeks (3 doses per cycle)* 5mg/kg bevacizumab
Bevacizumab + 5-FU/FA	Roswell Park (bolus)	8 weeks	*Weekly for 6 weeks, then 2 weeks rest (6 doses per cycle)* 500mg/m^2 5-FU 500mg/m^2 leucovorin *Once every two weeks (4 doses per cycle)* 5mg/kg bevacizumab
IFL	Roswell Park (bolus)	6 weeks	*Weekly for 4 weeks, then 2 weeks rest (4 doses per cycle)* 125mg/m^2 irinotecan 500mg/m^2 5-FU 20mg/m^2 leucovorin
5-FU/FA	Roswell Park (bolus)	8 weeks	*Weekly for 6 weeks, then 2 weeks rest (6 doses per cycle)* 500mg/m^2 5-FU 500mg/m^2 leucovorin
Oxaliplatin + 5-FU/FA	Modified de Gramont (infusional)	2 weeks	*Once every 2 weeks* 175mg folinic acid 400mg/m^2 5-FU 2800mg/m^2 5-FU 85mg/m^2 oxaliplatin
Mitomycin-C plus 5-FU	Protracted venous 5-FU	6 weeks	*Once every 6 weeks* 7mg/m^2 mitomycin *Daily* 300mg/m^2/24hours 5-FU

The two trials upon which the Assessment Group models are based used the Roswell Park bolus 5-FU/FA regimens; these are not commonplace in the UK. However, in order to maintain the internal validity of the resource use data collected within these trials, the costs associated with each of the chemotherapy regimens were modelled according to the Roswell Park regimen within the base case analysis. The impact of assuming an infusional 5-FU/FA regimen on the central estimates of cost-effectiveness, which better reflects UK clinical practice, was explored within the sensitivity analysis.

It should be noted that whilst the treatment options evaluated within these two cost-effectiveness models may be considered to be competing therapies, there are known

differences between the patient populations enrolled within the AVF2107g[58] and AVF2192g[60] trials (See Section 5.2.1.4). Owing to this heterogeneity, the costs and effects of the treatment options estimated within the two health economic models of bevacizumab should not be compared incrementally.

6.2.1.4 Cost-effectiveness analysis methods

6.2.1.4.1 Methods for estimating overall survival benefits for non-bevacizumab treatment arms

Kaplan-Meier curves giving empirical estimates of overall survival in each of the four treatment groups were obtained from the trial publications.[58,60] These empirical survival curves were digitally scanned using TECHDIG software, and subsequently imported into Microsoft EXCEL. As some patients were still alive at the end of the AVF2107g and AVF2192g trials (i.e. the curves were right-censored),[58,60] the final portion of each survival curve was extrapolated using regression analysis to estimate the parameters of a Weibull survival curve. Independent regression models were constructed to describe the probability of overall survival over time within each of the four treatment groups.

The Weibull survivor function $S(t)$ is given by the formula:

$$S(t) = \exp\{\lambda t^{\gamma}\}$$

where λ = scale parameter, t = time, and γ = shape parameter.

Transforming the survivor function $S(t)$ gives the linear relationship:

$$\Rightarrow \quad \ln\{-\ln S(t)\} = \ln\lambda + \gamma \ln t$$

where $\ln(t)$ is the independent variable and $\ln\{-\ln(S(t)\}$ is the dependent variable.

The application of this transformation to the Kaplan Meier survival estimates results in an approximately straight line whereby $\ln\{-\ln S(t)\} = y$, $\ln\lambda$ = intercept, γ = gradient and $\ln t$=x.

Figures 13 and 14 show the results of the regression-fitted survivor functions compared to the empirical overall survival observed within study AVF2107g.[58]

Figure 13 Empirical and modelled overall survival for bevacizumab+IFL and IFL treatment groups

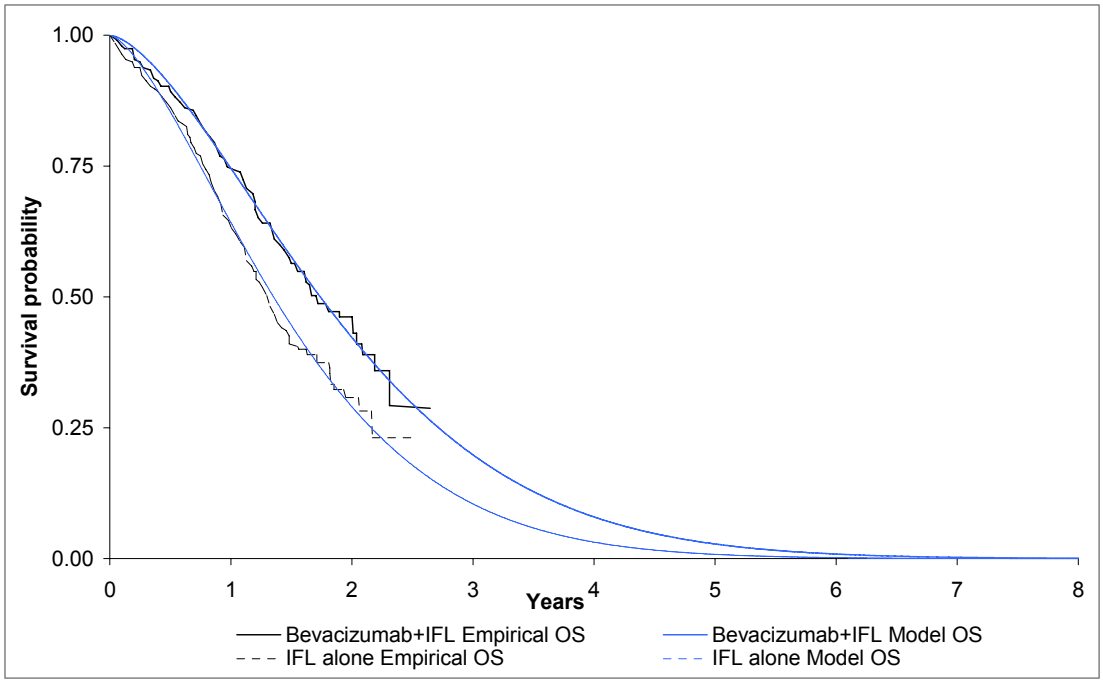
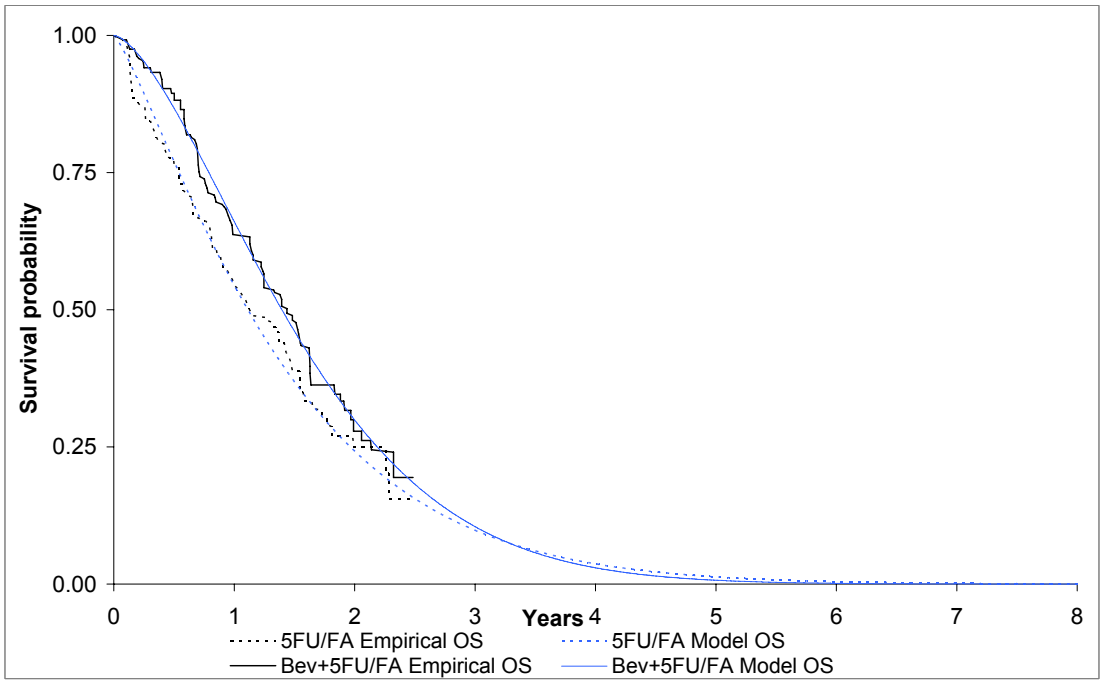


Figure 14 Empirical and modelled overall survival for bevacizumab+5-FU/FA and 5-FU/FA treatment groups



Figures 13 and 14 suggest that the fitted Weibull survivor functions provide a good fit to the empirical overall survival data. Notably, the empirical survival curves for patients receiving bevacizumab plus 5-FU/FA and 5-FU/FA alone intersect one another; the Weibull regression

model captures this relationship well. As noted in Section 6.1.3.4, the approach employed by Roche to estimate the progression-free and post-progression survival durations for patients in the two modelled bevacizumab trials included an adjustment to account for those patients who continued to receive bevacizumab following disease progression.[65] However, the analysis of post-progression survival estimates within studies AVF2107g and AVF2192g indicated that the overall survival of patients who received bevacizumab was not markedly different to the overall survival of patients who received some other chemotherapy following disease progression (See Table 28), and Roche's adjustment made very little difference to the empirical estimates.[65] For this reason, the Assessment Group's analysis is based upon the overall survival curves reported by Hurwitz et al[58] and Kabbinavar et al.[60]

The most appropriate measure of overall survival is the mean rather than the median; if the tail of the overall survival distribution is skewed, the median survival estimate is likely to be biased. Therefore, mean overall survival durations were estimated for each of the four modelled treatment groups using the following formula:

Mean survival = $(1/\lambda)^{(1/\gamma)} \times \Gamma\{1+(1/\gamma)\}$ where Γ is the mathematical gamma function.

6.2.1.4.2 Methods for estimating QALYs gained

Neither the AVF2107g study[58] or the AVF2192g study[60] included a direct assessment of HRQoL using a preference-based method through which health utilities could be estimated. On account of the absence of direct evidence of the utility of patients receiving bevacizumab and other chemotherapy regimens, systematic searches were undertaken to identify indirect evidence in order to estimate the utility associated with various states of health for patients with metastatic CRC. These search strategies are contained in Appendix 4. Four studies were identified which attempted to estimate utility scores for patients with metastatic CRC.[95,97,98,91] Details of these studies are reported in Table 33.

Table 33 Summary of characteristics of utility studies for metastatic CRC

Study	Study population	Method of elicitation and details of scenarios used
Ko et al[95]	Colon cancer subgroup included 169 patients.	The Health and Activities Limitation Index was mapped onto a utility scale. This does not appear to be preference-based but is a conversion of a numerical Likert rating scale.
Ness et al[97]	90 individuals who had previously undergone removal of colorectal adenoma. 81 of these patients were included in study.	Seven health states describing various states of severity of colon and rectal cancer. Scenarios F and G were *"Stage IV metastatic/unresectable disease with/without ostomy."* Preferences elicited using standard gamble.
Ramsey et al[98]	173 subjects with CRC (various stages) sampled from US SEER database completed the survey	Preferences elicited using the Health Utilities Index Mark 3 (HUI3)
Petrou and Campbell[91]	30 nurses experienced in oncology care	Utility scores for six chemotherapy-specific scenarios elicited using the standard gamble technique

Table 34 presents the utility scores reported for each of the scenarios used within the four identified studies.[91,95,97,98]

Table 34 Health state utility scores available within the literature

Health state description	Ko et al[95]	Ness et a[97]	Ramsey et al[98]	Petrou and Campbell[91]
<1yr post-diagnosis (no stage information available)	0.67 +/- 0.21			
1-5 yrs post-diagnosis (no stage information available)	0.68 +/- 0.24			
>5yrs post-diagnosis (no stage information available)	0.71 +/-0.25.			
Stage IV metastatic/unresectable disease without ostomy		0.24 (0.16, 0.32)		
Stage IV metastatic/unresectable disease with ostomy		0.27 (0.18, 0.36)		
Stage IV at 13-24months since diagnosis			0.95 (no range available, n=1)	
Stage IV at 25-36months since diagnosis			0.92 +/- 0.04	
Stage IV at 37-60months since diagnosis			0.76 +/- 0.11	
Stage IV at >60month since diagnosis			0.84 +/-0.13	
Chemotherapy in the previous month			0.80 (no range available)	
No chemotherapy in the previous month			0.84 (no range available)	
Best possible health				1.0 (no range available)
Worst possible health				0 (no range available)
Partial response				1.0 (no range available)
Stable disease				0.95 (no range available)
Progressive disease				0.575 (no range available)
Terminal disease				0.10 (no range available)

The lack of overlap in health states, and the highly variable utility scores for the studies presented in Table 34 highlights the paucity of good quality evidence relating to the impact of chemotherapy on HRQoL in patients with metastatic CRC. Notably, only two of these studies[98,91] elicited values for health states which explicitly concern treatment with cytotoxic therapies. The health economic model developed as part of the previous assessment of irinotecan and oxaliplatin[27] used unpublished evidence from the recent FOCUS trial[99] in order to value health utilities over time. The assessment of HRQoL, estimated using the EQ-5D

over a period of 48-weeks, suggested ***(CIC data removed)*** in patients receiving chemotherapy for metastatic CRC.[100]

The Assessment Group models assume that the quality of life of patients with metastatic CRC is determined primarily by their response to treatment. Only the study reported by Petrou and Campbell[91] attempted to estimate utility scores according to response on treatment as well as utility scores following the cessation of active therapy. Two health states were assumed in the Assessment Group models: *"progression-free"* and *"post-progression."* The utility score for stable disease reported by Petrou and Campbell[91] appears to be unrealistically close to a state of "perfect health" (utility = 0.95). The utility score associated with progression-free disease was instead assumed to be 0.80, the utility score for patients receiving chemotherapy as estimated by Ramsey et al.[98] The utility for patients with progressive disease was estimated by assuming a relative risk between the utility for stable disease and progressive disease. A beta distribution with a mean of 0.75 was used to describe this relative risk parameter. The use of the relative risk results in a utility score for the progressive disease state of 0.60.

The duration for which patients are free from disease progression whilst receiving first-line treatment was estimated using progression-free survival curves reported within studies AVF2107g[58] and AVF2192g.[60] Parametric Weibull curves were fitted to empirical Kaplan Meier progression-free survival curves using the same method described in Section 6.2.1.4.1. Mean progression-free survival durations for each treatment group were estimated by calculating the area under the progression-free survival curves. Second- and subsequent-line progression-free survival durations were not measured for patients following disease progression on first-line therapy within studies AVF2107g[58] or AVF2192g.[60] Second-line progression-free survival durations were assumed to reflect the experience of patients allocated to the FOLFIRI-FOLFOX treatment group within the GERCOR trial reported by Tournigand et al.[85] Given the absence of evidence to the contrary, the models assume that progression-free survival whilst receiving second-line treatment is the same for each treatment group, based upon the progression-free survival duration observed within the Tournigand trial.[85] Total time without disease progression was estimated by adding first-line and second-line progression-free survival durations. The duration for which patients experience progressive disease was calculated as the overall survival duration observed within treatment groups within studies AVF2107g[58] and AVF2192g[60] minus the estimated total progression-free survival periods calculated above.

It should be noted that the utility estimates describing alternative health states and the crude methods to estimate the proportion of time spent in these health states limit the validity of the

health economic analysis. Ideally, HRQoL evidence would have been assessed over the full duration of studies AVF2107g[58] and AVF2192g[60] using a suitable preference-based method.

6.2.1.4.3 Methods for estimating health care resource use and costs

Eleven groups of health resources and costs are included in the health economic models:

(1) Drug acquisition;

(2) Infusional pumps;

(3) Pharmacy costs;

(4) Hickman/PICC line insertion;

(5) Hospital resources for chemotherapy administration;

(6) Hospital admissions resulting from the incidence of adverse events;

(7) Drug used to manage adverse events;

(8) Diagnostic tests;

(9) Clinician consultations;

(10) Primary care costs;

(11) Supportive care costs following treatment cessation

With the exception of Hickman and PICC line insertion and supportive care costs, all costs were calculated on a cyclical basis such that mean costs for overall survival periods could be estimated for each chemotherapy regimen, and subsequently related to modelled overall survival benefits.

Drug acquisition costs

Unit costs of bevacizumab, irinotecan, oxaliplatin, 5-FU, FA and mitomycin were taken from the BNF.[89] In instances whereby multiple products were listed, the least expensive was used within the analysis. In keeping with recent guidance issued by NICE on the methods of health technology appraisal,[101] VAT was not added to unit costs within the health economic models. Data relating to the mean number of doses of bevacizumab, irinotecan, 5-FU and FA and the relative dose intensity of each drug administered during first-line treatment within studies AVF2107g[58] and AVF2192g[60] were obtained from the Roche submission to NICE[65] and from data contained within the mathematical models developed by Roche.

With the exception of bevacizumab, the mean acquisition cost of each chemotherapy component received was calculated using the following formula:

mean number of doses received x *mean dose (mg)* x *cost per mg* x *mean body size*

As the dose of bevacizumab is determined by body mass rather than surface area, the mean acquisition cost of bevacizumab was calculated using the following formula:
mean number of doses received x *mean dose (mg)* x *cost per mg* x *mean body mass*

The cost-effectiveness models assume that mean body mass in these patients is 75kg, and that mean body surface area is 1.75m^2.

Studies AVF2107g[58] and AVF2192g[60] did not collect information on chemotherapies received by patients enrolled within these trials following disease progression. In the UK, it is likely that the majority of patients would be offered oxaliplatin in combination with 5-FU/FA as second-line treatment if deemed sufficiently fit. It is further likely that if treated in the UK, a small proportion of patients would be offered further treatment with a third-line chemotherapy regimen (*Personal communication, Dr D Radstone, Consultant Oncologist, Weston Park Hospital, Sheffield)*.

Owing to the absence of evidence concerning subsequent-line chemotherapies received within studies AVF2107g[58] and AVF2192g,[60] assumptions were made concerning the expected time spent receiving further chemotherapies based upon data from previously identified studies of sequences of chemotherapies[99,85] and via expert opinion. Within the trial reported by Tournigand et al,[85] patients allocated to FOLFIRI/FOLFOX received a mean of 7.73 cycles of second-line oxaliplatin plus 5-FU. It was therefore assumed for all treatment groups that patients would receive a mean of 7.73 cycles of oxaliplatin plus 5-FU/FA as second-line treatment. It was further assumed that 10% of patients would subsequently receive third-line treatment with Mitomycin-C and protracted 5-FU for a period of 2-months (*Personal communication, Dr D Radstone, Consultant Oncologist, Weston Park Hospital, Sheffield)*. Given the absence of any empirical evidence, these assumptions were applied equally to all modelled treatment groups. Therefore, within the base case analysis, the costs associated with second- and subsequent-line chemotherapy use do not affect estimates of cost-effectiveness or cost-utility. These assumptions were tested within the sensitivity analysis.

Infusional pumps

The cost of disposable infusional pumps was taken from a study reported by Iveson and colleagues.[37] This was estimated as a weekly/cyclical cost and included the cost of the pharmacist's time. The model assumes that a new pump is required for each cycle of infusional 5-FU/FA received. The model assumes that six pumps are required for each cycle of protracted 5-FU plus mitomycin. A cost of £62.00 per infusor device was used within the analysis and uplifted using Health Service Inflation indices.[102]

Pharmacy costs

The estimated pharmacy costs per cycle of chemotherapy are summarised in Table 35. It was assumed that the handling cost for a simple i.v. infusion was £23.00, and the cost for a complex i.v. infusion was £38.00; this handling cost was assumed to be incurred for each cycle of treatment irrespective of the cycle length (*Personal communication, Michelle Rowe, Clinical Services, The Christie Hospital NHS Trust, Manchester, November 2005*). The cost of bevacizumab in combination with irinotecan and 5-FU/FA given according to the Roswell Park regimen was estimated to be £122, whilst the same regimen without bevacizumab was estimated to be £84. The cost of bevacizumab in combination with 5-FU/FA given according to the Roswell Park regimen was estimated to be £76, whilst the handling charge for 5-FU/FA alone was estimated to be £46. For second-line treatments, the handling charge for oxaliplatin plus 5-FU/FA was estimated to be £152. For the small proportion of patients who are assumed to receive third-line treatment with Mitomycin-C plus protracted 5-FU, the associated pharmacy cost was estimated to be £251 per cycle (*Personal communication, Michelle Rowe, Clinical Services, The Christie Hospital NHS Trust, Manchester, November 2005)*. All estimated pharmacy handling charges include the pharmacist's time for checking and the technician's time for dispensing.

Table 35 Pharmacy costs used in the health economic models

Chemotherapy drugs	Regimen	Simple components	Complex components	Pharmacy cost per cycle
Bevacizumab + IFL	Roswell Park	5-FU FA	Bevacizumab Irinotecan	£122
IFL	Roswell Park	5-FU FA	Irinotecan	£84
Bevacizumab + 5-FU/FA	Roswell Park	5-FU FA	Bevacizumab	£74
5-FU/FA	Roswell Park	5-FU FA	-	£46
Oxaliplatin + MdG	Modified de Gramont	-	Oxaliplatin 5-FU FA	£152
Mitomycin plus protracted 5-FU	6-weekly protracted cycle	Mitomycin-C	5-FU	£251

Hickman/PICC line insertion

The cost of line insertion was taken from the results of an RCT reported by Boland and colleagues.[103] This trial evaluated the effectiveness of image-guided Hickman line insertion versus unguided Hickman line insertion.[103] The cost of an unguided, rather than image-guided Hickman line insertion was used within the health economic models of bevacizumab. Cost estimates within the trial included the basic costs of insertion as well as unplanned events,

costs associated with misplaced insertions, serious adverse events and infections, and the costs of nurse, oncologist and radiologist assistance. A mean cost of £440.40 was used within the model[103] and uplifted using Health Service Inflation indices.[102] It should be noted that the cost associated with the insertion of a Hickman line is likely to be more expensive than the insertion of a PICC line; however, as this one-off cost is applied equally to both bevacizumab and non-bevacizumab treatment groups within the model, the resulting marginal cost-effectiveness estimates remain unaffected.

Administration costs

Unit costs of outpatient attendances were obtained from an earlier Personal Social Services Research Unit (PSSRU) report;[104] these costs are reported at 1999 prices, and were uplifted using Health Service Inflation indices.[102] It was assumed that these costs included nursing time for the administration of chemotherapy. The cost per medical oncology day case was not available and was hence assumed to be the same as a medical oncology outpatient attendance. A medical oncology inpatient day was reported to be £356 and a medical oncology outpatient day was reported to be £109;[104] this cost was uplifted to 2004 prices.[102] The hospitalisation resource use per cycle for each chemotherapy regimen assumed within the model is reported in Table 36.

Table 36 Hospitalisation resource use per cycle for chemotherapy regimens included in the health economic models of bevacizumab

Treatment regimen	Assumed hospitalisation requirements for chemotherapy administration per cycle
Bevacizumab+IFL (Roswell Park)	5 day case attendances every 6 weeks
IFL (Roswell Park)	4 day case attendances every 6 weeks
Bevacizumab+5-FU/FA (Roswell Park)	7 day case attendances every 8 weeks
5-FU/FA (Roswell Park)	6 day case attendances every 8 weeks
Oxaliplatin+5-FU/FA (Modified de Gramont)	1 day case attendance every 2 weeks
Mitomycin-C plus protracted 5-FU	6 day case attendances every 6 weeks (one administration day and 5 outpatient attendances for pump changes)

For the purpose of simplicity, the bevacizumab models presented here assume that all chemotherapy is administered within a day case setting. Indeed, this has been the increasing trend observed within usual clinical practice in England and Wales (*Personal communication: Dr D Radstone, Consultant Oncologist, Weston Park Hospital, Sheffield*). However, it should be noted that a small proportion of patients receive chemotherapy on an inpatient basis. It is likely that the impact of this simplification will have only a minimal impact upon the resulting estimates of cost-effectiveness and cost-utility.

Hospital admissions for chemotherapy-related adverse events

The cost associated with hospitalisation admission to manage chemotherapy-related adverse events was modelled using resource use evidence reported by Schmitt et al.[90] Schmitt et al[90] reported the mean number of days in hospital per patient per month whilst receiving chemotherapy. The study took the form of a retrospective case note review of patients enrolled within an RCT of irinotecan versus 5-FU/FA reported by Rougier.[105] Schmitt et al[90] estimated the mean number of days in hospital per month to be 1.2 and 0.8 days for irinotecan and 5-FU/FA respectively. In the absence of hospitalisation admission estimates specific to the treatment options evaluated within the models presented here, a mean estimate of 1.0 days per month is assumed for patients receiving all non-bevacizumab-containing chemotherapy regimens.

Data on the proportion of hospitalisations according to ward type were also reported by Schmitt et al;[90] these data were used together with the estimated days in hospital to calculate hospitalisation costs for chemotherapy-related adverse events, based upon unit costs reported by Netten and Dennett.[104] This resulted in an estimated cost per day in hospital of £258; this estimated cost was uplifted using HCHS inflation indices.[102] The calculations underpinning these estimates are presented in Table 37.

Table 37 Proportion of hospital days and unit costs by speciality

Department	Proportion of hospital days by specialty (Schmitt et al[90])			Cost per day [104]
	Irinotecan (n=127)	5-FU (n=129)	Average	
Medicine	51.5%	58.9%	55.2%	£222
Oncology	21.7%	10.1%	15.9%	£356
Surgery	19.3%	16.2%	17.8%	£301
ICU	0.4%	0.4%	0.4%	£359
Other	7.0%	14.2%	10.6%	£222
Mean cost per day	£257.54			

The additional hospitalisation resource use requirements associated with bevacizumab treatment was modelled using a relative risk of resource consumption estimated using data collected within the AVF2107g trial.[58] The relative risk of additional resource use required for treatment with bevacizumab was estimated to be approximately 1.13; this was assumed to be the same irrespective of the comparator treatment group.[65]

Drug costs for managing adverse events

Drug costs used to manage adverse events were estimated from a study reported by Kerr and O'Connor,[106] based on the average of the 5-FU and raltitrexed costs. An estimate of £9.74 per

month was assumed for the IFL and 5-FU/FA treatment options within the model; and uplifted using Health Service Inflation indices.[102] Additional drug costs associated with treatment with bevacizumab were estimated by assuming a relative risk of 1.13 as reported within the Roche submission.[65]

Cost of diagnostic tests

The cost of diagnostic tests was also taken from the study by Kerr and O'Connor.[106] This estimate included the cost of x-rays, blood tests and CT scans. A cost of £64.55 was assumed for each of the chemotherapy regimens, calculated as the mean of the raltitrexed and 5-FU/FA treatment arms.[106]

Clinician consultations

The cost of clinical consultations per cycle were estimated from the study reported by Iveson and colleagues.[37] A cost of £79.81 was used within the model and uplifted to 2004 prices using Health Service Inflation indices.[102]

Primary care costs

Primary care costs were taken from Kerr and O'Connor;[106] an estimate of £10.42 per month was assumed for all chemotherapy regimens.

