Cetuximab for recurrent and/or metastatic squamous cell carcinoma of the head and neck (SCCHN)

ERG Report

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Adrian Bagust carried out the critical appraisal of the manufacturer's economic model with assistance from Angela Boland and Claire McLeod. Angela Boland summarised the manufacturer's review of economic literature and described the economic model.

All authors read and commented on draft versions of the ERG report and provided useful feedback to the lead author (Janette Greenhalgh).

Contents

Abbreviations:

AE(s)	Adverse event(s)
ASCO	American Society of Clinical Oncology
BNF	British National Formulary
BSA	Body surface area
BSC	Best supportive care
BTS	Blood Transfusion Service
CEAC	Cost-effectiveness acceptability curve
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CTX	Chemotherapy treatment
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
EMEA	European Medicines Agency
EORTC QLQ-C30	Cancer-specific questionnaire for assessing quality of life
EQ-5D	EuroQol 5D is a standardised instrument used as a measure of health outcome
ERG	Evidence Review Group
EXTREME	Erbitux in First-Line Treatment of Recurrent or Metastatic Head and Neck Cancer Trial
HEED	Health Economic Evaluation Database
ICD 10	International Classification of Diagnosis
ICER	Incremental cost-effectiveness ratio
KPS	Karnofsky performance status
LYG	Life year gained
MS	Manufacturer submission
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Clinical Excellence
OS	Overall survival
PFS	Progression free survival
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Resource Unit
QALY	Quality adjusted life year
QLQ-H&N35	Tumour-specific questionnaire for assessing QoL in head and neck cancer
QoL	Quality of life
RCT	Randomised controlled trial
SA	Sensitivity analysis
SCCHN	Squamous cell carcinoma of the head and neck
SOPD	Sum of perpendicular dimensions
STA	Single Technology Appraisal
TGFα	Transforming growth factor-alpha
TTF	Time to treatment failure
WTP	Willingness to pay
5-FU	Fluorouracil

1 SUMMARY

1.1 Scope of the submission

The remit of the Evidence Review Group (ERG) is to comment on the clinical and cost-effectiveness evidence submitted to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal (STA) process. Clinical and economic evidence has been submitted to NICE from Merck Serono in support of the use of cetuximab (Erbitux®) for the first-line treatment of patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck (SCCHN). The manufacturer submission (MS) describes the use of cetuximab in combination with platinum-based chemotherapy (CTX: cisplatin or carboplatin plus 5-fluorouracil (5-FU)) compared with platinum-based CTX alone.

On 23rd October 2008, the Committee for Medicinal Products for Human Use (CHMP), European Medicines Agency (EMEA), adopted a positive opinion to extend the use of cetuximab (Erbitux®) to include the treatment of patients with recurrent and/or metastatic SCCHN. The CHMP positive opinion states that 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".

The ERG notes that neither the final scope issued by NICE, nor the positive opinion adopted by the CHMP, restricts the use of cetuximab to first-line treatment for this group of patients.

1.2 Summary of submitted clinical-effectiveness evidence

The clinical effectiveness evidence described in the MS is derived from a phase III open label randomised controlled trial (RCT) which compared the use of cetuximab plus CTX with CTX alone. The EXTREME trial was conducted in 80 centres within 17 European countries and included 442 patients. The results of the EXTREME trial showed significant effects of cetuximab plus CTX on the primary outcome of median overall survival (OS) compared to CTX: 10.1 months compared to 7.4 months. There was also a significant effect of cetuximab plus CTX on the secondary endpoints compared to CTX: median progression free survival (PFS), 5.6 months compared to 3.3 months; best overall response to therapy, 35.6% compared to 19.5%; disease control rate, 81.1% compared to 60%; median time to treatment failure (TTF), 4.8 months compared to 3.0 months. There was no significant difference in the median duration of response between the cetuximab plus CTX and CTX groups: 5.6 months compared to 4.7 months. The quality of life (QoL) data described in the MS were very limited; the manufacturer states that there was no difference in QoL found between the two

treatment groups. No safety issues related to cetuximab arose beyond those already previously documented for cetuximab.

1.3 Summary of submitted cost-effectiveness evidence

In the absence of UK-based economic evaluations of cetuximab plus CTX for patients with recurrent and/or metastatic SCCHN, the manufacturer conducted a *de novo* economic evaluation. A two-arm state-transition Markov model was developed by the manufacturer to evaluate the cost effectiveness of cetuximab plus CTX compared to CTX. The clinical data used in the economic evaluation are generated from the EXTREME trial. Although the economic evaluation is trial-based, there is also a modelling component with regard to the extrapolation of health effects beyond the period of the trial (24 months). The economic evaluation adopts a lifetime horizon for the consideration of costs and benefits and the perspective is that of the UK NHS and Personal Social Services (PSS).

The manufacturer reports an incremental cost-effectiveness ratio (ICER) of £121,367 per quality adjusted life year (QALY) gained and an incremental cost per life year (LY) gained of £92,226. In addition to the main results, ICERs for selected subgroups are also presented. Univariate sensitivity analysis (SA) shows that varying (i) the cost of day case infusion and (ii) the utility values in the stable/response health state of the cetuximab plus CTX arm have the greatest impact on the ICER. Probabilistic sensitivity analysis (PSA) was also conducted by the manufacturer. The PSA described in the MS illustrates that cetuximab plus CTX is unlikely to be cost effective for patients with recurrent and/or metastatic SCCHN even at, what would usually be considered, very high levels of willingness to pay (WTP) for an additional QALY.

The ERG made several corrections and/or adjustments to the model logic and parameter values. In general, the combined effect of ERG corrections and/or adjustments yielded less favourable economic results for cetuximab than described in the MS. The highest ICER estimated by the ERG for the amended base case was £208,266 per QALY. The economic modelling results submitted by the manufacturer and estimated by the ERG therefore do not support a case for the use of cetuximab with platinum-based CTX in recurrent and/or metastatic SCCHN, either for the whole population or for any identified patient subgroup.

1.4 Commentary on the robustness of submitted evidence

1.4.1 Strengths

The manufacturer cites evidence from a reasonably high quality trial (EXTREME) of the clinical benefit of cetuximab plus CTX compared with CTX. 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.

1.4.2 Weaknesses

The ERG notes that there is only one relevant RCT (EXTREME) which compares cetuximab plus CTX with CTX. This trial is an open label trial and relies on the unblinded assessment of clinical outcomes. Despite designing the trial to include a comprehensive analysis of QoL (e.g. utilising three relevant questionnaires over a number of pre-specified time points), very limited QoL data were collected and reported in the MS. Clinically, this may limit the ability of clinicians to select appropriate patients who would be able to tolerate and benefit from cetuximab plus CTX.

The ERG is confident that neither model assumptions nor parameter values are likely to introduce sufficient uncertainty to allow cetuximab plus CTX to be cost effective for this group of patients. For example, the results of the ERG threshold analysis indicate that cetuximab may not be cost effective at any price according to current NICE guidance.

The ERG has identified a number of different areas in the economic model where it has been appropriate to correct or revise model assumptions, which taken together have increased the size of the ICER.

1.4.3 Areas of uncertainty

The MS provides clinical and economic evidence for the first-line treatment of patients with recurrent and/or metastatic SCCHN only. The MS does not discuss the costs and benefits of second-line treatment options for this group of patients.

Some patients presenting with recurrent and/or metastatic SCCHN may have already received cetuximab (in combination with radiotherapy) for locally advanced SCCHN. There is no clinical evidence available to demonstrate the effectiveness of cetuximab plus CTX in patients who are not cetuximab-naive.

Some questions over the appropriateness and reliability of parametric survival projection beyond the duration of trial data could not be fully explored by the ERG due to lack of information; in particular, the appropriateness of employing Weibull modelling for all patient groups may benefit from further examination.

The ERG questions the appropriateness of economic modelling in this STA since many health economists would prefer to carry out direct evaluation of trial data when there is only evidence available from a single RCT.

The manufacturer argues that the assessment of quality of life associated with the use of cetuximab plus CTX may misrepresent the real health gain for patients with recurrent and/or metastatic SCCHN. The manufacturer would prefer that other indicators of benefit (e.g. socioeconomic status) are taken into account.

1.5 Key issues

Clinical:

The manufacturer provides clinical evidence to support the use of cetuximab as a first-line treatment for patients with recurrent and/or metastatic SCCHN. Neither the final scope issued by NICE nor the EMEA CHMP positive opinion limits the use of cetuximab to first-line treatment only.

The EXTREME trial demonstrates the superior clinical effectiveness of cetuximab plus CTX over CTX. However, whether or not the patients in the EXTREME trial are sufficiently similar (in terms of age and KPS) to patients in England and Wales with recurrent and/or metastatic SCCHN who require treatment is uncertain.

There is no clinical evidence available to demonstrate the effectiveness of cetuximab plus CTX in patients who are not cetuximab-naive.

Based on consideration of the manufacturer's responses to the ERG letter of clarification and subsequent further request, the ERG considers that patients with metastatic SCCHN have not been shown to receive a significant survival benefit from cetuximab plus CTX compared to CTX alone.

Economics:

The cost per QALY figures reported in the MS are high (in excess of £100,000 per QALY gained). Both the original model submitted by the manufacturer and the model corrected/adjusted by the ERG, yield ICERs which far exceed accepted values. Given the high cost of cetuximab plus CTX and the marginal health benefits gained in comparison to CTX, discussion of further economic issues within NICE's current acceptability range (£20,000 to £30,000 per QALY) seems unnecessary. The ERG concludes that even setting a lower price for cetuximab would not strengthen the manufacturer's case for cost effectiveness.

2 BACKGROUND

2.1 Critique of the manufacturer's description of the underlying health problem

In the context section of the MS, the manufacturer describes the key issues related to the decision problem. A summary of this section of the MS describing the underlying health problem and associated risk factors is presented in Box 2-1 and Table 2.1. All information was taken directly from the MS.

Box 2-1 Summary of the manufacturer's description of the underlying health problem

The term head and neck cancer covers a wide variety of different cancers occurring in the tissues of the head and neck. The full spectrum of cancers covers 30 different ICD10 codes and although each individual cancer is relatively uncommon when taken as a group they account for over 8000 cancer registrations and over 2000 deaths per year in England and Wales.[1, 2]

Squamous cell carcinoma of the head and neck most commonly arises in the oral cavity, pharynx and larynx. Tumours of the thyroid gland are mainly adenocarcinoma and are managed differently from SCCs. Around 90% of head and neck cancers are SCC.[3]

Tobacco and alcohol consumption are aetiological factors involved in the onset of SCCHN, which commonly affects middle-aged or older men. Incidence is associated with exposure to risk factors, and there are pronounced geographical variations. SCCHN tends to be a disease of deprivation and of men; the risk of men developing the disease is four times greater for men living in the most deprived areas.[4, 5]

The prognosis of recurrent and/or metastatic SCCHN subjects is extremely poor with a median survival time of only 6-9 months.

Table 2.1 SCCHN registrations relevant to the decision problem by tumour site

Site (ICD 10 code)	**Number of registrations in England (2005)**		**Number of registrations in Wales (2006)**	
	Males	Females	Males	Females
Oral cavity (C00-C06)	1341	1005	130	82
Pharynx (C09-C14)	1126	415	90	34
Larynx (32)	1432	297	89	21

2.1.1 Treatment options for patients with SCCHN

The MS states that "treatment is usually tailored to each individual patient and takes into account physical health and co-morbidities, nature and course of disease and previous treatments" (MS, pg15). This means that patients with recurrent and/or metastatic SCCHN are a heterogeneous population requiring diverse treatments including perhaps surgery or radiotherapy with curative intent, chemoradiotherapy, CTX and/or best supportive care (BSC). The MS states that when palliative CTX is administered to recurrent and/or metastatic patients, the most commonly used regimens include platinum compounds, 5-FU, methotrexate and bleomycin. In the UK, market research conducted on behalf of Merck Serono revealed that "cisplatin is the most common choice of platinum agent in England and Wales with very little use of carboplatin" (MS, Appendix MI).

2.1.2 Cetuximab

Cetuximab is the intervention of interest in the MS. The main body of clinical evidence is derived from the comparison of cetuximab plus CTX versus CTX in a phase III RCT for patients with recurrent and/or metastatic SCCHN. The MS explains the mode of action of cetuximab and this is summarised in Box 2-2.

Box 2-2 Cetuximab (Erbitux®)

The epidermal growth factor receptor (EGFR) is a commonly expressed transmembrane glycoprotein belonging to the tyrosine kinase growth factor receptor family. It is expressed widely in normal human body tissues and is over expressed in many types of tumour.

EGFR is highly expressed in nearly all SCCHN tumours and has a strong prognostic significance providing a strong rationale for testing anti-EGFR agents in this indication.

Cetuximab blocks binding of EGF and TGFα to the EGFR and inhibits ligand-induced activation of this receptor. Cetuximab also stimulates EGFR internalisation effectively removing the receptor from the cell surface for interaction with ligands. Cetuximab also induces antibody dependent cell cytotoxicity.

2.1.3 ERG's critique of the manufacturer's definition of the underlying disease

The MS provides a reasonable description of the underlying health problem including details of incidence, prevalence and aetiology. However, the ERG notes that there is no real consideration of the physical or psychological well-being of this patient group; this is surprising as most patients with recurrent and/or metastatic SCCHN are likely to have

experienced serious physical and emotional difficulties as a result of the disease and its treatments.

2.2 Critique of manufacturer's overview of current service provision

The manufacturer appointed an Advisory Board made up of four consultant oncologists and four representatives from Merck Serono (the manufacturer) to provide input to the MS. The meeting notes of the Advisory Board are embedded in the MS as Appendix H1. The Board agreed that "chemotherapy is the mainstay of treatment in patients who cannot be treated by local methods (surgery and radiotherapy) and are fit enough to receive it. This is most commonly cisplatin-based."

The ERG notes that many patients with recurrent and/or metastatic SCCHN are unsuitable for CTX.

3 CRITIQUE OF THE MANUFACTURER'S DEFINITION OF THE DECISION PROBLEM

The final scope issued by NICE and the manufacturer's definition of the decision problem are described in the MS (pg8-9) and the summary table is reproduced here (Table 3.1).

Table 3.1 Final scope issued by NICE and the manufacturer's definition of the decision problem

	Final scope issued by NICE	**Decision problem addressed in the MS**
Population	Adults with metastatic and/or recurrent squamous cell carcinoma of the head and neck for whom platinum-based chemotherapy is appropriate.	Adults with metastatic and/or recurrent squamous cell carcinoma of the head and neck for whom platinum-based chemotherapy is appropriate.
Intervention	Cetuximab plus platinum-based chemotherapy.	Cetuximab plus platinum-based chemotherapy.
Comparator(s)	Platinum-based chemotherapy regimens.	Platinum-based chemotherapy regimens. Specifically 5-flurouracil combined with cisplatin is the standard of care in the UK in this setting.
Outcomes	The outcome measures to be considered include: • overall survival • progression free survival • tumour response • adverse effects of treatment • health-related quality of life	The outcome measures to be considered include: • overall survival • progression free survival • tumour response • adverse effects of treatment • health-related quality of life
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The economic analysis should be based on a lifetime time horizon. Costs will be considered from an NHS and Personal Social Services perspective.	The cost effectiveness of treatments will be expressed in terms of incremental cost per quality-adjusted life year. Cost per life year will also be presented. The economic analysis will be based on a lifetime time horizon. Costs will be considered from an NHS and Personal Social Services perspective.
Special considerations and other issues	If the evidence allows, the appraisal should consider subgroups (e.g. by performance status or biomarkers), for whom the technology may be particularly effective. Guidance will only be issued in accordance with the marketing authorisation.	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.

3.1 Licensed indications of cetuximab and scope of the manufacturer submission

3.1.1 New licensed indication

The EMEA currently approves cetuximab in combination with radiotherapy for the treatment of locally advanced SCCHN. Merck Serono has submitted an application to extend this license to include the treatment of patients with recurrent and/or metastatic SCCHN with cetuximab plus CTX. On October 23rd 2008, the CHMP issued a positive opinion of cetuximab to recommend the variation to the terms of the marketing authorisation. The full indication will be for the use of cetuximab in combination with platinum-based CTX for patients with recurrent and/or metastatic SCCHN.

The MS provides clinical and economic evidence of first-line use of cetuximab plus CTX for patients with recurrent and/or metastatic SCCHN. The final scope issued by NICE does not limit the patient population to those receiving first-line treatment only, yet the MS presents clinical evidence describing first-line use of cetuximab only. This means that the MS does not provide clinical or economic evidence regarding the treatment of patients with recurrent and/or metastatic SCCHN who might require second-line care.

3.2 Population

The stated population in the final scope issued by NICE and discussed in the manufacturer's definition of the problem was described as "adults with metastatic and/or recurrent SCCHN for whom platinum-based CTX is appropriate." Neither NICE nor the manufacturer define what is meant by "appropriate". The ERG has assumed that the term "appropriate" refers to those patients whose health cannot be improved by surgery and/or radiotherapy and whose health state may be improved by more than BSC measures alone.

The clinical and economic evidence described in the MS is derived primarily from the EXTREME trial. The baseline characteristics from the EXTREME trial show that trial patients are perhaps younger (median age 56 years) and fitter (very high KP scores) than the patients expected to present for this type of treatment in the UK. A casemix bias towards younger and fitter patients in clinical trials is not uncommon, although in this instance the ERG cannot judge to what extent the need to select patients clinically suitable for chemotherapy might explain the observed differences.

Also, approximately 15% of patients in both arms of the EXTREME trial had not received prior radiotherapy. In the UK, it is unlikely that patients with recurrent SCCHN will NOT have had prior radiotherapy (Personal Communication, Richard Shaw, October 2008). In response to the ERG's letter of clarification, the manufacturer stated that "8% of patients in the cetuximab arm and 7% of the patients in the comparator arm initially presented with metastatic disease. Hence these patients would not be expected to have been previously treated with radiotherapy. It is also important to consider that clinical practice has evolved since the EXTREME trial was initiated in December 2004." How the effect of changes in clinical practice since 2004 may affect the anticipated clinical benefits of cetuximab plus CTX on patients treated in England and Wales today is unknown.

