NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

MERCK SERONO LTD.

SINGLE TECHNOLOGY APPRAISAL SUBMISSION:

ERBITUX® (CETUXIMAB) FOR THE FIRST-LINE TREATMENT OF RECURRENT and /or METASTATIC SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK

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Section A

1 Description of technology under assessment

1.1	Give the brand name, approved name and, where appropriate, therapeutic class. For devices please provide details of any different versions of the same device.

Brand name: Erbitux

Approved name: cetuximab

Therapeutic class: Antineoplastic agents, monoclonal antibodies

1.2	Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, please give the date on which authorisation was received. If not, please state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

No: This is subject to CHMP/EMEA opinion. We anticipate CHMP opinion by Q4 2008 if no major objections occur. Currently this dossier is scheduled for assessment at the September 2008 CHMP meeting.

1.3	What are the (anticipated) indication(s) in the UK? For devices, please provide the (anticipated) CE marking, including the indication for use.

Scientific assessment by the CHMP/EMEA is ongoing; the Company is not in the position to anticipate any decision on the indication by the EMEA. However at the current time the licence for head & neck cancer patients is anticipated to include the following;

"Erbitux is indicated for the treatment of patients with squamous cell cancer of the head and neck

• *in combination with radiation therapy for locally advanced disease*

• *in combination with platinum-based chemotherapy for recurrent and/or metastatic disease."*

1.4	To what extent is the technology currently being used in the NHS for the proposed indication? Include details of use in ongoing clinical trials. If the technology has not been launched, please supply the anticipated date of availability in the UK.

It is our understanding that the technology is not currently used in the NHS for the proposed indication (first-line treatment for recurrent and / or metastatic squamous cell carcinoma of the head and neck (SCCHN)) outside of clinical trials. However it is licensed in the UK in metastatic colorectal cancer and locally advanced squamous cell carcinoma of the head and neck as follows:

Erbitux is indicated in the treatment of patients with epidermal growth factor receptor (EGFR)-expressing, KRAS wild-type metastatic colorectal cancer

- *in combination with chemotherapy.*
- *as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan.*

Cetuximab in combination with radiation therapy is indicated for the treatment of patients with locally advanced squamous cell cancer of the head and neck (SCCHN)."

NICE have recently approved the use of cetuximab in combination with radiotherapy in locally advanced SCCHN for those patients not suitable for chemoradiotherapy.

1.5	Does the technology have regulatory approval outside the UK? If so, please provide details.

Yes, as of July 2008, cetuximab is approved in the EU for:

"The treatment of patients with epidermal growth factor receptor (EGFR)-expressing, KRAS wild-type metastatic colorectal cancer

- *in combination with chemotherapy.*
- *as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan.*

Cetuximab in combination with radiation therapy is indicated for the treatment of patients with locally advanced squamous cell cancer of the head and neck (SCCHN)."

Cetuximab is also approved outside of the EU in a number of other countries for the treatment of metastatic colorectal cancer and for the treatment of locally advanced squamous cell carcinoma of the head and neck (SCCHN).

1.6	Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

The NICE appraisal of cetuximab for the first line treatment of metastatic colorectal cancer in combination with chemotherapy is ongoing. The first appraisal committee meeting was held on 3rd September 2008.

1.7	For pharmaceuticals, what formulation(s) (for example, ampoule, vial, sustained-release tablet, strength(s) and pack size(s) will be available?

The following vial sizes are available:
100mg/20ml vial and 500mg/100ml vial.

1.8	What is the proposed course of treatment? For pharmaceuticals, list the dose, dosing frequency, length of course and anticipated frequency of repeat courses of treatment.

It is expected that in combination with platinum based chemotherapy for the treatment of recurrent and/or metastatic SCCHN, regimens will be used as detailed in the following regimen:

400 mg cetuximab per m^2 body surface area day 1. All subsequent weekly doses of cetuximab are 250 mg/m^2. Cetuximab treatment is continued until progression of the underlying disease.

1.9 What is the acquisition cost of the technology (excluding VAT)? For devices, provide the list price and average selling price. If the unit cost of the technology is not yet known, please provide details of the anticipated unit cost, including the range of possible unit costs.

The NHS list price for cetuximab is £159.02 /20ml (100mg) vial and £795.10 /100ml (500mg) vial. The acquisition cost to the NHS, however remains at the previous price of £136.50/20ml (100mg) vial and £682.50/100ml (500mg) vial by means of a procurement discount.

1.10 What is the setting for the use of the technology?

Treatment of patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck who are unsuitable for definitive local therapy. i.e. those who would be considered suitable for treatment with platinum containing regimens.

1.11 For patients being treated with this technology, are there any other aspects that need to be taken into account? For example, are there additional tests or investigations needed for selection, or particular administration requirements, or is there a need for monitoring of patients over and above usual clinical practice for this condition? What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

Premedication: Prior to the first infusion, patients must receive pre-medication with an antihistamine and corticosteroid. This pre-medication is recommended prior to all subsequent infusions.
Close monitoring is required during the infusion and for at least 1 hour after the end of the infusion.

Concomitant chemotherapy with platinum containing regimens is likely to be in 21-day cycles with cisplatin (100 mg/m^2) or carboplatin (AUC 5) given on day 1, plus infusional 5-FU (1000 mg/m^2/day) given on days 1 to 4.

A maximum duration of chemotherapy of 6 cycles was stipulated in the protocol for the pivotal study.

98% of head and neck cancer tumours express EGFR and 97% express wt K-RAS, thus it is not anticipated that either of these tests will need to be performed as a pre-requisite for treatment with cetuximab. It is not expected that EGFR or KRAS testing will be included in the licence for this indication.

2 Statement of the decision problem

	Final scope issued by NICE	**Decision problem addressed in the submission**
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.

Section B

3 Executive summary

- *The UK approved name, brand name, marketing status and principal pharmacological action of the proposed drug.*

Cetuximab (Erbitux®) is a chimerised monoclonal antibody to the Epidermal Growth Receptor (EGFR). By blocking EGFR in tumour cells, it decreases proliferation of the tumour. It is licensed in the UK for the treatment of EGFR expressing KRAS wild-type metastatic colorectal cancers in combination with chemotherapy and as a monotherapy in those metastatic colorectal cancers that have failed irinotecan or oxaliplain based chemotherapy and are intolerant to irinotecan. It is also licensed, in combination with radiotherapy, for locally advanced Squamous Cell Carcinomas of the Head and Neck (SCCHN).

An application for extension of marketing authorisation is currently being considered by the EMEA. This extension is for the treatment of patients with recurrent and/or metastatic SCCHN, in combination with platinum based chemotherapy. The dossier is scheduled for assessment at the September 2008 CHMP meeting.

- *The formulation(s), strength(s), pack size(s), maximum quantity(ies), anticipated frequency of any repeat courses of treatment and acquisition cost (see section 1.9).price.*

Cetuximab is available as solution for infusion in 100mg (20ml) and 500mg (100ml) vials. The acquisition costs are £136.50 and £682.50 respectively. Vials are supplied singly.

- *The indication(s) and any restriction(s).*

As yet the EMEA has not approved cetuximab for this licence extension. However, the indication relevant to the decision problem is anticipated to be:

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 recommended course of treatment.*

In the pivotal EXTREME trial cetuximab was administered on a weekly basis at a dose of 400mg/m^2 for the first infusion followed by 250 mg/m^2 for subsequent weekly infusions. It was given concurrently with combination chemotherapy using platinum and 5-FU for 18 weeks (6 cycles) and was continued as a monotherapy until progression.

- The main comparator(s).

The main comparator is combination chemotherapy using a platinum agent (carboplatin or cisplatin) in combination with 5-FU given in 3 weekly cycles for a total of 6 cycles.

- Whether the key clinical evidence in the submission comes from head to head randomised trials (RCTs), from an indirect comparison of two sets of randomised trials involving a common comparator (for example, placebo or other active therapy), or from non-randomised studies.

The key clinical evidence comes from the EXTREME trial which was a randomised controlled study comparing standard platinum based chemotherapy alone with the combination of chemotherapy and cetuximab in patients with recurrent and/or metastatic SCCHN.

- The main clinical results of the randomised trials and any relevant non RCTs.

Table ES1: Summary of results of EXTREME study

Response Variable	Number (%) of subjects, ITT population	
	Cetuximab + CTX (N=222)	**CTX (N=220)**
Overall survival		
Median (months)	10.1	7.4
Log rank p value	0.036	
Hazard Ratio [95%CI]	0.797 [0.644, 0.986]	
Progression free survival		
Median (months)	5.6	3.3
Log rank p value	<0.0001	
Hazard Ratio [95%CI]	0.538 [0.431, 0.672]	
Best overall response		
Complete response	15 (6.8)	2 (0.9)
Partial Response	64 (28.8)	41 (18.8)
Stable disease	101 (45.5)	89 (40.5)
Progressive disease	12 (5.4)	45 (20.5)
Not evaluable	30 (13.5)	43 (19.5)
Best overall response rate (%[95%CI])	35.6 [29.3, 42.3]	19.5 [14.5, 25.4]
CMH test		
P value	0.0001	
Odds ratio [95% CI]	2.326 [1.504, 3.600]	
Disease Control rate (% [95% CI])	81.1 [75.3, 86.0]	60.0 [53.2, 66.5]
CMH test		
P value	<0.0001	
Odds ratio [95% CI]	2.881 [1.870, 4.441]	

There was no significant difference in adverse event profile or detrimental effect in quality of life from the addition of cetuximab to conventional chemotherapy

- In relation to the economic evaluation, details of:

the type of economic evaluation and justification for the approach used

the pivotal assumptions underlying the model/analysis

the incremental ratios from the evaluation.

- A de novo economic evaluation is presented in this submission. The economic evaluation compares the costs and health outcomes of patients with recurrent and / or metastatic Head and Neck cancer (RMHNC) with the following treatment strategy:
    - cetuximab in combination with platinum and 5FU containing regimens compared to a platinum and 5FU containing regimens alone
- It is anticipated that the licence will be restricted to use *" in combination with* platinum-*based chemotherapy for recurrent and/or metastatic disease."*
- The term Head and Neck cancer encompasses a variety of relatively rare tumour sub-sites.
- This economic evaluation will focus on the expected licensed population and consider particular patient sub groups where greater clinical and economic benefit can be derived through the addition of cetuximab to platinum based treatment:
    - Patients with a good performance status.
    - Tumour sites where cetuximab in combination with chemotherapy has been shown to offer significant benefit over chemotherapy alone.

The economic evaluation is based upon a Markov model which simulates the disease progression and survival of patients with RMHNC through three health states using both overall survival data and progression free survival data from the EXTREME study. The evaluation is from the perspective of the NHS and covers the expected lifetime of this cohort of patients.

Key to the model is the assumption that the EXTREME data map onto both this patient group and UK clinical practice, which was confirmed by a UK advisory board comprising oncologists specialising in head and neck cancer (please see Appendix H1).

Table S1 below shows the ICERs for the overall population and for the oral cavity subgroup, full details are presented in the health economic section of this submission.

Table S1: Cost per QALY for whole population and for oral cavity patients.

EXTREME ITT population	
Cetuximab + standard treatment vs Standard treatment	**Cost/QALY**
Incremental cost utility ratio	£121,367
Oral cavity subgroup	
Incremental cost utility ratio	£63,927

4 Context

4.1	Please provide a brief overview of the disease/condition for which the technology is being used. Provide details of the treatment pathway and current treatment options at each stage.

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. [ONS MB1 – no 36]

Squamous cell carcinoma (SCC) 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 squamous cell carcinomas [Dobrossy 2005].

The relative incidences of cancers in England and Wales, relevant to this submission are given in the table below

Table B.1 SCCHN registrations relevant to decision problem by tumour site

Site	**ICD10 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	C32	1432	297	89	21

ref [ONS MB1 – no 36] : [www.wcisu.wales.nhs.uk]

Tobacco and alcohol consumption are aetiological factors involved in the onset of Squamous Cell Carcinoma of the Head and Neck (SCCHN), which commonly affects middle-aged or older men. [Blott 1988, ONS MB1 – no 36]. Incidence is associated with exposure to risk factors, and there are pronounced geographical variations

[Seiwert 2005]. 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 [Thorne 1997, Edwards 1999].

Approximately two-thirds of patients have locally advanced SCCHN [Argiris 2008]. At least 50% of patients with locally advanced SCCHN develop locoregional or distant relapses, which are usually detected within the first 2 years of treatment [Argiris 2008].

There is no standard treatment for all patients with recurrent or metastatic disease. Guidelines recommend the tailoring of therapy to the individual patient [NCCN 2008, SIGN 2006, ESMO 2008]. In some patients, the tumour may still be amenable to surgery or radiotherapy with curative intent. However in patients with metastatic disease or who have previously received radiotherapy for their initial tumour, this may not be possible. In this group of patients palliative chemotherapy (CTX) is the mainstay of treatment.

The most commonly used chemotherapeutic treatments for recurrent and/or metastatic SCCHN include methotrexate, bleomycin, 5-fluorouracil (5-FU), and platinum compounds. New agents such as taxanes have not yet demonstrated any efficacy advantage in randomised phase III trials [Gibson 2005]. In the UK, market research conducted on behalf of Merck Serono has shown that treatment with a platinum based regimen is the most common chemotherapeutic approach [A+A tracker 2008 – appendix M1]. Although both carboplatin and cisplatin have shown efficacy in this stage of the disease, there is data to suggest an efficacy advantage of using cisplatin over carboplatin [Forastiere 1992]. The market research conducted confirmed that cisplatin is the most common choice of platinum agent in England and Wales with very little use of carboplatin [A+A tracker 2008]. Cisplatin can either be given as a single agent or in combination with 5-FU.

4.2 What was the rationale for the development of the new technology?

The prognosis of recurrent and/or metastatic SCCHN subjects is extremely poor with a median survival time, of only 6-9 months. New treatments that may provide a more favourable outcome are therefore urgently awaited. The Epidermal Growth Factor Receptor (EGFR) is highly expressed in nearly all SCCHN tumours and has a strong

prognostic significance in SCCHN, providing a strong rationale for testing anti-EGFR agents in this indication [Dassonville 1993, Grandis 1998, Ang 2002].

One of the most important studies in the first-line setting of recurrent and/or metastatic SCCHN was performed by the Eastern Cooperative Oncology Group (ECOG) and compared cisplatin + cetuximab versus cisplatin + placebo in 121 subjects (E5397) [Burtness 2006]. All efficacy time parameters favoured the cetuximab containing arm, although not reaching statistical significance (overall survival [OS] time: 9.2 vs 8.0 months; progression-free survival [PFS] time: 4.2 vs 2.7 months). However, the overall response rate was superior (26% vs 10%) which was significantly relevant at the p=0.03 level. Notably, the safety profile of cisplatin was not modified by cetuximab.

4.3 What is the principal mechanism of action of the technology?

The Epidermal Growth Factor Receptor (EGFR) is a commonly expressed transmembrane glycoprotein belonging to the tyrosine kinase growth factor receptor family. EGFR is expressed widely in normal human body tissues, and is over expressed in many types of tumour. As a transmembrane glycoprotein, the extracellular domain of the EGFR is a ligand-binding site for Transforming Growth Factor alpha (TGFα), Epidermal Growth Factor (EGF) and other factors. Upon ligand binding, the intracellular domain of the EGFR is activated, thereby triggering cellular mechanisms that regulate cell growth, propensity to tumour cell invasion and angiogenesis [Yarden 1988, Baselga 2001].

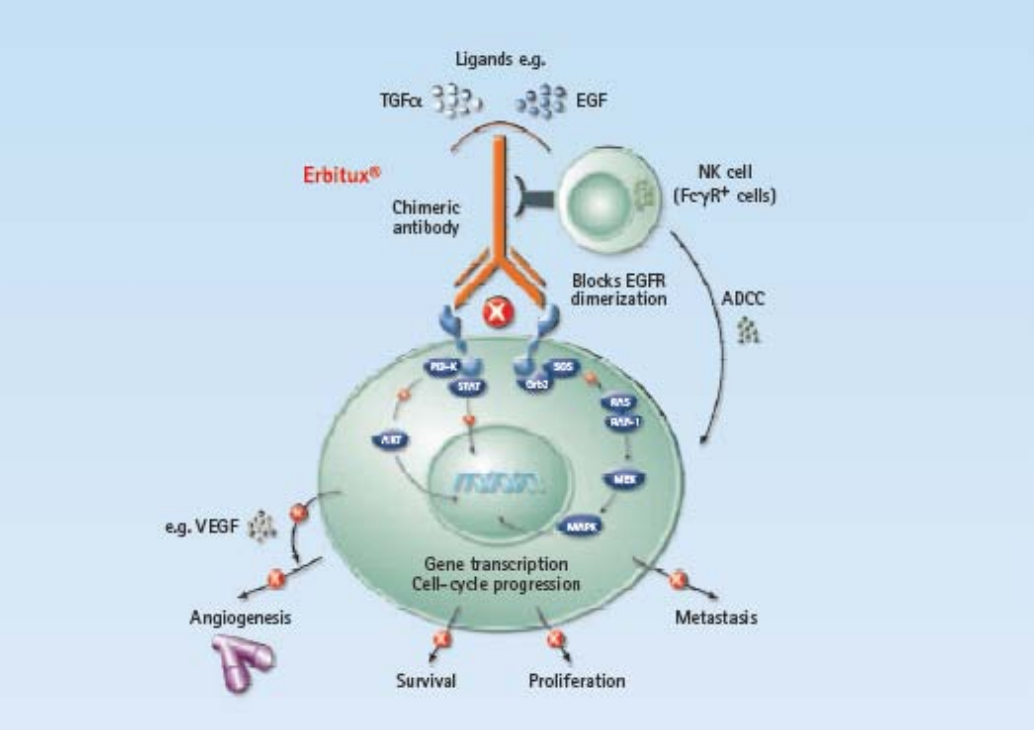
In vitro analysis using cells that express high numbers of EGFR and produce ligands for these receptors has shown that the EGFR may be activated through an autocrine pathway, thereby leading to the proliferation of cells in culture [Van de Vijver et al 1991.]

Cetuximab, a chimerised antibody of the IgG1 subclass, was originally derived from a mouse myeloma cell line. The chimerisation process resulted in an antibody with binding affinity to EGFR greater than the natural ligand EGF [Goldstein et al 1995].

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. [Waksal 1999]. Cetuximab also induces antibody dependent cell cytotoxicity (ADCC) [Roda et al 2007].

See Figure B1 overleaf;

Figure B1



Unlike the use of cetuximab in the treatment of metastatic colorectal cancer (mCRC), where testing for the presence of mutations to KRAS (Kirsten Rat Sarcoma) proteins is necessary to identify the group of patients who will respond, KRAS testing is not necessary in patients with SCCHN as the incidence of the mutation is less than 5% [Weber 2003].

4.4	What is the suggested place for this technology with respect to treatments currently available for managing the disease/condition?

Cetuximab in combination with platinum based chemotherapy is anticipated to be used in patients with recurrent and/or metatstatic squamous cell carcinoma of the

head and neck. It is anticipated to be licensed for patients who have not received chemotherapy for their recurrent/metastatic disease.

4.5 Describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

There is no single treatment that will be suitable for all patients with metastatic and/or recurrent SCCHN. Instead 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. In addition, the treatment of earlier stages of the disease, specifically locally advanced disease, have changed over recent years with increased use of combined chemoradiotherapy in this setting. However not all patients will have been considered suitable for this modality, additionally chemoradiotherapy is resource intensive and so not all patients in the recurrent setting will have received it. Therefore the nature of patients in the recurrent and/or metastatic group will inevitably be heterogeneous.

4.6 Provide details of any relevant guidelines or protocols.

"Improving Outcomes in Head and Neck Cancers" – NICE Guideline, 2004

"Diagnosis and management of Head and Neck Cancer – a national clinical guideline" – SIGN guideline no 90, 2006

"Squamous cell carcinoma of the head and neck: ESMO Clinical recommendations for diagnosis, treatment and follow-up" - Annals of Oncology 19 (Supplement 2): ii79–ii80, 2008

"NCCN Clinical Practice Guidelines in Oncology: Head and Neck Cancers" v.2 2008

5 Equity and equality

5.1 Identification of equity and equalities issues

Are there any issues relating to equity or equalities (consider issues relating to current legislation and any issues identified in the scope for the appraisal)?

Where an ICER is more than £20,000 per QALY gained, and particularly where it is more than £30,000, judgements on the acceptability of an intervention from a cost perspective must consider whether the assessment of the change in the quality of life *misrepresents* the real health gain. This can be clearly seen in this case where patients with RMHNC have a significantly compromised quality of life.

The age-standardised mortality rates from selected malignant neoplasms using the UK National Statistics Socioeconomic Classification (NS-SEC) aged 25-64 (2001-2003) for trachea, bronchus and lung conditions were examined. These ranged from 131 deaths for Class 1 (Higher managerial and professional) to 484 deaths for Class 7 (Routine occupations). Moreover, the average life expectancy at birth for men in England and Wales (2002-2005) ranged from 80 years for Class 1 (Professional) to 72.7 years for Class 5 (Unskilled).

Cetuximab will have proportionately greater effectiveness within those NS-SEC socioeconomic groups where trachea, bronchus and lung conditions are more prevalent or more severe, or where life expectancy is significantly below the national average. Where certain socioeconomic groups can derive additional or prolonged benefit from their use of cetuximab, such socioeconomic groups should be included as an indicator of benefit in the same way that age, sexual orientation and gender may be taken into account.

Principle 3 of '*Social Value Judgements: Principles for the development of NICE guidance*' requires NICE to consider other factors such as the need to distribute health resources in the fairest way within society as a whole, rather than the relative cost and benefits alone. 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 and, consequently, the cost effectiveness of an intervention is increased.

Principle 7 foresees the use of interventions by particular socioeconomic groups where there is evidence for the increased effectiveness of such interventions for such groups, or where there are other reasons relating to fairness for society in general. Principle 8 further requires NICE to actively consider reducing health inequalities, including those associated with socioeconomic status.

How has the analysis addressed these issues?

As the assessment of quality of life may misrepresent the real health gain for patients, results presented include both the cost per life year gained and the cost per QALY gained. Presentation of both sets of results side by side show clearly how quality of life misrepresents the benefits of cetuximab for RMHNC.

6 Clinical evidence

6.1 Identification of studies

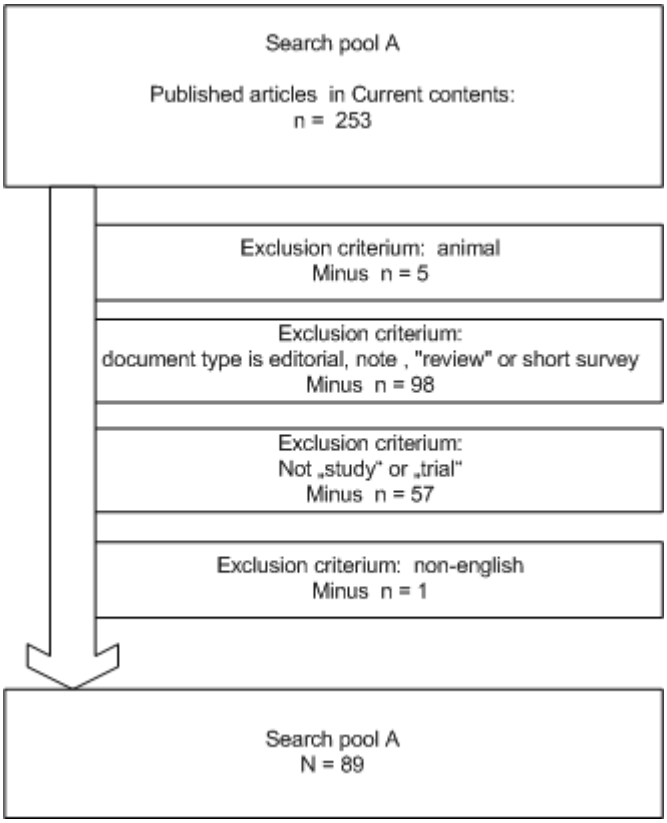
Exact details of the search strategy are provided in appendix 2, section 10.2.

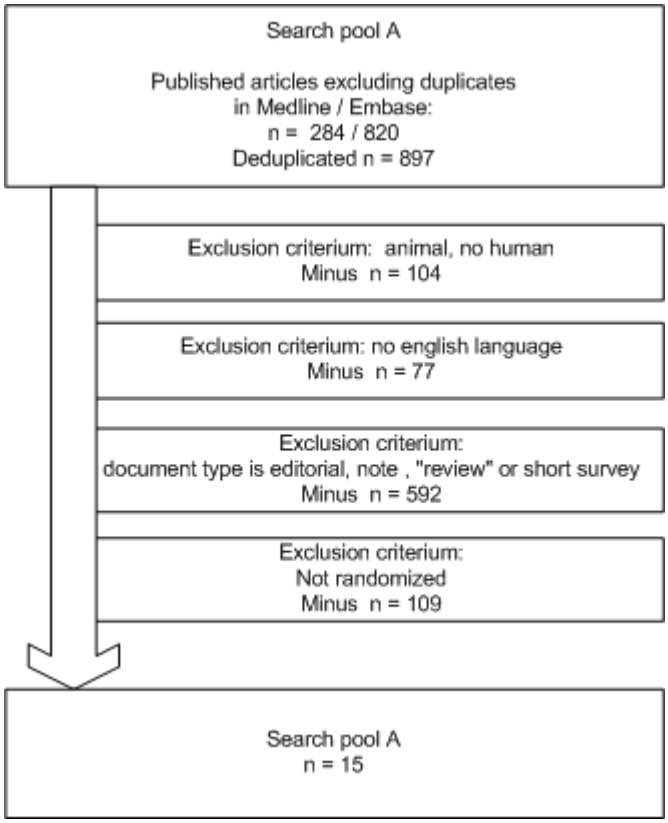
The scope of the search aimed to:

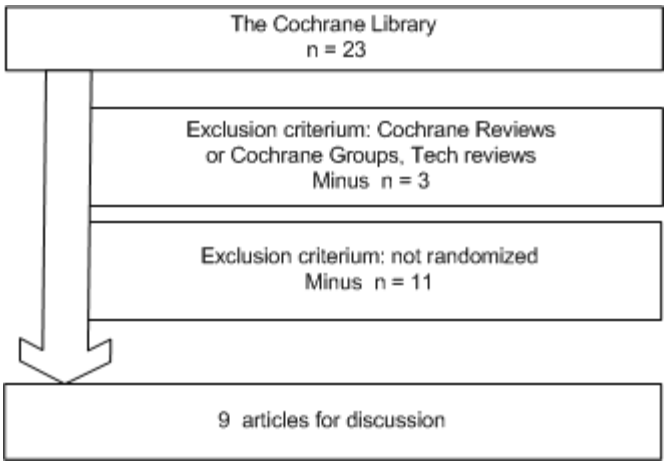
- Identify studies on the use of cetuximab in combination with platinum based chemotherapeutic regimens in the first line treatment of recurrent and/or metastatic SCCHN.

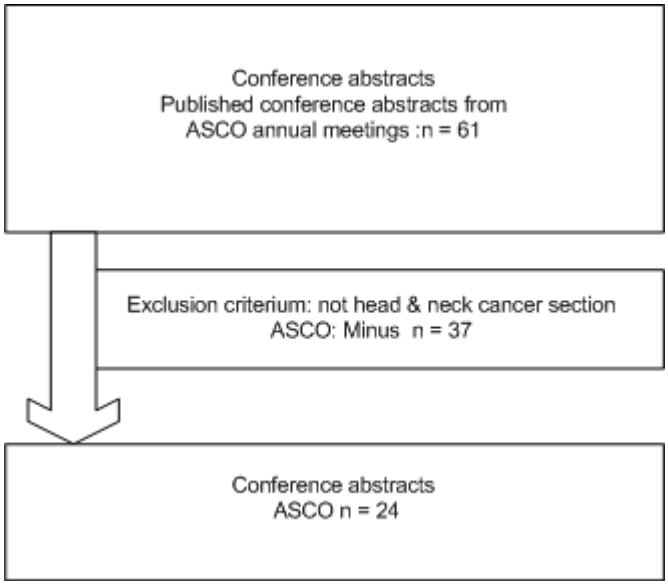
A range of sources were used to identify key clinical trial evidence for each of the main comparators. Abstracts were reviewed for all trials and if it was not clear if the trial met inclusion/exclusion criteria the full text article was then reviewed. Two independent reviewers were involved in the selection of studies for inclusion in the clinical evidence section. They selected studies independently and gave rationale for the inclusion and exclusion to the other reviewer. The studies included in the clinical evidence section have been agreed upon by both reviewers.

Summary of individual database searches









Medline + Embase + Current contents + Cochrane library + Conference searches revealed 137 published articles which were reviewed for potential inclusion

↓

110 Trials were excluded for the following reasons (includes duplicates).

Not a relevant population	41
Not a trial of treatment of interest	43
Not an RCT	10
Review article	16

↓

Duplicates removed

↓

3 studies were included in the systematic review

6.2 Study selection

6.2.1 Complete list of RCTs

Provide a list of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the assessors.

Study	**Design/ subject population**	**Phase**	**Study treatments**	**Sample size (N)**
ECOG 5397 [Burtness 2006]	1st line treatment of patients with recurrent and/or metastatic SCCHN	III	Cisplatin 100mg/m2 once every 4 weeks +/- Cetuximab	57 (active) 60 (placebo)
EMR 62202-008 [Bouhris 2006]	1st line treatment of patients with recurrent and/or metastatic SCCHN	I/II (safety and tolerability of combination regimen)	Cisplatin (100mg/m2) **or** Carboplatin (AUC 5) every 3 weeks **and** 5-Fluorouracil (escalating dose of 600, 800 and 1000mg/m2 per day for 5 days) **and** cetuximab	53
EXTREME [Vermorken 2008]	1st line treatment of patients with recurrent and/or metastatic SCCHN	III	Cisplatin (100mg/m2) **or** Carboplatin (AUC 5) every 3 weeks **and** 5-Fluorouracil 1000mg/m2 per day for 4 days every 3 weeks +/- cetuximab	222 (CTX + cetuximab) 220 (CTX alone)

6.2.2 Inclusion and exclusion criteria

Inclusion criteria

- Randomised controlled trials.
- Studies on the use of cetuximab in the 1st-line treatment of recurrent and/or metastatic head and neck cancer.
- Human only studies.
- Studies in English.

Exclusion criteria

- Studies which involved patients who had received previous treatment in the metastatic and/or recurrent head and neck cancer setting.
- Papers published in a language other than English.
- Letters and editorials.
- Review articles and conference summaries.
- Animal studies/preclinical data.

6.2.3 List of relevant RCTs

Study	Design/ subject population	Phase	Study treatments	Sample size (N)
EXTREME (EMR 62202-002) [Vermorken 2008]	1st line treatment of patients with recurrent and/or metastatic SCCHN	III	Cisplatin (100mg/m2) **or** Carboplatin (AUC 5) every 3 weeks **and** 5-Fluorouracil 1000mg/m2 per day for 4 days every 3 weeks +/- cetuximab	222 (CTX + cetuximab) 220 (CTX alone)

The ECOG 5397 study has been excluded from further discussion as cetuximab was only given in combination with chemotherapy and no allowance was made to continue cetuximab as a monotherapy until disease progression after the 6 cycles of platinum based chemotherapy, as is anticipated to be indicated in the forthcoming licence. The failure of this study to show a difference between treatment groups with regards overall survival despite a significant difference in response rates is probably due to this. In addition platinum was given as a single agent whereas the most common regimen in the UK is the combination of platinum with 5-Fluorouracil [A+A Tracker 2008 – appendix M1].

EMR 62202-008 has also been excluded from further discussion as this was primarily a safety study to examine the tolerability of combination of platinum, 5-FU and cetuximab and to determine the optimum dose of 5-FU to carry forward to the pivotal phase III study. It was conducted in only a small number of patients and had no control arm to examine the additional efficacy of the addition of cetuximab to conventional chemotherapy regimens.

6.2.4 List of relevant non-randomised controlled trials

None have been included.

6.2.5 Ongoing studies

We are not aware of any ongoing studies relevant to the decision problem.

6.3 Summary of methodology of relevant RCTs

6.3.1 Methods

EXTREME was an open-label, randomised, controlled multi-centre phase III study in subjects with recurrent and/or metastatic SCCHN who had not received previous CTX for this setting. Enrolment of 420 subjects was planned. 442 subjects were actually randomised at 80 centres in Europe: Austria (3), Belgium (5), Czech Republic (2), France (12), Germany (8), Hungary (4), Italy (5), Netherlands (4), Poland (5), Portugal (3), Russia (4), Slovakia (2), Spain (9), Sweden (3), Switzerland (3), UK (4), and Ukraine (4).

Subjects were randomised 1:1 to one of the following treatments:

Group A: Combination of cetuximab plus cisplatin or carboplatin and 5-FU
Group B: Cisplatin or carboplatin and 5-FU only.

Randomisation was performed centrally using an interactive voice response system (IVRS). Randomisation was stratified according to previous CTX (yes/no) and Karnofsky Performance Status (KPS) (<80/≥80).

Definition of treatment cycle: The ideal cycle in each group was defined as 21 days determined by CTX as follows:

> **Group A**: 1 treatment cycle consisted of dosing with CTX plus cetuximab on day 1, and doses of cetuximab on days 8 and 15, with follow-up through to day 20 of the cycle.
>
> **Group B**: 1 treatment cycle consisted of dosing with CTX on day 1 with follow-up through to day 20 of the cycle.

Cetuximab Regimen for Subjects in Group A

Cetuximab every 7 days	First infusion	All subsequent infusions
Cetuximab	400 mg/m² intravenous infusion over 120 min	250 mg/m² intravenous infusion over 60 min

Chemotherapy Regimen Every 21 Days in Groups A and B

Order of administration	Drug	Dose
First	**Cisplatin** 60-min infusion on day 1	100 mg/m²
Or	**Carboplatin** 60-min infusion on day 1	AUC 5
Then	**5-Fluorouracil** day 1 to day 4	1000 mg/m²/day continuous infusion

Duration of treatment for subjects in Group A: Subjects with absence of Progressive Disease (PD) and no unacceptable toxicity received 6 cycles of study treatment. Subjects with unacceptable toxicity due to one of the study drugs received the tolerated drug(s) until PD. Study treatment was discontinued earlier on occurrence of PD or unacceptable toxicity. If treatment with cetuximab was delayed because of related toxicity, the 21-day rhythm of CTX was retained. A maximum of 2 consecutive cetuximab infusions were able to be withheld (no more than 21 days without cetuximab infusions). After this, the subject had to be withdrawn, and all study treatments stopped. If treatment was delayed because of toxic effects of CTX, the 7-day rhythm of cetuximab infusions was retained. CTX was able to be delayed for a maximum of 21 days; after this, the subject had to be withdrawn from CTX, but cetuximab could be continued as monotherapy if the subject was still benefiting from treatment.

Duration of treatment for subjects in Group B: Subjects with absence of PD and unacceptable toxicity received a maximum of 6 cycles of CTX. Subjects with unacceptable toxicity due to one of the study drugs received the tolerated drug(s) until PD or up to a maximum of 6 cycles. Study treatment was discontinued earlier on occurrence of PD or unacceptable toxicity. CTX was able to be delayed for a maximum of 21 days, after this, the subject had to be withdrawn from CTX.

