

Bevacizumab and cetuximab for the treatment of metastatic colorectal cancer

Technology appraisal guidance

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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance are at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

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Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Guidance	4
2 Clinical need and practice	5
3 The technologies	7
3.1 Bevacizumab.....	7
3.2 Cetuximab	7
4 Evidence and interpretation	9
4.1 Clinical effectiveness	9
4.2 Cost effectiveness	13
4.3 Consideration of the evidence	17
5 Implementation	22
6 Recommendations for further research.....	23
7 Related guidance	25
8 Review of guidance	26
Appendix A. Appraisal Committee members and NICE project team	27
A. Appraisal Committee members	27
B. NICE Project Team	30
Appendix B. Sources of evidence considered by the Committee	31
Changes after publication.....	32
About this guidance.....	33

This guidance is partially replaced by TA242.

1 Guidance

This guidance has been partially updated by NICE technology appraisal guidance 242 (TA242) [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). See the guidance for more information.

- 1.1 Bevacizumab in combination with 5-fluorouracil plus folinic acid, with or without irinotecan, is not recommended for the first-line treatment of metastatic colorectal cancer.
- 1.2 This recommendation has been updated and replaced by [NICE technology appraisal guidance 242](#).
- 1.3 People currently receiving bevacizumab or cetuximab should have the option to continue therapy until they and their consultants consider it appropriate to stop.

2 Clinical need and practice

- 2.1 Colorectal cancer is a malignant neoplasm arising from the lining (mucosa) of the large intestine (colon and rectum). Colorectal cancer is the third most common cancer in the UK, with approximately 30,000 new cases registered in England and Wales in 2002. This represents 12% of all new cancer cases in women and 14% of all new cancer cases in men. The incidence of colorectal cancer increases with age. In people between the ages of 45 and 49 years the incidence is 20 per 100,000. Amongst those over 75 years of age, the incidence is over 300 per 100,000 for men and 200 per 100,000 per year for women. The median age of patients at diagnosis is over 70 years. The overall 5-year survival rate for colorectal cancer in England and Wales is approximately 50%; however, large differences in survival exist according to the stage of disease at diagnosis.
- 2.2 Metastatic colorectal cancer, where the tumour has spread beyond the confines of the lymph nodes to other parts of the body, is generally defined as stage IV of the American Joint Committee on Cancer (AJCC) tumour node metastases (TNM) system or stage D of Dukes' classification.
- 2.3 The population of patients with metastatic colorectal cancer includes both those who present with metastatic disease and those who develop metastatic disease after surgery. Estimates of people presenting with metastatic colorectal cancer range from 20% to 55% of new cases. Out of those who have undergone surgery for colorectal cancer with apparently complete excision, approximately 50% will eventually develop advanced disease and distant metastases (typically presenting within 2 years of initial diagnosis). The 5-year survival rate for metastatic colorectal disease is 12%.
- 2.4 The management of metastatic colorectal cancer is mainly palliative and involves a combination of specialist treatments (such as palliative surgery, chemotherapy and radiation), symptom control and psychosocial support. The aim is to improve both the duration and quality of the individual's remaining life. Clinical outcomes such as overall survival, response and toxicity are important, but alternative outcomes such as progression-free survival, quality of life, convenience, acceptability and patient choice are also important.
- 2.5 The most frequent site of metastatic disease is the liver. In up to 50% of patients with metastatic disease, the liver may be the only site of spread. For these

patients surgery provides the only chance of longer-term survival.

Approximately 10% of patients with metastatic colorectal cancer present with potentially resectable liver metastases and for approximately 14% chemotherapy may render unresectable liver metastases operable.

- 2.6 Individuals with metastatic disease who are sufficiently fit (normally those with World Health Organization performance status 2 or better) are usually treated with active chemotherapy as first- or second-line therapy. First-line active chemotherapy options include infusional 5-fluorouracil plus folinic acid or leucovorin (calcium folinate) (5-FU/FA, 5-FU/LV), oxaliplatin plus infusional 5-FU/FA (FOLFOX), and irinotecan plus infusional 5-FU/FA (FOLFIRI). Oral analogues of 5-FU (capecitabine and tegafur with uracil) may also be used instead of infusional 5-FU. For those patients first receiving FOLFOX, irinotecan may be a second-line treatment option, whereas for patients first receiving FOLFIRI, FOLFOX may be a second-line treatment option (in accordance with its licensed indication). Patients receiving 5-FU/FA or oral therapy as first-line treatment may receive treatment with FOLFOX and irinotecan as second-line and subsequent therapies.
- 2.7 Survival estimates for patients with metastatic colorectal cancer receiving best supportive care are approximately 6 months. The use of infusional 5-FU/FA can increase survival to approximately 10–12 months, whereas combinations of FOLFIRI followed by FOLFOX, or FOLFOX followed by irinotecan, have been reported to increase survival to 20–21 months.

