From: [redacted]
Sent: 20 February 2009 07:42
To: Jeremy Powell
Cc: [redacted]
Subject: Head and neck cancer (squamous cell carcinoma) - cetuximab - ACD & ER.....

Dear Jeremy

Thank you for the opportunity to comment on the Appraisal Consultation Document (ACD) and Evaluation Report (ER) for the above single technology appraisal.

I wish to confirm that the Department of Health has no substantive comments to
make, regarding this consultation.

Many thanks and best wishes

[redacted]
Department of Health

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE
Single technology appraisal (STA)
Cetuximab for the treatment of metastatic and/or recurrent squamous cell carcinoma of the head and neck
COMMENTS FROM NHS LEICESTER CITY

1.	**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.
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?** Yes. They represent a reasonable interpretation of evidence currently available and the practical resources required.
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, on the basis of the information presented.
4.	**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. .

National Institute for Health and Clinical Excellence

Single technology appraisal (STA)

Cetuximab for the treatment of metastatic and/or recurrent squamous cell carcinoma of the head and neck

Comments on the Appraisal consultation document

LET'S FACE IT SUPPORT NETWORK FOR FACIAL DISFIGUREMENT

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.

2. I do not feel qualified to be able to answer this question honestly.

3. 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.

4. 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?

Merck Serono response to NICE ACD advice: Erbitux® (cetuximab) for the first-line treatment of recurrent and /or metastatic squamous cell carcinoma of the head and neck.

NICE Single Technology Appraisal of cetuximab for the treatment of recurrent and /or metastatic squamous cell carcinoma of the head and neck

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.

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 1)
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

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?

Merck Serono response to NICE ACD advice: Erbitux® (cetuximab) for the first-line treatment of recurrent and /or metastatic squamous cell carcinoma of the head and neck.

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).

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.

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.

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.

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**.

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).

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.

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.

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.

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.

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.

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"

Merck Serono would like to request uniformity of approach across health technology assessments in the elements upon which a NICE appraisal committee bases decisions.

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]

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]

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.

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.

The appraisal of life-extending, end of life treatments

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.

(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.

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.

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.

(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.*

(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.

Conclusion

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.
- 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.)
- 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.
- Vermorken *el al* highlight that no significant advance in treatment of this group of patients has been achieved in the last 30 years.

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.

Appendix 1

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), and hope that the information will assist the committee in it's assessment of the STA. In line with the scope issued by NICE, Merck Serono had stated in the Decision Problem, Section 2 of the original STA submission that it would address "groups defined by performance status, previous treatments and response to previous treatments."

The additional data submitted here comprises further sub group analyses from the economic model based upon age and Karnofsky performance status (KPS**)** status (results are presented in Tables 2 and 3.

The original submission of evidence (in section 6.4) discussed performance status and age as prognostic factors. This information is copied below:

"A planned sensitivity analysis of overall survival was performed by prognostic factor. This demonstrated that previous exposure to chemotherapy had no prognostic relevance (HR of 0.999) but a KPS ≥ 80 notably reduced the risk of death by 49%."

"Pre planned subgroup analyses were also performed to search for any heterogeneity of response. These demonstrated little heterogeneity except in both older and less fit subjects, those receiving carboplatin chemotherapy, subjects whose tumours were located in the hypopharynx and larynx, poorly differentiated tumours and subjects whose tumours were metastatic, where benefit of the addition to cetuximab to standard chemotherapy was not demonstrable to a statistically significant degree.

The forest plots for these subgroup analyses are given in the tables below:"

Safety

The adverse events in this sub group would not be expected to differ from those presented in section 6.7 of the original submission.

Interpretation of Clinical Evidence

The EXTREME trial, covering 442 international intention-to-treat patients, includes UK patients and the A&A market research analysis includes data from 107 UK patients.

