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NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Bevacizumab and Cetuximab for the treatment of metastatic colorectal cancer

Response to consultee, commentator and public comments on the ACD

Consultee	Comment	Institute Response
Royal College of Pathologists	I have read through the NICE Appraisal Consultation Document on use of Bevacizumab and Cetuximab for Metastatic Colorectal Cancer and my comments on the document are as follows: 1) I would like to confirm that as far as I can judge all the relevant evidence has been taken into account to prepare the report. 2) The summaries of clinical and cost effectiveness provided in the report are reasonable interpretations of the evidence and that the preliminary views on the overall resources impact and implications for the NHS are appropriate. In case of bevacizumab it is to be noted however, that the statistically proven clinical effectiveness of the drug is unfortunately not balanced by its cost effectiveness due to its costliness. For cetuximab it is paramount that if the drug is to have any continued scientifically meaningful clinical use then more reliable clinically validated methods and criteria for identifying EGFR positive colorectal cancer are introduced to select patients compared to the current approach. 3) The provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of the guidance to the NHS.	Comments noted.
NHS: Quality Improvement Scotland	Reviewer 1 *Whether all the relevant evidence has been taken into account?* I do *Whether the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate?* I do consider the summary of the clinical effectiveness data is	Reviewer 1: Comments noted. Comments noted.

Consultee	Comment	Institute Response
	reasonable. I am not qualified to comment on the details of the cost effectiveness analysis. *Whether the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?* I agree in so much as the document acknowledges the effectiveness of these agents, but states that the "accepted" level of appropriate cost-effectiveness is not achieved. It is not for me to comment on the appropriateness of the "accepted" level threshold which has been applied. I would also comment that planned review in 3 years, should allow some flexibility for 1 or other agent to be reconsidered earlier if important new data are forthcoming.	The Committee considered that most ongoing research focused on bevacizumab and cetuximab in regimens outside of the current marketing authorisation. Additional bevacizumab and cetuximab regimens may be referred separately to the NICE technology appraisal programme if a licence is applied for accordingly. The review date therefore remains unchanged, but consultees can request an early review if relevant new data becomes available.
NHS: Quality Improvement Scotland (cont.)	Reviewer 2 *Whether all the relevant evidence has been taken into account?* Bowel Cancer UK has submitted comprehensive evidence of the efficacy of both these treatments, from the charity, clinician and patient perspectives. We hope that this and other evidence has been taken fully into account in both the NICE and SMC appraisals of these drugs. *Whether the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate?* Bowel Cancer UK believes, from the evidence that we have gathered and submitted, that both these treatments are extremely effective and should be made available to all patients that will benefit from them. Furthermore, the treatments should be made available on the basis of their efficacy and not be denied to patients on the grounds of cost – which seems to be the sole basis for the provisional negative guidance relating to them. *Whether you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?* Bowel Cancer UK is very disappointed with the provisional guidance because it indicates that these two biological agents will not be made available on the NHS, despite their proven efficacy and potential benefit to many bowel cancer patients. It is ironic that while the UK	Reviewer 2: The Committee considered all the evidence submitted, including evidence from clinical trials, patient experts and clinical specialists The Committee does not consider the affordability, that is cost alone, of new technologies but rather their cost effectiveness in terms of how its advice may enable the more efficient use of available healthcare resources (NICE Guide to the Methods of Technology Appraisal, paragraphs 6.2.6.1 – 6.2.6.3). Comment noted.

Consultee	Comment	Institute Response
	has been in the forefront of developing both these drugs, including the clinical trials, it looks as if we shall, once again, be at the very back of the queue when it comes to being able to make them available to patients. It is also very hard not to become frustrated and cynical when NICE appears to be making decisions on the basis of financial expediency rather than clinical efficacy. We shall continue to campaign for increased access to these valuable treatments and call on NICE to reconsider its decision and make these drugs available to patients that need them.	
NHS quality improvement Scotland (cont.)	Reviewer 3. This ACD advises that neither bevacizumab nor cetuximab be recommended for routine use in the NHS for first- or second line treatment of metastatic colorectal cancer respectively. The most necessary trial information is not available for cetuximab, in that direct comparisons of best standard treatment +/- cetuximab have not yet been reported. The survival benefits, although statistically significant, are marginal and bought at the expense of significant additional toxicity. The cost effectiveness estimates are therefore not compatible with the requirements for routine adoption and the case for further use to be confined to within research settings seems clear. I have no doubt that if the final recommendation is unchanged, it will be equally applicable in Scotland as in England and Wales.	Reviewer 3: Comments noted.
Cancerbackup	I write in response to the Appraisal Consultation Document (ACD) for the above appraisal. Cancerbackup is very disappointed at NICE's initial decision not to recommend these technologies, and we are particularly concerned at the provisional recommendation not to make bevacizumab available on the NHS for people with metastatic colorectal cancer. Colorectal cancer is common in England and Wales, with an estimated 30,909 new cases diagnosed each year. A NICE decision not to recommend the use of these two technologies would impact greatly on the length of life of a significant number of people. Bevacizumab and cetuximab offer increased active treatment options and provide patients and physicians the potential option to extend life as well as manage symptoms, in a sizeable proportion of patients. One study showed the median survival time for bevacizumab with bolus 5-FU/FA plus irinotecan as 20.3 months, compared to 15.6 months for a placebo with bolus 5-FU/FA plus irinotecan. The median time of progression free survival was 10.6 months compared with 6.2 months with the placebo. Colorectal cancer is difficult to treat once it has advanced,	Comments noted. This information was submitted to the Institute as part of the manufacturer's submission

Consultee	Comment	Institute Response
	with a wide range of physical and psychological symptoms resulting in decreased quality of life. Targeted compounds such as bevacizumab and cetuximab have the potential to be less toxic than other treatments, and may even reverse acquired drug resistance in some patients. The side effects of both bevacizumab and cetuximab are generally mild. Cancerbackup welcomes an early review of ongoing research relating to these technologies, as recommended in the ACD, to consider further evidence of clinical effectiveness. However, a decision not to recommend bevacizumab in particular would undoubtedly damage the UK's long-term ability to conduct research in this disease area.	The Committee considered that most ongoing research focused on bevacizumab and cetuximab in regimens outside of the current marketing authorisation. Additional bevacizumab and cetuximab regimens may be referred separately to the NICE technology appraisal programme if a licence is applied for accordingly. The review date therefore remains unchanged, but consultees can request an early review if relevant new data becomes available.
	Cetuximab: Cetuximab has already been recommended for use in the NHS in Wales. I hope that NICE will reconsider its decision to effectively withdraw this treatment from availability in Wales, and ensure its equal availability to patients across the UK.	The Institute recognises that guidance from other organisations may differ from its own guidance, because of different criteria for making decisions. NICE guidance supersedes guidance previously provided by the All Wales Medicines Strategy Group.
	Bevacizumab: Bevacizumab is considered to be the most beneficial technology for some years for treating colorectal cancer in a palliative setting. Our clinical advisers tell us that some clinicians in the UK are choosing to give bevacizumab intermittently over a period of three months, rather than eight months as referred to in the ACD. NICE does not consider this in its assessment of cost effectiveness, yet a recalculation of its cost based on the shorter time period would inevitably result in greater cost effectiveness. NICE must conduct	The Committee is required to make decisions within the context of the marketing authorisation. The dosing regimen specified in the SPC is once every fortnight until underlying disease progression.

