**NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE**

**Single Technology Appraisal**

# Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine for the treatment of metastatic colorectal cancer

**Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD2)**

## Comments received from consultees

| Consultee | Comment | Response |
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| Roche products | **Whether you consider that all of the relevant evidence has been taken into account**<br><br>No comments | Comment noted. |
| Roche products | **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**<br><br>2.1 Comments on the level of innovation of bevacizumab<br><br>'As a final consideration, the Committee did not consider bevacizumab represented a sufficiently innovative technology in the treatment of metastatic colorectal cancer because it did not result in a substantial improvement in progression-free or overall survival.' (Second ACD2 paragraph 4.17)<br><br>The committee appear to be confusing innovation with degree of | Comment noted. The FAD has been amended. The FAD now reads as follows: The Committee recognised the novel mode of action of bevacizumab but did not consider it to be a substantially innovative technology in the treatment of metastatic colorectal cancer. Please see the FAD section 4.21 for further details.<br><br>Comment noted No further changes have |

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| | clinical benefit. Something could be considered to provide modest clinical benefit and be innovative due the novel attributes of the technology; for instance that it provides an advance in science of treating a disease area. Bevacizumab was the first in an innovative class of drugs that act as anti-angiogenic agents, and the only one to show a statistically significant overall survival advantage in mCRC, which has been demonstrated in both 1st and 2nd line treatment (Hurwitz et al 2004 and the E3200 study). Since its launch in January 2005, bevacizumab has become the standard of care for 1st line mCRC in the vast majority of developed countries.<br><br>NICE STA process guide indicates 'the potential for long-term benefits to the NHS of innovation' should be accounted for by the committee. Other factors are also considered such as equity, as these factors are not considered to be adequately captured with the ICER calculation. Hence when considering innovation it is our understanding that this in relation to additional factors that haven't already been captured within the ICER. | been made in the FAD.<br><br>. |
| | Finally the wording in paragraph 4.17 in the ACD2 appears to comment on bevacizumab in mCRC generally rather than solely to the evidence considered as part of the scope of the appraisal (ie oxaliplatin containing regimens). The main source of evidence considered as part of this appraisal is the NO16966 study the result of which are inconsistent with the other pivotal trials of bevacizumab in mCRC, which demonstrated substantial and statistically significant improvement in both PFS and OS. The first pivotal study resulted in a median increase of 4.7 months in OS (Hurwitz et al, 2004) when bevacizumab was added to irinotecan-based therapy in 1st line. The | Comment noted. The Committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the manufacturers' submission and the Evidence Review Group report. It also carefully considered the comments received from consultees and commentators and the public in response to the Appraisal Consultation Documents. |

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| | other is the E3200 study which resulted in a median increase of 3 months from the addition of bevacizumab to oxaliplatin-based therapy in 2nd line where patients in the comparator arm had a median survival of only 12.8 months. | The Committee noted that bevacizumab gave modest clinical benefit as a first-line treatment and bevacizumab was clinically effective as part of second-line treatment. See FAD section 4.7. However, for both legal and bioethical reasons the Committee must take account economic considerations and cost effectiveness of the technologies (Social Value Judgments - Principles for the development of NICE guidance; principle 5). The Committee concluded that bevacizumab for the treatment of metastatic colorectal cancer would not be a cost-effective use of NHS resources. See FAD sections 4.21 and 4.22. |
| Roche Products | **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**<br><br>2.2. Interpretation of the evidence<br><br>The second ACD (refered to from hereon as ACD2) states that 'the Committee noted its earlier conclusions that all of the ICERs with and without the patient access scheme were likely to be underestimates.' Whilst not explicitly, it appears the committee were referring to the following elements of the economic model: | Comment noted. Please see detailed responses below. |

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| | • Pooling of the XELOX and FOLFOX arms for efficacy<br>• Adverse Event Costs<br>• Treatment duration<br>• PFS utility values<br>• Operating costs<br>• Incremental costs associated with administering bevacizumab<br>• Oxaliplatin price<br><br>Roche consider that the conclusion drawn by the committee that the elements above are all favourable to bevacizumab and that therefore all the ICERs are underestimated is not consistent with the evidence.<br><br>Whilst it is acknowledged that, as with any appraisal there is uncertainty around the ICERs, we consider the ICER's presented without the APAS to be reasonable central estimates and there are plausible reasons for why these in fact may be overestimates including the fact that no vial sharing has been assumed as well as that a reduction in the price of oxaliplatin would reduce the ICER's without the APAS.<br><br>Below, under a separate heading for each element, is the rational behind this statement. | |
| Roche Products | **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** | |

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| | **2.2.1 Pooling of the XELOX and FOLFOX arms for efficacy**<br><br>Referring to the 2*2 analysis excluding patients that had received prior adjuvant treatment:- *'The Committee heard from the manufacturer that the study was designed to pool the XELOX and FOLFOX arms and that interaction testing had been undertaken that demonstrated that pooling was appropriate. However, the Committee noted the original analysis and when the XELOX and FOLFOX arms were subsequently un-pooled the ICER for B-XELOX compared with XELOX increased slightly and the ICER for B-FOLFOX-6 compared with FOLFOX-6 increased markedly.'*<br><br>It is incorrect that the ICER for B-XELOX increased when the efficacy was unpooled. Table 3 (replicated below) of Roche's response to the ERG's clarification questions Part III shows that the ICER for B-XELOX vs XELOX decreases rather than increases (see figures highlighted in yellow).<br><br>This is consistent with what one might expect since if 'unpooling' the efficacy was to affect the ICER's, then one of the ICER's would increase and the other decrease, reflecting the fact that unpooling would cause the efficacy of one the comparisons to worsen and the other improve. Indeed this is what occurred when the efficacy was unpooled in the earlier analysis (ie the analysis when including patients with prior adjuvant treatment).<br>*Table provided, but not reproduced here.* | Comments noted. The FAD has been amended accordingly. Please see the FAD section 4.11 for further details.<br><br>The ERG believed that the most appropriate analysis was one using the 2 x 2 factorial design of the NO16966 study with XELOX and FOLFOX not pooled and patients who had received prior adjuvant therapy excluded. However, this analysis was not provided by the manufacturer despite requests by the ERG to do so. Please see the FAD section 3.23 for further details.<br><br>The Committee considered that pooling of the initial two-arm part of the study and the 2 x 2 factorial part of the study was inappropriate because of the different designs of the study and the imbalance of demographics between the two parts of the study. Please see the FAD section 4.10 for further details. |

