**NICE Single Technology Appraisal - cetuximab for head and neck cancer**

On behalf of Merck Serono, please find our response to questions posed by NICE on the 15th October 2007, with regards to the Single Technology Appraisal for cetuximab in Locally Advanced Squamous Cell Carcinoma of the Head and Neck (LA SCCHN).

The following evidence is presented in this document as requested by the Appeal panel:

**Section:**

1. Median survival data (including 95% confidence intervals) derived from the Bonner study, for each of the separate Karnofsky performance scores (KPS) – 100, 90, 80, 70 and less.
2. Incremental Cost Effectiveness Ratio estimates related to subgroup analyses presented in section 1.
3. Any other data in its possession that would enable the Appraisal Committee to assess the clinical and cost effectiveness of cetuximab according to the decision problem defined.

    3a. Median overall survival derived from the Bonner study stratified by KPS and for patients aged younger or older than 65 years.

    3b. Incremental Cost Effectiveness Ratios related to the subgroup analyses presented in section 3a above.

    3c. The implementation of a, ”cetuximab in head and neck cancer”, patient registry to collect patient outcomes in groups of patients with LA SCCHN determined inappropriate for treatment with cisplatin based chemoradiotherapy.

4a. Evidence on the efficacy and tolerability of carboplatin alone* in treating patients with locally advanced squamous cell cancer of the head and neck.

4b. Evidence on the efficacy and toxicity of carboplatin plus fluorouracil* in treating patients with locally advanced squamous cell cancer of the head and neck.

* We would assume that treatment in LA SCCHN would always be in combination with radiotherapy.

**1. Median survival data derived from the Bonner study, for each of the following Karnofsky performance scores – 100, 90, 80, 70 and less.**

Median survival data as requested from the Appeal panel for each of the individual Karnofsky performance scores is presented in Table 1 below. Please note, due consideration should be taken with regards to some of the subgroups due to the low patient numbers analysed.

**Table 1: Overall Survival (months) stratified by KPS at baseline.**

| Subgroup | | | | % Censored | Median | 95% CI | Hazard Ratio | 95% CI |
|---|---|---|---|---|---|---|---|---|
| Age | KPS | Treatment | N | | | | | |
| All | 100 | RT + CET | 34 | 70.6 | 62.6+ | (53.0, 62.6+) | 0.61 | (0.28, 1.31) |
| | | RT alone | 38 | 52.6 | 63.0+ | (27.1, 63.0+) | | |
| | 90-95 | RT + CET | 113 | 64.6 | 61.7+ | (55.2, 61.7+) | 0.58 | (0.39, 0.88) |
| | | RT alone | 103 | 48.5 | 42.9 | (24.3, 62.9+) | | |
| | 80 | RT + CET | 42 | 19.0 | 12.2 | ( 9.5, 18.6) | 1.11 | (0.69, 1.77) |
| | | RT alone | 49 | 26.5 | 14.8 | (10.1, 17.4) | | |
| | 70 | RT + CET | 15 | 20.0 | 12.2 | (10.7, 22.7) | 1.22 | (0.53, 2.78) |
| | | RT alone | 16 | 31.3 | 14.6 | ( 5.4, 54.0+) | | |
| | <70 | RT + CET | 6 | 16.7 | 4.4 | ( 0.8, 25.5) | 3.41 | (0.65, 17.7) |
| | | RT alone | 6 | 50.0 | 36.3 | ( 5.7, 36.3) | | |

**Key points to be noted from these analyses:**

- The number of patients available for analyses with a KPS of 100, 80, 70 and less than 70 are very low hence interpretation is limited.
- The Hazard Ratios for patients with a KPS of 100 and 90 are positive in favour of cetuximab in combination with radiotherapy.
- The Hazard Ratios reported for patients with a KPS of 80, 70 and less than 70 are not positive for cetuximab in combination with radiotherapy.

## 2. Incremental cost-effectiveness ratios for patient groups with a Karnofsky performance score of 100, 90, 80, 70 and less.

Incremental cost effectiveness ratios for each patient group by Karnofsky performance status is presented in Table 2 below.

