

# NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

## Overview

### Bevacizumab and cetuximab for metastatic colorectal cancer

The overview is written by members of the Institute's team of technical analysts. It forms part of the information received by the Appraisal Committee members before the first committee meeting. The overview summarises the evidence and views that have been submitted by consultees and evaluated by the Assessment Group, and highlights key issues and uncertainties. To allow sufficient time for the overview to be circulated to Appraisal Committee members before the first Appraisal Committee meeting, it is prepared before the Institute receives Consultees' comments on the Assessment Report. These comments are therefore not addressed in the overview. A list of the sources of evidence used in the preparation of this document is given in Appendix A.

**This overview contains academic in confidence information, which have been removed from the text**

## 1 Background

### 1.1 *The condition*

Colorectal cancer is a malignant neoplasm arising from the lining (mucosa) of the large intestine (colon and rectum). Colorectal cancer is the third most common cancer in the UK, with approximately 30,000 new cases registered in England and Wales in 2002, representing 12% of all new cancer cases in women and 14% of cancer cases in men. The incidence of colorectal cancer increases with age, from 20 per 100,000 in people between the ages of 45 and 59, to 200–300 in people aged over 75. The median age of patients at diagnosis is over 70 years.

The overall 5-year survival rate for colorectal cancer in England and Wales is approximately 50%; however, large differences in survival exist according to the stage of disease. On average, patients survive for 3 years after diagnosis.

Metastatic colorectal cancer where the tumour has spread beyond the confines of the lymph nodes to other parts of the body is generally defined as stage IV of the American Joint Committee on Cancer (AJCC) tumour node metastases (TNM) system or stage D of Dukes' classification. The population of patients with metastatic colorectal cancer includes both those who present with metastatic disease and those who experience a relapse following surgery. Estimates of the number of people presenting with metastatic colorectal cancer range from 20% to 55% of new cases, while approximately 50% of those who have undergone surgery for colorectal cancer with apparently complete excision will eventually develop advanced disease and distant metastases (typically presenting within 2 years of initial diagnosis). The 5-year survival rate for metastatic colorectal disease is 12%. Median survival after diagnosis of metastatic disease is approximately 6–9 months.

The most frequent site of metastatic disease is the liver. In as many as 50% of patients with metastatic disease, the liver may be the only site of spread. For these patients surgery provides the only chance of longer-term survival. Reported 5-year survival rates after resection of liver metastases range from 16% to 48%, and are 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.

## **1.2 Current management**

The management of metastatic colorectal cancer is mainly palliative, and involves a combination of specialist treatments (palliative surgery, chemotherapy and radiation), symptom control and psychosocial support. The aim is to improve both the duration and quality of the individual's remaining life, while also controlling symptoms. Clinical outcomes such as overall survival, response and toxicity are important, but alternatives such as progression-free survival, quality of life (QoL), convenience, acceptability and patient preferences are also important.

Early chemotherapy before onset of symptoms has been shown to prolong survival and improve overall QoL. Approximately 10% of patients with metastatic colorectal cancer present with potentially resectable liver metastases and for approximately

14% chemotherapy may render unresectable liver metastases operable. The assessment report suggests that resection may be successful with no further relapse in 40% of cases.

Individuals with metastatic disease who are sufficiently fit (those with World Health Organization [WHO] performance status 2 or better) are usually treated with active chemotherapy as first- or second-line therapy. In individuals with WHO performance status 3 or 4 the adverse effects of chemotherapy may often be judged to outweigh the potential benefits, although the decision depends on the individual’s clinical circumstances.

Possible first-line treatment options include 5-fluorouracil and folinic acid (5-FU/FA), oxaliplatin + 5-FU/FA (FOLFOX), or irinotecan + 5-FU/FA (FOLFIRI). Oral analogues of 5-FU, capecitabine and tegafur with uracil, are also recommended by NICE as first-line treatment options. For those patients receiving FOLFOX as first-line treatment, irinotecan may be a second-line treatment option, whereas for patients receiving FOLFIRI first line, FOLFOX may be a second-line treatment option. Patients receiving 5-FU/FA or oral therapy as first-line treatment may receive treatment with FOLFOX and irinotecan as second and subsequent line therapy. Current treatment options recommended by NICE are shown below (table 1).

**Table 1 Current treatment options for colorectal cancer recommended by NICE**

	<b>5-FU/FA/ oral</b>	<b>FOLFOX</b>	<b>FOLFIRI</b>	<b>Irinotecan</b>
First line	√	√	√	
Second and subsequent line		√		√

Survival estimates for patients with metastatic colorectal cancer receiving best supportive care are approximately 6 months. The use of infusional 5-FU/FA increases survival to approximately 10–12 months, whereas combinations of FOLFIRI followed by FOLFOX, or FOLFOX followed by irinotecan increases survival

to 20–21 months. The assessment report estimates that each year approximately 13,000 patients are treated with first-line therapy, while 6000 are subsequently treated with second-line therapy, and 300 will then receive third-line therapy.

Current NICE guidance on the treatment of colorectal cancer is given below<sup>1</sup>.

***NICE technology appraisal guidance no. 93***

‘Irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer’

1. Irinotecan and oxaliplatin, within their licensed indications, are recommended as treatment options for people with advanced colorectal cancer as follows:
  - Irinotecan in combination with 5-fluorouracil and folinic acid as first-line therapy, or irinotecan alone in subsequent therapy
  - Oxaliplatin in combination with 5-fluorouracil and folinic acid as first-line or subsequent therapy.
2. Raltitrexed is not recommended for the treatment of patients with advanced colorectal cancer. Its use for this patient group should be confined to appropriately designed clinical studies.

***NICE technology appraisal guidance no. 61***

‘Guidance on the use of capecitabine and tegafur with uracil for metastatic colorectal cancer’

1. Oral therapy with either capecitabine or tegafur with uracil (in combination with folinic acid) is recommended as an option for the first-line treatment of metastatic colorectal cancer.

