

# NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

## GUIDANCE EXECUTIVE (GE)

### Review of TA 118 Colorectal cancer (metastatic) - bevacizumab & cetuximab

This guidance published in January 2007 with a review date of May 2009.

#### Recommendation

- A part review of the guidance is carried out covering bevacizumab, cetuximab and (additionally)panitumumab for the treatment of metastatic colorectal cancer following the failure of first line chemotherapies (to include a part review of TA118 and a review of TA150). That we consult on this proposal.
- The decision to update the remaining guidance on bevacizumab plus irinotecan for first line treatment of metastatic colorectal cancer is deferred and it is considered for review with other first line treatment appraisals of metastatic colorectal cancer. That we consult on this proposal.

Consideration of options for recommendation:

Options	Comment
A review of the guidance proceed, pending consultation, and should be planned into the appraisal work programme.	The population for whom cetuximab is licensed has changed. The marketing authorisation now specifies EGFR positive and KRAS metastatic colorectal cancer. The population for cetuximab in TA118 (EGFR only) no longer reflects the population for whom cetuximab is considered to benefit. The technologies have received new licence extensions allowing their use with a number of combination therapies and with their position in the care pathway no longer specified. A number of these licence extensions are not subject to NICE guidance, or have been subject to terminated appraisals.
The decision to review the guidance should be deferred.	This is not an option for cetuximab, as the population licensed for one of the drugs has changed. This is an option for bevacizumab plus irinotecan for the first line treatment of metastatic colorectal cancer, as no new evidence was identified, and there is an ongoing appraisal of bevacizumab plus oxaliplatin for the first line treatment of metastatic colorectal cancer.
A review of the guidance should be combined with a review of a related technology and conducted at the scheduled time for the review of the related technology.	No relevant guidance review has been identified.
A review of the guidance should be combined with a	This is not an option, as there are no topics that have recently been referred to the Institute.

new appraisal that has recently been referred to the Institute.	
A review of the guidance should be incorporated into an on-going clinical guideline.	This is not an option, as both drugs have received new indications
A review of the guidance should be updated into an on-going clinical guideline.	Updating the guidance is not appropriate within the ongoing clinical guideline on colorectal cancer, as the topic does not match the prioritisations set for the guideline.
A review of the guidance should be transferred to the 'static guidance list'.	This is not an option, as both drugs have received licence extensions and for cetuximab the population in the marketing authorisation has changed and new evidence has been identified.

### Original remit(s)

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

### Current guidance

- 1.1 Bevacizumab in combination with 5-fluorouracil plus folinic acid, with or without irinotecan, is not recommended for the first-line treatment of metastatic colorectal cancer.
- 1.2 Cetuximab in combination with irinotecan is not recommended for the second-line or subsequent treatment of metastatic colorectal cancer after the failure of an irinotecan containing chemotherapy regimen.
- 1.3 People currently receiving bevacizumab or cetuximab should have the option to continue therapy until they and their consultants consider it appropriate to stop.

### Relevant Institute work

#### *Published/completed*

TA150 Cetuximab for the treatment of metastatic colorectal cancer following failure of oxaliplatin-containing chemotherapy (terminated appraisal - no evidence submission received from manufacturer)

TA61 Capecitabine and tegafur uracil for metastatic colorectal cancer. May 2003, review decision: static guidance

TA93 Irinotecan, oxaliplatin and raltitrexed for advanced colorectal cancer (review of TA33). August 2005, review decision: incorporate into on-going clinical guideline 'diagnosis and management of colorectal cancer'

#### *In progress*

Technology Appraisal (STA) - Cetuximab for the first line treatment of metastatic colorectal cancer, expected publication date August 2009

Technology Appraisal (STA) - Bevacizumab in combination with oxaliplatin and either 5FU or capecitabine for the treatment of metastatic colorectal cancer, expected publication date May 2010

Technology Appraisal (STA) - Panitumumab in combination with chemotherapy for the treatment of metastatic colorectal cancer, expected publication date TBC (referred as part of the 20<sup>th</sup> wave)

Clinical Guideline - Diagnosis and management of colorectal cancer. In progress, expected publication date July 2011

### Details of licence extensions

Technology	Original indication	New indication
Bevacizumab (Roche)	Use of bevacizumab in combination with intravenous 5-FU/FA with or without irinotecan for first-line treatment of metastatic colorectal cancer.	Use of bevacizumab in combination with any chemotherapy for treatment of metastatic colorectal cancer ( <i>no treatment line specification</i> ).
Cetuximab (Merck Serono)	Use of cetuximab in combination with irinotecan for the treatment of patients with EGFR-expressing metastatic colorectal cancer after failure of cytotoxic therapy that included irinotecan.	Use of cetuximab in combination with chemotherapy ( <i>no treatment line specification</i> ), or, as monotherapy after failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan, for treatment of EGRF-expressing, KRAS metastatic colorectal cancer.

