NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal

Cetuximab (review of TA176) and panitumumab (partial review of TA240) for the first line treatment of metastatic colorectal cancer

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of cetuximab and panitumumab within their licensed indications for previously untreated metastatic colorectal cancer (review of technology appraisal 176 and partial review of technology appraisal 240).

Background

Colorectal cancer is a malignant tumour arising from the lining of the large intestine (colon and rectum). Metastatic colorectal cancer refers to disease that has spread beyond the large intestine and nearby lymph nodes. This type of cancer most often spreads first to the liver, but metastases may also occur in other parts of the body including the lungs, brain and bones.

Colorectal cancer is the third most common cancer in England: in 2011, there were 34,000 people diagnosed with colorectal cancer and 12,900 deaths. Between 10% and 25% of people with colorectal cancer have metastatic disease when first diagnosed, and approximately 50% of people who have surgery for early stage disease will eventually develop metastases. The overall 5-year survival rate for metastatic colorectal cancer is 6.6%.

Treatment of metastatic colorectal cancer may involve a combination of surgery, chemotherapy, radiotherapy and supportive care. When possible, surgical removal (resection) or destruction of the primary tumour and metastases may be considered. For people with metastases only in their livers, complete resection appears to offer the best chance of long-term survival, providing 5-year survival rates ranging from 25% to 44%. Chemotherapy is an option to prolong survival and/or to make the primary tumour or metastases suitable for resection. NICE clinical guideline 131 recommends chemotherapy options including fluorouracil and folinic acid in combination with oxaliplatin (FOLFOX), tegafur in combination with fluorouracil and folinic acid, capecitabine in combination with oxaliplatin (XELOX), and capecitabine alone. In practice, fluorouracil and folinic acid may also be used in combination with irinotecan (FOLFIRI) in some people for whom oxaliplatin is not suitable. Chemotherapy may be combined with biological agents such as cetuximab (recommended for some people in technology appraisal 176), panitumumab and bevacizumab (available through the Cancer Drugs Fund).

The choice and effectiveness of some treatments for metastatic colorectal cancer may be influenced by genetic markers. Inhibitors of epidermal growth factor receptor (EGFR), such as cetuximab and panitumumab, appear to be less effective for treating tumours with mutations in genes in the *RAS* family (specifically *KRAS* and *NRAS*) than those without mutations (known as 'wild-type'). Approximately 50% of people with advanced colorectal cancer have mutations in the *KRAS* or *NRAS* genes.

At the time of technology appraisal 176, *RAS* wild-type status was defined based on a single part ('exon') of the *KRAS* gene. After the appraisal, evidence emerged which suggested that identifying further *RAS* genetic markers (the absence of mutations in the *NRAS* gene and in 2 further exons of *KRAS*), may improve the effectiveness of cetuximab and panitumumab. Consequently, the marketing authorisations of both drugs have been updated by the European Medicines Agency, consistent with this evidence, so that they are licensed for a smaller population based on a stricter definition of *RAS* wild-type status. It was therefore agreed to review technology appraisal 176 and partially review technology appraisal 240, to appraise cetuximab and panitumumab within their revised marketing authorisations for treating previously untreated metastatic colorectal cancer.

The technologies

Cetuximab (Erbitux, Merck Serono) is a recombinant monoclonal antibody that blocks EGFR and thereby inhibits the proliferation of tumour cells. It has a marketing authorisation in the UK for use in combination with FOLFOX or irinotecan-based chemotherapy, for treating previously untreated, EGFR-expressing, *RAS* wild-type metastatic colorectal cancer.

Panitumumab (Vectibix, Amgen) is a recombinant, fully human IgG2 monoclonal antibody that binds to EGFR, blocking its signalling pathway and inhibiting the growth of tumours. It has a marketing authorisation in the UK for use in combination with FOLFOX, for treating previously untreated, *RAS* wild-type metastatic colorectal cancer. Clinical trials have also measured the effectiveness of panitumumab in combination with FOLFIRI for previously untreated metastatic colorectal cancer.

The summaries of product characteristics for both cetuximab and panitumumab state that evidence of wild-type *KRAS* and *NRAS* status is required before starting treatment.

Interventions	Cetuximab, in combination with FOLFOX or irinotecan-based chemotherapy Panitumumab, in combination with fluorouracil-containing regimens
Population	People with previously untreated, *RAS* wild-type metastatic colorectal cancer

Comparators	The interventions should be compared with each other, and with: • FOLFOX • XELOX • FOLFIRI • Capecitabine • Tegafur, folinic acid and fluorouracil • Bevacizumab, in combination with oxaliplatin- or irinotecan-based chemotherapy (not recommended by NICE but funded via the Cancer Drugs Fund)
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rate • rate of resection of metastases • 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. The availability of any patient access schemes for the intervention or comparator technologies should be taken into account. Biosimilars are not expected to be in established NHS practice at the time of appraisal and are not included as comparators. Where comparator technologies are available through the Cancer Drugs Fund, the cost incurred by the Cancer Drugs Fund should be used in any economic analyses, rather than the list price.

Other considerations	If evidence allows, consideration may be given to subgroups based on the location of metastases (inside and/or outside the liver). The appraisal will include consideration of the costs and implications of *RAS* mutation testing, but will not make recommendations on specific diagnostic tests or devices. Guidance will only be issued in accordance with the marketing authorisations. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	Related Technology Appraisals: Technology Appraisal No. 242, Jan 2012, 'Cetuximab, bevacizumab and panitumumab for the treatment of metastatic colorectal cancer after first-line chemotherapy (review of TA150 and part review of TA118)'. Review proposal date Jan 2015. Technology Appraisal No. 240, Dec 2011, 'Panitumumab in combination with chemotherapy for the treatment of metastatic colorectal cancer (terminated appraisal)'. Partial review as part of this appraisal. Technology Appraisal No. 212, Dec 2010, 'Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine for the treatment of metastatic colorectal cancer'. Static list. Technology Appraisal No. 176, Aug 2009, 'Cetuximab for the first-line treatment of metastatic colorectal cancer'. Under review as part of this appraisal. Technology Appraisal No. 118, Jan 2007, 'Bevacizumab and cetuximab for the treatment of metastatic colorectal cancer'. Static list. Partial review conducted as part of TA242. Related Guidelines: Clinical Guideline No. 131, Nov 2011, 'The diagnosis and management of colorectal cancer'. An addendum to this guideline is being developed. Review proposal date Dec 2015. Related Interventional Procedures: Interventional Procedures Guidance No. 401, Jul 2011, 'Selective internal radiation therapy for non-resectable

	colorectal metastases in the liver'. Interventional Procedures Guidance No. 327, Dec 2009, 'Radiofrequency ablation for colorectal liver metastases'. Interventional Procedures Guidance No. 201, Dec 2006, 'Preoperative high dose rate brachytherapy for rectal cancer'. Related Quality Standards: Quality Standard No. 20, Aug 2012, 'Quality standard for colorectal cancer'. http://www.nice.org.uk/guidance/qualitystandards/qualitystandards.jsp Related NICE Pathways: NICE Pathway: Colorectal cancer, Pathway created: Nov 2011. http://pathways.nice.org.uk/pathways/colorectal-cancer
Related National Policy	Public Health England, National Screening Committee policy on bowel cancer screening in adults. http://www.screening.nhs.uk/bowelcancer NHS England, Cancer Drugs Fund list: http://www.england.nhs.uk/wp-content/uploads/2014/08/ncdf-list-july14.pdf