Consultee	Comment	Institute Response
	a further assessment of bevacizumab as soon as further evidence is available to evaluate its relative effectiveness. NICE's final recommendations must reflect the significant impact that bevacizumab can have on survival time for people with metastatic colorectal cancer. Further consideration must also be given to patients' quality of life when appraising bevacizumab and cetuximab. I urge NICE to consider these points and to recommend these technologies for use in the NHS.	The Appraisal Committee considered the quality of life of patients with metastatic colorectal cancer including utility data provided by one of the manufacturers (FAD 4.2.8) and case studies in submissions from consultees.
Royal College of Nursing	**Evidence** The evidence appears to be a very comprehensive and thorough review of the evidence available on the use of these drugs. As well as reviewing the relevant clinical trials, the Committee have sought opinions from specialists who are experts in the management of colorectal cancer. We do not consider that any evidence has been omitted. We welcome the Committee's consideration of the technology assessment report produced by the School of Health and Related Research (ScHARR). **Clinical effectiveness** The three randomised controlled trials using bevacizumab have been analysed thoroughly when looking at the effectiveness of bevazizumab as first-line treatment for metastatic colorectal cancer and appropriate outcomes have been identified. The Appraisal Committee addressed the use of cetuximab for second-line or subsequent treatment of metastatic colorectal cancer. No studies comparing cetuximab with current standard treatments were identified. The Committee therefore looked at one randomised controlled trial and three single-arm studies. These were analysed and interpreted appropriately. **Cost effectivenss** When considering the cost effectiveness of these two drugs the Committee have considered both the manufacturer's models and additionally the assessment group developed two models for each drug. This seems a very thorough evaluation and interpretation of the evidence. When considering the above evidence for both clinical and cost effectiveness, we consider	Comments noted. Comments noted. Comments noted.

Consultee	Comment	Institute Response
	that the Committee also took into account the technology assessment report produced by ScHARR. We would offer no further comments. **Resource impact and implications for NHS** It is accepted that when a new drug is prescribed, health care professionals have to take into account the supporting infrastructure such as sustaining increased patient through-put in clinics, pharmacy and nursing costs and all associated episodes such as in-patient admissions. These will obviously impact on the NHS resources. However, the NHS Cancer Plan (2000) pledged a commitment to improving treatment and reducing cancer mortality by providing patients with the best care and professional support by tackling inequalities in health and treatment. It would seem unethical to deny patients treatments that are more effective and which possibly could result in a longer survival time. **Provisional recommendations** The recommendations appear to be sound but it is disappointing that clinicians are not able to offer these treatments to patients who would be clinically eligible, thereby prolonging survival. It is frustrating for both patient and clinician. The review date of May 2009 seems unacceptably long although it is appreciated that further research is being carried out, we suggest that an earlier review date is considered.	The recommendations are not inconsistent with the NHS cancer plan. The NHS cancer plan pledges to make the most appropriate treatment available to patients, and specifically refers to NICE guidance and therefore the concept of using cost-effectiveness as a criterion for decision making. The Committee considered that most ongoing research focused on bevacizumab and cetuximab in regimens outside of the current marketing authorisation. Additional bevacizumab and cetuximab regimens may be referred separately to the NICE technology appraisal programme if a licence is applied for accordingly. The review date therefore remains unchanged, but consultees can request an early review if relevant new data becomes available.
Merck Pharmaceuticals	**i) whether we consider that all of the relevant evidence has been taken into account.** Merck Pharmaceuticals do not consider that all of the relevant evidence has been taken into account. We should like to: A. reply to certain specific points in the ACD (*in italics below*), with which we take issue. B. draw the appraisal committee's attention to additional evidence which supports the use of cetuximab + irinotecan as a 3rd line therapy for mCRC.	Cetuximab was appraised within the context of the current marketing authorisation and within the boundaries defined in the scope for this appraisal. The licensed indication does not stipulate that an oxaliplatin containing regimen has to have failed in order for the patient to receive cetuximab

Consultee	Comment	Institute Response
	A. Reply to specific points in the ACD **4.1 Clinical Effectiveness: Section 4.1.7** *"The assessment group identified no studies that compared cetuximab with current standard treatments (FOLFOX or active/ best supportive care)".* We would like to highlight that we do not consider FOLFOX to be a comparator to cetuximab + irinotecan therapy. We have proposed that patients who are eligible to receive cetuximab + irinotecan therapy have already received an oxaliplatin-containing regimen in addition to an irinotecan-containing regimen. Re-challenge with FOLFOX would not therefore be a treatment option for these patients and cannot be considered a comparator treatment in this 3rd line setting.	combined with irinotecan. It could therefore be used as a second line therapy for those patients who have received FOLFIRI first line. This was also highlighted in the manufacturer's comments on the scope of this appraisal which stated that cetuximab plus irinotecan could be compared to FOLFOX in those patients who have not previously progressed on oxaliplatin. The subgroups of patients receiving cetuximab and inrinotecan either as second line or as third line were discussed by the Committee – see FAD document section 4.3.6, 4.3.7.
Merck Pharmaceuticals (cont)	*"The participants included in the studies tended to be younger than the average age of patients receiving chemotherapy in England & Wales; a median age of 56 years was reported in two of the trials and a median age of 59 years in the other two. In all four studies, the populations tended to have good performance status (ECOG 0 to 1 or Karnofsky 80-100)".* Merck Pharmaceuticals challenged these statements in April 2006 when they appeared in the Technology Assessment Report and provided audit data from a total of 2337 UK patients with metastatic colorectal cancer receiving all lines of chemotherapy for mCRC collected in three "waves"; • May – June 2004 (n=791), • Dec 2004 – Jan 2005 (n=796) • October - November 2005 (n=750). The table below summarises the mean age and ECOG performance status for those patients who specifically received 3rd line treatment for their mCRC. This clinical practice ("real life") audit shows that the mean age of patients receiving chemotherapy in the 3rd line setting is 58.7 years - 62.8 years. In addition, between 74% and	The age of the participants in the cetuximab clinical trials was not a deciding factor in the guidance. The text in the FAD has been amended.

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87% of these patients have an ECOG performance status between 0 and 1.

<table>
<tr><th>3rd line patients</th><th>May – June 2004</th><th>December 2004 – January 2005</th><th>October - November 2005</th></tr>
<tr><td>n</td><td>52</td><td>69</td><td>49</td></tr>
<tr><td>Mean age (yrs)</td><td>62.3</td><td>62.8</td><td>58.7</td></tr>
<tr><td>ECOG 0 - 1 (%)</td><td>74</td><td>87</td><td>78</td></tr>
</table>

The studies included in the submitted dossier for cetuximab + irinotecan on August 23rd 2005 reflected the epidemiological data gained from these audits:

<table>
<tr><th></th><th>BOND trial</th><th>Saltz et al.,2001</th><th>Seitz et al., 2005</th></tr>
<tr><td>n</td><td>329</td><td>138</td><td>24</td></tr>
<tr><td>Median age: yrs [range]</td><td>59 [26-84]</td><td>56 [26-83]</td><td>53 [31-78]</td></tr>
<tr><td>KPS/ ECOG PS [range]</td><td>87.8% (80-100)</td><td>Median 90%</td><td>Median 1 [0-2]</td></tr>
</table>

In summary:

- The BOND trial data matches the findings from the audits very well.
- The number of patients in the Saltz and Seitz studies are too small to exactly reflect the audit data - median ages are lower, but the ranges are similar.