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<sup>1</sup> For more details, see the NICE website: [www.nice.org.uk](http://www.nice.org.uk)

## 2 The technologies

**Table 2 Summary description of technologies**

Generic name	Bevacizumab	Cetuximab
Proprietary name	Avastin	Erbix
Manufacturer	Roche Products	Merck Pharmaceuticals
Dose	5 mg/kg of body weight given once every 14 days as an intravenous infusion	An initial dose of 400 mg/m <sup>2</sup> of body surface area with subsequent weekly dose of 250 mg/m <sup>2</sup>
Acquisition cost excluding VAT ( <i>BNF</i> edition 50)	100mg vial £242.66 net 400mg vial £924.40 net	50 ml vial £136.50 net

Bevacizumab (Avastin, Roche Products) (table 2) is a recombinant humanised monoclonal IgG1 antibody that acts as an angiogenesis inhibitor by targeting the biological activity of human vascular endothelial growth factor (VEGF), which stimulates new blood vessel formation in the tumour. Bevacizumab is licensed in the UK:

- in combination with intravenous 5-fluorouracil/folinic acid or intravenous 5-fluorouracil/folinic acid/irinotecan
- for first-line treatment of patients with metastatic carcinoma of the colon or rectum.

The first dose of bevacizumab is given following chemotherapy as a 90-minute intravenous infusion. Subsequent doses may be given before or after chemotherapy initially as a 60-minute intravenous infusion, reduced to a 30-minute intravenous transfusion if bevacizumab is well tolerated. Bevacizumab treatment is recommended until underlying disease progression.

Cetuximab (Erbix, Merck Pharmaceuticals) (table 2) is a recombinant monoclonal antibody that blocks the human epidermal growth factor receptor (EGFR) and thus inhibits the proliferation of cells dependent on EGFR activation for growth. Cetuximab is licensed in the UK:

- in combination with irinotecan
- for the treatment of patients with EGFR-expressing metastatic colorectal cancer after failure of irinotecan-including cytotoxic therapy.

The first dose of cetuximab is given as an intravenous infusion over 120 minutes; subsequent weekly doses may be given over a period of 60 minutes. Irinotecan must not be administered earlier than 1 hour after the cetuximab infusion. Cetuximab treatment is recommended until underlying disease progression.

Before being treated with cetuximab patients should first be tested to identify whether or not the tumour is expressing EGFR. This is currently done using a commercially available DakoCytomation kit which uses immunohistochemistry (IHC) to identify EGFR expression (£995.00 for a set of 35 tests). (The assessment report states there is no information concerning sensitivity for this kit.) One common side effect of cetuximab therapy is the development of an acne-like rash.

## **3 The evidence**

### **3.1 Clinical effectiveness**

#### **3.1.1 Bevacizumab**

Systematic searches identified three randomised controlled trials that investigated the effectiveness of bevacizumab as a first-line treatment. AVF2107 investigated the effect of irinotecan, 5-fluorouracil and leucovorin (IFL) with and without the addition of bevacizumab. AVF0780 and AVF2192 investigated the effect of 5-fluorouracil and leucovorin (FU/LV) with and without bevacizumab. In all three trials the interventions were delivered as bolus regimens. For two of the trials the primary end point was overall survival, while in the other (AVF0780) the primary end points were time to disease progression and best tumour response. The participants included in AVF2107 had a mean age of 59, while those in AVF0780 had a median age of 64. In both trials participants had good performance status. The participants in AVF2192 tended to be older with a worse performance status (table 3).

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**Table 3 Characteristics of the bevacizumab trials<sup>a</sup>**

	<b>Hurwitz et al (AVF2107)</b>	<b>Kabbinavar (AVF0780)</b>	<b>Kabbinavar (AVF2192)</b>
<b>Population</b>	Mean age 59 years, 59.5% male ECOG 0, 56.5%; ECOG 1, 42.5%; ECOG 2 <1%	Median age 64 years, 62% male ECOG 0, 60.5%; ECOG 1, 39.5%; ECOG 2, 0%	Mean age 71 years, 53.5% male ECOG 0, 28.5%; ECOG 1, 66%; ECOG 2, 7%
<b>Tumour</b>	Colon 79%, rectum 21% 1 metastatic site 38% 2 metastatic sites 62%	1 metastatic site 60.5% 2 metastatic sites 27% 3 metastatic sites 12.5%	Colon 81%, rectum 19% 1 metastatic site 35% 2 metastatic sites 66%
<b>Treatment arm</b>	Bevacizumab 5 mg/kg once every 2 weeks + bolus IFL regimen Saltz regimen (see below) (n = 411)	Bevacizumab 5 mg/kg once every 2 weeks + FU (500 mg/m <sup>2</sup> ) + LV (500 mg/m <sup>2</sup> ) Roswell Park regimen (n = 35)	Bevacizumab 5 mg/kg once every 2 weeks + FU (500 mg/m <sup>2</sup> ) + LV (500 mg/m <sup>2</sup> ) Roswell Park regimen (n = 104)
<b>Control arm</b>	Placebo + bolus IFL regimen (125 mg/m <sup>2</sup> irinotecan, 500 mg/m <sup>2</sup> 5-FU by IV bolus injection, 20 mg/m <sup>2</sup> leucovorin by IV bolus) (n = 402)	FU (500 mg/m <sup>2</sup> ) + LV (500 mg/m <sup>2</sup> ) Roswell Park regimen (n = 36)	FU (500 mg/m <sup>2</sup> ) + LV (500 mg/m <sup>2</sup> ) Roswell Park regimen (n = 105)
<b>Primary outcomes</b>	Overall survival	Time to disease progression, best tumour response (complete or partial)	Overall survival
<b>Secondary outcomes</b>	Progression-free survival, response rate, health-related QoL	Overall survival, duration of response	Progression-free survival, objective response rate, response duration and change in FACT-C QoL
<b>Second-line treatments</b>	Approximately 55% received some form of second-line therapy: 25% received oxaliplatin, 10% irinotecan, 23% capecitabine, less than 2% underwent metastasectomy. Approximately 33% of participants in bevacizumab arms continued to receive bevacizumab second line	Patients who received bevacizumab and demonstrated a complete response, partial response or stable disease were eligible to receive additional bevacizumab in an open-label extension if their disease progressed within 6 months after their last dose in the study. 22 control patients who experienced disease progression crossed over to receive bevacizumab (10 mg/kg)	53% of patients received second-line treatment. 42% of patients were treated with oxaliplatin, irinotecan or both agents
<sup>a</sup> Data were averaged across control arm and intervention arms receiving bevacizumab at the licensed dose.			