Supportive care costs following treatment cessation

Evidence concerning the costs of supportive care of patients with metastatic CRC following treatment cessation is scant. A monthly cost of £600 for hospital and hospice care following cytotoxic treatment was assumed based upon a study which attempted to estimate the costs of managing women with stage IV breast cancer in the UK.[107] The Assessment Group model therefore assumes that supportive care costs for women with breast cancer are similar in patients with CRC. This estimate is subject to considerable uncertainty.

6.2.1.4.4 Discounting

Current guidance from NICE on the methods of Technology Appraisal[101] recommends that costs and benefits that occur in the future are given less weight than those that occur in the present. However, as the distribution of costs incurred over time is unknown, this means that the reliable application of discounting is problematic, and is not included in the Assessment Group models. Given the short time horizon used within the model, the omission of discounting is unlikely to have a substantial impact upon the estimates of cost-effectiveness and cost-utility.

6.2.1.4.5 Uncertainty analysis

The economic analysis of bevacizumab includes two types of uncertainty analysis: simple scenario analysis to explore the impact of alternative costing assumptions on the estimates of cost-effectiveness and cost-utility, and probabilistic sensitivity analysis to explore second-order uncertainty surrounding mean parameter values.

Scenario analysis

There exists a paucity of good quality evidence concerning resources required in the delivery of alternative chemotherapy regimens for metastatic CRC, and the resources required to manage adverse events associated with specific chemotherapy regimens. The earlier assessment of irinotecan, oxaliplatin and raltitrexed[27] identified several estimates of resources associated with chemotherapy administration. Scenario analysis was undertaken to explore the impact of assuming lower published cost estimates on central estimates of cost-effectiveness. As it is standard practice for chemotherapy for 5-FU/FA to be administered via infusion, scenario analysis was also undertaken to estimate the likely cost impact of assuming that first-line chemotherapy was given according to the modified de Gramont 5-FU/FA regimen. An additional sensitivity analysis was undertaken to explore the impact of assumptions concerning differential post-progression-free survival durations and associated costs on estimates of cost-effectiveness and cost-utility. Scenario analysis was also undertaken to consider the impact ***(CIC data removed)*** on the marginal cost-effectiveness estimates, based upon unpublished data from the FOCUS trial.[100]

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis was undertaken to explore the impact of second-order uncertainty surrounding mean parameter values on marginal costs and health effects. This was undertaken by describing parameter values within the model using probability distributions, and by propagating this uncertainty through the model using Monte Carlo sampling methods to produce information on the likelihood that each intervention is optimal (that is, the probability that the intervention produces more net benefit that the comparator). The results of these simulations are presented as cost-effectiveness planes and cost-effectiveness acceptability curves (CEAccs).

The overall survival curves and progression-free survival curves within the model were described by multivariate normal distributions of the form $X \sim N(m,V)$ where m is the vector of means (the scale and shape parameters of the baseline Weibull survivor function) and V is the covariance matrix of these means.

Standard errors surrounding the mean number of treatment cycles received during first-line therapy were taken from the Roche economic models:[65] these parameters were described by normal distributions. As chemotherapy acquisition costs and other administration costs are estimated on a cyclical basis, sample variation in the mean number of cycles received results in "knock-on" variation in the total costs of both drug acquisition and administration.

Uncertainty surrounding the difference in utility between the progression-free and progressive disease health states was modelled using a beta distribution. The parameters describing this distribution were subjectively selected such that the mean relative risk was 0.75, although the sampled relative risk could be as high as 1 (i.e. no difference in utility between progressive and stable disease states) or as low as 0.2 (i.e. utility in the progressive disease state is valued considerably lower than utility in the stable disease state).

As the bevacizumab trials did not collect further information on second- and subsequent-line therapies, there is uncertainty concerning the costs and health effects associated with these. The proportion of survival time spent in the second-line progression-free state was modelled using a beta distribution assuming a mean of 0.17.

Uncertainty surrounding the mean number of hospitalisations whilst receiving non-bevacizumab-including therapy was assumed to follow a lognormal distribution with a mean of 1 hospital day per month, and upper and lower limits of 2 days and 0.5 days respectively. Owing to the limitations of evidence concerning hospitalisation whilst receiving chemotherapy for metastatic CRC, the selection of these limits for the distribution was subjective. As the relative risk of hospital admission due to treatment-related toxicity and drug use for bevacizumab versus chemotherapy alone was estimated using resource data collected within study AVF2107g only,[58] the standard error surrounding this relative risk was doubled for the model based on study AVF2192g.[60]

Uncertainty surrounding the costs of supportive care was modelled using a lognormal distribution to allow for skewness. The parameters to this distribution were fitted such that the mean of the distribution was £600 per month, with upper and lower limits of £1,500 and £300 per month respectively. The selection of these limits for the distribution was subjective.

6.2.2 Methods to estimate the cost-effectiveness of cetuximab in combination irinotecan in the second- and subsequent-line treatment of patients with EGFR-expressing metastatic colorectal cancer after failure of irinotecan-including cytotoxic therapy

6.2.2.1 Overview of health economic model of cetuximab

The health economic analysis undertaken by the Assessment Group estimates the incremental cost-effectiveness of cetuximab in combination with irinotecan in comparison to active/best supportive care in the second- and subsequent-line treatment of patients with EGFR-expressing metastatic CRC after failure of irinotecan-including cytotoxic therapy. In line with the Merck submission to NICE,[35] *"active supportive care"* is defined as the best care available, as judged by the physician, and may include chemotherapy; supportive interventions may include antibiotics, analgesics, transfusions, corticosteroids, or any other symptomatic therapy and/or assistance of a psychotherapist, and localised radiation therapy to alleviate symptoms.[35] For the purpose of this model, *"best supportive care"* is assumed to include palliative interventions but explicitly excludes the use of active cytotoxic chemotherapy. Additional analysis was undertaken to estimate the incremental cost-effectiveness of cetuximab in combination with irinotecan in comparison to best supportive care alone, and oxaliplatin plus 5-FU/FA alone.

The mathematical model developed by the Assessment Group is centred around the methodology and data used within Merck's submission to NICE,[35] but incorporates more plausible assumptions concerning the expected survival of patients beyond the duration of the trial. The model also explores the impact of alternative assumptions concerning the survival of patients receiving active/best supportive care. It is crucial to note from the outset that the development of the Assessment Group model should be interpreted in the light of the absence of available evidence on the comparative efficacy of cetuximab plus irinotecan versus active/best supportive care. The review of the clinical effectiveness of cetuximab plus irinotecan (See Section 5.3) highlighted the complete absence of empirical evidence to demonstrate whether cetuximab plus irinotecan improves either health-related symptoms or overall survival in patients with EGFR-expressing metastatic CRC who have previously failed on irinotecan-containing therapy. Whilst cetuximab plus irinotecan has been demonstrated to impact upon tumour response rates,[73] the relationship between tumour response, and the impact of cetuximab treatment on HRQoL and overall survival remains unquantified.

The development of a health economic model to evaluate the potential cost-effectiveness of cetuximab plus irinotecan is by no means a substitute for methodologically rigorous clinical

trials, but instead represents a series of hypotheses to explore the potential cost-effectiveness of cetuximab in combination with irinotecan as compared to active/best supportive care.

Owing to the dearth of direct clinical evidence, the primary health economic analysis is presented as a threshold analysis, which attempts to elucidate the degree of additional overall survival benefit required in order for cetuximab plus irinotecan to achieve an acceptable level of cost-effectiveness and cost-utility in comparison to active/best supportive care. Indirect evidence from other clinical trials which have evaluated other chemotherapies in comparison to best supportive care is also considered in order to indicate the likely survival duration of patients without cetuximab treatment as second- or subsequent-line therapy. It should however, be noted that these comparisons are subject to known biases, as patients enrolled within these studies may have been either EGFR-positive or negative, and may or may not have previously received irinotecan-including therapy. Owing to the lack of clarity concerning the relationship between EGFR-expression and overall survival in patients with metastatic CRC, the magnitude of this bias on the resulting incremental effectiveness, cost-effectiveness and cost-utility estimates is unclear.

6.2.2.2 Health economic outcomes included in analysis

The mathematical model developed by the Assessment Group includes the following health economic outcomes:

- Cost per LYG
- Cost per QALY gained

6.2.2.3 Interventions included in health economic model

The health economic model compares the incremental costs and effects of cetuximab in combination with irinotecan versus active/best supportive care in patients with EGFR-expressing metastatic CRC who have failed on irinotecan-including cytotoxic therapy. The primary health economic analysis does not distinguish between patients who have received one or more previous lines of therapy; instead the analysis assumes that prognosis is independent of the number of previous treatment courses received. This is supported by *post hoc* analysis of Kaplan Meier survival estimates according to baseline patient characteristics within the BOND trial (See Appendix 10).[73]

A list of interventions included in the health economic model is presented in Table 38.

Table 38 List of chemotherapy regimens included in the health economic model

Chemotherapy regimen (treatment group)	Cycle duration	Chemotherapy regimen components and protocol dose
Cetuximab plus irinotecan (intervention group)	1 week	*Initial loading dose* 400mg/m^2 *Once every subsequent week* 250mg/m^2
Oxaliplatin+5-FU/FA (active supportive care group)	2 weeks (Modified de Gramont)	*Once every 2 weeks* 175mg folinic acid 400mg/m^2 5-FU 2800mg/m^2 5-FU 85mg/m^2 oxaliplatin
5-FU/FA (active supportive care group)	2 weeks (Modified de Gramont)	*Once every 2 weeks* 175mg folinic acid 400mg/m^2 5-FU 2800mg/m^2 5-FU
Mitomycin-C plus 5-FU/FA (active supportive care group)	6 weeks (protracted 5-FU)	*Once every 6 weeks* 7mg/m^2 mitomycin *Daily* 300mg/m^2/24hours 5-FU
Irinotecan monotherapy (active supportive care group)	3 weeks	*Once every 3 weeks* 350mg/m^2 irinotecan
Raltitrexed (active supportive care group)	3 weeks	*Once every 3 weeks* 3mg/m^2 raltitrexed

6.2.2.4 Cost-effectiveness analysis methods

6.2.2.4.1 Methods for estimating overall survival benefits for cetuximab plus irinotecan treatment group

The effectiveness of treatment with cetuximab plus irinotecan was estimated using patient-level data collected within the BOND trial.[73] Owing to the questionable validity of the extrapolation of overall survival outcomes for patients estimated within the Merck model (See Section 6.1.4.2), an alternative method of extrapolation using Weibull regression analysis was used to adjust for censoring of patients outcomes within the cetuximab plus irinotecan arm of the BOND trial.[73] Kaplan-Meier curves were constructed for patients allocated to the cetuximab plus irinotecan group of the BOND trial[73] using the empirical patient-level survival outcomes reported within the Merck cost-effectiveness model.[35] The parameters of a Weibull survivor function were then estimated using linear regression analysis.

The Weibull survivor function $S(t)$ is given by the formula:

$$S(t) = \exp\{-\lambda t^{\gamma}\}$$

where λ = scale parameter, t = time, and γ = shape parameter.

Transforming the survivor function $S(t)$ gives the linear relationship:

$$\Rightarrow \quad \ln\{-\ln S(t)\} = \ln\lambda + \gamma \ln t$$

where $\ln(t)$ is the independent variable and $\ln\{-\ln(S(t)\}$ is the dependent variable.

The results of the Assessment Group extrapolation are shown in Figure 15, together with the empirical overall survival estimates observed within the BOND trial[73] and the extrapolated survival outcomes estimated within the Merck model.[35]

Figure 15 Empirical and modelled overall survival curves for patients receiving cetuximab plus irinotecan

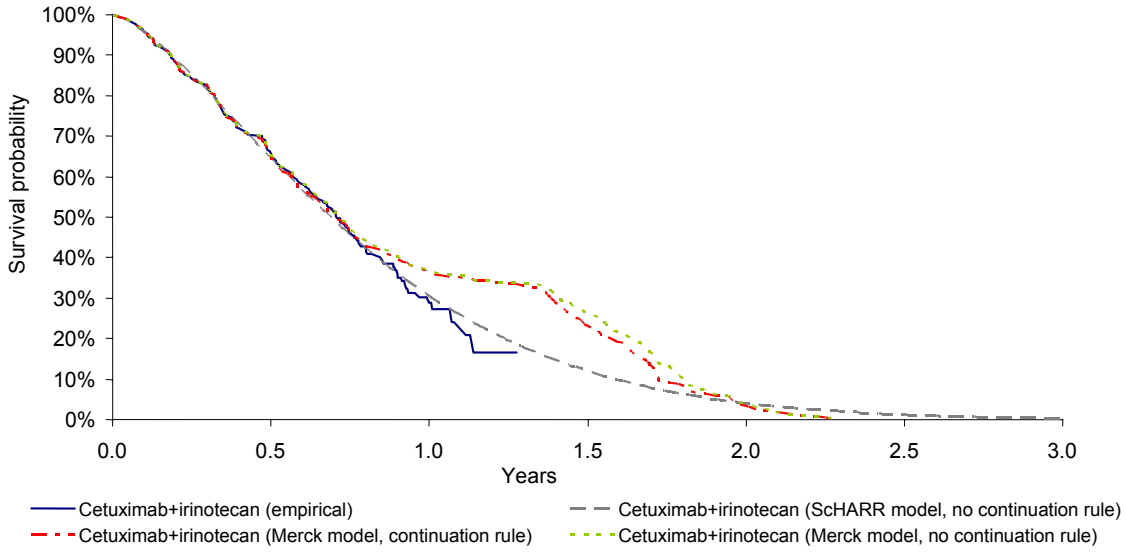


Figure 15 suggests that in comparison to the extrapolated survival curve produced by Merck, the Weibull extrapolation provides a considerably better fit to the empirical overall survival data observed within the BOND study.[73] The mean survival duration of patients receiving cetuximab in combination with irinotecan was calculated using the following formula.

Mean survival = $(1/\lambda)^{(1/\gamma)}$ x $\Gamma\{1+(1/\gamma)\}$ where Γ is the mathematical gamma function.

6.2.2.4.2 Methods for estimating overall survival benefits for patients receiving active/best supportive care

Active/best supportive care survival duration within the threshold analysis

The duration for which patients with EGFR-expressing metastatic CRC who have previously failed on irinotecan-including cytotoxic therapy may be expected to survive without second- or subsequent-line cetuximab therapy is unknown. Within the primary threshold analysis, the expected overall duration of patients receiving active/best supportive care is held as an unknown variable, and varied in order to indicate the likely incremental cost-effectiveness and cost-utility of cetuximab plus irinotecan versus active/supportive care.

Estimating the expected survival duration of patients receiving active/best supportive care using indirect sources

Systematic searches were undertaken in order to identify studies which included patients with metastatic CRC receiving active/best supportive care following one or more lines of active chemotherapy (See Appendix 4). The systematic searches identified three studies which included patients receiving active/best supportive care.[108,93,109] The study reported by Cunningham et al was a Phase III RCT of irinotecan versus best supportive care in patients with metastatic CRC who had failed 5-fluorouracil therapy.[93] Notably, 31% of the patients allocated to the best supportive care arm within this trial received further active chemotherapy.[93] The study reported by Rao and colleagues was a Phase III RCT of Farnesyl Transferase Inhibitor R115777 versus best supportive care in patients with refractory advanced CRC.[108] The third study, reported by Barni et al,[109] was a randomised study of low-dose subcutaneous interleukin-2 plus melatonin versus supportive care alone in patients with metastatic CRC who had previously failed on 5-FU treatment. Summary details of these studies are presented in Table 39. None of these three studies discriminated patients according to EGFR status.

Table 39 Summary of study characteristics of studies including best supportive care as second and subsequent-line treatments

	Cunningham et al[93]	Rao et al[108]	Barni et al[109]
Year of publication	1999	2004	1995
Median age (range)	62 yrs	61 yrs (25-82)	59 yrs (32-73)
Performance status (see Appendix 3)	WHO 31% 0 46% 1 23% 2	ECOG 93% 0-1 7% 2	KPS Median 80 Range 50-100
Previous treatment	5-FU	At least two prior chemotherapy regimens for advanced disease	5-FU/FA
Metastatic site	Liver (77%) Lung (30%) Peritoneum (10%)	-	Visceral lesions (88%) Bone (8% Soft tissues (4%)
Chemotherapy in BSC arm	Yes (31% patients)	No	No
Study setting	Prospective, multicenter non-blinded controlled trial	Multicenter, double-blind, randomised Phase III study, conducted in 64 centers in 18 countries	Single centre
Median OS (months)	6.5	6.1	9.0 (estimated from Kaplan Meier curve)
Median PFS (months)	Not reported	2.7	Not reported

6.2.2.4.3 Methods for estimating QALYs

The method used to estimate utility scores within the models of bevacizumab was also applied to the model of cetuximab plus irinotecan versus active/best supportive care. As with the bevacizumab model, two health states were defined: utility scores of 0.80 and 0.60 were applied to time in "stable disease" and "progressive disease" respectively (See 6.2.1.4.2). The progression-free survival duration for patients receiving cetuximab in combination with irinotecan was estimated using the empirical Kaplan Meier progression-free survival curve reported within the BOND trial. Progression-free survival curves for patients receiving active/best supportive care were available only for the trial reported by Rao et al.[108] Time without disease progression was estimated as the ratio of progression-free survival to overall survival (approximately 37% of overall survival) using outcomes for the control arm of this trial, based upon estimates of the area under the published Kaplan Meier curves.[108]

6.2.2.4.4 Methods for estimating health care resource use and costs

Acquisition costs

The acquisition costs of cetuximab and irinotecan were estimated using data on the number of vials administered within BOND trial as reported in the Merck submission to NICE.[73,35] Table 40 shows the observed chemotherapy resource use for patients receiving cetuximab plus irinotecan within the BOND trial. Unit costs for cetuximab and irinotecan were taken from the BNF.[89]

Table 40 Chemotherapy resource use for patients receiving cetuximab plus irinotecan within the BOND trial[35]

Drug	Number of vials administered	Mean vials per patient (n=218)
100mg cetuximab (including continuation rule)	18,849	86.46
2m-ml irinotecan (including continuation rule)	832	3.82
5m-ml irinotecan (including continuation rule)	4,229	19.40
100mg cetuximab (excluding continuation rule)	14,262	65.42
2m-ml irinotecan (excluding continuation rule)	1,037	4.76
5m-ml irinotecan (excluding continuation rule)	5,603	25.70

The acquisition costs associated with those patients who receive active supportive care were estimated using data collected from a subpopulation of patients who were eligible to participate in but were excluded from the BOND trial (as described in Section 6.1.4.5);[73] these data were reported within the Merck submission to NICE.[35] According to the Merck submission, this group represents a matched cohort of patients who were receiving active/best supportive care.[35] Table 41 shows the observed chemotherapy resource use for patients receiving active chemotherapy within the matched population resource use sample.

Table 41 Chemotherapy resource use for patients receiving active chemotherapy within the matched population resource use sample[35]

Drug	Total cycles	Mean dose per cycle
Oxaliplatin	130	185
Fluorouracil	139	5,125
Mitomycin C	23	10
Folinic acid	128	308
Capecitabine	12	2879
Irinotecan	30	303

Mean acquisition costs for each treatment group were estimated by multiplying the mg per dose of each drug administered by their respective unit cost, as shown in Table 42.[89]

Table 42 Acquisition costs used within cetuximab model

Drug	Mg per vial	Cost per vial	Cost per mg
Cetuximab	100	£136.50	£1.37
Irinotecan 2-ml vial	40	£53.00	£1.33
Irinotecan 5-ml vial	100	£130.00	£1.30
Oxaliplatin	100	£330.00	£3.30
5-FU	5,000	£64.00	£0.01
Mitomycin C	20	£36.94	£1.85
FA	350	£90.98	£0.26
Capecitabine	60,000	£295.06	£0.00
Raltitrexed	2	£121.86	£60.93

Administration costs

Hospitalisation resource use associated with the administration of cetuximab plus irinotecan was taken from the Merck cost-effectiveness model.[35] According to the Merck model, there were a total of 3,668 chemotherapy administrations within the combination arm of the BOND trial,[73] which corresponds to a mean of 16.83 administrations per patient. When the proposed continuation rule is employed, this would have resulted in 2,736 chemotherapy administrations, which corresponds to a mean of 12.55 administrations per patient.[35] Assuming a mean cost per day case attendance of £114.31 (uplifted from £109),[94] this results in a mean total administration cost of £1,435 when the proposed continuation rule is employed, and £1,923 when the proposed continuation rule is not included in the analysis.

The Merck submission to NICE reported that the mean number of day case attendances for chemotherapy administrations in the group of 19 patients receiving active supportive care was 5.8.[35] This however appears to be an underestimate, as one may expect the number of attendances for those patients receiving 5-FU/FA to be around 7.3 days (assuming a modified de Gramont regimen). As the total time receiving treatment for patients receiving active supportive care is unknown, treatment times for individual chemotherapy regimens were assumed to be independent. This may overestimate the total costs of administration on active supportive care, and therefore favours the cetuximab plus irinotecan treatment group. Based upon independent treatment times, the mean number of chemotherapy day case attendances was estimated to be 16.84, which results in a mean cost of hospitalisation for chemotherapy administration of £1,925.16.

The model also includes the costs of drugs to manage treatment-related adverse events, hospitalisations for adverse events, clinical consultations and tests and imaging whilst receiving chemotherapy. For the cetuximab plus irinotecan group, these costs were based upon a sample of 43 patients enrolled within the BOND trial;[73] for the active supportive care group, these costs were estimated from the sample of 20 patients within the resource use

sample described in 6.1.4.5.[35] The mean costs associated with the consumption of these resources in the two treatment groups are shown in Table 43.

Table 43 Monthly/cyclical costs of other resource use in cetuximab plus irinotecan and active supportive care treatment groups

Resource item	Cost	Source
Medical oncology outpatient visit for chemotherapy administration	£109.00	Netten and Dennett[104]
Pump cost per cycle	£62.00	Iveson[37]
Drug costs per month	£9.78	Kerr and O'Connor[106]
Pharmacy costs per cycle Cetuximab plus irinotecan	£46.00	*Personal communication, Michelle Rowe, The Christie Hospital, Manchester*
Pharmacy costs per cycle MdG + Oxaliplatin	£152.00	*Personal communication, Michelle Rowe, The Christie Hospital, Manchester*
Pharmacy costs per cycle MdG	£114.00	*Personal communication, Michelle Rowe, The Christie Hospital, Manchester*
Pharmacy costs per cycle mitomycin C	£251.00	*Personal communication, Michelle Rowe, The Christie Hospital, Manchester*
Pharmacy costs per cycle capecitabine	£12.00	*Personal communication, Michelle Rowe, The Christie Hospital, Manchester*
Pharmacy costs per cycle irinotecan monotherapy	£23.00	*Personal communication, Michelle Rowe, The Christie Hospital, Manchester*
Pharmacy costs per cycle raltitrexed	£23.00	*Personal communication, Michelle Rowe, The Christie Hospital, Manchester*
Consultation costs per month receiving cetuximab/irinotecan	£63.72	Merck submission[35]
Tests and imaging per month receiving cetuximab plus irinotecan	£38.45	Merck submission[35]
Hospitalisations per month receiving cetuximab plus irinotecan	£156.52	Merck submission[35]
Consultation costs per month whilst receiving active/best supportive care	£74.58	Merck submission[35]
Tests and imaging costs per month whilst receiving active/best supportive care	£17.25	Merck submission[35]
Hospitalisations costs per month whilst receiving active/best supportive care	£124.84	Merck submission[35]

The total costs of these resources in each treatment group were estimated by multiplying the resource use costs per month by the expected duration on treatment. For the cetuximab plus irinotecan treatment group, the mean time on treatment was estimated by multiplying the modelled overall survival duration by the proportion of survival time on treatment, estimated using outcomes and resource use data for uncensored patients within the BOND trial.[35] When

the continuation rule is included in the model, the BOND data suggests that patients remain on cetuximab plus irinotecan therapy for 45% of their total survival time. When the continuation rule is excluded in the model, the BOND data suggests that patients remain on cetuximab plus irinotecan for 51% of total survival time. Total treatment time in the active supportive care group was estimated by multiplying the number of cycles of each regimen received by their respective cycle lengths. It was assumed that all 5-FU/FA was given according to the Modified de Gramont regimen as this reflects usual clinical practice in England and Wales. The total costs of treatment for the active supportive care treatment group were then weighted by the assumed proportion of all patients who would receive active supportive care. Within the base case analysis, it was assumed that 31% of all active/best supportive care patients would receive further chemotherapy, based upon the trial reported by Cunningham et al.[93]

Supportive care costs

In line with the bevacizumab model described in Section 6.2.1, the cost associated with supportive care whilst not receiving active treatment was assumed to be £600 per month. The cost of supportive care in the cetuximab plus irinotecan group was estimated by multiplying the cost of supportive care by the estimated remaining survival time following cessation of treatment with cetuximab plus irinotecan. The same approach was employed to estimate the costs of supportive care for those patients receiving other active chemotherapy. The costs of supportive care in those patients who do not receive further chemotherapy was estimated by multiplying the mean overall survival duration by the annual costs of supportive care.

6.2.2.4.5 Discounting

As with the model of bevacizumab, the distribution of costs incurred over time is unknown, hence discounting is therefore not included in the model. Given the very short time horizon used within the analysis, the omission of discounting is unlikely to have a substantial impact upon the estimates of cost-effectiveness and cost-utility.

6.2.2.4.6 Uncertainty analysis

As the primary health economic analysis is presented as a threshold analysis, probabilistic uncertainty analysis is inappropriate. Scenario analyses are presented to consider the impact of alternative survival durations for patients receiving active/best supportive care, based upon published studies which have evaluated other chemotherapy versus best supportive care,[109,108,93] on the incremental cost-effectiveness of cetuximab in combination with irinotecan. In addition, the impact of alternative assumptions concerning the proportion of patients receiving active chemotherapy in the comparator group, and the impact of ***(CIC data***

removed) from the MABEL trial[72] on incremental estimates of cost-effectiveness and cost-utility are explored.