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| | The reason for the difference in ICER's seen between analysis 2 and 3 (table 3 above) is that in the 2*2 part of the study the placebo+FOLFOX arm performed implausibly well compared to the other arms in the study, thus reducing the observed difference in survival between the B-FOLFOX and placebo+FOLFOX arms, and when pooled with the placebo+XELOX arm, it also negatively affects the B-XELOX vs XELOX comparison. It was established that this anomaly in the results was as a result of an imbalance in an important prognostic factor, the importance of which was unknown at the time of the study. This point was accepted by the committee and it is noted in the ACD2 that removing the patients that had received prior adjuvant therapy removed this imbalance (see paragraph 4.4; ACD2).<br><br>With the imbalance removed there would be no reason to believe that XELOX and FOLFOX would result in different survival outcomes and likewise B-XELOX and B-FOLFOX would also be expected to have the same survival outcomes as each other. As discussed in the ACD2 this is supported by the statistical analysis which showed XELOX to be non-inferior to FOLFOX and no interaction between bevacizumab and the chemotherapy regimen used. This is further validated when comparing the ICERs for analyses 2,3, and 4 (table 3 above) the only instance where the ICER for B-XELOX *versus* XELOX comparison increases is where the placebo+FOLFOX arm including patients with prior adjuvant chemotherapy were pooled with the placebo+XELOX arm thus worsening the assumed treatment effect for B-XELOX vs XELOX. | The Committee considered that it was counter-intuitive for the analysis to pool the effects of treatment, but not to pool the duration of treatment in the XELOX and FOLFOX arms. Therefore the Committee concluded that the ICERs were associated with substantial uncertainty. Please see the FAD section 4.11 for further details. |

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| Roche Products | **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**<br><br>2.2.2. Adverse event costs<br><br>'The Committee was also aware that the costs of adverse events had not been included in the economic model' (paragraph 4.13 ACD2)<br><br>This is incorrect. The cost of adverse events are included in the economic model (see pages 138 to 140 in Roche's submission). Hence it is untrue to say that ICER is underestimated as a result of their exclusion. | Comment noted. The FAD has been amended accordingly. The FAD reads as follows: Disutility due to adverse events was not included in the economic model Please see the FAD section 4.15 for further details. |
| Roche Products | **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**<br><br>**2.2.3 Treatment duration**<br><br>**2.2.3.1 Longer treatment duration in clinical practice and the subsequent effect on the ICER**<br><br>Paragraph 4.12 the ACD states: *'The Committee noted that stopping oxaliplatin treatment 1 month before the other treatment agents or receiving bevacizumab for 1 month after oxaliplatin* | Comment noted. The Committee noted the information provided by the manufacturer and concluded that the economic model reflected the clinical evidence that was available (in terms of treatment duration). However, the Committee concluded that in practice bevacizumab treatment would be expected to continue until disease progression in patients treated with a continuous therapy policy. This could potentially increase the ICERs. Please see |

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| | *treatment had increased the ICERs. It noted that both analyses assumed no increase in progression-free or overall survival. However, the Committee considered that if such increases in progression-free and overall survival were accounted for, the extra bevacizumab costs would outweigh any additional survival benefits of bevacizumab, given the previously noted modest impact on progression-free and overall survival'…. 'in practice bevacizumab treatment would be expected to continue until disease progression in patients treated with a continuous therapy policy. This could potentially increase the ICERs.'*<br><br>The fact it is <u>possible</u> the ICER could increase with an increase in treatment duration is undeniable. However one cannot know for sure what the incremental benefit of treating for longer would be and it is equally plausible the ICER might decrease or remain the same. The above paragraph seems to imply that it is more likely that the ICER would increase based on the costs outweighing the benefits, but it is not clear what is precisely meant by 'outweigh' in this instance. The committee clearly consider that the high ICER for the comparison without the APAS demonstrates that the cost outweighs the benefit however if for each additional month of treatment patients received the same magnitude of benefit as the average observed across all patients in the NO16966 then this ICER would be expected to remain roughly the same. It is not clear whether the committee considered this.<br><br>In addition there are credible hypotheses for why the ICER might decrease with longer treatment:- Patients in the NO16966 study typically stopped treatment on bevacizumab at the same time as | the FAD section 4.12 for further details<br>Please see the FAD section 4.12 for further details. |

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| | oxaliplatin. This was primarily, either as a result of disease progression, or due to the cumulative toxicity of treatment with oxaliplatin, which typically can only be given for a maximum of around 6 months. Patients with PFS longer than 6 months then had a greater chance of stopping oxaliplatin, and thus bevacizumab prior to progression. This is borne out in the observed treatment durations in the study where the proportion of patients on treatment relative to those remaining in PFS reduces over time (see Figure 1 below). It is reasonable to consider that patients that remained in PFS for longer did so in part due to a greater response to bevacizumab. If this is the case then continued treatment with bevacizumab could result in greater incremental benefit than in the patients that stopped treatment due to disease progression. Hence treating to progression would lead to a reduction in the ICER as the patients that receive the greatest benefit would receive longer treatment. Indeed a possible reason for why the first appraisal of bevacizumab in mCRC resulted a lower ICER (~£62k) than seen in this appraisal may be a result of the fact that patients in the study being analysed in that appraisal were treated until progression.<br>*Figure provided, but not reproduced here.*<br><br>In conclusion whilst one cannot know for sure the incremental benefit of treating for longer, and thus how the ICER would be affected, there are plausible scenarios where treating to progression would either cause the ICER to remain the same or reduce. Hence paragraph 4.12 is misleading. | |

