NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Cetuxiamb for the treatment of recurrent and/or metastatic squamous cell cancer of the head and neck

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

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patient/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee. Where clinical specialists and patient experts make comments on the ACD separately from the organisations that nominated them, these are presented alongside the consultee comments in the tables below.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Comments received from consultees

Consultee	Comment	Response
Merck Serono	Introduction	
	Merck Serono appreciates the opportunity to comment on the NICE ACD for the Single Technology Appraisal for cetuximab in the treatment of recurrent and /or metastatic squamous cell carcinoma of the head and neck (RMHN). Please find herewith, our response.	Comment noted.
	We wish to address four issues raised in connection with the ACD which play a critical role in the appraisal, and may impact upon how the committee reviews the ACD. 1. Subgroup analyses based upon age and performance status (please see Appendix 2. Consistency of decision making across different Health Technology Assessments 3. Cetuximab addresses an unmet need 4. The appraisal of life-extending, end of life treatments	See below for response to detailed comments
	Our comments fall under sections i; ii and iii of the Appraisal Committee's general headings; i) Do you consider that all of the relevant evidence has been taken into account? ii) Do 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? iii) Do 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?	See below for response to detailed comments.

Consultee	Comment	Response
Merck Serono	**i) Do you consider that all of the relevant evidence has been taken into account?** Merck Serono values the appraisal committee's comments on the relevant evidence.	
	In order to support further the committee in it's assessment of the STA, Merck Serono wishes to submit additional data in Appendix 1 as per Section 4.5.2.10 of the NICE Guide to the Technology Appraisal Process (reference N0514). The original submission of evidence (Sept 25th 2008) included discussion of the impact of Karnofsky Performance Status (KPS) on overall survival, combined with analyses of subgroups defined by tumour location (descriptions of the pre-planned subgroups can be found on pages 46 & 47 and Table B3 of the original submission).	Comment noted.
	Following the publication of NICE supplementary advice, effective from 5 January 2009, concerning the appraisal of life-extending, end of life treatments, the significance of information revealing an extension of life by three months has increased. Merck Serono concludes that subgroup analyses which show extension of life by three months should be submitted for consideration by NICE. We would therefore like the appraisal committee to reconsider the data for cetuximab + chemotherapy for a sub-group of patients that now meets all of the end-of-life criteria.	Comment noted. The Committee considered the cost-effectiveness analyses submitted for the additional subgroups based on age and Karnofsky performance status (KPS). See FAD section 4.4.

Consultee	Comment	Response
Merck Serono	The additional data consists of further sub group cost-effectiveness analyses from the original economic model based upon • Age (under 65 years of age) • Karnofsky performance status (above KPS 90 and KPS 80) It is felt that the data for this proposed subgroup of patients is clinically relevant and for these patients there are no alternative treatment options which may confer similar benefit.	Comment noted. See FAD sections 3.19 and 3.20 for a summary of the cost effectiveness analyses for the subgroups combining age and Karnofsky performance status (KPS) and the ERG's critique of the analyses. The Committee considered the cost-effectiveness analyses for these subgroups. See FAD section 4.4.
	Analysis from the economic model for the subgroup of patients age<65 years and KPS>90 reveals incremental life years equating to an overall survival benefit of 3.77 months. This data is based upon a regression analysis.	Comment noted.
	Appendix 1 contains the more detailed cost-effectiveness analyses for the sub group defined above together with tabulations which show the proportion of RMHN patients by age and performance status (estimated from A+A market research analysis) and a calculation of the number of patients who would be eligible for treatment under NICE guidance for this sub group if approved.	
	It is estimated that the number of RMHN patients who are potentially eligible for treatment who satisfy the criteria age <65, KPS>90 is 209 per annum (see Table 6). Applying the incremental cost per patient from the original Merck Serono submission (please see appendix 1 below for further details) we would estimate a budget impact of £3,527,293 per annum assuming 100% uptake.	Comment noted.
	The estimated maximum number of patients who would be eligible for all licensed indications for cetuximab is calculated to be 2,841 patients per annum assuming 100% uptake in each indication (see Table 7).	Comment noted. The Committee noted that the number of patients eligible for cetuximab for this indication was approximately 3000. See FAD section 4.9.