The assessment group did not perform a meta-analysis on the data from the three trials because of differences in the comparators and populations. The individual trial results are summarised below (see also table 5). However, the trials have been combined in a meta-analysis by Kabbinavar and colleagues, and the results of this analysis are summarised in the fourth bullet point below.

- The addition of bevacizumab to IFL (AVF2107) led to a statistically significant increase in median overall survival compared with IFL alone (20.3 months vs 15.6 months, respectively,  $p < 0.001$ ). This was not demonstrated in AVF2192 and AVF0780, where the addition of bevacizumab to FU/LV showed no statistically significant increase in median overall survival (AVF2192: bevacizumab with FU/LV vs FU/LV, 16.6 months vs 13.2 months, respectively,  $p = 0.09$ ; and AVF0780: bevacizumab with FU/LV vs FU/LV, 17.7 months vs 13.6 months, respectively,  $p = 0.07$ )<sup>2</sup>.
- Progression-free survival measured as time from randomisation until tumour progression or death was measured in two trials. In both trials the addition of bevacizumab caused a statistically significant increase in median progression-free survival compared with control (AVF2107: 10.6 months vs 6.2 months, respectively,  $p < 0.001$ ; and AVF2192: 9.2 months vs 5.5 months, respectively,  $p < 0.0002$ ). The other trial (AVF0780) reported the median time to disease progression, which also favoured the bevacizumab-containing arm above control (9.0 months vs 5.2 months, respectively,  $p = 0.005$ ).
- All three trials measured tumour response rate (as partial or complete reduction in tumour size). Bevacizumab combined with IFL gave a higher tumour response rate compared with IFL alone (AVF2107), and this difference was statistically significant (44.8% vs 34.8%, respectively,  $p = 0.004$ ). Bevacizumab combined with FU/LV gave a higher tumour response rate compared with FU/LV (AVF0780), and this difference was also statistically significant (40.0% vs 16.7%, respectively,  $p = 0.029$ ). However, in AVF2192, the results on tumour response rate did not reach statistical significance (26.0% vs 15.2% for treatment and control arms, respectively;  $p = 0.055$ ).
- In a meta-analysis by Kabbinavar and colleagues, the combined results of the three trials showed a statistically significant impact on overall survival favouring the addition of bevacizumab (17.9 months vs 14.6 months for treatment and control arms, respectively;  $p = 0.008$ ). The effect was also seen for progression-free survival (8.8 months vs 5.6 months,  $p < 0.0001$ ) and response rate (34.1% vs 24.5%,  $p = 0.019$ ).

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<sup>2</sup> Results for AVF0780 and AVF2192 are taken from the Roche submission calculated directly from the Avastin clinical trials database. Earlier publications presented the following data for overall survival. AVF0780: FU/LV 13.8 months, FU/LV + bevacizumab 21.5 months, and AVF2192: FU/LV 12.9 months, FU/LV + bevacizumab 16.6 months.



In summary, across the three trials the addition of bevacizumab shows a consistent statistically significant increase in progression-free survival. However, the role of bevacizumab in overall survival and tumour response rate is less certain. Although both the outcomes were statistically significant in AVF2107, neither was statistically significant in AVF2192.

### 3.1.2 Cetuximab

Systematic searches identified no trials that compared cetuximab to current standard comparators (FOLFOX, active/best supportive care [ASC/BSC]). When the search was widened the following trials were identified: one randomised controlled trial that compared cetuximab monotherapy with cetuximab combined with irinotecan (BOND); and three single-arm trials, two of which measured the effect of cetuximab monotherapy (CP02-0144, CP02-0141) and one which measured the effect of cetuximab combined with irinotecan (CP02-9923). The primary outcome for all trials was tumour response rate. A median age of 56 years was reported in trials CP02-9923 and CP02-0141, while a median age of 59 years was reported in BOND and CP02-0144. In all four trials the populations had good performance status (table 4).

- Cetuximab combined with irinotecan (BOND) showed no statistically significant difference in median overall survival when compared with cetuximab monotherapy (8.6 months vs 6.9 months, respectively,  $p = 0.48$ ). The single-arm trials show results of a similar magnitude to those observed in the BOND study, median overall survival for cetuximab monotherapy; 6.4 months (CP02-0141), 6.6 months (CP02-0144) and cetuximab combined with irinotecan 8.4 months (CP02-9923).
- Cetuximab combined with irinotecan showed a statistically significant increase in median time to progression compared with cetuximab monotherapy (4.1 months vs 1.5 months, respectively,  $p < 0.001$ ). Median time to progression was reported in two of the single-arm trials – 1.4 months for cetuximab monotherapy (CP02-0144) and 2.9 months for cetuximab combined with irinotecan (CP02-9923).
- All four cetuximab trials measured tumour response rate. In the BOND trial cetuximab combined with irinotecan gave a higher response rate than cetuximab monotherapy, and this difference was statistically significant (22.9% vs 10.8%, respectively,  $p = 0.007$ ). The other single-arm trials showed similar rates of response: the cetuximab monotherapy trials CP02-0141 and CP02-0144 showed response rates of 8.8% and 12.0%, respectively, while cetuximab combined with irinotecan (CP02-9923 trial) showed a response rate of 15.2%.
- The cetuximab trials suggest that the response to cetuximab may be associated with acne-like rash. Pooled results for trials CP02-0141 (cetuximab monotherapy)

and BOND (n = 339) from the manufacturer's submission show that 50% of patients with stable disease at 6 weeks had an acne-like rash of grade 2 or above; 26% (n = 20) of these went on to get a partial response, as compared with 13% (n = 10) of those without an acne-like rash grade 2 or above (p = 0.043).

- In terms of survival, in the BOND trial patients in the combination therapy arm with an acne-like rash grade 2 or above had an overall survival of 10.8 months compared with 5.8 months for those with either no rash or a grade 1 acne-like rash. In trial CPO2-9923 patients receiving irinotecan and cetuximab and who had a grade 3 acne-like rash had a median survival of 13.1 months, compared with 10.6 months for those with grade 2, 6.2 months for those with grade 1 and 4.3 months for those with no rash (grade 0 vs grade 1–3, p = 0.0008) (see also page 63 of the assessment report).

