

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Review of TA212; Bevacizumab in combination with oxaliplatin and either 5-fluorouracil plus folinic acid or capecitabine for the treatment of metastatic colorectal cancer

This guidance was issued in December 2010.

The review date for this guidance is May 2013.

1. Recommendation

The guidance should be transferred to the 'static guidance list'. That we consult on this proposal.

2. Original remit(s)

"To appraise the clinical and cost effectiveness of bevacizumab within its licensed indication in combination with oxaliplatin and either 5FU or capecitabine for the treatment of metastatic colorectal cancer."

3. Current guidance

1.1 Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine is not recommended for the treatment of metastatic colorectal cancer.

1.2 People currently receiving bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine for the treatment of metastatic colorectal cancer should have the option to continue treatment until they and their clinicians consider it appropriate to stop.

4. Rationale¹

There is no significant new evidence that is likely to lead to a change in the recommendations in TA212, and no directly relevant ongoing studies. Therefore it is appropriate that the guidance be transferred to the static list.

5. Implications for other guidance producing programmes

There is no proposed or ongoing guidance development that overlaps with this review proposal.

¹ A list of the options for consideration, and the consequences of each option is provided in Appendix 1 at the end of this paper

6. New evidence

The search strategy from the original ERG report was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from June, 2009 onwards were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section below. See Appendix 2 for further details of ongoing and unpublished studies.

7. Summary of evidence and implications for review

Summary of TA212

In TA212, the Committee concluded that adding bevacizumab to oxaliplatin-containing regimens gave a modest clinical benefit in the first-line treatment of metastatic colorectal cancer and that bevacizumab was clinically effective as part of second-line treatment. No evidence of bevacizumab given after second-line treatment was submitted by the manufacturer. Given the high incremental cost effectiveness ratio estimates and their uncertainty, the Committee concluded that bevacizumab in combination with oxaliplatin-containing regimens could not be recommended as cost-effective use of NHS resources for the first-line or second-line treatment of metastatic colorectal cancer.

Updated summary of product characteristics

At the time of the TA212 appraisal, bevacizumab in combination with fluoropyrimidine-based chemotherapy had a UK marketing authorisation that included an indication for the treatment of patients with metastatic carcinoma of the colon or the rectum (although the remit of TA212 was for bevacizumab in combination with oxaliplatin and either 5-FU or capecitabine). The current indication for metastatic colorectal cancer is unaltered; however, the Summary of Product Characteristics for bevacizumab was updated in January 2013 to include efficacy and safety results from study ML1847.

Study ML18147 was a Phase III randomised, controlled, open-label trial that assessed continued use of bevacizumab plus standard second-line chemotherapy compared with chemotherapy alone in patients with metastatic colorectal cancer progressing after a first-line bevacizumab-containing treatment (Bennouna et al. 2013). Median overall survival was statistically significantly longer with bevacizumab plus chemotherapy (n=409) than chemotherapy alone (n=411) (112 months compared with 98 months, hazard ratio 0.81 [95% CI 0.69–0.94], p=0.0062).

This potential additional treatment setting is not considered relevant to current clinical practice in England and Wales (because first-line treatment with bevacizumab is not recommended by NICE).

The manufacturer has advised that no future extensions to the marketing authorisation for bevacizumab for the treatment of metastatic colorectal cancer are expected, and has therefore indicated that it believes a review of TA212 is unwarranted because of the lack of relevant new evidence.

Comparators

Comparators in TA212 were oxaliplatin-including chemotherapy regimens without bevacizumab and irinotecan-including chemotherapy regimens without bevacizumab. These chemotherapy combinations continue to be used as standard treatments in the UK (see [NICE clinical guideline 131](#) for details). No potential new comparators have been identified.