Of the 80 centres included in the EXTREME trial, four were based in the UK. The remaining centres were based in: France, Spain, Germany, Italy, Belgium, Netherlands, Portugal, Sweden, Switzerland, Austria, Poland, Hungary, Russia, Ukraine, Czech Republic and Slovakia. Upon request, the manufacturer asserted that even though only nine patients were enrolled from the UK, over half the total number of patients came from other European countries which would be expected to have similar practices and levels of care as observed in the UK. The countries named as similar to the UK were Belgium, France, Germany, Italy, Netherlands and Spain; the percentage of patients from these countries combined with UK patients is 59%.

Upon request, the manufacturer provided details of disease stage classification, tumour stage by disease site, the number of pre-treatments by tumour type and the modality of pre-treatment by tumour site. Clinical advisors to the ERG conclude that these data show sufficient comparability with UK data.

Finally, the ERG notes that the guidance issued by NICE[6] in 2008 recommends the use of cetuximab plus radiotherapy for the treatment of locally advanced SCCHN. 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 observes that as patients in the EXTREME trial were cetuximab-naive, there is no clinical evidence to support the use of cetuximab in this cohort of patients.

3.2.1 Intervention

The technology is cetuximab (Erbitux®) a monoclonal antibody that inhibits the actions of the epidermal growth factor receptor that is highly expressed in nearly all squamous cell tumours

and has a strong prognostic significance in SCCHN. Cetuximab is given in combination with CTX for up to six cycles and is continued as monotherapy until disease progression.

3.3 Comparators

The stated comparators in the final scope are platinum-based CTX regimens. In the definition of the decision problem, the manufacturer has narrowed this to a specific platinum-based CTX, cisplatin plus 5-FU. However, the patients in the EXTREME trial received cisplatin plus 5-FU or carboplatin plus 5-FU, not just cisplatin plus 5-FU.

The results of a Merck Serono SCCHN Erbitux® Tracking Study support the manufacturer's statement that cisplatin plus 5-FU is the standard of care in the UK for this patient group. This study is described in an embedded document in the MS (Appendix M1). In the study, 50 UK oncologists were interviewed between December 2007 and February 2008. The study analysed data from 332 patients who had locally advanced, recurrent from locally advanced or metastatic SCCHN and were treated with radiotherapy, CTX and/or targeted therapy.

The ERG is confident that where CTX is appropriate for this group of patients, cisplatin plus 5-FU is likely to be standard therapy in the UK. However, the ERG notes that CTX itself is not standard care for the group of patients as a whole, as many patients with recurrent and/or metastatic SCCHN are unsuitable for CTX.

3.4 Outcomes

The manufacturer adequately describes the outcomes of interest in relation to the relevant patient group and/or phase of treatment reflecting the single list of clinical outcomes identified in the final scope issued by NICE.

The relevant outcomes used to measure clinical effectiveness include: OS, PFS, tumour response, adverse events (AEs) of treatment and health related QoL.

In the clinical effectiveness section of the MS, the manufacturer describes the instruments that are used to measure QoL in the trial. However, the results of the QoL assessments are not reported in full in this section. The results are presented only in the EXTREME Study Final Quality of Life Report which was not referred to in the MS, but was provided by the manufacturer in the file containing electronic references.

3.5 Time frame

During the trial period, patients were followed up until death or discontinuation of treatment. Costs and outcomes are extrapolated beyond the trial follow up period. Overall survival and PFS are censored and do not provide information on the course of disease beyond 24 months.

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

3.6 Other relevant factors

No relevant subgroup analyses are explicitly stated in the final scope issued by NICE. However, in the manufacturer's definition of the decision problem, it is stated that pre-planned subgroup analyses, defined by performance status, previous treatments and response to previous treatments, would be carried out. The ERG is confident that the subgroup analyses are appropriate. The manufacturer provided separate subgroup cost-effectiveness analysis results for patients with recurrent cancer and for those patients with and without metastatic cancer in response to requests from the ERG.

The MS includes a section on "Equity and Equality" (MS, pg19-20). No equity or equality considerations were identified in the final scope issued by NICE. The manufacturer argues that for patients with recurrent and/or metastatic SCCHN, QoL assessments may misrepresent the real health gain experienced by patients. The manufacturer refers to Principles 7, 8 and 9 as described in "Social Value Judgements: Principles for the development of NICE guidance" and contends that "Where the life expectancy of a socio-economic group of patients is significantly below the national average, a one year QALY gain is proportionately of far greater benefit than may be the case in a more elevated group and consequently the cost effectiveness of an intervention is increased" (MS, pg19).

4 CLINICAL EFFECTIVENESS

Table 4.1 provides an outline of the key background/clinical information and its location within the MS. Its purpose is to signpost the reader to the main areas of background/clinical information within the MS.

Table 4.1 Key non-economic information in the MS

Key information	Pages in the MS	Key tables/figures in the MS
Description of technology	3	
Statement of decision problem	8-9	
Context/background	14-18	
Equity and equality	19-20	
Literature search:		
Search strategies	Appendix 2, Section 10.2	Appendix 2, Section 10.2
Study selection	24-26	
Clinical effectiveness evidence:		
Trial information	27-45	Table B2
Results: main and subgroups	45-49	Figure B3
Results: QoL analysis	51-52	Provided electronically in addition to MS
Results: safety	53-55	
Merck Serono Advisory Board	Appendix H1	
Merck Serono tracking study	Appendix M1	

4.1 Critique of manufacturer's approach

4.1.1 Description of manufacturer's search strategy and comment on the appropriateness of the chosen search strategy.

The stated aim of the literature search described in the MS was to identify studies describing the use of cetuximab in combination with platinum-based chemotherapeutic regimens in the first-line treatment of recurrent and/or metastatic SCCHN. The ERG re-emphasises that the limitation to first-line use was applied by the manufacturer and was not included in the NICE scope.

The search strategy was comprehensive and included the most appropriate databases: MEDLINE (1950 to August week 3 2008), EMBASE (1980 to week 5 2008), DataStar Current Contents (1995 to 3/9/2008), the Cochrane library (3/9/2008) and the American Society of Clinical Oncology (ASCO) abstracts from annual meetings. The manufacturer did

not search ISI Web of Knowledge which includes the Science Citation Index and conference proceedings.

The MS presented the search strategy and resulting articles in a self-contained embedded document. The flowchart relating to DataStar Current Contents shows a search total of 89, however the actual numbers quoted total 92. In addition, the file containing the search results contained only 63 references.

With reference to the ASCO search, the ERG found a conference presentation made by the principal investigator of the EXTREME trial at the 2007 ASCO conference which did not appear in the manufacturer's search results for ASCO.

4.1.2 Statement of the inclusion/exclusion criteria used in the study selection and comment on whether they were appropriate.

Table 4.2 shows the inclusion and exclusion criteria presented in the MS.

Table 4.2 Inclusion and exclusion criteria

Inclusion	Exclusion
Randomised controlled trials	Studies which involved patients who had received previous treatment in the metastatic and/or recurrent head and neck cancer setting
Studies of the use of cetuximab in the first-line treatment of recurrent and/or metastatic head and neck cancer	Papers published in a language other than English
Human only studies	Letters and editorials
Studies in English	Review articles and conference summaries

The inclusion/exclusion criteria described in the MS are appropriate to the manufacturer's stated objectives, focussed on cetuximab as a first-line treatment.

The MS lists three relevant RCTs (two phase III trials and one phase II trial). The EXTREME trial was included in the review. The results of the EXTREME trial have been published[7] recently and the trial characteristics are shown in Table 4.3. The remaining two trials were excluded from the literature review by the manufacturer and are summarised in Table 4.4.

Table 4.3 EXTREME trial characteristics

Design	Intervention	Inclusion criteria (main)	Exclusion criteria (main)	Outcomes
Multicentre, European phase III open label RCT comparing cetuximab plus platinum-based CTX versus platinum-based CTX. Patients (n=442) were randomised on a 1:1 ratio and were stratified according to receipt or non-receipt of previous CTX and KPS score	Cetuximab plus CTX (cisplatin plus 5-FU or carboplatin plus 5-FU) (n=222) or CTX (n=220). Treatment: cisplatin 100 mg m^2 of body-surface area as 1hr infusion on day 1. Carboplatin: an area under the curve of 5 mg per ml per minute, as 1hr infusion on day 1. 5-FU: 1000 mg per m^2 per day for 4 days every 3 weeks. Cetuximab: 400 mg m^2 as 2 hour infusion. Subsequent weekly doses of 250 mg m^2 at least 1hour before CTX. Maximum of six cycles of CTX. Dose modifications were allowed. After the six cycle maximum, patients in the cetuximab group with at least stable disease received cetuximab as a monotherapy until disease progression	18 years +; histologically or cytologically confirmed recurrent and/or metastatic SCCHN; ineligibility for local therapy; at least one lesion biodimensionally measurable; KPS $\geq$70; adequate hematologic, renal, hepatic function; tumour tissue available for evaluation of EGFR expression	Surgery or irradiation within the previous 4 weeks; previous systemic CTX unless part of multimodal treatment for locally advanced disease completed > 6 months before study entry; nasopharyngeal carcinoma; concomitant anticancer therapies	Primary: OS (time from randomisation to death) Secondary: PFS (time from randomisation to radiologic confirmation of disease progression, or death from any cause within 60 days after the last assessment or randomisation, whichever came first); best overall response (complete/partial response persisting $\geq$4 weeks); disease control (complete/partial response, or stable disease); TTF (time from randomisation until the date of the first occurrence of any event specified in the protocol; duration of response (time from first documentation of complete/ partial response until disease progression or death); safety; QoL

CTX=chemotherapy treatment; OS= overall survival; PFS = progression free survival; TTF =time to treatment failure; QoL = quality of life; SCCHN=squamous cell carcinoma of the head and neck; KPS=Karnofsky performance status; EGFR=epidermal growth factor receptor

Table 4.4 Excluded trials

Study	Design/population	Phase	Study treatments	Sample size
ECOG 5397[8] (Burtness 2005)	First-line treatment of patients with recurrent and/or metastatic SCCHN. Placebo controlled trial	III	Cisplatin 100mg/m^2 once every 4 weeks +/- cetuximab 200mL/m^2 initial dose, 125 mL/m^2 thereafter.	57 (active) 60 (placebo)
EMR 62202-008[9] (Bouhris 2006)	First-line treatment of patients with recurrent and/or metastatic SCCHN	I/II Safety and tolerability of combination regimen	Cisplatin (100mg /m^2) or carboplatin (AUC5) once every 3 weeks plus 5-FU (escalating dose of 600, 800 and 1000mg/m^2 per day for 5 days) plus cetuximab (400 mg/ m^2 initial dose and 250mg/ m^2 weekly thereafter)	53

AUC = area under the curve

The Burtness[8] trial (ECOG 5397) was excluded from the review in the MS on the grounds that cetuximab was only given in conjunction with CTX and not as a monotherapy after six cycles of CTX as was the case in the EXTREME trial and is likely to be indicated in the licence. In addition, the CTX was single agent platinum rather than with the addition of 5-FU as in the EXTREME trial and in common UK practice. The CTX cycles in the EXTREME trial ran over 3 weeks, whereas cycles in the Burtness[8] trial ran over 4 weeks.

The Bourhis[9] trial was excluded in the MS as it was a small trial with no control group, primarily testing for safety and dosage assessment.

4.1.3 Relevant studies that were not included in the submission

The ERG did not find any other relevant studies for inclusion in the review.

4.1.4 Description and critique of manufacturer's approach to validity assessment

The manufacturer commented on relevant aspects of the quality of the EXTREME trial, namely: allocation concealment; randomisation technique; powering; follow-up; blinding; relevance to the UK; baseline comparability of groups; statistical analyses; type of analysis. The manufacturer described the EXTREME trial as an open label RCT. Randomisation was stratified according to the most important prognostic factors: previous CTX and Karnofsky

performance score (KPS). A central stratified, permuted block randomisation procedure was used to balance prognostic factors and to minimise the predictability of treatment allocation.

The manufacturer notes that the baseline characteristics of the patients in the trial were balanced in respect of demographics, nature of disease and prior treatment. Standard statistical analyses for this kind of research were undertaken along with an intention to treat analysis. The manufacturer described the justification of the power, sample size and length of follow-up. Clinical data collection in the EXTREME trial was good. However, despite describing a comprehensive approach to the assessment of patient QoL, the proportion of evaluable questionnaires from the EXTREME trial was low, thus the QoL data reported in the MS were limited.

The manufacturer's approach to validity was reasonable in most respects, although the open label nature of the EXTREME trial warrants further discussion. It is well documented that open studies are more likely to favour experimental interventions over controls[10,11] and studies that are not double-blinded can exaggerate effect estimates by 17%.[11] The ERG notes that the manufacturer has attempted to address the lack of assessor blinding by providing "clear guidance for the assessment of response……..to minimise the possibility of bias" (MS, pg44). It is unclear how far the guidance would have limited any assessment bias.

Similarly, patient awareness of treatment allocation has also been shown to affect treatment outcomes,[10,11] although the use of a placebo control in this setting would be considered unethical. It could be further argued that since a common side-effect of cetuximab treatment is a rash, treatment allocation would become obvious to both patients and assessors over time, undermining any attempts at blinding. Sources of differences in patient experience between the two treatment arms (other than the intervention) are documented, with safety data being collected more frequently in the cetuximab plus CTX arm (weekly) than in the CTX arm (at the start of every treatment cycle). It is also likely that patients in the cetuximab plus CTX arm received more attention from medical staff due to their extra treatment.

In summary, the EXTREME trial was conducted as an open label RCT, with the inherent dangers of overestimation of treatment effects by assessors and altered patient expectations. A comprehensive critical appraisal using the CASP checklist[12] by the ERG of the EXTREME trial (supplemented by information from the published paper[7]) is described in Appendix 1.

4.1.5 Description and critique of manufacturers outcome selection

The outcome measures presented in the MS are shown in Table 4.5. These are standard outcomes for a trial of this type and match those specified in the scope.

Table 4.5 Outcome measures included in the EXTREME trial

Outcome	Definition
Overall survival (Primary)	Time from day of randomisation to death
Progression free survival	Time from randomisation to the first radiologic confirmation of disease progression, or death from any cause within 60 days after the last assessment or randomisation, whichever came first
The best overall response	Complete response or partial response persisting for at least four weeks
Disease control	Complete response, partial response or stable disease
Time to treatment failure	Time from randomisation until the date of the first occurrence of one of the protocol-specified events
Duration of response	Time from first documentation of a complete or partial response until the first occurrence of disease progression or until death

Quality of life was measured with two related assessment tools: EORTC QLQ-C30 (version 3); EORTC QLQ-H&N35. The EORTC QLQ-C30 is a cancer-specific questionnaire for assessing QoL in patients participating 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.

Assessments were scheduled to be made at six time points: at screening (baseline); day one of the third CTX cycle; first six weekly evaluation: six months; 12 months; final tumour assessment. The small proportion of patients responding at 12 months mitigated against any meaningful statistical analysis. No assessment of QoL was carried out in Hungary, Ukraine or Slovakia (81 patients) due to the lack of translated, validated questionnaires. In addition EuroQol EQ-5D questionnaires were used only in the UK; however no analyses were carried out on these data due to the very small number of patients and responses involved.

Safety outcomes included standard AE reporting, vital signs, physical examination, concomitant medication and procedures, electrocardiogram, ejection fraction, chest X-ray and clinical laboratory evaluations. According to the published paper[7] AEs were monitored

weekly throughout the study in the cetuximab plus CTX group and at the start of every treatment cycle in the CTX group.

4.1.6 Description and critique of the statistical approach used

Details of the statistical approach used in the conduct and analysis of the EXTREME trial were described in the published paper[7] and are repeated here in brief. In terms of powering, the EXTREME trial assumed a median survival of seven months and an approximate increase of 36% in median survival with the addition of cetuximab to the platinum-based CTX. It was calculated that an event-driven analysis after 340 deaths would provide the study with a power of 80% to detect a difference at a two-sided, 5% significance level. Random assignment to study groups of a total of 420 patients within 20 months would lead to estimated total study duration of 34 months (with the assumption that 5% of patients would be lost to follow-up).

Full details of the Cox regression modelling approach undertaken are also described in the published paper.[7] In contrast to the MS, the published paper[7] fully describes the statistical approaches and techniques used by the manufacturer and the ERG considers the methods to be appropriate.

4.1.7 Summary of submitted systematic review

The systematic review in the MS, which identified only one relevant study, was complete and reasonable. However, the stated aim of the literature search described in the MS was to identify studies describing the use of cetuximab in combination with platinum-based chemotherapeutic regimens in the first-line treatment of recurrent and/or metastatic SCCHN. The ERG re-emphasises that this limitation was applied by the manufacturer: the scope does not specify first-line treatment. The search strategy was adequately reported. All relevant clinical trials were identified and validity of the one included trial was discussed by the manufacturer.

The clinical outcomes reported in the single relevant RCT identified cover all clinical outcomes outlined in the final scope issued by NICE. Despite designing the trial to include a comprehensive analysis of QoL, very limited QoL data were collected and reported in the MS. Statistical methods were described in full and appropriately applied.

4.1.8 Summary of submitted clinical effectiveness evidence

The clinical effectiveness evidence described in the MS is derived from a phase III, open label RCT which compared the use of cetuximab plus CTX with CTX alone. The clinical evidence from the EXTREME trial is described in both the MS and in the recently published paper.[7] The EXTREME trial was conducted in 80 centres within 17 European countries and included 442 patients. Patients received cetuximab plus CTX for a maximum of six cycles and continued on cetuximab monotherapy until disease progression. The results of the EXTREME trial showed significant effects of cetuximab plus CTX on the primary and secondary clinical outcomes.

4.1.9 Summary of RCT outcome results

Data presented in this report have been extracted from the MS, the primary published peer-reviewed clinical paper[7] and the EXTREME Study Final Quality of Life Report. Additional information was provided by the manufacturer in clarification of questions raised by the ERG.

The baseline characteristics of randomised patients are shown in Table 4.6. It can be seen that the patients are well balanced between treatment arms in terms of key characteristics.

