NICE National Institute for Health and Care Excellence

NICE guidance

Cetuximab, bevacizumab and panitumumab for the treatment of metastatic colorectal cancer after first-line chemotherapy: Cetuximab (monotherapy or combination chemotherapy), bevacizumab (in combination with non-oxaliplatin chemotherapy) and panitumumab (monotherapy) for the treatment of metastatic

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Contents

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This guidance replaces TA150.

This guidance partially replaces TA118.

1 Guidance

This guidance updates and replaces NICE technology appraisal 150 (published in June 2008). It also updates and replaces recommendations in NICE technology appraisal guidance 118 (published in January 2007) on the use of cetuximab for the treatment of colorectal cancer that has progressed after first-line chemotherapy. For details see About this guidance.

1.1 Cetuximab monotherapy or combination chemotherapy is not recommended for the treatment of people with metastatic colorectal cancer that has progressed after first-line chemotherapy.

1.2 Bevacizumab in combination with non-oxaliplatin (fluoropyrimidine-based) chemotherapy is not recommended for the treatment of people with metastatic colorectal cancer that has progressed after first-line chemotherapy.

1.3 Panitumumab monotherapy is not recommended for the treatment of people with metastatic colorectal cancer that has progressed after first-line chemotherapy.

1.4 People currently receiving cetuximab monotherapy or combination chemotherapy, bevacizumab in combination with non-oxaliplatin chemotherapy, or panitumumab monotherapy for the treatment of metastatic colorectal cancer that has progressed after first-line chemotherapy should have the option to continue treatment until they and their clinician consider it appropriate to stop.

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2 Clinical need and practice

2.1 Colorectal cancer originates in the lower part of the digestive system, including the colon and rectum. In metastatic colorectal cancer, the tumour spreads beyond the local or regional lymph nodes to other parts of the body. Approximately 32,000 people were diagnosed with colorectal cancer in England and Wales in 2008. 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 over 75 years. The median age of people at diagnosis is over 70 years.

2.2 The overall 5-year survival rate for colorectal cancer in England and Wales is approximately 50%; however, large differences in duration of survival exist according to the stage of disease at diagnosis. In 2007, over 93% of people in the UK diagnosed with Stage A on the modified Dukes' classification system (the earliest stage of the disease) survived for 5 years compared with less than 7% of people with metastatic disease.

2.3 At the time of diagnosis, an estimated 20–55% of people with colorectal cancer already have metastatic disease. In addition, of the people who have undergone surgery for early-stage colorectal cancer, approximately 50–60% will eventually develop metastatic disease, most commonly in the liver.

2.4 Advanced, or metastatic, colorectal cancer is cancer that has spread beyond the colon to other areas of the body. The management of metastatic colorectal cancer is mainly palliative, that is, to relieve symptoms, and combines specialist treatments (such as palliative surgery, chemotherapy and radiation) with control of symptoms and psychosocial support. However, approximately 8% of people with metastatic colorectal cancer have potentially resectable liver metastases and, in some, chemotherapy may make these liver metastases operable.

2.5 The aim of treatment is to improve both the length and quality of the patient's remaining life. People with metastatic disease in sufficiently good health (World Health Organization performance status 2 or better)

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are usually treated with first-line chemotherapy and then, if their cancer progresses, second-line chemotherapy. For other people, the harms from chemotherapy may outweigh the potential benefits. Therefore treatment depends on the person's individual circumstances.

2.6 Characteristics of the tumour that influence outcomes of treatment in people with metastatic colorectal cancer include the presence of: epidermal growth factor receptor (EGFR) and the 'wild-type' (non-mutated) form of the v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (*KRAS*) gene. Drugs that target EGFR are more effective against tumours expressing EGFR and a normal (wild-type) *KRAS* gene compared with those not expressing EGFR and with a mutated *KRAS* gene. Around 80% of people with metastatic colorectal cancer have EGFR-expressing disease and 30–50% have the *KRAS* wild-type gene.

2.7 As first-line treatment options for advanced colorectal cancer, NICE has recommended oxaliplatin in combination with 5-fluorouracil plus folinic acid (FOLFOX) and irinotecan in combination with 5-fluorouracil plus folinic acid (FOLFIRI) ('Irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer' (review of technology appraisal 33) [NICE technology appraisal guidance 93; TA93]). Other first-line treatment options recommended for metastatic colorectal cancer are the oral analogues of 5-fluorouracil; capecitabine or tegafur with uracil (in combination with folinic acid) ('Guidance on the use of capecitabine and tegafur with uracil for metastatic colorectal cancer' [NICE technology appraisal guidance 61; TA61]). If metastatic disease is confined to the liver, and the patient has *KRAS* wild-type disease, the aim of first-line treatment is to make the metastases resectable surgically, and cetuximab may be given with FOLFOX or FOLFIRI ('Cetuximab for the first-line treatment of metastatic colorectal cancer' [NICE technology appraisal guidance 176; TA176]).

2.8 For second-line therapy in people whose disease has progressed despite first-line treatment, TA93 recommends monotherapy with irinotecan as an option for people who received FOLFOX as first-line treatment, and FOLFOX as an option for people who received FOLFIRI as first-line treatment.

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3 The technologies

3.1 Bevacizumab (Avastin, Roche Products) is a recombinant monoclonal antibody that inhibits angiogenesis by targeting the biological activity of human vascular endothelial growth factor, which stimulates formation of new blood vessels in the tumour. The UK marketing authorisation states that bevacizumab 'in combination with fluoropyrimidine-based chemotherapy is indicated for the treatment of patients with metastatic carcinoma of the colon or rectum'. Fluoropyrimidines are anti-metabolite drugs which include 5-fluorouracil (5-FU), folinic acid, capecitabine and tegafur.

3.2 Bevacizumab is contraindicated in people who have hypersensitivity to the active substance or to any of the excipients. The summary of product characteristics (SPC) lists the following as special warnings and precautions for use: gastrointestinal perforations, gastrointestinal fistulae, wound healing complications, hypertension, reversible posterior leukoencephalopathy syndrome, proteinuria, thromboembolism (arterial and venous), haemorrhage (including pulmonary haemorrhage and haemoptysis), congestive heart failure, neutropenia, hypersensitivity reactions (including infusion reactions), osteonecrosis of the jaw and eye disorders. For full details of side effects and contraindications, see the SPC.

3.3 Bevacizumab is administered by intravenous infusion. The recommended dosage is 5 or 10 mg/kg of body weight once every 2 weeks or 7.5 or 15 mg/kg of body weight once every 3 weeks. The price of a 100-mg vial is £242.66, and a 400-mg vial is £924.40 (excluding VAT; 'British national formulary' [BNF] edition 61). Costs may vary in different settings because of negotiated procurement discounts.

3.4 Cetuximab (Erbitux, Merck Serono) is a recombinant monoclonal antibody that blocks the human EGFR and inhibits the proliferation of cells that depend on activation of EGFR 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 FOLFOX (5-FU and folinic acid

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and oxaliplatin) or as a single agent in patients whose disease has failed to respond to oxaliplatin and irinotecan-based therapy, and who are intolerant to irinotecan.

3.5 Cetuximab is contraindicated in people with known severe (grade 3 or 4) hypersensitivity reactions to cetuximab. The SPC lists the following as special warnings and precautions for use: infusion-related reactions, respiratory disorders, skin reactions, electrolyte disturbances, neutropenia and cardiovascular disorders. For full details of side effects and contraindications, see the SPC.

3.6 Cetuximab is administered by intravenous infusion. The recommended dosage is an initial dose of 400 mg/m^2 of body surface area followed by 250 mg/m^2 once a week. The list price of a 20-ml vial (100-mg) is £178.10, and a 100-ml vial (500-mg) is £890.50 (excluding VAT; BNF edition 61). The manufacturer of cetuximab has agreed with the Department of Health that the price to the NHS will be £136.50 for a 20-ml vial and £682.50 for a 100-ml vial. Because the reduced prices are in the public domain and are available across the NHS, all calculations in the economic model are based on these reduced prices. Costs may vary in different settings because of negotiated procurement discounts.

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

3.8 Panitumumab is contraindicated in people with severe hypersensitivity to the active substance or to any of the excipients and in people with interstitial pneumonitis or pulmonary fibrosis. The SPC lists the following as special warnings and precautions for use: 'dermatologic reactions, pulmonary complications, electrolyte disturbances, infusion-related reactions, acute renal failure and keratitis'. For full details of side effects and contraindications, see the SPC.

3.9 Panitumumab is administered by intravenous infusion. The recommended

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dosage is 6 mg/kg of body weight once every 14 days. The price of a 100-mg vial is £379.29, and a 400-mg vial is £1517.16 (excluding VAT; BNF edition 61). Costs may vary in different settings because of negotiated procurement discounts.

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4 Evidence and interpretation

The Appraisal Committee (appendix A) considered evidence from a number of sources (appendix B).

4.1 The scope specified that this appraisal would evaluate the clinical and cost effectiveness of: cetuximab (monotherapy or in combination with chemotherapy); bevacizumab (in combination with non-oxaliplatin chemotherapy) and panitumumab monotherapy. The populations covered included people with EGFR-expressing and *KRAS* wild-type metastatic colorectal cancer that has progressed after first-line chemotherapy (cetuximab or panitumumab) and people with metastatic colorectal cancer that has progressed after first-line chemotherapy (bevacizumab). The comparators were chemotherapy with oxaliplatin or irinotecan. The interventions were compared with each other and with best supportive care. The relevant outcomes were overall survival, progression-free survival, response rate, adverse reactions to treatment, and health-related quality of life.

