# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

**Technology Appraisals and Guidance Information Services**

**Static List Review (SLR)**

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| **Title and TA publication number of static topic:** | **TA118; Bevacizumab and cetuximab for the treatment of metastatic colorectal cancer (recommendation 1.1)** |
| **Final decision:** | The guidance will remain on the 'static guidance list'. |

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| **1. Publication date:** | January 2007 |
| **2. Date added to static list:** | January 2010 |
| **3. Date the last searches were run:** | 26th May 2009 |
| **4. 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.<br>1.2 This recommendation has been updated and replaced by NICE technology appraisal guidance 242.<br>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. |
| **5. Research recommendations from original guidance:** | The Committee noted the following ongoing clinical trials related to this guidance; |

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| | NCT00063141 is an RCT comparing cetuximab combined with irinotecan with irinotecan alone as second-line treatment in patients with metastatic colorectal cancer.<br><br>NCT00079066 is an RCT comparing cetuximab combined with best supportive care with best supportive care alone in patients with metastatic colorectal cancer.<br><br>6.2 The Committee was aware of other ongoing clinical trials with bevacizumab and cetuximab as part of different treatment regimens.<br><br>The TREE-2 trial is a randomised multicentre study comparing three regimens of oxaliplatin plus bolus, infusional or oral 5-FU with bevacizumab to evaluate safety and tolerability in the first-line treatment of patients with advanced colorectal cancer.<br><br>The NO16966C trial is a randomised phase III study of intermittent oral capecitabine in combination with intravenous oxaliplatin (CAPOX) with or without bevacizumab for the first-line treatment of patients with advanced colorectal cancer.<br><br>The CONcePT trial aims to develop an optimised schedule of administration of FOLFOX plus bevacizumab in the first-line treatment of patients with advanced colorectal cancer.<br><br>The E3200 trial is a phase III RCT of oxaliplatin, 5-FU and leucovorin with or without bevacizumab, versus bevacizumab alone in patients previously treated for advanced or metastatic colorectal cancer. Preliminary data have been presented. The bevacizumab monotherapy arm was prematurely halted because of lack of efficacy.<br><br>The first-line use of cetuximab in combination with standard chemotherapy regimens is being investigated in a number of studies. One example is the COIN study (NCT00182715), which aims to determine whether the addition of cetuximab to continuous oxaliplatin and 5-FU improves overall survival when compared with either continuous oxaliplatin and 5-FU on its own, or intermittent oxaliplatin and fluoropyrimidine chemotherapy. Other examples include NCT00145314 (5-FU/FA + |

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| | oxaliplatin), NCT00286130 (FOLFIRI, FOLFOX) and NCT00215722 (capecitabine and oxaliplatin).<br><br>EXPLORE is an RCT comparing cetuximab combined with FOLFOX with FOLFOX alone as second-line treatment in patients with metastatic colorectal cancer. Recruitment to the trial was halted prematurely when the number of participants reached 102. Preliminary results were presented at the annual conference of the American Society for Clinical Oncology in 2005 for progression-free survival and response rate.<br><br>6.3 The Committee recommends research to investigate the predictive value of EGFR testing and the correlation of baseline and on-treatment markers with tumour response and survival.<br><br>6.4 Additionally, the Committee recommends studies to investigate the impact of bevacizumab and cetuximab treatment on health-related quality of life. |
| **6. Current cost of technology/ technologies:** | Bevacizumab: 100mg vial = £242.66; 400mg vial = £924.40 (BNF69) |
| **7. Cost information from the TA (if available):** | Bevacizumab: 100mg vial = £242.66; 400mg vial = £924.40 (BNF51) |
| **8. Alternative manufacturers:** | According to a UKMI Medicines Q&A (2013), bevacizumab's patent expired on 27/12/2014. It's UK regulatory status is: suspended. No generics or biosimilars. |
| **9. Changes to the original indication:** | Bevacizumab in combination with fluoropyrimidine-based chemotherapy is indicated for treatment of adult patients with metastatic carcinoma of the colon or rectum. (This is a change to the indication listed in TA118 but was included in the review of TA118 in 2009, where it was noted "*no treatment line specification*". In TA118 (2007) the indication was "Bevacizumab is licensed in the UK in combination with intravenous 5-FU/FA with or without irinotecan for first-line treatment of patients with metastatic |