**Table 2 Costs: health outcomes and cost-effectiveness ratios by KPS subgroups**

| | | KPS <70* | KPS 70 | KPS 80 | KPS 90 | KPS 100 |
|---|---|---|---|---|---|---|
| **Costs** | RT | £6,945 | £6,672 | £6,768 | £7,442 | £7,448 |
| | ERT | £10,349 | £13,618 | £12,262 | £14,706 | £13,584 |
| **QALYs** | RT | 2.2963 | 1.5950 | 2.0303 | 3.1846 | 3.4903 |
| | ERT | 2.3880 | 1.4864 | 2.1247 | 4.8107 | 3.9569 |
| **Life years** | RT | 4.3713 | 2.3967 | 2.9876 | 4.5994 | 4.7238 |
| | ERT | 2.8471 | 2.0990 | 2.6145 | 6.0936 | 5.4927 |
| **Cost per QALY gained** | | £37,089 | -£63,927 | £58,210 | £4,467 | £13,151 |
| **Cost per life year gained** | | -£2,233 | -£23,335 | -£14,725 | £4,862 | £7,979 |

* includes one patient with KPS50 in RT group

**Key points to be noted from these analyses:**

- All analyses were conducted using the Merck Cost Effectiveness model submitted to NICE in its original appraisal.
- Patients with a KPS of 100 or 90 report a cost per QALY gained of £13,151 and £4,467 respectively which are both well within NICE defined thresholds for cost effective use of NHS resource.

**3. Any other data in its possession that would enable the Appraisal Committee to assess the clinical and cost effectiveness of cetuximab according to the decision problem defined by Merck Serono.**

**3a. Median overall survival derived from the Bonner study stratified by KPS and for patients aged younger or older than 65 years.**

The cetuximab clinical data assessed by the EMEA and presented in section 5.1 of the cetuximab SPC [1] states:

> *"No clinical benefit could be demonstrated in patients with KPS <=80 who were 65 years of age or older".*

Presented below in Table 3 is an analysis of patients older and younger than 65 years, and stratified by KPS of 80 and less, and greater than 80.

**Table 3: Overall Survival [Months] stratified by Age and KPS at Baseline**

| Stratification | | | | | | % Cen- | Rates | | | Median | | Hazard Ratio |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1st Strata | | 2nd Strata | | Treatment | N | sored | 1 Year | 2 Years | 3 Years | 95% CI | | 95% CI |
| AgeGroup | <65 yrs | KPSGroup | <=80 | RT + CET | 44 | 27.3 | 56.8% | 36.4% | 26.3% | 15.7 | (10.3, 25.5) | 0.86 (0.53, 1.40) |
| | | | | RT alone | 47 | 27.7 | 53.0% | 32.2% | 27.4% | 13.2 | ( 8.3, 17.7) | |
| | | | >80 | RT + CET | 122 | 68.9 | 90.1% | 76.3% | 73.0% | 62.6+ | (56.7, 62.6+) | 0.61 (0.40, 0.93) |
| | | | | RT alone | 101 | 53.5 | 84.9% | 67.6% | 55.7% | 59.3 | (31.6, 63.0+) | |
| | >=65 yrs | KPSGroup | <=80 | RT + CET | 20 | 5.0 | 45.0% | 5.0% | | 11.7 | ( 6.0, 14.3) | 2.26 (1.14, 4.49) |
| | | | | RT alone | 24 | 33.3 | 66.7% | 40.2% | 31.3% | 15.9 | (11.7, 54.0+) | |
| | | | >80 | RT + CET | 25 | 52.0 | 80.0% | 76.0% | 68.0% | 53.0 | (26.6, 61.7+) | 0.63 (0.32, 1.27) |
| | | | | RT alone | 41 | 41.5 | 75.0% | 59.5% | 46.4% | 27.1 | (19.9, 62.9+) | |

**Key points to be noted from these analyses:**

- Hazard Ratios for patients with a KPS of greater than 80 (i.e. KPS of 100 and 90) are positive in favour of cetuximab in combination with radiotherapy regardless of age.
- Of the 4 groups assessed, the hazard ratio for patients aged older than 65 years and with a KPS of 80 and less (a Hazard Ratio of 2.26) would suggest no benefit for the use of cetuximab in combination with radiotherapy in this group only. This is in line with the cetuximab SPC.
- For patients aged less than 65 years and with a KPS of 80 or less, whilst the confidence intervals cross 1, the hazard ratio is positive in favour of cetuximab in combination with radiotherapy for this group of patients. Please note however, that the patient numbers assessed are low and data should be interpreted with this consideration.

In order to present data consistent with that requested in section 1 of this document, please find below in Table 4, data stratification by the individual KPS and aged older or younger than 65 years.