3 The technologies

3.1 *Bevacizumab*

- 3.1.1 Bevacizumab (Avastin, Roche Products) is a recombinant humanised monoclonal IgG1 antibody that acts as an angiogenesis inhibitor. It targets the biological activity of human vascular endothelial growth factor, which stimulates new blood vessel formation in the tumour. Bevacizumab is licensed in the UK in combination with intravenous 5-FU/FA with or without irinotecan for first-line treatment of patients with metastatic carcinoma of the colon or rectum.
- 3.1.2 Bevacizumab is contraindicated in patients who are pregnant, have untreated central nervous system metastases, have hypersensitivity to the active substance or to any of the excipients, or have hypersensitivity to products derived from Chinese hamster ovary cell cultures or other recombinant human or humanised antibodies. The summary of product characteristics (SPC) lists the following complications that may be associated with bevacizumab treatment: gastrointestinal perforation, wound-healing problems, hypertension, proteinuria, arterial thromboembolism, haemorrhage and cardiomyopathy. For full details of side effects and contraindications, see the SPC.
- 3.1.3 Bevacizumab is administered as an intravenous infusion at a dose of 5 mg/kg body weight once every 14 days. Bevacizumab treatment is recommended until there is underlying disease progression. Bevacizumab is available in 100-mg and 400-mg vials at net prices of £242.66 and £924.40 respectively (excluding VAT; 'British national formulary' edition 51 [BNF 51]). If vial wastage is assumed, a 75-kg person would receive a single 400-mg vial of bevacizumab per dose, equating to a cost of £924.40. Patients in the key registration trial received an average of 18.2 doses, equating to an average total cost of drug acquisition of £16,824.08 per patient. Costs may vary in different settings because of negotiated procurement discounts.

3.2 *Cetuximab*

- 3.2.1 Cetuximab (Erbix, Merck Pharmaceuticals) is a recombinant monoclonal antibody that blocks the human epidermal growth factor receptor (EGFR) and thus inhibits the proliferation of cells that depend on EGFR activation for

growth. Cetuximab is licensed in the UK in combination with irinotecan for the treatment of patients with EGFR-expressing metastatic colorectal cancer after failure of cytotoxic therapy that included irinotecan.

- 3.2.2 The UK marketing authorisation stipulates that before being treated with cetuximab patients should be tested to identify whether or not the tumour is expressing EGFR. This is currently done using the commercially available DakoCytomation kit, which uses immunohistochemistry to identify EGFR expression (£995.00 for a set of 35 tests [information supplied by manufacturer]).
- 3.2.3 One common side effect of cetuximab therapy is the development of an acne-like rash. The SPC notes that if a patient experiences a grade 3 or 4 skin reaction cetuximab treatment must be interrupted, with treatment being resumed only if the reaction resolves to grade 2. In addition, the SPC lists infusion-related reactions and respiratory disorders that may be associated with treatment with cetuximab. For full details of side effects and contraindications, see the SPC.
- 3.2.4 Cetuximab is given as an intravenous infusion with an initial loading dose of 400 mg/m² of body surface area and subsequent weekly doses of 250 mg/m². Cetuximab treatment is recommended until there is underlying disease progression. Cetuximab is provided in 50-ml vials containing 2 mg cetuximab per ml. The net price for a 50-ml vial is £136.50 (excluding VAT; BNF 51). Assuming vial wastage, an average person with a body surface area of 1.75 m² would receive seven vials per loading dose and five vials per maintenance dose, equating to a cost of £955.50 for the loading dose and £682.50 for each maintenance dose. Patients in the key registration trial received an average of 16.8 doses, equating to an average total drug acquisition cost of £11,739 per patient. Costs may vary in different settings because of negotiated procurement discounts.

4 Evidence and interpretation

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

4.1 Clinical effectiveness

Bevacizumab

4.1.1 Three randomised controlled trials (RCTs) have investigated the effectiveness of bevacizumab as a first-line treatment for metastatic colorectal cancer.

- One study (n = 813; median age 59 years) investigated the effect of irinotecan, bolus 5-FU and leucovorin (calcium folinate) (IFL) with and without the addition of bevacizumab.
- The other two studies (one n = 71, median age 64 years; one n = 209, median age 71 years) investigated the effect of bolus 5-FU and leucovorin (5-FU/LV) with and without bevacizumab.

For two of the studies the primary end point was overall survival, while in the smaller study that used 5-FU/LV as the comparator the primary end points were time to disease progression and best tumour response. In all three studies participants tended to have a good performance status (Eastern Cooperative Oncology Group [ECOG] status 0 or 1; unrestricted by disease or only restricted in strenuous physical activity), although in the larger study that used 5-FU/LV as a comparator, 7% had an ECOG status of 2 (ambulatory and capable of all self-care but unable to carry out any work activities).

4.1.2 Data taken from the manufacturer's submission are based on analyses carried out using data from the clinical trials database, which is subject to updates and revisions. Therefore in some instances the results presented here differ from the results in earlier published journal articles.

4.1.3 The addition of bevacizumab to IFL led to a statistically significant difference in median overall survival compared with IFL alone (20.3 months vs 15.6 months, respectively; hazard ratio [HR] 0.66, 95% confidence interval [CI] 0.54 to 0.81). In the studies that used 5-FU/LV as comparator there were no statistically significant differences in median overall survival. In the larger study the median

overall survival in the bevacizumab-containing arm was 16.6 months compared with 13.2 months in the control arm (HR 0.77, 95% CI 0.56 to 1.05). In the smaller study the median overall survival in the bevacizumab-containing arm was 17.7 months compared with 13.6 months in the control arm (HR 0.52, 95% CI not reported; $p = 0.07$).

