CETUXIMAB PLUS RADIOTHERAPY FOR THE TREATMENT OF LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK

THE EVIDENCE REVIEW GROUP'S REPORT

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The RDTC was established in 1991 to promote safe effective prescribing and economical drug usage, and to provide a source of independent authoritative advice on pharmaceutical and therapeutic issues throughout the former Northern and Yorkshire region. The RDTC co-ordinates prescribing activities, provides a poisons and medicine information service and is the teratology information service for the UK. The Centre is one of four NHS regional monitoring centres for the Medicines and Healthcare Regulatory Authority (MHRA).

CHE is a research unit of the University of York. The Centre's aim is to undertake high quality research that is capable of influencing health policy decisions. The largest programme of work at CHE is that on economic evaluation and health technology assessment which focuses on a range of methodological and applied work. This includes full technology assessment reviews and evidence review reports for the National Institute for Health and Clinical Excellence (NICE). Recent assessment reports for NICE include treatments for prostate and ovarian cancer, psoriasis and psoriatic arthritis.

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Conflicts of interest:

The authors to this report have no conflicts of interest.

List of Abbreviations

AIC	Akaike Information Criterion
BAHNO	British Association of Head and Neck Oncologists
BNF	British National Formulary
COSTART	Coding System for Thesaurus of Adverse Reaction Terms
DAHNO	Data for Head and Neck Oncology
EGFR	Epithelial growth factor receptor
EQ-5D	EuroQoL-5D
ERG	Evidence Review Group
ESMO	European Society of Medical Oncology
Gy	Grays
HRG	Health Resource Group
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
LA	Locally advanced
NCCN	National Comprehensive Cancer Network
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
PSS	Personal Social Services
QALY	Quality-adjusted life-year
RCT	Randomised controlled trial
RT	Radiotherapy
RT+C	Radiotherapy plus cetuximab
SCCHN	Squamous cell carcinoma of the head and neck
SIGN	Scottish Intercollegiate Guidelines Network
SMC	Scottish Medicines Consortium
SPC	Summary of product characteristics
STA	Single Technology Appraisal
VOI	Value of information

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Chapter 1
Summary

1. Introduction

This document critically evaluates the evidence submission, from Merck Pharmaceuticals, on the clinical and cost-effectiveness of cetuximab (Erbitux®) for the treatment of locally advanced squamous-cell carcinoma of the head and neck (LA SCCHN) [1]. This report identifies the submission's strengths and weaknesses, supplemented, where appropriate, with our own analysis. Two clinical experts in the field of head and neck cancer were asked to advise the Evidence Review Group (ERG) to help inform the review.

1.1 Scope of the submission

The perceived aim of Merck Pharmaceuticals' submission was to evaluate the clinical and cost-effectiveness of cetuximab in combination with radiotherapy relative to radiotherapy alone in patients with LA SCCHN who are considered inappropriate for chemoradiotherapy but appropriate for radiotherapy.

1.2 Summary of submitted clinical evidence

Only one study was included in the submission [2]. This study was a fully published, well designed and conducted, randomised controlled trial that compared radiotherapy plus cetuximab with radiotherapy alone in patients with stage III or IV, non-metastatic LA SCCHN of the oropharynx, hypopharynx or larynx. Efficacy was evaluated on an intention-to-treat basis and included all randomised patients. Safety was evaluated in all patients who received treatment. The trial demonstrated that the duration of locoregional control (the primary endpoint) was significantly longer with radiotherapy plus cetuximab than radiotherapy alone. With respect to secondary endpoints, both overall and progression-free survival were significantly longer, and the overall response rate was significantly better, with the combination than radiotherapy alone. Cetuximab did not exacerbate the common toxic effects associated with radiotherapy of the head and neck. Severe (grade 3 – 5) acneiform rash and infusion reaction occurred more frequently with radiotherapy plus cetuximab than with radiotherapy alone, whereas the converse applied to severe anaemia.

1.3 Summary of submitted cost-effectiveness evidence

No previous studies were identified by the manufacturer or by the ERG which would help inform this STA. Therefore, the manufacturer's economic evaluation is considered by the ERG to comprise the only relevant evidence to consider for the purposes of this STA.

The manufacturer's submission included a *de-novo* economic evaluation to estimate the cost-effectiveness of treatment with (i) cetuximab plus radiotherapy and (ii) radiotherapy alone. The economic model (including the comparator) was considered appropriate for the decision problem. The results from the manufacturers suggested that cetuximab plus radiotherapy was cost-effective compared to radiotherapy alone under a broad range of different assumptions on the basis of a cost-effectiveness threshold of £20,000. In the base-case the incremental cost-effectiveness ratio of cetuximab plus radiotherapy compared to radiotherapy alone in the treatment of patients with LA SCCHN was £6,390 per additional quality-adjusted life-year (QALY).

1.4 Commentary on the robustness of submitted evidence

1.4.1 Strengths

The ERG felt that Merck Pharmaceuticals' submission was generally of good quality. There were no major errors or omissions, and the majority of the data quoted within the submission were a fair and accurate representation of the original reference data.

1.4.2 Weaknesses

The main weakness of the submission is that the evidence for the clinical effectiveness of cetuximab plus radiotherapy is based on a single clinical trial. Therefore, no supporting evidence for the findings is available.

1.4.3 Areas of uncertainty

The ERG felt there were two major areas of uncertainty:

1. The patient population in the pivotal trial by Bonner *et al* (2006) [2] included a high proportion of patients who would be expected to be suitable for chemoradiotherapy, and, therefore, does not match the population that is the focus of the submission's decision problem, i.e. patients who are considered inappropriate for chemoradiotherapy. No data are available regarding the number of patients in the trial who would be considered inappropriate for radiotherapy, and hence no sub-group analysis on the population specified in

the decision problem has been carried out. Therefore, the trial results may not be directly applicable to the target population. However, the clinical experts consulted by the ERG [3] were of the opinion that the Bonner *et al* trial is a good source for the comparison of radiotherapy plus cetuximab with radiotherapy alone and use of the whole trial population is appropriate, because the factors that would lead to chemotherapy being inappropriate are highly variable.

2. The radiotherapy regimens used in the trial are not typical of current UK practice. Once daily radiotherapy, rather than altered-fractionation regimens, is the regimen most representative of current UK practice (used in about 80% of patients, according to a survey by the Royal College of Radiologists) [3]. In the Bonner *et al* trial, however, altered-fractionation regimens (twice daily and concomitant boost) were selected for 18% and 56% of patients, respectively (76% in total).

Another possible area of uncertainty is whether there are sub-groups of patients who may derive more benefit from cetuximab with radiotherapy than others. The Bonner *et al* trial was not powered to detect treatment-related differences for sub-groups, such as patients who received once daily radiotherapy or those with laryngeal or hypopharyngeal cancer [4], but some results for sub-groups are presented in the published paper, although with no confidence intervals or p-values. In view of the lack of power of the trial, caution needs to be exercised in drawing conclusion; however, the results presented raise questions as to whether there are sub-groups of patients who may derive more benefit from the combination therapy than others. In patients with oropharyngeal cancer, locoregional control and overall survival durations appeared to be longer than those in patients with laryngeal or hypopharyngeal cancer. Furthermore, the once daily radiotherapy regimen may have been less effective in terms of overall survival than the two altered-fractionation regimens, and overall survival appeared to be longer with radiotherapy plus cetuximab than radiotherapy alone in patients who received the concomitant boost regimen. Further clinical trials are needed to resolve these issues. Details of these sub-group analyses are included in the structured critical appraisal of the Bonner *et al* trial presented in Appendix 3.

A number of areas of uncertainty emerged in the manufacturer's cost-effectiveness modelling. These relate mainly to the extrapolation methods, and the assumptions

used to derive the utility and cost estimates. However, based on the sensitivity analyses undertaken by the manufacturers and some additional ERG analyses, these areas of uncertainty are unlikely to have a material effect on the conclusions of the cost-effectiveness analysis.

Chapter 2
Background

2.1 Cetuximab for locally advanced squamous-cell carcinoma of the head and neck

Head and neck cancer is a broad term that includes any cancer with its primary site anywhere from the base of the neck upwards [5]. The definition generally excludes tumours of the brain and related tissues and malignant melanomas [6, 7]. The most common histological type of head and neck cancer is a squamous cell carcinoma, particularly affecting the oral cavity and larynx although patients may present with more than one primary cancer [5, 7, 8]. Approximately 90% of oral cancers are primary squamous cell carcinomas arising from the lining mucosa of the mouth, most commonly the tongue and floor of the mouth [8]. There are several recognised or hypothesised risk factors, both environmental and genetic, with perhaps the most well recognised being tobacco use, especially in the presence of a high alcohol intake [5-8]. There is a wide distribution of other cancer sites and histologies providing a broad spectrum of disease, although many of these are extremely rare [5, 7]. Local metastases from head and neck cancer occur in a significant number of cases, usually spreading through the lymphatic system in the neck. Distant metastases occur less commonly, and metastases from other cancers to the head and neck are rare [7].

2.1.1 Incidence

There were over 5,000 new cases of cancers of the oral cavity, oropharynx, hypopharynx and larynx in England in 2003. Male prevalence dominates (70%), possibly due to lifestyle factors (smoking, drinking), as does increasing age (median 60 to 64 years). Only 1,965 of the above new cases related specifically to cancers of the oropharynx, hypopharynx, and larynx [9].

2.1.2 Diagnosis

Common presenting symptoms include hoarseness, sore throat, difficulty in swallowing, and ulceration or swellings of the oral mucosa and tongue with the majority of patients presenting with advanced disease [7]. Figures published in a recent audit of head and neck cancer treatment, specifically the oral cavity and larynx, indicate that 51% of all patients present with early stage disease although

these figures may be skewed by the fact that laryngeal cancer is often detected early due to patients presenting with voice alteration [7].

2.1.3 Prognosis

Prognosis is dependent on many factors, not least the origin of the cancer and stage at diagnosis [5]. There is considerable variation in the severity of the cancer at diagnosis or presentation. Laryngeal cancers have higher five-year survival rates compared with oral cancers because an obvious symptom of the cancer is voice alteration which often prompts patients to consult a doctor earlier than do patients with oral cancers which may only manifest as a painless ulcer. Ultimately patients with cancer diagnosed and treated at an earlier stage have a much better prognosis [5].

2.1.4 Treatment

Treatment will usually consist of a combination of surgery and radiotherapy, and may include chemotherapy [5]. Surgery is only suitable for patients for whom complete resections are considered possible and are in good enough overall health to undergo an operation. Radiotherapy may be administered with curative intent alone, typically at a dose of 2 Grays (Gy) in a single fraction per day, five days per week, for seven weeks. Novel radiotherapy regimens include hyperfractionation where a dose of about 1.2 Gy is administered twice daily over the same time frame resulting in a greater overall dose, and accelerated regimens where time frame is reduced but the total dose remains the same or is also reduced [10]. Regimens can be both hyperfractionated and accelerated [2]. A meta-analysis of altered radiotherapy regimens concluded that hyperfractionated regimens offer a significant absolute survival benefit at 5 years of about 8% over once daily radiotherapy [10]. No significant survival benefit was observed for other altered regimens. All altered regimens offer significant improvements in local control, and hyperfractionated and accelerated regimens with no dose reduction also demonstrated a significant absolute benefit in terms of locoregional control of about 7 to 9% [10].

During concomitant chemoradiotherapy patients receive both chemotherapy and radiotherapy at the same time. Several meta-analyses have demonstrated a small but significant survival benefit for chemoradiotherapy compared with radiotherapy alone in patients with squamous cell carcinoma of the head and neck, with the absolute survival benefit at 5 years estimated at between 5 and 14% [11]. The greatest reliable benefit is seen with platinum-based regimens where the absolute

survival benefit is estimated at 12%, and 15% when in combination with platinum and 5-fluorouracil [12]. The most recently published meta-analysis investigating this question, which excluded any studies not deemed relevant to current accepted practice, quantified the absolute survival benefit of chemoradiotherapy at two years as 13% [13]. Altered radiotherapy regimens appear to show an even greater benefit when combined with chemotherapy, but the relatively small numbers of patients and heterogeneity of the studies have prevented a single regimen from being adopted as anything but experimental practice [11-13]. As may be expected, the incidence and severity of adverse events is significantly greater for patients treated with chemoradiotherapy than those treated with radiotherapy alone [12]. Some patients may not be suitable for chemotherapy as well as radiotherapy, and for others it may not be appropriate - for example, less fit patients, those with metastatic disease, or patients with early tumours (which generally respond well to less toxic treatment) [5].

2.1.5 Epithelial growth factor receptor

Epithelial growth factor receptor (EGFR) is a transmembrane receptor which is activated by at least three endogenous ligands. Activation of EGFR stimulates epithelial cell proliferation. Overexpression of EGFR is reported to occur in almost all cases of squamous cell carcinoma of the head and neck (>90%) at a 70-fold increased level [14]. Overexpression of EGFR is associated with more aggressive tumour characteristics and worse prognosis, although the evidence is not conclusive [15]. Overexpression is also associated, in vitro, with resistance to radiation [16].

2.1.6 Cetuximab

Cetuximab is a chimeric IgG monoclonal antibody that competes for EGFR binding sites on the external surface of the cell membrane. Binding of cetuximab to EGFR prevents activation of tyrosine kinase within cells, eventually resulting in apoptosis. Cetuximab, in combination with radiotherapy, is specifically licensed only for the treatment of locally advanced squamous cell carcinomas of the head and neck [14]. Other drugs licensed for treating head and neck cancer include cisplatin, mitomycin, and vincristine; docetaxel is expected to gain a licence for neoadjuvant use with other agents within the next 12 months [17].

2.2 Critique of the manufacturer's description of the background

The Merck submission provided a reasonably comprehensive and detailed background. The disease and current treatment options were discussed in detail. However, the treatment modality prevalence data are derived from only 139 patients

and may not be an accurate reflection of practice. Nevertheless, the recommendations for eligible patients are in-line with the product licence.

The rationale for the development of the technology and its proposed place in therapy are detailed. However, the statement “Cetuximab is an IgG1 monoclonal antibody directed against the EGFR receptor and enhances the cytotoxic effects of radiation in squamous cell carcinoma” is based upon animal data and may not, therefore, be applicable to human patients in practice. Furthermore, the statement “Radiation increases the expression of EGFR in cancer cells and blockade of EGFR signalling sensitises cells to the effects of radiation” is not supported by the accompanying reference. Rather, the authors conclude that “overexpression of EGFR conferred cellular resistance to ionizing radiation”.

No information is provided concerning radiotherapy doses, treatment regimens, or regimen modifications. This may be significant as some radiotherapy regimens are associated with better outcomes than others.

Chapter 3
Defining the Decision Problem

3.1 Scope

The scope for this single technology appraisal (STA) was clearly defined in Merck Pharmaceuticals' submission. The decision problem considered was the clinical and cost-effectiveness of cetuximab plus radiotherapy relative to radiotherapy alone in patients with LA SCCHN who are considered inappropriate for chemoradiotherapy but suitable for radiotherapy.

3.2 Intervention

The intervention considered in the decision problem is cetuximab in combination with radiotherapy.

Cetuximab (Erbitux®) is manufactured by Merck Pharmaceuticals [14]. The list price (£136.50 for one 50-ml vial of cetuximab 2 mg per ml) is correct at the time of writing [18].

3.3 Patient population

The manufacturer states that the proposed use in the UK is cetuximab plus radiotherapy for the treatment of patients with LA SCCHN of the head and neck for which chemoradiotherapy is not considered an appropriate option. However, the licensed indication is cetuximab plus radiotherapy for the treatment of patients with LA SCCHN [14]. The patient population in the only trial included by the manufacturer (Bonner *et al* 2006 [2]) comprised patients with locoregionally advanced head and neck cancer (stage III or IV, non-metastatic, squamous-cell carcinoma of the oropharynx, hypopharynx or larynx). It is not stated in the published paper whether any of these patients were not suitable for chemoradiotherapy. However, a high proportion of patients in the trial would be expected to have been suitable for chemoradiotherapy. Therefore, the patient population in this clinical trial does not match the target population advocated by the company.

3.4 Comparators

The manufacturer chose radiotherapy alone as the most relevant comparator in the stated group of patients. Cetuximab is only licensed for use in combination with radiotherapy for patients with LA SCCHN. Independent expert clinical advice given to the ERG confirmed that there was no therapy other than radiotherapy alone that would be used in this group of patients [3]. Therefore, the choice of comparator seems appropriate.

3.5 Trial outcomes

The primary endpoint of the Bonner *et al* 2006 trial was duration of locoregional control of the patients' tumours. Secondary endpoints included overall survival, progression-free survival, overall response rate and safety. The clinical experts consulted by the ERG [3] considered overall survival to be a key endpoint. However, due to the high level of co-morbidities associated with this type of cancer (which is largely due to drinking and smoking), the main focus of end points has been on locoregional control. Although locoregional control does not equal progression-free survival it is thought that the majority of patients would be progression-free as metastatic relapse is unlikely with this type of cancer and, therefore, most recurrences would be local. Locoregional control can have a significant effect on health-related quality of life as the majority of these cancers arise in the airway and mouth leading to difficulty swallowing etc. The submission states that disease-specific health-related quality of Life (HRQoL) instruments (EQ5D, QLQC-30 with Head & Neck module) were used to collect HRQoL data. However, there is no reference to HRQoL assessment in the published paper, although details of HRQoL assessment are provided in the clinical trial protocol [19].

3.6 Key issues

The ERG felt that the key issues stated by the manufacturer were reasonable. With respect to treatment guidelines, the ERG has reviewed current treatment guidelines for LA SCCHN. A summary is presented later in this report and further details are provided in Appendix 4.

The ERG considered two other key issues to be that the patient population of the pivotal trial [2] was not representative of the target population stated in the decision problem, and that the proportions of patients receiving the three radiotherapy regimens used in the trial are not representative of current UK practice (discussed above in "Areas of uncertainty").