Consultee	Comment	Response
Merck Serono	**ii) Do 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?** **Consistency of decision making across different Health Technology Assessments** Merck Serono believes that decision making processes should be consistent across health technology assessments. Merck Serono would seek to clarify the definition of survival as applied in the end of life process, as there may be a difference in the way this criterion has been applied to cetuximab in head and neck cancer compared to other appraisals. For example in the recent FAD, "Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma" of February 2009, the NICE appraisal committee applied the end of life criteria when reaching a decision over its recommendation. For end of life criteria to be applied, there needs to be 'sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment.' When the appraisal committee assessed sunitinib, they appear to have used the sunitinib clinical trial as evidence for this increase in survival, whereas in the ACD for cetuximab in head and neck cancer, the Committee chose to apply the end of life criteria on the basis of life years gained from the economic model. Therefore there is uncertainty as to whether clinical trial data or data derived from the economic model should be used to justify the utilisation of the end-of-life criteria.	Comment noted. Comment noted. The supplementary advice to the Appraisal Committee states in 2.3.1 that 'The estimates of the extension to life are robust and can be shown or reasonably inferred from either progression free survival or overall survival (taking account of trials in which cross-over has occurred and been accounted for in the effectiveness review)'. The Committee accepted that the results for the whole study population suggested that cetuximab plus platinum-based chemotherapy extended median survival relative compared with platinum-based chemotherapy alone. However, the Committee was not persuaded that either the estimate of life extension obtained from the trial or the predicted life years gained from the economic modelling fulfilled the survival criterion. See FAD section 4.8.

Consultee	Comment	Response
Merck Serono	In the Merck Serono submission for first line use of cetuximab in recurrent and/ or metastatic Head and Neck cancer STA we presented results from the EXTREME study together with economic modelling.	Comment noted.
	The primary outcome of the EXTREME study was overall survival. For this measure, a statistically significant and clinically meaningful improvement in overall survival was demonstrated in the cetuximab + CTX arm over the CTX arm. Median overall survival observed in the clinical trial was increased from 7.4 months (95% CI: 6.4, 8.3) to 10.1 months (95% CI: 8.6, 11.2). The hazard ratio was 0.797 (95% CI 0.644, 0.986, p=0.0362). This is an improvement of 2.7 months.	Comment noted. The Committee accepted that the results for whole study population suggested that cetuximab plus platinum-based chemotherapy extended median survival relative compared with platinum-based chemotherapy alone. However, the Committee was not persuaded that either the estimate of life extension obtained from the trial or the predicted life years gained from the economic modelling fulfilled the survival criterion. See FAD section 4.8.
	Our health economic model for the same overall population estimates that patients treated with cetuximab plus platinum/5FU gain on average 0.142 QALYs and 0.187 life years compared to those treated with platinum/5FU alone	Comment noted. The Committee noted that the predicted life years gained from the model was 0.187. See FAD section 4.8.

Consultee	Comment	Response
Merck Serono	The appraisal committee used the Merck Serono **economic model** in section 4.7 of the ACD and stated that on the basis of the estimate of life years gained from the addition of cetuximab to chemotherapy of 0.187, which equates to an average of 68 days, the committee did not consider that the magnitude of this benefit was in keeping with the supplementary advice for consideration of life-extending, end-of-life treatments.	Comment noted.
	However, in the February 2009 FAD, "Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma", the NICE appraisal committee evaluated this submission on the basis of the clinical trial rather than a modelling estimate and states in section 4.3.11 "the committee also noted that evidence from the sunitinib trial suggested that sunitinib increased survival"	Comment noted.
	Merck Serono would like to request uniformity of approach across health technology assessments in the elements upon which a NICE appraisal committee bases decisions.	Comment noted. The Committee accepted that the results for the whole study population suggested that cetuximab plus platinum-based chemotherapy extended median survival relative compared with platinum-based chemotherapy alone. The Committee were concerned about the uncertainty associated with this estimate. The Committee was not persuaded that either the estimate of life extension obtained from the trial or the predicted life years gained from the economic modelling fulfilled the survival criterion. See FAD section 4.8.
	iii) Do 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? **Cetuximab addresses an unmet need**	
	Vermorken, Mesia et al. 2008 have pointed out that since the introduction of cisplatin for the treatment of recurrent and or metastatic squamous cell carcinoma of the head and neck (SCCHN) approximately 30 years ago, there has been little improvement in survival among patients with this disease. *[Platinum-Based Chemotherapy plus Cetuximab in Head and Neck Cancer. Vermorken JB, Mesia R. et al 2008 N Engl J Med 359;11]*.	Comment noted.