4.1.4 Progression-free survival (which was defined as time from randomisation until tumour progression or death) was measured in two of the studies. In both, there was a statistically significant difference in median progression-free survival. In the study comparing bevacizumab and IFL with IFL alone, the median progression-free survival was 10.6 months in the bevacizumab arm and 6.2 months in the control arm (HR 0.54, 95% CI 0.45 to 0.66). In the larger of the two studies comparing bevacizumab and 5-FU/LV with 5-FU/LV alone, the median progression-free survival was 9.2 months in the bevacizumab arm and 5.5 months in the control arm (HR 0.50, 95% CI 0.34 to 0.73). The smaller study that used 5-FU/LV as a comparator reported the median time to disease progression. There was a statistically significant difference favouring the bevacizumab arm over the control arm (9.0 months vs 5.2 months, respectively [HR 0.44, 95% CI not reported; $p=0.005$]).

4.1.5 All three studies measured tumour response rate (as partial or complete reduction in tumour size). In two studies, the differences in tumour response rate reached statistical significance. In the study with IFL as a comparator, the tumour response rate in the bevacizumab arm was 44.8% compared with 34.8% in the control arm (incremental difference 10.0%, 95% CI 3.3 to 16.7). In the smaller study that used 5-FU/LV as a comparator, the tumour response rate was 40.0% in the bevacizumab arm and 16.7% in the control arm (incremental difference 23.3%, 95% CI not reported; $p = 0.029$). In the larger study that used 5-FU/LV as a comparator, the difference in tumour response rate did not reach statistical significance (26.0% and 15.2% for treatment and control arms, respectively [incremental difference 10.8%, 95% CI not reported; $p = 0.055$]).

4.1.6 In all the studies there was a higher incidence of grade 3 and 4 adverse events in the groups receiving bevacizumab compared with the control groups:

- 84.9% vs 74.0%, respectively, with IFL as the comparator
- 74.3% vs 54.3% in the smaller study with 5-FU/LV as the comparator

- 87% vs 71% in the larger study with 5-FU/LV as the comparator.

Higher incidences of grade 3 and 4 hypertension were also reported in the groups receiving bevacizumab compared with the control groups:

- 11.0% vs 2.3%, respectively, with IFL as the comparator
- 8.6% vs 0% in the smaller study with 5-FU/LV as the comparator
- 16% vs 3% in the larger study with 5-FU/LV as the comparator.

For other grade 3 and 4 toxicities there were no consistent patterns of effects. An increased incidence of diarrhoea was reported in the study that used IFL as the comparator (32.4% vs 24.7%), and there was an increased incidence of thrombotic events in the smaller study that used 5-FU/LV as the comparator (14.3% vs 2.9%).

Cetuximab

- 4.1.7 The assessment group identified no studies that compared cetuximab with current standard treatments (which in the case of second- and subsequent-line treatment are FOLFOX and active/best supportive care [ASC/BSC], respectively). One RCT, the BOND study, was identified in which cetuximab combined with irinotecan was compared with cetuximab monotherapy (n = 329). In this study participants in the monotherapy arm could have irinotecan added to their treatment regimen upon disease progression. Three single-arm studies were also identified, of which two measured the effect of cetuximab monotherapy (one with 346 participants and one with 57 participants) and one measured the effect of cetuximab combined with irinotecan (n = 138). The primary outcome for all studies was tumour response rate. A median age of 56 years was reported in two of the trials and a median age of 59 years in the other two. In all four studies the populations tended to have good performance status (ECOG 0 to 1 or Karnofsky 80 to 100).
- 4.1.8 In the RCT there was no statistically significant difference in median overall survival between treatment groups. The median overall survival was 8.6 months in the cetuximab plus irinotecan arm and 6.9 months in the cetuximab monotherapy arm (HR 0.91, 95% CI 0.68 to 1.21). In the single-arm studies of cetuximab monotherapy, the median survival duration was 6.6 months (95% CI 5.6 to 7.6) in the larger and 6.4 months (95% CI 4.1 to 10.8) in the smaller study. In the single-arm study of cetuximab plus irinotecan, median overall survival

duration was 8.4 months (95% CI 7.2 to 10.3).

- 4.1.9 In the RCT there was a statistically significant difference in median time to progression between treatment groups. The median time to progression was 4.1 months in the cetuximab combined with irinotecan arm and 1.5 months in the cetuximab monotherapy arm (HR 0.54, 95% CI 0.42 to 0.71). Median time to progression was reported in two of the single-arm studies: 1.4 months (95% CI 1.3 to 2.8) in the larger cetuximab monotherapy study and 2.9 months (95% CI 2.6 to 4.1) for cetuximab combined with irinotecan.
- 4.1.10 All four cetuximab studies measured tumour response rate. In the RCT there was a statistically significant difference between treatment groups. The tumour response rate was 22.9% in the cetuximab combined with irinotecan arm and 10.8% in the cetuximab monotherapy arm (incremental difference 12.1%, 95% CI 4.1 to 20.2). The rates of response in the single-arm studies were 8.8% (95% CI 2.9 to 19.3) and 12.0% (95% CI 8.4 to 15.4) in the two cetuximab monotherapy studies and 15.2% (95% CI 9.7 to 22.3) in the study that combined cetuximab with irinotecan. The Institute also received data, following completion of the assessment report, from three additional single-arm studies of cetuximab. In two of these studies all patients had received two prior chemotherapy regimens. Results from these studies confirmed the effect seen in other studies of cetuximab.
- 4.1.11 Data from the manufacturer's submission suggest that the response to cetuximab may be associated with an acne-like rash. Post hoc analyses of pooled data from the two studies in which patients received cetuximab combined with irinotecan (combined total of 339 patients) show 153 patients had stable disease at 6 weeks, of whom 50% had an acne-like rash of grade 2 or above (n = 76). Of these, 26% (n = 20) went on to have a partial response compared with 13% (n = 10) of those without an acne-like rash of grade 2 or above (p = 0.043).
- 4.1.12 Data from the RCT show that patients in the cetuximab plus irinotecan arm with an acne-like rash of grade 2 or above had an overall survival of 10.8 months compared with 5.8 months for those with either no rash or a grade 1 rash. In the single-arm study of cetuximab plus irinotecan, patients who had a grade 3 acne-like rash had a median survival of 13.1 months, compared with 10.6 months for those with a grade 2 rash, 6.2 months for those with a grade 1 rash and

4.3 months for those with no rash ($p = 0.0008$, grade 0 vs grade 1–3).