Chapter 4
Clinical Effectiveness

4.1 Search Strategy

A systematic literature search was undertaken by the ERG to verify the completeness of the methodology used by the manufacturer to retrieve relevant clinical studies presented in the submission. Although the ERG identified no trials additional to those identified by the manufacturer, the ERG felt that the details of the search strategy provided in the manufacturer's submission were inadequate (a detailed critique is presented in Appendix 1), and carried out a literature search in accordance with the recommendations of NICE. The inclusion and exclusion criteria and the search strategy used by the ERG are included in Appendix 2.

Both searches identified one other randomised controlled trial (Burtness B, Goldwasser MA, Flood W, et al. Phase III randomized trial of cisplatin plus placebo compared with cisplatin plus cetuximab in metastatic/recurrent head and neck cancer: an Eastern Cooperative Oncology Group study. J Clin Oncol. 2005;23(34):8646-54) [20]. As cetuximab is not licensed to be used with cisplatin for patients with head and neck cancer, nor is cetuximab plus radiotherapy licensed for patients with metastatic/recurrent head and neck cancer, this trial is not relevant to the decision problem, and the ERG felt that its exclusion from the submission was, therefore, justified.

The manufacturer included only one randomised controlled trial (the trial by Bonner *et al*, 2006 [2], upon which the product licence was granted) in the submission. The trial data are summarised below in Table 4.1.

Table 4.1 Summary of Bonner *et al* 2006 [2]

Abbreviations key: **ADE:** adverse effect; **BSA:** body-surface area; **C:** cetuximab; **c.f.:** compared with; **CI:** confidence interval; **HR:** hazard ratio; **MC:** multicentre; **ITT:** intention-to-treat; **iv**: intravenous; **LRC:** locoregional control; **mo:** months; **OR:** odds ratio; **ORR:** overall response rate (i.e. rate of complete and partial responses); **OS:** overall survival; **PFS:** progression-free survival; **RRR:** relative risk reduction; **RT:** radiotherapy; **RT+C:** high-dose radiotherapy plus cetuximab; **SCC:** squamous cell carcinoma; **vs.** versus

Reference	Design	Intervention	Inclusion criteria	Exclusion Criteria	Outcomes	Results	Adverse Effects
Bonner *et al*. New Engl J Med 2006; 354:567-78 [2]	MC, multinational, randomised, phase 3 study comparing high-dose RT with high-dose RT+C. Patients were stratified according to Karnofsky performance status (60-80 vs. 90-100), nodal involvement (N0 vs. N+), tumour stage (T1-T3 vs. T4) and RT-fractionation regimen, and randomised (minimisation method) to RT or RT+C. Treatment was not blinded, but investigator-generated data were submitted for blinded review. Four randomised patients who received no treatment were included in the efficacy, but not the safety, analyses.	424 patients were randomly assigned to RT alone (n = 213) or RT+C (n = 211). All patients received a 7- to 8-week radiation-fractionation regimen: either once daily (70.0 Gy in 35 fractions); twice daily (72.0-76.8 Gy in 60-64 fractions) or concomitant boost (72.0 Gy in 42 fractions). The RT+C group received a loading dose of C iv (400 mg/m^2 BSA over 120 min) one week before RT, followed by weekly 60-min iv infusions of 250 mg/m^2 for duration of RT. Patients given C were pre-medicated with a histamine H_1-receptor antagonist iv.	Patients with stage III or IV, non-metastatic, measurable SCC of the oropharynx, hypopharynx or larynx. Other criteria: medical suitability for definitive radiotherapy, Karnofsky performance score ≥ 60, normal haematopoietic, hepatic and renal function.	Previous cancer, chemotherapy within preceding 3 years, surgery or previous RT for head and neck cancer.	Primary endpoint: duration of LRC. Secondary endpoints: OS; PFS; ORR; safety.	LRC median duration: RT+C = 24.4 mo, RT = 14.9 mo. HR for locoregional progression or death with RT+C c.f. RT = 0.68 (95%CI 0.52 to 0.89; p = 0.005). Median OS: RT+C = 49.0 mo, RT = 29.3 mo. HR for death with RT+C c.f. RT = 0.74 (95%CI 0.57 to 0.97; p = 0.03). Median PFS: RT+C =17.1 mo, RT = 12.4 mo. HR for disease progression with RT+C c.f. RT = 0.70 (95%CI 0.54 to 0.90; p = 0.006). ORR: RT+C = 74%; RT = 64% (OR = 0.57; 95%CI 0.36 to 0.90; p = 0.02)	Incidence rates of all grade 3 – 5 ADEs similar, except acneiform rash and infusion-related events more common with RT+C than RT. Grade 3 – 5 acneiform rash: RT+C = 17%, RT = 1% (p < 0.001); infusion reaction: RT+C = 3%, RT = 0% (p = 0.01); anaemia: RT+C = 1%, RT = 6% (p = 0.006). C did not exacerbate common toxic effects associated with RT of head and neck. 4 patients discontinued C due to hypersensitivity reactions after test or first dose. 8 of 9 other patients who discontinued did so due to grade 3 acneiform rash. Deaths: 12/213 in RT group and 11/211 in RT+C group died within 60 days after last RT or RT+C treatment.

4.2 Submission Trial Analysis

The Bonner *et al* 2006 [2] trial was subjected to a detailed critical appraisal (presented in Appendix 3), which was then compared with the data presented in the submission.

4.2.1 Trial summary

This fully published phase 3, multinational, randomised controlled trial compared the effects of radiotherapy plus cetuximab (RT+C) and radiotherapy alone (RT) on the duration of locoregional control (primary endpoint), overall survival, progression-free survival, overall response rate and safety in patients with stage III or IV, non-metastatic, measurable squamous-cell carcinoma of the oropharynx, hypopharynx or larynx. The trial was well designed, it included adequate numbers of patients in each treatment group to have 90% power to detect a difference in locoregional control at one year (44% to 57% or more) between the groups at a 5% significance level, and all the participants who entered the trial were accounted for at its conclusion. Efficacy was evaluated on an intention-to-treat basis and included all randomised patients, whereas four patients who received no treatment were not included in the safely analysis. Cetuximab was administered as described in the summary of product characteristics (SPC) [14].

4.2.2 Important trial points

- The estimated duration of locoregional control (the primary endpoint) was significantly longer (by 9.5 months) with RT+C (24.4 months) than RT (14.9 months).
- The estimated duration of overall survival (a secondary endpoint) was significantly longer with RT+C (49.0 months) than RT (29.3 months). The median duration of follow-up was 54 months.
- The estimated duration of progression-free survival (a secondary endpoint) was significantly longer with RT+C (17.1 months) than RT (12.4 months).
- The overall response rate during the first year (complete plus partial response rate; a secondary endpoint) was significantly higher with RT+C (74%) than RT (64%).
- The incidences of severe (grade 3 – 5) adverse effects did not differ significantly between the two groups, with the exception of acneiform rash (17% with RT+C vs. 1% with RT), infusion reaction (3% with RT+C vs. 0% with RT), and anaemia (1% with RT+C vs. 6% with RT). Cetuximab did not

exacerbate the common toxic effects associated with radiotherapy of the head and neck, including mucositis, xerostomia, grade 3 – 5 weight loss and performance status deterioration.

4.2.3 Critique of the submission

The majority of the submission was accurate according to the published trial data, and the interpretation of the trial was fair. However, the ERG considered that some points of interpretation were open to further debate; these are discussed first. There were a few minor points, such as information presented in the manufacturer's submission not being included in the published paper or references provided.

The major points are:

- Page 35. Question 50. With respect to clinical practice in the UK, the submission states that the Bonner *et al* 2006 study did allow for a range of radiotherapy regimens and this reflects well on the variation in practice in the UK, where all three types of radiotherapy schedule are in use for squamous-cell head and neck cancers. The reference quoted refers to data on file and gives details of a market research audit, which was carried out for the company between October and November 2005, of case notes of patients with LA SCCHN treated with radiotherapy and/or chemotherapy [21]. As far as the ERG is aware, this audit is unpublished, it has not been peer-reviewed and neither the full details of the methods used to conduct the review nor the full results of the review were provided by the manufacturer. No details of the types of radiotherapy regimens for 139 patients with LA SCCHN with tumours of the oropharynx, hypopharynx and larynx (i.e. the tumour sites of the patients in the Bonner *et al* trial) are presented in the reference provided. The average total doses and number of fractions planned are given, but whether radiotherapy was given once daily, twice daily or as a concomitant boost regimen is not stated. The reference does state that no one particular radiotherapy schedule appeared to be standard, but this refers to a total of 309 patients with SCCHN (not just the 139 described above) who received radiotherapy as part of their treatment regimen. Therefore, it is not clear from the information provided by the manufacturer whether the radiotherapy schedules used in the Bonner *et al* trial, or the proportions of patients with the same types and stages of LA SCCHN who received the three types of

radiotherapy schedule in the Bonner *et al* trial, are representative of practice in the UK.

- In the Bonner *et al* trial, the once daily radiotherapy regimen was selected before a patient registered for only 26% of the 424 randomised patients; 417 patients actually received radiotherapy (seven had no radiotherapy), and 25% of these received it once daily. The most frequently selected (and received) radiotherapy regimen was concomitant boost therapy (56% of patients), and the twice daily radiotherapy regimen was selected (and received) least often (18% of patients). These proportions of patients are not typical of the current UK situation. According to the two clinical experts in the field of head and neck cancer [3] consulted by the ERG, once daily radiotherapy is most representative of UK practice and used most frequently in the UK. One of the experts quoted a survey conducted by the Royal College of Radiologists, which found that once daily radiotherapy is used in about 80% of patients with head and neck cancer in the UK, and the average once daily regimen is 70 Gy in 35 fractions over seven weeks. This regimen is the same as the once daily regimen used in the Bonner *et al* trial [2]. Twice daily and concomitant boost radiotherapy are not used for various reasons, including resource issues. According to one of the clinical experts, altered-fractionation regimens give benefits over once daily, and concomitant boost radiotherapy (70 Gy in six weeks) is considered the best radiotherapy regimen. Disadvantages of the concomitant boost regimen are that the patient needs two doses of radiotherapy daily eight hours apart on five days a week and, in the UK, there are logistical problems with this due to lack of facilities and transport. Therefore, current UK practice with respect to radiotherapy regimens (predominantly once daily), differs from the predominant practice in the Bonner *et al* trial, in which altered-fractionation regimens (i.e. twice daily and concomitant boost) and once daily radiotherapy were pre-selected for 74% and 26% of patients, respectively.

- The Bonner *et al* [2] trial was not powered to detect treatment-related differences for sub-groups but results for sub-groups of patients who received once daily, twice daily and concomitant boost radiotherapy regimens are presented in the published paper, with hazard ratios (HRs) but with no confidence intervals or p values. In the 417 patients who received radiotherapy (seven patients did not), the median durations of overall survival

were 18.9 months with radiotherapy plus cetuximab vs. 15.3 months (HR 1.01) with radiotherapy alone in patients who received the once daily radiotherapy regimen (25%); 58.9 vs. 53.3 months (HR 0.74), respectively, in those who received the twice daily radiotherapy regimen (18%); and >66.0 vs. 31.0 months (HR 0.64), respectively, in those who received concomitant boost radiotherapy (56%). These results suggest that the once daily radiotherapy regimen may be less effective than the twice daily and concomitant boost regimens, and that radiotherapy plus cetuximab with the concomitant boost regimen may confer an overall survival advantage over concomitant boost radiotherapy alone. However, because the study was not powered to detect treatment-related differences for sub-groups, caution must be exercised in drawing conclusions from this analysis.

- Page 35. Question 51. The target population advocated by the manufacturer for cetuximab in combination with radiotherapy comprises patients who are considered inappropriate for chemoradiotherapy but suitable for radiotherapy. However, the Bonner *et al* trial [2] included a high proportion of patients who would be expected to be suitable for chemoradiotherapy. The two clinical experts consulted by the ERG [3] were of the opinion that the Bonner *et al* trial is a good source for the comparison of radiotherapy plus cetuximab with radiotherapy alone. They felt that the use of the whole trial was appropriate, partly because the clinical factors that would lead to chemoradiotherapy being inappropriate are highly variable (including renal impairment, i.e. a glomerular filtration rate < 50 ml/min; bad hearing; tinnitus; cardiac dysfunction; social factors; patient choice; and performance status, although the latter alone is not adequate for determining appropriateness for chemoradiotherapy, as other factors may be more important). One of the experts would only consider a small group of patients (those who cannot be given cisplatin or carboplatin) for radiotherapy plus cetuximab, and estimated that a plausible range of 10 – 20% of patients would be inappropriate for chemoradiotherapy. The other considered that about 50% of all patients get chemoradiotherapy and about 50% get radiotherapy alone, and estimated that about half of the latter (i.e. about a quarter of all patients) would be suitable for radiotherapy plus cetuximab. He estimated that about 20 - 25% of the patients in the Bonner *et al* trial would be ineligible for chemoradiotherapy. He also commented that a strength of the trial is that it included patients with a range of Karnofsky performance scores (60 – 100), and considered that all patients

with a score of 90 - 100 would be suitable for chemoradiotherapy, about a half of those with a score of 80 might be suitable and those with a score of 60 – 70 would not be suitable. As well as clinical reasons for patients not being suitable for chemoradiotherapy, practice in the UK and the choice of patients for whom chemoradiotherapy is considered inappropriate may vary according to treatment centre, clinician factors, resources available locally and local infrastructure.

The ERG asked the manufacturer to provide a clear definition and criteria for patients considered inappropriate for chemoradiotherapy. The manufacturer provided details of the responses of three clinical oncologists who were asked why they would not consider a patient to be appropriate for chemoradiotherapy, but suitable for radiotherapy [22]. Their reasons included those outlined by the clinical experts consulted by the ERG.

The ERG also asked the manufacturer to provide further information on the number of patients in the Bonner *et al* 2006 trial [2] who met the criteria of being "considered inappropriate for chemoradiotherapy but suitable for radiotherapy" and to provide any additional results which have been presented for this sub-group. If the latter were not available, the ERG requested that the manufacturer undertook this analysis. The manufacturer pointed out that the Bonner *et al* 2006 trial was not designed or statistically powered to assess for sub-groups of patients who may be inappropriate for chemoradiotherapy treatment [22]. The manufacturer also stated that impaired hearing, peripheral neuropathy, patients with SCCHN and under the age of 40 years, and patient choice were not exclusion criteria in the Bonner *et al* study, but the numbers of patients found in the data set were too small and hence not appropriate to carry out any further statistical analyses [22].

More minor points are:

- Page 26, Table 3. Study Schedule. The submission states that a HRQoL questionnaire (QLQ)C30/H&N35 was completed at randomisation, before starting the fourth week of radiotherapy, eight weeks following the completion of radiotherapy, and at the next two 4-month follow-up evaluations. The published paper makes no reference to a HRQoL questionnaire, although details of HRQoL assessment are provided in the clinical trial protocol [19]. To date any HRQoL findings from the Bonner *et al* study remain unpublished [2].

- Page 37. The A + A Healthcare audit data of patients treated provided [21] do not show that 77% of patients were male.

- Pages 44-45. This section is reported accurately, with the following minor exceptions: there is no mention in the published paper [2] that the groups were balanced for race (page 40); locoregional control results according to radiotherapy regimen presented in the manufacturer's submission (page 45) are not presented in the published paper; and, as discussed above, HRQoL data are not presented in the published paper.

- Page 51. The statement that the survival advantage of nearly 20 months is greater than the survival advantages of 7-18 months seen in large randomised studies of chemoradiotherapy versus radiotherapy is based on little convincing evidence. Direct comparisons among trials cannot be made, as factors such as different methodologies, patient populations and treatment regimens may vary. Furthermore, such comparison is not applicable to the decision problem, which relates only to patients for whom chemoradiotherapy is inappropriate.

4.2.4 ERG Summary

One, fully published, well conducted, randomised controlled trial was included in the manufacturer's submission [2]. The median duration of locoregional control (the primary endpoint) with radiotherapy plus cetuximab (24.4 months) was significantly longer (by 9.5 months) than that with radiotherapy alone (14.9 months) in patients with locoregionally advanced head and neck cancer, who had high performance status (nearly 90% of both groups had a Karnofsky performance score ≥ 80, and patients with a score < 60 were ineligible). With respect to secondary endpoints, the median duration of progression-free survival was significantly longer with radiotherapy plus cetuximab than radiotherapy (17.1 vs. 12.4 months), as was overall survival (49.0 vs. 29.3 months). The best overall response rate during the first year was also significantly better with radiotherapy plus cetuximab (74%) than radiotherapy (64%). The severe (grade 3 - 5) side effects experienced with the two regimens differed significantly only with respect to acneiform rash and infusion reaction, which occurred more frequently in the radiotherapy plus cetuximab than the radiotherapy group, and anaemia, which occurred more frequently in the

radiotherapy than the radiotherapy plus cetuximab group. Cetuximab did not exacerbate the common toxic effects associated with radiotherapy of the head and neck.

Although the trial was well conducted and the results for the primary endpoint appear robust, there are differences between the radiotherapy regimens used predominantly in UK practice and those used in the trial. Also, the trial patient population, which included patients who would have been suitable for chemoradiotherapy, does not match the population described in the decision problem.

4.3 Other relevant studies

No other relevant studies were identified by the ERG during a comprehensive literature search. See Appendix 2 for search strategy.

4.4 Relevant ongoing studies

All relevant trials were included in the manufacturer's submission. Other than the EXTREME (Cetuximab (Erbitux) in Combination With Cisplatin or Carboplatin and 5-Fluorouracil in the First Line Treatment of Subjects With Recurrent and/or Metastatic Squamous Cell Carcinoma of the Head and Neck) study which is now closed to recruitment, there are no ongoing studies examining the use of cetuximab in the treatment of head and neck cancer.

