NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

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

Premeeting briefing

This briefing presents major issues arising from the manufacturer's submission (MS), Evidence Review Group (ERG) report and statements made by consultees and their nominated clinical specialists and patient experts. Please note that although condensed summary information is included for ease of reference, this briefing should be read in conjunction with the full supporting documents.

The manufacturer was asked to provide further details and clarification of the following: the baseline characteristics of the patients in the EXTREME trial, survival analyses (both overall and progression-free survival) undertaken for the full trial cohort and modelled subgroups, the proportion of scheduled platinum chemotherapy doses given/omitted by cycle, whether the parameters for Weibull models for overall survival and progression-free survival were estimated independently or jointly in all cases, the meaning of the adverse event rates used in the model, separate incremental cost-effectiveness ratios for patients with recurrent cancer and patients with metastatic cancer.

Licensed indication

In October 2008, the marketing authorisation for cetuximab (Erbitux, Merck Serono) was extended. The additional licensed indication for cetuximab is:

- Cetuximab is indicated for the treatment of patients with squamous cell cancer of the head and neck in combination with platinum-based chemotherapy for recurrent and/or metastatic disease.

Key issues for consideration

- Neither the final scope nor the manufacturer's decision problem restricted the appraisal of cetuximab to first-line treatment only. However, the evidence presented here relates only to first-line treatment.

- Are the results of the clinical study applicable to patients seen in clinical practice in the UK? It has been suggested by the ERG that patients in the trial were younger and had higher Karnofsky performance-status scores than patients presenting for this type of treatment in the UK.

- What is the Committee's view on relevance of the subgroup analyses for overall survival? For several subgroups there appeared to be no survival benefit from cetuximab plus chemotherapy, although only the analysis for tumour location was reported as significant for interaction.

- Have the subgroup analyses in the cost-effectiveness analysis been carried out adequately? The ERG are concerned that it is likely that at least some of these subgroups are too small to yield reliable projection models.

- What is the Committee's view of the ERG's exploratory analysis around the uncertainty in the manufacturer's base-case and subgroup analyses?

- Does the Committee consider that criteria for special consideration for life-extending medicines for small populations with short-life expectancy have been fulfilled?

1 Decision problem

1.1 Decision problem approach in the manufacturer's submission

Population	Adults with metastatic and/or recurrent squamous cell cancer of the head and neck for whom platinum-based chemotherapy is appropriate.
Intervention	Cetuximab plus platinum-based chemotherapy.
Comparators	Platinum-based chemotherapy regimens. Specifically 5-fluorouracil combined with cisplatin is the standard of care in the UK in this setting.
Outcomes	Overall survival, progression-free survival, tumour response, adverse effects of treatment, health-related quality of life.
Economic evaluation	The cost effectiveness of treatments will be expressed in terms of incremental cost per QALY. Cost per life year will also be presented. Costs will be considered from an NHS and personal social services perspective (PSS).
Special considerations and other issues	There are no subgroups that have been defined by biomarkers. The submission will consider groups defined by performance status, previous treatments and response to previous treatments.

1.2 Evidence Review Group comments

1.2.1 Population

The population described in the final scope and in the manufacturer's definition of the problem was 'adults with metastatic and/or recurrent squamous cell cancer of the head and neck (SCCHN) for whom platinum-based chemotherapy is appropriate'. As 'appropriate' was not defined, the Evidence Review Group (ERG) has assumed that the term refers to those patients whose health cannot be improved by surgery and/or radiotherapy but may be improved by more than best supportive care measures alone.

Neither the final scope issued by NICE nor the decision problem submitted by the manufacturer limited the patient population to those receiving cetuximab in

combination with platinum-based chemotherapy as first-line treatment only. However the manufacturer only presented clinical evidence on the first-line use of cetuximab in combination with platinum-based chemotherapy.

1.2.2 Intervention

Cetuximab is a monoclonal antibody directed against the epidermal growth factor receptor (EGFR) that is highly expressed in nearly all squamous cell tumours. It is given in combination with platinum-based chemotherapy for up to six cycles and is continued as monotherapy until there is disease progression.

1.2.3 Comparators

The ERG was confident that when chemotherapy is appropriate for this group of patients, cisplatin plus 5-fluorouracil (5-FU) is likely to be the standard treatment in the UK. However, the ERG noted that chemotherapy is not always standard care for this group of patients as a whole, as it is considered unsuitable for many patients with recurrent and/or metastatic SCCHN.

1.2.4 Outcomes

The ERG considered the manufacturer to have adequately described the outcomes of interest for the relevant patient group and/or phase of treatment and reflected the list of clinical outcomes identified in the final scope issued by NICE.

1.2.5 Economic evaluation

In the economic model the time horizon chosen was a lifetime horizon in order to account for all relevant costs and benefits.