4.1.13 In the RCT the incidence of some adverse events was higher in patients receiving cetuximab plus irinotecan compared with those receiving cetuximab alone: grade 3 and 4 adverse events (65.1% vs 43.5%); diarrhoea (21.2% vs 1.7%); neutropenia (9.4% vs 0%); grade 3 or 4 acne-like rash (9.4% vs 5.2%).

4.2 *Cost effectiveness*

4.2.1 No published economic analyses of either bevacizumab or cetuximab were identified. The manufacturers of bevacizumab and cetuximab both submitted cost-effectiveness models, and the assessment group developed two models for each drug.

Bevacizumab – manufacturer's models

4.2.2 The manufacturer submitted two simple-state transition models with three health states: pre-progression, post-progression and death. Each model was based on data from a different bevacizumab study. The first was based on the study that compared bevacizumab plus IFL with IFL, while the second was based on the larger of the two studies that compared bevacizumab plus 5-FU/LV with 5-FU/LV. In both models the analysis was carried out from the perspective of the NHS. Data on progression-free survival for the treatment and control arms were taken from trial data, and an equal risk of death was applied following progression irrespective of treatment group. The models assumed equivalent utility scores for both the intervention and control groups, with a utility of 0.80 given to the pre-progression health state and 0.50 to the post-progression health state. Utility decrements associated with adverse events were not included. Pre-progression costs were calculated from the trials, augmented with data from other published sources. For post-progression costs an assumption of £2000 a month was used, applied equally to both arms.

4.2.3 With discounting of 6% for costs and 1.5% for benefits, the cost per quality-adjusted life year (QALY) gained was £88,364 for bevacizumab combined with IFL compared with IFL alone. With the same discounts, the cost per QALY gained for bevacizumab combined with 5-FU/LV was £56,628 compared with 5-FU/LV alone. One-way sensitivity analyses resulted in estimates of cost per QALY gained of between £82,577 and £106,770 for bevacizumab combined

with IFL, and between £39,136 and £69,439 for bevacizumab combined with 5-FU/LV. Probabilistic sensitivity analyses suggest that the likelihood of cost effectiveness at a willingness-to-pay of £30,000 per QALY is 0.16 for bevacizumab combined with IFL, and 0.24 for bevacizumab combined with 5-FU/LV.

Bevacizumab – assessment group models

- 4.2.4 The methods used for the models produced by the assessment group were similar to those used in the NICE appraisal of irinotecan, oxaliplatin and raltitrexed (NICE technology appraisal 93). The assessment group presented two models based on the same trials as used in the manufacturer's models. The models were simple-state transition models with costs and effects calculated from the perspective of the NHS. Unlike the manufacturer's models the outcome data were based on published overall survival curves from the two studies. The utility value for pre-progression was the same as was used in the manufacturer's models (0.80), whereas that for post-progression was slightly higher (0.60). Data on second-line and subsequent therapies were taken from a study that investigated the optimal sequence of FOLFOX and FOLFIRI as first- and second-line therapies, and were applied equally to treatment and control groups. Costs were calculated from study data and augmented from a range of sources including published literature and personal communications. Discounting was not used because the distribution of costs incurred over time was unknown and was not considered relevant by the assessment group because of the short time horizon in the model.
- 4.2.5 The base-case costs per QALY gained for the assessment group models were £62,857 for bevacizumab combined with IFL and £88,436 for bevacizumab combined with 5-FU/LV, compared with IFL or 5-FU/LV alone, respectively. One-way sensitivity analyses of the base case produced a cost per QALY gained of £60,430–£76,831 for bevacizumab combined with IFL, and £51,355 and higher for bevacizumab combined with 5-FU/LV. Probabilistic sensitivity analyses suggest that, with a willingness-to-pay threshold of £30,000, the likelihood of bevacizumab being cost effective is zero.
- 4.2.6 The differences in the cost per QALY gained between the assessment group's model and the manufacturer's model are likely to have been caused by the difference in the methods used to calculate survival. The manufacturer's model

resulted in more favourable estimates of the cost per QALY than did the assessment group's model when the comparator was 5-FU/LV because the difference in progression-free survival was greater than the difference in mean overall survival. Conversely, the assessment group's model resulted in more favourable cost per QALY estimates when the comparator was IFL, because the difference in overall survival was greater than the difference in progression-free survival.

