

## **Comments on Appraisal Consultation Document**

### **Appraisal of bevacizumab and cetuximab for the treatment of metastatic colorectal cancer**

- 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 10<sup>th</sup> ) that more information regarding these two agents might become available at the American Society of Clinical Oncology (ASCO) meeting at the beginning of July 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 This was the case although all the new data was either in abstract or presentation form and not peer-reviewed publications.**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 was 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 1<sup>st</sup> 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)**

**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.**

- 2. 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.**

**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.**

- 3. 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.