1.2.6 Subgroup analyses

The manufacturer stated that pre-planned subgroup analyses, defined by Karnofsky performance-status (KPS) score, previous treatments and

response to previous treatments, were to be carried out. The ERG was confident that the subgroup analyses were appropriate.

1.3 Statements from professional/patient groups and nominated experts

Professional and patient groups stated that head and neck cancer is difficult to treat and that people with this condition have a very poor prognosis. Current treatment depends on the stage of the cancer spread. Currently SCCHN with distant metastasis is often treated palliatively. Locally and regionally recurrent SCCHN can be treated by repeat surgical resection with or without reconstruction and with or without brachytherapy. In some cases additional external beam radiation can also be used. One professional group stated that for most distant metastatic lesions, there is no geographical variation in current practice. However, there are differences of opinion between professionals for the treatment of locally and regionally recurrent SCCHN which results in geographical variation in practice. This is because of the small number of people with this condition seen regularly by clinicians.

Professional groups stated that oncology services in the UK have experience of using cetuximab for head and neck cancer. Cetuximab is already available and has been licensed for use in locally advanced head and neck cancer and other cancers. As a result, one professional group stated that education or training would not be required.

2 Clinical effectiveness evidence

2.1 Clinical effectiveness in the manufacturer's submission

There are some differences between the clinical-effectiveness results presented in the manufacturer's submission (MS) and the published peer-

reviewed clinical paper (Vermorken J et al. 2008). Where there are differences, the ERG report and this document give the published data.

The manufacturer identified and presented data from one randomised controlled trial (RCT). This study (EXTREME) was an open-label study in patients with recurrent and/or metastatic SCCHN that included 442 patients at 80 centres in 17 European countries. Patients were randomised to the following:

Intervention Group: Combination of cetuximab plus cisplatin and 5-fluorouracil or carboplatin and 5-fluorouracil

Comparator Group: Cisplatin and 5-fluorouracil or carboplatin and 5-fluorouracil only

Patients received cetuximab in combination with chemotherapy for a maximum of six cycles and continued on cetuximab monotherapy until there was disease progression. Patients received chemotherapy only for a maximum of six cycles or until there was disease progression or unacceptable toxicity. Randomisation was stratified according to the most important prognostic factors: previous chemotherapy and KPS.

Patients in the study had recurrent and/or metastatic SCCHN that was considered unsuitable for local therapy and a KPS of at least 70 at study entry. Patients were excluded if they had previous systemic chemotherapy, except if given as part of a multimodal treatment for locally advanced disease which was completed more than 6 months before study entry, or if they had surgery (excluding prior diagnostic biopsy), or radiotherapy in the 4 weeks before study entry.

Statistical analyses were undertaken on the intention-to-treat population. The time-to-event variables were compared by using the stratified log-rank test with the factors used for randomisation (previous chemotherapy and KPS).

The Cox regression method, stratified according to the randomisation categories, was used to calculate the hazard ratios. The MS described the justification of the power, sample size and length of follow up in the trial. The baseline characteristics of the two treatment arms in the EXTREME study were balanced in terms of demographics, nature of disease and previous treatment.

Results of the full analysis set

The primary outcome of the EXTREME study was overall survival. A statistically significant improvement was demonstrated in the cetuximab plus chemotherapy group for all outcomes except duration of response. Median overall survival was increased from 7.4 months in the chemotherapy group (95% confidence interval [CI] 6.4 to 8.3) to 10.1 months in the cetuximab plus chemotherapy group (95% CI 8.6 to 11.2). The key results of the EXTREME study are shown in table 1. The data for the outcomes of time to treatment failure and duration of response were not presented in the MS as secondary outcomes. Data for time to treatment failure and duration of response were therefore taken from the published paper[1], as were the accompanying footnotes.

[1] Vermorken J et al. 2008

Table 1 Key results of the EXTREME trial

Outcome	Cetuximab plus CTX (n = 222)	CTX (n = 220)	Hazard ratio (HR)/odds ratio (OR)	p value
Primary				
OS (median; months) (95% CI)	10.1 (8.6–11.2)	7.4 (6.4–8.3)	HR for death 0.797 (0.644–0.986)	0.00362[a]
Secondary				
PFS (median; months) (95% CI)	5.6 (5.0–6.0)	3.3 (2.9–4.3)	HR for progression 0.538 (0.431–0.672)	< 0.001[a]
Best overall response	35.6% (29.3–42.3)	19.5% (14.5–25.4)	OR 2.326 (1.504–3.600)	< 0.001[b]
Disease control rate (95% CI)	81% (75.3–86)	60% (53.2–66.5)	OR 2.881 (1.870–4.441)	< 0.001[cd]
Time to treatment failure (months) (95% CI)	4.8 (4.0–5.6)	3.0 (2.8–3.4)	HR 0.59 (0.48–0.73)	< 0.001[ab]
Duration of response (months) (95% CI)	5.6 (4.7–6.0)	4.7 (3.6–5.9)	HR 0.76 (0.50–1.17)	0.21[be]

CTX: chemotherapy; OS: overall survival; PFS: progression-free survival; CI: confidence interval.

p values, hazard ratios and odds ratios are stratified according to receipt or non-receipt of previous chemotherapy and Karnofsky performance status at randomisation.

