NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Overview

Cetuximab (mono- or combination chemotherapy), bevacizumab (combination with non-oxaliplatin chemotherapy) and panitumumab (monotherapy) for the treatment of metastatic colorectal cancer after first-line chemotherapy (review of technology appraisal 150 and part-review of technology appraisal 118)

1.1.1	This document is a summary of the evidence and views submitted by consultees and the Assessment Group. It highlights key issues for discussion at the first Appraisal Committee meeting. NICE prepares the overview before it receives consultees' comments on the assessment report. The sources of evidence used in the preparation of this document are given in appendix A.

1.1.1.1 Background

1.2 The condition

Colorectal cancer is a malignant neoplasm arising from the lining (mucosa) of the large intestine (colon and rectum). It is the third most commonly diagnosed cancer in the UK, with approximately 32,000 new cases registered in England and Wales in 2008, accounting for 11% of all new diagnoses of cancer in women and 14% of all new diagnoses cancer in men. The prevalence of colorectal cancer increases with age, from 35 per 100,000 in people younger than 60 years, to 345 per 100,000 in people aged over 75 years. 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 at diagnosis.

In metastatic colorectal cancer the tumour has spread beyond the confines of the locoregional lymph nodes to other parts of the body. This is described as stage IV of the American Joint Committee on Cancer's tumour node metastases system or stage D of Dukes' classification. A substantial proportion of people with colorectal cancer already have metastatic disease at the time of diagnosis; estimates range from 20% to 55%. In addition, approximately 50–60% of patients who have undergone surgery for early-stage 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 cancer is around 7%.

The most frequent site of metastatic disease is the liver. For patients whose disease is confined to a limited area of the liver, surgery provides the possibility of longer-term cancer free survival. An estimated 80% of patients are eligible for surgery and, of those, 40% will remain disease free in the long term. Around 40– 50% of patients will develop liver metastases within 3 years of primary surgery.

In the past few years it has been established that two genetic factors can affect treatment outcomes in metastatic colorectal cancer: epidermal growth factor receptor (*EGFR*) and the v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (*KRAS*) gene. It has also been established that some types of chemotherapy have much more effective anti-tumour activity in tumours that express EGFR and a normal ('wild-type') *KRAS* gene. Global clinical trial data indicate that 80% of patients with metastatic colorectal cancer have EGFR-expressing disease and approximately 30–50% have the *KRAS* wild-type gene.

This review was initiated because of a change in the marketing authorisation for bevacizumab since 'Bevacizumab and cetuximab for the treatment of metastatic colorectal cancer' (NICE technology appraisal guidance 118). It was considered appropriate to also include the terminated appraisal

'Cetuximab for the treatment of metastatic colorectal cancer following failure of oxaliplatin-containing chemotherapy' (NICE technology appraisal 150) and to evaluate panitumumab for the treatment of metastatic colorectal cancer after first-line chemotherapy.

1.3 Current management

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

Early chemotherapy before onset of symptoms has been shown to prolong survival and improve overall quality of life. Approximately 8% of patients with metastatic colorectal cancer present with potentially resectable liver metastases and, in around 14% of patients, chemotherapy may render unresectable liver metastases operable. Liver resection may be successful with no further relapse.

People with metastatic disease who are sufficiently fit (those with World Health Organization [WHO] performance status 2 or better) are usually treated with chemotherapy as first-line and/or second-line therapy. In people 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 individual clinical circumstances.

First-line chemotherapy options include 5-fluorouracil and folinic acid (5-FU/FA), oxaliplatin plus 5-FU/FA (FOLFOX), or irinotecan plus 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 monotherapy may be a

second-line treatment option; for patients receiving first-line FOLFIRI, FOLFOX may be a second-line treatment option. Patients receiving 5-FU/FA or oral analogues as first-line treatment may receive treatment with FOLFOX or irinotecan as second- and subsequent-line therapy. Current treatment options recommended by NICE are shown below (Table 1).

Table 1 Current NICE technology appraisal recommendations for treatments of metastatic colorectal cancer

	First line	**Second and subsequent line**
IV 5-FU/FA or oral prodrug (capecitabine or tegafur-uracil) (TA61)	Yes	No guidance
IV 5-FU/FA + oxaliplatin (FOLFOX) (TA93)	Yes	Yes
IV 5-FU/FA + irinotecan (FOLFIRI) (TA93)	Yes	No guidance
Irinotecan monotherapy (TA93)	No guidance	Yes
Raltitrexed(TA93)	No	No
Bevacizumab + FOLFOX or capecitabine + oxaliplatin (XELOX) (TA212)	No	No guidance
Bevacizumab + IV 5-FU/FA ± irinotecan (TA118)	No	No guidance
Cetuximab + FOLFOX or FOLFIRI (KRAS wild type only) (TA176; TA150)	a	No
Cetuximab monotherapy (TA150)	No guidance	No [b]
Cetuximab + irinotecan (TA118)	No guidance	No

[a] only recommended if metastatic disease is confined to the liver and the aim of treatment is to make the metastases resectable.

[b] TA150 was terminated because the manufacturer did not provide a submission.