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| Roche Products<br><br>Roche Products | **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**<br><br>**2.2.3.2. PFS Utility values**<br><br>The ACD2, paragraph 4.13, indicates that the committee considered that the ICER's were underestimates due the utility values used in the economic analysis being overestimated, specifically:<br>• Patients on bevacizumab would have a worse PFS utility value than the comparator arm due to greater adverse events<br>• The utility values for both arms were overestimates<br><br>Disutility due to adverse events<br><br>Of the 5.1% excess of grade 3 and 4 tox 3.2% can be accounted for by hypertension, which in most cases will be measurable and treated but have little impact on patients utility.<br><br>The other important factor is that the adverse event rates reported for the NO16966 are not adjusted for time on treatment in the study. PFS, and hence treatment duration and OS, was longer in the bevacizumab arms so total AE's reported in this arm would increase disproportionately to any increase in AE's per unit time. Disutility / utility values are a measure of disutility / utility per unit of time. The fact that patients may experience disutility / utility for longer is already | Comment noted. Comment noted. The evidence section of the FAD includes a summary of the information provided by the manufacturer. The Committee agreed that the utility value of 0.77 was still high because it was similar to the utility values of people in the UK general population rather than people with metastatic colorectal cancer. The Committee also noted that the utility values were obtained from a small study of patients with metastatic colorectal cancer receiving cetuximab and chemotherapy using the EQ-5D. In addition, the utility values in the economic model were not regimen-specific. It further noted that decreasing the utility values by 20% had a large impact on increasing the ICERs. Please see the FAD section 4.14 for further details<br><br>In addition, the Committee concluded that in some cases, the adverse effects of bevacizumab could be serious and |

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| | captured in the model via the fact that it incorporates time in PFS and OS<br><br>There is an argument for separating out PFS into two distinct health states and applying separate utility values for each of these health states to capture the fact that when being treated patients probably experience lower quality of life than after treatment is stopped and before disease progression. This would then more accurately reflect any disutility of treating for longer in the bevacizumab arm. However conversely this would mean that any incremental utility from being in PFS without the side-effects of treatment for the time between treatment cessation and progression would also be captured. As the incremental treatment duration in the bevacizumab arm was less than the incremental time between treatment cessation to progression the impact of applying two different utility values actually reduces the ICER.<br><br>Finally a single utility value is currently applied to patients who are progression free, which incorporates patients with complete response (CR), partial response (PR) and stable disease (SD). Since tumour bulk is typically associated disutility it is reasonable to assume that the utility gain in PFS is greatest in patients with complete response and least in patients with stable disease. Adding bevacizumab to chemotherapy improves the degree of the response in patients (increased proportion of patients in non-progression have CR or PR). This increase in utility is not captured in the model and hence may underestimate the utility associated with bevacizumab thus overestimating the ICER. | disutility due to adverse events specific to bevacizumab treatment should have been incorporated into the model. The utility values used could not have accounted for the adverse effects of bevacizumab because they were obtained from a study that examined cetuximab. The Committee therefore concluded that the ICERs would increase if the disutility due to adverse events related to bevacizumab treatment was included. Please see the FAD section 4.15 for further details. |

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| | PFS utility value in both arms<br><br>'The Committee agreed that the utility value of 0.77 was still high because it was similar to the utility values of people in the UK general population aged 55–64 and 65–74 rather than people with metastatic colorectal cancer. The Committee also noted that the utility values were obtained from a small study of people with metastatic colorectal cancer receiving cetuximab and chemotherapy.' (ACD2 paragraph 4.13).<br><br>The paragraph above questions the credibility of the source of utility values, however it is important to note the PFS utility values came from the EQ-5D results of a pivotal randomised controlled trial (NICE's preferred approach) in the indication of interest from patients receiving first line chemotherapy until progression. | |
| Roche Products | **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**<br><br>**2.2.3.3. Modelling of treatment duration as observed in NO16966**<br><br>Whilst the 'ERG agreed that the manufacturer's economic model was an accurate replication of the NO16966 study' (paragraph 3.24), a minor criticism of the model was made in Paragraph 3.14 in that 'Duration of treatment varied between treatment arms and was longer with the addition of bevacizumab and longer in the FOLFOX than in | Comment noted. The FAD has been amended accordingly. The FAD reads as follows: Treatment duration was estimated and applied in the model for each arm of the NO16966 study. |

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| | the XELOX arms. However, the model assumed that the treatment duration was the same in the B-FOLFOX and BXELOX arms.'<br><br>Whilst a relatively minor point we wish to highlight any factual inaccuracies we identify in the document and this statement was noted as being incorrect. Treatment duration was in fact estimated and applied in the model for each arm of the NO16966. Please see pages 137 and 138 of our submission and also in response to question B6 page 91 of Roche's response to the second set of clarifications questions from the ERG.<br><br>The only simplification made was that, given that oxaliplatin is free of charge under the APAS, it was assumed to be given for same duration as bevacizumab. In the study the oxaliplatin treatment duration was slightly shorter in the bevacizumab arms than the bevacizumab treatment duration. Hence the model currently overestimates the treatment duration of oxaliplatin in the bevacizumab arms and correcting this would reduce the ICER's for when the APAS is not applied. There has no affect on the ICER's when the APAS is applied as oxaliplatin is free of change. | |
| Roche Products | **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**<br><br>**2.2.4 Administration costs** | Comment noted. |

