National Institute for Health and Clinical Excellence

Multiple Technology Appraisal (MTA)

Cetuximab (mono- or combination chemotherapy), bevacizumab (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 118)

Response to consultee and commentator comments on the draft scope (pre-referral)

Comment 1: the draft scope

Section	Consultees	Comments	Action
Background information	Greater Midlands Cancer Network (on behalf of NHS Telford and Wrekin)	This is accurate.	Comment noted.

Section	Consultees	Comments	Action
	Merck Serono	We feel that in terms of the review of TA 150 the evidence for cetuximab for the treatment of metastatic colorectal cancer following failure of oxaliplatin-containing chemotherapy has not changed therefore the terminated appraisal still stands. Although the scope is sufficiently broad to cover all technologies which are potentially part of this appraisal, we aim to focus the submission on the subgroup where evidence shows patients are most likely to benefit. For the purpose of this appraisal we will be submitting evidence for the use of cetuximab in combination with chemotherapy or as monotherapy in patients with EGFR-expressing KRAS wild-type metastatic colorectal cancer who have failed at least two previous chemotherapeutic regimens in the metastatic setting.	Comment noted.
	Amgen	No comment.	
	Roche	No comment.	
	Medical Research Council Clinical Trials Unit	OK	Comment noted.

Section	Consultees	Comments	Action
The technology/ intervention	Greater Midlands Cancer Network (on behalf of NHS Telford and Wrekin)	There should be consideration of cetuximab in combination with irinotecan as this is a treatment option (although not favoured in this Network)	NICE will only appraise drugs within their marketing authorisation. Combination regimens are covered within the marketing authorisation for cetuximab, which currently has a UK marketing authorisation for the treatment of colorectal cancer either in combination with chemotherapy, or as monotherapy in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan. Combination regimens are covered in the marketing authorisation for cetuximab.
	Merck Serono	It is not completely clear from the title and the 'intervention' section, however we assume that the appraisal seeks to evaluate both cetuximab monotherapy and cetuximab in combination with chemotherapy.	The appraisal intends to evaluate cetuximab in line with its marketing authorisation, that is, as monotherapy and also in combination with chemotherapy.
	Amgen	No comment.	

Section	Consultees	Comments	Action
	Roche	1. NICE has recently published negative provisional guidance for the bevacizumab in second-line mCRC, based upon the E3200 study. Therefore as a result of this negative guidance bevacizumzab has ceased to be a relevant intervention / comparator to the NHS. 2. The scope could currently be interpreted as suggesting that monotherapy bevacizumab is to be appraised, however this would be inappropriate as the license is in combination with fluoropyrimidine-based chemotherapy.	Comment noted. In technology appraisal 150, NICE was unable to recommend the use of cetuximab for the treatment of colorectal cancer following failure of oxaliplatin-containing chemotherapy The scope has been updated to consider bevacizumab only in combination with chemotherapy not containing oxaliplatin.
	Medical Research Council Clinical Trials Unit	OK	Comment noted.
Population	Greater Midlands Cancer Network (on behalf of NHS Telford and Wrekin)	Would add in chemo/radiotherapy for clarity.	Comment insufficiently clear.

Section	Consultees	Comments	Action
	Merck Serono	As described above we aim to focus the submission on the subgroup where evidence shows patients are most likely to benefit. For the purpose of this appraisal we will be submitting evidence for the use of cetuximab in combination with chemotherapy or as monotherapy in patients with EGFR-expressing KRAS wild-type metastatic colorectal cancer who have failed at least two previous chemotherapeutic regimens in the metastatic setting.	Comment noted.
	Amgen	The draft scope states that the relevant patient population would be “people with metastatic colorectal cancer that has progressed after first-line chemotherapy”. It is important to note that the licence for panitumumab is in monotherapy as it was studied in a patient population that had failed at least two prior therapies, i.e. 100% of patients in the panitumumab trial received two lines of prior chemotherapy.	Comment noted. The remit is for second-line and subsequent treatment regimens, as per TA118.
	Roche	No comment.	