IV = intravenous

Table 2 The appraisal scope

Interventions	• Cetuximab (monotherapy or in combination with chemotherapy) • Bevacizumab (in combination with chemotherapy not containing oxaliplatin) • Panitumumab (monotherapy)
Populations	• People with EGFR-expressing and KRAS wild-type metastatic colorectal cancer that has progressed after first-line chemotherapy (cetuximab and panitumumab population) • People with metastatic colorectal cancer that has progressed after first-line chemotherapy (bevacizumab population)
Comparators	• Irinotecan- or oxaliplatin-based chemotherapy regimens • Where appropriate, the interventions will be compared with each other • Best supportive care
Outcomes	• The outcome measures to be considered include: - overall survival - progression-free survival - response rate - adverse effects of treatment - health-related quality of life

1.3.1.1 The technologies

Table 3 Summary description of technologies

Non-proprietary name	Bevacizumab	Cetuximab	Panitumumab
Proprietary name	Avastin	Erbitux	Vectibix
Manufacturer	Roche Products	Merck Serono	Amgen
Dose	5 or 10 mg/kg of body weight given by intravenous infusion once every 2 weeks or 7.5 or 15 mg/kg of body weight given by intravenous infusion once every 3 weeks	Initial intravenous infusion of 400 mg/m^2 of body surface area followed by weekly intravenous infusions of 250 mg/m^2	6 mg/kg of body weight given by intravenous infusion once every 14 days
Acquisition cost (BNF edition 61)	100-mg vial £242.66 net 400-mg vial £924.40 net	100-mg vial £178.10 net 500-mg vial £890.50 net	100-mg vial £379.29 net 400-mg vial £1517.16 net

Bevacizumab

Bevacizumab (Avastin, Roche Products) 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 has a UK marketing authorisation:

- in combination with fluoropyrimidine-based chemotherapy for the treatment of metastatic carcinoma of the colon or rectum.

The SPC recommends that treatment is continued until disease progression.

Serious adverse events associated with bevacizumab include gastrointestinal perforation, wound healing complications, haemorrhage, arterial thromboembolic events, congestive heart failure and neutropenia. The most common adverse events in patients receiving bevacizumab are anorexia,

dysgeusia, headache, hypertension, stomatitis, constipation and exfoliative dermatitis.

Cetuximab

Cetuximab (Erbitux, Merck Serono) 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 has a UK marketing authorisation:

- for the treatment of patients with EGFR-expressing, KRAS wild-type metastatic colorectal cancer
  - in combination with irinotecan-based chemotherapy or FOLFOX4 (oxaliplatin, 5-FU and folinic acid)
  - as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan

The SPC recommends that treatment is continued until disease progression.

Hypomagnesaemia and skin reactions are very common side effects of cetuximab therapy. Other common adverse events include headache, dehydration, diarrhoea, nausea, vomiting and anaemia. Serious adverse events associated with cetuximab are congestive heart failure, pulmonary embolism, sepsis, hypertension, and deep vein thrombosis.

Panitumumab

Panitumumab (Vectibix, Amgen) is a recombinant monoclonal antibody that blocks EGFR, inhibiting the growth of tumours expressing EGFR. It has a UK marketing authorisation:

- as monotherapy for the treatment of EGFR-expressing metastatic colorectal cancer with non-mutated (wild-type) *KRAS* after failure of fluoropyrimidine-, oxaliplatin- and irinotecan-containing chemotherapy regimens.

The SPC does not specify an optimal treatment duration.

The most common adverse events were skin rash, hypomagnesaemia, paronychia, fatigue, abdominal pain, nausea, constipation and diarrhoea. The most serious toxicities identified in clinical studies of panitumumab were pulmonary fibrosis, severe dermatological toxicity complicated by infectious sequelae and septic death, infusion reactions, abdominal pain, hypomagnesaemia, nausea, vomiting, and constipation.

1.3.1.2 The evidence

1.4 Clinical effectiveness

1.4.1 Bevacizumab

The manufacturer of bevacizumab identified one randomised controlled trial (RCT) (Giantonio 2007), which investigated the effectiveness of bevacizumab in combination with an oxaliplatin-containing chemotherapy regimen as a second-line treatment for metastatic colorectal cancer (this is outside the scope of this appraisal). The RCT was a multinational study conducted in 221 centres in the USA and South Africa. The study included people (n = 829) with metastatic colorectal cancer who had previously been treated with fluoropyrimidine with or without irinotecan. Between November 2001 and April 2003, people were randomised to one of three groups receiving either FOLFOX4 with bevacizumab, FOLFOX4 without bevacizumab or bevacizumab as a single agent. The primary end point of the study was overall survival. The intent-to-treat analysis of the primary end point of overall survival included 286 patients in the FOLFOX4-plus-bevacizumab arm, 291 patients in the FOLFOX4-alone arm, and 243 patients in the bevacizumab-alone arm. Treatment assignment was balanced by sex, age, Eastern Cooperative Oncology Group (ECOG) performance status, and prior radiation therapy exposure. In February 2003, the bevacizumab-alone arm of the study

was closed after an interim analysis that suggested inferior survival when compared with the chemotherapy-containing arms of the study.