Table 4.6 Baseline characteristics of patients in the EXTREME trial

Characteristic		Cetuximab plus CTX (n=222)	CTX (n=220)
Gender	Male n (%)	197 (88.7)	202 (91.8)
	Female n (%)	25 (11.3)	18 (8.2)
Age (yrs)	Mean (sd)	57.1 (8.0)	56.7 (8.7)
	Median	56	57
	Q1-Q3	51-62	51-62
Age categories (yrs)	<65 n (%)	183 (82.4)	182 (82.7)
	≥65 n (%)	39 (17.6)	38 (17.3)
Primary tumour site	Oropharynx n (%)	80 (36.0)	69 (31.4)
	Hypopharynx n (%)	28 (12.6)	34 (15.5)
	Larynx n (%)	59 (26.6)	52 (23.6)
	Oral cavity n (%)	46 (20.7)	42 (19.1)
	Other n (%)	9 (4.1)	23 (10.5)
Tumour type	Recurrent not metastatic n (%)	118 (53.2)	118 (53.6)
	Metastatic inc recurrent n (%)	104 (46.8)	102 (46.4)
Karnofsky performance status	100	37 (16.7)	37 (16.8)
	90	69 (31.1)	62 (28.2)
	80	89 (40.1)	96 (43.6)
	75	1 (0.5)	1 (0.5)
	70	25 (11.3)	24 (10.9)
	50	1 (0.5)	0
Previous therapy	Radiotherapy n (%)	189 (85.1)	190 (86.4)
	Radiotherapy (exc. palliative) n (%)	174 (78.4)	176 (80)
	Surgery n (%)	143 (64.4)	135 (61.4)
	Chemotherapy n (%)	90 (40.5)	80 (36.4)
	Radiochemotherapy (exc. palliative) n (%)	69 (31.1)	60 (27.3)
	Neoadjuvant chemotherapy n (%)	24 (10.8)	33 (15.0)
	Other n (%)	1 (0.5)	2 (0.9)

sd=standard deviation; n=number; inc=included; exc=excluded; CTX=chemotherapy

The key results of the EXTREME trial are shown in Table 4.7. The data for the outcomes of TTF and duration of response were not presented in the MS although they were described within the MS as secondary outcomes. Data for TTF and duration of response were thus taken from the published paper,[7] as were the accompanying footnotes.

The outcomes were highly significant in favour of the cetuximab plus CTX arm for all outcomes except duration of response. The primary outcome of OS yielded a median 10.1 months in the cetuximab plus CTX arm compared to 7.4 months in the CTX arm. Further consideration of survival and mortality in the EXTREME trial from a health economics perspective is presented in sections 5.5.1 and 5.5.2.

Table 4.7 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 months (median) (95% CI)	10.1 (8.6-11.2)	7.4 (6.4-8.3)	HR 0.797 (0.644-0.986)	0.00362[a]
Secondary				
PFS months (median) (95% CI)	5.6 (5.0-6.0)	3.3 (2.9-4.3)	HR 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 (CI)	81 % (75.3-86)	60 % (53.2-66.5)	OR 2.881 (1.870-4.441)	<0.001[c d]
Time to treatment failure (mths) (95% CI)	4.8 (4.0-5.6)	3.0 (2.8-3.4)	HR 0.59 (0.48-0.73)	<0.001[a b]
Duration of response (mths) (95% CI)	5.6 (4.7-6.0)	4.7 (3.6-5.9)	HR 0.76 (0.50-1.17)	0.21[b e]

p values, hazard ratios and odds ratios are stratified according to receipt or non-receipt of previous chemotherapy and KPS at randomisation; CI=confidence interval; mths=months; CTX=chemotherapy

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.

Planned SAs were undertaken and the results are shown in Table 4.8. The significant prognostic factors were found to be a KPS above 80 ($p<0.0001$) and treatment with cetuximab ($p<0.0269$).

Table 4.8 Analysis of prognostic factors for the EXTREME trial

Prognostic factor	Level	n	p value	Hazard /Odds Ratio	95% CI
Type of primary tumour	Recurrent not metastatic Metastatic inc recurrent	236 206	0.0607	0.814	0.656-1.009
Karnofsky status	<80 ≥80	52 390	<0.0001	0.508	0.374-0.689
Previous CTX	Yes No	170 272	0.9934	0.999	0.802-1.245
Treatment group	CTX Cetuximab + CTX	220 222	0.0269	0.786	0.636-0.973

CTX=chemotherapy; CI=confidence interval

4.1.10 Subgroup analyses

The MS presents a number of subgroup analyses. A series of exploratory analyses were carried out to identify any heterogeneity of response in relation to OS and PFS. It should be noted that the published paper[7] emphasised that the trial was not powered to detect differences in treatment effects between subgroups and so the results of the analyses must be interpreted with caution.

The clinical subgroups explored were: age, KPS score, platinum regimen, previous treatment, primary tumour site, tumour grade, baseline QoL score and percentage EGFR-detectable cells. The results were depicted in standard forest plots.

For OS, most subgroups appeared to show a benefit of cetuximab treatment. The exceptions were: ≥65 years; KPS of <80; carboplatin therapy; tumour site in the hypopharynx; tumour sited in the larynx; poorly differentiated tumours; metastatic tumours. The hazard ratio (HR) for patients with metastatic disease (HR=0.99) suggests that this group of patients may not derive any survival benefit from cetuximab plus CTX (this is discussed further in section 6.2). No p values were cited in the MS; however, the published paper[7] states that only the interaction between treatment and primary tumour site was significant ($p<0.03$).

For PFS, most subgroups (with the exception of patients with KPS scores of <80) appeared to benefit from treatment with cetuximab.[7] No p values were presented in the MS; however, the published paper[7] states that the only interaction found to be significant was between treatment group and tumour site ($p<0.02$).

The MS provides a forest plot demonstrating that the benefits of cetuximab were most marked in patients with tumours of the oral cavity or oropharynx. There was no significant effect for patients with tumours located in the hypopharynx or larynx.

A second subgroup analysis assessed whether there were any differences in response rate between those patients treated with cisplatin and those treated with carboplatin within each treatment arm. Table 4.9 shows a significant improvement in response rate in the cetuximab plus CTX arm compared with CTX, irrespective of CTX type. However, the response rates for patients treated with carboplatin are, with the exception of disease control rate, lower than for those treated with cisplatin (perhaps because these patients were less fit). The ERG notes that the population in the table is 433 not the ITT figure of 442.

Table 4.9 Analysis of response rates according to platinum type

	Cetuximab plus CTX	CTX	p value	Odds Ratio
Cisplatin	**(n=149)**	**(n=135)**		
Best overall response rate (95% CI)	38.9% (31.1-47.2)	23% (16.2-31.0)	0.0035	2.181 (1.289-3.691)
Disease control rate (95% CI)	81.9% (74.7-87.7)	63.0% (54.2-71.1)	0.0004	2.631 (1.521- 4.551)
Carboplatin	**(n=69)**	**(n=80)**		
Best overall response rate (95% CI)	30.4% (19.9)	15.0% (8.0-24.7)	0.0267	2.452 (1.102-5.548)
Disease control rate (95% CI)	84.1% (73.3-91.8)	58.8% (47.2-69.6)	0.0007	3.879 (1.735-8.675)

CTX=chemotherapy; CI=confidence interval

4.1.11 Quality of life

The Final Quality of Life Report, submitted electronically by the manufacturer in addition to the MS, presents QoL data more comprehensively than the MS.

The proportion of evaluable questionnaires for both EORTC QLQ-C30 and QLQ-H&N35 was considered by the manufacturer to be low (61% in the cetuximab plus CTX group and 58% in CTX 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 showed that in general, the scores for the cetuximab plus CTX group were not significantly worse than the CTX group. Some significant differences in favour of the cetuximab plus CTX group were observed at cycle three on measures of pain, swallowing, speech problems and social eating; however, these differences were not apparent at month six, possibly due to the small sample size at this time.

The MS concludes that the addition of cetuximab to standard CTX has no adverse effect on QoL.

The Final Quality of Life Report cites the main reasons for the low response rates as 'random events' such as failure to distribute the questionnaire, patient felt it was inconvenient or an invasion of privacy. The ERG notes that in trials that involve end-of-life care for very ill patients, the assessment of patient QoL is of low priority compared to arranging treatment. However, given the importance of QoL to this patient group, it is noteworthy that so little emphasis was placed on collecting these key data. The manufacturer states that these low

response rates do not compare favourably with the Merck-sponsored Crystal study (first-line cetuximab therapy in addition to irinotecan-based therapy in metastatic colorectal cancer) in which 81% of questionnaires were considered evaluable.

4.1.12 Safety

The tables in the MS which relate to safety outcomes (MS, pg54-55) both cite 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[7] states that eight patients were not treated (five in the cetuximab plus CTX arm and three in the CTX arm).

The safety data in general were poorly reported in the MS: no p values were given, although these were found in the published paper.[7] Information on treatment compliance was also omitted in the MS though presented in the published paper.[7]

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. Compliance with CTX was similar in both groups.

Death was mainly due to progressive disease in both groups and none due to cetuximab-related AEs.[7]

Table 4.10 shows AEs reported by ≥ 10% of patients. The frequencies of most common AEs were comparable in both treatment groups except rash, acne, acneiform dermatitis, dry skin and anorexia which occurred more frequently in the cetuximab plus CTX group. In addition to those listed in Table 4.10, the MS states that AEs that occurred only in the cetuximab plus CTX group were: conjunctivitis, paronychia, pruritus, exfoliative rash and skin toxicity. The MS further states that with the exception of diarrhoea and anorexia, these findings are consistent with the known safety profile of cetuximab.

Table 4.11 shows Grade 3 or 4 AEs reported by ≥ 5% of patients and Grade 4 AEs reported by ≥ 1% of patients. The majority of events occurred with similar frequencies in both treatment groups except rash. According to Table 3 in the published paper,[7] there was a significant difference between the cetuximab plus CTX group and CTX on the following AEs (Grades 3 and 4 are combined): skin reactions ($p<0.001$); anorexia ($p<0.05$); hypomagnesaemia ($p<0.05$); sepsis ($p<0.02$). Of the Grade 4 events, septic shock and hypocalcaemia occurred only in the cetuximab plus CTX group and there were no Grade 4

skin reactions or vomiting in either group. The published paper[7] states that the main Grade 3 or 4 AEs were consistent with the side-effect profile of cetuximab.

Table 4.10 Adverse events reported in ≥10% patients

Event	Cetuximab plus CTX (n=219) n (%)	CTX (n=215) n (%)
Any adverse event	218 (99.5)	208 (96.7)
Nausea	119 (54.3)	101 (47.0)
Anaemia	93 (42.5)	114 (53.0)
Vomiting	87 (39.7)	81 (37.7)
Neutropenia	84 (38.4)	84 (39.1)
Rash	61 (27.9)	4 (1.9)
Asthenia	57 (26.0)	47 (21.9)
Diarrhoea	57 (26.0)	35 (16.3)
Anorexia	55 (25.1)	31 (14.4)
Fatigue	51 (23.3)	45 (20.9)
Mucosal inflammation	51 (23.3)	41 (19.1)
Pyrexia	49 (22.4)	28 (13.0)
Thrombocytopenia	48 (21.9)	52 (24.2)
Constipation	48 (21.9)	43 (20.0)
Acne	48 (21.9)	0
Leukopenia	42 (19.2)	34 (15.8)
Weight decreased	41 (18.7)	32 (14.9)
Dermatitis acneiform	32 (14.6)	0
Stomatitis	31 (14.2)	28 (13.0)
Dry Skin	30 (13.7)	1 (0.5)
Alopecia	27 (12.3)	15 (7.0)
Hypocalcaemia	27 (12.3)	10 (4.7)
Hypokalaemia	26 (11.9)	15 (7.0)
Hypomagnesaemia	24 (11.0)	11 (5.1)
Dysphagia	22 (10.0)	20 (9.3)
Cough	22 (10.0)	19 (8.8)
Dyspnoea	21 (9.6)	28 (13.0)

CTX=chemotherapy

Table 4.11 Grade 3 or 4 adverse events reported in ≥5% of patients or Grade 4 adverse events reported in ≥1% of patients

Event	Grade 3 or 4 events		Grade 4 events	
	Cetuximab plus CTX (n=219) n (%)	CTX (n=215) n (%)	Cetuximab plus CTX(n=219) n (%)	CTX (n=215) n (%)
Any adverse event	179 (81.7)	164 (76.3)	67 (30.6)	66 (30.7)
Neutropenia	49 (22.4)	50 (23.3)	9 (4.1)	18 (8.4)
Anaemia	29 (13.2)	41 (19.1)	2 (0.9)	2 (0.9)
Thrombocytopenia	24 (11.0)	24 (11.2)	0	3 (1.4)
Leucopenia	19 (8.7)	19 (8.8)	4 (1.8)	5 (2.3)
Hypokalaemia	16 (7.3)	10 (4.7)	2 (0.9)	1 (0.5)
Vomiting	12 (5.5)	6 (2.8)	0	0
Asthenia	11 (5.0)	12 (5.6)	1 (0.5)	1 (0.5)
Anorexia	11 (5.0)	3 (1.4)	2 (0.9)	1 (0.5)
Hypomagnesaemia	11 (5.0)	3 (1.4)	8 (3.7)	1 (0.5)
Rash	11 (5.0)	0	0	0
Febrile neutropenia	10 (4.6)	10 (4.7)	2 (0.9)	4 (1.9)
Dyspnoea	9 (4.1)	17 (7.9)	2 (0.9)	5 (2.3)
Pneumonia	9 (4.1)	4 (1.9)	3 (1.4)	1 (0.5)
Hypocalcaemia	9 (4.1)	2 (0.9)	5 (2.3)	0
Sepsis	6 (2.7)	1 (0.5)	3 (1.4)	1 (0.5)
Septic shock	3 (1.4)	0	3 (1.4)	0
Tumour haemorrhage	3 (1.4)	6 (2.8)	2 (0.9)	4 (1.9)
PS decreased	2 (0.9)	4 (1.9)	1 (0.5)	4 (1.9)
Respiratory failure	1 (0.5)	5 (2.3)	0	4 (1.9)

CTX=chemotherapy

4.1.13 Critique of submitted evidence syntheses

No evidence synthesis was carried out as the submitted clinical evidence was derived from a single RCT which reported relevant outcomes and comparators. In the main, the EXTREME trial was adequately designed and carried out, although the lack of blinding of outcome assessors and patients might be a cause for some concern. The quality of clinical outcomes data reporting for the main comparison was generally good with confidence intervals presented throughout. However, some secondary outcomes were not reported in the MS (for example, TTF and duration of response). The QoL and safety data were poorly reported in the MS.

4.2 Summary

4.2.1 Clinical results

Cetuximab plus CTX versus CTX

- The results of the EXTREME trial showed that adding cetuximab to platinum-based CTX with 5-FU prolonged the median OS from 7.4 months in the CTX group to 10.1 months in the group that received cetuximab plus CTX.

- All secondary outcomes except response duration were significant in favour of cetuximab plus CTX compared with CTX. Median PFS was 5.6 months compared to 3.3 months; best overall response to therapy was 35.6% compared to 19.5%; disease control rate was 81.1% compared to 60%; median TTF was 4.8 months compared to 3.0 months.

- Exploratory subgroup analyses indicated a general benefit of cetuximab in most subgroups (e.g. oral cavity patients, younger age, high KPS).

- The HR for patients with metastatic disease is 0.99.

- No difference in QoL was found between cetuximab plus CTX and CTX patients. The ERG notes that QoL data were limited. No safety issues related to cetuximab arose beyond those already previously documented for cetuximab.

4.2.2 Clinical issues

- The manufacturer submitted clinical evidence to support the use of cetuximab plus CTX for the first-line treatment of patients with recurrent and/or metastatic SCCHN. The final scope does not restrict the appraisal of cetuximab to first-line treatment for this group of patients.

- The patients in the EXTREME trial may not represent potentially eligible patients in England and Wales in terms of age and KPS.

- Patients with metastatic disease appear not to derive any survival benefit from cetuximab plus CTX.

- Collection and reporting of QoL data were poor. In particular the proportion of evaluable QoL questionnaire responses was low. This is disappointing as an improvement in QoL is a real treatment objective for these very seriously ill patients.

- There is no clinical effectiveness evidence available to support the use of cetuximab plus CTX in patients with SCCHN who are not cetuximab-naive.

5 ECONOMIC EVALUATION

5.1 Introduction

This section provides a structured critique of the economic evidence submitted by Merck Serono. The two key components of the economic evidence presented in the MS are (i) a systematic review of the relevant literature (ii) a report of the manufacturer's *de novo* economic evaluation. See Table 5.1 for a summary of key information points. The manufacturer also provided an electronic version of the Excel-based economic evaluation. Finally, the manufacturer also submitted an electronic version of sections of the EXTREME Clinical Study Report.

Table 5.1 Key information in the MS

Key information	**Pages in the MS**	**Key tables/figures in the MS**
Details of the systematic review of the literature	58-59; Appendix 3	
Technology, patients, comparator, perspective and time horizon	61-66	
Framework for model-based evaluation	67-75	H3-H5
Clinical evidence used in economic evaluation	75-77	
Measurement and valuation of health benefits	78-83	H6-H7
Resource identification, measurement and valuation	83-94	H8, H10, H11,H13
Methods of sensitivity analysis and statistical analysis	95-98	H14b
Results – base case analysis Probabilistic sensitivity analysis	98-100 100-103	H15,H17 Figures H5-H7
Results - subgroup analysis Forest plots	103-108 104-105	H20-H22 Figures H8-H9
Results – sensitivity analysis	109-111	H23-H24
Assessment of factors relevant to the NHS and other parties	112-116	BI1-BI3

5.2 Overview of manufacturer's cost-effectiveness review

The manufacturer conducted a review of the literature to retrieve cost-effectiveness studies relevant to the decision problem of cetuximab for the first-line treatment of patients with recurrent and/or metastatic SCCHN.