**Table 4: Overall Survival [Months] stratified by Age and KPS at Baseline**

| Subgroup | | | | % Censored | Median | 95% CI | Hazard Ratio | 95% CI |
|---|---|---|---|---|---|---|---|---|
| Age | KPS | Treatment | N | | | | | |
| <65 yrs | 100 | RT + CET | 30 | 73.3 | 62.6+ | (45.5, 62.6+) | 0.59 | (0.24, 1.46) |
| | | RT alone | 24 | 54.2 | 63.0+ | (31.0, 63.0+) | | |
| | 90-95 | RT + CET | 92 | 67.4 | 60.0+ | (56.7, 60.0+) | 0.62 | (0.38, 1.00) |
| | | RT alone | 77 | 53.2 | 59.3 | (30.2, 62.9+) | | |
| | 80 | RT + CET | 33 | 24.2 | 12.2 | ( 9.5, 20.4) | 0.91 | (0.52, 1.57) |
| | | RT alone | 34 | 23.5 | 11.8 | ( 7.1, 17.7) | | |
| | 70 | RT + CET | 6 | 33.3 | 29.2 | (20.4, 59.3+) | 0.55 | (0.15, 2.01) |
| | | RT alone | 8 | 25.0 | 10.7 | ( 4.4, 39.4+) | | |
| | <70 | RT + CET | 4 | 25.0 | 16.3 | ( 0.8, 36.0+) | 3.91 | (0.40, 37.8) |
| | | RT alone | 5 | 60.0 | 36.3 | ( 2.9, 36.3) | | |
| >=65 yrs | 100 | RT + CET | 4 | 50.0 | 53.0 | ( 6.4, 56.1+) | 0.91 | (0.19, 4.44) |
| | | RT alone | 14 | 50.0 | 60.8+ | (20.6, 60.8+) | | |
| | 90-95 | RT + CET | 21 | 52.4 | 52.1 | (26.6, 61.7+) | 0.53 | (0.24, 1.16) |
| | | RT alone | 26 | 34.6 | 24.3 | (14.7, 47.5) | | |
| | 80 | RT + CET | 9 | 0.0 | 12.5 | ( 8.7, 17.5) | 2.11 | (0.83, 5.38) |
| | | RT alone | 15 | 33.3 | 15.9 | (14.2, 52.8+) | | |
| | 70 | RT + CET | 9 | 11.1 | 11.9 | ( 4.1, 12.2) | 2.24 | (0.70, 7.20) |
| | | RT alone | 8 | 37.5 | 20.8 | ( 5.4, 54.0+) | | |
| | <70 | RT + CET | 2 | 0.0 | 1.1 | ( 0.4, 1.7) | 47E7 | (0.00, . ) |
| | | RT alone | 1 | 0.0 | 5.7 | ( 5.7+, 5.7+) | | |

**Key points to be noted from these analyses:**

- The patient numbers assessed in each subgroup are low, hence interpretation is limited.
- For patients aged less than 65 years:
  - Only those with a KPS of less than 70 report a hazard ratio greater than 1 (3.91), suggesting no benefit for the use of cetuximab in combination with radiotherapy.
  - All other subgroups report a hazard ratio of less than 1.
    - These results would suggest a trend towards benefit of cetuximab in combination with radiotherapy in this group of patients as validated by data presented in Table 3 of this document.
- For patients aged greater than 65 years, similar conclusions as presented for Table 3 can be drawn.

**3b. Incremental cost-effectiveness ratios stratified by individual KPS and aged older or younger than 65 years.**

The subgroup analysis in section 3a of this document would suggest that in addition to all patients with a KPS of 90 or 100, there is a strong trend for patients aged less than 65 years with a KPS of 80 or less to benefit from treatment with cetuximab in combination with radiotherapy. Table 5 below presents a cost-effectiveness analysis assessing this particular group of patients.

**Table 5: Costs, health outcomes and cost-effectiveness ratios for patients aged <65 years and KPS 80 or less**

| | | Patients aged <65 years and with a KPS of 80 or less |
|---|---|---|
| **Costs** | RT | £6,729 |
| | ERT | £12,147 |
| **QALYs** | RT | 1.7990 |
| | ERT | 2.6418 |
| **Life years** | RT | 2.5653 |
| | ERT | 3.2844 |
| **Cost per QALY gained** | | £6,729 |
| **Cost per life year gained** | | £7,534 |

**Key points to be noted from these analyses:**

- All analyses were conducted using the Merck Cost Effectiveness model submitted to NICE in its original appraisal.
- Patient numbers assessed in these analyses are limited and data should be interpreted with this consideration in mind.
- The cost per QALY gained of £6,729 is well within NICE defined thresholds for cost effective use of NHS resource.