As it is not yet known which regimen of radiation therapy is most effective for head and neck cancer, various phase III studies are underway comparing new methods of radiotherapy treatment with conventional radiotherapy treatments. Although several of these studies have been ongoing for a number of years, it is doubtful they will provide additional evidence within the next 6-12 months. See Appendix 2 for search strategy.

4.5 Review of current treatment guidelines for LA SCCHN

The manufacturer's submission states that there are no set treatment guidelines for patients with locally advanced SCCHN. This is based on data collected in the recent national head and neck cancer audit (Data for Head and Neck Oncology; DAHNO)[7]. The DAHNO report notes that, in the absence of nationally accepted clinical standards, professional bodies led by the British Association of Head and Neck Oncologists (BAHNO) and facilitated by DAHNO should evolve such standards. However, an indication as to how such standards should be established or what such

standards should focus on is not given in the audit. Both the manufacturer's submission [1] and DAHNO [7] highlight only NICE guidance [5] issued in November 2004, and the positive advice issued by the Scottish Medicines Consortium (SMC) [23] issued in July 2006 as relevant guidelines or protocols.

NICE recommends that head and neck cancer teams within each network should agree local guidelines for the treatment of each form of cancer within this group [5]. The guidance states that many patients are treated with radiotherapy alone, but those with more advanced disease may require both radiotherapy and surgery or chemoradiation. In addition, the interval between surgery and radiotherapy should be as short as possible, ideally less than six weeks, and radiotherapy departments should make every effort to ensure that each patient receives a complete and unbroken course of the prescribed treatment. Synchronous chemoradiation or altered fractionation regimens (more intensive forms of treatment appropriate for patients with advanced disease who are fit enough to cope with their adverse effects) should also be available for selected patients. No specific recommendations are made on which radiotherapy or chemotherapy regimens should be used as primary treatment.

Although the manufacturer's submission cited only two guidelines for the treatment of LA SCCHN, other guidelines are available and include the Royal College of Radiologists [24], the National Comprehensive Cancer Network (NCCN) [25], the European Society of Medical Oncology (ESMO) [26], the 2004 national meeting draft of the Scottish Intercollegiate Guidelines Network (SIGN) [27] (SIGN guidelines on head and neck cancer were due to be published in the summer of 2006, but at the time of writing, they had not been published [28]), and Cancer Care Ontario [29].

All of the above groups agree with NICE recommendations [5] that treatment guidelines must be established locally and take into account individual patient needs and toxicity. However, SIGN, NCCN and the Royal College of Radiologists provide more detailed guidance with respect to specific head and neck cancer subsets and suggest specific radiotherapy and chemotherapy regimens that should be implemented in the various stages of hypopharyngeal, oropharyngeal and laryngeal cancer [24, 25, 27].

Other than the positive opinion given by the SMC [23] on the clinical and cost-effectiveness of cetuximab in LA SCCHN, there is no other specific reference to cetuximab within the aforementioned guidelines.

Further details of these guidelines are presented in Appendix 4.

Chapter 5
Economic Evaluation

5.1 Introduction

This section provides a structured critique of the cost-effectiveness evidence submitted by Merck Pharmaceuticals (the manufacturer). As part of the STA process, manufacturers are expected to perform a systematic review of existing cost-effectiveness evidence for the health care technology or process being assessed. Where there is no existing evidence or the existing evidence is insufficient, manufacturers may perform their own *de-novo* cost-effectiveness analysis.

The manufacturer's economic submission to NICE includes:

(i) a description of the search undertaken in an attempt to identify cost-effectiveness literature relevant to the decision problem (p53-58);

(ii) a report on the economic evaluation undertaken by the manufacturer and presented specifically for the NICE STA process (p58-86, in particular Figure 3, p66 the schematic of the model and Tables 13-15, p68-77 which provide information on the model's inputs and assumptions);

(iii) base-case costs and effectiveness results from the model (Tables 20,22 and 23, p97-98 and p100);

(iv) stochastic sensitivity analysis results from the model (Table 24, p101 and Figures 7-8, p101-102);

(v) results from the deterministic one-way sensitivity analysis conducted (Table 25, p103);

(vi) an Excel-based model comprising the manufacturer's economic model provided electronically;

(vii) a report on the resource utilisation and cost variables used to inform the decision problem (Technical Appendix 1); and

(viii) a report on the health state valuation study conducted in order retrospectively to estimate utility values from the Bonner *et al* [2] study (Technical Appendix 3).

Following a list of questions posed by the ERG to the manufacturers, two addenda were submitted. The manufacturer's addenda include:

(i) a statement that a sub-group analysis of those patients in the Bonner *et al* [2] study who were not appropriate for chemoradiotherapy was not possible (SCCHN NICE STA response letter1, responses A2 and B3);
(ii) further information on the approach used to extrapolate survival data (Merck response on survival extrapolation);
(iii) the STATA statistical code used for the survival analysis (sample.do);
(iv) individual patient data relating to the extrapolation (Observed.txt);
(v) life table survival probabilities (Life table survival probabilities (pat).txt);
(vi) information about the estimation of hazard ratios in the Bonner *et al* [2] trial (SCCHN NICE STA response letter for comments of 26th September 2006, A1);
(vii) details of the number of centres providing each radiotherapy regimen (SCCHN NICE STA response letter for comments of 26th September 2006, A1);
(viii) details of the derivation of the general population hazard (SCCHN NICE STA response letter for comments of 26th September 2006, A2); and
(ix) an Excel file containing the requested spread sheets "oscalcs" and "imputed data" (imputed data – os and pfs cure NICE STA v1.xls).

This section focuses on the economic evidence submitted by the manufacturer. The submission is subject to a critical review on the basis of the manufacturer's report and by direct examination of the electronic version of the economic model. The critical appraisal is conducted with the aid of a checklist to assess the quality of economic evaluations and a narrative review to highlight key assumptions and possible limitations.

5.2 Existing cost-effectiveness evidence

As part of the manufacturer's submission a systematic search was undertaken with the aim of identifying all studies evaluating the cost-effectiveness of cetuximab for head and neck squamous cell carcinoma (SCCHN). The date range and sources searched to identify the primary studies were appropriate for this purpose. The results of the search identified no studies which met the inclusion criteria (reasons for exclusion can be found in Table 10 p58).

The searches undertaken by the manufacturer were replicated by the ERG in order to validate the evidence base considered. The ERG found that the search was reproducible, and the results were consistent with the original search. However,

some of the search terms used by the manufacturer would not have retrieved records as intended. For example, Line 2 in the original search write-up was (((squamous cell carcinoma$ or squamous-cell carcinoma$) adj head and neck$) or HNSCC).ti,ab. This line produces a syntax error in Ovid. Using the same strategy but amending the search terms resulted in more records being identified. However, none of these was deemed by the ERG to match the inclusion criteria. Therefore, the ERG concurs with the manufacturer that there are no existing published cost-effectiveness studies evaluating the use of cetuximab for SCCHN.

5.3 Overview of manufacturer's economic evaluation

The manufacturer's submission is based on a *de-novo* economic evaluation to estimate the cost-effectiveness of treatment with (i) radiotherapy and (ii) cetuximab plus radiotherapy. A brief overview of the key assumptions used in the analysis, alongside a narrative description of the main approach used, is reported below. This is followed by a more detailed critique of the economic evaluation and its assumptions.

The key assumptions used in the model include:

(i) That the population relevant to the pivotal trial (Bonner *et al* 2006 [2]) is representative of /appropriate for the population of interest for the company's definition of the decision problem (i.e. those patients with LA SCCHN in the UK who are considered inappropriate for chemo-radiotherapy but suitable for radiotherapy).

(ii) That patient HRQoL is best represented by ranking the health states associated with adverse events into a hierarchy (Table 18, p82) with the worst state taking precedence in the estimation of QALYs. This assumes that the states are utility independent (i.e. only the utility from the worst adverse event being experienced matters, and there are no utility interaction effects between adverse events).

(iii) It is appropriate to include only adverse events that have been found to differ between treatment with cetuximab plus radiotherapy and cisplatin plus radiotherapy in the calculation of utility in the model. This seems to be the case as the HRQoL study conducted by the manufacturer which appears to relate to a comparison of cetuximab plus radiotherapy and cisplatin plus radiotherapy.

(iv) It is appropriate to exclude post treatment adverse events from the model.

(v) That only adverse events identified as the most significant cost drivers were included in the costing for the model. This accounts for only 64% of all adverse events experienced in the Bonner *et al* [2] trial.

(vi) That the use of the 'Cure model' for the extrapolation of the individual patient data over a lifetime time horizon is the most appropriate model for extrapolation.

(vii) That UK oncology nurses represent a good proxy for patients with LA SCCHN so that their responses to the EQ-5D provide a good estimate of the HRQoL experienced by the patients.

(viii) That there is no uncertainty with regards to the extrapolation methods for each patient.

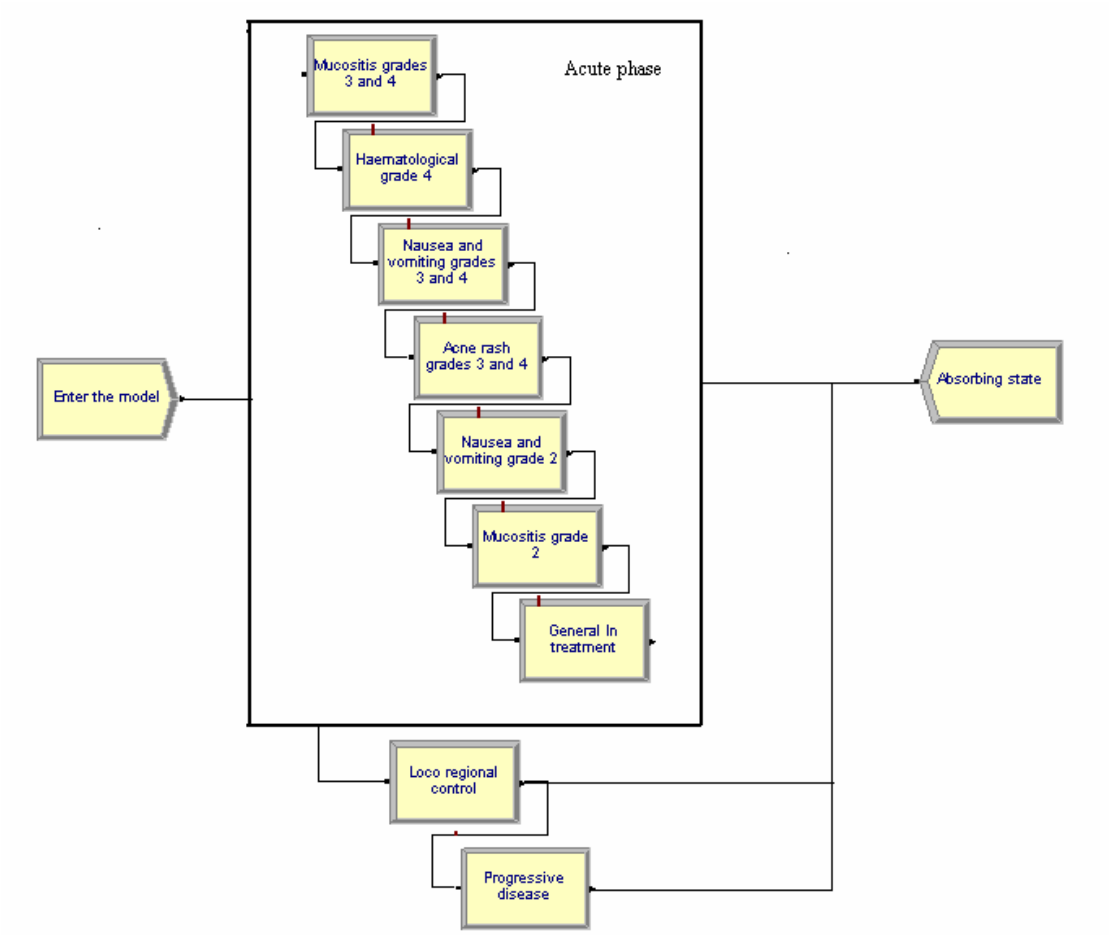
The results for the economic evaluation are presented for the base-case, and thereafter for several other scenarios through sensitivity analysis. A stochastic sensitivity analysis has also been undertaken.

5.3.1 Natural history

The model uses individual patient data from the Bonner *et al* trial [2] to estimate costs and health effects during the trial period for each patient. Where the data are censored the model extrapolates costs and health effects. Patients enter the model in the acute treatment stage at the beginning of the trial period. In the acute stage patients reside in the health state relating to the worst adverse event(s) they experience during treatment (details discussed later).

Following the acute treatment stage, patients enter the locoregional control state and remain in this state until they experience disease progression at which point they enter the progressive disease state. These flows between states are uni-directional: patients are unable to return to the progressive disease or acute treatment states once they have left them. At any point in the model, patients may die and exit to the absorbing death state. A schematic of the model is presented in Figure 5.1.

Figure 5.1 Schematic of manufacturer's model



5.3.2 Extrapolation methods

The manufacturers extrapolated censored survival times (i.e. in patients remaining alive at the end of the trial) using parametric survival models for progression-free and overall survival. To do this the manufacturers used a 'cure model', which allows a non-zero cure fraction. In other words, the survival model estimated the proportion of patients who were 'cured' (survival probability equal to 1) and who would never experience the event of interest (progression or death). This allowed the manufacturers separately to estimate the overall survival probability of cured and non-cured patients. The overall survival probability of cured patients was estimated from UK life tables together with an estimate of the proportional increase in mortality hazard for patients who have experienced LA SCCHN. The cure model predicts the progression-free or overall survival probability for the proportion of patients not cured. A log-normal distribution with a logistic link function was selected for the cure model. This is appropriate for characterising patterns of survival where the hazard is initially increasing, but then begins to decrease.

Survival times beyond censoring were imputed using the survival probabilities from the cure model corresponding to the censored time, multiplied by a random uniform probability. Predictions for censored overall survival were constrained to be at least as great as observed progression-free survival. Correspondingly, any predictions for progression-free survival that were greater than predicted overall survival were re-estimated. A single, deterministic imputation of progression-free and overall survival was calculated for each patient where necessary due to censoring. The survival model is discussed further in Section 5.3.8 and critically reviewed in Section 5.5.2.

5.3.3 Treatment effectiveness

The clinical data used in the economic evaluation is the individual patient data recorded in the Bonner *et al* [2] clinical trial and extrapolation of the censored data using the cure model discussed above. Disease progression is based on the individual patient data where it is recorded, and is imputed via the cure model where it is not. A summary and critique of the trial are provided in Chapter 4 and Appendix 3. Table 5.1 below shows summary statistics for efficacy outcomes from the trial based on an intention to treat analysis.

Table 5.1 Efficacy outcomes for the intention to treat trial population

Variable	**Radiotherapy Alone.** **ITT population N=213**	**Radiotherapy plus Cetuximab** **ITT population N=211**
Locoregional control Median duration in months	14.9	24.4
Progression Free Survival Median duration in months	12.4	17.1
Overall Survival Median duration in months	29.3	49.0
Response Rate (Complete Response + Partial Response) Total number (%)	137 (64%)	155 (74%)

Adverse events reflected in the individual patient data have been included in the model. However, due to censoring of some endpoints for adverse events, an expected time per adverse event is included. This is discussed further below.

5.3.4 Health-related quality of life

HRQoL in terms of utility values for the health states was estimated from a study of oncology nurses in the UK using the EQ-5D. Fifty nursing staff from oncology centres around the UK were recruited for the study and screened to ensure they were suitable to act as proxies for the patients (details of the screening criteria are provided in Technical Appendix 3 of the manufacturer's submission). The nurses were asked to complete the EQ-5D's 5-dimensional classification system [30] for each health state which was described to them to reflect their judgement about a patient's HRQoL when experiencing each health state. Utility values were derived based on the 'UK social values' [31].

The study aimed to estimate utility values for a series of health states describing major side effects and post-treatment outcomes that may be experienced by patients undergoing treatment for stage III and IV head and neck cancer. Seven health states for the acute phase were identified which described different grades of the acute toxicities (these were based on the National Cancer Institute common toxicity criteria [32]). Two health states were identified that described toxicities post treatment; however, these were then excluded from the economic model. Two further states described possible final outcomes of treatment in terms of the success or failure of treatment (post treatment loco-regional control or progressive disease). The health states and the assigned utility values are presented in Table 5.2.

Table 5.2 Model health states and assigned utility values

Health state	Definition	Utility
Acute phase health states		
A	General in–treatment – range of ≤ grade 1 adverse events	0.659
B	As health state A plus grade 3 or 4 mucositis, stomatitis and dysphagia	0.062
C	As health state A plus grade 2 mucositis, stomatitis and dysphagia	0.608
D	As health state A plus grade 3 or 4 nausea and vomiting	0.108
E	As health state A plus grade 2 nausea and vomiting	0.573
F	As health state A plus grade 3 or 4 acne and rash	0.226
G	As health state A plus grade 4 haematological toxicity	0.101
Post-acute phase health states		
J	Post–treatment loco–regional control	0.862
K	Post–treatment progressive or worsening disease	0.129

With regards to the acute states, the manufacturer assumes that patient HRQoL would be best represented by ranking the health state (adverse event) into a hierarchy with the worst health state (in terms of utility score) taking precedence (state B), followed by the second worst health state etc. Each patient's acute phase health states (i.e. the adverse events they experienced during treatment) were then compiled to assess which of the acute health states they would have spent time in and how many times each adverse event occurred. Each patient was then assigned the utility value for the worst health state they experienced for the average duration of that health state/adverse event (calculated across all patients) multiplied by the number of times that worst state occurred for that patient. Any remaining time in the acute treatment state (i.e. the length of time in the acute treatment state for each patient minus the average time (across all patients) of the worst adverse event experienced by that patient) was assigned the utility for the next worst adverse event the individual experienced and so on. The manufacturer argued that this is a conservative approach to the estimation of utility as each patient is allocated their worst possible utility score within the parameters of the modelled health state. The ERG's view on the limitations of this approach are discussed later.