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| | carcinoma of the colon or rectum.” |
| **10. New relevant trials:** | 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<br>Estimated Enrolment: 350; Estimated Study Completion Date: June 2017<br><br>An Exploratory Study of Treatment Sensitivity and Prognostic Factors in a Phase III, Randomized, Controlled Study Comparing the Efficacy and Safety of mFOLFOX6 + Bevacizumab Therapy vs. mFOLFOX6 + Panitumumab Therapy in Patients With Chemotherapy-naïve Wild-type RAS(KRAS/NRAS) Unresectable Advanced or Recurrent Colorectal Cancer NCT02394834<br>Estimated Enrolment: 800; Estimated Study Completion Date: September 2018<br><br>Sequential Treatment Strategy for Metastatic Colorectal Cancer (ITACa) NCT01878422<br>Estimated Enrolment: 350; Estimated Study Completion Date: March 2016<br><br>Multicenter Phase III Randomized Study of FOLFIRI Plus Bevacizumab Following or Not by a Maintenance Therapy With Bevacizumab in Patients With Non-Pretreated Metastatic Colorectal Cancer NCT00952029<br>Estimated Enrolment: 492; Estimated Study Completion Date: July 2016<br><br>Multicenter Randomized Trial Evaluating FOLFIRI Plus Cetuximab Versus FOLFIRI Plus Bevacizumab in First Line Treatment of Metastatic Colorectal Cancer NCT00433927<br>Estimated Enrolment: 568; Estimated Study Completion Date: December 2016<br><br>A Multi-center, Single-arm, Pilot Study of 5-FU Based Doublet Chemotherapy Plus Bevacizumab as Neoadjuvant Therapy for Patients With Previously Untreated Unresectable Liver-only Metastases From Colorectal Cancer NCT01695772 |

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| | Enrolment: 51; Estimated Study Completion Date: April 2016<br><br>Randomized, Open, Multicenter Phase III Study With Capecitabine Plus Bevacizumab Versus Capecitabine Plus Irinotecan Plus Bevacizumab as First-line Therapy in Patients With Metastatic Colorectal Cancer NCT01249638<br>Estimated Enrolment: 516; Estimated Study Completion Date: December 2016<br><br>Folfoxiri Plus Bev Followed by Reintroduction of Folfoxiri Plus Bev at Progression Versus Folfox Plus Bev Followed by Folfiri Plus Bev in mCRC (TRIBE2) Folfoxiri Plus Bev Followed by Reintroduction of Folfoxiri Plus Bev at Progression Versus Folfox Plus Bev Followed by Folfiri Plus Bev in mCRC (TRIBE2)<br>Estimated Enrolment: 654; Estimated Study Completion Date: February 2021<br><br>Study of Avastin in Combination With Chemotherapy for the First Treatment of Metastatic Colorectal Cancer NCT01972490<br>Estimated Enrolment: 150; Estimated Study Completion Date: March 2016 |
| **11. Relevant NICE guidance (published or in progress):** | NICE technology appraisal guidance [TA307] Aflibercept in combination with irinotecan and fluorouracil-based therapy for treating metastatic colorectal cancer that has progressed following prior oxaliplatin-based chemotherapy Published date: March 2014. Review date: August 2016<br><br>NICE technology appraisal guidance [TA285] Bevacizumab in combination with gemcitabine and carboplatin for treating the first recurrence of platinum-sensitive advanced ovarian cancer Published date: May 2013 Review: June 2016<br><br>NICE technology appraisal guidance [TA242] Cetuximab, bevacizumab and panitumumab for the treatment of metastatic colorectal cancer after first-line chemotherapy: 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 technology appraisal 150 and part review of technology appraisal guidance 118) |