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| | Paragraph 3.30 of the ACD states *'The ERG noted that the source of the recalculated administration costs and patient access scheme operating costs were unclear.'*<br><br>Section 4.14 goes on to state, when referring to the administration costs, that the committee noted that *'in particular, the sources of the unit costs were unclear'*.<br><br>The source of the revised administrations costs was described in our response to the ACD under the heading *'The incremental pharmacy and administration cost associated with adding bevacizumab to XELOX or FOLFOX'* . The source of the unit costs was clearly stated as being the PSSRU (see table 7 from Roche response to the 1st ACD below). Full details of the time and motion study which these unit costs were then applied were also provide in the our response.<br>*Table provided, but not reproduced here.* | |
| Roche Products | **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**<br><br>**2.2.5. Operating costs of the APAS**<br><br>Paragraph 3.30 of the ACD states 'The ERG noted that the source of the recalculated administration costs and patient access scheme operating costs were unclear.' | Comment noted. |

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| | A detailed description of the methods and sources of timings and costs are provide under the heading of 'The NHS resource cost of operating APAS and the subsequent effect on the ICER'.<br><br>Section 3.26 states 'The manufacturer revised the time per patient of operating the patient access scheme to 131 minutes and 152 minutes for the XELOX and FOLFOX regimens, respectively, based on research within the NHS. This equated to a cost per patient over years 1 to 3 of £57 and £67 for B-XELOX and B-FOLFOX, respectively.'<br><br>The above paragraph could be misunderstood to suggest that the cost per patient was only accounted for from years 1 to 3. This is not the case. The ongoing costs of running the scheme were based on the mean duration patients are expected to be on APAS, although admittedly patients are not expect to be on the scheme for more than 3 years.<br><br>The mention of years 1 to 3 in our response to the first ACD was with regards to the average number of patients that would be expected to be enrolled on APAS in trust during the first 3 years from commencing the scheme. This was required to convert the one-off cost of a trust setting up the scheme and the monthly accounting activities associated with the APAS to a per patient cost that could then be applied to the economic model. | Comment noted. The FAD has been amended accordingly. Please see the FAD section 3.26 for further details. |
| Roche Products | **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** | |

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| | **2.2.6. Oxaliplatin Price**<br><br>Paragraph 4.16 of the ACD2 states 'the Committee noted the view of the ERG that if the substantial price reduction of oxaliplatin was included in the model then the ICERs would also be greatly increased.'<br><br>It is not clear from the above paragraph which ICER's are being referred to. It is not the case that all the ICERs would increase. The ICER's without APAS applied would decrease should the price of oxaliplatin reduce since patients were treated for longer on oxaliplatin in the bevacizumab arm. | Comment noted. The Committee noted the ERG's exploratory analyses, which showed that when the oxaliplatin list price was discounted by 90% the ICERs with the patient access scheme were greatly increased to £68,100 per QALY gained for B-XELOX compared with XELOX, and to £70,500 per QALY gained for B-FOLFOX compared with FOLFOX-6. See FAD section 4.18 for further details. |
| Roche Products | **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**<br><br>Roche do not agree the ACD is a currently a fair reflection of the evidence. As detailed above, under heading 2, there a number of areas where the ACD is either factually incorrect or does not provide a reasonable interpretation of the evidence. | Comment noted. Please see detailed responses above. |
| Roche Products | **Are there any equality related issues that need special consideration that are not covered in the ACD?**<br><br>No comments. | Comment noted. |
| Department of Health | Thank you for the opportunity to comment on the appraisal consultation document for the above single technology appraisal. | Comment noted. |

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| | I wish to confirm that the Department of Health has no substantive comments to make, regarding this consultation. | |
| Bowel Cancer UK | **Comments on individual sections of the ACD:**<br><br>**Section 1:**<br><br>We disagree strongly with this preliminary recommendation. Bevacizumab is a highly effective treatment that is widely available throughout Europe, the USA and other parts of the world. It has helped thousands of patients live longer and feel better with advanced bowel cancer. There is overwhelming evidence for its efficacy, including in the outcomes of various trials and studies, such as PRiME, which NICE has chosen to ignore in reaching this negative verdict | Comment noted. The Committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the manufacturers' submission and the Evidence Review Group report. It also carefully considered the comments received from consultees and commentators and the public in response to the Appraisal Consultation Documents.<br><br>The Committee noted that bevacizumab gave modest clinical benefit as a first-line treatment and bevacizumab was clinically effective as part of second-line treatment. See FAD section 4.7. However, for both legal and bioethical reasons the Committee must take account economic considerations and cost effectiveness of the technologies (Social Value Judgments - Principles for the development of NICE guidance; principle 5). The Committee concluded that bevacizumab for the treatment of metastatic colorectal cancer would not be a cost-effective use of NHS resources. See FAD sections 4.21 and 4.22. |

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| Bowel Cancer UK | **Comments on individual sections of the ACD:**<br><br>**Section 2:**<br><br>Once again, NICE appears to be making a negative decision on the basis of bureaucratic principals, rather than clinical ones. The priority for NICE should be for it to fully assess the clinical efficacy of a treatment, rather than get bogged down in the ease or difficulty and cost of patient access schemes. I was frankly shocked in the NICE appraisal meeting that so much time was spent on the minuatiae of the patient access schemes and so little time spent on the treatments clinical efficacy. Once again, patients are suffering because NICE seems unable and unwilling to put people not processes first in reaching its verdicts. | Comment noted. The Committee noted that bevacizumab gave modest clinical benefit as a first-line treatment and bevacizumab was clinically effective as part of second-line treatment. See FAD section 4.7. However, for both legal and bioethical reasons the Committee must take account economic considerations and cost effectiveness of the technologies (Social Value Judgments - Principles for the development of NICE guidance; principle 5). The Committee concluded that bevacizumab for the treatment of metastatic colorectal cancer would not be a cost-effective use of NHS resources. See FAD sections 4.21 and 4.22. |
| Bowel Cancer UK | **Comments on individual sections of the ACD:**<br><br>**Section 3:**<br><br>NICEs negative assessment of Bevacizumabs clinical efficacy - its claim of an average of only six weeks added benefit - is based solely on one flawed study, completed in 2006, the NO16966 study, which stopped patients receiving Bevacizumab when the chemotherapy they were on stopped working. Subsequent studies, including the comprehensive PRiME study published at ASCO this summer, show that patients can live up to 27 months with advanced mCRC, if they stay on Bevacizumab with a second chemotherapy agent if the first | Comment noted. The Committee considered all the relevant evidence submitted, including evidence from clinical trials, patient and clinical experts, the manufacturers' submission and the Evidence Review Group report. It also carefully considered the comments received from consultees and commentators and the public in response to the Appraisal Consultation Documents.<br><br>The Committee noted that bevacizumab gave modest clinical benefit as a first-line |