6.2.3 Cost-effectiveness results for bevacizumab in the first-line treatment of metastatic colorectal cancer

6.2.3.1 Overview of results

This section presents the results of the health economic models of bevacizumab in the first-line treatment of metastatic CRC. The results for bevacizumab in combination with IFL are presented in terms of the marginal cost per QALY gained as compared with IFL alone; the results for bevacizumab in combination with 5-FU/FA are presented in terms of the marginal cost per QALY gained as compared with 5-FU/FA alone. Section 6.2.3.2 reports the estimated costs and consequences of adding bevacizumab to two standard chemotherapy regimens. Median overall survival estimates presented within the trial publications,[58,60] are compared with the mean empirical estimates of overall survival and the parametric Weibull survival curves. The inclusion of utility adjustments to account for different states of HRQoL is also reported within this section. A breakdown of costs associated with drug acquisition, chemotherapy administration, and supportive care is reported separately for each assumed line of therapy over the lifetime of the population. Section 6.2.3.3 presents the central estimates of cost-effectiveness under the base case model assumptions. Section 6.2.3.4 details the results of a series of scenario analyses used to test the structural and parametric assumptions within the model, as well as the results of the probabilistic sensitivity analysis. Sections 6.2.3.5 and 6.2.3.6 present the findings of the cost-effectiveness analysis and the estimated costs to the NHS respectively. Section 6.2.3.7 highlights areas for further research.

6.2.3.2 Costs and consequences of treatment with bevacizumab

Table 44 shows a comparison of median and estimated mean overall survival together with the results of the Weibull regression analysis. Due to the censoring of the survival curves, it should be noted that the mean AUC estimates calculated using the empirical Kaplan Meier curves are downwardly biased. The Weibull models account for this additional survival beyond the durations of studies AVF2107g[58] and AVF2192g.[60]

Table 44 Median and mean overall survival estimated using empirical Kaplan Meier overall survival curves and Weibull modelled survival curves

	Median overall survival (years)	AUC mean overall survival estimate (years)	Weibull overall survival estimate (years)
Study AVF2107g[58]			
Bevacizumab+IFL	1.69	1.68	1.98
IFL+placebo	1.30	1.41	1.57
Incremental	**0.39**	**0.27**	**0.41**
Study AVF2192g[60]			
Bevacizumab+5-FU/FA	1.38	1.43	1.59
5-FU/FA	1.08	1.26	1.41
Incremental	**0.31**	**0.18**	**0.19**

The AUC mean estimates of overall survival presented in Table 44 are lower than the median survival estimates reported within the trial publications for studies AVF2107g[58] and AVF2192g.[60] However, when the censoring in the tail of the curves is accounted for using Weibull regression modelling, the difference in overall survival for bevacizumab plus IFL versus IFL alone is estimated to be 0.41 years, whilst the incremental difference in overall survival for bevacizumab plus 5-FU/FA versus 5-FU/FA alone is estimated to be 0.19 years. It should be noted that the regression models of overall survival for study AVF2107g[58] appear to slightly underestimate the survival of patients receiving IFL alone, therefore the marginal survival benefit for patients receiving bevacizumab plus IFL over IFL may be overestimated.

Table 45 presents the estimated number of QALYs gained within the treatment groups included in the health economic models, based upon the methods reported in Section 6.2.2.4.3. The estimates of effectiveness employed within the model are based upon the Weibull survival curves, rather than the AUC analysis of the empirical survival curves.

Table 45 Estimated QALYs gained for modelled treatment options

Trial arm	Estimated time with stable disease (years)*	Estimated LYGs	Estimated time with progressive disease (years)	QALYs gained stable disease	QALYs gained progressive disease	Total QALYs gained	Marginal QALYs gained
Study AVF2107g[58]							
Bevacizumab+IFL	1.27	1.98	0.70	1.02	0.42	1.44	**0.31**
IFL	0.97	1.57	0.59	0.78	0.35	1.13	
Study AVF2192g[60]							
Bevacizumab+ 5-FU/FA	1.16	1.59	0.43	0.93	0.26	1.19	**0.18**
5-FU/FA	0.83	1.41	0.57	0.67	0.34	1.01	

**Includes estimate of progression-free survival duration whilst receiving first- and second-line therapy*

Table 46 presents a breakdown of the cost estimates for the four treatment options included in the health economic models; for the purpose of transparency, these are differentiated according to the individual line of therapy within the assumed modelled treatment sequences.

Table 46 Breakdown of cost components estimated within the cost-effectiveness models

Cost component	First-line bevacizumab +IFL	First-line IFL	First-line bevacizumab+ 5-FU/FA	First-line 5-FU/FA
Estimated first-line acquisition costs	£20,157.86	£4,500.28	£17,556.65	£3,569.81
Assumed second-line acquisition costs*	£4,269.68	£4,269.68	£4,269.68	£4,269.68
Assumed third-line acquisition costs*	£34.84	£34.84	£34.84	£34.84
Estimated first-line administration costs	£8,399.69	£5,509.51	£7,032.45	£4,375.60
Estimated second-line administration costs*	£4,351.34	£4,351.34	£4,217.82	£4,217.82
Estimated third-line administration costs*	£395.12	£395.12	£395.12	£395.12
Line insertion costs	£456.36	£456.36	£456.36	£456.36
Supportive care costs	£5,075.21	£4,262.24	£3,111.36	£4,140.12
Total costs	**£43,140.09**	**£23,779.36**	**£37,074.28**	**£21,459.35**

**Assumed to be the same across all treatment options in the base case analysis. This assumption is tested in the sensitivity analysis*

Table 46 demonstrates that the most substantial cost component within both models is the acquisition cost associated with bevacizumab; this represents an additional cost of around £14,000 - £15,700 when added to non-bevacizumab containing chemotherapy regimens. Further costs are also incurred due to the additional administration requirements for the two bevacizumab-containing treatment options. Post-progression treatment costs are assumed to be the same for all treatment groups within the base case analysis.

6.2.3.3 Central estimates of cost-effectiveness and cost-utility

Table 47 presents the central estimates of the marginal cost-effectiveness and cost-utility of first-line bevacizumab in combination with IFL versus IFL alone, and bevacizumab in combination with 5-FU/FA versus 5-FU/FA alone.

Table 47 Central estimates of cost-effectiveness and cost-utility

Treatment arm	Mean LYG	Mean QALYs gained	Mean total cost	Marginal cost per LYG	Marginal cost per QALY gained
***Study AVF2107g*[58]**					
Bevacizumab+IFL	1.98	1.44	£43,140.09	**£46,853.48**	**£62,857.10**
IFL+placebo	1.57	1.13	£23,779.36		
Difference	0.41	0.31	£19,360.73		
***Study AVF2192g*[60]**					
Bevacizumab+5-FU/FA	1.59	1.19	£37,074.28	**£84,395.74**	**£88,435.85**
5-FU/FA	1.41	1.01	£21,459.35		
Difference	0.19	0.18	£15,614.94		

Table 47 suggests that treatment with bevacizumab plus IFL costs approximately £19,361 more than treatment with IFL over the lifetime of the average patient, and results in an estimated 0.41 additional LYGs. The model suggests that bevacizumab in combination with IFL costs an estimated £46,854 for each additional LYG when compared to IFL alone. When survival is adjusted to account for differences in HRQoL between different disease states, the addition of bevacizumab to IFL is estimated to produce an additional 0.31 QALYs. The model suggests that bevacizumab in combination with IFL costs an estimated £62,857 per QALY gained when compared to IFL alone.

The health economic model based upon study AVF2192g[60] suggests that treatment with bevacizumab plus 5-FU/FA costs approximately £15,615 more than treatment with 5-FU/FA alone over the lifetime of the patient, and results in an estimated 0.19 additional LYGs. The model suggests that bevacizumab in combination with 5-FU/FA costs an estimated £84,396 per LYG when compared to 5-FU/FA alone. When survival is adjusted to account for differences in HRQoL between disease states, the addition of bevacizumab to 5-FU/FA is estimated to produce an additional 0.18 QALYs. The model suggests that bevacizumab in combination with 5-FU/FA costs an estimated £88,436 per QALY gained when compared to 5-FU/FA alone.

6.2.3.4 Simple sensitivity analyses

The cost-effectiveness models of first-line bevacizumab are hinged upon numerous structural and parametric assumptions. This section explores the potential impact of this uncertainty on the central estimates of cost-effectiveness and cost-utility.

6.2.3.4.1 Cost-effectiveness results based upon estimates of overall survival generated by Roche[65]

The central estimates of cost-effectiveness and cost-utility reported in Section 6.2.3.3 are based upon the overall survival durations using empirical evidence observed within studies AVF2107g[58] and AVF2192g.[60] However, as patients within the intervention groups of these two studies were allowed to continue receiving bevacizumab beyond disease progression, the reported overall survival estimates may be biased in favour of the intervention groups (although the evidence of post-progression survival presented in Table 28 does not indicate the presence of this bias). Consequently, the central estimates of cost-effectiveness and cost-utility presented in Section 6.2.3.3 are more favourable for bevacizumab plus IFL and less favourable for bevacizumab plus 5-FU/FA than those presented within the Roche submission.[65] These differences are a direct result of the adjustments made by Roche to the overall survival estimates observed within studies AVF2107g[58] and AVF2192g.[60] Table 48 presents alternative cost-effectiveness and cost-utility estimates based upon the Assessment Group models, assuming the levels of survival benefit estimated within the Roche models.[65]

Table 48 Sensitivity analysis - marginal cost-effectiveness estimates assuming modelled survival benefits estimated by Roche[65]

Treatment arm	Mean LYG	Mean QALYs gained	Mean total costs	Marginal cost per LYG	Marginal cost per QALY gained
Study AVF2107g[58]					
Bevacizumab+IFL	2.02	1.48	£43,087.57	**£62,532.28**	**£76,831.68**
IFL+placebo	1.73	1.24	£24,687.04		
Marginal difference	0.29	0.24	£18,400.52		
Study AVF2192g[60]					
Bevacizumab+5-FU/FA	2.01	1.47	£38,760.25	**£42,409.68**	**£51,355.34**
5-FU/FA	1.63	1.16	£22,473.68		
Marginal difference	0.38	0.32	£16,286.57		

The results shown in Table 48 suggests that the assumptions concerning overall survival for each of the treatment options results in less favourable estimates of cost-effectiveness and cost-utility for bevacizumab plus IFL. However, the approach adopted by Roche resulted in a greater marginal impact upon survival for bevacizumab plus 5-FU/FA versus 5-FU/FA than suggested by the Assessment Group model; this is because the difference in mean progression-free survival duration observed for the treatment groups within study AVF2192g was greater than the difference in mean overall survival. Consequently, the use of survival estimates from the Roche model result in considerably more favourable estimates of cost-effectiveness and cost-utility for bevacizumab plus 5-FU/FA versus 5-FU/FA.

6.2.3.4.2 Alternative assumptions concerning second- and subsequent-line treatment resource use

The base case analysis assumes that the duration of second- and subsequent line treatment and the benefits attributable to this are the same for all treatment groups. As data concerning the resources consumed beyond disease progression within each of the treatment groups were not collected within either study AVF2107g[58] or study AVF2192g;[60] the true impact of second-line therapy is uncertain. Table 49 presents the results of a sensitivity analysis whereby the number of treatment cycles and the progression-free survival benefits attributable to such treatment are assumed to be directly related to the duration of overall survival observed within the trials, based upon resource and outcome data from the trial reported by Tournigand et al.[85] Within the model based upon study AVF2107g,[58] this sensitivity analysis assumes that patients allocated to bevacizumab plus IFL subsequently receive a mean of 6.9 cycles of oxaliplatin plus 5-FU/FA as second-line treatment; patients allocated to IFL alone are assumed to subsequently receive a mean of 5.5 cycles of oxaliplatin plus 5-FU/FA as second-line treatment. Within the model based upon study AVF2192g,[60] this sensitivity analysis assumes that patients allocated to the bevacizumab plus 5-FU/FA arm receive a mean of 5.6 cycles of oxaliplatin plus 5-FU/FA as second-line treatment; patients allocated to the 5-FU/FA arm are assumed to receive a mean of 4.9 cycles of oxaliplatin plus 5-FU/FA as second-line treatment.

Table 49 Sensitivity analysis – marginal cost-effectiveness estimates assuming differential chemotherapy benefits following disease progression

Treatment arm	Mean LYG	Mean QALYs gained	Mean total costs	Marginal cost per LYG	Marginal cost per QALY gained
Study AVF2107g[58]					
Bevacizumab+IFL	1.98	1.45	£41,810.56	**£49,458.04**	**£63,272.84**
IFL+placebo	1.57	1.13	£21,373.58		
Marginal difference	0.41	0.32	£20,436.99		
Study AVF2192g[60]					
Bevacizumab+5-FU/FA	1.59	1.19	£34,775.82	**£86,939.72**	**£87,766.28**
5-FU/FA	1.41	1.00	£18,690.20		
Marginal difference	0.19	0.18	£16,085.63		

Table 49 demonstrates that the assumptions concerning differential chemotherapy use following disease progression has only a minor impact upon the marginal costs and effects of bevacizumab plus IFL compared to IFL and bevacizumab plus 5-FU/FA compared to 5-FU/FA.

6.2.3.4.3 Scenario analysis assuming lower published cost estimates

Numerous potential cost sources to inform the resource parameters included within the two health economic models are available within the literature. In line with the approach used within the earlier assessment of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced CRC,[27] the base case analysis uses high cost estimates. A comparison of high and low cost estimates for resource components is presented in Table 50.

Table 50 Alternative cyclical costs used in scenario analysis

Parameter	Base case cost (high estimate)	Source	Scenario analysis cost (low estimate)	Source
Days in hospital per month*	1.00	Schmitt[90]	0.38	Analysis of progression-free survival reported in de Gramont trial[110]
Cost per hospital day*	£258	Iveson[37]	£300	Unpublished data from de Gramont trial[110]
Monthly cost of diagnostic tests	£65.00	Kerr and O'Connor[106]	£3.16	Iveson[37]
Monthly primary care cost	£10.42	Iveson[37]	£1.14	Kerr[106]
Line insertion cost	£440.40	Boland[103]	£250.00	Iveson[37]

**Cost per day and number of hospital days relate to same source*

The resulting marginal cost-effectiveness estimates assuming lower cost estimates are presented in Table 51.

Table 51 Sensitivity analysis – marginal cost-effectiveness estimates assuming lower published cost estimates

Treatment arm	Mean LYG	Mean QALYs gained	Mean total costs	Marginal cost per LYG	Marginal cost per QALY gained
Study AVF2107g[58]					
Bevacizumab+IFL	1.98	1.44	£39,801.33	**£45,323.78**	**£60,804.90**
IFL+placebo	1.57	1.13	£21,072.70		
Marginal difference	0.41	0.31	£18,728.63		
Study AVF2192g[60]					
Bevacizumab+5-FU/FA	1.59	1.19	£34,111.46	**£80,862.82**	**£84,733.80**
5-FU/FA	1.41	1.01	£19,150.18		
Marginal difference	0.19	0.18	£14,961.28		

Table 51 suggests that the use of lower cost estimates has only a limited impact upon the marginal costs of bevacizumab, thus the estimates of cost-effectiveness and cost-utility remain broadly similar to those reported within the base case analysis (see Section 6.2.3.3).

6.2.3.4.4 Scenario analysis assuming all 5-FU/FA chemotherapy is administered as an infusional regimen

Within studies AVF2107g[58] and AVF2192g,[60] all first-line chemotherapy was given according to the Roswell Park bolus regimen, which is not commonly used in clinical practice in England and Wales. Table 52 presents marginal cost-effectiveness and cost-utility results if all 5-FU/FA regimens are assumed to be given according to the Modified de Gramont regimen. The model therefore assumes that for each cycle, patients receive up to 3,200mg/m^2 5-FU, 200mg FA, and 180mg/m^2 irinotecan where applicable. The number of cycles of first-line chemotherapy received within each treatment group is estimated according to the estimated time spent receiving first-line chemotherapy within studies AVF2107g[58] and AVF2192g.[60]

Table 52 Sensitivity analysis – marginal cost-effectiveness estimates assuming all 5-FU/FA treatment is given according to the infusional Modified de Gramont regimen

Treatment arm	Mean LYG	Mean QALYs gained	Mean total costs	Marginal cost per LYG	Marginal cost per QALY gained
Study AVF2107g[58]					
Bevacizumab+IFL	1.98	1.44	£40,306.06	**£45,044.74**	**£60,430.55**
IFL+placebo	1.57	1.13	£21,692.73		
Marginal difference	0.41	0.31	£18,613.33		
Study AVF2192g[60]					
Bevacizumab+5-FU/FA	1.59	1.19	£28,662.98	**£70,475.16**	**£73,848.88**
5-FU/FA	1.41	1.01	£15,623.63		
Marginal difference	0.19	0.18	£13,039.35		

Table 52 suggests that there is little difference in the marginal cost of bevacizumab plus IFL versus IFL alone whether given according to the bolus Roswell Park regimen, or whether 5-FU/FA is administered according to the infusional Modified de Gramont regimen. When all 5-FU/FA regimens are assumed to be administered according to the Modified de Gramont regimen, the marginal cost of IFL plus bevacizumab versus IFL is reduced by approximately £750. The assumption of infusional rather than bolus 5-FU/FA has a greater impact upon the marginal cost-effectiveness and cost-utility of bevacizumab plus 5-FU/FA compared to 5-FU/FA alone, leading to a reduction in marginal cost of approximately £2,580. The results of this sensitivity analysis should be interpreted with caution, as the relative impact of Modified de Gramont and Roswell Park regimens on overall survival is unclear.

6.2.3.4.5 Higher day case cost estimate

There is uncertainty surrounding the unit costs associated with different types of hospital

attendance. In line with the earlier assessment of the clinical effectiveness and cost-effectiveness of irinotecan, oxaliplatin and raltitrexed in the treatment of advanced CRC,[27] the cost associated with day case hospital attendance was derived from an early PSSRU report;[104] within the base case analysis, the cost per day case attendance was assumed to be £109. The NHS Reference Costs[94] report the cost of a day case attendance for chemotherapy with a digestive system primary diagnosis to be £255. Table 53 reports the impact of this higher cost estimate on the marginal cost-effectiveness results.

Table 53 Sensitivity analysis – marginal cost-effectiveness estimates assuming a higher cost for day case attendances

Treatment arm	Mean LYG	Mean QALYs gained	Mean total costs	Marginal cost per LYG	Marginal cost per QALY gained
Study AVF2107g[58]					
Bevacizumab+IFL	1.98	1.44	£49,151.60	**£51,163.91**	**£68,639.83**
IFL+placebo	1.57	1.13	£28,009.71		
Marginal difference	0.41	0.31	£21,141.88		
Study AVF2192g[60]					
Bevacizumab+5-FU/FA	1.59	1.19	£42,639.22	**£93,346.70**	**£97,815.30**
5-FU/FA	1.41	1.01	£25,368.18		
Marginal difference	0.19	0.18	£17,271.05		

Table 53 suggests that the use of a higher day case attendance cost results in less favourable cost-effectiveness estimates than those presented within the base case analysis. This is due to the additional resource use associated with bevacizumab treatment. The use of the higher day case attendance cost is estimated to increase the marginal cost of treatment by around £1,700 within both models.

6.2.3.4.6 Uncertainty surrounding HRQoL

There is a paucity of robust evidence relating to the HRQoL associated with alternative states of health whilst receiving chemotherapy in patients with metastatic CRC. The earlier assessment of irinotecan, oxaliplatin and raltitrexed in the treatment of advanced CRC[27] used evidence collected within the MRC-sponsored FOCUS trial.[100] Within this study, patients were asked to complete the EQ-5D health status instrument at 6-week intervals over a period of 48 weeks. Early analysis of these data suggested that the mean utility of patients with metastatic CRC whilst receiving chemotherapy is ***(CIC data removed)***.[100] Table 54 ***(CIC data removed)*** for all patients who are alive.

Table 54 Sensitivity analysis - impact *(CIC data removed)*the FOCUS trial on marginal cost-utility

Treatment arm	Mean LYG	Mean QALYs gained	Mean total costs	Marginal cost per LYG	Marginal cost per QALY gained
***Study AVF2107g*[58]**					
Bevacizumab+IFL	1.98	***(CIC data removed)***	£43,140.09	**£46,853.48**	***(CIC data removed)***
IFL+placebo	1.57		£23,779.36		
Marginal difference	0.41		£19,360.73		
***Study AVF2192g*[60]**					
Bevacizumab+5-FU/FA	1.59	***(CIC data removed)***	£37,074.28	**£84,395.74**	***(CIC data removed)***
5-FU/FA	1.41		£21,459.35		
Marginal difference	0.19		£15,614.94		

Table 54 suggests that the assumption of ***(CIC data removed)***for patients prior to progression and following disease progression has little impact upon the marginal cost-utility of bevacizumab plus IFL versus IFL alone. However, the impact upon the cost-utility of bevacizumab plus 5-FU/FA versus 5-FU/FA alone is substantial; the use of ***(CIC data removed)*** is estimated to result in a marginal cost-utility estimate of ***(CIC data removed)*** per QALY gained for bevacizumab plus 5-FU/FA versus 5-FU/FA alone.

6.2.3.4.7 Alternative assumptions concerning palliative and supportive care costs

There is considerable uncertainty surrounding the costs of supportive care given to patients following cessation of chemotherapy. Tables 55 and 56 present the marginal cost-effectiveness and cost-utility results assuming half (£300) and double (£1,200) the cost of supportive care assumed in the base case analysis.

Table 55 Sensitivity analysis - marginal cost-effectiveness results assuming supportive care costs of £300 per month

Treatment arm	Mean LYG	Mean QALYs Gained	Mean total costs	Marginal cost per LYG	Marginal cost per QALY gained
***Study AVF2107g*[58]**					
Bevacizumab+IFL	1.98	1.44	£40,600.28	**£45,868.91**	**£61,536.24**
IFL+placebo	1.57	1.13	£21,646.39		
Marginal difference	0.41	0.31	£18,953.89		
***Study AVF2192g*[60]**					
Bevacizumab+5-FU/FA	1.59	1.19	£35,517.25	**£87,178.27**	**£91,351.58**
5-FU/FA	1.41	1.01	£19,387.49		
Marginal difference	0.19	0.18	£16,129.76		

Table 56 Sensitivity analysis - marginal cost-effectiveness results assuming supportive care costs of £1200 per month

Treatment arm	Mean LYG	Mean QALYs gained	Mean total costs	Marginal cost per LYG	Marginal cost per QALY gained
Study AVF2107g[58]					
Bevacizumab+IFL	1.98	1.44	£48,206.48	**£48,817.49**	**£65,491.95**
IFL+placebo	1.57	1.13	£28,034.18		
Marginal difference	0.41	0.31	£20,172.30		
Study AVF2192g[60]					
Bevacizumab+5-FU/FA	1.59	1.19	£40,180.23	**£78,845.21**	**£82,619.60**
5-FU/FA	1.41	1.01	£25,592.26		
Marginal difference	0.19	0.18	£14,587.98		

Tables 55 and 56 clearly demonstrate that the assumptions concerning the costs associated with supportive care following chemotherapy treatment cessation have only a minor impact upon the cost-effectiveness and cost-utility of bevacizumab.

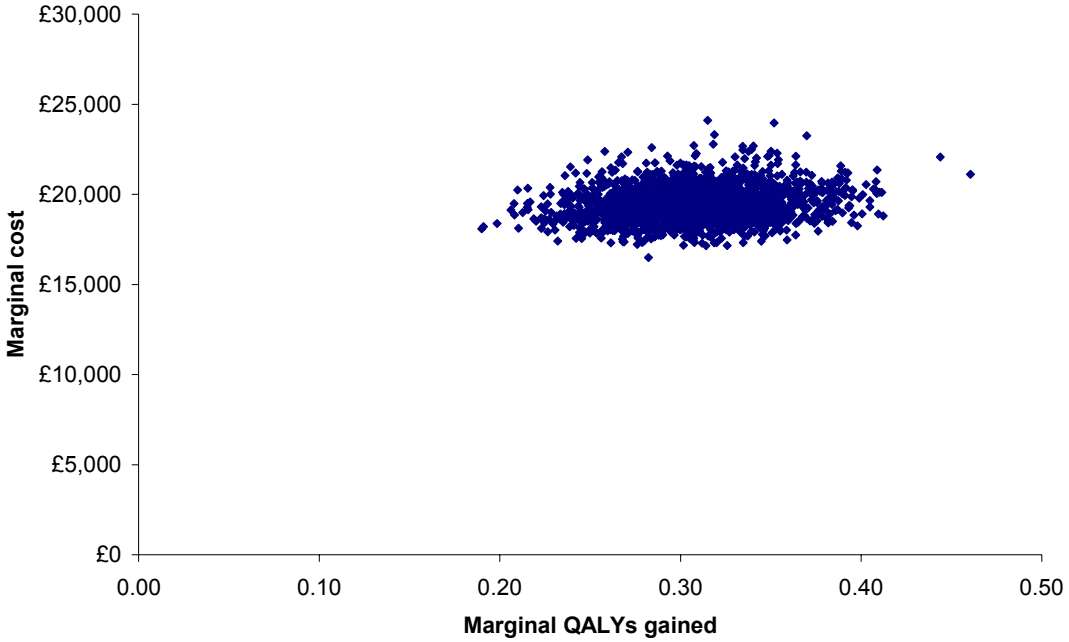
6.2.3.4.8 Probabilistic sensitivity analysis results

This section presents the results of the probabilistic sensitivity analysis for the cost-effectiveness models based upon study AVF2107g[58] and study AVF2192g.[60]

Probabilistic sensitivity analysis results for bevacizumab plus IFL versus IFL

Figure 16 presents a marginal cost-effectiveness plane for bevacizumab plus IFL versus IFL, based upon study AVF2107g[58] based upon 2,000 random model iterations.

Figure 16 Marginal cost-effectiveness plane for bevacizumab plus IFL versus IFL



The marginal cost-effectiveness plane suggests that bevacizumab plus IFL is always expected to result in greater costs and a greater number of QALYs gained when compared to IFL alone (i.e. the marginal cost-effectiveness estimate always lies in the North-East quadrant of the plane). It should be noted that use of independent regression models for bevacizumab plus IFL and IFL alone may underestimate the true uncertainty in marginal costs and effects. The 5th and 95th percentiles for marginal QALYs gained are estimated to be 0.25 and 0.37 respectively. The 5th and 95th percentiles for marginal cost are estimated to be approximately £18,000 and £21,100 respectively.

Figure 17 presents CEAccs for bevacizumab plus IFL versus IFL alone. These curves describe the probability that bevacizumab plus IFL and IFL have a cost per QALY ratio that is better than a given willingness to pay threshold (λ).