Following the cessation of treatment, the remainder of each patient's overall survival was allocated between post-treatment phase health states J and K, representing progression-free survival and survival with progressive disease, respectively, based on the time spent in each of the two states.

5.3.5 Resource utilisation and costs

Resource utilisation was based on individual patient data from the Bonner *et al* [2] trial as well as on assumptions reached following advice from a panel of 6 UK clinical experts and two further clinical experts (Prof Chris Boshof and Dr Tova Prior, University College London). The regimen of radiotherapy, the number of fractions received by each patient and the dose of cetuximab administered were recorded in the Bonner *et al* [2] clinical data set. Assumptions were made regarding other resource utilisation, full details of which are provided in Table 15 p 72-77 and in q104 p91-2 of the manufacturer's submission. In particular it is worth emphasising the following assumptions:

(i) Although radiotherapy is administered daily, contact time with a specialist occurs approximately once a week for about 15 minutes. Therefore, separate outpatient visits are only included for these weekly sessions.

(ii) Cetuximab is administered in an outpatient setting with one outpatient visit allocated for each dose.

(iii) Resource use parameters used to calculate the expected cost of each adverse event are derived from the UK expert panel.

(iv) Only adverse events identified (by Prof Chris Boshof) as the most significant cost drivers with respect to a combination of frequency of occurrence and intensity of resource use associated with treatment were included in the cost analysis.

Unit costs were derived from the NHS reference costs, details of the derivation are given in Technical Appendix 1 of the manufacturer's submission. In particular, it is worth noting that adverse event costs were based on the expected cost of the average episode (in terms of time) for each type of event and severity grade. This was due to missing and censored end dates of events. This assumption is discussed further below.

Only NHS costs were considered, and no account was taken of any costs imposed on personal social services (PSS).

5.3.6 Discounting

The manufacturer's submission has used an annual discount rate of 3.5% for future costs and QALYs.

5.3.7 Sensitivity analyses

The manufacturer's submission includes one-way sensitivity analysis and stochastic sensitivity analysis based on a bootstrapping approach.

5.3.8 Model validation

The manufacturer's submission reports that where assumptions were necessary, expert opinion was sought to validate these using an expert panel of 6 or Prof Chris Boshoff and Dr Tova Prior. The submission claims the cure model used to impute censored progression-free and overall survival has been validated by providing details of a Weibull model fitted to the data which shows the cure model results are conservative towards the cetuximab plus radiotherapy arm, and an exponential model to show that it is consistent with the cure approach.

The manufacturers explored a number of survival models for extrapolation. Survival was modelled using a Weibull distribution, which resulted in estimates more favourable to cetuximab plus radiotherapy in comparison to the cure model, and so the manufacturers state that their use of the cure model is conservative. In addition, the results of the cure model were compared to a simple extrapolation assuming an exponential survival distribution. The results of the simple extrapolation are described as very similar to the results of the cure model, but are not provided. This could potentially indicate that the cure model was poorly estimated on the overall survival data, and this model may have added little to a simple extrapolation assuming a constant hazard of death. The reason why the cure model may have fit the survival data poorly are discussed further in Section 5.5.2.

The shape parameter of the Weibull distribution for the estimation of overall survival was not significantly different from 1, indicating that an exponential distribution may equally be able to describe the survival data. The shape parameter for overall survival was estimated to be 0.93, indicating that the hazard was, if anything, slightly decreasing with time. The shape parameter of the Weibull distribution for progression-free survival was estimated to be 0.81, and was significantly different from 1, indicating that the hazard for progression-free survival was, on average, decreasing with time.

The manufacturer states that the observed survival curves appeared concave, indicating that a log-logistic or log-normal model would be more appropriate than an exponential model that assumed a constant hazard, or a Weibull model that assumes

a monotone hazard. The ERG considers this to be appropriate. The manufacturers also compared the Akaike Information Criterion (AIC), a statistic based on the log-likelihood, between models estimated using an exponential, Weibull, log-normal and log-logistic distribution, and found this to be lowest for the log-normal survival distribution.

Whilst the use of the cure model may have been conservative with respect to the use of a Weibull model, the choice of distribution for the cure model was not conservative. The log likelihood for each of the distributions tested within the cure model was lowest for the logistic distribution, but the log-normal distribution was selected. The manufacturers chose to use the log-normal distribution, as it resulted in the lowest cure fraction (estimated proportion of patients cured) compared to the Weibull, logistic, gamma or exponential. While this is true, it also resulted in the biggest difference in cure fraction between the treatment groups (11.7% in favour of cetuximab plus radiotherapy) compared to the alternative distributions (smallest difference 8.4%). See Table 5.3 for the log-likelihood and estimated cure fractions of the distributions.

Table 5.3 Estimated cure fractions

Survival curve model	Log-likelihood	Estimated cure fraction		
		RT arm	***RT + C arm***	***difference***
Weibull	-1096.6	36.3%	45.5%	9.2%
Log-normal (Used in base-case analysis)	**-1093.7**	**23.5%**	**35.2%**	**11.7%**
Logistic	-1092.4	28.7%	39.7%	11.0%
Gamma	-1095.0	35.8%	45.3%	9.5%
Exponential	-1101.7	30.0%	38.4%	8.4%

A sensitivity analysis was conducted in which no extrapolation was performed. As greater proportions of patients receiving cetuximab plus radiotherapy were progression-free or alive at the end of the trial period, this analysis will underestimate the benefit of cetuximab plus radiotherapy. However, it does provide a useful extreme case scenario for comparison with the extrapolated results.

5.4 Critique of the manufacturer's economic evaluation

The ERG has considered the methods applied in the manufacturer's economic evaluation in the context of the critical appraisal questions listed in Table 5.4 which are drawn from common checklists for economic evaluation methods [33].

Table 5.4 Critical appraisal checklist

Item	Critical Appraisal	Reviewer Comment
Is there a well defined question?	Yes ?	The manufacturer advocates the use of cetuximab plus radiotherapy for those patients with locally advanced SCCHN who are considered inappropriate for chemoradiotherapy but appropriate for radiotherapy.
Is there a clear description of alternatives?	?	Cetuximab plus radiotherapy vs radiotherapy alone (however there are issues over the radiotherapy regime which is not clearly defined for either treatment).
Has the correct patient group/ population of interest been clearly stated?	?	The population of interest is those patients with locally advanced SCCHN who are considered inappropriate for chemo-radiotherapy, such a population is not clearly defined (see clinical effectiveness section).
Is the correct comparator used?	Yes	In the specified patient population, our clinical specialists have advised radiotherapy is the only appropriate comparator.
Is the study type reasonable?	Yes	Cost-effectiveness analysis used using QALYs as the measure of treatment benefit.
Is the perspective of the analysis clearly stated?	Yes	Perspective stated as costs to NHS and health benefits to patients.
Is the perspective employed appropriate?	Costs- Yes Outcomes-Yes	The manufacturer's submission adopts a UK NHS perspective for costs, although they fail to take account of costs to PSS, so it is only partially consistent with the NICE reference case. Perspective on outcomes is that of the patient with treatment health effects to the individuals being captured by QALYs.
Is effectiveness of the intervention established?	?	The CEA is based on data from the Bonner *et al* [2] trial of which only a sub-group represent individuals who were not suitable for chemoradiotherapy. When further analysis of this sub-group only was requested by the ERG, the manufacturer stated that it was too small to run statistical analysis on. There are also issues with the radiotherapy regimes used in the trial.
Item	Critical Appraisal	Reviewer Comment
Has a lifetime horizon been	Yes	A lifetime horizon has been used in the

used for analysis (has a shorter horizon been justified)?		model.
Are the costs and consequences consistent with the perspective employed?	Yes	Costs are consistent with an NHS perspective although some costs, e.g. pre-medication costs, are excluded. Consequences are measured in QALYs although there are some concerns over the way that utility decrements from adverse events have been included.
Is differential timing considered?	Yes	Discounted has been implemented at an appropriate rate.
Is incremental analysis performed?	Yes	
Is sensitivity analysis undertaken and presented clearly?	Yes	One-way sensitivity analysis has been undertaken and the results clearly presented (Table 25, p103 of submission). Probabilistic sensitivity analysis was not undertaken due to the trial-based modelling approach adopted. Instead, stochastic sensitivity analysis has been undertaken by using a bootstrapping approach.

Table 5.5 below compares the manufacturer's submission to that of the NICE reference case.

Table 5.5 NICE reference case checklist

Attribute	Reference Case	Included in submission	Comment on whether *de-novo* evaluation meets requirements of NICE reference case
Comparator(s)	Alternative therapies including those routinely used in NHS	Yes	Radiotherapy alone is the appropriate comparator for the population of interest.
Perspective - costs	NHS and PSS	?	NHS costs have been taken into account but no consideration of PSS costs has been undertaken.
Perspective - benefits	All health effects on individuals	Yes	QALY benefits to treated individuals are considered, wider health effects are not considered but are unlikely to be relevant.
Time horizon	Sufficient to capture differences in costs and outcomes	Yes	The economic model has a lifetime time horizon.
Synthesis of evidence	Systematic review	?	The model uses individual patient data from a single study which could be considered the most relevant.
Outcome measure	QALYs	Yes	
Attribute	Reference Case	Included in submission	Comment on whether *de-novo* evaluation meets requirements of

			NICE reference case
Health states for QALY measurement	Described using a standardised and validated instrument	Yes	Utility values for the health states were estimated from a study of oncology nurses in the UK using the EQ-5D (which is considered an appropriate instrument by NICE). The preferences for the EQ-5D scoring function were measured by a time trade off technique of approximately 3000 UK adults and therefore represent preferences of a sample of the public.
Benefit valuation	Time Trade Off or Standard Gamble	Yes	
Source of preference data	Sample of public	Yes	
Discount rate	Health benefits and costs	Yes	Benefits and costs have both been discounted at 3.5%.
Equity	No special weighting	Yes	No special weighting was undertaken.
Sensitivity analysis	Probabilistic sensitivity analysis	No	Probabilistic sensitivity analysis has not been undertaken. Instead stochastic sensitivity analysis has been performed by the method of bootstrapping and this allows for the presentation of a cost-effectiveness acceptability curve. However, there are concerns that the manufacturer has failed to take account of uncertainty around the method of extrapolation when undertaking the bootstrapping.

5.5 Detailed critique of evaluation methods

A critical review of the methods used in the manufacturer's economic evaluation has been undertaken. The review has used the previous checklists as a basis for the analysis.

5.5.1 Decision problem, perspective and assumptions

The decision problem and objective are clearly stated within the manufacturer's submission, including details of:

1) Disease – LA SCCHN.
2) Patient group – the manufacturer's proposed population is those patients in England and Wales with LA SCCHN who are considered inappropriate for chemotherapy plus radiotherapy.
3) Options compared – cetuximab plus radiotherapy versus radiotherapy alone.

As described in Section 4.2.3, although the decision problem is clearly stated, the data used in the model relate to a different patient group from that stated in the original decision problem. In particular, the economic model is based directly on the entire dataset from the Bonner *et al* trial [2] and this trial included patients who would

have been suitable for chemotherapy plus radiotherapy. The ERG has been unable to ascertain exactly what proportion of the patients in this trial would be unsuitable for chemotherapy plus radiotherapy. However, our clinical advisers have stated it would be between 10 and 25% (see Section 4.2.3). The ERG requested that the manufacturer provide clinical and cost-effectiveness results for the sub-group of patients unsuitable for chemotherapy. However, in the addendum provided by the manufacturer they stated that such a sub-group would be too small and hence it was not appropriate to carry out further statistical analysis. However, the ERG's clinical advisers have also suggested that the overall results from the trial are likely to be directly relevant to the decision problem.

The perspective on costs taken by the manufacturer is that of the NHS, this differs from the NICE reference case as no account is taken of the costs relating to PSS. However, the exclusion of PSS costs is considered by the ERG to be unlikely to affect the current results significantly as the costs should be broadly equivalent across the treatment arms. It may even be biased against cetuximab plus radiotherapy as PSS costs are more likely to occur in the disease progression state which occurs later, on average, in the cetuximab plus radiotherapy trial arm, and also less frequently due to the higher cure rate, and hence would have a lower present value due to discounting.

The perspective on benefits is health effects on treated individuals. Although, the NICE Reference Case requires estimation of health effects to individuals (including, for example, patients' families), the focus on patients would seem reasonable. The base-case model includes 9 health states which have been valued using the EQ-5D instrument using oncology nurses as a proxy for patients. The ERG has concerns that these health states might not fully capture the HRQoL experience of patients. These concerns are discussed further below. The model uses a lifetime time horizon which is consistent with the NICE methods guidance [34] which states that the time horizon should be sufficiently long to reflect any differences in costs or outcomes between the options.

The submitted economic evaluation assumes that all the important factors related to the disease, in terms of costs and HRQoL, can be captured in the seven adverse event health states and the two post treatment health states. However, it is reported in the manufacturer's submission that, at least with respect to the acute health states, these only cover 68% of adverse events experienced and do not take account of

patients having more than one adverse event at a time. Further potential weaknesses with this approach are discussed in the HRQoL section below.

The HRQoL study conducted on behalf of the manufacturer also identified two adverse events that occur following the cessation of treatment: peripheral neuropathy and ototoxicity. These two states have been excluded from the manufacturer's economic model, This may be due to the HRQoL study being based on the treatment of cisplatin plus radiotherapy and these adverse events may not be relevant to either of the treatment arms considered in the manufacturer's cost-effectiveness analysis. If the prevalence of these two states differs between the treatment arms then the analysis may be biased. However, the ERG does not have the data to examine their prevalence so cannot indicate whether such a bias exists and, if present, its direction.

5.5.2 Survival analysis

The data from the Bonner *et al* trial [2] provides an estimate of median progression-free and overall survival. In order to estimate the *expected* costs and health benefits it is necessary to have an estimate of mean survival duration. Therefore, the manufacturers extrapolated the censored survival times using parametric survival models for progression-free and overall survival. The manufacturers applied a survival model that allowed a non-zero cure fraction, which can be termed a cure model. In other words, the survival model estimated the proportion of patients who were 'cured' (survival probability equal to 1) and who would never experience the event of interest (progression or death). This allowed the manufacturers separately to estimate the overall survival probability of cured and non-cured patients. The cure model predicts the progression-free and overall survival probability for the proportion of patients not cured.

In order to estimate the overall survival probability of cured patients, the manufacturers used age-adjusted mortality risks for UK males (http://www.gad.gov.uk/Life_Tables/Interim_life_tables.htm) and applied a proportional hazard to account for the higher risk of death among patients who have experienced LA SCCHN in comparison to the general population. This proportional hazard was calculated by comparing the survival in a published meta-analysis of trials comparing radiotherapy to chemotherapy plus radiotherapy in patients with LA SCCHN [35] to the survival probabilities calculated from UK life tables. The published meta-analysis and the use of UK life tables seem to be reasonable data

sources. However, approximately 20% of the trial population were female, and so the use of male life-expectancy will underestimate the expected survival in the general population, and lead to a corresponding overestimate of the proportional hazard of death for patients who have experienced SCCHN. As the greatest proportion of cured patients is in the cetuximab plus radiotherapy group, this is unlikely to bias the model results in favour of cetuximab plus radiotherapy. Following a request by the ERG, the manufacturer provided an explanation of how the proportional hazard was calculated (see addendum "SCCHN NICE STA response letter for comments of 26th September 2006"); however, this has resulted in some confusion as it appears to suggest that the age-adjusted life expectancy has also been based on both male and female life tables. The ERG has been unable to replicate the calculation and, therefore, it remains unclear whether the possible bias described above will be an issue.

The published meta-analysis provided survival curves that incorporated data up to 10 years follow-up. The manufacturer assumed that patients still alive after 5 years were cured. The clinical advisor to the ERG thought this to be a reasonable assumption. The manufacturers then estimated a straight line of 'best fit' between the published curves (loco-regional treatment plus chemotherapy compared to loco-regional treatment alone) and extended this line until it intercepted the x-axis (i.e. the survival probability was 0). The method by which this line was fitted to the published curves is not reported. The point of intercept for the fitted line was estimated to be 19 years. The mean hazard rate was then estimated by dividing the slope of the line by the survival probability in each year from 5 to 19 and pooling the results. The calculated mean hazard (0.1167) was divided by the estimated mean hazard in the general population (0.04188) to calculate a hazard ratio of 2.786.

The initial survival time was set to equal the mean age (57 years) of the trial participants. For progression-free survival, the time to progression was imputed using the survival probabilities estimated in the cure model. The manufacturers state that the cure rate probability that corresponded as closely as possible to the observed censored time was multiplied by a random uniform probability. The survival time corresponding to this resulting probability was then taken as the imputed failure time. Adding this failure time to the censored time gave the estimated progression-free survival. A similar procedure was used to estimate overall survival, but using probabilities generated by the cure model for proportion of patients not cured and adjusted probabilities from UK life tables for the proportion cured.

The use of a random uniform probability in this way assumes that nothing is known about the probability of each patient surviving beyond the observed censored time. This would contrast with other possible multivariate approaches that might incorporate the effect of patient covariates in the probability of survival, such as age, gender and co-morbidity. However, so long as the treatment effect of cetuximab does not differ according to these characteristics, the results of the economic model should not be biased. The use of a single draw from a random uniform probability could mean that, if the analysis were run again, the results would be quite different. In addition, the cure model predicts survival with uncertainty. The 95% confidence interval around treatment effect on the estimated cure fraction incorporated zero. This uncertainty could have been characterised in the economic evaluation by making use of the standard errors around predicted survival or the upper and lower confidence limits. The survival extrapolation is likely to be the main source of uncertainty in the economic evaluation but this is not reflected in the model results.