### Details of new products

Panitumumab is currently licensed as monotherapy for EGFR-expressing metastatic colorectal carcinoma with KRAS after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-based therapy. It is also being studied in combination with chemotherapy for the first line treatment of metastatic colorectal cancer. Panitumumab in combination with chemotherapy is not currently licensed but was referred to NICE as part of the 20<sup>th</sup> wave.

### Update of trials in the current guidance

Trial	Details
NCT00063141 A Phase III Randomized, Open-Label, Multicenter Study of Irinotecan and Cetuximab vs. Irinotecan as Second-Line Treatment in Patients With Metastatic, EGFR-Positive Colorectal Carcinoma.	Study completed October 2007.
NCT00079066 A Phase III Randomized Study of Cetuximab (Erbix, C225) and Best Supportive Care	This study is completed and results have been published.

Versus Best Supportive Care in Patients With Pretreated Metastatic Epidermal Growth Factor Receptor (EGFR)-Positive Colorectal Carcinoma.	
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### Other on-going trials

Trials	Details
NCT00433927 Multicenter Randomized Trial Evaluating FOLFIRI Plus Cetuximab Versus FOLFIRI Plus Bevacizumab in First Line Treatment of Metastatic Colorectal Cancer.	Phase III Currently recruiting Estimated Enrolment: 568 Estimated Completion Date: December 2015.
NCT00265850 A Phase III Trial of Irinotecan / 5-FU / Leucovorin or Oxaliplatin / 5-FU/ Leucovorin With Bevacizumab, or Cetuximab (C225), or With the Combination or Bevacizumab and Cetuximab for Patients With Untreated Metastatic Adenocarcinoma of the Colon or Rectum.	Phase III Currently recruiting Estimated Enrolment: 2300 Estimated Primary Completion Date: June 2008.

### Proposed Timing for updating the guidance

If the guidance was updated as an appraisal the scoping work would start in October 2009, the Appraisal Committee would consider the appraisal in November 2010 with expected publication in March 2011 (subject to appeal).

### New evidence

The search strategy from the original assessment report was re-run on the Cochrane Library, Medline, Medline(R) In-Process and Embase. References from 2005 onwards were reviewed.

### Implementation

A submission from Implementation is attached at the end of this paper.

### Equality and diversity issues

None

### Appraisals comment

TA118 provides guidance on two specific indications each used at different points in the treatment pathway:

- Bevacizumab in combination with irinotecan for the first line treatment of metastatic colorectal cancer (MCRc) and,
- Cetuximab in combination with irinotecan for EGFR expressing MCRc after the failure of an irinotecan containing regimen.

In July 2008 cetuximab had an amendment to its marketing authorisation limiting the population for which it is indicated from people whose MCRc is EGRF expressing to people

whose MCrC is both EGFR expressing and KRAS. This reflects increased knowledge about the action of cetuximab and the people likely to benefit. Further targeting of cetuximab therapy will alter the cost effectiveness profile of this agent and suggests a need to review the original cetuximab guidance.

In addition, to the change in the licensed population, cetuximab is now licensed in addition to any chemotherapy (but usually oxaliplatin or irinotecan) as a first line treatment or as a subsequent line treatment (usually second or third line) following failure of first line chemotherapy. It is also licensed as monotherapy following failure of other chemotherapy treatments where a patient is intolerant to further irinotecan. There is an ongoing appraisal of first line cetuximab treatment (due for publication August 2009), but the indications for subsequent line treatment additional to that in TA118 have either been subject to terminated appraisal (TA150 cetuximab plus oxaliplatin), or have not been subject to NICE guidance (cetuximab monotherapy). NICE is unable to provide timely guidance on the use of cetuximab monotherapy and the population indicated is a relatively small subgroup of the MCrC population, therefore an STA of this indication in isolation may not add value to the NHS. The use of cetuximab after the failure of first line chemotherapy can be considered distinct from first line use, and therefore from the first line treatment appraisal. However, the indications for treatment after the failure of first line chemotherapy in TA118 (combination with irinotecan), TA150 (combination with oxaliplatin) and the monotherapy indication may be considered together as reflecting the available options for adding cetuximab to standard treatment. These treatment options could be considered together in a single appraisal.