Other relevant clinical evidence

Another Phase III trial, the MACRO TTD study, compared the efficacy and safety of bevacizumab alone with bevacizumab and capecitabine plus oxaliplatin (XELOX) as maintenance treatment following induction chemotherapy with XELOX plus bevacizumab in the first-line treatment of 480 patients with metastatic colorectal cancer (Diaz-Rubio et al. 2012). There were no statistically significant differences in the median progression-free survival or overall survival times or in the response between the two arms. Several ongoing studies are investigating bevacizumab as a potential maintenance treatment (see '[Registered and unpublished trials](#)' in appendix 2).

Further evidence from NO16966 (a Phase III trial in the manufacturer's submission for TA212) showed that there were no statistically significant differences in resection rates or overall survival in patients treated with bevacizumab versus placebo who underwent surgery with curative intent (Okines et al. 2009).

Although not in the metastatic setting (and therefore outside of the remit for TA212), recent results from a Phase III study that investigated bevacizumab in combination with oxaliplatin-based chemotherapy in the adjuvant treatment of patients with resected stage III or high-risk stage II colon carcinoma suggested that the addition of bevacizumab to adjuvant chemotherapy did not provide any benefit. The authors stated that they did not recommend the use of bevacizumab in the adjuvant treatment of patients with curatively resected stage III colon cancer (de Gramont A. et al. 2012).

Summary: impact of new evidence

The cost-effectiveness estimates for first-line treatment with bevacizumab in combination with oxaliplatin-containing chemotherapy are unlikely to have changed substantially since the time of the appraisal. There is no new evidence to suggest that the size of the clinical benefit would be increased and the price of bevacizumab is unchanged from the time of the appraisal.

Although Study ML18147 showed a survival benefit with continued use of bevacizumab plus standard second-line chemotherapy compared with chemotherapy alone in patients with metastatic colorectal cancer progressing after a first-line bevacizumab-containing treatment, this is not considered relevant to clinical practice in England and Wales because first-line treatment with bevacizumab has not been recommended by NICE. In the absence of other strong evidence, the cost-effectiveness estimates for second-line treatment with bevacizumab in combination with oxaliplatin-containing chemotherapy are unlikely to have changed substantially since the time of the appraisal.

Given the lack of evidence that would be likely to alter Committee's original decision, it is concluded that it would not be good use of NHS resources to carry out a review of TA212 at this time.

8. Implementation

A submission from Implementation is included in Appendix 3.

It is not possible to draw any conclusions from these data because bevacizumab has a UK marketing authorisation for more than one indication and these data are not specific to the colorectal cancer indication.

9. Equality issues

No equality issues were raised during the scoping, evidence submissions or consultation stages of TA212 so no specific issues relating to equality needed to be taken into account.

GE paper sign off: Helen Knight, Associate Director, 18 April 2013

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Appendix 1 – explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

Options	Consequence	Selected – ‘Yes/No’
A review of the guidance should be planned into the appraisal work programme.	A review of the appraisal will be planned into the NICE’s work programme.	No
The decision to review the guidance should be deferred to [specify date or trial].	NICE will reconsider whether a review is necessary at the specified date.	No
A review of the guidance should be combined with a review of a related technology appraisal.	A review of the appraisal(s) will be planned into NICE’s work programme as a Multiple Technology Appraisal, alongside the specified related technology.	No
A review of the guidance should be combined with a new technology appraisal that has recently been referred to NICE.	A review of the appraisal(s) will be planned into NICE’s work programme as a Multiple Technology Appraisal, alongside the newly referred technology.	No
The guidance should be incorporated into an on-going clinical guideline.	<p>The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review.</p> <p>This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.</p>	No
The guidance should be updated in an on-going clinical guideline.	<p>Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn.</p> <p>Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).</p>	No

Options	Consequence	Selected – ‘Yes/No’
The guidance should be transferred to the ‘static guidance list’.	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review.	Yes

NICE would typically consider updating a technology appraisal in an ongoing guideline if the following criteria were met:

