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

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Abstract

This paper presents a summary of the evidence review group (ERG) report into the clinical effectiveness and cost-effectiveness of cetuximab for recurrent and/or metastatic squamous cell carcinoma of the head and neck (SCCHN) based upon a review of the manufacturer's submission to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal (STA) process. The submission's evidence came from a single reasonably high-quality randomised controlled trial (RCT) [EXTREME (Erbitux in First-Line Treatment of Recurrent or Metastatic Head and Neck Cancer); $n = 442$] comparing cetuximab plus chemotherapy (CTX) with CTX alone. Cetuximab plus CTX had significant effects compared with CTX alone on the primary outcome of overall survival (10.1 versus 7.4 months respectively) and the secondary outcomes of progression-free survival (PFS) (5.6 versus 3.3 months), best overall response to therapy (35.6% versus 19.5%), disease control rate (81.1% versus 60%) and time-to-treatment failure (4.8 versus 3.0 months), but not on duration of response (5.6 months versus 4.7 months). No safety issues with cetuximab arose beyond those already previously documented. The manufacturer developed a two-arm state-transition Markov model to evaluate the cost-effectiveness of cetuximab plus CTX versus CTX alone, using clinical data from the EXTREME trial. The ERG recalculated the base-case cost-effectiveness results taking changes in parameters and assumptions into account. Subgroup and threshold analyses were also explored. The manufacturer reported

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Discussion of ERG reports is invited. Visit the HTA website correspondence forum (www.hta.ac.uk/correspond).

an incremental cost-effectiveness ratio (ICER) of £121,367 per quality-adjusted life-year (QALY) gained and an incremental cost per life-year gained of £92,226. Univariate sensitivity analysis showed that varying the cost of day-case infusion and the utility values in the stable/response health state of the cetuximab plus CTX arm had the greatest impact on the ICER. Probabilistic sensitivity analysis illustrated that cetuximab plus CTX is unlikely to be cost-effective for patients with recurrent and/or metastatic SCCHN, even at what would usually be considered very high levels of willingness to pay for an additional QALY. With regard to the economic model the appropriateness and reliability of parametric survival projection beyond the duration of trial data could not be fully explored because of lack of information. The ERG also questioned the appropriateness of economic modelling in this STA as evidence is available only from a single RCT. In conclusion, the ERG considers that patients with metastatic SCCHN were not shown to receive a significant survival benefit from cetuximab plus CTX compared with CTX alone and that even setting a lower price for cetuximab would not strengthen the manufacturer's case for cost-effectiveness.

Introduction

The National Institute of Health and Clinical Excellence (NICE) is an independent organisation within the NHS that is responsible for providing national guidance on the treatment and care of people using the NHS in England and Wales. One of the responsibilities of NICE is to provide guidance to the NHS on the use of selected new and established health technologies, based on an appraisal of those technologies.

NICE's single technology appraisal (STA) process is specifically designed for the appraisal of a single product, device or other technology, with a single indication, for which most of the relevant evidence lies with one manufacturer or sponsor.[1] Typically, it is used for new pharmaceutical products close to launch. The principal evidence for an STA is derived from a submission by the manufacturer/sponsor of the technology. In addition, a report reviewing the evidence submission is submitted by the evidence review group (ERG), an external organisation independent of NICE. This paper presents a summary of the ERG report for the STA of cetuximab for recurrent and/or metastatic squamous cell carcinoma of the head and neck (SCCHN).[2]

Description of the underlying health problem

The term head and neck cancer covers a wide variety of different cancers [30 different International Classification of Diseases (ICD) codes] occurring in the tissues of the head and neck. As a group they account for over 8000 cancer registrations in England and Wales.[3] Around 90% of head and neck cancers are squamous cell. SCCHN most commonly arises in the oral cavity, pharynx and larynx.[3] The number of registrations for these subgroups was 5833 in England in 2005[4] and 446 in Wales in 2006,[5] with a ratio of male to female cases of approximately 70:30.