In summary, the assessment group identified no trials that compared cetuximab with current standard comparators. One randomised controlled trial (BOND) was identified that compared cetuximab monotherapy with cetuximab combined with irinotecan. The trial results show that cetuximab combined with irinotecan significantly improved time to progression and tumour response rate when compared with cetuximab monotherapy (table 5). There is some evidence to suggest that the degree of response to cetuximab may be associated with acne-like rash.

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**Table 4 Characteristics of the cetuximab trials**

	<b>BOND</b>	<b>CP02-0141</b>	<b>CP02-0144</b>	<b>CP02-9923</b>
<b>Population</b>	Median age 59 years (range 26–84), 63% male  87.8% = Karnofsky 80–100	Median age 56 years (range 26–80), 61% male  Median ECOG = 0	Median age 59 years (range 29–85), 53% male  ECOG 0, 42%; ECOG 1, 57%	Median age 56 years (range 26–83)  Median Karnofsky = 90
<b>Tumour</b>	Colon 58%, rectum 40%  1 metastatic site 50%, 2 metastatic sites 32%, ≥3 metastatic sites 5%	Colon 77%, rectum 23%  2 metastatic sites 33%, ≥3 metastatic sites 14%	Not reported	Colon approx. 80%, rectum approx. 20%
<b>Treatment arm</b>	Cetuximab 400 mg/m <sup>2</sup> , followed by weekly transfusions of 250 mg/m <sup>2</sup> , and also irinotecan at the same dose as that given in their most recent pre-study therapy (n = 218)	Initial dose of cetuximab 400 mg/m <sup>2</sup> , followed by weekly transfusion of 250 mg/m <sup>2</sup> (n = 57)	Initial dose of cetuximab 400 mg/m <sup>2</sup> , followed by weekly transfusion of 250 mg/m <sup>2</sup> (n = 346)	Initial dose of cetuximab 400 mg/m <sup>2</sup> , followed by weekly transfusion of 250 mg/m <sup>2</sup> , and also irinotecan 125 mg/m <sup>2</sup> weekly for 4 wks then 2 wks rest or 350 mg/m <sup>2</sup> every 3 wks (n = 138)
<b>Control arm</b>	Cetuximab only as above (n = 111)	Not applicable (NA)	NA	NA
<b>Primary outcomes</b>	Tumour response rate	Tumour response rate	Tumour response rate	Tumour response rate
<b>Secondary outcomes</b>	Time to progression, duration of response, overall survival, incidence of adverse events	Duration of response, survival duration, toxicity	Not reported	Not reported
<b>Previous cancer treatment</b>	One 21%, two 37%, more than two 43%, 63% prior oxaliplatin therapy	One 28%, two or more 72%, 100% irinotecan refractory, 14% prior oxaliplatin therapy	Participants were irinotecan, oxaliplatin and 5-FU refractory	Participants were irinotecan refractory, 10% prior oxaliplatin therapy

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**Table 5 Summary of the results of the bevacizumab and cetuximab controlled trials**

<b>Study</b>	<b>N</b>	<b>Arms</b>	<b>Survival median (95% confidence interval [CI])</b>	<b>Progression-free survival median (95% CI)<sup>3</sup></b>	<b>Tumour response rate % (95% CI)</b>
<b>Bevacizumab</b>					
AVF2107	923	Bolus IFL	15.6 (14.3 to 17.0)	6.2 (5.6 to 7.7)	34.8 (30.2 to 39.6)
		Bolus IFL + bevacizumab	20.3 (18.5 to 24.2)	10.6 (9.0 to 11.0)	44.8 (39.9 to 49.8)
Hazard ratio (p value)			0.66 (p < 0.001)	0.54 (p < 0.001)	NA (p = 0.004)
AVF0780	104	5-FU/FA	13.6 (not reported)	5.2 (3.5 to 5.6)	16.7 (7.0 to 33.5)
		5-FU/FA + bevacizumab	17.7 (not reported)	9.0 (5.8 to 10.9)	40.0 (24.4 to 57.8)
Hazard ratio (p value)			0.52 (p = 0.07)	0.44 (p = 0.005)	NA (p = 0.029)
AVF2192	209	5-FU/FA	13.2 (10.4 to 17.0)	5.5 (5.4 to 6.1)	15.2 (9.2 to 23.9)
		5-FU/FA + bevacizumab	16.6 (13.6 to 19.3)	9.2 (7.0 to 10.6)	26.0 (18.1 to 35.6)
Hazard ratio (p value)			0.77 (p = 0.09)	0.50 (p = 0.0002)	NA (p = 0.055)
<b>Cetuximab</b>					
BOND	329	Cetuximab	6.9 (5.6 to 9.1)	1.5 (1.4 to 2.0)	10.8 (5.7 to 18.1)
		Cetuximab and irinotecan	8.6 (7.6 to 9.6)	4.1 (2.8 to 4.3)	22.9 (17.5 to 29.1)
Hazard ratio (p value)			0.91 (p = 0.48)	0.54 (p < 0.001)	NA (p = 0.007)

<sup>3</sup> AVF0780 and BOND measured time to progression not progression-free survival.

### 3.1.3 Adverse events

In the three bevacizumab trials there was a higher incidence of grade 3 and 4 adverse events in the arms receiving bevacizumab compared with control: AVF2107 84.9% vs 74.0%, respectively; AVF0780 74.3% vs 54.3%; and AVF2192 87% vs 71%. Higher incidences of grade 3 and 4 hypertension were also reported, compared with control: AVF2107 11.0% vs 2.3%, respectively; AVF0780 8.6% vs 0%; and AVF2192 16% vs 3%. For other grade 3 and 4 toxicities there were no consistent patterns of effects. An increased incidence of diarrhoea was reported in trial AVF2107 (32.4% vs 24.7%), and thrombotic events in trial AVF0780 (14.3% vs 2.9%). All three trials reported that other clinical trials of bevacizumab have identified haemorrhage, thromboembolism, proteinuria and hypertension as possible adverse events associated with bevacizumab.