Incremental cost effectiveness calculations relating to data presented in Table 4 of section 3a can be found in appendix 1.

**3c. <u>The implementation of a cetuximab head and neck cancer patient registry.</u>**

As communicated at the appeal meeting, we wish to inform the Appraisal Committee that Merck Serono has engaged with the Department of Health to establish a, "Coverage with Evidence Development" program based on the broader recommendation of the report from Sir David Cooksey[2]. We believe this initiative is the only possibility to address the remaining uncertainties in the three subgroups identified as inappropriate for cisplatin based chemoradiotherapy by the Appraisal Committee in the published FAD for this appraisal:

- *Active peripheral, cerebral or coronary vascular disease and any form of myelosuppression.*
- *Contraindications to cisplatin (conditions predisposing the patient to thrombocytopaenia, impaired renal function, impaired hearing and peripheral neuropathy).*
- *Previous cisplatin therapy for any malignancy.*

At the same time, this patient registry will provide access to appropriate treatment for this tiny and deserving patient group. Given the small number of patients defined, clinical data to answer the questions posed by NICE will never be collected, and as a result, this group of LA SCCHN patients will never have access to cetuximab in the UK.

Merck Serono proposes the initiation of a patient registry for the treatment of patients who may fall into one of these subgroups as a joint initiative with the NHS to collect effectiveness and cost effectiveness data. Cetuximab would not be available for NHS patients with LA SCCHN outside of this scheme and this would ensure that the most appropriate patients receive the treatment.

Information on clinical and cost effectiveness could then be provided to NICE for when the guidance on this technology is considered for re-review. Such an initiative would allow NICE to provide either a positive recommendation for the use of cetuximab in particular populations of patients within the registry only, or provide a "within research" recommendation.

## 4. Literature review of carboplatin monotherapy or in combination with fluorouracil treatment for LA SCCHN

**Key findings**

- The literature review identified a range of studies from different phases of research and with inconsistent reporting of study outcomes and tolerability.
- As a result, it is difficult to make firm conclusions on the use of carboplatin plus radiotherapy with and without 5-FU in locally advanced SCCHN.

**Carboplatin* in combination with radiotherapy**

- The literature review failed to identify any phase III studies and no published peer-reviewed meta-analyses of carboplatin alone or in combination with radiotherapy.
- The most robust overall survival estimate was published by Jeremic et al where the 53 patients treated with carboplatin reported a median overall survival of 30 months.
- No studies were identified which had a greater loco regional control (months) or median overall survival than found in the Bonner study (49 months median overall survival).

**Carboplatin* in combination with fluorouracil and radiotherapy**

- Three studies reported median overall survival of around 20 months.
- No studies were identified which provided a greater loco regional control (months) or median overall survival than found in the Bonner study (49 months median overall survival).
- The phase III research of carboplatin in combination with fluorouracil and radiotherapy identified high rates of grade 3/4 mucositus/ stomatitis, radiation dermatitis/ skin problems, haematological toxicities and dysphagia.

* We would assume that treatment in LA SCCHN would always be in combination with radiotherapy.

**Methods:**

A literature review was carried out to assess the efficacy and tolerability of carboplatin alone in combination with 5-fluorouracil for the treatment of patients with LA SCCHN.

The literature search was conducted on the week commencing 22nd October 2007.

Table 6 below presents the databases searched, the search terms utilised and the number of references found.

**Table 6:**

| **Database** | **Search Term** (free text search) | **Number of references found** |
|---|---|---|
| Medline | Carboplatin, head + neck. | 113 |
| Datastar: Medical research database. | Carboplatin, locally, advanced, squamous, head + neck. | 707 when duplicates removed = 186 |
| ASCO: head and neck abstracts database | Carboplatin | 100 |

Where possible the search included MESH and EMBASE subject headings.

Studies were included if the reference assessed patients with stage 3/4 (locally advanced SCCHN). Studies which assessed stage 1/2 were not included unless the research focused upon stages 3/4 and the minority of patients were stage 1 or 2.

**4a. Evidence on the efficacy and tolerability of carboplatin alone in treating patients with locally advanced squamous cell cancer of the head and neck.**

22 published studies were determined appropriate for review:

- 1 Meta analysis
- 1 Phase II/III study
- 10 Phase II studies
- 4 Phase I/II studies
- 3 Phase I studies
- 3 Retrospective reviews

The majority of these papers declare what stage of research this publication is in, however where no phase is given, research is considered to be phase II if efficacy is a research objective either as a randomised or as a single arm trial.