Information on performance status in the EXTREME study uses the Karnofsky Performance Status criteria, while the A&A market research analysis uses ECOG scale. The comparability of the two is based on a table adapted from Common Terminology Criteria for adverse events (CTCAE) Version 2 US DCTD NCI NIH and is presented in Table 1 below. (CTCAE version 3 does not present this chart) and from research by Verger *et al* 1992. Verger *et al* showed in a study of 150 consecutive oncology patients assessing KPS and ECOG score in a population of mean age 60 years, excellent correlations between the two scales for KPS 100 and 90 and ECOG 0 and 1, although lesser performance statuses do not correlate so well.

Table1: Mapping of performance status measures: ECOG to KPS.

PERFORMANCE STATUS CRITERIA Karnofsky scores are multiples of 10			
ECOG		**KARNOFSKY**	
Description		Description	
Score 0	Fully active, able to carry on all pre-disease performance without restriction.	Score 100	Normal, no complaints, no evidence of disease.
		Score 90	Able to carry on normal activity; minor signs or symptoms of disease.
Score 1	Restricted in physically strenuous activity but ambulatory and able to carry out light work of a light or sedentary nature e.g., light housework or office work.	Score 80	Normal activity with effort; some signs or symptoms of disease.
		Score 70	Cares for self, unable to carry on normal activity or do work.

Table adapted from Common Terminology Criteria for adverse events (CTCAE) Version 2 US DCTD NCI NIH

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. (Details of the regression analysis can be found in Appendix 2).

Studies have shown that patients are likely to choose treatment that will give them only marginal life prolongation in the eyes of health care professionals [Matsuyama 2006].

It is to be expected that younger patients with good performance status might be offered and might accept aggressive anti-cancer therapy.

Applicability

The sub group proposed of those less than 65 years of age and with a KPS of 90 or above would be a natural group at which to target more aggressive combination chemotherapies. Intuitively one would expect such patients to be able to tolerate intense therapy better than those patients who were older or with a lower performance status and hence that the results of such treatment would be more favourable, This is confirmed by the forest plot presented below in Fig B3 where both the age under 65 subgroup and the KPS $\geq$ 80 subgroup have hazard ratios which show significant benefit under cetuximab treatment.

Figure B3: Forest plots for hazard ratios of overall survival for pre-planned subgroups in EXTREME study (copied from original submission of evidence).

