NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Consideration of consultation responses on review proposal

Review of TA176; Cetuximab for the first line treatment of metastatic colorectal cancer, and TA240; Panitumumab for the first-line treatment of metastatic colorectal cancer

This guidance was issued August 2009.

The review date for this guidance is August 2012.

TA176 was considered for review along with TA61 in 2011 and it was decided that Clinical Guideline CG131 should refer to but not incorporate TA176.

Background

At the GE meeting of 5 November 2013 it was agreed we would consult on the review plans for this guidance. A four week consultation has been conducted with consultees and commentators and the responses are presented below.

Proposal put to consultees:	A review of the guidance (TA176) should be combined with a review of a related technology appraisal (TA240).
Rationale for selecting this proposal	At the time of the development of TA176 cetuximab was licensed for treating KRAS wild type metastatic colorectal cancer. TA176 recommends cetuximab only for treating a small subgroup; treatment is not recommended for the majority of people covered in the marketing authorisation. Evidence has emerged that identifying further RAS biomarkers improves the effectiveness of the anti-EGFR agents cetuximab and panitumumab. This has already led to a change in the wording of the marketing authorisation for panitumumab. Therefore we propose that a review of TA176 is combined with a review of TA240 'Panitumumab in combination with chemotherapy for the treatment of metastatic colorectal cancer' (terminated appraisal). This new evidence related to additional RAS biomarkers makes other new published evidence on cetuximab less relevant (both for the overall population and for the benefit of cetuximab in enabling resection of previously inoperable liver metastases).

GE is asked to consider the original proposal in the light of the comments received from consultees and commentators, together with any responses from the appraisal team. It is asked to agree on the final course of action for the review.

Recommendation post consultation:	A review of the guidance (TA176) should be combined with a part review of a related technology appraisal (TA240) and cover cetuximab and panitumumab for the treatment of previously untreated metastatic colorectal cancer

Respondent	Response to proposal	Details	Comment from Technology Appraisals
Bladder & Bowel Foundation		B&BF will not be participating in this review.	Comment noted.
Sanofi	Agree	The proposal to review this guidance and to consider panitumumab and cetuximab within the same appraisal appears reasonable given the evolution of the evidence base for EGFR inhibitors. In addition to the studies described in the Guidance Executive paper, we would also draw attention to the CALGB 80405 trial, which is a Phase III trial evaluating cetuximab, bevacizumab, and cetuximab plus bevacizumab (three arms) used in combination with FOLFOX or FOLFIRI in previously untreated mCRC, with OS as a primary endpoint. This trial is expected to report at ASCO in 2014 and should provide additional relevant information on the efficacy of cetuximab.	Comment noted. Thank you for highlighting expected publication of the CALGB 8405 trial results at ASCO in 2014. (This trial is listed by its registration number [NCT00265850] in the table of ongoing/registered studies in the proposal paper.)
Medicines and Healthcare Products Regulatory Agency	No comment	As this is a proposal to update the guidance (to bring the recommendations closer to the licensed indications), we have no comment on the proposal.	Comment noted.

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National Cancer Research Institute Royal College of Physicians Royal College of Radiologists Association of Cancer Physicians	Agree	The experts of the NCRI/RCP/RCR/ACP/JCCO believe that this review is appropriate. The new data which is available will come from results of the FIRE3 study.	Comment noted.
Amgen		We support the recommendation proposed by the Institute that TA176 should be updated within a multiple technology appraisal combined with a review of 'panitumumab in combination with chemotherapy for the treatment of metastatic colorectal cancer' (TA240). The proposal paper provides, as the rationale for review, the recent identification of further RAS mutations beyond KRAS exon 2 that are predictive of patient response to treatment with anti-EGFR agents. Amgen has led the research on the targeted selection of patients for treatment with anti-EGFR agents according to tumour-specific genetic biomarkers; from first pioneering the publication of results in patients with wild-type	Comments noted. A response to each of the three points that were raised is given below. 1. This will be a review of TA176 and a part review of TA 240 for previously untreated metastatic colorectal cancer (first line). 2. Thank you for highlighting this additional study. The proposal paper summarises only critical developments since guidance publication: the additional analyses of the Phase III PRIME study and described in panitumumab's summary of product characteristics.