5.5.3 Health-related quality of life

Due to a lack of a preference based HRQoL measurement in the Bonner *et al* trial [2] (the trial included 2 disease-specific HRQoL measures - the EORTC QLQ-C30 and the EORTC QLQ H&N35) the manufacturer conducted its own HRQoL study (details of which can be found in Technical Appendix 3 of the submission). Fifty nursing staff from oncology centres around the UK were recruited for the study and screened to ensure they had suitable experience. Although the selection into the study appears well conducted (with, for example, well defined screening criteria etc.), no information is given on how the nurses who were asked to complete the original screening questionnaire were selected. There may also be a concern that oncology nurses are not good proxies for patients. However, it may be considered that, due to the selection criteria setting out a minimum amount of experience with LA SCCHN patients, the nurses are reasonable proxies.

The company developed seven health states to represent the acute stage of treatment. However, there is little clarification of why these health states have been chosen. The manufacturer states that:

"To avoid cognitive overload for respondents taking part in the valuation, the number of health states included in the utility valuation were limited to those describing a combination of major adverse events and their severities that could be substantiated

to distinguish between different comparator treatments to be included in the economic evaluation associated with this study. Furthermore, due to the limitations of the number of health states to be included in the study, the series of health states were designed to reflect increases in severity of only one adverse side effect at a time rather than increases in severity of combinations of side effects." (Technical Appendix 3, p10).

Of particular interest is the suggestion that health states were included if they could distinguish between the different treatment options. The sources they have used to achieve this are listed in Technical Appendix 3 (Appendix 2) of the submission. The specific methods are unclear, but it appears that they have actually identified the adverse events that differ between cetuximab plus radiotherapy and radiotherapy plus cisplatin. This would not account for adverse events that may differ between cetuximab plus radiotherapy and radiotherapy alone, which is the comparison in the model. As a result, relevant adverse events may have been excluded. The study also states that it excluded the adverse event of an allergic reaction to intravenous drug treatment which is more common with cetuximab plus radiotherapy. The rationale for this exclusion was that the clinician would be available to treat it immediately. As long as such a reaction is over in a very brief period this should not bias the results significantly but, if there are longer-term effects, then exclusion may bias the results in favour of the cetuximab plus radiotherapy option.

The manufacturer also states that the health states were selected to reflect increases in severity of only one side effect at a time rather than a combination of side effects (i.e. the study did not consider interaction effects between adverse events). When combined with the algorithm of hierarchy of health states used by the manufacturer (where only the health state with the lowest utility is taken into account), this implies that the adverse events are utility independent of one another. This is a strong assumption, and it is possible that having two or more adverse events at the same time could lead to a lower utility score than that of the adverse events with the lowest utility taken separately. It is not clear what effect this assumption could have on the analysis, but if multiple adverse events are more common in the cetuximab plus radiotherapy arm, the current model's cost-effectiveness results may be biased in favour of the combination therapy.

The ERG has further concerns over the algorithm of health state utilities which has been used by the manufacturer (details of which are set out in Table 18, p82 of the

submission). Due to censored data and missing end-dates for adverse events, the model has simply used the average duration for each event calculated across all patients. This has resulted in the possibility that, what the manufacturer considers to be, a conservative approach to the estimation of HRQoL might not actually be conservative. For example, if an individual experiences both Health State D (nausea and vomiting grade 3 or 4) and Health State F (acne/rash grade 3 or 4) they are assumed to have the utility of D for its average time of 14 days and then the utility of F only for the remainder of the treatment period. In contrast, if they only experience Health State F they would be given the utility for the state for longer than the treatment period as the average time spent in F is 72 days. Those patients experiencing states F and D in the cetuximab treatment arm (in which the acute treatment stage lasts 56 days) and who, during the post treatment period, achieved loco-regional control, would be assigned a health effect of 25.7 quality-adjusted days over the first 72 days. If the same individual only experienced adverse event state F, they would achieve a health effect of 16.5 quality-adjusted days over the same period. This shows a weakness with the approach as it would appear that a patient with less severe toxicity (i.e. one who only experienced a single adverse event) experiences a worse health effect. However, it is not clear in which direction this will bias the cost-effectiveness results.

The issue of censored / missing endpoints of adverse events could also result in bias if these are not missing / censored at random. The average time of an adverse event from the observed endpoint data will only provide an unbiased estimate if the data are missing / censored completely at random. This may not be the case, particularly with censored data, where the end-date of an adverse event is missing due to the adverse event extending beyond the monitoring period. If these adverse events are longer than the average length of those observed fully (i.e. where the end-point is observed), then the method used will underestimate the average length of adverse events and hence the health decrements, in terms of utility, that will be experienced. Given that there are more adverse events in the cetuximab plus radiotherapy arm of the trial (705) compared to the radiotherapy alone arm (678), it may be the case that the use of this average will bias the cost-effectiveness results in favour of cetuximab plus radiotherapy, although the extent of this bias is unclear.

5.5.4 Resource use and costs

Radiotherapy treatment resource use and costs

The total cost of radiotherapy is based on the type of radiotherapy regimen (once daily, twice daily or concomitant boost) and the actual number of fractions received. For costing, the resource use for patients was converted to the nearest similar health resource group (HRG) from the NHS Reference costs. The manufacturer sought advice from Dr Tova Prior to assign the patient population to the most appropriate HRGs. In particular, it was informed that patients would be required to be immobilised in a shell, meaning that the HRGs which contained "technical support" were the most appropriate. Full details of the HRGs used and the costs applied to radiotherapy are provided in Technical Appendix 1, Section 1.1 of the submission.

An estimation of the type and cost of radiotherapy administration was arrived at from the recommendation of the manufacturer's UK expert panel. The panel indicated that radiotherapy was always administered on an outpatient basis with individual administrations requiring only a small amount of time for the technical delivery of treatment. It was assumed that contact time with a specialist was once a week for approximately 15 minutes. Only one outpatient visit per week is included in the cost analysis. However, the courses of radiotherapy are daily, so it is not clear whether costing only one outpatient visit a week is appropriate. As both treatment arms receive radiotherapy, and hence the same cost, this should not affect the cost-effectiveness results.

Cetuximab acquisition and administration

The Bonner *et al* trial [2] recorded the doses of cetuximab administered to all patients in the cetuximab plus radiotherapy treatment arm. These doses were rounded up to the nearest 100mg (to allow for wastage through the non-reuse of vials), then multiplied by the acquisition cost of £136.50 (taken from the *British National Formulary*). It was assumed that cetuximab would be administered once per week over a period of one hour in an outpatient setting. Therefore, patients were assigned the full cost of a medical oncology outpatient visit in addition to the cost of the radiotherapy administration.

The manufacturer also mentions that, prior to the infusion of cetuximab, patients should receive premedication with antihistamine. These costs do not appear to have been included in the manufacturer's cost analysis. However, these costs are likely to be small and to make very little difference to total costs (for example, injectable

chlorphenamine maleate costs only £1.62 per 1ml amp of 10mg/ml, from the *British National Formulary*).

Adverse event treatment costs

Frequencies of adverse events of grade 3 or 4 were similar in both treatment groups (reported in 84.4% of patients in radiotherapy and in 90.4% patients in cetuximab plus radiotherapy) with the exception of acneiform rash which was more common in the cetuximab treatment arm.

Due to the large size of the adverse event dataset from the Bonner *et al* trial [2] (the dataset reported 8,207 separate events which comprised over 300 types of event by Coding System for Thesaurus of Adverse Reaction Terms (COSTART) definition), the manufacturer considered that costing all adverse events would be prohibitive. Therefore, following advice from Prof Chris Boshof, those events which were considered to be the most significant cost drivers with respect to a combination of frequency of occurrence and the resources required for their treatment have been identified. These identified adverse events are presented in Table 15, p74 of the submission. However, it must be noted that the identified events account for only approximately 64% of all adverse events reported and, if the other 36% are unevenly split between treatment groups (by either type or total number), then their exclusion could bias the results of the subsequent cost-effectiveness analysis, although the direction of any bias is unknown.

In Technical Appendix 3 of their submission, the manufacturer states that the risk of allergic reaction following intravenous drug infusion is higher with cetuximab, but that the adverse event has been excluded from the utility states as immediate treatment would be received, suggesting that such an event would be transitory and hence would not have any significant effect on HRQoL. However, such adverse events do not appear to have been included in the cost analysis either. One of the ERG's clinical advisors suggests serious adverse reactions are rare and, in the main, managed inexpensively.

The manufacturer has also assumed that mucositis, stomatatis and dysphagia can be grouped together, acne can be grouped with rash and nausea can be grouped with vomiting. This is justified, following advice by Chris Boshoff, on the basis that it is desirable to incorporate any simplifying assumptions that would not introduce bias

into the analysis. One of our clinical advisors agrees that these adverse events would be managed in a similar manner suggesting that this grouping is reasonable.

The costs were based on the expected cost of the average episode for each type of event and its severity grade rather than on the recorded duration of each event for each patient in the trial database. This was done due to missing / censored endpoints of adverse events. However, this will only provide an unbiased estimate if the data is missing / censored completely at random and this may not be the case, particularly with censored data where the end-date of an adverse event is missing due to the adverse event having extended beyond the monitoring period. If these adverse events are longer than the average length of those observed fully (i.e. where the endpoint is observed) then the method used will underestimate the average length of adverse events and hence the costs. As there were more adverse events in the cetuximab plus radiotherapy arm (705 compared to 678 in the radiotherapy arm) then this may bias the result in favour of cetuximab.

In Technical Appendix 1 Section 1.5 of the submission, the manufacturer describes the elimination of duplicated and overlapping events. This removal was undertaken if all of the following four criteria were satisfied: (i) the events were assigned to the same patient; (ii) the events had the same COSTART term; (iii) the events had the same toxicity grade; and (iv) the events had overlapping or matching onset dates. The removal of duplicated terms seems perfectly reasonable as it would be inappropriate to double-count costs for treatment of one event. However, the removal of overlapping events is a cause for concern. It would seem more appropriate for the two overlapping events to be counted as one with the earliest start point and latest endpoint used. If this has not been done then the estimates for the expected length of event (based on the average length of event) would be shorter than the actual expected length of event and thus costs will be artificially low. As there were more events in the cetuximab plus radiotherapy arm, then this would appear to bias the result in favour of cetuximab plus radiotherapy.

The treatment costs for the selected adverse events were then estimated by the UK expert panel based on medication costs and appropriate HRGs.

Routine monitoring

Costs of routine monitoring of patients performed by a specialist post treatment are included in the economic model. As information on such monitoring was not

available from the Bonner *et al* trial [2], estimates were made based on the recommendations of the manufacturer's UK expert panel. The panel indicated that routine monitoring may continue until the 4th year after cessation of treatment.

Salvage / palliative care

Following disease progression, patients receive palliative or salvage therapy. Data on resource use for this care were recorded in the Bonner *et al* trial [2] based on the type of therapy. Unit costs were then sourced from these to arrive at estimates of the cost of these therapies (these estimates were the expected cost for each patient, based on the proportion of patients in the arm in the dataset who received the specific therapy). Further information on these is provided in Technical Appendix 1-Table 9 of their submission. However, the data provided in the trial on these types of care is limited due to the truncated follow up – that is, some individuals would have received these types of care further into the future. Therefore, the costs for salvage / palliative care for both the radiotherapy and the cetuximab plus radiotherapy arms will be under estimated.

The costs for salvage / palliative care are applied at the point of progression. This may be an inappropriate method as it seems reasonable to assume that these costs would be spread over the whole period that the individual spends in the progressive disease state. By applying the costs at the beginning of this period, it will tend to overestimate cost as these will not be discounted appropriately.

5.6 Consistency

5.6.1 Internal consistency

Random checking has been carried out on formulae in the electronic model provided with the manufacturer's submission. The macros used for the sampling simulation and the creation of the cost-effectiveness acceptability curve have also been checked. A comprehensive checking process against all cells in the model has not been undertaken by the ERG given time and resource limits.

It was not possible to reproduce the calculation of the proportional hazard applied to the life table survival probabilities from the information provided by the manufacturer in the submission. The description of how the figure of 0.0167 for the mean hazard among patients with LA SCCHN was obtained from the published meta-analysis appears reasonable. No description was provided of how the corresponding figure of 0.004188 was calculated from the life tables. Attempts to calculate this figure from

the life tables were unsuccessful. However the manufacturer clarified this in the addendum "SCCHN NICE STA response letter for comments 26th September 2006". They stated that "For the general UK population, the average hazard of death was obtained by pooling the yearly hazard (death rate) of time intervals from 67 years upwards using an inverse-variance of the death rate estimate for each year as a weight". The ERG has not had time to replicate this approach but the explanation seems reasonable.

It was possible to re-run the survival models in STATA to calculate the probability of survival from both the cure model and the other parametric models evaluated by the manufacturer. The use of a random uniform probability in the single imputation procedure is not explained. However, the use of a random uniform probability prevents accurate re-estimation of the imputed survival as the imputed times are, therefore, themselves random.

5.6.2 External consistency

As the Bonner *et al* trial [2] is the pivotal published trial comparing cetuximab plus radiotherapy and radiotherapy alone and it is individual patient data from this trial that are used directly in the model, the ERG is unable to validate the external consistency of the model with other sources. Discussion of the consistency of this trial with previous clinical evidence can be found in Chapter 4 and Appendix 3.

With regards to the cost analysis, the estimates for the costs of the courses of radiotherapy, cetuximab etc. appear reasonable. In terms of HRQoL, the ERG has not been able to identify other studies in order to validate the utility values applied in the model.

5.7 Results

5.7.1 Summary

The results of the model are presented in the manufacturer's submission from p96 to 105. In particular, it is worth noting that the submission includes: (i) the base-case results showing ICERs of £6,930 per additional QALY for cetuximab plus radiotherapy vs radiotherapy alone; (ii) results from the stochastic sensitivity analyses (Table 24 and Figures 7 and 8, p101-2); and (iii) results from the one-way sensitivity analyses conducted in the company's submission (details of which can be found from p102-4 and results on Table 25, p103).

5.7.2 Base-case analysis

The costs and QALYs from the base-case are presented in Tables 5.6 and 5.7 respectively. Table 5.8 contains the incremental costs and QALYs and the resulting incremental cost-effectiveness ratio.

Table 5.6 Average costs associated with each phase per patient

Regimen	Acute phase	Locoregional control	Progressive disease	Expected total
Radiotherapy	£4,434.88	£1,628.76	£1,131.34	**£7,194.99**
Cetuximab plus radiotherapy	£10,875.07	£1,867.58	£1,077.89	**£13,820.55**

Table 5.7 Average QALYs associated with each phase per patient

Regimen	Acute phase	Locoregional control	Progressive disease	Expected total
Radiotherapy	0.0366	2.6253	0.1543	2.8163
Cetuximab plus radiotherapy	0.0333	3.7118	0.1082	3.8532

Table 5.8 Incremental cost per quality adjusted life year

	Incremental Cost	Incremental QALY	Incremental cost per QALY
Cetuximab plus radiotherapy vs radiotherapy alone	£6,626	1.26	£6,390

In the base-case analysis, treatment with cetuximab plus radiotherapy instead of radiotherapy alone increased costs by approximately £6,626 and QALYs by 1.6 per patient, giving an ICER of £6,390 per additional QALY.

5.7.3 Sensitivity analyses

The results of the one-way sensitivity analysis contained in the manufacturer's submission are presented in Table 5.9. In summary, the ICERs are largely unaffected by the majority of these analyses. An interesting result is that, if no extrapolation is undertaken (i.e. the time horizon is reduced from a lifetime to simply the period of the

trial follow-up), the ICER increases to £19,951. Progression free and overall survival were significantly higher in the cetuximab plus radiotherapy arm than radiotherapy alone arm, so using no extrapolation could be considered to be a conservative estimate of the cost-effectiveness of cetuximab plus radiotherapy. This sensitivity analysis demonstrates that cetuximab plus radiotherapy could still be considered cost-effective (with a cost per QALY of less than £20,000) with no extrapolation.

Table 5.9 One-way sensitivity analysis

Sensitivity analysis	Description of sensitivity analysis and variable(s) tested	Values used in sensitivity analysis	ICER (£/QALY)	Change (£/QALY)
	Base case result		6389.71	
A	No discounting	0% (costs), 0% (outcomes)	4905.20	-1484.51
B	Outcomes not discounted	3.5% (costs), 0% (outcomes)	4858.95	-1530.76
C	Decrease discount rate to 2.5%	2.5 (costs), 2.5% (outcomes)	5936.62	-453.09
D	Increase discount rate to 5%	5% (costs), 5% (outcomes)	7109.71	720.01
E	Increase discount rate to 10%	10% (costs), 10% (outcomes)	9821.80	3432.09
F	Remove radiotherapy administration cost	No specialist visits allocated to RT admin	6386.64	-3.06
G	Double cost of mucositis treatment	£189.45 (grade 2), £614.36 (3), £6,071.39 (4)	6424.77	35.07
H	Halve cost of mucositis treatment	£47.36 (grade 2), £153.59 (3), £1,517.85 (4)	6372.17	-17.53
I	Double cost of nausea & vomiting treatment	£161.35 (grade 2), £666.59 (3), £2,198.12 (4)	6382.12	-7.58
J	Halve cost of nausea & vomiting treatment	£40.34 (grade 2), £166.65 (3), £549.53 (4)	6393.50	3.79
K	Set all acute health state utilities as general in-treatment	0.659 (health states B, C, D, E, F & G)	6380.20	-9.51
L	Set all acute health state utilities to worst acute utility	0.062 (health states B, C, D, E, F & G)	6369.91	-19.79
M	Set length of event to 10 days for health state B	10 days (health state B)	6377.43	-12.28
N	Set length of event to 20 days for health state B	20 days (health state B)	6377.62	-12.08
O	Set length of event to 10 days for health states B & D	10 days (health state B), 10 days (health state D)	6377.47	-12.24
P	Set length of event to 20 days for health states B & D	20 days (health state B), 20 days (health state D)	6377.55	-12.16

Sensitivity analysis	Description of sensitivity analysis and variable(s) tested	Values used in sensitivity analysis	ICER (£/QALY)	Change (£/QALY)
Q	Set length of event to 10 days for all acute health states	10 days (health states B, C, D, E, F & G)	6382.34	-7.37
R	Set length of event to 20 days for all acute health states	20 days (health states B, C, D, E, F & G)	6381.57	-8.14
S	Halve increment between locoregional control and progressive disease utility	0.67875 (health state J), 0.31225 (health state K)	8948.74	2559.04
T	Equalise locoregional control and progressive disease utilities to the average	0.4955 (health state J & K)	14926.76	8537.05
U	Analysis Timeframe: No imputation	Use unextrapolated trial data.	19950.99	13561.28
V	Analysis Timeframe: 10 years	Cap economic analysis after 10 years.	9207.51	2817.80
X	Survival analysis: Weibull model	Use Weibull model to extrapolate trial survival	5868.18	-521.52

5.7.4 Stochastic sensitivity analysis

A summary of results from the stochastic sensitivity analysis using a bootstrap approach is presented in Table 5.10. It is worth noting that these results are based on bootstrapping from the individual patient data under the base case assumptions (e.g. extrapolation by cure model).