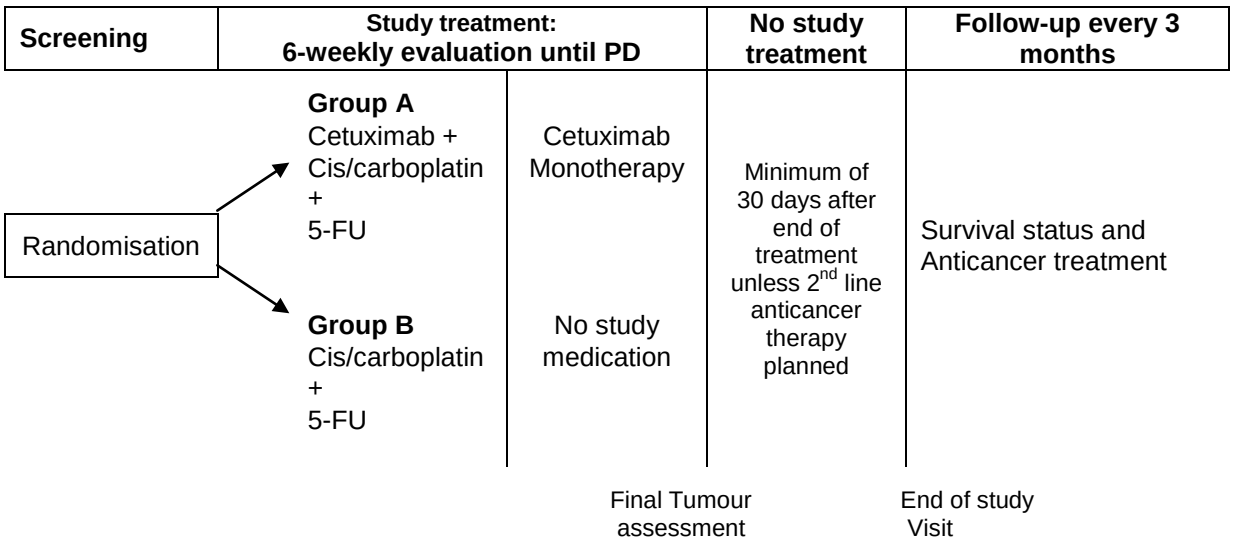
Subjects who stopped treatment in either treatment group before the occurrence of PD remained in the study and continue to be assessed for response every 6 weeks until PD. Upon occurrence of PD, all study medication was discontinued, and a final tumour assessment (FTA) visit was carried out. This was followed by an end-of-study (EoS) visit no earlier than 30 days after the last study treatment, but always before the start of any new anticancer therapy.

For patients who responded (complete response [CR] or partial response [PR]), confirmation by computed tomography (CT) or magnetic resonance imaging (MRI) had to be done at the earliest 4 weeks later (could be included in the next 6-weekly evaluation visit). If the investigator suspected PD at any time, CT or MRI was permitted at any time.

Follow-up for survival: After the EoS visit, follow-up evaluations were performed in all subjects every 3 months to collect information on further anticancer treatment and OS time.

Quality of life: The EORTC QLQ-C30 questionnaire and its head and neck symptomatic module, the EORTC QLQ-H&N35 were used to assess QoL in both treatment groups throughout the study.

The overall study design is summarised in the following diagram.



All subjects remained in the study until PD, unacceptable toxicity, or withdrawal of consent (whichever occurred first).

The recruitment period lasted from December 2004 to December 2005 (first patient in: 21 December 2004; last patient in: 30 December 2005). The data cut-off point for the study was 12 March 2007.

6.3.2 Participants

Inclusion Criteria

All of the following criteria had to be fulfilled for inclusion in the study:

- Signed written informed consent before any study-related activities.
- Men or women aged ≥18 years.
- Histologically or cytologically confirmed diagnosis of SCCHN.
- Recurrent and/or metastatic SCCHN, not suitable for local therapy.
- At least 1 bi-dimensionally measurable lesion either by CT scan or MRI.
- KPS of ≥70 at study entry.
- Neutrophils ≥1500/mm^3, platelet count ≥100000/mm^3, and haemoglobin ≥9 g/dL.
- Total bilirubin ≤2 x upper limit of normal (ULN); aspartate-aminotransferase (AST) and alanine-aminotransferase (ALT) ≤3 x ULN.
- Creatinine clearance >60 mL/min.
- Tumour tissue available for immunohistochemical evaluation of EGFR expression.
- Effective contraception for both male and female subjects if risk of conception exists.

Exclusion Criteria

Subjects who fulfilled one or more of the following criteria were not eligible for the study:

- Prior systemic chemotherapy, except if given as part of a multimodal treatment for locally advanced disease which was completed more than 6 months prior to study entry.
- Surgery (excluding prior diagnostic biopsy), or irradiation within 4 weeks before study entry.

- Presence of nasopharyngeal carcinoma.
- Active infection (infection requiring IV antibiotics), including active tuberculosis, and known and declared human immunodeficiency virus infection.
- Uncontrolled hypertension defined as systolic blood pressure ≥180 mmHg and/or diastolic blood pressure ≥130 mmHg under resting conditions.
- Pregnancy (absence confirmed by serum β-human chorionic gonadotropin test) or lactation period.
- Concomitant chronic systemic immune therapy, or hormonal therapy as cancer therapy.
- Other concomitant anticancer therapies.
- Documented or symptomatic brain or leptomeningeal metastasis.
- Clinically relevant coronary artery disease or history of myocardial infarction in the last 12 months or high risk of uncontrolled arrhythmia or uncontrolled cardiac insufficiency.
- Previous treatment with monoclonal antibody therapy, or other signal transduction inhibitors or EGFR targeting therapy.
- Previous or current other squamous cell carcinoma.
- Evidence of previous other malignancy within the last 5 years.
- Any investigational medication within 30 days before study entry.
- Medical or psychological condition that would not permit the subject to complete the study or sign informed consent.
- Known drug abuse (except alcohol abuse).
- Known allergic reaction against any of the components of the study treatment.

The baseline characteristics of subjects in each group were comparable and are detailed in table B.2 overleaf. As can be seen the two groups were well balanced by baseline demographics and nature of disease.

Table B2: Baseline characteristics of subjects in EXTREME study

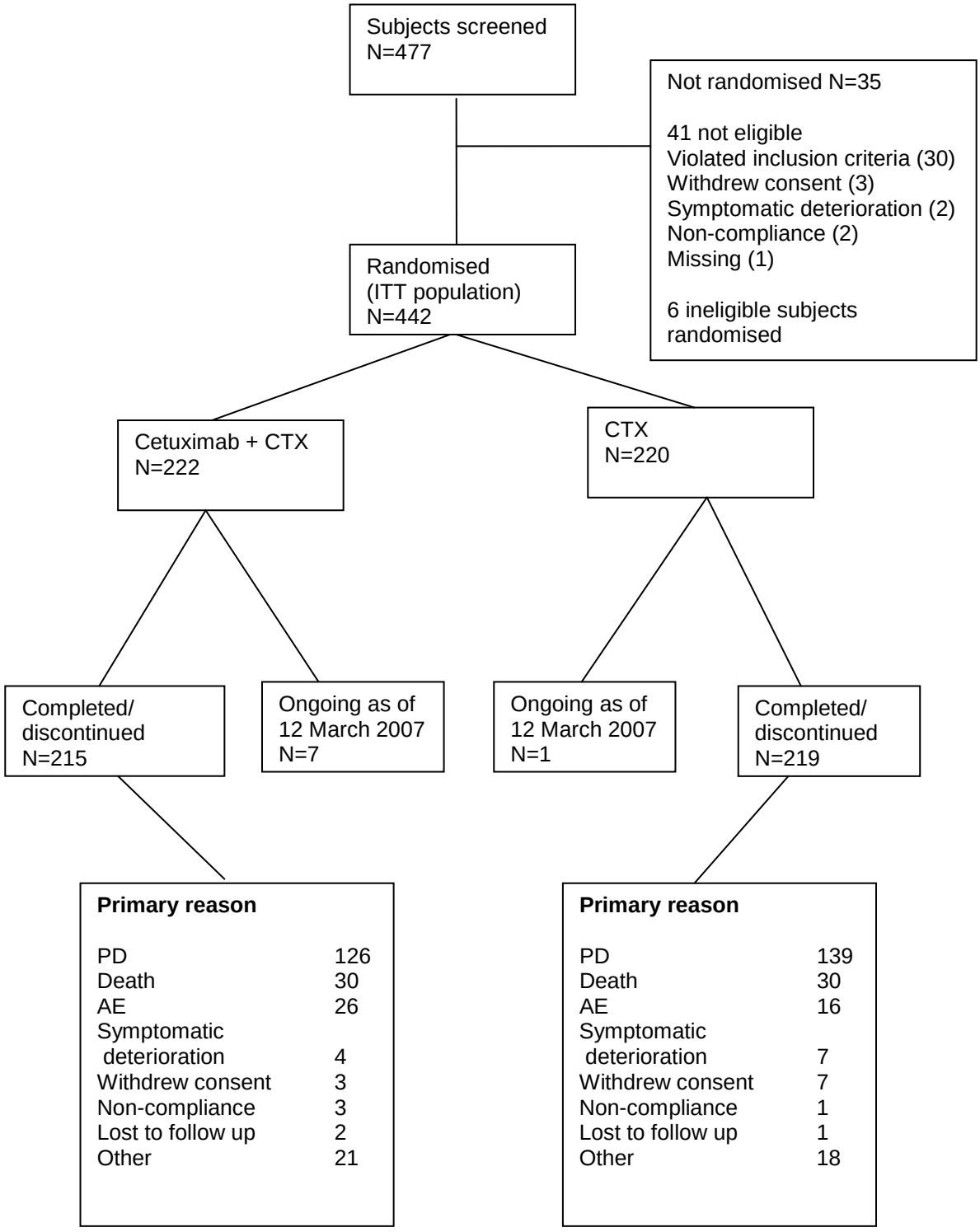
Characteristic		Cetuximab + CTX N=222 (%)	CTX N=220 (%)
Gender	Male	197 (88.7)	202 (91.8)
	Female	25 (11.3)	18 (8.2)
Age (years)	Mean ± SD	57.1 ± 8.0	56.7 ± 8.7
	Median	56	57
	Q1-Q3	51 – 62	51 – 62
Age categories (years)			
	< 65	183 (82.4)	182 (82.7)
	≥ 65	39 (17.6)	38 (17.3)
Site of primary tumour	Oropharynx	80 (36.0)	69 (31.4)
	Hypopharynx	28 (12.6)	34 (15.5)
	Larynx	59 (26.6)	52 (23.6)
	Oral Cavity	46 (20.7)	42 (19.1)
	Other	9 (4.1)	23 (10.5)
Type of tumour	Recurrent, not metastatic	118 (53.2)	118 (53.6)
	Metastatic, including recurrent	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	202 (91.0)	201 (91.4)
	Radiotherapy (excluding palliative)	189 (85.1)	190 (86.4)
	Surgery	174 (78.4)	176 (80.0)
	Chemotherapy	143 (64.4)	135 (61.4)
	Radiochemotherapy (excluding palliative)	90 (40.5)	80 (36.4)
	Neoadjuvant chemotherapy	69 (31.1)	60 (27.3)
	Other	24 (10.8)	33 (15.0)
		1 (0.5)	2 (0.9)

6.3.3 Patient numbers

477 subjects were screened at 81 centres. 41 subjects were not eligible for treatment at the end of screening .The reasons were: inclusion or exclusion criteria not fulfilled (30), death and withdrawal of consent (3 each), symptomatic deterioration (2), non-compliance with study timelines (1), refusal to continue study procedures but willing to have further data collected (1), missing (1). 436 patients were therefore eligible for treatment. However, 6 of the ineligible patients were randomised, leaving 442 subjects at 80 centres. Therefore only 35 screened subjects were not randomised.

A flow diagram of the disposition of subjects throughout the study is given overleaf.

Flow Diagram Showing Number of Subjects in Each Stage of the Study



6.3.4 Outcomes

EXTREME **EMR 62202-002**
Primary outcome measure
Overall survival time defined as the time from day of randomisation to death
Secondary outcome measures
Progression free survival time
Best overall response and disease control
Duration of response
Time to treatment failure
Quality of life
Safety
Drug exposure
Adverse events
Reasons for deaths
Safety Laboratory values
Vital signs

Response Criteria per Timepoint

Overall response was based on the assessments for index and non-index lesions and on the occurrence of new lesions. Definitions were as follows:

Evaluation of response based on index lesions.

Complete Response (CR)	Disappearance of all index lesions
Partial Response (PR)	A 50% or more decrease in the SOPD of index lesions compared to the baseline SOPD, with no evidence of PD
Stable Disease (SD)	Neither sufficient decrease to qualify for PR nor sufficient increase to qualify for PD
Progressive disease (PD)	A 25% or more increase in the SOPD of index lesions, compared to the smallest SOPD recorded for the study period (nadir SOPD)

SOPD = sum of the product of diameters

Evaluation of response based on non-index lesions

Complete Response (CR)	Disappearance of all non-index lesions. No new lesions
No change (NC)	No significant change in non-index lesions to qualify for either CR or PD. No new lesions.
Progressive disease (PD)	Appearance of one or more new lesions, and/or unequivocal progression of existing non-index lesions (worsening or new effusions or ascites was not considered radiologic progression)

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of PD at the time point in question were classified as having “symptomatic deterioration”. Every effort was to be made to document the objective progression even after discontinuation of treatment.
If residual disease had to be distinguished from normal tissue, residual lesion was to be further investigated by fine-needle aspiration or biopsy before confirming the CR status.

The overall response per time point was derived from the tumour response assessments obtained for index lesions and non-index lesions with or without appearance of new lesions at the respective time point. Overall responses for all possible combinations of tumour responses are provided in the following table. Assessments of overall response were provided for each visit at which response evaluation is scheduled.

Overall Response per Timepoint Assessment

Index lesions	Non-index lesions	New lesions	Overall response
CR	CR	No	CR
CR	NC	No	PR
PR	CR or NC	No	PR
SD	CR or NC	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

If no technically adequate baseline imaging data were available for one or more regions (e.g. abdomen and chest):

- The response assessment was based on the available scans from other regions if no lesions were detected in follow-up scans of unavailable regions at baseline.
- If one or more lesions were detected on follow-up scans of unavailable regions at baseline, then these lesions were regarded as new lesions, resulting in an overall response of PD for this time point.

If at any time point no technically adequate scans were available for one or more regions that were involved at baseline, and there was no evidence of PD on the available scans:

- If unavailable regions at a follow-up time point contained no index lesions, then the response assessment was based on the lesions of the available scans.

- If one or more index lesions were located in previously unavailable regions at a follow up, then an overall response of PD was assigned at the time point when not all scans were available. This assignment was subject to review and change before determination of the best overall response across all time points.

Confirmation Criteria and Best Overall Response According to Modified WHO Criteria

The best overall response was to be derived from the assessments of overall response at the individual time points using the following algorithm.

- To be assigned a status of CR, changes in tumour measurements must have been confirmed to show disappearance of all lesions by a repeat, directly consecutive CR assessment no less than 4 weeks after the criteria for CR were first met.
- To be assigned a status of PR, changes in tumour measurements must have been confirmed to show a 50% decrease in SOPD compared to baseline by a repeat CR or PR assessment (not necessarily consecutive) no less than 4 weeks after the criteria for PR were first met.
- If the best response was SD, measurements must have met the SD criteria at least once no less than 6 weeks after first dose of treatment, otherwise the best response was classed as not evaluable (NE).

If an overall response of PD was assigned to a time point due to unavailable scans, and was followed by a timepoint with no evidence of PD, then the timepoint with unavailable scans was overruled in determination of the best overall response. Otherwise the response remained as PD.

The best possible overall response is CR, followed by PR, SD and PD. The confirmation process is summarised in the following table where the best two timepoints are considered. Except for CR, the two time points did not have to be consecutive. The second column applies only when the best response at the earlier time point was either CR or a PR. If there was only one follow-up time point, the second column does not apply. The best response can only be SD as confirmation was missing.

Best Overall Response

Earlier best response (not yet confirmed)	Later best response (confirmation)	Best overall response
CR	CR	CR
CR	No CR or missing	SD
PR	CR or PR	PR
PR	SD or PD or missing	SD
SD	not applicable	SD
PD	not applicable	PD

Once a CR was observed (confirmed or unconfirmed), any unequivocal reappearance of disease resulted in a classification of PD.

Once a PR was confirmed, the status remained PR until the criteria for PD were met.

If no baseline scans were available (or readable) or no follow-up scans were available (or readable), the best overall response was NE.

If no index lesion was present at baseline (protocol violation) and there was no evidence of PD at the first follow-up time point, the best overall response was NE.

In subjects with a confirmed CR or PR, the date of response was the date when the criteria for CR or PR were first met. The date of the scans determined the date of the response evaluation (CR, PR, SD). The date of PD was determined either by the date of the corresponding scan or by the date of the assessment of clinical deterioration.

6.3.5 Statistical analysis and definition of study groups

The efficacy analyses were ranked according to their clinical relevance as follows:

1. OS time.
2. Progression-free survival time.
3. Best overall response.
4. Disease control.
5. Time to treatment failure.
6. Duration of response.

The effect of this procedure is that no confirmatory claim can be based on variables that have a rank lower or equal to that variable whose null hypothesis was the first not to be rejected.

Primary Analysis: Overall Survival Time

Survival time was defined as the time in months from randomisation to the date of death. If a subject had not died, the survival time was censored at the last date the subject was known to be alive or if this date was after data cut-off, the date of data cut-off. The primary analysis tested the equality of OS time between treatment groups, applying the two-sided stratified log-rank test (ά=5%) taking into account strata used for randomisation (previous CTX: no/yes and KPS: <80/≥80).

The following null-hypothesis was tested:

$H0: \lambda_A(t)=\lambda_B(t)$ *versus* $H1: \lambda_A(t)=\theta\lambda_B(t), \theta\neq 1$

where $\lambda(t)$ represents the hazard at time t and θ the unknown constant of proportionality of hazards in treatment groups A and B.

Determination of Sample Size

The sample size calculation was based on the following assumptions:

- α=0.05 (two-sided).
- Power=80%.
- Increase of the median OS time from 7 months to 9.5 months (i.e. about 36% increase in median survival time).

This resulted in a required number of 340 deaths (events).

Further assumptions:

- Average randomisation of 21 subjects per month.
- 14 months of follow-up after randomizing the last subject.
- Median OS time of 7 months in the control arm.
- 5% of subjects lost to follow-up.

These assumptions resulted in a requirement for 420 subjects to be randomised within 20 months to observe the required number of deaths approximately 34 months after randomisation of the first subject.
The duration of the study was determined by the time point when 340 deaths had been reported. A study duration of between 32 and 36 months was expected, depending on the median OS time of the CTX group, which was expected to lie between 6 and 8 months.
However, the number of 340 events was selected to ensure an 80% power to detect an increase in median OS time of about 36%, regardless of the median OS time in the CTX group.

The following subgroup analyses were conducted and are listed in table B3 overleaf.

Table B3: Planned subgroup analyses for EXTREME study

Variable	Categories				
Age (years)	<65		>65		
Gender	Male		Female		
Ethnic origin	Caucasian		Other		
KPS	<80		≥80		
Previous chemotherapy	Yes		No		
Previous neoadjuvant chemotherapy	Yes		No		
Prior radiotherapy	Yes		No		
Prior radiochemotherapy	Yes		No		
Prior surgery	Yes		No		
Start of platinum therapy	Cisplatin		Carboplatin		
EGFR staining (%)	0	>0 to <40	≥40	missing	
Type of primary tumour	Recurrent, not metastatic		Metastatic, including recurrent		
Site of origin of primary	Oropharynx	Hypopharynx	Larynx	Oral Cavity	Other
Disease stage at first diagnosis	<III	III	IV		
Histology	Well or moderately differentiated	Poorly differentiated	None otherwise specified/ missing		
On-study skin reaction (highest grade)	0	1or 2	3 or 4	1-4	2-4
On-study acne-like rash (highest grade)	0	1or 2	3 or 4	1-4	2-4
FISH Test	Positive		Negative		
Global quality of life at baseline: as estimated by items 29 and 30 of the EORTC QLQ-C30	≤ median		≥ median		

6.3.6 Critical appraisal of relevant RCTs

How was allocation concealed?

This randomised, controlled study was open-label. A central, stratified, permuted-block randomisation procedure was used to balance prognostic factors between treatment groups and to minimise the predictability of treatment allocation in this open-label study.

• What randomisation technique was used?

All subjects were assigned a 4-digit subject number in ascending order (first subject in a centre is 0001, second 0002, etc.) by the investigator at the screening visit. Subjects who entered the study retained this number throughout. Subjects from different centres were identified by a unique 8-digit number (0101-0001, 0101-0002 etc.). The first 2 digits of this number indicate the country, the 3rd and 4th digits indicate the centre number, and the last 4 digits are the number assigned to the subject at the screening visit.

Once an eligible subject was identified and informed consent had been obtained, the centre called an interactive voice-response randomisation and received instructions regarding treatment allocation. Allocation to the 2 treatment groups was in the ratio 1:1.

Randomisation was stratified for the most important prognostic factors (previous CTX [yes/no] and KPS [<80 vs ≥80]) using randomised permutated blocks to balance these factors across the treatment groups and thus improve comparability of the results.

• Was a justification of the sample size provided?

Yes, the sample size was calculated to provide the statistical power necessary to show the difference in treatment groups as described in section 5.3.5.

• Was follow-up adequate?

All subjects were followed up until death or discontinuation which allowed the study to accurately determine overall survival.

• Were the individuals undertaking the outcomes assessment aware of allocation?

Investigators making assessments of outcomes were aware of allocation as this was an open label study. Clear guidance for the assessment of response was given in the protocol to minimise the possibility of bias.

• Was the design parallel-group or crossover? Indicate for each crossover trial whether a carry-over effect is likely.

This study was a parallel group study.

• Was the RCT conducted in the UK (or were one or more centres of the multinational RCT located in the UK)? If not, where was the RCT conducted, and is clinical practice likely to differ from UK practice?

The EXTREME study (EMR 62202-002) was a multinational trial with 4 centres located in the UK.

• How do the included in the RCT participants compare with patients who are likely to receive the intervention in the UK? Consider factors known to affect outcomes in the main indication, such as demographics, epidemiology, disease severity and setting.

The population treated in the EXTREME study is comparable to the population of patients in the UK anticipated to be treated with cetuximab in combination with platinum based chemotherapy.

• For pharmaceuticals, what dosage regimens were used in the RCT? Are they within those detailed in the Summary of Product Characteristics?

The cetuximab regimen used was 400 mg cetuximab per m^2 body surface area on day 1. Then, subsequent weekly doses of 250 mg/m^2. Cetuximab treatment is continued until progression of the underlying disease. This is consistent with the anticipated dosage regimen in the Summary of product characteristics for cetuximab.

The regimens for carboplatin, cisplatin and 5-FU are consistent with the summary of characteristics for those drugs.

• Were the study groups comparable?

The baseline characteristics are balanced between the two treatment arms with respect to baseline demographics, nature of disease and prior treatment.

• Were the statistical analyses used appropriate?

Yes, they are the standard analyses undertaken for this type of research.

• Was an intention-to-treat analysis undertaken?

Yes an ITT analysis was undertaken for this study.

• Were there any confounding factors that may attenuate the interpretation of the results of the RCT(s)?

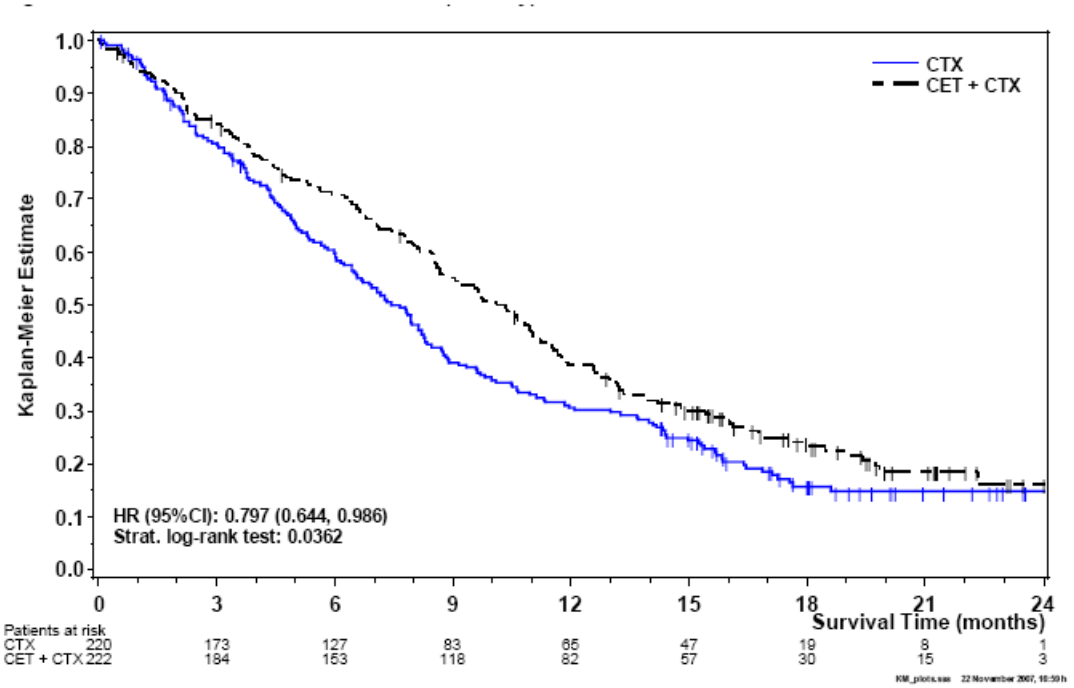
No.

6.4 Results of the relevant comparative RCTs

Overall Survival

The primary outcome of the EXTREME study was overall survival. For this measure, a statistically significant and clinically significant improvement in overall survival was demonstrated in the cetuximab + CTX arm over the CTX arm. Median overall survival was increased from 7.4 months (95% CI:6.4, 8.3) to 10.1 months (95% CI:8.6, 11.2). The hazard ratio was 0.797 (95% CI 0.644, 0.986, p=0.0362).

Figure B2 – Kaplan Meier graph of overall survival for EXTREME study



A planned sensitivity analysis of overall survival was performed by prognostic factor. This demonstrated that previous exposure to chemotherapy had no prognostic relevance (HR of 0.999) but a KPS ≥ 80 notably reduced the risk of death by 49%. In addition subjects with metastatic SCCHN had a reduced risk of death compared to those with only locally recurrent SCCHN (HR 0.814, 95%CI – 0.656, 1.009). The full details of the sensitivity analysis are given below:

Prognostic factor	Statistic			
	N	P value	HR	95% CI
Type of primary tumour				
Recurrent, not metastatic	236			
Metastatic, inc recurrent	206	0.0607	0.814	[0.656, 1.009]
Karnofsky performance status				
<80	52			
≥80	390	<0.0001	0.508	[0.374, 0.689]
Previous Chemotherapy				
Yes	170			
No	272	0.9934	0.999	[0.802, 1.245]
Treatment group				
CTX	220			
Cetuximab + CTX	222	0.0269	0.786	[0.636, 0.973]

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

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

Figure B3: Forest plots for hazard ratios of overall survival for pre-planned subgroups in EXTREME study

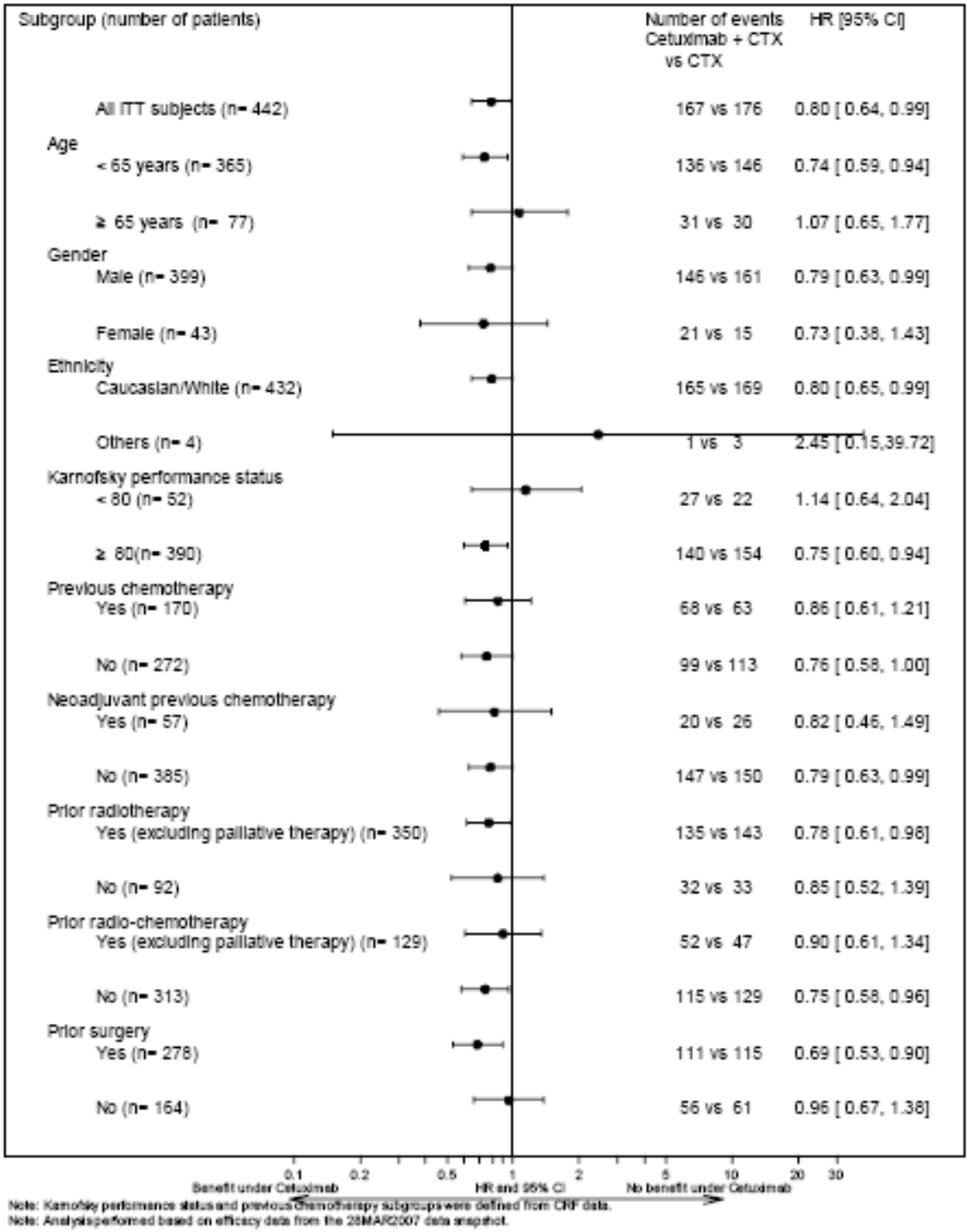
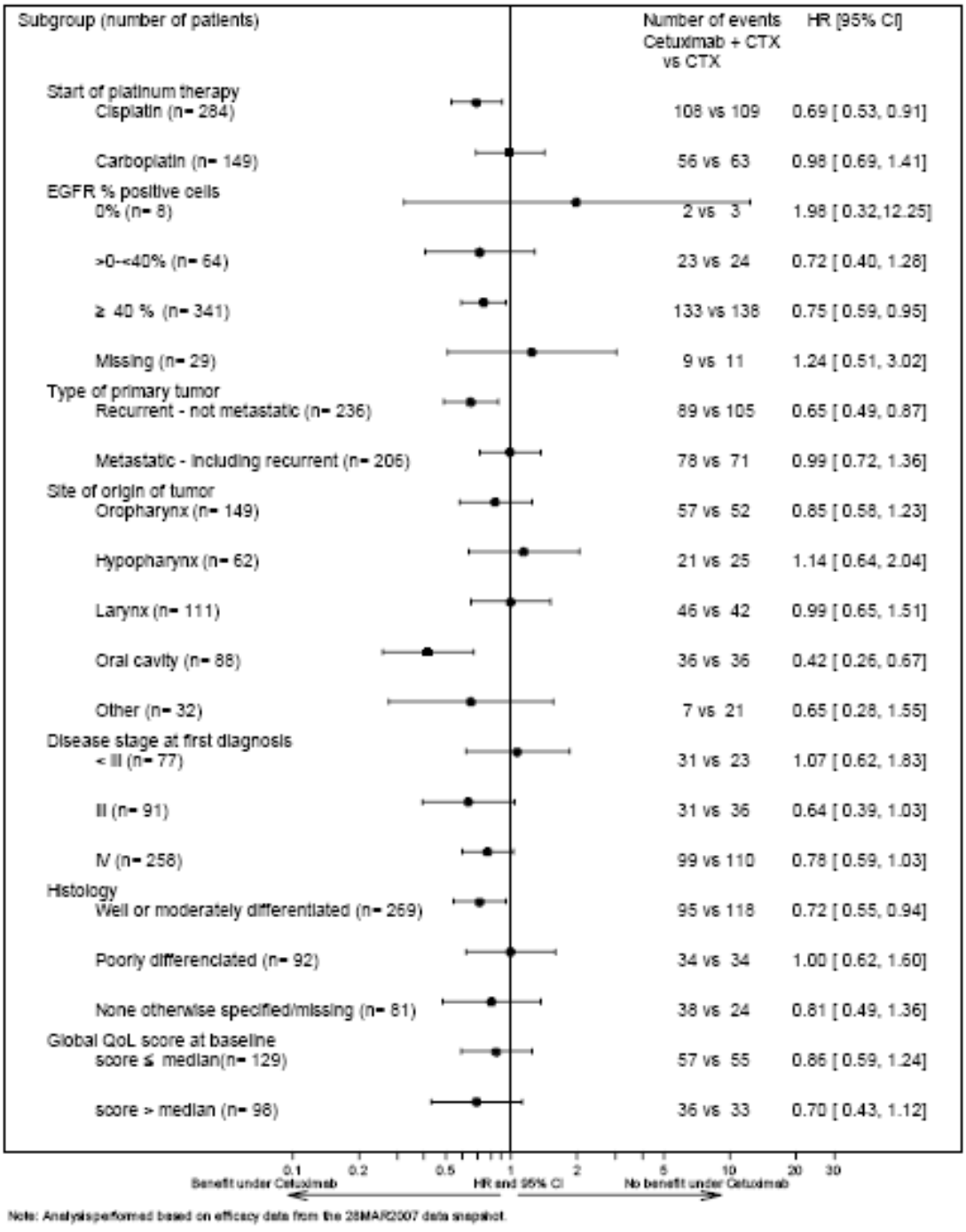


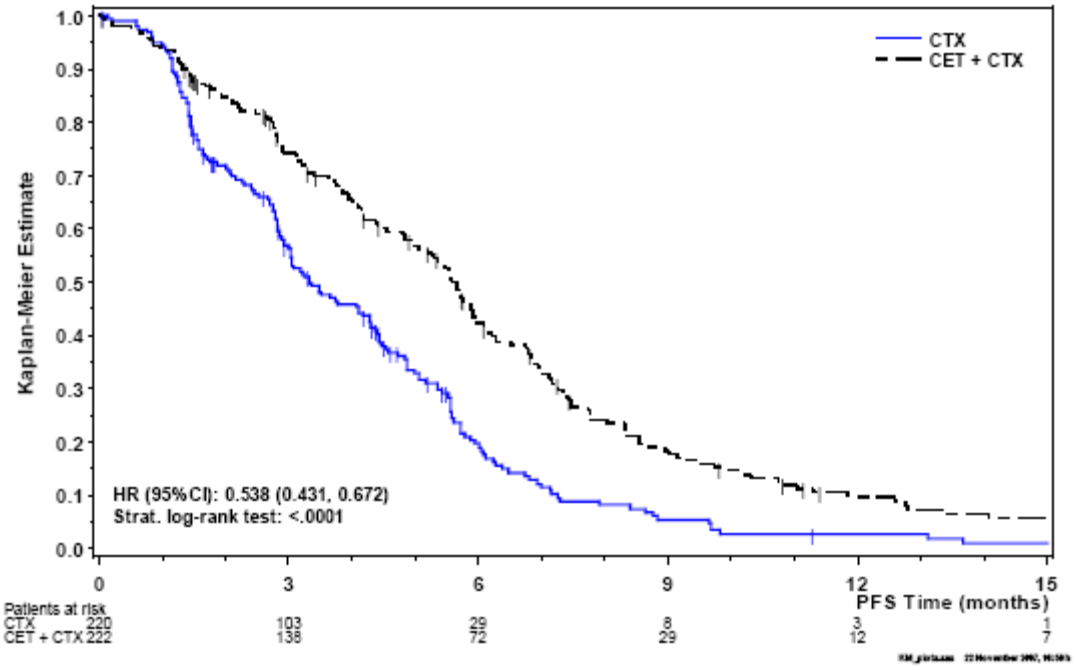
Figure B3: (cont). Forest plots for hazard ratios of overall survival for pre-planned subgroups in EXTREME study



Progression free survival

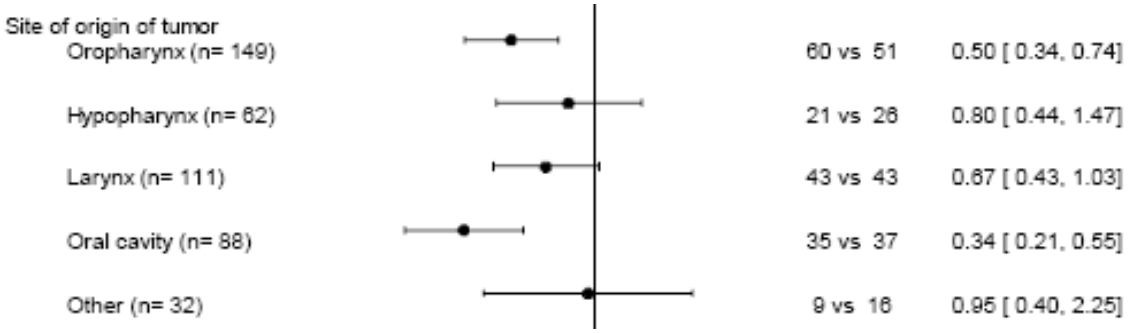
There was a significant prolongation of progression-free survival (PFS) time in the cetuximab + CTX arm compared to the CTX alone arm. The median PFS in the CTX group was 3.3 months and in the cetuximab+CTX group it was 5.6 months. The hazard ratio was 0.538 (95% CI 0.431, 0.672). The Kaplan Meier estimates are given in the figure below:

Figure B4. Kaplan Meier graph for progression free survival (PFS) for EXTREME study.