Table 4 Results from the RCT in the manufacturer's submission evaluating bevacizumab in combination with FOLFOX as a second-line therapy

	FOLFOX4 + bevacizumab (n = 286)	Bevacizumab alone (n = 243)	FOLFOX4 (n = 291)
Medium overall survival (months)	12.9	10.2	10.8
Median progression-free survival (months)	7.3	2.7	4.7
Response rate (%)	22.7	8.6	3.3

The incremental overall survival for FOLFOX4 plus bevacizumab compared with FOLFOX4 was 2.1 months with a resulting hazard ratio (HR) of 0.75. The incremental progression-free survival for FOLFOX4 plus bevacizumab compared with FOLFOX4 was 2.6 months (p = 0.011).

The Assessment Group did not identify any studies that met their criteria to be included in their review, that is, bevacizumab in combination with non-oxaliplatin-based chemotherapy. For bevacizumab, studies were eligible for inclusion in the review if the population with metastatic colorectal cancer had progressed after first-line chemotherapy. No stipulation for EGFR expression or KRAS status was required, because this has been shown to have no influence on bevacizumab activity. It pointed out that a phase II clinical trial (SPIRITT) is currently underway comparing bevacizumab with FOLFIRI against panitumumab with FOLFIRI after first-line treatment (expected study completion is August 2012).

The manufacturer (Roche Products) identified three RCTs that investigated the effectiveness of bevacizumab as a first-line treatment for metastatic

colorectal cancer. The manufacturer stated that while no RCTs compare bevacizumab with a fluoropyrimidine with or without irinotecan in the second-line setting, these RCTs provide evidence that bevacizumab would be an effective second-line treatment for metastatic colorectal cancer.

One RCT (Hurwitz 2004) compared bevacizumab plus irinotecan, bolus 5-fluorouracil, and folinic acid (IFL) (n = 402) with placebo plus IFL (n = 411). The primary end point was overall survival.

The second RCT (Kabbinavar 2005) compared bevacizumab plus bolus fluorouracil, and folinic acid (5-FU/FA) (n = 104) with bolus 5-FU/FA (n = 105).

The third RCT (Saltz 2008) compared bevacizumab plus oxaliplatin-based chemotherapy (FOLFOX or XELOX) (n = 699) with oxaliplatin-based chemotherapy (FOLFOX or XELOX) (n = 667). The primary end point was progression-free survival. Results are summarised in Table 3 below.

Table 5 Results from the three RCTs in the manufacturer's submission of bevacizumab as a first-line therapy

Study	n	Intervention /comparator	Overall survival (months)	Hazard ratio	Median progression free survival (months)	Hazard ratio
Hurwitz (2004)	813	BEV + IFL vs PLA + IFL	20.3 vs 15.6	0.66 p < 0.001	10.6 vs 6.2	0.54 p < 0.001
Kabbinavar (2005)	209	BEV + 5-FU/FA vs PLA + 5-FU/FA	16.6 vs 12.9	0.79 p = 0.16	9.2 vs 5.5	0.50 p = 0.002
Saltz (2008)	1401	BEV + XELOX or FOLFOX4 vs PLA + XELOX or FOLFOX4	21.3 vs 19.9	0.89 p = 0.77	9.4 vs 8.0	0.83 p = 0.002

BEV = bevacizumab. IFL = irinotecan + 5-fluorouracil (5-FU) + folinic acid. PLA = placebo. FU/FA = 5-FU + folinic acid. XELOX = capecitabine + oxaliplatin. FOLFOX4 = oxaliplatin+ 5-FU + folinic acid.

1.4.2 Cetuximab

The manufacturer and the assessment group included one randomised controlled trial (the CO.17 study), Au 2009 which compared the efficacy of cetuximab in combination with best supportive care with best supportive care alone. The RCT was a multinational study conducted in Canada and Australia. The study population was patients (n = 572) with metastatic colorectal cancer who had previously been treated with fluoropyrimidine, irinotecan, and oxaliplatin or had contraindications to these treatments. A total of 394 tumour specimens (198 from the cetuximab group and 196 from the best supportive care group) were examined for KRAS-mutation status (accounting for 68.9% of the total study population (Karapetis 2008). The Assessment Group stated that treatment assignment was balanced by sex, age and ECOG performance status, but as is usually the case with cancer trials, the study population was significantly younger (median age 62–64) compared with the general population presenting with colorectal cancer (median age 70–79 for men and 75–85 or older for women). The primary end point of the study was overall survival. The Assessment Group judged that the trial was of good quality, but pointed out that although the median duration of follow-up was reported (14.6 months), no range is given and it is not clear if this is for both arms of the trial.

The median overall survival in the whole trial population was 6.1 months in the cetuximab group and 4.6 months in the best supportive care group with an HR of 0.77 (95% CI 0.64 to 0.92; p = 0.005). The Assessment Group noted that only 7% of patients receiving best supportive care were given cetuximab after cross-over. No significant differences were seen in the benefit of cetuximab on the basis of ECOG performance status at baseline, age or sex in subgroup analysis. However, an unplanned analysis indicated that grade of rash in patients receiving cetuximab was correlated with overall survival, with median survival of 2.6 months in patients with no rash, compared with 4.8 months in patients with Grade 1 rash and 8.4 months in patients with Grade 2 rash (p < 0.001).

For patients with KRAS mutations, a median overall survival of 4.5 months for cetuximab and 4.6 months for best supportive care with an HR of 0.98 (95% CI 0.70 to 1.37; p = 0.89). For patients with the *KRAS* wild-type gene, the median overall survival was 9.5 months in the cetuximab group compared with 4.8 months in the best supportive care group with an HR of 0.55 (95% CI 0.41 to 0.74; p < 0.001). Subsequent to adjustment for potential prognostic factors, the HR increases to 0.62 (95% CI 0.44 to 0.87; p = 0.006).