Consultee	Comment	Response
Merck Serono	Cetuximab represents a step-change in first-line treatment of recurrent and /or metastatic squamous cell carcinoma of the head and neck. The currently available treatment options for recurrent and/or metastatic disease are limited (Vermorken, Herdst et al 2008); "Patients who receive first-line platinum-based regimens for recurrent and/or metastatic disease generally have a survival of 6 months to 9 months. Because current treatment options are so limited, there is a clear need for new therapies for patients with recurrent and/or metastatic SCCHN. EGFR generally is expressed at high levels in SCCHN and is associated with a poor prognosis in terms of disease-free survival and overall survival." (*Overview of the Efficacy of Cetuximab in Recurrent and/or Metastatic Squamous Cell Carcinoma of the Head and Neck in Patients Who Previously Failed Platinum-based Therapies. Vermorken JB, Herbst RS 2008 CANCER June 15, Volume 112 / Number 12, 2710-2719]*	See below for response to detailed comments. Comment noted.
	Patients who receive first-line platinum-based regimens for recurrent and/or metastatic disease generally have a survival of just 6 months to 9 months, so there are currently no treatments that reliably cure recurrent and/or metastatic squamous cell carcinoma of the head and neck. Therefore Merck Serono would contend that cetuximab addresses an unmet need.	Comment noted. The Committee noted from the EXTREME clinical trial that life expectancy for those patients treated with chemotherapy alone (that is without the addition of cetuximab) was unlikely to be more than 24 months and could be as low as 7 months. See FAD section 4.8.
	In the recent FAD, "Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma" of February 2009, the NICE appraisal committee take into account "There are currently no treatments that reliably cure advanced and/or metastatic RCC". Merck Serono request that, for cetuximab, the absence of alternative curative treatment is also taken into account.	Comment noted. The Committee accepted that the results for the whole study population suggested that cetuximab plus platinum-based chemotherapy extended median survival relative compared with platinum-based chemotherapy alone. However the Committee did not consider that this gain in overall survival met the criterion that the addition of cetuximab represented a 'marked change' from current treatment for recurrent and/or metastatic SCCHN. See FAD Section 4.8.

Consultee	Comment	Response
Merck Serono	**<u>The appraisal of life-extending, end of life treatments</u>** Merck Serono would like the committee to consider if the application of end of life criteria for cetuximab in recurrent/metastatic head and neck cancer is congruent with recently published appraisals: There are two other appraisals (although guidance is not final as yet) in which the end-of-life criteria have been applied. We believe that there are commonalities between these appraisals and therefore the end-of-life criteria should be applied to cetuximab in recurrent and/or metastatic head and neck cancer.	Comments noted.
	(a) Life expectancy and Survival benefit Appraisals thus far: • **Lenalidomide** in multiple myeloma - When assessing lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy (ACD2), the Appraisal Committee, took note of data that normal life expectancy without lenalidomide was unlikely to be greater than 24 months and was potentially as low as 9 months. The committee also stated that trials suggested that lenalidomide increased survival by more than 3 months compared to dexamethasone. • **Sunitinib** in renal cell carcinoma - The Appraisal Committee also recently assessed sunitinib and noted that normal life expectancy with IFNα treatment alone was unlikely to be greater than 24months and was potentially as low as 12 months. The committee also considered that the sunitinib trial suggested that sunitinib increased survival by more than three months compared to IFNα alone.	Comment noted.

Consultee	Comment	Response
Merck Serono	While cetuximab in the treatment of recurrent and/ or metastatic squamous cell carcinoma has an incremental cost effectiveness ratio in excess of the upper end of the range normally approved by the Appraisal Committees, currently patients who receive first-line platinum-based regimens for recurrent and/or metastatic disease generally have a survival of just 6 months to 9 months as there are no treatments that reliably cure recurrent and/or metastatic squamous cell carcinoma of the head and neck. Clinical trial results from the EXTREME study show a median overall survival increase from 7.4 months (95% CI: 6.4, 8.3) to 10.1 months (95% CI: 8.6, 11.2). This is an improvement of nearly 3 months (2.7 months). If we consider results from the economic model for the subgroup of patients age<65 years and KPS>90 then we see an overall survival benefit of 3.77 months.	Comment noted. The Committee accepted that the trial results for the whole study population suggested that cetuximab plus platinum-based chemotherapy extended median survival relative compared with platinum-based chemotherapy alone. However, the Committee was not persuaded that either the estimate of life extension obtained from the trial or the predicted life years gained from the economic modelling fulfilled the survival criterion. See FAD section 4.8. The Committee considered the additional cost-effectiveness analyses submitted by the manufacturer for subgroups based on age and KPS score (KPS of 90 or more and KPS of 80 or more). The Committee concluded that the estimates of cost-effectiveness for the subgroup of patients who were younger than 65 years with a KPS score of 90 or more could not be considered reliable. See FAD section 4.4.
	On the basis of both life expectancy of the individuals in question and the additional survival benefit from cetuximab, Merck Serono would like to request that the application of the end of life criteria should be reviewed for this appraisal.	Comment noted. The Committee was not persuaded that either the estimate of life extension obtained from the trial or the predicted life years gained from the economic modelling fulfilled the survival criterion. The Committee therefore did not consider that the estimate of gain in overall survival was in keeping with the criteria relating to extension of life. See FAD sections 4.8 and 4.10.