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		KRAS tumours in September 2007, to most recently, demonstrating that clinical benefit is enhanced in patients with wild-type RAS (KRAS or NRAS) tumors (1,2). We believe that it is important to note, that we re-initiated terminated appraisal TA240 ('panitumumab in combination with chemotherapy for the treatment of metastatic colorectal cancer') with the Institute in September 2013 as a result of the new RAS analysis and the improved benefit-risk profile of panitumumab in patients with wild-type RAS. We have outlined below our comments and clarifications points on the proposal. 1. Proposed review remit to cover first-line use of cetuximab and panitumumab We would like to seek clarification on the indications that would be considered in the remit of this proposed review. In August 2009, the Institute published TA176 which assessed the first-line use of cetuximab in metastatic colorectal cancer (mCRC). In January 2012, TA242 was published which assessed bevacizumab, cetuximab and panitumumab in mCRC that has progressed after first-line therapy. A key rationale for conducting TA242 was to combine post first-line treatments in a single review within a multiple technology appraisal (MTA).	3. Thank you for providing these Cancer Drugs Fund statistics on the use of bevacizumab for previously untreated metastatic colorectal cancer. A draft scope will be developed and at this stage all potentially relevant comparators will be identified and included, and comments received from consultation on this review proposal paper will be considered when developing the draft scope. At consultation, consultees and commentators will be invited to provide feedback on aspects such as the selection of appropriate comparators.

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		The original remit of the terminated appraisal for panitumumab TA240 included the appraisal of both first and second-lines of treatment. In this proposed review, we recommend consistency of approach with that taken for TA176 and TA242. In line with original TA176, we recommend that the proposed review considers both cetuximab and panitumumab in first-line use only. We would further recommend that panitumumab in the second-line treatment setting be considered as part of TA242 when it is up for review, in line with the rationale provided by the Institute that all post first-line treatments be appraised within a single MTA. 2. Efficacy of panitumumab in patients with wild-type RAS tumours It is noteworthy that the recent publication of the RAS analysis is based on the pivotal phase III PRIME study which compared panitumumab plus FOLFOX to FOLFOX alone; a comparator that is in line with that recommended by the Institute for first-line use in its most up to date clinical guideline on colorectal cancer CG131**Error! Bookmark not defined.** (2,3). Indeed, the review proposal states that in the most recent survival analysis of the phase III PRIME study, an improvement in overall survival of almost 6 months was shown with the	

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		addition of panitumumab to FOLFOX in patients with wild-type RAS tumours (HR 0.77, 95%CI 0.64 to 0.94, p=0.009). We would like to highlight that there is additional evidence of panitumumab's efficacy in patients with wild-type RAS tumours in the first-line setting which is absent from the summary of evidence in the review proposal. The PEAK study (NCT00819780), a randomised phase II study evaluating panitumumab plus FOLFOX versus bevacizumab plus FOLFOX as first-line treatment in mCRC patients, assessed the effect on progression free survival (PFS) and overall survival (OS) in patients with wild-type RAS mutations (4). The PFS and OS hazard ratios favoured the panitumumab arm as follows: • Median PFS: 13.0 months versus 10.1 months = 2.9 months (HR 0.66, 95%CI 0.46 to 0.95, p= 0.03) • Median OS: 41.3 months versus 28.9 months = 12.4 months (HR 0.63, 95%CI 0.39 to 1.02, p= 0.06) The results of the PEAK study are consistent with the results of the analysis of RAS mutations in the pivotal phase III PRIME study. This expands the evidence base demonstrating that activation of RAS mutations is predictive of treatment effect with	

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		panitumumab. 3. Relevant comparators within the proposed review reflecting routine clinical practice The proposal paper states that "There are currently no other changes to potential comparators since the original guidance was issued, because guidance for the first-line use of another targeted treatment, bevacizumab (TA212; anti-VEGF agent) did not recommend their use". We would like to underscore the widespread use of targeted treatments for colorectal cancer for first-line use, such as bevacizumab, since the inception of the cancer drugs fund (CDF) in 2010. Consequently it would be important to regard treatments available and routinely used under the CDF as appropriate comparators for first-line mCRC. Disregarding these treatments as relevant comparators would be to disregard current clinical practice within England. Bevacizumab is one such example of a routinely used first-line treatment for mCRC which is recommended by the CDF. The national CDF list was established in April 2013 following rationalisation of the 10 regional CDF lists. The national availability of bevacizumab was evident before the set-up of the national list, as it was included in 9 out of the 10 regional lists for first-line	

