

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal

Cetuximab and panitumumab for previously untreated metastatic colorectal cancer (review of TA176 and partial review of TA240)

Draft scope (post-referral)

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 35% to 40% of people with advanced colorectal cancer have mutations in the *KRAS* gene.

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 more targeted 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 (Erbix, 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.

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.

Intervention(s)	Cetuximab, in combination with FOLFOX or irinotecan-based chemotherapy Panitumumab, in combination with FOLFOX
Population(s)	People with previously untreated, <i>RAS</i> wild-type metastatic colorectal cancer

Comparators	<p>The interventions should be compared with each other, and with:</p> <ul style="list-style-type: none"> • FOLFOX • XELOX • FOLFIRI • Capecitabine • Tegafur, folinic acid and fluorouracil • Bevacizumab, in combination with oxaliplatin- or irinotecan-based chemotherapy
Outcomes	<p>The outcome measures to be considered include:</p> <ul style="list-style-type: none"> • overall survival • progression-free survival • response rate • rate of resection of metastases • adverse effects of treatment • health-related quality of life.
Economic analysis	<p>The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.</p> <p>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.</p> <p>Costs will be considered from an NHS and Personal Social Services perspective.</p> <p>The availability of any patient access schemes for the intervention or comparator technologies should be taken into account.</p> <p>Biosimilars are not expected to be in established NHS practice at the time of appraisal and are not included as comparators.</p> <p>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.</p>

<p>Other considerations</p>	<p>If evidence allows, consideration may be given to subgroups based on the location of metastases (inside and/or outside the liver).</p> <p>The appraisal will include consideration of the costs and implications of <i>RAS</i> mutation testing, but will not make recommendations on specific diagnostic tests or devices.</p> <p>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.</p>
<p>Related NICE recommendations and NICE Pathways</p>	<p>Related Technology Appraisals:</p> <p>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.</p> <p>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.</p> <p>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.</p> <p>Technology Appraisal No. 176, Aug 2009, 'Cetuximab for the first-line treatment of metastatic colorectal cancer'. Under review as part of this appraisal.</p> <p>Technology Appraisal No. 118, Jan 2007, 'Bevacizumab and cetuximab for the treatment of metastatic colorectal cancer'. Partial review conducted as part of TA242.</p> <p>Related Guidelines:</p> <p>Clinical Guideline No. 131, Nov 2011, 'The diagnosis and management of colorectal cancer'. Review proposal date Nov 2014.</p> <p>Related Interventional Procedures:</p> <p>Interventional Procedures Guidance No. 401, Jul 2011, 'Selective internal radiation therapy for non-resectable colorectal metastases in the liver'.</p> <p>Interventional Procedures Guidance No. 327, Dec 2009,</p>

	<p>'Radiofrequency ablation for colorectal liver metastases'. Interventional Procedures Guidance No. 201, Dec 2006, 'Preoperative high dose rate brachytherapy for rectal cancer'.</p> <p>Related Quality Standards: Quality Standard No. 20, Aug 2012, 'Quality standard for colorectal cancer'. http://www.nice.org.uk/guidance/qualitystandards/qualitystandards.jsp</p> <p>Related NICE Pathways: NICE Pathway: Colorectal cancer, Pathway created: Nov 2011. http://pathways.nice.org.uk/pathways/colorectal-cancer</p>
<p>Related National Policy</p>	<p>Public Health England, National Screening Committee policy on bowel cancer screening in adults. http://www.screening.nhs.uk/bowelcancer</p> <p>NHS England, Cancer Drugs Fund decision summaries for cetuximab and panitumumab. http://www.england.nhs.uk/wp-content/uploads/2014/02/Cetuxi-rasmcra-jan14.pdf http://www.england.nhs.uk/wp-content/uploads/2014/02/panitum-rasmcra-jan14.pdf</p>

Questions for consultation

Have all relevant comparators for cetuximab and panitumumab been included in the scope? Which treatments are considered to be established clinical practice in the NHS for previously untreated metastatic colorectal cancer?

Are the outcomes suggested in the scope appropriate? Do they capture all the relevant potential benefits of these technologies for people with metastatic colorectal cancer?

Are the subgroups suggested in 'other considerations' appropriate?

- Are there any other subgroups of people in whom cetuximab and panitumumab are expected to be more clinically effective and cost effective or other groups that should be examined separately?
- Should the appraisal consider subgroups based on clinical characteristics of the cancer (for example, whether the primary tumour or metastases have been, or may be, resected)?
- Should the appraisal consider any other genetic markers (for example, EGFR or BRAF mutation status)?

Where do you consider cetuximab and panitumumab will fit into the existing NICE pathway, [Colorectal cancer](#)?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which cetuximab and panitumumab are licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technologies;
- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Do you consider cetuximab and panitumumab to be innovative in their potential to make a significant and substantial impact on health-related benefits and how they might improve the way that current need is met (are they a 'step-change' in the management of the condition)?

Do you consider that the use of cetuximab and panitumumab can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.