Figure 17 Marginal CEAccs for bevacizumab plus IFL versus IFL

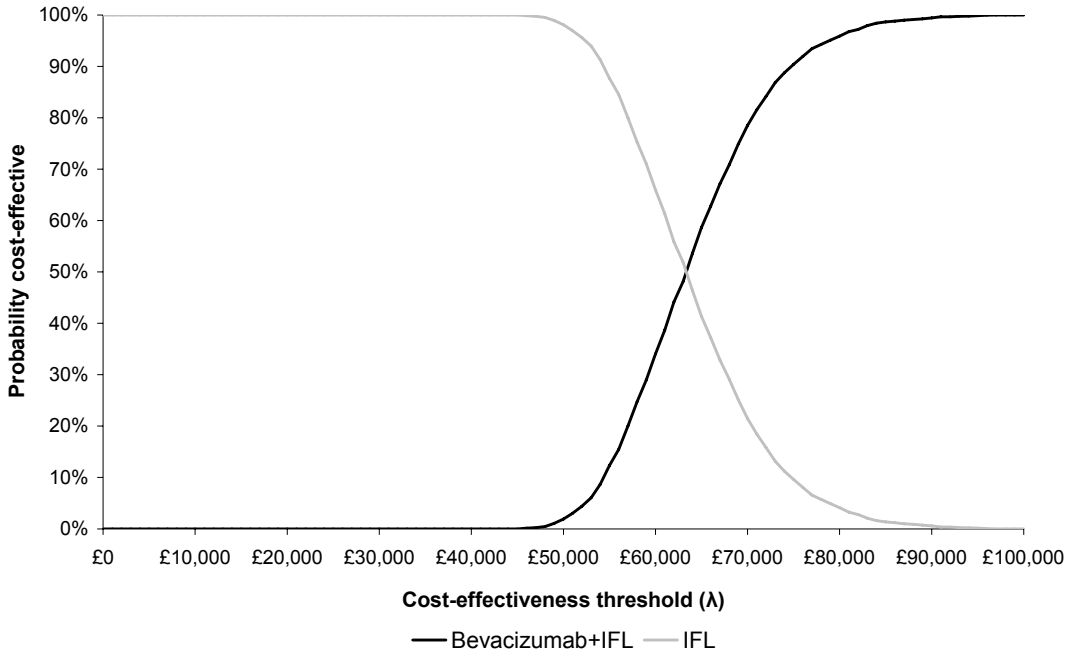


Figure 17 suggests that for willingness to pay thresholds less than £30,000 per QALY gained, the probability that bevacizumab plus IFL is cost-effective is close to zero.

Probabilistic sensitivity analysis results for bevacizumab plus 5-FU/FA versus 5-FU/FA alone

Figure 18 presents a marginal cost-effectiveness plane for bevacizumab plus 5-FU/FA versus 5-FU/FA, based upon study AVF2192g.[60]

Figure 18 Marginal cost-effectiveness plane for bevacizumab plus 5-FU/FA versus 5-FU/FA

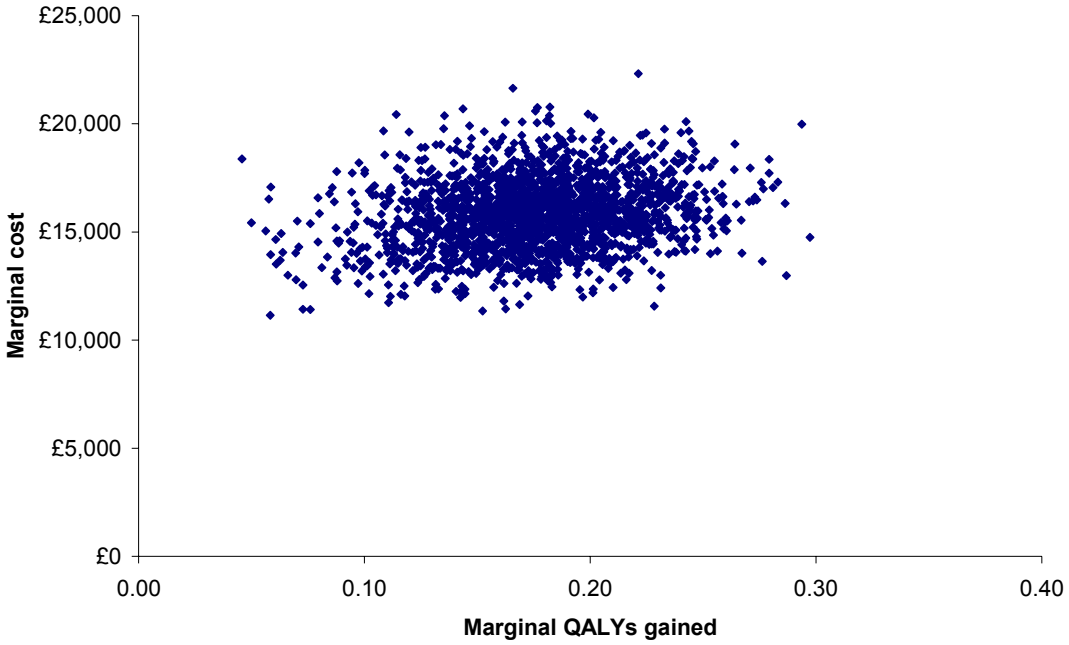


Figure 18 suggests that bevacizumab plus 5-FU/FA is likely to result in greater costs and QALYs gained when compared to 5-FU/FA alone. The 5th and 95th percentiles for marginal QALYs gained are estimated to be 0.11 and 0.24 respectively. The 5th and 95th percentiles for marginal cost are estimated to be approximately £13,300 and £18,500 respectively. Figure 19 presents CEAccs describing the probability that bevacizumab plus 5-FU/FA results in the greatest degree of net benefit over a range of willingness to pay thresholds (λ).

Figure 19 Marginal CEAccs for bevacizumab plus 5-FU/FA versus 5-FU/FA

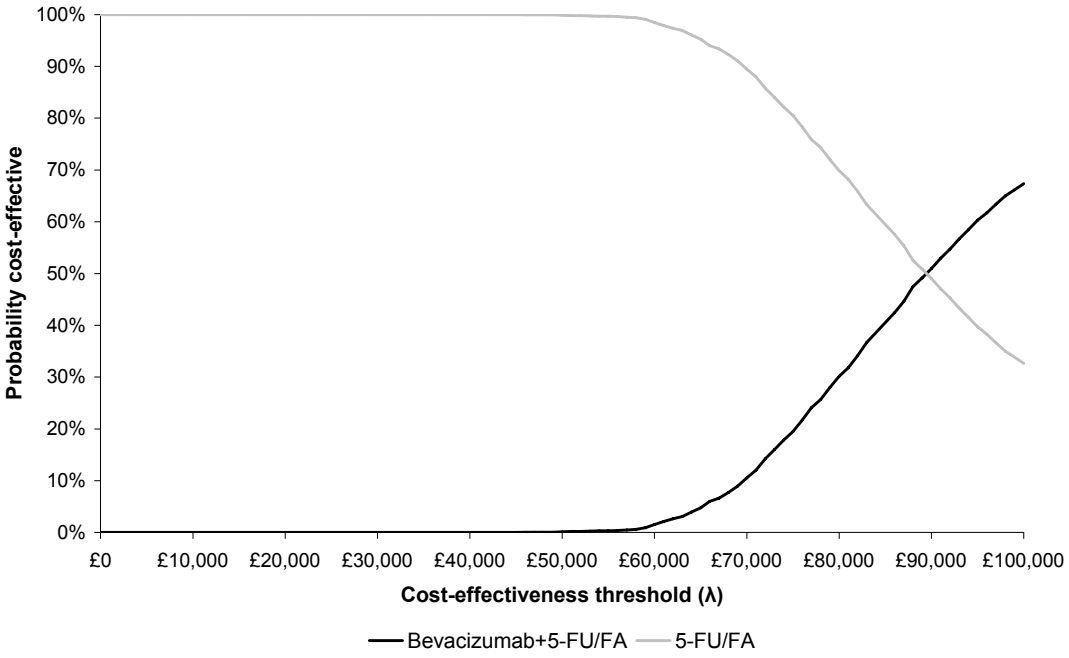


Figure 19 suggests that the probability that bevacizumab plus 5-FU/FA has a marginal cost-utility that is better than £30,000 per QALY gained is close to zero.

6.2.3.5 Discussion of bevacizumab cost-effectiveness and cost-utility results

The health economic models developed for use in this study are broadly similar to the models submitted by Roche.[65] Crucially, the Assessment Group models use the published data on the efficacy of bevacizumab plus IFL and bevacizumab plus 5-FU/FA as reported within the trial publications.[60,58] When compared to IFL alone, the addition of bevacizumab is expected to cost approximately £46,853 for each additional LYG, and approximately £62,857 for each additional QALY gained. When compared to 5-FU/FA alone, the addition of bevacizumab is expected to cost approximately £84,396 for each additional LYG, and approximately £88,436 for each additional QALY gained.

The sensitivity analysis suggests that the cost-effectiveness and cost-utility of bevacizumab is unlikely to be markedly better than those presented within the base case analysis. Unsurprisingly, the key determinant of cost-effectiveness and cost-utility is the acquisition cost of bevacizumab. Assumptions concerning differential costs associated with second-line treatment did not have a substantial impact upon the estimates of cost-effectiveness and cost-utility. The results of the probabilistic sensitivity analysis suggest that the probability that bevacizumab in combination with IFL versus IFL alone has a marginal cost-effectiveness that is better than £30,000 is close to zero. The probability that bevacizumab in combination with 5-FU/FA versus 5-FU/FA alone has a marginal cost-effectiveness that is better than £30,000 is also close to zero.

6.2.3.6 Estimated annual cost of bevacizumab to the NHS

Figure 1 (See Section 3.2.2) presented a treatment pathways model to estimate the number of patients receiving chemotherapy for metastatic CRC; this was developed using evidence available within the literature and current clinical opinion.[27] The model suggests that approximately 12,300 patients undergo first-line chemotherapy for metastatic disease. The proportion of patients who receive 5-FU/FA and irinotecan was taken from a report of the resources associated with metastatic CRC undertaken by Kendle International Inc. on behalf of Merck Pharmaceuticals.[111] As the data within this study were collected between 2001 to 2004, it is possible that these represent underestimates. However, it should also be noted that bevacizumab may not be appropriate for all patients who are fit enough to receive irinotecan and/or 5-FU/FA. Additional costs associated with drug acquisition and administration were

taken from the Assessment Group models. Table 57 presents the estimated additional annual cost to the NHS of providing bevacizumab as a first-line treatment.

Table 57 Estimated annual cost of first-line bevacizumab to the NHS

	Value	Comment
Number of patients receiving first-line chemotherapy	12,323	See Figure 1
Percentage of patients who currently receive 5-FU/FA (excluding oral 5-FU/FA)*	32%	Taken from Kendle International CRC report[111]
Percentage of patients who currently receive 5-FU/FA plus irinotecan	6%	Taken from Kendle International CRC report[111]
Number of patients who currently receive 5-FU/FA	3,943	
Number of patients who currently receive 5-FU/FA plus irinotecan	739	
Additional acquisition cost for bevacizumab per patient (plus 5-FU/FA)	£16,435	Taken from Assessment Group model of study AVF2192g
Additional acquisition cost for bevacizumab per patient (plus 5-FU/FA+irinotecan)	£18,398	Taken from Assessment Group model of study AVF2107g
Additional administration costs for bevacizumab per patient (plus 5-FU/FA)	£2,657	Taken from Assessment Group model of study AVF2192g
Additional administration costs for bevacizumab per patient (plus 5-FU/FA+irinotecan)	£2,890	Taken from Assessment Group model of study AVF2107g
Total additional cost of bevacizumab	**£91,024,013**	

** Outside of current licensed indications*

Based upon the assumptions employed within the Assessment Group model and the treatment pathways model and current estimates of the use of 5-FU/FA and irinotecan, the estimated additional acquisition cost resulting from the provision of bevacizumab is approximately £78million per year. The additional administration cost associated with first-line bevacizumab is estimated to be approximately £13million. This results in an estimated additional annual cost to the NHS of around £91 million.

6.2.3.7 Areas for further research on the use of bevacizumab in the treatment of metastatic colorectal cancer

The development of the health economic models of bevacizumab highlights a number of areas for further research.

- The central uncertainty surrounding the cost-effectiveness and cost-utility of bevacizumab concerns the true efficacy of using bevacizumab alongside first-line infusional 5-FU/FA regimens, without subsequent bevacizumab treatment following disease progression, in prolonging the overall survival of patients with metastatic CRC in patients who are representative of the NHS CRC population. As patients who

were allocated to the intervention groups within studies AVF2107g[58] and AVF2192g[60] were allowed to continue to receive bevacizumab following disease progression, the relative impact of first-line bevacizumab compared to standard chemotherapy is not clear. The approach adopted by Roche[65] may provide a reasonable estimate of the survival benefits associated with adding bevacizumab to IFL. However, the assumption that progression-free survival and overall survival benefits are identical appears to overestimate the marginal survival benefits within study AVF2192g.[60] Consequently, the economic analysis of study AVF2192g is presented by Roche is likely to be biased in favour of the bevacizumab treatment group. Whilst the use of the reported overall survival data from studies AVF2107g[58] and AVF2192g[60] may improve the robustness of the health economic modelling, the resulting estimates of cost-effectiveness and cost-utility may in fact be optimistic. Further research is indicated to explore the impact of adding bevacizumab to standard cytotoxic regimens within rigorous high quality RCTs; the findings of such research may enhance the robustness of any subsequent cost-effectiveness analysis.

- Current evidence relating to the impact of cytotoxic therapy on HRQoL is weak. There is no evidence to demonstrate the impact of bevacizumab treatment on HRQoL. The systematic searches undertaken by the Assessment Group identified only two studies which attempted to quantify the impact of treatment response on HRQoL. Further valuation studies are merited in order to elucidate the relationship between cytotoxic therapy, treatment response and HRQoL.
- A further source of uncertainty within the model derives from the absence of data collection following disease progression on first-line treatment within studies AVF2107g[58] and AVF2192g.[60] In order to obtain an accurate depiction of the costs and consequences resulting from treatment with bevacizumab, empirical evidence concerning actual resource use and outcomes beyond disease progression may be valuable.

6.2.4 Cost-effectiveness results for cetuximab in the second- and subsequent-line treatment of patients with metastatic colorectal cancer

This section reports the results of the cost-effectiveness analysis of cetuximab plus irinotecan in the second- and subsequent-line treatment of EGFR-expressing patients with metastatic CRC who have previously failed on irinotecan-including cytotoxic therapy undertaken by the Assessment Group. Section 6.2.4.1 presents estimates of the costs and consequences of second- and subsequent-line treatment with cetuximab in combination with irinotecan, and active/best supportive care.

As there is no direct evidence to demonstrate whether cetuximab plus irinotecan improves overall survival and/or HRQoL as compared to active/best supportive care within the specific licensed subgroup of patients for whom cetuximab plus irinotecan is indicated, the primary results of the health economic analysis are presented as a threshold analysis. The threshold analysis presents the necessary improvement in overall survival that patients receiving cetuximab plus irinotecan would have to demonstrate compared to active/best supportive care in order to achieve a given level of incremental cost-effectiveness and cost-utility. This analysis is presented in Sections 6.2.4.2 and 6.2.4.3. Section 6.2.4.4 presents estimates of overall survival for patients with metastatic CRC whilst receiving active/best supportive care drawn from indirect sources. Section 6.4.2.5 presents the results of the sensitivity analysis. The corresponding estimates of incremental cost-effectiveness and cost-utility for each of these indirect survival estimates are indicated. Section 6.2.4.6 presents a discussion of the findings of the analysis of cost-effectiveness and cost-utility. Section 6.2.4.7 presents the estimated annual cost to the NHS cetuximab plus irinotecan. Section 6.2.4.8 highlights areas in which further research is indicated.

6.2.4.1 Costs and consequences of treatment with cetuximab plus irinotecan and active/best supportive care

6.2.4.1.1 Consequences of treatment with cetuximab plus irinotecan

The empirical AUC overall survival duration for patients receiving cetuximab plus irinotecan, as shown in Figure 15, is estimated to be 0.72 life years (approximately 8.6 months). This estimate is downwardly biased due to the right-censoring in the final portion of the curve. As noted in Section 6.1.4, the validity of Merck's extrapolation of overall survival data within the BOND study[73] appears to be questionable, as the extrapolated curve and empirical Kaplan Meier estimates diverge at around 0.80 years. The Weibull regression analysis undertaken by the Assessment Group appears to present a more reasonable fit to the survival outcomes observed within the BOND trial.[73] The mean overall survival duration estimated using the

Weibull survival curve is estimated to be 0.81 life years (9.7 months); this is likely to represent a more accurate estimate of mean overall survival for these patients.

Figure 15 suggests that the incorporation of the Merck's proposed continuation rule has only a minor impact upon the overall survival of patients receiving cetuximab plus irinotecan. The Merck model suggested that overall survival duration for these patients with and without the continuation rule were 0.89 and 0.91 life years respectively.[35] Assuming the same relative impact on survival outcomes, the mean survival duration of patients receiving cetuximab plus irinotecan according to the proposed continuation rule estimated by the Assessment Group was 0.79 life years (0.81 x 0.98).

6.2.4.1.2 Costs of treatment with cetuximab plus irinotecan

Table 58 presents estimates of the costs of treatment for patients receiving cetuximab plus irinotecan.

Table 58 Expected costs for patients receiving cetuximab plus irinotecan

Cost component	Cetuximab plus irinotecan (with continuation rule)	Cetuximab plus irinotecan (without continuation rule)
Acquisition costs for cetuximab plus irinotecan	£11,654.26	£15,395.59
Administration costs whilst receiving cetuximab plus irinotecan	£3,166.48	£4,024.06
Supportive care costs following treatment cessation	£2,780.44	£3,169.00
Total cost	**£17,601.18**	**£22,588.65**

Table 58 suggests that the acquisition costs for cetuximab plus irinotecan represent the most substantial cost component over the remaining lifetime of patients. The cost of cetuximab accounts for between 76% and 77% of the total acquisition cost, depending on whether Merck's proposed continuation rule is applied.

6.2.4.1.3 Costs associated with active/best supportive care

Table 59 presents the estimated mean costs associated with active/best supportive care.

Table 59 Expected costs associated with active supportive care and best supportive care

Cost component	Expected cost
Patients receiving further active chemotherapy (31% of patients)	
Lifetime chemotherapy acquisition cost	£5,865.67
Lifetime chemotherapy administration cost	*Dependent on assumed survival duration*
Monthly supportive care cost	£600.00*
Patients receiving best supportive care (69% of patients)	
Monthly supportive care cost	£600.00

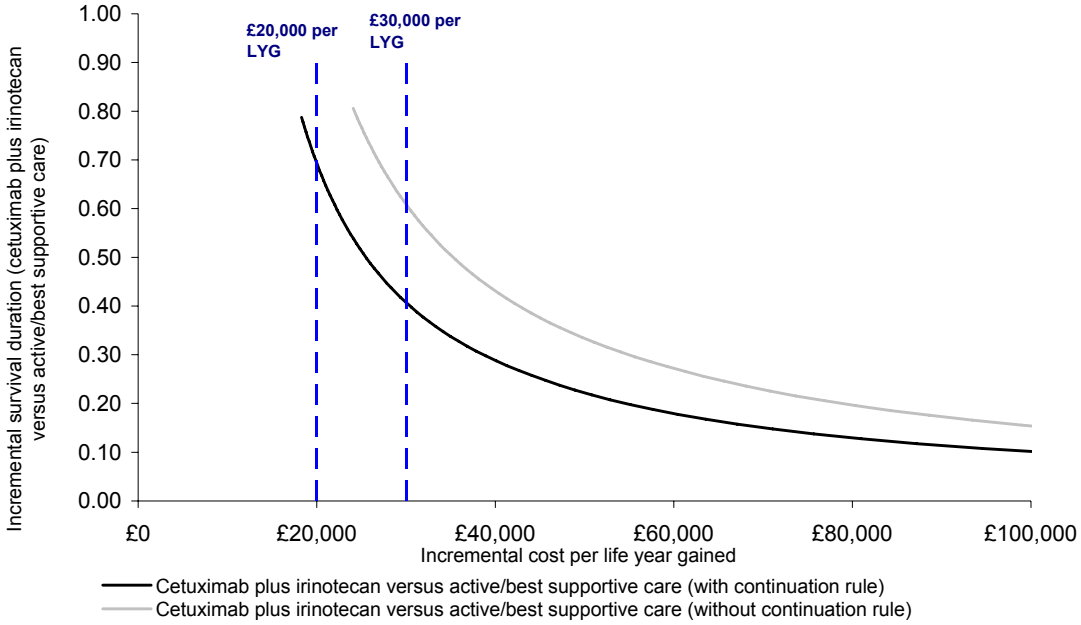
** Additional supportive care costs are included if mean survival is assumed to be greater than estimated time on active treatment*

The difference in overall survival between patients receiving further active chemotherapy and those receiving best supportive care alone following one or more previous lines of chemotherapy is unknown. For the 31% of patients who are assumed to receive further active chemotherapy, a single one-off cost is assumed irrespective of mean overall survival duration. Additional supportive care costs are assumed if the mean survival duration is greater than the modelled time on treatment. This assumption favours the cetuximab plus irinotecan group. For the remaining 69% of patients who do not receive active chemotherapy but instead receive best supportive care alone, the model assumes a mean monthly cost of £600.

6.2.4.2 Threshold analysis results based on incremental cost per LYG

Figure 20 presents the incremental survival difference of cetuximab plus irinotecan compared to active/best supportive care necessary in order to achieve a range of levels of cost-effectiveness. The vertical axis represents the incremental survival benefit attributable to cetuximab plus irinotecan in comparison to active/best supportive care, and thus has a maximum value of 0.79 or 0.81 life years depending on whether Merck's proposed continuation rule is applied. The horizontal axis shows the estimated cost per LYG associated with the given level of incremental survival benefit.

Figure 20 Graphical threshold analysis based on incremental cost per LYG



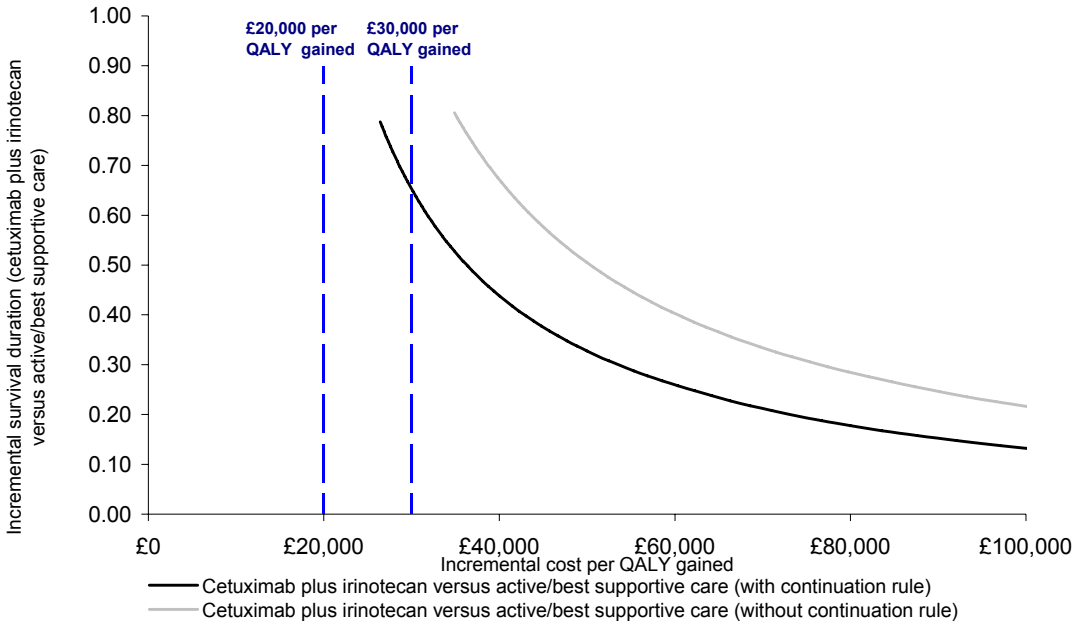
When the proposed continuation rule is applied to patients treated with cetuximab plus irinotecan, the novel therapy must provide an additional 0.70 life years when compared to active/best supportive care in order to achieve an incremental cost-effectiveness ratio of £20,000 per LYG. In other words, a matched cohort of patients receiving active/best supportive care must have an expected survival duration of 0.09 life years or less in order for cetuximab plus irinotecan to have a cost-effectiveness of £20,000 per LYG. In order to obtain an incremental cost-effectiveness ratio of £30,000 per LYG, the model suggests that cetuximab plus irinotecan given under the proposed continuation rule must provide an additional 0.41 life years over treatment with active/best supportive care. In other words, a matched cohort of patients receiving active/best supportive care must have an expected survival duration of 0.38 life years or less in order for cetuximab plus irinotecan to have a cost-effectiveness of £30,000 per LYG.

When the proposed continuation rule is not applied, the model suggests that it is not possible for cetuximab plus irinotecan to achieve an incremental cost-effectiveness ratio of £20,000 per LYG when compared to active/best supportive care. In order to obtain an incremental cost-effectiveness ratio of £30,000 per LYG, the model suggests that cetuximab plus irinotecan given without the proposed continuation rule must provide an additional 0.61 life years over active/best supportive care. In other words, a matched cohort of patients receiving active/best supportive care must have an expected survival duration of 0.20 life years or less in order for cetuximab plus irinotecan to have a cost-effectiveness of £30,000 per LYG.

6.2.4.3 Threshold analysis results based on incremental cost per QALY gained

Figure 21 presents the incremental survival difference required for cetuximab plus irinotecan to achieve a range of levels of cost-utility when compared to active/best supportive care. The vertical axis represents the incremental survival benefit attributable to cetuximab plus irinotecan in comparison to active/best supportive care, and thus has a maximum value of 0.79 or 0.81 life years depending on whether the continuation rule is applied. As this analysis includes adjustments for different states of HRQoL, the horizontal axis shows the estimated cost per QALY gained associated with the given level of incremental survival benefit.

Figure 21 Graphical threshold analysis based on incremental cost per QALY gained



The model suggests that it is not possible for cetuximab plus irinotecan to have a cost per QALY ratio of less than £20,000 irrespective of whether the continuation rule is applied. When the proposed continuation rule is applied, cetuximab plus irinotecan must provide 0.65 additional life years when compared to active/best supportive care in order to achieve an incremental cost per QALY ratio of £30,000. When the continuation rule is not applied, the model suggests that it is not possible for the incremental cost-utility of cetuximab plus irinotecan versus active/best supportive care to be below £30,000 per QALY gained.

6.2.4.4 Estimates of overall survival for metastatic colorectal cancer patients receiving active/best supportive care

As noted in Section 6.2.2.4.2, three studies were identified which allowed for the estimation of overall survival duration whilst receiving active/best supportive care[93] or best supportive care alone.[109,108] Table 60 presents the mean AUC estimates of overall survival based upon

these three studies alongside the corresponding cost-effectiveness and cost-utility estimates for cetuximab plus irinotecan given according to the proposed continuation rule versus active/best supportive care. The reader should note that these three studies did not discriminate according to EGFR status.