Consultee	Comment	Response
Merck Serono	**(b) Alternative treatments** Appraisals thus far: • **Lenalidomide in multiple myeloma** – The Appraisal Committee felt that there were potential alternatives to lenalidomide i.e. thalidomide and bortezomib for previously treated multiple myeloma however the Committee felt that these two drugs were unlikely to be routinely available on the NHS • **Sunitinib in renal cell carcinoma** – Although the FAD does not explicitly document the Committee discussions on alternative treatments when applying the end-of-life criteria, it was stated that sunitinib was a step-change in treatment As discussed previously, since the introduction of cisplatin approximately 30 years ago for the treatment of recurrent and or metastatic squamous cell carcinoma of the head and neck, there has been little improvement in survival among patients with this disease (Vermorken, Mesia et al. 2008). *Consequently, not only is there no alternative curative treatment, but, analogous to sunitinib in renal cell carcinoma, cetuximab can be considered a step-change in treatment*.	 Comment noted. Comment noted. Comment noted. The Committee was not persuaded that either the estimate of life extension obtained from the trial or the predicted life years gained from the economic modelling fulfilled the survival criterion. The Committee therefore did not consider that the estimate of gain in overall survival equated to a marked change from current treatment for recurrent and/or metastatic SCCHN. See FAD sections 4.8 and 4.10.

Consultee	Comment	Response
Merck Serono	**(c) Eligible Population** Appraisals thus far: • **Lenalidomide in multiple myeloma** –The Committee accepted that the estimated eligible population was approximately 2100. • **Sunitinib in renal cell carcinoma** - The Committee accepted the total number of people with advanced and/or metastatic RCC in England and Wales was approximately 4000 and therefore the eligible population can be considered small. In the ACD for cetuximab for head and neck cancer, it was noted that 3000 people per year are diagnosed with recurrent and/or metastatic squamous cell carcinoma of the head and neck, and that only a proportion of these would be appropriate for the therapy in question. If we focus on the sub- population (as presented in Appendix 1) of those patients who are under 65 years of age and with a KPS of 90 or above the population has been calculated to be just 209 patients per annum. Given the details outlined above, and the similarity of this appraisal to both the appraisal of lenalidomide in multiple myeloma and the appraisal of sunitinib in renal cell carcinoma, Merck Serono consider that the recurrent and/or metastatic squamous cell carcinoma of the head and neck population and the cetuximab technology meet the criteria of a life-extending, end-of-life treatment and that the justification for this consideration is supported by robust evidence.	 Comment noted. Comment noted. Comment noted. The Committee accepted that an estimated 3000 people in England and Wales per year are diagnosed with recurrent and/or metastatic SCCHN every year and that cetuximab plus platinum-based chemotherapy would be appropriate for only a small proportion of these patients. See FAD section 4.9. Comment noted. The Committee accepted that the eligible population was small. However, in considering the application of the end-of-life policy, the Committee understood that it should take into account the cumulative population for each product and noted that cetuximab was licensed for a number of other indications involving much larger patient groups. See FAD sections 4.9 and 4.10.

Consultee	Comment	Response
Merck Serono	**<u>Conclusion</u>** Merck Serono believes that cetuximab for first line treatment of recurrent and / or metastatic head and neck cancer should be considered a step-change treatment. Merck Serono would also request that end-of-life criteria should be applied to this intervention on the basis that: • Cetuximab (the treatment) is indicated for patients with a short median life expectancy of 7.4 months (i.e. less than 24 months) as per the control arm of the EXTREME clinical trial. • There is sufficient evidence (please refer to appendix 1) to indicate that the treatment offers an extension to life particularly for the subgroup of patients age<65 years and KPS>90 which produces an overall survival benefit of 3.77 months in the economic model. Regression analysis is undertaken to inform the process of considering the relevance of the outcomes assessed in the EXTREME clinical trial to the clinical benefits experienced by patients in UK practice. The overall survival benefit from cetuximab observed in the pivotal EXTREME trial is 2.7 months and therefore is only slightly less (9 days less) than the additional 3 months normally expected under the end-of-life criteria.	Comment noted. Comment noted. The Committee accepted that people with recurrent and/or metastatic SCCHN have a short life expectancy. See FAD section 4.8. Comment noted. The Committee was not persuaded that the evidence provided supported the predicted life years gained for the combined age and KPS score subgroup. In addition the Committee was not persuaded that the estimate of life extension obtained from the subgroup analysis was robust. The Committee therefore considered the criteria only in relation to the estimate of overall survival based on the whole study population because it did not consider the subgroup data to be robust. The Committee was not persuaded that either the estimate of life extension obtained from the trial or the predicted life years gained from the economic modelling for the whole study population fulfilled the survival criterion. . See FAD sections 4.4, 4.8, and 4.10.