The BOND trial comparing cetuximab monotherapy with cetuximab plus irinotecan reported a higher incidence of the following in the cetuximab combination therapy arm: grade 3 and 4 adverse events (65.1% vs 43.5%); diarrhoea (21.2% vs 1.7%) and neutropenia (9.4% vs 0%). Cetuximab is also associated with an increased incidence of an acne-like rash (9.4% vs 5.2%) grade 3 or 4 (see previous section on effectiveness).

## 3.2 Cost effectiveness

No published economic analyses of either bevacizumab or cetuximab were identified. Both manufacturers submitted cost-effectiveness models and the assessment group developed two models for bevacizumab and two models for cetuximab.

### 3.2.1 Bevacizumab manufacturer's model

Roche submitted two simple-state transition models in which patients moved around three health states: pre-progression, post-progression, death. Each model was based on data from a different bevacizumab trial; AVF2107 compared bevacizumab combined with IFL with IFL, and AVF2192 compared bevacizumab combined with FU/LV with FU/LV. In both models the analysis was carried out from the perspective

of the NHS. Data on progression-free survival were taken from each of the trials for the treatment and control arms, to which an equal risk of death following progression was applied regardless of treatment group. The models assumed equivalent utility scores for both the intervention and control groups with a utility of 0.80 given to the pre-progression health state and 0.50 given to the post-progression health state. Utility decrements associated with adverse events were not included. Pre-progression costs were calculated from the trials augmented with data from other published sources, while an assumption of £2000 a month was used for post progression costs applied equally across both arms.

The incremental cost effectiveness ratios (ICERs) were £88,364 per quality adjusted life year (QALY) for bevacizumab combined with IFL (discounted at 6% for costs and 1.5% for benefits) or £93,128 per QALY (discounted at 3.5% for costs and benefits). The ICER for bevacizumab combined with FU/LV was £56,628<sup>4</sup> per QALY (discounted at 6% for costs and 1.5% for benefits) or £59,894 per QALY (discounted at 3.5% for costs and benefits).

When considering these base case results it is important to remember that direct incremental comparisons between the two models should not be carried out because of known differences in the populations of trials AVF2107 and AVF2192.

One-way sensitivity analyses resulted in estimates of cost utility of between £82,577 and £106,770 for bevacizumab combined with IFL, and between £39,136 and £69,439 for bevacizumab combined with FU/LV. Probabilistic sensitivity analyses suggest that the probability of cost effectiveness at a willingness-to-pay threshold of £30,000 was 0.16 for bevacizumab combined with IFL, and 0.24 for bevacizumab combined with FU/LV. The manufacturer submission notes that the models are particularly sensitive to utility values.

### **3.2.2 Bevacizumab assessment group models**

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<sup>4</sup> Figure provided by assessment group obtained directly from the Roche economic model.

The models produced by the assessment group followed a similar methodology to that used in the earlier NICE appraisal of irinotecan, oxaliplatin and raltitrexed. The key difference in the assessment group models from the models presented by Roche is the use of overall survival data from studies AVF2107 and AVF2192 rather than progression-free survival. Other significant differences are the sources of the utility values and the explicit sourcing of costs for second and subsequent line therapies.

Like Roche the assessment group presented two models – one based on trial AVF2107 and one based on trial AVF2192. The models are simple-state transition models with costs and effects calculated from the perspective of the NHS. Unlike the Roche models the outcomes data are based on published overall survival curves from the two trials. The utility values for pre-progression are the same as used in the Roche models (0.80), whereas that for post-progression is slightly higher (0.60). Data on second and subsequent line therapies were taken from a trial by Tournigand and colleagues that investigated the optimal sequencing of FOLFOX and FOLFIRI as first- and second-line therapies, and applied equally to treatment and control groups. Costs were calculated from trial data and augmented from a range of sources including published literature and personal communication. No discounting was used in the models because the distribution of costs incurred over time was unknown. However, given the short time horizon used in the models it is unlikely that this would have a large impact on the results. Uncertainties surrounding the costs and benefits were captured using one way and probabilistic sensitivity analyses.

The base case ICERs for the assessment group models were £62,857 per QALY for bevacizumab combined with IFL and £88,436 per QALY for bevacizumab combined with FU/LV.

The difference in the ICERs between the assessment group and Roche models reflects the use of progression-free survival versus overall survival. The approach adopted by Roche resulted in greater marginal impact on survival than the assessment group models because the difference in mean progression-free survival was greater than the difference in mean overall survival in trial AVF2192. This means that the Roche model resulted in more favourable estimates of cost

effectiveness than the assessment group model when the comparator was FU/LV. Conversely, the assessment group model results in more favourable estimates of cost effectiveness when the comparator is IFL.

When the assessment group models are run using the survival benefits estimated by Roche, the ICERs are lower than those obtained in the Roche base case, showing that other adjustments made by the assessment group in relation to utility values and second-line costs have a favourable impact on the ICER (table 6).

**Table 6 Summary of the base case results of the bevacizumab economic models**

<b>Trial</b>	<b>Roche model</b>	<b>Assessment group model</b>	<b>Assessment group with Roche survival benefits</b>
<b>AVF2107</b>			
ICER	£93,128	£62,857	£76,832
Incremental costs	£20,535	£19,360	£18,400
Incremental QALY	0.22	0.31	0.24
<b>AVF2192</b>			
ICER	£59,894	£88,436	£51,355
Incremental costs	£18,056	£15,615	£16,286
Incremental QALY	0.30	0.18	0.32
The base case ICER in the Roche model is discounted at 3.5% for both costs and QALYs. The assessment group model is not discounted.			

One-way sensitivity analyses produced ICERs of £60,430–£76,831 per QALY for bevacizumab combined with IFL, and £51,355- **(CIC information removed)** per QALY for bevacizumab combined with FU/LV. Probabilistic sensitivity analyses



suggest that with a willingness-to-pay threshold of £30,000, the likelihood of bevacizumab being cost effective is zero.