Table 60 Cost-effectiveness and cost-utility estimates for cetuximab plus irinotecan versus active/best supportive care including continuation rule

Treatment option	Per patient results			Incremental results				
	Estimated LYGs	Estimated QALYs gained	Total cost	LYGs	QALYs gained	Cost	Incremental cost per LYG (Cet+Ir vs. A/BSC)	Incremental cost per QALY gained (Cet+Ir vs. A/BSC)
Cetuximab plus irinotecan	0.79	0.55	£17,601	-	-	-	-	-
Active/best supportive care (Cunningham et al)[93]	0.60	0.41	£6,798	0.19	0.14	£10,804	**£58,048**	**£77,210**
Best supportive care (Rao et al)[108]	0.67	0.45	£7,341	0.12	0.09	£10,260	**£86,752**	**£108,934**
Best supportive care (Barni et al)[109]	0.77	0.52	£8,124	0.02	0.03	£9,477	**£462,889**	**£335,358**

The calculation of the mean overall survival durations for the active/best supportive care treatment groups range from 0.60 life years[93] to 0.77 life years.[109] Based upon these indirect estimates of overall survival, the cost per LYG for cetuximab plus irinotecan given according to the proposed continuation rule may be as low as £58,048 per LYG or as high as £462,889 per LYG. When health outcomes are measured in terms of QALYs, the equivalent range is likely to be £77,210 to £335,358 per QALY gained.

Table 61 presents the equivalent analysis when the proposed continuation rule is not applied in the model.

Table 61 Cost-effectiveness and cost-utility estimates for cetuximab plus irinotecan versus active/best supportive care excluding continuation rule

Treatment option	Per patient results			Incremental results				
	Estimated LYGs	Estimated QALYs gained	Total cost	LYGs	QALYs gained	Cost	Incremental cost per LYG (Cet+Ir vs. A/BSC)	Incremental cost per QALY gained (Cet+Ir vs. A/BSC)
Cetuximab plus irinotecan	0.81	0.56	£22,589	-	-	-	-	-
Active/best supportive care (Cunningham et al)[93]	0.60	0.41	£6,798	0.2042	0.15	£15,791	**£77,345**	**£104,747**
Best supportive care (Rao et al)[108]	0.67	0.45	£7,341	0.1363	0.11	£15,248	**£111,853**	**£145,192**
Best supportive care (Barni et al)[109]	0.77	0.52	£8,124	0.0385	0.04	£14,465	**£375,487**	**£370,044**

Table 61 suggests that based upon the indirect evidence on the expected survival duration of patients with metastatic CRC who receive active/best supportive care,[93,108,109] the cost per LYG for cetuximab plus irinotecan given according to the proposed continuation rule may be as low as £77,345 per LYG or as high as £375,487 per LYG. When health outcomes are measured in terms of QALYs, the equivalent range is likely to be £104,747 to £370,044 per QALY gained.

6.2.4.5 Sensitivity analysis

This section presents the results of simple sensitivity analysis to explore the impact of alternative assumptions ***(CIC data removed)*** for patients with metastatic CRC and alternative assumptions concerning the proportion of patients who receive further chemotherapy within the active/best supportive care group.

(CIC data removed)

Figure 22 Sensitivity analysis – threshold analysis using data from the MABEL study (including continuation rule)

(CIC data removed)

6.2.4.5.2 Comparing cetuximab plus irinotecan against BSC or oxaliplatin plus 5-FU/FA alone

The scope issued by NICE specified that the comparators for the assessment of cetuximab plus irinotecan are oxaliplatin plus 5-FU/FA and active/best supportive care. In reality, it is likely that those patients receiving active supportive care will receive oxaliplatin plus 5-FU/FA, as reflected in the central analysis. Figure 23 shows the equivalent cost-utility threshold analysis assuming that a) all patients receive oxaliplatin plus 5-FU/FA, and b) all patients receive BSC alone.

Figure 23 Sensitivity analysis – cost-utility threshold analysis comparing cetuximab plus irinotecan against oxaliplatin plus 5-FU/FA or BSC (including continuation rule)

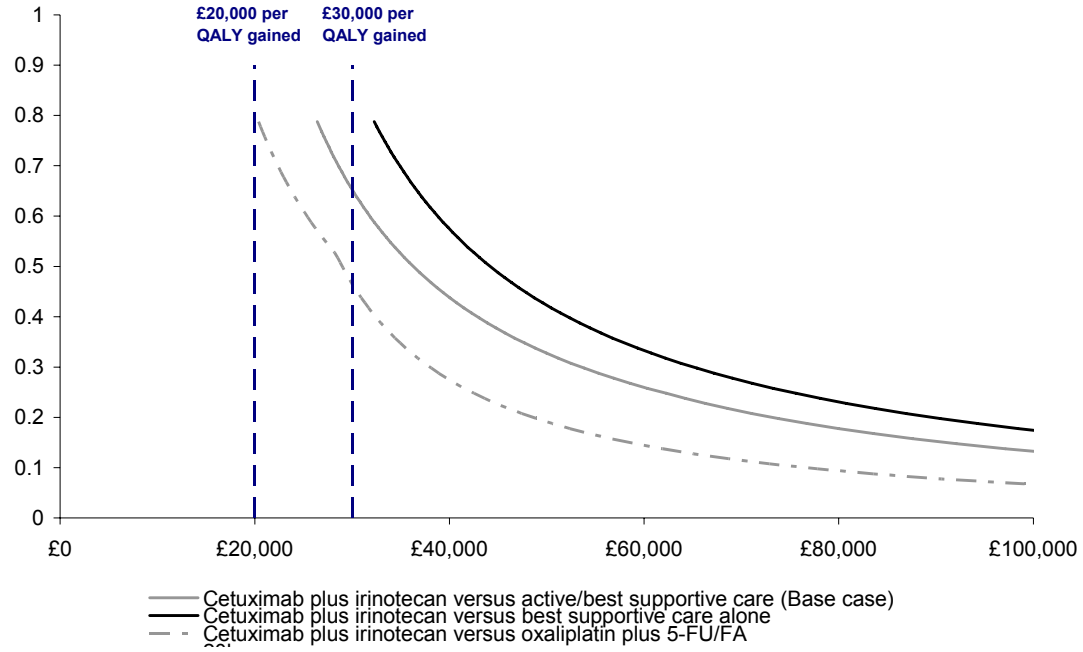


Figure 23 suggests that a more favourable cost per QALY ratio is possible when all patients in the comparator group are assumed to receive oxaliplatin plus 5-FU/FA. The results of the sensitivity analysis demonstrate that if all patients are assumed to receive oxaliplatin plus 5-FU/FA, the necessary incremental survival benefit required for cetuximab plus irinotecan decreases, owing to the greater costs associated with the active/supportive care group. If all patients are assumed to receive BSC alone, the model suggests that it is not possible for cetuximab plus irinotecan to have a cost per QALY ratio which is better than £30,000.

6.2.4.6 Discussion of cetuximab cost-effectiveness and cost-utility results

The absence of comparative evidence to demonstrate whether cetuximab plus irinotecan improves either disease-related symptoms or overall survival means that the interpretation of the health economic results is problematic. Ultimately, it is very difficult to suggest whether a health intervention represents value for money when its comparative efficacy remains unknown.

The health economic model suggests that cetuximab plus irinotecan results in approximately 0.79 life years when Merck's proposed continuation rule is applied, and approximately 0.81 life years when the proposed treatment rule is not applied. Based upon the assumptions employed within the health economic model, cetuximab plus irinotecan is expected to generate approximately 0.55 and 0.56 QALYs gained respectively. These health gains are expected to cost approximately £17,601 if cetuximab plus irinotecan is given according to the

proposed continuation rule; the cost of treatment is estimated to be approximately £22,589 if the proposed continuation rule is not applied.

The inclusion of the proposed continuation rule represents the most favourable economic profile for treatment with cetuximab plus irinotecan. The threshold analysis suggests that in order to achieve an incremental cost-effectiveness ratio that is better than £20,000 per LYG, cetuximab plus irinotecan must provide an additional 0.70 LYGs (around 8.4 months) over treatment with active/best supportive care. Given that patients receiving cetuximab plus irinotecan are expected to survive for approximately 0.79 years (around 9.5 months), this suggests that a population matched to patients enrolled within the BOND trial[73] who would receive treatment with active/best supportive care must live for a modest 0.09 years of life or less (approximately 1.1 months) in order for cetuximab plus irinotecan to achieve this level of cost-effectiveness. In order to achieve a cost-effectiveness ratio that is better than £30,000 per LYG, cetuximab plus irinotecan must provide an additional 0.41 LYGs (around 4.9 months) over treatment with active/best supportive care. This suggests that a population matched to patients enrolled within the BOND trial[73] who receive treatment with active/best supportive care must live for 0.38 years or less (approximately 4.6 months) in order for cetuximab plus irinotecan to achieve this level of cost-effectiveness.

The inclusion of indirect evidence in the health economic model suggests that it is unlikely that cetuximab plus irinotecan has a cost-utility of less than £20,000 per QALY gained. In order for cetuximab plus irinotecan to achieve a cost per QALY gained of £30,000 or less, expected survival in the active/best supportive care group must be 0.14 life years (1.7 months) or less.

It should be reiterated that there is a complete dearth of published evidence concerning the expected survival of patients with metastatic CRC who are EGFR-positive who receive active/best supportive care following failure on previous irinotecan-including cytotoxic therapy. The synthesis of indirect evidence on the expected survival duration of this subgroup of patients suggests that the cetuximab plus irinotecan may cost between £77,210 per QALY gained and £335,358 per QALY gained when compared to active/best supportive care alone. Whilst the economic profile for cetuximab plus irinotecan does not appear favourable within this analysis, the reader should note that the true survival duration of patients with EGFR-expressing metastatic CRC may differ from the estimates obtained from these indirect sources, hence this analysis should be approached with caution. Owing to the lack of clarity concerning the relationship between EGFR-expression and prognosis, and the relationship

between the presence of the acne-like rash and HRQoL, these two factors have not been incorporated into the health economic model, which restricts the validity of the model.

6.2.4.7 Estimated annual cost to the NHS for cetuximab plus irinotecan

Table 62 presents the estimated annual costs to the NHS of providing cetuximab in combination with irinotecan in the treatment of patients with EGFR-expressing metastatic CRC. The estimated number of patients with metastatic CRC is drawn from the treatment pathways model presented in Figure 1 (See Section 3.2.2). The analysis assumes that only patients who test positive for EGFR-expression would be treated with cetuximab plus irinotecan; this is assumed to be 82%.[73] It is assumed that 5-FU/FA is contraindicated for 10% of these patients, therefore second-line treatment with oxaliplatin would not be considered a viable option, and cetuximab plus irinotecan may be given instead. The treatment pathways model also indicates that approximately 308 patients may receive third-line treatment.

Table 62 Estimated annual cost to the NHS for cetuximab plus irinotecan

	Value	Reference
Number of patients receiving any chemotherapy	12,323	Treatment pathways model
Number of patients who receive second-line chemotherapy	6,162	Treatment pathways model
Number of patients who receive third-line chemotherapy	308	Treatment pathways model
Percentage of patients who are EGFR-positive	82%	Merck submission,[35] Cunningham et al[73]
Percentage of patients intolerant to 5-FU	10%	Assumption
Estimated number of EGFR-positive patients who may receive cetuximab plus irinotecan as second-line therapy	505	
Estimated number of EGFR-positive patients who may receive cetuximab plus irinotecan as third-line therapy	253	
Total estimated number of patients receiving cetuximab plus irinotecan	758	
Estimated cost per patient (acquisition, administration and supportive care costs)	£19,641	
Estimated annual cost to the NHS	**£14,885,006.24**	

The estimated annual cost to the NHS of providing cetuximab in combination with irinotecan as an option for the second- and third-line treatment of metastatic CRC is approximately £15million. This estimate is subject to considerable uncertainty.

6.2.4.8 Areas for further research on the use of cetuximab in the second- and subsequent-line treatment of metastatic colorectal cancer

Further research is required to determine the impact of cetuximab in combination with irinotecan as compared to active/best supportive care in terms of overall survival 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 these patients, and as the BOND study has demonstrated that cetuximab has clinically significant activity in terms of response rates in patients with irinotecan-refractory CRC, further RCTs are unlikely to be considered ethically viable. Further research is also required to explore the impact of the current exclusion of patients in whom EGFR is not detected on the cost-effectiveness of cetuximab in combination with irinotecan according to its licensed indications.

7. ASSESSMENT OF FACTORS RELEVANT TO THE NHS AND OTHER PARTIES

7.1 Financial impact for patient and others

Sculpher and colleagues[112] reported an analysis of the travel costs for patients and their carers for patients treated with chemotherapy. The report showed that many patients had their carers accompany them when undergoing chemotherapy, and that between 79% and 85% of carers took time off from work or household duties to do this. The burden for carers may be affected by the number and duration of hospital visits as well as the cytotoxic agent received.

7.2 Quality of life for family and carers.

Family members and other carers play an important role in the care of cancer patients, but may experience high levels of anxiety and depression that can adversely affect aspects of their physical and mental health as well as their social and family lives.[113] The impact of the therapy on family and carers will depend on their opinion concerning its effectiveness, their perception of its favourable and adverse effects, as well as the logistics of the delivery of care.

7.3 Age of patients

The patient's age has an important influence on the choice of cytotoxic therapy. Younger patients are more likely to be fitter and may be able to better tolerate any treatment-related adverse effects/toxicities than older patients; this issue is relevant for all chemotherapies.

NICE guidance on the principles of Social Value Judgements[114] states that "*NICE clinical guidance should only recommend the use of a therapeutic or preventative measure for a particular age group when there is clear evidence of differences in the clinical effectiveness of the measure in different age groups that cannot be identified by any other means."*

7.4 Administration of therapy

Within the trials of bevacizumab included in this assessment, treatment was administered according to the Roswell Park regimen whereby patients receive bolus 5-FU/FA once weekly for four out of every six weeks, or for six out of every eight weeks.[58,60] These regimens may have different effectiveness profiles and resource implications to the typical infusional 5-FU/FA regimens which are commonplace in the UK.

7.5 Availability of alternative therapies

The indications of bevacizumab and cetuximab considered within this assessment are not competing therapies; bevacizumab is currently licensed only as a first-line therapy, and

cetuximab is currently licensed as a second- and subsequent-line therapy in the treatment of patients with metastatic CRC.

7.6 Targeting patients who are EGFR-positive for treatment with cetuximab

Treatment with cetuximab is currently licensed only for use in patients with metastatic CRC whose tumours are EGFR-positive. The process of identifying this population of patients is currently undertaken using the Dakocytomation PharmDx testing kit. The true sensitivity of this test is unknown, and the differential benefit of treating EGFR-expressing and non-EGFR-expressing patients with cetuximab is unclear. Irrespective of these uncertainties, the use of cetuximab carries with it an associated cost of EGFR-testing (approximately £995.00 for a set of 35 tests, *personal communication, Jeremy White, Market Development Manager, Merck Pharmaceuticals*), as well as additional resource implications and increased pathology workload.

7.7 Monitoring of patients

There is a need to monitor patients closely when they are initially placed on bevacizumab and cetuximab due to the possibility of allergic reactions to these new antibodies. This necessitates an increased burden on both medical and nursing time. Ideally there should be a nurse available to monitor such patients undergoing treatment and to liaise with the medical staff if necessary.[115]

7.8 Equity issues

There was significant overall improvement in survival for bowel cancer during the 1990s, but the deprivation gap has also widened significantly. Survival for rectal cancer in the latest period analysed (1996-1999) was 9.4 per cent higher for the richest patients than the poorest patients in men and 8.3 per cent higher in women. Between 1986 and 1999, this gap widened by an average of 2.5 per cent every five years. The deprivation gap in survival was also large for colon cancer - 5.7 per cent in men and 7.3 per cent in women in the period 1996-1999. The gap widened by an average of 1.9 per cent in men and 2.2 per cent in women every five years during the three successive five-year periods studied.[116]

8. DISCUSSION

8.1 Clinical effectiveness findings

8.1.1 The clinical effectiveness of bevacizumab in the first-line treatment of metastatic colorectal cancer

8.1.1.1 Number and type of studies included in the review

Three RCTs were included in the assessment of bevacizumab. One of these studies compared bevacizumab in combination with IFL versus IFL alone (study AVF2107g[58]); the remaining two studies compared bevacizumab in combination with 5-FU/FA versus 5-FU/FA (studies AVF2192g[60] and AVF0780g[59]). As far as can be determined from the published studies, all of the trials included within the review of bevacizumab were reasonably well-designed and conducted, and, with the exception of study AVF0780g,[59] appear to have included balanced populations. The main issue of concern is that the population of the Phase III trial (study AVF2107g[58]) is relatively younger than the UK NHS population of CRC patients.

8.1.1.2 Impact on overall survival

Overall survival was used as the primary endpoint within studies AVF2107g[58] and AVF2192g.[60] Within study AVF2107g, the addition of 5mg/kg bevacizumab to irinotecan in combination with 5-FU/FA (IFL) resulted in a statistically significant increase in median overall survival of 4.7 months (hazard ratio = 0.66, $p<0.001$).[58]

Within study AVF2192g, the addition of 5mg/kg bevacizumab to 5-FU/FA resulted in a non-significant increase in median overall survival of 3.7 months (hazard ratio = 0.79, $p=0.16$).[60]

Within study AVF0780g, the addition of 5mg/kg bevacizumab to 5-FU/FA resulted in a non-significant increase in median overall survival of 7.7 months (hazard ratio = 0.63).[59] A p-value was not available to determine whether this difference was statistically significant.

The combined analysis of studies AVF2107g,[58] AVF2192[60] and AVF0780[59] reported a 26% reduction in daily risk of death with bevacizumab plus FU/LV, compared to FU/LV or IFL alone, with a hazard ratio of 0.742 (95% CI: 0.59-0.93, $p=0.0081$).[61] Owing to the heterogeneity between the studies included within this combined analysis, the reader should interpret these results with caution.

8.1.1.3 Impact of treatment on progression-free survival

Within study AVF2107g, the addition of 5mg/kg bevacizumab to IFL resulted in a statistically significant increase in median progression-free survival of 4.4 months (hazard ratio = 0.54, p<0.001).[58]

Within study AVF2192g, the addition of 5mg/kg bevacizumab to 5-FU/FA resulted in a statistically significant increase in median progression-free survival of 3.7 months (hazard ratio = 0.50, p=0.0002).[60]

Study AVF0780g[59] did not report progression-free survival but reported time to progression, where time to progression is defined as the time from randomisation until objective tumour progression. Time to progression was used as a primary endpoint within this trial. The results of this study showed that the addition of bevacizumab at 5 mg/kg resulted in a statistically significant increase of 3.8 months in time to disease progression compared to FU/FA alone (9.0 months compared to 5.2 months, p=0.005).

The combined analysis of studies AVF2107g,[58] AVF2192[60] and AVF0780[59] reported a significant benefit in terms of median duration of PFS in patients who received FU/LV plus bevacizumab compared to FU/LV or IFL (8.77 months versus 5.55 months, 95% CI: 0.50-0.78, p=0.001).[61] As noted above, the presence of heterogeneity between the studies included within this combined analysis should direct the reader to interpret these results with caution.

8.1.1.4 Impact of treatment on tumour response

Within study AVF2107g,[58] an overall tumour response rate of 44.8% was reported for bevacizumab plus IFL compared to 34.8% for IFL plus placebo (p=0.004).

Within study AVF2192g,[60] the addition of bevacizumab to 5-FU/FA did not result in a statistically significant difference in overall tumour response rates between bevacizumab plus FU/FA and FU/FA plus placebo (p=0.055).

Best (confirmed) tumour response rate was used as a primary endpoint within study AVF0780g.[59] Within this study, there was a statistically significant difference between bevacizumab administered at 5 mg/kg dose with FU/FA compared to FU/FA (p=0.029), but not when the bevacizumab was administered at 10 mg/kg (p=0.434).

8.1.1.5 Treatment-related adverse events

Within study AVF2107g[58] it was reported that clinical benefit was accompanied by a relatively modest increase in adverse events of treatment, which were easily managed. Only the incidence of hypertension was significantly increased in the bevacizumab plus IFL group ($p<0.01$), with all episodes of hypertension being manageable with standard oral antihypertension agents.

Within study AVF2192g,[60] it was reported that the results should be viewed in the context of the study population (i.e. specifically selected patients who were deemed by the treating physician to be sub-optimal candidates for first-line irinotecan-containing therapy), and that despite this higher risk study population, the regimen of bevacizumab plus FU/LV seemed to have been well tolerated.

Within study AVF0780g,[59] it was reported that more patients in the bevacizumab arms experienced at least one NCI common toxicity criteria grade 3 or 4 adverse event. The authors related this increase in incidence of grade 3 and 4 events seen in the bevacizumab arms compared with the control arm as a possible result of patients in these arms being on the study intervention for a longer duration

8.1.1.6 Impact of treatment on quality of life

None of the studies reported the impact of bevacizumab treatment on HRQoL.

8.1.2 The clinical effectiveness of cetuximab in the treatment of patients with EGFR-expressing metastatic colorectal cancer who have previously failed on irinotecan-including therapy

8.1.2.1 Number and type of studies included in the review

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 overall survival in patients with EGFR-expressing metastatic colorectal cancer who have previously failed on irinotecan-containing therapy. One Phase II trial,[73] three single arm studies[74,76,77,75] and a pooled analysis[78] were the only identified studies which included cetuximab as a second- or subsequent-line therapy.

8.1.2.2 Impact on overall survival

Two studies reported overall survival estimates for patients receiving cetuximab in combination with irinotecan. The BOND trial[73] reported a median overall survival duration of

8.6 months for patients receiving cetuximab plus irinotecan. Study IMCL CP02-9923[75] reported a median overall survival duration for patients receiving cetuximab plus irinotecan of 8.4 months.

8.1.2.3 Impact on progression-free survival

The BOND trial[73] reported a median time to progression of 4.1 months for patients receiving cetuximab plus irinotecan. Study IMCL CP02-9923[75] reported a median time to progression for patients receiving cetuximab plus irinotecan of 2.9 months.

8.1.2.4 Impact of treatment on tumour response

The BOND trial[73] reported a tumour response rate of 22.9% (17.5%-29.1%) for patients receiving cetuximab plus irinotecan. Study IMCL CP02-9923[75] reported a tumour response rate of 15.2% (9.7%-22.3%) for patients receiving cetuximab plus irinotecan. Without further active treatment, one would have expected a tumour response rate of zero within the selected populations.

8.1.2.5 Treatment-related adverse events

Cetuximab in combination with irinotecan, had significantly more adverse events (any grade 3 or grade 4 adverse event) than cetuximab monotherapy, 65.1% compared to 43.5% ($p<0.001$) in the BOND trial.[73] Key toxicities associated with treatment with cetuximab plus irinotecan were the presence of an acne-like rash, diarrhoea, nausea and vomiting, neutropenia, anaemia, and asthenia. Toxicity data from study IMCL CP02-9923[75] was not available.

(CIC data removed)

Merck provided an addendum to their full submission to NICE[71] outlining early ***(CIC data removed)*** results from the MABEL trial.[72] ***(CIC data removed)*** Due to the timing of the submission of the addendum[71] the MABEL trial has not been subjected to a methodologically rigorous assessment of validity.

8.2 Cost-effectiveness and cost-utility findings

8.2.1 The cost-effectiveness of bevacizumab in the first-line treatment of metastatic colorectal cancer

The systematic searches did not identify any published studies relating to the cost-effectiveness of bevacizumab in the first-line treatment of metastatic CRC. The Roche industrial submission to NICE included details of two cost-effectiveness models of bevacizumab based upon studies AVF2107g[58] and AVF2192g.[60] These models assume that the costs and effects of treatment with bevacizumab are accrued within the progression-free survival period; this is likely to produce conservative estimates for the economic analysis of study AVF2107g and optimistic estimates for the economic analysis of study AVF2192g. The Roche models suggested that first-line treatment with bevacizumab plus IFL versus IFL costs approximately £71,101 per LYG and £88,364 per QALY gained, whilst bevacizumab plus 5-FU/FA versus 5-FU/FA costs approximately £47,792 per LYG and £56,628 per QALY gained.

The Assessment Group model based upon study AVF2107g[58] suggests that treatment with bevacizumab plus IFL costs approximately £19,360 more than treatment with IFL over the lifetime of the average patient, and results in an estimated 0.41 LYGs. The cost-effectiveness model suggests that bevacizumab in combination with IFL costs an estimated £46,853 for each additional LYG when compared to IFL alone. When survival is adjusted to account for differences in HRQoL between different disease states, the addition of bevacizumab to IFL is estimated to produce an additional 0.31 QALYs gained. The model suggests that bevacizumab in combination with IFL costs an estimated £62,857 per QALY gained when compared to IFL alone. The probabilistic sensitivity analysis suggests that the probability that bevacizumab in combination with IFL versus IFL alone has a marginal cost-effectiveness that is better than £30,000 is close to zero.

The Assessment Group model based upon study AVF2192g[60] suggests that treatment with bevacizumab plus 5-FU/FA costs approximately £15,615 more than treatment with 5-FU/FA alone over the lifetime of the patient, and results in an estimated 0.19 additional years of life. Bevacizumab in combination with 5-FU/FA is estimated to cost an additional £84,396 per LYG when compared to 5-FU/FA alone. When survival is adjusted to account for differences in HRQoL, the addition of bevacizumab to 5-FU/FA is estimated to produce an additional 0.18 QALYs gained. The model suggests that bevacizumab in combination with 5-FU/FA costs an estimated £88,436 per QALY gained when compared to 5-FU/FA alone. The probability that bevacizumab in combination with 5-FU/FA versus 5-FU/FA alone has a marginal cost-effectiveness that is better than £30,000 is close to zero.

The analysis of cost-effectiveness and cost-utility undertaken by the Assessment Group are based upon the published evidence, and uses assumptions which favour treatment with

bevacizumab over standard chemotherapy. The Assessment Group models suggest that it is unlikely that bevacizumab in combination with either 5-FU/FA or IFL has a cost-utility that is better than £60,000 per QALY gained.

8.2.2 The cost-effectiveness and cost-utility of cetuximab in the treatment of patients with EGFR-expressing metastatic colorectal cancer who have previously failed on irinotecan-including therapy

The systematic searches did not identify any studies relating to the cost-effectiveness of cetuximab in the second- and subsequent-line treatment of patients with metastatic CRC. The model submitted to NICE by Merck was subject to flaws in the methods used to extrapolate the survival data from the BOND trial. A new model was developed using more robust survival analysis methods. Owing to the absence of direct evidence on the relative effectiveness of cetuximab plus irinotecan versus active/best supportive care, threshold analysis was undertaken to demonstrate the necessary improvement in survival required in order for cetuximab plus irinotecan to achieve a range of levels of cost-effectiveness and cost-utility.

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. The threshold analysis suggests that in order to achieve an incremental cost-effectiveness ratio that is better than £20,000 per LYG, cetuximab plus irinotecan must provide an additional 0.70 LYGs (around 8.4 months) over treatment with active/best supportive care. This suggests that a population matched to patients enrolled within the BOND trial[73] who receive treatment with active/best supportive care must live for 0.09 years of life or less (approximately 1.1 months) in order for cetuximab plus irinotecan to achieve this level of cost-effectiveness. In order to achieve a cost-effectiveness ratio that is better than £30,000 per LYG, cetuximab plus irinotecan must provide an additional 0.41 LYGs (around 4.9 months) over treatment with active/best supportive care. This suggests that a population matched to patients enrolled within the BOND trial[73] who receive treatment with active/best supportive care must live for 0.38 years or less (approximately 4.6 months) in order for cetuximab plus irinotecan to achieve this level of cost-effectiveness. The model suggests that it is not possible for cetuximab plus irinotecan to have a cost-utility of less than £20,000 per QALY gained. In order for cetuximab plus irinotecan to achieve a cost per QALY gained of £30,000 or less, expected survival in the active/best supportive care group must be 0.14 life years (1.7 months) or less.