Sub group analysis of the progression free survival results again indicated heterogeneity of response with less fit patients showing less benefit of the addition of cetuximab to standard chemotherapy. Also, the differences in the responses, dependent on tumour site, were evident. The increase in progression free survival by the addition of cetuximab to chemotherapy was seen most markedly in the patients with tumours of the oral cavity and oropharynx and was not statistically significant in patients with tumours located in the hypopharynx and larynx. The forest plot for PFS for the tumour location sub-groups is given in the figure below.

Figure B5: Selected Forest plot of progression free survival (PFS) by tumour locations for EXTREME study.



Response rate

A secondary outcome was response rate. Analyses show that the response rate in the cetuximab + CTX arm is significantly greater than in the CTX alone arm. Detail of the response rates is given in the figure below:

Response Variable	**Number (%) of subjects, ITT population**	
	Cetuximab + CTX (N=222)	**CTX (N=220)**
Best overall response		
Complete response	15 (6.8)	2 (0.9)
Partial Response	64 (28.8)	41 (18.6)
Stable disease	101 (45.5)	89 (40.5)
Progressive disease	12 (5.4)	45 (20.5)
Not evaluable	30 (13.5)	43 (19.5)
Best overall response rate (%[95%CI])	35.6 [29.3, 42.3]	19.5 [14.5, 25.4]
CMH test		
P value	0.0001	
Odds ratio [95% CI]	2.326 [1.504, 3.600]	
Disease Control rate (% [95% CI])	81.1 [75.3, 86.0]	60.0 [53.2, 66.5]
CMH test		
P value	<0.0001	
Odds ratio [95% CI]	2.881 [1.870, 4.441]	

A subgroup analysis of response rates was performed according to whether subjects were initially treated with either carboplatin or cisplatin based chemotherapy in the study. These sub-analyses showed that there was a significant improvement in

response rate in the cetuximab arm compared with the CTX arm irrespective of chemotherapy chosen. However the absolute response rates for subjects treated with carboplatin are lower in all groups than for those treated with cisplatin. This may reflect a lower efficacy of carboplatin or a bias towards using carboplatin in those patients with lower performance status or other co morbidities. Details of this sub-analysis are given in the table below:

Response variable	**Number (%) of subjects, ITT population**	
	Cetuximab + CTX	**CTX**
Therapy started with CISPLATIN	(N=149)	(N=135)
Best overall response rate (%[95%CI])	38.9 [31.1, 47.2]	23.0 [16.2, 31.0]
P value (CMH test)	0.0035	
Odds ratio [95% CI]	2.181 [1.289,3.691]	
Disease Control rate (% [95% CI])	81.9 [74.7, 87.7]	63.0 [54.2, 71.1]
P value (CMH test)	0.0004	
Odds ratio [95% CI]	2.631 [1.521,4.551]	
Therapy started with CARBOPLATIN	(N=69)	(N=80)
Best overall response rate (%[95%CI])	30.4 [19.9, 42.7]	15.0 [8.0, 24.7]
P value (CMH test)	0.0267	
Odds ratio [95% CI]	2.452 [1.102,5.458]	
Disease Control rate (% [95% CI])	84.1 [73.3, 91.8]	58.8 [47.2, 69.6]
P value (CMH test)	0.0007	
Odds ratio [95% CI]	3.879 [1.735,8.675]	

Quality of Life

Special attention was given to the EORTC QLQ-C30 social functioning scale as it was expected that this scale was likely to be impacted by skin reactions related to cetuximab. However, no statistically significant differences were observed between the treatment groups for the social functioning scale suggesting that the addition of cetuximab did not have a negative effect on social functioning. In the analysis of the worst score post baseline, generally the results favoured the cetuximab arm however none of the differences were considered statistically significant.

For the QLQ-H&N35 questionnaire the results were in general favourable to the cetuximab + CTX treatment arm. Longitudinal analyses were also carried out for the QLQ-H&N35 and statistically significant differences were found at cycle 3 in the pain, swallowing, speech problems and social eating items. These results were confirmed by the analysis of the change from baseline to worst post-baseline in which significant differences for the pain and swallowing items were found.

Thus there is evidence to suggest that the addition of cetuximab helps in alleviating the symptoms associated with H&N cancer. There was no evidence of a statistically significant difference in treatment groups in any of the items at month 6. However, this may be due to the small sample size at month 6.

In conclusion, when using summary measures to compare the treatment groups the differences indicated that the addition of cetuximab exhibited trends towards a better QoL. The treatment differences obtained from the longitudinal model and the analyses using pattern-mixture modelling yielded some statistically significant findings consistently indicating lower levels of symptoms and a better QL in the cetuximab+CTX group compared with CTX alone. Importantly, the addition of cetuximab did not impair the social functioning as was initially hypothesized.

Thus, it could be concluded that the addition of cetuximab to CTX had a positive impact on the QoL of patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck.

However the proportion of completed QLQ-C30 questionnaires which were considered evaluable was quite low and the more conservative assumption is that the addition of cetuximab to standard chemotherapy has no adverse effect on quality of life.

6.5 Meta-analysis

No meta analyses were conducted.

6.6 Indirect/mixed treatment comparisons

No indirect/mixed treatment comparisons were conducted.

6.7 Safety

The incidence of adverse events in each group was broadly similar indicating that the addition of cetuximab to standard chemotherapy does not significantly increase toxicity of treatment. The exceptions to this were rash, acne, acneiform dermatitis, dry skin and anorexia which occurred more frequently (≥10% difference) in the cetuximab + CTX group than in the CTX group.

The following AEs also occurred more frequently in the cetuximab + CTX group, but the difference was less than 10%: nausea, diarrhoea. Pyrexia, hypocalcaemia and hypomagnesemia. In addition the following AEs occurred only in the cetuximab + CTX group: conjunctivitis, paronychia, pruritus, exfoliative rash, and skin toxicity.

These findings are consistent with the known safety profile of cetuximab except diarrhoea and anorexia.

The full listing of adverse events occurring in ≥10% of subjects in either group is given in the following table:

Adverse events reported in ≥10% of subjects in either group.

Preferred term	Number (%) of subjects	
	Cetuximab + CTX (N=219)	CTX (N=215)
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)
Neutropaenia	84 (38.4)	84 (39.1)
Rash	61 (27.9)	4 (1.9)
Aesthaenia	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)
Thrombocytopaenia	48 (21.9)	52 (24.2)
Constipation	48 (21.9)	43 (20.0)
Acne	48 (21.9)	0
Leukopaenia	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)
Hypomagnasaemia	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)

The majority of more severe AEs (Grade 3 or 4) including haematological toxicities occurred with similar frequencies in both treatment groups. As expected, rash was reported only for the cetuximab treatment group. The full listing of the most common severe AEs is given in the table below.

Grade 3 or 4 adverse events reported in ≥5% of subjects or grade 4 AEs reported in ≥1% of subjects in either group.

Preferred term	Number (%) of subjects			
	Grade 3 or 4 events		Grade 4 events	
	Cetuximab + CTX (N=219)	CTX (N=215)	Cetuximab + CTX (N=219)	CTX (N=215)
Any event	179 (81.7)	164 (76.3)	67 (30.6)	66 (30.7)
Neutropaenia	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)
Thrombocytopaenia	24 (11.0)	24 (11.2)	0	3 (1.4)
Leukopaenia	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)
Hypomagnasaemia	11 (5.0)	3 (1.4)	8 (3.7)	1 (0.5)
Rash	11 (5.0)	0	0	0
Febrile Neutropaenia	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)

6.8 Non-RCT evidence

6.8.1 Summary of methodology of relevant non-RCTs

Not applicable.

6.8.2 Critical appraisal of relevant non-RCTs

Not applicable.

6.8.3 Results of the relevant non- RCTs

Not applicable.

6.9 Interpretation of clinical evidence

6.9.1 Provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

As described, the prognosis for patients with recurrent and/or metastatic SCCHN is poor. There have been no new therapies that have demonstrated an increase in overall survival beyond standard chemotherapy until the EXTREME study. The increase in overall survival represents a 36% (2.1/7.4 months) increase in overall survival in a group of patients who are over-represented by the socially disdvantaged.

Studies have shown that patients are far more likely to choose treatment that will give them only marginal life prolongation in the eyes of health care professionals [Matsuyama 2006]. An increase in life expectancy of 36% is very significant in this group of patients.

6.9.2 Identify any factors that may influence the applicability of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select suitable patients based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the Summary of Product Characteristics?

All data presented in this submission is within the anticipated licence wording and dosing regimen to be identified in the upcoming SPC.

There are no issues that have been identified that could affect the applicability of these results to patients in UK practice who would be likely to receive this treatment in combination with platinum based chemotherapy.

Although the averge patient in the EXTREME study is younger and fitter than the avearge patient in the UK with SCCHN. Only fitter and therefore possibly younger patients would be suitable for aggressive combined chemotherapy regimens for the treatment of their disease.

7 Cost effectiveness

7.1 Published cost-effectiveness evaluations

7.1.1 Identification of studies

Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided in appendix 3, section 9.3.

The literature review strategy was designed to retrieve cost effectiveness studies which were relevant to the decision problem of cetuximab (Erbitux) for the treatment of first line metastatic/recurrent head and neck cancer (RMHNC). OVID advanced search was used for both Embase and Medline and searches were carried out on Tueday 26th August 2008. The criterion utilised are presented below. All searches were limited to English and human:

- Metastatic head & neck cancer.
- Recurrent head and neck cancer.
- Metastatic/recurrent SCCHN (Squamous Carcinoma of the Head and Neck).
- Cetuximab.

These terms were combined together and searched with each of the following 'health economic' search criteria:

- Cost effectiveness analysis.
- Cost benefit analysis.
- QALY.
- Cost effectiveness.
- Quality of life.

All search terms were mapped to subject heading.

HEEDS was searched on 26/8/08 using the terms cetuximab and metastatic recurrent head & neck cancer.

The Centre for Reviews and Dissemination (CRD) website was also searched (**http://www.crd.york.ac.uk/CRDWeb/Search.aspx?DefaultOr=No&RPP=10&SessionID=538291&SearchID=538291&D=1&H=11&E=2&SearchFor=cetuximab&DB**=) using cetuximab as a search term.

7.1.2 Description of identified studies

Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. Where studies have been identified and not included, justification for this should be provided.

Neither the Medline nor the Embase reviews identified any economic analyses in the treatment of recurrent/metastatic head and neck cancer (RMHNC). The HEEDS search returned 3 papers;

1. A review the efficacy of cetuximab in this setting.
2. An overview of biomarkers in head and neck cancer.
3. On the subject of molecular pathogenesis of head and neck cancers.

The CRD database identified15 studies:

- 10 assessed second line or later therapy in metastatic colorectal cancer.
- The remaining 5 were horizon scanning documents.

Therefore this review did not identify any economic analyses in the RMHNC setting. Please see Appendix 3 for tables showing the full search strategy.

7.2 De novo economic evaluation(s)

In the absence of a relevant published economic evaluation, manufacturers or sponsors should submit their own economic evaluation. When estimating cost effectiveness, particular emphasis should be given to adhering to the 'reference case' (see the NICE document 'Guide to the methods of technology appraisal'). Reasons for deviating from the reference case should be clearly explained. Particularly important features of the reference case include those listed in the table below.

Element of health technology assessment	Reference case	Section in 'Guide to the methods of technology appraisal'
Defining the decision problem	The scope developed by the institute	5.2.5 & 5.2.6
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	5.2.5 & 5.2.6
Perspective costs	NHS and Personal Social Services	5.2.7 to 5.2.10
Perspective benefits	All health effects on individuals	5.2.7 to 5.2.10
Type of economic evaluation	Cost-effectiveness analysis	5.2.11 to 5.2.12
Synthesis of evidence on outcomes	Bases in a systematic review	5.3
Measure of health effects	QALYs	5.4
Source of data for measurement of HRQL	Reported directly by patients and carers	5.4
Source of preference data for valuation of changes in HRQL	Representative sample of the public	5.4
Discount rate	An annual rate of 3.5% on both costs and health effects	5.6
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	5.12

HRQL, health related quality of life; NHS, National Health Service; QALYs, quality-adjusted life years

Introduction

- A de novo economic evaluation is presented in this submission. The economic evaluation compares the costs and health outcomes of patients with recurrent and / or metastatic Head and Neck cancer (RMHNC) with the following treatment strategy:
    - Cetuximab in combination with platinum and 5FU containing regimens compared to a platinum and 5FU containing regimens alone.
- It is anticipated that the licence will be restricted to use *" in combination with* platinum-*based chemotherapy for recurrent and/or metastatic disease."*
- The term Head and Neck cancer encompasses a variety of relatively rare tumour sub-sites.
- This economic evaluation will focus on the expected licensed population and consider particular patient sub groups where greater clinical and economic benefit can be derived through the addition of cetuximab to platinum based treatment:
    - Patients with a good performance status.
    - Tumour sites where cetuximab in combination with chemotherapy has been shown to offer significant benefit over chemotherapy alone.
- The economic evaluation simulates the disease progression and survival of patients with RMHNC through three health states using both overall survival data and progression free survival data from the EXTREME study.
- Patients with recurrent/ metastatic SCCHN are predominantly those who are of a lower socioeconomic status and with a disease where there has been no innovation or improvement in outcome in recent years.

7.2.1 Technology

7.2.1.1 How is the technology (assumed to be) used within the economic evaluation? For example, give indications, and list concomitant treatments, doses, frequency and duration of use.

The purpose of this *de novo* economic evaluation is to estimate the cost-effectiveness of cetuximab in combination with chemotherapy (CCTX) compared to chemotherapy alone (CTX), in the treatment of recurrent/metastatic head and neck cancer and in those patients who are considered inappropriate for definitive (potentially curative) treatment with radiotherapy or surgery. Although the economic evaluation is trial-based, there is also a modelling component with regards to the extrapolation of health effects beyond the trial period.

It is assumed that the treatment regimens are as set out in the trial protocol of the pivotal EXTREME (EMR 62202-002) trial. Cetuximab was administered on a weekly basis at a dose of 400mg/m^2 for the first infusion followed by 250 mg/m^2 for subsequent infusions. It was given concurrently with combination chemotherapy using platinum and 5-FU for 21 weeks and was continued as a monotherapy until progression.

The ideal cycle in each group was defined as 21 days as follows:

Group A: 1 treatment cycle consisted of dosing with CTX plus cetuximab on day 1, and doses of cetuximab on days 8 and 15, with follow-up through to day 20 of the cycle.

Group B: 1 treatment cycle consisted of dosing with CTX on day 1 with follow-up through to day 20 of the cycle.

Tables H1 and H2 below present the planned dose regimens administered in the EXTREME study.

Table H1: Cetuximab Regimen for Subjects in Group A.

Cetuximab every 7 days	First infusion	All subsequent infusions
Cetuximab	400 mg/m² intravenous infusion over 120 min	250 mg/m² intravenous infusion over 60 min

Table H2: Chemotherapy Regimen Every 21 Days in Groups A and B.

Order of administration	Drug	Dose
First Or	**Cisplatin** 60-min infusion on day 1 **Carboplatin** 60-min infusion on day 1	100 mg/m² AUC 5
Then	**5-Fluorouracil** day 1 to day 4	1000 mg/m²/day continuous infusion

In accordance with the clinical trial protocol:

- Subjects with absence of Progressive Disease (PD) and no unacceptable toxicity received 6 cycles of study treatment.
- Subjects with unacceptable toxicity due to one of the study drugs received the tolerated drug(s) until PD.
- Study treatment was discontinued earlier on occurrence of PD or unacceptable toxicity.

- If treatment with cetuximab was delayed because of related toxicity, the 21-day schedule of CTX was retained.
- A maximum of 2 consecutive cetuximab infusions were able to be withheld (no more than 21 days without cetuximab infusions).
- After this, the subject had to be withdrawn, and all study treatments stopped.
- If treatment was delayed because of toxic effects of CTX, the 7-day schedule of cetuximab infusions was retained.
- CTX was able to be delayed for a maximum of 21 days; after this, the subject had to be withdrawn from CTX, but cetuximab could be continued as monotherapy if the subject was still benefiting from treatment.

7.2.1.2 Has a treatment continuation rule been assumed? Where the rule is not stated in the SmPC this should be presented as a separate scenario, by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.

A continuation rule has not been assumed in this economic model.

- the costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required)

Not applicable.

- the robustness and plausibility of the endpoint on which the rule is based

Not applicable.

- whether the 'response' criteria defined in the rule can be reasonably achieved

Not applicable.

- the appropriateness and robustness of the time at which response is measured

Not applicable.

- whether the rule can be incorporated into routine clinical practice

Not applicable.

- whether the rule is likely to predict those patients for whom the technology is particularly cost effective

Not applicable.

- issues with respect to withdrawal of treatment from non-responders and other equity considerations

Not applicable.

7.2.2 Patients

7.2.2.1 What group(s) of patients is/are included in the economic evaluation? Do they reflect the licensed indication? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem?

As yet the EMEA has not approved cetuximab for its licence extension and at the time of this submission, the CHMP decision has not yet commented on the proposed licence wording. However, the indication relevant to the decision problem is anticipated to be:

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 population of the pivotal clinical trial (EXTREME) is considered in the economic evaluation, that is, those eligible for treatment for 1st line treatment of recurrent and/or metastatic SCCHN.

7.2.2.2 Was the analysis carried out for any subgroups of patients? If so, how were these subgroups identified? If subgroups are based on differences in relative treatment effect, what clinical information is there to support the biological plausibility of this approach? For subgroups based on differences in baseline risk of specific outcomes, how were the data to quantify this identified? How was the statistical analysis undertaken?

Head and Neck cancer covers a varied group of relatively rare cancers.

This economic evaluation will also consider sub groups with the following characteristics:

- Good Karnofsky performance status i.e. 90 or above.
- Those tumour sites which have been shown in the EXTREME clinical trial to derive statistically significant benefit when cetuximab is added to platinum based chemotherapy.

These particular patient sub groups have been identified as where greater clinical and economic benefit can be shown through the addition of cetuximab to the standard platinum based treatment compared to the overall ITT population from the EXTREME clinical trial.

Good Karnofsky performance status i.e. 90 or above.

Patients who are fitter are more likely to tolerate aggressive chemotherapy regimens and not discontinue therapy due to adverse events. Therefore we have looked specifically at the group with Karnofsky Performance status of greater than or equal to 90.

Those tumour sites which have been shown in the EXTREME clinical trial to derive statistically significant benefit when cetuximab is added to platinum based chemotherapy.

- In the sub group analysis of overall survival in the EXTREME study it was not possible to demonstrate a statistically significant difference in survival from the addition of cetuximab to platinum based chemotherapy in patients whose tumours were located in the larynx or hypopharynx.
- This was not the case for tumours of the oral cavity and oropharynx where a statistically significant difference in PFS was shown in both in the cetuximab + CTX group compared with the CTX group alone.
- In addition a statistically significant difference was observed in overall survival in patients with tumours of the oral cavity. For tumours located in the oropharynx the difference in OS was not quite significant but given the significant difference in PFS it is reasonable to assume that these patients derive benefit from the addition of cetuximab to chemotherapy.

Therefore for the economic analysis we have also concentrated on patients whose tumours were located in the oral cavity and oropharynx alone.
(Please see Appendix H1 advisory board).

7.2.2.3 Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Refer to the subgroups identified in the scope.

Sub groups based upon age are not presented, it was considered by the Advisory board panel (see Appendix H1) that results based upon age may be a surrogate for other factors e.g. performance status or fitness for treatment.

7.2.2.4 At what points do patients 'enter' and 'exit' the evaluation? Do these points differ between treatment regimens? If so, how and why?

Patients 'enter' into the evaluation in the Stable/Response state. The model has a cycle length of 3 weeks and a patient can move to the *Progressive* state, remain in the *Stable/Response* state or die (i.e. transition to the *Death* state). All patients 'exit' the evaluation in the *death* health state.

7.2.3 Comparator technology

What comparator(s) was/were used and why was it/were they chosen? The choice of comparator should be consistent with the summary of the decision problem (Section A).

The comparator therapy in the economic evaluation is platinum-based chemotherapy regimens. Specifically 5-Flurouracil combined with cisplatin is the standard of care in the UK in this setting (Please see Appendix H1 advisory board).

7.2.4 Study perspective

If the perspective of the study did not reflect NICE's reference case, provide further details and a justification for the approach chosen.

The perspective of the economic evaluation matches that of the NICE reference case. Costs are estimated from the perspective of the NHS and all relevant disease and treatment health effects to the individual are captured via quality-adjusted life years (QALYs).

7.2.5 Time horizon

The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect all important differences in costs or outcomes between the technologies being compared.

What time horizon was used in the analysis, and what was the justification for this choice?

The time horizon chosen was a lifetime horizon so all relevant benefits and costs are accounted for in the economic model. This equates to 29 cycles covering 608 days / 1.6 years.

7.2.6 Framework

The purpose of this section is to provide details of the framework of the analysis. Section a) below relates to model-based evaluations, and section b) below relates to evaluations conducted alongside clinical trials. Please complete the section(s) relevant to the analysis.

a) Model-based evaluations

7.2.6.1 Please provide the following.

- A description of the model type.

A two-arm state-transition Markov model was developed to evaluate the cost-effectiveness of cetuximab in addition to standard platinum based chemotherapy as first-line management for metastatic/recurrent SCCHN relative to standard platinum based chemotherapy alone.

The course of disease is reflected with three mutually exclusive health states:

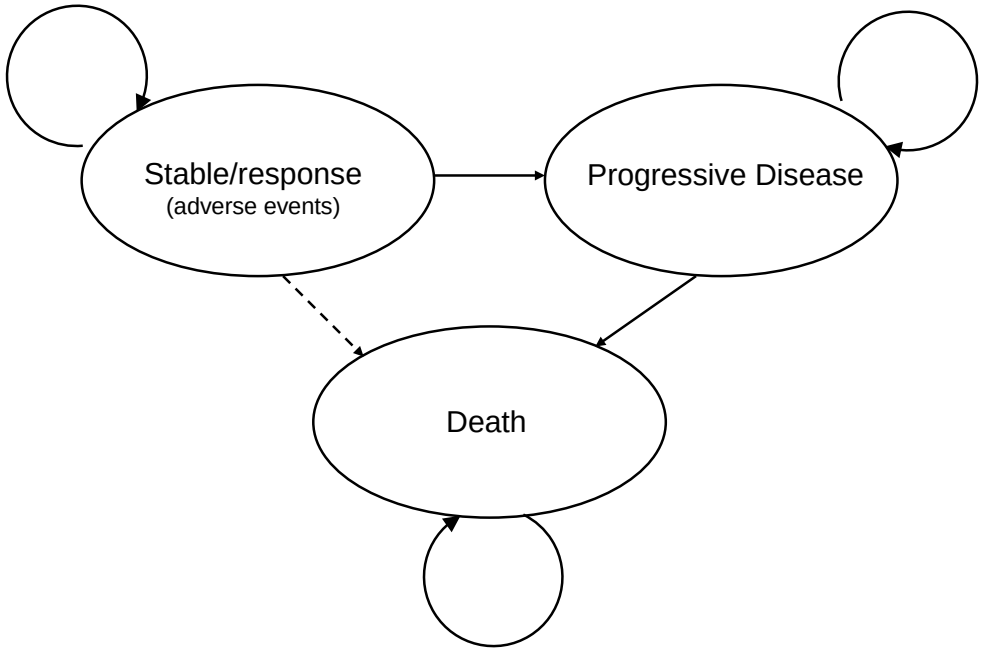
- **Stable/Response:** No sufficient increase to qualify for progressive disease in the index lesions; Disappearance or no significant change in non-index lesions. No new lesions.
- **Progressive:** A 25% or more increase in the Sum of the Perpendicular Dimensions (SOPD) of index lesions, compared to the smallest SOPD recorded for the study period. Appearance of one or more new lesions and/or unequivocal progression of existing non-index lesions.
- **Death:** Death from any cause.

In both arms of the model patients start in the Stable/Response state. Every 3 weeks a patient can move to the *Progressive* state, remain in the *Stable/Response* state or die (i.e. transition to the *Death* state). The distribution of patients over the 3 health states over time was imputed using the Weilbull method for both progression free survival (PFS) and overall survival (OS) as estimated from the EXTREME trial. Patients were assumed to receive cetuximab with cisplatin/carboplatin + (5-FU) or cisplatin/carboplatin + (5-FU) only when in the stable/response health state. Patients in the health state ‘progressive disease’ receive palliative care, which is a mixture of various chemotherapy, surgery and radiation therapy as observed in the EXTREME trial.

- A schematic of the model. For models based on health states, direction(s) of travel should be indicated on the schematic on all transition pathways.
- A list of all variables that includes their value, range (distribution) and source.

The Health Economic Model is presented in Figure H1 below.

Figure H1: Health Economic Model Schematic.



No transition probabilities were calculated to describe the distribution of health states over time. The fitted (and extrapolated) Weibull survival curves describe the proportion of patients in each health state at the beginning of each 3-week cycle. See section 7.2.6.8 for further information on extrapolation techniques employed.
Tables H3, H4 and H5 below contain chemotherapy resource use, other resource use independent of treatment and cost estimates for adverse events respectively. Table H3 is based upon Hopper *et al,* H4 is based upon clinical opinion and the costs in Table H5 are derived from the Merck Pharmaceutical submission for cetuximab in locally advanced squamous cell carcinoma of the head and neck.

Table H3: Chemotherapy related resource use per 3-week cycle (source Hopper *et al.*).

	Stay in medical oncology ward per cycle [average days per cycle]			**Outpatient drug administration visit [number per cycle]**		
	Base	*Low*	*High*	*Base*	*Low*	*High*
Cetuximab + Carboplatin + 5-FU	4.0	3.2	4.8	2.0	1.6	2.4
Cetuximab + Cisplatin + 5-FU	4.0	3.2	4.8	2.0	1.6	2.4
Cetuximab	0.0	0.0	0.0	3.0	2.4	3.6
Carboplatin + 5-FU	4.0	3.2	4.8	0.0	0.0	0.0
Cisplatin + 5-FU	4.0	3.2	4.8	0.0	0.0	0.0
5-FU	4.0	3.2	4.8	0.0	0.0	0.0
Bleomycin	0.0	0.0	0.0	3.0	2.4	3.6
Carboplatin	0.0	0.0	0.0	1.0	0.8	1.2
Cisplatin	0.0	0.0	0.0	1.0	0.8	1.2
Docetaxel	0.0	0.0	0.0	1.0	0.8	1.2
Gefitinib	0.0	0.0	0.0	0.0	0.0	0.0
Methotrexate	0.0	0.0	0.0	1.0	0.8	1.2
Paclitaxel	0.0	0.0	0.0	1.0	0.8	1.2
Vinorelbine	0.0	0.0	0.0	1.0	0.8	1.2

Table H4: Resource use and cost by health state (independent of treatment) expressed per 3 week cycle (estimated by members of advisory panel).

	Stable / Response			Progressive		
	Base	**Low**	**High**	**Base**	**Low**	**High**
Consultant oncologist	0.3	0.2	0.4	3.0	1.8	4.2
Nurse visits [hours per cycle]	0.0	0.0	0.0	0.0	0.0	0.0
GP	0.0	0.0	0.0	0.0	0.0	0.0
CT-scan	0.5	0.3	0.7	0.0	0.0	0.0
MRI	0.2	0.1	0.2	0.0	0.0	0.0

Table H5: Cost estimates for adverse events (average episode costs)

Adverse Event	Toxicity Grade	Expected episode cost	How calculated
Mucositis/stomatitis/dysphagia	2	£94.72	HRG C37 multiplied by 5% plus medication[1]
Mucositis/stomatitis/dysphagia	3	£307.18	HRG C36 multiplied by 10% plus medication[2]
Mucositis/stomatitis/dysphagia	4	£3,035.70	HRG C36 multiplied by 100%
Nausea/vomiting	2	£80.68	HRG F47 multiplied by 10% plus medication[3]
Nausea/vomiting	3	£333.29	HRG F46 multiplied by 30% plus medication[4]
Nausea/vomiting	4	£1,099.06	HRG F46 multiplied by 100%
Radiation dermatitis	3/4	£6.36	Cost of tube of betamethasone
Acne/rash	3/4	£43.38	Cost of course of topical and oral anti-bacterials
Dehydration	3/4	£1,519.05	HRG K09 multiplied by 100%
Thrombocytopenia	3/4	£84.22	Cost of platelets transfusion
Febrile neutropenia	3/4	£1,337.42	HRG P23 multiplied by 100%
Anaemia	3/4	£930.04	HRG S06 multiplied by 50%
Fever/Infection/ Pyrexia	3/4	£1,103.37	HRG P05 multiplied by 50% plus medication[5]

Notes:

1. For mucositis/stomatitis/dysphagia grade 2, the expected value of the event is equal to 5% multiplied by the HRG cost plus 95% multiplied by the cost of benzydamine rinse.

- A separate list of all assumptions and a justification for each assumption.

Please see Table H13 in Section 7.2.9.10.

7.2.6.2 Why was this particular type of model used?

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.

7.2.6.3 What was the justification for the chosen structure? How was the course of the disease/condition represented? Please state why any possible other structures were rejected.

The modelling structure was designed to reflect the natural disease progression of advanced head and neck cancer.

7.2.6.4 What were the sources of information used to develop and inform the structure of the model?

Several sources of information were used to develop the model. Firstly, an in-depth literature review was carried out to search for publication of other economic evaluations in the first line treatment of recurrent/metastatic Head and Neck cancer. This included a review of all NICE published Technical Assessment Reports (TAR) for review of methods employed in the appraisal of H&N treatments.

The EXTREME trial data 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 were utilised to test assumptions and validate the approach.

7.2.6.5 Does the model structure reflect all essential features of the condition that are relevant to the decision problem? If not, why not?

This particular choice of model was used to make the full use of the clinical data available. Overall survival is extrapolated from the available Kaplan Meier OS curves beyond the trial period. Progression free survival curves were extrapolated to inform the transition from the stable responding health state to either progressive or death health states using survival analyses.
In addition, it was decided to utilise a Markov model design to adequately capture the costs, benefits and adverse events associated with the treatment of recurrent/metastatic squamous head and neck cancer.

7.2.6.6 For discrete time models, what was the model's cycle length, and why was this length chosen? Does this length reflect a minimum time over which the pathology or symptoms of a disease could differ? If not, why not?

The model cycle length is 3 weeks. This reflects the length of one cycle of platinum based chemotherapy. It also represents one half of the time interval between planned tumour assessments in the EXTREME trial which were at 6 weekly intervals. The minimum interval between scans allowed in the trial was 4 weeks.

7.2.6.7 Was a half-cycle correction used in the model? If not, why not?

A half cycle correction has not been used. As noted in 7.2.6.6 it was not thought necessary since the three week cycle in the model is half of one interval between planned tumour scans.

7.2.6.8 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer-term difference in effectiveness between the technology and its comparator?

Costs and clinical outcomes are extrapolated beyond the trial follow up period. The overall survival and progression free survival are censored and do not provide information on the course of disease beyond 24 months. For the economic evaluation a lifetime horizon is employed, all patients are followed up until death. Hence, the OS and PFS curves as observed in the trial were extrapolated by fitting a 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. Figures H2 and H3 show the results of the fitted survivor functions compared with the empirical OS and PFS observed.