Section	Consultees	Comments	Action
	Medical Research Council Clinical Trials Unit	Interventions should be assessed within patients known to express wild type KRAS as there is now fairly widespread evidence that cetuximab and panitumumab are only of potential benefit in these patients (NB most RCTs included patients with both wild type and mutant KRAS).	We can only appraise interventions in line with their marketing authorisation (note that cetuximab and panitumumab are only for KRAS positive patients). The following populations will be considered: 1) People with EGFR-expressing and KRAS wild-type metastatic colorectal cancer that has progressed after first-line chemotherapy (cetuximab & panitumumab population) 2) People with metastatic colorectal cancer that has progressed after first-line chemotherapy (bevacizumab population)
Comparators	Greater Midlands Cancer Network (on behalf of NHS Telford and Wrekin)	No – could include mitomycin which is used as 3rd line treatment.	As outlined in the SPC, mitomycin 'has a possible role in combination with other cytotoxic drugs in colorectal cancer'. Combination regimens are currently listed in the scope.

Section	Consultees	Comments	Action
	Merck Serono	Irinotecan and oxaliplatin-based therapy have been included within the comparators. These comparators are unlikely to be relevant for a population who have failed at least two chemotherapeutic regimens in the metastatic setting. For these patients optimised standard of care is the most appropriate alternative, combining palliative care, as well as supportive and active treatments.	Comment noted. Irinotecan- or oxaliplatin-based chemotherapy regimens are considered appropriate comparators as this appraisal is considering second-line (and subsequent) treatment options. If a patient has failed one type of chemotherapy regimen (either oxaliplatin or irinotecan-containing regimen) that they may try the alternative chemotherapy regimen as their subsequent treatment option. Best supportive care has been added to the list of comparators.

Section	Consultees	Comments	Action
	Amgen	The comparators stated in the draft scope include irinotecan- or oxaliplatin-based chemotherapy regimens; cetuximab, bevacizumab and panitumumab monotherapy will be compared with each other. Panitumumab is licensed as monotherapy for the treatment of patients with metastatic colorectal cancer after failure of fluoropyrimidine, oxaliplatin and irinotecan-containing chemotherapy regimens. Indeed, all patients in the panitumumab pivotal phase III study, which compared panitumumab plus best supportive care versus BSC alone (in patients with metastatic colorectal cancer who had progressed after standard chemotherapy) received two lines of prior chemotherapy and 37% of patients received three lines of prior chemotherapy. Therefore the relevant comparator for these patients who have developed resistance to existing chemotherapies would be best supportive care (BSC) and not irinotecan- or oxaliplatin-based chemotherapy regimens, and consequently, BSC should be included in the list of comparators.	Comment noted. The scope now states 'Where appropriate, the interventions will be compared with each other'. Best supportive care has been added to the list of comparators.
	Roche	Please see comment on the technology / intervention above regarding both the relevance of bevacizumab as either an intervention or comparator and also the comment regarding the use of "monotherapy"	Comment noted (see response above).
	Medical Research Council Clinical Trials Unit	I am unaware of any randomised controlled trials that have compared monotherapy with cetuximab or panitumumab versus chemotherapy with with either oxaliplatin-based or irinotecan based regimens in second line treatment of metastatic colorectal cancer patients who have progressed after first line treatment	Comment noted.