8.3 Limitations of the assessment

8.3.1 Limitations of the assessment of bevacizumab

There exists a reasonable body of evidence to demonstrate the clinical benefits associated with the treatment with bevacizumab. However, there is potential confounding of overall survival outcomes within the included RCTs, as patients who were allocated to the intervention arm were allowed to continue to receive bevacizumab-including therapy beyond disease progression. Consequently, the true impact of bevacizumab as a first-line therapy in the treatment of metastatic CRC is uncertain. This is a problem for both the evaluation of clinical effectiveness as well as cost-effectiveness. Due to this uncertainty, the use of published clinical effectiveness estimates within the cost-effectiveness and cost-utility analysis undertaken by the Assessment Group represents the most favourable economic case for bevacizumab.

8.3.2 Limitations of the assessment of cetuximab

No studies met the inclusion for the review of clinical effectiveness of cetuximab plus irinotecan. The review of the clinical effectiveness of cetuximab plus irinotecan highlighted the complete absence of empirical evidence to demonstrate whether cetuximab plus irinotecan improves either health-related symptoms or overall survival in patients with EGFR-expressing metastatic colorectal cancer who have previously failed on irinotecan-containing therapy as compared to active/best supportive care. Whilst cetuximab plus irinotecan has been demonstrated to impact upon tumour response,[73] the relationship between tumour response, the impact of cetuximab treatment on HRQoL and overall survival remains equivocal. The necessary use of indirect comparisons to estimate the incremental costs and clinical effects of cetuximab plus irinotecan as compared to active/best supportive care should be approached with caution.

8.4 Outstanding issues surrounding the use of bevacizumab and cetuximab in the treatment of metastatic colorectal cancer

8.4.1 Issues surrounding the use of bevacizumab

The assessment of the clinical effectiveness and cost-effectiveness of bevacizumab in the treatment of metastatic CRC highlights several important uncertainties:

- The true impact of bevacizumab on overall survival and disease-related symptoms within the first-line treatment setting is uncertain.
- The true costs of treatment following disease progression are uncertain; these data were not collected within the included RCTs of bevacizumab.

- None of the included RCTs presented information relating the impact of treatment with bevacizumab on HRQoL.

8.4.2 Issues surrounding the use of cetuximab

There are a number of important unresolved issues and uncertainties surrounding the clinical effectiveness and cost-effectiveness of cetuximab plus irinotecan in the second- and subsequent-line treatment of patients with EGFR-expressing metastatic CRC who have previously failed on irinotecan-including therapy.

- The incremental benefit of cetuximab in comparison to active/best supportive care has not been demonstrated within any clinical trials.
- There is some evidence to suggest that cetuximab treatment may be active in patients in whom EGFR is not detected, who would currently be considered ineligible for treatment within current licensed indications in England and Wales.
- There is increasing uncertainty surrounding the predictive value of the DakoCytomation EGFR Pharm DX testing kit. Anecdotal evidence from the principal investigator of study IMCL CP02-9923 suggests that the IHC EGFR test has *"no predictive value"*,[83] and that *"there is no medical basis for ordering the test, since the test does not predict who is or is not likely to respond."*[83]
- There is evidence of a correlation between the presence of the acne-like rash and observed survival duration. However, this was not specified prospectively within the trials. In addition, the clinical implementation of Merck's proposed continuation rule may be questionable, as there may be doubt concerning whether the presence of stable disease represents a viable criterion for the cessation of treatment with cetuximab and irinotecan.

9. CONCLUSIONS

9.1 Conclusions on the use of bevacizumab in the treatment of metastatic colorectal cancer

The addition of 5mg/kg bevacizumab to IFL resulted in a statistically significant increase in median overall survival, progression-free survival and overall tumour response rate. The addition of 5mg/kg bevacizumab to 5-FU/FA resulted in a statistically significant increase in median progression-free survival and overall tumour response rate. The addition of bevacizumab to IFL or 5-FU/FA does result in an increase of grade 3/4 adverse events but these were generally manageable. The cost-effectiveness of bevacizumab plus IFL versus IFL is unlikely to be better than £46,853 per LYG; the cost-utility of bevacizumab plus IFL versus IFL is unlikely to be better than £62,857 per QALY gained. The probabilistic sensitivity analysis suggests that 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 £84,396 per LYG; the cost-utility of bevacizumab plus 5-FU/FA versus 5-FU/FA is unlikely to be better than £88,436 per QALY gained. The probabilistic sensitivity analysis suggests that the probability that bevacizumab plus 5-FU/FA has a marginal cost-utility that is better than £30,000 is close to zero.

A key consideration which should be borne in mind when interpreting the results of the assessment of clinical effectiveness and cost-effectiveness is that the patients recruited into two of the three included RCTs were of a lower age than the typical population of patients with metastatic CRC in England and Wales. Therefore, the external validity of the assessment may be compromised.

9.2 Priorities for further research on bevacizumab

The uncertainties surrounding the use of bevacizumab in the treatment of metastatic CRC outlined in Section 8.4.1 give rise to four potential areas for further research; ongoing clinical research studies concerning the use of bevacizumab in the treatment of metastatic CRC is outlined in Appendix 11.

- 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 overall survival in patients with metastatic CRC who are representative of the typical population of CRC patients in the 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. Further research concerning the optimal role of bevacizumab alongside sequences of oxaliplatin, irinotecan and 5-FU/FA would be valuable. The findings of the TREE-2, the NO16966C trial, the CONcePT trial, and the E3200 trial may elucidate this issue (See Appendix 11).

- Further research concerning the impact of treatment with bevacizumab on HRQoL is warranted. This may be undertaken as part of an RCT.
- Further evidence on the specific resource implications associated with bevacizumab would be valuable.

9.3 Conclusions on the use of cetuximab in the treatment of metastatic colorectal cancer

The studies identified for inclusion in the review suggest that treatment with cetuximab plus irinotecan results in a median overall survival duration of between 8.4 months and 8.6 months, a time to progression period of between 2.9 months and 4.1 months, and a tumour response rate of 22.9%. Key treatment-related toxicities include the presence of an acne-like rash, diarrhoea, nausea and vomiting, neutropenia, anaemia, and asthenia. The threshold analysis suggests that in order to obtain an incremental cost-effectiveness ratio of £30,000 per LYG, cetuximab plus irinotecan given under the proposed continuation rule must provide an additional 0.41 life years over treatment with active/best supportive care. In order to achieve a cost-utility ratio of £30,000 per QALY gained, cetuximab plus irinotecan must provide at least 0.65 additional life years over active/best supportive care. Indirect evidence concerning the survival duration of patients without treatment suggest that this magnitude of incremental benefit is unlikely, although there are clear biases in drawing evidence from these sources. The absence of direct comparative evidence to demonstrate whether cetuximab plus irinotecan improves either disease-related symptoms or overall survival means that the evaluation of the cost-effectiveness and cost-utility is problematic. Whilst, it is difficult to suggest whether cetuximab represents value for money, as its comparative efficacy remains unknown, indirect comparisons suggest that the incremental cost-effectiveness of cetuximab plus irinotecan is unlikely to be better than £30,000 per QALY gained.

9.4 Priorities for further research on cetuximab

The uncertainties surrounding the use of cetuximab in the treatment of metastatic CRC outlined in Section 8.4.2 give rise to four potential areas for further research; ongoing clinical research studies concerning the use of cetuximab in the treatment of metastatic CRC is outlined in Appendix 11.

- Further research is required to determine the impact of cetuximab in combination with irinotecan as compared to active/best supportive care in terms of overall survival 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 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 also 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 may be merited. The findings of the COIN trial, the NCT00063141 trial, and the BOND-2 and BOND-3 trials may elucidate this issue (See Appendix 11).

Appendix 1 Numbering system for the different factors of TNM staging

Tumour (T)

- TX = Primary tumour cannot be assessed
- TO = No evidence of primary tumour
- TiS = Carcinoma in situ
- Ta = Tumour invades epithelium
- T1 = Tumour invades lamina propria
- T2a = Tumour invades superficial detrusor muscle (inner half)
- T2b = Tumor invades deep muscle (outer half)
- T3 = Tumour invades perivesical fat
    - T3a = Microscopic invasion perivesical tissue
    - T3b = Macroscopic invasion perivesical tissue
- T4 = Tumour invades prostate, uterus, vagina, pelvic wall or abdominal wall
    - T4a = Tumour invades prostate, uterus, vagina
    - T4b = Tumour invades pelvic or abdominal wall

Node (N)

- NX = Regional lymph nodes cannot be assessed
- N0 = No regional lymph node metastasis
- N1 = Metastasis in a single lymph node, 2 cm or less in greatest dimension
- N2 = Metastasis in a single lymph node, more than 2 cm but not more than 5cm in greatest dimension, or multiple lymph nodes, none more than 5 cm in greatest dimension
- N3 = Metastasis in a lymph node more than 5 cm in greatest dimension

Metastasis (M)

- MX = Presence of distant metastasis cannot be assessed
- M0 = No distant metastasis
- M1 = Distant metastasis

Appendix 2 Summary of survival and progression free survival observed in clinical trials of irinotecan and oxaliplatin for the treatment of advanced colorectal cancer[27]

The original remit from the Department of Health was *"To appraise the clinical and cost effectiveness of irinotecan, oxaliplatin, raltitrexed, cetuximab and bevacizumab in the treatment of advanced colorectal cancer."*

For completeness, the results of the assessment of irinotecan, oxaliplatin and raltitrexed in the treatment of advanced colorectal cancer are presented in the tables below.

Overall survival: first-line therapies for colorectal cancer

Study	Median overall survival (months)				
	Irinotecan+ 5-FU	5-FU	Oxaliplatin+5-FU	Ralttitrexed	P-value
Douillard et al 2000[117]	17.4	14.1			0.036
Kohne et al 2003[118]	20.1	16.9			0.278
Saltz et al 2000[119]	14.8	12.6			0.037
Cornella et al 2004[120]	15.7		18.9		0.032
Goldberg et al 2004[121]	15.0		19.5		0.0001
Tournigand et al 2004[85]	21.5		20.6		0.99
De Gramont et al 2000[110]		14.7	16.2		0.12
Giacchetti et al 2000[122]		19.9	19.4		NS
Grothey et al 2002[123]		16.1	20.4		0.19
Cocconi et al 1998[124]		12.3			
Cunningham et al 1996[125]		10.3			
Maughan et al 2002[126]		8.9			
Pazdur et al 1997[127]		9.7			
Cocconi et al 1998[124]		12.3		10.9	0.197
Cunningham et al 1996[125]		10.3		10.3	0.44
Maughan et al 2002[126]		8.9		9.8	0.94
Pazdur et al 1997[127]		9.7		12.7	0.0109

Progression-free survival: first-line therapies for colorectal cancer

Study	Progression-free survival (months)				
	Irinotecan+5-FU	5-FU	Oxaliplatin+5-FU	Raltitrexed	P-value
Douillard et al 2000[117]	6.7	4.4			0.001
Kohne et al 2003[118]	8.5	6.4			0.0001
Saltz et al 2000[119]	7.0	4.3			<0.001
Cornella et al 2004 [120]	7.5		8.2		0.169
Goldberg et al 2004[121]	6.7		8.7		0.0014
Tournigand et al 2004[85]	8.5		8.0		0.26

De Gramont et al 2000[110]		6.2	9.0		0.0003
Giacchetti et al 2000[122]		6.1	8.7		0.048
Grothey et al 2002[123]		5.3	7.9		0.0001
Cocconi et al 1998[124]		5.1			
Cunningham et al 1996[125]		3.6			
Maughan et al 2002[126]		6.2			
Pazdur et al 1997[127]		Not reported			
Cocconi et al 1998[124]		5.1		3.9	<0.005
Cunningham et al 1996[125]		3.6		4.7	0.44
Maughan et al 2002[126]		6.2		5.3	0.057
Pazdur et al 1997[127]		Not reported			

Overall survival: second-line therapies for colorectal cancer

Study	Median overall survival (months)					
	Irinotecan	Irinotecan+ BSC	Oxaliplatin +5-FU	5-FU	BSC	P-value
Rougier et al 1998[128]	10.8			8.5		0.035
Cunningham et al 1999[93]		9.2			6.5	0.0001
Rothenberg et al 2003[129]			9.8	8.7		<0.07

Progression-free survival: second-line therapies for colorectal cancer

Study	Progression-free survival (months)					
	Irinotecan	Irinotecan+ BSC	Oxaliplatin +5-FU	5-FU	BSC	P-value
Rougier et al 1998[128]	4.2			2.9		0.03
Cunningham et al 1999[93]		Not reported			Not reported	
Rothenberg et al 2003[129]			4.2	2.1		0.0001

Appendix 3 Performance status scales

WHO performance status

The most common performance status is the World Health Organisation scale which ranges from 0 (fully active) to 4 (bedridden).

0	Able to carry out normal activity
1	Restricted in activity, but ambulatory
2	Confined to bed part of, up and about for more than 50% of waking hours
3	Confined to bed for more than 50% of waking hours
4	Totally confined to bed

Eastern Cooperative Oncology Group (ECOG) performance status

0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Karnofsky Performance Scale Index

The Karnofsky Performance Scale Index (KPS) allows patients to be classified as to their functional impairment. This can be used to compare effectiveness of different therapies and to assess the prognosis in individual patients. The lower the KPS score, the worse the survival for most serious illnesses.

KARNOFSKY PERFORMANCE STATUS SCALE DEFINITIONS RATING (%) CRITERIA

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.

Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

Appendix 4 Search strategies

Search strategy clinical effectiveness

Database: Ovid MEDLINE(R) <1966 to April Week 2 2005>

Search Strategy:

---

1 (bevacizumab or avastin).af. (177)
2 216974-75-3.rn. (0)
3 Recombinant humanised monoclonal antibody to VEGF.af. (0)
4 (cetuximab or erbitux).af. (246)
5 or/1-4 (380)
6 exp Colorectal Neoplasms/ (82082)
7 NEOPLASMS/ (139140)
8 CARCINOMA/ (44988)
9 ADENOCARCINOMA/ (84122)
10 or/7-9 (260268)
11 Colonic Diseases/ (10019)
12 Rectal Diseases/ (4997)
13 exp COLON/ (36936)
14 exp RECTUM/ (25629)
15 or/11-14 (68404)
16 10 and 15 (3097)
17 (carcinoma adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw. (19771)
18 (neoplasia adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw. (1435)
19 (neoplasm$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw. (2109)
20 (adenocarcinoma adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw. (6911)
21 (cancer$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw. (47335)
22 (tumor$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw. (14668)
23 (tumour$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw. (3728)
24 (malignan$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw. (4260)
25 or/17-24 (78583)
26 6 or 16 or 25 (105981)
27 randomized controlled trial.pt. (198570)
28 controlled clinical trial.pt. (67854)
29 Randomized Controlled Trials/ (36257)
30 Random Allocation/ (52720)
31 Double-Blind Method/ (80748)
32 Single-Blind Method/ (8758)

33 or/27-32 (337506)

34 clinical trial.pt. (400686)

35 exp Clinical Trials/ (162978)

36 (clin$ adj25 trial$).ti,ab. (107454)

37 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab. (79972)

38 PLACEBOS/ (23504)

39 placebos.ti,ab. (1088)

40 random.ti,ab. (78029)

41 Research Design/ (40035)

42 or/34-41 (638420)

43 33 or 42 (667083)

44 5 and 26 and 43 (100)

45 from 44 keep 1-100 (100)

Search strategy for cost effectiveness evidence

Database: Ovid MEDLINE(R) <1966 to April Week 3 2005>

Search Strategy:

---

1 (bevacizumab or avastin).af. (181)

2 216974-75-3.rn. (0)

3 Recombinant humanised monoclonal antibody to VEGF.af. (0)

4 (cetuximab or erbitux).af. (251)

5 or/1-4 (387)

6 exp Colorectal Neoplasms/ (82207)

7 NEOPLASMS/ (139290)

8 CARCINOMA/ (45030)

9 ADENOCARCINOMA/ (84214)

10 or/7-9 (260550)

11 Colonic Diseases/ (10026)

12 Rectal Diseases/ (5000)

13 exp COLON/ (36978)

14 exp RECTUM/ (25647)

15 or/11-14 (68464)

16 10 and 15 (3099)

17 (carcinoma adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw. (19791)

18 (neoplasia adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw. (1436)

19 (neoplasm$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw. (2110)

20 (adenocarcinoma adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw. (6923)

21 (cancer$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw. (47428)

22 (tumor$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw. (14692)

23 (tumour$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw. (3731)

24 (malignan$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw. (4268)

25 or/17-24 (78715)

26 6 or 16 or 25 (106150)

27 ECONOMICS/ (23805)

28 exp "Costs and Cost Analysis"/ (114641)

29 "Value of Life"/ (4410)

30 exp Economics, Hospital/ (13268)

31 exp Economics, Medical/ (9610)

32 Economics, Nursing/ (3638)

33 Economics, Pharmaceutical/ (1449)

34 exp Models, Economic/ (4122)

35 exp "Fees and Charges"/ (21396)

36 exp BUDGETS/ (8711)

37 ec.fs. (196197)

38 (Costs or cost or costed or costly or costing$).tw. (144451)

39 (economic$ or pharmacoeconomic$ or price$ or pricing).tw. (72193)

40 Quality-Adjusted Life Years/ (2111)

41 economic burden.tw. (969)

42 "Cost of Illness"/ (6769)

43 exp quality of life/ (45694)

44 Quality of Life.tw. (45697)

45 life quality.tw. (1451)

46 hql.tw. (55)

47 (Sf36 or sf36 or sf thirtysix or sf thirty six or short form 36 or short term thirty six or short form thirtysix or shortform 36).tw. (1717)

48 Qol.tw. (4497)

49 (Euroqol or eq5d or eq 5d).tw. (578)

50 Qaly$.tw. (1109)

51 Quality adjusted life year$.tw. (1342)

52 Hye$.tw. (343)

53 Health$ year$ equivalent$.tw. (30)

54 Health utilit$.tw. (279)

55 HUI.tw. (249)

56 Quality of wellbeing$.tw. (2)

57 Qwb.tw. (94)

58 Quality of well being.tw. (506)

59 (Qald$ or qale$ or qtime$).tw. (34)

60 or/27-59 (441793)

61 5 and 26 and 60 (17)

62 from 61 keep 1-10 (10)

Search strategy for literature on quality of life in patients with colorectal cancer

Database: Ovid MEDLINE(R) <1966 to April Week 3 2005>

Search Strategy:

---

1 exp Colorectal Neoplasms/

2 Neoplasms/

3 Carcinoma/

4 Adenocarcinoma/

5 or/2-4

6 Colonic Diseases/

7 Rectal Diseases/

8 exp Colon/

9 exp Rectum/

10 or/6-9

11 5 and 10

12 (carcinoma adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.

13 (neoplasia adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.

14 (neoplasm$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.

15 (adenocarcinoma adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.

16 (cancer$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.

17 (tumor$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.

18 (tumour$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.

19 (malignan$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.

20 or/12-19

21 1 or 11 or 20

22 health related quality of life.tw.

23 hrql.tw.

24 hrqol.tw.

25 hql.tw.

26 sf 36.tw.
27 sf thirtysix.tw.
28 sf thirty six.tw.
29 short form 36.tw.
30 short form thirty six.tw.
31 short form thirtysix.tw.
32 shortform 36.tw.
33 shortform thirty six.tw.
34 shortform thirty six.tw.
35 sf36.tw.
36 medical outcomes survey.tw.
37 mos.tw.
38 euroqol.tw.
39 eq 5d.tw.
40 eq5d.tw.
41 qaly$.tw.
42 quality adjusted life years/
43 quality adjusted life year$.tw.
44 hye$.tw.
45 health$ year$ equivalent$.tw.
46 psychological general well being index.tw.
47 psychological general wellbeing index.tw.
48 pgwb$.tw.
49 health utilit$.tw.
50 hui.tw.
51 quality of wellbeing$.tw.
52 quality of well being.tw.
53 qwb$.tw.
54 rosser.tw.
55 trade off$.tw.
56 standard gamble.tw.
57 tto.tw.
58 "Quality of Life"/
59 "Outcome Assessment (Health Care)"/
60 (preference$ or utilit$).tw. and (58 or 59)
61 ((preference$ or utilit$) and quality of life).tw.
62 (preference$ adj2 (elicit$ or patient$ or population$ or measure$ or based or cost$)).tw.

63 (utilit$ adj2 (elicit$ or patient$ or population$ or measure$ or based or cost$)).tw.

64 or/22-57,60-63

65 21 and 64

Search strategy to identify studies which included patients with metastatic CRC receiving active/best supportive care following one or more lines of active chemotherapy

Database: Medline

Date undertaken: 19.10.05, 7.11.05

Scope of search: Survival following 2nd , 3rd or 4th line treatment for colorectal cancer

Search technique: Browsing or 'berrypicking'.

1 (3rd line or third line or 4th line or fourth line).tw.

2 Colorectal Neoplasms/

3 1 and 2

4 supportive care.ti.

5 survival.tw.

6 2 and 4 and 5

7 Drug Resistance, Neoplasm/

8 2 and 5 and 7

9 from 3 keep 2,4-7,10-12,23,25

10 salvage.tw.

11 2 and 10

12 from 11 keep 4,6-7,19,22,45

13 from 8 keep 1-2,8

14 compassionate.tw.

15 2 and 14

16 from 15 keep 1

17 survival.ti.

18 refractory.tw.

19 2 and 5 and 18

20 from 19 keep 4,6,8,14,21,54

21 or/9,12-13,16,20

22 from 21 keep 1

23 (2nd line or second line).ti.

24 2 and 23

25 limit 24 to clinical trial

26 (2nd line or second line).tw.

27 2 and 26

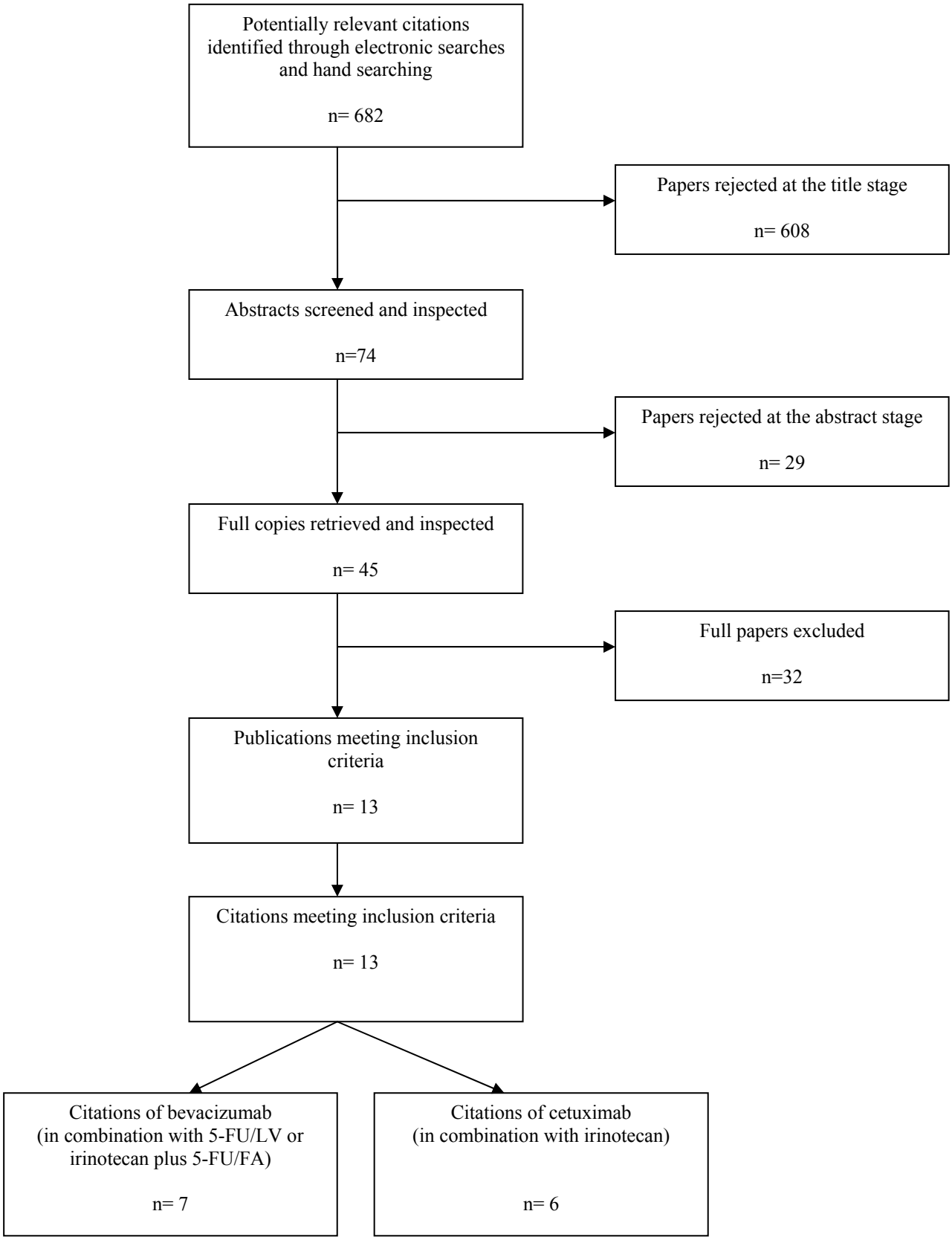
28 limit 27 to clinical trial

29 28 not 25

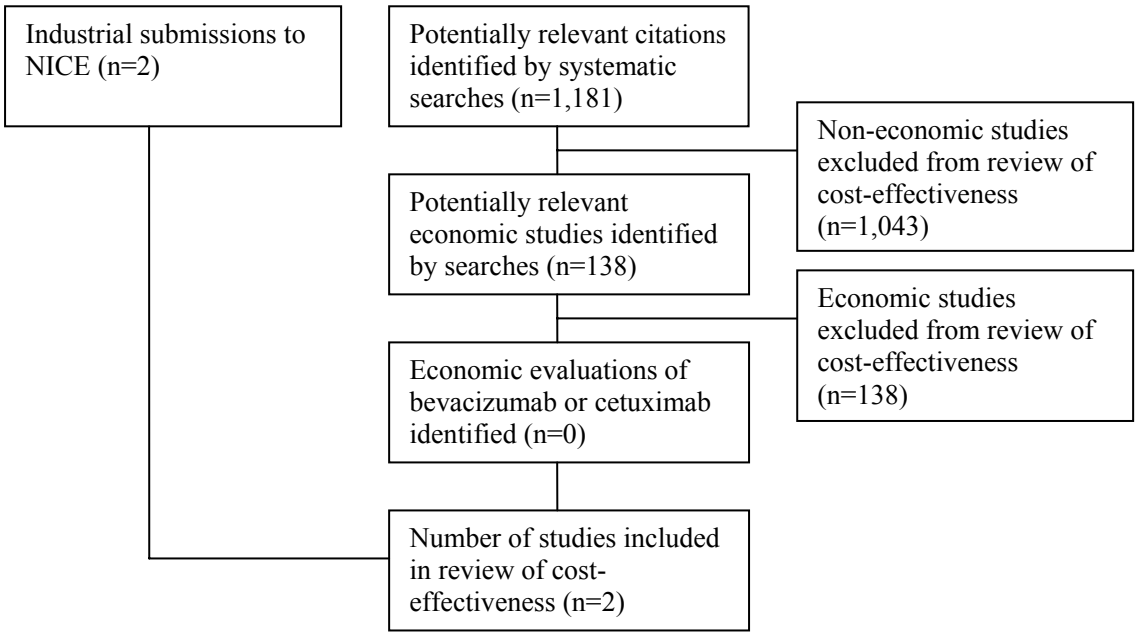
30 22 or 28

Appendix 5 QUOROM trial flow chart

Clinical effectiveness review



Cost-effectiveness review



Appendix 6 Quality assessment

Quality assessment summary

Assessment criteria	Hurwitz 2004[58]	Study AVF0780G[59]	Study AVF2192[60]	Cunningham[73]
Was the method used to assign participants to the treatment groups really random?	Y	U	Y	Y
What method of assignment was used?	CG	U	U	U
Was the allocation of treatment concealed?	Y	U	Y	U
What method was used to conceal treatment allocation?	CR	U	U	U
Was the number of participants who were randomised stated?	Y	Y	Y	Y
Were details of baseline comparability presented?	Y	Y	Y	Y
Was baseline comparability achieved?	Y	N	Y	U
Were the eligibility criteria for study entry specified?	Y	Y	Y	Y
Were any co-interventions identified that may influence the outcomes for each group?	Y	U	Y	Y
Were the outcome assessors blinded to the treatment allocations?	Y	U	U	U
Were the individuals who administered the intervention blinded to the treatment allocation?	Y	U	U	U
Were the participants who received the intervention blinded to the treatment allocation?	Y	Y	Y	U
Was the success of the blinding procedure assessed?	Y	U	U	U
Were at least 80% of the participants originally included in the randomised process followed up in the final analysis?	Y	Y	U	U
Were the reasons for withdrawal stated?	Y	Y	N	U
Was an intention-to-treat analysis included?	Y	U	N	Y

Abbreviations:
Y = yes;
N = no;
U = unclear;
CG = computer-generated;
CR = Central randomisation
N/A = not applicable

Appendix 7 Data extraction form

Randomised controlled trials data extraction form based on NHS CRD Report No. 4. [NHS Centre for reviews and Dissemination. Report 4: Undertaking systematic reviews of research on effectiveness; CRD's guidance for those carrying out or commissioning reviews. York: University of York; 2001.]