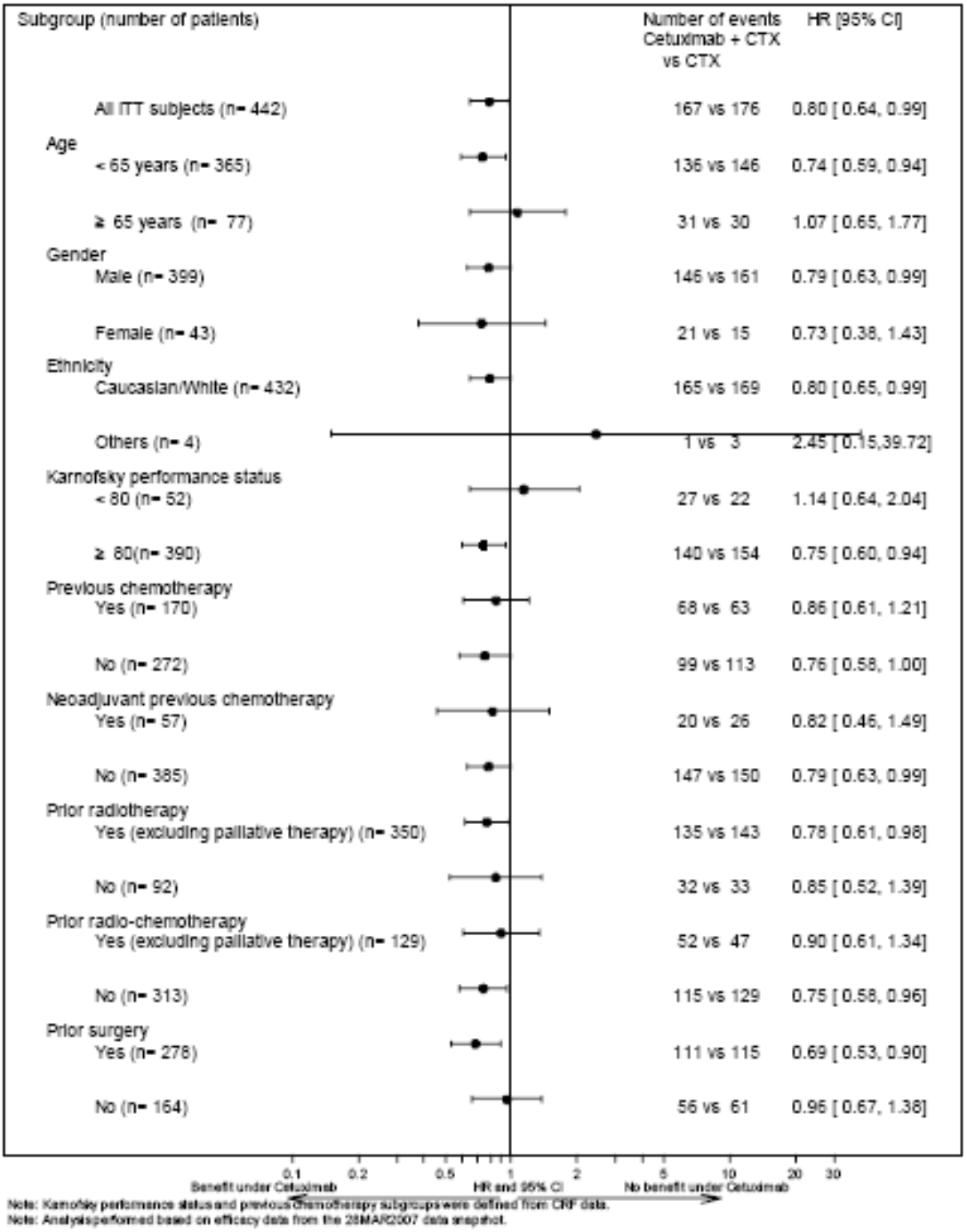

Table 2 shows mean overall survival gains for the subgroup of patients age <65 years and with a KPS ≥ 90 which exceed the 3 month threshold for consideration under the end of life criteria. These analyses are based upon regression analyses of the EXTREME data.

It is felt that this proposed sub group is clinically relevant and there are no alternative treatment options for this group of patients which may confer similar benefit.

It is to be expected that younger, fitter patients might be offered and might benefit from the more intense treatments such as a combination of chemotherapy and cetuximab.

For the subgroup of RMHN patients age <65 years with KPS >90 the results from the economic model are presented in Table 1 below.

Table 2: Analysis of the subgroup for age<65 years and KPS≥90

Cost-effectiveness			
Cetuximab + standard treatment vs Standard treatment	mean	p2.5	p97.5
Incremental costs	£19,744	£13,772	£26,427
Incremental life-years	0.314	-0.131	0.790
Incremental QALYs	0.213	-0.281	0.713
Incremental cost effectiveness ratio	£62,893		
Incremental cost utility ratio	£92,804		

The incremental life years here equate to an overall survival benefit of 3.77 months

For further information a second iteration of the above analysis including those patients with a slightly lower KPS (age <65 years with KPS≥80) produces results as shown below in Table 3. This is based upon the cut offs used in the pre-planned analysis of the EXTREME trial data, which were presented in section 6.4 of the original Merck Serono submission to NICE (see pages 46 & 47, and Figure B3 – copied above).

Table 3: Analysis of the subgroup for age<65 years and KPS≥80

Cost-effectiveness			
Cetuximab + standard treatment vs Standard treatment	mean	p2.5	p97.5
Incremental costs	£17,815	£12,195	£23,648
Incremental life-years	0.188	-0.283	0.650
Incremental QALYs	0.143	-0.282	0.614
Incremental cost effectiveness ratio	£94,887		
Incremental cost utility ratio	£124,400		

The incremental life years here equate to an overall survival benefit of 2.25 months

Clearly the scenario in Table 2 above shows mean overall survival above 3 months; however the number of patients with RMHN cancer who fit the criteria of under 65 years of age and

with a Karnofsky performance status of more than 90 is expected to be small (see Table 6 below).

