**NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE**
**Cetuximab for the treatment of head and neck cancer – comments on appraisal consultation document**

## Response to consultee, commentator and public comments on the ACD

| Consultee or Commentator | Comment | Institute response |
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| Merck | Our comments fall under points 1 and 3 of the general headings requested:<br>i) whether you consider that all of the relevant evidence has been taken into account;<br>iii) whether you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS.<br><br>We wish to address three issues raised in the ACD which play a critical role in the appraisal, and may determine how the preliminary decision may have been reached. We do not believe that all the relevant evidence has been taken into account, or at least may have been misinterpreted which has resulted in a provisional recommendation which is not sound and suitable basis for guidance to the NHS:<br><br>1. <u>The proposed patient population for the treatment with cetuximab plus radiotherapy:</u><br>a. The definition of patient "fitness" described by NICE in the ACD and the relationship to Karnofsky Performance Status (KPS)<br>b. NICE proposed alternative treatments for SCCHN: the licensing and contraindications associated with the use of cisplatin and carboplatin<br>c. Proposed criteria for the selection of patients for whom the use of cetuximab in combination with radiotherapy would be appropriate to ensure that clinical and cost effectiveness measures are met in clinical practice<br><br>2. <u>Radiotherapy treatment patterns for the treatment of LA SCCHN in the UK</u><br>3. <u>Critique of the decision problem</u><br>a. Medical ethics governing the choice of treatment with radiotherapy alone<br>b. Clinical research timelines and the use of current standard treatment<br>c. Implications for clinical research in the UK | See below for response to detailed comments |

| Consultee or Commentator | Comment | Institute response |
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| Merck (continued) | **In summary:**<br>• Patient, "fitness" for treatment with Chemoradiotherapy, according to the NICE ACD, is defined by KPS, but this is not a measure of concomitant conditions. It is possible for a patient to have a high KPS (90 or above), have a concomitant condition, and be unsuitable for cisplatin based chemoradiotherapy treatment. The A+A market audit conducted by Merck Pharmaceuticals shows that the size of this population is approximately 14% of the total locally advanced and non resectable population of patients with SCCHN. | The Appraisal Committee considered the criteria submitted by the consulttees for identifying patients for whom chemoradiotherapy is unsuitable (see FAD section 4.10) |
| | • Carboplatin is not licensed for the treatment of SCCHN. In addition there is no large scale clinical data to support the use of carboplatin in the treatment of LA SCCHN. Hence, carboplatin should be removed from this technology appraisal as inclusion gives an impression that NICE are endorsing an unlicensed treatment, which is inappropriate. | Chemoradiotherapy is only considered as a comparator in this appraisal, that is, an alternative treatment with which the treatment under appraisal is compared. Consideration of comparator treatments 'off licence' is appropriate when such treatment is considered part of current practice in the NHS (see section 2.2.3.1 of the Guide to the Methods of Technology Appraisal). The Appraisal Committee does not make recommendations about comparator treatments |
| | • A simple criterion can be applied and recommended by NICE to the NHS for the treatment of LA SCCHN with cetuximab in combination with radiotherapy. This criterion would be as follows, "Cetuximab in combination with radiotherapy is recommended for use in patients with a good performance status and who are medically inappropriate to receive cisplatin plus radiotherapy". This is similar to guidance issued by the Scottish Medicines Consortium. A list of reasons why cisplatin based chemoradiotherapy may be deemed to be medically inappropriate is included later in this response to the ACD. | The Appraisal Committee considered the criteria submitted by the consultees for identifying patients for whom chemoradiotherapy is unsuitable (see FAD section 4.10) |
| | • The ACD critiques the radiotherapy schedules used in the Bonner study and suggests that the regimens used are not representative of treatment in the UK. This critique is flawed, as to the knowledge of Merck Pharmaceuticals, there is no published source which describes UK clinical practice and once a day standard treatment. The A+A audit conducted by Merck Pharmaceuticals showed that radiotherapy schedules in the UK vary by total number of Grays and fractions given, according to hospital and region, based upon clinician preference and available resources. It is therefore inaccurate to assume that once a day radiotherapy treatment is standard for the UK. | Acknowledged by the Appraisal Committee in the ACD (See section 4.4) No action required for the FAD<br>These comments relate to the ERG report rather than the ACD. No action required for FAD |

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| Merck (continued) | Merck Pharmaceuticals A+A audit data of patients treated for SCCHN in the UK shows that of those patients whose condition is locally advanced and non resectable, 21% receive radiotherapy alone. 14% of the overall LA SCCHN non resectable population could be termed as having a high performance status (ECOG of 0 or 1) and it would be medically appropriate for cetuximab to be added into their radiotherapy treatment regimen. Indeed use of cetuximab in this group of patients represents a cost-effective use of NHS resource in comparison to using radiotherapy alone given the publication of the Bonner et al2 study which clearly demonstrates significant clinical benefit for cetuximab in this setting.<br><br>**1a) <u>The definition of patient "fitness" described by NICE in the ACD and the relationship to Karnofsky performance status</u>**<br><br>Section 4.8 of the ACD[1] states:<br><br>*"The Committee considered the possibility that the subgroup with lower performance status might best represent the population for whom chemoradiotherapy would be considered inappropriate in clinical practice"*<br><br>The ACD presents an incorrect ***assumption*** that all patients in the Bonner study would have been suitable for chemoradiotherapy (CRT) since the average Karnofsky Performance Status (KPS) in the study was >80[2]. Patient, "fitness" for treatment can be defined by a Karnofsky performance score (KPS), but this is not a measure of concomitant conditions. It is possible for a patient to have a high KPS (90 or above), have a concomitant condition, and be unsuitable for cisplatin based chemoradiotherapy treatment. Hence it is incorrect to assume that "fitness" is the only determinant by which a patient would, or would not be prescribed cisplatin as part of their treatment. | The Appraisal Committee considered the criteria submitted by the consultees for identifying patients for whom chemoradiotherapy is unsuitable (see FAD section 4.10) |

1 National Institute for Clinical Excellence. Appraisal Consultation Document – cetuximab for cancer of the head and neck. Issue data: January 2007

2 Bonner JA et al. Radiotherapy plus Cetuximab for Squamous- Cell Carcinoma of the Head and Neck. N Engl J Med 2006;354:567-78.

| Consultee or Commentator | Comment | Institute response |
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| Merck (continued) | Section 4.7 of the ACD states:<br>*"The Committee concluded that there were likely to be few patients with a Karnofsky performance score of 90 or more who have contraindications to both chemoradiotherapy options."*<br>It is clear from the above quote that NICE acknowledge that this population of patients, albeit a small population, does exist. However, it is incorrect to assume there are ***only a few*** patients who would have a good performance status (i.e. KPS >80) and not be appropriate for cisplatin based chemoradiotherapy, since such patients could have concomitant conditions which preclude the use of cisplatin based chemoradiotherapy. Again this is the use of a flawed assumption which states that patient "fitness" is determined by the presence or absence of a concomitant condition. Indeed comorbidity and Karnofksy Performance score have been shown to be independent prognostic factors in the treatment of cancer [3].<br>In summary, if the appraisal committee conclude there are likely to be few patients with a KPS of 90 or more who have contraindications to cisplatin based chemoradiotherapy, then it could be considered unethical and medically indefensible to deny treatment to this particular group of patients and unreasonable of NICE to ignore the treatment needs of this group of patients | The Committee considered both cisplatin and carboplatin were suitable comparators. While acknowledging that cisplatin had contraindications that could be consistent, in some cases, with a high performance status, the Committee noted that carboplatin had fewer contraindications than cisplatin. The Committee concluded that conditions that are contraindications for chemoradiotherapy with carboplatin would generally be associated with impaired performance status. See FAD 4.10 |

[3] Firat et al, Int J Radiat Oncol Biol Phys. 2002 Oct 1;54(2):357-64).

| Consultee or Commentator | Comment | Institute response |
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| Merck (continued) | Reasons why a patient may be inappropriate for cisplatin based chemoradiotherapy treatment are presented below:<br>• **Comorbidity:**<br>o Active peripheral, cerebral or coronary vascular disease<br>o Any form of myelosuppression<br>• **Contraindication:**<br>o Condition that may be exacerbated by the risks associated with thrombocytopenia<br>o Impaired renal function<br>o Impaired hearing<br>o Peripheral neuropathy<br>• **Other reasons:**<br>o Previous cisplatin therapy<br>o Patient choice for treatment<br>Merck Pharmaceuticals have carried out an audit of the treatment of patients with SCCHN in the UK (A+A Merck KGaA[4] market research audit) over two time periods: Wave 1 was in November 2005; Wave 2 was in the period of November 2006 to January 2007. The objective of this audit was to assess the heterogeneity of the SCCHN patient group and treatment differences in the UK. This audit was conducted because such detailed information was not available in any publicly available database.<br>Information from the November 2005 audit (Wave 1) was presented in Merck's original submission to NICE. The questionnaire for this audit was further refined for Wave 2 of the market research audit, in order to collect information on the concomitant conditions patients presented with prior to treatment. | See above and FAD 4.10 |

[4] Data on file - A+A Healthcare market research audit Merck KgaA UKEHN06005

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<tr><th>Consultee or Commentator</th><th>Comment</th><th>Institute response</th></tr>
<tr><td>Merck (continued)</td><td>
The key demographic data from both “waves” are shown in table 1 below:<br><br>
Table 1: Merck Pharmaceuticals A+A audit of SCCHN
<table>
<tr><th>Parameter collected</th><th>Wave 1 (Nov ‘05)</th><th>Wave 2 (Nov ‘06 –Jan ‘07)</th></tr>
<tr><td>Number of participating physicians</td><td>52</td><td>51</td></tr>
<tr><td>Number of patient records</td><td>405</td><td>412</td></tr>
<tr><td>Number of patients with locally advanced non-resectable disease</td><td>133 (33%)</td><td>154 (37%)</td></tr>
<tr><td>Patients who are LA & non resectable</td><td></td><td></td></tr>
<tr><td>Who received RT alone</td><td>51 (38%)</td><td>32 (21%)</td></tr>
<tr><td>% patients with ECOG 0-1</td><td>84%</td><td>68%</td></tr>
<tr><td>Mean age</td><td>62 yrs</td><td>61.2yrs</td></tr>
<tr><td>Comorbidities prior to treatment</td><td>Information not collected</td><td>Observed in 17/22 pts. See Table 2 for details</td></tr>
</table>
Data presented in table 1 shows that this actual patient population compares well with those patients treated in the Bonner study.<br><br>
The research conducted from November 2006 – January 2007[5] reflects how the treatment of SCCHN has developed in a one year time frame.<br><br>
A full description of methods and comprehensive results are presented in Appendix 1, but in summary this data was collected from 51 physicians across the UK between November 2006 and January 2007. To give greater external validity to this data Merck Pharmaceuticals consulted with a number of oncologists. The general opinion was that this data was representative of their practice, with full comments presented in Appendix 2.
</td><td>See above and FAD 4.10</td></tr>
</table>

[5] Data on file - A+A Healthcare market research audit 2006- 2007 Merck KgaA UKEHN07001

| Consultee or Commentator | Comment | Institute response |
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| Merck (continued) | Each physician provided data from case notes of their last 7-8 patient cases treated with radiotherapy and/or chemotherapy for SCCHN.<br>• In total, data from **412 patient cases** treated with radiotherapy and/or chemoradiotherapy were collected<br>• **154 patient cases (37%)** described the treatment of patients who were termed as locally advanced and non resectable<br>• **32 patient cases (21%)** described the treatment of patients who were termed as locally advanced and non resectable and treated with radiotherapy<br>Data presented focuses upon a particular group of patients for whom the addition of cetuximab to a radiotherapy treatment regimen would be medically appropriate, that is:<br>• Locally advanced SCCHN<br>• Non resectable<br>• Treated with radiotherapy<br>• Reporting an ECOG performance score of 0 or 1 (i.e. a high performance status)<br>**This group consists of 22 patient cases which is 14% of the LA nopn resectable patients treated**.<br>• The mean age of patients in this group was 71 years<br>• 7 (32%) of these patients were under the age of 65<br>• Tumour location:<br>o Oral cavity: 3 14%<br>o Nasopharynx: 1 5%<br>o Oropharynx: 6 27%<br>o Hypopharynx: 5 23%<br>o Larynx: 7 32%<br>• A concomitant condition was found in 17 patients (77%). Further details of the concomitant conditions reported are detailed below in table 2. | See above and FAD 4.10 |

| Consultee or Commentator | Comment | Institute response |
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| Merck (continued) | **Table 2: Concomitant conditions found in patients with LA SCCHN, non resectable and receiving radiotherapy treatment alone** | See above and FAD 4.10 |

| Concomitant conditions | Number | % |
|---|---|---|
| Coronary arterial disease | 2 | 9.1 |
| Coronary arterial disease / Other CV disease | 2 | 9.1 |
| Coronary arterial disease / Other CV disease / Other | 0 | 0.0 |
| Coronary arterial disease / Other CV disease / Renal impairment | 1 | 4.5 |
| Coronary arterial disease / Renal impairment | 2 | 9.1 |
| Coronary arterial disease / Renal impairment / Pulmonary disease | 1 | 4.5 |
| Other | 0 | 0.0 |
| Other CV disease | 2 | 9.1 |
| Other CV disease / Pulmonary disease | 0 | 0.0 |
| Peripheral vascular disease | 1 | 4.5 |
| Peripheral vascular disease / Coronary arterial disease | 1 | 4.5 |
| Peripheral vascular disease / Other CV disease | 0 | 0.0 |
| Peripheral vascular disease / Other CV disease / Other | 0 | 0.0 |
| Peripheral vascular disease / Renal impairment | 1 | 4.5 |
| Pulmonary disease | 3 | 13.6 |
| Renal impairment | 1 | 4.5 |
| Renal impairment / Other | 0 | 0.0 |
| **Total** | **17** | **77.3** |

<table>
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<tr><td>Merck (continued)</td><td>

- 22 patients received radiotherapy alone. Of these patients the rationale for not prescribing chemoradiotherapy is presented in table 3 below.

**Table 3: Rationale not to prescribe any chemotherapy to this patient?**

| Rationale | Number | % |
|---|---|---|
| No indication | 9 | 40.9 |
| Patient performance status/general state does not allow to prescribe CT / Toxicity of CT would be too great | 1 | 4.5 |
| Patient is not compliant | 1 | 4.5 |
| Patient performance status/general state does not allow to prescribe CT | 8 | 36.4 |
| Toxicity of CT would be too great | 3 | 13.6 |
| **Total** | **22** | **100** |

**1b) <u>NICE proposed alternative treatments for SCCHN: the licensing and contraindications associated with the use of cisplatin and carboplatin</u>**

Section 4.3 of the ACD states;

*“Chemoradiotherapy (concomitant chemotherapy being either cisplatin or carboplatin-based) carries a high risk of adverse effects and requires patients to be willing and fit enough to cope with these.”*

Carboplatin is not licensed for the treatment of SCCHN and wording for such is not included in section 4.1 of the carboplatin SPC[6 7 8]. In addition there are no large scale clinical data to support the use of carboplatin in the treatment of LA SCCHN. Hence, carboplatin should be removed from consideration for this technology appraisal as inclusion gives an impression that NICE are endorsing an unlicensed treatment, and this is inappropriate.

