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

Premeeting briefing

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

The manufacturer was asked to provide additional information on the clinical and cost effectiveness data, structure of the economic model and uncertainty in the economic analysis.

Abbreviations

CR	complete response
ERG	evidence review group
HRQoL	Health-related quality of life
ICER	incremental cost-effectiveness ratio
ITT	intention to treat
PR	partial response
QALY	quality-adjusted life year

Licensed indication

Cetuximab (Erbitux, Merck) in combination with radiotherapy is licensed in the UK for the treatment of patients with locally advanced squamous cell carcinoma of the head and neck.

Key issues for consideration

Decision problem/scope

- Is the population defined in the decision problem appropriate given the issues facing the NHS (proportion of patients receiving chemoradiotherapy)?

- If so, can we define the patient population for which chemoradiotherapy is considered inappropriate?

Clinical effectiveness

- Is it appropriate to extrapolate the results reported in the pivotal trial to the population in the decision problem? (Note: the population in the trial includes a substantial number of patients for whom chemoradiotherapy would be appropriate).

- Do the baseline characteristics of the population in the pivotal trial represent those seen in clinical practice? (Note: people in the trial population had, on average, higher Karnofsky performance scores than those patients considered unsuitable for chemoradiotherapy in UK clinical practice; in UK practice radiotherapy regimens are predominantly once daily, which differs from the predominant use altered-fractionation regimens in the trial).

Cost effectiveness

- Given the differences between the populations in the pivotal trial and the decision problem, do the reported cost-effectiveness results apply?
- If not, can the Committee estimate the cost effectiveness of cetuximab and radiotherapy for patients for whom chemoradiotherapy is not considered an appropriate option?

1 Decision problem

1.1 Decision problem approach in the manufacturer's submission

Population	Patients with locally advanced squamous cell carcinoma of the head and neck for whom chemoradiotherapy is not considered an appropriate option.[a]
Intervention	Cetuximab plus radiotherapy weekly until the end of the radiation therapy (usually 7 to 8 weeks) with an initial dose of 400 mg/m^2 of cetuximab without radiotherapy followed by 250 mg/m^2 of cetuximab and 10 Gy radiation therapy per week.
Comparators	Radiotherapy alone in three different dosing schedules.
Outcomes	Duration of locoregional control[b], overall survival, progression-free survival and response rate.

[a] Technical Lead comment: This is a restricted interpretation of the licence that was not justified by the manufacturer.

[b] Defined as the time from the date of randomisation until the first documented progression, recurrence of locoregional disease or death from any cause.

1.2 Evidence Review Group comments on the manufacturer's submission

1.2.1 **Decision problem**: the decision problem and objectives were clearly defined.

1.2.2 **Population**: The manufacturer's submission states that the proposed use in the UK is cetuximab in combination with radiotherapy for the treatment of patients with locally advanced squamous cell carcinoma of the head and neck for whom chemoradiotherapy is not considered an appropriate option. The population in the only trial included by the manufacturer (Bonner et al. 2006) comprised patients with locoregionally advanced head and neck cancer (stage III or IV, non-metastatic, squamous-cell carcinoma of the oropharynx, hypopharynx or larynx) who had good performance status (nearly 90% of both groups had a Karnofsky performance score of 80 or more; patients with a score of less than 60 were excluded). It is not stated in the published paper whether any of these patients were unsuitable for

chemoradiotherapy; however, a high proportion of patients in the trial would be expected to have been suitable. Therefore, the patient population in this clinical trial does not match the target population proposed by the company.

1.2.3 **Comparators**: the comparator treatment considered is valid. However, the proportions of patients receiving the three radiotherapy regimens used in the trial are not representative of current UK practice.

1.2.4 **Outcomes**: the primary endpoint was duration of locoregional control of tumours (see section 1.1 for definition). Secondary endpoints included overall survival, progression-free survival, overall response rate and safety. The clinical specialists consulted by the ERG considered overall survival to be a key endpoint.