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| | chemotherapy fails, either irinotecan or oxaliplatin, with 5FU and leucovorin - the FOLFIRI and FOLFOX regimens. Once again, NICE appears to have been determined to make a negative decision and to find the "evidence" to justify doing so, rather than seek to make a positive decision and find the evidence for doing so. | treatment and bevacizumab was clinically effective as part of second-line treatment. See FAD section 4.7. However, for both legal and bioethical reasons the Committee must take account economic considerations and cost effectiveness of the technologies (Social Value Judgments - Principles for the development of NICE guidance; principle 5). The Committee concluded that bevacizumab for the treatment of metastatic colorectal cancer would not be a cost-effective use of NHS resources. See FAD sections 4.21 and 4.22. |
| Bowel Cancer UK | **Comments on individual sections of the ACD:**<br><br>**Section 4:**<br><br>It is a great shame that NICE didn't take the opportunity it was given to approve Bevacizimab for the treatment of metastatic CRC. In producing negative guidance, once again, for what is a very effective treatment, NICE has shown that it is out of tune with the mood of the times, which has been set by the Coalition Government - very much one of prioritising those most in need, including patients with advanced conditions. If NICE could learn to trust clinicians in its decisions it would find that the reality of approving treatments like Bevacizumab would be much less costly and time consuming than declining them. Clinicians will not give Bevacizumab to a patient if | Comment noted. The Committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the manufacturers' submission and the Evidence Review Group report. It also carefully considered the comments received from consultees and commentators and the public in response to the Appraisal Consultation Documents.<br>The Committee noted that bevacizumab gave modest clinical benefit as a first-line treatment and bevacizumab was clinically effective as part of second-line treatment. |

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| | they arent going to benefit from it or tolerate it. Neither will they keep a patient on the drug if it stops working for them. If clinicians are allowed to make decisions in the best interests of their patients the system will work better for everyone and, above all, those most in need will be helped to live longer anf feel better with an advanced disease. | See FAD section 4.7. However, for both legal and bioethical reasons the Committee must take account economic considerations and cost effectiveness of the technologies (Social Value Judgments - Principles for the development of NICE guidance; principle 5). The Committee concluded that bevacizumab for the treatment of metastatic colorectal cancer would not be a cost-effective use of NHS resources. See FAD sections 4.21 and 4.22. |
| Bowel Cancer UK | **Comments on individual sections of the ACD:**<br><br>**Section 5:**<br>One would hope that the soon to be introduced Interim Drugs Fund and Cancer Drugs Fund from next year, which will be allocated | Comment noted. |
| Bowel Cancer UK | **Comments on individual sections of the ACD:**<br><br>**Section 7:**<br><br>Nothing to add to this section | Comment noted. |
| Bowel Cancer UK | **Comments on individual sections of the ACD:**<br><br>**Section 8:**<br><br>Three more years of injustice, unnecesary pain and reduced life | The Institute recognises that guidance from other organisations may differ from its own guidance, because of different criteria for making decisions. The Committee |

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| | expectancy for patients with advanced bowel cancer. Three more years of the UK falling further and further behind the rest of Europe in the treatment of advanced bowel cancer. Three more years of millions of pounds and hours being wasted by clinicians, their patients and organisations like ourselves trying to gain access to bevacizumab for patients who can benefit from it. | considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the manufacturer's submission and the Evidence Review Group Report. The Committee noted that bevacizumab gave modest clinical benefit as a first-line treatment and bevacizumab was clinically effective as part of second-line treatment. See FAD section 4.7. However, for both legal and bioethical reasons the Committee must take account economic considerations and cost effectiveness of the technologies (Social Value Judgments - Principles for the development of NICE guidance; principle 5). The Committee concluded that bevacizumab for the treatment of metastatic colorectal cancer would not be a cost-effective use of NHS resources. See FAD sections 4.21 and 4.22. |
| Royal College of Nursing | **The Royal College of Nursing welcomes the opportunity to review this document. The RCN's response to the four questions on which comments were requested is set out below:**<br><br>**i) Has the relevant evidence has been taken into account?**<br><br>The evidence considered seems comprehensive. | Comment noted. |

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| Royal College of Nursing | **ii) Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence, and are the preliminary views on the resource impact and implications for the NHS appropriate?**<br><br>We would ask that the summaries of the clinical and cost effectiveness of this appraisal should be aligned to the clinical pathway followed by patients with metastatic colorectal cancer. The preliminary views on resource impact and implications should be in line with established standard clinical practice. | Comment noted. |
| Royal College of Nursing | **iii) Are the provisional recommendations of the Appraisal Committee sound and do they constitute a suitable basis for the preparation of guidance to the NHS?**<br><br>Nurses working in this area of health have reviewed the recommendations of the Appraisal Committee and do not have any other comments to add. | Comment noted. |
| Royal College of Nursing | **iv) Are there any equality related issues that need special consideration that are not covered in the ACD?**<br><br>None that we are aware of at this stage. We would however, ask that any guidance issued should show that equality issues have been considered and that the guidance demonstrates an understanding of issues concerning patients' age, faith, race, gender, disability, cultural | Comment noted. No equality issues had been raised during the scoping, evidence submissions or consultation stages. Therefore, it concluded that there were no |

| Consultee | Comment | Response |
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| | and sexuality where appropriate. | specific issues relating to equality that needed to be taken into account. |

