Bevacizumab and cetuximab for treatment of advanced colorectal cancer – table of consultee comments draft scope

Section	Consultees	Comments	Response
Objective	CancerBACUP	We recommend that the word advanced used in the title of the appraisal and under the 'Objectives' heading is removed and replaced with 'metastatic'. Both bevacizumab and cetuximab are licensed for use in metastatic colorectal cancer rather than advanced cancer.	Although the Institute has in the past treated the term 'advanced' to mean the same as 'metastatic' it appreciates that the licenses of bevacizumab and cetuximab use 'metastatic' and thus decided to change the draft scope accordingly.
	ScHARR	Bevacizumab and cetuximab should be considered as two separate appraisals. The choice of which intervention should be appraised first should be led by the maturity of clinical trial data, and the timescales for the completion of current ongoing trials of these therapies. Our initial scoping searches suggest that 2 Phase III trials of bevacizumab have been completed. However, the two key phase III trials for Cetuximab (Cunningham et al - irinotecan and cetuximab vs irinotecan, and Maughan et al – the COIN trial), have not yet been completed.	The Institute decided to combine the appraisal of these two drugs for the following reasons: efficient use of Assessment Group resources by using one background section and if possible one model and the recent review of irinotecan, oxaliplatin and raltitrexed was able to combine 1st and 2nd line treatment option in one economic modelling framework. The Institute is not aware of a study that plans to compare cetuximab in combination with irinotecan versus irinotecan alone.
Background	Colon Cancer Concern	Can we add the following text - in italics - in the middle of the second paragraph of this section: *Although the disease is very treatable if caught early,* approximately 30% of those individuals diagnosed with colorectal cancer present with the advanced disease*.*	The scope is not the place to comment on the 'treatability' of a specific disease.
The technologies	ScHARR	The intervention is appropriately defined by the draft scope as *"bevacizumab (in combination with 5-FU/FA or with irinotecan plus 5-FU/FA."*	Noted.
	ScHARR	The scope appropriately defines the intervention for the appraisal as *"Cetuximab in combination with irinotecan."*	Noted.
Population	Colon Cancer Concern	Shouldn't the "For bevacizumab" section read: People with untreated advanced *metastatic* colorectal cancer	See above. The scope has been amended.

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	Merck Pharmaceuticals	*For bevacizumab: People with untreated advanced colorectal cancer' (p.2)* - The Summary of Product Characteristics for bevacizumab states that it is 'indicated for first-line treatment of patients with *metastatic* carcinoma of the colon or rectum' (our emphasis). It is important to clarify the distinction between advanced and metastatic stages of the disease.	See above. The scope has been amended.
	ScHARR	The population for the appraisal [of bevacizumab] is slightly unclear. The scope defines the population as *"people with untreated advanced colorectal cancer."* It would be useful for NICE to clarify that these patients may have received adjuvant treatment for earlier disease, although their advanced disease is untreated.	See above. The scope has been amended. Currently, adjuvant treatment is licensed for Dukes' C colon cancer only, which does not include metastatic cancer.
	ScHARR	The population for the appraisal [of cetuximab] is defined as "People with EGFR-expressing metastatic colorectal cancer who failed irinotecan-including therapy." We would like NICE to clarify whether this population includes patients who have previously failed on adjuvant irinotecan in non-advanced colorectal cancer or those patients who have failed on first-line irinotecan for advanced colorectal cancer. The title for the appraisal should reflect the fact that this intervention is indicated only for a specific subgroup of colorectal cancer patients. To avoid confusion, the title of the appraisal should be changed to *"The use of cetuximab for the second-line treatment of patients with EGFR-expressing metastatic colorectal cancer."* It should also be noted that the licensing for cetuximab may be extended to include patients who have failed using oxaliplatin in the future.	Irinotecan is currently not licensed in the UK for adjuvant treatment of 'non-advanced colorectal cancer'. The Institute thus interpreted the license of cetuximab to only include patients with EGFR-expressing metastatic colorectal cancer after failure of irinotecan-including cytotoxic therapy *for their metastatic colorectal cancer* [addition NICE (not in text of SmPC)]. The license of cetuximab allows it to be used in second- and third-line treatment of metastatic colorectal cancer. This is addressed in the scope in the sections that describe the population eligible for cetuximab and current standard treatments for the comparison. The interventions will be appraised in accordance with their existing license.