We therefore believe that the population included in the clinical trials with cetuximab + irinotecan are representative of the metastatic colorectal cancer population in England and Wales who would be considered for 3rd line treatment.

All three trials showed significant efficacy of cetuximab + irinotecan in the 3rd line clinical practice setting:

- A consistent response rate of 15.2 - 22.9%
- A consistent median PFS of 2.9 - 4.1 months
</td><td>
The report by Seitz et al. is a retrospective analysis of 24 patients from two of the phase II cetuximab trials. It was not included in the submission by the manufacturer.

The Committee recognised that cetuximab demonstrated some clinical effectiveness, but that it is currently not possible to
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A consistent median OS of 8.4 - 8.6 months (excluding the Seitz study since the OS figure given includes 1st line of chemotherapy)
The BOND study showed that the grade of skin rash is correlated with improved response rate and survival.

</td><td>establish the relative effectiveness compared with standard care. (see FAD section 4.3.7)</td></tr>
<tr><td>Merck Pharmaceuticals (cont)</td><td>4.1 Clinical Effectiveness: Section 4.1.8

“In the RCT there was no statistically significant difference in median overall survival between the treatment groups. The median overall survival was 8.6 months in the cetuximab plus irinotecan arm and 6.9 months in the cetuximab monotherapy arm”
The Appraisal Committee have failed to acknowledge that 56 of the 111 patients in the monotherapy arm subsequently had irinotecan added back into their treatment regimen upon progression of disease. This high level of cross-over into the cetuximab + irinotecan arm, undoubtedly had a negative impact on the statistical significance in survival between the two arms.</td><td>The incremental survival benefit seen in the cetuximab BOND study was not a deciding factor in the guidance because cetuximab monotherapy was not considered to reflect current standard care within the NHS in England and Wales. However, a statement has been added to section 4.1.7 to state that cross over was allowed in this trial.</td></tr>
<tr><td>Merck Pharmaceuticals (cont)</td><td><u>B. Additional evidence which supports the use of cetuximab + irinotecan as a 3rd line therapy for mCRC</u>

a) Further publications for cetuximab + irinotecan
Since Merck Pharmaceuticals submitted it’s dossier for cetuximab + irinotecan on August 23rd 2005, there have been several publications which further support the efficacy and safety results observed in the primary RCT (BOND) and the supporting trials (Saltz + Seitz).
The key population data from these trials are summarised in the tables below:

<table>
<tr><th></th><th>Vincenzi et al., 2006</th><th>Gebbia et al., 2006</th></tr>
<tr><td>n</td><td>55</td><td>60</td></tr>
<tr><td>Median age (yrs) [range]</td><td>63 [27-79]</td><td>62 [37-81]</td></tr>
<tr><td>ECOG PS</td><td>0-2</td><td>1-2</td></tr>
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</td><td>The manufacturer included four trials in their submission (BOND, CP02 9923, CP02 0141, CP02 0144) which the Committee believed showed some evidence of the effectiveness of cetuximab. The concern of the Committee was the relative effectiveness of cetuximab against current standard care. The additional studies referred to by the consultee support the evidence of effect and have been mentioned in section 4.1.10 of the FAD, but they do not answer the question of relative effect.</td></tr>
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<tr><td>Previous Treatment</td><td>• 58.2% with adjuvant 5FU/LV chemotherapy
• 1st line:
o XELOX 69%
o FOLFOX 31%,
• 2nd line:
o FOLFIRI 100%</td><td>• 98% Surgery
• 90% adjuvant chemotherapy
• 1st and 2nd line:
o all with oxaliplatin and irinotecan
• Number of lines of previous chemotherapy:
o 65% 2 lines;
o 35% ≥3 lines;</td></tr>
</table>

In summary,
• While the numbers of patients are small, the population data reflect the audit data very well in terms of age and performance status
• These patients were heavily pre-treated.

Importantly, these two trials confirmed the efficacy of cetuximab + irinotecan in the 3rd line setting:

<table>
<tr><th>Study</th><th>Vincenzi et al., 2006</th><th>Gebbia et al., 2006</th></tr>
<tr><td>ORR %
[95% CI]</td><td>25.4%
[21.7-39.6%]</td><td>20%
[11-32%]</td></tr>
<tr><td>PFS (months)
[95% CI]</td><td>4.7
[2.5 - 7.1]</td><td>3.1
[1.2 - 9]</td></tr>
<tr><td>OS (months)
[95% CI]</td><td>9.8
[3.9 - 10.1]</td><td>6
[2 - 13]</td></tr>
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In addition, the study by Vincenzi confirmed the correlation between acne-like rash and</td><td></td></tr>
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tumour response reported by Cunningham in the BOND study.

Furthermore, Merck Pharmaceuticals has conducted the following international study (MABEL) which included 148 patients from 24 centres in the UK.

<table>
<tr><th>Study</th><th>MABEL</th></tr>
<tr><td>n</td><td>1147</td></tr>
<tr><td>Median age [95% CI]</td><td>62 yrs [25-84yrs]</td></tr>
<tr><td>Previous treatment lines
1 line
2 lines
3 or more lines</td><td>
17%
37%
46%</td></tr>
<tr><td>KPS</td><td>Majority 80-100%</td></tr>
<tr><td>ORR [95% CI]</td><td>20% [18-23%]</td></tr>
<tr><td>PFS
12 weeks
24 weeks
36 weeks
48 weeks</td><td>
61%
34%
17%
6%</td></tr>
<tr><td>OS (months) [95% CI]</td><td>9.2 [8.7-9.9]</td></tr>
</table>

Therefore the MABEL trial confirms previously reported efficacy parameters for the combination of cetuximab + irinotecan in a clinical practice setting:

• A consistent response rate of 15.2 - 25.4% across all trials
• A consistent median PFS of 2.9 - 4.7 months
• A consistent median OS of 6 - 9.8 months