[a] number of months estimated using Kaplan-Meier method

[b] p value calculated using the log-rank test

[c] p value calculated using Cochrane-Mantel-Haenszel test

[d] disease control includes complete response, partial response and stable disease

[e] data on duration of response were available for 62 patients in the cetuximab group and 36 patients in the chemotherapy-alone group; data on disease progression in these patients were available at the time of analysis. The number of months was estimated with the use of the Kaplan-Meier method

Results of the pre-planned subgroup analysis

A number of protocol-defined subgroup analyses were also reported. The clinical subgroups included: age, performance status, platinum regimen, previous treatment, primary tumour site, tumour grade, baseline quality of life

score and percentage of EGFR-detectable cells. Forest plots for these subgroups are provided in figure B3 on pages 47–48 of the MS.

For overall survival, a benefit of cetuximab treatment was shown in most subgroups. The exceptions were: patients aged 65 years or older, KPS of less than 80, carboplatin therapy, tumour sites in the hypopharynx or larynx, poorly differentiated tumours and metastatic tumours. No statistical tests for interaction were reported in the MS. According to the published paper[2] only the interaction for primary tumour site was statistically significant ($p = 0.03$). It can be seen in figure B3 (forest plot on pages 47–48 of the MS) that the effect of adding cetuximab to chemotherapy was most marked in the group with primary tumours located in the oral cavity. No effect at all was demonstrated on tumours located in the hypopharynx or larynx. However, the authors advise caution because, given repeated testing, this result could have occurred by chance.

For progression-free survival, all subgroups appeared to benefit from treatment with cetuximab. Again, the benefit of treatment with cetuximab was most marked in patients with tumours of the oral cavity. There was no significant effect for patients with tumours located in the hypopharynx or larynx. The forest plot for progression-free survival for the tumour location subgroups is shown in figure B5 on page 50 of the MS.

The manufacturer undertook further subgroup analysis of response rates according to whether patients were initially treated with either cisplatin- or carboplatin-based chemotherapy in the trial. The analysis showed a significant improvement in response rate in the cetuximab plus chemotherapy group compared with chemotherapy alone, irrespective of chemotherapy type. However, the response rates for patients treated with carboplatin were (with the exception of disease control rate) lower than for those treated with

[2] Vermorken J et al. 2008

cisplatin. Details of the response rates are provided in table 4.9 on page 30 of the ERG report.

Quality of life

Health related quality of life (HRQoL) was measured with two related assessment tools, EORTC QLQ-C30 (version 3) and EORTC QLQ-H&N35. The QLQ-C30 is a cancer-specific questionnaire for assessing quality of life in patients in clinical trials. The EORTC QLQ-H&N35 is a tumour-specific module questionnaire which has been developed for use in patients with head and neck cancer. In the EXTREME study, assessments were scheduled to be made at six time points: at screening (baseline), on day one of the third chemotherapy cycle, at the first six weekly evaluation, at six months, at 12 months, and at the final tumour assessment. The small proportion of patients responding at 12 months prevented any meaningful statistical analysis. In addition another type of questionnaire was used only in the UK (the EuroQoL EQ-5D). No analyses were carried out on these data due to the very small number of patients and responses involved.

The proportion of evaluable questionnaires for EORTC QLQ-C30 and QLQ-H&N35 was considered by the manufacturer to be low (61% in the cetuximab plus chemotherapy group and 58% in the chemotherapy-only group). On the EORTC QLQ-C30 social functioning scale, no statistically significant differences were observed between the treatment groups. Results of the QLQ-H&N35 questionnaire showed that in general, the scores for the cetuximab plus chemotherapy group were not significantly worse than for the chemotherapy-only group. Some significant differences in favour of the cetuximab plus chemotherapy group were observed at cycle three for measures of pain, swallowing, speech problems and social eating; however, these differences were not apparent at month six.

Safety

The tables in the MS showing safety outcomes (see pages 54 and 55 in the MS) include a total of 434 patients, eight less than the 442 originally randomised. The safety population was not defined in the MS. However, the published paper[3] states that eight patients were not treated (five in the cetuximab plus chemotherapy arm and three in the chemotherapy-only arm).

Information on adherence to the planned regimen was not reported in the MS, although it was presented in the published paper[3]. More than 90% of patients received more than 90% of the planned initial dose of cetuximab, and more than 70% of patients received more than 90% of subsequent doses. Adherence to the planned chemotherapy regimen was similar in both groups.