### 3.2.3 Cetuximab manufacturer's model

The model developed by Merck uses survival modelling to estimate the lifetime costs and benefits for patients receiving cetuximab combined with irinotecan compared with ASC/BSC. Two sets of analyses are presented. The first is based directly on data from the BOND trial with an extrapolation to take into account censored values. In the second analysis further adjustments are made to the survival data to reflect a proposed continuation rule. Under the continuation rule patients only continue to receive cetuximab beyond 6 weeks if there is either a partial or complete tumour response or an acne-like rash of grade 2 or above. This is based on evidence outlined in the effectiveness section suggesting that the response to treatment may be associated with acne-like rash.

The modelling was carried out from the perspective of the NHS, and economic outcomes were presented as life years gained with two sensitivity analyses to examine the impact of using QALYs (assuming constant utility of either 0.95 or 0.71 taken from published literature). **(CIC information removed)** Costs and resource data were taken from the BOND study and augmented from the published literature. Costs and benefits were discounted at an annual rate of 3.5%. The assessment group reanalysed the data using discount rates of 6.0% and 1.5%.

Survival data from the BOND trial were adjusted to account for censored data. This estimated that the mean overall survival duration of patients given cetuximab and irinotecan was 11.01 months (undiscounted) without the continuation rule and 10.76 months (undiscounted) with the continuation rule. The assessment report states that the survival curves modelled by the manufacturer diverge from the empirical overall survival curve at around 9 months post randomisation and therefore may overestimate the actual survival duration of these patients. In the absence of direct comparisons of cetuximab with ASC/BSC, the survival of patients receiving ASC/BSC was modelled from data taken from a randomised controlled trial of second-line irinotecan versus ASC/BSC by Cunningham and colleagues. Within this

study the hazard ratio describing relative survival of patients receiving ASC/BSC compared with irinotecan was 1.71; this ratio was then applied to the observed relative survival duration of the patients receiving cetuximab monotherapy in the BOND trial to net out the impact of receiving cetuximab monotherapy. The expected overall survival duration of patients receiving ASC/BSC was estimated to be 5.64 months. The model assumes that the relative hazard of overall survival between cetuximab monotherapy and ASC/BSC as second and subsequent line treatment is exactly equivalent to the relative survival hazard between irinotecan and ASC/BSC as second-line treatment.

A series of one-way sensitivity analyses was carried out to consider uncertainty around unit costs and hazard ratios. Bootstrapping techniques were used to explore other areas of uncertainty.

The base case analysis suggests an incremental cost per life year gained of £33,263 with the continuation rule. One-way sensitivity analyses present incremental cost-effectiveness estimates of £35,014 per QALY with a utility value of 0.95 and £46,849 per QALY with a utility value of 0.71 (table 7).

**Table 7 Summary of the results of the cetuximab manufacturer submission**

Continuation rule	Utility value	Incremental costs	Incremental QALYs	ICER
+	0.95	13,971	0.40	35,014
+	<i>(CIC information removed)</i>			
-	0.95	18,902	0.42	45,237
-	<i>(CIC information removed)</i>			

Values in the table are discounted at 3.5%. *(CIC information removed)*

Cost-effectiveness acceptability curves suggest that with a willingness to pay £30,000 per *life year gained* the probability of cost effectiveness is 0.10. The

manufacturer submission notes that the model is sensitive to the continuation rule and the outcomes of chemotherapy relative to ASC/BSC.

### **3.2.4 Cetuximab assessment group model**

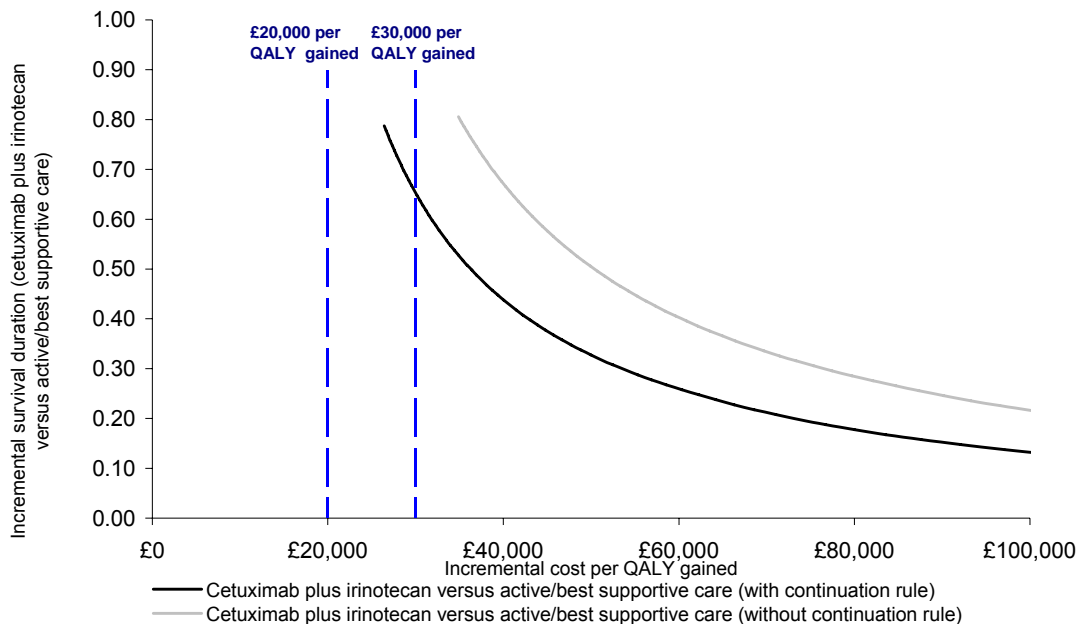
Without any direct comparisons of cetuximab combined with irinotecan versus ASC/BSC or FOLFOX, the assessment group developed two different models. The first is a threshold analysis considering the necessary incremental benefit cetuximab combined with irinotecan would have to provide over ASC/BSC to be considered cost effective. The second is an indirect comparison of data from the BOND trial with data from other published trials of second-line ASC/BSC.