Figure H2: Fitted Weibull survival curve for overall survival, total patient group

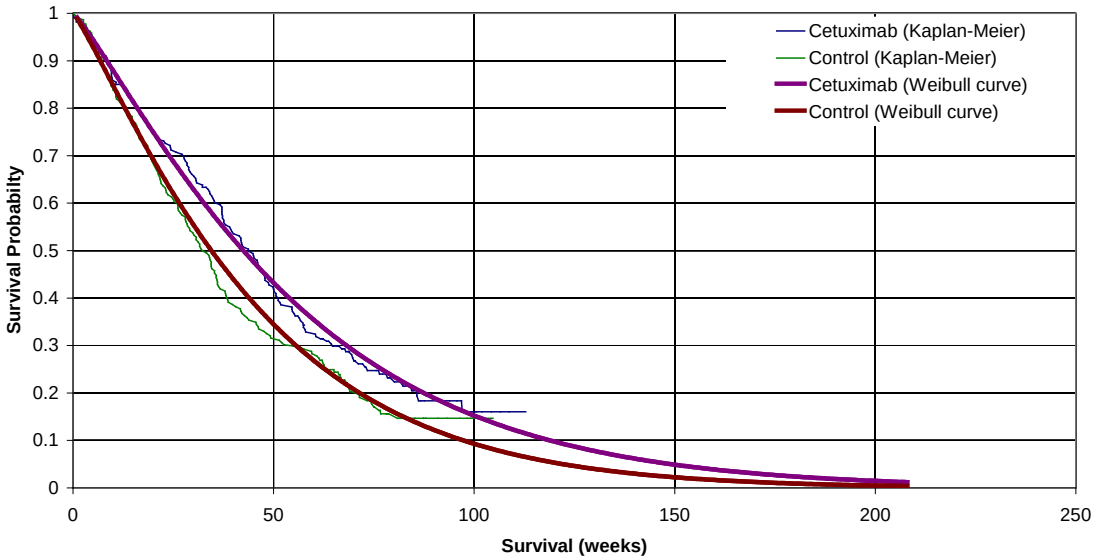
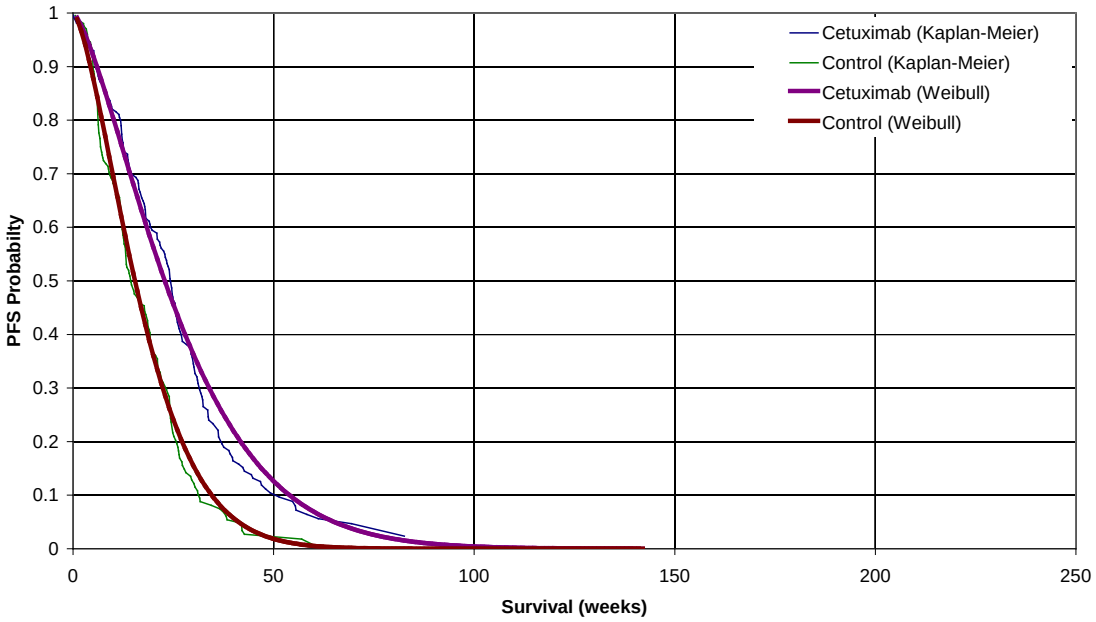


Figure H3: Fitted Weibull survival curve for progression free survival, total patient group



Figures H2 and H3 suggest that the fitted Weibull survivor functions provide a good fit to the empirical OS and PFS data.

While goodness-of-fit statistics were used to assess how well the functions fit the observed trial data they cannot be interpreted as assessing the fit for the time after the evaluation period. Therefore, the choice of the final function should also be assessed by clinical expertise, to ensure that the fit of the curves for the time period after the evaluation period makes sense. (The choice of the Weibull function is therefore based on two assessments:

- Goodness-of-fit for the data of the evaluation period.
- Clinical expertise for the estimated values for time points after the evaluation period.

The parameters for the scale and shape of the Weibull curves are presented in Appendix H3. The Weibull survival curve for PFS was used to determine the distribution of patients in the Stable/Response health state over time. The OS curve was used to determine the proportion of patients that were in the health state death at any point in time. The difference between these two curves gives the proportion of patients experiencing progressive disease. In addition to the total population OS and PFS curves were fitted to the oral cavity, oral cavity plus oropharynx and oropharynx subgroups considered in the evaluation.

b) Non-model-based economic evaluations

7.2.6.9 Was the evaluation based on patient-level economic data from a clinical trial or trials?

Not applicable.

7.2.6.10 Provide details of the clinical trial, including the rationale for its selection.

Not applicable.

7.2.6.11 Were data complete for all patients included in the trial? If not, what were the methods employed for dealing with missing data for costs and health outcomes?

Not applicable.

7.2.6.12 Were all relevant economic data collected for all patients in the trial? If some data (for example, resource-use or health-related utility data) were collected for a subgroup of patients in the trial, was this subgroup prespecified and how was it identified? How do the baseline characteristics and effectiveness results of the subgroup differ from those of the full trial population? How were the data extrapolated to a full trial sample?

Not applicable.

7.2.6.13 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about any longer-term differences in effectiveness between the technology and its comparator?

Not applicable.

7.2.7 Clinical evidence

Where relevant, answers to the following questions should be derived from, and consistent with, the clinical evidence section of the submission (section 5). Cross-references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided and a justification for the approach provided.

7.2.7.1 How was the baseline risk of disease progression estimated? Also state which treatment strategy represents the baseline.

The risk of disease progression was based upon the EXTREME trial data set. Baseline treatment in the trial was either cisplatin or carboplatin with 5FU. Cetuximab was added to these regimens in the experimental arm of the trial. In UK clinical practice Cisplatin/5FU is the treatment of choice (Please see Appendix M1 A+A Market research for more information). Please see Appendix H1 advisory board for validation of comparator choice.

7.2.7.2 How were the relative risks of disease progression estimated?

In order to model the short and long-term outcomes of treatment in patients within the cost effectiveness model, survival analysis using the Weibull technique has been undertaken as a means of estimating the progression between the three health states. This is based upon both the progression free survival and overall survival Kaplan Meier curves from the EXTREME trial. The number of patients in the health state 'death' at any time point was estimated using the OS survival extrapolation. The number of patients at any time point who were in the health state 'stable/response' was estimated using the PFS extrapolation curve. The 'progressive disease' health state was calculated as the difference between 'death' and 'stable/response' as outlined above.

7.2.7.3 Were intermediate outcome measures linked to final outcomes (such as patient survival and quality-adjusted life years [QALYs])? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

No, intermediate outcome measures were not linked to final outcomes. The overall survival and progression free survival data from the EXTREME study were used in the economic model.

7.2.7.4 Were the health effects or adverse effects associated with the technology included in the economic evaluation? If not, would their inclusion increase or decrease the estimated cost effectiveness of this technology?

Health and adverse effects of treatment have been included in the economic analysis. The utility values utilised in the economic evaluation are derived from quality of life data collected in the EXTREME trial using the EORTC QLQ-C30 questionnaire. The utilities were calculated using a cross walking method previously described by Kind *et al* 2005. This is described in section 7.2.8.3.

7.2.7.5	Was expert opinion used to estimate any clinical parameters? If so, how were the experts identified, to which variables did this apply, and what was the method of elicitation used?

Expert opinion was obtained from a Merck Serono health economic advisory board held on 22nd July 2008, and subsequently by use of specific questions to the delegates. Please see Appendix H1 advisory board for further details.

Attendees at this advisory board were a cross section of Senior Consultant Clinical Oncologists based in England who specialise in the treatment of Head and Neck Cancer.

Expert opinion was used to confirm:

The applicability of the EXTREME trial data to the UK setting.

That the patients in the EXTREME trial are representative of the patient group who would be considered for platinum based chemotherapy.

That cisplatin/5FU is the standard comparator for this patient group in the UK.

That the list of active 'best supportive care' treatments used in the model would not be expected to alter the survival outcomes in the EXTREME trial.

That the incidence of adverse events in the trial was considered comparable in both arms of the trial.

That resource use assumptions were reasonable, with the exception of resource use independent of treatment which was felt to be too high in the cetuximab arm vs. the comparator arm of the model.

Please see Appendix H1 for details of advice given during the health economic advisory board.

7.2.7.6	What remaining assumptions regarding clinical evidence were made? Why are they considered to be reasonable?

All assumptions were validated by the health economic advisory board as described in section 7.2.7.5 above.

7.2.8 Measurement and valuation of health effects

The value of health effects should be expressed in terms of QALYs for the appropriate time horizon. For the reference case, the measurement of changes in HRQL should be reported directly from patients and the value of changes in patients' HRQL (that is, utilities) should be based on public preferences using a choice-based method. The EQ-5D is the preferred measure of HRQL in adults. The methods to elicit EQ-5D utility values should be fully described. When EQ-5D data are not available or are inappropriate for the condition or effects of treatment, the valuation methods should be fully described and comparable to those used for the EQ-5D. Data collected using condition-specific, preference-based measures may be presented in separate analyses. The use of utility estimates from published literature must be supported by evidence that demonstrates that they have been identified and selected systematically.

All parameters used to estimate cost effectiveness should be presented clearly in tabular form and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

7.2.8.1 If health effects were not expressed using QALYs, what health outcome measure was used and what was the justification for this approach?

The health effects were expressed using QALYs.

7.2.8.2 Which health effects were measured and valued? Health effects include both those that have a positive impact and those with a negative impact, such as adverse events.

The health effects measured were:

- Adverse events for each arm of the trial, derived from the clinical trial dataset (EXTREME).
- Progression-free and overall survival, based upon the Kaplan Meier survival curves from the EXTREME clinical study (imputed where censored via the statistical extrapolation model).

7.2.8.3 How were health effects measured and valued? Consideration should be given to all of the following:

- State whether the EQ-5D was used to measure HRQL or provide a description of the instrument/s used.

The EORTC QLQ-C30 questionnaire and its head and neck symptomatic module, the EORTC QLQ-H&N35 were used to assess QoL in both treatment groups throughout the EXTREME study. The QLQ-C30 is a cancer specific questionnaire for assessing QoL in patients participating in clinical trials. The QLQ-C30 questionnaire (version 3) comprises 30 items, organised into the following:

- Global Health Status / QoL scale (QL2, items 29 and 30), which can be used as an overall summary measure.
- Five functional scales.
- Three symptom scales.
- Six single items.

Please see Appendix H2 for further details.

Whilst the QLQ C30 is a cancer scale it is still described as a 'generic' instrument, hence the use of a head and neck cancer specific scale (in this case EORTC QLQ-H&N35) was utilised to capture quality of life specific to this area.

- Provide details of the population in which health effects were measured. Include information on recruitment of sample, sample size, patient characteristics and response rates.

The health effects utilised were based upon the EXTREME clinical trial:

- EXTREME was an open-label, randomized, controlled multi-centre phase III study in subjects with recurrent and/or metastatic SCCHN who had not received previous CTX for this setting.
- Enrolment of 420 subjects was planned. 442 subjects were actually randomized at 80 centres in Europe.

Table H6 below presents the patient sample and characteristics information from the EXTREME study.

Table H6: EXTREME trial Patient Characteristics.

Characteristic		Cetuximab + CTX N=222 (%)	CTX N=220 (%)
Gender	Male	197 (88.7)	202 (91.8)
	Female	25 (11.3)	18 (8.2)
Age (years)	Mean ± SD	57.1 ± 8.0	56.7 ± 8.7
	Median	56	57
	Q1-Q3	51 – 62	51 – 62
Age categories (years)	< 65	193 (82.4)	182 (82.7)
	≥ 65	39 (17.6)	38 (17.3)
Site of primary tumour	Oropharynx	80 (36.0)	69 (31.4)
	Hypopharynx	28 (12.6)	34 (15.5)
	Larynx	59 (26.6)	52 (23.6)
	Oral Cavity	46 (20.7)	42 (19.1)
	Other	9 (4.1)	23 (10.5)
Type of tumour	Recurrent, not metastatic	118 (53.2)	118 (53.6)
	Metastatic, including recurrent	104 (46.8)	102 (46.4)
Karnofsky performance status	100	37 (16.2)	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	202 (91.0)	201 (91.4)
	Radiotherapy (excluding palliative)	189 (85.1)	190 (86.4)
	Surgery	174 (78.4)	176 (80.0)
	Chemotherapy	143 (64.4)	135 (61.4)
	Radiochemotherapy (excluding palliative)	90 (40.5)	80 (36.4)
	Neoadjuvant chemotherapy	69 (31.1)	60 (27.3)
	Other	24 (10.8)	33 (15.0)
		1 (0.5)	2 (0.9)

- Were the data collected as part of a RCT? Refer to section 5.3 as necessary and provide details of respondents.

Yes, the data were collected as part of the EXTREME study.

- How were health effects valued? If taken from the published literature, state the source and describe how and why these values were selected. What other values could have been used instead?

Health effects were based upon EORTC QLQ C30 data completed during the pivotal clinical trial. Please see below for a description of the methodology used to convert these results into EQ-5D utility values.

- Was a mapping mechanism (or 'cross-walk') generated to estimate health-related utilities of patients in the trials? Provide details of the rationale for the analysis, the instruments used, the sample from which the data were derived and the statistical properties of the mapping mechanism.

In order to obtain EQ-5D estimates, QLQ-C30 scores as measured in the EXTREME trial were mapped onto the EQ-5D scores using an algorithm previously developed by Kind *et al* 2005.

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

Please see Appendix H8 for the parameter estimates and standard error values for the cross walk algorithm.

This algorithm was developed in patients with pancreatic cancer; the key assumption which makes it appropriate to apply this algorithm to the recurrent/metastatic SCCHN population in this study, 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. Since these items reflect Quality of life and global health status this is thought to be a reasonable assumption.

The QLQ-C30 scores for the stable/responsive state and progressive/disease state were calculated from the EXTREME trial and the utility scores were calculated using the above regression equation. Items Q3-Q26 were dichotomized (with not at all = 0; a little to very much = 1). For item 29, values were used as reported in the trial.

All available data for patients on study treatment (n=157) were used to estimate the utility value for patients in the stable/responsive health state, with the exception of baseline data. Baseline data were not utilised in the model as patients cannot be defined as responsive at baseline. The baseline utility values (and confidence intervals) were as follows:

Overall	0.62 (0.25-1.00; n=227).
Standard arm	0.61 (0.24-0.98; n=106).
Cetuximab arm	0.64 (0.26-1.00; n =121).

The confidence intervals for the baseline utility values show a high level of uncertainty as suggested by the high level of overlap, this is expected given the use of the raw data from the EORTC QLQ-C30 questionnaires completed during the trial in the cross walking exercise described above. We have addressed the potential impact of this

uncertainty in the sensitivity analysis in section 7.3.3 and in particular in Table H23 and sub section 7.3.3.1.
Analyses were performed for both the cetuximab-with-standard-treatment-arm and the standard-treatment-arm in order to capture potential differences in adverse events between the treatment groups and its impact on QLQ-C30 and utility. The rationale behind this is that if adverse events have an impact on quality of life it will be captured with the QLQ C-30 global question. Dis-utilities associated with adverse events were not accounted for separately.

For patients with progressive disease, utility estimates were obtained from the QLQ-C30 recorded at the Final Tumour Assessment (FTA) visit with stratification by treatment group. Since cetuximab is discontinued once a patient reaches progressive disease, no differences in adverse events are expected between the treatment groups, and therefore no differences in utility due to adverse events are expected in this health state.

The overall QLQ-C30 global health status scores for the health states "stable/responsive disease" and "progressive/disease" were calculated from the EXTREME trial. The utility scores were mapped onto EQ-5D values using the regression equation above (See Table H7 for values).

The model allows for a choice of utility values based upon the mapping exercise described above:

- Overall values.
- Treatment specific values.

The treatment specific values are utilised in the stable/responsive health state in order to capture the differences in quality of life during active treatment caused by either benefit from treatment or resulting from the adverse effects of treatment. Table H7 below shows the values used in the model.

Table H7: Utility values utilized in the economic model.

	Value
Stable/response with cetuximab	0.69
Stable/response with standard treatment	0.65
Progressive disease	0.52

- Were health states directly valued? If so, provide details of the rationale for the analysis, the HRQL measures that were valued, the population who produced the values and full details of the methods used. Explain the rationale for the analysis and the choice of instruments used.

Utilities were derived from a cross walking exercise based on the EXTREME study as described above.

7.2.8.4 Were any other generic or condition-specific preference based measures used in the clinical trials? Provide a description of the data below. The results should be considered in a sensitivity analysis (see Section 6.2.11).

EQ-5D data were collected only in patients from the UK in the EXTREME study. Only 12 assessments were returned from the 7 patients who completed questionnaires hence the need to perform the cross walking exercise for the EORTC QLQ-C30.

7.2.8.5 Were any health effects excluded from the analysis? If so, why were they excluded?

All relevant health effects were included in the analysis.

7.2.9 Resource identification, measurement and valuation

7.2.9.1 What resources were included in the evaluation? (The list should be comprehensive and as disaggregated as possible.)

The categories of resources in the model include:

- Cost of chemotherapy drugs in the 1st line (cetuximab, cisplatin, carboplatin, folinic acid, 5-fluorouracil).
- Cost of administration in the 1st line.
- Cost of treatment of adverse events.
- Cost of palliative intent chemotherapy drugs.
- Cost of palliative intent surgery.
- Cost of palliative intent radiotherapy.

Information on healthcare resources other than the distribution of chemotherapy regimens surgery and radiotherapy were not collected in the EXTREME trial. As a result estimates obtained from the literature and key opinion leaders (KOLs) treating SCCHN have been used. Hopper *et al* (2004) reported the resource utilization associated with chemotherapy and surgery in patients with advanced head and neck

cancer in the UK. Costs for treatment of adverse events are shown in Table H12 below and are based upon those submitted for the use of cetuximab in locally advanced head and neck cancer.

Distribution of treatment by health state

In Table H8 the distribution of treatments by model arm and health state are presented. These estimates were obtained from the EXTREME trial and assumed applicable to the UK setting. This distribution of chemotherapy regimens over time is used to estimate the total costs incurred due to drug acquisition. Palliative radiotherapy and surgery were offered to patients who had progressed from trial treatment. The model considers both palliative radiotherapy and surgery as independent of cetuximab prescription and as a result these were applied equally to the cetuximab plus standard treatment and the standard treatment arms. The proportions applied in the model are as follows:

- Palliative radiotherapy for 10.2% of patients.
- Palliative surgery for 3.2% of patients.

Table H8: Distribution of treatments by health state.

Treatment	**cetuximab plus standard treatment arm**				**Standard Treatment arm**			
	First 6 cycles		Cycle 7+		First 6 cycles		Cycle 7+	
	Stable	Progressive	Stable	Progressive	Stable	Progressive	Stable	Progressive
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%

7.2.9.2 How were the resources measured?

Drug utilisation and radiotherapy resources were measured in the EXTREME clinical trial. Administration and other resources were estimated using data from Hopper *et al.* The study by Hopper *et al* aimed to analyse the cost-effectiveness of Foscan mediated photodynamic therapy (Foscan-PDT) compared with palliative chemotherapy, extensive palliative surgery or 'no treatment' for patients with advanced head and neck cancer in the UK. Where possible, Hopper utilised published resource use information. In the absence of such information, Hopper utilised expert opinion. It is thought to be appropriate as the study by Hopper *et al* assesses advanced SCCHN in the UK setting, which is the same setting as this appraisal. We have specifically utilised data from Hopper *et al* about treatment delivery resources for chemotherapy i.e. the number of days of inpatient stay and the number of outpatient visits for administration of treatment.

7.2.9.3 Were the resources measured using the same source(s) of evidence as the baseline and relative risks of disease progression?

Yes, the EXTREME trial provides data for both resources and relative risk of disease progression.

Resources measured by EXTREME include:

- Drug utilisation.
- 'Best supportive care' treatment modality.
- Surgery.
- Radiotherapy.
- 'Other' chemotherapies on progression.

Further resource utilisation data were derived from Hopper *et al* associated with administration of the treatment modalities listed above.

The model has been validated against cetuximab usage in the EXTREME clinical trial. The extrapolation techniques utilised in the model overestimates the number of vials of cetuximab used per patient. To correct for this an adjustment has been made in the model, details are contained in Appendix H5.

7.2.9.4 Were resources used to treat the disease/condition included for all relevant years (including those following the initial treatment period)? Provide details and a justification for any assumptions that were made (for example, assumptions regarding types of subsequent treatment).

Yes, resources used to treat the condition were included for all relevant years. It was assumed that items such as GP visits, speech therapy and dietician time would be consistent between both arms of the trial hence these have not been included in the model.

7.2.9.5 What source(s) of information were used to value the resources? Were alternative sources of information available? Provide a justification for the preferred source and explain any discrepancies between the alternatives.

The costs in the model were estimated from a health service perspective and use UK NHS reference costs and list prices from BNF 55 for drugs used.
See Tables H10 and H11 below and Table H5 in section 7.2.6.1 for full details.
Table H5 presents cost estimates for adverse events incurred in the model. These costings were taken directly from those calculated for the appraisal of cetuximab in locally advanced SCCHN. It was deemed appropriate to utilise this costing due to the similarities in adverse event presentation in the different stages of head and neck cancer and that the resources and costs to treat these events would be similar.
Please see Appendices H1 for Advisory board validation of this decision and H9 for further details of how these costs were calculated.

7.2.9.6 What is the unit cost (excluding VAT) of the intervention(s) included in the analysis? Does this differ from the (anticipated) acquisition cost reported in section 1? If price discounts are presented in sensitivity analyses provide details of formal agreements regarding the discount including the period over which the discount is agreed and confirmation of national organisations with which the discount has been agreed for the whole of the NHS in England and Wales.

As of September 2008 the published list price of cetuximab is £159.02 / 20ml vial. Merck Serono has agreed with the Department of Health to maintain the old list price (£136.50/ 20ml vial) for all patients within the NHS. This price of £136.50 will be

uniform and applicable for all NHS prescriptions. As a result of this agreement the old list price should be utilised within this appraisal.

Table H10: Unit costs for drug acquisition surgery and radiotherapy applied in the model.

	cost per unit	description of unit	dose [mg]	no. of units / vials	Cost for the 3-week cycle			Source	Remarks
					Base	Low	High		
Cetuximab (initial cycle)	£136.50	per vial; 100 mg; 20ml, 5 mg/ml	1,530	16.00	£2,184.00	£2,184.00	£2,184.00	EXTREME; Drug prices based on BNF55, available at www.bnf.org	400 mg/m2 for initial dose + 250 mg/m2 for subsequent weekly dose; Body surface area of 1.7 m^2
Cetuximab (cycle 2-6)	£136.50	per vial; 100 mg; 20ml, 5 mg/ml	1,275	13.00	£1,774.50	£1,774.50	£1,774.50		
Cetuximab (cycle 7+)	£136.50	per vial; 100 mg; 20ml, 5 mg/ml	1,275	13.00	£1,774.50	£1,774.50	£1,774.50		
Carboplatin	£260.00	per vial 600 mg; 60 ml, 10 mg/ml	1,098.6	2.00	£520.00	£520.00	£520.00	BNF55	EXTREME: dose of AUC 5, for a male, 60 years, 70kg, 170 cm, serum creatine 0.595 mg/dl, use of Chatelut formula, at each cycle
Cisplatin	£50.22	per vial 100 mg; 100ml, 1 mg/ml	170	2.00	£100.44	£100.44	£100.44	BNF55	EXTREME: 100 mg/ m^2 for each cycle; BSA chosen of 1.7m^2
5-FU	£64.00	per vial 2500 mg; 100 ml, 25 mg/ml	6,800	3.00	£192.00	£192.00	£192.00	BNF55	EXTREME: 1000 mg/ m^2/day during 4 days at each cycle
Cetuximab + Carboplatin + 5-FU (initial cycle)					£2,896.00	£2,896.00	£2,896.00		
Cetuximab + Cisplatin + 5-FU (initial cycle)					£2,476.44	£2,476.44	£2,476.44		
Cetuximab + Carboplatin + 5-FU (cycle 2-6)					£2,486.50	£2,486.50	£2,486.50		

Table H10 (continued): Unit costs for drug acquisition surgery and radiotherapy applied in the model.

	cost per unit	description of unit	dose [mg]	no. of units / vials	Cost for the 3-week cycle			Source	Remarks
Cetuximab + Cisplatin + 5-FU (cycle 2-6)					£2,066.94	£2,066.94	£2,066.94		
Carboplatin + 5-FU					£712.00	£712.00	£712.00		
Cisplatin + 5-FU					£292.44	£292.44	£292.44		
Bleomycin	£15.56	per vial 15 mg/15 units	78.57	5.00	£77.80	£77.80	£77.80	BNF55	Rx list: 0.25 to 0.50 units/kg (10 to 20 units/ m^2) given intravenously, intramuscularly, or subcutaneously weekly or twice weekly; BSA assumed of 1.7 m^2 (1 unit bleomycin equals 1 mg.)
Docetaxel	£534.75	per vial 80 mg; 2ml, 40 mg/ml	130.95	2.00	£1,069.50	£1,069.50	£1,069.50	BNF55	Rx list: 75 mg/ m^2 as a 1 hour intravenous for each cycle; BSA chosen of 1.7 m^2
Gefitinib	£0.00	not yet licensed	5250	0.00	£0.00	£0.00	£0.00		n/a
Methotrexate	£9.03	per tablets 10 mg	200	20.00	£180.60	£180.60	£180.60	BNF55	RX list: 25 mg/day orally for 4 to 8 days plus 7-10 days of no treatment (8 days of 25 mg/day assumed)
Paclitaxel	£500.86	per vial 150 mg; 25 ml, 6 mg/ml	235.71	2.00	£1,001.72	£1,001.72	£1,001.72	BNF55	given every 3 weeks, administered intravenously over 24 hours at a dose of 135 mg/ m^2, BSA =1.7 m^2 assumed

Table H10 (continued): Unit costs for drug acquisition surgery and radiotherapy applied in the model.

	cost per unit	description of unit	dose [mg]	no. of units / vials	Cost for the 3-week cycle			Source	Remarks
Vinorelbine	£153.98	per 50 mg; 5ml,10mg/ml	157.14	4.00	£615.92	£615.92	£615.92	BNF55	Rx list: 30 mg/ m^2 administered weekly. The recommended method of administration is an intravenous injection over 6 to 10 minutes; BSA=1.7 m^2 assumed
Radiotherapy	£1,135.93	>3 and <13 fractions	1	1.00	£1,135.93	£1,135.93	£1,135.93	NICE STA report for locally advanced SCCHN	Reference Costs 2004, HRG w21 Teletherapy with Technical Support, >3 <13 Fractions
Surgery	£1,180.66		1	1.00	£1,180.66	£1,180.66	£1,180.66	NICE STA report for locally advanced SCCHN	Reference Costs 2004. It is equal to a weighted average of 3 elective inpatient HRGs (C54, C57 and C58: Mouth or Throat procedures). C54: unit cost £6,845.84, 1,194 procedures. C57: unit cost £2,063.40, 13,781 procedures. C58: unit cost £970.06, 89,882 procedures.

Table H11: Unit costs other resource use.

	cost per unit	description of unit	source
Inpatient stay in medical oncology ward per day	£296.00	per day	X99OST: 2007-08 Chemotherapy Indicative tariff Other Solid Tumour Cancer Chemotherapy : All Drugs, NHS National Tariffs
Outpatient drug administration visit	£124.66	per visit	Reference cost 2004: Outpatient specialty code 370 (Medical Oncology) - Subsequent visit
Consultant oncologist	£87.00	per consultation	2007-08 Outpatient Mandatory Tariff, 370 Medical Oncology Adult Follow-up Attendance tariff
General Practitioner	£34.00	Per surgery consultation of 11.7 min	PSSRU 2007 p127
(Clinical) nurse specialist per hour	£38.00	per hour	PSSRU 2007 p125, nurse advanced
CT-scan	£77.00	per procedure	Reference Costs 2005/6, RBC5 'Band C5 - CT Other
MRI	£244.00	per procedure	Reference Costs 2005/6, RBF1 Band F1 - MRI
Nurse community	£26.00	per hour	PSSRU 2007 p122

7.2.9.7 Does the technology require additional infrastructure to be put in place? Provide details of data sources used to inform resource estimates and values.

The addition of cetuximab to standard chemotherapy in this indication is not expected to lead to the need for additional infrastructure. It is envisaged that cetuximab would be delivered using the outpatient chemotherapy suites or inpatient facilities which currently exist within the NHS.

7.2.9.8 Were the resources measured and valued in a manner consistent with the reference case? If not, how and why do the approaches differ?

All resources are measured and valued from the perspective of the NHS and Personal Social Services in England and Wales.

7.2.9.9 Were resource values indexed to the current price year?

In all cases, the most recently published (at the time of analysis) unit cost source was utilised; therefore it was not necessary to index costs to the current price year.

7.2.9.10 Provide details of and a justification for any assumptions that were made in the estimation of resource measurement and valuation.

Table H13: Description of model section and assumption employed

Section of the model	Description of the state in the model	Outcomes and data sources	Service use and costs
Model structure	Two-arm state transition model.	The cost-effectiveness model followed the treatment regimen adopted in the Phase III EXTREME trial which is representative of the routine care in the UK.	The EXTREME trial is a head-to-head comparison with relevant comparator, the patient population in the trial is representative of the UK population, and trial design reflects the routine practice.
	Health states.	The health states chosen in the cost-effectiveness model are based on the WHO criteria for measuring objective response used in the EXTREME trial. Patients are assumed to receive the treatments of interest (i.e cetuximab and cisplatin/carboplatin + 5-FU) only when in the stable/response health state. Patients in the health state 'progressive disease' receive palliative care, which is a mixture of various chemotherapy, surgery and radiation therapy as observed in the EXTREME trial.	EXTREME.
	Cycle length.	Each cycle was 3 weeks long; this is equivalent to a chemotherapy treatment cycle and is half of one of the assessment scan intervals.	EXTREME.
Efficacy and safety data.	Progression free survival and overall survival data.	Patient level efficacy results from the Phase III trial were extrapolated to a lifetime horizon using a Weibull curve.	EXTREME.
	Adverse events.	Adverse events are assumed to occur in the stable/responsive health state. The choice of adverse event was is based upon grade 3 and grade 4 adverse events and those which were considered most clinically relevant.	EXTREME trial, NICE STA for locally advanced SCCHN.

Table H13 (continued): Description of model section and assumption employed

Section of the model	Description of the state in the model	Outcomes and data sources	Service use and costs
Cost data	Drug acquisition cost wastage.	Since drug acquisition cost was based on complete vials, wastage was accounted for. The chemotherapy dose was calculated using the BSA of 1.7m^2.	EXTREME.
	Accurate calculation of vial usage.	The model has been validated against cetuximab usage in the EXTREME clinical trial. The extrapolation techniques utilised in the model overestimates the number of vials of cetuximab used per patient. To correct for this an adjustment has been made in the model.	See Appendix H5.
	Adverse events lump sum cost.	When calculating the cost of treatment, only adverse events that are costly to treat were accounted for in the model. For example, cost of treating fatigue was not included in the model. Costing was assumed to be in line with the NICE STA for locally advanced SCCHN.	NICE STA for locally advanced SCCHN. See table H5, section 7.2.6.1 and Appendix H9 for further details.
	Resource utilisation.	Resource utilisation was mainly based on the treatment pathway that was observed in the EXTREME trial, complemented with other literature and input from the advisory board and sensitivity analyses were conducted to the resources that were identified as important to the cost-effectiveness model.	EXTREME trial, Hopper *et al* 2004 for treatment regimes including 5-FU. Advisory board.
Quality of life	Mapping of utility values from QLQ-C30 data.	Utilities by health states were derived from the responses to the QLQ C-30 global question in the EXTREME trial. Treatment arm specific utility scores were used for the stable/responsive health state. Utility values collected at the final tumour assessment were assumed to be valid for patients with progressive disease, independent of treatment arm.	EXTREME. Kind *et al* 2005.
	Disutilities for adverse events.	Disutilities associated with adverse events were not accounted for separately because the utilities were calculated based on the responses to the QLQ C-30 global questionnaire. The patients' response to the QLQ C-30 global question is assumed to capture the impact of adverse events on the patients' quality of life.	An assumption based upon the utility cross walking exercise.

7.2.10 Time preferences

Were costs and health benefits discounted at the rates specified in NICE's reference case?

All costs and health benefits have been discounted at 3.5% as stated in the reference case.

Sensitivity analysis

Sensitivity analysis should be used to explore uncertainty around the structural assumptions used in the analysis. Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

The uncertainty around the appropriate selection of data sources should be dealt with through sensitivity analysis. This will include uncertainty about the choice of sources for parameter values. Such sources of uncertainty should be explored through sensitivity analyses, preferably using probabilistic methods of analysis.

All inputs used in the analysis will be estimated with a degree of imprecision. Probabilistic sensitivity analysis is preferred for translating the imprecision in all input variables into a measure of decision uncertainty in the cost effectiveness of the options being compared.

For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

7.2.10.1 Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated including a description of alternative scenarios included in the analysis.

Assumptions related to structural uncertainty can be found in Table H14 below.

Table H14: Commentary on Structural uncertainty

Structural Uncertainty	Comment
Inclusion/ exclusion of potentially relevant comparators.	The issue of comparators is addressed by modelling available evidence from the EXTREME trial. As observed in the A+A market research and confirmed by the Merck Serono Health Economic advisory board the relevant UK comparator is cisplatin in combination with 5FU.
Inclusion/ exclusion of potentially relevant events.	The model captures the events that correspond to the key endpoints in the trials, and includes: • Overall survival. • Progression free survival. • Progression. • Death. • Palliative intent surgery. • Palliative intent radiotherapy.
Statistical models to estimate specific parameters.	Various methods for survival analysis were assessed. Considerations included clinical relevance and statistical fit. The Weibull method was selected as being most appropriate.
Clinical uncertainty or lack of clinical evidence.	The primary clinical uncertainties lay in: • The applicability of the EXTREME data to the UK setting. The UK HE advisory board confirmed that this data is applicable to the UK.

7.2.10.2 Which variables were subject to sensitivity analysis? How were they varied and what was the rationale for this?

The following variables were subject to sensitivity analysis as presented below in Table H14b:

Table H14b: Inputs for sensitivity analyses

Variable	Base	Low input	High Input
Annual discount rate for effects	3.5%	0.0%	
Annual discount rate for costs	3.5%	0.0%	
Proportion of patients with acne like rash in cetuximab arm	7.3%	4.3%	10.3%
Utilities			
Cetuximab arm			
Stable/response	0.69	0.59	0.79
Standard arm			
Stable/response	0.65	0.55	0.75
Overall (independent of assessment)			
Progressive disease	0.52	0.42	0.62
Cost of an outpatient attendance for grade 3/4 AE	£43.38	£36.87	£49.89
Cost of infusion (varied between half day and inpatient and inpatient day)	£124.66	£62.33	£296.00

Utilities were varied by plus or minus 0.1, costs were varied by 15% either side of the value utilised in the model unless otherwise stated. The proportion of patients with the typical cetuximab acne like rash was varied by +/- 3%.

7.2.10.3 Was probabilistic sensitivity analysis (PSA) undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated; including the derivation and value of 'priors'.

Probabilistic sensitivity analysis was undertaken in the economic model.

7.2.11 Statistical analysis

7.2.11.1 How were rates or probabilities based on intervals transformed into (transition) probabilities?

The OS and PFS curves as observed in the trial were extrapolated by fitting a 2-parameter Weibull survival curve through the empirical patient level data.
The 2-parameter Weibull survivor function S(t) is given by the equation:

$$S(t) = \exp(-\lambda t^{\gamma})$$

where λ = scale parameter, t = time and γ = shape parameter.

The scale and shape parameters of the Weibull distribution were estimated with least-square regression methods. The Weibull survival curve for PFS was used to determine the distribution of patients in the 'Stable/Response' health state over time. The OS curve was used to determine the proportion of patients that were in the health state 'death' at any point in time. The difference between these two curves gives the proportion of patients experiencing 'progressive disease'.

7.2.11.2 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

Since Weibull curves describe the trial data better than exponential curves, it can be concluded that the hazard rates and progression rates are not constant over time. Since the Weibull PFS and OS survival curves have been used to estimate the proportion of patients in each health state at each model cycle it can be stated that this has been included in the model.