Cetuximab – manufacturer's model

- 4.2.7 The manufacturer's model for cetuximab used survival modelling to estimate the lifetime costs and benefits for patients receiving cetuximab combined with irinotecan compared with ASC/BSC. Two sets of analyses were presented. The first was based directly on survival data from the RCT, whereas in the second analysis adjustments were made to the survival data to reflect a proposed continuation rule. Under the continuation rule patients would only continue to receive cetuximab beyond 6 weeks if there were either a partial or complete tumour response or an acne-like rash of grade 2 or above.
- 4.2.8 The duration of survival of patients receiving cetuximab combined with irinotecan was extrapolated from data in the RCT. The survival of patients receiving ASC/BSC was calculated from the survival of the patients in the cetuximab monotherapy arm of the RCT. The data from the monotherapy arm were adjusted to remove the impact of cetuximab using an HR taken from an RCT of second-line irinotecan compared with ASC/BSC. Therefore the model assumes that the relative hazard of overall survival between cetuximab monotherapy and ASC/BSC as second-line and subsequent treatment is exactly equivalent to the relative survival hazard between irinotecan and ASC/BSC as second-line treatment. The modelling was carried out from the perspective of the NHS, with costs and resource data taken from the RCT comparing cetuximab monotherapy with cetuximab plus irinotecan and augmented from the published literature. Outcomes were presented as life years gained, with sensitivity analyses to examine the impact of quality of life using alternative utilities for metastatic colorectal cancer of 0.95 and 0.71, both constant over the lifetime and based on published data. Additional data were presented using a utility of 0.73, constant over the lifetime, based on data collected as part of a single-arm study that investigated the effectiveness of cetuximab as a second- and subsequent-line treatment for patients with metastatic colorectal cancer

(MABEL). Costs and benefits were discounted at an annual rate of 3.5%.

- 4.2.9 The base-case analysis suggests a cost per life year gained of £33,263 if the continuation rule were applied. One-way sensitivity analyses with the application of the continuation rule result in cost per QALY estimates of £35,014 with a utility value of 0.95 and £45,566 with a utility value of 0.73. Without the continuation rule, cost per QALY estimates are £45,237 and £58,870 respectively. Cost-effectiveness acceptability curves suggest that at a willingness-to-pay threshold of £30,000 per life year gained the likelihood of cost effectiveness is 0.10.

Cetuximab assessment group models

- 4.2.10 In the absence of direct comparisons of cetuximab plus irinotecan with ASC/BSC or FOLFOX, the assessment group developed two models. The first was a threshold analysis considering the incremental benefit that cetuximab combined with irinotecan would have to provide over ASC/BSC in order to be considered cost effective. The second model was an indirect comparison of data from the arm receiving cetuximab and irinotecan in the RCT with data from other published studies of second-line ASC/BSC.
- 4.2.11 In both models overall survival for patients receiving cetuximab was estimated from patient-level data in the RCT. In the threshold analysis, the survival of patients receiving ASC/BSC was held as an unknown variable, whereas in the indirect comparisons different values for overall survival, ranging from 6 to 9 months, were taken from three published studies. Health-related quality of life was estimated in the same way as in the bevacizumab model, applying a utility of 0.80 to pre-progression disease states and 0.60 to post-progression states. For the cetuximab arm, measures of the duration of pre-progression survival as a proportion of overall survival were estimated using data from the RCT. For the comparator arm, they were derived from a trial that compared tipifarnib (a farnesyl transferase inhibitor) with BSC in refractory advanced colorectal cancer. In this study the duration of pre-progression survival was approximately 37% of overall survival. Resource use and costs were taken from the RCT as reported in the manufacturer's submission and augmented from the published literature and personal communication with clinical experts. Discounting was not used in the model because the distribution of costs incurred over time was unknown and was not considered relevant by the

assessment group because of the short time horizon in the model.

4.2.12 The base-case threshold analysis suggests it is not possible for cetuximab combined with irinotecan to have a cost per QALY gained of less than £20,000, irrespective of the application of the continuation rule. When the proposed continuation rule is applied, cetuximab plus irinotecan must provide 0.65 additional life years (7.8 months) compared with ASC/BSC in order to achieve a cost per QALY gained of £30,000. This would imply that survival for patients receiving ASC/BSC would have to be 0.14 life years (1.7 months) or less. It was not possible to achieve a cost per QALY gained of less than £30,000 without the continuation rule. A sensitivity analysis using utility values from the MABEL study suggested that with the continuation rule applied cetuximab plus irinotecan must provide 0.60 additional life years (7.2 months) compared with ASC/BSC in order to achieve a cost per QALY gained of £30,000. Indirect comparisons are associated with a high level of uncertainty, but they yielded estimates of the cost per QALY gained that ranged from £77,210 to £370,044.

4.3 *Consideration of the evidence*

4.3.1 The Committee reviewed the data available on the clinical and cost effectiveness of bevacizumab and cetuximab for metastatic colorectal cancer, having considered evidence on the nature of the condition and the value placed on the benefits of bevacizumab and cetuximab by people with metastatic colorectal cancer, those who represent them, and clinical experts. It was also mindful of the need to take account of the effective use of NHS resources.

4.3.2 The Committee heard from clinical specialists that it is accepted that multiple chemotherapy treatments lead to incremental gains in survival if patients are sufficiently fit to receive therapy. The Committee further heard from clinical specialists that treatment regimens frequently involve combination therapy of 5-FU/FA either with irinotecan or with oxaliplatin as first-line therapies, followed, where patients are sufficiently fit, by irinotecan as a second-line therapy where oxaliplatin has been given and by oxaliplatin plus 5-FU/FA as a second-line therapy where irinotecan has been given. The experts suggested that it would be of merit to add further options and lines of therapy to this sequence.