- i. The technology falls within the scope of a clinical guideline (or public health guidance)
- ii. There is no proposed change to an existing Patient Access Scheme or Flexible Pricing arrangement for the technology, or no new proposal(s) for such a scheme or arrangement
- iii. There is no new evidence that is likely to lead to a significant change in the clinical and cost effectiveness of a treatment
- iv. The treatment is well established and embedded in the NHS. Evidence that a treatment is not well established or embedded may include;
 - Spending on a treatment for the indication which was the subject of the appraisal continues to rise
 - There is evidence of unjustified variation across the country in access to a treatment
 - There is plausible and verifiable information to suggest that the availability of the treatment is likely to suffer if the funding direction were removed
 - The treatment is excluded from the Payment by Results tariff
- v. Stakeholder opinion, expressed in response to review consultation, is broadly supportive of the proposal.

Appendix 2 – supporting information

Relevant Institute work

Published

Cancer service guidance CSGCC Improving outcomes in colorectal cancer Issued: June 2004. Review proposal (November 2012) - The sections of the colorectal cancer service guidance relating to organisation and management of services for early rectal cancer and arrangement of services for the management of bowel obstruction caused by colon cancer should be considered for an update.

Clinical guidelines CG131 Colorectal cancer: the diagnosis and management of colorectal cancer Issued: November 2011 Review date: November 2014

Technology appraisals TA61 Capecitabine and tegafur uracil for metastatic colorectal cancer Issued: May 2003. Review decision (June 2011) was that TA61 be incorporated into CG131 Colorectal cancer: the diagnosis and management of colorectal cancer

Technology appraisals TA176 Cetuximab for the first line treatment of metastatic colorectal cancer. Issued: August 2009. Review date: June 2011 TA176 should not be incorporated verbatim into CG131 Colorectal cancer: the diagnosis and management of colorectal cancer as the results of the further subgroup analyses of the COIN study could potentially lead to the need to update the recommendations in the future. Therefore, NICE proposed it should instead be cross-referenced.

Clinical guidelines CG118 Colonoscopic surveillance for prevention of colorectal cancer in people with ulcerative colitis, Crohn's disease or adenomas Issued: March 2011. Review date: March 2014

Technology appraisals TA242 Cetuximab (monotherapy or combination chemotherapy), bevacizumab (in combination with non-oxaliplatin chemotherapy) and panitumumab (monotherapy) for the treatment of metastatic colorectal cancer after first-line chemotherapy (review of TA150 and part review of TA118) Issued: January 2012. Review date: January 2015

Technology appraisals TA118 Bevacizumab and cetuximab for the treatment of metastatic colorectal cancer Issued: January 2007 (This guidance has been partially updated by TA242 Colorectal cancer (metastatic) 2nd line - cetuximab, bevacizumab and panitumumab (review)). The review decision from TA118 (published January 2010) stated that a separate appraisal of the remaining recommendations in TA118 (bevacizumab plus irinotecan for first line treatment of metastatic colorectal cancer) should be carried out (subject to a patient access scheme being referred to NICE for consideration by the Department of Health).

Technology appraisals TA100 Capecitabine and oxaliplatin in the adjuvant treatment of stage III (Dukes' C) colon cancer Issued: April 2006. Review date: June 2011 incorporated into CG131 Colorectal cancer: the diagnosis and management of colorectal cancer

Clinical guidelines CG27 Referral guidelines for suspected cancer Issued: June 2005. Review date: February 2011 – Concluded that some areas of the guideline may need updating.

Quality Standard QS20 Colorectal cancer Issued: August 2012. Review date: August 2017

In development

Technology appraisal Aflibercept for the treatment of metastatic colorectal cancer which has progressed following prior oxaliplatin-based chemotherapy. In development. Expected date of issue: October 2013

Proposed appraisal

Regorafenib for the treatment of metastatic colorectal cancer.

Suspended/terminated

Technology appraisals TA240 Panitumumab in combination with chemotherapy for the treatment of metastatic colorectal cancer Issued: December 2011 NICE was unable to recommend the use in the NHS of panitumumab in combination with chemotherapy for the treatment of metastatic colorectal cancer because no evidence submission was received from the manufacturer or sponsor of the technology.