Non-RCT evidence

The manufacturer also presented a retrospective analysis (De Roock et al, 2008), which combined data from four RCTs (The BOND, EVEREST, SALVAGE and BABEL trials). This analysis compared the efficacy of cetuximab in combination with best supportive care with cetuximab in combination with irinotecan according to KRAS status. The Assessment Group excluded this study from their review because it was judged to have a number of key limitations: it is a retrospective analysis of four studies, KRAS status has been retrospectively determined for a selection of patients, and the SALVAGE and BABEL trials appear to be single arm studies (for further details, see pages 115–16 of the Assessment Group's report).

1.4.3 Panitumumab

The assessment report included one randomised controlled trial (Van Cutsem et al 2007), which compared the efficacy of panitumumab in combination with best supportive care with best supportive care alone. The RCT was a multinational study conducted in Western Europe, Central Europe, Eastern Europe, Canada, Australia and New Zealand. The study population was patients (n = 463) with metastatic colorectal cancer which had progressed after standard chemotherapy (fluoropyrimidine, irinotecan, and oxaliplatin). The Assessment Group stated that treatment assignment was balanced by sex, age and ECOG performance status, but that there was a slight imbalance by disease status (46% of participants had ECOG performance status 0 and

41% ECOG performance status 1 in the treatment arm compared with 34% ECOG performance status 0 and 50% ECOG performance status 1 in the best supportive care arm). The Assessment Group also stated that reporting of disease status was confined to ECOG performance status and no details of primary or metastatic sites were provided. The Assessment Group also judged that, as is usually the case with cancer trials, the study population was significantly younger (median age 62–64) compared with the general population presenting with colorectal cancer (median age 70–79 for men and 75–85 or older for women). The primary end point of the study was overall survival. The Assessment Group judged the study to be generally of good quality, but noted that it was unclear whether assignment to each treatment group was random, and there was a lack of clinician and investigator blinding because of expected skin toxicity; however, to mitigate this, tumour assessments were performed by blinded central review.

A total of 427 (92%) of the trial population, were put forward for KRAS testing. In the KRAS wild-type population, median progression-free survival was 12.3 weeks in the panitumumab arm compared with 7.3 weeks in the best supportive care arm (Amado et al 2008). The manufacturer explained that, to compensate for tumour-assertion bias in the best supportive care arm of the trial, an interval-censored sensitivity analysis was performed whereby radiological event times were moved to the closest assessment time pre-specified in the protocol; the resulting median progression-free survival times were 16 weeks and 8 weeks for panitumumab and best supportive care respectively (HR = 0.44; 95% CI 0.30 to 0.63).

The median overall survival (unadjusted for crossover) in the KRAS wild-type population was 8.1 months with panitumumab compared with 7.6 months with best supportive care. A statistically significant difference in median overall survival between panitumumab and best supportive care in this population was not demonstrated (HR = 0.99; 95% C.I 0.75 to 1.29).

The manufacturer explained that 76% of patients assigned to receive best supportive care only crossed over to the panitumumab arm of the study. Therefore, the manufacturer adjusted the overall survival results for the crossover that occurred by use of the following method (see page 5 of the manufacturer's submission for an explanation of the rationale behind this method):

- Patients receiving best supportive care with mutant KRAS, regardless of whether they crossed over to receive panitumumab treatment after disease progression, were included in the analysis. The manufacturer's rationale for use of this method was that the trial showed that patients with mutant KRAS did not benefit from treatment with panitumumab, and patients with mutant KRAS in the best supportive care arm who crossed over to receive panitumumab after disease progression also did not benefit from it. The manufacturer's explained that inclusion of all patients receiving best supportive care with mutant KRAS (regardless of crossover) in the survival analysis would provide a larger sample of patients and would reduce the risk of bias because patients who crossed over generally seemed to have a better prognosis than those who did not.
- Patients with wild-type KRAS in the best supportive care arm who crossed over to receive panitumumab were excluded from the estimation of overall survival in the best supportive care arm in the analysis.
- Overall survival was estimated using two mutually exclusive time periods separated by the primary endpoint of the study, disease progression: a) mean time to disease progression, and b) mean time from progression to death.
- Best supportive care survival estimates were based on patients randomised to best supportive care with mutant KRAS or wild type KRAS for the time until disease progression (before any treatment crossover occurred), and based on patients randomised to best supportive care with mutant KRAS for time from disease progression until death.

- Mean times to disease progression and from progression to death were estimated by fitting survival models to patient-level data from the clinical trial and then estimating the area under the best-fit curves.
- Mean survival was estimated for each distribution.

The manufacturer's analysis showed that the average survival gain adjusted for crossover was between 2.74 months (overall survival estimated by splitting response rates) and 3.13 months (overall survival estimated by aggregating survival across response rates) for panitumumab compared with best supportive care.