Further, cetuximab monotherapy has been shown to be active (this is a licensed indication in the USA). It is important to consider the absolute survival in a group of patients being treated
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Consultee	Comment	Institute Response
	largely in the third and fourth-line setting for metastatic colorectal cancer who were progressing at the time of study entry – a group with a very limited life expectancy.	
Merck Pharmaceuticals (cont)	Based on these clinical efficacy data, cetuximab has been granted reimbursement status in the European countries listed in the section below. **b) Positive endorsement of cetuximab + irinotecan as a 3rd line treatment for mCRC from other Health Technology Appraisal Bodies** **AWMSG** Following deliberation at the All Wales Medicines Strategy Group meeting on 2nd March 2006, a recommendation was made to the Minister for Health and Social Services in Wales that *"cetuximab, in combination with irinotecan, should be endorsed for use within NHS Wales (with specific restrictions) for the treatment of EGFR-expressing metastatic colorectal cancer after failure of irinotecan-including cytotoxic therapy. Treatment must only be initiated and administered under the supervision of a physician experienced in the use of chemotherapeutic agents*." On June 14th 2006, the Minister for Health and Social Services in Wales endorsed this decision. This recommendation and details of the restrictions applied can be found in Reference attached. In brief, patients eligible for treatment must meet the following criteria: • Irinotecan-refractory disease (i.e. progression of disease within 12 weeks of stopping an irinotecan-containing schedule) • received and discontinued a prior oxaliplatin-containing schedule • EGFR-expressing disease • a performance status of 0 or 1 and not have any contraindications to receiving further irinotecan therapy Monitoring requirements ensure that non-responding patients do not continue treatment	The patient population considered in the economic modelling by both the AWMSG and the Appraisal Committee was based on the trial data from the BOND study. The economic modelling provided by the manufacturer was considered at the Appraisal Committee meeting (see FAD sections 4.3.11, 4.3.12, 4.3.13). The Assessment Report on cetuximab commissioned for the AWMSG also states that the case for cost effectiveness has not been made. The Appraisal Committee has not received evidence that the intervention criteria proposed by the AWMSG leads to more cost-effective treatment than that seen in the BOND study. The Institute recognises that guidance from other organisations may differ from its own guidance, because of different criteria for making decisions.

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beyond 6 weeks. Further monitoring will be at 6-8 week intervals. Patients will be registered with the Welsh Medicines Partnership within 28 days of starting treatment and outcomes will be audited.

Merck Pharmaceuticals are in agreement with this recommendation and support these restrictions.

<u>Belgium</u>
The “Moniteur Belge” dated 20th June 2006 (No 196) listed cetuximab + irinotecan for patients who have failed irinotecan-containing therapy as a reimbursed medication[i]. The reimbursement will come into effect on July 1st 2006.

The conditions associated with this reimbursement are similar to those endorsed by the AWMSG on June 14th 2006.

This recommendation and details of the restrictions applied are attached in the original language together with a précis English translation.

c) Other European countries that reimburse the use of cetuximab + irinotecan for mCRC patients

The table below shows the reimbursement status for cetuximab + irinotecan for mCRC patients in 20 European countries.

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<tr><td rowspan="2">Merck Pharmaceuticals (cont)</td><td>ii) whether we consider the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate.</td><td rowspan="2"></td></tr>
<tr><td>Merck Pharmaceuticals would like to draw the attention of the Appraisal Committee to the following points:

a) The proposed positioning of cetuximab + irinotecan in the treatment of mCRC following irinotecan failure.
We believe that the positioning proposed by NICE is too broad. The evidence upon which the licence for cetuximab is based clearly positions cetuximab + irinotecan as a 3rd line treatment in the UK setting. The proposed wording by NICE – “use of cetuximab + irinotecan for the second-line or subsequent treatment of mCRC” is misleading.
We would propose that NICE refrain from making a recommendation of the use cetuximab +</td><td>The appraisal was carried out in line with the marketing authorisation and the scope of the appraisal.

Consultees can request an early review if</td></tr>
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Consultee	Comment	Institute Response
	irinotecan in the 2nd line setting until the evidence from the EPIC study are available ***- CIC removed***	relevant new data that may affect the guidance become available.
	We would propose that NICE carefully evaluate the "restrictions for use" detailed in the AWMSG document and consider whether approval for use in the UK could be based on such parameters.	See detailed response above.
Merck Pharmaceuticals (cont)	**b) comments on the models used by NICE in its decision making process** We agree with NICE that the level of uncertainty in the "indirect analysis" economic model means it should not be used to aid decision making and would request that all reference to this model and the results it produced is removed from the assessment report to avoid confusion.	The assessment report is a document produced independently for NICE to inform the Appraisal Committee. As such it is a document that cannot be changed after the Appraisal Committee meeting, and the information cannot be removed from the assessment report by NICE.
Merck Pharmaceuticals (cont)	However, we dispute the manner in which evidence from the "threshold analysis" was used, especially the conclusion from the threshold analysis*; "it was not possible (for cetuximab) to achieve a cost per QALY of less than £30,000"* (ACD Section 4.2.12). Such a conclusion implies that the only parameter of interest to NICE is the survival of patients in ASC/BSC. The results of the "threshold analysis" assume that the costs of ASC/BSC are assumed constant, as are the utility values. We believe there are two conditions in which cetuximab + irinotecan is a cost effective treatment option (ie: incremental cost per QALY < £30,000) and compatible with the best use of NHS resources: • when a utility value of 0.95 is utilised; and, • when the survival benefit of ASC/BSC is less than 4.5 months. The NICE presented "threshold analysis" (ACD section 4.2.11) uses utility values of 0.8 and 0.6 for progression free and progressive disease, respectively. To assess the impact of such a "threshold analysis", we modified the Merck cost effectiveness model to replicate NICE analyses and results. We found that if a utility value of 0.95 is used (Petrou and Campbell 1997) it is possible for cetuximab (with or without the continuation rule) to have a cost per QALY of less than £30,000 (see Figure 1).	The utility value of 0.95 (Petrou and Campbell) is an estimate of utility for stable disease, and the Committee did not consider that it adequately captured the HRQoL of a patient with metastatic colorectal cancer through the course of the illness. Petrou and Campbell provide further utility estimates of 0.575 for progressive disease and 0.10 for terminal disease. Merck has published their own utility estimates collected through the MABEL study with a baseline utility of 0.73 and an average utility of 0.75.

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Merck Pharmaceuticals (cont)	Figure 1 also shows that when using a utility value of 0.95 in a "threshold analysis", the survival advantage required over ASC/BSC for cetuximab + irinotecan could be as low as 0.4 years to be cost-effective. Therefore, cetuximab + irinotecan can achieve cost-effectiveness if survival with ASC/BSC is less than 4.5 months (not 2 months as per the ACD; Section 4.3.12). It is difficult to argue that survival of 4.5 months or less is an unrealistic assumption in the same way NICE have assumed that survival of 2 months or less is unrealistic (ACD; Section 4.3.12). Consequently, there is a reasonable likelihood that cetuximab + irinotecan has a cost per QALY of less than £30,000.	Assumptions about the maximum survival duration of patients receiving ASC/BSC are informed by the studies of best supportive care included in the assessment report. Three studies were identified which gave estimates of median survival ranging from 6-9 months. The six month estimate reflects patients who had had two previous lines of therapy. The Committee was also aware of the estimate in the manufacturer's economic model which gave a mean overall survival of 5.6 months (FAD section 4.3.13). The Committee was therefore not persuaded that maximum survival of 4.5 months of less in ASC/BSC was a realistic assumption.
Merck Pharmaceuticals (cont)	**Figure 1: Threshold analysis of the Merck cost-effectiveness analysis when a utility value of 0.95 is used**	The Institute has taken the utility estimates provided by the manufacturer into account (see FAD section 4.3.12). A sensitivity analysis of the threshold model was carried out by the assessment group using the utility data from the MABEL study. This was commercial in confidence at the time of the Committee meeting and release of the ACD but has been seen and considered by the Committee.