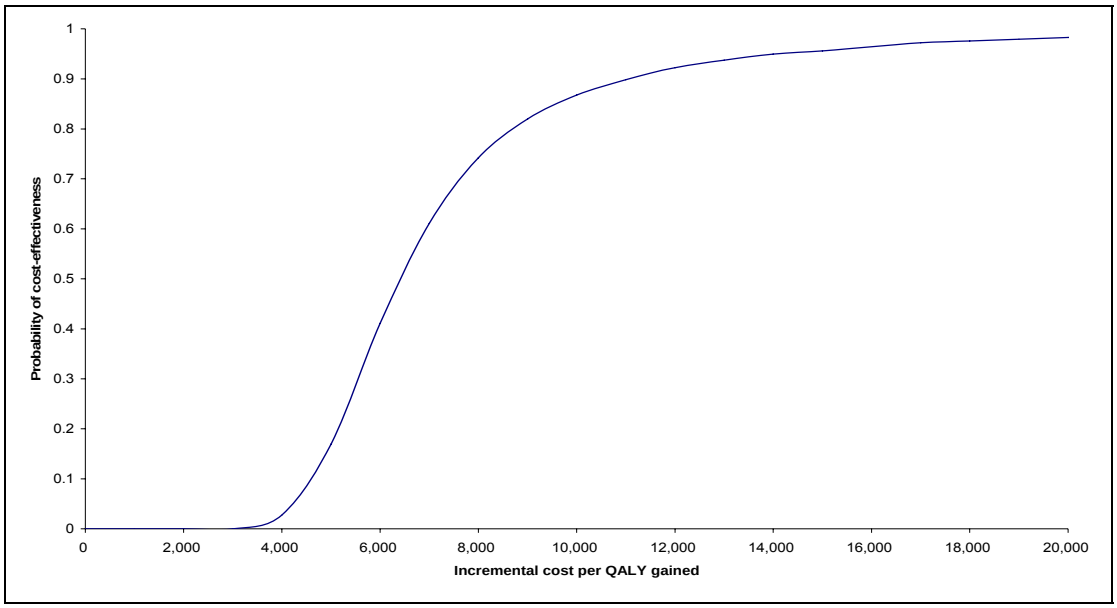
Table 5.10 Bootstrap summary

	Cost (£)	**QALYs**
Radiotherapy alone	7,046.20	3.2693
Cetuximab plus radiotherapy	13,697.51	4.42916
Incremental	6,651.31	1.15986
Standard error of incremental values		
95% Bias-Corrected Lower Confidence Limit	6,155.11	0.23
95% Bias-Corrected Upper Confidence Limit	6,973.75	1.65246

The central estimate for the ICER of cetuximab plus radiotherapy vs radiotherapy alone from the stochastic sensitivity analysis is lower than under the base-case (£5,375 vs £6,390) suggesting cetuximab plus radiotherapy to be more cost-effective than under the deterministic model.

The cost-effectiveness acceptability curve for cetuximab plus radiotherapy vs radiotherapy alone is presented in Figure 5.2 below.

Figure 5.2 Cost-effectiveness acceptability curve



5.8 Summary of uncertainties and issues

In general, the ERG considered the manufacturer's economic submission to be of good quality. The approach undertaken was considered appropriate for the decision problem. Sensitivity analysis performed by the manufacturer was deemed generally appropriate by the ERG. The manufacturer's submission contains a good description of the data sources and justification for the assumptions used. An electronic copy of the model was provided, which allowed a more detailed assessment of the approaches undertaken to estimate the cost-effectiveness of cetuximab plus radiotherapy versus radiotherapy alone for the treatment of patients with LA SCCHN. However, there are a number of uncertainties and issues, and these may bias the model results; these are summarised in Table 5.11.

Table 5.11 Summary of uncertainties and issues with the manufacturer's cost-effectiveness analysis identified by the ERG

Uncertainty or issue	Details	Available sensitivity analysis	Likely influence on results of model
Decision problem			
The data in the model includes trial data which does not match the defined population in the decision problem.	The manufacturer's proposed population is those patients with LA SCCHN who are considered inappropriate for chemoradiotherapy. However, the Bonner *et al* trial's inclusion criteria were not limited to these patients. (see Chapter 4 and Appendix 3).	The ERG requested sub-group analysis based on those in the proposed population but the manufacturer responded that such a group was too small and hence such analyses would be inappropriate.	Uncertain

Extrapolation			
Use of male life-expectancy will underestimate expected survival in general population.	Manufacturer stated in original submission that male life-expectancy had been used to calculate the proportional hazard for cured patients. This would underestimate the expected survival in the general population and lead to an overestimate of the proportional hazard of death for those patients who have experienced LA SCCHN. (Note- the ERG is unsure which life tables have been used to calculate expected survival in general population)	The ERG is unable to provide any sensitivity analysis to examine this issue.	If male life-expectancy was actually used the ERG anticipates that this would bias results against cetuximab plus radiotherapy as a greater percentage of individuals treated with that combination were cured at the end of the trial. The extent of bias is likely to be small. The ICER without extrapolation was less than £20,000 so assumptions relating to extrapolation are unlikely to be important.

Exclusion of a multivariate approach to modelling survival following censoring.	The approach undertaken within the model assumes that nothing is known about the probability of each patient surviving beyond the observed censored time. Multivariate approaches to extrapolation could have been used incorporating effects of extrapolation etc.	The ERG is unable to provide any sensitivity analysis to examine this issue.	If the treatment effect of cetuximab differs according to covariates then the results may be biased.
The choice of distribution for the cure model was not conservative.	The manufacturers chose to use the log-normal distribution for the cure model, as it resulted in the lowest cure fraction compared to the Weibull, logistic, gamma or exponential. While this is true, it also resulted in the biggest difference in cure fraction between the treatment groups (11.7% in favour of cetuximab plus radiotherapy) compared to the alternative distributions (smallest difference 8.4%)	The ERG is unable to provide any sensitivity analysis to examine this issue.	The ICER without extrapolation was less than £20,000 so assumptions relating to extrapolation are unlikely to be important.

Health-related quality of life			
Possible inappropriate adverse events considered for HRQoL study.	The HRQoL study identifies adverse events that differ in prevalence between treatment with cetuximab plus radiotherapy and cisplatin plus radiotherapy. However, as the economic evaluation conducted compares cetuximab plus radiotherapy and radiotherapy alone it would have been more appropriate to identify the adverse events which differ in prevalence between these two treatments.	See Section 6.2	Uncertain
No HRQoL interactions between health states were considered.	The health states were selected to reflect increases in severity in one side effect at a time rather than a combination of side effects.	See Section 6.2	Uncertain
Approach to HRQoL can lead to one adverse event being worse for health than two.	The use of average length of time for worst event and then a maximum of only the rest of the treatment period for another adverse event can result in a worse HRQoL with one event than with two which is counterintuitive.	See Section 6.2	Uncertain

HRQoL and costs				
Censored / missing endpoints may be informative.	If censored / missing endpoints are informative then the use of average durations for adverse events based on fully observed events is inappropriate and will bias the analysis in terms of both costs and HRQoL.	See Section 6.2 and 6.3	Uncertain direction, likely to be small.	
Exclusion of post treatment adverse event states.	States representing peripheral neuropathy and ototoxicity have been excluded from the analysis despite being identified in the HRQoL study.	See section 6.2 and 6.3	Uncertain direction, likely to be small.	
Possible inappropriate method of removal of overlapping adverse events.	The manufacturer has removed adverse events of same type and grade if they overlap one another. However, it is not clear if they have taken the latest end date of the two which would be most appropriate.	See section 6.2 and 6.3	Uncertain direction, likely to be small.	
Resource use and costing				
Exclusion of PSS costs.	The analysis has not taken account of costs relating to PSS.	See Section 6.3	Likely to bias results in favour of radiotherapy alone. The extent of bias is likely to be small.	

Exclusion of pre-medication costs.	The costs of pre-medication with an antihistamine for the cetuximab patients appears to be excluded.	See Section 6.3	Exclusion of such costs would bias results in favour of cetuximab plus radiotherapy. But the extent of bias is expected to be small.
Salvage / Palliative care costs / resources underestimated.	Salvage / Palliative care costs are based on average observed in trial but, as trial follow up is truncated, many patients will not have required it during the trial and, therefore, costs / resources will not represent average required.	See Section 6.3	Bias will favour radiotherapy alone arm as these individuals experience progression earlier on average and hence the present value of any underestimation will be higher. The extent of bias is not clear.

Chapter 6

Additional work to be undertaken by ERG

The ERG has undertaken additional work to address several of the issues and uncertainties identified during the structured critique of the manufacturer's submission in the previous chapter. This additional work has been undertaken to examine the potential robustness of the base-case results to several of the assumptions made in the manufacturer's cost-effectiveness analysis. There were areas of uncertainty that the ERG could not further analyse and these will also be discussed.

6.1 Decision problem

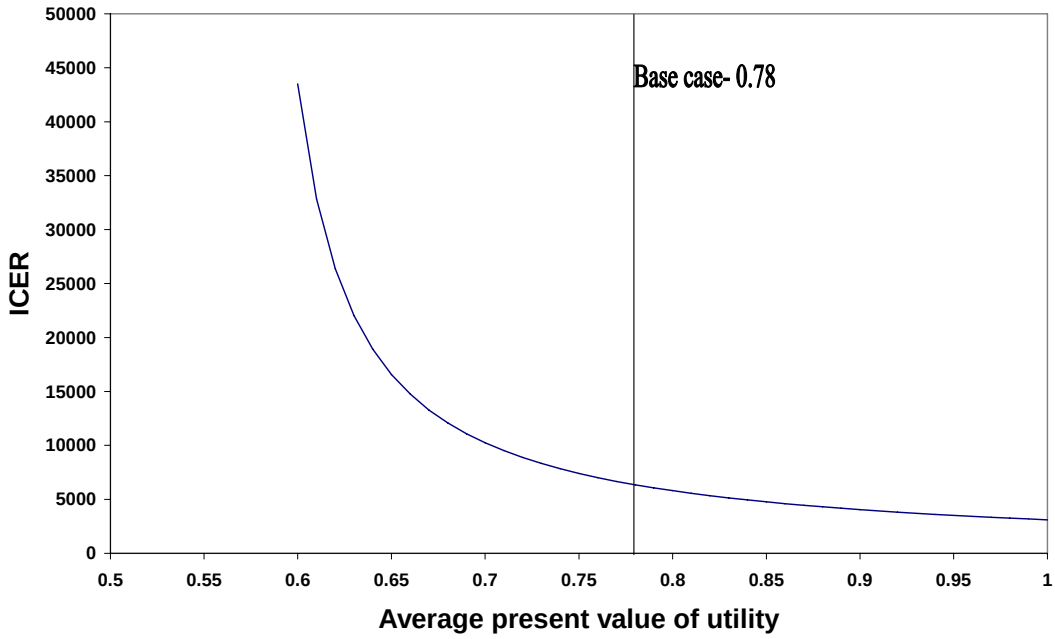
As discussed previously, the ERG requested sub-group analyses to be performed on those individuals in the trial who would be considered inappropriate for chemoradiotherapy and would thus be part of the proposed population. However, the manufacturer stated that this group would be too small on which to perform sub-group analysis. The ERG is unable to do anything to resolve this uncertainty further, and is also unable to provide any suggestion of what, if any, bias the use of this wider group of patients may introduce.

6.2 Health-related quality of life

The summary table in Chapter 5 highlights some of the issues that the ERG identified with the HRQoL study and inputs for the model. As no other sources for utility values for LA SCCHN patients were identified and the restructuring of the model to allow for hypothetical adverse event interactions (e.g. multiplicative or additive) is beyond the scope of the ERG report, the ERG has undertaken a simple sensitivity analysis to examine the robustness of the results. This has been achieved by examining what change in the average utility value for patients in the cetuximab plus radiotherapy arm would be required to increase the incremental cost per QALY gained of cetuximab plus radiotherapy to levels which may not be considered cost-effective. The base-case average utility in the two groups has been identified by dividing the estimated QALYs in each group by the estimated life-years. It should be noted that this ignores discounting, so the results are approximate. These results are presented in Figure 6.1

below.

Figure 6.1 Average utility with cetuximab plus radiotherapy arm and its impact on the incremental cost per QALY gained for the combination therapy. The average utility with radiotherapy alone remains at 0.69.



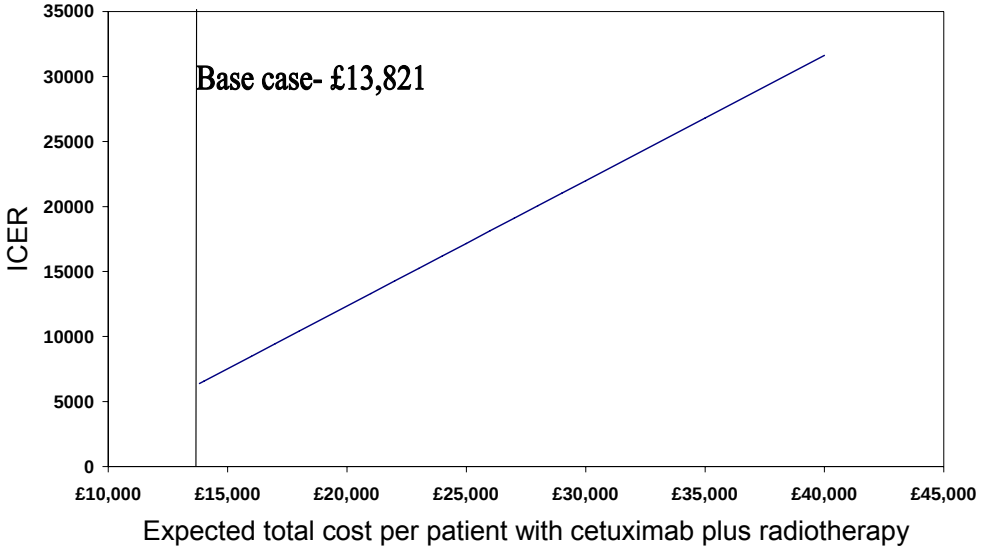
As Figure 6.1 shows, it would require a large decrease in the average utility of a patient treated with cetuximab plus radiotherapy, *ceteris paribus,* for the drug not to be considered cost-effective (e.g. it requires a decrease in average utility of larger than 0.17 for cetuximab plus radiotherapy not to be considered cost-effective at a threshold value of £30,000 per QALY gained). The average utility in the radiotherapy alone group is fixed at the base-case value of 0.69. This suggests that any biases caused by the issues identified by the ERG in relation to HRQoL estimation would have to be very large and in favour of cetuximab plus radiotherapy to have a material effect on the conclusions on the cost-effectiveness analysis.

6.3 Resource use and costing

The ERG identified several issues and uncertainties with the approach taken to estimate resource use and costs in the manufacturer's submission. More details of these can be found in Section 5.5.4 as well as in Table 5.11 in Section 5.8. As with the HRQoL, the ERG has been unable to identify any other sources to help examine the concerns raised and is unable to restructure the model as it is beyond the scope of the ERG report. However, as with the HRQoL additional analyses, the ERG has carried

out a simple sensitivity analysis examining what change in total average costs for the cetuximab plus radiotherapy arm would be required, *ceteris paribus*, for cetuximab plus radiotherapy not to be considered cost-effective. The mean cost per patient in the radiotherapy group alone remains fixed at £7,195. Again, the analysis ignores discounting, so the results are approximate. These results are presented in Figure 6.2 below.

Figure 6.2 Average total cost with cetuximab plus radiotherapy and its impact on the incremental cost per QALY gained for the combination therapy. The average cost with radiotherapy alone remains at £7,195.



The figure shows that it would require large increases in average total costs per patient in the cetuximab plus radiotherapy arm, *ceteris paribus*, for cetuximab plus radiotherapy not to be considered cost-effective (e.g. it would take nearly a three-fold increase in average total cost, from £13,800 to £40,000, for cetuximab plus radiotherapy not to be considered cost-effective at a threshold of £30,000 per QALY gained). The results of this basic sensitivity analysis suggest that any biases resulting from the costing and resource use issues identified by the ERG would have to be very large and in favour of cetuximab plus radiotherapy to have a material effect on the conclusions of the cost-effectiveness analysis.

Chapter 7
Discussion and conclusions

7.1 Summary of clinical effectiveness issues

The manufacturer's submission was considered to comprise the most relevant clinical effectiveness evidence for the purpose of this STA. Only one study [2], the basis upon which the licence for use in LA SCCHN was granted, was included. More trial data would have been useful to assess radiotherapy plus cetuximab but, unfortunately, no other trials relevant to the decision problem are available.