Overall survival was estimated from patient level data collected in the BOND study using Weibull regression analysis to adjust for censoring. The assessment group estimated the mean overall survival duration as 0.81 (9.7 months) without the continuation rule and 0.79 (9.5 months) with the continuation rule. In the threshold analysis the survival duration of patients receiving ASC/BSC was held as an unknown variable, whereas in the indirect comparisons different values for mean overall survival were taken from three published trials (table 8). Health-related QoL was estimated in the same way as in the bevacizumab model applying a utility of 0.80 to pre-progressive disease states and 0.60 post-progressive disease states. Measures of the quantity of pre-progression survival were estimated using the BOND study for the cetuximab arm and derived from a trial by Rao and colleagues for the comparator arm (approximately 37% of overall survival).

Resource use and costs were taken from the BOND trial as reported in the manufacturer submission and augmented from the published literature and personal communication with clinical experts. Discounting was not used in the model, but as with bevacizumab the short time horizon means this is unlikely to have a substantial impact on the ICER. Probabilistic sensitivity analysis was not appropriate for the threshold analysis so a series of scenario analyses were presented to explore the impact of uncertainty.

The base case threshold analysis suggests it is not possible for cetuximab combined with irinotecan to have a cost per QALY of less than £20,000 irrespective of the application of the continuation rule. When the proposed continuation rule is applied cetuximab combined with irinotecan must provide 0.65 additional life years (7.8 months) when compared with ASC/BSC to achieve an incremental cost per QALY ratio of £30,000 (figure 1). It was not possible to achieve a cost per QALY of less than £30,000 without the continuation rule.

**Figure 1 Additional life years cetuximab therapy must provide over ASC/BSC to be cost effective at a willingness-to-pay threshold of £20,000 and £30,000**



The results from the indirect comparisons are presented in table 8, but for methodological reasons these analyses are associated with a high level of uncertainty. Importantly, none of the studies used as the comparator discriminated on the basis of patient’s EGFR status.

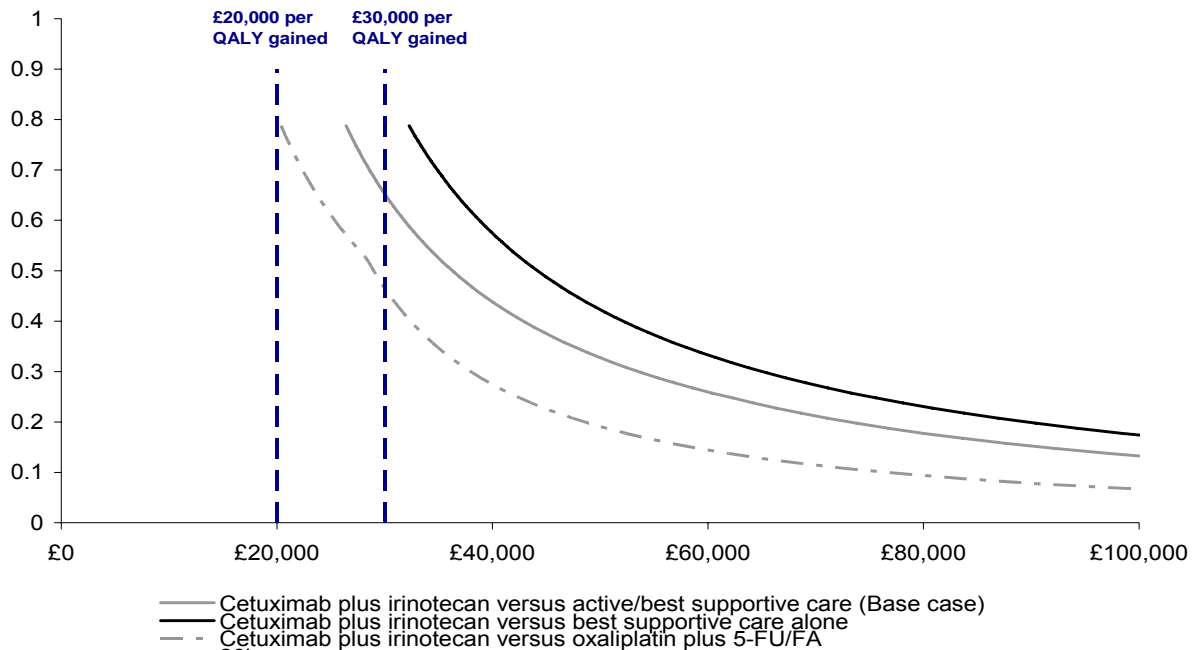
**Table 8 Summary of the indirect comparisons**

Comparator	Median survival duration of BSC arm <sup>a</sup>	Continuation rule	Incremental QALY	Incremental cost	ICER
Cunningham and colleagues	6.5 months	+	0.14	£10,804	£77,210
		-	0.15	£15,791	£104,747
Rao and colleagues	6.1 months	+	0.09	£10,260	£108,934
		-	0.11	£15,248	£145,192
Barni and colleagues	9.0 months	+	0.03	£9,477	£335,358
		-	0.04	£14,465	£370,044

<sup>a</sup> ICERs are calculated using mean and not median survival values.

Scenario analyses suggest that a more favourable cost per QALY ratio is possible if all people in the comparator arm are assumed to receive oxaliplatin combined with 5-FU/FA due to the greater associated costs. However, if all people in the comparator arm are assumed to get best supportive care it is not possible for cetuximab combined with irinotecan to have a cost per QALY ratio of less than £30,000 (figure 2).

**Figure 2 Additional life years cetuximab therapy must provide over current standard care to be cost effective at a willingness-to-pay threshold of £20,000 and £30,000**



## 4 Issues for consideration

### Effectiveness

- With the exception of the bevacizumab study AVF2192, the populations in both the bevacizumab and cetuximab trials were relatively younger and fitter than the England and Wales population of patients with metastatic colorectal cancer. Can the treatment effects seen in the studies be considered transferable to clinical practice?

### Bevacizumab

Bevacizumab is currently licensed as a first-line therapy for metastatic colorectal cancer.

- Although bevacizumab consistently demonstrates a statistically significant impact on progression-free survival/time to progression this did not always lead to a statistically significant difference in overall survival or tumour response in individual studies. Has bevacizumab demonstrated sufficient clinical effectiveness across the clinical outcomes measured in the trials?
- All three trials compare the addition of bevacizumab to bolus chemotherapy regimens rather than the infusional regimens more commonly used within

England and Wales. The relative effectiveness of infusional versus bolus regimens is unclear.