5.2.1 Identification and description of studies

The MS included full details of the electronic search strategy used in the review by the manufacturer. The databases searched were described with dates and included MEDLINE, EMBASE, NHS Economic Evaluation Database (NHS EED) and Health Economic Evaluation Database (HEED). All searches were conducted over relevant time periods.

Stated clinical related inclusion criteria were: metastatic head and neck cancer, recurrent head and neck cancer, metastatic/recurrent SCCHN and cetuximab. These terms were combined with the following economic related terms: cost effectiveness analysis, cost benefit analysis, QALY, cost effectiveness and QoL.

Using these criteria no relevant studies were identified for inclusion in the review. Neither the MEDLINE nor the EMBASE searches identified any economic analyses in the treatment of recurrent and/or metastatic head and neck cancer. Several studies were identified by the NHS EED (n=3) and the HEED (n=15) searches. The manufacturer excluded these studies from the review.

5.2.2 Summary and conclusions

The manufacturer's review of the cost-effectiveness evidence available for cetuximab as a first-line treatment of recurrent and/or metastatic SCCHN is adequate. The ERG is confident that the manufacturer did not miss any relevant articles in its searches of the published literature. No details of any searches undertaken to identify unpublished data held by the manufacturer were presented in the MS; therefore the ERG cannot comment further on this issue.

5.3 Overview of manufacturer's economic evaluation

The purpose of the manufacturer's *de novo* economic evaluation is to estimate the cost effectiveness of cetuximab plus CTX compared to CTX alone in the treatment of recurrent and/or metastatic SCCHN and in those patients who are considered inappropriate for definitive (potentially curative) treatment with radiotherapy or surgery.

5.3.1 Description of manufacturer's economic model

A two-arm state-transition Markov model was developed to evaluate the cost effectiveness of cetuximab in addition to standard CTX alone. The course of disease is reflected by three mutually exclusive health states (stable/response; progressive; death).

Table 5.2 Classification of health states

Health state	Definition of health state	Treatment
Stable/response	No sufficient increase to qualify for progressive disease in the index lesions; AND disappearance or no significant change in non-index lesions; AND no new lesions	Patients only receive chemotherapy when in the stable/response state
Progressive	25% or more increase in the SOPD of index lesions, compared to the smallest SOPD recorded for the study period; OR Appearance of one or more new lesions and /or unequivocal progression of existing non-index lesions	Patients in the progressive disease health state receive palliative care
Death	Death from any cause	

SOPD=sum of the perpendicular dimensions

The structure of the manufacturer's model is shown in Figure 5-1.

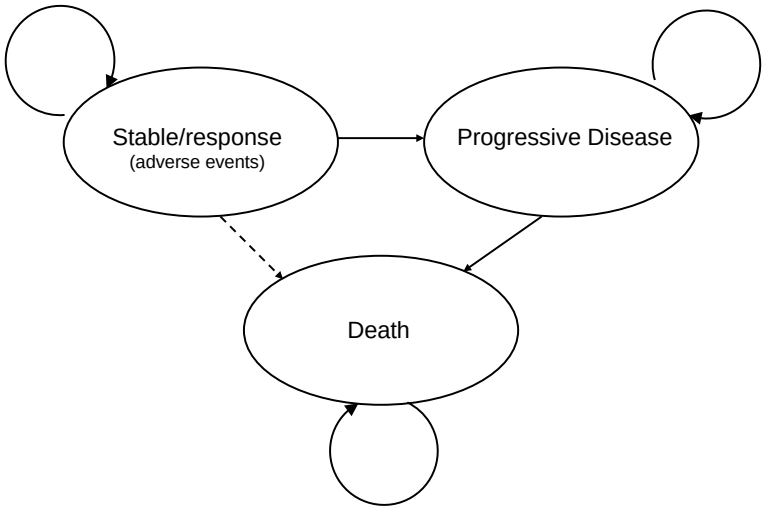

Figure 5-1 Structure of manufacturer's model

In both arms of the model patients start in the stable/response state. Every three weeks a patient can move to the progressive state, remain in the stable/response state or die (i.e. transition to the death state). No return to the stable/response state is permitted from the progressive state. The distribution of patients over the three health states over time was imputed using Weibull survival models for both PFS and OS estimated using individual patient data (IPD) from the EXTREME trial. No transition probabilities were calculated to describe the distribution of health states over time, these being implicit within the parametric survival functions. The fitted (and extrapolated) Weibull survival curves describe the proportion of patients in each health state at the beginning of each three week cycle (a half cycle correction was not used). All patients exit the evaluation in the death state.

Clinical data from the EXTREME trial were used to inform the timings, costs and transition between health states in the model. Additionally, consultation with individual clinical experts and a UK Advisory Board was undertaken to test assumptions and validate the approach.

5.3.2 Parameters and values

Key parameters and values used in the economic model are presented in Table 5.3 to Table 5.6.

Table 5.3 Distribution of patients receiving treatments by health state and treatment phase

Treatment	**Cetuximab plus CTX**				**CTX**			
	First 6 cycles		Cycle 7+		First 6 cycles		Cycle 7+	
	Stable	PD	Stable	PD	Stable	PD	Stable	PD
Cetuximab + Carboplatin + 5-FU	31.7%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Cetuximab + Cisplatin + 5-FU	68.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Cetuximab	0.0%	1.5%	100%	1.5%	0.0%	3.7%	0.0%	3.7%
Carboplatin + 5-FU	0.0%	0.0%	0.0%	0.0%	37.2%	0.0%	0.0%	0.0%
Cisplatin + 5-FU	0.0%	0.0%	0.0%	0.0%	62.8%	0.0%	0.0%	0.0%
5-FU	0.0%	4.4%	0.0%	4.4%	0.0%	2.9%	0.0%	2.9%
Bleomycin	0.0%	2.6%	0.0%	2.6%	0.0%	2.9%	0.0%	2.9%
Carboplatin	0.0%	4.4%	0.0%	4.4%	0.0%	3.7%	0.0%	3.7%
Cisplatin	0.0%	3.6%	0.0%	3.6%	0.0%	4.0%	0.0%	4.0%
Docetaxel	0.0%	4.1%	0.0%	4.1%	0.0%	4.0%	0.0%	4.0%
Gefitinib	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Methotrexate	0.0%	7.0%	0.0%	7.0%	0.0%	5.9%	0.0%	5.9%
Paclitaxel	0.0%	5.7%	0.0%	5.7%	0.0%	5.1%	0.0%	5.1%
Vinorelbine	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%

CTX=chemotherapy; PD=progressive disease; 5-FU=fluorouracil

Table 5.4 Mean utility values by health state

	Utility	Low*	High*	Source
Cetuximab plus CTX				
Stable/response	0.69	0.38	0.99	QLQ-C3O EXTREME trial
Progressive disease	0.53	0.13	0.93	QLQ-C3O EXTREME trial
CTX				
Stable/response	0.65	0.31	0.99	QLQ-C3O EXTREME trial
Progressive disease	0.51	0.10	0.91	QLQ-C3O EXTREME trial
Overall (independent of treatment)				
Stable/response	0.67	0.35	0.99	QLQ-C3O EXTREME trial
Progressive disease	0.52	0.11	0.93	QLQ-C3O EXTREME trial

*Low and high values are based on 95% confidence intervals; CTX=chemotherapy

Table 5.5 Patients receiving other treatments in progressive disease

Model variable	Value	Source
Radiotherapy in progressive disease	10.2%	EXTREME trial
Surgery in progressive disease	3.2%	EXTREME trial

Table 5.6 Costs used in economic evaluation

Model variable	Value	Source
Drug costs per 3 week cycle (base case)		
Cetuximab (initial cycle)	£2,184.00	EXTREME trial; Drug prices based on BNF55
Cetuximab (cycle 2-6)	£1,774.50	
Cetuximab (cycle 7+)	£1,774.50	
Carboplatin	£520.00	BNF55
Cisplatin	£100.44	BNF55
5-FU	£192.00	BNF55
Cetuximab + Carboplatin + 5-FU (initial cycle)	£2,896.00	
Cetuximab + Cisplatin + 5-FU (initial cycle)	£2,476.44	
Cetuximab + Carboplatin + 5-FU (cycle 2-6)	£2,486.50	
Cetuximab + Cisplatin + 5-FU (cycle 2-6)	£2,066.94	
Carboplatin + 5-FU	£712.00	
Cisplatin + 5-FU	£292.44	
Bleomycin	£77.80	BNF 55
Docetaxel	£1,069.50	BNF 55
Gefitinib	£0.00	n/a
Methotrexate	£180.60	BNF 55
Paclitaxel	£1,001.72	BNF 55
Vinorelbine	£615.92	BNF55
Radiotherapy	£1,135.93	Previous cetuximab STA report 2008 (TA145)
Surgery	£1,180.66	Previous cetuximab STA report 2008 (TA145)
Inpatient stay in medical oncology ward per day	£296.00	Chemotherapy Indicative Tariff (2007/08)
Outpatient drug administration visit	£124.66	NHS Reference cost 2004
Consultant oncologist	£87.00	Outpatient Mandatory Tariff (2007/08)
General Practitioner	£34.00	PSSRU 2007
(Clinical) nurse specialist per hour	£38.00	PSSRU 2007
CT-scan	£77.00	NHS Reference cost (2005/06)
MRI	£244.00	NHS Reference cost (2005/06)
Nurse community	£26.00	PSSRU 2007

5-FU=fluorouracil

5.3.3 Treatment effectiveness within the MS

The clinical data used in the economic evaluation are generated from the EXTREME trial and are as described in section four of this ERG report. Although the economic evaluation is trial-based, there is also a modelling component to allow extrapolation of health effects beyond the period of the trial.

Survival

As the trial data for OS and PFS were censored at 24 months and do not provide full information on the course of disease for patients still alive at that time, the manufacturer chose to extrapolate both outcomes beyond the trial period. In particular PFS curves were extrapolated to inform the transition from the stable/response health state to either progressive or death health states. The choice of the Weibull function is said to be based on two assessments: (i) goodness-of-fit and (ii) clinical expertise for the estimated values for time points after the evaluation period.

The MS (pg74) states that "...the OS and PFS curves as observed in the trial were extrapolated by fitting 2-parameter Weibull survival curves to the empirical patient level data. The scale and shape parameters of the Weibull distribution were estimated with least-square regression methods." The ERG notes that these two statements appear to be contradictory, or at best confusing. From additional information provided by the manufacturer regarding model fitting, it seems that the Maximum Likelihood method was used for model fitting (the normal procedure when analysing IPD), rather than least squares minimisation (more commonly employed when only aggregate Kaplan-Meier analysis results are available).

5.3.4 Population

The population in the economic evaluation is based on the population in the EXTREME trial. The manufacturer considers that this patient population is relevant for the economic evaluation because it reflects the population likely to be eligible for first-line treatment of recurrent and/or metastatic SCCHN. However, the ERG notes that all of the patients in the EXTREME trial are cetuximab-naive.

In the statement of the decision problem, the manufacturer states that the economics component of the MS will consider groups defined by performance status, previous treatments and response to previous treatments. The submitted economic evaluation therefore considers the following subgroups of patients: good KPS (i.e. 90 or above) and tumour sites which have been shown in the EXTREME trial to derive statistically significant benefit when cetuximab is added to CTX (i.e. oral cavity and oropharynx alone).

5.3.5 Comparator technology

The comparator assumed in the economic evaluation reflects the comparator used in the EXTREME trial (i.e. platinum based CTX). Specifically, the Merck Serono Advisory Board for Cetuximab Submissions to NICE advised the manufacturer that cisplatin plus 5-FU is the standard of care in the UK for patients in this setting.

5.3.6 Health related quality of life

The EORTC QLQ-C30 questionnaire and its head and neck module (EORTC QLQ-H&N35) were used to assess health related QoL in both arms of the EXTREME trial and the data are used in the economic evaluation. In order to express the QoL scores in QALYs, the EORTC QLQ-C30 data collected in the trial were converted into EQ-5D scores. This conversion was performed using the following cross walk algorithm:

EQ-5D = 0.633 + 0.047*Q29 - 0.124*Q3 -0.167*Q5 -0.086*Q11 -0.102*Q20 - 0.082*Q26

The manufacturer cites a published reference to a conference abstract[13] and provides details of the parameter estimates and standard error values for the cross walk algorithm. The manufacturer states that "although this algorithm was developed in patients with pancreatic cancer, the key assumption which makes it appropriate to apply this algorithm to the recurrent and/or metastatic SCCHN population in the economic evaluation, is that the type of cancer is not an effect-modifier of the relationship between EQ-5D and QLQ-C30 items outlined in the equation."(MS, pg81)

Utility values for patients in the stable/response health state were derived from all available data for patients on study treatment (n=157) excluding baseline data as patients cannot be defined as responsive at baseline. In the economic model, treatment specific utilities or overall (independent of treatment) utilities can be used for the stable/response and progressive health states (Table 5.7). In the base-case analysis, treatment specific utilities are used for stable/response, and an overall utility for progressive disease.

For patients with progressive disease, utility estimates were obtained via the QLQ-C30 global questionnaire at the final tumour assessment and were assumed in the submitted base case to be valid independent of treatment arm (Table 5.7).

Table 5.7 Utility values utilized in the economic model

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

CTX=chemotherapy

Disutilities associated with AEs were not accounted for separately because the utilities were calculated based on the responses to the QLQ-C30 global questionnaire. The patients' response to the QLQ-C30 global questionnaire is assumed to capture the impact of AEs on the patients' QoL.

5.3.7 Resources and costs

The categories of costs used in the economic model include: CTX drugs at first-line (cetuximab, cisplatin, carboplatin, folinic acid 5-FU), drug administration at first-line, treatment of AEs, palliative intent CTX drugs, palliative intent surgery, palliative intent

radiotherapy. The ERG notes that costs for treatment of adverse events are based upon those submitted to NICE by Merck Serono for consideration in the appraisal of cetuximab for locally advanced head and neck cancer.[6] Information on health care resources other than (i) drug utilisation and (ii) frequency of CTX regimens, surgery and radiotherapy were **not** collected in the EXTREME trial.

Table 5.8 Resource use employed in the model

Cost item	Description/source
Drug utilisation	Compared with data from the EXTREME trial, the extrapolation technique used in the model overestimates the number of vials of cetuximab used per patient. An adjustment was made to correct for this. Chemotherapy dose was calculated using a BSA of $1.7m^2$
Treatment related resource use	For example: inpatient stays and outpatient visits. Administration and other resources were estimated using data from Hopper et al.[14]
Adverse events	For example: pyrexia grade 3, anaemia grade 4. Costings were taken directly from those calculated for the appraisal of cetuximab in locally advanced SCCHN. Advisory Board agreed with this approach.
Other resource use (independent of treatment)	For example: consultant oncologist appointment, MRI scan, CT scan. Resource use was estimated by key opinion leaders (Advisory Board).
Palliative care	For example: palliative chemotherapy, surgery, radiotherapy. Treatment delivery resources were estimated using data from Hopper et al.[14]

MRI=magnetic resonance imaging; CT=computer tomography; SCCHN=squamous cell carcinoma of the head and neck; BSA=body surface area

The costs in the manufacturer's model are based on UK NHS reference costs and list prices from the British National Formulary 55[15] for drugs used. Merck Serono has agreed with the Department of Health to maintain the old list price of cetuximab for all patients within the NHS. This list price of £136.50/20ml vial will be uniform and applicable for all NHS prescriptions.

5.3.8 Perspective, time horizon and discounting

Costs are estimated from the **perspective** of the NHS and all relevant disease and treatment health effects to the individual are captured via QALYs. The **time horizon** chosen was a lifetime horizon so all relevant costs and benefits are accounted for in the economic model. In the model, costs and benefits are **discounted** at a rate of 3.5% in line with current NICE guidance.

5.3.9 Model validation

The manufacturer states that the model structure and assumptions were validated by a UK expert panel and provides the supporting meeting notes from the Merck Serono Health Economic Advisory Board Meeting.

5.3.10 Results included in the MS

The main results of the manufacturer's economic model are presented in Table 5.9 and Table 5.10. Incremental cost-effectiveness ratios were also calculated for subgroups and are shown in Table 5.11.

Table 5.9 Cost-effectiveness results (QALYs)

Treatment group	Total costs	QALYs gained	
Cetuximab plus CTX	£30,678	0.65	
CTX	£13,392	0.51	**Incremental cost per QALY gained**
Incremental	£17,286	0.142	**£121,367**

CTX=chemotherapy; QALY=quality adjusted life year

Table 5.10 Cost-effectiveness results (LYG)

Treatment group	Total costs	Life years gained	
Cetuximab plus CTX	£30,678	1.07	
CTX	£13,392	0.88	**Incremental cost per LY gained**
Incremental	£17,286	0.187	**£92,226**

CTX=chemotherapy; LY=life year

Table 5.11 Incremental cost-effectiveness ratios for subgroups

Incremental costs	Incremental QALYs/LYG	Cost per QALY gained/Cost per LY gained
Cetuximab plus CTX versus CTX: Oropharynx and oral cavity		
£19,867	0.189/0.254	£105,069/£78,301
Cetuximab plus CTX versus CTX: Oropharynx and oral cavity, KPS>=90		
£21,683	0.222/0.316	£97,702/£68,717
Cetuximab plus CTX versus CTX: Oropharynx		
£17,915	0.071/0.041	£250,597/£434,568
Cetuximab plus CTX versus CTX: Oropharynx, KPS>=90		
£18,242	0.059/0.026	£309,735/£695,475
Cetuximab plus CTX versus CTX: Oral cavity		
£22,658	0.354/0.550	£63,927/£41,224
Cetuximab plus CTX versus CTX: Oral cavity, KPS>=90		
£27,688	0.505/0.818	£54,791/£33,855

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

5.3.11 Sensitivity analyses

Univariate SA and PSA were conducted by the manufacturer for selected model parameters. The results of the main SA are presented in Table 5.12. Varying the cost of day case infusion and changing the utility values in the stable/response health state of the cetuximab arm have the greatest impact on the ICER.