Assessment Group comments

The Assessment Group commented on the approach used by the manufacturer of panitumumab to adjust for cross-over was reasonable and explained that the method employed relies on two assumptions. First, panitumumab plus best supportive care is not effective for patients with KRAS mutant status. Second, similarities in progression-free survival between patients with KRAS mutations and wild-type KRAS randomised to best supportive care can predict similarities in overall survival between these two groups of patients. The Assessment Group judged that the evidence in the Amado (2008) study (presented in the manufacturer's submission) supported these assumptions, and therefore they considered them reasonable. For further details, see pages 128–132 of the Assessment Group's report.

1.5 Mixed treatment comparison of all three interventions

Neither the Assessment Group nor the manufacturers identified any RCTs that directly compared the interventions included in this appraisal with each other.

The manufacturers of panitumumab and bevacizumab did not submit a mixed treatment comparison. They explained that it was not possible to conduct a robust indirect comparison of the three intervention technologies under

assessment. Both the Assessment Group and the manufacturer of cetuximab carried out a mixed treatment comparison using the Bucher approach, to estimate the relative effectiveness of the interventions relevant to the decision problem.

Merck Serono's mixed treatment comparison

Data from the De Roock analysis and CO.17 (Karapetis 2008) study for cetuximab and the Amado (2008) study for panitumumab were used to assess comparative clinical effectiveness of cetuximab in combination with chemotherapy against panitumumab or best supportive care and cetuximab monotherapy against panitumumab in the KRAS wild-type population. The manufacturer explained that it had not identified any evidence for bevacizumab which could be used in the mixed treatment comparison.

The resulting HR for overall survival for cetuximab plus irinotecan versus best supportive care was 0.29 (95% CI 0.14 to 0.59). However, Merck Serono stated that on the advice of a clinical expert, the parametric model fitted to the Kaplan–Meier curve for overall survival Weibull function) was deemed to insufficiently match the original data. The manufacturer therefore obtained data on additional patients in the De Roock study (n = 364 compared with n = 80 in the original analysis). The resulting overall survival HR for cetuximab plus irinotecan was 0.32 compared with best supportive care. The manufacturer used the 95% confidence intervals from the original analysis derived from 80 patients, that is 95% CI = 0.14 to 0.59.

The resulting HR for overall survival for cetuximab monotherapy was 0.56 (95% CI = 0.37 to 0.83) compared with panitumumab monotherapy.

Assessment Group comments

The Assessment Group expressed a number of concerns about the validity of the manufacturer's mixed treatment comparison analysis. For further details, see pages 117 to 119 of the assessment group report. These were:

- Data from an RCT and a non-RCT were combined and these different study designs are subject to different sources of bias and confounding.
- There was no explicit assessment of the similarities between patient populations in the studies.
- It was unclear why model fit was determined by clinical experts rather than by statistical methods and there is no explanation as to how this adjustment was made.
- Use of the 95% CI for the adjusted hazard ratio from the initial indirect comparison will lead to more favourable overall survival estimates for cetuximab, even though the mean value is slightly different.
- Unadjusted hazard ratios from the CO.17 study were used when adjusted (for patient characteristics) HRs would have been more appropriate.
- There appeared to be no accounting for the cross-over in the BOND data used in De Roock and colleagues 2008.
- The Amado study had a large amount of cross-over and therefore bias, but there is no published analysis available that addresses this issue.

Assessments Group's mixed treatment comparison

The Assessment Group carried out a mixed treatment comparison analysis using the data from CO.17 (Karapetis 2008) study and De Roock (2008) study for cetuximab and the Amado (2008) study for panitumumab. The Assessment Group explained that although the manufacturer of panitumumab addressed the issue of cross-over in the Amado study in their submission, these adjusted results could not be used in the analyses because no HRs were presented.

The Assessment Group also specified that its analysis comparing cetuximab and panitumumab was based on the assumption that people receiving best supportive care in the CO.17 (Karapetis) and Amado study had equivalent care and treatment.

The Assessment Group analysis differed from the Merck Serono's analysis in that hazard ratios were adjusted for patient characteristics (For further details of the rationale for this decision, see pages 70 and 71 of the assessment report). Also, hazard ratios obtained from the indirect comparison were not adjusted using data from the De Roock study.

Table 6 The results of the Assessment Group's mixed treatment comparison analyses – direct and indirect HRs (and 95% CIs) for overall survival and progression-free survival

Outcome	HR from Karapetis et al	CET+BSC vs BSC	PAN+BSC vs BSC	CET+BSC vs PAN+BSC (calculated by Assessment Group)
Progression-free survival	Unadjusted	0.40 (0.30 to 0.54)	0.45 (0.34 to 0.59)	0.89 (0.59 to 1.33)
	Adjusted	0.42 (0.30 to 0.58)		0.93 (0.61 to 1.43)
Overall survival	Unadjusted	0.55 (0.41 to 0.74)	0.99 (0.75 to 1.29)	0.56 (0.37 to 0.83)
	Adjusted	0.62 (0.44 to 0.87)		0.63 (0.41 to 0.97)
BSC = best supportive care. CET = cetuximab. HR = hazard ratio. PAN = panitumumab. PFS = progression-free survival.				