Section	Consultees	Comments	Action
Outcomes	Greater Midlands Cancer Network (on behalf of NHS Telford and Wrekin)	Yes.	Comment noted.
	Merck Serono	All reasonable outcome measures have been included in the scope.	Comment noted.
	Amgen	The outcomes listed in the draft scope exclude a key outcome measures that is important in capturing key health-related benefits, namely liver resection rates. It is acknowledged that chemotherapy may render unresectable liver metastases operable and result in longer term survival for a proportion of patients: TA 176 recommended cetuximab for the first-line treatment of metastatic colorectal cancer on condition that the metastatic disease is confined to the liver and is unresectable. Although the rates of liver resection are lower in the second and third line setting, we understand from expert opinion the resection does take place (albeit on a small proportion of patients). We therefore recommend that the outcome of liver resection rates be added in the scope for this review.	Comment noted. 'If evidence allows, liver resection rates should be considered' has been added to the scope (see other considerations section).
	Roche	No comment.	
	Medical Research Council Clinical Trials Unit	I think the key outcomes are included.	Comment noted.

Section	Consultees	Comments	Action
Economic analysis	Greater Midlands Cancer Network (on behalf of NHS Telford and Wrekin)	No comment.	
	Merck Serono	No further comments other than the economic analysis will focus on the subpopulation described above.	Comment noted.
	Amgen	No comment.	
	Roche	No comment.	
	Medical Research Council Clinical Trials Unit	This is outside my area of expertise therefore I have no comment to make.	Comment noted.
Equality and Diversity	Greater Midlands Cancer Network (on behalf of NHS Telford and Wrekin)	No comment.	

Section	Consultees	Comments	Action
	Merck Serono	A number of networks in the UK have already approved the use of cetuximab as a third line treatment for KRAS wild type mCRC patients ahead of NICE guidance. Consequently, potential inequity could exist across current NHS clinical practice. Effectively, in some Trusts, patients would have access to cetuximab therapy in the third line setting, whilst in other areas patients would only have the option of appealing to an exceptional cases panel creating inequity for patients in accessing newer and more effective treatment options. In addition, many patients are currently dying prematurely each year due to health inequalities and social differences (partly as a result of late diagnosis in patients) therefore action is required in reducing survival differences for metastatic colorectal cancer patients.	Comment noted. NICE guidance helps to standardise access to healthcare across the country. The NHS is legally obliged to fund and resource medicines and treatments recommended by NICE's technology appraisals.
	Amgen	No comment.	
	Roche	No comment.	
	Medical Research Council Clinical Trials Unit	This is outside my area of expertise therefore I have no comment to make.	Comment noted.
Innovation			
Other considerations	Greater Midlands Cancer Network (on behalf of NHS Telford and Wrekin)	No comment.	

Section	Consultees	Comments	Action
	Merck Serono	We feel that the supplementary advice for appraisal end of life treatments should be applied for the subpopulation of patients with EGFR-expressing KRAS wild-type metastatic colorectal cancer who have failed at least two previous chemotherapeutic regimens in the metastatic setting. These represent a small population of patients where life expectancy is generally below 24 months and where cetuximab offers an extension of life of more than 3 months.	Comment noted. The committee will consider the appraisal of end of life treatments when all the following criteria are met: 1. The treatment is indicated for patients with a short life expectancy, normally less than 24 months and; 2. There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment, and; 3. The treatment is licensed or otherwise indicated for small patient populations.
	Amgen	No comment.	
	Roche	No comment.	

Section	Consultees	Comments	Action
	Medical Research Council Clinical Trials Unit	No comment.	
Questions for consultation	Greater Midlands Cancer Network (on behalf of NHS Telford and Wrekin)	No comment.	

Section	Consultees	Comments	Action
	Merck Serono	1) Most appropriate comparators? See 'comparators' section. 2) Other comparators? See 'comparators' section. 3) Subgroups, equality and equity? As described above, we aim to focus the submission on the subgroup where evidence shows patients are most likely to benefit. For the purpose of this appraisal we will be submitting evidence for the use of cetuximab in combination with chemotherapy or as monotherapy in patients with EGFR-expressing KRAS wild-type metastatic colorectal cancer who have failed at least two previous chemotherapeutic regimens in the metastatic setting 4) Clinical outcomes and health-related benefits See 'outcomes' section. 5) Nature of the data The evidence for the effectiveness of cetuximab as monotherapy is based upon a randomised controlled trial 'CO17' which compares the intervention against, the most appropriate comparator in this setting. In terms of evidence for cetuximab in combination with chemotherapy, various sources can be used including. □ Pivotal randomised controlled trials undertaken prior to original license for mCRC □ Systematic review and meta-analysis of randomised controlled trials □ Retrospective KRAS analysis of some patients within the pivotal trials. The KRAS analysis was not part of original trial protocols.	Comment noted.