Additionally section 4.7 of the ACD states;

*“The Committee concluded that there were likely to be few patients with a Karnofsky performance score of 90 or more who have contraindications to both chemoradiotherapy options.”*

</td><td>Chemoradiotherapy is only considered as a comparator in this appraisal, that is, an alternative treatment with which the treatment under appraisal is compared. Consideration of comparator treatments ‘off licence’ is appropriate when such treatment is considered part of current practice in the NHS (see section 2.2.3.1 of the Guide to the Methods of Technology Appraisal). The Appraisal Committee does not make recommendations about comparator treatments</td></tr>
</table>

6 Carboplatin 10 mg/ml Intravenous Infusion (SPC) (Mayne Pharma plc). http://emc.medicines.org.uk/
7 Carboplatin 10mg/ml Concentrate for Solution for Injection (SPC) (Wockhardt). http://emc.medicines.org.uk/
8 Paraplatin 10mg/ml Concentrate for Solution for Infusion. (SPC)(Bristol Myers Squibb) http://emc.medicines.org.uk/

<table>
<tr><th>Consultee or Commentator</th><th>Comment</th><th>Institute response</th></tr>
<tr><td>Merck (continued)</td><td>Table 4 below compares contraindications for cisplatin and carboplatin.<br><br>Table 4: An assessment of SPC contraindications and warnings for cisplatin and carboplatin
<table>
<tr><th>Reason why a patient may be medically inappropriate</th><th>Cisplatin[9]</th><th>Carboplatin</th></tr>
<tr><td>Active peripheral, cerebral or coronary vascular disease.</td><td>Section 4.8. Undesirable effects. Anaemia is reported as an undesirable effect. (This is a concern for pts who have moderate to severe cardiac disease or COPD)</td><td>Section 4.8 Undesirable effects. Anaemia is reported as an undesirable effect. (This is a concern for pts who have moderate to severe cardiac disease or COPD)</td></tr>
<tr><td>Impaired renal function (given the nephrotoxicity profile of cisplatin).</td><td>Section 4.3. Contraindication in renal impairment.</td><td>Section 4.3. Contraindication in severe renal impairment (CrCL <20ml/min).</td></tr>
<tr><td>Impaired hearing (given ototoxicity).</td><td>Section 4.3. Contraindication in ototoxicity</td><td>Section 4.8 Undesirable effects. Ear and Labyrinth disorders</td></tr>
<tr><td>Peripheral neuropathy.</td><td>Section 4.8 Undesirable effects. Neurotoxicity including peripheral neuropathy</td><td>Section 4.8 Undesirable effects. Mild peripheral neuropathy</td></tr>
<tr><td>Any form of myelosuppression.</td><td>Section 4.3 Contraindicated in myelosuppressed patients</td><td>Section 4.3 Contraindicated in severe myelosuppressed patients</td></tr>
</table></td><td>The Committee considered both cisplatin and carboplatin were suitable comparators. While acknowledging that cisplatin had contraindications that could be consistent, in some cases, with a high performance status, the Committee noted that carboplatin had fewer contraindications than cisplatin. The Committee concluded that conditions that are contraindications for chemoradiotherapy with carboplatin would be associated with impaired performance status. See FAD 4.10.</td></tr>
</table>

[9] Cisplatin 1 mg/ml Sterile Concentrate (SPC).(Mayne Pharma plc). http://emc.medicines.org.uk/

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| Merck (continued) | Table 4 shows that the SPC's for both cisplatin and carboplatin contain contraindications or warnings for active peripheral, cerebral or coronary vascular disease, impaired renal function, impaired hearing and any form of myelosuppression.<br><br>Furthermore with regards to patients who may be inappropriate for cisplatin based chemoradiotherapy, section 4.3 of the ACD states;<br><br>*"Chemoradiotherapy (concomitant chemotherapy being either cisplatin or carboplatin-based) carries a high risk of adverse effects and requires patients to be willing and fit enough to cope with these."*<br><br>If NICE are acknowledging the high risk of adverse effects associated with cisplatin based chemoradiotherapy and that a patient would have to be willing to cope with such treatment, then patient choice of treatment must be considered here as a reason not to receive chemoradiotherapy.<br><br>One of the cornerstones of the Government's health strategy is patient choice, and we are sure that NICE are mindful of this in their recommendations to the Department of Health[10]. | See above |

[10] Building on the best: Choice, responsiveness and equity in the NHS Department of Health 09/12/2003 http://www.dh.gov.uk/PublicationsAndStatistics/Publications/PublicationsPolicyAndGuidance/PublicationsPolicyAndGuidanceArticle/fs/en?CONTENT_ID=4075292&chk=xhE5pS

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| Merck (continued) | **1c) <u>Proposed criteria for the selection of patients for whom the use of cetuximab in combination with radiotherapy is appropriate to ensure that clinical and cost effectiveness measures are met in clinical practice</u>**<br><br>After consultation with UK oncologists Merck Pharmaceuticals would propose that the following patient selection criteria should be used in the consideration of prescribing cetuximab plus radiotherapy to ensure that clinical and cost effectiveness as presented in the original Merck submission and Bonner et al are transferred to the naturalistic setting.<br><br>1. Patient is to receive a radiotherapy regimen:<br><br>2. The patient is of good performance status (KPS>80 or ECOG 0-1)<br><br>3. The patient is considered medically inappropriate to receive cisplatin based chemoradiotherapy or the patient's choice of treatment/ unwilling to receive chemoradiotherapy<br><br>Based upon input from UK oncologists, the following are reasons by which a patient may be considered medically inappropriate to receive cisplatin based chemoradiotherapy:<br><br>• Active peripheral, cerebral or coronary vascular disease<br>• Any condition that may be exacerbated by the risks of thrombocytopenia (commonly observed with high-dose cisplatin treatment)<br>• Impaired renal function (cisplatin can induce nephrotoxicity)<br>• Impaired hearing (cisplatin can induce ototoxicity )<br>• Peripheral neuropathy (cisplatin can induce neuropathy)<br>• Previous cisplatin therapy for any malignancy<br>• Any form of myelosuppression | The Appraisal Committee considered the criteria submitted by consultees for identifying patients for whom chemoradiotherapy is unsuitable (see FAD section 4.10) |

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| Merck (continued) | **2. <u>Radiotherapy treatment patterns for the treatment of LA SCCHN in the UK</u>**<br>Section 3.6 of the ACD states;<br>*"Furthermore, there are differences between the radiotherapy regimens used predominantly in UK clinical practice and those that were used in the trial".*<br>Radiotherapy schedules in the UK vary by total number of Grays (Gy) and fractions given, according to hospital and region, based upon clinician preference and available resources. It is therefore inaccurate to assume that once a day radiotherapy treatment is standard for the UK.<br>We have been unable to find a published source to validate NICE's claim that radiotherapy regimens in the UK are standardised. The ERG report[11] states the following:<br>*"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]".*<br>However the reference for such a survey appears to be referenced incorrectly as:<br>"*Telephone conference calls 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."*<br>Merck Pharmaceuticals would appreciate correction of this inaccuracy and provision of the actual publication of the Royal College of Radiologists survey to assess methods used within this survey. The A+A audit data collected on behalf of Merck Pharmaceuticals clearly demonstrate that radiotherapy schedules in the UK vary across the country based upon clinician preference and local resource constraints. Data from the two waves of the audit of the UK treatment of patients with SCCHN (A+A Merck KGaA market research audit) conducted in November 2005 and in the period of November 2006 to January 2007 validates this. | Acknowledged by the Appraisal Committee in the ACD (See ACD, section 4.4) No action required for the FAD |

[11] Evidence Review Group Report prepared by Centre for Health Economics, University of York & NHS Northern and Yorkshire Regional Drug and Therapeutics Centre. ERBITUX® (CETUXIMAB) FOR THE TREATMENT OF LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA OF THE HEAD & NECK (LA SCCHN)

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| Merck (continued) | In Wave 1 of the audit conducted in November 2005, of the 79 patients with LA SCCHN non resectable disease who received radiotherapy as part of their treatment regimen, there was no one particular radiotherapy schedule with regards to Gy total dose and number of fractions planned.<br>• The average total dose was 62 Gy (with 79% between 60 and 70)<br>• The average number of fractions planned was 29 (with 79% between 30 and 35)<br>In wave 2 of the audit, in the 35 patients with LA SCCHN non resectable disease that received radiotherapy a similar picture was observed:<br>• The average total dose was 65 Gy (with 79% between 65 and 70)<br>• The average number of fractions planned was 31 (with 79% between 30 and 35)<br>Furthermore this is supported by the national head and neck cancer audit (Data for Head and Neck Oncology; DAHNO)[12] which states that there are no set treatment guidelines for patients with locally advanced SCCHN. In addition, guidelines published by SIGN[13] do not include reference to current once daily usage. The Royal College of Radiologists report[14] made recommendations for stage III and IV disease (LA SCCHN) as follows:<br>*"Fit patients with Stage III or IV head and neck cancer treated with definitive radiotherapy should not be treated with conventional fractionation alone (10 Gy per week)".*<br>Given such data it is incorrect to state that the radiotherapy regimens used in Bonner are not reflective of UK treatment and unreasonable to question the reported efficacy of Bonner et al due to differences in radiotherapy.<br>**3. <u>Critique of the decision problem</u>**<br>**a) Medical ethics governing the choice of treatment with radiotherapy alone**<br>**b) Clinical research timelines and the use of current standard treatment**<br>**c) Implications for clinical research in the UK** | |

[12] NHS Health and Social Care Information Centre. DAHNO (Data for Head and Neck Oncology) first annual report: key findings from the national head and neck cancer audit, January 2004 – November 2005. National Clinical Audit Support Programme, Leeds.
[13] SIGN Guideline 90- Diagnosis and management of head and neck cancer (October 2006). www.sign.ac.uk
[14] Radiotherapy Dose Fractionation. Royal College of Radiologists. (June 2006) www.rcr.ac.uk

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| Merck (continued) | **a) <u>Medical ethics governing the choice of treatment with radiotherapy alone</u>**<br>Section 3.6 of the ACD states;<br>*"The Committee considered the decision problem described in the manufacturer's submission to be reasonable, but noted that the population specified excluded people for whom chemotherapy is suitable. Therefore the decision problem did not reflect the entire population of people with locally advanced squamous cell cancer of the head and neck for whom cetuximab might be considered as a treatment option."*<br>The Bonner study was initiated in 1999. The primary objective of this research was to examine the duration of locoregional control in subjects with locally advanced SCCHN treated with either radiotherapy or cetuximab in combination with radiotherapy. This study produced clinically significant results with regards to the treatment of LA SCCHN. Indeed it could be deemed <u>medically unethical</u> to give radiotherapy alone following the publication of the Bonner et al study which clearly demonstrates significant clinical benefit as follows:<br>• Improved median duration of locoregional control by 9.5 months (from 14.9 months (RT) to 24.4 months (ERT) (p=0.005)).<br>• Prolonged median overall survival by 19.7 months (from 29.3 months (RT) to 49.0 months (ERT) (p=0.03)) with a 26% reduction in the risk of death.<br>• Significantly improved progression-free survival, with a median of 17.1 months compared to 12.4 months in those patients treated with radiotherapy alone (p=0.006).<br>• When used in combination with radiotherapy, cetuximab does not significantly exacerbate the toxicities associated with radiotherapy.<br>When cisplatin based chemoradiotherapy is deemed to be inappropriate for a patient, it could be regarded as medically unethical to withhold cetuximab from a patient's radiotherapy based treatment regimen. | The committee acknowledged that the trial was initiated at a time when radiotherapy was still the standard treatment (see FAD section 4.5) |

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| Merck (continued) | **b) <u>Clinical research timelines and the use of current standard treatment</u>**<br><br>In 1999 when the Bonner study was initiated, the current standard treatment for locally advanced SCCHN was radiotherapy, and hence the Bonner study was designed to compare cetuximab plus radiotherapy against this standard treatment and not against cisplatin based chemoradiotherapy. Therefore, the collection of data on patients who were considered medically inappropriate for cisplatin based chemoradiotherapy was not a consideration at the time the trial was initiated. Pivotal analyses of the benefits of cisplatin based chemoradiotherapy began in 2000 with the publication of the MACH NC data[15], although this did not start to become integrated into UK clinical practice until 2001/ 2002.<br><br>**c) <u>Implications for clinical research in the UK</u>**<br><br>Due to the timelines incurred in completing large randomised Phase III trials, it is not uncommon for there to be a paradigm shift in the interim period between design of the study and publication of results and marketing authorisation being received, as we observe here with the use of chemoradiotherapy becoming the new current standard treatment for locally advanced SCCHN.<br><br>In this light it is unreasonable of the appraisal committee to not consider such implications and to give a negative recommendation for a treatment which can provide significant clinical benefit to those patients who are inappropriate to receive chemoradiotherapy. | The Committee acknowledged that the trial was initiated at a time when radiotherapy was standard treatment (See FAD section 4.5)<br><br>The Committee concluded that the evidence did not provide a robust demonstration of the clinical effectiveness of cetuximab plus radiotherapy compared with radiotherapy alone in the relevant subgroup of patients. |
| Clinical Expert Dr Nick Slevin | I welcome the opportunity to comment on the Evaluation Report and Appraisal Consultation Document (ACD) for Cetuximab in locally advanced head and neck cancer.<br><br>The simple logic adopted in the ACD seems to be that patients considered unfit for the "standard" of chemoradiotherapy were <u>not</u> the patient group which dominated the Bonner Phase 3 Study such that there is insufficient evidence to justify the use of Cetuximab in this less fit patient group. It was obvious to me from the session where I offered verbal evidence to the Committee that there was considerable ignorance around issues of radiotherapy fractionation, variations in chemoradiotherapy practice as well as treatment toxicity which, I believe, undermines the above "logic pathway". I consider that the Committee <u>has not</u> taken into account all of the relevant evidence. | Comment noted |