Table 5.12 Univariate sensitivity analysis results

Variable	Base	Low input	High input	Low input ICER	High input ICER	Range of ICER from low to high inputs
Annual discount rate for effects	3.5%	0.0%		£118,009		
Annual discount rate for costs	3.5%	0.0%		£121,971		
Proportion of patients with acne like rash in cetuximab arm	7.3%	4.3%	10.3%	£121,358	£121,377	-£19
Utility - stable/response (Cetuximab arm)	0.69	0.59	0.79	£197,466	£87,606	£109,860
Utility - stable/response (Standard arm)	0.65	0.55	0.75	£96,238	£164,257	-£68,019
Utility - overall (independent of assessment) Progressive disease	0.52	0.42	0.62	£122,264	£120,484	£1,780
Cost of an outpatient attendance for grade 3/4 AE	£43.38	£36.87	£49.89	£121,364	£121,371	-£7
Cost of infusions half day outpatient and inpatient day	£124.66	£62.33	£296.00	£111,040	£149,756	-£38,716

ICER= incremental cost effectiveness ratio; AE=adverse event

The manufacturer conducted further SA in order to assess the impact of higher or lower AE costs. The AE profile report rates are similar across both treatment arms and changing the cost of an AE does not affect the size of the ICER.

For the PSA, scatter plots (incremental cost versus life years, incremental cost versus QALYs) and a cost-effectiveness acceptability curve (CEAC) were calculated as shown in Figure 5-2 and Figure 5-3.

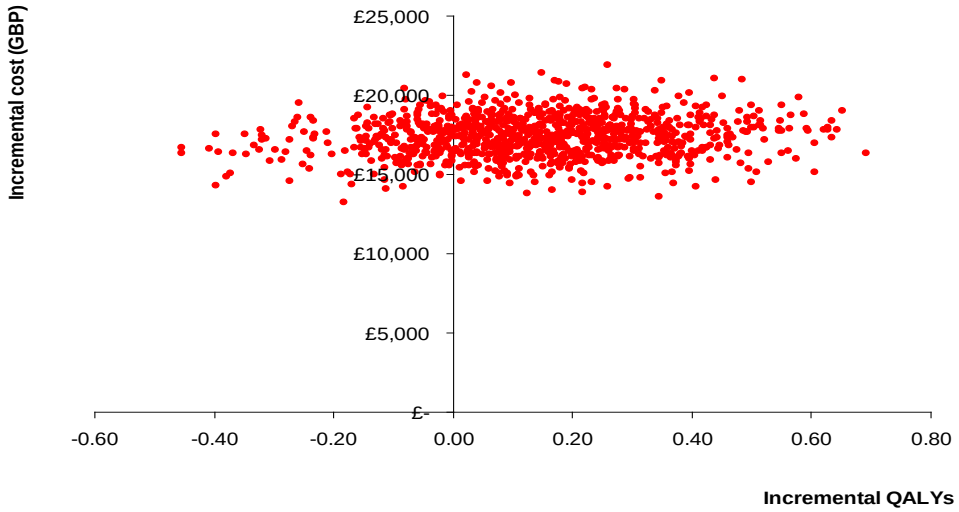

Figure 5-2 Scatter plot for incremental cost versus incremental QALY

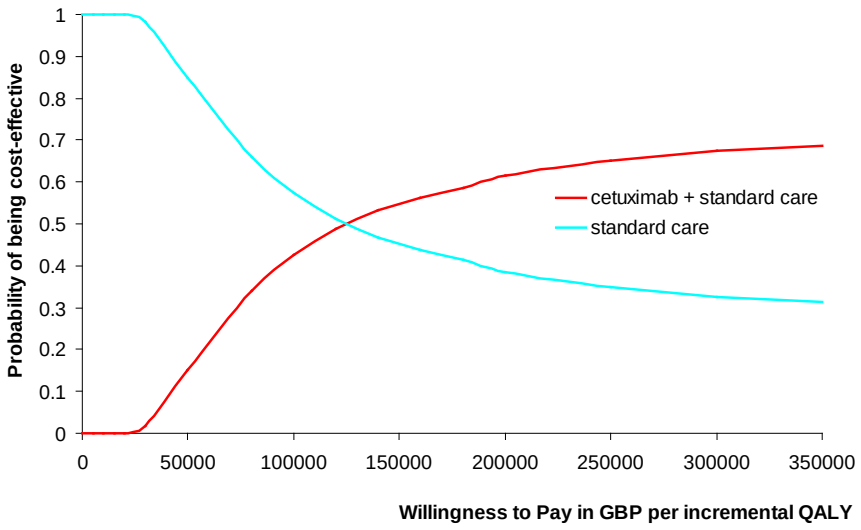

Figure 5-3 Cost-effectiveness acceptability curve

The CEAC illustrates that cetuximab plus standard CTX is unlikely to be cost effective for this group of patients even at what would usually be considered very high levels of WTP for an additional QALY.

5.4 Assessment of the manufacturer's economic model

Table 5.13 tests how closely the manufacturer's submitted economic evaluation accords with the requirements for a base case analysis as set out in the NICE reference case checklist.[16] Table 5.14 summarises the ERG's appraisal of the economic evaluation conducted by the manufacturer using the Drummond 10-point checklist.[17]

Table 5.13 NICE reference case checklist[16]

Attribute	Reference case	Does the *de novo* economic evaluation match the reference case?
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	The comparator, as confirmed by the manufacturer's Advisory Board, would be cisplatin in the NHS **IF** chemotherapy were planned for these patients
Perspective costs	NHS and Personal Social Services (PSS)	Economic evaluation is carried out from the perspective of the NHS. No PSS costs are described in the MS
Perspective benefits	All health effects on individuals	Health effects to the individual are captured via QALYs
Form of economic evaluation	Cost-effectiveness analysis	Cost-effectiveness analysis
Time horizon	Sufficient to capture differences in costs and outcomes	The time horizon chosen was a lifetime horizon so all relevant benefits and costs are accounted for in the economic model
Synthesis of evidence on outcomes	Systematic review	All outcome data are derived from a single phase III RCT (EXTREME). This is appropriate
Outcome measure	Quality adjusted life years (QALYs)	Quality of life data from the EXTREME trial were collected using the QLQ-C30 and the QLQ-H&N35. Data were cross walked into EQ-5D scores
Health states for QALY	Described using a standardised and validated instrument	Patients in the EXTREME trial completed QoL questionnaires for conversion into EQ-5D scores
Benefit valuation	Time-trade off or standard gamble	QLQ-C30 scores were converted to EQ-5D scores. Valuations within the EQ-5D are calculated using time-trade off techniques
Source of preference data for valuation of changes in HRQL	Representative sample of the public	QLQ-C30 scores were converted to EQ-5D scores. EQ-5D scores were originally estimated by a representative sample of the public
Discount rate	An annual rate of 3.5% on both costs and health effects	Benefits and costs, where appropriate, have been discounted using the 3.5% rate
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	All QALYs estimated by the economic model have the same weight
Sensitivity analysis	Probabilistic sensitivity analysis (PSA)	PSA was undertaken by the manufacturer. The ERG believes the results of the PSA to be unreliable as the degree of sample uncertainty in the model is overestimated

PSS= Personal Social Services; MS=manufacturer submission; RCT=randomised controlled trial; QoL=quality of life; QLQ=quality of life questionnaire; QALYs=quality adjusted life years; PSA=probabilistic sensitivity analysis; ERG=Evidence Review Group

Table 5.14 Critical appraisal checklist[17]

Item	Critical appraisal	ERG comment
Was a well-defined question posed in answerable form?	Yes	However, the ERG notes that the manufacturer restricted the evaluation to first-line treatment only
Was a comprehensive description of the competing alternatives given?	Yes	The manufacturer describes cisplatin plus 5-FU as the relevant comparator. In the EXTREME trial, cisplatin plus 5-FU or carboplatin plus 5-FU is administered to patients.
Was the effectiveness of the programme or services established?	Yes	Evidence from the EXTREME trial demonstrated the clinical effectiveness of cetuximab plus CTX over CTX for the trial period. The manufacturer failed to provide adequate information regarding projective modelling. As a result, the ERG was not able to test its concerns about some of the assumptions used by the manufacturer to extrapolate costs and benefits
Were all the important and relevant costs and consequences for each alternative identified?	Not always	For example, price adjustments were performed for cetuximab vial use but no similar analyses were performed for cisplatin or carboplatin CTX
Were costs and consequences measured accurately in appropriate physical units?	Not always	For example, the BSA value used to calculate CTX costs was underestimated in the MS
Were the cost and consequences valued credibly?	Not always	For example, a wide range of diverse and out-of-date cost sources were used for the calculation of adverse events in the MS
Were costs and consequences adjusted for differential timing?	Mostly	The method of discounting was not employed appropriately at all times (e.g. when treatment cycles bridged two years)
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	ICERs (cost per QALY gained and cost per LYG) have been presented for the base case and several subgroups. As a result, the clinical effectiveness of cetuximab plus CTX for patients with metastatic disease has been raised by the ERG
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	Univariate SA and PSA have been undertaken by the manufacturer. The ERG believes the results of the PSA to be unreliable as the degree of sample uncertainty in the model is overestimated
Did the presentation and discussion of study results include all issues of concern to users?	No	Very limited quality of life data were presented in the MS. Given that patients with recurrent and/or metastatic disease are seriously ill, this omission is noticeable.

ERG= Evidence Review Group; CTX=chemotherapy; BSA=body surface area; MS = manufacturer submission; SCCHN=squamous cell head and neck cancer; QALY=quality adjusted life year; LYG=life year gained; SA=sensitivity analysis; PSA=probabilistic sensitivity analysis; ICER=incremental cost-effectiveness ratio

5.5 Detailed critique of manufacturer's economic model

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

5.5.1 Structure and assumptions

Modelling rationale

There is a basic question to be considered concerning the validity of creating an economic model for this STA, particularly since there is only one set of clinical trial results showing mortality in the follow-up period covering 75-80% of enrolled patients (Table 14.2-6.1 of the EXTREME Clinical Study Report). The justification for projective modelling in the MS (pg 71) is as follows:

"This type of model was used to make full use of the available clinical trial data. The model estimates overall survival through an extrapolation of trial results beyond the trial period in order to capture costs and benefits for the expected duration of the patients' life time."

Although at first sight this argument appears to be appropriate in relation to the NICE Reference Case[16] (lifetime assessment), the use of simulation derived from a single data source rather than employing the observed data directly is vulnerable to challenge, since the modelling process introduces additional uncertainty to that already inherent in the trial itself. Moreover, there is little to be gained by evidence synthesis in this situation since there is only one source of outcomes data. The potential problem with projective modelling of OS in such a case is that it is more likely to exaggerate health gains than to underestimate them, leading to an overoptimistic result. This is particularly relevant for late-stage disease where no claim is made to provide a cure, merely to modify the timing and process of progression. In such cases, benefit often takes the form of a limited period of reduced risk after which disease progression resumes as before, so that virtually all the outcome gain will have been realised well before the final patient dies.

This issue is discussed in section 5.5.2 in relation to the details of the projective modelling carried out to inform the submitted model. However, the ERG notes that there is a strong theoretical case to be answered here as to the appropriateness of modelling since many health economists would prefer to carry out direct evaluation of trial data when there is only evidence from a single RCT available.

Health states

The model is based on a very simple Markov structure involving two health states for surviving patients - stable/response and progressive disease. Once a patient has entered the latter state no return to the stable/response state is allowed. This basic structure is probably adequate for this group of patients with very advanced disease, and a generally poor prognosis.

Mid-cycle correction

No mid-cycle correction was employed in the submitted model, on the grounds that the cycle length is short (21 days). The omission of this feature in Markov models may affect cost-effectiveness results directly through systematically over or under-estimating costs and outcomes (depending on whether values for the start or end of a cycle are taken as representative of the whole cycle). However, it can also result in confusion over which quantities represent point estimates and which are appropriate for period calculations leading to unpredictable consequences.

To test the direct effect of omitting a mid-cycle correction on the submitted base case results, the logic for OS and QALYs was amended, averaging estimates for the start and end of each cycle. Similarly, costs for all cycles beyond the trial period (cycles 7+) were recalculated based on the average number of patients alive in each cycle. Costs in the first six cycles required more specific adjustments. Platinum treatment costs including drug administration were related to the number of patients alive at the beginning of each cycle, whereas the cost of cetuximab and the extra cost of administering cetuximab were re-estimated for the number of patients treated at the beginning of each relevant week in cycles 1-6.

These alterations led to a reduction in overall incremental costs of £1,101 per patient and a very small reduction in outcomes (-0.0011 QALYs). As a result the cost-effectiveness ratio is reduced by £6,884/QALY to £114,484 per QALY gained.

Adverse event frequency

Where a clinical trial is the source of information on the frequency, duration and severity of AEs for an economic model, some detailed and complex analysis of the individual patient data is required if the model is to fairly represent the impact of AEs on treatment costs and patient outcomes. Evidence submitted,[18] by Merck Serono, to inform the earlier NICE technology appraisal of cetuximab for the treatment of loco-regional SCHNN[6] described a detailed analysis of this type. This allowed the modellers to take account of multiple AEs for

the same patient, of AEs of different severity and duration, and of coincident AEs with combined effects on QoL and treatment costs (i.e. avoidance of double-counting).

The AE frequency parameter values used in the manufacturer's model for this current appraisal are drawn from a single table in the EXTREME Clinical Study Report (Table 14.3.1-3.3). The Clinical Study Report was provided electronically by the manufacturer. The ERG requested in its letter of clarification to the manufacturer further information concerning the definitions relating to the results displayed in the table as follows: "Please provide further clarification of the meaning of the AE rates used in the model (for example does the AE data refer to the number of events, or the number of patients for whom any event occurred at any time?"). However, no clarification was provided by the manufacturer, who responded "The clinical relevance of these rates was validated by the Merck Serono Health economic advisory board held on 22nd July 2008."

In the absence of a full analysis of AE experience, some caution may be necessary in interpreting the various aspects of the economic model results which rely on the aggregate AE frequencies.

5.5.2 Treatment effectiveness

Parametric modelling of overall survival and progression free survival

Data collection in the EXTREME trial was stopped at 24 months follow-up, and the model has been constructed using parametric survival projection models of OS and PFS to extend the analysis until death for all patients. The use of this procedure may be questioned on two grounds:

1) *Can the choice of functional form of each survival model (2 trial arms x 2 outcomes) be justified on objective grounds?*

The MS did not provide an adequate explanation of why the Weibull function was chosen for all survival models in the base case, as well as in all six subgroup analyses. It is normal to carry out comparative model-fitting exercises for a range of candidate models, using objective criteria for assessing suitability on statistical grounds. Moreover, graphical evidence of the appropriateness of the fitted models was only provided in relation to the base case overall analysis.

Further detailed information was requested by the ERG via the original letter of clarification and charts were then provided by the manufacturer showing the Weibull model survival

function superimposed on the Kaplan-Meier survival curve for each of the populations used in the submitted economic model. However, none of the requested supporting statistical information from the Kaplan-Meier analyses was made available by the manufacturer, notably the estimated mean survival with confidence limits, and the number of patient records included in each analysis. The manufacturer explained that the Weibull model was found to fit the available data slightly better than either the lognormal or the log-logistic functions for the overall trial population, and to provide more clinically realistic projected mean survival values.

Visual examination of the subgroup charts suggests that there may be a systematic mismatch between the Weibull model and the observed data in the middle time period (150-400 days), especially for PFS, and that this may result in an overestimate of the mean expected PFS in both control and intervention arms, though it is not clear whether this would seriously impact on the incremental PFS.

It is apparent that there are small numbers of patients within some of the subgroups and that model-fitting in these instances may not be reliable.

2) *Is projection of differential outcomes and costs beyond the observed data valid?*

It can be argued that in some cases projection modelling of outcomes and costs may not be appropriate, especially where the Kaplan-Meier survival curves have converged closely, and there is no *a priori* reason to expect them to diverge significantly at a later time. Under such circumstances, truncating the analysis at the point when the trial was terminated may be considered necessary to avoid the risk of spurious artefactual differences arising from ill-advised projection.

An analysis was carried out by the ERG using the submitted base case model to compare costs and outcomes at 24 months (end of the follow-up period). Both net discounted incremental costs per patient and incremental patient utility were considerably reduced (-£526 per patient and -0.029 QALYs per patient) resulting in a large increase in the estimated ICER from £121,367 to £147,817 per QALY gained. This indicates the sensitivity of cost-effectiveness estimates to assumptions concerning projection modelling.

5.5.3 Health related quality of life and utility

Selection of health state utilities

Utility values were not measured directly in the EXTREME trial. However the EORTC generic cancer quality of life instrument (QLQ-C30) with head and neck specific module (QLQ-H&N35) was administered, and a basic mapping exercise was carried out in which selected generic items were used to estimate EQ-5D values.

The submitted baseline model uses different mean utility values for patients in the two trial arms when in the stable/response state, but uses a single overall average utility estimate for all patients in the progressive disease state. At the same time, no disutility is accounted for from AEs occurring under CTX. This is justified on the assumption that these are automatically included in the state values. The importance of these assumptions can be seen by comparing cost-effectiveness results under the four different combinations of overall or treatment-specific values available in the model.

Table 5.15 Health state utilities and cost per QALY

Utility values in stable/response: progressive states	Incremental QALYs	Incremental cost/QALY gained
Treatment-specific : Overall (submitted base case)	0.142	£121,367
Treatment-specific : Treatment-specific	0.153	£113,149
Overall : Treatment-specific	0.134	£128,658
Overall : Overall	0.124	£139,390

The weaknesses of the QoL aspect of the EXTREME trial are evident from the poor response rates and the wide confidence limits reported for baseline observations which cover most of the available scale range (0.25-1.00). In addition, this uncertainty is compounded by the uncertainty inherent in the mapping function used to convert EORTC QLQ-C30 data to EQ-5D values. It is clear that the difference between trial arms cannot be considered statistically significant at any stage - at trial baseline, in the stable/response state or in the progressive disease state. It is therefore difficult to justify using separate estimates at any point in the analysis. If combined estimates are used throughout, the estimated outcome gains are noticeably lower than in the submitted results, and the cost-effectiveness ratio rises to over £139,000 per QALY gained. However, this also calls into question the assumption that any disutility difference associated with CTX is included in separate treatment-specific state utility values.