The pivotal study, which is fully published and was of good quality, compared the durations of locoregional control (the primary endpoint), overall survival and progression-free survival, and the overall response rates in patients with LA SCCHN who were treated with high-dose radiotherapy alone or in combination with cetuximab. For all these endpoints, radiotherapy plus cetuximab was significantly superior to radiotherapy alone. Comparative safety was also assessed. Cetuximab did not exacerbate the common toxic effects associated with radiotherapy of the head and neck, including mucositis, xerostomia, grade 3 – 5 weight loss, and performance status deterioration. The only differences among the severe (grade 3 - 5) adverse effects experienced by the two groups were: acneiform rash, which is a very common side effect of cetuximab (skin reactions may develop in > 80% of patients and mainly present as acne-like rash) [14] and infusion reaction occurred more frequently with radiotherapy plus cetuximab than radiotherapy, whereas the converse applied to anaemia.

Although the pivotal trial results for the primary endpoint appear robust, the ERG felt that there are two main areas of uncertainty with respect to the decision problem considered in the submission. The pivotal trial population included a high proportion of patients who would have been suitable for radiotherapy and, therefore, do not match the population advocated in the decision problem, i.e. patients who are considered inappropriate for chemoradiotherapy. In current UK practice, once daily radiotherapy is given to the majority of patients with head and neck cancer, whereas in the trial, the majority of patients received altered-fractionation radiotherapy (concomitant boost or twice daily). In the light of these differences, it is not clear how applicable to the UK population the trial results are.

7.2 Summary of cost-effectiveness issues

No previous studies were identified which would help inform this STA. Therefore, the manufacturer's economic evaluation is considered by the ERG to comprise the only relevant evidence to consider for the purposes of this STA.

The manufacturer's submission included a *de-novo* economic evaluation to estimate the cost-effectiveness of treatment with (i) cetuximab plus radiotherapy and (ii) radiotherapy alone. The economic model (including the comparator) was considered appropriate for the decision problem. The results from the manufacturers demonstrated that cetuximab plus radiotherapy was cost-effective compared to radiotherapy alone under a broad range of different assumptions assuming a threshold of £20,000 per QALY gained.

The ERG identified a number of potential issues related to the manufacturer's economic submission. Perhaps the most important of these is common with the clinical review: the fact that the only randomised trial informing the economic analysis does not match the patient population which is the focus of the manufacturer's decision problem and which is reflected in their model. In addition, a series of issues relating to the analysis of extrapolation, HRQoL and resource use/costs were identified. To the extent that the methods used were inappropriate, these may introduce basis to the results. The ERG was unable to conclude, in the majority of cases, in which way direction any bias would affect the results. Following additional analysis by the ERG (see Chapter 6) it was concluded that any biases would have to be very large to have a material effect on the conclusions of the manufacturer's cost-effectiveness analysis.

7.3 Implications for future research

From the clinical perspective, there are areas where future research would be helpful to establish which patients are likely to derive most benefit from cetuximab in conjunction with radiotherapy to enable therapy to be targeted most appropriately. For example, trials designed to establish whether treatment efficacy varies according to LA SCCHN tumour site and with radiotherapy regimen, and whether tumour EGFR expression levels affect responses to radiotherapy plus cetuximab would be useful.

One of the clinical experts consulted by the ERG suggested that setting up a patient register to collect post-treatment observational data of patients treated with cetuximab would be useful.

Although the majority of the issues identified by the ERG could be clarified by additional research, it is worth stressing that it would require large changes in parameter values to result in cetuximab plus radiotherapy not being cost-effective. Although no formal value of information analysis (VOI) [36] has been undertaken by the manufacturer or the ERG, this may suggest the VOI would be low and hence further research would not be a priority. The most important issue relates to the appropriateness of the use of the Bonner *et al* trial [2]for the patient population of interest. Further evidence on the clinical-effectiveness of cetuximab plus radiotherapy in those patients with locally advanced SCCHN who are considered inappropriate for chemoradiotherapy would help to clarify the results of the submitted economic evaluation. In addition to this a more comprehensive HRQoL study, for example one which considers interactions between adverse events, would also help to improve the accuracy of the cost-effectiveness estimates.

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Appendix 1 Critique of the manufacturer's search strategy

Point 28 requires a description of the search strategy employed to retrieve relevant published and unpublished trials, quote "Describe the strategies used to retrieve relevant clinical data both from the published literature and from unpublished data held by the company. The methods used should be justified with reference to the decision problem. Sufficient details should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided."

The details provided by the company are inadequate. There is no indication as to whether their searches included the wider treatment of locally advanced SCCHN or whether they focused only on cetuximab. As the only comparator treatment identified by the company is radiotherapy it may be appropriate to search beyond the technology and include literature pertaining to the effectiveness of radiotherapy compared to other treatments for example chemotherapy or chemo-radiotherapy.

Point 29 specifies the minimum set of databases that should be interrogated for a literature search (Medline, Embase, Medline (R) In-Process, and the Cochrane Library).

The company's response does not specifically indicate whether the Medline In-Process database was searched, although subsequent comment indicates that it was. Additionally the ASCO website was searched.

Points 30 and 31 require details of the date of any searches; these are adequately described. All searches were conducted over the period 1993 to date, except the ASCO search which had a cut-off of 1995. The reason for a 1993 cut-off date is not stated but is assumed to relate to the discovery of cetuximab. Further, the cut-off dates are not identified as relating to the date of publication or the date of indexation within the database.

Point 32 requires details of the complete search strategies used. These are described with the omission of some minor but potentially significant points. For example, where indexed search terms have been used there is no indication as to whether the terms were 'exploded', i.e. whether the searches also included all of the terms below that searched in the hierarchical index, and Embase appears to have

been searched using free text for cetuximab and Erbitux, whereas these are indexed terms. The restrictions applied (English language, clinical trials, relating to humans) seem logical and fair. Reference is made to a search of the Embase Alert database which was not specifically referred to previously. Reference is also made to exclusion and inclusion criteria described subsequently; some of these are not suitable for searches of unpublished data, for example the inclusion relating to published papers or abstracts.

Point 33 requires details of any additional searches that were carried out. Reference is made to searches of two company databases without the details of the searches, for example search terms and restrictions applied.

Point 34 requires details of the inclusion and exclusion criteria. These seem logical and fair although the restriction applying to randomised controlled trials could reasonably have been omitted due to a general paucity of data concerning the specific decision problem.

Point 35 requires details concerning the data abstraction strategy. This is adequately described with reference to earlier points although no details are provided concerning the criteria used when manually eliminating trials that were deemed not relevant to the search, neither is it stated how many personnel were involved in the manual filtering of trials and whether a decision to eliminate a trial was peer reviewed.

Appendix 2 Search strategy undertaken by ERG for cetuximab STA for the clinical effectiveness literature review

Database: Medline 1950 to date (MEZZ)

Host: Dialog DataStar

Access: via NHS trust internet

Date search performed: 18th August 2006

Search strategy:

#1.	Search "Head-and-neck-neoplasms" as an exploded term	170502
#2.	Search "erbitux OR cetuximab" as text terms	565
#3.	Search "1 AND 2"	65
#4.	Search "3" with restrictions (clinical-trials# OR clinical-trial OR controlled-clinical-trial OR multicenter-study OR randomized-controlled-trial) AND (language = English) AND (human = Yes)	28

Database: Embase 1974 to date (EMZZ)

Host: Dialog DataStar

Access: via NHS trust internet

Date search performed: 18th August 2006

Search strategy:

#1.	Search "cetuximab" as an indexed term	2133
#2.	Search "cetuximab" as a text term	2147
#3.	Search "erbitux" as a text term	774
#4.	Search "Head-and-neck-tumour" as an exploded term	84963
#5.	Search "1 OR 2 OR 3"	2153
#6.	Search "4 AND 5"	242
#7.	Search "6" with restrictions (clinical-trial#) AND (language = English) AND (human = Yes)	177
#8.	Search "review = Yes"	811282
#9.	Search "7 NOT 8"	80

Database: Medline (R) In-Process

Host: Ovid

Access: via Newcastle University library internet website

Date search performed: 23rd August 2006

Search strategy:

#1.	Search “cetuximab OR erbitux” as text terms	54
#2.	Search “1 NOT colon NOT colorectal” as text terms	26

Database: Cochrane Database of Systematic Reviews

Host: Wiley InterScience

Access: via National Electronic Library for Health internet website

Date search performed: 24th August 2006

Search strategy:

#1.	Search “cetuximab OR erbitux” as text terms	2

The following databases were searched for current/ongoing research: Cancer research UK, National Cancer Research Network, Current Controlled Trials register (searched across multiple registers, including, ISRCTN, MRC NHS, and the National Institutes of Health registers), proceedings of the American Society for Clinical Oncology, National Research Register, National Cancer Institute and Scirus, using the free text term ‘Head & Neck’

Appendix 3 Structured critical appraisal of Bonner et al 2006[2]

CRITICAL APPRAISAL

Name of Trial: Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck

Reference: Bonner J A, Harari P M, Giralt J et al. N Engl J Med 2006; 354:567-78

Question: Is radiotherapy plus cetuximab (RT+C) more effective than radiotherapy (RT) alone in patients with locoregionally advanced head and neck cancer?

Summary: The median duration of locoregional control (the primary endpoint) with RT+C (24.4 months) was significantly longer (by 9.5 months) than that with RT alone (14.9 months) in patients with locoregionally advanced head and neck cancer, who had high performance status (nearly 90% of both groups had a Karnofsky performance score ≥ 80, and patients with a score < 60 were ineligible). With respect to secondary endpoints, the median duration of progression-free survival was significantly longer with RT+C than RT (17.1 vs. 12.4 months), as was overall survival (49.0 vs. 29.3 months). The best overall response rate during the first year was also significantly better with RT+C (74%) than RT (64%). The severe (grade 3 – 5) side effects experienced with the two regimens differed significantly only with respect to acneiform rash and infusion reaction, which occurred more frequently in the RT+C than the RT group, and anaemia, which occurred more frequently in the RT than the RT+C group. C did not exacerbate the common toxic effects associated with radiotherapy of the head and neck.

Did the study ask a clearly focussed question?

Yes – This trial was designed to compare the effectiveness of high-dose radiotherapy (RT) alone with high-dose RT plus cetuximab (RT+C) in patients with locoregionally advanced head and neck cancer. The population studied, interventions given and outcomes considered are clearly stated.

Was the study design appropriate?

Yes – A randomised controlled trial (RCT) design was appropriate, as this trial (a phase 3, multinational RCT) compared RT+C with a control, i.e. RT alone.
Eligible patients had stage III or IV, non-metastatic, measurable squamous-cell carcinoma of the oropharynx, hypopharynx or larynx. Patients had to be medically suitable for definitive RT, have a Karnofsky performance score ≥ 60 and normal haematopoietic, hepatic and renal function. Patients who had previously had cancer, received chemotherapy within the preceding three years, undergone surgery or previously received RT for head and neck cancer were ineligible.

The interventions given were a 7- to 8-week RT regimen alone or RT+C. The investigators were required to select one of three RT regimens, either once-daily fractionation (26%), twice-daily fractionation (18%) or concomitant boost radiotherapy (56%), before a patient registered. The RT+C group received C 400 mg/m^2 body-surface area intravenously (iv) as a loading dose over 120 min one week before RT, followed by weekly 60-min iv infusions of 250 mg/m^2 for the duration of RT. Patients assigned to C were given a test dose of 20 mg over 10 min and observed for 30 min, and if they experienced grade 3 or 4 hypersensitivity reactions, C was discontinued. C was not delayed if patients experienced RT-related toxic effects, nor was RT delayed due to C-related toxic effects. Patients who received C were premedicated with an iv histamine H_1-receptor antagonist (50 mg diphenhydramine or equivalent).

The primary endpoint was duration of locoregional control (LRC), defined as the absence of progression of locoregional disease at the scheduled follow-up visits. Secondary endpoints included: overall survival (OS), calculated from the time of randomisation until death due to any cause; progression-free survival (PFS), i.e. time from the day of randomisation until first documented progression (locoregional or distant) or until death due to any cause; overall response rate (ORR), i.e. complete plus partial responses (the best overall response was derived from investigators' assessments of response during the first year) and safety.

Were participants appropriately allocated to intervention and control groups?

Probably – Patients were stratified according to their Karnofsky performance status (60 to 80 vs. 90 to 100; the higher the number, the better the performance), nodal involvement (N0 vs. N+), tumour stage (T1 to T3 vs. T4) and radiation-fractionation regimen (concomitant boost vs. once daily vs. twice daily), and randomised by a minimisation method to receive RT or RT+C. The authors do not state who carried out the randomisation, where it was done or how the randomisation schedule was generated. The treatment groups were well balanced with respect to their demographic and tumour-related characteristics. There were no significant differences between the groups at entry (calculated using Fisher's exact test).

Were participants, staff and study personnel 'blind' to participants study group?

No – In view of the obvious differences between the RT and RT+C regimens, blinding was not possible. However, the investigator-generated data were submitted for blinded review by an independent committee of experts. This committee determined the dates of a first documented locoregional progression or recurrence, distant metastasis or second primary tumour. As the outcome criteria were clearly defined, observer bias is unlikely for these outcomes.

Were all of the participants who entered into the trial accounted for at its conclusion?

Yes – All randomised patients (including four who received no treatment) were included in the efficacy analyses, which were performed on an intention-to-treat (ITT) basis. The four untreated patients were not included in the safety analysis. There was no loss to follow-up. The median and mean RT doses did not differ between the two groups, and compliance with therapy was balanced. The use of salvage surgery and subsequent chemotherapy was also balanced between the treatment groups. In total, 208 patients were treated with C, 90% of whom received all planned doses (median of eight).

Were the participants in all groups followed up and data collected in the same way?

Yes – History taking, physical examination, and monitoring of adverse events and routine haematology and chemical variables were performed weekly during RT. Disease assessments were performed at weeks 4 and 8 after RT, every four months thereafter for two years, and then semi-annually during years 3, 4 and 5. Acute toxic effects were assessed up to the eighth week after treatment and late radiation effects were assessed thereafter.

Was the study large enough?

Yes – According to historical data, patients treated with RT alone were expected to have a LRC rate of 44% at one year, and the one-year LRC rate with RT+C was hypothesised to be ≥ 57%. The authors assumed a constant hazard rate with a uniform accrual rate for 18 months and additional follow-up of 12 months. They calculated that 208 patients per treatment group would provide 90% power to detect a difference in the LRC duration at the 5% level with the use of a 2-sided log-rank test. Efficacy evaluations were performed on an ITT basis; 213 patients were randomly assigned to RT and 211 to RT+C. The distribution of time-to-event variables was estimated by the Kaplan-Meier method, treatment effects were compared by means of a stratified log-rank test, and the 3-year rates were compared with the use of a Z-test. The Cox regression method was used to estimate the hazard ratio (HR), and the Cochran-Mantel-Haenszl test was used to compare the response rates of the groups.

How are the results presented and what is the main result?

The LRC, OS and PFS results are presented as median durations with a HR, 95% confidence interval (CI) and a p value. The ORR results are presented as percentages with an odds ratio (OR), 95% CI and a p value.

LRC (primary endpoint): The estimated median duration of LRC was significantly longer in the RT+C group (24.4 months) than the RT group (14.9 months). The HR for locoregional progression or death was 0.68 (95% CI 0.52 to 0.89; p = 0.005), which equates to a relative reduction in the risk of locoregional progression of 32% in favour of RT+C. The 3-year rates of LRC achieved were 47% with RT+C and 34% with RT (p < 0.01), which equates to an absolute risk reduction (ARR) of 13% with RT+C compared with RT alone.

The secondary endpoint results were:

OS: The median duration of follow-up was 54 months. The estimated median survival time was significantly longer with RT+C than RT (49.0 vs. 29.3 months; HR 0.74, 95% CI 0.57 to 0.97; p = 0.03). The 3-year survival rates were 55% with RT+C and 45% with RT alone (p = 0.05), which equates to an ARR of 10% in favour of RT+C.
PFS: The estimated median PFS duration was significantly longer with RT+C than RT (17.1 vs. 12.4 months; HR 0.70, 95% CI 0.54 to 0.90; p = 0.006). The 3-year PFS rates were 42% with RT+C and 31% with RT (p = 0.04), which equates to an ARR of 11% in favour of RT+C.
ORR: The best ORR was 74% with RT+C and 64% with RT (OR 0.57, 95% CI 0.36 to 0.90; p = 0.02). This equates to an ARR for the best overall response during the first year of 10% in favour of RT+C.

How safe were the regimens?

All adverse events that occurred in at least 10% of patients in either group, regardless of cause, and severe (grades 3-5) adverse effects are presented. The p-values for differences between adverse event rates in the two groups were determined using Fisher's exact test. The incidences of severe reactions were similar in the two groups, with the exception of acneiform rash (17% with RT+C vs. 1% with RT; p < 0.001), infusion reaction (3% with RT+C vs. 0% with RT; p = 0.01) and anaemia (1% with RT+C vs. 6% with RT; p = 0.006). C did not exacerbate the common toxic effects associated with radiotherapy of the head and neck, including mucositis, xerostomia, pain, grade 3 – 5 weight loss and performance-status deterioration. The incidences of all grades of ADEs that differed significantly between the two groups are shown below in Table 1.