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		use. With the formation of a national list, bevacizumab is now included on that national list for mCRC and is therefore routinely available for use by NHS England. It is noteworthy that around 17% of all notifications for new patients (1,430 patients) to the national CDF between April 2013 and September 2013 were for bevacizumab in mCRC. Three quarters of these applications were for first-line use, equating to approximately 1,096 patients (5). Additionally, the manufacturer submission for TA212, which appraised the first-line use of bevacizumab, estimated that 20% of the incident population, approximately 6,000 patients, with mCRC could be eligible for first-line treatment (6). Assuming that the proportion of notifications to the national CDF during these 6 months is representative of the full year, approximately 2,200 patients are likely to receive bevacizumab in 2013. This implies that over a third of patients eligible for first-line treatment are receiving bevacizumab, demonstrating its significant use in clinical practice for patients with mCRC. Given the availability and routine use of targeted treatments such as bevacizumab in the NHS (funded through the CDF), we recommend that the Institute consider including comparators that are commonly used in clinical practice in the scope of	

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		this proposed review. **References** 1. Amado RG, Wolf M, Peeters M, et al. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. J Clin Oncol 2008;26: 1626-34 2. Douillard JY, Oliner KS, Siena S, et al. Panitumumab–FOLFOX4 treatment and RAS mutations in colorectal cancer. N Engl J Med 2013;369:1023-34 3. Colorectal cancer: the diagnosis and management of colorectal cancer. Clinical Guideline. CG131. Published: November 2011. 4. Schwartzberg LS, Rivera F, Karthaus M, et al. Analysis of KRAS/NRAS mutations in PEAK: A randomized phase II study of FOLFOX6 plus panitumumab or bevacizumab as first-line treatment for wild-type (WT) KRAS (exon 2) metastatic colorectal cancer (mCRC). J Clin Oncol 31, 2013 (suppl; abstr 3631) 5. National Cancer Drugs Fund http://www.england.nhs.uk/ourwork/pe/cdf/ 6. Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine for the treatment of metastatic colorectal cancer. Technology Appraisal. TA212. Published: December 2010.	
Royal College of Nursing	Agree	Nurses caring for people with colorectal cancer reviewed the consultation document on behalf of the RCN. The RCN notes the proposal that TA176 should be updated within a multiple technology appraisal along with 'panitumumab in combination with chemotherapy for the treatment of metastatic	Comments noted. The results of the FIRE-3 study will be considered as part of the review of guidance.

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		colorectal cancer' (terminated appraisal, TA240). It is noted that evidence has emerged that identifying further RAS biomarkers improves the effectiveness of the anti-EGFR agents cetuximab and panitumumab. We agree that there is recent evidence supporting the proposal. European Society For Medical Oncology (ESMO) conference at the European Cancer Congress 2013, reported that: Phase III FIRE -3 Trial Data show most patients with wild-type RAS metastatic colorectal cancer benefit from first-line Folfiri plus cetuximab. Treatment findings from a pre-planned analysis by mutational status done on data from the FIRE-3 trial, that expanded KRAS testing as a predictive factor of resistance to more rare NRAS gene and BRAF, confirmed previously reported results that first line treatment with Folfiri plus the anti-EGFR (epidermal growth factor receptor) agent cetuximab achieve benefit in terms of overall response rate and overall survival in most patients with KRAS wild type (exon 2) metastatic colorectal cancer (mCRC). But the benefit encompasses also those with wild type KRAS exon 3/4 and wild type NRAS exon 2/3/4. However, a subgroup of patients with mutated RAS did not show similar benefit and achieved improved progression-free survival following treatment with Folfiri plus the	

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		anti-VEGF (vascular endothelial growth factor) agent bevacizumab. In our view, the proposals for the review of this guidance is warranted and welcomed.	

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Merck Serono	Agree	Merck Serono welcomes the opportunity to update the existing guidance and supports the Institute's proposal for review of Technology Appraisal 176 (TA176). We appreciate that NICE has recognised that cetuximab in combination with capecitabine-containing regimens such as XELOX is no longer covered by the European marketing authorisation. NICE's acknowledgement that "*this has no bearing on the review decision because combination therapy with capecitabine-containing regimens is not recommended in TA176*", is welcome and this prudence should be maintained when considering COIN within the review. We would also like to draw attention to the inclusion of the NORDIC-VII trial in NICE's summary of information. The only form of 1st line oxaliplatin based treatment within the European marketing authorisation for cetuximab is FOLFOX. Therefore we would also like to mention that the use of bolus 5-FU/folinic acid and oxaliplatin (Nordic FLOX) administered continuously or intermittently, is neither a licensed combination nor a standard combination used in NHS practice and also should not be considered relevant to the proposal.	Comment noted. The review of TA176 will focus on using cetuximab within its European marketing authorisation for the treatment of previously untreated metastatic colorectal cancer and this will depend on the marketing authorisation at the time of the appraisal. All relevant evidence will be considered when developing recommendations, including different combination regimens that are used in clinical practice in England.