[15] Pignon J P, Bourhis J, Domenge C et al. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. Lancet 2000; 355: 949-55

| Consultee or Commentator | Comment | Institute response |
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| Clinical Expert Dr Nick Slevin (continued) | Radiotherapy Fractionation<br>It is well recognised that improvements in locoregional control of head and neck cancer (excepting the elderly) usually translate into benefits in overall survival if salvage options are not available, because systemic metastases are relatively uncommon. This relationship has been analysed and calculated to equate to a 6.7% improvement in 5 year survival for a 10% improvement in 2 year locoregional control (Wadsley, Bentzen IJROBP 2004 60 (5) 1405-9). In the large Radiotherapy Oncology Group (RTOG) head and neck fractionation study (Fu et al IJROBP 2000 48(1) 7-16) the accelerated concomitant boost regimen of 72Gy in 6 weeks (1.8 x 30 + boost of 1.5 x 12) gave an improved 2 year locoregional control of 8.5% and improved overall survival at 2 years of 4.8% (not statistically significant) compared to the international standard of 70Gy in 7 weeks. This accelerated regimen had significantly greater acute side effects compared to the standard fractionation but no significant increase in late (enduring) morbidity. This modestly accelerated 1 week shorter than conventional (6 ½ - 7) schedule maintained a conventional total dose of approximately 70Gy (72). Concomitant boost accelerated radiotherapy was adopted as fractionation of choice by the RTOG. Another regimen of modest acceleration (used in some UK centres) is the DAHANCA 6 fraction per week schedule giving (as for the RTOG concomitant boost) a conventional total dose of approximately 70Gy over an overall time 1 week shorter than the conventional (6 ½ - 7) ie 5 ½ weeks. The local control absolute benefit was 10% (Overgaard J Lancet 2003 362. 933-940). Very consistent with the RTOG trial, the DAHANCA regimen had greater acute toxicity (mucositis) but no significant difference in late (enduring) side effects.<br><br>Variations in Chemoradiotherapy Practice<br>Synchronous chemoradiotherapy versus radiotherapy alone gave an absolute improvement in 5 year survival of 8% in the landmark metaanalysis of 63 head and neck trials involving over 10,000 patients (Pignon JP et al Lancet 2000 355 (9208) 949 – 955). An update of this analysis adding 24 trials (Pignon, personal communication) suggested a particular benefit for platinum compared to other cytotoxics such that the survival benefit was 12% (using the 2 to 3 Wadsley/Bentzen guide, this would equate to 18% gain in locoregional control).<br><br>A direct comparison between the international standard of 70Gy in 7 weeks and adding synchronous Cisplatinum (100mg/$m^2$ 3 weekly) in larynx cancer (a site for which salvage options ARE available) showed an 18% gain in locoregional control (70 to 88%) from chemoradiotherapy (Forastiere AA NEJM 2003 349 2091-2098).<br><br>What then happens if synchronous chemotherapy is added to a modestly accelerated concomitant boost radiotherapy schedule? | Comment noted.<br><br>Comment noted. |

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| Clinical Expert Dr Nick Slevin (continued) | A Phase 2 Study was subsequently performed using RTOG concomitant boost radiotherapy with single agent Cisplatin (Ang et al J Clin Oncol 2005 23(13) 3008-15) in acknowledgment that Cisplatin with radiotherapy was an international standard of care. Although the authors suggested "good compliance", 4% of patients died of treatment complications, (within 30 days) 25% had severe (ulceration, haemorrhage, necrosis) acute side effects and the 2 year cumulative incidence of severe late (enduring) morbidity was 51%. These levels of severe toxicity would be totally unacceptable to the UK community of head and neck oncologists and their patients.<br><br>Other investigators have used their own concomitant boost schedules with chemotherapy (eg German study of 70Gy in 5 ½ weeks) and found improvements in tumour control (12% improvement in locoregional control) and overall survival (10% at 3 years). (Semrau R et al IJROBP 2006 and Starr IJROBP 2001 50 (5): 1161 – 1171).<br><br>Treatment Toxicity<br>I have previously emphasised concerns about chronic dysphagia as a consequence of chemoradiotherapy; in a recent review of 63 patients treated by chemoradiotherapy, 5 died of aspiration during/after treatment, the prevalence of severe aspiration was 33% and 39% of patients required prolonged enteral nutritional support for severe dysphagia (Nguyen NP et al Radiother Oncol 2006 80(3) 302-6; Nguyen NP et al Ann Oncol 2004 15(3) 383-8).<br><br>In the Ang Phase 2 Study of RTOG concomitant boost with chemotherapy, 41% of patients still had a feeding tube at 1 year post treatment. In the German concomitant boost and chemotherapy study (Starr 2001), 51% of patients still had a feeding tube at 2 years. The toxic death rate from chemoradiotherapy trials (ie within 30 days) is consistently at least 4% (Adelstein et al J Clin Oncol 2003 21 92 – 98). | Comments noted. The Appraisal Committee acknowledged the high risk of adverse effects of chemoradiotherapy.(see ACD, section 4.3) |

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| Clinical Expert Dr Nick Slevin (continued) | Bonner Study<br>The radiotherapy regimen used in the Bonner Study was this same RTOG accelerated concomitant boost in the majority. We know that choosing an accelerated schedule is advantageous in this disease group with high expression of EGFR, as EGFR expression predicts for benefit from accelerated radiotherapy as compared to conventional (Bentzen J Clin Oncol 2005 23(24) 5560-7). In the Bonner Study addition of Cetuximab gave a 3 year improvement in locoregional control of 13% (34-47) which translated to an (expected) overall survival benefit of 10% at 3 years. These benefits are virtually identical to other concomitant boost radiotherapy trials using chemotherapy (albeit with a different schedule to the RTOG) (eg Budach et al J Clin Oncol 2005 23(6) 1125-35) with a gain in 3 year locoregional control of 13% (39-52) and 3 year survival benefit of 9%; Starr et al above 12% improvement LRC, 10% overall survival gain.<br>In the absence of a randomised trial of a direct comparison between Cetuximab and Cisplatin:<br>Benefit in LRC<br>(i) Conventional fractionation (CF) v concomitant boost (CB) 8.5% (RTOG Study)<br>(ii) CF v CF + Cisplatin approx 15% - 20%<br>(update of IGR meta analysis/Forastiere study)<br>(iii) RTOG CB + Cisplatin too toxic for routine use (Ang study)<br>(iv) RTOG CB v CB + Cetuximab (Bonner Study) 13%<br>(v) Variations in concomitant boost + chemo 13% (Budach/Starr studies)<br>ie benefit in LRC (8.5% + 13%) with CB + Cetuximab versus conventional fractionation likely to be at least as great as with chemoradiotherapy versus conventional fractionation. The local control benefit from adding Cetuximab to RTOG CB is likely to be very similar to that from adding chemotherapy to CB (13%). However, crucially for the patients, both the RTOG CB used in the Bonner Study as well as the Cetuximab would not increase late (enduring toxicity) compared to conventional fractionation alone. This is in contrast to adding chemotherapy. Other experts suggest that Cetuximab gives a superior median survival advantage compared to chemoradiotherapy (Bernier J, Eur J Cancer 2007 43 35 – 45)<br><br>Recommendation to do Clinical Trial<br>Having been Chair of the NCRI head and neck research group it would be IMPOSSIBLE to get agreement on trial design and/or funding to do a clinical trial of RT + Cetuximab versus RT + chemo as recommended in the ACD: | Comment noted<br><br>Comment noted (See FAD section 6.1) |

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| Clinical Expert Dr Nick Slevin (continued) | Option A<br>Accelerated RT schedule + Cetuximab v accelerated schedule + synchronous Cisplatin – latter would be considered too toxic; differences in tumour control likely to be very small (see above: 13% v 13%)/numbers required too large.<br><br>Option B<br>Accelerated RT schedule + Cetuximab v conventional RT + Cisplatin – would not be considered scientific (2 variables) and likely differences would be in late toxicity (would not be funded).<br><br>Option C<br>Conventional RT + Cetuximab v conventional RT + chemo – former would be regarded as substandard as Cetuximab does not increase mucositis; conventional RT is no longer optimum fractionation and randomised trial evidence confirms that acceleration gives better outcomes for EGFR positive cancer than conventional fractionation. | |

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| Clinical Expert Dr Nick Slevin (continued) | <u>How do we choose which Stage 3/4 patients should have Cetuximab?</u><br>1. A 75 year old KP 60 patient alcoholic smoker<br>Is likely to struggle even with conventional RT alone.<br>No evidence for benefit from modified fractionation, chemotherapy nor indeed Cetuximab.<br>2. A 50 year old KP 90 patient with myocardial infarct 6 months ago.<br>Should not have Cisplatin with its recognised vasculopathic toxicity.<br>Would be suitable for Cetuximab.<br>3. A 50 year old KP 90 patient with hypertension and GFR of 50.<br>Should be considered for Cetuximab accepting that renal function and general toxicities should be closely monitored.<br>4. A 30 year old KP 100 patient having significant RT dose to the inner ear (with resultant risk of sensorineural deafness/tinnitus).<br>Should have Cetuximab rather than Cisplatin (recognised ototoxicity).<br>5. A 50 year old depressed KP 90 patient living alone with poor nutrition/prior weight loss.<br>Should be wary of chemoradiotherapy on account of likely poor patient acceptance of severe mucositis and difficulty in coping with likely medium/long term feeding tube dependence.<br>Would be suitable for Cetuximab.<br>6. A 50 year old KP 100 patient with N2/N3 disease.<br>Use adjuvant chemotherapy on account of significant risk of systemic metastases; no evidence that Cetuximab reduces metastatic disease.<br>7. A 50 year old KP 100 patient, NICE Committee Chair, with T2pN1 tonsil cancer.<br>Patient concerned about severity of mucositis/weight loss/debilitation and its impact on Committee work that would ensue from chemoradiotherapy. Having been informed of relevant data, <u>the patient</u> opts for accelerated RT + Cetuximab.<br>Patients 1, 2, 3, 4, 5 and 7 are <u>"UNSUITABLE"</u> for Cisplatin chemotherapy.<br>Patient 1 is unsuitable for chemoradiotherapy and Cetuximab.<br>Patient 6 is <u>better</u> treated with adjuvant chemotherapy.<br>Patients 2, 3, 4, 5 and 7 are <u>better</u> treated with Cetuximab. | The Appraisal Committee considered the criteria submitted by consultees for identifying patients in whom chemoradiotherapy is unsuitable (see FAD section 4.10) |

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| Clinical Expert Dr Nick Slevin (continued) | In other words it is not possible to pigeon-hole the exact indications for accelerated RT + Cetuximab except to say that some patients are UNSUITABLE for chemoradiotherapy (in my own practice, about 1 patient in 3). It would be extremely useful to be able to select patients on the basis of their tumour EGFR status but, unfortunately, this requires methodological refinement to become a useful therapeutic predictive test.<br><br>Conclusion<br>The Bonner Study should be regarded as a proof of principle study. I have previously estimated the proportion overall of head and neck cancer patients likely to be suitable for Cetuximab is 10-20% only (or about 30% of non-surgical patients who might be considered for chemotherapy but who are "unsuitable" for this). Head and neck patients are a "Cinderella" speciality because they receive little media focus or prioritisation for health funding (contrast this with the preliminary 3% survival benefit at 3 years for adjuvant Herceptin in the HERA breast trial – NICE approved).<br><br>I propose that accelerated radiotherapy with Cetuximab is approved as a CURATIVE option for patients with locally advanced head and neck cancer. If I was a head and neck cancer patient with heavy node positive disease (which predicts for systemic metastases) I would choose chemotherapy as adjuvant treatment; without heavy node positive Stage 3/4 disease I WOULD CHOOSE accelerated radiotherapy with Cetuximab as THE TREATMENT OF CHOICE (particularly in relation to toxicity). I hope the Appraisal Committee will consider these comments and approve the use of Cetuximab. I genuinely believe that lack of approval of Cetuximab will REDUCE the cure rate for this patient group and that the provisional recommendations of the Appraisal Committee are unsound.<br><br>POST SCRIPT<br>If I have previously been at fault for failing to recognise the need to detail complex fractionation issues to the Committee then I apologise. If details of reasons behind the variation in head and neck management have previously been omitted from my evidence this was due to a complacent assumption on my part that Cetuximab WOULD be approved – again I apologise. I have quoted "high impact" recent literature pertinent to key issues (accepting all the inconsistencies of the medical literature). | Comment noted. As above<br><br>The Appraisal Committee accepted that (see section 4.5 ACD). No action required for FAD |

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| British Association of Head and Neck Oncologists | I have been asked by the British Association of Head and Neck Oncologists to reply to the initial assessment for Cetuximab in advanced head and neck cancer. I wanted to reply after the ESTRO Head and neck meeting last week because I wanted to ensure a representative reply rather than a personal one.<br><br>As you know Cetuximab is the first drug in head and neck cancer that has been licenced by the FDA for over forty years. There is a lot of scientific evidence as to why it may be effective and a lot of interest generally. Prognosis for advanced head and neck cancer has not really improved significantly over the years, and local control as well as survival is a major issue with quality of survival in this group. The current standard of care is chemoradiotherapy with several well designed trials plus updated meta analysis to support its use. However the latest update presented at ASCO in 2006, noted the relative lack of improvement in outcomes in the over 71 year age group. The toxicity of chemoradiotherapy has always been noted and some of the American trials have suggested mortality rates of up to 6%, which with a surival benefit of 10 - 12 % is significant. The patient group also have considerable co morbidities.<br><br>The advantages of Cetuximab is said to be the lack of increase in radiation induced toxicity such as dysphagia or mucositis although other side effects partiuclarly the rash are well know and rash presence indicates benefit. | Comment noted |
| | The request for licensing by Merck however relates to only one study. While this Bonner et all study has been very well conducted, its age means it did not compare chemoradiotherpay plus or minus cetuximab. Therefore Merck have extrapolated the patient population to apply for a licence in those unfit for chemoradiotherapy. While there is general scientific support for such a drug there is very limited experience in the UK with some centres having treated about 10 patients. The major sticking point is that Merck are trying to have the NICE badge for a group of patients which have not been specifically targetted in the Bonner study. Most patients unfit for chemoxrt are unfit on t he basis of performance status, extreme age, poor cardiac or renal function. The study required patients to have good performance stage and normal renal function and the median age was 58 years. Therefore we are reliant on limited UK practice plus lack of evidence for chemoradiotherapy in 71 years or more. The practice does however seem to favour the tolerability of the drug but of course is not being audited etc. | Comment noted |
| | Minor points about the study also include the preponderance for oropharyngeal cancers, whereas in the elderly the laryngeal and hypopharyngeal are more common. Over 56% had hyperfractionated treatments with radiotherapy which are quite tough and therefore go with the expected good performance status. Those schedules are rarely used in the UK. | Comment noted |
| | Although the study was well received, even at ESTO head and neck conference where Cetuximab was being billed as an option for patients, Kian Ang who was one of the authors of the trial, would not be drawn into when to specifically use the drug, pointing out the experience in less than five hundred patients. | Comment noted |