STUDY & DESIGN	DATA EXTRACTION	
Trial	REVIEW DETAILS	
	Author, year	
Study design	**Objective**	
	Publication type **(ie full report or abstract)**	
	Country of corresponding author	
	Language of publication	
	Sources of funding	
	INTERVENTIONS	
	Focus of interventions (comparisons)	
	Description	
	T1: Intervention group, dose, timings	
	T2: Control group, dose, timings	
	T3: Additional group, dose, timings	
	Intervention site (health care setting, country)	
	Duration of intervention	
	Length of follow up	
	STUDY CHARACTERISTICS	
	Method of randomisation	
	Description	
	Generation of allocation sequences	
	Allocation concealment?	
	Blinding level	
	Numbers included in the study	
	Numbers randomised	
	POPULATION CHARACTERISTICS	
	Target population (describe)	
	Inclusion / exclusion criteria (n)	
	Recruitment procedures used (participation rates if available)	
	Characteristics of participants at baseline	
	Age (mean yr.)	

	Gender (male/female)	
	Performance scale/status	
	Tumor stage	
	Other information	
	Were intervention and control groups comparable?	
	OUTCOMES	
	Definition of primary outcomes	
	Definition of secondary outcomes	
	Definition of tertiary outcomes	
	Definition of other outcomes	
	ANALYSIS	
	Statistical techniques used	
	Intention to treat analysis	
	Does technique adjust for confounding?	
	Power calculation (priori sample calculation)	
	Attrition rates (overall rates) i.e. Loss to follow-up	
	Was attrition adequately dealt with?	
	Number (%) followed-up from each condition	
	Compliance with study treatment	
	Adherence to study treatment	
	RESULTS	
	Quantitative (e.g. estimates of effect size); qualitative results; effect of the intervention on other mediating variables *(Example Outcomes: overall survival, relapse-free survival, disease free survival, response rates etc)*	
	Overall survival	
	Progression-free survival	
	Toxicity/adverse effects	
	Time to treatment failure	
	Quality of life	
	Tumour response rate	
	Cost information	
	Other information	
	SUMMARY	
	Authors' overall conclusions	
	Reviewers comments	

Appendix 8 List of study exclusions

Studies excluded from the review of clinical effectiveness for bevacizumab and cetuximab

Author/Study	Reason for exclusion
NIH 2005[130]	Clinical study synopsis of Hurwitz study - no information
NIH 2005[131]	Clinical study synopsis of Kabbinavar study - no information
Susman E 2005[132]	Letter/Comment/Editorial
Dittrich C 2004[133]	Letter/Comment/Editorial
Feagler R et al. 2004[134]	Letter/Comment/Editorial
Giantonio et al. 2002[135]	Early data, mature data presented later
Kabbinavar et al. 2004[136]	Early data, mature data presented later
Price 2004[137]	Review – not systematic
Parvez T et al. 2004[138]	Review – not systematic
Croom K et al. 2004[139]	Review – not systematic
Grem J 2002[140]	Review – not systematic
D'Orazio A et al. 2003[141]	Review – not systematic
CCOHTA 2004[142]	Review – not systematic
Piche T 2005[143]	Summary information from main paper
Choite M 2004[144]	Summary information from main paper
Hurwitz H et al. 2004[145]	Summary information from main paper
Fyfe G et al. 2004[146]	Summary information from main paper
Hendrick E et al. 2004[147]	Summary information from main paper
Hurwitz H et al. 2003[148]	Summary information from main paper
Kabbinavar F et al. 2004[149]	Summary information from main paper
Bergsland E et al. 2001[150]	Summary information from main paper
Benson A et al. 2003[151]	Wrong comparator
NIH 2005[152]	Wrong intervention/comparator
NIH 2005[153]	Wrong intervention/comparator
Baselg J et al 2002[154]	Letter/Comment/Editorial
Zielinski SL et al 2004[155]	Letter/Comment/Editorial
Cunningham et al 2005[156]	Clinical study synopsis of Cunningham - no information
Wang L et al 2003[157]	Letter/Comment/Editorial
Cunningham et al 2003[158]	Summary information from main paper
Cunningham et al 2003[159]	Summary information from main paper
Rosenberg A.H. et al 2002[160]	Wrong population (cetuximab)
Raoul J.L et al 2003[161]	Wrong population (cetuximab)

Appendix 9 FACT-C questionnaire

Below is a list of statements that other people with your illness have said are important. By circling one number per line, please indicate how true each statement has been for you during the past 7 days.

PHYSICAL WELL-BEING	not at all	a little bit	Some-what	Quite a bit	Very much
During the past 7 days:					
1. I have a lack of energy……..	0	1	2	3	4
2. I have nausea…….....	0	1	2	3	4
3. Because of my physical condition, I have trouble meeting the needs of my family……	0	1	2	3	4
4. I have pain…….....	0	1	2	3	4
5. I am bothered by side effects of treatment……	0	1	2	3	4
6. I fell sick……	0	1	2	3	4
7. I am forced to spend time in bed……...	0	1	2	3	4
8. Looking at the above 7 questions, how much would you say your PHYSICAL WELL-BEING affects your quality of life?.....	Not at all	(circle one number) 0 1 2 3 4 5 6 7 8 9 10			Very much so

SOCIAL/FAMILY WELL-BEING	not at all	a little bit	Some-what	Quite a bit	Very much
During the past 7 days:					
9. I feel distant from my friends……	0	1	2	3	4
10. I get emotional support from my family…….	0	1	2	3	4
11. I get support from my friends and neighbours……..	0	1	2	3	4
12. My family has accepted my illness…….	0	1	2	3	4
13. Family communication about my illness is poor……	0	1	2	3	4
14. I feel closer to my partner (or the person who is my main support)……	0	1	2	3	4
15. Have you been sexually active during the past year? No__Yes__ If yes: I am satisfied with my sex life……...	0	1	2	3	4
16. Looking at the above 7 questions, how much would you say your SOCIAL/FAMILY WELL-BEING affects your quality of life?.....	Not at all	(circle one number) 0 1 2 3 4 5 6 7 8 9 10			Very much so

RELATIONSHIP WITH DOCTOR	not at all	a little bit	Some-what	Quite a bit	Very much
During the past 7 days:					
17. I have confidence in my doctor(s)……..	0	1	2	3	4
18. My doctor is available to answer my questions	0	1	2	3	4
19.. Looking at the above 2 questions, how much would you say your RELATIONSHIP WITH THE DOCTOR affects your quality of life?.....	Not at all	(circle one number) 0 1 2 3 4 5 6 7 8 9 10			Very much so

EMOTIONAL WELL-BEING	not at all	a little bit	Some-what	Quite a bit	Very much
During the past 7 days:					
20. I feel sad……..	0	1	2	3	4
21. I am proud of how I'm coping with my illness……...	0	1	2	3	4
22. I am losing hope in the fight against my illness……..	0	1	2	3	4
23. I feel nervous……...	0	1	2	3	4
24. I worry about dying…….	0	1	2	3	4
25. I worry about my condition will get worse…….	0	1	2	3	4
26. Looking at the above 6 questions, how much would you say your EMOTIONAL WELL-BEING affects your quality of life?.....	Not at all	(circle one number) 0 1 2 3 4 5 6 7 8 9 10			Very much so

FUNCTIONAL WELL-BEING	not at all	a little bit	Some-what	Quite a bit	Very much
During the past 7 days:					
27. I am able to work (include work in home)……..	0	1	2	3	4
28. My work (include work in home) is fulfilling……	0	1	2	3	4
29. I am able to enjoy life…….	0	1	2	3	4
30. I have accepted my illness……..	0	1	2	3	4
31. I am sleeping well……...	0	1	2	3	4
32. I am enjoying the things I usually do for fun…….....	0	1	2	3	4
33. I am content with the quality of my life right now…….	0	1	2	3	4
34. Looking at the above 7 questions, how much would you say your FUNCTIONAL WELL-BEING affects your quality of life?.....	(circle one number) 0 1 2 3 4 5 6 7 8 9 10 Not at all Very much so				

ADDITIONAL CONCERNS	not at all	a little bit	Some-what	Quite a bit	Very much
During the past 7 days:					
35. I have swelling or cramps in my stomach area……...	0	1	2	3	4
36. I am losing weight……...	0	1	2	3	4
37. I have control of my bowels……	0	1	2	3	4
38. I can digest my food well……	0	1	2	3	4
39. I have diarrhea…….	0	1	2	3	4
40. I have a good appetite…….	0	1	2	3	4
41. I like the appearance of my body……	0	1	2	3	4
Do you have an ostomy appliance? No__Yes__ If yes: answer #42 & 43. If no, go to #44					
42. I am embarrassed by my ostomy appliance	0	1	2	3	4
43. Caring for my ostomy appliance is difficult…….	0	1	2	3	4
44. Looking at the above 9 questions, how much would you say these ADDITIONAL CONCERNS affects your quality of life?.....	(circle one number) 0 1 2 3 4 5 6 7 8 9 10 Not at all Very much so				

Appendix 10 Statistical analysis of baseline study characteristics within BOND

The tables below present the results of an analysis of patient-level data from the both treatment groups within BOND trial undertaken by the Assessment group. Statistical analysis was undertaken to explore whether the observed Kaplan Meier estimates of survival were affected by baseline patient characteristics. Differences in survival between patients groups were tested using log-rank analysis.

Comparison of overall survival outcomes for cetuximab plus irinotecan group according to patient characteristics at baseline

	Number of patients (N)	Mean survival duration (years)	Standard error	Log-rank statistic	Significance (p)
Sex					
Male	143	0.63	0.03	**0.17**	**0.6813**
Female	75	0.61	0.03		
Karnofsky performance score					
<80	25	0.45	0.08	**2.56**	**0.1096**
80-100	193	0.64	0.02		
Age					
<60 years	116	0.62	0.03	**0.09**	**0.7605**
≥60 years	102	0.62	0.03		
Number of previous therapies					
1	41	0.63	0.04	**3.2**	**0.6688**
2	79	0.61	0.03		
3	61	0.6	0.04		
4	21	0.69	0.05		
5	13	0.66	0.12		
6	3	0.59	0.22		

The statistical analysis suggests that sex, performance score, patient age, and the number of previous lines of chemotherapies received by patients did not significantly affect overall survival.

Comparison of overall survival outcomes for cetuximab monotherapy group according to patient characteristics at baseline

	Number of patients (N)	Mean survival duration (years)	Standard error	Log-rank statistic	Significance (p)
Sex					
Male	63	0.65	0.04	**7.59**	**0.0059**
Female	48	0.51	0.04		
Karnofsky performance score					
<80	15	0.37	0.08	**8.82**	**0.003**
80-100	96	0.63	0.03		
Age					
<60 years	59	0.60	0.04	**0.43**	**0.511**
≥60 years	52	0.58	0.05		
Number of previous therapies					

1	27	0.64	0.06	**3.14**	**0.5353**
2	41	0.53	0.05		
3	20	0.56	0.07		
4	18	0.69	0.09		
5	5	0.63	0.10		

Within the monotherapy treatment group, patient sex and Karnofsky performance score significantly affected observed survival, although patient age and the number of previous lines of therapy did not.

Appendix 11 Ongoing clinical research studies on the use of cetuximab and bevacizumab in the treatment of metastatic colorectal cancer

First-line bevacizumab in combination with oxaliplatin plus 5-FU/FA

The TREE-2 trial

The TREE-2 study is a randomised multicentre study comparing three regimens of oxaliplatin plus bolus, infusional or oral 5-FU and bevacizumab in order to evaluate safety and tolerability in the first-line treatment of patients with advanced CRC. Preliminary results from this study were presented at the 2006 ASCO annual meeting,[162] however, mature overall survival outcomes were not available at the time of publication.

NO16966C trial

The NO16966C trial is a randomized phase III study of intermittent oral capecitabine in combination with intravenous oxaliplatin with or without intravenous bevacizumab versus bolus and continuous infusion 5-FU/FA with intravenous oxaliplatin with or without intravenous bevacizumab as first-line treatment for patients with metastatic CRC. Results are not yet available for this study.

The CONcePT trial

The primary aim of this study is to develop an optimized schedule of administration of FOLFOX plus bevacizumab that maximizes the efficacy and safety of this regimen when administered to patients with advanced colorectal cancer.

Second-line bevacizumab for metastatic CRC

The E3200 trial

The E3200 study is a phase III randomized trial of oxaliplatin, 5-FU, and leucovorin calcium with or without bevacizumab versus bevacizumab alone in patients with previously treated advanced or metastatic colorectal adenocarcinoma. This trial was sponsored by the National Cancer Institute (NCI) and conducted by a network of researchers led by the ECOG. Study results were presented at the 2005 ASCO annual meeting.[86]

First-line cetuximab for metastatic CRC

The COIN trial

The COIN trial aims 1) to determine whether the addition of cetuximab to continuous chemotherapy (oxaliplatin plus 5-FU combination chemotherapy) improves overall survival

when compared with continuous combination chemotherapy alone; 2) to determine whether intermittent palliative chemotherapy (given in 12-week episodes with intervals off treatment between active treatment, until evidence of progression) results in non-inferiority in terms of overall survival, when compared with continuous chemotherapy given (until progression or cumulative toxicity). This study opened for accrual in March 2005.

Second-line cetuximab for metastatic CRC

NCT00063141 trial

The NCT00063141 study is a phase III study of irinotecan and cetuximab Vs irinotecan alone as second-line treatment in patients with metastatic, EGFR-positive CRC. The objective of this study is to determine whether overall survival is improved in subjects with metastatic, EGFR-positive colorectal cancer treated with cetuximab in combination with irinotecan compared with irinotecan alone as second-line therapy following treatment with a fluoropyrimidine and oxaliplatin based, non-irinotecan-containing regimen. This study opened for accrual in April 2003.

Combination use of bevacizumab and cetuximab

BOND 2 and BOND 3

The BOND-2 study was a phase II randomised trial which investigated the effect of adding bevacizumab to either cetuximab monotherapy or cetuximab in combination with irinotecan in the treatment of patients with metastatic CRC who have EGRF-positive tumours who have previously failed on irinotecan-including therapy. A further study, the BOND-3 trial has been initiated to evaluate the utility of bevacizumab/cetuximab with or without irinotecan in bevacizumab-refractory patients.

12. References

1. Statisitcs: colorectal cancer. Cancer Research UK 2005;

2. Cooper, N., Gautrey, M, and Quinn, M. Cancer registrations in England, 2002. 2005;

3. Welsh Cancer Intelligence and Surveillance Unit. 2005 Triennial Report: Cancer Incidence, Mortality and Survival in Wales. 2005;

4. Quinn, M., Babb, M., Broch, A., and et al Cancer Trends in England and Wales 1950-1999. Studies in Medical and Population Subjects 2001;

5. Bethune, A., Brown, J, Harding, S., and et al Population Trends 1998; 94

6. Willett, W. The search for the causes of breast and colon cancer. Nature 1989;389-394.

7. Reddy, B., Engle, A, Katsifis, S, and et al Biochemical epidemiology of colon cancer: effect of types of dietry fiber on fecal mutagens, acid, and neutral sterols in healthy subjects. Cancer Res 1989;4629-4635.

8. Potter, J. D. Reconciling the epidemiology, physiology, and molecular biology of colon cancer. Journal of the American Medical Association 1992;1573-1577.

9. Vasen, H. F., Mecklin, J. P., and Khan, P. M. The International Collaborative Group on Hereditart Non-Polyposis Colorectal Cancer (ICG-HNPCC). Dis Colon Rectum 1991; 34 424-425.

10. Hill, M. J., Morson, B. C., and Bussey, H. J. Aetiology of adenoma - carcinoma sequence in large bowel. Lancet 1992; 1 245-247.

11. Doll, R and Peto, R. The causes of cancer: quantitative estimates of aviodable risks of cancer in the United States today. Journal of the National Cancer Institute 1981;1191-1308.

12. Muto, T., Bussey, H. J., and Morson, B. C. The evolution of cancer of the colon and rectum. Cancer 1975;2251-2270.

13. Hoff, G. and Vatn, M. H. Colonic Adenoma: Natural History. Digestive Diseases 1991;61-69.

14. Atkin, W. S. and Saunders, B. P. Surveillance guidelines after removal of colorectal adenomatous polyps. Gut 2002; 51 6-9.

15. Stryker, S. J., Wolff, B. G., Culp, C. E., Libbe, S. D., Ilstrup, D. M., and MacCarthy, R. L. Natural History of Untreated Colonic Polyps. Gastroenterology 1987;1009-1013.

16. American Joint Committee on Cancer Collaborative Staging Manual and Coding Instructions AJCC 2004;

17. Rudy, D. R. and Zdon, M. J. Update on Colorectal Cancer. American Family Physician 2000; 61 1759-1770.

18. Boyle, P. and Langman, J. S. ABC of colorectal cancer: Epidemiology. BMJ 2000;805-808.

19. The management of colorectal cancers. Effective Health Care 1997; 8

20. NHS Executive Improving outcomes in colorectal cancer: the research evidence. NHS Executive London 2000;

21. Seymour, M. T., Stenning, S. P., Cassidy, J., and et al Attitudes and practice in the management of metastatic colorectal cancer in Britain. Clin Oncol (R Coll Radiol) 1997;248-251.

22. Young, A. and Rea, D ABC of colorectal cancer: treatment of advanced disease. BMJ 2000;1278-1280.

23. Midgley, R. and Kerr, D. Colorectal Cancer. Lancet 2003;245-247.

24. Ward, S., Kaltenhaler, E., Cowan, J, and Brewer, N. Clinical and cost-effectiveness of capecitabine and tegafur with uracil for the treatment of metastatic colorectal cancer: Systematic review and econnomic evaluation. Health Technology Assessment 2003;

25. National Institute for Clinical Excellence Guidance on the use of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer. Technology Appraisal Guidance No.33 2003;

26. National Institute for Clinical Excellence Guidance on the use of capecitabine and tegafur with uracil for metastatic colorectal cancer. Technology Appraisal Guidance No.61 2003;

27. Hind, D., Tappenden, P., Tumur, I., Eggington, S., Sutcliffe, P., and Ryan, A. The use of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer: systematic review and economic evaluation (review of Guidance No. 33). NICE 2005;

28. Atkin, W. Single flexible sigmoidoscopy screening to prevent colorectal cancer: baseline findings of a UK multicentre reandomised trial. Lancet 2002; 359 1291-1300.

29. Rowan, S., Gautrey, M, and Quinn, M. Cancer registrations in ENGland, 2001. National Cancer Intelligence Centre, Office for National Statisitcs 2004;

30. Cancer Incidence in Wales 1992-2001. Welsh Cancer Intelligence and Surveillance Unit 2004;

31. South West Cancer Intelligence Service. Data held on fi;e: Audit study of patients with colorectal cancer undeertaken in the Wessex region 1991-. 1995;

32. Cassidy, J. Capecitabine vs bolus 5-FU/leucovorin as adjuvant therapy for colon cancer (the X-ACT study): positive efficacy results of a phase III trial. Journal of Clinical Oncology 2004; 22 (oral presentation)

33. Adam, R., Avisar, E., Ariche, A., Giachetti, S., Azoulay, D., Castaing, D., Kunstlinger, F., Levi, F., and Bismuth, F. Five-year survival following hepatic resection after neoadjuvant therapy for nonresectable colorectal [liver] metastases. Annals of Surgical Oncology 2001; 8 347-353.

34. Seymour, M. Optimizing the use and sequencing of fluorouracil and oxaliplatin in advanced colorectal cancer (ACRC): the UK MRC FOCUS (CR08) Trial. Euorpean Society of Medical Oncology 2004;

35. Merck Pharmaceuticals Cetuximab (Erbitux®). Submission to the National Institute for Health and Clinical Excellence. 2005;i-73.

36. National Institute for Clinivcal Excellence Guidance on Cancer Services: Improving Outcomes in Coloractal Cancers (Manual Update). NICE 2004;

37. Iveson, T. J., Hickish, T., Schmitt, C., and Van Cutsem E. Irinotecan in second-line treatment of metastatic colorectal cancer: improved survival and cost-effect compared with infusional 5-FU. European Journal of Cancer 1999; 35 1796-1804.

38. Jonker, D. J., Maroun, J. A., and Kocha, W. Survival benefit of chemotherapy in metastatic colorectal cancer; a meta-analysis of randomized controlled trials. British Journal of Cancer 2000;1789-1794.

39. Poon, M. A., O'Connell, M. J., Wieand, H. S., and et al Biochemical modulation of fluorouracil with leucovorin: confirmatory evidence of improved therapeutic efficacy advanced colorectal cancer. Journal of Clinical Oncology 1991;1967-1972.

40. Machover, D., Goldschmidt, E., Chollet, P., and et al Treatment of advanced colorectal and gastric adenocarcinoma with 5-fluorouracil and high-dose folinic acid. Journal of Clinical Oncology 1986;685-696.

41. Madajewicz, S., Petrelli, N., and Rustum, Y. M. Phase I-II trial of high-dose calcium leucovorin and 5-fluorouracil in advanced colorectal cancer. Cancer Res 1984;4667-4669.

42. Lokich, J. J., Ahlgren, J. D., Gullo, J. J., and et al Prospective randomized comparison of continuous infusion flourouracil with a conventional bolus schedule in metastatic colorectal carcinoma. A Mid Atlantic Oncology Programme Study. Journal of Clinical Oncology 1989;425-432.

43. de Gramont, A., Bosset, J. F., Milan, C., and et al Randomized trial comparing monthly low-dose leucovorin and fluorouracil bolus with bimonthly high-dose leucovorin and fluorouracil bolus plus continuous infusion for advanced colorectal cancer. A French intergroup Study. Journal of Clinical Oncology 1997;808-815.

44. Leonard, P., Seymour, M. T., James, R., Hochhauser, D., and Ledermann, J. A. Phase II study of irinotecan with bolus and high dose infusional 5-FU and folinic acid (modified de Gramont) for first or second line treatment of advanced or metastatic colorectal cancer. British Journal of Cancer 2002;1216-1220.

45. Aranda, E., Diaz-Rubio, E., Cervantes, A., and et al Randomized trial comparing monthly low-dose leucovorin and fluorouracil for advanced colorectal cancer: a Spanish Cooperative Group for Gastro-Intestinal Tumor Therapy (TTD) Study. Annals of Oncology 1998;727-731.

46. Kohne, C. H., Schoffski, P., Kaufer, C., and et al Effective biomodulation by leucovorin of high-dose infusion fluorouracil given as a weekly 24-hour infusion: results of a randmized trial in patients with advanced colorectal cancer. Journal of Clinical Oncology 1998;418-426.

47. Levi, F. Chronopharmacology of anticancer agents. - 1997;229-331.

48. Irinotecan: Summary of Product Characteristics. Electron Medicines Compendium 2005;

49. Joint Formulary Comittee. British National Formulary 2004;

50. Electron Medicines Compendium 2004;

51. Oxaliplatin: Summary of Product Characteristics. Electron Medicines Compendium 2005;

52. Cars, A. New Developments in systemic Chemotherapy in Advanced Colorectal Cancer. Scandinavian Journal of Gastroenterology 2003; (Suppl 239)

53. Damjanovic, D., Thompson, P., and Findlay, M. Evidence-based update of chemotherapy options for metastatic colorectal cancer. ANZ Journal of Surgery 2004;781-787.

54. EMEA European Medicines Agency Website. EMEA 2006;

55. Ciardiello, F. and Tortora, G. Epidermal growth factor receptor (EGFR) as a target in cancer therapt: understnading the role of receptor expression and other molecular determinants that could influence the response to anti-EGFT drugs. European Journal of Cancer 2003;1348-1354.

56. Moher, D., Cook, D. J., Eastwood, S., Olkin, I., Rennie, D., and Stroup, D. F. Improving the quality of reports of meta-analyses of randomised controlled trials: the Quorom Statement. Lancet 1999; 354 1896-1900.

57. Therasse, P., Arbuck, S. G., Eisenhauer, E. A., Wanders, J., Kaplan, R. S., Rubinstein, L., Verweij, J., Van Glabbeke, M., van Oosterom, A. T, Christian, M. C., and Gwyther, S. G. New Guidelines to Evaluate the Response to Treatment in Solid Tumors. Journal of the National Cancer Institute 2000; 92 205-216.