There is no standard treatment for all patients with recurrent or metastatic disease; guidelines recommend the tailoring of therapy to the individual patient.[3,6] In some patients the tumour may still be amenable to surgery or radiotherapy with curative intent; however, in patients with metastatic disease or who have previously received radiotherapy for the initial tumour, this may not be possible. For this group of patients palliative CTX is the mainstay of treatment if they are able to tolerate it. The most commonly used chemotherapeutic treatments for recurrent and/or metastatic SCCHN include methotrexate, bleomycin, 5-fluorouracil (5-FU) and platinum compounds. The prognosis for recurrent and/or metastatic SCCHN subjects is poor with a median survival time of only 6–9 months.

Scope of the ERG report

The ERG report presents the results of the assessment of the manufacturer (Merck Serono) evidence submission regarding the use of cetuximab with platinum-based CTX (cisplatin plus fluorouracil or carboplatin plus fluorouracil) compared with platinum-based CTX alone for the first-line treatment of recurrent and/or metastatic SCCHN. The report includes an assessment of both the clinical effectiveness and cost-effectiveness evidence submitted by the manufacturer. The primary clinical outcome measure was overall survival (OS), with secondary outcomes of progression-free survival (PFS), response to therapy, safety and quality of life (QoL). The cost-effectiveness measures were incremental cost-effectiveness ratio (ICER) and incremental cost per life-year (LY) gained.

Cetuximab (Erbitux®) is a monoclonal antibody that inhibits the action of the epidermal growth factor receptor (EGFR), which is highly expressed in nearly all SCCHN tumours. Whilst the ERG report was in progress, a positive opinion from the European Medicines Agency (EMEA) Committee for Medicinal Products for Human Use (CHMP) to extend the use of cetuximab to include the treatment of patients with recurrent and/or metastatic SCCHN in combination with platinum-based CTX was issued. Final approval was given by the EMEA after the submission of the ERG report. Neither the EMEA nor NICE limited the indication to first-line use; this limitation was imposed by the manufacturer.

Methods

The ERG report comprised a critical review of the evidence for the clinical effectiveness and cost-effectiveness of the technology based upon the manufacturer's/sponsor's submission to NICE as part of the STA process.

The ERG evaluated the quality of the manufacturer's clinical effectiveness review. Searches conducted by the manufacturer were assessed for completeness and the single trial put forward as evidence of effectiveness was critically appraised using a standard tool (CASP[7] – Critical Appraisal Skills Programme). With regard to cost-effectiveness evidence, the ERG assessed the manufacturer's searches for completeness, critically appraised the submitted economic model using a standard assessment tool (Drummond and Jefferson[8]) and conducted a detailed evaluation of the model. The ERG recalculated the base-case cost-effectiveness results taking changes in parameters and assumptions into account, for example revised drug costs, mid-cycle correction, overall PFS utility value. Subgroup and threshold analyses were also explored by the ERG.

Results

Summary of submitted clinical evidence

The clinical effectiveness evidence described in the manufacturer's submission was derived from a single phase III open-label randomised controlled trial (RCT) that compared the use of cetuximab plus CTX with CTX alone. The EXTREME (Erbitux in First-Line Treatment of Recurrent or Metastatic Head and Neck Cancer) trial was conducted in 80 centres within 17 European countries and included 442 patients. The results of the EXTREME trial showed significant effects of cetuximab plus CTX compared with CTX alone on the primary outcome of OS (10.1 months versus 7.4 months respectively). There was also a significant effect of cetuximab plus CTX compared with CTX alone on the secondary end points of median PFS (5.6 months versus 3.3 months), best overall response to therapy (35.6% versus 19.5%), disease control rate (81.1% versus 60%) and median time-to-treatment failure (TTF) (4.8 months versus 3.0 months). No significant difference was noted in the median duration of response between the cetuximab plus CTX and CTX alone groups (5.6 months versus 4.7 months). The results are summarised in *Table 1*. The QoL data described were very limited; the manufacturer states that there was no difference in QoL between the two treatment groups. No safety issues related to cetuximab arose beyond those already previously documented.