ADE	**RT+C (n = 208)**	**RT (n = 212)**	**p value**
Acneiform rash	87%	10%	< 0.001
Weight loss	84%	72%	= 0.005
Nausea	49%	37%	= 0.02
Fever	26%	13%	= 0.001
Headache	19%	8%	= 0.001
Pruritis	16%	4%	< 0.001
Infusion reaction	15%	2%	< 0.001
Chills	11%	5%	= 0.03
Anaemia	3%	13%	< 0.001

Table 1 Significantly different incidences of all grades of ADEs

Four patients discontinued C due to hypersensivity reactions after the test or first dose, and nine others discontinued, eight due to grade 3 acneiform rash. Dose reduction was required in < 5% of patients. Twelve and 11 patients in the RT and RT+C groups, respectively, died within 60 days of their last RT or C treatment, but no death was known to be related to C.

How precise are the results?

The 95% CI for the HR (0.68) for the primary endpoint (LRC) was 0.52 to 0.89. This means that with 95% certainty the true value lies within this range, i.e. the true effect may be a relative risk reduction of 11-48%. The 95% CI does not cross the line of no effect and the p value is highly significant (p = 0.005). The numbers of patients in each arm (RT+C n = 211, RT n = 213) were in excess of the 208 per treatment group the authors calculated was needed to provide 90% power to detect a difference in the LRC duration at the 5% significance level. Efficacy analyses were carried out on the ITT population. Therefore, in terms of the primary endpoint, the results for superiority of RT+C compared with RT alone in the study population appear robust. With respect to the secondary endpoints (OS, PFS, and ORR) RT+C appeared superior to RT alone, but the power the study had for these endpoints is not stated.

No pre-planned sub-group analyses were carried out, but some results, including HR values, for patients with cancer of the oropharynx, larynx and hypopharynx are presented, although with no accompanying CI or p values. Patients with oropharyngeal cancer were in the majority, 135/213 (63%) of the RT group and 118/211 (56% of the RT+C group). The respective values for the patients with laryngeal cancer were 51/213 (24%) and 57/211 (27%) and for those with hypopharyngeal cancer were 27/213 (13%) and 36/211 (17%). However, the trial was not sufficiently powered to detect treatment-related differences for sub-groups,[1] and due to the lack of statistical analysis and small numbers of patients (particularly of those with laryngeal and hypopharyngeal cancer), it is not possible to have any degree of certainty, there may be some differences in some endpoints among these three groups of patients. E.g. for the patients with oropharyngeal cancer, the median duration of LRC was 49.0 months with RT+C vs. 23.0 months with RT (HR 0.61), whereas the LRC durations were 12.9 months with RT+C and 11.9 months with RT (HR 0.69) for patients with laryngeal cancer and 12.5 months with RT+C and 10.3 months with RT (HR 0.92) for those with hypopharyngeal cancer. Median duration of OS showed similar differences: > 66.0 months with RT+C vs. 30.3 months with RT in patients with oropharyngeal cancer (HR 0.62), whereas the values were 32.8 months and 31.6 months (HR 0.87), respectively, for patients with laryngeal cancer and 13.7 months and 13.5 months (HR 0.94), respectively, for those with hypopharyngeal cancer.

Furthermore, OS results with the different RT regimens are presented (with HRs, but with no CI or p values). In the 417 patients who received radiotherapy (seven patients did not), the median durations of OS were 18.9 months with RT+C vs. 15.3 months (HR 1.01) with RT alone in patients who received the once daily RT regimen (25%); 58.9 vs. 53.3 months (HR 0.74), respectively, in those who received the twice daily RT regimen (18%); and >66.0 vs. 31.0 months (HR 0.64), respectively, in those who received concomitant boost RT (56%). Although the study was not powered to detect treatment-related differences for sub-groups,[1] the once daily RT regimen may be less effective than the twice daily and concomitant boost regimens, and RT+C with the concomitant boost regimen may confer an OS advantage over concomitant boost RT alone.

Can the results be applied to the local population?

This multinational study was carried out at cancer centres in the USA, 10 European countries (including the UK), South Africa, Australia, New Zealand and Israel. The patients' performance status were high, with nearly 90% of both groups having a Karnofsky performance score of ≥80. The majority of patients (49% and 54% in the RT and RT+C groups, respectively) had a Karnofsky score of 90, with 18% and 16%, respectively, having a score of 100. Only 11% and 10%, respectively, had scores of 60-70. As the RT regimens are clearly stated, if similar regimens were to be used in the UK, it would seem likely that similar results could be achieved with RT+C in UK patients with a similar disease profile (in terms of the proportions with oropharyngeal, laryngeal and hyopharyngeal cancer) and who fulfil the trial criteria. However, it is not clear how applicable to the UK population the trial results are, as there are differences between current clinical practice in the UK and the trial. The proportions of patients who received the RT regimens used in the trial differ from those in UK practice. In the trial, the majority (74%) of patients received either twice daily (18%) or

concomitant boost (56%) RT regimens, with only 25% receiving once daily RT. According to two clinical experts in the field of head and neck cancer, the once daily RT regimen is the most representative of current UK practice; one quoted a survey by the Royal College of Radiologists, which found that once daily RT is used in about 80% of head and neck cancer patients.[2] The clinical experts considered that only a small proportion of the patients in this trial would be considered for RT+C, as chemoradiotherapy is the treatment of choice for patients who are fit enough to receive it. The experts considered that about 10 – 20% and about a quarter of UK patients, and about 20 - 25% of those in the trial would be inappropriate for chemoradiotherapy, although the proportion may vary according to centre, clinician and resources available locally.[2] The reasons why chemoradiotherapy are inappropriate are highly variable, and include contraindications to chemotherapy (e.g. renal failure, cardiac dysfunction, poor hearing, tinnitus), poor performance status, and other patient factors, including social factors and patient choice. If the majority of patients in the UK who would be considered for RT+C therapy have lower performance status (i.e. Karnofsky score < 80) than the majority of those in this trial, then as so few patients in this trial had scores below 80, it is not clear whether similar results could be expected.

Summary

The median duration of LRC (the primary endpoint) with RT+C (24.4 months) was significantly longer (by 9.5 months) than that with RT alone (14.9 months) in patients with locoregionally advanced head and neck cancer. With respect to the secondary endpoints, the median duration of PFS was significantly longer with RT+C than C (17.1 vs. 12.4 months), as was OS (49.0 vs. 29.3 months). The best overall response rate during the first year was also significantly better with RT+C (74%) than RT (64%). The severe (grade 3 – 5) side effects experienced with the two regimens differed significantly only with respect to acneiform rash and infusion reaction, which occurred more frequently in the RT+C than the RT group, and anaemia, which occurred more frequently in the RT than the RT+C group. C did not exacerbate the common toxic effects associated with radiotherapy of the head and neck.

Critical Appraisal References

1. Bonner, JA et al. Correspondence. Cetuximab plus radiotherapy for head and neck cancer. The authors and a colleague reply. New Engl J Med 2006; 354:2187.
2. Teleconferences with Professor Christopher Nutting, Consultant Clinical Oncologist, Head and Neck Unit, Royal Marsden NHS Foundation Trust, and Dr Mehmet Sen, Consultant Clinical Oncologist (Sub-specialist in Head and Neck Cancer), The Leeds Teaching Hospitals NHS Trust. 31st August, 13th September and 25th September 2006.

Appendix 4 Treatment guidelines for LA SCCHN

NICE 2004 [5] – The guidance states that careful assessment of each patient's clinical, nutritional and psychological state is crucial to inform treatment planning. Multi-disciplinary teams (MDTs) should therefore establish multi-disciplinary pre-admission clinics at which all aspects of the case can be considered by appropriate specialists, and members of the MDT can discuss the way forward with individual patients and their carers. All patients with upper aerodigestive tract (UAT) cancers should have chest X-rays. Other forms of imaging are necessary to assess the stage and spread of the tumour, and specialist ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI) should be available. Suggestions about treatment strategies for individual patients should be made and developed in the context of MDT meetings at which all relevant clinical specialists should be present.

The optimum form of primary treatment for patients with UAT cancers depends on two crucial issues: whether the tumour is sufficiently localised to permit complete resection, and the general fitness of the patient. Other important issues are the probability of long-term disease control and the anticipated impact of the treatment on the patient's quality of life. Either radiotherapy or surgery may be appropriate as primary treatment; but some patients will require both. Head and neck cancer teams within each network should agree guidelines for the treatment of each form of cancer within this group. Many patients are treated with radiotherapy alone, but those with more advanced disease may require both radiotherapy and surgery or chemoradiation. The interval between surgery and radiotherapy should be as short as possible, ideally less than six weeks. Radiotherapy departments should make every effort to ensure that each patient receives a complete and unbroken course of the prescribed treatment.

Scottish Medicines Consortium 2006 [23] – The SMC issued positive advice on the use of cetuximab in combination with radiation therapy for the treatment of patients with LA SCCHN. The SMC restricted cetuximab to patients who are not appropriate for or unable to tolerate chemo-radiotherapy and who are of good performance status with no evidence of distant metastases. Cetuximab is also restricted to use by specialists in the management of head and neck cancer. An initial loading dose in week one of 400mg/m^2 followed by a weekly maintenance infusion of 250mg/m^2 for 2-8 weeks is recommended. Radiotherapy should start in week 2.

Although only the above two guidelines were cited in the manufacturer's submission, other guidelines on the management of head and neck cancer are available and include:

Royal College of Radiologists 2006[24] – Alternatives to the international standard doses of radiotherapy (60 - 70 Gy given daily in fractions of 1.8 - 2 Gy over 6.5 - 7 weeks) are discussed. Four major modified fractionation radiotherapies can be identified:

(1) Hyper-fractionation – same treatment time, higher total dose, and more than 5 fractions per week.
(2) Moderate acceleration – similar total dose, reduction of treatment time by 1 - 2 weeks, and more than 5 fractions per week.
(3) Marked acceleration plus hyper-fractionation – reduction of treatment time by more than 2 weeks, reduced total dose, and more than 5 fractions per week
(4) Marked acceleration with hypo-fractionation – less than conventional number of large-sized fractions.

Induction chemotherapy with full-dose cisplatin and 5-FU may produce a small survival benefit. Patients with stage I or stage II laryngeal cancer can be treated effectively with both short and conventional regimens:

(1) 64 - 70 Gy in daily 2 Gy fractions over 6.5 - 7 weeks
(2) 54 - 55 Gy in 20 daily fractions over 4 weeks
(3) 50 - 52.5 Gy in 16 daily fractions over 3 weeks

For fit patients with stage III or IV head and neck cancer offered definitive radiotherapy, the following regimens are recommended:

(1) Moderately accelerated radiotherapy (e.g. 66 - 68 Gy in 2 Gy fractions 6 times a week over 5.5 weeks
(2) 72 Gy in 6 weeks using concomitant boost
(3) 66 - 70 Gy in 6.5 - 7 weeks plus synchronous chemotherapy

National Comprehensive Cancer Network 2006[25]

<u>*Cancer of the oropharynx*</u> – Treatment should be based on clinical stage of disease. This is divided into three staging categories (1) T1-2, NO-1; (2) T3-4, N0; and (3) any T3-4, N+ or any T, N2-3.

(1) Early stage disease (T1-2, NO-1) - Definitive radiotherapy (conventional fractionation 70 Gy: 2.0 Gy/day) or concurrent chemotherapy/radiotherapy (e.g. carboplatin plus 5-FU) or excision of primary with or without unilateral or bilateral neck dissection.
(2) More advanced disease (T3-4, N0) – Concurrent chemotherapy (e.g. carboplatin plus 5-fluorouracil (5-FU)) is preferred; or surgery plus chemotherapy and radiotherapy for adverse features; or induction chemotherapy followed by concurrent chemotherapy/radiotherapy that includes function evaluation or induction chemotherapy followed by chemo/radiotherapy off protocol.
(3) T3-4, N+ or any T, N2-3 - Concurrent chemotherapy/radiotherapy is preferred for treatment of locally advanced (T3-4 of N2-3) cancer of the oropharynx.

Cancer of the hypopharynx – Patients with resectable disease are divided into two groups: those with early-stage cancer (most T1, N0-1; small T2, N0) who do not require total laryngectomy and those patients with advanced resectable cancer (T1, N2-3; T2-4, any N) who do require laryngectomy.

(1) T1, N0-1; small T2, N0 - Initial treatment with definitive radiotherapy without chemotherapy (primary and gross adenopathy > 70 Gy, 2.0 Gy/day or neck > 50 Gy, 2.0 Gy/day) followed by surgery for residual neck disease.
(2) T1, N2-3; T2-4, any N - May be managed with induction chemotherapy, surgery, concurrent chemoradiation or multimodality clinical trial of induction chemotherapy followed by concurrent chemoradiation that includes function evaluation.

Cancer of the larynx – Treatment of patients with laryngeal cancer is divided into three categories: (1) tumours of the glottic larynx, (2) tumours of the supraglottic larynx without positive nodes (N0), and (3) tumours of the supraglottic larynx with positive nodes (N+). For invasive cancer, surgery (partial laryngectomy through earlier endoscopic or open approaches) and radiotherapy are equally effective for early-stage glottic or supraglottic cancers. Participation in clinical trials is preferred for patients with locally advanced laryngeal cancer requiring total laryngectomy. Resectable, advanced-stage supraglottic and glottic primaries can be managed surgically with a combined modality approach consisting of either total laryngectomy or concurrent chemoradiation. In patients with laryngeal cancer, radiotherapy with concurrent administration of cisplatin is superior either to induction chemotherapy

followed by radiotherapy or to radiotherapy alone for laryngeal preservation and locoregional control.

European Society for Medical Oncology (ESMO) 2005[26] – A multidisciplinary treatment schedule should be established in all cases. The patient's nutritional status must be corrected and maintained. Treatment depends on primary tumour location and extension. Standard options are surgery with post-operative radiotherapy (stages I and II) or chemoradiotherapy (stages III, IV and lower stages with high risk features). Adjuvant chemotherapy has demonstrated no benefit. Adjuvant chemoradiotherapy with single agent platinum following surgery increases disease-free and overall survival in comparison with post-operative radiotherapy alone. Neoadjuvant chemotherapy has demonstrated no effect on disease-free survival or overall survival. Neoadjuvant chemotherapy followed by radiotherapy allows organ preservation in advanced larynx and hypopharynx cancer otherwise requiring total laryngectomy. Cisplatin with 5-FU is the chemotherapy of choice in this indication.

Scottish Intercollegiate Guidelines Network 2004 (Draft)[27] (SIGN guidelines on head and neck cancer were due to be published in the summer of 2006, but at the time of writing, they had not been published[28]) – Definitive, curative treatment of head and neck cancers involves surgery and radiotherapy alone or in combination. Chemotherapy may be used in addition but not as a single modality. Little good quality evidence exists to guide the choice of definitive local therapy for each tumour subsite. The choice of definitive local therapy must take into account the individual factors relating to the tumour and patient including likely functional outcome of treatment, resectability of the tumour, general medical condition of the patient, and the patient's wishes.

In patients with non-metastatic SCCHN concurrent chemotherapy should be considered in all patients receiving non-surgical treatment, with single agent cisplatin as the chemotherapeutic agent. The routine use of neoadjuvant chemotherapy prior to radiotherapy is not recommended except in locally advanced hypopharyngeal cancer when induction chemotherapy followed by radiotherapy in responders is appropriate. The routine use of neoadjuvant or adjuvant chemotherapy in combination with surgery is not recommended. The routine use of adjuvant chemotherapy following radiotherapy is not recommended. If external beam radiotherapy is used as the sole treatment modality without the addition of

chemotherapy, a short overall treatment schedule is recommended (e.g. 50 - 55Gy in 15 - 20 fractions) for patients with early laryngeal cancer. Moderately accelerated schedules (6 fractions/week), or hyperfractionated schedules with increased total dose, are recommended for patients with tumours at other subsites.

Locally advanced laryngeal cancer – Total laryngectomy followed by postoperative radiotherapy or an organ preservation strategy may both be used in the treatment of locally advanced laryngeal cancer, depending on the patient's desire for organ preservation and general performance status. Patients with T4 tumours extending through cartilage into soft tissue may be best treated by total laryngectomy and postoperative radiotherapy. In patients who wish to pursue organ preservation the treatment of choice is concurrent chemoradiation with single agent cisplatin with salvage surgery as required. For those patients unsuitable for chemotherapy who wish to pursue organ preservation, radiotherapy with a modified fractionation schedule is recommended.

Hypopharyngeal cancer – In resectable locally advanced hypopharyngeal cancer, treatment may be either by surgical resection or an organ conservation approach. Patients who wish to preserve their larynx may be treated with induction chemotherapy (cisplatin and 5FU) and radical radiotherapy in complete responders, with surgical resection reserved for those who show less than a complete response to two cycles of chemotherapy. Resectable locally advanced disease should not be treated by conventional radiotherapy alone. Non-resectable locally advanced disease should be treated by conventionally fractionated concurrent chemoradiation using single agent cisplatin. Non-resectable locally advanced disease in those patients unsuitable for chemotherapy should be considered for treatment with radiotherapy using a modified fractionation.

Locally advanced oropharyngeal cancer – There is no evidence for superior survival following any particular therapeutic strategy. As the function of the oropharynx is complex and plays a major role in breathing, speaking and swallowing it may be preferable to adopt an organ conservation approach to treatment. Locally advanced oropharyngeal cancer may be treated by concurrent conventionally fractionated chemoradiotherapy using single-agent cisplatin. Locally advanced disease in those patients unsuitable for chemotherapy should be considered for treatment with radiotherapy using a modified fractionation. The routine use of neoadjuvant or adjuvant chemotherapy in combination with surgery is not recommended.

Cancer Care Ontario 2000[29] – Concomitant chemotherapy with conventional fractionated radiotherapy should be the treatment of choice for patients with advanced squamous-cell head and neck cancer. At this time there are insufficient data to recommend the use of concomitant chemotherapy with altered fractionation schedules. The choice of concomitant therapy should take into account the toxicity produced by various regimens and the convenience of treatment administration. Reasonable options outside a clinical trial include either single agent daily cisplatin or carboplatin with conventional radiotherapy, or alternating split-course radiotherapy with cisplatin plus infusional 5-FU.