To apply an end of life adjustment to the outcome of the analysis presented in Table 2 for those patients who were less than 65 years of age and who had a KPS of 90 or above the assumption is made that all of the extra survival accrued is experienced at a health utility value which is equivalent to that of the average population for the same age. Therefore we would utilise the incremental life years value of 0.314 and multiply this by the average utility value for the age group in the analysis. Petrou *et al* [2005] calculated an average utility value by age for the general population as presented in Table 4.

Table 4: EQ-5D utility scores reported for the general population.

Age	Overall utility score
16-24	0.904
25-34	0.907
35-44	0.882
45-54	0.847
55-64	**0.789**
65-74	0.778
>75	0.724

The age range which best estimates the under 65 years of age group proposed is 55-64 year old which yields an overall utility score of 0.789.

Therefore the QALY gain under this assumption is 0.314x0.789 = 0.248 QALYs.

The cost per adjusted QALY is calculated from the incremental costs/adjusted QALYs:

The point estimate of the adjusted cost per QALY is then £19,744/0.248 = £79,613.

Based upon this calculation, the weighting required to hit the £20,000/QALY approval threshold is estimated at 3.98, while the weight applied for the £30,000 threshold is estimated to be 2.65.

Budget impact estimate.

The analyses for expected patients numbers are based on figures from the A&A market research (see Table 5 below) since the Baseline Demographics for EXTREME do not include the numbers of patients who are both age<65 years and KPS≥80 or 90. And while the EXTREME trial covers 442 international intention-to-treat patients, including UK patients, the A&A market research analysis includes data from 107 UK patients.

Data from 107 recurrent and/or metastatic H&N (RMHN) patients from the A+A database (Appendix 1 of original Merck Serono submission) are summarised below, in Table 5, for the proportion of patients above and below the age of 65, then stratified by ECOG performance status.

Table 5: Proportion of RMHN patients by age and performance status from A+A data.

23 - Q10. Current performance status (ECOG)	Age<65	Age>65	Total
ECOG 0	8,41%	1,87%	10,28%
ECOG 1	38,32%	21,50%	59,81%
ECOG 2 and over	13,08%	16,82%	29,91%
Total	59,81%	40,19%	100,00%

To calculate the number of patients in the subgroup age <65, KPS≥90 we will assume that ECOG 0 is equivalent to KPS 90 or above. The number of patients who would be eligible for treatment under NICE guidance can be calculated as shown in Table 6:

Table 6: Patient number calculation for the subgroup age <65, KPS≥90.

Population definition	Estimated number	Comments
Total case of head and neck cancer in England	7,765	Source: NICE TA145 costing template
Proportion of patients with recurrent/ metastatic H&N cancer (RMHN)	32%	A+A Healthcare market Research
Number of patients with RMHN	2,485	32% of 7,765
Proportion of RMHN patients who are <65 years of age	59.8%	Source: A+A Healthcare market Research
Proportion of RMHN patients who are <65 years of age and KPS≥90	8.4%	Source: A+A Healthcare market Research
Number of RMHN patients who are <65 years of age and KPS≥90	**209**	**8.4% of 2,485**

The results presented in Table 6 show that nearly 60% of patients in this real-life sample for RMHN are under the age of 65, this is compared to 82% of patients in the EXTREME clinical trial who were aged under 65 years of age. The majority of patients who would be subject to a clinical approach where the most intense treatments are offered would be expected to be less than 65 years of age. It is worth noting that the information from EXTREME contains 4 UK patients while the information from the A+A market research reflects the actual case notes from 107 UK patients treated by 71 UK physicians. Merck Serono believes that the A+A data are representative of the UK population.

It is estimated that the number of patients who are potentially eligible for treatment for RMHN who satisfy the criteria age <65, KPS≥90 is 209 per annum. Applying the incremental cost per patient from the original Merck Serono submission of £16,877 (calculated by dividing total cost for the year 2009 in Table BI1 by the 169 patients estimated to be treated) we would estimate a budget impact of £3,527,293 per annum **assuming 100% uptake**.

