NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

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)

Final Scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of cetuximab (mono- or combination chemotherapy), bevacizumab (combination with non-oxaliplatin chemotherapy) and panitumumab (monotherapy) within their licensed indications for the treatment of metastatic colorectal cancer after first-line chemotherapy.

Background

Colorectal cancer is a malignant neoplasm arising from the lining of the large intestine (colon and rectum). Approximately 34,000 new cases of colorectal cancer were diagnosed in England and Wales in 2007, and approximately 14,000 deaths registered in 2008. The median age of patients at diagnosis is over 70 years.

In metastatic colorectal cancer the tumour has spread beyond the confines of the locoregional lymph nodes to other parts of the body. This is described as stage IV of the American Joint Committee on Cancer (AJCC) tumour node metastases (TNM) system or stage D of Dukes' classification. Between 20% and 55% of people first diagnosed with colorectal cancer have metastatic disease. In addition, approximately 50% to 60% of patients who have undergone surgery for early stage colorectal cancer with apparently complete excision will eventually develop advanced disease and distant metastases (typically presenting within 2 years of initial diagnosis). The 5-year survival rate for metastatic colorectal disease is 12%.

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.

NICE currently recommends oxaliplatin in combination with infusional 5-fluorouracil plus folinic acid (FOLFOX) and irinotecan in combination with infusional 5-fluorouracil plus folinic acid (FOLFIRI) as first-line treatment options for advanced colorectal cancer. FOLFOX or irinotecan alone are

recommended as subsequent therapy options (technology appraisal 93). The oral analogues of 5-fluorouracil, capecitabine and tegafur, in combination with uracil (and folinic acid) are also recommended as first-line treatment options for metastatic colorectal cancer (technology appraisal 61).

Cetuximab in combination with FOLFOX, or in combination with FOLFIRI, is recommended as an option for the first-line treatment of metastatic colorectal cancer where the metastatic disease is confined to the liver and the aim of treatment is to make the metastases resectable (technology appraisal 176).

In technology appraisal 118, bevacizumab in combination with 5-fluorouracil plus folinic acid, with or without irinotecan, as a first-line treatment and cetuximab in combination with irinotecan, as a second and subsequent line treatment were not recommended for metastatic colorectal cancer.

In technology appraisal 150, NICE was unable to recommend the use of cetuximab for the treatment of colorectal cancer following failure of oxaliplatin-containing chemotherapy because no evidence submission was received from the manufacturer of the technology (terminated appraisal).

The technologies

Cetuximab (Erbitux, Merck Serono) is a recombinant monoclonal antibody that blocks the human epidermal growth factor receptor (EGFR), inhibiting the growth of tumours expressing EGFR. Cetuximab has a UK marketing authorisation for the treatment of patients with EGFR-expressing, KRAS wild-type metastatic colorectal cancer either in combination with chemotherapy; or as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan.

Bevacizumab (Avastin, Roche Products) is a recombinant monoclonal antibody that acts as an angiogenesis inhibitor by targeting the biologic activity of human vascular endothelial growth factor (VEGF), which stimulates new blood vessel formation in the tumour. It has a UK marketing authorisation in combination with fluoropyrimidine-based chemotherapy for the treatment of patients with metastatic carcinoma of the colon or rectum.

Panitumumab (Vectibix, Amgen) is a recombinant monoclonal antibody that blocks the EGFR, inhibiting the growth of tumours expressing EGFR. It has a UK marketing authorisation as monotherapy for the treatment of EGFR expressing metastatic colorectal cancer with non-mutated (wild-type) KRAS after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens.

Intervention(s)	• cetuximab (monotherapy or in combination with chemotherapy) • bevacizumab (in combination with

	chemotherapy not containing oxaliplatin) • panitumumab (monotherapy)
Population(s)	• People with EGFR-expressing and KRAS wild-type metastatic colorectal cancer that has progressed after first-line chemotherapy (cetuximab & panitumumab population) • People with metastatic colorectal cancer that has progressed after first-line chemotherapy (bevacizumab population)
Comparators	• Irinotecan- or oxaliplatin-based chemotherapy regimens. • Where appropriate, the interventions will be compared with each other. • Best supportive care.
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rate • adverse effects of treatment • health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. If evidence allows the appraisal should consider the use of continuation rules based on tumour response. If evidence allows, liver resection rates should be

	considered.
Related NICE recommendations	Related Technology Appraisals: Technology Appraisal, No 176, August 2009, Cetuximab for the first line treatment of metastatic colorectal cancer. Review date: August 2012. Technology Appraisal, No. 150, June 2008. Cetuximab for the treatment of metastatic colorectal cancer following failure of oxaliplatin-containing chemotherapy (terminated appraisal). Under review. Technology Appraisal, No. 118, January 2007. Bevacizumab and cetuximab for the treatment of metastatic colorectal cancer. Under review. Technology Appraisal, No. 93, August 2005 (review of TA33). Irinotecan, oxaliplatin and raltitrexed for advanced colorectal cancer. Currently being incorporated in an on-going clinical guideline, "Diagnosis and management of colorectal cancer". Expected date of publication July 2011. Technology Appraisal, No. 61, May 2003. Capecitabine and tegafur uracil for metastatic colorectal cancer. Moved to static list in April 2006. Technology appraisal in preparation, Bevacizumab in combination with oxaliplatin and either 5-FU or capecitabine for the treatment of metastatic colorectal cancer. Expected date of publication December 2010 Technology Appraisal in Preparation, Panitumumab in combination with chemotherapy within its licensed indication for the treatment of metastatic colorectal cancer. Earliest anticipated date of publication tbc. Related Guidelines: Clinical Guideline in preparation, Diagnosis and management of colorectal and anal cancer. Expected date of publication: October 2011 Guidance on Cancer Services, June 2004, Improving outcomes in colorectal cancers.