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	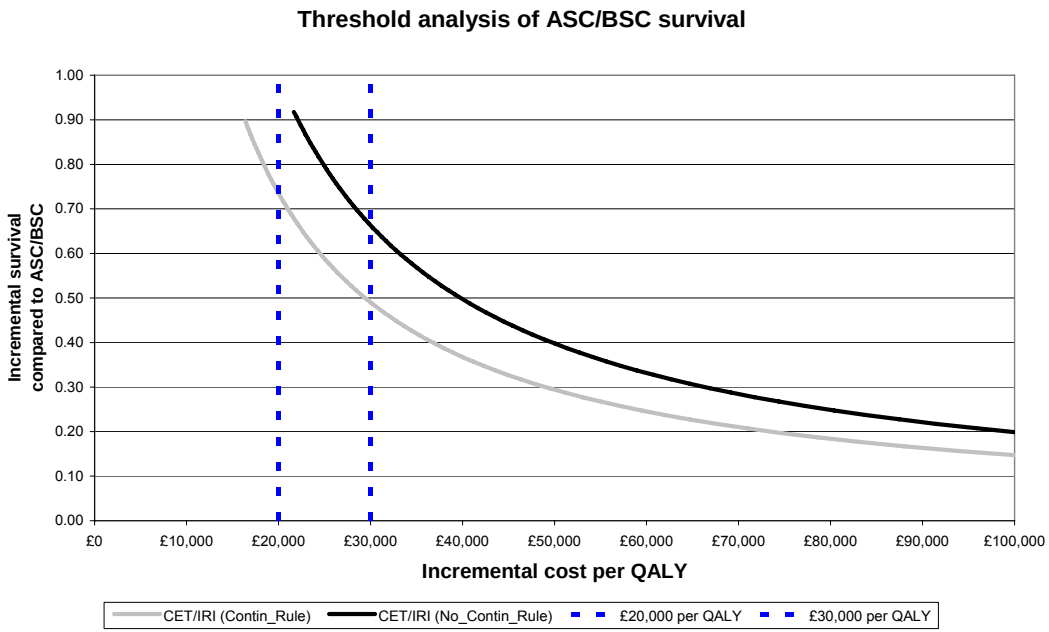 Given the level of uncertainty both in the model used by Merck Pharmaceuticals and the "indirect analysis" provided by the assessment group, NICE appear to rely on a "threshold analysis" to determine whether or not it is possible for cetuximab to be cost-effective; *"The Committee therefore considered the threshold analysis completed by the assessment group"* (ACD Section 4.3.12). However, our assessment of a "threshold analysis" suggests that results are based on a single variable (i.e. survival in ASC/BSC). When other variables are taken into account (e.g. utilities) there is a distinct possibility that cetuximab + irinotecan has an incremental cost per QALY of less than £30,000 and therefore is compatible with the best use of NHS resources. It is appreciated that there exists a reasonable amount of uncertainty in this decision and so	

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	NICE have attempted to minimise the level of uncertainty by using the "threshold analysis". However, in doing so it is assumed that some uncertain parameters (eg: utility values) are certain. These assumptions have been biased against cetuximab. When these assumptions are relaxed, as in the threshold analysis presented here, it is found that there is a possibility that cetuximab is a cost-effective intervention.	
Merck Pharmaceuticals (cont)	**c) cost implications of non-implementation of cetuximab + irinotecan therapy** A pertinent point was made by Dr Levine on behalf of The Association of Coloproctologists in their submission to NICE; that the cost of non-implementation of cetuximab + irinotecan therapy should not be underestimated. He highlights that a minimum of 2 - 3 hours is taken up by clinicians and a wide variety of other hospital staff in explaining to a fit patient why a licensed drug cannot be used to treat their cancer because of financial reasons, which could be argued is not a good use of NHS resources. Further, the costs of such non-implementation are not taken into account in the analysis of cost effectiveness conducted by NICE.	The cost to be included in an economic evaluation are specified in the in the Guide to the Methods of Technology Appraisal section 5.6 (Available from URL http://www.nice.org.uk/page.aspx?o=201974) Costs included need to be evidence-based, and the Institute has not received any evidence on the potential costs referred to by the consultee.
Merck Pharmaceuticals (cont)	**iii) whether we consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS** Merck Pharmaceuticals do not consider that the provisional recommendations are sound and constitute a suitable basis for the preparation of guidance to the NHS for the following reasons: **Positioning of cetuximab in the treatment pathway** NICE's positioning of cetuximab + irinotecan in the treatment of mCRC is too broad. We would not advocate it's use as a 2nd line treatment based on current evidence but would support its use as a 3rd line agent with restrictions applied as detailed in the AWMSG decision.	The appraisal was carried out within the context of the original scope and the current marketing authorisation which may include second line treatment. The Committee considered the fact that for a proportion of patients cetuximab would be a last line therapy (e.g. third line agent) when they made their decisions – see FAD document section 4.3.6
Merck Pharmaceuticals (cont)	**Incomplete evidence base** The evidence base to support the use of cetuximab + irinotecan in the licensed setting has expanded since the original dossier was submitted. This new evidence consistently supports	The Committee acknowledges that cetuximab demonstrates clinical efficacy. However, the relative effect of cetuximab in

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	the efficacy of cetuximab + irinotecan as a 3rd line treatment option in patients who have exhausted other chemotherapy options	comparison to standard care remains unknown – see FAD document section 4.3.7
Merck Pharmaceuticals (cont)	**Uncertainty surrounding the use of the "threshold model"** There is reasonable uncertainty in assessing the cost-effectiveness of cetuximab. We appreciate that this response does not eliminate this uncertainty, however, it is argued that with a relatively small budget impact (approximately £3.6m for 410 patients rising to £10m for 1125 patients) NICE should feel comfortable making a decision even with this uncertainty when the potential benefits of cetuximab are so highly valued as evidenced by the submissions made by the Patient Groups, expert clinicians and clinician groups to NICE. Furthermore we have shown that there exists a reasonable likelihood that the cost per QALY for cetuximab + irinotecan is less than £30,000.	See detailed responses above.
Merck Pharmaceuticals (cont)	**NICE's opinion of what constitutes "Cost-effectiveness"** NICE appear to have made their recommendation because they do not believe that cetuximab has a cost per QALY of less than £30,000. This belief has two fundamental flaws: i) It is a belief based on an interpretation of the "threshold analysis" that has no evidence base – *"This (a cost per QALY of less than £30,000) could only be achieved if survival with ASC/BSC is less than 2 months, which was agreed to be an unrealistic assumption"* ACD Section 4.3.12 ii) It is a belief built upon a "threshold analysis" which considers only one variable (survival in ASC/BSC) and therefore regards as certain all other variables in the assessment of cost-effectiveness (eg: utility values). The model proposed by Merck Pharmaceuticals takes more variables into account and is therefore not subject to the high risk of being inaccurate associated with dependency on one particular variable. We therefore consider that the guidance with respect to cost-effectiveness is based upon an interpretation which lacks any evidence base, i.e. that of a flawed "threshold analysis" and does not, therefore, constitute a suitable basis for the preparation of guidance to the NHS.	See detailed responses above.
Merck Pharmaceuticals (cont)	**Timelines for re-review** We would strongly oppose the recommendation that this TA is considered for review in May	The Committee considered that most ongoing research focused on bevacizumab and cetuximab in regimens outside of the