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Current Standard Treatments (comparators)	CancerBACUP	We would also recommend that the section detailing comparators is amended to read: **Current standard treatments (comparators):** For bevacizumab and cetuximab: • Established fluorouracil containing regimen • Irinotecan • Oxaliplatin • Combination chemotherapy • Best supportive care	The scope has not been amended. Bevacizumab and cetuximab are licensed for use in different patient groups and as a result standard treatments differ.
	Merck Pharmaceuticals	*'For bevacizumab: established fluorouracil-containing or releasing regimen' (p.2).* - We believe it would be helpful to clarify the above statement in terms of specifically available actual treatment options: a. established fluorouracil-containing regimen alone b. capecitabine c. oxaliplatin in combination with 5-FU/FA d. irinotecan in combination with 5-FU-FA	The scope has not been amended. The actual comparisons will depend on the available evidence but the definition used in the scope covers the treatments listed by the consultee.

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	Merck Pharmaceuticals	*'For cetuximab: irinotecan alone' (p.2)* - NICE Technology Appraisal No. 33 (issued March 2002) recommends the use of irinotecan monotherapy following the failure of 5-FU/FA. In clinical practice, irinotecan monotherapy is the recommended 2nd-line of chemotherapy for metastatic colorectal cancer patients. Cetuximab, in combination with irinotecan, is licensed for the treatment of patients who have *progressed* on irinotecan-including cytotoxic therapy, and therefore constitutes a new (3rd-line) treatment. Under the current marketing authorisation, cetuximab can only be used in patients who have failed irinotecan; therefore irinotecan monotherapy can not be used as a comparator to cetuximab in combination with irinotecan. - Colorectal cancer patients who have experienced a treatment break from irinotecan may be *re-challenged* with irinotecan. Patients who have progressed on irinotecan therapy will not be re-challenged with irinotecan, due to the lack of evidence to support this clinical approach. Re-challenging patients who have progressed on irinotecan is not a part of standard clinical practice.	The scope has been amended to delete irinotecan monotherapy as it is indeed unlikely that patients who received irinotecan as part of their treatment in first-line will receive irinotecan monotherapy in second-line. Noted.
	Merck Pharmaceuticals	*'For cetuximab: oxaliplatin in combination with 5-FU/FA by infusion' (p.2)* - Patients in the pivotal cetuximab clinical trial - Bowel Oncology with Cetuximab Antibody (BOND) – represent a heavily *pre-treated* cohort. The majority of patients in BOND (62%) had already progressed on oxaliplatin, in addition to progression on irinotecan therapy. Oxaliplatin with 5-FU/FA can be compared to cetuximab plus irinotecan only in those patients who have not previously progressed on oxaliplatin.	Noted.

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	Merck Pharmaceuticals	*'For cetuximab: active supportive care' (p.2)* - The clinical literature often refers to 'active supportive care', 'supportive care' or 'best supportive care'. The terminology can vary between clinical papers and national healthcare systems. Active supportive care, and the role of palliative chemotherapy within active supportive care, needs to be clearly defined in the final scoping document. - Following disease progression with irinotecan monotherapy, metastatic colorectal cancer patients currently have no further established lines of therapy available, with the exception of adding cetuximab to irinotecan. Cetuximab plus irinotecan therefore addresses an unmet clinical need for which there is no alternative.	The scope has been amended to read active/best supportive care (that is without chemotherapy) Noted.
	ScHARR	The draft scope defines the current standard treatment [for bevacizumab] as *"established fluorouracil-containing or releasing regimen."* We would suggest that the comparators for the appraisal should reflect the Appraisal Committee's recommendations following the review of irinotecan, oxaliplatin and raltitrexed in the treatment of advanced colorectal cancer. We would also suggest that active supportive care should be put forward as a relevant comparator for the appraisal.	The current list of standard treatments represents all licensed possibilities for the patient group that is eligible for bevacizumab. Active supportive care does not appear to be an appropriate standard treatment option for first-line treatment of metastatic colorectal cancer. The scope has not been amended.
	ScHARR	The list of current standard treatments defined within the scope [for cetuximab] is restrictive. We suggest that the relevant comparator should reflect the Appraisal Committee's recommendations following the review of irinotecan, oxaliplatin and raltitrexed in the treatment of advanced colorectal cancer.	The current list of standard treatments represents all licensed possibilities for the patient group that is eligible for cetuximab. The scope has been amended to delete irinotecan monotherapy.
	Colon Cancer Concern	Where it says 'For cetuximab: irinotecan alone': As we understand it, current NICE guidance says that cetuximab can only be used in patients who have failed irinotecan. Consequently, irinotecan monotherapy cannot be compared to cetuximab in combination with irinotecan.	NICE has not issued guidance on cetuximab. The scope has been amended to delete irinotecan monotherapy as it is indeed unlikely that patients who received irinotecan as part of their treatment in first-line will receive irinotecan monotherapy in second-line.