7.2.12 Validity**.** Describe the measures that have been undertaken in order to validate and check the model.

The model structure and assumptions were validated by a UK Expert Panel; please see Appendix H1 advisory board.

7.3 Results

Provide details of the results of the analysis. In particular, results should include, but are not limited to, the following:

- costs, QALYs and incremental cost per QALY
- disaggregated results such as life years gained, costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment
- a statement as to whether the results are based on a probabilistic sensitivity analysis
- cost-effectiveness acceptability curves including a representation of the cost-effectiveness acceptability frontier
- scatterplots on cost-effectiveness quadrants
- a tabulation of the mean results (costs, QALYs, ICERs) the probability that the treatment is cost-effectiveness a thresholds of £20,000-£30,000 per QALY gained and the error probability.

7.3.1 Base-case analysis

7.3.1.1 What were the results of the base-case analysis?

Cost Results.

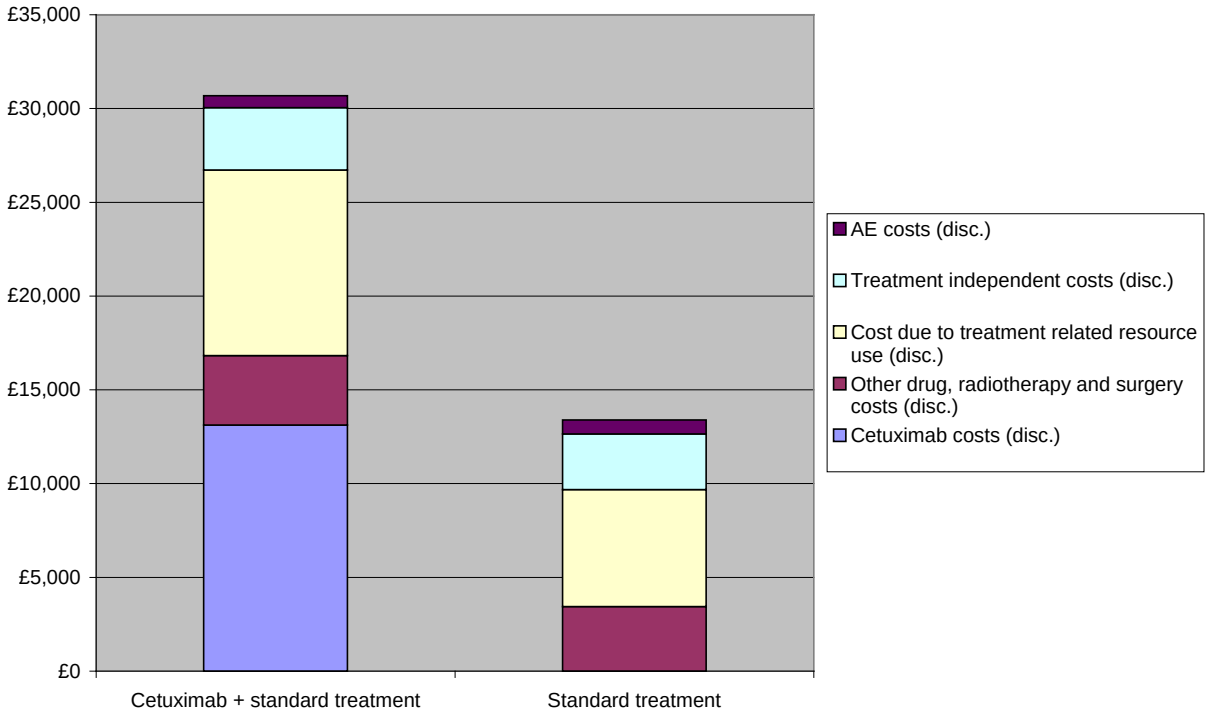
The economic model estimated that the cetuximab plus platinum combination regimen is associated with an incremental cost per patient of £17,286 and a total expected mean cost per patient of £30,678 in comparison to £13,392 in the platinum combination alone arm.

A breakdown of cost by major components is presented in Table H15 and Figure 4 below.

Table H15: Number of Vials used and discounted costs by trial arm.

Costs		
	Cetuximab + standard treatment	**Standard treatment**
Cetuximab vials	96.26	0.00
Cetuximab costs (disc.)	£13,126	£0
Other drug, radiotherapy and surgery costs (disc.)	£3,695	£3,445
Subtotal of treatment costs (disc.)	***£16,821***	***£3,445***
Cost due to treatment related resource use (disc.)	£9,896	£6,231
Treatment independent costs (disc.)	£3,327	£2,969
AE costs (disc.)	£635	£747
Total costs (disc.)	***£30,678***	***£13,392***

Figure 4: discounted costs by resource type.



Health Outcome results.

The economic model estimates that patients treated with cetuximab plus platinum/5FU gain on average 0.142 QALYs and 0.187 life years compared to those treated with platinum/5FU alone. Table H16 below present's incremental QALYs and life years gained.

Table H16: Discounted LY and QALY by trial arm.

Outcomes		
	Cetuximab + standard treatment	**Standard treatment**
Life years (disc.)	1.07	0.88
Quality adjusted life years (disc.)	0.65	0.51

Incremental cost-effectiveness ratio results:

The economic model estimates that cetuximab plus platinum/5FU patients are estimated to gain 0.142 QALYs and have an incremental cost of £17,286 per patient compared to platinum/5FU alone patients.

This translates into an incremental cost effectiveness ratio (ICER) of cetuximab plus platinum/5FU in comparison with platinum/5FU alone of £121,367.

Table H 17: Cost Effectiveness Results.

Cost-effectiveness	
Cetuximab + standard treatment vs Standard treatment	**mean**
Incremental costs	**£17,286**
Incremental life-years	0.187
Incremental QALYs	0.142
Incremental cost per life year gained	£92,226
Incremental cost utility ratio	**£121,367**

Probabilistic Sensitivity Analyses.

In order to address uncertainty around the observed cost and effect values utilised in the model, Probabilistic Sensitivity Analyses (PSA) was undertaken. Statistics and cost effects for 1,000 simulations are presented below in Table H18, Table H19 and Figure H5 and H6. Please see Appendix H6 for a full description of PSA distribution type and values applied in the model. The p2.5 and p97.5 columns in the tables below represent the 95% confidence interval values.

Table H18: PSA Statistics.

Cost-effectiveness			
Cetuximab + standard treatment vs Standard treatment	**mean**	**p2.5**	**p97.5**
Incremental costs	£17,286	£14,916	£19,922
Incremental life-years	0.187	0.013	0.372
Incremental QALYs	0.142	-0.235	0.523
Incremental cost effectiveness ratio	£92,226		
Incremental cost utility ratio	£121,367		

Table H18 above shows the breakdown of incremental costs and benefits with distributions for the base case analysis. Table 19 below shows the PSA costs with 95% confidence interval values.

Table H19: Overview of cost estimates per treatment arm.

	Cetuximab + Standard Treatment			**Standard Treatment**		
	mean	**2.5% limit**	**97.5% limit**	**mean**	**2.5% limit**	**97.5% limit**
Cetuximab vials	96.26	86.91	106.55	0.00	0.00	0.00
Cetuximab costs (disc.)	*£13,126*	*£11,861*	*£14,524*	*£0*	*£0*	*£0*
Other drug, radiotherapy and surgery costs (disc.)	£3,695	£3,705	£3,356	£3,445	£3,191	£3,713
Treatment costs (disc.)	£16,821	£15,610	£18,095	£3,445	£3,191	£3,713
Cost due to treatment related resource use (disc.)	£9,896	£8,796	£11,219	£6,231	£5,450	£7,140
Treatment independent costs (disc.)	£3,327	£2,272	£4,809	£2,969	£2,027	£4,168
AE costs (disc.)	£635	£538	£736	£747	£638	£870
Total costs (disc.)	**£30,678**	**£28,560**	**£33,394**	**£13,392**	**£11,926**	**£14,979**

Figures H5 and H6 below show respectively the scatter plots for incremental cost vs incremental life years and incremental costs vs incremental QALYs.

Figure H5: Scatter plot of incremental cost versus incremental LYs

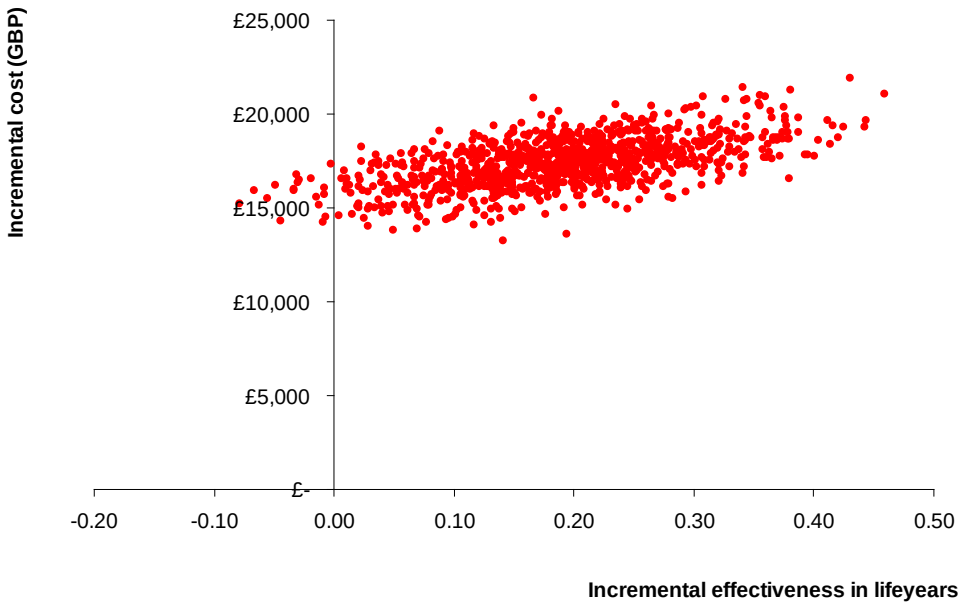
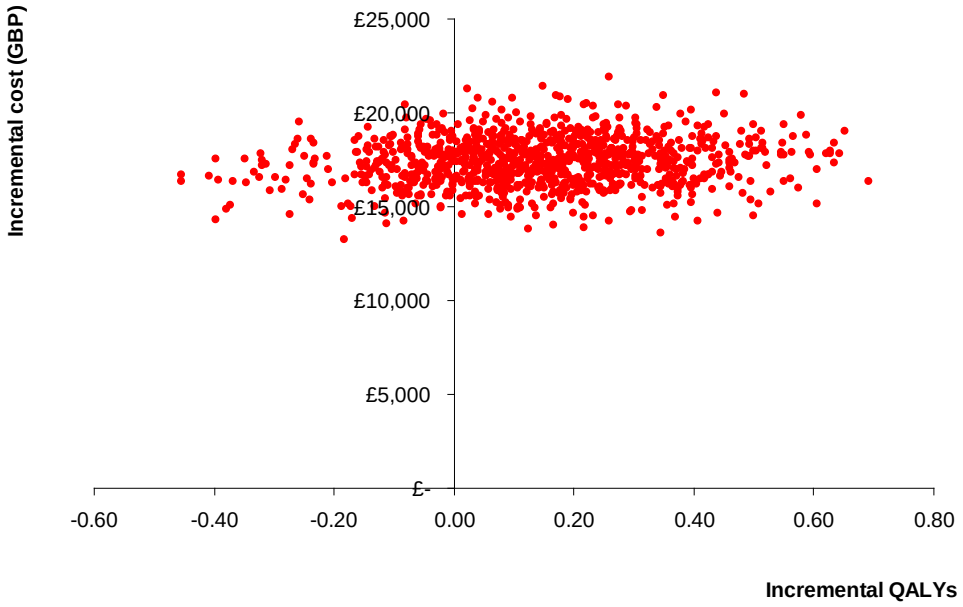


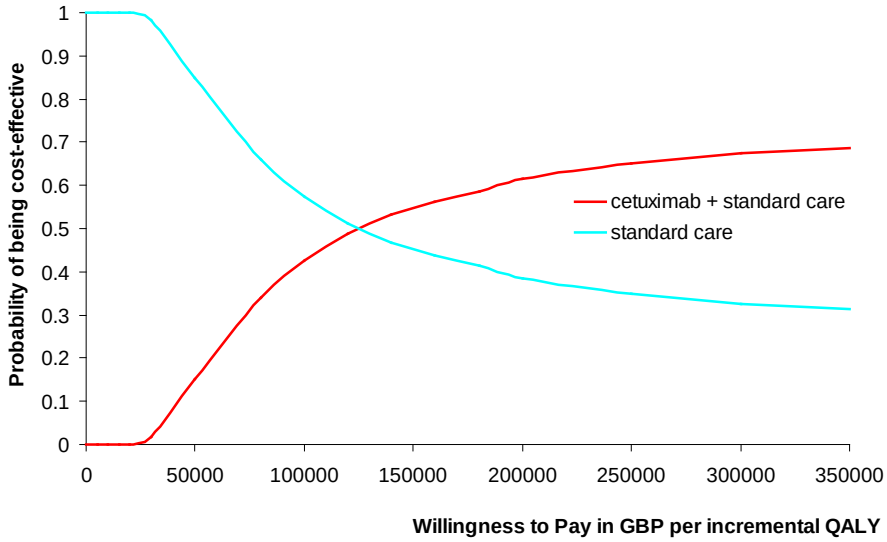
Figure H6: Scatter plot of incremental cost versus incremental QALYs



It is clear from figures H5 and H6 the impact of quality of life and how this misrepresents and undervalues the clinical benefit demonstrated. The spread of data presented in H5 clusters together representing the positive overall survival benefits of cetuximab in combination with chemotherapy. However the spread of data in figure H6 crosses the Y axis representing the impact of the quality of life of

this patient group. Figure H7 shows the cost effectiveness acceptability curve.

Figure H7: Cost effectiveness acceptability curve



7.3.2 Subgroup analysis

7.3.2.1 What were the results of the subgroup analysis/analyses if conducted?

As described in the clinical section and the introduction to the health economic section of this submission, subgroups are based upon location of tumour site and performance status. Figure H8 and H9 Show the forest plots for overall survival in the EXTREME trial and highlight where greater clinical value can be demonstrated. These have been marked on the forest plot for clarity.

Figure H8: Forest plot for subgroups in EXTREME.

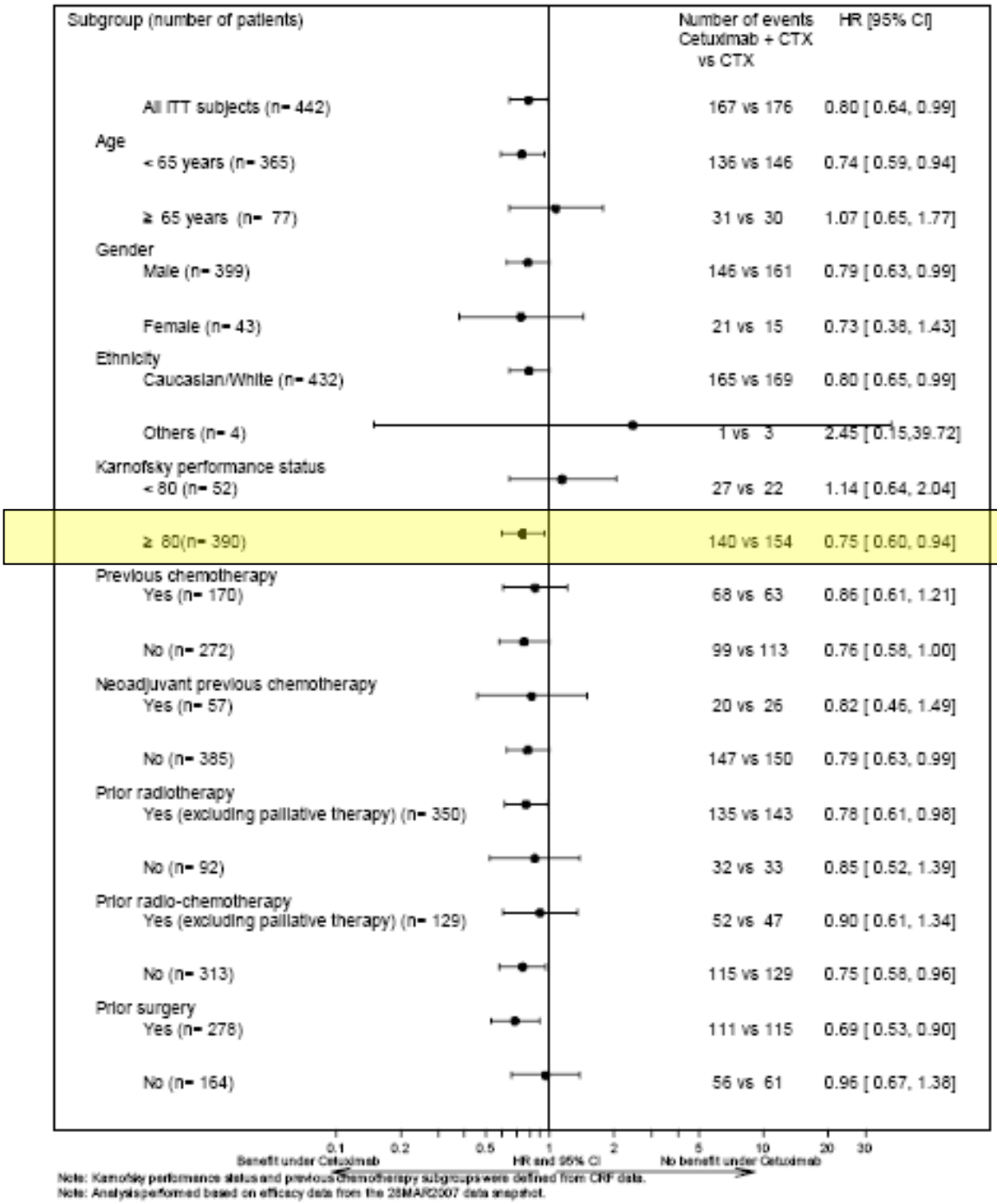
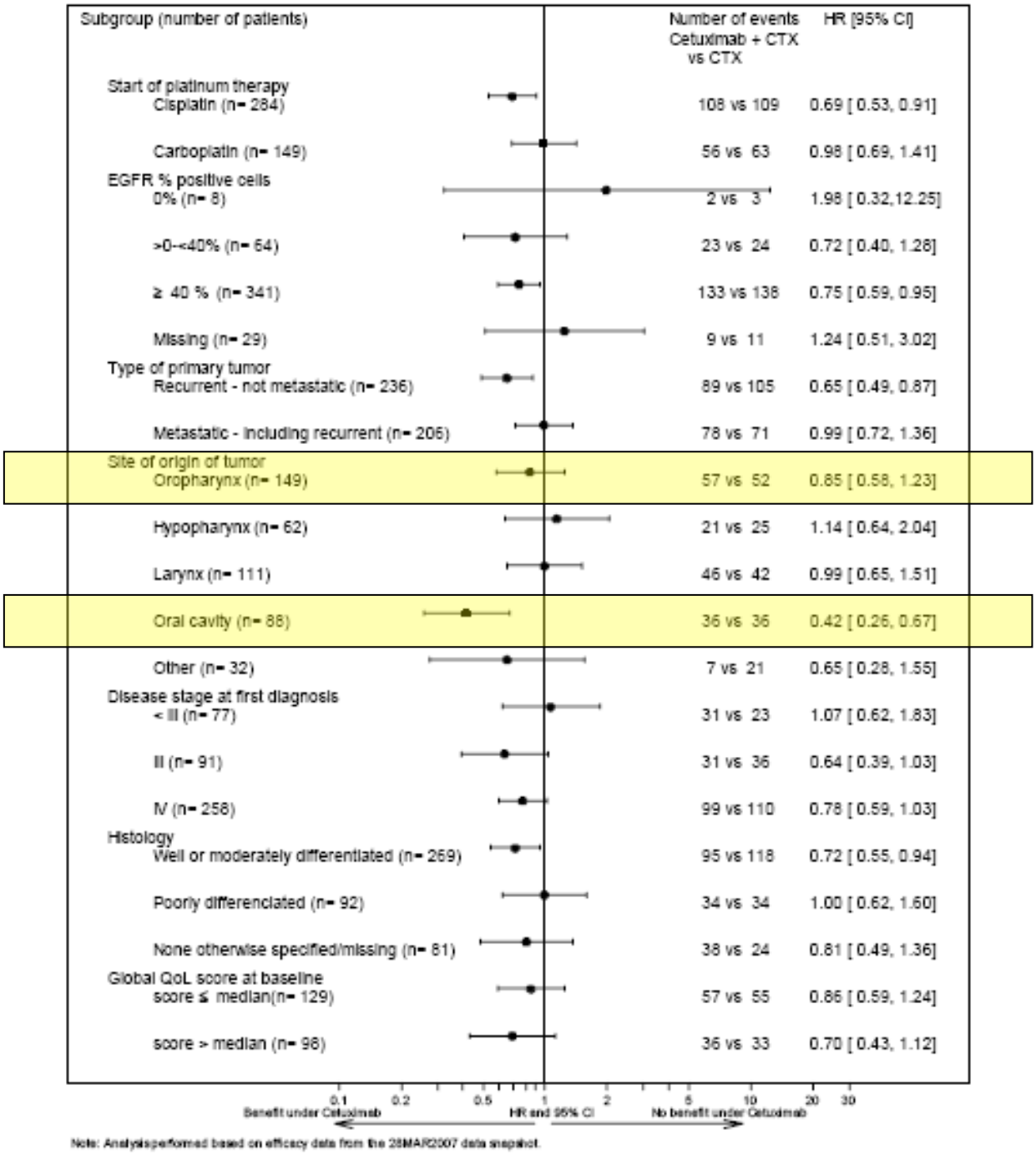


Figure H9: Forest plot for subgroups in EXTREME.



Key points from Figures H8 and H9:

- Results for those patients whose tumours were located in the hypopharynx and larynx showed that the benefit of the addition to cetuximab to standard chemotherapy was not demonstrable to a statistically significant degree.
- Patients with a higher performance status, in this case KPS of 80 and above, did show statistically significant benefit from the addition of cetuximab to standard chemotherapy.

- While sub group analysis on patient age may suggest that younger patients derive more benefit, advice from the Merck Serono advisory board suggests that this may be a surrogate for other prognostic factors.

Hence the sub groups we have focussed on are by tumour site and performance status.

Tables H20, H21 and H22 below provide an exploratory analysis of the following subgroups respectively:

- Oropharynx and oral cavity.
- Oropharynx.
- Oral cavity.

For each of the subgroups data is also presented for those patients with a Karnofsky performance status of 90 or above.

Oropharynx and oral cavity subgroups.

Table H20: Incremental cost effectiveness ratios for the oral cavity and oropharynx subgroups

Oropharynx and oral cavity		
Cetuximab + standard treatment vs Standard treatment	Incremental costs and effects	ICER
Incremental costs	£19,867	
Incremental life-years	0.254	£78,301
Incremental QALYs	0.189	£105,069
Oropharynx and oral cavity, KPS>= 90		
Cetuximab + standard treatment vs Standard treatment		
Incremental costs	£21,683	
Incremental life-years	0.316	£68,717
Incremental QALYs	0.222	£97,702

The scenario above presents results for the combined tumour sites oropharynx and oral cavity subgroup and for patients with a Karnofsky performance status of greater than or equal to 90. This latter group provides a cost per QALY of £97,702. While this analysis may capture a large proportion of patients from the total cohort of patients in the EXTREME study it was apparent from the forest plots shown in Figures H7 and H8 that the individual tumour sites may show different clinical benefit, these scenarios are shown below in Tables H21 and H22.

Oropharynx Subgroups.

Table H21: Incremental cost effectiveness ratios for the oropharynx subgroup.

Oropharynx		
Cetuximab + standard treatment vs Standard treatment	Incremental costs and effects	**ICER**
Incremental costs	£17,915	
Incremental life-years	0.041	£434,568
Incremental QALYs	0.071	£250,597
Oropharynx with KPS>=90		
Cetuximab + standard treatment vs Standard treatment		
Incremental costs	£18,242	
Incremental life-years	0.026	£695,475
Incremental QALYs	0.059	£309,735

The presented incremental cost per QALY gained is lower than the incremental life year gained. It is important to realise that the absolute OS difference per treatment arm for life years is higher than that calculated for QALYs, however the incremental difference is not.

As described in section 7.2.7.2, incremental life years are calculated using the extrapolated OS Kaplan Meier curves and QALYs are calculated by taking into account for the time to progression and the time from progression to death.

For incremental life years, the area under the curves for each treatment arm reflects the mean survival. There is only a small difference in survival as the lines from the Weibull curves cross.

The calculation of QALYs accounts for the time to progression and the time from progression to death. The time to progression is longer for cetuximab treated patients and also the utility value is higher for cetuximab treated patients. Please note that a treatment arm independent utility value is used for the progressive patients, and although the time from progression to death is expected to be longer for patients not treated with cetuximab, this does not have a big impact. Please see Appendix H7 oropharynx results description for more information.

It can be seen from Table H21 that the ICERs for all of the oropharynx subgroups are unlikely to be considered cost-effective.

Oral cavity subgroups.

Table H22: Incremental cost effectiveness ratios for the oral cavity subgroups.

Oral cavity		
Cetuximab + standard treatment vs Standard treatment	Incremental costs and effects	ICER
Incremental costs	£22,658	
Incremental life-years	0.550	£41,224
Incremental QALYs	0.354	£63,927
Oral cavity, KPS>= 90		
Cetuximab + standard treatment vs Standard treatment		
Incremental costs	£27,688	
Incremental life-years	0.818	£33,855
Incremental QALYs	0.505	£54,791

The results Table H22 show that the oral cavity subgroups are approaching a more reasonable cost per life year in the £30,000 to £40,000 range. The impact of the morbidity of advanced head and neck cancer is demonstrated by the increase in ICER value when considering the cost per QALY. These range between £54,791 and £63,927 dependent upon consideration of patients fitness (oral cavity KPS>=90 and oral cavity subgroups respectively).

7.3.3 Sensitivity analyses

Table H23 below shows the results of the univariate sensitivity analysis. Utilities were varied by plus or minus 0.1, costs were varied by 15% either side of the value utilised in the model unless otherwise stated. It can be seen that varying the cost of day case infusion and the utility values in stable/responsive health state of the cetuximab arm of the trial has the greatest impact on the ICER.

Table H23: Univariate sensitivity analysis.

Variable	Base	Low input	High input	Low input ICER	High input ICER	Spread L->H
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
Utilities						
Cetuximab arm						
Stable/response	0.69	0.59	0.79	£197,466	£87,606	£109,860
Standard arm						
Stable/response	0.65	0.55	0.75	£96,238	£164,257	-£68,019
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 out patient and inpatient day	£124.66	£62.33	£296.00	£111,040	£149,756	-£38,716

Table H24 below shows the results of a further univariate sensitivity analysis assessing the impact of higher and lower adverse event costs. Costs were varied plus or minus 25%. It is clear from these results that the modification of these costs has very little impact upon the ICER this is because the adverse event profile report rates are similar across both treatment arms assessed.

Table H24: Cost of adverse event sensitivity analysis.

	Base	Low	High	Low input ICER	High input ICER
Anaemia grade 3	£930	£698	£1,163	£121,485	£121,249
Anaemia grade 4	£930	£698	£1,163	£121,353	£121,382
Neutropenia grade 3	£1,337	£1,003	£1,672	£121,278	£121,457
Neutropenia grade 4	£1,337	£1,003	£1,672	£121,467	£121,267
Thrombocytopenia grade 3	£84	£63	£105	£121,368	£121,367
Thrombocytopenia grade 4	£84	£63	£105	£121,369	£121,365
Mucositis/ stomatitis/ dysphagia grade 2	£95	£71	£118	£121,358	£121,377
Mucositis/ stomatitis/ dysphagia grade 3	£307	£230	£384	£121,371	£121,364
Mucositis/ stomatitis/ dysphagia grade 4	£3,036	£2,277	£3,795	£121,443	£121,292
Nausea/ vomiting grade 2	£81	£61	£101	£121,360	£121,375
Nausea/ vomiting grade 3	£333	£250	£417	£121,355	£121,380
Nausea/ vomiting grade 4	£1,099	£824	£1,374	£121,385	£121,349
Pyrexia grade 3 or 4	£1,103	£828	£1,379	£121,385	£121,349
Acne/ rash grade 3 or 4	£43	£33	£54	£121,362	£121,373

7.3.3.1 What were the main findings of the sensitivity analyses?

It can be seen that varying the cost of day case infusion and the utility values in stable/responsive health state of the cetuximab arm of the trial has the greatest impact on the ICER. Costs of palliative treatment do not affect the ICER. The model is not very sensitive to the 3.5% discount rate applied to costs and outcomes.

To further explore the impact of utility, two further analyses were carried out and in particular assessed the overall group and the oral cavity subgroup with a KPS >=90. For the overall group a comparison was made between the base case analysis (use of treatment specific utilities) in the stable response health state and the use of the overall utility value in this health state. The costs per QALY produced were £121,367 and £139,390 respectively.

For the oral cavity sub group:

a) To assess the utility value for the stable response health state required to produce a more attractive ICER.
b) To assess the impact of using a non treatment specific response value (i.e. the same in both the cetuximab plus chemotherapy and comparator arms).

Firstly, for the oral cavity group, when a utility of 0.9 and 0.85 is utilised in the stable/ response health states for the cetuximab plus chemotherapy and standard treatment arms respectively, the cost per QALY is £46,819.
Secondly, when a non treatment specific utility value is applied the cost per QALY for the overall group is £57,160 for the oral cavity group (compared to £54,791 as presented in Table H22 in the base case subgroup analysis).

7.3.3.2 What are the key drivers of the cost effectiveness results?

The key driver of cost effectiveness is the acquisition cost of cetuximab and utility value applied.

7.3.4 Interpretation of economic evidence

7.3.4.1 Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

There are no other published data in this setting for head and neck cancer.

7.3.4.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology?

Yes, the economic evaluation is relevant to all groups of patients who could potentially use this technology.

7.3.4.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

One of the main weaknesses of this evaluation would be the lack of EQ-5D data collected directly from the clinical trial. The use of the cross walking methodology from EORTC QLQ-C30 is thought to give utility values which are consistent and reasonable considering the health status of patients with recurrent/metastatic head and neck cancer. The smaller sample size of the oral cavity subgroup described above (n=88) may impact on the robustness of the evidence.

7.3.4.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

Two items may have enhanced the robustness of the model:

- Utility data collected in a larger number of patients and by a different method i.e. collected using EQ-5D in a clinical trial.
- A clinical trial looking at separate tumour location – however due to small patient numbers this would be both difficult to recruit to and take years to complete.

8 Assessment of factors relevant to the NHS and other parties

The purpose of this section is to provide an analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical effectiveness and cost effectiveness. This will facilitate the subsequent evaluation of the budget impact analysis. Such factors might include issues relating to service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

8.1 What is the estimated annual budget impact for the NHS in England and Wales?

For the population defined as oral cavity and oropharynx:

- The estimated budget impact for the NHS in England and Wales is a total of £2,852,184 in year one.
- In the first year of launch this consists of treating 169 patients in combination with platinum based chemotherapy. For the oral cavity subgroup this would be 127 patients.
- This would rise £2,852,184 to £14,260,919 treating a total of 845 patients in years one to five respectively. For the oral cavity subgroup costs would rise from £2,148,730 in year one to £10,743,652 in year five.
- Costs presented above represent the additional cost of cetuximab plus associated administration costs over and above the costs of usual care for this group of patients.

Table BI1 below presents total budget impact, purchase costs of cetuximab and other modelled costs including administration, treatment of adverse events and costs incurred for radiotherapy and surgical procedures.

Table BI1: Estimated budget impact for whole eligible population.

Estimated Budget Impact Overview				
	Patient numbers	**Cetuximab cost**	**Administration cost**	**Total cost**
2009	169	£2,220,374	£631,810	£2,852,184
2010	338	£4,440,748	£1,263,619	£5,704,368
2011	507	£6,661,123	£1,895,429	£8,556,552
2012	676	£8,881,497	£2,527,239	£11,408,736
2013	845	£11,101,871	£3,159,048	£14,260,919

As can be seen from Table BI2 below the budget impact for the oral cavity subgroup in year one is estimated at £2,220,374 acquisition cost for cetuximab and total cost including administration of £2,852,184.

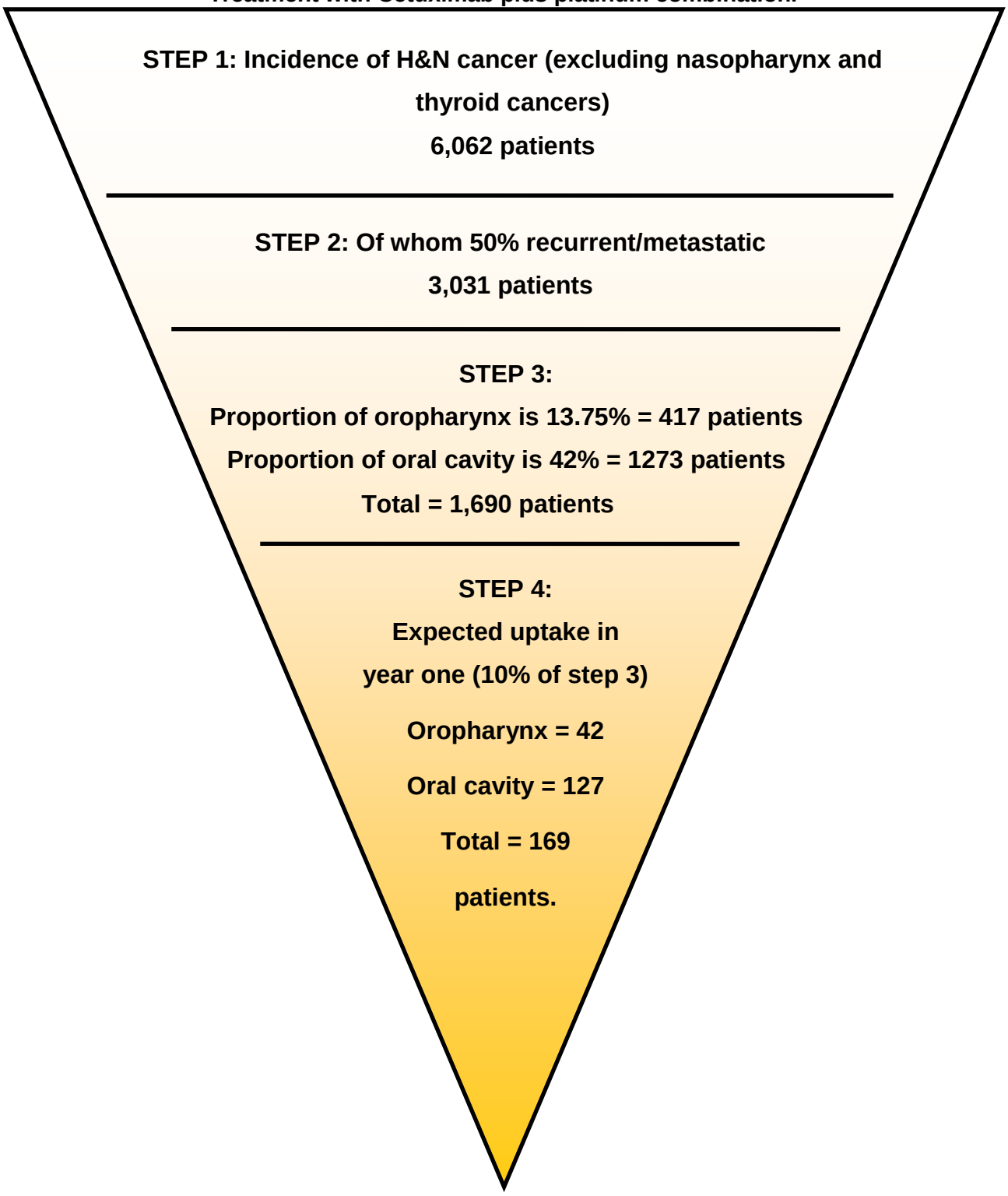
Table BI2: Estimated budget impact for oral cavity sub group.