1.3 Clinical specialists and patient experts' statements

1.3.1 According to a clinical specialist, most clinicians feel that cetuximab should be added to radiotherapy and reserved for less fit patients until further clinical evidence is available on the effectiveness of cetuximab added to chemoradiotherapy.

2 Clinical effectiveness evidence

2.1 Evidence from the manufacturer's submission

2.1.1 The table below shows the main results of the randomised controlled trial discussed in the manufacturer's submission.

Table 1 Summary of results (Bonner et al. 2006)

Variable	Radiotherapy alone ITT population (n = 213)	Radiotherapy plus cetuximab ITT population (n = 211)	p value	Hazard ratio	95% CI
Locoregional control, median duration in months	14.9	24.4	0.005	0.68	0.52–0.89
Progression-free survival, median duration in months	12.4	17.1	0.006	0.70	0.54–0.90
Overall survival, median duration in months	29.3	49.0	0.03	0.74	0.57–0.97
Response rate (CR+PR) Total number (%)	137 (64%)	155 (74%)	0.02	0.57 (odds ratio)	0.36–0.90

ITT intention to treat; CR complete response; PR partial response.

See page 43 of the manufacturer's submission.

2.1.2 Analyses of subgroups by tumour site, tumour stage (III or IV) and radiotherapy regimen all showed a trend in favour of the combination therapy for both overall survival and locoregional control (see section 2.5 table 6 of the manufacturer's submission), although the study was not statistically powered to detect differences in these subgroups.

2.1.3 ***Technical Lead comment*** In patients who received the once daily regimen the hazard ratio for the median duration of overall survival with radiotherapy plus cetuximab versus radiotherapy alone was 1.01. No confidence interval and no p value are presented in the trial by Bonner and colleagues for this hazard ratio, or for any of the other subgroup results presented.

2.2 Evidence Review Group comments

2.2.1 The ERG judged the one trial (Bonner et al. 2006) reported in the manufacturer's submission to be of good methodological quality and did not identify any others.

2.2.2 The manufacturer's submission states that the relevance of the subject population in the trial by Bonner and colleagues to that in the UK is demonstrated by an audit of case notes of 139 patients with locally advanced squamous cell carcinoma of the head and neck. This audit was carried out for the manufacturer and, as far as the ERG was aware, was not published and had not been peer-reviewed. Neither the full details of the methods used to conduct the review nor the full results of the review were provided by the manufacturer.

2.2.3 In the manufacturer's report of the audit findings no details of the types of radiotherapy regimens were provided. Therefore, it is not clear whether the radiotherapy schedules used and the proportions of patients with the same types and stages of locally advanced squamous cell carcinoma of the head and neck in the Bonner et al trial are representative of practice in the UK.

2.2.4 In the trial by Bonner and colleagues, investigators were required to select one of the three radiotherapy-fractionation regimens before patient registration. The most frequently selected regimen was concomitant-boost therapy (received by 56% of patients); the once-daily radiotherapy regimen was selected for 26% of patients (received by 25% of patients); the twice-daily radiotherapy regimen was selected least often (received by 18% of patients). These proportions are not typical of the current UK situation. According to two clinical specialists in the field of head and neck cancer consulted by the ERG, once-daily radiotherapy is most frequently used in the UK.

2.2.5 The ERG asked the manufacturer to provide clear definitions and criteria for patients for whom chemoradiotherapy is considered inappropriate. The manufacturer provided details of the responses of three clinical oncologists who were asked why they would consider radiotherapy but not chemoradiotherapy to be appropriate for a patient. Their reasons included those outlined by the clinical specialists consulted by the ERG.

2.2.6 The trial by Bonner and colleagues included a high proportion of patients who would be expected to be suitable for chemoradiotherapy. The two clinical specialists consulted by the ERG were of the opinion that the trial was a good source for the comparison of cetuximab in combination with radiotherapy with radiotherapy alone, partly because the clinical factors that would lead to chemoradiotherapy being inappropriate are highly variable. Chemoradiotherapy may also be considered inappropriate for non-clinical reasons, including the resources available locally and local infrastructure.