Details of changes to the indications of the technology

Indication considered in original appraisal	Proposed indication (for this appraisal)
Bevacizumab (Roche)	Bevacizumab's indication in metastatic colorectal cancer is unchanged from the time of the TA212 appraisal. In January 2013 the Summary of Product Characteristics for bevacizumab in mCRC was updated to include the results of an additional clinical trial (ML18147), which investigated continued use of bevacizumab plus standard second-line chemotherapy in patients with metastatic colorectal cancer progressing after standard first-line treatment containing bevacizumab.

Details of new products

Drug (manufacturer)	Details (phase of development, expected launch date,)
Regorafenib (Bayer)	FDA approved regorafenib to treat patients with metastatic colorectal cancer (Sept, 2012)

Drug (manufacturer)	Details (phase of development, expected launch date,)
OncoVAX (Vaccinogen)	It is estimated that OncoVAX® will achieve FDA approval in 2015. Upon approval, OncoVAX® would become commercially available in North America and Europe. Source: Vaccinogen website
Talaporfin sodium with Light Infusion Therapy (Litx)	For metastatic colorectal cancer (4334) CCPHA checking
Sorafenib (Nexavar)	For metastatic colorectal cancer (5029) NHSC monitoring
Bevacizumab (Avastin)	For colorectal cancer (5936) CCPHA checking

Registered and unpublished trials

Trial name and registration number	Details
Maintenance Treatment Versus Observation After Induction in Advanced Colorectal Carcinoma (CAIRO3) (NCT00442637)	Estimated Enrolment: 635 Estimated Study Completion Date: June 2013
Adjuvant Xeloda Plus Eloxatin +/- Avastin After Radical Resection of Liver Metastasis of Colorectal Cancer (NCT00394992)	Estimated Enrolment: 500 Estimated Study Completion Date: December 2013
Optimal Maintenance Therapy With Bevacizumab After Induction in Metastatic Colorectal Cancer (CRC) (NCT00973609)	Estimated Enrolment: 840 Estimated Study Completion Date: December 2013
Study of 5-Fluorouracil/Leucovorin/Oxaliplatin (FOLFOX) + Bevacizumab Versus 5-Fluorouracil/Leucovorin/Oxaliplatin/Irinotecan (FOLFOXIRI) + Bevacizumab as First Line Treatment of Patients With Metastatic Colorectal Cancer Not Previously Treated and With Three or More Circulating Tumoral Cells (VISNU-1) (NCT01640405)	Estimated Enrolment: 350 Estimated Study Completion Date: June 2017

Trial name and registration number	Details
A Study of Avastin (Bevacizumab) in Combination With 5-FU Based Doublet Chemotherapy in Patients With Colorectal Cancer And Previously Untreated Unresectable Liver-Only Metastases (NCT01695772)	Estimated Enrolment: 50 Estimated Study Completion Date: April 2016
Second-Line Combination Chemotherapy With or Without Bevacizumab in Treating Patients With Metastatic Colorectal Cancer Who Have Received First-Line Chemotherapy and Bevacizumab (NCT00720512)	Estimated Enrolment: 262 Estimated Study Completion Date: March 2014
First Line Metastatic Colorectal Cancer Therapy in Combination With FOLFOX (HORIZON III) (NCT00384176)	Enrolment: 1805 Estimated Study Completion Date: August 2013
A Translational Study of Avastin (Bevacizumab) in Patients With Metastatic Colorectal Cancer (ASCENT) (NCT01588990)	Estimated Enrolment: 150 Estimated Study Completion Date: November 2017
A Study of Avastin (Bevacizumab) Plus Crossover Fluoropyrimidine-Based Chemotherapy in Patients With Metastatic Colorectal Cancer (NCT00700102)	Enrolment: 821 Estimated Study Completion Date: October 2013
Cetuximab and/or Bevacizumab Combined With Combination Chemotherapy in Treating Patients With Metastatic Colorectal Cancer (NCT00265850)	Estimated Enrolment: 2900 Estimated Primary Completion Date: March 2013
A Study of Avastin (Bevacizumab) in Combination With Xeloda (Capecitabine) in Elderly Patients With Metastatic Colorectal Cancer (NCT00484939)	Enrolment: 281 Estimated Study Completion Date: June 2013
Optimization of Bevacizumab Scheduling With Chemotherapy for Metastatic Colorectal Cancer (OBELICS) (NCT01718873)	Estimated Enrolment: 230 Estimated Study Completion Date: August 2015
Avastin and Chemotherapy Followed by a KRAS Stratified Randomization to Maintenance Treatment for First Line Treatment of Metastatic Colorectal Cancer. (ACT2) (NCT01229813)	Estimated Enrolment: 181 Estimated Primary Completion Date: December 2013