- Patients allocated to the intervention arm of the bevacizumab studies were allowed to continue with bevacizumab including therapy after disease progression. Consequently the true impact of bevacizumab as a first line treatment is uncertain.
- One consideration for first-line treatments for metastatic colorectal cancer is the extent to which they may render unresectable metastases resectable, thus presenting the opportunity for long-term survival. There is no evidence presented for resection in the manufacturer's submission; the published paper for trial AVF2107 reports that less than 2% of people across both arms underwent metastasectomy. As an outcome are resection rates important for people with metastatic colorectal cancer? What are resection rates for other first line therapies?

### **Cetuximab**

Cetuximab is currently licensed in combination with irinotecan for patients who have previously failed on an irinotecan including regimen.

- Without studies comparing cetuximab therapy to current standard treatment it is difficult to accurately assess the relative effectiveness of cetuximab therapy compared to current standard care.
- Although the license indicates patients have to be EGFR positive, expert submissions note concerns about guidance being based on EGFR status. EGFR presence does not reliably predict the response to cetuximab (see page 61 of the assessment report). Do uncertainties around who may benefit from cetuximab impact on the formulation of guidance?
- Submissions note that available data show that cetuximab combined with irinotecan appears to demonstrate anti-tumour activity. They state that for ethical reasons this means it is unlikely that a significant number of further trials investigating last line use compared to ASC/BSC will be completed. The assessment group identified one ongoing trial.

### **Cost effectiveness**

- Both submissions note concerns about the uncertainty surrounding utility values which affect the estimates of costs per QALY.
- Submissions note that both bevacizumab and cetuximab are monoclonal antibodies and as such represent an innovative approach to cancer therapy.

## Bevacizumab

- In their response to the assessment report Roche propose to set up the Avastin registry programme and to pay for administration costs of bevacizumab and associated infusional costs given as part of bevacizumab containing regimens. Analyses run by the assessment group including the proposed cost reductions provide ICERs of £49,197 per QALY for bevacizumab combined with IFL and £69,045 per QALY for bevacizumab combined with FU/FA. How do the proposals for a registry affect the committee decisions?

## Cetuximab

- Within the licensed indication cetuximab may be given as a second or subsequent line therapy after failing on irinotecan including therapy. For some patients ASC/BSC may be the only treatment option. The assessment report notes that in those patients where ASC/BSC is the only treatment option, progression-free survival and tumour response are likely to be close to zero.
- The manufacturer's submission requests that cetuximab be appraised for the subset of the population for who cetuximab could be considered a last active treatment option, either as a third line therapy or as a second line therapy for those patients for whom oxaliplatin is contraindicated.
- The manufacturer's submission proposes a continuation rule (see section 3.2.3) and requests that cetuximab is appraised within the context of the continuation rule. However, the SPC notes that if a patient experiences a grade 3 skin reaction then cetuximab treatment must be interrupted and may only be resumed if the reaction resolves to grade 2. The impact of this on the outcomes is unclear.
- There is uncertainty surrounding the estimates of cost effectiveness of cetuximab due to the lack of evidence about its relative effectiveness compared to current standard treatment.

## 5 Ongoing research

### *Bevacizumab*

#### First line

The TREE-2 trial is a randomised multicentre study comparing three regimens of oxaliplatin plus bolus, infusional or oral 5-FU with bevacizumab to evaluate safety



and tolerability in the first-line treatment of patients with advanced colorectal cancer. Preliminary results have been presented and survival data will be available June 2006.

The NO16966C trial is a randomised phase III study of intermittent oral capecitabine in combination with intravenous oxaliplatin (CAPOX) with or without bevacizumab for the first-line treatment of patients with advanced colorectal cancer.

The CONcePT trial aims to develop an optimised schedule of administration of FOLFOX plus bevacizumab in the first-line treatment of patients with advanced colorectal cancer.

### **Second and subsequent line**

The E3200 trial is a phase III randomised controlled trial of oxaliplatin, 5-FU and leucovorin with or without bevacizumab, versus bevacizumab alone in patients previously treated for advanced or metastatic colorectal cancer.

## ***Cetuximab***

### **First line**

There are several studies currently investigating the first-line use of cetuximab in combination with standard chemotherapy regimens (for example, FOLFOX, FOLFIRI, CAPOX). One example is the COIN study, which aims to determine if the addition of cetuximab to continuous oxaliplatin and 5-FU improves overall survival when compared either to continuous oxaliplatin and 5-FU on its own or to intermittent oxaliplatin and fluoropyrimidine chemotherapy.

### **Second and subsequent line**

NCT00063141 is a randomised controlled trial comparing cetuximab combined with irinotecan with irinotecan alone as second-line treatment in patients with metastatic colorectal cancer.

NCT00079066 is a randomised controlled trial comparing cetuximab combined with best supportive care with best supportive care alone in patients with metastatic colorectal cancer.

EXPLORE is a randomised controlled trial comparing cetuximab combined with FOLFOX with FOLFOX alone as second-line treatment in patients with metastatic colorectal cancer. Preliminary results were presented at ASCO 2005.

### ***Bevacizumab and cetuximab in combination***

The BOND 2 study was a phase II randomised trial which investigated the effect of adding bevacizumab to either cetuximab monotherapy or cetuximab combined with irinotecan in patients with metastatic colorectal cancer who had previously failed on irinotecan including therapy. Preliminary results for this study are available. A further study (BOND 3) has been initiated to evaluate the use of bevacizumab combined with cetuximab with or without irinotecan in bevacizumab refractory patients.

## **6 Authors**

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## Appendix A: Sources of evidence considered in the preparation of the overview

- A The Assessment Report: Tappenden P, Jones R, Paisley S, Carroll C, SchARR, *The use of bevacizumab and cetuximab for the treatment of metastatic colorectal cancer*. February 2006
- B Submissions from the following organisations:
- I Manufacturer/sponsors:
- Roche Products
  - Merck Pharmaceuticals
- II Professional/specialist and patient/carer groups:
- Colon Cancer Concern
  - Cancer BACUP
  - Royal College of Nursing
  - Beating Bowel Cancer
  - Association of Coloproctologists of Great Britain
  - Royal College of Pathologists
  - Royal College of Physicians