Estimated Budget Impact for oral cavity sub group				
	Patient numbers	**Cetuximab cost**	**Administration cost**	**Total cost**
2009	127	£1,672,748	£475,982	£2,148,730
2010	255	£3,345,497	£951,964	£4,297,461
2011	382	£5,018,245	£1,427,947	£6,446,191
2012	509	£6,690,993	£1,903,929	£8,594,922
2013	637	£8,363,741	£2,379,911	£10,743,652

8.2	What number of patients were assumed to be eligible? How was this figure derived?

Figure BI1 shows the patient flow, the assumptions are listed below for each step.

Figure BI1: Estimated Number of Patients Assumed to Be Eligible for Treatment with Cetuximab plus platinum combination.



Step 1: The 6,062 patients in step one consist of the sum total of the ICD10 code registrations specific to the tumour sub groups pertinent to the decision problem. Please see Table BI3 which provides a breakdown of the number of patients by tumour type in England and Wales.

Step 2: As noted in section 4.1 at least 50% of patients with locally advanced SCCHN develop locoregional or distant relapses, which are usually detected within the first 2 years of treatment [Argiris 2008].

Step 3: Based upon the proportion of patients who were enrolled into the EXTREME trial the proportion of oropharynx patients is13.75%. This was calculated by assuming that the oropharynx group represents 50% of patients with pharynx cancer. Oral cavity patients was found to be 42.2%.

Step 4: The uptake assumption in year one of 10% is based upon a market introduction mid year and slow local approval processes as observed with the locally advanced head and neck approval for cetuximab.

Table BI3: SCCHN registrations relevant to decision problem by tumour site

Site	**ICD10 code**	**Number of registrations in England 2005**		**Number of registrations in Wales 2006**		**Total**
		males	*females*	*males*	*females*	**(%)**
Oral cavity	C00-C06	1341	1005	130	82	2558 (42.2%)
Pharynx	C09-C14	1126	415	90	34	1665 (27.5%)
Larynx	C32	1432	297	89	21	1839 (30.3%)
total		3899	1717	309	137	6062

ref [ONS MB1 – no 36] : [www.wcisu.wales.nhs.uk]

8.3 What assumption(s) were made about current treatment options and uptake of technologies?

It was assumed that the uptake of cetuximab would be 10% in year one. This is based upon:

- The estimated timing of NICE guidance coming part way through year one.
- Relatively slow uptake of current NICE guidance in H&N cancer.

8.4 What assumption(s) were made about market share (where relevant)?

Market share is not thought to be relevant in this context, there are no competitor products in this indication.

8.5 What unit costs were assumed? How were these calculated?

Unit costs are as described in Tables H10, H11 and H12 and include unit costs for drug treatment and NHS reference costs for administration.

8.6 In addition to drug costs, consider other significant costs associated with treatment. What is the recommended treatment regime – for example, what is the typical number of visits, and does treatment involve daycase or outpatient attendance? Is there a difference between recommended and observed doses? Are there likely to be any adverse events or a need for other treatments in combination with the technology?

The budget impact model takes into account drug costs and the costs of administration. Follow up therapies including 'best supportive care' chemotherapy and radiotherapy plus palliative surgical interventions are not included as they are not contingent on the introduction of cetuximab.

8.7 Were there any estimates of resource savings? If so, what were they?

There were no estimates of resource savings.

8.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

No opportunities for resource savings have been identified at this time.

9 References

[ONS MB1 – no 36] - http://www.statistics.gov.uk/downloads/theme_health/MB1_36/MB1_No36_2005.pdf

[Welsh cancer statistics] - http://www.wales.nhs.uk/sites3/Documents/242/incpub2006%5F31Jan08.pdf

[NCCN 2008] - http://www.nccn.org/professionals/physician_gls/PDF/head-and-neck.pdf

[SIGN 2006] - http://www.sign.ac.uk/pdf/sign90.pdf

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10 Appendices

Appendix M1: A+A data tracker market research

Appendix H1: Advisory Board.

Appendix H2: EORTC QLQ C30 and H&N 35.

Appendix H3: Parameters of the Weibull distribution for overall survival and progression free survival by treatment arm and subgroups

	cetuximab + Standard Treatment		Standard Treatment	
	Shape	**Scale**	**Shape**	**Scale**
Progression Free Survival				
Total population	1.399	0.000571	1.490	0.000646
Patients with oral cavity as primary tumour site	1.351	0.000614	1.220	0.003556
and KPS>90	1.398	0.000384	1.013	0.008636
Patients with oropharynx as primary tumour site	1.629	0.000143	1.446	0.000752
and KPS>90	1.958	0.000023	1.770	0.000121
Patients with oral cavity or oropharynx as primary tumour site	1.499	0.000282	1.323	0.001636
and KPS>90	1.645	0.000115	1.292	0.001663
Overall Survival				
Total population	1.165	0.000911	1.158	0.000128
Patients with oral cavity as primary tumour site	1.402	0.000194	1.026	0.004303
and KPS>90	2.113	0.000022	1.214	0.001905
Patients with oropharynx as primary tumour site	1.557	0.000082	1.184	0.000862
and KPS>90	1.689	0.000031	1.493	0.000108
Patients with oral cavity or oropharynx as primary tumour site	1.353	0.000269	1.006	0.003151
and KPS>90	1.815	0.000013	1.180	0.001040

Appendix H4: Table of papers retrieved from CRD search.

Appendix H5: cetuximab vial use correction

Appendix H6: Distributions for probabilistic sensitivity analysis

Appendix H7: Oropharynx results description.

Appendix H8: Parameter estimates for cross-walk algorithm from QLQ-C30 to EQ-5D utility

	Unstandardized Coefficients	Standard Error
Constant	0.633	.071
Q29 Overall health	0.047	.013
Q3 trouble with short walk	-0.124	.031
Q5 help with dressing washing	-0.167	.047
Q11 trouble sleeping	-0.086	.032
Q20 difficulty concentrating	-0.102	.033
Q26 physical family life impact	-0.082	.031

Source: P Kind. Measuring the value of quality of life in cancer: An index based on EORTC QLQC-30 Journal of Clinical Oncology, 2005 ASCO Annual Meeting Proceedings. Vol 23, No 16S, 2005: 6013

Appendix H9: Breakdown of cost components for treatment of adverse events

10.1 Appendix 1

Summary of Product Characteristics or Technical Manual or drafts

Please note that the attached SPC is in a draft form submitted to EMEA and may therefore be subject to revision.

10.2 Appendix 2: search strategy for section 6

The following information should be provided.

10.2.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

10.2.2 The date on which the search was conducted.

10.2.3 The date span of the search.

10.2.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

10.2.5 Details of any additional searches, for example searches of company databases (include a description of each database).

10.2.6 The inclusion and exclusion criteria.

10.2.7 The data abstraction strategy.

10.3 Appendix 3: search strategy for section 7

The following information should be provided.

10.3.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- Health Economic Evaluation Database
- NHS Economic Evaluation Database (NHS EED).

10.3.2 The date on which the search was conducted.

10.3.3 The date span of the search.

10.3.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Table AP1 and AP2 below show the results from the searches performed using OVID on 26th August 2008.

The search strategy and date span can be found under section 7.1.1.

Table AP1: Copy of search results from OVID for Medline

OVID Medline (R) 1950 to present carried out 26/8/08			
# ▲	**Searches**	**Results**	**Search Type**
1	recurrent head & neck cancer {Including Related Terms}	531	Basic
2	limit 1 to (human and english language)	469	Advanced
3	metastatic head & neck cancer {Including Related Terms}	623	Basic
4	limit 3 to (human and english language)	510	Advanced
5	metastatic recurrent SCCHN {Including Related Terms}	214	Basic
6	limit 5 to (human and english language)	196	Advanced
7	6 or 4 or 2	1027	Advanced
8	cost effectiveness analysis {Including Related Terms}	592	Basic
9	limit 8 to (human and english language)	465	Advanced
10	cost benefit analysis {Including Related Terms}	780	Basic
11	limit 10 to (human and english language)	518	Advanced
12	QALY {Including Related Terms}	542	Basic
13	limit 12 to (human and english language)	489	Advanced
14	cost effectiveness {Including Related Terms}	1384	Basic
15	limit 14 to (human and english language)	1303	Advanced
16	quality of life {Including Related Terms}	504	Basic
17	limit 16 to (human and english language)	503	Advanced
18	cetuximab {Including Related Terms}	491	Basic
19	limit 18 to (human and english language)	357	Advanced
20	7 and 9 and 19	0	Advanced
21	11 and 7 and 19	0	Advanced
22	7 and 13 and 19	0	Advanced
23	7 and 19 and 15	0	Advanced
24	7 and 19 and 17	0	Advanced

Table AP2: Copy of search results from OVID for Embase

OVID Embase 1980 to 2008 week 34 carried out 26/8/08			
# ▲	**Searches**	**Results**	**Search Type**
1	recurrent head & neck cancer {Including Related Terms}	565	Basic
2	limit 1 to (human and english language)	494	Advanced
3	metastatic head & neck cancer {Including Related Terms}	693	Basic
4	limit 3 to (human and english language)	598	Advanced
5	metastatic recurrent SCCHN {Including Related Terms}	61	Basic
6	limit 5 to (human and english language)	56	Advanced
7	6 or 4 or 2	958	Advanced
8	cost effectiveness analysis {Including Related Terms}	1261	Basic
9	limit 8 to (human and english language)	916	Advanced
10	cost benefit analysis {Including Related Terms}	576	Basic
11	limit 10 to (human and english language)	312	Advanced
12	QALY {Including Related Terms}	1783	Basic
13	limit 12 to (human and english language)	1509	Advanced
14	cost effectiveness {Including Related Terms}	4675	Basic
15	limit 14 to (human and english language)	3777	Advanced
16	quality of life {Including Related Terms}	16584	Basic
17	limit 16 to (human and english language)	14122	Advanced
18	cetuximab {Including Related Terms}	247	Basic
19	limit 18 to (human and english language)	215	Advanced
20	7 and 9 and 19	0	Advanced
21	11 and 7 and 19	0	Advanced
22	7 and 13 and 19	0	Advanced
23	7 and 19 and 15	0	Advanced
24	7 and 19 and 17	0	Advanced

HEEDS was searched on 26/8/08 using the terms cetuximab and recurrent metastatic head & neck cancer.
NHS EED was searched on 26/8/08 using cetuximab as the search term.

10.3.5 Details of any additional searches, for example searches of company databases (include a description of each database).

1From: Nicola Hay
Sent: 06 November 2008 12:19
To: '[redacted]'
Cc: Jeremy Powell; David Bevan; Janet Robertson; Meindert Boysen
Subject: Cetuximab for the treatment of metastatic and/or recurrent SCCHN - follow up to clarification letter

Dear [redacted],

Further to your response to our questions of clarification dated 24th October 2008, the Evidence Review Group, Liverpool Reviews & implementation Group (LRiG), would like to request further details as follows:

For the additional subgroup analyses considering recurrent (excluding metastatic) disease and any metastatic disease, please provide further details of the survival analyses as follows:

· Kaplan-Meier analysis including OS and PFS survival charts.

· Kaplan-Meier mean OS and PFS at 24 months with confidence limits.

· If possible a detailed printout of Kaplan-Meier events and censoring by time in the EXTREME trial.

· Weibull model parameter values used in the cost-effectiveness analysis.

· Any related clinical effectiveness data comparisons (e.g. hazard ratios and forest plots)

It would be appreciated if you would provide the above information to the Institute by 20th November 2008.

Kind Regards

Nicola

Nicola Hay

Analyst - Centre for Health Technology Evaluation

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10th October 2008

[redacted]
Merck Serono
Bedfont Cross
Stanwell Road
Feltham
Middlesex
TW14 8NX

Dear [redacted],

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

The Evidence Review Group, Liverpool Reviews and Implementation Group (LRiG), and the technical team at NICE have now had an opportunity to take a look at submission by Merck Serono. In general terms they felt that it is well presented and clear. However the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both LRiG and the technical team at NICE will be addressing these points in their reports. As there will not be any consultation on the evidence report prior to the Appraisal Committee meeting you may want to do this work and provide further discussion from your perspective at this stage.

We request you to provide a written response to this letter to the Institute by 24th October 2008. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

If you present data that is not already reference in the main body of your submission and that data is seen to be academic/commercial in confidence

information, please complete the attached checklist for in confidence information.

Yours sincerely

Meindert Boysen, Pharmacist MScHPPF
Associate Director - STA
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

Section A. Clarification on effectiveness data

A1. *Please provide a break down of patient numbers in the EXTREME trial by country.*

A2. *Please provide clarification as to why 15% of patients in the cetuxiamb arm and 16% of patients in the chemotherapy arm in the EXTREME trial had not previously been treated with radiotherapy.*

A3. *Please provide details of the stage of disease at diagnosis and previous treatment for each tumour site (oropharynx, hypopharynx, larynx, oral cavity and other) in the EXTREME trial.*

A4. *Please provide the proportion of unavailable or unreadable scans in each of the trial arms in the EXTREME trial for each time point.*

A5. *Please provide overall survival time (OS) and progression free survival time (PFS) data for patients in the cetuximab plus cisplatin arm and cisplatin arm in the EXTREME trial.*

Section B. Clarification on cost-effectiveness data

B1. *Please provide further details of the survival analyses undertaken for the full trial cohort and all six modelled subgroups for the following:*

- *Kaplan-meier analysis including OS and PFS survival charts, estimated mean OS and PFS at 24 months with confidence limits, and if possible a detailed printout of kaplan-meier events and censoring by time in the EXTREME trial.*
- *Performance statistics for all functional forms (including Weibull) tested for modelling OS and PFS for each modelled population.*
- *Correlation between Weibull parameter estimates for each modelled population.*

B2. *Please indicate whether the parameters for Weibull models for OS and PFS were estimated independently or jointly in all cases.*

B3. *Please provide further details of the proportion of scheduled platinum chemotherapy doses given/omitted by cycle.*

B4. *Please provide further clarification of the meaning of the adverse event rates used in the model (for example does the adverse event data refer to the number of events, or the number of patients for whom any event occurred at any time).*

B5. *Please provide separate incremental cost-effectiveness ratios for patients with recurrent cancer and for those patients with metastatic cancer.*

Cetuximab for the treatment of metastatic and/or recurrent squamous cell carcinoma of the head and neck:
Merck Serono Response to NICE clarification Letter

Please find on behalf of Merck Serono the answers to questions of clarification from the evidence review group of the 10th October 2008 for the appraisal of cetuximab in the treatment of metastatic and/or recurrent squamous cell carcinoma of the head and neck. These questions are as set out below.

Section A. Clarification on effectiveness data

A1. *Please provide a break down of patient numbers in the EXTREME trial by country.*

A2. *Please provide clarification as to why 15% of patients in the cetuximab arm and 16% of patients in the chemotherapy arm in the EXTREME trial had not previously been treated with radiotherapy.*

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A5. *Please provide overall survival time (OS) and progression free survival time (PFS) data for patients in the cetuximab plus cisplatin arm and cisplatin arm in the EXTREME trial.*

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B1. *Please provide further details of the survival analyses undertaken for the full trial cohort and all six modelled subgroups for the following:*

- *Kaplan-meier analysis including OS and PFS survival charts, estimated mean OS and PFS at 24 months with confidence limits, and if possible a detailed printout of kaplan-meier events and censoring by time in the EXTREME trial.*
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B3. *Please provide further details of the proportion of scheduled platinum chemotherapy doses given/omitted by cycle.*

B4. *Please provide further clarification of the meaning of the adverse event rates used in the model (for example does the adverse event data refer to the number of events, or the number of patients for whom any event occurred at any time).*

B5. *Please provide separate incremental cost-effectiveness ratios for patients with recurrent cancer and for those patients with metastatic cancer.*

Section A. Clarification on effectiveness data

A1: Please provide a break down of patient numbers in the EXTREME trial by country.

Table A1 below presents the breakdown of patient numbers both by country and by arm of the trial. It can be seen that while a small number of patients were enrolled in the UK over half of the total came from other European countries which would be expected to have similar practices and levels of care for the treatment of head and neck cancer (Belgium, France, Germany, Italy, Netherlands, Spain) as observed in the UK.

Table A1: Breakdown of patients by country and arm of trial

Country	Cetuximab + CTX	CTX	**Total**
Austria	4	10	14
Belgium	14	16	30
Czech Republic	4	5	9
France	45	31	76
Germany	18	14	32
Hungary	19	24	43
Italy	14	12	26
Netherlands	4	6	10
Poland	18	18	36
Portugal	3	6	9
Russia	9	7	16
Slovakia	3	1	4
Spain	38	41	79
Sweden	3	4	7
Switzerland	4	4	8
Ukraine	18	16	34
United Kingdom	4	5	9
Total	**222**	**220**	**442**

A2: *Please provide clarification as to why 15% of patients in the cetuximab arm and 16% of patients in the chemotherapy arm in the EXTREME trial had not previously been treated with radiotherapy.*

Information from the EXTREME trial states that of these patients, 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. However, this data does not account for the remaining 7% and 9% of patients in each arm and why these patients did not receive radiotherapy.

The EXTREME clinical trial report forms did not collect this particular information hence Merck Serono can only postulate that either the previous treatment episode did not clinically warrant treatment with radiotherapy or that it was judged more appropriate to use another modality of treatment. For example, for some patients with locally advanced disease it may be that surgery was thought to provide a better clinical outcome than radiotherapy, and in EXTREME this was common with 62.9% of all patients having had some form of surgical intervention as pre-treatment.

It is also important to consider that clinical practice has evolved since the EXTREME trial was initiated in December 2004.

A3: *Please provide details of the stage of disease at diagnosis and previous treatment for each tumour site (oropharynx, hypopharynx, larynx, oral cavity and other) in the EXTREME trial.*

Table A2 below describes how the staging referred to in Table A3 is derived from the TNM classification.

Table A2: Key to the staging used in Table A3

Stage	Tumour	Nodal involvement	Metastases
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
Stage III	any T	N1	M0
Stage IV	T4	N0, N1	M0
Stage IV	any T	N2, N3	Any M
Stage IV	any T	any N	M1
Unknown	any unknown, or TX, NX, MX which could not be solved by the definition above		
MIssing	Any data not available.		

It can be seen from Table A3 below that the majority of patients in each tumour site sub group present with Stage IV disease (258/442); a further 95 out of 442 patients present with stage III disease. For both stage III and stage IV disease this represents just under 80% of all the patents enrolled into the EXTREME trial.

Table A3: Tumour stage at diagnosis by site

Tumour site Summary	n=
Hypopharynx	62
Larynx	111
Oral cavity	88
Oropharynx	149
Other	32
Total	**442**

Tumour site/stage	n=
Hypopharynx	**62**
Stage I	1
Stage II	3
Stage III	9
Stage IV	48
Unknown	1
Larynx	**111**
Stage 0	1
Stage I	9
Stage II	13
Stage III	25
Stage IV	58
Missing	1
Unknown	4
Oral cavity	**88**
Stage I	7
Stage II	12
Stage III	24
Stage IV	42
Unknown	3
Oropharynx	**149**
Stage I	7
Stage II	22
Stage III	29
Stage IV	85
Unknown	6
Other	**32**
Stage II	2
Stage III	4
Stage IV	25
Unknown	1
Total	**442**

Table A4 below presents the number (and percentage) of patients receiving pre-treatment by tumour type.

Table A4: Number of pre-treatments by tumour type – patient numbers.

Number of pre – treatments	Site of origin of tumor											
	Hypopharynx		Larynx		Oral cavity		Oropharynx		Other		Total	
0	10	(16.1%)	7	(6.3%)	1	(1.1%)	16	(10.7%)	5	(15.6%)	39	(8.8%)
1	16	(25.8%)	23	(20.7%)	16	(18.2%)	30	(20.1%)	7	(21.9%)	92	(20.8%)
2	19	(30.6%)	34	(30.6%)	39	(44.3%)	59	(39.6%)	9	(28.1%)	160	(36.2%)
3	9	(14.5%)	33	(29.7%)	16	(18.2%)	23	(15.4%)	7	(21.9%)	88	(19.9%)
4	6	(9.7%)	8	(7.2%)	11	(12.5%)	9	(6.0%)	2	(6.3%)	36	(8.1%)
5	2	(3.2%)			2	(2.3%)	3	(2.0%)	1	(3.1%)	8	(1.8%)
6			5	(4.5%)	1	(1.1%)	5	(3.4%)	1	(3.1%)	12	(2.7%)
7			1	(0.9%)	2	(2.3%)	1	(0.7%)			4	(0.9%)
8							3	(2.0%)			3	(0.7%)
Total	**62**	**(100.0%)**	**111**	**(100.0%)**	**88**	**(100.0%)**	**149**	**(100.0%)**	**32**	**(100.0%)**	**442**	**(100.0%)**

For each of the tumour site subgroups, data is presented below in Table A5 showing which types of pre-treatment were administered.

Table A5: Modality of pre-treatment

Anti cancer pre-treatment: Immunotherapy

Site of origin of tumor	Not received	Received	Total
Hypopharynx	100.0%	0%	100.0%
Larynx	100.0%	0%	100.0%
Oral cavity	100.0%	0%	100.0%
Oropharynx	100.0%	0%	100.0%
Other	100.0%	0%	100.0%
Total	**100.0%**	0%	**100.0%**

Anti cancer pre-treatment: Hormonal

Site of origin of tumor	Not received	Received	Total
Hypopharynx	100.0%	0%	100.0%
Larynx	100.0%	0%	100.0%
Oral cavity	100.0%	0%	100.0%
Oropharynx	100.0%	0%	100.0%
Other	100.0%	0%	100.0%
Total	**100.0%**	0%	**100.0%**

Anti cancer pre-treatment: Radiotherapy

Site of origin of tumor	Not received	Received	Total
Hypopharynx	16.1%	83.9%	100.0%
Larynx	15.3%	84.7%	100.0%
Oral cavity	9.1%	90.9%	100.0%
Oropharynx	13.4%	86.6%	100.0%
Other	25.0%	75.0%	100.0%
Total	**14.3%**	**85.7%**	**100.0%**

Table A5: Modality of pre-treatment (continued).

Anti cancer pre-treatment: Radiotherapy (excluding palliative)

Site of origin of tumor	Not received	Received	Total
Hypopharynx	27.4%	72.6%	100.0%
Larynx	23.4%	76.6%	100.0%
Oral cavity	12.5%	87.5%	100.0%
Oropharynx	18.8%	81.2%	100.0%
Other	31.3%	68.8%	100.0%
Total	**20.8%**	**79.2%**	**100.0%**

Anti cancer pre-treatment: Other

Site of origin of tumor	Not received	Received	Total
Hypopharynx	100.0%	0.0%	100.0%
Larynx	100.0%	0.0%	100.0%
Oral cavity	98.9%	1.1%	100.0%
Oropharynx	98.7%	1.3%	100.0%
Other	100.0%	0.0%	100.0%
Total	**99.3%**	**0.7%**	**100.0%**

Anti cancer pre-treatment: Surgery

Site of origin of tumor	Not received	Received	Total
Hypopharynx	58.1%	41.9%	100.0%
Larynx	23.4%	76.6%	100.0%
Oral cavity	20.5%	79.5%	100.0%
Oropharynx	47.7%	52.3%	100.0%
Other	40.6%	59.4%	100.0%
Total	**37.1%**	**62.9%**	**100.0%**

Table A5: Modality of pre-treatment (continued).

Anti cancer pre-treatment: Chemotherapy

Site of origin of tumor	Not received	Received	Total
Hypopharynx	51.6%	48.4%	100.0%
Larynx	67.6%	32.4%	100.0%
Oral cavity	72.7%	27.3%	100.0%
Oropharynx	54.4%	45.6%	100.0%
Other	62.5%	37.5%	100.0%
Total	**61.5%**	**38.5%**	**100.0%**

Anti cancer pre-treatment: Radio-chemotherapy

Site of origin of tumor	Not received	Received	Total
Hypopharynx	69.4%	30.6%	100.0%
Larynx	77.5%	22.5%	100.0%
Oral cavity	79.5%	20.5%	100.0%
Oropharynx	61.7%	38.3%	100.0%
Other	68.8%	31.3%	100.0%
Total	**70.8%**	**29.2%**	**100.0%**

Key points from Table A5:

- Immunotherapy and hormonal treatments were not offered to patients prior to entry into the EXTREME trial and the options shown capture the majority of possible pre-treatments since the 'other' category has a total of just 0.7%.
- For head and neck cancer treatments, nearly 86% of patients had received pre-treatment with radiotherapy. This figure decreases slightly to 79.2% when the palliative intent radiotherapy is removed from the analysis.
- Surgery was another common modality of pre-treatment with 62.9% of all patients having had some form of surgical intervention.
- 38.5% of patients were pre-treated with chemotherapy alone, while the proportion of patients who had been given radio-chemotherapy was 31.3%.

A4: *Please provide the proportion of unavailable or unreadable scans in each of the trial arms in the EXTREME trial for each time point.*

The proportion of unavailable or unreadable scans in each of the trial arms as requested is presented as a table in Appendix 2.

A5: *Please provide overall survival time (OS) and progression free survival time (PFS) data for patients in the cetuximab plus cisplatin arm and cisplatin arm in the EXTREME trial.*

If we understand the question correctly, the overall survival and progression free survival data were presented in the original Merck Serono submission of evidence (section 6.4 Page 45 to 49) in Figures B2 and B4. Figure B3 presented the forest plots of hazard ratios of pre-planned subgroups in EXTREME. These data are included in appendix A1 below. If this is not the correct interpretation of this question, we would please request further clarity as to the exact requirements of this request.

Section B. Clarification on cost-effectiveness data

B1: *Please provide further details of the survival analyses undertaken for the full trial cohort and all six modelled subgroups for the following:*

- *Kaplan-meier analysis including OS and PFS survival charts, estimated mean OS and PFS at 24 months with confidence limits, and if possible a detailed printout of kaplan-meier events and censoring by time in the EXTREME trial.*

A visual representation of the Kaplan-Meier analyses including overall survival and progression free survival are presented below in Figures H1 to H12. These are presented for each tumour site sub-group and by treatment arm. The 24-month overall survival and progression free data with corresponding lower and upper limits are given below in Table H1 and H2 respectively.

Figure H1: PFS overall population.

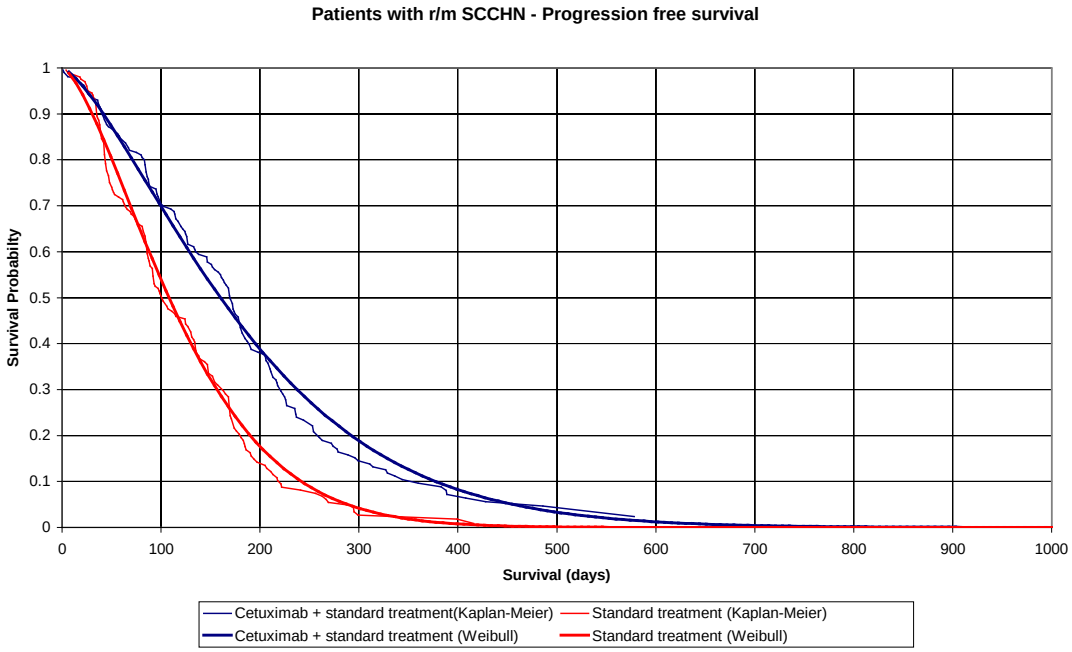


Figure H2: OS overall population.

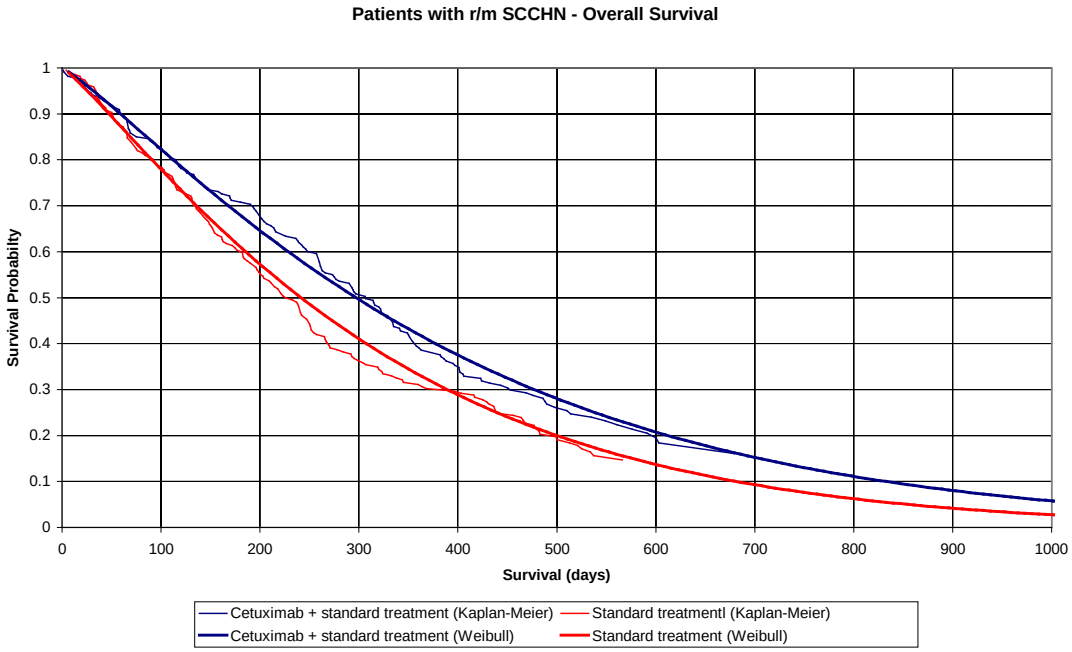


Figure H4: PFS oral cavity subgroup

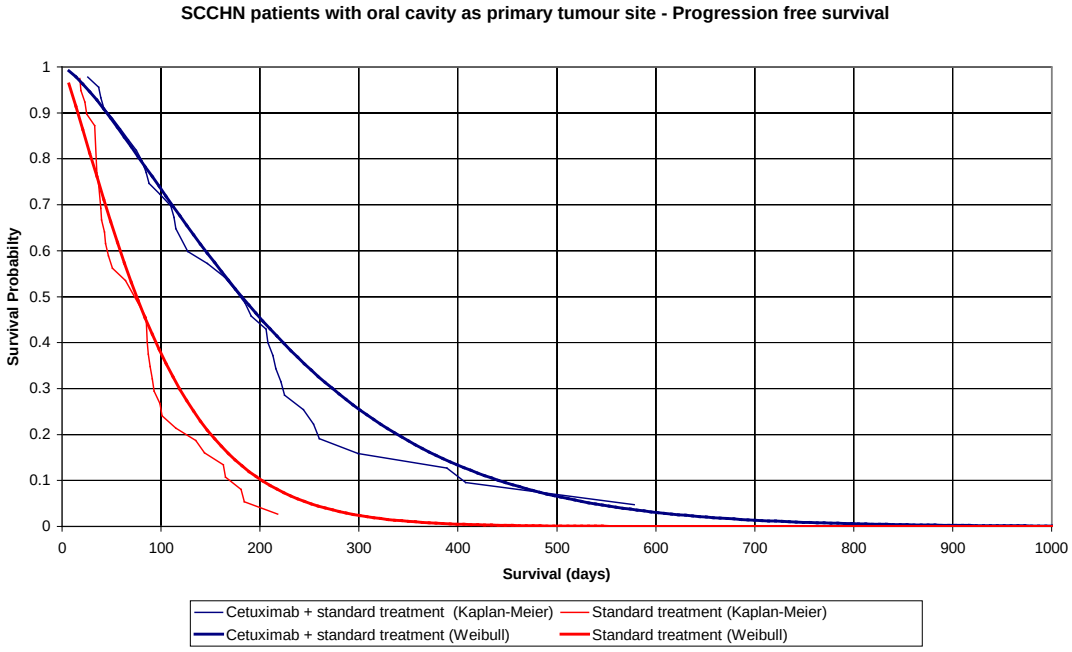


Figure H5: OS oral cavity subgroup

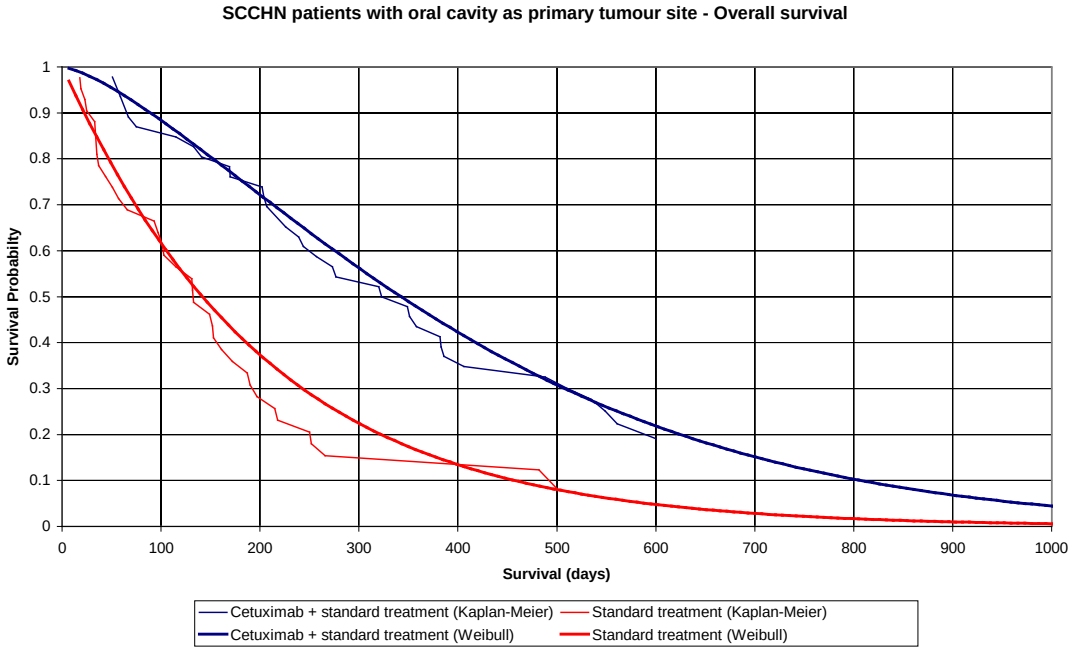


Figure H6: PFS oral cavity; KPS>=90.