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| British Association of Head and Neck Oncologists (continued) | I could not comment on whether the economics of improving survival by 10% in a heavily co morbid and older group is cost effective. Local control would be a huge benefit clinically. I note the significant difference in QALYs assessment by NICE and Merck.<br><br>While I struggle with this group of patients clinically and can see potential benefits for patients, I would be concerned that a positive NICE outcome would not be linked to a prospective audit. I would advocate that a group such as the NCRN or even BAHNO via the DAHNO audit already set up should be heavily involved.<br><br>A number of us have proposed that a trial in intermediate cancers, ie the group with no benefit from the addition of chemotherapy would benefit from the Bonner style approach. We are of course awaiting the RTOG trial in advanced disease.<br><br>Overall with so few options available in head and neck cancer and such a scientifically sound drug I would like to see Cetuximab move into clinical practice. The data extrapolation from the Bonner study into the group of patients Merck are proposing is however very contentious and only anecdotally safe. I would like to see more trials in the particular patient group, plus robust audit. The international community also seem to see this drug as a step forward, but it's exact role remains undetermined by the current literature. | Comment noted<br><br>Comment noted<br><br>Comment noted<br><br>Comment noted |
| Cancer Research UK | Advanced local head and neck cancer is a highly distressing condition for patients and their carers. It is also very difficult to treat.<br><br>Non-surgical treatment options for patients with advanced head and neck cancer are radiation therapy or chemotherapy combined with radiation treatment. The current standard of care is chemoradiotherapy using platinum.<br><br>Currently, there is no alternative treatment to radiotherapy alone in those unfit for the relatively toxic platinum-based regimens. Cetuximab, therefore, offers a clinically important therapeutic gain for a subset of patients, both for their quality and duration of life.<br><br>NICE has stated in its Appraisal Consultation Document that it does not recommend cetuximab for patients with locally advanced squamous cell cancer of head and neck. Cancer Research UK considers this recommendation, if finalised, could deny certain patients and their oncologists the opportunity to utilise the first new drug for head and neck cancer for 20 years which has been shown significantly to improve survival rates when used alongside radiotherapy. | Comment noted<br><br>Comment noted<br><br>Comment noted<br><br>Comment noted |

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| Cancer Research UK (continued) | In July last year the Scottish Medicines Consortium approved cetuximab for use within NHS Scotland for the treatment of patients with head and neck cancer who are not appropriate for or unable to tolerate chemoradiotherapy. Clearly, it would be unfair if patients in Carlisle were not entitled to the same treatment options as those over the boarder in Dumfries. | In addition to the manufacturer's submission, an independent Evidence Review Group Report, statements of personal views by patient experts and clinical specialists are considered by the Committee in reaching its recommendations. The Committee cannot speculate about the deliberations of another body. Submissions to SMC and NICE may not have been identical |
| | **We believe that patients who are not suitable for cisplatin should be able to receive cetuximab for head and neck cancer.** | The Appraisal Committee considered the criteria submitted by consultees for identifying patients in whom chemoradiotherapy is unsuitable (see FAD section 4.10). The committee also noted that carboplatin has fewer contraindications than cisplatin |
| | **Clinical evidence**<br>The main source of evidence considered by the appraisal committee is from the Bonner trial, which commenced in 1999. It is worth noting that much of the shift from radiotherapy alone to chemoradiotherapy occurred in routine clinical practice after this trial was designed. At the time the trial commenced the research question 'does cetuximab improve overall survival and locoregional control in advanced head and neck squamous cell carcinoma compared to radiotherapy alone' was a valid demonstration of efficacy. | The Appraisal Committee acknowledged that the trial was initiated at a time when radiotherapy was standard treatment (see FAD section 4.5) |
| | Given the setting, we can therefore understand why the appraisal committee has come to the conclusion that patients entering the study would today be considered fit for chemoradiotherapy. However, as the clinical environment has changed the challenge is to make best sensible deductions from studies whose designs are, without any ability to foresee this on the part of the investigators, no longer in line with new and emerging clinical practice. | The Committee concluded that the evidence did not provide a robust demonstration of the clinical effectiveness of cetuximab plus radiotherapy compared with radiotherapy alone in the relevant subgroup of patients. |

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| Cancer Research UK (continued) | NICE's Evidence Review Group and appraisal committee have rejected the manufacturer's proposal that cetuximab should be considered for patients who are not suitable for chemoradiotherapy, on the basis that trial data are only available for patients with good performance status and who would therefore be 'expected to be suitable for chemoradiotherapy'. However, it is not always the case that only patients who have poor performance status are those who are platinum intolerant. Many patients are unable to tolerate cisplatin due to conditions such as sensorineural hearing loss, peripheral neuropathy, and renal impairment, as well as having poorer performance status. | The Appraisal Committee considered the criteria submitted by consultees for identifying patients for whom chemoradiotherapy is unsuitable (see FAD section 4.10) |
| | We also note the predominance of oropharyngeal patients in the population of the Bonner trial. While cetuximab clearly showed efficacy at this site, this was not reflected in the other subsites studied (larynx, hypopharynx) but the trial was not powered to allow subset analyses, so firm conclusions cannot be drawn. As NICE"s appraisal is designed to cover 'head and neck' cancer, it should be recognised that this is a heterogeneous group of biologically different cancers and the Bonner findings might not accurately indicate how all primary tumour sites respond. We suggest that NICE might therefore consider the value of cetuximab in oropharyngeal cancer patients only. | Comment noted |
| | **Financial implications**<br>The subset of patients for whom a positive outcome to this appraisal would be beneficial is only small, comprising about 20% of patients. According to NICE's own expert adviser, the impact for most centres would be the treatment of about one additional patient per week, with no requirement for specific haematological or biochemical monitoring. | The Committee does not consider budget impact in its deliberations |
| | The ICER analysis varied, depending on criteria used, but was accepted to be most unlikely to increase above £20,000. This would appear favourable in the light of the disease and its effects on patients and their carers. | Comment noted |
| | **We therefore ask NICE to reconsider its decision to ensure that those patients who might benefit from cetuximab are afforded the opportunity to do so.** | Comment noted |
| | **Further research**<br>We believe there more recommendations for future research should be added to this appraisal. There is a clear need for a large post-licensing surveillance trial, powered to give adequate information for robust outcomes depending on performance status, age, site of tumour, and stage of tumour. NICE approval should be revised in the light of those findings. | Comment noted |

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| Cancer Research UK (continued) | We agree with NICE's recommendation for head to head trials of cetuximab in combination with radiotherapy versus standard chemoradiotherapy. Careful consideration particularly needs to be given to the design of such a study where there might not be equipoise in the management of young patients with large volume nodal disease. There is likely to be a definable 'cut off' in terms of fitness, toxicity, progression free survival, overall survival and disease staging, especially nodal, where cetuximab plus radiotherapy becomes best therapy compared with standard chemoradiotherapy. Determination of that patient and disease profile may require an incremental approach, through serial studies, taking the above factors into account. Consideration should also be given to the place of cetuximab in post-surgical relapse.<br><br>We hope you find these comments useful. We look forward to a final decision by NICE which will have taken into consideration the points made here and so approves the use of cetuximab for patients who are not considered suitable for standard chemoradiotherapy treatment. | Comment noted |
| Kings College Hospital | Comments on the evaluation report<br><br>Overall the effects of cetuximab in the clinical setting have been disappointing with the clearest benefit shown for patients with locally advanced head and neck cancer. There is some evidence that cases with mutation of the EGFR or gene amplification show the highest benefit. The evaluation report outlines that >90% of cases with head and neck cancer over express the EGFR by a factor of 70. However this information is not included in the reference cited and may be incorrect as most studies suggest an amplification factor of about 2 when tumours are compared to the matched normal tissues.<br><br>There is no published trial data comparing cetuximab plus radiotherapy with chemoradiotherapy. The RTOG0552-phase 3 study will compare adding cetuximab to chemoradiotherapy. The evaluation does not refer to the fact that the promising results seen combining cetuximab with radiation have led to the development of new trials adding cetuximab to chemoradiation followed by maintenance with Cetuximab for advanced disease (ECOG E3303-phase 2), or delivering cetuximab and chemotherapy followed by Cetuximab and chemoradiation (NCT00226239-phase 2). The possible benefit of adding Cetuximab to post surgical adjuvant regimes with chemoradiotherapy is also being evaluated (RTOG0234-phase 2). Interim analysis from phase 2 studies using Gefitinib is available and suggests that adding EGFR inhibitors to standard treatment regimes may be beneficial and there is clearly a need for more research in this area particularly in terms of defining the benefit of biological agents with the different fractionation regimes.<br><br>In their submission Merck propose that Cetuximab might be added to radiotherapy for the 60% of cases that do not receive chemoradiation at present. The reasons why these cases do not receive chemoradiation are complex and will include clinician preference and access to facilities. | Comment noted<br><br>The Appraisal Committee considered research currently in progress and subsequently reduced the time period for review (See FAD section 8)<br><br>The Appraisal Committee considered the criteria submitted by consultees for identifying patients for whom chemoradiotherapy is unsuitable (see FAD section 4.10) |

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| Kings College Hospital (continued) | It may also be helpful to add a paragraph outlining the rationale for combining Cetuximab with radiotherapy. Exposure to radiation induces cell death but it may also induce a proliferative response and increased EGFR expression is one of the pathways that play a role in this post treatment proliferative response. Adding treatment with cetuximab may block this radiation-induced activation of EGFR thereby augmenting the effect of radiation. Blocking the EGFR may also have effects on angiogenesis and cell motility. Thus there is a sound biological basis for introducing this therapy and this is strengthened by the very significant late toxicity associated with the use of cisplatin and radiotherapy. | Section 2.1 of the ACD only provides a brief summary of the technology to be appraised. Readers are directed to the summary of product characteristics for further information. |
| | Comments on the Appraisal consultation document | |
| | The ACD bears the title cetuximab for the treatment of locally advanced squamous cell cancer of the head and neck. However, the appraisal focuses on the use of cetuximab for the treatment of locally advanced squamous cell cancer of the head and neck for whom chemoradiotherapy is contraindicated, a restricted interpretation of the licence used by the manufacturer. This discrepancy suggests that it would be helpful to define the scope of any future appraisals more precisely. | Comment noted |
| | Intuitively it makes good sense to allow treatments to evolve towards more targeted and multiple tumour targeted treatments. As outlined in the evaluation the clearest benefit following treatment with Cetuximab reported to date is when this agent is combined with radiotherapy to treat locally advanced head and neck cancer. The downside of the Bonner study, on which most of the critique is based, is that it was designed at a time when radiation alone was considered as the standard treatment for patients with advanced head and neck cancer. There is thus no comparison of cetuximab and radiation versus chemotherapy and radiation. However, the Bonner study does show that Cetuximab can augment the response to radiotherapy. This trial provided important “proof of principle “ data illustrating that targeting a key signalling pathway can improve the response to radiotherapy. Indeed the benefit of cetuximab plus radiotherapy in achieving a 10% improvement in overall survival over 3 years is broadly similar to the estimated 5-14% improvement in survival with chemoradiation over 5 years, with the estimate being 12% for cisplatin. This point is understated in the evaluation report but the picture is complicated by the fact that many cases included in the Bonner study were treated by accelerated or boost radiotherapy regimes. | The Appraisal Committee accepted that the Bonner trial had shown cetuximab with radiotherapy to be more effective than radiotherapy alone in the patient population included in that study (see section 4.5 ACD). No action required for FAD |
| | The ACD concludes that cetuximab should not be approved for cases for which chemoradiotherapy is contraindicated but arguably this is not the context in which the appraisal should be conducted if head and neck cancer patients are to benefit from this agent. The report has considered the Bonner study in detail and summaries the clinical and cost effectiveness and resource implications for the NHS in the context of radiotherapy alone versus erbitux and radiotherapy and these data seem reasonable. | Comment noted |

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| Kings College Hospital (continued) | The Evaluation report presupposes that cetuximab would be reserved for those cases that were not considered fit for chemoradiation. At present chemoradiation is evolving to be the standard of care in the UK but less than half of all cases that might benefit from combined treatment receives cisplatin. As highlighted by Dr Slevin, difficulty swallowing is the major problem after chemoradiation. The results following attempted salvage surgery for recurrence after chemoradiation are also poor and overall surgical morbidity is very high such that there is a need to find effective alternatives to cisplatin. Thus if Cetuximab were available, considering the relatively favourable toxicity profile, this agent might be used increasingly for those cases considered most likely to benefit from aggressive adjuvant therapy. Any recommendations should be considered in the context of the potential broader application of the drug since radiation therapy alone is no longer the standard of care for cases with locally advanced head and neck tumours. | Comment noted |
| | The ongoing clinical trials do not address the requirement to compare cetuximab and radiotherapy with chemoradiation, and the acute and chronic toxicities associated with Cisplatin will preclude use of this drug with accelerated fractionation and boost regimes that may be beneficial when cetuximab is given. | Comment noted |
| | It makes sense to look for alternatives to cisplatin and consider treatment with Cetuximab for cases who are too old, have a poor performance status or unlikely to tolerate the side effects of cisplatin and radiotherapy. | The Appraisal Committee considered the criteria submitted by consultees for identifying patients for whom chemoradiotherapy is unsuitable (see FAD section 4.10) |
| | Cetuximab is currently available in Scotland for these indications. It is generally accepted that we will see a transition towards more and multiple targeted therapies and there may also be merit in allowing Cetuximab to be considered as an alternative to cisplatin and radiotherapy in the management of locally advanced disease in view of the good response rate and favourable toxicity profile. | In addition to the Manufacturer's submission, an independent Evidence Review Group Report, statements of personal views by patient experts and clinical specialists are considered by the Committee in reaching its recommendations. The Committee cannot speculate about the deliberations of another body. Submissions to SMC and NICE may not have been identical. |
| | In conclusion, there is good evidence that this treatment improves outcome for head and neck cancer patients with radiotherapy to justify recommending approval for this agent in the treatment of locally advanced disease together with radiotherapy. | Comment noted |