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	2009. The evidence base and further indications for cetuximab and bevacizumab are rapidly expanding but at a different pace.	current marketing authorisation. Additional bevacizumab and cetuximab regimens may be referred separately to the NICE technology appraisal programme if a licence is applied for accordingly. The review date therefore remains unchanged, but consultees can request an early review if relevant new data becomes available.
Merck Pharmaceuticals (cont)	We should like to propose that the two technologies are not appraised together in the future, but are subject to individual STAs (as in the case of paclitaxel and docetaxel for early breast cancer). Merck Pharmaceuticals are able to provide NICE with anticipated 2nd and 1st line indication dates in order to plan the timing of these STA's.	Comments noted.
Roche Products LTD	We have a number of important points of feedback which are set out below in the three response sections required by the Committee.	
	1. "Whether you consider that all of the relevant evidence has been taken into account"	
	Roche believes that all of the relevant evidence has been taken into account during the appraisal. However, as might be expected for a new and innovative drug such as bevacizumab, the evidence base is rapidly being added to and new data are constantly emerging. This was demonstrated most recently, for example, by the large number of research presentations at the recent ASCO meeting which took place earlier in June. Across the current and upcoming indications for bevacizumab presently being studied, a total of 74 abstracts were presented at ASCO of which 23 were in colorectal cancer and five in other GI related tumours. As a result of the rapidly developing clinical and cost effectiveness evidence base both in metastatic colorectal cancer and in the other upcoming indications for bevacizumab, Roche	Comments noted. The Committee considered that most ongoing research focused on bevacizumab and cetuximab in regimens outside of the current marketing authorisation. Additional bevacizumab and cetuximab regimens may be referred separately to the NICE technology appraisal programme if a licence is applied for accordingly. The review date therefore remains unchanged, but consultees can request an early review if relevant new

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	would like to request that bevacizumab be considered for an early re-review in one years time via the NICE technology appraisal programme.	data becomes available.
	2. "Whether you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate"	
	Roche strongly concurs with the conclusions drawn by the Committee that bevacizumab offers significant clinical benefits for patients with metastatic colorectal cancer when added to first-line fluoropyrimidine + / - irinotecan containing chemotherapy regimens.	Comments noted.
	3. "Whether you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS"	
	Roche very much welcomed the consideration by the Appraisal Committee of the Avastin Registry Programme (ARP) as we had requested and which was submitted alongside the economic modelling undertaken for this particular appraisal. However, since the Appraisal Consultation Document was issued, we have now received updated information regarding earlier timelines for the launch of additional licensed indications for bevacizumab which are now expected in 2007 for metastatic breast cancer (high dose indication); non-small cell lung cancer (high and low dose indications); renal cell carcinoma (high dose indication); and for combination treatment with oxaliplatin and fluoridopyrimidine-based regimens for metastatic colorectal cancer (low dose indication). Each of these indications is at various stages of progression through the NICE topic selection process. In the light of these timelines, Roche considers it important to re-evaluate the overall position of bevacizumab's future use in the NHS with a view to being able to satisfactorily address the UK issues of cost effectiveness on a broader basis.	The FAD has been amended accordingly.

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	CIC removed *CIC removed* *CIC removed* *CIC removed* *CIC removed* *CIC removed* *CIC removed* *CIC removed* *CIC removed* *CIC removed* *CIC removed* *CIC removed* *CIC removed* *CIC removed* *CIC removed* *CIC removed* *CIC removed* The new indications referred to above for breast, lung and renal cancer are already at various stages of the horizon scanning process for NICE topic referral and we remain supportive of them being brought forward in due course for appraisal as part of the new Single Technology Appraisal (STA) process at the earliest possible opportunity.	
Bowel Cancer UK	**i. Whether you consider that all the relevant evidence has been taken into account** Bowel Cancer UK has submitted comprehensive evidence of the efficacy of both these treatments, from the charity, clinical and patient perspectives. We hope that this and other evidence has been taken fully into account in NICE's appraisals of these drugs.	The Committee considered all the evidence submitted, including evidence from clinical trials, patient experts and clinical specialists.

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	ii. Whether you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate Bowel Cancer UK believes, from the evidence that we have gathered and submitted, that both these treatments are extremely effective and should be made available to all patients that will benefit from them. Furthermore, we believe that the treatments should be made available on the basis of their efficacy and not be denied to patients on the grounds of cost - which seems, sadly, to be the sole criteria for the provisional negative guidance that NICE has made relating to them. In the case of Erbitux, it is clear that NICE's guidance is inconsistent on clinical grounds, as your equivalent organisation in Wales, the All Wales Medicines Strategy Group (AWMSG), has approved the treatment's use to bowel cancer patients on the NHS in Wales. While we are glad that Welsh patients will benefit from the drug, it is galling for patients in England and Scotland to know they can't receive it - a situation that is not just grossly unfair but also takes postcode or in this case country prescribing to new extremes. **iii. Whether you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS** Bowel Cancer UK is very disappointed with the provisional guidance, because it indicates that these two biological agents will not be made available on the NHS, despite their proven efficacy and potential benefit to many bowel cancer patients. It is ironic that while the UK has been in the forefront of developing both these drugs, including in clinical trials, it looks as if we shall, once again, be at the very back of the queue when it comes to being able to make them available to patients. It is also very hard not to become angry and cynical when NICE appears to be making decisions on the basis of financial expediency rather than clinical efficacy. We shall continue to campaign for increased access to these valuable treatments and call on NICE to reconsider its decision and make these drugs available to patients that need them. **Additional Comments** As you know, Bowel Cancer UK has invested considerable time and effort in preparing our submission to NICE with regard to these treatments: our submission included a	The Committee does not consider the affordability, that is cost alone, of new technologies but rather their cost effectiveness in terms of how its advice may enable the more efficient use of available healthcare resources (NICE Guide to the Methods of Technology Appraisal, paragraphs 6.2.6.1 – 6.2.6.3). The Institute recognises that guidance from other organisations may differ from its own guidance, because of different criteria for making decisions. NICE guidance supersedes guidance previously provided by the All Wales Medicines Strategy Group Comments noted. The Committee does not consider the affordability of new technologies, that is costs alone, but rather their cost effectiveness in

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	comprehensive summary of the evidence of the treatments' efficacy from three leading clinicians; a dozen case studies of patients who have benefited from them; and our own considered appraisal of both drugs. We have made these efforts, not just because we are stakeholders in this appraisal, but also because we and the clinicians we work with believe in these treatments; because we know patients who have benefited from them - in terms of improved quality of life and increased length of life; and because both drugs represent a new era in the treatment of colorectal cancer: the era of targeted therapies that will, one day, enable each individual patient to have a tailored treatment for the disease. As NICE will be aware, things have moved on somewhat since we prepared our submission last year, particularly as a result of the significant growth in the profile of targeted therapies - including these treatments - including in the media. Much of this publicity has been generated as a result of individual patients' high profile campaigns to gain access to these treatments and/or raise the funds to pay for them privately through donations. Bowel Cancer UK has been privileged to get to know and work with some of these patients and we have been deeply moved by their heroic efforts to fight for what they believe in and in circumstances that would deter many people, i.e. when they were in the advanced stages of the disease and had only weeks to live. It is, frankly, tragic that these patients were forced to fight bureaucracy when they should have been focussing all their efforts on fighting bowel cancer; and that the system that they helped to support throughout their lives - through taxes and other contributions - failed them when they needed it most. No decision, even one made by NICE, is made in a vacuum and NICE's negative guidance has to be put into the wider context of CRC patients being more willing to campaign for treatments and for the media more willing to help them publicise them. There's no doubt that these campaigns will grow in number and volume if these treatments remain unavailable to those who can and should benefit from them. It will come as no surprise to NICE to know that Bowel Cancer UK is also going to continue to campaign for access to these treatments, including in support of individual patients who have been recommended them and yet cannot receive them on the NHS. We have been encouraged by and have publicly welcomed NICE's positive guidance regarding a number of CRC treatments, including oxaliplatin and capecitabine in the	terms of how its advice may enable the more efficient use of available healthcare resources (NICE Guide to the Methods of Technology Appraisal, paragraphs 6.2.6.1 – 6.2.6.3). Comments noted.