Summary of submitted cost-effectiveness evidence

In the absence of UK-based economic evaluations, the manufacturer conducted a de novo economic evaluation. A two-arm state-transition Markov model was developed to evaluate the cost-effectiveness of cetuximab plus CTX compared with CTX alone. The clinical data used in the economic evaluation were generated from the EXTREME trial. Although the economic evaluation was trial based there was also a modelling component with regard to the extrapolation of health effects beyond the period of the trial (24 months). The economic evaluation adopted a lifetime horizon for the consideration of costs and benefits and the perspective is that of the UK NHS and personal social services.

The manufacturer reported an ICER of £121,367 per quality-adjusted life-year (QALY) gained and an incremental cost per LY gained of £92,226. In addition to the main results, ICERs for selected subgroups were also presented. Univariate sensitivity analysis showed that varying (1) the cost of day-case infusion and (2) the utility values in the stable/response health state of the cetuximab plus CTX arm had the greatest impact on the ICER. Probabilistic sensitivity analysis illustrated that cetuximab plus CTX is unlikely to be cost-effective for patients with recurrent and/or metastatic SCCHN, even at what would usually be considered very high levels of willingness to pay for an additional QALY.

TABLE 1 *Key results of the EXTREME trial*

Outcome	Cetuximab plus CTX (*n* = 222)	CTX (*n* = 220)	Hazard ratio (HR)/ odds ratio (OR)	*p*-value
Primary				
OS (months), median (95% CI)	10.1 (8.6–11.2)	7.4 (6.4–8.3)	HR 0.797 (0.644–0.986)	0.00362[a]
Secondary				
PFS (months), median (95% CI)[a]	5.6 (5.0–6.0)	3.3 (2.9–4.3)	HR 0.538 (0.431–0.672)	< 0.001
Best overall response	35.6% (29.3–42.3)	19.5% (14.5–25.4)	OR 2.326 (1.504–3.600)	< 0.001[b]
Disease control rate (95% CI)[c]	81% (75.3–86.0)	60% (53.2–66.5)	OR 2.881 (1.870–4.441)	< 0.001[d]
Time to treatment failure (months) (95% CI)[a]	4.8 (4.0–5.6)	3.0 (2.8–3.4)	HR 0.59 (0.48–0.73)	< 0.001[b]
Duration of response (months) (95% CI)[e]	5.6 (4.7–6.0)	4.7 (3.6–5.9)	HR 0.76 (0.50–1.17)	0.21[b]

CI, confidence interval; CTX, chemotherapy; OS, overall survival; PFS, progression-free survival.
p-values, hazard ratios and odds ratios are stratified according to receipt or non-receipt of previous chemotherapy and Karnofsky Performance Status at randomisation.

a Number of months estimated using Kaplan–Meier method.
b *p*-value calculated using the log-rank test.
c Disease control includes complete response, partial response and stable disease.
d *p*-value calculated using Cochrane–Mantel–Haenszel test.
e Data on duration of response were available for 62 patients in the cetuximab group and 36 patients in the CTX alone group; data on disease progression in these patients were available at the time of analysis. The number of months was estimated using the Kaplan–Meier method.

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

Commentary on the robustness of submitted evidence

The manufacturer cited evidence from a reasonably high-quality trial (EXTREME) of the clinical benefit of cetuximab plus CTX compared with CTX alone. The trial was well designed, used robust randomisation techniques and was suitably powered to show differences between the treatment groups. Appropriate exploratory subgroup analyses were carried out and statistical reporting was generally good.

However, the clinical effectiveness evidence was based only on this single trial, which was open label and relied on the unblinded assessment of clinical outcomes. Despite designing the trial to include a comprehensive analysis of QoL, very limited QoL data were collected and reported.