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| Merck Serono | I am writing to confirm that Merck Serono does not have any comments in relation to the above bevacizumab Single Technology Appraisal. | Comment noted. No actions required. |
| Medicines and Healthcare products Regulatory Agency | Thank you for your invitation to the MHRA for the above appraisal. This was passed on to our experts in the Licensing and Vigilance Risk Management of Medicines divisions who have confirmed that they will not be participating in this appraisal but would like to be kept informed for future.<br>Please contact us again if you need further assistance with this, or any other queries. | Comment noted. No actions required. |
| National Collaborating Centre for Cancer | **Has all of the relevant evidence been taken into account?**<br><br>Yes | Comment noted. |
| National Collaborating Centre for Cancer | **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**<br><br>-Section 3.1, 2nd sentence – The GDG do not think that this statement is true. | Comment noted. The manufacturer stated that the use of irinotecan in combination with folinic acid and 5-flourouracil (FOLFIRI) is decreasing and that it is mainly used in the small minority of patients who cannot tolerate oxaliplatin. |

| Consultee | Comment | Response |
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| | -Section 3.4, last sentence – the GDG felt that this statement was true of all trials and therefore didn't really add anything | Comment noted. |
| | -Section 4.12, last sentence – the GDG queried where the evidence was to support this statement? | Comment noted. Comment noted. The Committee noted the information provided by the manufacturer and concluded that the economic model reflected the clinical evidence that was available (in terms of treatment duration). However, the Committee concluded that in practice bevacizumab treatment would be expected to continue until disease progression in patients treated with a continuous therapy policy. This could potentially increase the ICERs. Please see the FAD section 4.12 for further details. |
| | -Section 4.13 – the GDG questioned whether or not the higher incidence rates of grade 3 and 4 toxicity were actually statistically significant | Comment noted. The Committee concluded that in some cases, the adverse effects of bevacizumab could be serious and disutility due to adverse events specific to bevacizumab treatment should have been incorporated into the model. The utility values used could not have accounted for the adverse effects of bevacizumab because they were obtained from a study that examined cetuximab. The |

| Consultee | Comment | Response |
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| | -Section 4.14, penultimate sentence – what was the basis for this conclusion – not clear as is. | Committee therefore concluded that the ICERs would increase if the disutility due to adverse events related to bevacizumab treatment was included. Please see the FAD section 4.15 for further details.<br><br>Comment noted. |
| National Collaborating Centre for Cancer | **Are the provisional recommendations sound and a suitable basis for guidance to the NHS?**<br><br>Yes | Comment noted. |
| National Collaborating Centre for Cancer | **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?**<br><br>No | Comment noted. |

**Comments received from members of the public**

| Role* | Section | Comment | Response |
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| NHS professional 1 | 1 | I fully support this recommendation. In particular, the evidence for overall survival benefit is lacking, the ICERs are high, and the benefits of the patient access scheme are doubtful, given its complexity. Funding a treatment for which the costs are so high, in relation to the benefits, is likely to have a significant impact on my PCT, and makes the likelihood of other service developments much less likely. Particularly vulnerable areas include treatments for lymphoedema, health promotion support for early cancer detection and the identification and early management of people at high risk of heart disease | Comment noted. No action required. |
| NHS Professional 1 | 2 | The DoH concerns about the patient access scheme are highly significant, and a complex scheme could easily founder and not deliver the benefits to the NHS needed. | Comment noted. No action required. |
| NHS Professional 1 | 3 | The weaknesses of the original case- using data which and been rejected as unreliable by the EMA- is a mater of great concern. The use of data on administration costs which are so lacking in robustness also undermines the case. | Comment noted. No action required. |

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patient', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

| Role* | Section | Comment | Response |
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| NHS Professional 1 | 4 | The Committees considerations seem completely reasonable, The base line ICERs are very high, and the likely numbers of cases to be treated should the recommendation change will have a substantial impact on the ability of my PCT to fund other developments with better evidence of cost effectiveness. | Comment noted. No action required. |
| NHS professional 2 | 1 | NHS North Yorkshire and York (NHS NYY) strongly endorses the preliminary recommendations made by NICE. This regimen provides a marginal increase in progression-free survival, but no increase in overall survival at a significant increase in cost. Improvements in PFS may not necessarily provide a better quality of life, noting no QoL data was provided. Approximate annual incidence of metastatic bowel cancer of 13/100,000, we estimate that 98 patients annually locally would qualify for this. At £24,000/year, this would represent approximately £2,350,000 in drug cost, with an assumed increase in imaging, diagnostics and other associated activity. The current financial climate means that to fund this treatment, disinvestment in other therapies, with more robust patient-orientated outcomes would be extremely likely. This would lead to a net health loss to the PCT residents. We recognise that by using bevacizumab, there are likely to be changes in other areas of the pathway, but the evidence suggests it is not cost-effective and is only effective in increasing PFS by 1.4 months on average with no statistically significant evidence to show improvements in overall survival. | Comment noted. No action required. |

| Role* | Section | Comment | Response |
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| NHS professional 2 | 3 | The evidence for first-line use comes from a phase III RCT, initially designed to show non-inferiority of capecitabine and oxaliplatin (XELOX) compared with oxaliplatin, folinic acid and 5-Fluorouracil (FOLFOX-4) with a subsequent addition of bevacizumab or placebo to the regimens. NHS NYY is sceptical over the use of non-inferiority trials. It is our view that it is relatively easy to subtly but significantly alter the odds of a treatment, which is difficult to detect without intense scrutiny. The initial results presented were derived from pooling of the data from both parts of the study, and we support that this was not considered to be appropriate by the European Medicines Agency and by NICE due to an imbalance in prognostic factors between the two parts of the study. First-line treatment including the use of bevacizumab resulted in a statistically significant progression-free survival benefit of 1.4 months, but no statistically significant benefit on overall survival in the secondary analysis of the study data, which utilised data from the second part of the study only. Adverse events were common. A significant percentage of the participants withdrew from the study due to adverse events. NHS NYY believes that this might have a significant adverse impact on the external validity of the evidence reviewed. | Comment noted. No action required. |