Consultee	Comment	Response
Merck Serono	• No alternative treatment with comparable benefit is available through the NHS for the patient population as a whole (or for the subgroup of patients age<65 years and KPS>90 under consideration.)	The Committee considered the criteria only in relation to the estimate of overall survival for the whole study population because it did not consider the subgroup data to be robust. The Committee was not persuaded that either the estimate of life extension obtained from the trial or the predicted life years gained from the economic modelling reresented a marked change from current treatment for SCCHN. See FAD sections 4.4, 4.8, and 4.10.
	• Cetuximab is licensed or otherwise indicated for a small population. Whilst 3000 people annually are diagnosed with recurrent and/or metastatic head and neck cancer, the number of patients eligible for cetuximab in the proposed sub group (age<65 years and KPS>90) is estimated to be approximately 209 per annum. Furthermore the total number of patients who may receive treatment with cetuximab for any of its licensed indications in a given year is estimated to be fewer than 3,000 at 2,841.	Comment noted. The Committee accepted that an estimated 3000 people in England and Wales per year are diagnosed with recurrent and/or metastatic SCCHN every year and that cetuximab plus platinum-based chemotherapy would be appropriate for only a small proportion of these patients. However, in considering the application of the end-of-life policy, the Committee understood that it should take into account the cumulative population for each product and noted that cetuximab was licensed for a number of other indications involving much larger patient groups. See FAD section 4.9.
	• Vermorken el al highlight that no significant advance in treatment of this group of patients has been achieved in the last 30 years.	Comment noted.
	Merck Serono feels that taking these considerations into account would result in reasonable interpretations of the evidence and would allow sound preparation of guidance to the NHS that cetuximab in combination with platinum-based chemotherapy may be recommended for the treatment of recurrent and/or metastatic squamous cell cancer of the head and neck under the end-of-life criteria.	Comment noted. The Committee was not persuaded that the use of cetuximab plus platinum-based chemotherapy fulfilled all the criteria to be considered as a life extending, end-of-life treatment. See FAD sections 4.8, 4.9 and 4.10.
	Appendix 1 and 2 (not reproduced here)	

Consultee	Comment	Response
Vinidh Paleri, Clinical Expert	I agree with the contents of the ACD	Comment noted.
Dr Chris Nutting, Clinical Expert	I don't have any comments to make on this document. The paper is self explanatory	Comment noted.
Marilyn Jones, Patient Expert	1) I believe all the available and relevant evidence has been taken into account including the one randomised controlled trial provided by manufacturer. 3.2 2) I consider the summaries of clinical cost effectiveness are reasonable interpretations of the evidence, which should that in some instances the subgroups were too small casting doubt of the results of cost effectiveness 3.14 Cetuximab requires more frequent administration than chemotherapy and if the disease responds treatment has to continue until disease progression occurs incurring greater costs, and patients tend to survive longer. Other treatments and palliative care can involve additional NHS costs. 3.18 3) The provisional recommendations of the Appraisal Committee, are, I believe sound - they pointed out that life years gained with the addition of cetuximab to chemotherapy was the equivalent of 68 days. 4.7 4) Personally I do not feel there are any equality related issues not covered in the ACD.	Comments noted

Consultee	Comment	Response
Lets Face It t	**1. I do not think that all the relevant evidence has been taken into account.** With reference to 4.6 I value the details and statistics for patients with a short life expectancy, normally less than 24 months. That the treatment will extend the life of the patient normally of at least 3 months. What is most important and fails to have been addressed is the quality of life for the patients in the final months, and the difference Erbitux makes compared to the treatment available for the majority of head and neck cancer patients. I believe the committee must take these facts into account along with all the other advantages, the extension of life and quality of life that is gained by treating with Erbitux or, the adverse side effects now being experienced with platinum based chemotherapy. It feels to me as a patient, that this area has not been explored adequately; maybe because there are no statistics or records? My judgment not only as a patient but with the experience gained by sharing the deaths of hundreds of head and neck cancer patients; I assure you it is not a dignified death for either the patient or the carer. I would urge the committee to take this into consideration along with the financial cost. If Erbitux can provide a quality of life for those extended months, then please, consider it for the small number of patients who require it.	Comment noted. The Committee took into account a patient's quality of life through the QALYs (The QALY is a measure of a person's length of life weighted by a valuation of their health related quality of life over that period) estimated by the manufacturer's economic model. See section 5.4 of the Guide to methods of technology appraisal. Available at: http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf The Committee took into account the extension of life and quality of life through its consideration of the supplementary advice from the Institute, to be taken into account when appraising treatments which may be life-extending for patients with short life expectancy, and which are licensed for indications affecting small numbers of patients with incurable illnesses. See FAD sections 4.7 and 4.8.
	I**2. Do 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?** I do not feel qualified to be able to answer this question honestly.	Comment noted.
	3. Do 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? Yes, I do consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS with the additional exploration of my comments on quality of life in the final months**.**	Comment noted.