No tests of statistical significance were reported in the MS for the safety data, although these were presented in the published paper[3]. The incidence of adverse events in each group was similar, indicating that the addition of cetuximab to chemotherapy did not significantly increase treatment toxicity. The exceptions to this were rash, acne, acneiform dermatitis, dry skin and anorexia which occurred more frequently (a 10% or greater difference) in the cetuximab plus chemotherapy group than in the chemotherapy-only group. In addition the following adverse events occurred only in the cetuximab plus chemotherapy group: conjunctivitis, paronychia, pruritis, exfoliative rash and skin toxicity. For the full listing of adverse events occurring in 10% or more patients in either group, see table 4.10 on page 32 of the ERG report.

Most of the more severe adverse events (grade 3 or 4) including haematological toxicities, occurred with similar frequencies in both treatment groups. Rash was reported only for the cetuximab plus chemotherapy group. For a full listing of the most common severe adverse events, see table 4.11 on page 33 of the ERG report. The published paper[3] states that the main grade 3

[3] Vermorken J et al 2008

or 4 adverse events were consistent with the known side-effect profile of cetuximab.

2.2 Evidence Review Group comments

The systematic literature review conducted by the manufacturer was designed to identify the clinical evidence available to assess the efficacy of first-line use of cetuximab plus chemotherapy in patients with recurrent and/or metastatic SCCHN. The ERG stated that the MS provided clinical and economic evidence of first-line use of cetuximab plus chemotherapy for patients with recurrent and/or metastatic SCCHN only and that it did not provide clinical or economic evidence about those who might require second-line treatment.

The ERG stated that the literature search in the MS, which identified only one relevant study, was complete and reasonable. The ERG was confident that all relevant published trials were identified by the manufacturer.

The ERG judged the one study (EXTREME) reported in the MS to be a well-conducted RCT. The trial was well-designed, used robust randomisation techniques and was suitably powered to show differences between the treatment groups. Appropriate exploratory subgroup analyses were carried out and statistical reporting was generally good. However, the study was an open-label trial that relied on the unblinded assessment of clinical outcomes. The ERG stated that this may lead to the over estimation of treatment effects by assessors and altered patient expectations.

Of the 80 centres included in the EXTREME study, four were based in the UK. The manufacturer was asked to provide a breakdown of patient numbers by country, details of the stage of disease at diagnosis and previous treatment for each tumour site. The manufacturer stated that only nine patients were enrolled from the UK, but over half of the total number of patients came from other European countries. These countries would be expected to have similar practices and levels of care as in the UK. The total percentage of patients

from other European countries and from the UK was 59%. The manufacturer also provided details of disease stage, tumour stage by disease site, the number of pretreatments by tumour type and the method of pretreatment by tumour site. The ERG considered that these data showed sufficient comparability with UK data.

The ERG stated that the patients in the EXTREME study may be younger (median age 56 years) and fitter (high KPS) than patients presenting with recurrent and/or metastatic SCCHN in UK clinical practice. The ERG stated that while a case-mix bias towards younger and fitter patients in clinical trials was not uncommon, there was uncertainty as to whether similar clinical-effectiveness rates could be replicated for patients in the UK with this condition.

Approximately 15% of patients in both groups in the EXTREME study had not received previous radiotherapy. The ERG stated that in UK clinical practice, it was unlikely that patients with recurrent SCCHN would not have had previous radiotherapy. In response to the letter of clarification, the manufacturer stated that 8% of patients in the cetuximab plus chemotherapy group and 7% in the chemotherapy-only group initially presented with metastatic disease. Therefore these patients would not be expected to have been previously treated with radiotherapy.

The ERG noted that 'Cetuximab for the treatment of locally advanced squamous cell cancer of the head and neck' (NICE technology appraisal guidance 145) recommends the use of cetuximab plus radiotherapy for the treatment of locally advanced SCCHN. The ERG stated that this means that in England and Wales, there will be some patients with recurrent and/or metastatic SCCHN who have previously received cetuximab as part of their treatment. The ERG stated that as patients in the EXTREME study were cetuximab naive, there was no clinical evidence to support the use of cetuximab in this group of patients.

The clinical outcomes reported in the EXTREME study covered all clinical outcomes outlined in the final scope issued by NICE. However, despite designing the trial to include a comprehensive analysis of HRQoL, the ERG considered the collection and reporting of the HRQoL data to be poor. In particular the proportion of evaluable HRQoL questionnaires was low. The ERG stated that given the importance of HRQoL to this patient group, it was noteworthy that so little emphasis was placed on collecting these key data.

2.3 Statements from professional/patient groups and nominated experts

One professional group stated that as patients with metastatic and/or recurrent disease have incurable cancer, the outcome measures to be considered should be progression-free survival, symptomatic relief and improvement in quality of life.