4.2 Clinical effectiveness

4.2.1 The Assessment Group completed a systematic review of the efficacy of the technologies as second- and third-line treatments for metastatic colorectal cancer that has progressed after first-line chemotherapy. For cetuximab and panitumumab, the population of interest was limited to people with *KRAS* wild-type disease. For the three therapies under consideration, only two randomised clinical trials (RCTs) met the inclusion criteria and were judged to be of good quality. In neither study did people have their *KRAS* mutation status determined at the beginning of the trial. However, both trials retrospectively analysed this and reported results for the subgroup of people with *KRAS* wild-type tumours.

Bevacizumab

4.2.2 The manufacturer identified one RCT (the E3200 trial) of bevacizumab as

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second-line treatment for metastatic colorectal cancer. The trial investigated the effectiveness of bevacizumab plus an oxaliplatin-containing chemotherapy regimen, which is outside the scope of this appraisal. People with metastatic colorectal cancer (n = 829) who had previously been treated with a fluoropyrimidine with or without irinotecan were randomised to receive bevacizumab plus FOLFOX4 (oxaliplatin plus 5-fluorouracil 400 mg, fluorouracil 600 mg and folinic acid), FOLFOX4 alone or bevacizumab alone. The primary endpoint was overall survival.

4.2.3 Median overall survival was 12.9 months in people randomised to bevacizumab plus FOLFOX4 (n = 286), 10.8 months in people randomised to FOLFOX4 alone (n = 291), and 10.2 months in people randomised to bevacizumab alone (n = 252). The incremental overall median survival for bevacizumab plus FOLFOX4 compared with FOLFOX4 was 2.1 months, with a hazard ratio (HR) of 0.75 (95% confidence interval [CI] not provided, p = 0.001). Median progression-free survival was 7.3 months in the bevacizumab plus FOLFOX4 arm, 4.7 months in the FOLFOX4 alone arm, and 2.7 months in the bevacizumab alone arm. The incremental median progression-free survival for bevacizumab plus FOLFOX4 compared with FOLFOX4 alone was 2.6 months (p < 0.0001). The bevacizumab alone arm of the study closed early after an interim analysis suggested inferior overall survival compared with the other arms.

4.2.4 The manufacturer identified three RCTs (Hurwitz et al. 2004, Kabbinavar et al. 2005, Saltz et al. 2008) that investigated the effectiveness of bevacizumab as first-line treatment for metastatic colorectal cancer. However, the scope for this appraisal specifies that bevacizumab should be considered as second-line and subsequent treatment. The manufacturer stated that, because no RCTs for metastatic colorectal cancer in the second-line setting studied bevacizumab in combination with chemotherapy regimens not containing oxaliplatin, these RCTs in the first-line setting only provide evidence to 'indicate that bevacizumab is safe and effective in combination with irinotecan in second-line metastatic colorectal cancer'. One study (Hurwitz et al. 2004) compared bevacizumab plus irinotecan, bolus 5-fluorouracil and folinic acid (n = 402) with placebo plus irinotecan, bolus 5-fluorouracil and folinic acid (n = 411). The primary endpoint was median overall survival, which was

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20.3 months for people randomised to bevacizumab plus irinotecan, bolus 5-fluorouracil and folinic acid compared with 15.6 months for people randomised to placebo plus folinic acid (HR = 0.66, p < 0.001). The median progression-free survival was 10.6 months for people randomised to bevacizumab plus irinotecan, bolus 5-fluorouracil and folinic acid and 6.2 months for people randomised to placebo plus folinic acid (HR = 0.54, p < 0.001). The second RCT (Kabbinavar et al. 2005) evaluated bevacizumab plus bolus 5-fluorouracil and folinic acid (n = 105) compared with placebo plus bolus 5-fluorouracil and folinic acid (n = 104). Median overall survival was 16.6 months in people randomised to bevacizumab plus bolus 5-fluorouracil and folinic acid compared with 12.9 months in people randomised to placebo plus 5-fluorouracil and folinic acid (HR = 0.79, p = 0.16). The third RCT (Saltz et al. 2008) compared bevacizumab plus oxaliplatin-based chemotherapy (FOLFOX or capecitabine plus oxaliplatin [XELOX], n = 699) with oxaliplatin-based chemotherapy alone (FOLFOX or XELOX, n = 667). Progression-free survival (the primary endpoint) was significantly greater in people randomised to bevacizumab plus chemotherapy compared with chemotherapy alone (median progression-free survival 9.4 months versus 8.0 months; HR = 0.83, p = 0.002). There was no significant difference in overall median survival between the two arms (21.3 months versus 19.9 months for the bevacizumab plus chemotherapy arm and chemotherapy alone arm respectively; HR = 0.89, p = 0.77).

4.2.5 The manufacturer identified two observational cohort studies that investigated the effectiveness of bevacizumab as second-line treatment for metastatic colorectal cancer in people with progressed disease. One study, which used data from the 'Bevacizumab Regimens: Investigation of Treatment Effects and Safety' (BRiTE) registry compared overall survival in people treated with bevacizumab as first- and second-line therapy (n = 642), with people treated with bevacizumab as first-line therapy but with other chemotherapy treatments in the second-line setting (n = 531). Overall survival was significantly greater in people who received bevacizumab as a second-line treatment compared with those receiving other second-line chemotherapy regimens (median overall survival post progression 31.8 months compared with 19.9 months; HR = 0.48, p < 0.001). The other observational study used data from the ARIES registry and compared overall survival in people with metastatic

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colorectal cancer who received bevacizumab as first- and second-line treatment (n = 208) with people treated with bevacizumab in the second-line setting only (n = 255). Overall survival was significantly greater in people who received bevacizumab as first- and second-line treatment compared with those who received it in the second-line setting only (median overall survival post progression 21.7 months (95% CI 17.8 to 27.0) compared with 17.5 months (95% CI 15.9 to 21.5). The manufacturer noted that the data from the registries were not available by type of chemotherapy, and therefore specific information about the effect of bevacizumab in combination with non-oxaliplatin-based chemotherapy could not be provided.

4.2.6 The Assessment Group did not identify any trials that met the inclusion criteria for its review (that is, bevacizumab plus non-oxaliplatin-based chemotherapy for the treatment of people with metastatic colorectal cancer whose disease had progressed after first-line chemotherapy).

Cetuximab

4.2.7 The manufacturer and the Assessment Group identified one RCT (the CO.17 trial), which compared cetuximab plus best supportive care with best supportive care alone in people (n = 572) with metastatic colorectal cancer who had previously been treated with a fluoropyrimidine, irinotecan and oxaliplatin or who had contraindications to these treatments. This trial was mainly a trial of third-line and subsequent therapy, because 96–98% of people had received both irinotecan and oxaliplatin. Nearly half of the participants had received four or more chemotherapy regimens. The primary endpoint was overall survival.

4.2.8 The median overall survival in the whole trial population (irrespective of *KRAS* mutation status of the tumour) was 6.1 months with cetuximab plus best supportive care and 4.6 months with best supportive care alone, with an HR of 0.77 (95% CI 0.64 to 0.92; p = 0.005). Approximately 7% of people randomised to best supportive care alone were given cetuximab after crossover.

4.2.9 A total of 394 (68.9%) tumour specimens were retrospectively examined for *KRAS* mutation status after completion of the trial (Karapetis et al.

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2008). Limiting analyses to people with *KRAS* wild-type status, the median overall survival was 9.5 months for people randomised to cetuximab plus best supportive care compared with 4.8 months for people randomised to best supportive care alone (HR = 0.55, 95% CI 0.41 to 0.74; p < 0.001). In an analysis that adjusted for both randomisation and potential prognostic factors (age, Eastern Cooperative Oncology Group performance status, previous chemotherapy), the HR increased to 0.62 (95% CI 0.44 to 0.87; p = 0.006).

4.2.10 To compare cetuximab plus best supportive care with cetuximab plus irinotecan in people with *KRAS* wild-type status, the manufacturer presented a published retrospective observational analysis (De Roock et al. 2008, referred to as the De Roock analysis) that analysed data on Belgian participants combined from four studies (EVEREST n = 50, BOND n = 44, SALVAGE n = 17 and BABEL n = 2). Approximately one-quarter of people had been treated with cextuximab monotherapy, and three-quarters with cetuximab (at varying dosages) plus irinotecan. The phase II EVEREST trial investigated the effect of cetuximab dose escalation on EGFR expression in people with metastatic colorectal cancer whose disease had not responded to prior treatment with irinotecan. The BOND study was a randomised open-label multicentre phase II RCT of cetuximab plus irinotecan versus cetuximab monotherapy in people with metastatic EGFR-expressing colorectal adenocarcinoma. The SALVAGE study was an uncontrolled trial of monotherapy with cetuximab in people with metastatic colorectal cancer, whose tumours expressed EGFR and were refractory to irinotecan, oxaliplatin and fluoropyrimidines. The BABEL study was an uncontrolled trial of cetuximab monotherapy in people with *KRAS* wild-type metastatic colorectal cancer. The De Roock analysis provided data for a total of 113 people (67 with *KRAS* wild-type status, 46 with the *KRAS* mutation) with irinotecan refractory metastatic colorectal cancer who had been treated with cetuximab monotherapy. The Assessment Group excluded the De Roock analysis from its review because it judged the analysis to have a number of limitations: the people selected may not have been representative of people treated in UK clinical practice, and two of the studies (BABEL and SALVAGE) were single arm (that is, uncontrolled) studies. Only the BOND study compared cetuximab plus irinotecan with cetuximab monotherapy.