The licence for bevacizumab has also been extended to include its use in any chemotherapy combination and in any line of therapy. There is an ongoing appraisal of bevacizumab plus oxaliplatin, which focuses on first line treatment. This is a distinct combination from that in TA118 which appraised bevacizumab plus irinotecan for first line treatment. There would not appear to be any significant new evidence that would alter the guidance on first line treatment of bevacizumab plus irinotecan, and therefore there may not be urgency to review this aspect of TA118. Bevacizumab is, however, now licensed for treatment after failure of first line chemotherapies and this has not been subject to NICE guidance. These indications may be included in any appraisal of treatments after failure of first line chemotherapy. However, the population for bevacizumab is a larger population than that indicated for cetuximab because no biomarkers are specified.

Finally, searches identified an additional product, panitumumab, which is currently referred to the Institute for appraisal in combination with chemotherapy, and is anticipated to focus on first line treatment, dependent on the receipt of appropriate marketing authorisation. Panitumumab currently has a monotherapy licence (obtained in December 2007) for use after the failure of oxaliplatin, and irinotecan containing chemotherapy regimens, with the same biomarkers (EGFR, KRAS) as cetuximab. As for cetuximab, NICE is unable to provide timely guidance and the population indicated is a relatively small subgroup of the MCrC population, therefore an STA of this indication in isolation may not add value to the NHS. However, as this treatment is indicated for the same population as cetuximab, for a similar point in the care pathway it would be appropriate to combine this indication with any appraisal of cetuximab for treatment subsequent to first line therapy.

The table below shows how the proposed review relates to published or in progress guidance on treatments for metastatic colorectal cancer.

<b>Guidance</b>	<b>Status</b>	<b>Suggestion</b>
Bevacizumab and cetuximab for MCrC (TA118)	Review proposal	Partial review of TA118 (review cetuximab but not bevacizumab first line)
Cetuximab for MCrC following failure of oxaliplatin-containing chemotherapy (TA150)	Terminated	Included in review of TA118
Cetuximab for first line treatment of EGRF expressing KRAS MCrC	In progress (expected August 2009)	No overlap with review of TA118 because this is first-line treatment
Panitumumab in combination with chemotherapy for first line treatment of EGRF expressing KRAS MCrC	In progress (expected TBC)	No overlap with review of TA118 because this is first-line treatment
Bevacizumab (with oxaliplatin and either 5FU or capecitabine) for MCrC (no line specification)	In progress (expected May 2010)	No overlap with review of TA118 because this is first line treatment & is bevacizumab with oxaliplatin & either 5FU or capecitabine (not with irinotecan)

## Summary

A part review of the TA118 guidance is required to reflect the change in the licensed population for cetuximab. In addition it is appropriate to include further indications where these are not currently subject to NICE guidance and to appraise as an MTA, cetuximab for the treatment of MCrC following the failure of first line chemotherapies to include a part review of TA118 and TA150 and an appraisal of cetuximab monotherapy. This should include the indication for panitumumab monotherapy because it reflects the same licensed population as cetuximab and will not be included in the STA of panitumumab combination therapy.

A review of bevacizumab in combination with irinotecan for first line treatment is not required because no new evidence is available.

An appraisal of bevacizumab following failure of first line chemotherapy may be appropriate to include in the proposed MTA review, although it is recognised there are differences in the licensed populations.

## GE paper sign off:

Nina Pinwill, Associate Director, CHTE  
18 August 2009

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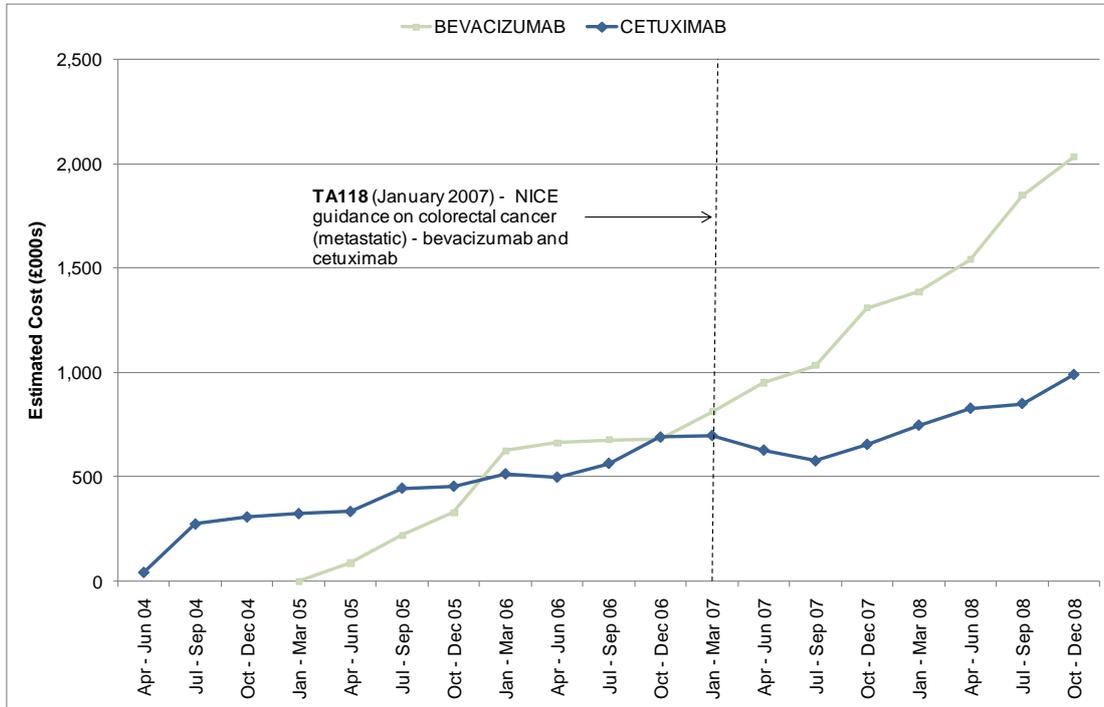
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## IMPLEMENTATION DIRECTORATE