One patient group stated that the results of the EXTREME study showed that treatment with cetuximab plus chemotherapy significantly increased adverse effects (sepsis, hypomagnesemia). Professional and patient groups reported that the other side effects of cetuximab (skin rash, vomiting, diarrhoea and infusion-related reaction) shown in the EXTREME trial were consistent with the well known adverse effects of cetuximab.

While patient groups welcomed any improvement in overall survival rates, one group questioned whether the increase in overall survival seen in the EXTREME study (2.7 months) was a significant improvement.

3 Cost effectiveness

3.1 Cost effectiveness in the manufacturer's submission

The manufacturer developed a two-arm state-transition Markov model to evaluate the cost effectiveness of cetuximab plus chemotherapy with standard chemotherapy. The clinical data used in the economic evaluation were

generated from the EXTREME study. Although the economic evaluation was trial-based, there was a modelling component to allow extrapolation of health effects beyond the period (24 months) of the study. A simplified model structure is shown in figure 5-1 on page 37 of the ERG report, with a written description on page 38.

The data from the EORTC QLQ-30 questionnaire and its head and neck module (EORTC QLQ-H&N35) were used in the economic evaluation. In order to express the HRQoL scores in QALYs, the EORTC QLQ-30 data collected in the trial were converted into EQ-5D scores. This conversion was performed using a cross walk algorithm. For the utility values used in the economic model, see table 2 below.

Table 2 Utility values used in the economic model

Health state	Value (95% confidence intervals)
Stable/response with cetuximab plus chemotherapy	0.69 (0.38–0.99)
Stable/response with chemotherapy	0.65 (0.31–0.99)
Overall stable/response	0.67 (0.35–0.99)
Progressive disease following cetuximab plus chemotherapy	0.53 (0.13–0.93)
Progressive disease following chemotherapy	0.51 (0.10–0.91)
Overall progressive disease	0.52 (0.11–0.93)

Disutilities associated with adverse events were not accounted for separately. This was because the utilities calculated were based on the responses to the QLQ-30 global questionnaire. The patient's response to the QLQ-30 global questionnaire was assumed to capture the impact of adverse events on the patient's HRQoL.

The categories of costs used in the economic model included: chemotherapy drugs (cetuximab, cisplatin, carboplatin, 5-flurouracil), drug administration as first-line, treatment of adverse events, palliative-intent chemotherapy drugs, palliative-intent surgery, palliative-intent radiology. Information on health care

resources other than drug use and frequency of chemotherapy regimens, surgery and radiotherapy were not collected in the EXTREME study. The manufacturer therefore estimated the cost of these resources from the literature and key opinion leaders treating SCCHN. For further details of the unit costs used in the economic model, see table 5.6 on page 40 of the ERG report.

Results

The main results of the manufacturer's economic model are presented in tables 3–5 below.

Table 3 Cost-effectiveness results (QALYs)

Treatment group	Total costs	QALYs gained	
Cetuximab plus chemotherapy	£30,678	0.65	
Chemotherapy alone	£13,392	0.51	Incremental cost per QALY gained
Incremental costs/benefits	£17,286	0.142	£121,367

QALY: quality adjusted life year

Table 4 Cost-effectiveness results (life years gained)

Treatment group	Total costs	Life years (LY) gained	
Cetuximab plus chemotherapy	£30,678	1.07	
Chemotherapy alone	£13,392	0.88	Incremental cost per life year gained
Incremental costs/benefits	£17,286	0.187	£92,226

Table 5 Cetuximab plus CTX versus CTX alone - incremental cost-effectiveness ratios for subgroups

Incremental costs	Incremental QALYs/LYs	Incremental cost per QALY gained/ incremental cost per LY gained
Oropharynx and oral cavity		
£19,867	0.189/0.254	£105,069/£78,301
Oropharynx and oral cavity, KPS ≥90		
£21,683	0.222/0.316	£97,702/£68,717
Oropharynx		
£17,915	0.071/0.041	£250,597/£434,568
Oropharynx, KPS ≥90		
£18,242	0.059/0.026	£309,735/£695,475
Oral cavity		
£22,658	0.354/0.550	£63,927/£41,224
Oral cavity, KPS ≥90		
£27,688	0.505/0.818	£54,791/£33,855
Recurrent disease[a]		
£18,758	0.215/0.308	£87,099/£60,939
Metastatic disease (including those with recurrent SCCHN)[a]		
£14,539	0.026/–0.015	£562,849/dominated
Metastatic disease (excluding those with recurrent SCCHN)[a]		
£13,469	–0.046/–0.088	dominated

CTX: chemotherapy; QALY: quality adjusted life year; LY: life year;

KPS: Karnofsky performance status

[a] incremental costs and benefits, cost per life year and cost per QALY taken from the manufacturer's response to request for clarification, 24 October 2008

The manufacturer conducted both univariate and probabilistic sensitivity analyses (PSA) for selected model parameters. The results of the main sensitivity analyses are presented in table 5.12 on page 46 of the ERG report. Varying the cost of the day-case infusion and changing the values in the stable/response health state of the cetuximab arm had the greatest impact on the incremental cost-effectiveness ratio (ICER).