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| | Published date: January 2012 Review: June 2016 Review decision - March 2015 - TA214 will now be moved to the static list.<br><br>NICE guidelines [CG131] Colorectal cancer: The diagnosis and management of colorectal cancer Published date: November 2011. Guideline currently being updated (no review date on website)<br><br>NICE technology appraisal guidance [TA212] Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine for the treatment of metastatic colorectal cancer Published date: December 2010. Review decision - July 2013 - TA212 will now be moved to the static list.<br><br>NICE technology appraisal guidance [TA176] Cetuximab for the first-line treatment of metastatic colorectal cancer Published date: August 2009. Review decision: TA176 was reviewed with TA240 and the decision made that TA176 should be updated, along with a related technology appraisal (TA240).<br><br>NICE technology appraisal guidance [TA61] Guidance on the use of capecitabine and tegafur with uracil for metastatic colorectal cancer Published date: May 2003. reviewed: June 2011 A61 and it can therefore be incorporated into the on-going clinical guideline for the diagnosis and management of colorectal cancer<br><br>**In development**<br><br>Colorectal cancer (metastatic) - cetuximab (review TA176) and panitumumab (part review TA240) (1st line) ID794 Anticipated publication date: April 2016<br><br>**Suspended/terminated**<br><br>Colon cancer (adjuvant) - irinotecan [ID379] Status: Suspended. Irinotecan is not currently licensed in the UK for the adjuvant treatment of colon cancer<br><br>NICE technology appraisal guidance [TA240] Panitumumab in combination with chemotherapy for the treatment of metastatic colorectal cancer (terminated appraisal) - no evidence submission was received from the manufacturer or sponsor of the |

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| | technology<br><br>NICE technology appraisal guidance [TA334]Regorafenib for metastatic colorectal cancer after treatment for metastatic disease (terminated appraisal) - no evidence submission was received from the manufacturer or sponsor of the technology |
| **12. Relevant safety issues:** | MHRA/CHM advice (BNF69)<br><br>Bevacizumab and sunitinib: risk of osteonecrosis of the jaw (January 2011)<br><br>Treatment with bevacizumab or sunitinib may be a risk factor for the development of osteonecrosis of the jaw. |
| **13. Any other additional relevant information or comments:** | The review of TA118 (May 2009) suggested an appraisal of bevacizumab following failure of first line treatment |
| **14. Technical Lead comments and recommendation:** | Since TA118, bevacizumab has received a broad marketing authorisation, which includes any fluoropyrimidine-based chemotherapy and does not specify a line of treatment, whereas in TA118, bevacizumab was licensed in combination with intravenous 5-FU/FA with or without irinotecan for first-line treatment of metastatic colorectal cancer. However, this does not affect this review because other bevacizumab combinations for first- or subsequent-line treatment have been covered by separate technology appraisals (TA212: bevacizumab in combination with oxaliplatin-containing, fluoropyrimidine-based chemotherapy; TA242: bevacizumab for metastatic colorectal cancer that has progressed after first-line chemotherapy).<br><br>This review identified new trials of first-line bevacizumab. However, these trials evaluated various combinations of bevacizumab, most of which do not match the combination in TA118 (bevacizumab in combination with 5-fluorouracil plus folinic acid, with or without irinotecan).<br><br>The current cost of bevacizumab remains the same as that from TA118. Bevacizumab's patent expired on 27/12/2014. However, no biosimilars to bevacizumab have been |

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| | identified in this review.<br><br>Given that no substantial new evidence has been identified in this review, and the cost of bevacizumab remains the same, the cost effectiveness of bevacizumab in combination with 5-fluorouracil plus folinic acid, with or without irinotecan, for the first-line treatment of metastatic colorectal cancer is unlikely to change compared with the original appraisal. In view of that, it is considered that recommendation 1.1 in TA118 should remain on the static list. |

**SLR paper sign off:** Janet Robertson – Associate Director, Technology Appraisals

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Date of IS searching: July 2015

## Appendix 1 – explanation of options

| Options | Consequence | Selected – 'Yes/No' |
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| The guidance will remain on 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 |
| The decision to review the guidance will be deferred to specify date or trial | NICE will consider whether a review is necessary at the specified date. NICE will actively monitor the evidence available to ascertain when a consideration of a review is more suitable. | No |
| A full consideration of a review will be carried out through the Review Proposal Process | There is evidence that could warrant a review of the guidance. NICE will schedule a consideration of a review, including a consultation with relevant consultees and commentators. | No |
| The guidance will be withdrawn | The guidance is no longer relevant and an update of the existing recommendations would not add value to the NHS. NICE will schedule a consideration of a review, including a consultation with relevant consultees and commentators. | No |