The manufacturer provided clinical evidence to support the use of cetuximab as a first-line treatment for patients with recurrent and/or metastatic SCCHN; hence, there is no discussion of the costs and benefits of second-line treatment options for this patient group. Neither the final scope issued by NICE nor the EMEA CHMP positive opinion limits the use of cetuximab to first-line treatment only.

The ERG was confident that neither model assumptions nor parameter values were likely to introduce sufficient uncertainty to allow cetuximab plus CTX to be cost-effective for this group of patients. A number of key issues and parameters in the economic model did not seem to be justified. The results of the ERG's threshold analysis indicate that cetuximab plus CTX may not be cost-effective at any price according to current NICE guidance. The ERG identified a number of different areas in the economic model in which it was appropriate to correct or revise model assumptions, which taken together increased the size of the ICER (*Table 2*).

Conclusions

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

TABLE 2 *ERG modifications to manufacturer's economic model*

Model/amendment	Incremental costs	Incremental survival	Incremental QALYs	Incremental cost/LY gained	Incremental cost/QALY gained
Base case	£17,286	0.1874	0.1424	£92,226	£121,367
Mid-cycle correction	£16,185 (–£1101)	0.1874	0.1414 (–0.0011)	£86,353 (–£5873)	£114,484 (–£6884)
Limit to 24 months	£16,760 (–£526)	0.1318 (–0.0556)	0.1134 (–0.0290)	£127,149 (+£34,923)	£147,817 (+£26,449)
Overall PFS utility value	£17,286	0.1874	0.1240 (–0.0184)	£92,226	£139,390 (+£18,023)
Adverse event utility adjustment	£17,286	0.1874	0.1443 (+0.0019)	£92,226	£119,808 (–£1560)
Revised drug costs	£20,441 (+£3155)	0.1874	0.1424	£109,059 (+£16,833)	£143,519 (+£22,152)
100% cisplatin use	£17,332 (+£46)	0.1874	0.1424	£92,473 (+£247)	£121,692 (+£325)
Cetuximab dose adjustment	£17,404 (+£118)	0.1874	0.1424	£92,858 (+£632)	£122,199 (+£831)
Cisplatin dose adjustment	£17,259 (–£27)	0.1874	0.1424	£92,081 (–£145)	£121,177 (–£191)
Rebase unit costs	£18,852 (+£1566)	0.1874	0.1424	£100,580 (+£8354)	£132,361 (+£10,993)
Revised discounting	£17,283 (–£3)	0.1873(–0.0002)	0.1423 (–0.0001)	£92,297 (+£71)	£121,437 (+£69)
Base case + all changes – full life	£20,932 (+£3646)	0.1873 (–0.0002)	0.1259 (–0.0166)	£111,784 (+£19,558)	£166,307 (+£44,939)
Base case + all changes – 24 months	£20,331 (+£3045)	0.1317 (–0.0558)	0.0976 (–0.0449)	£154,420 (+£62,194)	£208,266 (+£86,899)

LY, life-year; PFS, progression-free survival; QALY(s), quality-adjusted life-year(s).
Numbers in parentheses indicate the change relative to the base case.

is uncertain. There is also no clinical evidence available to demonstrate the effectiveness of cetuximab plus CTX in patients who are not cetuximab naive. Finally, the ERG considered that patients with metastatic SCCHN were not shown to receive a significant survival benefit from cetuximab plus CTX compared with CTX alone.

With regards to the economic model, some questions over the appropriateness and reliability of parametric survival projection beyond the duration of trial data could not be fully explored by the ERG because of lack of information; in particular, the appropriateness of employing Weibull modelling for all patient groups may benefit from further examination. The ERG also questioned the appropriateness of economic modelling in this STA as many health economists would prefer to carry out direct evaluation of trial data when evidence is available only from a single RCT.

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

Summary of NICE guidance issued as a result of the STA

At the time of writing, the guidance has not been issued by NICE.

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