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| Let's Face It | I do not consider that all of the relevant evidence has been taken into account on this evaluation report on Cetuximab. The lack of awareness of the needs of the H&N cancer patients who are suffering from this disease. seems to have been overlooked. The cost of hospital care, ongoing allied health care in the community need to be taken into account when assessing the financial cost to the NHS<br><br>Dying of squamous cell cancer is ugly, horrific and terrifying not only for the patient, but their families and carers. Without Erbitux patients are left to die agonising deaths. Facial cancer affects the ability to eat, drink, communicate. The invading tumours cannot be treated and patients are left to die either from suffocation or carotid haemorrhage - drowning in their own blood.<br><br>My experience as the founder of Let's Face It, a charity supporting H&N cancer patients and families, has been one of abject horror at the lack of understanding and care of these people. You can imagine my thankfulness in knowing there is a new drug available that will shrink the invading tumours and give these patients a dignified end to their lives.<br><br>There is always a price to pay for care. Taking into account the cost of community care and hospitals and hospice care for these patients, I believe that Erbitux will balance out the cost, releasing hospital beds, and professionals care in hospitals. | Comment noted |
| Royal College of Nurses | Nurses working in this area of health have reviewed the Appraisal Consultation Document for the technology appraisal of Cetuximab for the treatment of locally advanced squamous cell cancer of the head and neck and on behalf of the RCN support the recommendations contained in the document. | Comment noted |
| Royal College of Pathologists | As far as can be judged from the information provided in the Evaluation Report and a recent Mini Review on the subject (Reuter et al British Journal of Cancer 2007;96:408-416) all of the relevant evidence appears to have been taken into account by the Appraisal Committee to provide its provisional recommendations for the preparation of the guidance to the NHS. The ACD points out that the success of cetuximab plus radiotherapy over radiotherapy alone recorded by a single randomised clinical trail (RCT) is not appropriate to recommend extrapolation of its use for patients otherwise eligible for chemoradiotherapy, which is the current standard care. To cover this weakness the Committee has recommended conduction of "head-to-head trials of cetuximab in combination with radiotherapy versus chemoradiotherapy" to allow a more objective assessment of the benefit of cetuximab plus radiotherapy as a novel therapy for head and neck cancer. This message is echoed by the Minireview. | Comment noted |
| Royal College of Paediatricians and Child Health | Thank you for inviting the RCPCH to comment on this Appraisal Consultation Document.<br><br>We did not receive any comments from paediatricians, other than this cancer is extremely rare in paediatrics | Comment noted |

CONFIDENTIAL
Reply received but no comments:
Welsh Assembly Government
Department of Health

## Comments received from website consultation:

| Commentator | Section of ACD | Comment | Institute response |
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| NHS Professional 1 | Section 1 | Quite an astonishing outcome. This is a very poor reading of the literature when such good Phase III data is available. Survival from Head and Neck cancer has improved little over the last 10 years and it will be extraordinarily disappointing not to be able to prescribe cetuximab for our patients. If this was breast cancer, cetuximab would have been approved. Who is going to be the patient lobby for this often disadvantaged group of patients, who don't have young, pretty women to advertise their cause? Our head and neck cancer patients are older, from lower socioeconomic classes and often with alcohol related problems. I guess our society values them less than young women with breast cancer. Really shocking. | Comment noted. The Appraisal Committee is required to issue guidance based on a consideration of the technology's clinical and cost effectiveness relative to appropriately defined comparators – treatments that are standard practice in the NHS. See FAD 4.7 to 4.10 |
| | Section 4 | Were there any clinical oncologists on the panel who actually treat Head and Neck cancer? Could you show me please the randomised Phase III data showing that concomitant chemotherapy with carboplatin is as effective as cisplatin. Is it? Why is this assumed? I have a good number of patients who are fit and over 70, whom I would love to offer cetuximab who I know I could never get through radical chemoradiation. Have any of the panel actually put patients through a course of radical chemoradiation? It is very tough indeed. | The Appraisal Committee considered the criteria submitted by consultees for identifying patients for whom chemoradiotherapy is unsuitable (see FAD section 4.10) |
| | Section 6 | Of course these trials are ongoing. Again the reason that this has been turned down is bizarre and the literature has been poorly understood. Chemoradiation in Head and neck cancer means treatment with cisplatin based regimens. Carboplatin-cisplatin equivalence has not been proven in phase 3 trials to my knowledge. Please could you show me your literature references to show their equivalence? Therefore there is a distinct group of patients of good PFS who need an alternative - and that is cetuximab. I would be grateful for a response to this and advice as to what to tell my older patients who are not eligible for chemoradiation (incidentally, I rarely give chemoradiation to patients above 65 as it is just too tough). This is such a highly specialised area - my impression is that the panel's understanding of chemoradiation is of a very low level. | The Appraisal Committee considered the trials currently in progress and subsequently reduced the time period for review (See FAD section 8) |

| Commentator | Section of ACD | Comment | Institute response |
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| NHS Professional 2 | Section 3 | Suitability for chemotherapy is not based on Performance status alone. Other factors such as age, co morbidity, impaired renal function, impaired hearing among other factors would be considered. In the UK the number of treatment fractions and overall time is in many centres less than the average 8 weeks as in the USA which would potentially result in a shorter course of Cetuximab, and the cost per patient. The manufacturers have been modest in their application, in view of the low toxicity it should be considered as a replacement for chemotherapy in all patients where combined therapy is indicated, irrespective of KPS. | The Appraisal Committee considered the criteria submitted by consultees for identifying patients for whom chemoradiotherapy is unsuitable (see FAD section 4.10) |
| | Section 4 | The major benefit of this drug appears to be lost in all this "scientific" evaluation. We can at present only make an assumption that cetuximab plus radiotherapy is at least equally effective as chemotherapy and radiotherapy. Comparative trials are difficult to conduct in Head & Neck cancer for many reasons and this question may never be answered. However combining radiotherapy with chemotherapy, although recognised to be more effective than Radiotherapy alone, does result in considerable increase in overall toxicity and morbidity, both acute and long term, which adversely affects quality of life and swallowing. Dry mouth, pain and difficulty or inability to swallow can be the price to pay for a cure from cancer. Here we have a new drug, demonstrated to enhance the efficacy of radiotherapy alone, without the added toxicity and morbidity. This group of patients require considerable support to get through treatment and cope with life afterwards, and any treatment that reduces their suffering should be considered a significant breakthrough and benefit and not a financial irritation. This group of patients can end up with a miserable existence and are a vocal minority. | Comment noted (see FAD section 4.3) |
| | Section 5 | This drug has been approved by the SMC. Are we going the end up with an inter UK lottery | In addition to the manufacturer's submission, an independent Evidence Review Group Report, statements of personal views by patient experts and clinical specialists are considered by the Committee in reaching its recommendations. The Committee cannot speculate about the deliberations of another body. Submissions to SMC and NICE may not have been identical |
| | Section 6 | In view of numbers of patients required this would be difficult to implement in the UK, and any result would be long into the future. If Cetuximab and radiotherapy become the standard practice in USA and Europe, such a trial will never happen and once again the UK falls behind in cancer therapy. | Comment noted |

| Commentator | Section of ACD | Comment | Institute response |
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| | Section 8 | If the decision stands there needs to be mechanism for early review if new or relevant evidence becomes available. | The Appraisal Committee considered the trials currently in progress and subsequently reduced the time period for review (See FAD section 8) |
| NHS Professional 3 | Section 1 | The ERG has dismissed this application for the patient subgroup for whom cisplatin RT is unsuitable based purely on poor performance status, but there are other patients for whom chemoRT is not suitable or appropriate (see below). The ERG accepts the RCT presented is of high quality and acceptthe significant benefit for patients treated within the trial. It therefore seems unethical to refuse cetuximab with RT for all patients. | The Appraisal Committee considered the criteria submitted by consultees for identifying patients for whom chemoradiotherapy is unsuitable (see FAD section 4.10) |
| | Section 4 | Patients are unsuitable for cisplatin chemoradiotherapy for reasons other than poor performance status. I have treated a young female with cetuximab RT who wanted to maintain fertility, another with pre-existing sensorineural deafness, and another with cirrhosis. The data quoted above regarding lack of effect in poorer ps is not in the public domain and should be subject to scrutiny | The 'European Public Assessment Report' is available on the European Medicines Agency (EMEA) website http://www.emea.eu.int/. The subgroup data are presented in this document. |
| | Section 6 | I strongly support a head-to-head trial, but we already know from the RCT that the level of survival benefit is similar to chemoRT | Comment noted |
| Patient 1 | | Having suffered from cancer of the Tonsil, I would like to think that if the cancer re-occurred the newly developed treatment combining radiotherapy and erbitux would be available to me. I also would like this treatment to be available to new patients suffering from head and neck cancer, especially as this is becoming more common in younger people, where a possibility of a cure could give them many more happy years of life, | Comment noted |
| | Section 2 | The side effects of the drug are minimal in comparison to the side effects of the standard radiotherapy treatment for head and neck cancer. The cost also seems acceptable, costing less than 5,000 for a standard 4 week radiotherapy treatment, this is surely worth while when compared against the cost of treating possible recurrences of the original cancer. | The Committee does not consider budget impact in its deliberations |
| | Section 3 | The drug has been shown to be effective in prolonging the life of patients with head and neck cancer, and should not be denied to those who could benefit from it. No advance has been made in the treatment of head and neck cancer for 25 years, and only a small proportion of the population suffer from this, so patients who have this cancer feel that they are not receiving the maximum benefit from the latest investigations, and new developments | Comment noted (see FAD section 4.5) |

| Commentator | Section of ACD | Comment | Institute response |
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| | Section 4 | I was 45 years old when I had chemoradiotherapy, and the side effects from the treatment prevented me from working for a year after the end of my treatment. A less toxic treatment might have allowed me to return to work earlier, which would have decreased the benefits I claimed, and increased the tax and NI I paid, with a net increase to the government of approximately 600 a month. In a few months this would have paid for the increased cost of the treatment | Comment noted |
| Patient 2 | | I am currently in treatment with cisplatin and radiotherapy to prevent recurrence of squamous cell carcinoma, following surgical removal of the tumour and lymph nodes | Comment noted |
| | Section 1 | This seems to be commonly used in the US and I feel that it ought to be offered to patients who could benefit from it here. | Comment noted |
| | Section 3 | It would seem that this treatment could be of help to certain categories of patients and so should be made available | The trial was not designed or statistically powered to assess for subgroups of patients (see page 44 of the manufacturer's submission) |
| | Section 4 | Although I appreciate that cost has to be taken into account when making these decisions, it is most distressing, as a patient, to find that a treatment which could save or prolong your life will not be offered despite clinical evidence showing the benefits | Comment noted |
| Patient 3 | | I was diagnosed with a squamous cell carcinoma and i would like to say the treatment available to me is completely limited what i did receive did not give me the all clear but left me in a predicament that i will not be able to have any more radiotherapy considering i am only 23 the more options available to me the better my chance of survival and combating the disease why is it only patients in England and whales who suffer the consequences of ones persons judgement who has more than likely never had to battle with this disease. | In addition to the manufacturer's submission, an independent Evidence Review Group Report, statements of personal views by patient experts and clinical specialists are considered by the Committee in reaching its recommendation. The Committee cannot speculate about the deliberations of another body. Submissions to SMC and NICE may not have been identical |
| Patient 4 | Section 4 | I would like to see cetuximab funded on the NHS for Head and Neck cancer suffers as this is the only drug we have had in a long time which gives hope of some extension and quality of life. If Scotland and Europe can have it then why can't England and Wales? | In addition to the manufacturer's submission, an independent Evidence Review Group Report, statements of personal views by patient experts and clinical specialists are considered by the Committee in reaching its recommendations. The Committee cannot speculate about the deliberations of another body. Submissions to SMC and NICE may not have been identical |

| Commentator | Section of ACD | Comment | Institute response |
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| NHS Professional 4 | Section 4 | It is expected for cetuximab to replace the use of chemotherapy in combination with radiotherapy in patients with advanced Head & Neck Cancer not only who are considered unfit to receive chemotherapy, but also for those who are expected to develop intolerable side effects in particular with large radiation fields. In these patients, the severe painful mucositis and xerostomia are inevitable in case of use of chemotherapy compared to cetuximab or radiotherapy alone. The nutritional consequences and the co-morbidity of pain and lack of saliva are remarkable and worth considering. The treatment of these complications, the long term recovery and the need for wide inputs from the supporting team raise the cost of chemotherapy remarkably high. The quality of life of patients and their carers are remarkably affected. This effect was accepted in view of the better survival and the lack of other alternatives that can reduce these toxicities. In the presence of good alternative that doesn1t compromise the efficacy of treatment, I believe that our patients deserve better option. | The Appraisal Committee considered the criteria submitted by consultees for identifying patients for whom chemoradiotherapy is unsuitable (see FAD section 4.10) |
| NHS Professional 5 | Section 1 | These patients frequently have significant co-morbidities due to the high incidence of social deprivation and the common and significant risk factors in the aetiology of this disease of heavy smoking and alcohol consumption. These co-morbidities may have already ruled out the possibility of radical surgical management due to anaesthetic risks or concerns regarding rehabilitation following major resections that compromise or alter speech, swallowing, breathing and body image This patient group therefore often have contraindications to platinum based chemotherapy due to renal impairment, ischaemic heart disease, peripheral and cerebrovascular disease. Therefore the availability of an alternative radical concurrent regime that utilises cetuximab and avoids the risks associated with vascular and renal toxicity has great potential. These patients frequently have a lack of social support and concerns often arise regarding their ability to cope with the significantly enhanced toxicities of chemoradiotherapy regimes and their safety in the event of an episode of significant myelosuppression following chemotherapy (this would not be a risk with cetuximab). Even for those patients of excellent performance status, with no significant co-morbidities and with excellent social support only about 2/3s complete the concurrent chemoradiotherapy schedule due to the degree of toxicity experienced. | The Appraisal Committee considered the criteria submitted by consultees for identifying patients for whom chemoradiotherapy is unsuitable (see FAD section 4. 10) |
| | Section 4 | By using a regime with reduced toxicity, compared to concurrent chemoradiotherapy, and with the potential for improving local control and survival, there is the potential to reduce subsequent health care costs involved in frequent inpatient admissions for pain control and enteral feeding during and after the concurrent chemoradiotherapy regime, surgical salvage procedures for residual or relapsed disease and palliative chemotherapy. There is the increased potential to maintain normal physiological functions and body image and thereby maintain/improve QOL | There are currently no trials available that compare cetuximab plus radiotherapy directly with chemoradiotherapy. In the absence of evidence comparing cetuximab plus radiotherapy with chemoradiotherapy, the Committee could not recommend it as an alternative to chemoradiotherapy (see FAD section 4.6) |