The manufacturer conducted further sensitivity analyses in order to assess the impact of higher or lower adverse event costs. The adverse event profile rates

were similar across both treatment arms and changing the cost of adverse events did not affect the size of the ICER.

For the probabilistic sensitivity analyses, the manufacturer presented scatter plots (incremental costs versus life years, incremental costs versus QALYs) and a cost-effectiveness acceptability curve; see figures 5-2 and 5-3 on page 47 of the ERG report.

3.2 Evidence Review Group comments

The ERG considered the economic model submitted by the manufacturer to be implemented to a generally high standard and clearly presented. The layouts of the various elements of the model were generally logical, and the formulae employed were straightforward.

The ERG highlighted a number of key issues about the economic model submitted by the manufacturer.

- The ERG questioned the validity of creating an economic model for this appraisal, since there was only one set of clinical trial results showing mortality in the follow-up period, covering 75–80% of enrolled patients. The ERG stated that although the approach to the economic modelling appeared to be appropriate in relation to the NICE reference case (see the NICE 'Guide to the methods of technology appraisal') the use of simulation derived from a single data source rather than using the observed data directly introduces additional uncertainty to that already inherent in the trial. The ERG stated that the potential problem with projective modelling of overall survival data is that it is more likely to exaggerate health gains than to underestimate them, leading to an over optimistic result. The ERG stated that this is particularly relevant for late-stage disease where no claim is made to provide a cure, merely to delay progression.

- The ERG noted that a mid-cycle correction had been omitted from the manufacturer's model. The ERG stated that such an omission may affect

cost-effectiveness results directly through systematically over or underestimating costs and outcomes depending on whether values for the start or end of a cycle are taken as representative of the whole cycle.

- The manufacturer's economic model has been constructed using parametric survival projection models of overall survival and progression-free survival to extend the analysis until death for all patients. Of particular concern to the ERG was the appropriateness of Weibull modelling to all patient groups. The ERG stated that it could not fully explore the appropriateness and reliability of the parametric survival projection models as the manufacturer chose not to provide all the requested information.

- The submitted baseline model used different mean utility values for patients in the two treatment arms when in the stable response state, but used a single overall average utility estimate for all patients in the progressive disease state. The ERG stated that given the limited HRQoL data available from the EXTREME study and the uncertainty inherent in the mapping function used to convert the EORTC QLQ-C30 data to EQ-5D values, it was difficult to justify using separate estimates at any point in the analysis.

- The ERG stated that most of the chemotherapy treatments for patients with head and neck cancer are given on the basis of the body surface area (BSA) of the individual patient. The manufacturer's model does not take account of BSA differences between patients, including those due to gender. The ERG considered that the fixed average value used in the model (1.7 m^2) significantly underestimates the value found for patients with head and neck cancer in the UK (males: 1.85 m^2, females: 1.65 m^2).

- The ERG noted that the unit costs used in the manufacturer's submitted model were drawn from a number of different sources and were based on different years. The sources used were: NHS reference costs for 2004 and 2005/06; inpatient indicative tariff and outpatient mandatory tariff for

2007/08, Personal Social Services Research Unit (PSSRU) 2007, British National Formulary (BNF) 50 and 55 for drug costs and a published paper for platelet transfusion costs in 2000/01 (Varney and Guest 2003). The ERG stated that it has identified more appropriate sources.

- The MS contains two tables (H23 and H24 on pages 109 and 110 respectively) showing results of variations in a selection of model parameters. The ERG stated that it was notable that no univariate sensitivity analyses were carried out for the most important aspects of the analysis: the estimated overall survival time, and the effect of inter-patient dosing variability on treatment costs.

- The ERG highlighted that the manufacturer had not incorporated any uncertainty in the assumed value of the mean BSA, used in the calculation of treatment costs, in the PSA. The ERG stated that this can have an important influence on model results and should feature in any PSA.

- The ERG stated that there was no indication in the MS of the number of patients in the EXTREME study available for analysis in each subgroup. The ERG considered that it was likely that at least 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.

3.2.1 Exploratory analysis

The ERG undertook exploratory analysis using alternative assumptions and parameters in the economic model. The key amendments made by the ERG were as follows:

- Inclusion of a mid-cycle correction on the submitted base-case results. For further details see page 52 of the ERG report.

- Replacing the projection modelling of costs and outcomes used in the base case with a comparison of the costs and outcomes at 24 months (end of

follow-up period in the EXTREME study). For further details see page 54 of the ERG report.

- Using combined estimates of mean utility values throughout the analysis. For further details see page 55 of the ERG report.

- The ERG replaced the fixed mean BSA value (1.7 m^2) used in the manufacturer's model with a mean BSA of 1.83 m^2 (based on results of a UK audit study and weighted for the gender balance in the EXTREME study). For further details see page 57 of the ERG report.