Table 6 above shows that there is no statistically significant difference in progression-free survival between those receiving cetuximab plus best supportive care and those receiving panitumumab plus best supportive care, regardless of whether the adjusted or unadjusted HRs are used. There was a statistically significant difference in overall survival between cetuximab plus best supportive care and panitumumab plus best supportive care, with patients receiving cetuximab plus best supportive care having longer overall survival. The assessment group pointed out that the Amado study had a large number of patients randomised to receive best supportive care actually

receiving panitumumab plus best supportive care during the progressed disease stage, potentially biasing the results against cetuximab. Thus, the HR for overall survival from this study is subject to confounding.

1.6 Cost effectiveness

Amgen and Roche Products did not submit economic models.

Roche Products submitted cost calculations for bevacizumab plus FOLFIRI compared with cetuximab plus FOLFIRI. Roche estimated the total incremental cost of cetuximab plus FOLFIRI compared with bevacizumab plus FOLFIRI to be £5408 (with KRAS testing costs of £462, drugs costs of £3357 and administration costs of £1589) (see pages 127–28 of the Assessment Group's report).

1.7 The Merck Serono model

Merck Serono model structure

A Markov model was used to compare cetuximab plus best supportive care with best supportive care; cetuximab plus irinotecan with best supportive care; cetuximab plus best supportive care with panitumumab plus best supportive care and cetuximab plus irinotecan with panitumumab plus best supportive care. The population was people with EGFR-expressing KRAS wild-type metastatic colorectal cancer who had received at least two lines of chemotherapy in the metastatic disease stage. The model had a 10-year time horizon and a UK NHS perspective. The model had three health states: progression-free disease, progressive disease and death. Transitions between health states were based on parametric approximations of Kaplan–Meier estimates of progression-free survival and overall survival (with time in progressive disease defined as the difference between the two).

For the comparison of cetuximab monotherapy with best supportive care, for which patient-level data were available, the manufacturer estimated separate

probabilities of death for people in progression-free and post-progression disease, as well as for time to progression. Different functions were selected for each transition (log-normal for time to progression; log-logistic for pre-progression death; Weibull for post-progression death), on the basis of goodness-of-fit measures.

For the comparison of cetuximab plus irinotecan with best supportive care, progression-free survival and overall survival were modelled using a two-stage process. First, progression-free survival and overall survival in the best supportive care arm were simulated using a Weibull curve fitted to data extracted from the key RCT comparing cetuximab with best supportive care. The corresponding cetuximab plus irinotecan functions were then estimated by applying HRs drawn from the mixed treatment comparison of cetuximab plus irinotecan with best supportive care.

Table 7 Summary of the efficacy estimates used in Merck Serono's economic model

Treatment comparisons	Overall survival HR (95% CI)	Overall survival HR (95% CI) estimated	Progression-free survival HR (95% CI)	Progression-free survival HR (95% CI) estimated
CET vs BSC	0.55 (0.41 to 0.74)	N/A	0.40 (0.30 to 0.54)	N/A
CET + IRI vs CET	0.53 (0.28 to 1.01)	N/A	0.47 (0.23 to 0.94)	N/A
CET + IRI vs BSC	N/A	0.32 (0.14 to 0.59)	N/A	0.24 (0.12 to 0.52)
PAN vs BSC	0.99 (0.75 to 1.29)	N/A	0.45 (0.34 to 0.59)	N/A
CET vs PAN	N/A	0.56 (0.37 to 0.83)	N/A	0.89 (0.59 to 1.33)
CET + IRI vs PAN	N/A	0.32 (0.15 to 0.71)	N/A	0.53 (0.24 to 1.17)

HR = hazard ratio. CET = cetuximab. BSC = best supportive care. IRI = irinotecan. PAN = panitumumab. N/A = not applicable.

Assumptions in the model were:

- Cycle length would be 1 week, and therefore a half-cycle correction was not necessary.
- The mean time on treatment with cetuximab plus BSC would be 2.6 months and 4.4 months for cetuximab plus ironotecan
- People with progressive disease would not receive any active treatment and active treatment would cease at set cut-off time points (13 weeks for cetuximab plus best supportive care and 24 weeks for cetuximab plus irinotecan) even if disease had not progressed.
- People who dropped out of active treatment would be allocated to the progressive disease state.

Utility estimates were obtained by use of the HUI scale (a generic preference-based measure) in the CO.17 study of cetuximab monotherapy. These utility values were then also applied to cetuximab plus irinotecan and panitumumab plus best supportive care.

Table 8 Utility values used in the model

	Cetuximab	**Best supportive care**
Before progression (used in progression-free state)		
Mean utility	0.809	0.746
After progression (used in progressive disease state)		
Mean utility	0.789	0.693

Merck Serono results

Merck Serono presented the results as individual pairwise comparisons rather than in an incremental analysis (table 9).

Table 9 Merck Serono base-case results: individual pairwise comparisons

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Cetuximab plus best supportive care compared with best supportive care					
Best supportive care	£7580	0.359	N/A	N/A	N/A
Cetuximab plus best supportive care	£21,836	0.662	£14,256	0.303	£47,095
Cetuximab plus irinotecan versus best supportive care					
Best supportive care	£7947	0.391	N/A	N/A	N/A
Cetuximab plus irinotecan plus best supportive care	£37,248	1.059	£29,301	0.68	£43,887
Cetuximab plus best supportive care versus panitumumab plus best supportive care					
Panitumumab plus best supportive care	£24,465	0.469	N/A	N/A	N/A
Cetuximab plus best supportive care	£21,836	0.662	£574	0.193	Dominant
Cetuximab plus irinotecan versus panitumumab plus best supportive care					
Panitumumab plus best supportive care	£23,810	0.443	N/A	N/A	N/A
Cetuximab plus irinotecan	£37,248	1.059	£13,438	0.616	£21,819
ICER = incremental cost-effectiveness ratio. QALY = quality-adjusted life year. N/A = not applicable.					