Disutility from adverse events

Four AEs were identified in the EXTREME trial report for which important differences in incidence occurred between the trial arms; anaemia (7.2% less with cetuximab), mucositis/stomatitis/dysphagia (3.4% more with cetuximab), nausea/vomiting (6.4% more with cetuximab) and acne/rash (7.3% more with cetuximab). No mapping exercises have been reported between EORTC QLQ-C30 and EQ-5D at this level of detail, and the mapping algorithm used in the MS did not involve the items in the EORTC instrument relating to these specific AEs. However, a study[19] on lung cancer patients reported details of a linearised quality of life scale derived from the EORTC questions, which provides specific weights for most of the QLQ-C30 items. A comparison between weights in the Kind[13] mapping algorithm and those in the Bagust paper[19] indicate close correspondence for those items not related to mobility, suggesting that the Bagust weights[19] could be useful to proxy missing disutility estimates for key AEs. An exploratory analysis of overall AE impact on estimated EQ-5D was carried out by the ERG on this basis, which indicated that the net difference is probably very small amounting to an improvement of about 0.005 on the EQ-5D scale for patients receiving cetuximab (disutility of 0.051 for cetuximab plus CTX versus 0.056 for CTX). A justification offered by the manufacturer in support of using treatment-specific utility estimates is that this incorporates improvements from a better AE profile. The ERG exploratory exercise suggests that the size of difference between values employed in the model (0.04 in the stable/response state) is much larger (eight times) than that which could reasonably be expected.

If the manufacturer's argument for treatment-specific utilities in the pre-progression state is rejected, then a minor adjustment for AEs may be applied to the overall utility for the cetuximab arm. Applying this difference to the six cycles of trial medication yields a net expected utility gain from use of cetuximab of about 0.00185 per patient. The impact of this amendment can be gauged by applying it to the submitted base case leading to a smaller ICER by about £1,500 per QALY (from £121,367 to £119,808 per QALY gained).

5.5.4 Resources and costs

Chemotherapy costs

Most of the CTX treatments administered to head and neck cancer patients are dosed on the basis of the body surface area (BSA) of the individual patient. The submitted model does not take account of BSA differences between patients, including those due to gender. In addition, the fixed average value used ($1.7m^2$) significantly underestimates the values found for UK

head and neck cancer patients (males: 1.85 m^2; females: 1.65$m^{2)}$ which were identified from a recent survey[20] of three UK cancer centres. These figures, weighted for the gender balance shown in the EXTREME trial, yield a mean BSA of 1.83m^2. The costs of CTX drugs per cycle in 13 regimens were re-estimated using this BSA value and are shown in Table 5.16.

Table 5.16 Chemotherapy costs per cycle

Treatment	Submitted cost per cycle	Re-estimated cost per cycle
Cetuximab + carboplatin + 5-FU (initial cycle)	£2896.00	£3229.14
Cetuximab + cisplatin + 5-FU (initial cycle)	£2476.44	£2819.70
Cetuximab + carboplatin + 5-FU (cycle 2-6)	£2486.50	£2854.07
Cetuximab + cisplatin + 5-FU (cycle 2-6)	£2066.94	£2444.64
Cetuximab	£1774.50	£2453.05
Carboplatin + 5-FU	£712.00	£776.09
Cisplatin + 5-FU	£292.44	£366.65
5-FU	£192.00	£256.09
Bleomycin	£77.80	£90.83
Cisplatin	£100.44	£110.56
Docetaxel	£1069.50	£1104.22
Paclitaxel	£1001.72	£1013.81
Vinorelbine	£615.92	£828.53

The overall effect on the submitted base case analysis of using these improved parameter estimates is to increase the incremental cost per patient by £3,155 per patient, resulting in an increase in cost-effectiveness ratio of £22,152 per QALY gained to a revised base case ICER of £143,519 per QALY gained.

Choice of platinum-based chemotherapy

The EXTREME trial allowed clinicians a choice between cisplatin and carboplatin for platinum-based CTX, and the base case model analysis uses the observed trial proportions (31.7% carboplatin in the intervention arm and 37.2% in the control arm). Clinical advice indicates that cisplatin is used in almost all cases in the UK. Substituting 100% cisplatin use into the submitted model increases the incremental cost per patient by £46, and the cost-effectiveness ratio by £325 per QALY gained.

Adjustment for missed doses of cetuximab

The submitted model incorporates a reduction factor which is applied to the full calculated use of cetuximab (based on the number of patients alive at the beginning of each cycle) to approximate to the lower actual use recorded in the EXTREME trial. This accounts for the combined effects of missing or delayed doses and dose reductions, and is fully justified when carrying out a cost-effectiveness analysis. However, the functional form of the fitted equation

is not well-suited to the data, being based on a quadratic polynomial function of the patients alive at the start of each cycle. The ERG has calibrated an alternative formulation, which involves an exponential function with a non-zero 'floor' to model the observed proportion of full usage; and this was found to fit the observed trial data better. Substitution of the ERG revised adjustment factor in place of the factor originally proposed leads to increased incremental costs by £118 per patient and an increase of £831 per QALY in the base case cost-effectiveness ratio.

Adjustment for missed doses of cisplatin/carboplatin

In principle the same sort of adjustment should be made for actual trial use of carboplatin and cisplatin to ensure that costs for both the intervention and the comparator are being estimated on the same basis. Information available from the EXTREME Clinical Study Report allowed the ERG to estimate the size of this effect for the first six cycles of treatment. This amendment reduces the incremental cost in the base case by £27 per patient, reducing the ICER by £191 per QALY gained.

N.B. These two adjustments relate only to the costs of the therapeutic agents, and not to the costs of administration. The reprogramming required to adjust the latter element is too complex to be undertaken by the ERG in the time available.

Radiotherapy and surgery costs

The costs of post-trial radiotherapy and surgery are estimated from Table 14:1-14 of the EXTREME Clinical Study Report, which shows the number of patients receiving various interventions after the trial treatment. There are two potential problems with the use of these data.

1) The proportions used do not relate to the number of treatment events, and therefore costs calculated on this basis attach only to the first such event, any subsequent events not being accounted for. This approach may understate the true cost of such interventions, and potentially result in bias if the total number of resource consuming events is not evenly balanced between the trial arms. It is not possible to draw any conclusions on this issue without access to more accurate trial data, however the size of any bias is likely to be too small to influence cost-effectiveness results.

2) The model authors have assumed that radiotherapy and surgery costs are equivalent between the trial arms and have pooled the observed data to obtain a single incidence rate to

be applied equally to both arms of the evaluation. The reported differences in proportions of affected patients are not statistically significant suggesting that this assumption is probably valid.

Unit costs

The unit costs used in the manufacturer's submitted model are drawn from the MS[18] (Table 5 of Technical Appendix 1 for adverse event costs) for the previous technology appraisal of cetuximab for locally advanced SCCHN.[6] They are based on an eclectic mix of sources, using different years: NHS Reference Costs for 2004 and 2005/6, Inpatient Indicative tariff and Outpatient Mandatory tariff for 2007/8, PSSRU 2007, BNF 50 and 55 for drug costs and a published paper[21] for platelet transfusion costs in 2000/1. In order to assess the effect of using a reasonably consistent price base for costs, the ERG has identified more appropriate sources as follows:

- NHS Reference Costs for 2006/7[22] for inpatient, outpatient and investigations

- PSSRU 2007[23] for primary care costs

- British National Formulary 56[24] (2008) for drug costs

- Blood Transfusion Service prices for 2007/8[25], adjusted to 2006/7 prices assuming 4% inflation for transfusions.

The submitted unit prices are compared with the updated prices in Table 5.17 and Table 5.18, and show increases in all hospital costs except for imaging procedures which shows price falls. The combined effect of these changes to the submitted base case is to increase the incremental cost per patient by £1,566, resulting in an increase in the cost-effectiveness ratio of £10,993 to £132,361 per QALY gained.

Table 5.17 Unit cost revisions updating to consistent price base - hospital and community costs

Item	Submitted unit cost	ERG revised unit cost	Source
Inpatient stay - medical oncology	£296.00 per day	£320.92 per day	**2006/7 NHS Reference Costs for non-elective inpatient episodes** a) CZ23W/X/Y Major Head, Neck & Ear Disorders 19+ years OLS model to estimate daily rate of £296.82 b) CZ24O/P/Q Complex Major Head, Neck & Ear Disorders 19+ years OLS model to estimate daily rate of £411.90 Weighted average by casemix volumes of (a) & (b) = £320.92
Outpatient drug administration visit	£124.66 per visit	£189.44 per visit	**2006/7 NHS Reference Costs for outpatients** SB15Z Deliver subsequent element of a chemotherapy cycle
Consultant Oncologist	£87.00 per consultation	£106.71 per consultation	**2006/7 NHS Reference Costs for outpatients** 370 Medical Oncology (attendance without treatment)
General Practitioner	£34.00 per consultation	£34.00 per consultation	**PSSRU 2007** p.127 (unchanged)
Nurse Specialist	£38.00 per hour	£38.00 per hour	**PSSRU 2007** p.125 nurse advanced (unchanged)
CT scan	£77.00 per procedure	£71.88 per procedure	**2006/7 NHS Reference Costs** CT Scan of one area - weighted average of RA08Z/RA09Z/RA10Z by casemix volume
MRI	£244.00 per procedure	£146.84 per procedure	**2006/7 NHS Reference Costs for outpatients** MRI Scan of one area - weighted average of RA01Z/RA02Z/RA03Z by casemix volume
Nurse community	£26.00 per hour	£26.00 per hour	**PSSRU 2007** p.122 (unchanged)

Table 5.18 Unit cost revisions updating to consistent price base - adverse event cost components

Component	Submitted unit cost	ERG revised unit cost	Source
Hospitalisation episodes			
Anaemia (grade 3/4)	£930.04	£943.74	**2006/7 NHS Reference Costs for non-elective inpatient** PA48B Blood Cell Disorder without complicating condition
Febrile neutropenia (grade 3/4)	£1,337.42	£2,867.69	**2006/7 NHS Reference Costs for non-elective inpatient** PA45Z Febrile Neutropenia with Malignancy
Non-febrile neutropenia (grade 3/4)	Not used - all neutropenia costed as febrile	£599.25	**2006/7 NHS Reference Costs for non-elective inpatient** WA02Y Disorders of immunity without HIV/AIDS or complications
Fever/infection (grade 3/4)	£2,206.53	£2,001.74	**2006/7 NHS Reference Costs for non-elective inpatient** Weighted average of PA16A & PA16B Major infection with/without complications
Mucositis/stomatitis/ dysphagia (grade 2)	£1,818.27	£1,967.88	**2006/7 NHS Reference Costs for non-elective inpatient** CZ24Q Complex major Head, Neck or Ear diagnoses without complications
Mucositis/stomatitis/ dysphagia (grade 3/4)	£3,035.70	£2,817.21	**2006/7 NHS Reference Costs for non-elective inpatient** Weighted average of CZ24O & CZ24P Complex major Head, Neck or Ear diagnoses with complications
Nausea & vomiting (grade 2)	£702.40	£748.11	**2006/7 NHS Reference Costs for non-elective inpatient** FC05C General Abdominal Disorders without complications
Nausea & vomiting (grade 3/4)	£1,099.06	£1,128.93	**2006/7 NHS Reference Costs for non-elective inpatient** Weighted average of FC05A & FC05B General Abdominal Disorders with complications
Medications			
Anti-fungal mouth rinse	£4.01	£4.01	**BNF 56**: Difflam 300ml
Anti-emetic	£4.86	£3.48	**BNF 56**: Domperidone 10mg x 100
Anti-pyretic	£0.21	£0.17	**BNF 56**: Paracetamol 500mg x 16
Topical anti-bacterial	£22.24	£22.24	**BNF 56**: Zineryt 90 ml
Oral anti-bacterial	£21.24	£21.14	**BNF 56**: Minocin MR 100mg x 56
Topical corticosteroid	£6.36	£6.36	**BNF 56**: Diprosone 100mg
Procedures			
Platelet transfusion[#]	£84.22	£200.00	**BTS 2007/8 price list:** £208.46 - remove inflation from 2006/7 of about 4%

This only accounts for the cost of one therapeutic dose of platelets. The submitted model does not include the cost of delivering the transfusion.

5.5.5 Discounting

Adverse event costs

All AE costs are estimated as a single average figure per patient and attributed to the first treatment cycle. As a result, there is no discounting applied in the submitted model to any AEs, regardless of when they occur. In view of the relatively small differences in AE rates between trial arms, most of which occur in the first few months, it is unlikely that this simplification will have any material effect on the economic results.

Discounting method

The method used for discounting both costs and outcomes involves assigning a treatment year number to the time (in days) of the first day of each cycle. This method is accurate for costing treatments delivered only on the first day of each cycle (such as CTX), however for costs spread across the cycle (including cetuximab treatment) and also for outcomes, this method is inaccurate for those cycles which begin in one discounting year and end in the next. The original logic for calculating the discounting year has been amended by the ERG to allow a more accurate discounting factor to be used and this has been applied to all costs and outcomes.

This change has no effect on costs of trial medication given in the first year. Using the revised logic produces minor changes in results for the submitted base case: both discounted incremental costs and outcomes are reduced slightly, resulting in a small increase in the cost-effectiveness ratio (+£69 per QALY gained).

5.5.6 Sensitivity analysis

Univariate sensitivity analysis

The MS contains two tables (H23 and H24) showing results of variations in a selection of model parameters. These include discount rates, utility values, the incidence of rash when treated with cetuximab, the costs of administering treatments, and the costs of AEs. The analysis shows that ICERs are most sensitive to administration costs and to utility values in the pre-progression state.

It is notable that no univariate SAs were carried out in relation to the most important aspects of the analysis: the estimated OS time, and the effect of inter-patient dosing variability on treatment costs.

Probabilistic sensitivity analysis

The outcome gains obtained from the submitted economic model are dependent on the Weibull model parameters used for projecting OS and PFS until death. In order to incorporate uncertainty in these parameters into the PSA, estimated standard errors for each parameter are employed independently to simulate uncertainty about central estimates. However, parameter estimates for the Weibull distribution obtained by fitting to observed data are often strongly negatively correlated, and should be simulated jointly taking full account of covariance. Additional information provided by the manufacturer has allowed parameter correlations to be calculated for nine separate patient populations/subgroups drawn from the EXTREME trial. These show moderately significant correlations ($p < 0.1$) affecting all nine patient groups, and strongly significant correlations ($p < 0.05$) affecting five patient groups. Progression free survival models are more frequently implicated than OS models (nine PFS models are affected versus two OS models).

Furthermore Weibull parameters for OS and PFS have been estimated separately from the same patient data. It is highly likely that OS and PFS will be strongly positively correlated (since PFS is part of OS), so that covariance between the two sets of Weibull parameter estimates cannot be ignored and, ideally, model parameters for PFS and OS should be jointly estimated. The manufacturer has confirmed that OS and PFS models were developed independently in all cases. The central estimate of the cost-effectiveness ratio may not be affected to any great degree by this problem, but any assessment of the associated uncertainty will not be trustworthy, since variance in the distribution of uncertainty is most probably overstated within the PSA.

No attempt was made to incorporate uncertainty in the assumed value of the mean BSA, used in the calculation of treatment costs, in the PSA. As noted above this can have an important influence on model results and should feature in any PSA.

Taken together, these omissions suggest that the submitted PSA results should not be considered reliable for decision-making.

5.5.7 Model validation

The MS reports that validity of the model structure and assumptions was endorsed by the Advisory Board of consultant oncologists and manufacturer representatives. No information was provided to describe what steps were taken to ensure internal validity of the model with respect to the realisation of the design and assumptions in the Excel workbook, or the verification of specific model outputs against published trial results. The model itself does not show evidence of built-in validation features.

6 SUMMARY OF ADDITIONAL WORK BY ERG

6.1 Base case results

Table 6.1 shows the submitted base case cost-effectiveness results for cetuximab plus CTX versus CTX, together with the individual effect of applying the ten separate model amendments recommended by the ERG. Finally the combined effects of these amendments are presented. Full details are available in Appendix 2.

Table 6.1 ERG modifications

Model / amendment	Incremental costs	Incremental survival	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 most influential changes to costs arise from the recalculation 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 is the main alteration to outcomes. If the analysis is limited to 24 months, outcome gains are reduced proportionately more than incremental costs, resulting in larger increases in the calculated ICERs.

6.2 Subgroup analyses

Six patient subgroups identified from the EXTREME trial are featured in the manufacturer's submitted model, based on three tumour site groups divided between two performance status categories. Table 6.2 presents cost-effectiveness results for each, as submitted and also incorporating ERG preferred corrections and/or amendments. Full details are available in Appendix 2. In all cases the results indicate that cetuximab is less cost-effective with ERG model and parameter corrections and/or amendments incorporated, than when submitted. The most promising subgroup (oral cavity with good KPS) remains outside the range which would normally be considered cost effective by NICE.

It is also worth noting that no indication is given in the MS of the number of EXTREME patients available for analysis in each subgroup. The ERG considers it likely that at least some of these subpopulations are too small to yield reliable projection models, casting doubt on the credibility of these cost-effectiveness results.

Table 6.2 Summary of cost effectiveness for patient subgroups included within the manufacturer's original submitted model

Subgroup / model	Incremental costs	Incremental survival	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

In the original letter of clarification the manufacturer was asked to provide additional cost-effectiveness results for subgroups defined by the presence/absence of metastatic disease. The results supplied are summarised in Table 6.3. However, without further information on the model survival parameters used to generate these results it was not possible to apply the ERG recommended corrections and/or adjustments to these subgroups. Therefore the ERG made a second request for further details relating to the metastatic and recurrent (non metastatic) patient subgroups. The manufacturer provided new information which allowed the ERG to extend the submitted model to include these additional subgroup populations, leading to new results based on the ERG recommended corrections and/or adjustments to the submitted model. These are displayed in Table 6.4 and indicate worsened economic results, as might be anticipated from results for other subgroups (Table 6.2). Full details are available in Appendix 2.