Trial name and registration number	Details
Cap+Bev vs Cap+Iri+Bev 1st-line Therapy in mCRC (NCT01249638)	Estimated Enrolment: 516 Estimated Study Completion Date: December 2016
Fluorouracil, Leucovorin, and Oxaliplatin With or Without Bevacizumab in Treating Patients Who Have Undergone Surgery for Stage II or Stage III Colon Cancer (NCT00096278)	Enrolment: 2710 Estimated Study Completion Date: March 2014
The Role of Surgery of the Primary Tumour With Few or Absent Symptoms in Patients With Synchronous Unresectable Metastases of Colon Cancer (CAIRO4) (NCT01606098)	Estimated Enrolment: 360 Estimated Primary Completion Date: August 2015

References

1. Bennouna J, Sastre J, Arnold D et al. (2013) Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): A randomised phase 3 trial. *The Lancet Oncology*. 14 (1) (pp 29-37), 2013. Date of Publication: January 2013. (1): 29-37.
2. de Gramont A., Van Cutsem E., Schmoll HJ et al. (Dec. 2012) Bevacizumab plus oxaliplatin-based chemotherapy as adjuvant treatment for colon cancer (AVANT): a phase 3 randomised controlled trial. *Lancet Oncology*. 13 (12): 1225-1233.
3. Diaz-Rubio E, Gomez-Espana A, Massuti B et al. (2012) First-line XELOX plus bevacizumab followed by XELOX plus bevacizumab or single-agent bevacizumab as maintenance therapy in patients with metastatic colorectal cancer: the phase III MACRO TTD study. *Oncologist*. 17 (1): 15-25.
4. Okines A, Del PO, Cunningham D et al. (2009) Surgery with curative-intent in patients treated with first-line chemotherapy plus bevacizumab for metastatic colorectal cancer First BEAT and the randomised phase-III NO16966 trial. *British Journal of Cancer*. 101 (7) (pp 1033-1038), 2009. Date of Publication: 2009. (7): 1033-1038.

Implementation feedback: review of NICE technology appraisal guidance 212

NICE Technology Appraisal 212 Colorectal cancer (metastatic) - bevacizumab
Implementation input required by 04/03/2013
Please contact Rebecca Lea regarding any queries rebecca.lea@nice.org.uk