Consultee	Comment	Response
Lets Face It	**4. Are there any equality related issues that need special consideration that are not covered in the ACD?** The equality related issues that need special consideration that have not been covered in the ACD are the one of quality of life for the terminally ill patient. Does Erbitux improve the life for the patient compared to platinum based chemotherapy alone?	Comment noted. The Committee took into account a patient's quality of life through the QALYs (The QALY is a measure of a person's length of life weighted by a valuation of their health related quality of life over that period) estimated by the manufacturer's economic model. See section 5.4 of the Guide to methods of technology appraisal. Available at: http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf
The Mouth Cancer Foundation	The Mouth Cancer Foundation is disappointed with the preliminary recommendation of the Appraisal Committee not to recommend the use of Cetuximab in combination with platinum-based chemotherapy for the treatment of recurrent and/or metastatic squamous cell cancer of the head and neck. Here are our comments on the ACD, in response to the following general questions: **i. Do you consider that all of the relevant evidence has been taken into account?** **ii. Do 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?** The Mouth Cancer Foundation considers that while the relevant evidence has been taken into account, the ERG's reasoning is faulty in its interpretation of the material it considered. It appears to be biased and adversarial to material evidence in the manufacturer's submission. Our more detailed comments, keyed to various sections in the ACD, are below: 3.12 As a patient organisation, we would be disappointed if the manufacturer had not submitted clinical evidence to support the use of cetuximab plus platinum-based chemotherapy for the first-line treatment of patients with recurrent and/or metastatic SCCHN if its evidence shows that the added use of cetuximab improves outcome. Why does the ERG consider this a problem?	Comment noted. Comment noted. Comment noted. This comment was considered by the Appraisal Committee. Only formal responses from the Appraisal Committee to the comments on the ACD are included here.

Consultee	Comment	Response
The Mouth Cancer Foundation	The ERG states that patients in the EXTREME trial may be younger and fitter (indicated by very high KPS scores) than patients with recurrent and/or metastatic SCCHN in the UK. However, perusal of the age categories in Table 4.6 of participants in the EXTREME trial shows that 82.4% were <65 years and 17.6% were >65 years. We would not read this to mean patients in the trial were younger unless ERG thinks those between 55 -64 are young! Our experience with patient members reflects very much the picture that most Head and Neck cancer patients are not over 65 years. **There are increasing numbers of cases of younger patients in their 20's – 40's with recurrent and/or metastatic SCCHN and they should have access to this treatment that can prolong their life**. The ERG also expresses concern that no evidence was provided by the manufacturer to support the use of cetuximab plus platinum-based chemotherapy in patients with recurrent and/or metastatic SCCHN who were not cetuximab-naive. Is ERG not aware that the use of cetuximab for Head and Neck cancer patients is relatively new and not routinely available to them? One should expect that most patients with recurrent and/or metastatic SCCHN would inevitably be cetuximab-naive. The ERG highlighted that for several subgroups, including metastatic disease, there appeared to be no survival benefit from cetuximab plus platinum-based chemotherapy. The corollary is that there is a survival benefit for some subgroups. As a patient organisation, we expect the ERG to support the use of cetuximab for these groups of patients but do not find the ERG doing this.	Comments noted. This comment was considered by the Appraisal Committee. Only formal responses from the Appraisal Committee to the comments on the ACD are included here.

Consultee	Comment	Response
The Mouth Cancer Foundation	3.13 We feel that the ERG's own critique of the economic model submitted by the manufacturer is badly flawed. The ERG felt that the average BSA value of 1.7m2 used was incorrect and worked out a higher mean BSA of 1.83m2 to use in their own model from a 'recent survey of three UK cancer centres.' The reference (no 20) given in its Evaluation Report is to a BMJ awareness article on "Squamous Cell Carcinomas of the Head and Neck", not a survey. However, the average UK male BMA is 1.98 (based on average height of 178cm and weight of 80kg) and the average UK female BMA is 1.72 (based on average height of 162cm and weight of 67kg) and the average of the two gives 1.85. However derived, we would like to know if this 'survey' was of (1) Head and Neck cancer patients and (2) whether their BSA was recorded after initial treatment (surgery, radiotherapy) or before. Our patient members' experience is that they lost a lot of their normal weight after surgery and radiotherapy and their BSA was most definitely below the average UK male or female figure. **3**.14 We feel that for rarer cancers like recurrent and/or metastatic SCCHN where patient numbers are smaller, the ERG should not readily dismiss data presented by saying that "some of the subgroups were too small to yield reliable projection models, casting doubt on the credibility of the cost-effectiveness results for those subgroups." If so dismissed, rarer cancers will always be disadvantaged by the approach employed. We submit that exploratory analysis done using the ERG model amendments on all the patient subgroups were flawed and its conclusion that the use of cetuximab plus chemotherapy may not be cost effective at any price is perverse	Comments noted. This comment was considered by the Appraisal Committee. Only formal responses from the Appraisal Committee to the comments on the ACD are included here.

Consultee	Comment	Response
The Mouth Cancer Foundation	**iii. Do 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?** The Mouth Cancer Foundation is of the opinion that the Appraisal Committee's decision is unsound especially when it says in the ACD that: 4.2 Overall the Committee accepted the evidence from the clinical specialists that the results of the EXTREME trial would be applicable to the UK population. 4.3 The Committee accepted that the trial demonstrated the efficacy of cetuximab plus platinum-based chemotherapy in patients with recurrent and/or metastatic SCCHN. 4.4 The clinical specialists and a patient expert advised the Committee that the adverse events reported for the trial were consistent with those seen in clinical The practice where cetuximab had been used for locally advanced SCCHN and colorectal cancer.	Comment noted. Comment noted. Comment noted. The Committee observed that the trial data suggested that cetuximab plus platinum-based chemotherapy extended median survival by 2.7 months compared with platinum-based chemotherapy alone. However, the Committee was not persuaded that either the estimate of life extension obtained from the trial or the predicted life years gained from the economic modelling fulfilled the survival criterion. See FAD section 4.8. Comment noted.