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Panitumumab

4.2.11 The manufacturer and the Assessment Group identified one RCT (the 'Amgen' trial) that compared panitumumab plus best supportive care with best supportive care alone in 463 people with metastatic colorectal cancer that had progressed after standard first- and second-line chemotherapy (a fluoropyrimidine, irinotecan and oxaliplatin). The primary endpoint of the trial was progression-free survival. Overall survival was analysed as a secondary endpoint. No statistically significant difference was observed in overall survival in the whole population (irrespective of *KRAS* mutation status) (HR = 1.00, 95% CI 0.82 to 1.22).

4.2.12 Tumour samples from 427 (92%) people in the Amgen trial were retrospectively obtained for *KRAS* mutation status testing after the end of the trial. In the *KRAS* wild-type population, median progression-free survival was 12.3 weeks in people randomised to panitumumab plus best supportive care compared with 7.3 weeks in people randomised to best supportive care alone. When calculating overall survival in people randomised to the best supportive care arm, the manufacturer excluded people with wild-type *KRAS* who crossed over to receive panitumumab. Overall survival was estimated using two mutually exclusive time points: mean time to disease progression and mean time from progression to death. Survival estimates for best supportive care were based on people randomised to best supportive care with a *KRAS* mutation or wild-type *KRAS* for the time until disease progression (before any treatment crossover occurred), and people randomised to best supportive care with a *KRAS* mutation for the time from disease progression to 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 and the mean survival for each distribution. The median overall survival from an intention-to-treat analysis in the *KRAS* wild-type population was 8.1 months for people randomised to panitumumab plus best supportive care compared with 7.6 months for people randomised to best supportive care alone. No statistically significant difference in median overall survival after disease progression between panitumumab and best supportive care was shown in this *KRAS* wild-type population (HR = 0.99;

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95% CI 0.75 to 1.29).

4.2.13 There was significant crossover in the Amgen trial; of 219 people randomised to best supportive care alone, 166 (76%) crossed over after disease progression to receive treatment with panitumumab. Because panitumumab lengthened progression-free survival, and many people randomised to best supportive care also received panitumumab after progression, the estimates of effectiveness from intention-to-treat analyses (see section 4.2.11) were considered by the manufacturer to underestimate the effectiveness of panitumumab. Therefore, in an attempt to adjust for this bias, the manufacturer adjusted the overall survival results by including people with *KRAS* mutations randomised to best supportive care in the analysis, regardless of whether they crossed over to receive panitumumab treatment after disease progression. The manufacturer's rationale for this method was that the trial showed that people with a *KRAS* mutation did not benefit from treatment with panitumumab. Therefore people with a *KRAS* mutation in the best supportive care arm who crossed over to receive panitumumab after disease progression would also be less likely to benefit from it. 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. The Assessment Group judged that the manufacturer's approach and assumptions to adjust for crossover were reasonable.

Mixed treatment comparisons

4.2.14 The Assessment Group and the manufacturers did not identify any RCTs that directly compared each of the technologies included in this appraisal. 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 technologies relevant to the decision problem. Without clinical evidence for the use of bevacizumab as specified by the scope, there were four treatments or comparators:

- best supportive care

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- monotherapy with cetuximab plus best supportive care
- monotherapy with panitumumab plus best supportive care, and
- cetuximab plus chemotherapy plus best supportive care.

The manufacturers of panitumumab and bevacizumab did not submit a mixed treatment comparison because they did not consider it possible to conduct a robust mixed treatment comparison of the three technologies based on the evidence available.

Manufacturer's (Merck Serono) mixed treatment comparison

4.2.15 To compare the clinical effectiveness of cetuximab plus chemotherapy with panitumumab plus best supportive care and best supportive care alone, the manufacturer (Merck Serono) used data from the CO.17 trial and from the Amgen trial. Although the scope of this appraisal covers cetuximab plus chemotherapy, the only evidence available was for cetuximab plus irinotecan. The manufacturer used data from 80 people in a retrospective analysis of the De Roock analysis to compare cetuximab plus best supportive care with cetuximab plus irinotecan in the *KRAS* wild-type population. The manufacturer did not identify any relevant evidence for bevacizumab.

4.2.16 The resulting HR for overall survival for cetuximab plus irinotecan and best supportive care compared with best supportive care alone was 0.29 (95% CI 0.14 to 0.59). Following advice from clinical specialists, the manufacturer concluded that the parametric model it had fitted to the Kaplan–Meier curve for overall survival (Weibull function) did not match the original data. The manufacturer therefore obtained additional data from the retrospective analysis of the De Roock analysis for 364 people. The resulting HR for overall survival for cetuximab plus irinotecan compared with best supportive care changed to 0.32 (confidence interval not reported). The manufacturer used the 95% CI from the original retrospective analysis of the De Roock analysis (that is, 95% CI 0.14 to 0.59). The resulting HR for overall survival for cetuximab plus best supportive care compared with panitumumab plus best supportive care was 0.56 (95% CI 0.37 to 0.83).

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4.2.17 The Assessment Group expressed concerns about the validity of the manufacturer's approach to calculating progression-free survival and overall survival hazard ratios from the mixed treatment comparison because:

- it combined randomised and non-randomised evidence, subjecting it to bias and confounding
- it did not assess whether the populations in the chosen studies were comparable
- for calculating the overall survival HR for cetuximab plus irinotecan compared with best supportive care, the manufacturer used data from a non-comparative study to adjust the HR to fit the model, but the statistical fit of the model was determined by clinical specialists rather than statistical testing, and the manufacturer did not clarify how adjustments were made to fit the data to the model
- the manufacturer used unadjusted HRs from the cetuximab CO.17 RCT instead of values adjusted for patient characteristics, which may have overestimated the effectiveness of cetuximab
- the BOND study, which was included in the observational retrospective analysis that combined four studies (the De Roock analysis) did not account for crossover, and this could have led to an underestimation of overall survival gain for cetuximab plus best supportive care compared with cetuximab plus irinotecan.

Assessment Group's mixed treatment comparison

4.2.18 The Assessment Group also carried out a mixed treatment comparison for the four treatments: best supportive care, cetuximab monotherapy plus best supportive care, panitumumab monotherapy plus best supportive care, and cetuximab plus irinotecan and best supportive care. The Assessment Group used data from the two RCTs used by the manufacturer of cetuximab in its mixed treatment comparison: the CO.17 trial (cetuximab plus best supportive care compared with best supportive care alone) and the Amgen trial (panitumumab plus best supportive care compared with best supportive care alone). It also used data from the

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retrospective analysis of four studies (the De Roock analysis). The Assessment Group assumed that best supportive care was equivalent between the CO.17 trial and the Amgen trial. Unlike the manufacturer's analysis, the Assessment Group adjusted HRs in its mixed treatment comparison for the patient characteristics in the *KRAS* wild-type population. However, the HRs obtained from the indirect comparison were not adjusted using data from the retrospective analysis (De Roock analysis).

4.2.19 Results of the mixed treatment comparison showed that patients who received cetuximab plus best supportive care would be expected to have significantly longer overall survival than those receiving panitumumab plus best supportive care (unadjusted HR 0.56, 95% CI 0.37 to 0.83; adjusted HR 0.63, 95% CI 0.41 to 0.97). The Assessment Group highlighted that the HR for overall survival for panitumumab from the Amgen trial may have underestimated the effectiveness of panitumumab relative to best supportive care because most people randomised to best supportive care also received treatment with panitumumab after their disease had progressed. The Assessment Group reported an overall survival estimate of 16.2 months for cetuximab plus irinotecan in an appendix to the assessment report.

4.3 Cost effectiveness

Manufacturer's submission

4.3.1 Amgen and Roche Products did not submit health economic models. Roche Products submitted calculations outlining the treatment costs for bevacizumab plus FOLFIRI compared with cetuximab plus FOLFIRI. The treatment cost for cetuximab plus FOLFIRI was estimated to exceed that for bevacizumab plus FOLFIRI by £5408, with an incremental cost for *KRAS* testing of £462, additional drugs costs of £3357 and additional administration costs of £1589.

4.3.2 Merck Serono provided a Markov model to make four comparisons:

- cetuximab plus best supportive care compared with best supportive care alone

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- cetuximab plus irinotecan plus best supportive care compared with best supportive care alone
- cetuximab plus best supportive care compared with panitumumab plus best supportive care
- cetuximab plus irinotecan plus best supportive care compared with panitumumab plus best supportive care.

4.3.3 The population modelled by Merck Serono included people with EGFR-expressing *KRAS* wild-type metastatic colorectal cancer who had received second- or subsequent-line chemotherapy for metastatic disease. The model had a 10-year time horizon and a UK National Health Service (NHS) perspective. The cycle length was 1 week and a half-cycle correction was not applied. The model had three health states: progression-free disease, progressive disease and death. Merck Serono based the transitions between health states on parametric approximations of Kaplan–Meier estimates of progression-free survival and overall survival from the relevant arms of the RCTs (with time spent by a patient in progressive disease defined as the difference between the two).