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	Colon Cancer Concern	Where it says: 'For cetuximab: oxaliplatin in combination with 5-FU/FA by infusion': As we understand it, oxaliplatin with 5-FU/FA can only be compared to cetuximab with irinotecan in patients who have not previously progressed on oxaliplatin.	Noted.
	Colon Cancer Concern	It should also be pointed out that cetuximab with irinotecan currently addresses an unmet clinical need, which there is currently no alternative to. After disease progression with irinotecan monotherapy, metastatic colorectal cancer patients currently have no further established lines of therapy available, with the exception of adding cetuximab to irinotecan. Consequently, could you add a bullet point to reflect this; such as: • No current standard treatment comparators to cetuximab with irinotecan (which meets an otherwise unmet clinical need)	The scope has not been amended because active/best supportive care sufficiently describes third-line treatment options.
Outcomes	ScHARR	The outcomes for the appraisal include survival, progression-free survival, tumour response rate, time to tumour failure, adverse events/toxicity and health-related quality of life. These are identical to the set of outcomes used in the appraisal of irinotecan, oxaliplatin and raltitrexed, and are thus relevant within this appraisal.	Noted.
Economic Analysis	Cancer Services Collaborative	We would be keen to ensure that the appraisal contains a detailed analysis of the pharmacy, medical, nursing and clinic resources required to deliver the new therapies. Issues concerning staffing and facilities are becoming as, if not more important, than actual drug costs and we need to know exactly what impact on the service a new treatment is likely to have before it is introduced. We are about to conduct a national survey of capacity and demand for chemotherapy services which we hope will provide data that can be used to inform this and future appraisals.	Noted.

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	Merck Pharmaceuticals	*'The cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year' (p.2)* - The validity of generic utility scores for patients with 'end-stage' metastatic colorectal cancer (i.e. cetuximab eligible patients) has not been established. There is strong evidence that patients, given their poor prognosis, will re-frame their utility scores, possibly no-longer trading-off quantity vs. quality of life. - While we recognise the methodological advantages of expressing cost effectiveness as a cost per quality-adjusted life year for public health decision-makers, the limitations of this approach for a critical illness such as metastatic colorectal cancer should be acknowledged, and should not be the sole basis for decision-making in regard to cost effectiveness. - Alternative pharmacoeconomics outcomes, potentially more sensitive to the disease area of metastatic colorectal cancer, should be given equal consideration by decision-makers (i.e. cost per progression-free life year, cost per life-year-gained).	Noted.
	ScHARR	The outcomes for the analysis should be broader and should include the cost per life year gained. It is unclear whether NICE are proposing an incremental economic analysis of bevacizumab and cetuximab versus all other comparators (i.e. the economic evaluation of the FOCUS and Tournigand trials), or a marginal analysis of bevacizumab and cetuximab against the comparators used in the trials.	The scope has been amended to include the word 'ideally' before the sentence on cost effectiveness. If evidence allows it would be appropriate to make those comparisons.
Other Considerations	Merck Pharmaceuticals	*'It is anticipated that individuals receiving interventions first-line may subsequently receive other interventions as second-line treatment' (p.3)* - Between 'second-line' and 'treatment' please add the words 'and third-line'. As noted above, cetuximab plus irinotecan, active supportive care, and oxaliplatin in combination with 5-FU/FA by infusion, are all potential third-line treatment options in clinical practice.	The scope has been amended to include reference to third-line treatment.

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	ScHARR	A review of bolus/infusional 5-FU/FA regimens has already been explored as part of the update of Guidance no. 33 - The use of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer.	Noted.
	Royal College of Pathologists	Since cetuximab is only given to people with EGGER-expressing tumours it will be important to evaluate the histopathological methodology used to demonstrate EGFR-expression, especially in relation to its reproducibility and quality control.	Noted.
	Colon Cancer Concern	Where it says: 'It is anticipated that individuals receiving interventions first-line may subsequently receive other interventions as second-line treatment': Can you please amend the end of this paragraph to say '….as second-line and third-line treatment' because cetuximab with irinotecan and oxaliplatin in combination with 5-FU/FA by infusion, are potential third-line treatment options in clinical practice.	The scope has been amended to include reference to third-line treatment.

Consultees of which response was received but with no specific comments on the draft scope:

Roche Products Ltd	Beating Bowel Cancer	Welsh Assembly Government
Pfizer Ltd	Department of Health	Royal Pharmaceutical Society of Great Britain
MRC Clinical Trials Unit	Mayne Pharma	Royal College of General Practitioners
Wyeth Pharmaceuticals	CORE	Marie Curie Cancer Care
Royal College of Surgeons	Association of Coloproctology of Great Britain and Ireland	
Board of Community Health Councils in Wales		