Consultee	Comment	Response
The Mouth Cancer Foundation	The Mouth Cancer Foundation hopes that the Appraisal Committee's will reconsider its decision as the concerns raised by the ERG in relation to its exploratory analyses undertaken by the ERG using alternative assumptions and parameters in the economic model (see section 3.16) are flawed. It is important that the Appraisal Committee recognise that oncologists who provide the treatment always consider the individual patient on a case-by-case-basis as not all patients will be suitable for this treatment. We are not sure if the model of costs reflects this. **iv. Are there any equality related issues that need special consideration that are not covered in the ACD?** The Mouth Cancer Foundation considers that all the following criteria in the supplementary advice from the Institute when appraising treatments which may be life-extending for these patients with short life expectancy, and which are licensed for indications affecting small numbers of patients with incurable illnesses, were met: • The treatment is indicated for patients with a short life expectancy, normally less than 24 months. • No alternative treatment with comparable benefits is available through the NHS. • The treatment is licensed, or otherwise indicated, for small patient populations. • In addition, when taking these into account the Committee must be persuaded that the estimates of the extension to life are robust and the assumptions used in the reference case economic modelling are plausible, objective and robust. • There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Comment noted. NICE issues guidance for the whole population with a specific condition. The economic model reflects the costs of and benefits obtained from cetuximab for the 'average' patient on the 'average' treatment pathway. Individual patient variation is accounted for through the probabilistic sensitivity analysis. Comment noted. The Committee took into account the extension of life and quality of life through its consideration of the supplementary advice from the Institute, to be taken into account when appraising treatments which may be life-extending for patients with short life expectancy, and which are licensed for indications affecting small numbers of patients with incurable illnesses. See FAD section 4.7.

Consultee	Comment	Response
The Mouth Cancer Foundation	We would argue that the criteria that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment is only guidance and so should be applied flexibly. The Committee observed that the trial data suggest that cetuximab plus platinum-based chemotherapy extends survival relative to platinum-based chemotherapy alone. The EXTREME trial showed a statistically significant increase in median overall survival for cetuximab plus chemotherapy of 2.7 months or 81 days. It would be perverse if this treatment is denied just because patients in the trial failed to live for an additional 9 days longer in order to meet this criteria. This is the first time in 30 years that a study has shown an increase in overall survival for these patients. The Committee should consider that the magnitude of this benefit is in keeping with the spirit of the supplementary advice for consideration of life-extending, end-of-life treatments. The Committee should conclude that cetuximab for recurrent and/or metastatic SCCHN be recommended. The Mouth Cancer Foundation feels that it is important that clinicians are able to provide this current treatment modality if they decided it as most appropriate for their patient.	Comment noted. The supplementary advice to the Appraisal Committee states in 2.3.1 that 'The estimates of the extension to life are robust and can be shown or reasonably inferred from either progression free survival or overall survival (taking account of trials in which cross-over has occurred and been accounted for in the effectiveness review)'. The Committee were concerned about the uncertainty associated with the estimate of overall survival from the trial because of the wide confidence interval. It was also aware that the predicted life years gained from the economic modelling was lower reflecting a gain in overall survival of approximately 2.2 months. The Committee therefore did not consider that this estimate of gain in overall survival was in keeping with the criteria relating to extension of life or that the addition of cetuximab represented a marked change from current treatment for SCCHN. See FAD section 4.8. .

Consultee	Comment	Response
Royal College of Nursing	**Introduction** With a membership of over 400,000 registered nurses, midwives, health visitors, nursing students, health care assistants and nurse cadets, the Royal College of Nursing (RCN) is the voice of nursing across the UK and the largest professional union of nursing staff in the world. RCN members work in a variety of hospital and community settings in the NHS and the independent sector. The RCN promotes patient and nursing interests on a wide range of issues by working closely with the Government, the UK parliaments and other national and European political institutions, trade unions, professional bodies and voluntary organisations. The Royal College of Nursing welcomes the opportunity to review the Appraisal Consultation Document of the health technology appraisal of Cetuximab for the treatment of head and neck cancer (squamous cell carcinoma). **Response to the Appraisal Consultation Document** Nurses working in this area of health have reviewed this appraisal consultation document and have no additional comments to make on this document. The RCN will welcome national guidance to the NHS on the use of this health technology	Comment noted. Comment noted. Comment noted.
Royal College of Pathologists	The College notes that the NICE evaluation has concluded that cetuximab treatment has not been recommended as a cost-effective use of NHS resources, and recognises that although some patients may show benefit, in the absence of any validated biomarkers to predict which patients are more likely to respond to this type of targeted treatment, the treatment will not be recommended for general use for head and neck cancer patients.	Comment noted.
Leicester City NHS	**Do you consider that all of the relevant evidence has been taken into account?** Yes. We note the report of the Liverpool Implementation Group and consider that all of the relevant evidence has been taken into account. However, we note that the number of studies conducted is relatively small and share the concerns expressed about the generalisability of results, particularly when considering a diverse population such as Leicester.	Comment noted.
	Do 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? Yes. They represent a reasonable interpretation of evidence currently available and the practical resources required.	Comment noted.