The total number of patients eligible for cetuximab in all its currently licensed indications is calculated based upon the assumptions in Table 7 as follows:

Table 7: Calculation of eligible patients for cetuximab by indication.

Indication	**Patient numbers**	**Source**
Locally advanced H&N cancer	621	NICE TA145, costing template
RMHN cancer	209	Table 5 above
Metastatic colorectal cancer (mCRC)	2,011	Figure BI1, Merck Serono submission for mCRC
Total for all indications	**2,841**	

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.**

Appendix 2: Details of the Multivariate regression analysis

A multivariate Cox-regression model was estimated based on the complete dataset with following variables based on the complete patient dataset: treatment, age, KPS>80, KPS>90, recurrent and metastatic, metastatic not recurrent, recurrent not metastatic, cisplatin-treated, carboplatin-treated, pre-progression free>12 months and the pre-progression free>12 months and chemonaive group as well as the interaction factors between the treatment group and the other variables. Only the first four variables (treatment, age, KPS>80, KPS>90) are of relevance to this submission.

Four multivariate 2-parameter Weibull regression models were fitted using the statistical software package R: one for each arm (cetuximab in addition to Standard Treatment/ Standard Treatment) and outcome (PFS and overall survival) combination. For example, the regression equation for PFS for the cetuximab arm is given by

Alpha = -0.22 * catage + 0.28 * KPS80 + 0.12 * KPS90 + 0.13 * catptum2 - 0.13 * catptum3 – 0.06 * platireg + 0.01 * prechemo - 0.11 *PFS12m + 0.40 * PFS12mchemonaive + 5.12

with log “scale” equal to -0.37. From these values, the survival curve can be obtained:

Survival = exp(-exp(-ALPHA/”scale”) *time^(1/”scale”)) eq. 3

Tables A2 and A3 present the parameters and their coefficients for the multivariate analyses. Please note that the survival and progression free survival curves are described using the following formula: Survival = exp(-exp(-ALPHA/”scale”) *time^(1/”scale”)). Where: exp(-ALPHA/”scale”)= SCALE and 1/”scale”=SHAPE.

Table A2. Overview of included characteristics and their coefficients for the multivariate analysis for PFS by treatment arm

Coefficients	Erbitux® + Standard Treatment Coefficients	Standard Treatment Coefficients
Age category (catage)	-0.22	-0.23
KPS>80	0.28	0.63
KPS>90	0.12	0.07
Recurrent not metastatic (catptum2)	0.13	0.00
Metastatic not recurrent(catptum3)	-0.13	0.38
Cisplatin or Carboplatin (platireg)	-0.06	-0.07
Chemonaive or not (prechemo)	0.01	-0.05
Progression free for > 12 months (PFS12)	-0.11	0.22
Progression free for > 12 months and chemonaive (PFS12chemonaive)	0.40	0.20
Intercept	5.12	4.24
log “scale”	-0.37	-0.52

Table A3. Overview of included characteristics and their coefficients for the multivariate analysis for OS by treatment arm

Coefficients	Erbitux® + Standard Treatment Coefficients	Standard Treatment Coefficients
Age category (catage)	-0.13	0.07
KPS>80	0.48	0.33
KPS>90	0.31	0.09
Recurrent not metastatic (catptum2)	0.12	0.11
Metastatic not recurrent(catptum3)	-0.01	0.41
Cisplatin or Carboplatin (platireg)	-0.12	0.06
Chemonaive or not (prechemo)	0.02	0.04
Progression free for > 12 months (PFS12)	0.01	-0.06
Progression free for > 12 months and chemonaive (PFS12chemonaive)	0.23	0.44
Intercept	5.57	5.41
log “scale”	-0.34	-0.26

Reference

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ukfe1dat01.eu.merck

From: [redacted] - Mouth Cancer Foundation
[[redacted]]
Sent: 18 February 2009 21:11
To: Jeremy Powell
Cc: David Bevan; [redacted]; [redacted]; [redacted]; [redacted]; [redacted]; [redacted]
Subject: Re: ACD - Cetuximab for the treatment of recurrent and/or metastatic
squamous cell cancer of the head and neck

Dear Mr Powell
Thank you for giving the Mouth Cancer Foundation the opportunity to respond to the Appraisal
Consultation Document (ACD) and the supporting Evaluation Report (ER) on Cetuximab for the
treatment of recurrent and/or metastatic squamous cell cancer of the head and
neck (link:
http://www.nice.org.uk/guidance/index.jsp?action=folder&o=42906).
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. i. Do you consider that all of the relevant evidence has been taken into account?
ii. 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?
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.