| Commentator | Section of ACD | Comment | Institute response |
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| | Section 6 | This patient population often have poor levels of literacy and education therefore recruitment to trials is often impeded. The likelihood of a randomised head to head trial of cetuximab with radiotherapy vs. chemoradiotherapy, as proposed by the Committee, is unlikely to recruit a representative population of head and neck cancer patients as all patients in order to be eligible will need to be fit enough to receive and have no contraindications to chemoradiotherapy. It is the significant number of patients not suitable for chemoradiotherapy who need a more effective management strategy than radiotherapy alone in whom cetuximab seems to offer the increased chance of better quality of life through improved locoregional control and median overall survival. | Comment noted |
| Patient 5 | | I am concerned to highlight public awareness of the damage that traditional head and neck cancer treatment causes and have done this here at my main site. NICE has recently published the first draft of its guidance on the use of Erbitux in combination with radiation therapy for the treatment of locally or regionally advanced squamous cell carcinoma of the head and neck. The initial draft recommends that the treatment should NOT be funded on the NHS. I object to this lack of funding for Erbitux. Erbitux treatment should be available on the NHS. I can never have more radiotherapy in the case of cancer reoccurrence. This treatment might save my life and the lives of others. Anyone who has had traditional radiotherapy head and neck treatment would know how dreadful it is and how painful it is in the mouth and throat. I feel very strongly about this and believe Erbitux should be made available for use through UK via the NHS. It is an amazing move forward in head and neck cancer treatment. Please allow use of Erbitux at NHS centres in UK. | Comment noted. |
| | | Erbitux has been approved for use in Scotland as well as Europe. So should this draft guidance remain unchanged, then people with head and neck cancer in England and Wales will be denied access to a treatment which is available in other areas of the UK. Please allow use of Erbitux at NHS centres in UK. | In addition to the manufacturer's submission an independent Evidence Review Group Report, statements of personal views by patient experts and clinical specialists are considered by the Committee in reaching its recommendations. The Committee cannot speculate about the deliberations of another body. Submissions to SMC and NICE may not have been identical |
| | | Erbitux should be recommended for use in all NHS centres for head and neck patients | Comment noted |

| Commentator | Section of ACD | Comment | Institute response |
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| NHS Professional 6 | Section 1 | "In patients undergoing radical radiotherapy for locally advanced head and neck cancer, who are medically unfit for concurrent chemoradiotherapy, concurrent administration of cetuximab with radiotherapy should be considered." SIGN Guideline 2006 - Level of evidence 1++ Grade A recommendation | In addition to the manufacturer's submission, an independent Evidence Review Group Report, statements of personal views by patient experts and clinical specialists are considered by the Committee in reaching its recommendations. The Committee cannot speculate about the deliberations of another body. Submissions to SMC and NICE may not have been identical |
| | Section 3 | Karnofsky Performance Status is a subjective assessment of patient fitness, but Head and Neck cancer patients commonly have other smoking and alcohol related co-morbidities which may preclude their medical fitness to receive combined chemoradiotherapy. In such patients, radiotherapy plus cetuximab may be a viable treatment option. | The Appraisal Committee considered the criteria submitted by consultees for identifying patients for whom chemoradiotherapy is unsuitable (see FAD section 4.10) |
| NHS Professional 7 | Section 1 | This is the first of such agents to be examined in phase three trial. The findings of the Bonner study are already been implemented in other centres outside of the UK. However overall at this point I agree with the initial recommendation as I feel more data is required. We are relying on one trial with extrapolation of the results to a particular groups of patients who were not specifically targeted as the research population. We have limited experience of this drug in the UK. Although assured of its relative lack of toxicity the majority of patients with advanced head and neck cancer unsuitable for chemoradiotherapy will be unsuitable for cardiac or renal reasons. Otherwise they will be unsuitable by age and or performance status. This high risk group of patients may benefit from this treatment but that is a presumption rather than proof in this trial. Further support is required, independent of the manufacturer to bring this drug into clinical use. Nearly all Clinical Oncologists who treat head and neck cancer are however interested in proceeding with this given the dismal outcome of advanced uncontrolled head and neck cancer and the current limited options | Comment noted |
| | | This is feasible in current clinical setting. The health economics of someone with a very poor predicted outcome and the additional benefit would appear to me to be tiny- but that is not my area of expertise. | Comment noted |
| | Section 2 | I agree with above that translation of the Bonner data into an unselected and poor prognostic group of patients with high risk co morbidities is of interest but on this data alone is difficult to support. | Comment noted |

| Commentator | Section of ACD | Comment | Institute response |
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| | Section 3 | There are so few ways forward for patients with advanced head and neck cancer and local control as well as survival is vital. Clinical Oncologists are therefore desperately seeking for newer strategies. This appears to hold a lot of promise and is being used in an ad hoc way in other countries. In Scotland where approval has been given for performance status 0-1 clinicians freely admit the flexibility ie inhomogeneity of their treated population. Allowing Nice approval at this date will probably lead to the same piecemeal approach. | Comment noted |
| | Section 4 | My recommendation would be to have a large scale prospective audit of the use of cetuximab- indications performance status and toxicity, with very detailed co morbidity analysis- validated data is available. Parallel research trials of course should also be considered. NCRN/ NICE etc may need to consider how to implement this eg alongside DAHNO. i feel it should not be the responsibility of the manufacturer. | Comment noted |
| | Section 8 | Radiotherapy plus cetuximab versus surgery plus xrt? altered fractionation radiotherapy plus or minus cetuximab. ( not cetuximab plus xrt versus chemoxrt as probably unethical nor chemorad plus mjnus xrt as that is RTOG study).<br>Appropriate. ESTRO head and neck meeting is next week 22-24th of Feb so more progress may be made then | Comment noted |
| NHS Professional 8 | Section 4 | Not all patients with Karnofsky score of 90 are suitable for chemoradiotherapy. One third of patients in the study had a lower Karnofsky score. Although radiotherapy schedules do not tally with those used in the UK the results are still valid. | The Appraisal Committee considered the criteria submitted by consultees for identifying patients for whom chemoradiotherapy is unsuitable (see FAD section 4.10) |
| NHS Professional 9 | Section 1 | There is a significant number of people with locally advanced H&NSCC who for a variety of reasons are not suitable for combined chemoradtherapy but who achieve a significant benefit from cetuximab + RT compared to RT alone. | The Appraisal Committee considered the criteria submitted by consultees for identifying patients for whom chemoradiotherapy is unsuitable (see FAD section 4.10) |
| | Section 4 | There will always be a group of patients who are very fit - KP score of 90+ but still have contraindications to cisplatin - namely hearing difficulties. It would be useful to know from the RCT if the proportion was known as the use of cetuximab + RT in this group would be very relevant | The Appraisal Committee considered the criteria submitted by consultees for identifying patients for whom chemoradiotherapy is unsuitable (see FAD section 4.10) |
| | Section 6 | Absolutely agree with this | Comment noted |

| Commentator | Section of ACD | Comment | Institute response |
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| NHS Professional 10 | Section 1 | There is very little else to offer patients with advanced disease: here is an agent, a monoclonal antibody which can be given to enhance radiotherapy significantly, without the toxicity that chemotherapy would cause. I think that ANY patient in the advanced / metastatic phase would welcome having something else to support their fight against the disease. | Comment noted |
| | Section 2 | The side effects are transitory, treatable and will not normally require the patient to be admitted; The treatment is simple to give, once the two initial courses have been given; these patients are in the department anyway for their radiotherapy. | Comment noted |
| | Section 3 | This product was trialled at a time when Chemo-Radiation was not the Gold Standard. Therefore, the data presented was a comparison of radiotherapy alone versus Erbitux. 2. There is a small group of patients who cannot receive Chemo-radiation for a range of reasons other than a low KPS score, and these people deserve to have the proven benefit of this drug, when they cannot have the benefit of chemo-radiation. | The Appraisal Committee acknowledged that the trial was initiated at a time when radiotherapy was standard treatment (see FAD section 4.5) |
| | Section 4. | KPS of 90 is not alone, the basis for acceptance for chemotherapy. As mentioned already, this product was trialled before chemo-radiation was adopted as the Gold Standard, so there was no analysis on the basis of comparison with chemo-radiation, this was not an issue at that time. I would draw your attention to 4.3 above, where the clinical specialists recognise a use for this drug, in a select group of patients. Erbitux is NOT an alternative to chemotherapy / chemo-radiation; it is an adjunctive treatment for those patients who cannot tolerate chemo-radiation re 4.8 Karnofsky status is not the over-riding criterion for decisions about using chemotherapy or not. There is some evidence that a group of patients offered chemo-radiation will fail to complete their treatment because of cheo-toxicity: these patients could also benefit from use on Erbitux. This will have a positive psychological effect for these patients, who are usually very distressed that they cannot complete what they perceive to be life-saving treatment. | The Appraisal Committee considered the criteria submitted by consultees for identifying patients for whom chemoradiotherapy is unsuitable (see FAD section 4.10) |
| | Section 5 | We should be able to start using this drug immediately - or at least begin putting the plans for funding in place ASAP to minimise the bureaucratic delay that seems to tag onto to every decision made in high places! Patients with advanced H&N cancers do not have the luxury of waiting three months to start treatment. | Comment noted |
| | Section 6 | Anything that can be developed to treat this Cinderella group of patients would be welcome: Tumours in this region cause the most amount of symptomatic distress: one cannot ‘rest’ an airway/food passage"" easily. The long-term effects of xerostomia are devastating and research in this area is to be welcomed. Companies that are prepared to research in this small clinical area ought to be encouraged, not blocked! | Comment noted |

| Commentator | Section of ACD | Comment | Institute response |
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| | Section 8 | June 2010? Just think for a moment of how many patients this will adversely affect i.e. HOW MANY PATIENTS WILL HAVE DIED MISERABLE DEATHS, in that time. | The Appraisal Committee considered research currently in progress and subsequently reduced the time period for review (See FAD section 8) |
| NHS Professional 11 | Section 4 | The standard chemo/radiotherapy, is not at all certain with regards to the actual drugs that should be used for chemo/radiotherapy. There is considerable variation in practice as to whether Cisplatin is a drug of choice, Carboplatin or Cisplatin 5FU or Capecitabine etc. Doses of drugs are also extremely uncertain. The advantage of the Bonner data is that Cetuximab was given in a uniform way with different fractionations but this would occur in any multi-centre trial as fractionation schemes have been developed empirically. The Bonner data answered the scientific question of whether Cetuximab is a real radiosensitizer i.e. increased effectiveness with no obvious increase in acute or late toxicity. | Comment noted (see FAD sections 4.3 and 4.4) |
| | | Merck's assessment with regards to the performance status is valid and certainly in our centre i.e. Preston Cancer Centre, we have found giving chemo/radiotherapy problematic. I believe that NICE's document is well thought out but feel that interpretation is misguided although we can easily see why. I hope that NICE strongly reconsider their decision. | The Appraisal Committee considered the criteria submitted by consultees for identifying patients for whom chemoradiotherapy is unsuitable (see FAD section 4.10) |
| Other | Section 1 | As a clinical Oncologist I am required to discuss treatment options with patients. Currently there are two pharmacological interventions proven to improve survival over radiotherapy alone: synchronous chemotherapy and synchronous cetuximab. Chemotherapy is associated with an enhancement of the mucosal reaction which is the main dose limiting toxicity in head and neck cancer, cetuximab is not. Chemotherapy is only the standard of care because it was investigated first. There is not a direct comparison and there is unlikely to be one. The current state of evidence suggests roughly similar benefits form chemotherapy and cetuximab with the key side effect, mucositis, not being enhanced by cetuximab. I cannot underestimate the importance of the latter: I would suggest chemoradiation to the head and neck is the most unpleasant nonsurgcal treatment in solid tumour oncology. | Comment noted (See FAD section 4.3) |
| | | Given the evidence base of an extra 10 people cured per 100 and the small cost relative to other drugs NICE has approved in the non curative setting I simply cannot understand why NICE is asking me to give a more painful treatment. In addition there is widespread ignorance of the vascular side effects of cisplatin | The Appraisal Committee does not consider budget impact in its deliberations |

| Commentator | Section of ACD | Comment | Institute response |
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| | Section 4 | 'might be expected to be considerably less'-can you show me robust evidence for the validity of this statement? As above there is widespread ignorance of the vascular toxicities of cisplatin: Are we to give pts with a history of MI or PVD chemort based on this guidance or rt alone? Will it be NICE or the PCTs who carry the risk when these patients need an amputation following cisplatinRT or relapse following RT alone. The clinician can only tell the patients the options but given a 10% difference in cure rate compared to RT alone from past experience of other cancer sites I would be very worried about litigation. | The Appraisal Committee is required to make decisions on the basis of clinical and cost effectiveness (See Guide to the methods of technology appraisals section 6.2) |
| NHS Professional 12 | Section 4 | CETUXIMAB FOR THE TREATMENT OF LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK The BONNER paper is a sentinel paper in the management of locally advanced head and neck cancer. Head and neck cancer is relatively uncommon and 424 patients represent a large study. The absolute overall survival benefit at 3 years (approx 10%) is much larger than that demonstrated so far with adjuvant Herceptin in breast cancer. | Comment noted |
| | | Many patients with advanced head and neck cancer are from a poor socio-economic class with considerable co-morbidity from smoking and alcohol which make then unsuitable for treatment with concurrent chemo-radiotherapy. When treatment fails palliative care options are complex and because of difficulties in swallowing and breathing include consideration of tracheostomy and feeding tubes. This group of patients are also at risk of terminal haemorrhage from fungating neck disease. The cost of palliative care is many orders of magnitude higher than the cost of a course of cetuximab. Multiple subgroup analyses are probably inappropriate in a study of this size but all groups including once daily fractionation most commonly used in the United Kingdom showed overall survival benefit. Though chemo-radiotherapy remains the gold standard for locally advanced head and neck cancer, there is no clear consensus with regard to dose and scheduling of chemotherapy or radiotherapy when used in combination. What is clear however is that toxicity is significantly enhanced by the addition of chemotherapy to radiotherapy, which is not the case with cetuximab. | Comment noted |
| | | I believe on the basis of the BONNER study, that it is entirely appropriate to allow the use of cetuximab concurrently with radiotherapy for patients with locally advanced head and neck cancer NOT suitable for treatment with concurrent chemo-radiotherapy, who are frequently some of the most disadvantaged members of society. | The Appraisal Committee is required to make decisions on the basis of clinical and cost effectiveness (See Guide to the methods of technology appraisals section 6.2) |