4.3.4 To compare cetuximab plus best supportive care with best supportive care alone, Merck Serono estimated separate probabilities for time to disease progression and time to death for people in the progression-free disease and progressive disease health states using patient-level data. Merck Serono chose different functions on the basis of goodness-of-fit measures for each transition (log-normal for time to progression; log-logistic for death from the health state of pre-progression; Weibull for death from the health state of progressive disease).

4.3.5 For the comparison of cetuximab plus irinotecan and best supportive care with best supportive care alone, Merck Serono modelled progression-free survival and overall survival using a two-stage process. First, it simulated progression-free survival and overall survival for people treated with best supportive care alone using a Weibull curve and then validated this curve using data from the best supportive care arm of the CO.17 trial. The corresponding values for progression-free survival and overall survival for cetuximab plus irinotecan and best supportive care

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were then estimated by applying the overall survival HRs for cetuximab plus irinotecan and best supportive care with the HR for best supportive care being drawn from the mixed treatment comparison. Merck Serono obtained estimates of utility for each health state using the Health Utility Index (HUI) scale (a generic preference-based measure of quality of life) by reanalysing data by health state in the CO.17 trial. These utility values were then applied to cetuximab plus irinotecan and best supportive care and panitumumab plus best supportive care. The manufacturer used utility values of 0.809 for progression-free disease, 0.789 for progressive disease and 0.000 for death.

4.3.6 The following assumptions were made in the model: the mean time on treatment with cetuximab plus best supportive care is 2.6 months and the mean time for cetuximab plus irinotecan is 4.4 months; active treatment stops at set cut-off time points, that is, 13 weeks for cetuximab plus best supportive care and 24 weeks for cetuximab plus irinotecan plus best supportive care, even if a patient's disease has not progressed.

4.3.7 Merck Serono produced a series of pairwise comparisons of cost effectiveness in people with *KRAS* wild-type metastatic colorectal cancer:

- Cetuximab plus best supportive care compared with best supportive care alone produced a base-case incremental cost-effectiveness ratio (ICER) of £47,095 per quality-adjusted life year (QALY) gained.
- Cetuximab plus irinotecan plus best supportive care compared with best supportive care alone produced a base-case ICER of £43,887 per QALY gained.

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- Cetuximab plus irinotecan plus best supportive care compared with panitumumab plus best supportive care produced a base-case ICER of £21,819 per QALY gained.

  When cetuximab plus best supportive care was compared with panitumumab plus best supportive care, panitumumab was associated with higher costs and fewer QALYs (–0.193 incremental QALYs and £2629 incremental costs). Merck Serono completed one-way sensitivity analyses on all the model parameters and the only factor found to significantly change the ICERs was varying the cost of cetuximab (which included changes to the price of the drug, its administration costs, and/or the duration of treatment).

4.3.8 Merck Serono's probabilistic sensitivity analyses indicated that, compared with best supportive care alone, cetuximab plus best supportive care and cetuximab plus irinotecan had a 64.7% and a 68% chance respectively of being cost effective at £50,000 per QALY gained. Compared with panitumumab plus best supportive care, cetuximab plus best supportive care had a 100% chance of being cost effective at £15,000 per QALY gained. Cetuximab plus irinotecan compared with panitumumab plus best supportive care has a 73.8% chance of being cost effective at £30,000 per QALY gained and a 93% chance of being cost effective at £50,000 per QALY gained.

Assessment Group's report

4.3.9 From a literature review the Assessment Group identified one cost-effectiveness analysis of bevacizumab in previously untreated metastatic colorectal cancer, which was not relevant to this appraisal. It also identified a study by Mittman et al. (2008) which was a trial-based cost-effectiveness analysis that used data from the cetuximab CO.17 trial. The Assessment Group also identified three studies (Annemans et al. 2007, Norum et al. 2006, Starling et al. 2007) which assessed the cost effectiveness of cetuximab plus irinotecan compared with best supportive care. The base-case ICER in the Annemans et al. study was €40,273 per life year gained (based on 12 weeks of treatment). The base-case ICER was €205,536 per life year gained in the Norum et al. study and £57,608 per QALY gained in the Starling et al. study.

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4.3.10 The Assessment Group noted that the Merck Serono model did not attempt to compare cetuximab plus irinotecan plus best supportive care with cetuximab plus best supportive care. Moreover, Merck Serono assessed the cost effectiveness of cetuximab only as third-line treatment and did not consider it as second-line treatment, but the scope for this appraisal allows any of the technologies to be considered as second-line treatment. The Assessment Group questioned the validity of the utility values obtained from the CO.17 trial by Merck Serono because they exceeded the values produced by the health economic evaluation that accompanied the CO.17 trial (Mittman et al. 2008).

4.3.11 The Assessment Group provided an area under the curve model that compares cetuximab plus best supportive care with best supportive care alone, cetuximab plus irinotecan plus best supportive care with best supportive care alone, and panitumumab plus best supportive care with best supportive care alone in people with EGFR-expressing *KRAS* wild-type metastatic colorectal cancer who had received at least second-line chemotherapy for metastatic disease. The Assessment Group did not include bevacizumab in the economic analysis because no clinical effectiveness evidence was available for bevacizumab plus chemotherapy without oxaliplatin in people who had received previous chemotherapy. The model had a 10-year time horizon and a UK NHS perspective. The cycle length was 1 month and a half-cycle correction was applied.

4.3.12 The model had three health states: progression-free disease, progressive disease and death. The Assessment Group used an 'area under the curve' or 'cohort partition' method to determine the number of people in each health state at each cycle of the model, rather than using transition probabilities. The Assessment Group obtained estimates of utility from the Mittman et al. (2008) study that used individual patient-level data and HUI data from the CO.17 trial. The Assessment Group used utility values for progression-free disease of 0.81 for cetuximab plus best supportive care, 0.75 for best supportive care, 0.75 for cetuximab plus irinotecan, and 0.87 for panitumumab plus best supportive care; a utility value of 0.69 was used for progressive disease (for all treatments).

4.3.13 The Assessment Group's model differed from the Merck Serono model in

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the following ways for the comparison of cetuximab plus best supportive care versus best supportive care alone:

- the estimates of mean time on cetuximab varied: Assessment Group 4.8 months, Merck Serono 2.6 months
- the estimates of drug costs varied because of differences in estimates of treatment duration: Assessment Group £14,400, Merck Serono £8200
- the estimates of drug administration costs varied because of differences in estimates of treatment duration: Assessment Group £5500, Merck Serono £2000
- the estimates of utility were taken directly from Mittman et al. (2008) by the Assessment Group; reanalysed estimates from the CO.17 trial were used by Merck Serono
- the Assessment Group model included an adjustment for crossover for the overall survival HR for panitumumab compared with best supportive care whereas the Merck Serono model did not.

4.3.14 For the comparison of cetuximab plus irinotecan versus best supportive care, the main differences between the Assessment Group's model and the Merck Serono model were the:

- estimates of mean time on cetuximab plus irinotecan varied: Assessment Group 8.8 months, Merck Serono 4.4 months
- estimates of drug costs varied because of differences in estimates of treatment duration: Assessment Group £32,000, Merck Serono £17,400
- estimates of drug administration costs varied because of differences in estimates of treatment duration: Assessment Group £12,700, Merck Serono £3800.

4.3.15 The Assessment Group produced a series of pairwise comparisons of cost effectiveness in people with *KRAS* wild-type metastatic colorectal cancer:

- Cetuximab plus best supportive care compared with best supportive care alone produced a base-case ICER of £98,000 per QALY gained.

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- Cetuximab plus irinotecan plus best supportive care compared with best supportive care alone produced a base-case ICER of £88,000 per QALY gained.

- Panitumumab plus best supportive care compared with best supportive care alone produced a base-case ICER of £150,000 per QALY gained.

  The Assessment Group completed deterministic one-way sensitivity analyses on model parameters and the only factor found to substantially change the ICER was the estimate of overall survival. The ICER for cetuximab plus best supportive care compared with best supportive care alone was more than £70,000 per QALY gained in all scenarios, the ICER for cetuximab plus irinotecan compared with best supportive care was more than £55,000 per QALY gained, and the ICER for panitumumab plus best supportive care compared with best supportive care was more than £110,000 per QALY gained. When the unadjusted progression-free survival estimates from the Amgen trial were used, the ICER for panitumumab plus best supportive care compared with best supportive care was reduced to £109,000 per QALY gained. In an additional analysis conducted in response to comments received from the manufacturers during consultation on the assessment report, the overall survival estimate for best supportive care was increased from 6.8 months to 7.2 months. This gave an ICER of £119,000 per QALY gained for panitumumab plus best supportive care compared with best supportive care.

4.3.16 The Assessment Group's probabilistic sensitivity analyses indicated that below £60,000 per QALY gained, none of the drugs appraised is the most cost-effective treatment for second-line or subsequent chemotherapy of metastatic colorectal cancer. Above £90,000 per QALY gained, cetuximab plus irinotecan is likely to be the most cost-effective treatment compared with best supportive care. Cetuximab monotherapy or panitumumab are never the most cost-effective option when compared with best supportive care.