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.
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.
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:
o The treatment is indicated for patients with a short life expectancy, normally less than
24 months.

o No alternative treatment with comparable benefits is available through the NHS.
o The treatment is licensed, or otherwise indicated, for small patient populations.
o 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.
o 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.

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.

Kind regards

Vinod

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[redacted]

Mouth Cancer Foundation

http://www.mouthcancerfoundation.org

Mouth Cancer Foundation is a registered charity No. 1109298
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Mouth Cancer Foundation website: UK based mouth cancer website portal that provides patients, carers and health professionals with easy access to comprehensive information on head and neck cancers and mouth cancer awareness campaigns.
http://www.mouthcancerfoundation.org/

Mouth Cancer Foundation Online Support Group: Provides practical advice and
support for cancer patients, their families and carers.
http://chat.mouthcancerfoundation.org

National Institute for Health and Clinical Excellence

Cetuximab for the treatment of head and neck cancer (squamous cell carcinoma)

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.

February 2009

The Royal College of Pathologists
Pathology: the science behind the cure

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single technology appraisal (STA)

Cetuximab for the treatment of metastatic and/or recurrent squamous cell carcinoma of the head and neck

Comments on the Appraisal Consultation Document (ACD)

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.

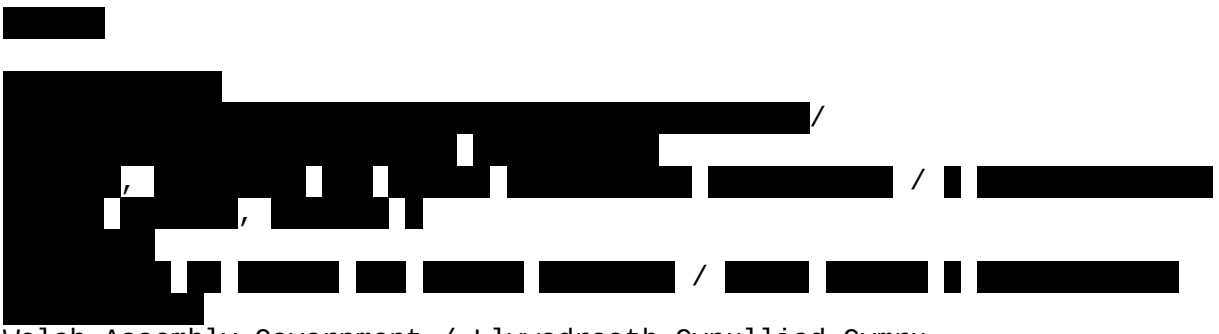
[redacted]

From: [redacted], [redacted] ([redacted]) [[redacted]]
Sent: 16 February 2009 08:59
To: Jeremy Powell
Subject: RE: Head and neck cancer (squamous cell carcinoma) - cetuximab - ACD

Good morning.

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.

Kind regards



Welsh Assembly Government / Llywodraeth Cynulliad Cymru
Tel / Ffon [redacted]
Fax / Ffacs [redacted]
E-mail / E-bost [redacted]

Welsh Association of Head and Neck Oncologists

Name	[redacted]
Role	NHS Professional
Other role	Welsh Association of Head and Neck Oncologists [redacted]
Location	Wales
Conflict	No
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	1.1 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.
Section 2 (the technology)	2.2 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.
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.
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. 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.
Section 5 (implementation)	
Section 6 (proposed recommendations for further research)	
Section 7 (related NICE guidance)	
Section 8 (proposed date of review of guidance)	
Date	

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