| Role* | Section | Comment | Response |
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| NHS professional 2 | 4 | The Committee concluded that “bevacizumab in combination with oxaliplatin-containing regimens could not be recommended as a cost-effective use of NHS resources for the first-line treatment of metastatic cancer”. NHS NYY concurs with this analysis. There is insufficient evidence of overall survival and the evidence presented did not show a substantial improvement in progression-free survival. The incremental cost-effectiveness ratios (ICERs) are uncertain, and on the basis of the evidence presented are likely to be much higher when considering duration of treatment in real-world use is likely to be longer, additional costs of managing bevacizumab toxicity which was excluded from the economic model, lower procurement costs of oxaliplatin, implementation of PAS scheme, utility values thus increasing the ICER. Roche has described a Patient Access Scheme (PAS) which the Department of Health is concerned may be too complex and lead to increased administrative costs, making it more expensive to implement than the Roche economic model suggests. We would ask that every effort is made to ensure implementation of such schemes are made simple without excessive financial transactions as evidence suggests that these schemes are convoluted and a substantial additional administrative burden, with the NHS not achieving the benefits and incurring additional costs whilst in pursuit of delivering quality patient care. The manufacturer did not collect any quality of life data, and the utility values are derived from previous NICE guidance for cetuximab which are unreliable in this context and likely to be overvalued, therefore we remain uncertain whether the PFS reported results in an improved QoL. Without the PAS, the revised ICERs for 1st line treatment were estimated at £105,000 per QALY when compared with the XELOX regimen alone, and £108,000 per QALY when compared to the FOLFOX-6 regimen alone. These are much higher than the usually accepted thresholds for the use of NHS resources. With the PAS, these were reduced to £30,000 per QALY and £24,600 per QALY respectively. The ICER for 2nd | Comment noted. No action required. |

| Role* | Section | Comment | Response |
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| NHS professional 2 | | per QALY and £24,600 per QALY respectively. The ICER for 2nd line use was reported as £103,000, again far greater than what is usually considered acceptable, furthermore, small benefits were achieved at the cost of increased adverse effects. | |
| NHS professional 3 | 1 | I fully support the Appraisal Committees preliminary recommendations. | Comment noted. No action required. |
| NHS professional 3 | 2 | Given that simple Patient Access Schemes place a considerable burden on NHS Trusts and Commissioning organisations, complex schemes need to be avoided and should not be supported. | Comment noted. No action required. |
| NHS professional 3 | 4 | I fully support the information included in this section. In particular:- 1. Pooling of the trial evidence is inappropriate. 2. First-line treatment including bevacizumab resulted in a progression free survival (PFS) benefit of only 1.4 months and no statistically significant benefit in overall survival (OS). 3. Adverse effects were common. A significant percentage of participants withdrew from study due to adverse effects. 4. Uncertainties around the ICERs - likely to be higher than those stated by the manufacturer. 5. Uncertainty around the costs to NHS of implementing the Patient Access Scheme. | Comment noted. No action required. |

| Role* | Section | Comment | Response |
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| NHS professional 4 | 1 | First line treatment including bevacizumab resulted in a progression free survival (PFS)benefit of 1.4 months and no statistically significant benefit in overall survival (OS) in the secondary analysis of the study data (using data only from the latter part of the study). This is poor value for money - money which could be far better spent on either basic clinical research into actual cures or for expanding and improving local palliative care services. | Comment noted. No action required. |
| NHS professional 4 | 4 | The revised ICERs without the patient access scheme amount to £105,000 per QALY compared to XELOX regimen alone and £108,000 compared with the FOLFOX-6 regimen, (much higher than usually accepted thresholds for use of NHS resources). With the PAS the ICERs were reduced to £30,000 and £24,600 respectively, but there is uncertainty about these estimates and the true ICERs could be higher. • The ICERs are uncertain and likely to be higher as treatment duration in real life use is likely to be longer. The PAS is likely to be more expensive to implement than estimated, and utility values derived from previous NICE guidance for cetuximab (TA 176) are unreliable and likely to be overvalued. No quality of life data were collected by the manufacturer. • For 2nd line treatment with oxaliplatin containing regimens there was a statistically significant OS and PFS benefit of three months from a single study. • There was no evidence presented for treatment later than second line. • Manufacturer reported ICER for second line use is Â£103,000 much higher than what is usually considered a cost effective use of NHS resources. There is no evidence for use after 2nd line. | Comment noted. No action required. |

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| NHS professional 4 | 5 | The Department of Health has expressed uncertainty about the costs to the NHS of implementing the patient access scheme (PAS), due to its complexity. If NICE were to reverse its decision and were to recommend the funding of the above regimes, the PCT would struggle to find the necessary funds, given the very tough financial cuts that it is currently having to make. | Comment noted. No action required. |
| NHS professional 4 | 7 | If NICE were to reverse its decision and were to recommend the funding of the above regimes, the PCT would struggle to find the necessary funds, given the very tough financial cuts that it is currently having to make. | Comment noted. No action required. |

| Role* | Section | Comment | Response |
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| NHS professional 5 | 1 | NHS Bradford and Airedale strongly endorse this preliminary recommendation by NICE. This drug confers a marginal progression free survival advantage, and NO overall survival advantage at a significant cost. It is not worth it. Indeed this drug at the current price is not affordable. Were we required to invest in this drug. We estimate that there will be approx 72 patients that will fit this indication in NHSBA in any given year (based on estimated incidence of 13 / 100,000). At £24,000 per course of treatment this would equate to approx £1,730,000 of investment in drug cost with additional significant investment in diagnostics, imaging and other activity. We assume the £24,000 covers the cost of Avastin, and not the other drugs it will be used with thus further increasing the cost. It is impossible to overstate the gravity of the financial position within NHS commissioners at this time. The £1.5m (plus activity costs) would need to be found inevitably it would be found from disinvestments in other services – probably more clinically effective and cost effective services – this would represent a net loss of health to the population of Bradford and Airedale and the population. | Comment noted. No action required. |