4.4 Consideration of the evidence

4.4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of bevacizumab in combination with non-oxaliplatin chemotherapy, cetuximab either in combination with chemotherapy or as

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monotherapy, and panitumumab monotherapy. The Committee did so having considered evidence on the nature of metastatic colorectal cancer and the value placed on the benefits of bevacizumab, cetuximab and panitumumab by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

4.4.2 The Committee heard from the clinical specialists and patient experts that there are limited treatment options for people with metastatic colorectal cancer that has progressed after treatment with first-line chemotherapy (progression being defined as radiological evidence of tumour growth or spread, and/or by clinical symptoms). The second-line treatment options that NICE recommends currently (in TA93) are irinotecan monotherapy and FOLFOX. Irinotecan monotherapy is offered to people who received FOLFOX as first-line treatment, and FOLFOX is offered to people who received FOLFIRI as first-line treatment. TA93 also specifies that people may receive treatment with either FOLFOX or irinotecan as second-line and subsequent-line therapy if they have received 5-fluorouracil and folinic acid or oral analogues as first-line treatment. The Committee heard from the clinical specialists that frail people and older adults were more likely to be offered as first-line therapy 5-fluorouracil and folinic acid over FOLFIRI or FOLFOX, with FOLFOX (or the same combination of oral analogues) being less toxic than FOLFIRI. The Committee also heard that as second-line therapy, clinicians prefer to offer combination chemotherapy (for example, FOLFOX) over irinotecan monotherapy (partly because of irinotecan's toxicity), but that clinicians consider offering irinotecan monotherapy as third-line therapy after second-line combination chemotherapy.

4.4.3 The Committee heard from the clinical specialists that EGFR testing was not routinely carried out in clinical practice for people with colorectal cancer because the results had not been found to correlate with response to specific chemotherapy regimens. The Committee further heard from the clinical specialists that *KRAS* testing is now routinely offered in the NHS in some parts of England and Wales, that several proprietary test kits are available, and that NHS pathology laboratories can carry out this testing at low cost. The Committee was also aware that Merck Serono offers *KRAS* testing for free, and that accepting Merck

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Serono's test did not prevent clinicians from prescribing treatments from other manufacturers. The Committee concluded that the *KRAS* testing required by the marketing authorisations for treatment with cetuximab and panitumumab would not be a barrier to treatment.

4.4.4 The Committee heard from the patient experts that people who need to have second- and third-line chemotherapy particularly value even very small increases in life expectancy because this extra time allows them to put their affairs in order and help family and friends. The Committee also heard from the patient experts that the opportunity to receive active treatment rather than palliative care alone is very important to people with metastatic colorectal cancer. In addition, the Committee heard that people with colorectal cancer in England are becoming increasingly worried about what they perceive to be unequal access to treatment with biological drugs, which are currently only provided to some people through the Cancer Drugs Fund.

Bevacizumab

4.4.5 The Committee discussed the clinical effectiveness of bevacizumab in people with metastatic colorectal cancer who have received first-line chemotherapy. The Committee discussed the results of the three RCTs (see section 4.2.4) presented in the Roche Products submission, which investigated the effectiveness of bevacizumab as first-line treatment for metastatic colorectal cancer. The Committee agreed that these trials demonstrated that bevacizumab is an effective first-line treatment for metastatic colorectal cancer, but recognised that the scope of this appraisal was to consider bevacizumab in the second- and third-line setting. The Committee understood that Roche Products, the regulatory authorities and the clinical specialists considered that if bevacizumab plus a non-oxaliplatin-containing regimen is effective in the first-line setting, the combination would also likely be effective in second- and third-line settings, despite not having been tested in these situations. The Committee heard that this assumption was the basis of the regulatory approval for bevacizumab as a second-line therapy. However, the Committee agreed that people receiving bevacizumab as second-line therapy would have more advanced disease than people receiving bevacizumab for first-line therapy. Therefore, the Committee concluded

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that people receiving bevacizumab as second-line therapy would likely have smaller gains in survival than people who have not previously received chemotherapy.

4.4.6 The Committee noted the results of two registry-based observational studies, BRiTE and ARIES. The Committee understood that Roche Products could not provide data from these registries specifically for bevacizumab in combination with non-oxaliplatin chemotherapy. In line with this, the manufacturer also informed the Committee that these registries were unlikely to inform the Committee's decision regarding the use of bevacizumab as second-line or subsequent therapy in combination with non-oxaliplatin chemotherapy. The Committee concluded that the observational evidence presented in the manufacturer's submission could not be used to establish the magnitude of the overall survival gain with bevacizumab plus non-oxaliplatin chemotherapy for people with metastatic colorectal cancer which had not responded to first-line chemotherapy.

4.4.7 The Committee then discussed the E3200 RCT presented in the Roche Products submission (see section 4.2.2), which investigated the effectiveness of bevacizumab plus an oxaliplatin-containing chemotherapy regimen as second-line treatment compared with placebo plus folinic acid for metastatic colorectal cancer. The Committee acknowledged that 'Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine for the treatment of metastatic colorectal cancer' (NICE technology appraisal guidance 212 [TA212]) has already evaluated the clinical and cost effectiveness of bevacizumab plus oxaliplatin-containing chemotherapy in metastatic colorectal cancer, and that the remit of the current appraisal is to appraise bevacizumab plus non-oxaliplatin chemotherapy. The Committee agreed that the results of the E3200 trial could not be used to establish the overall survival gain with bevacizumab plus non-oxaliplatin chemotherapy as second- or third-line treatment for people with metastatic colorectal cancer who had not responded to first-line or second-line chemotherapy. The Committee noted that this conclusion was supported by one of the clinical specialists, who pointed out that the effectiveness of biological drugs plus oxaliplatin differs from the effectiveness of biological drugs plus irinotecan. The Committee

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acknowledged that there is an ongoing RCT of bevacizumab plus FOLFIRI compared with panitumumab plus FOLFIRI as second-line treatment of metastatic colorectal cancer, which is due to finish in August 2012. However it agreed that it was not aware of any currently available evidence on which to base a decision about the clinical effectiveness of bevacizumab plus non-oxaliplatin chemotherapy in people with metastatic colorectal cancer who had previously received chemotherapy.

4.4.8 The Committee discussed the likely cost effectiveness of bevacizumab plus non-oxaliplatin chemotherapy compared with best supportive care and noted the Assessment Group's view that lack of relevant evidence on clinical effectiveness meant that it was not feasible to carry out a cost-effectiveness evaluation of bevacizumab. The Committee also heard from Roche Products that it had not submitted an economic model because it did not believe it would be possible to establish that bevacizumab plus non-oxaliplatin chemotherapy is cost effective as a second-line treatment for metastatic colorectal cancer. The Committee noted that previous NICE technology appraisal guidance (TA212 and 'Bevacizumab and cetuximab for the treatment of metastatic colorectal cancer' [NICE technology appraisal guidance 118; TA118]) had not found bevacizumab to be a cost-effective first-line or second-line treatment for metastatic colorectal cancer. In view of its previous judgement that bevacizumab is likely to be less effective as second-line therapy than as first-line therapy, on balance, the Committee felt that it was unlikely that bevacizumab would be a cost-effective treatment for people with metastatic colorectal cancer who had received first-line therapy. The Committee therefore concluded that the available clinical and cost-effectiveness evidence does not justify a positive recommendation for bevacizumab plus non-oxaliplatin chemotherapy as second-line treatment for metastatic colorectal cancer.

Cetuximab

4.4.9 The Committee discussed the clinical effectiveness of cetuximab (monotherapy or combination chemotherapy) in people with *KRAS* wild-type metastatic colorectal cancer that has progressed after first-line chemotherapy. The Committee noted that the people in the CO.17 trial had previously received oxaliplatin- and irinotecan-based therapy, that

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is, cetuximab was used in the third-line or later setting. The trial had shown a median overall survival of 9.5 months for cetuximab plus best supportive care compared with 4.8 months for best supportive care alone. The Committee was aware that only 68.9% of people in the CO.17 trial were tested for *KRAS* mutation status, and was concerned that there may have been selection bias related to the *KRAS* mutation testing if those people tested were fundamentally different in a way which influenced their response to treatment. The Committee noted the Assessment Group's comment that the age of people in the trial, including people whose tumour displayed *KRAS* mutations and those not tested, averaged 63 years (range 28–88 years), which was on average 10 years younger than people with metastatic colorectal cancer typically seen in clinical practice in the NHS. The Committee heard from the clinical specialists that age at of the start of treatment was unlikely to affect clinical response. The Committee therefore agreed that although the trial population did not fully represent people seen in clinical practice in the NHS, the evidence of clinical effectiveness for cetuximab monotherapy was generalisable to UK clinical practice. The Committee concluded that there was sufficient evidence to show that cetuximab plus best supportive care gave greater benefit in terms of both progression-free survival and overall survival than best supportive care alone.

4.4.10 The Committee discussed the evidence available for the clinical effectiveness of cetuximab plus irinotecan chemotherapy. The Committee noted that there were no head-to-head trials of cetuximab plus irinotecan compared with best supportive care in *KRAS* wild-type colorectal cancer. The Committee therefore discussed the results of the manufacturer's mixed treatment comparison that compared cetuximab plus chemotherapy with panitumumab or best supportive care and cetuximab monotherapy with panitumumab in the *KRAS* wild-type population. The Committee noted the Assessment Group's concerns about the validity of the mixed treatment comparison (see section 4.2.17). The Assessment Group was particularly concerned about the reliance on the retrospective observational analysis (the De Roock analysis) for the effectiveness estimate for cetuximab plus irinotecan, which combined data from RCTs and non-RCTs (single-arm trials), not all of which included treatment with cetuximab plus irinotecan. The

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Committee therefore agreed that the results of the mixed treatment comparison should be interpreted with caution. The Committee concluded that the estimates of overall survival for cetuximab plus irinotecan were subject to a high degree of uncertainty.