Table 6.3 Additional subgroup cost-effectiveness results provided by the manufacturer (without ERG corrections and adjustments)

Subgroup	Incremental costs	Incremental survival	Incremental QALYs	Incremental cost/LY gained	Incremental cost/QALY gained
Metastatic (including recurrent)					
Submitted	£14,539	-0.015	0.026	-£947,649	£562,849
Metastatic (excluding recurrent)					
Submitted	£13,469	-0.088	-0.046	-£153,122	-£295,134
Recurrent patients (non metastatic)					
Submitted	£18,758	0.308	0.215	£60,939	£87,099

QALYs=quality adjusted life years; LY=life years

Table 6.4 Additional subgroup cost-effectiveness results provided by the manufacturer with ERG corrections and adjustments applied

Subgroup / model	Incremental costs	Incremental survival (years)	Incremental QALYs	Incremental cost/ LY gained	Incremental cost/ QALY gained
Metastatic disease					
Submitted	£14,539	-0.015	0.026	-£947,649	£562,849
ERG - full life	£15,800	-0.015	0.013	-£1,037,600	£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

Within the second set of responses provided by the manufacturer, anonymised IPD were available for OS and PFS for metastatic and recurrent (non metastatic) subgroups. This allowed the ERG to carry out Kaplan-Meier analyses and derive clinical effectiveness

estimates and confidence intervals directly from the EXTREME trial observations, without modelling assumptions. These are shown in Table 6.5 and reveal quite different patterns of treatment responses between the two subgroups:

- for patients with recurrent disease a significant and similar survival benefit is evident for both OS and PFS, implying that the effect of cetuximab is to delay the onset of disease progression, without affecting the course of the disease post progression;

- for patients with metastatic disease there is a small and statistically non-significant improvement in OS and a larger significant gain in PFS, implying that the effect of cetuximab is to delay the onset of disease progressions but results in a reduction in survival after disease progression.

Table 6.5 Kaplan-Meier estimates of OS and PFS effectiveness for metastatic and recurrent disease subgroups

Patient population	**Overall survival (months)**			**Progression free survival (months)**		
	Mean cetuximab +CTX	Mean CTX only	Gain due to cetuximab (95% CI)	Mean cetuximab +CTX	Mean CTX only	Gain due to cetuximab (95% CI)
All patients	11.71	9.73	1.98 (0.90, 3.06)	6.25	4.09	2.16 (1.58, 2.74)
Metastatic disease	11.66	11.18	0.48 (-1.21, 2.17)	5.81	4.55	1.26 (0.49, 2.04)
Recurrent disease (non metastatic)	11.40	8.49	2.91 (1.62, 4.21)	6.56	3.66	2.90 (2.10, 3.70)

CI=confidence interval; CTX=chemotherapy

The results for the metastatic subgroup appear to be counter-intuitive. In particular it is noticeable that the reason for the lack of OS gain for this group is the very strong performance of patients in the control arm and not lack of clinical effect of cetuximab in the intervention arm. Several possible factors may be contributing to this phenomenon. Metastatic patients may have only been considered for CTX if they were exceptionally fit relative to recurrent patients. Alternatively, there may be a casemix bias operating in relation to prior treatments, (e.g. some metastatic patients may not have had prior radiotherapy).

In summary, on economic grounds the EXTREME trial does not appear to support the use of cetuximab for patients with metastases (with or without recurrence), since the modelling lends no support to a meaningful clinical benefit (either in terms of survival or QoL) from its use in addition to CTX. Moreover, there are grounds to question the reliability of the clinical outcomes reported for metastatic patients as a whole since they appear to be a heterogenous

group (evidenced by greater in-group variance in the control arm). Nor does the EXTREME trial appear to support the use of cetuximab for patients with recurrent disease despite evident health gains as the ICER falls outside of NICE's current acceptability range (£20,000 to £30,000 per QALY).

6.3 Threshold analysis

It is instructive to consider what unit cost for a vial of cetuximab would generate an estimated ICER within the NICE guidance range of cost effectiveness (£20,000 - £30,000 per QALY gained). Based on the amended base case with full life projection shown in Table 6.1, an incremental cost of £20,932 per patient from use of cetuximab with CTX can be expected. This can be analysed to its constituent parts as follows:

Cost of cetuximab	+ £16,223
Cost of other treatments	+ £7
Cost of CTX administration	+ £4,480
Treatment independent costs	+ £334
Adverse events costs	- £112
Total incremental cost per patient	**+ £20,932**
Overall outcome gain per patient	+0.1259 QALYs

Thus £4,709 per patient of the overall incremental cost is independent of the price of cetuximab. The minimum possible ICER achievable (corresponding to zero cost of cetuximab acquisition) is therefore £4,709 / 0.1259 or £37,403. Since this falls outside the 'willingness to pay' range considered cost-effective within the NICE methods guide[16] (£20,000 to £30,000 per QALY gained) it appears that use of cetuximab may not be cost-effective at any price. There are three contributory processes influencing this result:

- since cetuximab requires more frequent administration than CTX 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 is associated with better survival, patients experience a longer period during which they are eligible to gain benefit from other follow-on treatments and palliative care, all of which involve additional NHS costs.

6.4 Summary of cost-effectiveness evidence

6.4.1 Economic evaluation results

Base-case: Manufacturer

- The manufacturer reports an ICER of £121,367 per QALY gained for the comparison of cetuximab plus CTX versus CTX. The manufacturer reports an ICER of £92,226 per LYG for the comparison of cetuximab plus CTX versus CTX.

- Results of the PSA conducted by the manufacturer suggest that, based on current assumptions and evidence available, cetuximab plus CTX is unlikely to be cost-effective at a WTP of £30,000 per QALY gained.

Base-case: ERG

- A number of key issues and parameters in the economic model do not seem to be justified. After individual model assumptions are corrected and /or adjusted, the ICER for the base case comparison ranges from £114,484 to £147,817 per QALY gained.

- When all of the corrections and/or adjustments are made simultaneously using a lifetime model the ICER is approximately £166,307 per QALY gained. When all of the corrections and/or adjustments are made simultaneously at 24 months (i.e. no extrapolation), the ICER is approximately £208,266 per QALY gained.

- The ERG does not consider the manufacturer's PSA to be reliable as it excludes some important variables and fails to account for potentially important parameter covariances.

6.4.2 Economic issues and uncertainties

- The ICERs submitted by the manufacturer are high and fall outside of the cost-effectiveness threshold range used by NICE. The results of the ERG's threshold analysis indicate that cetuximab plus CTX may not be cost-effective at any price.

- The ERG questions the appropriateness of economic modelling in this STA since many health economists would prefer to carry out direct evaluation of trial data when there is only evidence from a single RCT available.

- Lack of information precluded the ERG from testing some concerns over the appropriateness and reliability of parametric survival projection beyond the duration of trial data.

- Based on the evidence presented in the two sets of responses from the manufacturer, the ERG considers that cetuximab plus CTX may not confer any survival benefit to patients with metastatic disease.

- The model included some logic and parameter value errors (e.g. method of costing CTX, updating unit costs to a consistent price base and using a non-treatment specific utility value for progression-free survival). No univariate SAs were carried out in relation to the most important aspects of the analysis: the estimated overall survival time, and the effect of inter-patient dosing variability on treatment costs.

7 DISCUSSION

The manufacturer presents a case for the use of cetuximab plus CTX versus CTX in patients with recurrent and/or metastatic SCCHN. In the statement of the decision problem, the manufacturer restricts the use of cetuximab plus CTX to first-line treatment for this group of patients. Neither the final scope issued by NICE, nor the positive opinion adopted by the CHMP, restricts the use of cetuximab in this way.

The systematic literature review conducted by the manufacturer was designed to identify the clinical evidence available for the assessment of efficacy for the first-line use of cetuximab plus CTX in patients with recurrent and/or metastatic SCCHN. The ERG is confident that all relevant published trials were identified by the manufacturer. The literature search identified a single relevant RCT (EXTREME) conducted by the manufacturer comparing cetuximab plus CTX versus CTX. The MS also included details of two other trials (ECOG 5397 and EMR 62202-008); both trials were appropriately excluded from the literature review by the manufacturer.

Results from the EXTREME trial furnish the principal clinical evidence presented in the MS. For the most part, the EXTREME trial appears to be a well-conducted phase III open label RCT, the results of which seem to demonstrate that cetuximab plus CTX is more clinically effective that CTX in a specific patient population. Clinical outcomes (including OS, PFS and tumour response) are improved in the cetuximab plus CTX arm. The QoL data analysed from the trial were limited, with the manufacturer concluding that "...the addition of cetuximab to standard chemotherapy has no adverse effect on quality of life" (MS, pg52).

The patients in the EXTREME trial appear to be younger and fitter than patients in England and Wales with recurrent and/or metastatic SCCHN. If this is the case, it is uncertain whether similar clinical effectiveness rates could be replicated for patients in England and Wales with this condition.

As noted by the ERG, some patients with recurrent and/or metastatic SCCHN will have received cetuximab (in combination with radiotherapy) for locally advanced SCCHN. There is no clinical evidence available to demonstrate the effectiveness of cetuximab plus CTX in patients who are not cetuximab-naive.

The cost-effectiveness section of the MS considers the same treatment comparison: cetuximab plus CTX versus CTX. The ICERs estimated by the manufacturer are extremely high (over £100,000 per QALY gained); as such they fall far outside the cost-effectiveness threshold range used by NICE (£20,000 to £30,000 per QALY). The ERG is certain that neither model assumptions nor parameter values are likely to introduce sufficient uncertainty to allow cetuximab plus CTX to be cost effective for the first-line treatment of patients with recurrent and/or metastatic SCCHN. To illustrate, the ERG considered what the unit cost of a cetuximab vial would have to be to generate an estimated ICER within the range of the NICE cost-effectiveness threshold. The results of the ERG's threshold analysis indicate that cetuximab plus CTX may not be cost effective at any price according to current NICE guidance.

The manufacturer argues that for patients with recurrent and/or metastatic SCCHN, the assessment of QoL may misrepresent the real health gain for patients, and therefore submits cost per LYG estimates as well as ICERs. A number of reasons are presented to support the case for misrepresentation. In particular, the manufacturer highlights that "…where the life expectancy of a socioeconomic group of patients is significantly below the national average, a one year QALY gain is proportionately of far greater benefit than may be the case in a more elevated group…"(MS, pg19). The ERG agrees that the life expectancy of patients with recurrent and or/metastatic SCCHN is below the national average, but also points out that using prognosis without treatment as a modifier in economic evaluations requires further research[26] and consultation and is not an approach currently adopted by NICE.[16] To conclude, the ERG is of the opinion that the justification for the misrepresentation of health gain for patients made by the manufacturer is unconvincing. The manufacturer does not present a coherent argument, fails to provide any supporting evidence, and seems to allude to a line of argument which does not fit with past or present NICE decision-making processes.

The ERG considered the cost per LYG estimates for the overall population and for subgroups. The manufacturer's cost per LYG for the overall population is high (£92,226 per LYG). Of all of the subgroups described in the MS, the ERG is confident that the oral cavity patient population with a KPS score of 90 or better is the most promising in cost-effectiveness terms. The ERG estimates a cost per LYG of about £40,000, which is higher than the manufacturer's estimate of £33,855 per LYG. However, cautious interpretation of the cost per LYG estimates is required. In England and Wales the KPS scoring system is more commonly used in clinical research (e.g. trials) than in clinical practice which means there may be many health professionals who are unfamiliar with its use. Also, as the scoring system is subjective and

patients are assessed at the discretion of the attending health professional, there exists the potential for misuse of the instrument.

In the original letter of clarification, the ERG asked the manufacturer to provide additional information to allow the ERG to consider more fully the appropriateness and reliability of parametric survival projection beyond the duration of trial data. However, as the manufacturer chose not to provide all of the requested information, the ERG could not fully explore these concerns. Of particular interest to the ERG was the appropriateness of Weibull modelling to all patient groups and both outcome variables (OS and PFS). From the additional information that the manufacturer did submit, the ERG concluded that use of cetuximab plus CTX might not be associated with a meaningful outcome benefit for patients presenting with metastatic disease (whether or not previously treated). In order to test further whether patients with metastatic SCCHN receive any health benefit from cetuximab plus CTX, the ERG repeated its request for additional information specifically relating to metastatic disease. From the second set of responses provided by the manufacturer, the ERG is more confident in its viewpoint that cetuximab plus CTX would not be considered cost effective under any assumptions for patients with metastatic disease.

The ERG made several corrections and/or adjustments to the model logic and parameter values. In general, the combined effect of ERG corrections and/or adjustments yields less favourable economic results for cetuximab than those described in the MS. The economic modelling results submitted by the manufacturer and estimated by the ERG therefore do not sufficiently support a case for the use of cetuximab with platinum-based CTX in recurrent and/or metastatic SCCHN, either for the whole population or for any identified patient subgroup.

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Appendix 1: Structured critical appraisal of EXTREME trial

Name of Trial: Platinum-based Chemotherapy plus Cetuximab in Head and Neck Cancer
Reference: Vermorken JB, Mesia R, Rivera F, et al. NEJM 2008; 359 (11) 1116-1126
Question: Is platinum-based CTX with fluorouracil plus cetuximab more effective than platinum-based CTX alone in the treatment of patients with recurrent or meta-static squamous cell carcinoma of the head and neck that are ineligible for local therapy?
Summary: Adding cetuximab to platinum-based CTX with fluorouracil significantly prolonged median OS (primary endpoint) from 7.4 months in the CTX alone group to 10.1 months in the group which received cetuximab in addition to CTX. With respect to secondary endpoints, the addition of cetuximab prolonged the median PFS from 3.3 months to 5.6 months and the number of patients who showed the best overall response to treatment was greater in the cetuximab group (36% compared to 20%). Moreover, in the cetuximab group, significantly more patients had controlled disease (81% compared to 60%) and time to treatment failure was longer (5.6 months compared to 4.7 months). Grade 3 or 4 AEs in the cetuximab group differed significantly in regard to skin reactions, anorexia, hypomagnesaemia, hypocalcaemia and sepsis. Reported QoL did not differ between the two groups.

Did the study ask a clearly focussed question?
Yes. The trial was designed to compare the effectiveness of platinum-based CTX with fluorouracil plus cetuximab compared to platinum-based CTX alone in the treatment of patients with recurrent or meta-static squamous cell carcinoma of the head and neck who were ineligible for local therapy (surgery or radiotherapy). The population studied, the interventions given and the outcomes considered are clearly stated.

Was the study design appropriate?
Yes. The trial was a Phase III multi-centred RCT. The design was appropriate as it allowed the investigators to assess the effects of the intervention (cetuximab) using a treatment and control group.

Eligible patients had recurrent and/or metastatic squamous cell cancer of the head and neck. These patients were not suitable for local therapy and had a KPS score of ≥70 at study entry. Other criteria were at least one lesion biodimensionally measurable by computed tomography or magnetic resonance imaging, adequate haemotologic, renal and hepatic function and tumour tissue that was available for evaluation of EGFR expression. Patients were excluded if they had undergone surgery or irradiation within the previous four weeks or previous systemic CTX (unless it was part of a multimodal treatment for locally advanced disease that had been completed more than six months prior to study entry). Other grounds for exclusion were: nasopharyngeal carcinoma; brain or leptomeningeal metastasis; taking other cancer therapies; active infection; uncontrolled hypertension; pregnancy; documented coronary artery disease; other malignancies within the previous five years; investigational medication in previous 30 days; known drug abuse (except alcohol); known allergic reaction to study treatments.

Patients received either cisplatin (at a dose of 100 mg/m^2 of BSA as a 1-hour intravenous infusion on day 1) or carboplatin (at an area under the curve of 5 mg per millilitre per minute, as a 1-hour intravenous infusion on day 1) and an infusion of fluorouracil (at a dose of 1000

mg/m^2 per day for four days) every three weeks. The use of cisplatin or carboplatin was at the discretion of the investigator. Cetuximab was administered at an initial dose of 400 mg/m^2 given as a 2-hour intravenous infusion, followed by subsequent weekly doses of 250 mg/m^2 given as a 1-hour intravenous infusion, ending at least one hour before the start of CTX. Dose modifications of CTX and cetuximab were permitted according to protocol-specified criteria. Patients received a maximum of six cycles of CTX. Patients with unacceptable toxic effects of one of the study drugs received only the tolerated drugs until disease progression. Patients who discontinued treatment before disease progression remained in the study and continued to undergo assessments at 6-week intervals until disease progression. After a maximum of six cycles of CTX, patients in the cetuximab group who had at least stable disease received cetuximab monotherapy until the disease progressed or there were unacceptable toxic effects, whereas patients in the CTX-alone group received no further active treatment but remained in the study until disease progression.

The primary outcome was overall survival time (OS) defined as the time from day of randomisation until death. Secondary outcomes included: progression free survival (PFS), (the time from randomization to the first radiologic confirmation of disease progression, or death from any cause within 60 days after the last assessment or randomization, whichever came first), the best overall response (a complete response or partial response persisting for at least four weeks), disease control (defined as a complete response, a partial response, or stable disease), the time to treatment failure (the time from randomization until the date of the first occurrence of one of the events specified in the protocol as constituting treatment failure), the duration of the response (the time from the first documentation of a complete or partial response until the first occurrence of disease progression or until death), QoL and safety.

Were participants appropriately allocated to intervention and control groups?
Yes. Patients were assigned a 4-digit subject number in ascending order by the investigator at the screening visit. Once an eligible patient was identified, the participating centre called an interactive voice-response randomisation and received instructions regarding treatment allocation. Allocation to the two treatment groups was 1:1. A central, stratified, permuted-block randomisation procedure was used to balance prognostic factors (previous CTX, and KPS) between treatment groups and to minimise the predictability of treatment allocation. The groups were well balanced with regard to their demographic, nature of the disease and KPS.