| Role* | Section | Comment | Response |
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| NHS professional 5 | 2 | There is an important methodological weakness involved in all Non Inferiority Trials (NIFTS) – that has an important bearing on this appraisal – and all others that depend on NIFT trials. Under the current standards for conducting a NIFT, in order to be non-inferior, one simply needs a 95% CI for the preferred [and usually proprietary] agent with an upper boundary which does not include delta in favour of the comparator (scenario A in the figure). For your preferred agent to be declared inferior, the LOWER 95% CI for the difference between the two agents must exclude the delta in favour of the comparator. For that to ever happen, the preferred/proprietary agent is going to have to be WAY worse than standard treatment. It is no wonder that such results are very, very rare, especially since deltas are generally much larger than is reasonable. We are not aware of any recent trial in a major medical journal where inferiority was declared. Inferiority is thus very difficult to declare, but superiority is relatively easy to declare, because for superiority your 95% CI doesn't have to exclude an obese delta, rather must just exclude zero with point estimate in favour of the preferred tx | Comment noted. No action required. |

| Role* | Section | Comment | Response |
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| NHS professional 5 | 3 | The evidence for first line use comes from a phase III RCT initially designed to show no inferiority of XELOX (capecitabine and oxaliplatin) compared with FOLFOX-4 regimens (Oxaliplatin, Folinic Acid and 5-Fluorouracil), with a subsequent addition of bevacizumab or placebo to the regimens. NHSBA is deeply skeptical of the validity of non inferiority trials. Our view is that it is very easy to subtly (and without VERY hard scrutiny difficult to detect) but significantly alter the odds of a treatment. Initial results reported by the manufacturer were derived from pooling of the data from both parts of the study, and this was not considered appropriate due to imbalance in prognostic factors in the two parts of the study. First line treatment including bevacizumab resulted in a progression free survival (PFS) benefit of 1.4 months and no statistically significant benefit in overall survival (OS) in the secondary analysis of the study data (using data only from the latter part of the study). The manufacturer initially pooled data from the two parts of the study and this was not considered appropriate by EMA and the NICE committee due to imbalance in prognostic factors in the two arms | Comment noted. No action required. |

| Role* | Section | Comment | Response |
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| NHS professional 5 | 4 | The Department of Health has expressed uncertainty about the costs to the NHS of implementing the patient access scheme (PAS), due to its complexity. NHSBA shares these deep concerns. The patient access scheme with its 4 elements: an upfront payment to the relevant NHS trust (undisclosed amount) for each patient, free avastin after 1year, oxaliplatin provided free by Roche and avastin to be purchased at full list price) seems excessively complex. Implementing an access scheme is administratively difficult has cost (thus further increasing the cost to the NHS) and in our experience doesn't work – thus increasing the likelihood that the NHS is not benefiting from the price quoted in the access scheme – making the ICERS even poorer than those cited in the draft review. The ICERs are uncertain and likely to be higher as treatment duration in real life use is likely to be longer. The PAS is likely to be more expensive to implement than estimated, and utility values derived from previous NICE guidance for cetuximab (TA 176) are unreliable and likely to be overvalued. No quality of life data were collected by the manufacturer. | Comment noted. No action required. |
| NHS professional 6 | 1 | I fully agree with the Appraisal Committees preliminary recommendations. | Comment noted. No action required. |
| NHS professional 6 | 2 | This is an accurate reflection of the technology. | Comment noted. No action required. |

| Role* | Section | Comment | Response |
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| NHS professional 6 | 3 | I agree with the ERG that the manufacturer's submission has weaknesses such as the lack of clarity about the operating costs of the access scheme and that the costs from the small private provider may not accurately represent the real costs from other providers. | Comment noted. No action required. |
| NHS professional 6 | 4 | I agree that there is a small clinical benefit but the large costs mean that NHS resources would achieve more if spent in other, more cost-effective areas. | Comment noted. No action required. |
| NHS professional 6 | 5 | No comment | Comment noted. No action required. |
| NHS professional 6 | 6 | There are other cost effective treatments available for this condition | Comment noted. No action required. |
| NHS professional 6 | 7 | No comment | Comment noted. No action required. |

| Role* | Section | Comment | Response |
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| Other | 1 | I have a 29-year-old sister who lives in Israel with her husband and two children. She was diagnosed with metastatic bowel cancer in March 2009. Unfortunately, she has a 21cm tumour in her liver and two much smaller ones elsewhere. Since the diagnosis and surgery to remove the primary tumour, she has been treated with bevacizumab together with chemotherapy. Even though her liver tumour is apparently incurable, her treatment has succeeded in keeping her tumours the same size. There are many cases like this where bevacizumab has succeeded in enhancing the quantity and quality of precious lives. This is why so many Western, forward-looking countries provide this drug to patients. Our new government coalition is determined to provide up-to-date and effective healthcare to cancer patients in desperate need. Whilst NICE attempts to ration drugs on a cost-effectiveness basis, any decision to withhold treatment from patients who will benefit from it is ultimately (albeit unintentionally) hubristic. Money is a necessary evil. Lets use compassion, not financial concern, as the primary basis for making choices about other peoples lives. Please reconsider your decision. | Comment noted. The Committee noted that bevacizumab gave modest clinical benefit as a first-line treatment and bevacizumab was clinically effective as part of second-line treatment. See FAD section 4.7. However, for both legal and bioethical reasons the Committee must take account economic considerations and cost effectiveness of the technologies (Social Value Judgments - Principles for the development of NICE guidance; principle 5). The Committee concluded that bevacizumab for the treatment of metastatic colorectal cancer would not be a cost-effective use of NHS resources. See FAD sections 4.21 and 4.22. |