- The ERG re-analysed the unit costs used in the manufacturer's model by using a more consistent price base for costs. The ERG used the following sources: NHS reference costs for 2006/07 for inpatient, outpatient and investigations; PSSRU 2007 for primary care costs; BNF 56 (2008) for drug costs and Blood Transfusion Service prices for 2007/08, adjusted to 2006/07 prices assuming 4% inflation for transfusions. For further details see page 59 of the ERG report.

Table 6 below presents a summary of the submitted base-case cost-effectiveness results for cetuximab plus chemotherapy compared with chemotherapy only, together with the individual effect and combined effects of the amendments made by the ERG. The ERG stated that the most influential changes to cost arose from the re-calculation of drug doses by BSA, partially offset by the introduction of a mid-cycle correction. The use of an overall pre-progression utility value in place of treatment-specific values was the main alteration to outcomes.

Table 6 Summary of the cost effectiveness results provided by the manufacturer with ERG amendments applied.

Model / amendment	Incremental costs	Incremental LY	Incremental QALYs	Incremental cost/LY gained	Incremental cost/QALY gained
Base case	£17,286	0.1874	0.1424	£92,226	£121,367
Mid-cycle correction	£16,185 [-£1,101]	0.1874	0.1414 [-0.0011]	£86,353 [-£5,873]	£114,484 [-£6,884]
Limit to 24 months	£16,760 [-£526]	0.1318 [-0.0556]	0.1134 [-0.0290]	£127,149 [+£34,923]	£147,817 [+£26,449]
Overall PFS utility value	£17,286	0.1874	0.1240 [-0.0184]	£92,226	£139,390 [+£18,023]
Adverse event utility adjustment	£17,286	0.1874	0.1443 [+0.0019]	£92,226	£119,808 [-£1,560]
Revised drug costs	£20,441 [+£3,155]	0.1874	0.1424	£109,059 [+£16,833]	£143,519 [+£22,152]
100% cisplatin use	£17,332 [+£46]	0.1874	0.1424	£92,473 [+£247]	£121,692 [+£325]
Cetuximab dose adjustment	£17,404 [+£118]	0.1874	0.1424	£92,858 [+£632]	£122,199 [+£831]
Cisplatin dose adjustment	£17,259 [-£27]	0.1874	0.1424	£92,081 [-£145]	£121,177 [-£191]
Rebase unit costs	£18,852 [+£1,566]	0.1874	0.1424	£100,580 [+£8,354]	£132,361 [+£10,993]
Revised discounting	£17,283 [-£3]	0.1873 [-0.0002]	0.1423 [-0.0001]	£92,297 [+£71]	£121,437 [+£69]
Base case + all changes - full life	£20,932 [+£3,646]	0.1873 [-0.0002]	0.1259 [-0.0166]	£111,784 [+£19,558]	£166,307 [+£44,939]
Base case + all changes - 24 months	£20,331 [+£3,045]	0.1317 [-0.0558]	0.0976 [-0.0449]	£154,420 [+£62,194]	£208,266 [+£86,899]
QALYs=quality adjusted life years; LY=life year; PFS=progression free survival					

The ERG also carried out exploratory analysis to determine the effect of its model amendments on all the patient subgroups. For full details of the effects of the ERG's parameter corrections and/or amendments on the

manufacturer's submitted subgroup cost-effectiveness results, see table 7 below.

Table 7 Summary of subgroup cost-effectiveness results provided by the manufacturer with ERG corrections and adjustments applied.

Subgroup/ model	Incremental costs	Incremental LY	Incremental QALYs	Incremental cost/LY gained	Incremental cost/QALY gained
Oral – all					
Submitted	£22,658	0.5496	0.3544	£41,223	£63,927
ERG - full life	£26,825	0.5492	0.3379	£48,844	£79,382
ERG - 24 months	£26,072	0.4785	0.3022	£54,486	£86,264
Oral - KPS 90+					
Submitted	£27,688	0.8178	0.5053	£33,855	£54,790
ERG - full life	£32,318	0.8172	0.4863	£39,547	£66,461
ERG - 24 months	£31,717	0.7658	0.4604	£41,415	£68,889
Oropharynx – all					
Submitted	£17,915	0.0412	0.0715	£434,568	£250,597
ERG - full life	£21,201	0.0412	0.0537	£514,150	£394,548
ERG - 24 months	£21,558	0.0821	0.0746	£262,583	£288,916
Oropharynx - KPS 90+					
Submitted	£18,242	0.0262	0.0589	£695,475	£309,735
ERG - full life	£21,311	0.0262	0.0403	£812,749	£528,387
ERG - 24 months	£21,427	0.0422	0.0484	£508,270	£441,913
Oral or Oropharynx – all					
Submitted	£19,867	0.2537	0.1891	£78,301	£105,069
ERG - full life	£18,561	0.2535	0.1898	£73,209	£137,024
ERG - 24 months	£18,396	0.2391	0.1827	£76,939	£141,701
Oral or Oropharynx - KPS 90+					
Submitted	£21,683	0.3155	0.2219	£68,717	£97,702
ERG - full life	£25,406	0.3153	0.2033	£80,576	£124,989
ERG - 24 months	£25,329	0.3106	0.2014	£81,543	£125,792

QALYs=quality adjusted life year; KPS=Karnofsky performance score; LY=life year; ERG=Evidence Review Group

Table 7 (continued) Summary of subgroup cost-effectiveness results provided by the manufacturer with ERG corrections and adjustments applied.