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	adjuvant setting. We hope that NICE will follow its conscience and reconsider its decision with regard to bevacizumab and cetuximab, making these revolutionary and invaluable treatments available to the patients who will benefit from them.	
Clinical expert 1	In the appraisal consultation document the relevant evidence as of the date of writing has been included. It was pointed out at the Appraisal Committee meeting (May 10th) that more information regarding these two agents might become available at the American Society of Clinical Oncology (ASCO) meeting at the beginning of June 2006. This was the case although all the new data was either in abstract or presentation form and not peer-reviewed publications. For Cetuximab there were more than 15 abstracts of studies looking at its role in treatment of colorectal cancer. Of these most were phase II studies with immature data. Of interest were preliminary results from the CALGB 80203 study (a randomised phase III study) of cetuximab in combination with FOLFOX and FOLFIRI compared to either regimen on their own. Preliminary data suggested enhanced response rates by addition of cetuximab in the first line setting but no data on survival as yet. Another interesting abstract was looking at trying to predict which patients would actually get benefit from cetuximab by looking at markers other than just EGFR status (Razis E. Abstract # 13500). The results of this study were not helpful but indicate a beginning to try and better target these agents. For Bevacizumab there were even more abstracts presented. Many of these were immature data on efficacy and safety from large trials of combinations including bevacizumab e.g. TREE, BEAT etc. However, abstracts from the BRITE study (#3537) which is a community based survey of 1st line bevacizumab combination therapy suggested that the efficacy and toxicity seen in the published trials is confirmed in a community setting. Another smaller study looking at risk factors for bevacizumab in an elderly population with colorectal cancer could exclude many patients from treatment due to concerns regarding toxicity (Pasetto LM, #13589). In addition an abstract looking at the influences of bevacizumab on national health care costs for colorectal cancer in Canada show significant increases in spending if the drug was widely implemented (Druker A, #6044)	Comments noted.

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	In summary, these abstracts continue to show evidence that the effectiveness of cetuximab and bevacizumab in combination therapy is real and at levels observed in published trials to date. No significant new toxicities have been shown and concerns about health care costs remain. The summaries of clinical data represent what is currently observed with cetuximab and bevacizumab. As mentioned above newly presented data tends to support improved response rates by addition of these drugs to standard therapy. As for cost-effectiveness, although not a health economist the fact that by both manufacturer's models and assessment group's models the costs per QALY are significantly above the willingness-to-pay threshold of £30,000 indicates to me that the cost-effectiveness conclusion is sound. I agree that the section 4.3 (Consideration of the evidence) is a fair reflection of the discussion had at the Appraisal Committee meeting. As to the proposals for further research, much of what is proposed is based around ongoing studies (many of which updated at ASCO 2006). The outcomes of these studies are likely to reinforce the clinical benefit of bevacizumab and cetuximab in a wider range of settings and with more understanding of toxicities. However, as the Appraisal Committee have already agreed that bevacizumab and cetuximab show evidence of clinical effectiveness (4.3.3; 4.3.4;4.3.8) I am unclear as to how in future these will alter the cost-effectiveness argument unless (which is unlikely) showing substantially better results than the data used in the current appraisal. I agree that more data is required on both agents in trying to identify those patients who are likely to benefit more from these treatments. A proper prospective trial using skin rash and early assessment of response to determine early stopping rules for cetuximab treatment might result in selection of patients and hence improve cost-effectiveness. These types of studies are difficult as many of the markers of response are not known or only weakly predictive.	This section has been amended in the FAD (section 6) Comments noted.

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	Undoubtedly more health –related costs and quality of life studies are required (as integral parts of effectiveness studies) but it is unlikely that these will get priority. In terms of simply assessing these drugs as good value for money for the NHS then the logic behind the provisional recommendations is sound. However, undoubtedly there are a cohort of patients who could have their life expectancy extended significantly (with toxicity acceptable to the patient) by use of these drugs. These are the patients with the prolonged responses on use of these drugs. The difficulty is we cannot predict who these patients are up front although there are some indicators. Using the same data as seen in this appraisal (although significantly different conclusions were drawn on cost-effectiveness) the All Wales medicines Strategy Group have approved cetuximab use in very strictly limited situations (still to be determined). A similar approach in England, potentially by using strict application to licensed indications plus additional parameters based on clinical evidence (as suggested in the submission by Professors Cunningham and Maughan and Dr Glynne Jones) would reduce overall NHS costs but allow those patients potentially more likely to benefit to have access to these agents. I think that the time for the next review of these agents should be once the results of the trials recommended in the section on further research are mature and published. Although I have no prior knowledge as to when this will be my guess is that 2008 would be more realistic than 2009.	The patient population considered in the economic modelling by both the AWMSG and the Appraisal Committee was based on the trial data from the BOND study. The economic modelling provided by the manufacturer was considered at the Appraisal Committee meeting (see FAD sections 4.3.11, 4.3.12, 4.3.13.). The Assessment Report on cetuximab commissioned for the AWMSG also states that the case for cost effectiveness has not been made. The Appraisal Committee has not received evidence that the intervention criteria proposed by the AWMSG or those by Professors Cunningham, Maughan and Dr Glynne-Jones leads to more cost-effective treatment than that seen in the BOND study. The Institute recognises that guidance from other organisations may differ from its own guidance, because of different criteria for making decisions. The Committee considered that most ongoing research focused on bevacizumab and cetuximab in regimens outside of the current marketing authorisation. Additional bevacizumab and cetuximab regimens may be referred separately to the NICE technology appraisal programme if a licence