2.2.7 The ERG asked the manufacturer to provide further information on the number of patients in the trial by Bonner and colleagues for whom chemoradiotherapy is considered inappropriate and to provide any additional results that have been presented for this subgroup. If additional results were not available, the ERG requested that the manufacturer undertake this analysis. The manufacturer stated that the trial was not designed or statistically powered to assess for subgroups of patients for whom chemoradiotherapy treatment may be inappropriate.

2.3 Clinical specialists and patient experts' statements

2.3.1 According to the patient expert's written statement most patients with advanced head and neck cancer would be prepared to tolerate the actual or perceived side effects of cetuximab. The most common side effect is a skin rash; its severity is an indication of the treatment's effect. In the opinion of the patient expert, most patients would welcome the rash as an indication that the treatment was working.

2.3.2 According to a clinical specialist, patients in the trial by Bonner and colleagues were generally representative of those seen in routine non-selected practice. The Karnofsky performance status of patients in the trial ranged from 60 to 100 but was most commonly 90. Therefore, it is necessary to extrapolate the clinical benefit from the

fitter group of patients in the clinical trial to the less fit patients for whom cetuximab in combination with radiotherapy is being proposed.

3 Cost effectiveness evidence

3.1 Cost effectiveness in the manufacturer's submission

3.1.1 Table 2 (below) shows the main results of the economic evaluation presented in the manufacturer's submission.

3.1.2 The results of the one-way sensitivity analysis are presented on pages 103–104 of the manufacturer's submission. The ICERs are largely unaffected by the majority of the analyses. However, if no extrapolation is undertaken (that is, the time horizon is reduced from a lifetime to simply the period of the trial follow-up), the ICER increases to £19,951.

Table 2 Summary of results of economic evaluation in the manufacturer's submission

Treatment	Radiotherapy	Cetuximab plus radiotherapy	Differences in costs/effects
Cost (£)	7,195	13,821	6,626
QALY	2.8162	3.8532	1.0369
ICER			6,390

See pages 50–85 of the manufacturer's submission for more details.

3.2 Evidence Review Group comments

3.2.1 There are no existing published cost-effectiveness studies evaluating the use of cetuximab in combination with radiotherapy for locally advanced squamous cell carcinoma of the head and neck.

3.2.2 In general, the ERG considered the manufacturer's economic submission to be of good quality and the sensitivity analysis undertaken to be appropriate. The submission contains a good description of the data sources and the justification for the assumptions. However, the ERG identified a number of uncertainties and other issues (see table 5.11 of the ERG report).

3.2.3 The ERG considered that the most important problem with manufacturer's economic submission was that the only randomised controlled trial informing the economic analysis does not match the patient population specified in the manufacturer's decision problem and this discrepancy was reflected in the manufacturer's model. The ERG was uncertain of the likely influence of this on the results of the economic model.

3.2.4 The ERG identified a series of issues relating to the analysis of extrapolation, HRQoL and resource use/costs. The ERG concluded that the methods used were probably appropriate but in the majority of cases were unable to determine the likely influence of using alternative methods on the results of the economic model. The methods used for the extrapolation were complex and not well described; as a result the ERG could not repeat the analysis. In addition, the uncertainty inherent to the extrapolation was not reflected in the results of the manufacturer's model. However, the ERG concluded that altering the method of extrapolation would be unlikely to cause the ICER to increase above £20,000.

3.2.5 The ERG undertook additional work to examine the potential robustness of the base-case results to the assumptions made in the manufacturer's cost-effectiveness model for HRQoL and resource use and cost (see pages 63 to 65 of the ERG report). The ERG concluded that any bias would have to be very large to have a material effect on the conclusions of the manufacturer's cost-effectiveness submission.

4 Author

Nicola Hay on behalf of the Committee Chair (Andrew Stevens), and the Lead Team (Peter Clark, Jonathan Michaels and Simon Mitchell).