4.4.11 The Committee discussed the economic model submitted by the manufacturer of cetuximab, and the Assessment Group's comments on this model. The Committee concluded that using best supportive care as one of the comparators in the model was appropriate. However, the Committee was concerned that the manufacturer had not submitted an economic comparison of cetuximab plus best supportive care versus cetuximab plus irinotecan plus best supportive care, despite having submitted estimates of clinical effectiveness, and had not given a reason for this. The Committee discussed two concerns about the total cost estimated by the manufacturer for cetuximab; that is, the administration costs and costs associated with duration of treatment. The Committee was aware that the Assessment Group model had used estimated administration costs for cetuximab that were two to three times higher than those estimated by the manufacturer. The Committee discussed its concerns about the assumptions in the manufacturer's model about the duration of treatment; particularly whether in clinical practice people would receive cetuximab for a fixed treatment period (as modelled) rather than until disease progresses (as specified in the SPC). The Committee heard from the clinical specialists that clinicians would offer people treatment with cetuximab monotherapy until their disease progressed, but would likely offer cetuximab plus irinotecan for a fixed period in view of the increased toxicity of combined treatment. The Committee therefore concluded that it did not accept the assumption in the manufacturer's model that a fixed treatment period for cetuximab represented UK clinical practice. The Committee also noted a comment made by Amgen during consultation that the NICE 'Guide to the methods of technology appraisal' states a preference for the use of the public list price for a technology and not the negotiated price to the NHS. The Committee noted that the lower NHS price for cetuximab was previously used in NICE technology appraisal 176 rather than the list price. It agreed that the most relevant price to be considered in this appraisal is the one that is nationally available and in the public domain, and therefore considered it appropriate to use the NHS price for cetuximab in the

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economic model.

4.4.12 The Committee discussed the utility estimates in the manufacturer's model, which were obtained from the CO.17 trial. The Committee was aware that using HUI deviated from the NICE reference case, which encourages the use of EQ-5D. However, it agreed that the HUI was a valid measure of utility and that values obtained from the trial population were likely to be generalisable to patients in the UK. The Committee noted that the utility estimates for each of the disease states were not consistent with the expectation that quality of life worsens with progression of disease. The Committee was aware of the Assessment Group's concern that the values of utility recalculated by the manufacturer from the CO.17 trial were higher for progression-free disease than those of Mittman et al. from the same trial. The Committee also noted that the utility estimates used in the model (for example, 0.81 for progression-free disease for cetuximab plus best supportive care) were similar to those expected for people of the same age without metastatic colorectal cancer. The Committee concluded that the utility values in the manufacturer's model were highly uncertain.

4.4.13 The Committee discussed the results of the manufacturer's sensitivity analyses and noted that the estimate of cost effectiveness was most sensitive to the estimate of overall drug costs, which was determined by the time on cetuximab treatment. The Committee heard from the manufacturer that the estimates of time on treatment in the model were based on clinical opinion rather than direct estimates from the CO.17 trial. The Committee agreed that the assumption of a fixed treatment period for cetuximab in the manufacturer's model did not represent UK clinical practice (see section 4.4.11).

4.4.14 The Committee considered the Assessment Group's economic model for cetuximab. The Committee heard that the utility estimates in the Assessment Group's model had been obtained from a published cost–utility study of the CO.17 trial (Mittman et al. 2008) and were in general lower than those used in the manufacturer's model. The Committee agreed that the utility values used by the manufacturer were implausibly high because they were similar to those of the general population of the same age without metastatic colorectal cancer. The

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Committee also noted that because the manufacturer did not provide an estimate of the average length of cetuximab treatment in the CO.17 trial, the Assessment Group contacted Dr Mittman to obtain this estimate after the assessment report had been submitted to the Committee. This estimate was provided to the Committee as an addendum, and is not given in this document because it is considered academic-in-confidence. The Committee agreed that this estimate of time on treatment was more appropriate because it was derived from trial data rather than from an assumption.

4.4.15 The Committee noted that one of the main factors affecting the cost effectiveness of cetuximab was the assumption about the duration of treatment. The Committee agreed that using the values provided as academic-in-confidence in the Assessment Group's analyses gave the most plausible ICER for cetuximab plus best supportive care of £90,000 per QALY gained and for cetuximab plus irinotecan plus best supportive care of £88,000 per QALY gained, both compared with best supportive care. The Committee was aware of another cost–utility analysis of the CO.17 trial (Mittman et al. 2008) that had estimated an ICER of £101,000 per QALY gained for cetuximab plus best supportive care compared with best supportive care. The Committee was also aware that the manufacturer, Merck Serono, noted in its comments during consultation that cetuximab 'is not cost effective under the usual threshold range for acceptability'.The Committee concluded that the most plausible ICERs for cetuximab monotherapy and cetuximab in combination chemotherapy did not represent a cost-effective use of NHS resources.

Panitumumab

4.4.16 The Committee discussed the clinical effectiveness of panitumumab monotherapy in people with *KRAS* wild-type metastatic colorectal cancer that has progressed after first-line chemotherapy. It noted that the only trial evidence available applied to people who had previously received both oxaliplatin- and irinotecan-based therapy, that is, in the third-line or subsequent setting (the Amgen trial). The Committee heard from the manufacturer that over 90% of people in the trial were assessed for the *KRAS* mutation and concluded that selection bias associated with testing was unlikely. The Committee noted that although a benefit in

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progression-free survival of 5 weeks was associated with panitumumab monotherapy relative to best supportive care, no statistically significant effect on overall survival was observed in the trial. The Committee heard from one of the clinical specialists that in trials of metastatic colorectal cancer, gains in progression-free survival cannot reliably translate to gains in overall survival. The Committee was aware that most people in the study who had been randomised to receive best supportive care crossed over to receive panitumumab. The Committee noted that one consultee proposed that analyses adjusting for crossover did not adjust for the adverse reactions related to panitumumab treatment. It heard the Assessment Group's view that the manufacturer's analyses to adjust for crossover reflected a reasonable approach. The Committee concluded that panitumumab provided a survival benefit relative to best supportive care, but that the magnitude of this benefit was uncertain.

4.4.17 The Committee discussed the results of the Assessment Group's economic analysis for panitumumab, which was based on the HRs for panitumumab from the Assessment Group's mixed treatment comparison, adjusted for crossover. The Committee also noted the analyses carried out by the Assessment Group after public consultation on the assessment report, which used unadjusted HRs from the Amgen trial directly. These analyses resulted in a decrease in the ICER from £150,000 to £109,000 per QALY gained when panitumumab plus best supportive care was compared with best supportive care alone. The Committee also noted that the results of the Assessment Group's one-way sensitivity analyses showed that increasing the mean overall survival estimate for panitumumab plus best supportive care from the base-case value of 6.8 months to 7.2 months (based on an increase of 2 standard errors) resulted in an ICER of £110,000 per QALY gained. The Committee concluded that it was not possible to specify a precise ICER for panitumumab plus best supportive care compared with best supportive care alone, but that the most plausible ICER was likely to be between £110,000 and £150,000 per QALY gained.

End-of-life considerations

4.4.18 The Committee considered supplementary advice from NICE that should be taken into account when appraising treatments that may extend the

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life of patients with short life expectancy and that are licensed for indications that affect small numbers of people with incurable illnesses. For this advice to be applied, all the following criteria must be met:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months.
- 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.
- The treatment is licensed or otherwise indicated for small patient populations.

In addition, when taking these criteria into account, the Committee must be persuaded that the estimates of the extension to life are robust and that the assumptions used in the reference case of the economic modelling are plausible, objective and robust.

4.4.19 The Committee discussed whether the technologies appraised fulfil the criteria for consideration as life-extending, end-of-life treatments. For metastatic colorectal cancer that has progressed after first-line treatment, the Committee agreed that the technologies fulfil the first criterion related to life expectancy, because estimates of life expectancy from people randomised to best supportive care in the second-line setting were less than 12 months.

4.4.20 For bevacizumab, the Committee agreed that there was no evidence to show how much bevacizumab plus non-oxaliplatin chemotherapy given as second-line treatment extends survival. In addition, the Committee understood that it should take into account all populations which are covered by all indications of the marketing authorisation for a given technology when considering the size of the patient population. The Committee noted that bevacizumab has a marketing authorisation for a number of indications and therefore does not fulfil the criterion of being indicated for a small patient group. The Committee concluded that bevacizumab plus non-oxaliplatin chemotherapy does not meet all of the criteria for a life-extending, end-of-life treatment.