Bevacizumab

- 4.3.3 The Committee reviewed the clinical effectiveness evidence from the bevacizumab studies and noted that the age of the population in the largest study was lower than the age of patients normally receiving chemotherapy in England and Wales. However, clinical specialists agreed that fitness, rather than age, is the primary factor when considering whether chemotherapy is appropriate. The Committee therefore agreed that the patients included in the bevacizumab trials could be considered to reflect a population of relatively fit patients with metastatic colorectal cancer in England and Wales.
- 4.3.4 The Committee noted that all bevacizumab studies demonstrated statistically significant gains in progression-free survival and that some studies also demonstrated statistically significant gains in overall survival and tumour response rate. However, the Committee noted that the comparators in the studies cannot be considered current standard practice in the NHS in England and Wales because the 5-FU treatment schedules involved administration by bolus rather than administration by infusion. It heard from clinical specialists that the benefits associated with bevacizumab in combination with bolus 5-FU are expected to be seen in infusional regimens because the two drugs have different mechanisms of action and their effects are therefore likely to be independent. This was also said to be supported by interim results from ongoing clinical studies. The Committee was therefore persuaded that the results seen in the studies could be considered generalisable to NHS practice in England and Wales.
- 4.3.5 The Committee then considered the estimates of cost effectiveness of bevacizumab. It noted that the models from the manufacturer and from the assessment group were similar in their methods and data sources; the models differed chiefly in their use of progression-free survival and overall survival, respectively, as the primary outcome data. The Committee noted that this difference resulted in different estimates of cost effectiveness from the manufacturer and the assessment group. However, the Committee considered that neither source resulted in a cost-effectiveness estimate that was compatible with the best use of NHS resources. The Committee noted that a proposal from the manufacturer for a registry programme could not be taken into further consideration because the Committee had been informed of imminent additional license extensions for bevacizumab, which would need to

be taken into account of in any such scheme. It concluded that bevacizumab in combination with 5-FU/FA, with or without irinotecan as a first-line treatment for metastatic colorectal cancer would not be a cost-effective use of NHS resources.

Cetuximab

- 4.3.6 The Committee considered the clinical effectiveness evidence from the cetuximab studies. The Committee understood that cetuximab plus irinotecan could be given in its current licensed indication either as a second-line treatment following failure of an irinotecan-containing regimen or as a subsequent-line treatment following failure of both irinotecan- and oxaliplatin-containing regimens. The Committee recognised that in both cases, some patients may still have a high performance status, meaning that further chemotherapy regimens could be considered appropriate.
- 4.3.7 The Committee was concerned that there were no studies that compared cetuximab with current standard care either in second- or subsequent-line therapy, or with any therapy not including cetuximab. The Committee noted that there were currently no clinical studies available comparing cetuximab with FOLFOX, and therefore the relative clinical effectiveness of cetuximab as a second-line treatment could not as yet be determined. The Committee heard testimonies from clinical specialists that subsequent to second-line treatment progression-free survival and tumour response would be negligible if further active treatment was not available. Therefore the results seen in the single-arm cetuximab studies for these outcomes could be interpreted as an effect of the drug. It also heard that clinical specialists believed that cetuximab, in this situation, where no other active treatment was available, could prolong survival for a number of months if the disease responded to the drug. The Committee was therefore persuaded that cetuximab in this situation demonstrated some evidence of effectiveness. However, the relative effectiveness against current standard care remains uncertain.
- 4.3.8 The Committee heard from patient experts and clinical specialists about the impact of the acne-like rash associated with treatment on patients' quality of life. They heard from patient experts that, for some patients, the side effects of the drugs were tolerated willingly because of the perceived benefit, whereas for others the side-effect profile may be more of a consideration. The Committee

heard from clinical specialists that the acne-like rash was generally well managed with antibiotics, treatment breaks or dose reduction. The Committee was therefore satisfied that the side-effect profile of cetuximab should not be a determining factor in its deliberations.

- 4.3.9 The Committee noted the contradiction that although the UK marketing authorisation stipulates that patients need to be tested for the presence of EGFR, a positive test for the presence of EGFR did not predict response to treatment. The Committee heard from clinical specialists that there is increasing knowledge of the mechanism of action of cetuximab and that it is now thought that the antibody identified through EGFR testing is different from the one targeted by cetuximab. The Committee noted the difficulties in identifying patients who were likely to respond to cetuximab, but was fully aware that decisions about its use in the NHS would have to be based on the current marketing authorisation.
- 4.3.10 The Committee considered the continuation rule proposed by the manufacturer. The Committee expressed concern about conflicts with the SPC, but it agreed that this would only be an issue for the small proportion of patients who experience grade 3 and 4 acne rash. Although it acknowledged that there was some evidence to suggest that the presence of a rash may predict response to cetuximab, the Committee had reservations about using it to decide whether to continue or discontinue treatment because no studies have so far tested prospectively this continuation rule.
- 4.3.11 The Committee considered the cost-effectiveness evidence for cetuximab. It noted that the economic modelling from both the manufacturer and the assessment group had been completed using effectiveness data from the RCT of cetuximab where approximately 80% of patients received cetuximab plus irinotecan as a third-line or subsequent therapy. It was also aware that the comparator used in both models was ASC/BSC, which meant the modelled scenario and corresponding estimates of cost effectiveness more closely resembled third-line or subsequent use of cetuximab rather than second-line use.
- 4.3.12 The Committee discussed the uncertainties around the estimates of utility for patients with metastatic colorectal cancer. The manufacturer had provided estimates between 0.95 and 0.71, both constant over the lifetime of the patient.