Were participants, staff and study personnel 'blind' to participants in the study group?
No. The trial was described as open label. Since placebo procedures were not employed, patients would be aware of the cetuximab infusion as would staff. Outcome assessors likewise were not blinded to treatment allocation, although it is stated that clear guidance for response assessment was given in the protocol to minimise the possibility of bias. This element should emphasised since open studies are more likely to favour experimental interventions and studies that are not double blinded can exaggerate effect estimates by 17%.[10,11]

Were all of the participants who entered the trial accounted for at its conclusion?
Yes. The number of randomised patients was 442, of these, eight were not treated but were included in the ITT analysis. The safety population comprised 434 patients. Three patients were lost to follow-up. The mean duration of treatment in the cetuximab group was 18 weeks (interquartile range, eight to 29). For 84% of patients, the relative dose intensity of cetuximab was 80% or more after the initial dose of 400 mg/m^2. The median duration of treatment with fluorouracil was 17 weeks (interquartile range six to 18) in the CTX alone group; the relative dose intensity of fluorouracil was 80% or more in 83% and 84% of patients in the two groups.

Were the participants in all groups followed up and data collected in the same way?
Yes and no. Patients were given a maximum of six cycles of CTX and were assessed by CT or MRI at baseline and at 6-week intervals after the start of the study until disease progression at which point the treatment was withdrawn. Those who stopped treatment before the occurrence of progressive disease remained in the study and continued to be assessed for response every six weeks. When progressive disease occurred, all study medication was discontinued and a final tumour assessment was carried out. This was followed by an end-of-study visit no earlier than 30 days after the last study treatment, but always before the start of any new anticancer therapy. After the end of study visit, follow-up evaluations were performed in all patients every three months to collect information on further anticancer treatment and OS time.

Concomitant medications and AEs were monitored weekly in the cetuximab group and at the start of every cycle in the CTX alone group. The questionnaires used to assess QoL in both treatment groups, was administered to both groups throughout the study. There was no placebo procedure in the trial and so the cetuximab patients are likely to have received more attention from health providers, as this treatment was extra to the platinum-based CTX. In addition, the cetuximab patients were followed weekly to monitor AEs: again the extra attention may have had some effect on the outcomes.

Did the study have enough participants to minimise the play of chance?
Yes. The trial assumed a median survival of seven months and an approximate increase of 36% in median survival with the addition of cetuximab to the platinum-based CTX. It was calculated that an event-driven analysis after 340 deaths would provide the study with a power of 80% to detect a difference at a two-sided, 5% significance level. Random assignment to study groups of a total of 420 patients within 20 months would lead to estimated total study duration of 34 months (with the assumption that 5% of patients would be lost to follow-up).

How are the main results presented and what is the main result?
The primary endpoint was OS defined as time from randomisation to death. The secondary endpoints were: PFS (time from randomisation to the first radiologic confirmation of disease progression or death from any cause within 60 days of the last assessment or randomisation); best overall response (a complete or partial response persisting for at least four weeks); disease control (complete or partial response, stable disease); TTF (time from randomisation until the date of the first occurrence of one of the events specified in the protocol as constituting treatment failure); duration of response (time from first documentation of a complete or partial response until the first occurrence of disease progression or until death); safety; quality of life. Time to event variables were compared by using the stratified log-rank test with the strata used for randomisation. The Cox regression method, stratified according to the randomisation categories was used to calculate hazard ratios.

Overall survival: median OS was significantly greater in the cetuximab group compared to the CTX alone group. Median OS was increased from 7.4 months (95% CI: 6.4, 8.3) to 10.1 months (95% CI, 8.6, 11.2). The HR was 0.797 (95% CI, 0.644, 0.986, $p<0.0362$).

Progression free survival: median PFS was significantly prolonged in cetuximab group compared to the CTX alone group. Median PFS was 5.6 months in the cetuximab group and 3.3 months in the CTX alone group. The HR was 0.538 (95% CI, 0.431, 0.672 $p<0.001$).

Overall response rate: response rate in the cetuximab group was significantly greater than in the CTX alone group, 35.6% (95% CI, 29.3, 42.3) compared with 19.5% (95% CI, 14.5, 25.4). The odds ratio was 2.33 (95% CI, 1.50-3.60 p<0.001).
Disease control rate: disease control rate was significantly greater in the cetuximab group than in the CTX alone group 81% (95% CI, 75.3, 86.0) compared with 60% (95% CI, 53.2, 66.5). The odds ratio was 2.88 (1.87-4.44 p<0.001)

Time to treatment failure: significantly greater in the cetuximab group compared to the CTX alone group 4.8 months (95% CI, 4.0, 5.6) compared with 3.0 months (95% CI, 2.8, 3.4 p<0.001)

Duration of response: this did not differ significantly between the two groups, 5.6 months in the cetuximab group compared with 4.7 months in the CTX alone group.

Safety: the incidence of any AE reported by ≥10% of patients was broadly similar in the 26 categories. The exceptions were rash, diarrhoea, anorexia, pyrexia, acne, dermatitis acneiform, dry skin, alopecia, hypocalcaemia, hypokalaemia, hypomagnesaemia. These were all reported by a greater number of patients in the cetuximab group.

Grade 3 or 4 AEs reported in≥5% of patients were listed as were Grade 4 events that were reported in≥1% of patients. Significant differences were found between the cetuximab and CTX alone groups for skin reactions (p<0.001), anorexia (p<0.5), hypomagnesaemia (p<0.05) and sepsis. Grade 3 skin reactions were seen in 9% of the cetuximab group, but no Grade 4 reactions were noted. There were four Grade 3 infusion reactions and two Grade 4 reactions within the cetuximab group. There were no infusion reactions in the CTX group.

Adverse events led to discontinuation of CTX or cetuximab in approximately 20% of patients in each group. Ten deaths (three in the cetuximab group and seven in the CTX alone group were considered to be treatment-related).

QoL: measured using the EORTC QLQ-C30 with the EORTC QLQ-H&N35 symptomatic module and the EQ5D. No assessment of QoL was carried out in Hungary, Ukraine or Slovakia due to the lack of translated, validated questionnaires. EQ-5D scores were not assessed due to the small proportion of patient respondents. The proportion of completed questionnaires which were considered evaluable was quite low and the more conservative assumption is that the addition of cetuximab to standard CTX has no adverse effect on QoL.

The results of the trial show that cetuximab combined with platinum-based CTX significantly increased OS, PFS, overall response rate, disease control and time to treatment failure, compared to CTX alone. QoL was not significantly affected, although the data regarding this outcome were poor.

How precise are the results?
The 95% confidence intervals are presented for all outcomes along with p values.

Overall survival: the HR was 0.80 with a CI of 0.64-0.99 indicating a 95% certainty that the true value lies within this range. The CI does not include 1, demonstrating the effectiveness of the intervention. The p value was 0.04, signifying that the result is significant and not likely to have been a chance finding.

Progression free survival: the HR was 0.54 with a CI of 0.43-0.67, indicating a 95% certainty that the true value lies within this range. The CI does not include 1, demonstrating the

effectiveness of the intervention. The p value was 0.001, signifying that the result is significant and unlikely to have been a chance finding.

Overall response to therapy: the odds ratio was 2.33 with a CI of 1.50-3.60 indicating a 95% certainty that the true value lies within this range. The CI does not include 1, demonstrating the effectiveness of the intervention. The p value was 0.001, signifying that the result is significant and unlikely to have been a chance finding.

Disease control: the odds ratio was 2.88 with a CI of 1.87-4.44 indicating a 95% certainty that the true value lies within this range. The CI does not include 1, demonstrating the effectiveness of the intervention. The p value was 0.001, signifying that the result is significant and unlikely to have been a chance finding.

Time to treatment failure: the HR was 0.59 with a CI of 0.48-0.73 indicating a 95% certainty that the true value lies within this range. The CI does not include 1, demonstrating the effectiveness of the intervention. The p value was 0.001, signifying that the result is significant and unlikely to have been a chance finding.

Duration of response: the HR was 0.76 with a CI of 0.50-1.17 indicating a 95% certainty that the true value lies within this range. The CI include 1, demonstrating there was no effect of the intervention. The p value was 0.21, signifying that the result is not significant and could be a chance finding.

In the subgroup analyses, several subgroups appear to benefit from cetuximab. These analyses were purely exploratory as the trial was not powered to show differences.

Can the results be applied?
All important and relevant outcomes were considered: OS; PFS; overall response rate; disease control; time to treatment failure; QoL of life; safety.

The trial was conducted in 80 centres in 17 countries in Europe, four of which were in the UK (n=9 patients). According to the manufacturer, 59% of patients were drawn from countries with similar practices to those of the UK (Belgium, France, Germany, Italy, Netherlands and Spain). The majority of the patients had a Karnofsky score greater than 80; however Karnofsky scoring can be open to interpretation and is not generally used in clinical practice, performance status is generally assessed through interaction with the patient.

Summary
The results of the trial show that cetuximab combined with platinum-based CTX significantly increased OS, PFS, overall response rate, disease control and time to treatment failure, compared to CTX alone. QoL was not significantly affected, although the data regarding this outcome were poor. No safety issues related to cetuximab arose beyond those already previously documented for cetuximab.

The 10 questions are adapted from Guyatt GH, Sackett DL, and Cook DJ, Users' guides to the medical literature. II. How to use an article about therapy or prevention. *JAMA* 1993; 270 (21): 2598-2601 and *JAMA* 1994; 271(1): 59-63

Appendix 2: Detailed economic analysis results

The following tables provide full details of the results reported in Tables 6.1, 6.2 and 6.4.

Table A2.1 ERG modifications

	Cetuximab + CTX			*CTX*							
Model / amendment	*Cost per patient*	*Estimated survival (years)*	*Estimated QALYs*	*Cost per patient*	*Estimated survival (years)*	*Estimated QALYs*	*Incremental costs*	*Incremental survival*	*Incremental QALYs*	*Incremental cost/LY gained*	*Incremental cost/QALY gained*
Base case	**£30,678**	**1.0714**	**0.6504**	**£13,392**	**0.8839**	**0.5080**	**£17,286**	**0.1874**	**0.1424**	**£92,226**	**£121,367**
Mid-cycle correction	£29,502 *[-£1,176]*	1.0714	0.6308 *[-0.0196]*	£13,317 *[-£75]*	0.8839	0.4895 *[-0.0185]*	£16,185 *[-£1,101]*	0.1874	0.1414 *[-0.0011]*	£86,353 *[-£5,873]*	£114,484 *[-£6,884]*
Limit to 24 months	£29,728 *[-£951]*	0.9636 *[-0.1078]*	0.5943 *[-0.0562]*	£12,968 *[-£425]*	0.8318 *[-0.0521]*	0.4809 *[-0.0271]*	£16,760 *[-£526]*	0.1318 *[-0.0556]*	0.1134 *[-0.0290]*	£127,149 *[£34,923]*	£147,817 *[£26,449]*
Overall PFS utility value	£30,678	1.0714	0.6394 *[-0.0110]*	£13,392	0.8839	0.5154 *[0.0074]*	£17,286	0.1874	0.1240 *[-0.0184]*	£92,226	£139,390 *[£18,023]*
Adverse event utility adjustment	£30,678	1.0714	0.6523 *[0.0019]*	£13,392	0.8839	0.5080	£17,286	0.1874	0.1443 *[0.0019]*	£92,226	£119,808 *[-£1,560]*
Revised drug costs	£34,203 *[£3,524]*	1.0714	0.6504	£13,762 *[£369]*	0.8839	0.5080	£20,441 *[£3,155]*	0.1874	0.1424	£109,059 *[£16,833]*	£143,519 *[£22,152]*
100% cisplatin use	£29,998 *[-£680]*	1.0714	0.6504	£12,666 *[-£727]*	0.8839	0.5080	£17,332 *[£46]*	0.1874	0.1424	£92,473 *[£247]*	£121,692 *[£325]*
Cetuximab dose adjustment	£30,797 *[£118]*	1.0714	0.6504	£13,392	0.8839	0.5080	£17,404 *[£118]*	0.1874	0.1424	£92,858 *[£632]*	£122,199 *[£831]*
Cisplatin dose adjustment	£30,026 *[-£652]*	1.0714	0.6504	£12,767 *[-£625]*	0.8839	0.5080	£17,259 *[-£27]*	0.1874	0.1424	£92,081 *[-£145]*	£121,177 *[-£191]*
Rebase unit costs	£33,205 *[£2,526]*	1.0714	0.6504	£14,353 *[£960]*	0.8839	0.5080	£18,852 *[£1,566]*	0.1874	0.1424	£100,580 *[£8,354]*	£132,361 *[£10,993]*
Revised discounting	£30,672 *[-£6]*	1.0708 *[-0.0006]*	0.6501 *[-0.0003]*	£13,389 *[-£3]*	0.8835 *[-0.0004]*	0.5078 *[-0.0002]*	£17,283 *[-£3]*	0.1873 *[-0.0002]*	0.1423 *[-0.0001]*	£92,297 *[£71]*	£121,437 *[£69]*
Base case + all changes - full life	**£34,465** ***[£3,787]***	**1.0708** ***[-0.0006]***	**0.6220** ***[-0.0284]***	**£13,534** ***[£141]***	**0.8835** ***[-0.0004]***	**0.4961** ***[-0.0119]***	**£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	**£33,382** ***[£2,704]***	**0.9631** ***[-0.1083]***	**0.5677** ***[-0.0827]***	**£13,051** ***[-£341]***	**0.8314** ***[-0.0525]***	**0.4701** ***[-0.0379]***	**£20,331** ***[£3,045]***	**0.1317** ***[-0.0558]***	**0.0976** ***[-0.0448]***	**£154,420** ***[£62,194]***	**£208,266** ***[£86,899]***

QALYs=quality adjusted life years; LY=life year; PFS=progression free survival

Table A2.2 Summary of cost effectiveness for all patient subgroups (within the manufacturer's submitted model and later additions)

	Cetuximab + CTX			*CTX*							
Model / amendment	*Cost per patient*	*Estimated survival (years)*	*Estimated QALYs*	*Cost per patient*	*Estimated survival (years)*	*Estimated QALYs*	*Incremental costs*	*Incremental survival*	*Incremental QALYs*	*Incremental cost/LY gained*	*Incremental cost/QALY gained*
Oral - all patients											
Submitted	£32,931	1.1271	0.6926	£10,272	0.5775	0.3382	£22,658	0.5496	0.3544	£41,224	£63,927
ERG - full life	£36,992	1.1265	0.6626	£10,166	0.5773	0.3247	£26,825	0.5492	0.3379	£48,844	£79,382
ERG - at 24 months	£36,127	1.0437	0.6210	£10,055	0.5652	0.3187	£26,072	0.4785	0.3022	£54,486	£86,264
Oral - KPS 90+											
Submitted	£36,846	1.2942	0.7955	£9,158	0.4763	0.2901	£27,688	0.8178	0.5053	£33,855	£54,791
ERG - full life	£41,164	1.2935	0.7636	£8,846	0.4763	0.2774	£32,318	0.8172	0.4863	£39,547	£66,461
ERG - at 24 months	£40,557	1.2412	0.7373	£8,840	0.4753	0.2769	£31,717	0.7658	0.4604	£41,415	£68,889
Oropharynx - all patients											
Submitted	£32,357	1.0597	0.6517	£14,441	1.0185	0.5802	£17,915	0.0412	0.0715	£434,568	£250,597
ERG - full life	£35,951	1.0592	0.6224	£14,750	1.0180	0.5686	£21,201	0.0412	0.0537	£514,150	£394,548
ERG - at 24 months	£35,510	1.0142	0.6002	£13,951	0.9321	0.5256	£21,558	0.0821	0.0746	£262,583	£288,916
Oropharynx - KPS 90+											
Submitted	£34,034	1.1624	0.7053	£15,792	1.1362	0.6464	£18,242	0.0262	0.0589	£695,475	£309,735
ERG - full life	£37,479	1.1618	0.6760	£16,169	1.1356	0.6356	£21,311	0.0262	0.0403	£812,749	£528,387
ERG - at 24 months	£36,931	1.1054	0.6483	£15,503	1.0633	0.5998	£21,427	0.0422	0.0485	£508,270	£441,913
Oral or Oropharynx - all patients											
Submitted	£32,755	1.1097	0.6800	£12,889	0.8560	0.4909	£19,867	0.2537	0.1891	£78,301	£105,069
ERG - full life	£36,589	1.1091	0.6504	£13,049	0.8556	0.4786	£23,540	0.2535	0.1718	£92,846	£137,024
ERG - at 24 months	£35,735	1.0240	0.6078	£12,390	0.7849	0.4431	£23,345	0.2391	0.1648	£97,642	£141,701
Oral or Oropharynx - KPS 90+											
Submitted	£34,868	1.2096	0.7374	£13,185	0.8941	0.5155	£21,683	0.3155	0.2219	£68,717	£97,702
ERG - full life	£38,729	1.2090	0.7072	£13,323	0.8937	0.5039	£25,406	0.3153	0.2033	£80,576	£124,989
ERG - at 24 months	£38,178	1.1529	0.6797	£12,849	0.8423	0.4784	£25,329	0.3106	0.2014	£81,544	£125,792
Metastatic disease *											
Submitted	-	-	-	-	-	-	£14,539	-0.015	0.026	-£947,649	£562,849
Submitted (approx. ERG re-estimate)	£27,940	1.0726	0.6314	£14,904	1.0878	0.6057	£13,036	-0.0153	0.0257	-£854,794	£507,290
ERG - full life	£31,279	1.0720	0.6053	£15,489	1.0872	0.5926	£15,789	-0.0152	0.0127	-£1,037,645	£1,241,001
ERG - at 24 months	£30,125	0.9564	0.5471	£14,158	0.9453	0.5208	£15,968	0.0111	0.0262	£1,443,175	£608,473
Recurrent disease (non metastatic) *											
Submitted	-	-	-	-	-	-	£18,758	0.308	0.215	£60,939	£87,099
Submitted (approx. ERG re-estimate)	£30,983	1.0509	0.6446	£12,173	0.7432	0.4292	£18,810	0.3077	0.2154	£61,131	£87,334
ERG - full life	£34,871	1.0504	0.6156	£12,196	0.7430	0.4165	£22,675	0.3074	0.1991	£73,759	£113,878
ERG - at 24 months	£34,030	0.9682	0.5743	£12,051	0.7271	0.4087	£21,978	0.2411	0.1656	£91,141	£132,732

* Survival model parameter estimates provided by manufacturer for these subgroups lacked sufficient precision to allow exact reproduction by ERG of submitted results. Approximate figures were generated by adjusting values to replicate outcome results as closely as possible.

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