4.4.21 For cetuximab, the Committee acknowledged that cetuximab plus best

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supportive care prolonged life by a median of 4.7 months in the third-line or later setting relative to best supportive care alone and therefore met the second end-of-life criterion. The Committee was aware from the manufacturer's data that approximately 7600 people have EGFR-positive, *KRAS* wild-type metastatic colorectal cancer in England and Wales, and only a small proportion of these (approximately 260 to 390 people) would be fit enough for third or subsequent lines of treatment. However, the Committee noted that cetuximab has a marketing authorisation for people with any stage of EGFR-positive *KRAS* wild-type metastatic colorectal cancer, and also for people with locally advanced and recurrent and/or metastatic head and neck cancer, which has previously been estimated to be a population of about 3000 (NICE technology appraisal guidance 172 [TA172]). The Committee discussed the decisions from two previous NICE technology appraisal appeals and noted that the Appeal Panel recognised that the criterion in the supplementary advice for end-of-life treatments for small patient populations indicated that 'Sufficient regard should be given to recognition of the desirability of developing new treatments in smaller disease areas and that higher prices, and therefore reduced cost effectiveness, were more likely to be justified given the need to recoup costs of development of the product from more limited licences'. The Appeal Panel had concluded that it was appropriate, according to the supplementary advice, to add together the potential patient populations covered by the marketing authorisation for different indications rather than on the basis of actual or recommended use. The Committee therefore concluded that the true size of the cumulative population covered by the marketing authorisation for cetuximab was likely to be over 10,000 patients and was not small, and that cetuximab does not meet all of the criteria for a life-extending, end-of-life treatment.

4.4.22 The Committee considered whether panitumumab provides a life extension of about 3 months. It noted that the manufacturer estimated that the mean life extension (after adjusting for crossover) was between 2.7 and 3.2 months, and that the Assessment Group judged the method used to derive this estimate to be reasonable. The Committee also noted that the progression-free survival benefit for panitumumab was similar to that for cetuximab and therefore there was sufficient evidence to indicate that panitumumab offers an extension to life of approximately 3

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months compared with best supportive care alone. The Committee noted that panitumumab has a marketing authorisation for people with *KRAS* wild-type and EGFR-expressing metastatic colorectal cancer in whom both irinotecan- and oxaliplatin-containing chemotherapy has failed. The Committee agreed that this represents a small patient population. However, the Committee was aware that the Committee for Medicinal Products for Human Use recently recommended an extension of the marketing authorisation for panitumumab in combination therapy for *KRAS* wild-type metastatic colorectal cancer to first-line and second-line settings. Therefore it is expected that in the near future panitumumab will be licensed for the treatment of metastatic colorectal cancer in a patient population of similar size to that estimated for cetuximab. The Committee noted the most plausible ICER for panitumumab monotherapy lies between £110,000 and £150,000 per QALY gained. Therefore, the Committee concluded that, even if panitumumab monotherapy met all the criteria for a life-extending, end-of-life treatment, the additional weight that would need to be assigned to the QALY benefits would be too great to justify it as an appropriate use of limited NHS resources.

4.4.23 The Committee noted that testing tumour characteristics, such as the *KRAS* mutation, allowed clinicians to identify people who were more likely to respond to treatment with cetuximab or panitinumab, and agreed that this was an innovation in the treatment of metastatic colorectal cancer. The Committee also heard from the clinical specialists that in the future, the identification of further *KRAS* andalso *BRAF* mutations will allow even better identification of people who are likely to benefit from therapy. The Committee considered whether any of the technologies in this appraisal could be considered innovative. It concluded that it had not been presented with a case, substantiated by data, that the treatments add demonstrable and distinctive benefits of a substantial nature that had not already been adequately captured in the QALY measure.

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Summary of Appraisal Committee's key conclusions

TA242	**Appraisal title: Cetuximab (monotherapy or combination chemotherapy), bevacizumab (in 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 guidance 118)**	**Section**
Key conclusion		
Cetuximab monotherapy or combination chemotherapy, bevacizumab in combination with non-oxaliplatin (fluoropyrimidine-based) chemotherapy, and panitumumab monotherapy are not recommended for the treatment of people with metastatic colorectal cancer that has progressed after first-line chemotherapy. This is because:		1.1–1.3
• It was not possible to confirm by how much bevacizumab in combination with non-oxaliplatin (fluoropyrimidine-based) chemotherapy would extend life when used as second-line therapy, and evidence from previous assessments of bevacizumab with other combination regimens or for first-line treatment does not allow a justification for a positive recommendation in this appraisal.		4.4.5, 4.4.6, 4.4.7
• The ICERs for cetuximab monotherapy or combination chemotherapy and for panitumumab monotherapy were very high (£90,000, £88,000 and £110,000–£150,000 per QALY gained respectively) and therefore these technologies did not represent a cost-effective use of NHS resources.		4.4.15 4.4.17
Current practice		
Clinical need of patients, including the availability of alternative treatments	The Committee heard from the clinical specialists and patient experts that there are limited treatment options for people with metastatic colorectal cancer that has progressed after treatment with first-line chemotherapy.	4.4.2

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	For second-line therapy in people whose disease has progressed despite first-line treatment, NICE technology appraisal guidance 93 recommends monotherapy with irinotecan as an option for people who received FOLFOX as first-line treatment, and FOLFOX as an option for people who received FOLFIRI as first-line treatment.	2.8, 4.4.2
The technology		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The Committee agreed that *KRAS* testing was an innovation in the treatment of metastatic colorectal cancer. The Committee was not presented with a case, substantiated by data, that the technologies under consideration add demonstrable and distinctive benefits of a substantial nature that have not already been adequately captured in the QALY measure.	4.4.23
What is the position of the treatment in the pathway of care for the condition?	The UK marketing authorisation for bevacizumab is in combination with fluoropyrimidine-based chemotherapy for the treatment of patients with metastatic carcinoma of the colon or rectum.	3.1
	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 FOLFOX (5-FU and folinic acid and oxaliplatin) or as a single agent in patients whose disease has failed to respond to oxaliplatin and irinotecan-based therapy, and who are intolerant to irinotecan.	3.4

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	Panitumumab has a UK marketing authorisation as a 'monotherapy for the treatment of patients with EGFR-expressing metastatic colorectal cancer with non-mutated (wild-type) *KRAS* after failure of fluoropyrimidine-, oxaliplatin- and irinotecan-containing chemotherapy regimens'.	3.7
Adverse reactions	The Committee did not discuss specific issues around the adverse reactions to the technologies appraised but it was aware of the special warnings and precautions for use outlined in the SPCs for bevacizumab, cetuximab and panitumumab.	3.2, 3.5, 3.8
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The Committee noted the only evidence identified for the clinical effectiveness of bevacizumab as second-line treatment for metastatic colorectal cancer was one RCT (the E3200 trial) in which bevacizumab was given with oxaliplatin-containing chemotherapy, and two non-randomised observational studies using data from the BRiTE and ARIES patient registries. The Committee agreed that the evidence presented by the manufacturer could not be used to establish the overall survival gain with bevacizumab plus non-oxaliplatin chemotherapy as second- or third-line treatment for people with metastatic colorectal cancer that had not responded to first-line or second-line chemotherapy.	4.2.2, 4.2.5, 4.4.5, 4.4.6
	The only evidence for the clinical effectiveness of cetuximab was one RCT (the CO.17 trial) in people with *KRAS* wild-type metastatic colorectal cancer that had progressed after first-line chemotherapy. The Committee noted that the people in the CO.17 trial had previously received oxaliplatin- and irinotecan-based therapy, and that the trial had shown a median overall survival of 9.5 months for cetuximab plus best supportive care compared with 4.8 months for best supportive care alone.	4.4.9

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	The Committee noted that there were no head-to-head trials of cetuximab plus irinotecan compared with best supportive care in *KRAS* wild-type colorectal cancer. The Committee agreed that the results of the mixed treatment comparisons should be interpreted with caution, and concluded that the estimates of overall survival for cetuximab plus irinotecan were subject to a high degree of uncertainty.	4.4.10
	The only evidence for the clinical effectiveness of panitumumab monotherapy came from one RCT (the Amgen trial) in people with *KRAS* wild-type metastatic colorectal cancer that had progressed after first-line chemotherapy. However, people in the trial had previously received both oxaliplatin- and irinotecan-based therapy, that is, panitumumab was given as third-line or subsequent therapy. The Committee noted that although a benefit in progression-free survival of 5 weeks was associated with panitumumab monotherapy relative to best supportive care, no statistically significant effect on overall survival was observed and therefore the magnitude of this benefit was uncertain.	4.4.16
Relevance to general clinical practice in the NHS	The Committee did not discuss specific issues around the relevance to general clinical practice in the NHS.	-
Uncertainties generated by the evidence	The uncertainties were:	
	• the overall survival gain with bevacizumab plus non-oxaliplatin chemotherapy in people with metastatic colorectal cancer who had previously received chemotherapy	4.4.7
	• the estimates of overall survival for cetuximab plus irinotecan based on the mixed treatment comparison	4.4.10

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	• the magnitude of the survival benefit of panitumumab relative to best supportive care.	4.4.16
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	None considered.	-
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The Committee concluded that there was sufficient evidence to show that cetuximab plus best supportive care gave greater benefit in terms of both progression-free survival and overall survival than best supportive care alone.	4.4.9
	The Committee concluded that panitumumab provided a survival benefit relative to best supportive care, but that the magnitude of this benefit was uncertain.	4.4.16
Evidence for cost effectiveness		
Availability and nature of evidence	Two economic models were available for this appraisal, one from the manufacturer of cetuximab and one from the Assessment Group.	4.3.2, 4.3.11
Uncertainties around and plausibility of assumptions and inputs in the economic model	The uncertainties were:	
	• the mean time on cetuximab treatment	4.4.13
	• the overall survival estimates used in the economic models for panitumumab and cetuximab in combination with irinotecan, which were based on the mixed treatment comparison.	4.4.10, 4.4.16