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		is applied for accordingly. The review date therefore remains unchanged, but consultees can request an early review if relevant new data becomes available.
Website Comment 1	Adding monoclonal antibodies to chemotherapy regimen has made difference in outcomes in breast cancer. The trials were not properly designed and therefore it may not look viable on health economics. I have taken part in Mabel trial and had couple of patients who responded very well with their survival more than a year. I feel clinician should be given freedom to use these drugs in patients who show response to above medicines. No clinician will continue to use these drugs in absence of response.	Comments noted.
Website Comment 2	Both, bevacizumab and cetuximab have been shown to be effective drugs in colorectal cancer. Survival benefit has particularly been shown for the combination of bevacizumab and chemotherapy versus chemotherapy alone in well conducted clinical trials. Efficacy has also been shown for cetuximab but the number of patients likely to benefit based on the current body of evidence is smaller. Rejection of these drugs puts NHS patients suffering from colorectal cancer at significant disadvantage compared to patients treated in the private sector and to patients treated in other countries with comparable gross national product. As a medical oncologist treating patients with colorectal cancer I regard access to both drugs as vital, since they both represent a significant improvement of the available treatment options and have potential of significantly prolonging survival.	For both legal and bioethical reasons those undertaking technology appraisals and developing clinical guidelines must take account of economic considerations" (Social Value Judgements - Principles for the development of NICE guidance; principle 5)
Website Comment 3	It is invalid to call the evidence for cetuximab flawed because it has not been compared to standard treatment, since there is no standard treatment for progressive disease following treatment with oxaliplatin and irinotecan (i.e. the licensed indication). Both these recommendations are disappointing and bad news for patients. It will take England further out of step with the rest of Europe and the US. The case for bevacizumab is strong based on the survival benefits and even stronger for cetuximab based on the smaller numbers involved and the lack of any effective therapy in the licensed indication. I do not understand how AWMSG can approve cetuximab and NICE decline it, although I note the guidance of the latter supersedes the former. Thus a patient today could receive the drug in	The current marketing authorisation does not stipulate that a patient has to have failed on an oxaliplatin containing regimen to receive cetuximab plus irinotecan. Consultees stated that both oxaliplatin and active/best supportive care could be considered as comparators for cetuximab. The Institute recognises that guidance from other organisations may differ from its own guidance, because of different criteria for

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	Cardiff but not in Bristol, but by the end of the year this could well change. It is postcode prescribing and timetable lottery. I'll tell my patients where and when to get ill from now on and with which disease. As with previous NICE appraisals it seems colorectal cancer patients will be seen as a poor relation and not have breakthrough drugs approved in a timely fashion. There never will be a comparison of cetuximab in this setting since there is no standard therapy for irinotecan refractory disease, and it was considered unethical at the design stage of the BOND trial to have a BSC arm as it was known even then (5 years ago) that the agent was active. The majority of patients will already have received FOLFOX, so this is not an option. TREE-2 final results were presented at ASCO this year. NO16966C will be at ESMO in October. COIN will offer no data on cetuximab in the licensed indication (who wrote this list?!) Number 93 was three years late and a lot of patients suffered as a consequence. Please don't make the same mistake again.	making decisions. The Committee is required to make decisions on the basis of clinical and cost effectiveness. There are a number of ongoing trials that compare cetuximab as a second and subsequent line therapy to standard treatments – see FAD Section 6. The list of ongoing research does not reflect the licensed indications rather it indicates the direction in which research into these agents is going. The list has been amended to reflect this more clearly (FAD section 6). Comment noted.
Summary of letter 1	• The responder was diagnosed with colorectal cancer in 2003 and has been on cetuximab and irinotecan as a third line treatment since October 2005, since February 2006 they have received cetuximab monotherapy to which their cancer has shown a positive response with few side effects. • The responder questions the decision that cetuximab is not cost effective, questioning whether it is considered cost effective to treat drug addicts and immigrants who have not contributed to the system. • In addition they question why research into these drugs is funded, if they are not then made available on the NHS. • The believe that the guidance issued by NICE does not take into account the original concept of the NHS and that by making a decision that goes against cetuximab they are failing in their duty and condemning patients to a miserable existence. • They urge us to 'throw caution to the wind' and think about the patient rather than the	The Committee is required to make decisions on the basis of clinical and cost effectiveness. In developing clinical guidance for the NHS, no priority should be given based on individuals' income, social class or position in life and individuals' social roles, at different ages, when considering cost effectiveness (SVJ principle 8). For both legal and bioethical reasons those undertaking technology appraisals and developing clinical guidelines must take

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	government budget.	account of economic considerations" (Social Value Judgements - Principles for the development of NICE guidance; principle 5)
Summary of letter 2	• The responder was diagnosed with colorectal cancer in 2002. They have been refused bevacizumab after requesting they have it with FOLFOX chemotherapy. They believe that oncologists must be allowed to work with all the drugs available and given the autonomy to prescribe as they perceive is appropriate. • Cancer is an NHS and government priority, however, this is not at any price. The cost of bevacizumab and cetuximab is too great and the economic case cannot be demonstrated. • It does not matter about the patients even the young ones, as it does not represent good value for money. But how can you value an addition four or five months of life? Neither NICE nor the SMC appear to take this into consideration, or if they do they dismiss them in an instant when they consider the drug to be too expensive. • Not all new drugs will be suitable for everyone, but the decision should be made by oncologists who make these decisions every day. • There are three points to be made: 1. By not supporting revolutionary and exciting drugs which show clear promise on the basis of phase three trials the government is potentially stifling future development. 2. Senior medics and surgeons support the introduction of these new cancer drugs 3. The government is making a value judgement that no patient in the UK deserves the chance of a longer life. • The sad truth is that these drugs have been rejected on the basis of cost alone. Younger bowel cancer sufferers are not being given the chance they deserve. People have been refused bevacizumab, these people are not being given the right chance at the right time. • Those who have worked in the health care sector know that difficult decisions have to be made. But where there is a will there is a way. It is not about limited resources. It is not about throwing money at an issue. It is about making the best use of what you have got every minute of the day.	The Committee is required to make decisions on the basis of clinical and cost effectiveness. NICE clinical guidance should only recommend the use of an intervention for a particular age group when there is clear evidence of differences in clinical effectiveness in different age groups that cannot be identified by any other means (SVJ Principle 6). Although individual choice is important for the NHS and its users, they should not have the consequence of promoting the use of interventions that are not clinically and/or cost effective" (Social Value Judgements - Principles for the development of NICE guidance; principle 5) The Committee does not consider the affordability of new technologies, that is costs alone, but rather their cost effectiveness in terms of how its advice may enable the more efficient use of available healthcare resources (NICE Guide to the Methods of Technology Appraisal, paragraphs 6.2.6.1 –

Consultee	Comment	Institute Response
		6.2.6.3).
Summary of letter 3	• The responder is a patient who has been diagnosed with colorectal cancer and has been refused cetuximab, even though their clinician said it may benefit them. This is distressing for them and their family. • The provisional guidance by NICE places financial considerations above clinical ones and they are sure the organization was not established to make decisions on that basis. • The guidance by NICE is also inconsistent with that published by Wales which has approved the use of cetuximab in people with colorectal cancer. This is postcode prescribing taken to extremes and further emphasises how wrong the guidance is.	The Committee does not consider the affordability of new technologies, that is costs alone, but rather their cost effectiveness in terms of how its advice may enable the more efficient use of available healthcare resources (NICE Guide to the Methods of Technology Appraisal, paragraphs 6.2.6.1 – 6.2.6.3). The Institute recognises that guidance from other organisations may differ from its own guidance, because of different criteria for making decisions.
Summary of letter 4	• Is the partner of a person diagnosed with colorectal cancer, they and their family are disappointed that NICE is not going to recommend bevacizumab for use on the NHS • They have been told by their oncologist that they may benefit from bevacizumab, but that he wasn't allowed to prescribe it on the grounds of cost, a situation which has been made worse by the negative decision from NICE. • They have worked all their lives and paid their taxes. They believe that bevacizumab is the only hope of survival and that NICE is in a position to help her.	Comment noted.