The Committee considered that the utility for a patient with metastatic colorectal cancer was more likely to reflect the lower end of this range, based on additional data submitted by the manufacturer from the MABEL study. The Committee concluded that, using the most realistic utility estimates, the cost-effectiveness estimates provided by both the manufacturer and the assessment group were not compatible with the best use of NHS resources. The Committee also noted that these estimates were associated with a high level of uncertainty because they were based on indirect comparisons.

4.3.13 The Committee therefore considered threshold analyses completed by the assessment group, where the survival in the comparator arm was held as unknown. The base-case threshold analysis suggested that, with the application of the continuation rule, a cost per QALY gained of £30,000 could only be achieved if survival with ASC/BSC is less than 2 months. A sensitivity analysis adjusting the assumptions to reflect utility values from the MABEL study did not materially alter the results. The Committee noted that the manufacturer had provided an estimate of mean survival of 5.6 months for patients receiving ASC/BSC in their economic model, while studies of ASC/BSC identified in the assessment report provided estimates of median survival ranging from 6 to 9 months. The Committee therefore considered that an estimate of mean survival while receiving ASC/BSC of approximately 2 months was an unrealistic underestimate. Considering all the available evidence on clinical and cost effectiveness, the Committee therefore concluded that cetuximab, either as a second-line or a subsequent-line treatment for metastatic colorectal cancer would not be a cost-effective use of NHS resources.

5 Implementation

- 5.1 The Healthcare Commission assesses the performance of NHS organisations in meeting core and developmental standards set by the Department of Health in 'Standards for better health' issued in July 2004. The Secretary of State has directed that the NHS provides funding and resources for medicines and treatments that have been recommended by NICE technology appraisals normally within 3 months from the date that NICE publishes the guidance. Core standard C5 states that healthcare organisations should ensure they conform to NICE technology appraisals.
- 5.2 'Healthcare Standards for Wales' was issued by the Welsh Assembly Government in May 2005 and provides a framework both for self-assessment by healthcare organisations and for external review and investigation by Healthcare Inspectorate Wales. Standard 12a requires healthcare organisations to ensure that patients and service users are provided with effective treatment and care that conforms to NICE technology appraisal guidance. The Assembly Minister for Health and Social Services issued a Direction in October 2003 which requires Local Health Boards and NHS Trusts to make funding available to enable the implementation of NICE technology appraisal guidance, normally within 3 months.
- 5.3 NICE has developed tools to help organisations implement this guidance (listed below).
- Audit criteria to monitor local practice.

6 Recommendations for further research

6.1 The Committee noted the following ongoing clinical trials related to this guidance.

- NCT00063141 is an RCT comparing cetuximab combined with irinotecan with irinotecan alone as second-line treatment in patients with metastatic colorectal cancer.
- NCT00079066 is an RCT comparing cetuximab combined with best supportive care with best supportive care alone in patients with metastatic colorectal cancer.

6.2 The Committee was aware of other ongoing clinical trials with bevacizumab and cetuximab as part of different treatment regimens.

- The TREE-2 trial is a randomised multicentre study comparing three regimens of oxaliplatin plus bolus, infusional or oral 5-FU with bevacizumab to evaluate safety and tolerability in the first-line treatment of patients with advanced colorectal cancer.
- The NO16966C trial is a randomised phase III study of intermittent oral capecitabine in combination with intravenous oxaliplatin (CAPOX) with or without bevacizumab for the first-line treatment of patients with advanced colorectal cancer.
- The CONcePT trial aims to develop an optimised schedule of administration of FOLFOX plus bevacizumab in the first-line treatment of patients with advanced colorectal cancer.
- The E3200 trial is a phase III RCT of oxaliplatin, 5-FU and leucovorin with or without bevacizumab, versus bevacizumab alone in patients previously treated for advanced or metastatic colorectal cancer. Preliminary data have been presented. The bevacizumab monotherapy arm was prematurely halted because of lack of efficacy.
- The first-line use of cetuximab in combination with standard chemotherapy regimens is being investigated in a number of studies. One example is the COIN study (NCT00182715), which aims to determine whether the addition of cetuximab to continuous oxaliplatin and 5-FU improves overall survival when compared with either continuous oxaliplatin and 5-FU on its own, or intermittent oxaliplatin and fluoropyrimidine chemotherapy. Other examples include NCT00145314 (5-FU/FA + oxaliplatin), NCT00286130 (FOLFIRI, FOLFOX) and NCT00215722 (capecitabine and oxaliplatin).

- EXPLORE is an RCT comparing cetuximab combined with FOLFOX with FOLFOX alone as second-line treatment in patients with metastatic colorectal cancer. Recruitment to the trial was halted prematurely when the number of participants reached 102. Preliminary results were presented at the annual conference of the American Society for Clinical Oncology in 2005 for progression-free survival and response rate.
- 6.3 The Committee recommends research to investigate the predictive value of EGFR testing and the correlation of baseline and on-treatment markers with tumour response and survival.
- 6.4 Additionally, the Committee recommends studies to investigate the impact of bevacizumab and cetuximab treatment on health-related quality of life.