Subgroup / model	Incremental costs	Incremental LY	Incremental QALYs	Incremental cost/LY gained	Incremental cost/QALY gained
Metastatic disease					
Submitted	£14,539	-0.015	0.026	dominated	£562,849
ERG - full life	£15,800	-0.015	0.013	dominated	£1,241,000
ERG - 24 months	£16,000	0.011	0.026	£1,443,200	£608,500
Recurrent disease (non metastatic)					
Submitted	£18,758	0.308	0.215	£60,939	£87,099
ERG - full life	£22,700	0.308	0.199	£73,800	£113,900
ERG - 24 months	£22,000	0.241	0.166	£91,100	£132,700
QALYs=quality adjusted life years; LY=life years; ERG=Evidence Review Group					

The ERG stated that in all cases the results of the analyses indicated that cetuximab plus chemotherapy was less cost-effective with the ERG amended model and parameter corrections than when originally submitted by the manufacturer.

The ERG undertook threshold analysis to determine the cost for a vial of cetuximab that would generate an ICER below £30,000 per QALY gained (for details of the analysis, see page 69 of the ERG report). The ERG stated that it appears that the use of cetuximab plus chemotherapy may not be cost effective at any price. The ERG reported that there are three contributory processes influencing this result:

- Since cetuximab requires more frequent administration than chemotherapy, it incurs additional infusion costs twice every cycle, regardless of the price charged for the drug.

- The trial protocol requires patients achieving a response to continue receiving cetuximab until disease progression occurs, incurring greater drug and administration costs.

- Because cetuximab plus chemotherapy is associated with better survival, patients experience a longer period during which they receive other follow-on treatments and palliative care, all of which involve additional NHS costs.

3.3 Further considerations following premeeting briefing teleconference

The manufacturer has estimated that there are approximately 3000 patients with recurrent and/or metastatic head and neck cancer in England and Wales. The EXTREME study reported a statistically significant difference in median overall survival (primary outcome measure) favouring cetuximab plus chemotherapy over chemotherapy alone (10.1 months versus 7.4 months, HR 0.797 [95% CI 0.644-0.986], p = 0.00362).

NICE guidance 'Cetuximab for the treatment of locally advanced squamous cell cancer of the head and neck' (NICE technology appraisal guidance 145) includes a recommendation to address equality issues arising from the Karnofsky performance-status score.

4 Authors

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Appendix A: Sources of evidence considered in the preparation of the premeeting briefing

A The evidence review group (ERG) report for this appraisal was prepared by Liverpool Reviews & Implementation Group, University of Liverpool:

- Greenhalgh J, Bagust A et al, Cetuximab for recurrent and/or metastatic squamous cell carcinoma of the head and neck (SCCHN), November 2008.

B Submissions or statements from the following organisations:

I Manufacturer/sponsor

- Merck Serono

II Professional/specialist, patient/carer and other groups:

- British Association of Head and Neck Oncology Nurses
- British Association of Otorhinolaryngologists - Head and Neck Surgeons
- Let's Face It
- Mouth Cancer Foundation
- Royal College of Nursing
- Royal College of Pathologists

C Additional references used:

Blood Transfusion Service (2008). National prices – Impact of cost pressures, developments and cost reduction programmes for the final year 2008/09 (cited November 2008). Available from: http://hospital.blood.co.uk/library/pdf/NCG_BC_Cost_Impact_0809.pdf

National Institute of Health and Clinical Excellence (2008). Guide to the methods of technology appraisal. London: National Institute for Health and Clinical Excellence. Available from: www.nice.org.uk/media/TAMethodsGuide

National Institute of Health and Clinical Excellence (2008). Cetuximab for the treatment of locally advanced squamous cell cancer of the head and neck. Technology appraisal guidance145. London: National Institute for Health and Clinical Excellence. Available from: www.nice.org.uk/TA145

Varney SJ and Guest JF (2003). The annual cost of blood transfusions in the UK. Transfusion Medicine Reviews, 13:205–18.

Vermorken J, Mesia R, Rivera F, et al. (2008) Platinum-based chemotherapy plus cetuximab in head and neck cancer. New England Journal of Medicine, 359:1116–27.