Consultee	Comment	Response
Leicester City NHS	**Do 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?** Yes, on the basis of the information presented.	Comment noted.
	Are there any equality related issues that need special consideration that are not covered in the ACD? From the information presented we are not aware of any equality related issues that require special consideration. However, we note the absence of a formal health equity impact assessment and suggest that a systematic approach (such as a health equity impact assessment) would help to assess equality related issues by making this dimension more explicit.	Comment noted. Health equity impact assessments are outside the remit of the Health Technology Appraisal Programme.
Welsh Assembly Government	Thank you for giving the Welsh Assembly Government the opportunity to comment on the above appraisal. We are content with the technical detail of the evidence supporting the appraisal and have no further comments to make at this stage.	Comment noted.

Comments received from commentators

Commentator	Comment	Response
Welsh Association of Head and Neck Oncologists	**Section1: Appraisal Committee's preliminary recommendations** This recommendation is regrettable. The therapeutic options in this situation are limited. Uncontrolled recurrent/metastatic squamous cell cancer of the head and neck is a particularly unpleasant condition. The number of patients suitable for this treatment will be relatively small, and there is reasonable evidence that this select group can derive useful benefit from the addition of cetuximab to standard platinum-based chemotherapy without undue additional toxicity	Comment noted.
Welsh Association of Head and Neck Oncologists	**Section 2: The technology** The skin rash, and other side effects are mild in most cases, and in general patients are willing to put up with them if they perceive a benefit from the treatment. The side effect profile of cetuximab is usually more acceptable than that of the chemotherapy options.	Comment noted.

Commentator	Comment	Response
Welsh Association of Head and Neck Oncologists	**Section 3: Manufacturer's submission** 3.12"...no evidence was provided by the manufacturer to support the use of cetuximab plus platinum-based chemotherapy in patients with recurrent and/or metastatic SCCHN who were not cetuximab-naive." Cetuximab is a relatively new drug. The population of relapsed patients previously treated with cetuximab is small. The effect of cetuximab pre-treatment on cetuximab re-treatment is not clear at present, but could potentially confound the results of a trial such as EXTREME. Indeed, other trials of biological agents in this situation (e.g. ZALUTE, an NCRI-badged trial) specifically exclude patients pretreated with Cetuximab. Data on this clinical scenario is likely to accumulate very slowly. "The ERG highlighted that for several subgroups, including metastatic disease, there appeared to be no survival benefit from cetuximab plus platinum-based chemotherapy, although only the subgroup for tumour location showed a statistically significant interaction with treatment." This statement does not make complete sense. There will always be a problem with subsite analysis in H&N cancer studies, where n is almost invariably smaller than desirable	Comments noted. This comment was considered by the Appraisal Committee. Only formal responses from the Appraisal Committee to the comments on the ACD are included here.

Commentator	Comment	Response
Welsh Association of Head and Neck Oncologists	**Section 4: Consideration of the Evidence** 4.2 There is increasing evidence of an epidemiological shift in H&N patients towards a younger population without the usual risk factors or comorbidities.	Comment noted.
	4.7 Gain of 68 days may represent a benefit of significant magnitude if symptoms are controlled. Response to, and tolerance of treatment is usually quick and easy to evaluate in this disease. Non-responders will be discontinued at an early stage. Those patients who have a good response may well derive a significant long-term benefit from this treatment which cannot be produced with cytotoxic chemotherapy.	Comment noted. The supplementary advice to the Appraisal Committee states in 2.3.1 that 'The estimates of the extension to life are robust and can be shown or reasonably inferred from either progression free survival or overall survival (taking account of trials in which cross-over has occurred and been accounted for in the effectiveness review)'. The Committee were concerned about the uncertainty associated with the estimate of overall survival from the trial because of the wide confidence interval. It was also aware that the predicted life years gained from the economic modelling was lower reflecting a gain in overall survival of approximately 2.2 months. The Committee therefore did not consider that this estimate of gain in overall survival was in keeping with the criteria relating to extension of life or that the addition of cetuximab represented a marked change from current treatment for SCCHN. See FAD section 4.8.

NB: The Welsh Association of Head and Neck Oncologists are a commentator organisation, however these comments were submitted through the public web site