7 Related guidance

7.1 NICE has issued the following related guidance.

- Irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer. NICE technology appraisal guidance 93 (2005).[Replaced by [NICE clinical guideline 131](#)]
- [Improving outcomes in colorectal cancers: manual update](#). NICE cancer service guidance (2004).
- [Guidance on the use of capecitabine and tegafur with uracil for metastatic colorectal cancer](#). NICE technology appraisal guidance 61 (2003).

8 Review of guidance

- 8.1 The review date for a technology appraisal refers to the month and year in which the Guidance Executive will consider whether the technology should be reviewed. This decision will be taken in the light of information gathered by the Institute, and in consultation with consultees and commentators.
- 8.2 The guidance on this technology was considered for review in January 2010. Details are on the [NICE website](#).

Andrew Dillon
Chief Executive
January 2007

Appendix A. Appraisal Committee members and NICE project team

A. Appraisal Committee members

The Appraisal Committee is a standing advisory committee of the Institute. Its 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. The Appraisal Committee meets regularly and membership is split into two branches, with the chair, vice-chair and a number of other members attending meetings of both branches. Each branch considers its own list of technologies and ongoing topics are not moved between the branches.

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 Darren Ashcroft

Senior Clinical Lecturer, School of Pharmacy and Pharmaceutical Sciences, University of Manchester

Professor David Barnett

Professor of Clinical Pharmacology, University of Leicester

Dr Peter Barry

Consultant in Paediatric Intensive Care, Leicester Royal Infirmary

Mr Brian Buckley

Vice Chairman, InContact

Professor John Cairns

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

Professor Mike Campbell

Statistician, University of Sheffield

Professor David Chadwick

Professor of Neurology, Walton Centre for Neurology and Neurosurgery

Dr Mark Chakravarty

Head of Government Affairs and NHS Policy, Procter and Gamble Pharmaceuticals (UK) Ltd

Dr Peter I Clark

Consultant Medical Oncologist, Clatterbridge Centre for Oncology, Merseyside

Dr Mike Davies

Consultant Physician, University Department of Medicine & Metabolism, Manchester Royal Infirmary

Mr Richard Devereaux-Phillips

Public Affairs Manager, Medtronic Ltd

Professor Jack Dowie

Health Economist, London School of Hygiene

Dr Fergus Gleeson

Consultant Radiologist, The Churchill Hospital, Oxford

Ms Sally Gooch

Former Director of Nursing & Workplace Development, Mid Essex Hospital Services NHS Trust

Mr Sanjay Gupta

Stroke Services Manager, Basildon and Thurrock University Hospitals NHS Trust

Professor Philip Home

Professor of Diabetes Medicine, University of Newcastle upon Tyne

Dr Peter Jackson

Clinical Pharmacologist, University of Sheffield

Professor Peter Jones

Professor of Statistics and Dean of the Faculty of Natural Sciences, Keele

Dr Mike Laker

Medical Director, Newcastle Hospitals NHS Trust

Dr George Levvy

Chief Executive, Motor Neurone Disease Association

Ms Rachel Lewis

Nurse Advisor to the Department of Health

Mr Terence Lewis

Mental Health Consultant, National Institute for Mental Health in England

Professor Jonathan Michaels

Professor of Vascular Surgery, University of Sheffield

Dr Neil Milner

General Medical Practitioner, Sheffield

Dr Ruairidh Milne

Senior Lecturer in Health Technology Assessment, National Coordinating Centre for Health Technology

Dr Rubin Minhas

General Practitioner, CHD Clinical Lead, Medway Primary Care Trust

Dr Rosalind Ramsay

Consultant Psychiatrist, Adult Mental Health Services, Maudsley Hospital

Mr Miles Scott

Chief Executive, Bradford Teaching Hospitals NHS Foundation Trust

Dr Lindsay Smith

General Practitioner, East Somerset Research Consortium

Mr Roderick Smith

Director of Finance, Adur, Arun and Worthing Primary Care Trust

Dr Ken Stein

Senior Lecturer, Peninsula Technology Assessment Group (PenTAG), University of Exeter

Professor Andrew Stevens (Chair)

Professor of Public Health, University of Birmingham

B. NICE Project Team

Each appraisal of a technology is assigned to a Health Technology Analyst and a Technology Appraisal Project Manager within the Institute.

Zoe Garrett

Technical Lead, NICE project team

Elisabeth George

Technical Adviser, NICE project team

Emily

Project Manager, NICE project team

Appendix B. Sources of evidence considered by the Committee

A. The assessment report for this appraisal was prepared by School of Health and Related Research (ScHARR), The University of Sheffield:

I) Tappenden P, Jones R, Paisley S, Carroll C. The use of bevacizumab and cetuximab for the treatment of metastatic colorectal cancer, 21 February 2006.

B. The following organisations accepted the invitation to participate in this appraisal. They were invited to make submissions and comment on the draft scope, assessment report and the appraisal consultation document (ACD). Consultee organisations are provided with the opportunity to appeal against the final appraisal determination.

II) Manufacturers/sponsors:

III) Professional/specialist and patient/carer groups:

IV) Commentator organisations (without the right of appeal):

B. The following individuals were selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups. 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 and cetuximab for metastatic colorectal cancer by attending the initial Committee discussion and/or providing written evidence to the Committee. They were also invited to comment on the ACD.

Changes after publication

March 2014: minor maintenance

March 2012: minor maintenance

January 2012: This guidance has been partially updated by NICE technology appraisal guidance 242 (TA242) [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). See the guidance for more information.

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.

The recommendations from this guideline have been incorporated into a [NICE Pathway](#). 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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