Merck Serono completed univariate one-way sensitivity analyses on all the model parameters and the only factor found to significantly change the incremental cost effectiveness ratios (ICERs) was varying the cost of cetuximab (for further details, see appendix 12 of the manufacturer's submission).

The manufacturer also carried out a series of scenario analyses, to assess which factors resulted in changes to the cost-effectiveness estimate, compared to the manufacturer's base-case ICERs (for further details see pages 138–41 of the manufacturers submission).

Merck Serono's probabilistic sensitivity analyses indicated that, compared with best supportive care and at a threshold of £50,000 per quality-adjusted life

year (QALY) gained, cetuximab plus best supportive care had a 64.7% chance of being cost effective, and cetuximab plus irinotecan had a 68% chance of being cost effective. Compared with panitumumab plus best supportive care, cetuximab plus best supportive care had a 100% chance of being cost effective at a threshold of £15,000 per QALY gained, and cetuximab plus irinotecan best supportive care had a 93% chance of being cost effective threshold of £50,000 per QALY gained.

The Assessment Group identified the following limitations of the Merck Serono model:

- Merck Serono did not include the full range of possible comparators. No attempt was made to compare cetuximab plus irinotecan with cetuximab plus best supportive care despite the data being available.
- Merck Serono only assessed the cost effectiveness of cetuximab as a third-line treatment and do not consider it in a second-line scenario, but the scope for this appraisal allows it to be considered as a second-line treatment.
- The sensitivity analyses did not include an assessment of the impact of changing the clinical effectiveness estimates in the model.
- There were shortcomings in the internal validity of the model that may have led to inaccurate estimates of costs (for further details see page 103 of the Assessment Group's report).
- Estimates of drug administration costs may be too low, because only drug administration costs at first delivery were considered but subsequent delivery of chemotherapy cycles may be more relevant.
- The estimates of time on treatment for cetuximab and irinotecan may be too low.
- The utilities from the CO.17 study reported in the submission do not always tally with those reported in the published study.

1.8 The Assessment Group model

Assessment Group model structure

The Assessment Group did not include bevacizumab in the economic analysis because no clinical effectiveness evidence was available for bevacizumab in combination with chemotherapy not containing oxaliplatin, in people who had received previous chemotherapy.

A Markov model was used to compare cetuximab monotherapy with best supportive care, cetuximab plus irinotecan with best supportive care and panitumumab plus best supportive care with best supportive care in people with EGFR-expressing KRAS wild-type metastatic colorectal cancer who had received at least two lines of chemotherapy in the metastatic disease stage. The model had a 10-year time horizon and a UK NHS perspective. The cycle length was one month and a half-cycle correction was applied.

The model had three health states: progression-free disease, progressive disease and death. An 'area under the curve' / 'cohort partition' method was used to determine state populations at each cycle of the model, rather than using transition probabilities. (For further details, see page 135 of the Assessment Group's report). Utility estimates were obtained from the Mittman (2008) study, which reported the HUI data from the CO.17 study.

Key similarities and differences between the Merck Serono and Assessment Group model

The similarities were:

- clinical effectiveness for cetuximab plus best supportive care and best supportive care
- health states progression free and progressive disease
- cost per mg of cetuximab
- dose intensity of 98% for cetuximab

- costs of treating adverse events
- similar utilities are used, except a lower utility was assumed for cetuximab plus best supportive care in progressed disease state in the assessment group model.

The differences were:

- estimates of drug costs due to differences in estimates of treatment duration, £14,400 Assessment Group, Merck Serono £8200
- estimate of drug administration costs due to differences in estimates of treatment duration, Assessment Group £5500, Merck Serono £2042
- estimate of mean time on cetuximab 4.8 months Assessment Group, Merck Serono 2.6 months
- Assessment Group model does not assume a cap on treatment time.

Assessment Group results

Table 10 Assessment Group's base case results for each intervention compared with best supportive care

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Best supportive care	£6256	0.36	N/A		N/A
Cetuximab plus best supportive care	£30,800	0.61	£24,500	0.25	£98,000
Cetuximab plus irinotecan	£59,348	0.97	£53,100	0.60	£88,000
Panitumumab plus best supportive care (does not include HR adjusted for cross-over)	£35,213	0.56	£29,000	0.19	£150,000
ICER = incremental cost-effectiveness ratio. QALY = quality-adjusted life year. N/A = not applicable.					

Table 2. PenTAG base case incremental results vs BSC for patients with KRAS WT status
Table 3. PenTAG base case results – patients with KRAS WT status

Assessment Group comments

The Assessment Group stated that the difference between the manufacturer's and Assessment Group estimate of cost-effectiveness is caused by the large difference in the estimates of total mean costs of acquisition and administration of cetuximab. The Assessment Group also noted that these differences were mostly due to the fact that they estimated a far higher mean time on cetuximab treatment than Merck Serono. For further details, see section 7.1.3.1.4, page 148, of the Assessment Group's report.