Section	Consultees	Comments	Action
Additional comments on the draft scope.	Greater Midlands Cancer Network (on behalf of NHS Telford and Wrekin)	No comment.	
	Merck Serono	No comment.	
	Amgen	No comment.	
	Roche	As indicated above bevacizuamab has ceased to be a relevant comparator as a result of the recent provisional negative guidance. However even if it were still considered relevant the following should be considered:-- 1. The pivotal trial evidence for cetuximab 2nd line is in combination with irinotecan-based therapy whilst for bevacizumab 2nd line pivotal trial was in combination with oxaliplatin-based therapy. Patients would typically not be retreated with the same chemotherapy 2nd line as they received 1st line; hence it would be of little clinical relevance to compare bevacizumab in combination with oxaliplatin-based therapy with cetuximab in combination with irinotecan-based treatment. 2. The license for cetuximab and panitumumab are for use in EGFR expressing KRAS-Wild-Type patients whereas the license, and trial data, for bevacizumab is for all mCRC patients creating additional difficulties in making any cross trial comparison required to compare these drugs.	Comment noted. In technology appraisal 150, NICE was unable to recommend the use of cetuximab for the treatment of colorectal cancer following failure of oxaliplatin-containing chemotherapy The scope has been updated to consider bevacizumab only in combination with chemotherapy not containing oxaliplatin.

Section	Consultees	Comments	Action
	NCC for cancer	The view of the NCC for Cancer (on behalf of the Colorectal Cancer Guideline Development Group) is that an MTA would be of little value to the NHS as cetuximab and bevacizumab are seldom used as single agents. Cetuximab and bevacizumab have already been appraised in combination and an appraisal of their use as single agents is unlikely to be of value. An STA of panitumumab would be useful.	Comment noted.

Section	Consultees	Comments	Action
	Medical Research Council Clinical Trials Unit	I think that in treatment of patients with metastatic colorectal cancer who have progressed after first line treatment, it is more likely that RCTs will have made a comparison of cetuximab or panitumumab in combination with chemotherapy versus the same chemotherapy alone; rather than cetuximab or panitumumab monotherapy versus chemotherapy. The review with regards to cetuximab and panitumumab assessment should include all randomised patients, but with emphasis on those known to express wild type KRAS. Along with a group of co-authors from within the MRC Clinical Trials Unit and externally, we have been conducting a full systematic review and meta-analysis of RCTs comparing the anti-EGFR monoclonal antibodies, Cetuximab and Panitumumab either as monotherapy (versus best supportive care) or in combination with chemotherapy (versus the same chemotherapy alone) in patients with advanced or metastatic colorectal cancer. We conducted extensive literature searches (according to Cochrane Collaboration methods) and identified all relevant studies. We did not identify any studies of antibody monotherapy versus conventional chemotherapy. The systematic review and meta-analysis has now been compelted and we are preparing a manuscript for publication presently. Should you require further details I would be happy to provide this information.	Comment noted. NICE will only appraise drugs within their marketing authorisation. Cetuximab currently holds a UK marketing authorisation for treatment either in combination with chemotherapy; or as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan, and will be appeaised as both a monotheraspy and in combination with chemoptherapy. Panitumumab is currently licensed for use as a monotherapy only (within this indication).

The following consultees/commentators indicated that they had no comments on the draft scope

Royal college of Nursing

NHS QIS

Macmillan Cancer Support

WAG
Department of Health
Pfizer
UKONS