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Incorporation of health-related quality-of-life benefits and utility values	The Committee noted that the utility estimates for each of the disease states were not consistent with the expectation that quality of life worsens with progression of disease. The Committee also noted that the utility estimates in the model (for example, 0.81 for progression-free disease for cetuximab plus best supportive care) were similar to those expected for people of the same age without metastatic colorectal cancer. The Committee concluded that the utility values in the manufacturer's model were highly uncertain.	4.4.12
Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	None considered.	
Are there specific groups of people for whom the technology is particularly cost effective?	None considered.	-
What are the key drivers of cost effectiveness?	The Committee noted that one of the main factors affecting the cost effectiveness of cetuximab was the assumption about the mean duration of treatment.	4.4.15

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	For panitumumab, the estimate of overall survival was the main factor found to substantially change the ICER.	4.4.17
Most likely cost-effectiveness estimate (given as an ICER)	The most plausible ICER for cetuximab plus best supportive care was £90,000 per QALY gained and for cetuximab plus irinotecan plus best supportive care the ICER was £88,000 per QALY gained, both compared with best supportive care.	4.4.15
	It was not possible to specify a precise ICER for panitumumab plus best supportive care compared with best supportive care alone, but this would likely lie between £110,000 and £150,000 per QALY gained.	4.4.17
Additional factors taken into account		
Patient access schemes (PPRS)	N/A	-
End-of-life considerations	The Committee agreed that the life expectancy of people with metastatic colorectal cancer treated with best supportive care in the second-line setting was less than 12 months.	4.4.19
	The Committee concluded that bevacizumab plus non-oxaliplatin chemotherapy did not meet all of the criteria for a life-extending, end-of-life treatment. This was because there was no evidence to show by how much bevacizumab plus non-oxaliplatin chemotherapy given as second-line treatment extended survival and bevacizumab has a marketing authorisation for a number of indications and therefore does not fulfil the criterion of being indicated for a small patient group.	4.4.20
	The Committee concluded that cetuximab did not meet all of the criteria for a life-extending, end-of-life treatment because the cumulative population covered by the indications in the marketing authorisation for cetuximab was likely to be over 10,000 patients and was not small.	4.4.21

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	The Committee noted that in the near future, panitumumab will be licensed for the treatment of metastatic colorectal cancer in a patient population of similar size to that for cetuximab. The Committee noted that the most plausible ICER for panitumumab monotherapy lies between £110,000 and £150,000 per QALY gained. Therefore, the Committee concluded that, even if all the criteria for a life-extending, end-of-life treatment were met for panitumumab monotherapy, the additional weight that would need to be assigned to the QALY benefits would be too great to justify it as an appropriate use of limited NHS resources.	4.4.22
Equalities considerations and social value judgements	The Committee heard that people with colorectal cancer in England are becoming increasingly worried about what they perceive to be unequal access to treatment with biological drugs, which are currently only provided to some patients through the Cancer Drugs Fund.	4.4.4

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5 Implementation

5.1 The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the NHS in England and Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must usually provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding direction, details will be available on the NICE website. When there is no NICE technology appraisal guidance on a drug, treatment or other technology, decisions on funding should be made locally.

5.2 NICE has developed tools to help organisations put this guidance into practice (listed below).

- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.

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6 Recommendations for further research

6.1 The Committee was aware that a phase II clinical trial (SPIRITT) comparing bevacizumab plus FOLFIRI with panitumumab plus FOLFIRI after first-line treatment is under way. The expected study completion date is August 2012. The Committee noted that the results of this trial should be considered in any future review decision for this appraisal.

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7 Related NICE guidance

Published

- Diagnosis and management of colorectal cancer. NICE clinical guideline 131 (2011)
- Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine for the treatment of metastatic colorectal cancer. NICE technology appraisal guidance 212 (2010).
- Cetuximab for the first-line treatment of metastatic colorectal cancer. NICE technology appraisal guidance 176 (2009).
- Bevacizumab and cetuximab for the treatment of metastatic colorectal cancer. NICE technology appraisal guidance 118 (2007).
- Irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer (review of technology appraisal 33). NICE technology appraisal guidance 93 (2005).
- Guidance on the use of capecitabine and tegafur with uracil for metastatic colorectal cancer. NICE technology appraisal guidance 61 (2003).

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8 Review of guidance

8.1 The guidance on this technology will be considered for review by the Guidance Executive in January 2015. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Andrew Dillon
Chief Executive
January 2012

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Appendix A: Appraisal Committee members and NICE project team

A Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Their members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are four Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Amanda Adler (Chair)
Consultant Physician, Addenbrooke's Hospital, Cambridge

Dr Ray Armstrong
Consultant Rheumatologist, Southampton General Hospital

Dr Jeff Aronson
Reader in Clinical Pharmacology, University Department of Primary Health Care, University of Oxford

Dr Michael Boscoe
Consultant Cardiothoracic Anaesthetist, Royal Brompton and Harefield NHS Foundation Trust

Professor John Cairns

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Professor of Health Economics Public Health and Policy, London School of Hygiene and Tropical Medicine

Dr Mark Chakravarty
External Relations Director – Pharmaceuticals and Personal Health, Oral Care Europe

Mr Mark Chapman
Health Economics and Market Access Manager, Medtronic UK

Mrs Eleanor Grey
Lay member

Dr Neil Iosson
General Practitioner

Mr Terence Lewis
Lay member

Professor Ruairidh Milne
Director of Strategy and Development and Director for Public Health Research at the NIHR Evaluation, Trials and Studies Coordinating Centre at the University of Southampton

Dr Rubin Minhas
General Practitioner and Clinical Director, BMJ Evidence Centre

Professor Stephen Palmer
Professor of Health Economics, Centre for Health Economics, University of York

Dr Sanjeev Patel
Consultant Physician and Senior Lecturer in Rheumatology, St Helier University Hospital

Dr John Pounsford
Consultant Physician, Frenchay Hospital, Bristol

Dr John Rodriguez
Assistant Director of Public Health, NHS Eastern and Coastal Kent

Mr Navin Sewak

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Primary Care Pharmacist, NHS Hammersmith and Fulham

Mr Roderick Smith
Finance Director, West Kent Primary Care Trust

Mr Cliff Snelling
Lay member

Professor Ken Stein (Vice Chair)
Professor of Public Health, Peninsula Technology Assessment Group (PenTAG), University of Exeter

Professor Andrew Stevens
Professor of Public Health, Department of Public Health and Epidemiology, University of Birmingham

Mr Tom Wilson
Director of Contracting and Performance, NHS Tameside and Glossop

B NICE project team

Each technology appraisal is assigned to a team consisting of one or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Helen Tucker
Technical Lead

Fiona Rinaldi
Technical Adviser

Jeremy Powell
Project Manager

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Appendix B: Sources of evidence considered by the Committee

1. The assessment report for this appraisal was prepared by 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

2. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, assessment report and the appraisal consultation document (ACD). Organisations listed in I, II and III were also invited to make written submissions and have the opportunity to appeal against the final appraisal determination.

I Manufacturers/sponsors:

- Amgen
- Merck Serono
- Roche Products

II Professional/specialist and patient/carer groups:

- Beating Bowel Cancer
- Bowel Cancer UK
- Cancer Research UK
- europacolon
- Royal College of Nursing

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- Royal College of Pathologists
- Royal College of Physicians
- United Kingdom Oncology Nursing Society

III Other consultees:

- Department of Health
- NHS Telford and Wrekin
- Welsh Government

IV Commentator organisations (without the right of appeal):

- British National Formulary
- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- Medac UK
- MRC Clinical Trials Unit
- National Cancer Research Institute
- Pfizer
- Sanofi

C The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer/sponsor consultees and commentators. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on bevacizumab, cetuximab and panitumumab by attending the initial Committee discussion and/or providing written evidence to the Committee. They were also invited to comment on the ACD.

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- Professor Mohammad Ilyas, Professor of Pathology, University of Nottingham, nominated by the Royal College of Pathologists – clinical specialist
- Professor Daniel Hochhauser, Consultant in Medical Oncology, University College London, nominated by Healthcare Improvement Scotland – clinical specialist
- Ian Beaumont, Director of Public Affairs, Bowel Cancer UK, nominated by Bowel Cancer UK – patient expert
- Barbara Moss, nominated by Bowel Cancer UK – patient expert

Professor Daniel Hochhauser also attended the second Committee discussion.

D Representatives from the following manufacturers/sponsors attended Committee meetings. They contributed only when asked by the Committee Chair to clarify specific issues and comment on factual accuracy.

- Amgen
- Merck Serono
- Roche Products

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Changes after publication

February 2014: minor maintenance

June 2012: minor maintenance

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About this guidance

NICE technology appraisal guidance is about the use of new and existing medicines and treatments in the NHS in England and Wales.

This guidance was developed using the NICE multiple technology appraisal process.

It updates and replaces NICE technology appraisal 150 (published June 2008). It also partially updates NICE technology appraisal guidance 118 (published in January 2007). This guidance updates and replaces recommendation 1.2 of TA118. The review and re-appraisal of cetuximab for the treatment of metastatic colorectal cancer that has progressed after first-line chemotherapy has resulted in a change in the guidance. Cetuximab is not recommended for the treatment of metastatic colorectal cancer that has progressed after any first-line chemotherapy (rather than specifically irinotecan-based chemotherapy).

We have produced a summary of this guidance for patients and carers. Tools to help you put the guidance into practice and information about the evidence it is based on are also available.

Your responsibility
This guidance represents the views of NICE and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way which would be inconsistent with compliance with those duties.

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