Assessment Group addendum

The Assessment Group explained that Merck Serono did not provide details of the mean treatment duration for cetuximab from the RCT of cetuximab vs. BSC (Karapetis 2008) and this information was not available from the literature. The Assessment Group therefore contacted the author of the Mittman (2008) study who stated that the median treatment duration with cetuximab for people with KRAS wild type disease in the CO.17 trial was [redacted]

The Assessment Group explained that this figure was the difference between the last and first dates of cetuximab infusions in the Mittman study. Given that cetuximab was given once per week, the Assessment Group estimated that of those patients with wild type KRAS who received at least one dose of cetuximab, the mean number of doses given was [redacted]

The Assessment Group estimated the mean undiscounted cetuximab administration cost as [redacted] The Assessment Group explained that [redacted]

When these revisions were made, the overall effect was to lower the base-case ICER for cetuximab plus best supportive care from £98,000 to £90,000 per QALY gained. For further details, see table 1 and 2, pages 4 and 5, of the Assessment Group's addendum document.

2 End of life criteria

1. The treatment is indicated for patients with a short life expectancy, normally less than 24 months.
   Overall survival in CO.17 study in best supportive care arm of KRAS wild type population: median 4.6 months

   Overall survival in Amado et al 2008 study in best supportive care arm of KRAS wild type population: median 7.6 months

2. There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment.
   Cetuximab: Overall survival gain in CO.17 study with cetuximab (compared with BSC) in KRAS wildtype population: mean 3.9 months, median 4.7 months

   Panitumumab: Overall survival gain in Amado et al 2008 study (unadjusted for crossover) in the KRAS wild-type population 0.5 months; average survival gain (adjusted for cross over): 2.74 - 3.13 months

   Bevacizumab: no trial information

3. The treatment is licensed or otherwise indicated for small patient populations.
   MerckSerono states that there are approximately 17,675 patients in England and Wales with metastatic colorectal cancer, 54% have KRAS wildtype and 80% express EGFR. The licence for cetuximab covers

treatment at all stages. Cetuxumab is also licensed for locally advanced and for recurrent and/or metastatic head and neck cancer. In TA172 this indication was considered to cover approximately 3000 patients.

Panitumumab monotherapy is licensed for 2nd and subsequent line treatment of KRAS wildtype metatstatic colorectal cancer. Panitumumab has also received a positive CHMP opinion for the treatment of wild-type KRAS metastatic colorectal cancer for 1st line treatment in combination with FOLFOX, and in 2nd line treatment in combination with FOLFIRI for patients who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan). This implies that the cumulative population would be similar to cetuximab CRC population.

Bevacizumab: has previously been discussed in this context as being licensed for large populations.

4. The estimates of the extension to life are robust – for Committee discussion

3 Equalities issues

Consultees raised the issue that inequality currently exists in access to treatment with cetuximab in the NHS. Some Trusts allow access to cetuximab in the third-line setting (for example, through the Cancer Drugs Fund) and others through the exceptional case process. No information relating to equality issues was included in the submissions from the two of the manufacturers and the Assessment Group's report. One of the manufacturers highlighted that are differences in survival among people with metastatic colorectal cancer in different socio-economic groups; however, no evidence was provided to suggest different access to treatment among these subgroups.

3.1.1.1 Issues for consideration

Clinical effectiveness

- How long do patients receive treatments in clinical practice – until progression of disease, or for a fixed period as assumed in modelling?
- Do clinicians use the therapies under consideration both 2nd line and 3rd line or only 2nd or only 3rd line?
- What is the 'correct' dose of bevacizumab + FOLFIRI – 10 mg/kg or 5 mg/kg?
- Does the NHS provide adequate infrastructure for KRAS testing, and, if required, EGFR testing?
- Is it realistic that vial sharing is assumed for irinitecan in NHS but not for cetuximab?

Cost effectiveness

- Do the modelled values have 'face validity'?
- Merck Serono reanalysed utility data from Mittman and achieved higher values. Was the means by which this was done reasonable?
- Does the Committee feel that a patient's utility is likely to differ by KRAS status?
- Is it reasonable to assume, as the model does, that utility is higher in the progression-free disease state in patients who had receive cetuximab + BSC compared with patient who had received BSC only?

3.1.1.2 Ongoing research

Hecht JR, Cohn AL. SPIRITT: A study of second-line treatment of metastatic colorectal cancer with FOLFIRI plus panitumumab or bevacizumab. Community Oncology. 2008; 5: 1–4. Study completion expected August 2012

3.1.1.3 Authors

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Technical Leads

July 2011

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

A The assessment report for this appraisal was prepared by the Peninsula Technology Assessment Group (PenTAG), University of Exeter:

- Hoyle M, Crathorne L, Peters J et al, The effectiveness and cost-effectiveness of cetuximab (mono- or combination chemotherapy), bevacizumab (combination with (non-oxaliplatin chemotherapy) and panitumumab (monotherapy) for the treatment of metastatic colorectal cancer after first-line chemotherapy (review of technology appraisal 150 and part review of technology appraisal 118): a systematic review and economic model, June 2011

B Submissions or statements were received from the following organisations:

I Manufacturers/sponsors

- Amgen
- Merck-Serono
- Roche

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

- Beating Bowel Cancer
- Bowel Cancer UK