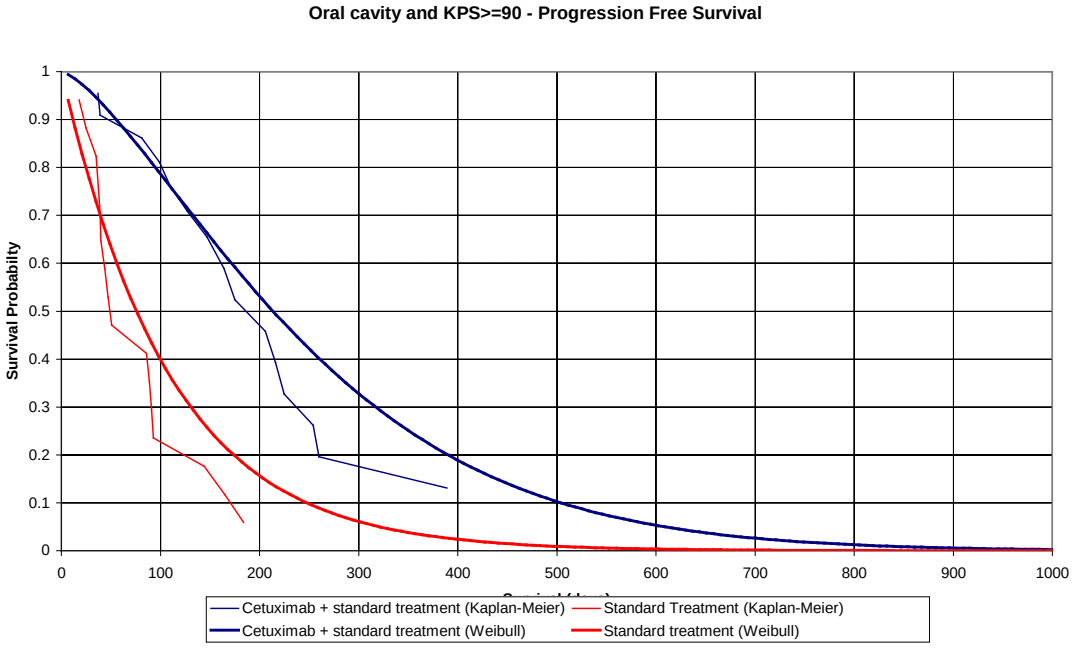


Figure H7: OS oral cavity; KPS>=90.

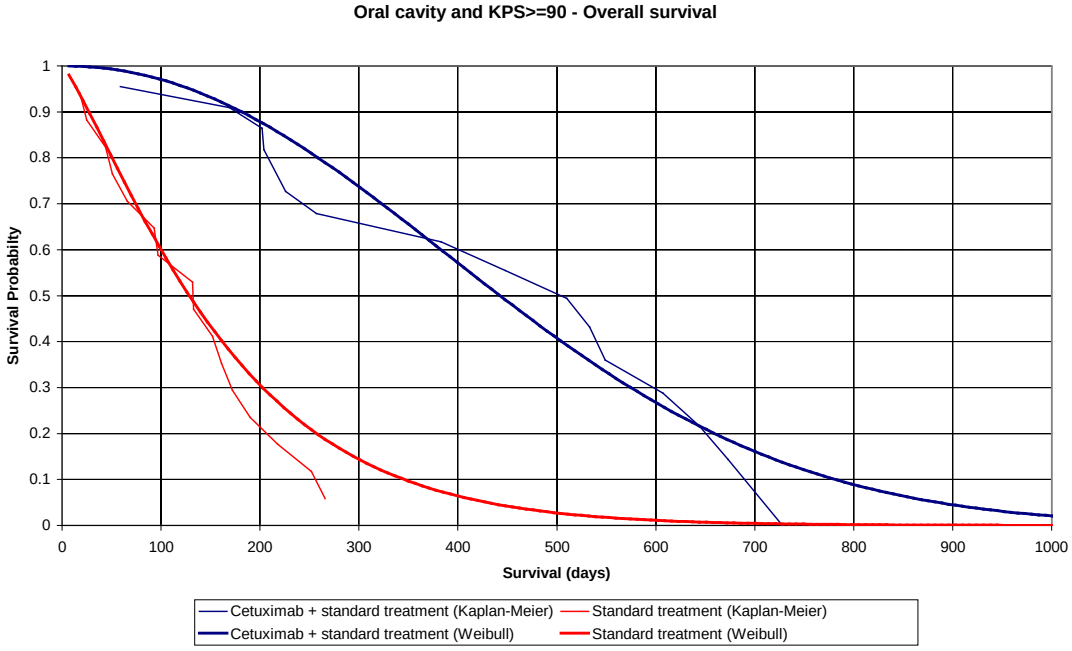


Figure H8: PFS oropharynx.

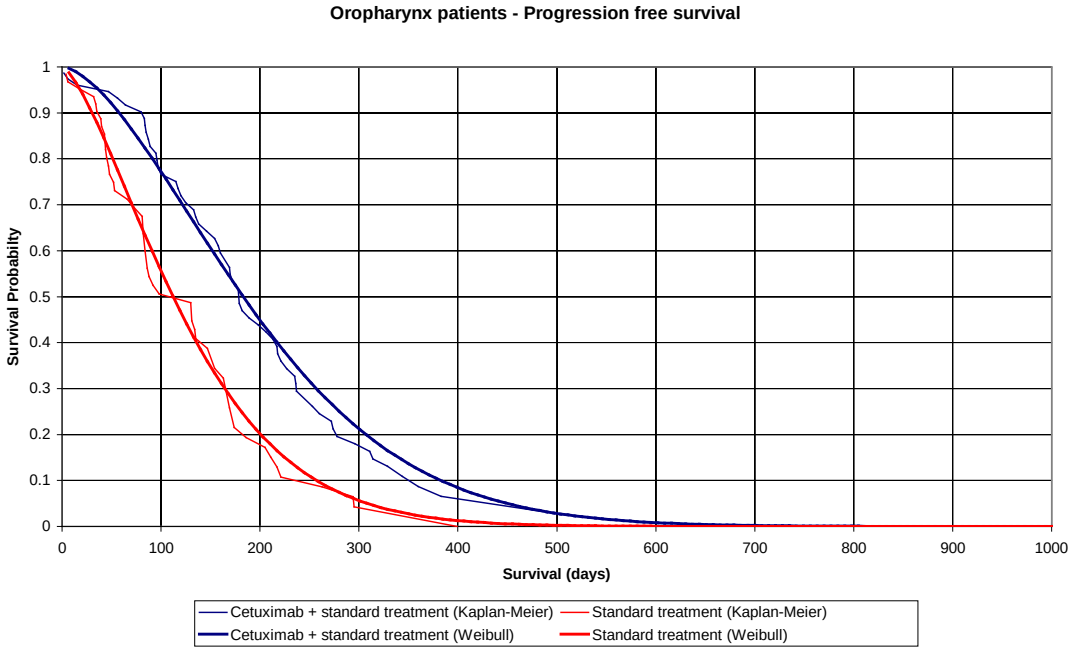


Figure H9: OS oropharynx.

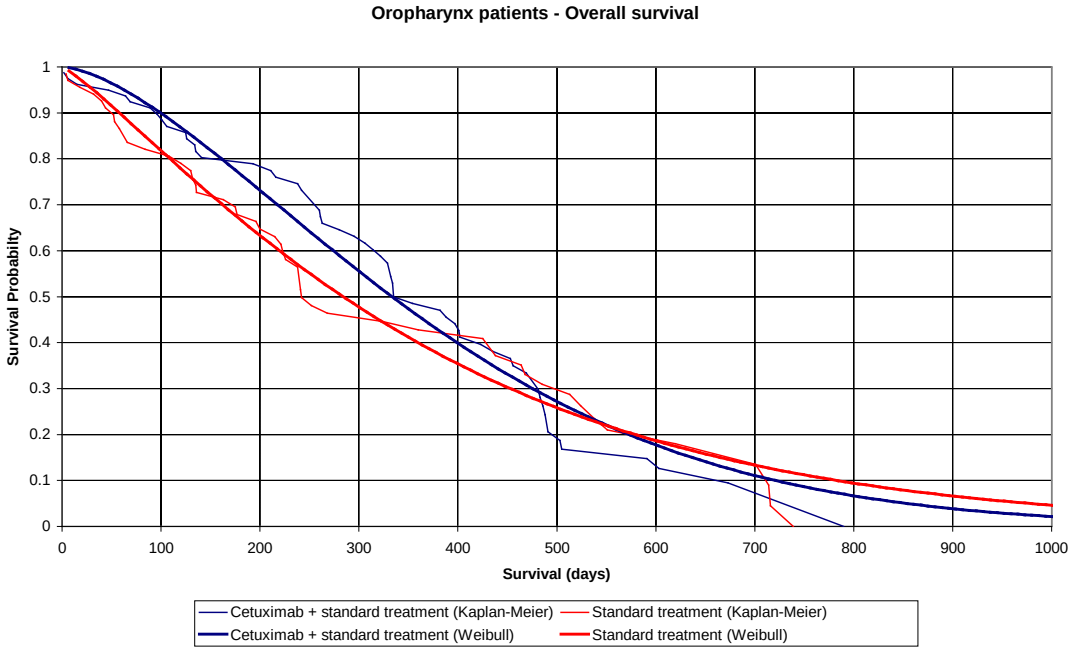


Figure H10: PFS oropharynx; KPS>=90

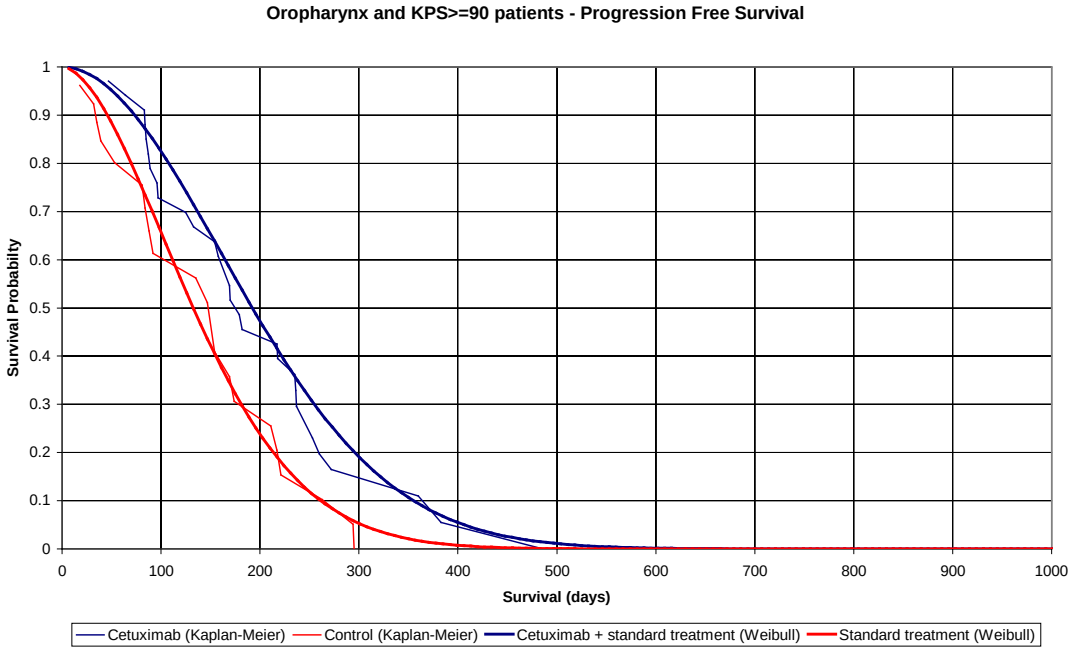


Figure H11: OS oropharynx; KPS>=90

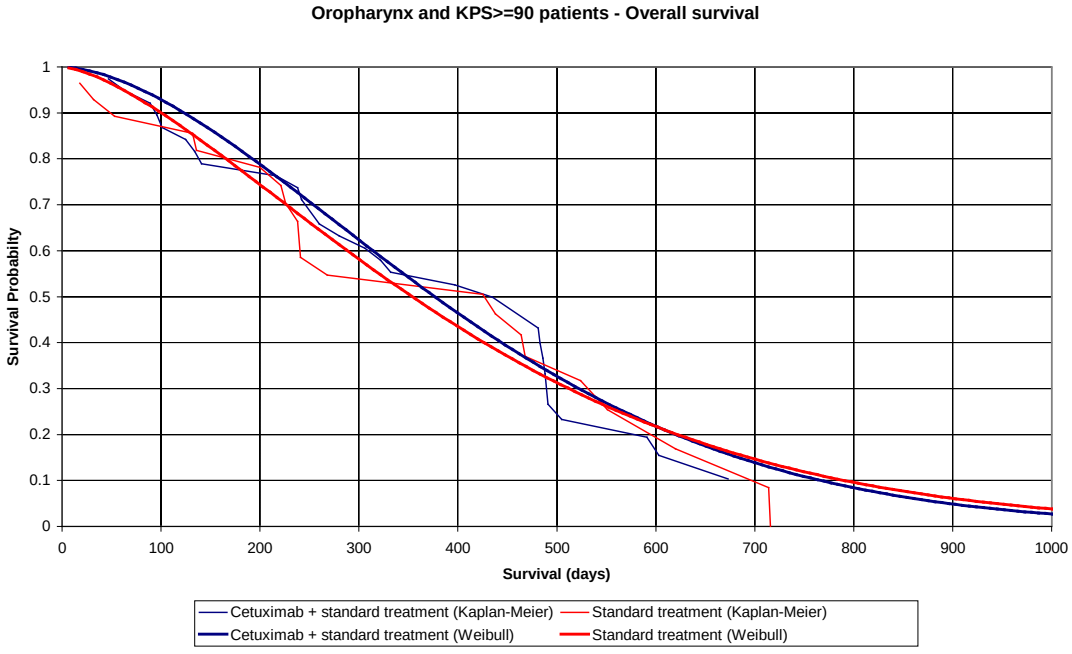


Figure H12: PFS oral cavity or oropharynx.

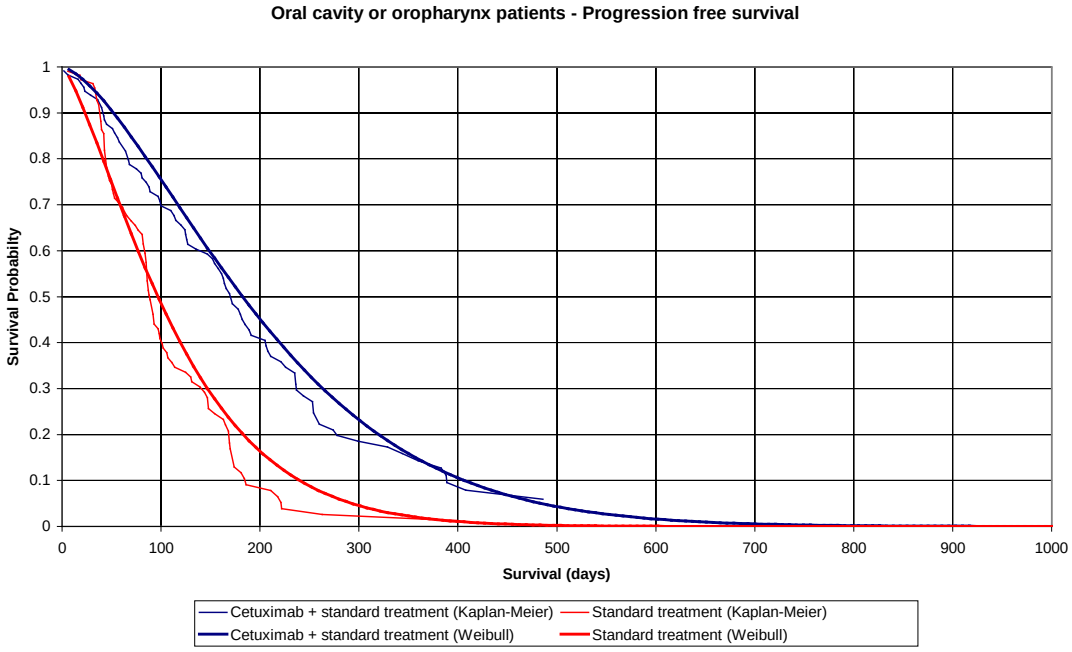


Figure H13: OS oral cavity or oropharynx.

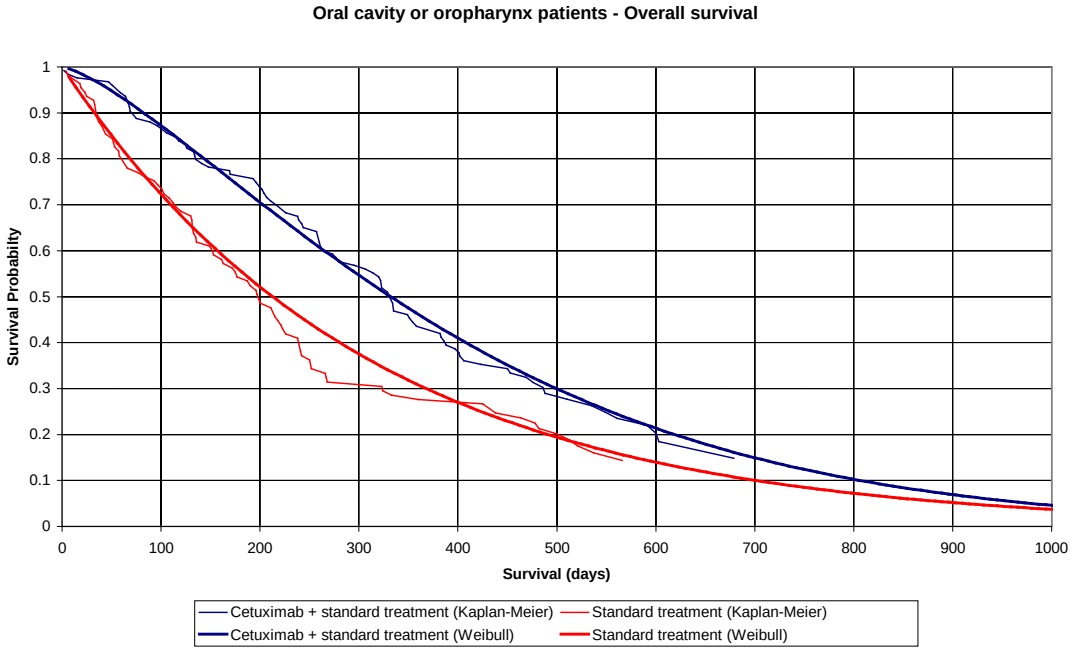


Figure H13: PFS oral cavity or oropharynx; KPS>=90.

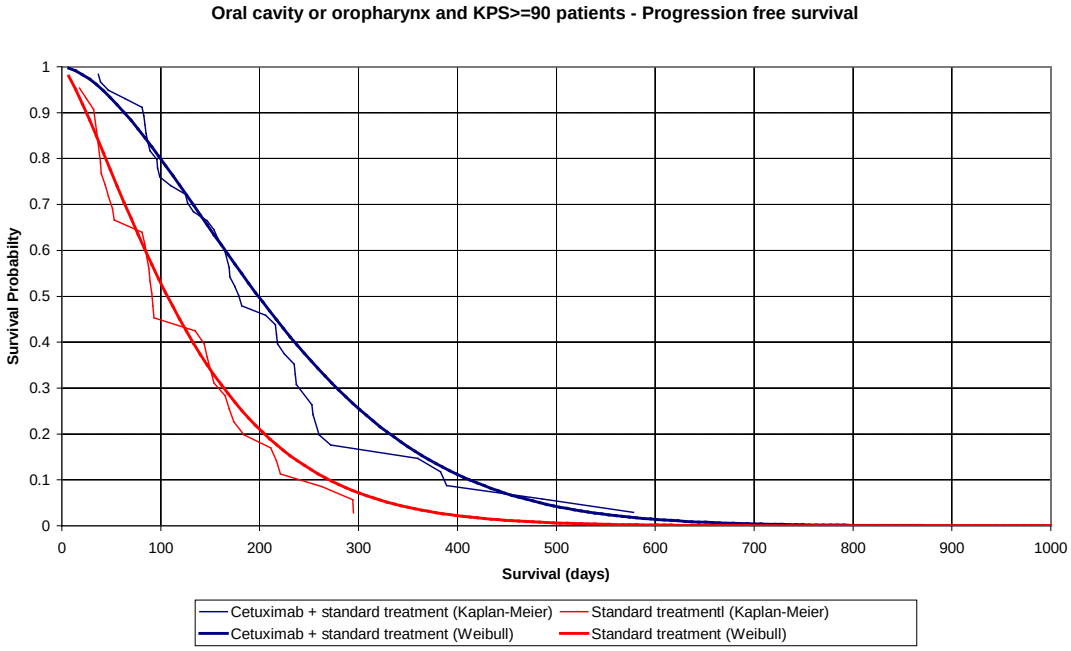


Figure H14: OS oral cavity or oropharynx; KPS>=90.

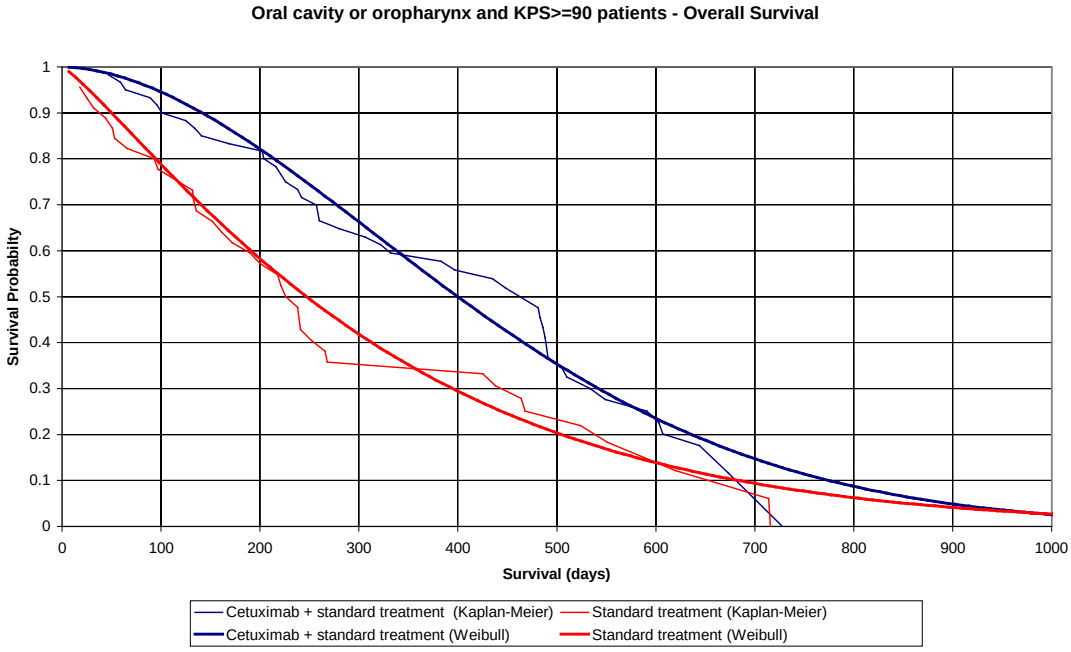


Table H1: Probability of being alive at 2 years based on the Weibull curves by subgroup.

	Cetuximab + platinum/5-FU			Platinum-5FU		
	value	**low CI**	**High CI**	**value**	**low CI**	**High CI**
Patients with recurrent/metastatic SCCHN	13.96%	7.63%	20.46%	8.33%	3.65%	14.05%
Patients with oral cavity as primary tumour site	13.62%	2.19%	26.79%	2.45%	0.02%	11.82%
Patients with oral cavity as primary tumour site and KPS>=90	13.76%	0.31%	31.97%	0.34%	0.00%	9.71%
Patients with oropharynx as primary tumour site	9.65%	1.99%	19.83%	12.11%	2.70%	23.29%
Patients with oropharynx as primary tumour site and KPS>=90	12.12%	1.12%	26.41%	13.05%	0.59%	29.57%
Patients with oral cavity or oropharynx as primary tumour site	13.47%	5.43%	22.04%	9.15%	2.70%	17.44%
Patients with oral cavity or oropharynx as primary tumour site and KPS>=90	12.80%	2.64%	24.62%	8.38%	0.69%	20.89%
Patients with recurrent SCCHN	13.21%	5.07%	21.97%	3.67%	0.62%	9.51%
Patients with metastatic SCCHN including those who are recurrent	14.75%	5.69%	24.09%	15.84%	6.12%	25.55%
Patients with metastatic SCCHN NOT those who are recurrent	10.73%	2.32%	21.36%	12.86%	2.76%	24.54%

Table H1 above presents the probability of being alive at 2 years based on the modelled Weibull curves and by subgroup. The values in the cetuximab + platinum / 5FU arm are reasonably consistent with the percentage probability of being alive ranging from approximately 10% to 15%, whilst the platinum / 5FU arm percentages range from below 1% to nearly 16%.

Table H2 below presents the probability of being progression free at 2 years based on the modelled Weibull curves and by subgroup. The probability of being progression free at 2 years with platinum/ 5FU treatment is either zero or approaching zero. In the cetuximab + platinum/ 5FU groups, a patient in the oral cavity subgroup has between a 1% and 2% chance of being progression free at 2 years depending upon performance status. The other tumour site subgroups show a value which is consistently below 1% of patients who are progression free at 2 years.

Table H2: Probability of being progression free at 2 years based on the Weibull curves by subgroup.

	Cetuximab + platinum/5-FU			Platinum-5FU		
	value	**low CI**	**High CI**	**value**	**low CI**	**High CI**
Patients with recurrent/metastatic SCCHN	0.31%	0.02%	1.57%	0.00%	0.00%	0.03%
Patients with oral cavity as primary tumour site	1.08%	0.00%	8.12%	0.00%	0.00%	0.55%
Patients with oral cavity as primary tumour site and KPS>=90	2.13%	0.00%	16.19%	0.10%	0.00%	6.59%
Patients with oropharynx as primary tumour site	0.14%	0.00%	2.23%	0.00%	0.00%	0.49%
Patients with oropharynx as primary tumour site and KPS>=90	0.01%	0.00%	1.54%	0.00%	0.00%	0.77%
Patients with oral cavity or oropharynx as primary tumour site	0.40%	0.01%	2.62%	0.00%	0.00%	0.25%
Patients with oral cavity or oropharynx as primary tumour site and KPS>=90	0.28%	0.00%	3.64%	0.03%	0.00%	1.69%
Patients with recurrent SCCHN	0.74%	0.02%	3.99%	0.00%	0.00%	0.02%
Patients with metastatic SCCHN including those who are recurrent	0.08%	0.00%	1.21%	0.00%	0.00%	0.26%
Patients with metastatic SCCHN NOT those who are recurrent	0.12%	0.00%	2.24%	0.01%	0.00%	0.97%

- *Performance statistics for all functional forms (including Weibull) tested for modelling OS and PFS for each modelled population.*

To overcome the issue of censored trial data and to extrapolate the trial results beyond the period of evaluation, the progression free survival and overall survival curves were fitted by three commonly used survival functions:

- the Weibull.
- log-normal.
- log-logistic.

The log likelihood for each of these functions is presented below in Table H3 for the total SCCHN population by treatment arm.

Table H3: Overview of log likelihoods for OS and PFS for the Weibull, log-logistic and the lognormal functions for the total SCCHN population.

		Weibull distribution	Loglogistic Distribution	Lognormal distribution
Cetuximab plus platinum/5-FU	Overall survival	-1169.7	-1186.8	-1200.3
	Progression free survival	-1046.8	-1052.8	-1066.5
Platinum/5-FU	Overall survival	-1173.6	-1181.5	-1182.9
	Progression free survival	-996.7	-997.5	-997.7

The decision to choose the Weibull function was based on the interpretation of the log likelihoods (minimizing the negative log-likelihood) of the evaluated curves and a clinical evaluation of the extrapolation beyond the trial period. The goodness of fit performance statistics only measure the fit to the observed trial data, but is not informative for the extrapolation of the survival curve. Therefore, a clinical evaluation of the curves for the time after the evaluation period was conducted.

The log-logistic and log-normal functions resulted in a heavy tail which possibly overestimated the mean estimates of survival and were not considered realistic in recurrent and metastatic SCCHN patients. For example, the mean survival for patients treated with cetuximab plus platinum/5-FU was estimated at 56, 88 and 100 weeks using the Weibull, lognormal and log-logistic functions respectively. Corresponding mean survival for patients treated with platinum/5-FU only were 46, 57, and 67 weeks respectively.

A 2-parameter Weibull function appeared to fit the observed data for the total population best and provided a reasonable extrapolation of the trial results across the evaluated subgroups, as can be seen the illustrations on the previous pages (p10 to p16).

- *Correlation between Weibull parameter estimates for each modelled population.*

Scale and shape were estimated jointly for each function. Therefore, the correlation is accounted for in the estimates of the shape and scale, but not in the probabilistic sensitivity analysis of the economic model. Table H4 below presents an overview of the variance-covariance matrix for the parameters alpha and log (scale) of the Weibull function by survival curve and treatment arm.

Table H4: Overview of the variance-covariance matrix for the parameters alpha and log(scale) of the Weibull function by survival curve, treatment and arm.

			Cetuximab+Platinum/5-FU		Platinum/5-FU	
			Alpha	***Log(scale)***	***Alpha***	***Log(scale)***
Total population	**OS**	**Alpha**	0.00427	-0.00036	0.00441	0.00003
		log(scale)	-0.00036	0.00390	0.00003	0.00444
	PFS	**Alpha**	0.00273	-0.00064	0.00311	-0.00050
		log(scale)	-0.00064	0.00323	-0.00050	0.00353
Oral cavity	**OS**	**Alpha**	0.01415	-0.00061	0.01415	-0.00061
		log(scale)	-0.00061	0.01997	-0.00061	0.01997
	PFS	**Alpha**	0.01986	-0.00472	0.01600	-0.00245
		log(scale)	-0.00472	0.01310	-0.00245	0.01561
Oral cavity + KPS>90	**OS**	**Alpha**	0.04536	-0.01037	0.01403	-0.00103
		log(scale)	-0.01037	0.03660	-0.00103	0.04219
	PFS	**Alpha**	0.06578	-0.01252	0.03254	-0.00417
		log(scale)	-0.01252	0.03185	-0.00417	0.03280
Oropharynx	**OS**	**Alpha**	0.01400	-0.00061	0.00689	-0.00043
		log(scale)	-0.00061	0.01361	-0.00043	0.01180
	PFS	**Alpha**	0.00975	-0.00207	0.00644	-0.00128
		log(scale)	-0.00207	0.01135	-0.00128	0.01002
Oropharynx + KPS>90	**OS**	**Alpha**	0.02139	-0.00083	0.01170	-0.00078
		log(scale)	-0.00083	0.03416	-0.00078	0.02472
	PFS	**Alpha**	0.01604	-0.00490	0.00909	-0.00276
		log(scale)	-0.00490	0.02876	-0.00276	0.01907
Oral cavity/ oropharynx	**OS**	**Alpha**	0.01131	-0.00082	0.00587	0.00013
		log(scale)	-0.00082	0.00770	0.00013	0.00789
	PFS	**Alpha**	0.00687	-0.00153	0.00480	-0.00086
		log(scale)	-0.00153	0.00615	-0.00086	0.00600

Table H4: Overview of the variance-covariance matrix for the parameters alpha and log (scale) of the Weibull function by survival curve, treatment and arm (continued).

			Cetuximab+Platinum/5-FU		Platinum/5-FU	
			Alpha	***Log(scale)***	***Alpha***	***Log(scale)***
Oral cavity/ oropharynx +KPS >90	**OS**	**Alpha**	0.01971	-0.00233	0.00661	-0.00040
		log(scale)	-0.00233	0.01827	-0.00040	0.01562
	PFS	**Alpha**	0.01717	-0.00376	0.00832	-0.00179
		log(scale)	-0.00376	0.01453	-0.00179	0.01131
Recurrent SCCHN	**OS**	**Alpha**	0.00611	-0.00121	0.00784	0.00003
		log(scale)	-0.00121	0.00636	0.00003	0.00842
	PFS	**Alpha**	0.00664	-0.00081	0.00495	-0.00117
		log(scale)	-0.00081	0.00704	-0.00117	0.00533
Metastatic, including recurrent SCCHN	**OS**	**Alpha**	0.01275	0.00061	0.01001	0.00011
		log(scale)	0.00061	0.01003	0.00011	0.00940
	PFS	**Alpha**	0.00581	-0.00137	0.00567	-0.00116
		log(scale)	-0.00137	0.00790	-0.00116	0.00702

OS: overall survival; PFS progression free survival

The presented correlations are based on the Alpha and log (scale) statistics as given by R statistical software. Please note that the survival and progression free survival curves are described using the following formula:

*Survival = exp(-exp(-ALPHA/"scale") *time^(1/"scale")). Where: exp(-ALPHA/"scale")= SCALE and 1/"scale"=SHAPE and "scale" = log(scale)*

B2: *Please indicate whether the parameters for Weibull models for OS and PFS were estimated independently or jointly in all cases*

Weibull models for OS and PFS were estimated independently.

B3: Please provide further details of the proportion of scheduled platinum chemotherapy doses given/omitted by cycle.

Please find below the tables from the EXTREME clinical trial reports for cisplatin and carboplatin based treatments respectively.

Cisplatin based treatments

From the tables below:

- The mean dose intensity overall is 92.1mg/m^2.
- At cycle 1 the mean dose intensity is 99.6 mg/m$^{2;}$ it ranges for cycles 2-6 of platinum treatment from 98.3 mg/m^2 to 94.6 mg/m^2 and at cycle 7 it drops more markedly to 89.6 mg/m^2.
- This is consistent with patients near the end of the active treatment phase being less able to tolerate the cumulative toxicity associated with cisplatin chemotherapy.