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| | | I understand that the Scottish Medicines Group has accepted the use of cetuximab for this indication. To decline this application will put the treatment of head and neck cancer in England back by a number of years. | In addition to the manufacturer's submission an independent Evidence Review Group Report, statements of personal views by patient experts and clinical specialists are considered by the Committee in reaching its recommendations. The Committee cannot speculate about the deliberations of another body. Submissions to SMC and NICE may not have been identical |
| NHS Professional 13 | Section 1 | In response to your preliminary statements, I want to say that there are a few patients each year at our centre who are ineligible for chemo-RT due to various reasons such as cardiac, renal co-morbidities and PS, who receive only radical/tolerance doses of RT. Given the high response rates with RT + cetuximab in comparison with RT alone in the Bonner study albeit in a slightly different population, it seems only fair that these patients who are ineligible for chemo-RT but can tolerate this treatment should be offered this. I agree that there will not be a huge number of such patients each year, but this treatment should be available for such patients. In addition, since the numbers will not be great, the financial implications as a whole should be affordable. | The Appraisal Committee does not consider budget impact in its deliberations |
| | Section 2 | Except for mild to moderate infusion-related reactions and skin reactions, the side effects are minimal and tolerable and hence can be used in the subset of patients who are unfit for Chemo-RT. The cost is very reasonable when compared to the efficacy as demonstrated in the Bonner trial, although the subset of patients are different. It has to be extrapolated. | Comment noted |
| | Section 3 | Although the population in the trial was different to the population for whom the treatment is proposed, it should be stressed that the treatment in combination with cetuximab should still be superior. Of course the best way to define it would be to construct trials answering these specific questions, but patient numbers will be a problem, it has to be a multi-central trial. | Comment noted |
| | Section 4.8 | In response to 4.8 there are patients with high PS who may be ineligible to have chemo-RT due to various reasons such as cardiac and renal co-morbidities, so they could benefit. | The Appraisal Committee considered the criteria submitted by consultees for identifying patients for whom chemoradiotherapy is unsuitable (see FAD section 4.10) |
| | Section 6 | Chemo-RT is the gold standard; it would be unethical at the present to do a RCT with chemo-RT versus RT + cetuximab. However in patients ineligible for whatever reasons, a RCT could be done after stratification of RT versus RT+cetuximab. In addition, Chemo-RT+/-Cetuximab can also be done. | Comment noted |

| Commentator | Section of ACD | Comment | Institute response |
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| Health Professional 14 | Section 1 | There are subsets of patients with locally advanced head and neck cancer who would benefit from the combination of radiotherapy and cetuximab in a cost effective way and a blanket statement such as this is not appropriate. | The Appraisal Committee considered the criteria submitted fby consultees or identifying patients for whom chemoradiotherapy is unsuitable (see FAD section 4.10) |
| | Section 2 | The information appears accurate. | Comment noted |
| | Section 3 | It is notable that the ERG thought the trial data robust. Whilst the trial population included a majority of patients with good performance status it is not necessarily the case that all of these would have been suitable for chemoradiotherapy. In UK practice a significant proportion of patients are treated with radiotherapy alone because of co-morbidities such as renal or cardiac disease or the responsible Oncologist believes that the patient would not tolerate the considerable additional toxicity of chemoradiotherapy. Many of these patients would be described as "good performance status" by standard criteria. It is therefore not true that the trial data cannot be extrapolated to the defined group. Whilst the radiotherapy regimens used in the trial were different to those used predominantly in UK practice there is no logical reason to believe that cetuximab would be any less effective with the fractionation regimes commonly used in the UK | The manufacturer was unable to provide information on either the number of patients in the RCT for whom chemordaiotherapy was considered inappropriate but suitable for radiotherapy or the effectiveness of cetuximab plus radiotherapy in this group (see FAD sections 3.7 and 4.7). The Appraisal Committee is required to make decisions on the basis of clinical and cost effectiveness (See Guide to the methods of technology appraisals section 6.2) |
| | Section 4 | I agree with all the comments from the clinical specialist and that cetuximab plus radiotherapy is not an alternative to chemoradiotherapy which must currently remain the standard of care for those patients who are deemed fit enough for it. However, fitness for chemoradiotherapy remains difficult to define and there remain a significant number of patients in the UK who receive radiotherapy alone but who cannot be regarded as poor performance cases by standard criteria. The trial data strongly suggest that these patients would benefit from the addition of cetuximab. | The Appraisal Committee considered the criteria submitted by consultees for identifying patients for whom chemoradiotherapy is unsuitable (see FAD section 4.10) |
| | Section 6 | Data from such trials would be welcome to determine the relative effectiveness of these two approaches to treatment but ongoing trials are examining the impact of adding cetuximab to chemoradiotherapy. | Comment noted |
| | Section 7 | The cancer service guidance recognises that this is a particularly disadvantaged group of patients where more research evidence is required to improve outcomes. Compared with other tumour sites large clinical trials are difficult to perform in head and neck cancer and new technologies are few and far between. The use of combined cetuximab and radiotherapy for a subset of patients who are deemed unfit for chemoradiotherapy provides one of the few opportunities to improve treatment outcome for this group of patients. | Comment noted. Only guidance issued by NICE are included in the FAD |

| Commentator | Section of ACD | Comment | Institute response |
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| | Section 8 | If there is no change in the recommendations then more than 3 years is a long time to wait before such a potentially beneficial treatment can be used within the NHS. | The Appraisal Committee considered research currently in progress and subsequently reduced the time period for review (See FAD section 8) |
| NHS Professional 15 | Section 1 | I think that cetuximab in combination with radiotherapy should be available for patients who are at serious risk that they cannot tolerate chemoradiotherapy despite is indicated. This approach is accepted in Scotland and in numerous countries in European Union. | In addition to the manufacturer's submission, an independent Evidence Review Group Report, statements of personal views by patient experts and clinical specialists are considered by the Committee in reaching its recommendations. The Committee cannot speculate about the deliberations of another body. Submissions to SMC and NICE may not have been identical |
| | Section 4 | There is a patient population which despite of good performance score are not good candidates for chemoradiotherapy, because of advanced age (older than 75) or comorbidity which are contraindication to platinium based regimens. | The Appraisal Committee considered the criteria submitted by consultees for identifying patients for whom chemoradiotherapy is unsuitable (see FAD section 4.10) |
| | Section 6 | I agree that such as RCT is required but until that Cetuximab should be an treatment option for head and neck cancer patient who on clinical assessment are considered not fit enough for concurrent chemo-radiotherapy | Comment noted |
| | Section 8 | The review of this technology should be considered earlier, because there is a great interest among the oncology community in this treatment which should end up with more scientific data on this subject. | The Appraisal Committee considered research currently in progress and subsequently reduced the time period for review (See FAD section 8) |
| Public | Section 1-8 | Available through NHS in Scotland and in Europe. Why not for patients in England and Wales | In addition to the manufacturer's submission, an independent Evidence Review Group Report, statements of personal views by patient experts and clinical specialists are considered by the Committee in reaching its recommendations. The Committee cannot speculate about the deliberations of another body. Submissions to SMC and NICE may not have been identical |

| Commentator | Section of ACD | Comment | Institute response |
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| Carer | | Please be equitable and make this treatment available immediately in all areas of England and Wales. Think about you or your relatives. | In addition to the manufacturer's submission, an independent Evidence Review Group Report, statements of personal views by patient experts and clinical specialists are considered by the Committee in reaching its recommendations. The Committee cannot speculate about the deliberations of another body. Submissions to SMC and NICE may not have been identical |
| NHS Professional 16 | Section 1 | I would ask the committee to reconsider its decision. The trial has clearly demonstrated value in patients with locally advanced head and neck cancer where radiotherapy would have been considered the only treatment option. Concurrent chemotherapy is not suited to a number of patients due to its attendant additional morbidity (and indeed mortality) as judged by the treating clinician. | Comment noted |
| | Section 2 | One of the major attractions of cetuximab is the selective nature of its activity. At a very basic level cetuximab is chemotherapy, it is simply selective in its site of action and this needs to be considered in defining its place in our treatment armamentarium. | Comment noted |
| | Section 3 | The application to use cetuximab where concurrent chemotherapy is considered inappropriate is a pragmatic one. The trial was designed when there was less enthusiasm for concurrent chemotherapy and it clearly shows its value when used with altered fractionation. The panel are correct in their observation that the main fractionation arm used in the study is not used in the U.K. However this misses two crucial points: (1) Altered fractionation for locally advanced head and neck cancers should be routine! (the evidence for the 2006 meta-analysis is there)(2)It is possible to "manipulate" the once daily schedule to achieve an effect of altered fractionation (a concept in IMRT called simultaneous integrated boost). | Comment noted |
| | Section 4 | It remains to be proven unequivocally that concurrent chemo-radiation should be "standard" for locally advanced head and neck cancers. Until the GORTEC trial publishes its results (?late 2007), altered fractionation remains a serious alternative option and the choice between these two approaches will rest with the treating clinician (who will judge this based on their assessment of the patient as well as their "belief" of the two approaches). Moreover there is much debate as to what "standard" chemoradiotherapy really is i.e. what is delivered in the real world from that in patients put into clinical trials. Therefore it is inappropriate to assume that good P.S. patients will automatically be guided towards chemoradiotherapy | The Appraisal Committee considered the criteria submitted by consultees for identifying patients for whom chemoradiotherapy is unsuitable (see FAD section 4.10) |

| Commentator | Section of ACD | Comment | Institute response |
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| | Section 6 | This principle is fine provided that the control arm can be agreed on! Since this defied previous attempts at trial development in the U.K. for a number of years I see this as a major challenge. Trials are ongoing or proposed in mainland Europe and the U.K. should perhaps consider supporting these. However a considerable time will pass until these trials are completed and non-approval of this agent will deny patients an alternative to the toxicity of concurrent chemoradiotherapy | Comment noted |
| | Section 8 | The guidance document is woefully short on the detail of what a radiotherapy department in the 21st century should provide for its head and neck cancer patients | Comment noted. The trial was not designed or statistically powered to assess for sub-groups of patients (see page 44 of the manufacturer's submission). |
| | | I suspect that proposed or ongoing trials will be very preliminary in their findings at this point. On the other hand this is a rapidly changing field and an early review perhaps in two years will be helpful irrespective of the panels final decision | The Appraisal Committee considered research currently in progress and subsequently reduced the time period for review (see FAD section 8) |
| NHS Professional 17 | Section 4 | The consideration that patients not suitable for radical chemoradiotherapy have not been examined in the study is the flaw in your recommendation. For radical radiotherapy on its own, patients require a good performance status; noone would give radical radiotherapy to patients with a poor performance status. Therefore patients not suitable for chemoradiotherapy are those in whom the toxicity would lead to them not completing the treatment. This is the case in patients with renal impaiment including the elderly. With this judgement, NICE is denying these patients a chance of better survival. Do also note that this is one of the few head and neck studies to have demonstrated an improved overall survival - most do not. | The Appraisal Committee considered the criteria submitted by consultees for identifying patients for whom chemoradiotherapy is unsuitable (see FAD section 4.10) |
| NHS Professional 18 | Section 1 | I disagree with this judgment (see below for details). The Bonner paper itself suggest otherwise. Apart from the paper (Bonner), a separate review in European Journal Cancer (EJC, 07; 43:35-45 have concluded quite the opposite, that patients with advanced head and neck cancer benefit from concurrent cetuximab with radiotherapy without the risk of acute and long term effects with chemoradiotherapy. | Comment noted |
| | Section 2 | In bigger cancer centres that may treat a few patients at the same time, the cost is lower as there is less drug wastage with drug preparation. | Comment noted |

| Commentator | Section of ACD | Comment | Institute response |
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| | Section 3 | Many patients with performance status KP>70 may still not be suitable for concurrent chemoradiotherapy due to other co-morbidities including ischaemic heart disease, renal impairment, diabetes, intolerance of chemotherapy related toxicities (eg intractable nausea) etc. At the moment these patients have no other options to improve the curative outcome of radiotherapy. Therefore it is important for NICE to realise that patients who "are not fit for chemoradiotherapy" may well be "Karnofsky performance score ranged from 60 to 100 but was most commonly 90". It is wrong to assume that those who are not fit for chemoradiotherapy must therefore be different from the patients included in the Bonner study. Eg one could have ischaemic heart disease but KP80 | Comment noted This comment related to the ERG report rather than the ACD (see ERG report section 3.3) No action required for the FAD |
| | | Many centres in UK use hypofractionated radiotherapy given over 4 weeks which is akin to the accelerated radiotherapy arms (if one truly believes that this subgroup to benefit more from cetuximab, but see below). In addition, the fact that the radiotherapy is hypofractionated, the total doses of cetuximab will be less (ie 5 doses per patient rather than 8 doses for a 4 week regime) which will increase the cost effectiveness tremendous | Comment noted |
| | Section 4 | The suggestion that lower KP do not benefit (because majority of the study subjects were good performance status and the subgroup analysis in those with poorer performance status did not seem to benefit) is flawed: one cannot draw conclusions from subgroup analysis, as study is not powered to look into this issue. Therefore treatment policy should not be drawn from subgroup analysis. | Comment noted. The manufacturer was required by the European Medicines Agency (EMEA) to highlight this apparent lack of efficacy in this subgroup within the SPC (see SPC section 5.1) http://emc.medicines.org.uk/emc/industry/default.asp?page=displaydoc.asp&documentid=14625 |
| | | The suggestions that single daily fractionation do not seem to benefit from concurrent cetuximab: again it is flawed because one cannot draw conclusions from subgroup analysis, as study is not powered to look into this issue. Therefore treatment policy should not be drawn from subgroup analysis. Unlike the issue of use of cetuximab in other settings (eg colorectal), the use of cetuximab in head and neck is with curative intent (ie not palliative treatment). This chance of cure is likely associated with less long term toxicity given that the acute toxicity is not increased. The ultimate long term cost effectiveness will be extremely high if in takes into consideration that those who are cured remains cured even beyond 5 and 10 years following treatment. | Comment noted |

| Commentator | Section of ACD | Comment | Institute response |
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| | | It is important to have cetuximab as an option that clinician can use where the above applies. Unlike other cancer sub-sites, there are limited pharmaceutical options to improve outcome. Head and neck cancer has been a Cinderella sub-site in terms of drug development. Now that we have one additional effective option, it is so disappointing that clinicians are denied this option. The number of patients is not large compared to applications for new drugs for other subsites, and in addition this treatment option is a curative option rather than a simply palliative one. | Comment noted |
| | Section 6 | There is no study addressing this at the moment, and there is no pharmaceutical impetus to do such a study. Meanwhile in the 5-10 years it takes before results become available, patients who would benefit form concurrent cetuximab but cant have concurrent chemo (see reasons above) will have a lesser chance of cure (these patients would not be suitable for the trial anyway). Again remember someone could have renal impairment (not suitable for chemo) but still performance status 80. There are many of these patients around. Don't forget when these patients (who could have been cured) return with disease recurrence because cetuximab is unavailable, the cost of treating them (admission for symptom control, further surgery, palliative care, inpatient stay in hospice, days off work) is going to be tremendous; and is likely to be more than the cost of the cetuximab treatment. | Comment noted |
| NHS Professional 19 | Section 1 | The recommendation takes a dismissive and unrealistic view of the significant proportion of patients with locally advanced head and neck cancer of good performance status in whom combined radical chemoradiotherapy is contra-indicated because of co-morbidity. Currently these patients receive radical radiotherapy alone. There is good evidence from a well conducted randomised controlled trial that radical dose radiotherapy plus cetuximab improves local control and mortality over radiotherapy alone. This trial has been the subject of extensive learned discussion and the emerging European and International consensus is that combined Cetuximab-radiation should be offered to those patients of good performance status in whom concurrent chemoradiotherapy (the current gold standard) is contraindicated. | Comment noted |
| | Section 3.6 | There are a significant number of patients of good performance status (fit enough to justify consideration of radical radiotherapy) who will not be suitable for concurrent chemotherapy by virtue of co-morbidity (renal disease, cardiovascular disease pulmonary disease etc.) These patients may well fit the characteristics of the trial population. The implicit assumption of 3.6 is that patients who are not suitable for radical concurrent chemoradiotherapy are necessarily of poor performance status is false. Poor performance status patients in the head and neck clinic are unlikely to be considered for radical therapy in any case. | Comment noted This comment related to the ERG report rather than the ACD (see ERG report section 3.3) No action required for the FAD |