No response received from:

Patient/carer groups	General
• Action for Children • Action For Sick Children • Afiya Trust • Beating Bowel Cancer • Black Health Agency • Bowel Cancer Information • Bowel Cancer UK • Cancer Black Care • Cancer Equality • Childhood Cancer Parents Alliance (formerly National Alliance of Childhood Cancer Parent Organisations) • Children with Cancer • CLIC Sargent • Colostomy Association • Equalities National Council • Helen Rollason Cancer Charity • Help Adolescents with Cancer • IA: Ilesostomy and Internal Pouch Support Group • Independent Cancer Patients Voice • Macmillan Cancer Support • Maggie's Centres • Marie Curie Cancer Care • Muslim Council of Britain • Muslim Health Network • National Children's Bureau • Ostomy Lifestyle • South Asian Health Foundation	• Allied Health Professionals Federation • Board of Community Health Councils in Wales • British National Formulary • Care Quality Commission • Commissioning Support Appraisals Service • Department of Health, Social Services and Public Safety for Northern Ireland • Healthcare Improvement Scotland • National Association of Primary Care • National Pharmacy Association • NHS Alliance • NHS Commercial Medicines Unit • NHS Confederation • Scottish Medicines Consortium Comparator manufacturers • Accord Healthcare (fluorouracil, irinotecan, oxaliplatin) • Actavis UK (irinotecan, oxaliplatin) • Hospira UK (irinotecan, oxaliplatin, fluorouracil) • Medac UK (irinotecan, oxaliplatin, fluorouracil, disodium levofolinate) • Merck Serono (tegafur uracil) • Mylan UK (irinotecan, oxaliplatin) • Pfizer (irinotecan, calcium levofolinate) • Roche Products (capecitabine) • Sandoz (fluorouracil, irinotecan) • Teva UK (irinotecan, oxaliplatin) • Wockhardt UK (fluorouracil, oxaliplatin)

- Specialised Healthcare Alliance
- Teenage Cancer Trust
- Tenovus
- Together For Short Lives
- WellChild

Professional groups

- Association of Anaesthetists of Great Britain and Ireland
- Association for Cancer Surgery
- Association of Coloproctologists of Great Britain
- Association of Surgeons of Great Britain and Ireland
- Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland (AUGIS)
- British Association for Services to the Elderly
- British Association of Surgical Oncology
- British Geriatrics Society
- British Institute of Radiology
- British Psychosocial Oncology Society
- British Society of Gastroenterology
- Cancer Network Pharmacists Forum
- Cancer Research UK
- Royal College of Anaesthetists
- Royal College of General Practitioners
- Royal College of Pathologists
- Royal College of Surgeons
- Royal Pharmaceutical Society
- Royal Society of Medicine
- Society and College of Radiographers
- UK Health Forum
- United Kingdom Clinical Pharmacy Association

- Zentiva (oxaliplatin)

Relevant research groups

- Cochrane Upper Gastrointestinal and Pancreatic Diseases Group
- CORE- Digestive Disorders Foundation
- Health Research Authority
- Institute of Cancer Research
- MRC Clinical Trials Unit
- National Cancer Research Network
- National Institute for Health Research
- Research Institute for the Care of Older People

Assessment Group

- Assessment Group tbc
- National Institute for Health Research Health Technology Assessment Programme

Associated Guideline Groups

- National Clinical Guidelines Centre
- National Collaborating Centre for Cancer

Associated Public Health Groups

- Public Health England
- Public Health Wales NHS Trust

• United Kingdom Oncology Nursing Society <u>Others</u> • Department of Health • NHS Crawley CCG • NHS England • NHS Surrey Heath CCG • Welsh Government	

GE paper sign-off: Elisabeth George, Associate Director – Technology Appraisals Programme

Contributors to this paper:

Technical Lead: Linda Landells

Project Manager: Andrew Kenyon

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