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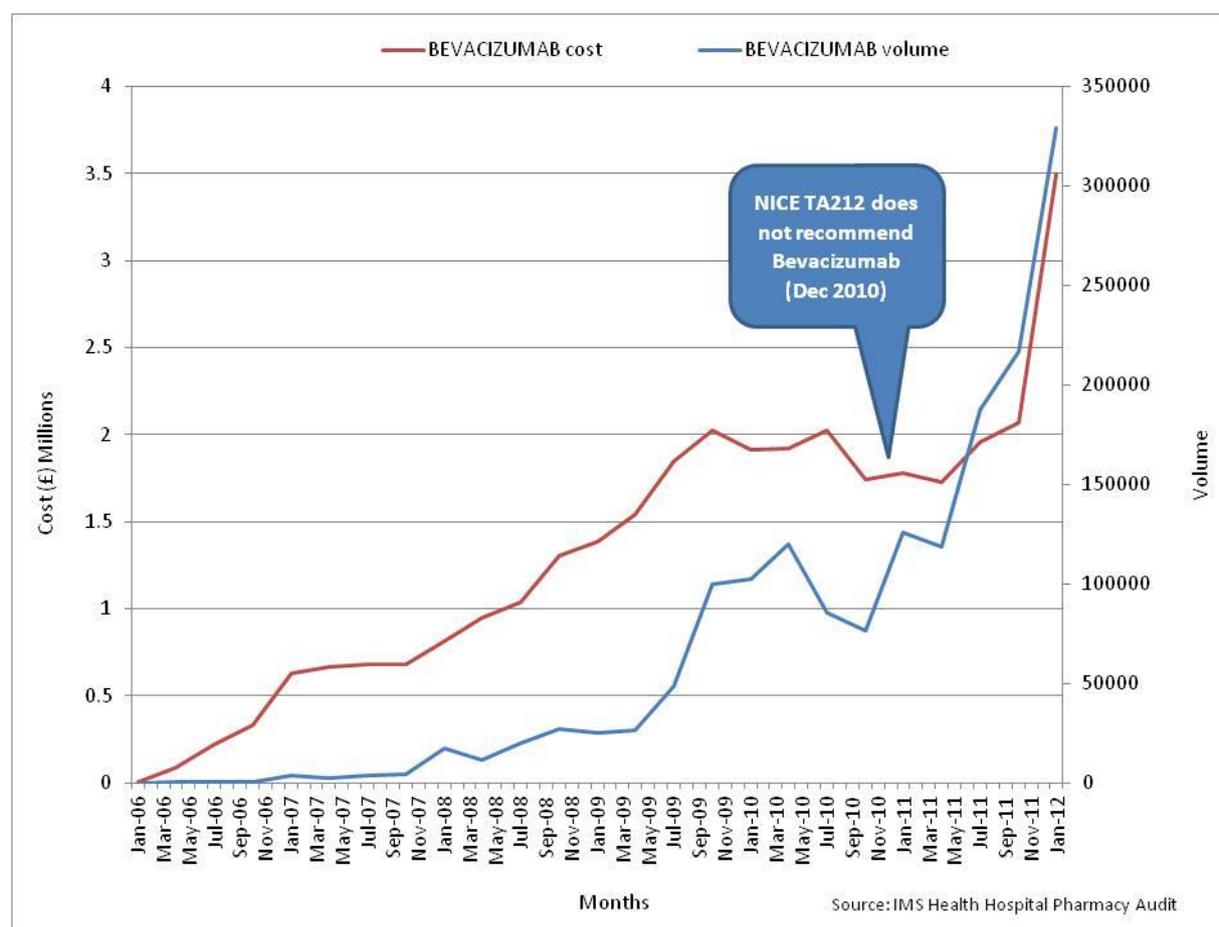
1 Routine healthcare activity data

1.1 Hospital Pharmacy Audit Index data

This section presents Hospital Pharmacy Audit Index data on the net ingredient cost (NIC) and volume of bevacizumab prescribed and used in hospitals in England.

These data need to be treated with caution as bevacizumab has indications other than for colorectal cancer.

Figure 1 Cost and volume of bevacizumab prescribed in hospitals in England



2 Implementation studies from published literature

Information is taken from the uptake database ([ERNIE](#)) website.

2.1 Richards, M (2010) [Extent and causes of international variation in drug usage: A report for the Secretary of State for Health by Professor Sir Mike Richards CBE](#)

This report looks at medicines usage between countries, using IMS Health data. The WHO defined daily dose or the maximum or prescribed daily dose was used to measure usage. Results rank the UK relative to other countries usage and present calculations showing how close or otherwise the UK is to the average use across groups of other countries. It should be noted that countries other than the UK would not be expected to adhere to NICE guidance making comparisons between countries not possible.

3 Qualitative input from the field team

The implementation field team have recorded the following feedback in relation to this guidance.

Nothing to add at this time.