NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

The use of bevacizumab and cetuximab for the treatment of metastatic colorectal cancer

Final Scope

Objective:
To establish the clinical and cost effectiveness of bevacizumab (Avastin, Roche Products Ltd), and cetuximab (Erbitux, Merck Pharmaceuticals) for the treatment of metastatic colorectal cancer, and to provide guidance to the NHS in England and Wales[i].

Background:
Colorectal cancer is a malignant neoplasm arising from the lining (mucosa) of the large intestine (colon and rectum). Metastatic colorectal cancer is generally defined as stage IV of the American Joint Committee on Cancer (AJCC or TNM) system or stage D of the Dukes' classification.

Colorectal cancer is the third most common cancer in the UK, with almost 30,000 new cases registered in England and Wales in 2001, representing 12% of all new cancer cases. Colorectal cancer predominantly affects older people and over half of all deaths occur in people older than 75 years of age. Approximately 30% of those individuals diagnosed with colorectal cancer present with the advanced disease. Approximately 30% of those individuals who do not have the advanced disease at presentation will subsequently develop this condition. The 5-year survival rate of advanced colorectal cancer is, on average, less than 5%.

The technologies:
Bevacizumab is a recombinant humanized monoclonal IgG1 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. Bevacizumab, in combination with intravenous 5-fluorouracil/folinic acid or intravenous 5-fluorouracil/folinic acid/irinotecan, is indicated for first-line treatment of patients with metastatic carcinoma of the colon or rectum.

Cetuximab is a recombinant monoclonal antibody that blocks the human epidermal growth factor receptor (EGFR) and thus inhibits the proliferation of cells dependent on EGFR activation for growth. Cetuximab in combination with irinotecan is indicated for the treatment of patients with EGFR-expressing metastatic colorectal cancer after failure of irinotecan-including cytotoxic therapy.

Intervention(s)	Bevacizumab (in combination with 5-FU/FA or with irinotecan plus 5-FU/FA) Cetuximab (in combination with irinotecan)
Population(s)	For bevacizumab: • People with untreated metastatic colorectal cancer For cetuximab: • People with EGFR-expressing metastatic colorectal cancer who failed irinotecan-including therapy
Current standard treatments (comparators)	For bevacizumab: • established fluorouracil-containing or -releasing regimen For cetuximab: • oxaliplatin in combination with 5-FU/FA by infusion • active/best supportive care (that is without chemotherapy)
Outcomes	Outcomes to be considered include: • Survival • Progression-free survival • Tumour response rate • Time to treatment failure • Adverse events / toxicity • Health-related quality of life
Economic analysis	Ideally, the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. Costs will be considered from an NHS and Personal Social Services perspective.
Other considerations	The interventions will be appraised in accordance with their existing licensed indications. Guidance will only be issued in accordance with the marketing authorisation. It is anticipated that individuals receiving interventions first-line or second-line may

	receive subsequent treatment during clinical trials. Any confounding that results from this should be taken into account if possible particularly with respect to choice of endpoint. Consideration should be given to different methods of delivering treatment such as infusion, bolus injection, or oral regimens.
Related NICE recommendations	**Completed appraisals** Guidance on the use of laparoscopic surgery for colorectal cancer. Technology Appraisal Guidance No. 17. Issued December 2000 Guidance on the use of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer. Technology Appraisal Guidance No. 33. Issued March 2002. Guidance on the use of capecitabine and tegafur with uracil for metastatic colorectal cancer. Technology Appraisal 61. Issued May 2003. **Appraisals in progress** Review of the Guidance on the use of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer. Expected date of issue August 2005. The use of oxaliplatin and capecitabine for the adjuvant treatment of colon cancer. Technology Appraisal. Expected date of issue May 2006. The use of irinotecan for the adjuvant treatment of colon cancer. Technology Appraisal. Expected date of issue January 2007. **Guidelines** Guidance on Cancer Services. Improving Outcomes in Colorectal Cancer. Issued June 2004

[i] Remit of the Department of Health: 'To appraise the clinical and cost effectiveness of irinotecan, oxaliplatin, raltitrexed, cetuximab and bevacizumab in the treatment of advanced colorectal cancer'.