58. Hurwitz, H., Fehrenbacher, L., Novotny, W., Cartwright, T., Hainsworth, J., Heim, W., Berlin, J., Baron, A., Griffing, S., Holmgren, E., Ferrara, N., Fyfe, G., Rogers, B., Ross, R., and Kabbinavar, F. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. New England Journal of Medicine 3-6-2004; 350 2335-2342.

59. Kabbinavar, F., Hurwitz, H. I., Fehrenbacher, L., Meropol, N. J., Novotny, W. F., Lieberman, G., Griffing, S., and Bergsland, E. Phase II, randomized trial comparing bevacizumab plus fluorouracil (FU)/leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer.[see comment]. Journal of Clinical Oncology 1-1-2003; 21 60-65.

60. Kabbinavar, F., Schulz, J, McCleod, M, Pattel, T, Hamm, J., Hecht, J. R., Mass R.D., Perrou, B, Nelson, B, and Novotny Addition of Bevacizumab to Bolus Flourouracil and Leucovorin in First-Line Metastatic Colorectal Cancer: Results of a Randomized Phase II Trial. Journal of Clinical Oncology 2005; 23 3697-3705.

61. Kabbinavar, F., Hambleton J., Mass R.D., Hurwitz, H., Bergsland, E., and Sarkar, S Combined Analysis of Efficacy: The Addition of Bevacizumab to Florouracil/Leucovorin Improves Survival for Patients With Metastatic Colorectal Cancer. Journal of Clinical Oncology 2005; 23 3706-3712.

62. Giantonio, B. Bevacizumab (anti-VEGF) plus IFL (irinotecan, fluorouracil, leucovorin) as front-line therapy for advanced colorectal cancer (advCRC): Updated results from the Eastern
Cooperative Oncology Group (ECOG) Study E2200. 2004 Gastrointestinal Cancers Symposium Abstract No: 289 2004;

63. Giantonio, B. Bevacizumab (anti-VEGF) plus IFL (irinotecan, fluorouracil, leucovorin) as front-line therapy for advanced colorectal cancer (advCRC): Results from the Eastern Cooperative Oncology Group (ECOG) Study E2200. 2003 ASCO Annual Meeting Abstract No: 1024 2003;

64. Mass R.D. Bevacizumab in combination with 5-FU/leucovorin improves survival in patients with metastatic colorectal cancer: A combined analysis. 2004 ASCO Annual Meeting Abstract No: 3616 2004;

65. Roche, Achieving clinical excellence in the treatment of metastatic colorectal cancer: Avastin (bevacizumab). Submission to the National Institute for Health and Clinical Excellence . 2005;i-98.

66. Ward, W. L, Hahn, E. A., Mo, F., Henandez, L., Tulsky, D. S., and Cella, D. Reliability and validity of the Functional Assessment of Cancer Therapy-Colorectal (FACT-C) quality of life instrument. Quality of Life Research 1998; 8 181-195.

67. Yoo, H. J., Kim, J. C., Eremenco, S., and Han, O. S. Quality of life in Colorectal Cancer Patients with Colectomy and the Validation of the Functional Assessment of Cancer Therapy-Colorectal (FACT-C), Version 4. Journal of Pain and Symptom Management 2005; 30 24-32.

68. Chapuis, P. H., Dent, O. F., Fisher, R., and et al A multivariate analysis of clinical and pathological variables in prognosis after resection of largr bowel cancer. Br J Surg 1985; 72 689-702.

69. Koch, M., McPherson, T. A., and Egedahl, R. D. Effect of sex and reproductive history on the survival of patients with colorectal cancer. J Chron Dis 1982; 35 69-72.

70. Hutchins, L. F., Unger, J. M., Crowley, J. J., Coltman, C. A. Jr., and Albain, KS Underreppresentation of Patients 65 Years of Age or Older in Cancer-Treatment trials. New England Journal of Medicine 1999; 341 2061-2067.

71. Merck Pharmaceuticals Manufacturer's addendum to the Merck submission for cetuximab in metastatic colorectal cancer: January 2006. 2006;1-19.

72. Corrie P The MABEL study. An open, uncontrolled, multicentre, phase II study of Erbitux. (cetuximab) in combination with irinotecan in patients with metastatic colorectal carcinoma expressing the epidermal growth factor receptor and having progressed on a
defined irinotecan-based regimen as most recent treatment. 2005;

73. Cunningham, D., Humblet, Y., Siena, S., Khayat, D., Bleiberg, H., Santoro, A., Bets, D., Mueser, M., Harstrick, A., Verslype, C., Chau, I., and Van Cutsem, E. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. New England Journal of Medicine 22-7-2004; 351 337-345.

74. Saltz, L. B., Meropol, N. J., Loehrer, P. J., Sr., Needle, M. N., Kopit, J., and Mayer, R. J. Phase II trial of cetuximab in patients with refractory colorectal cancer that expresses the epidermal growth factor receptor. Journal of Clinical Oncology 1-4-2004; 22 1201-1208.

75. Saltz, L. B. Cetuximab (IMC-C225) Plus Irinotecan (CPT-11) is Active in CPT-11-Refractory Colorectal Cancer (CRC) that Expresses Epidermal Growth Factor Receptor (EGFR). 2001 ASCO Annual Meeting Abstract No: 7 2001;

76. Lenz, H. J., Mayer, R. J., Gold, P. J., Mirsching, B., Stella, P. J., Cohn, A. L., Pippas, A. W., Azarnia, N., Needle, M. N., and Van Cutsem, E. Activity of cetuximab in patients with colorectal cancer refractory to both irinotecan and oxaliplatin. Journal of Clinical Oncology 2004; 22 3510-

77. Lenz, H. J. Activity of Erbitux (cetuximab) in patients with colorectal cancer refractory to a fluoropyrimidine, irinotecan, and oxaliplatin. 2005 Gastrointestinal Cancers Symposium Abstract No: 225 2005;

78. B.C.Mirtsching Cetuximab in refractory metastatic colorectal cancer: Analysis of efficacy and response by patient and disease variables. 2005 Gastrointestinal Cancers Symposium Abstract No: 205 2005;

79. FDA summary of safety and effectiveness data for DakoCytomation. 2005;

80. Chung, K. Y., Shia, J., Kemeny, N. E., Shah, M., Schwartz, G. K., Tse, A., Hamilton, A., Pan, D., Schrag, D., Schwartz, L., Klimstra, D. S., Fridman, D., Kelsen, D. P., and Saltz, L. B. Cetuximab shows activity in colorectal cancer patients with tumors that do not express the epidermal growth factor receptor by immunohistochemistry. Journal of Clinical Oncology 2005; 23 1803-1810.

81. Hidalog, M., Siu, L. L., Nemunaitis, J. J., Rizzo, J., Hammond, L. A., Takimoto, C., Eckhardt, S. G., Talcher, A., Britten, C. D., Denis, L., Ferrante, K., Van Hoff, D. D., Silberman, S., and Rowinsky, E. K. Phase I and Pharacologic Study of OS1-774, an Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor, in Patients With Advanced Solid Malignancies. Journal of Clinical Oncology 2001; 19 3267-3279.

82. Nygren, P., Sorbye, H., Osterlund, P., and Pfeiffer, P. Targeted drugs in metastatic colorectal cancer with special emphasis on guidelines for the use of bevacizumab and cetuximab: an Acta Oncologica expert report. Acta Oncologica 2005; 44 203-217.

83. Biedrzycki, B Current Topics in Colorectal Cancer: Targeting EGFR. Targeted Therapies 2005;19-20.

84. Perez-Soler, R. and Saltz, L. B. Cutaneous Adverse Effects With HER1/EGFR-Targeted Agents: Is There a Silver Lining? Journal of Clinical Oncology 2005; 23 5235-5246.

85. Tournigand, C., Andre, T., Achille, E., Lledo, G., Colin, P., Louvet, C., and de Gramont, A. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. Journal of Clinical Oncology 2004; 22 229-237.

86. Giantonio, B. The addition of bevacizumab (anti-VEGF) to FOLFOX4 in previously treated advanced colorectal cancer (advCRC): An updated interim toxicity analysis of the Eastern Cooperative Oncology Group (ECOG) study E3200. 2004 Gastrointestinal Cancers Symposium Abstract No: 241 2004;

87. Smith RD, Hall J, and Gurney H A cost-utility approach to the use of 5-fluorouracil and levamisole as adjuvant chemotherapy for Dukes' C colonic carcinoma. Med J Aust 1993; 158 319-322.

88. Brown ML, Nayfield SG, and Shibley LM Adjuvant therapy for stage III colon cancer: economics return to research and cost- effectiveness of treatment. J Nat Cancer Inst 1994; 86 424-430.

89. Royal Pharmaceutical Society of Great Britain British National Formulary No. 50. 2005;

90. Schmitt, C., Blijham, G., Jolain, B., Rougier, P., and Van Cutsem, E. Medical care consumption in a phase III trial comparing irinotecan with infusional 5-fluorouracil (5-FU) in patients with metastatic colorectal cancer after 5-FU failure. Anti-Cancer Drugs 1999; 10 617-623.

91. Petrou S and Campbell N Stabilisation in colorectal cancer. Int J Palliat Nurs 1997; 3 275-280.

92. Gelber RD, Goldhirsch A, and Cole BF Parametric Extrapolation of Survival Estimates with Applications to Quality of Life Evaluation of Treatments. Controlled Clinical Trials 1993; 14 485-499.

93. Cunningham, D. and Glimelius, B a phase III study of irinotecan (CPT-11) versus best supportive care in patients with metastatic colorectal cancer who have failed 5-fluorouracil therapy. V301 Study Group. Seminars in Oncology 1999; 26 6-12.

94. Department of Health NHS Reference Costs 2004. 2005;

95. Ko CY, Maggard M, and Livingston EH Evaluating Health Utility in Patients with Melanoma, Breast Cancer, Colon Cancer, and Lung Cancer: A Nationwide, Population-Based Assessment. Journal of Surgical Research 2003; 114 1-5.

96. National Insitute for Health and Clinical Excellence National Institute for Clinical Excellence Guidance on the use of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer. 2005;

97. Ness RM, Holmes AM, Klein R, and Dittus R Utility Valuations for Outcome States of Colorectal Cancer. The American Journal Of Gastroenterology 1999; 94 1650-1657.

98. Ramsey SD, Andersen MR, Etzioni R, Moinpour C, Peacock S, Potosky A, and et al Quality of Life in Survivors of Colorectal Carcinoma. Cancer 2000; 88 1294-1303.

99. Medical Research Council Flourouracil, Oxaliplatin and Irinotecan: Use and Sequencing. (FOCUS) Clinical protocol (version 6). 2003; CR08 1-90.

100. Medical Research Council Academic in confidence data from the FOCUS trial submitted by the Clinical Trials Unit. 2004;

101. National Institute for Clinical Excellence Guide to the methods of technology appraisal. 2004;

102. Netten, A. and Curtis, L. Unit costs of health and social care. Personal Social Services Research Unit 2004; Kent

103. Boland, J., Haycox, A., Bagust, A., and Fitzsimmons, L. A randomised controlled trial to evaluate the clinical and cost-effectiveness of Hickman line insertions in adult cancer patients by nurses. Health Technology Assessment 2003; 7 i-112.

104. Netten, A., Dennett, J., and Knight, J. Unit costs of health and social care. 1999;

105. Rougier, P. Cetuximab+FOLFIRI as first-line treatment for metastatic colorectal CA. 2004 ASCO Annual Meeting Abstract No: 3513 2004;

106. Kerr, D. and O'Connor, K. M. An economic comparison of the net clinical benefit and treatment costs of raltitrexed and 5-fluorouracil + leucovorin (Mayo regimen) in advanced colorectal cancer. Journal of Medical Economics 1999; 2 123-132.

107. Remak, E. and Brazil, L. Cost of managing women presenting with stage IV breast cancer in the United Kingdom. British Journal of Cancer 2004; 91 77-83.

108. Rao, S., Cunningham, D., de Gramont, A., Scheithauer, W., Smakal, M., Humblet, Y., and et al Phase III double-blind placebo-controlled study of farnesyl transferase inhibitor R115777 in patients with refractory advanced colorectal cancer. Journal of Clinical Oncology 2004; 22 3950-3957.

109. Barni, S., Lissoni, P., Cazzaniga, M., Ardizzoia, A., Meregali, S., Fossati, V., and et al A randomized study of low-dose subcultaneous interleukin- 2 plus mealtonin versus supportive care alone in metastatic colorectal cancer patients progressin under 5-fluorouracil and folates. Oncology 199; 52 243-245.

110. de Gramont, A., Figer, A., Seymour, M., Homerin, M., Hmissi, A., Cassidy, J., Boni, C., Cortes-Funes, H., Cervantes, A., Freyer, G., Papamichael, D., Le Bail, N., Louvet, C., Hendler, D., de Braud, F., Wilson, C., Morvan, F., and Bonetti, A. Leucovorin and flurouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. Journal of Clinical Oncology 2000; 18 2938-2947.

111. Kendle International Inc. Metastatic colorectal cancer: Treatment practice and costs of care in four European countries and modelling the economic impact of Erbitux. 2004; Draft Study Report prepared for Merck Pharmaceuticals

112. Sculpher, M., Palmer, M. K., and Heyes, A. Costs incurred by patients undergoing advanced colorectal cancer therapy: A comparison of raltitrexed and fluorouracil plus folinic acid. PharmacoEconomics 2000; 17 361-370.

113. Storey, L., Pemberton, C., Howard, A., and O'Donnell, L. Place of Death: Hobson's Choice or patient's choice? Cancer Nursing Practice 2003; 2 33-38.

114. National Institute for Health and Clinical Excellence Social Value Judgements. Priciples for the development of NICE guidance. 2005;

115. Levine, E on behalf of the Association of Coloproctologists of Great Britain and Ireland Formal submission in the health technology appraisal for the use of

bevacizumab and cetuximab for the treatment of advanced colorectal cancer. Submission to NICE. 2006;

116. Coleman, M. P., Rachet, B., Woods, L. M., Mitry, E., Riga, M., Cooper, N., and et al Trends and socioeconomic inequalities in cancer survival in England and Wales up to 2001. British Journal of Cancer 2004; 90 1367-1373.

117. Douillard, J. Y., Cunningham, D., Roth, A. D., Navarro, M., James, R. D., Karasek, P., Jandik, P., Iveson, T., Carmichael, J., Alakl, M., Gruia, G., Awad, L., and Rougier, P. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. Lancet 2000; 355 1041-1047.

118. Kohne, C. H., Van Cutsem E., Wils, J. A., and et al Irinotecan improves the activity of the AIO regimen in metastatic colorectal cancer: Results of EORTC GI Group study 40986. Proceedings of the American Society of Clinical Oncology 2003; 22 254-Abstract 1018-

119. Saltz, L. B., Cox, J. V., Blanke, C., Rosen, L. S., Fehrenbacher, L., Moore, M. J., Maroun, J. A., Ackland, S. P., Locker, P. K., Pirotta, N., Elfring, G. L., and Miller, L. L. Irinotecan plus fluororacil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. New England Journal of Medicine 2000; 343 905-914.

120. Comella, P., Massidda, B., and Farris, A. Oxaliplatin vs irinotecan plus leucovorin/fluorouacil i.v. bolus as first-line treatment of advanced colorectal carcinoma. European Society of Medical Oncology Annual Meeting 2004;

121. Goldberg, R. M., Sargent, D. J., Morton, R. F., Fuchs, C. S., Ramanathan, R. K., Williamson, S. K., Findlay, B. P., Pitot, H. C., and Alberts, S. R. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. Journal of Clinical Oncology 2004; 22 23-30.

122. Giacchetti, S., Perpoint, B., Zidani, R, Le Bail, N., Faggiuolo, R., Focan, C., Chollet, P., Llory, J. F., Letourneau, Y., Coudert, B., Berheaut-Cvitkovic, F., Larregain-Fournier, D., Le Rol, A., Walter, S., Adam, R., Misset, J. L., and Levi, F. Phase III multicenter reandomized trial of oxaliplatin added to chronomodulated fluorouracil-leucovorin as first-line treatment of metastatic colorectal cancer. Journal of Clinical Oncology 2000; 18 136-147.

123. Grothey, A., Deschler, B., and Kroening, H. Phase III study of bolus 5-fluorouracil (5-FU)/folinic acid (FA) (Mayo) vs weekly high-dose 24h 5-FU infusion/ FA + oxaliplatin (OXA) (FUFOX) in advanced colorectal cancer (ACRC). Proceedings of the American Society of Clinical Oncology 2002;Abstract 512-

124. Cocconi, G., Cunningham, D., Van Cutsem, E., Francois, E., Gustavsson, B., Van Hazel, G., Kerr, D., Possinger, K., and Hietschold, S. M. Open, randomized trial of raltitrexed versus fluoouracil plus high-dose leucovorin in patients with advanced colorectal cancer. Journal of Clinical Oncology 1998; 16 2943-2952.

125. Cunningham, D., Zalcberg, J. R., Rath, U., Oliver, I., Van Cutsem, E., Svensson, C., Seitz, J. F., Harper, P., Kerr, D., and Perez-Manga, G. Final results of a randomised trial comparing 'Tomudex' (raltitrexed) with 5-fluorouracil plus leucovorin in advanced colorectal cancer. 'Tomudex' Colorectal Cancer Study Group. Annals of Oncology 1996; 7 961-965.

126. Maughan, T. S., James, R. D., Kerr, D. J., Ledermann, J. A., McArdle, C., Seymour, M. T., Cohen, D., Hopwood, P., Johnston, C., and Stephens, R. J. Comparison of survival, palliation, and quality of life with three chemotherapy regimens in metastatic colorectal cancer. A multicentre reandomised trial. Lancet 2002; 359 1555-1563.

127. Pazdur, R. and Vincent, M. Raltitrexed (Tomudex) versus 5-flurouracil and leucovorin (5FU+LV) in patients with advanced colorectal cancer (ACC): results of a randomized, multicenter, North American trial. Proceedings of the American Society of Clinical Oncology 1997; 16 228a-Abstr 801-

128. Rougier P, Van Cutsem E, Bajetta E, Niederle N, Possinger K, Labianca R, Navarro M, Morant R, Bleiberg, H., Wils, J., Awad, L., Herait, P., and Jacques, C. Randomised trial of irinotecan versus fluorouracil by continuous infusion after fluorouracil failure in patients with metastatic colorectal cancer. Lancet 31-10-1998; 352 1407-1412.

129. Rothenberg ML, Oza AM, Burger B, Berlin J, Marshall JL, Ramanathan RK, Hart LL, Gupta S, Garay CA, and Haller DG Final results of a phase III trial of 5-FU/leucovorin versus oxaliplatin versus the combination in patients with metastatic colorectal cancer following irinotecan, 5-FU, and leucovorin. Proc Am Soc Clin Oncol 2003; 22 Abstract 1011-

130. NIH A Study to Evaluate Avastin in Combination with Standard Chemotherapy to Treat Colorectal Cancer. Current Controlled Trials database 2005;

131. NIH Combination Chemotherapy With or Without Bevacizumab in Treating Patients With Metastatic Colorectal Cancer. Current Controlled Trials database 2005;

132. Susman, E. Bevacizumab adds survival benefit in colorectal cancer. Lancet Oncology 1-3-2005; 6 136-2045.

133. Dittrich, Ch Targeted therapy - How successful has it been? European Journal of Cancer 2004; 40 2016-2021.

134. Feagler, R. J., Sano, H. S., Waddell, J. A., and Solimando-Jr, D. A. Bevacizumab: Cetuximab. Hospital Pharmacy 2004; 39 747-751.

135. Giantonio, B. Incorporating angiogenesis inhibition with bevacizumab (anti-VEGF) into frontline chemotherapy with irinotecan (CPT-11), fluorouracil and leucovorin (FU/LV) for advanced colorectal cancer (advCRC): a toxicity analysis of ECOG study E2200. 2002 ASCO Annual Meeting Abstract No: 503 2002;

136. Kabbinavar, F., Schulz, J, McCleod, M, and et al. Bevacizumab (Avastin), a monoclonal antibody to vascular endothelial growth factor, prolongs progression-free survival in first-line colorectal cancer in subjects who are not suitable candidates for first-line CPT-11 (TRC-0301). Proceedings of the American Society of Clinical Oncology 2004; 22

137. Price, N. Bevacizumab improves the efficacy of 5-fluorouracil/leucovorin in patients with advanced colorectal cancer. Clinical Colorectal Cancer 2004; 4 89-91.

138. Parvez, T., Mahrous, A.-R. S., and Fawazi, A. Meta-analysis of new treatment strategies for metastatic colorectal cancer. Journal of the College of Physicians and Surgeons Pakistan 2004; 14 638-642.

139. Croom, K. F. and Foster, R. H. Bevacizumab: In the treatment of colorectal cancer. American Journal of Cancer 2004; 3 187-194.

140. Grem, J. L. Mature results of adjuvant colon cancer trials from the Fluorouracil- only era. Journal of the National Cancer Institute 19-5-2004; 96 727-729.

141. Orazio, A., Lee, D., Ellis, L., and Chu, E. Adding a humanized antibody to vascular endothelial growth factor (Bevacizumab, Avastin(trademark)) to chemotherapy

improves survival in metastatic colorectal cancer. Clinical Colorectal Cancer 2003; 3 85-88.

142. CCOHTA Bevacizumab for Advanced colorectal Cancer. CCOHTA 2004;

143. Piche, T. Bevacizumab, irinotecan, fluorouracil combination and folinic acid for metastatic colorectal cancer. Hepato-Gastro 2005; 12 79-7020.

144. Choti, M. A. Bevacizumab in combination with irinotecan plus fluorouracil plus leucovorin chemotherapy prolongs survival but increases adverse events in people with metastatic colorectal cancer. Cancer Treatment Reviews 2004; 30 715-720.

145. Hurwitz, H. Bevacizumab in combination with 5-fluorouracil and leucovorin: A promising regimen for first-line metastatic colorectal cancer. 2004 Gastrointestinal Cancers Symposium Abstract No: 286 2004;

146. Fyfe, G. Bevacizumab plus irinotecan/5-FU/leucovorin for treatment of metastatic colorectal
cancer results in survival benefit in all pre-specified patient subgroups. 2004 ASCO Annual Meeting Abstract No: 3617 2004;

147. Hendrick E.E. Post-progression therapy (PPT) effect on survival in AVF2107, a phase III trial of bevacizumab in first-line treatment of metastatic colorectal cancer (mCRC). 2004 ASCO Annual Meeting Abstract No: 3517 2004;

148. Hurwitz, H. Bevacizumab (a monoclonal antibody to vascular endothelial growth factor) prolongs survival in first-line colorectal cancer (CRC): Results of a phase III trial of bevacizumab in combination with bolus IFL (irinotecan, 5-fluorouracil, leucovorin) as first-line therapy in subjects with metastatic CRC. 2003 ASCO Annual Meeting Abstract No: 3646 2003;

149. Kabbinavar, F. Bevacizumab (a monoclonal antibody to vascular endothelial growth factor) to prolong progression-free survival in first-line colorectal cancer (CRC) in subjects who are not
suitable candidates for first-line CPT-11. 2004 ASCO Annual Meeting Abstract No: 3516 2004;

150. Bergsland, E. Bevacizumab (BV) + Chemotherapy (CT) May Improve Survival in Metastatic Colorectal Cancer (MCRC) Subjects with Unfavorable Prognostic Indicators. 2001 ASCO Annual Meeting Abstract No: 2247 2001;

151. Benson, A. B., Catalano, P. J., Meropol, N. J., O'Dwyer, P. J., and Giantonio, B. J. Bevacizumab (anti-VEGF) plus FOLFOX4 in previously treated advanced colorectal cancer (advCRC): an interim toxicity analysis of the Eastern Cooperative Oncology Group (ECOG) study E3200 [abstract]. Proceedings of the American Society of Clinical Oncology 2003;243-

152. NIH Safety/Efficacy of Camptosar, Avastin, & 5-FU/LV 2-Schedules w/ Celebrex/Placebo as Colorectal Cancer Initial Treatment. Current Controlled Trials database 2005;

153. NIH Monoclonal Antibody Therapy Plus Combination Chemotherapy in Treating Patients With Metastatic Colorectal Cancer. Current Controlled Trials database 2005;

154. Baselga J. EGF receptor as a target: Preclinical and clinical studies. Proceedings-of-the-American-Association-for-Cancer-Research-Annual-Meeting 2002; 43 1142-1143.

155. Zielinski, S. L. and Travis, K. Cetuximab for advanced colorectal cancer gives months, but cost high. Journal of the National Cancer Institute 18-8-2004; 96 1199-8874.

156. Cunningham, D. Open, Randomised, Multicentre, Phase II Study of Cetuximab Alone or In Combination with Irinotecan in Patients with Metastatic Colorectal Adenocarcinoma Expressing the Epidermal Growth Factor Receptor and Progressing on a Defined Irinotecan-Based Reg. NRR Records from Research Centres: Lead Centres for Multi-Centre Projects 2005;

157. Wang, L. and Arnold, K. Chemo-cetuximab combo studied in patients with metastatic colorectal cancer. Journal of the National Cancer Institute 2-7-2003; 95 939-8874.

158. Cunningham, D. and Chau, I. Epidermal growth factor receptor (EGFR) therapies in colorectal carcinoma: The European data. Ejc Supplements 2003; 1 S106-S106.

159. Cunningham, D. Cetuximab (C225) alone or in combination with irinotecan (CPT-11) in patients with epidermal growth factor receptor (EGFR)-positive, irinotecan-refractory metastatic colorectal cancer (MCRC). 2003 ASCO Annual Meeting Abstract No: 1012 2003;

160. Rosenberg A.H. Erbitux (IMC-C225) plus weekly irinotecan (CPT-11), fluorouracil (5FU) and leucovorin (LV) in colorectal cancer (CRC) that expresses the epidermal growth factor receptor (EGFr). 2002 ASCO Annual Meeting Abstract No: 536 2002;

161. Raoul J.L., Van Laethem J.., Mitry E., Brezault C., Husseini F., Cals L., Peeters M., Vedovato J.C., Mueser M., and Rougier, P. Phase II study of cetuximab combined with FOLFIRI (bi-weekly irinotecan plus infusional 5-FU and folinic acid (FA)) in patients (pts) with metastatic, epidermal growth factor receptor (EGFR)- expressing colorectal cancer (CRC). Ejc Supplements 2003; 1 S89-S89.

162. Hochster, H., Hart LL, Ramanathan RK, Hainsworth, J., Griffing, S., Mass R.D., Nagarwala, Y., Jirau-Lucca, G., Shpilsky, A., and Childs, B. H. Results of the TREE-2 cohort: safety, tolerability and efficacy of bevacizumab addedd to three oxaliplatin/fluoropyrimidine regimens as first-line treatment of metastatic colorectal cancer. 2006 ASCO Annual Meeting Abstract N0: 244 2006;