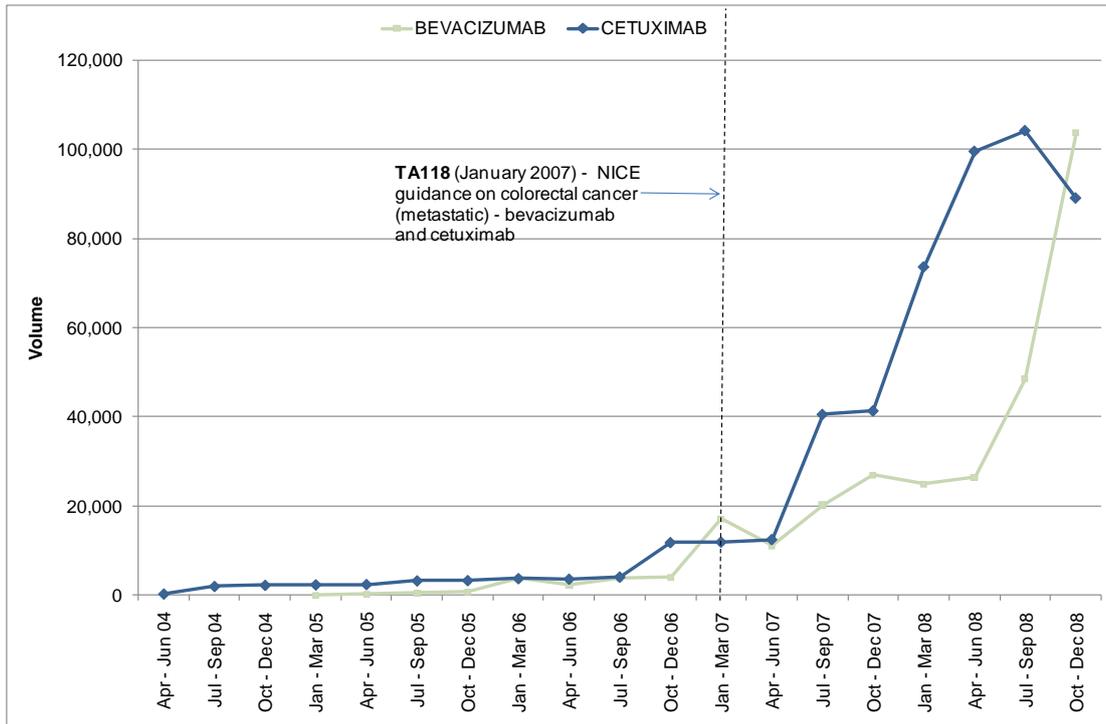
### Guidance Executive Review: TA118 Guidance on the use of bevacizumab and cetuximab for the treatment of colorectal cancer

Data showing trends in prescribing costs and volume are presented below. Unfortunately this data does not link to diagnosis or stage of cancer so needs to be treated cautiously in relation to the specific recommendations of the guidance. Additionally, the HPAI database measures volume in packs and a drug may be available in different pack sizes and pack sizes can vary between medicines. Estimated costs are also calculated by IMS using the drug tariff and other standard price lists. Many hospitals receive discounts from suppliers and this is not reflected in the estimated cost.

#### Estimated Cost



## Volume



## Data source

IMS Health: Hospital Pharmacy Audit.