Table 14.3.0-2.2: Cisplatin
Cumulative Dose, Dose Intensity, Relative Dose Intensity
Safety Population Treated with Cisplatin

	Cetuximab + CTX N = 149 (100%)	CTX N = 135 (100%)
Cumulative dose (mg/m²)		
N	149	135
Mean	399.6	342.9
Median	402.7	300.1
SD	184.89	190.45
Q1-Q3	200.5 - 595.6	194.8 - 541.4
Min-Max	96.3 - 618.3	97.1 - 626.0
Dose intensity (mg/m²/3 weeks)		
N	149	135
Mean	92.1	91.1
Median	95.6	94.6
SD	9.67	9.80
Q1-Q3	86.5 - 99.8	84.3 - 99.2
Min-Max	61.2 - 103.1	60.2 - 104.7
Dose intensity per cycle (mg/m²/cycle)		
Cycle 1: day 1 to day 18		
N	149	135
Mean	99.6	99.0
Median	99.8	99.7
SD	1.48	2.71
Q1-Q3	99.1 - 100.2	98.4 - 100.1
Min-Max	91.3 - 103.9	79.8 - 104.7

Table 14.3.0-2.2: Cisplatin
Cumulative Dose, Dose Intensity, Relative Dose Intensity
Safety Population Treated with Cisplatin

	Cetuximab + CTX N = 149 (100%)	CTX N = 135 (100%)
Cycle 2: day 19 to day 39		
N	128	106
Mean	98.3	97.2
Median	99.8	99.7
SD	5.50	7.70
Q1-Q3	98.6 - 100.3	98.5 - 100.2
Min-Max	74.8 - 105.6	49.7 - 104.1
Cycle 3: day 40 to day 60		
N	105	75
Mean	97.7	97.4
Median	99.9	99.7
SD	6.72	6.68
Q1-Q3	98.6 - 100.4	98.6 - 100.1
Min-Max	74.2 - 105.6	74.1 - 104.7
Cycle 4: day 61 to day 81		
N	82	61
Mean	97.2	95.9
Median	99.8	99.4
SD	7.04	8.75
Q1-Q3	97.9 - 100.3	97.1 - 100.1
Min-Max	74.0 - 103.1	73.9 - 110.8

Table 14.3.0-2.2: Cisplatin
Cumulative Dose, Dose Intensity, Relative Dose Intensity
Safety Population Treated with Cisplatin

	Cetuximab + CTX N = 149 (100%)	CTX N = 135 (100%)
Cycle 5: day 82 to day 102		
N	68	46
Mean	96.4	94.3
Median	99.7	99.2
SD	7.81	9.66
Q1-Q3	97.3 - 100.1	81.6 - 100.0
Min-Max	73.6 - 103.1	74.9 - 106.6
Cycle 6: day 103 to day 123		
N	58	40
Mean	94.6	93.1
Median	99.9	99.6
SD	10.02	12.00
Q1-Q3	95.0 - 100.4	81.0 - 100.3
Min-Max	59.8 - 103.1	51.0 - 106.6
Cycle 7: day 124 to day 144		
N	17	16
Mean	89.6	87.9
Median	99.1	96.9
SD	11.48	15.95
Q1-Q3	79.0 - 99.7	79.5 - 100.0
Min-Max	73.3 - 101.4	49.9 - 102.3

Carboplatin based treatment

From the tables below:

- The mean dose intensity overall is 323.3 mg/m^2.
- At cycle 1 the mean dose intensity is 348.6 mg/m^2 ; it ranges for cycles 2-6 of platinum treatment from 353.4 mg/m^2 to 325.6 mg/m^2 and at cycle 7 it increases to 333.1 mg/m^2.
- The cycle 7 number is counterintuitive and may be related to the small number of patients (n=17) left in this sample rather than a genuine increase in the dose intensity at this point.

Table 14.3.0-3.2: Carboplatin
Cumulative Dose, Dose Intensity, Relative Dose Intensity
Safety Population Treated with Carboplatin

	Cetuximab + CTX N = 69 (100%)	CTX N = 80 (100%)
Cumulative dose (mg/m²)		
N	69	80
Mean	1660.5	1205.5
Median	1636.8	1203.6
SD	717.31	591.90
Q1-Q3	1018.5 - 2059.9	776.2 - 1603.4
Min-Max	223.6 - 2954.7	233.9 - 2777.8
Dose intensity (mg/m²/3 weeks)		
N	69	80
Mean	323.3	277.1
Median	325.4	277.8
SD	66.52	63.47
Q1-Q3	279.9 - 359.4	235.1 - 317.2
Min-Max	142.0 - 489.7	81.1 - 425.8
Dose intensity per cycle (mg/m²/cycle)		
Cycle 1: day 1 to day 18		
N	69	80
Mean	348.6	306.1
Median	336.2	297.4
SD	74.32	60.75
Q1-Q3	291.7 - 395.3	262.5 - 342.2
Min-Max	206.5 - 531.6	160.9 - 434.9

Table 14.3.0-3.2: Carboplatin
Cumulative Dose, Dose Intensity, Relative Dose Intensity
Safety Population Treated with Carboplatin

	Cetuximab + CTX N = 69 (100%)	CTX N = 80 (100%)
Cycle 2: day 19 to day 39		
N	60	72
Mean	353.4	303.8
Median	337.5	300.0
SD	75.52	61.02
Q1-Q3	295.8 - 397.3	260.9 - 335.6
Min-Max	248.2 - 568.8	184.2 - 511.7
Cycle 3: day 40 to day 60		
N	52	56
Mean	336.8	309.5
Median	331.2	307.6
SD	71.01	62.01
Q1-Q3	287.6 - 391.1	262.3 - 341.1
Min-Max	196.9 - 508.5	206.8 - 502.4
Cycle 4: day 61 to day 81		
N	48	46
Mean	337.8	308.3
Median	329.3	301.7
SD	67.98	66.62
Q1-Q3	287.0 - 388.8	263.7 - 344.9
Min-Max	196.9 - 482.5	135.1 - 452.7

Table 14.3.0-3.2: Carboplatin
Cumulative Dose, Dose Intensity, Relative Dose Intensity
Safety Population Treated with Carboplatin

	Cetuximab + CTX N = 69 (100%)	CTX N = 80 (100%)
Cycle 5: day 82 to day 102		
N	38	30
Mean	338.2	292.2
Median	342.6	293.1
SD	64.73	68.99
Q1-Q3	292.1 - 378.8	237.4 - 334.3
Min-Max	196.9 - 497.1	163.8 - 413.7
Cycle 6: day 103 to day 123		
N	31	23
Mean	325.6	301.0
Median	325.4	295.2
SD	75.20	75.03
Q1-Q3	268.1 - 356.6	249.1 - 347.1
Min-Max	169.6 - 521.4	180.1 - 511.7
Cycle 7: day 124 to day 144		
N	13	6
Mean	333.1	323.8
Median	353.8	308.4
SD	66.34	65.57
Q1-Q3	285.5 - 376.3	275.6 - 385.3
Min-Max	196.4 - 444.4	247.0 - 417.9

B4: *Please provide further clarification of the meaning of the adverse event rates used in the model (for example does the adverse event data refer to the number of events, or the number of patients for whom any event occurred at any time).*

The adverse event rates have been chosen on the basis of the incidence of Grade III and IV events reported in the EXTREME clinical trial. The clinical relevance of these rates was validated by the Merck Serono Health economic advisory board held on 22nd July 2008.

B5: *Please provide separate incremental cost-effectiveness ratios for patients with recurrent cancer and for those patients with metastatic cancer.*

Incremental cost effectiveness ratios for patients with recurrent disease and patients with metastatic disease are presented below in Tables H5 – H7.

Table H5: Recurrent patients: Incremental costs and benefits, ICER & ICUR

Cetuximab + standard treatment vs Standard treatment	**mean**	**p2.5**	**p97.5**
Incremental costs	£18,758	£15,620	£21,977
Incremental life-years	0.308	0.116	0.523
Incremental QALYs	0.215	-0.122	0.560
Incremental cost per lie year gained	£60,939		
Incremental cost per QALY	£87,099		

Table H5 above presents the ICERS for patients with recurrent SCCHN. The cost per life year gained for this subgroup is £60,939 and the ICER is £87,099.

Table H6 below presents the ICERS for patients with metastatic SCCHN, including those patients were disease has recurred.

Table H6: Metastatic patients (including those who are recurrent): Incremental costs and benefits, cost per life year and cost per QALY.

Cetuximab + standard treatment vs. Standard treatment	**mean**	**p2.5**	**p97.5**
Incremental costs	£14,539	£10,680	£18,401
Incremental life-years	-0.015	-0.350	0.300
Incremental QALYs	0.026	-0.447	0.439
Incremental cost per life year	-£947,649		
Incremental cost per QALY	£562,849		

Table H6 above presents the ICER for patients with metastatic SCCHN, including those patients were disease has recurred. The cost per life year gained for this subgroup is -£947,649 and the ICER is £562,849. The cost per life year is negative and this is driven from the negative incremental life years presented above, however the ICER is positive based upon the 0.026 QALYs gained. This result is driven from greater time being spent in the progression free setting where greater utility can be gained, and this is represented in QALYs gained rather than life years.

Table H7 below presents the ICERS for patients with metastatic SCCHN, excluding those patients were disease has recurred.

Table H7: Metastatic patients (excluding those who are recurrent): Incremental costs and benefits, cost per life year and cost per QALY.

Cetuximab + standard treatment vs. Standard treatment	mean	p2.5	p97.5
Incremental costs	£13,469	£9,787	£17,397
Incremental life-years	-0.088	-0.356	0.203
Incremental QALYs	-0.046	-0.245	0.138
Incremental cost per life year	-£153,122		
Incremental cost per QALY	-£295,134		

Table H7 above presents the ICERS for patients with metastatic SCCHN, including those patients were the disease has recurred. The cost per life year gained and ICER are negative (-£153,122 and -£295,134 respectively) which is driven from the negative cost per life year and QALYS gained.

Appendices

Appendix A1 EXTREME overall survival and progression free survival

Appendix 2: The proportion of unavailable or unreadable scans in each of the trial arms in the EXTREME trial for each time point.

EMR 62202 - 002 EXTREME —— DRAFT ——

Patients with Missing or Unevaluable Tumor Assessments
Intent to Treat Population

	Cetuximab + CTX		CTX alone	
	Expected number of pts for tumor assessment (100 %)	Pts with missing or unevaluable tumor assessment	Expected number of pts for tumor assessment (100 %)	Pts with missing or unevaluable tumor assessment
Patients with at least one missing or unevaluable scan visit	222	51 (23.0%)	220	57 (25.9%)
Baseline	222	1 (0.5%)	220	1 (0.5%)
Week 6	184	5 (2.7%)	153	7 (4.6%)
Week 12	142	6 (4.2%)	107	5 (4.7%)
Week 18	102	7 (6.9%)	57	7 (12.3%)
Week 24	65	2 (3.1%)	26	1 (3.8%)
Week 30	46	7 (15.2%)	12	0 (0.0%)
Week 36	31	1 (3.2%)	9	2 (22.2%)
Week 42	24	2 (8.3%)	7	1 (14.3%)
Week 48	16	2 (12.5%)	6	2 (33.3%)
Week 54	12	2 (16.7%)	5	0 (0.0%)
Week 60	10	1 (10.0%)	2	0 (0.0%)
Week 66	7	0 (0.0%)	2	0 (0.0%)
Week 72	6	2 (33.3%)	2	0 (0.0%)
Week 78	6	0 (0.0%)	1	0 (0.0%)
Week 84	4	1 (25.0%)	1	0 (0.0%)
Week 90	3	0 (0.0%)	1	0 (0.0%)
Week 96	2	1 (50.0%)	1	0 (0.0%)
Week 102	1	0 (0.0%)	0	0 (0.0%)
FTA *	130	3 (2.3%)	142	3 (2.1%)
Patients with at least one missing tumor assessment before FTA or Discontinuation #		31		38

* Upon occurrence of PD, I.E. patients who went off-study or died prior to PD have no FTA visit.
\# Derived as patients for whom the time between last scan before FTA and FTA scan > 60 days.
For patients without FTA scan the discontinuation date was used.

Missing scan:

- No scans (target lesions, non-target lesions, new lesions) were performed at the respective 6-weekly evaluation visit, but overall response assessments were filled out by the investigator.
- No scans (target lesions, non-target lesions, new lesions) and no overall response assessment were available for the respective 6-weekly evaluation visit.

Unreadable scan (overall response assessment at the respective time point not assessable / not known / not available):

- For at least one target or non-target lesion no scan was performed at the respective 6-weekly evaluation visit.

Cetuximab for the treatment of metastatic and/or recurrent squamous cell carcinoma of the head and neck:
Merck Serono response to NICE further clarification questions.

Please find on behalf of Merck Serono the answers to the further questions of clarification from the evidence review group of the 7th November 2008 for the appraisal of cetuximab in the treatment of metastatic and/or recurrent squamous cell carcinoma of the head and neck. These questions are as set out below.

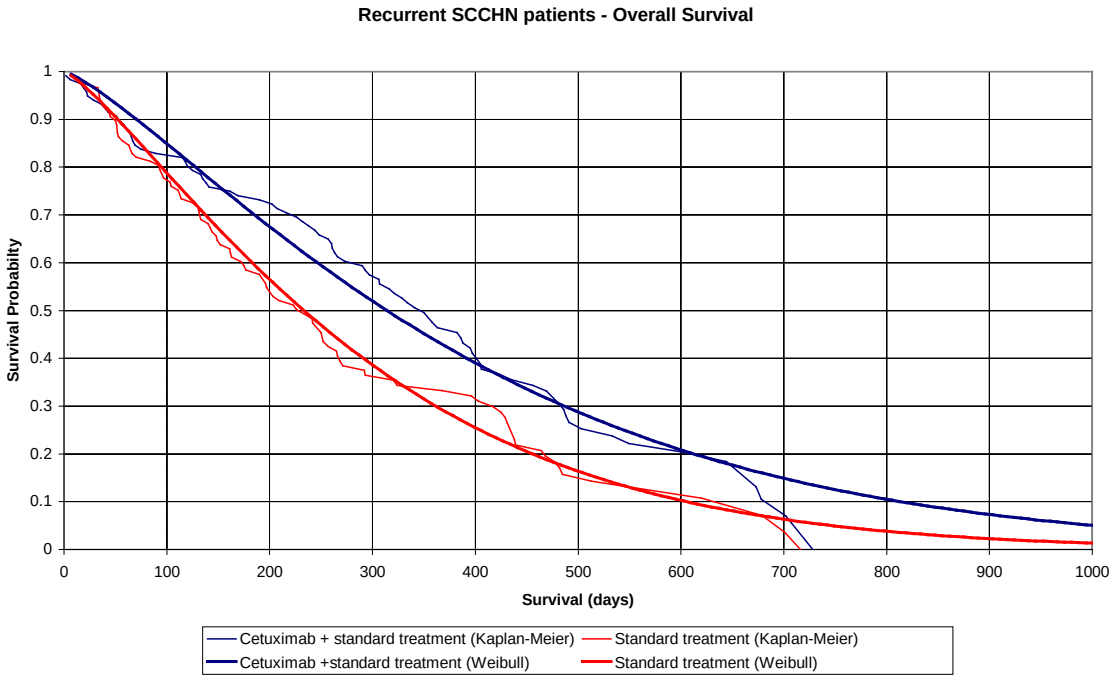
For the additional subgroup analyses considering recurrent (excluding metastatic) disease and any metastatic disease, please provide further details of the survival analyses as follows:

1. *Kaplan-Meier analysis including OS and PFS survival charts.*
2. *Kaplan-Meier mean OS and PFS at 24 months with confidence limits.*
3. *If possible a detailed printout of Kaplan-Meier events and censoring by time in the EXTREME trial.*
4. *Weibull model parameter values used in the cost-effectiveness analysis.*
5. *Any related clinical effectiveness data comparisons (e.g. hazard ratios and forest plots).*

1. Kaplan-Meier analysis including OS and PFS survival charts. Recurrent (excluding metastatic) SCCHN and any metastatic disease SCCHN.

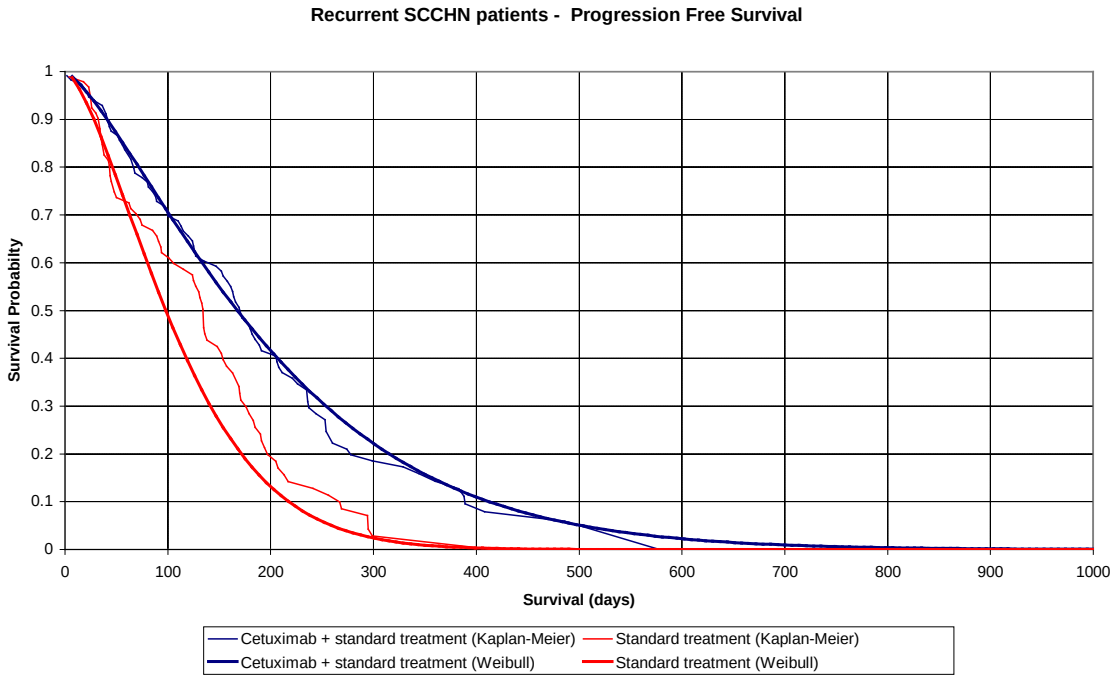
Figures 1-4 below present the Kaplan Meier and Weibull fitted curves for the recurrent and metastatic settings. Figures 1 and 2 show overall survival (OS) and progression free survival (PFS) respectively. Figures 3 and 4 show the same data in the metastatic setting.

Figure 1 Kaplan Meier and Weibull OS curves in the recurrent setting



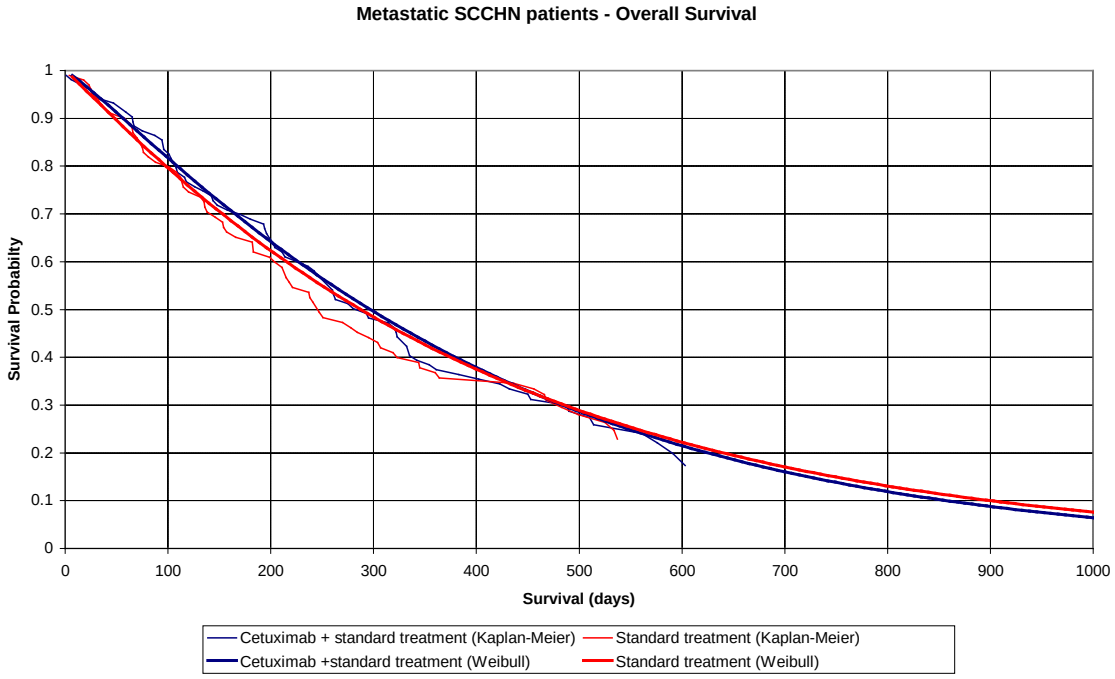
It can be seen from the Figures 1 and 2 that the fit of the Weibull curves to the Kaplan Meier (KM) curves is reasonable; however there is some variation in closeness of fit between 200 and 400 days of survival.
In Figure 1 the extrapolated curves seem to have longer tails than the KM data would suggest despite being quite a reasonable fit across the first 600 days of data.

Figure 2 Kaplan Meier and Weibull PFS curves in the recurrent setting



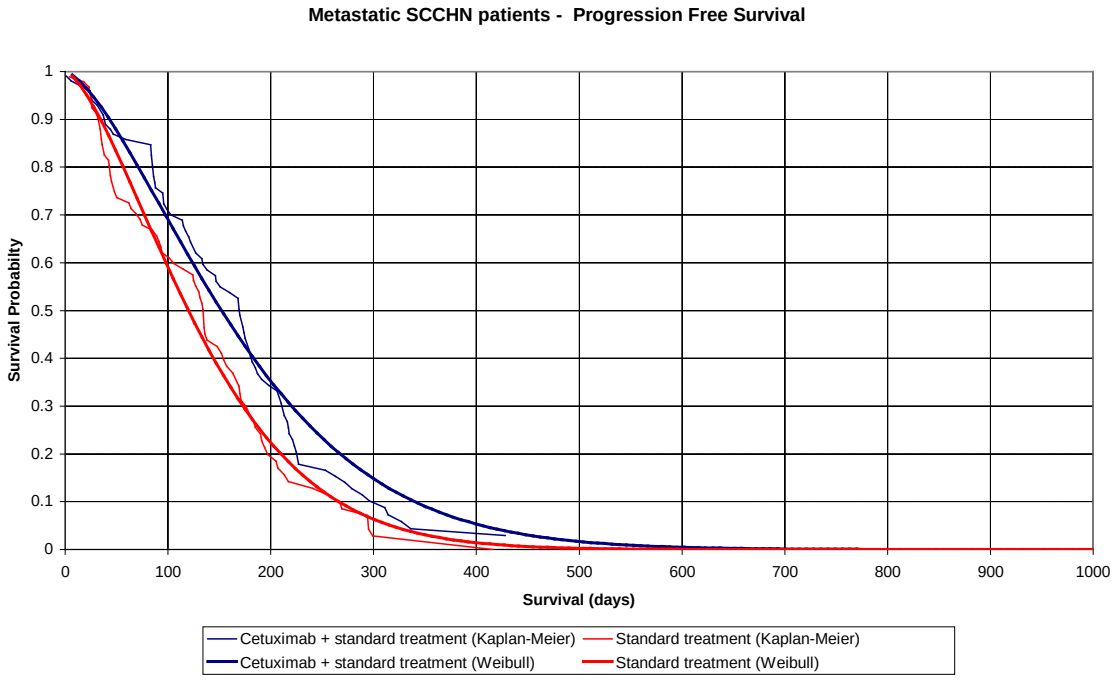
In Figure 2 above, the Weibull curve seems to be a good fit for the cetuximab arm but may underestimate the effects for PFS in the mid portion of the KM curve for the chemotherapy arm.

Figure 3 Kaplan Meier and Weibull OS curves in the metastatic setting



In Figure 3, while there is a modest separation of the Kaplan Meier OS curves, the Weibull curves seem almost to overlay each other.
Figure 4 below presents the Kaplan Meier and Weibull curves for the metastatic setting. The fitted Weibull curves seem to be a reasonable approximation to the KM curves for PFS.

Figure 4 Kaplan Meier and Weibull PFS curves in the metastatic setting



2. Kaplan-Meier mean OS and PFS at 24 months with confidence limits.

Due to either censoring of data or death of patients, no data were available for the Kaplan Meier curves at 24 months. The only data which we can therefore present is based upon the extrapolation of the Kaplan Meier curves. Tables 1 and 2 below present the estimates based on the Weibull extrapolation.

Table 1 Probability of being alive at 2 years based on the Weibull by subgroup

	Cetuximab + platinum/5-FU			Platinum-5FU		
	value	**low CI**	**High CI**	**value**	**low CI**	**High CI**
Patients with recurrent SCCHN	13.21%	5.07%	21.97%	3.67%	0.62%	9.51%
Patients with metastatic SCCHN including those who are recurrent	14.75%	5.69%	24.09%	15.84%	6.12%	25.55%

Table 2 Probability of being progression free at 2 years based on the Weibull curves by subgroup

	Cetuximab + platinum/5-FU			Platinum-5FU		
	value	**low CI**	**High CI**	**value**	**low CI**	**High CI**
Patients with recurrent SCCHN	0.74%	0.02%	3.99%	0.00%	0.00%	0.02%
Patients with metastatic SCCHN including those who are recurrent	0.08%	0.00%	1.21%	0.00%	0.00%	0.26%

3. If possible a detailed printout of Kaplan-Meier events and censoring by time in the EXTREME trial.

Figures 5, 6, 7 and 8 below present the charts of censoring by time in the EXTREME trial. Please note that as the number of censored data is not accounted for in the graph we have embedded an excel worksheet which contains patient level data for both PFS and OS censoring as appendix 1.

Figure 5 Censored OS data for recurrent patients

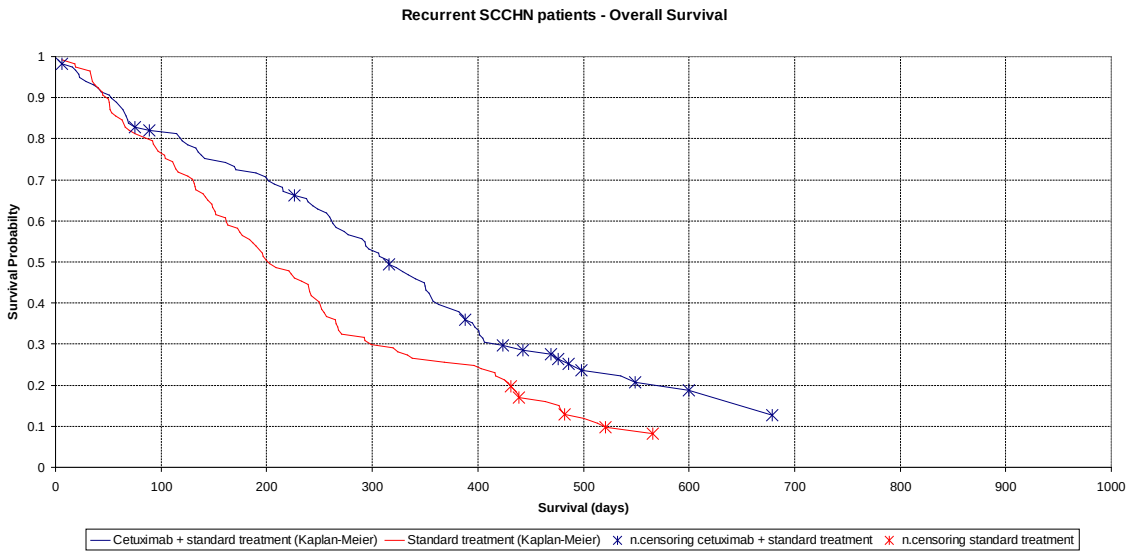


Figure 6 Censored PFS data for recurrent patients

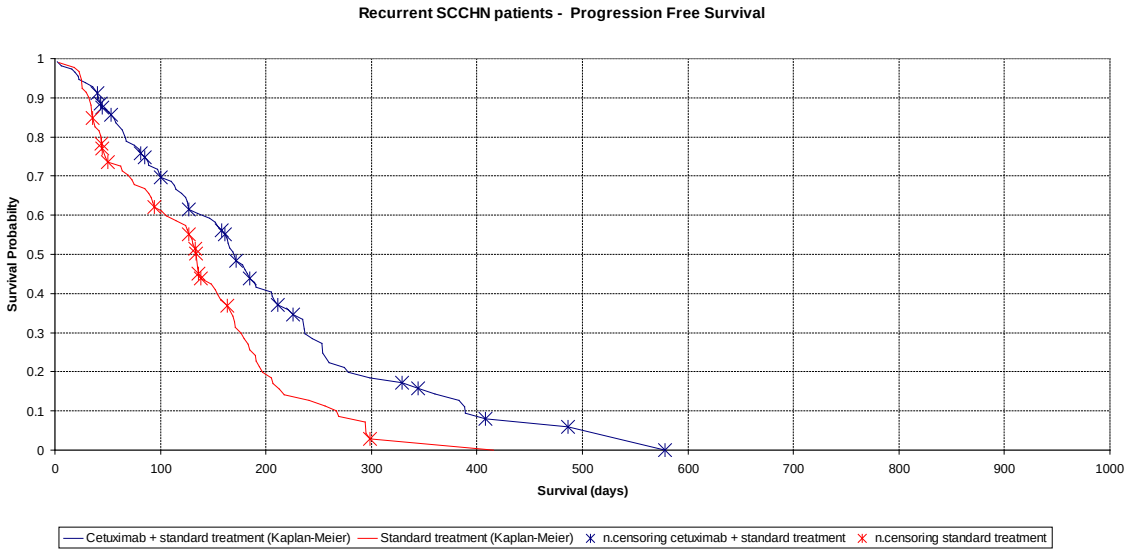


Figure 7 Censored OS data for metastatic patients

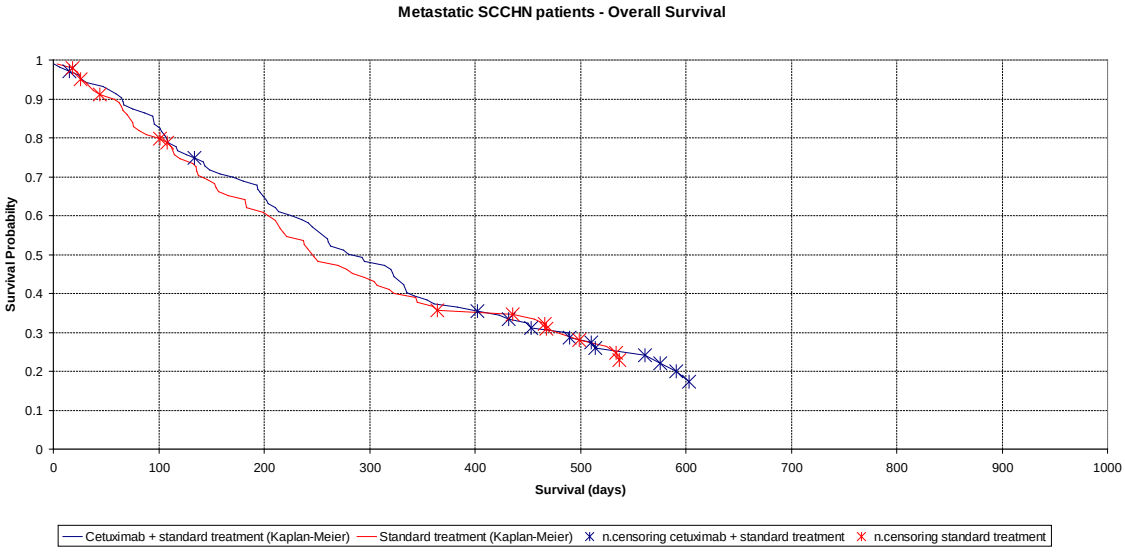
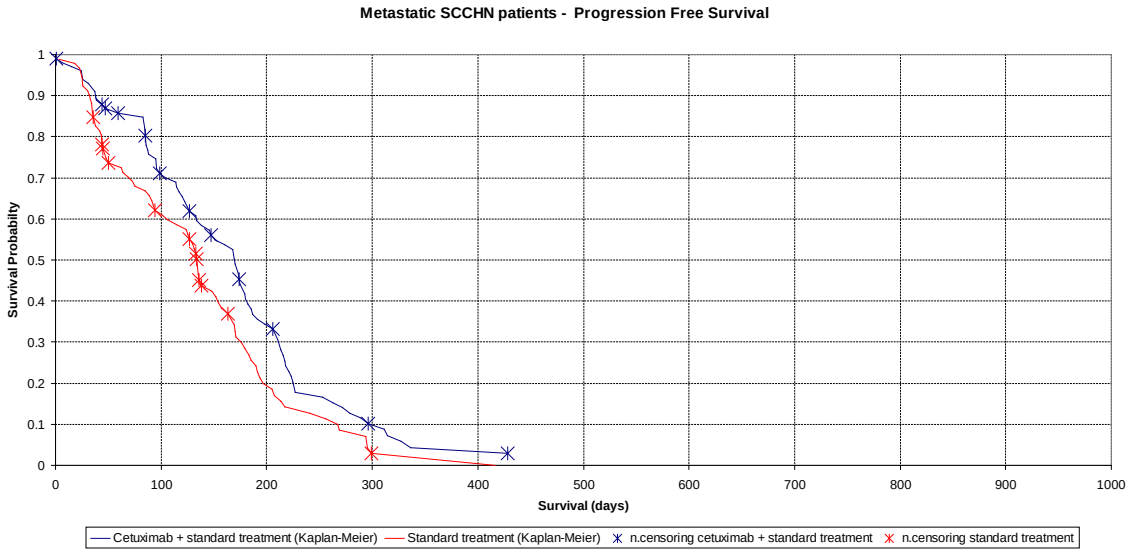


Figure 8 Censored PFS data for metastatic patients



4. Weibull model parameter values used in the cost-effectiveness analysis.

The Weibull model parameter values are presented in Tables 3 and 4 below.

Table 3 Overview of Weibull parameters used in the CE analysis by subgroup

	Cetuximab + platinum/5-FU		Platinum-5FU	
	shape	**scale**	**shape**	**scale**
Recurrent SCCHN				
OS	1.261	0.000	1.259	0.001
PFS	1.334	0.001	1.505	0.001
Metastatic SCCHN including those who are recurrent				
OS	1.132	0.001	1.052	0.002
PFS	1.492	0.000	1.507	0.001

Scale and shape were estimated jointly for each function. Therefore, the correlation is accounted for in the estimates of the shape and scale, but not in the probabilistic sensitivity analysis of the economic model.

Table 4 Overview of the variance-covariance matrix for the parameters alpha and log (scale) of the Weibull function by survival curve, treatment and arm

			Cetuximab+Platinum/5-FU		Platinum/5-FU	
			Alpha	***Log(scale)***	***Alpha***	***Log(scale)***
Recurrent SCCHN	**OS**	**Alpha**	0.00611	-0.00121	0.00784	0.00003
		log(scale)	-0.00121	0.00636	0.00003	0.00842
	PFS	**Alpha**	0.00664	-0.00081	0.00495	-0.00117
		log(scale)	-0.00081	0.00704	-0.00117	0.00533
Metastatic, including recurrent SCCHN	**OS**	**Alpha**	0.01275	0.00061	0.01001	0.00011
		log(scale)	0.00061	0.01003	0.00011	0.00940
	PFS	**Alpha**	0.00581	-0.00137	0.00567	-0.00116
		log(scale)	-0.00137	0.00790	-0.00116	0.00702

OS: overall survival; PFS progression free survival

The presented correlations are based on the Alpha and log(scale) statistics as given by R statistical software. Please note that the survival and progression free survival curves are described using the following formula:
Survival = *exp(-exp(-ALPHA/"scale") *time^(1/"scale")). Where: exp(-ALPHA/"scale")= SCALE and 1/"scale"=SHAPE and "scale" = log(scale)*

5. Any related clinical effectiveness data comparisons (e.g. hazard ratios and forest plots).

Table 5 below lists the hazard ratios for both OS and PFS and for patients who are recurrent and metastatic (including recurrent patients).

Table 5 Overview of hazard ratios by subgroup

	OS		PFS	
	HR	**95%CI**	**HR**	**95%CI**
Recurrent SCCHN				
Unstratified	0.65	0.49-0.87	0.44	0.33-0.60
Stratified (KPS score and previous chemotherapy)	0.68	0.51-0.91	0.44	0.32-0.60
Metastatic SCCHN including those who are recurrent				
Unstratified	0.99	0.72-1.36	0.71	0.52-0.97
Stratified (KPS score and previous chemotherapy)	0.96	0.70-1.33	0.70	0.51-0.97

Appendices

Appendix 1 patient level censoring data