| Commentator | Section of ACD | Comment | Institute response |
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| | Section 4.4 | Whilst there are differences in practice in the UK, there is a broad consensus that combined chemoradiotherapy represents the best practice in the primary radical treatment of locally advanced squamous cell cancer of the head and neck. This reflects the growing European and international consensus, and is demonstrated by the increasing use of evidence-based guidelines to standardise practice across cancer networks and wider regions. For example the recent Scottish Intercollegiate Guidelines for Head and Neck Cancer: http://www.sign.ac.uk/pdf/sign90.pdf 4.7 There is a significant minority of patients of good PS who are not fit for chemotherapy but who are accepted for radical radiotherapy. This population has a characteristic set of co-morbidities often related to very heavy alcohol and tobacco use, such that whilst of apparently good PS, they may not tolerate chemotherapy. | The Appraisal Committee considered the criteria submitted by consultee for identifying patients for whom chemoradiotherapy is unsuitable (see FAD section 4.10) |
| NHS Professional 20 | Section 1 | During my years of experience supporting head and neck cancer patients, I have seen how current chemoradiotherapy regimes are extremely difficult for many of them to tolerate. As they are already suffering with their disease and have difficulties with eating, swallowing, speaking and even breathing, any treatment that has lower toxicity has got to be justified not only in terms of longer survival but also treatment tolerance and adherence and, most importantly, quality of life. I therefore strongly recommend that Cetuximab be available where indicated. | Comment noted |
| | Section 4 | When considering the evidence, I feel a far greater emphasis should be put on the quality of life of this group of already very distressed patients. | Health related quality of life was discussed by the Appraisal Committee (See FAD sections 3.8 and 4.2) |
| NHS Professional 21 | Section 4 | NICE infers that Carboplatin could be an alternative to CDDP. i) There are no data showing that Carboplatin is as effective as CDDP in this setting ii)Carboplatin is not licensed for this indication iii)There is no randomised trial showing Carboplatin+RT improve survival compared to RT alone NICE states that " there were likely to be few patients with a Karnofsky performance score of 90 or more who have contraindications to both chemoradiotherapy options." Does NICE suggest that these patients should not receive optimal therapy, because they are in the minority? This statement is ambiguous. 1. The current standard treatment for patients with locally advanced head and neck cancer should be CDDP 100mg/m2 q21 x 3. 2. For good performance status patients (Karnofsky >90) and not eligible for high dosage CDDP, RT + Erbitux should be considered (NICE accepted that cetuximab with radiotherapy had been shown to be more effective than radiotherapy alone.) * Not eligible: a Previous CDDP b Peripheral neuropathy c Hearing impairment d Contra-indicated to receive high volume fluid hydration e Existing immunodeficiency f Concurrent use of potential nephrotoxic agents | The Appraisal Committee considered the criteria submitted by consultees for identifying patients for whom chemoradiotherapy is unsuitable (see FAD section 4.10) |

| Commentator | Section of ACD | Comment | Institute response |
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| | Section 6 | Unfortunately this is unlikely to happen: major trials are ongoing comparing Cisplatin and RT versus Cisplatin, RT and Cetuximab. Other trials compare neoadjuvant chemo with Cetuximab and RT. Any randomised data will only be helpful to patients in 5-6 years time. 1) Pharmacogenetic analyses of head and neck cancers to predict response to anti-EGFR therapies should be possible in the near future. Up to 40% of these cancers harbour variant III mutations of EGFR1 (EGFRvIII) ( Sok et al, Clin Cancer Research 2006, 12: 5064) and these are likely to be more resistant to anti-EGFR blockade. Such analyses in the future might further reduce the number of patients eligible for treatment with Erbitux (akin to Herceptin use). 2) Longer term use of anti-EGFR therapies (antibody or small molecule) is unlikely to be as effective as short term concomitant use with RT. During continuous anti-EGFR treatment, compensatory HER3 transphosphorylation leads to AKT/PI3K activation (Sergina et al, Nature. 2007 Jan 25;445(7126):437-41). The short term use of anti-EGFR blockade during RT therefore makes biological sense. | Comment noted |
| Other 2 | Section 1 | Surely any combination which "could" prolong the life of a Cancer Sufferer would be a positive thing | Comment noted |
| | Section 2 | Cost should not be a factor in the fight to save lives - it would be prudent to assess each individual case i agree however the cost of prescriptions sometimes exceed the charge to the NHS to make certain medications, this meaning any excess costs should be put towards research into how to reduce the cost of making medication more affordable to not only the NHS but also to the general public. | The Appraisal Committee does not consider budget impact in its deliberations |
| | Section 4 | So it would seem they think it would be feasible for this to be used by persons with the illness regardless of the cost factor and also if it would be productive/prolong the sufferers life expectancy. | Comment noted |
| | Section 6 | It is always a plus point for further trials but as this is available already elsewhere why is it that the UK have to wait for possible life saving treatment and possibly have to pay for it when it is being happily used by other suffers elsewhere in the country. | Comment noted. In addition to the manufacturer's submission an independent Evidence Review Group Report, statements of personal views by patient experts and clinical specialists are considered by the Committee in reaching its recommendations. The Committee cannot speculate about the deliberations of another body. Submissions to SMC and NICE may not have been identical |

| Commentator | Section of ACD | Comment | Institute response |
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| | Section 8 | Sooner the better, | The Appraisal Committee considered research currently in progress and subsequently reduced the time period for review (See FAD section 8) |
| | | I know little or nothing about the technology behind this treatment, but from information I have received it seems as though the U.K has been let down some what, in what could be a major breakthrough in Head & Neck cancer, Ii would like to pass comment that should anyone have to go through this illness knowing that there is treatment available, yet our NHS will not allow it to be paid for, it can only be a lead for many court cases, and for the cost of legal fees for 1 case with the NHS they could have saved at least 15 lives in a year. | Comment noted The Appraisal Committee is required to issue guidance based on a consideration of the technology's clinical and cost effectiveness |
| NHS Professional 22 | Section 1 | I agree that there is not sufficient data to recommend it routinely in all head and neck cancer patients but there is a selected group of patient in which denying the access to this drug is not appropriate. Two examples are patient who are pretreated with chemotherapy and do not have sufficient bone marrow reserve and patients with stable chronic renal failure who would not tolerate platinum based chemotherapy. | The Appraisal Committee considered the criteria submitted by consultees for identifying patients for whom chemoradiotherapy is unsuitable (see FAD section 4.10) |
| | Section 4 | Fair point but as stated the study was not sufficiently powered to show the difference in poor performance patients | Comment noted |
| | Section 6 | This would be a very informative and pivotal trial if at all possible | Comment noted |
| NHS Professional 23 | Section 1 | I believe that for the (small) patients who are not appropriate for Chemotherapy and Radiotherapy for advanced oropharyngeal cancer that the use of cetuximab and radiotherapy represents a real advantage over radiotherapy alone. | Comment noted. The trial was not designed or statistically powered to assess for sub-groups of patients (see page 44 of the manufacturer's submission) |
| | | Patients may not be suitable for Chemo RT due to co-mordities (e.g risk of sepsis, ischaemic heart disease, renal disease precluding cisplatin based chemotherapy) or may decline chemotherapy for other reasons. | The Appraisal Committee considered the criteria submitted by consultees for identifying patients for whom chemoradiotherapy is unsuitable (see FAD section 4.10) |
| | | At the time of the pivotal study, chemoRT was not the standard of care whilst RT was. The study showed a significant statistical and clinical improvement in median overall survival and progression free survival in a patient group where effective treatment options are limited and where local relapse is a significant practical problem. Median survival benefits are considerably greater than e.g single agent herceptin in advanced breast cancer which has previously been approved by NICE | Comment noted (see FAD section 4.5) |
| | Section 4 | See above for comments on standard of care at the time of the study | Comment noted |

| Commentator | Section of ACD | Comment | Institute response |
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| | Section 6 | Comparison of ChemoRT and cetuximab-RT especially on advanced oropharyngeal squamous cell carcinoma | Comment noted |
| NHS Professional 24 | Section 1 | The Bonner's study showing 10% survival benefit at 3 years in the group receiving cetuximab is a landmark achievement for head and neck cancer patients. There are only two drugs licensed for head and neck cancers in the UK namely Erbitux and taxotere unlike other cancers e.g. breast and bowel cancer. Furthermore, this drug is used in radical or curative intent, one would expect the potential lives saved outweigh the cost needed to provide palliative care for patients with disease progression. | Comment noted |
| | | The decision on how fit a patient is for concurrent chemoradiation is a complex one. As a radiation oncologist, I feel strongly that cetuximab should be available as an alternative for patients not suitable for chemoradiotherapy. Many patients with advanced head and neck cancer have many co-morbidities and chemoradiotherapy is not always be the best for some patients. Most UK centres use hypofractionated radiotherapy which is a form of accelerated radiotherapy which derived the most benefit in the Bonner study. I urged the NICE committee to consider approving Erbitux favourably for head and neck cancer patients who often do not have powerful lobby group to make their voice heard. | The Appraisal Committee considered the criteria submitted by consultees for identifying patients for whom chemoradiotherapy is unsuitable (see FAD section 4.10) |
| | Section 6 | Study for cetuximab in intermediate stage head and neck cancer should be welcomed | Comment noted |
| NHS Professional 25 | Section 1 | I would recommend in locally advanced SCCHN management radiotherapy alone should not be standard. All patients should be considered for chemoradiotherapy but when the chemoradiotherapy is not the choice of treatment according to the decision of the Multi-Disciplinary Team (MDT) for that individual patient (reasons need to be justified by the MDT) Cetuximab and radiotherapy should be offered as an alternative approach. | Comment noted |
| | Section 4 | The current standard management of locally advanced squamous cell carcinoma of Head and Neck (SCCHN) includes chemoradiotherapy. However early toxicity of this approach is quite severe and limits the implementation of this approach on a routine basis for all patients. The findings of this study are very important and clinically very relevant to the management of locally advanced SCCHN patients. The disadvantage of the study is that the experimental drug was tested against radiotherapy alone. | Comment noted |

| Commentator | Section of ACD | Comment | Institute response |
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| | Section 6 | Currently in locally advanced SCCHN head to head comparison of this drug against gold standard chemoradiotherapy is being tested by French Group and additional North American study (RTOG 0522) is testing the role of the drugs in combination with chemoradiotherapy against chemoradiotherapy. During the NCRI Head & Neck clinical studies systemic treatments and radiotherapy subgroup meeting on 23/02/07 the outline protocol of the intermediate stage group was discussed and the decision made to apply for CTAAC approval with the currently accepted gold standard altered radiotherapy fractionation versus altered radiotherapy fractionation and Cetuximab. Targeted treatments with radiotherapy are active research areas for SCCHN and potentially able to improve the outcome without increasing the radiation related mucositis which is the commonest reason for poor compliance. | Comment noted |
| | | I agree with the following statement which was included in the above guidance. "These more intensive forms of treatment are appropriate for patients with advanced disease who are fit enough to cope with their adverse effects." The above definition of ""fit enough to cope"" is unclear as it does not define which patients would be chosen for chemoradiotherapy. The treatment decision for chemoradiotherapy in this patient population is quite complex and may vary. | Comment noted. The Appraisal Committee considered the criteria submitted by consultees for identifying patients for whom chemoradiotherapy is unsuitable (see FAD section 4.10) |
| Other 2 | Section 1 | There have been very few developments in the treatment of head and neck cancer over the years, so any treatment options are very important to those who could benefit. Furthermore, cetuximab has been approved for use in Scotland as well as Europe. So should this draft guidance remain unchanged, then people with head and neck cancer in England and Wales will be denied access to a treatment which is available in other areas of the UK. | Comment noted. In addition to the manufacturer's submission, an independent Evidence Review Group Report, statements of personal views by patient experts and clinical specialists are considered by the Committee in reaching its recommendations. The Committee cannot speculate about the deliberations of another body. Submissions to SMC and NICE may not have been identical |
| | Section 2 | It is not a costly drug and the side effects are mild to moderate | The Appraisal Committee does not consider budget impact in its deliberations |
| | Section 3 | The manufacturer's submission was as good as it was possible | Comment noted |

| Commentator | Section of ACD | Comment | Institute response |
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| | Section 4 | Any criticisms are just plain nit-picking by non-clinicians to show that they understand the finest points of their specialisms! They appear to have no idea of what it means to a patient to have extra months of life. The clinicians and patients views appear to have been discounted. Our overall view on the draft is that the committee has not looked at this scenario in a pragmatic way or from the patient's point of view. It comes across from the recommendation that by denying access to this treatment, NICE does not truly understand the issues that are important to patients. As NICE points out, the trial involving Erbitux resulted in robust findings that are very significant to patients in England and Wales with regard to the fact they will live months longer and will have an alternative should they not be able to tolerate chemoradiotherapy.<br><br>NICE also notes that the treatment is cost effective. As you will appreciate, there are a small number of patients with Head and Neck Cancer who are set to lose a large amount if NICE does not approve the use of this treatment. | The Appraisal Committee is required to issue guidance based on a consideration of the technology's clinical and cost effectiveness. The Committee concluded that whilst cetuximab with radiotherapy had been shown to be more effective than radiotherapy alone in the patient population included in a single study, the evidence did not provide a robust demonstration of the clinical effectiveness of cetuximab plus compared with radiotherapy alone in the relevant subgroup of patients (see FAD section 4.10) |
| | Section 5 | As it should be. | Comment noted |
| | Section 6 | The evidence already shows a benefit to patients. There is no compelling need to make them wait for another trial. | Comment noted |
| | Section 8 | The only realistic response from a cancer patient to waiting another 3 years to find out if the treatment might become available is: "You must be joking!" | The Appraisal Committee considered research currently in progress and subsequently reduced the time period for review (See FAD section 8) |