Budach *et al*[3] published the only Meta analysis found on-line in Biomed Central. This publication assessed carboplatin and cisplatin based treatment compared to radiotherapy

alone and reported 6.7 months and 16.8 months prolongation of overall survival versus radiotherapy alone respectively. While this meta-analysis is included in this review, there is only one study of carboplatin in combination in combination with radiotherapy included (Jeremic *et al* 1997[4]) and results should be interpreted with this consideration. Jeremic *et al* is also considered below separately.

The Phase II/III study reported was published by Jeremic *et al* (1997) and assessed 159 patients treated with cisplatin or carboplatin plus radiotherapy versus radiotherapy alone. 53 patients were treated with carboplatin in combination with radiotherapy in this study and reported a median overall survival of 30 months.

Further details of all literature assessed is presented in Appendix 3 and 4 with a summary of all reported efficacy and tolerability. Key points are as follows:

- Reported overall survival rates vary from 36.2 months (Fuwa N et al[5]) assessing 35 patients to Jacobs MC[6] et al with 10.8 months assessing 26 patients.
- The most reliable overall survival estimate may be considered from Jeremic et al where the 53 patients treated with carboplatin reported a median overall survival of 30 months.
- Reporting of tolerability issues was inconsistent, however mucositis/ stomatitis, radiation dermatitis/ skin problems and haematological toxicities were the most commonly reported.
- In the vast majority of studies the exclusion criteria is not stated therefore it was not possible to ascertain if any patients with hearing, renal or cardiovascular impairment were excluded.
- The drop out rate due to toxicity is not stated in most of the studies.

**4b. Evidence on the efficacy and toxicity of carboplatin plus fluorouracil in treating patients with locally advanced squamous cell cancer of the head and neck.**

9 published studies were deemed appropriate for review:

- 3 Phase III studies
- 4 Phase II studies
- 1 Phase I/II studies
- 1 Phase I study

In addition, Bourhis et al[7] presented the MACH - NC meta-analysis at ASCO 2004 and concluded that the addition of fluorouracil to platinum based therapy added no benefit. The Three phase III studies identified were published by Fallai C et al[8], Denis et al[9] and Staar et al[10].

Fallai C et al assessed 192 patients and found no statistically significant difference between conventional radiotherapy, accelerated radiotherapy and carboplatin in combination with conventional radiotherapy. This included 64 patients treated with carboplatin in combination with fluorouracil and radiotherapy.

Denis et al assessed 226 patients. This study assessed the 5 year survival of carboplatin in combination with fluorouracil and radiotherapy versus radiotherapy alone. This study reported a statistically significant 5 year survival rate of 22% versus 16% in favour of carboplatin in combination with fluorouracil and radiotherapy. Late toxicities reported included 56% with grade 3/4 adverse events versus 30% in the radiotherapy alone group. These included assessmenrt for neurological, taste teeth, mandibula and hearing toxicity. Ototoxicity was found to be 0% in the radiotherapy group versus 6% for treatment with the combination.

Staar et al assessed 240 patients. The primary endpoint was 1 year survival with local control. The primary endpoint was met, however there was no statistically significant difference in 1 and 2 year loco-regional control rates. The overall 2 year survival rates were 48% for the chemoradiotherapy arm versus 39% for the radiotherapy alone arm.

Presented in Appendix 5 and 6 is a summary of all studies reporting carboplatin related efficacy and tolerability. Key points are as follows:

- Reported median overall survival is around 20 months. In the phase III research identified this varies from 23 months (Staar et al) assessing 113 patients treated with carboplatin in combination with fluorouracil and radiotherapy to 19 months (Fallai et al) assessing 64 patients. Denis et al also reports a median overall survival of 20 months.
- Reporting of tolerability issues was inconsistent, however in the phase III research identified, this included acute grade 3/4 toxicities of:
    - Mucositis/ stomatitis: 68% - 48%
    - Radiation dermatitis/ Skin problems: 30% - 16%
    - Haematological toxicities: 29.5% - 23%
    - Dysphagia: 51% (all grades)
- In the vast majority of studies the exclusion criteria is not stated therefore it was not possible to ascertain if any patients with hearing, renal or cardiovascular impairment were excluded.
- The drop out rate due to toxicity is not stated in most of the studies.

## Conclusion

### Carboplatin in combination with radiotherapy

- The literature review failed to identify any phase III studies and only one reviewed meta-analyses of carboplatin alone or in combination with radiotherapy.
- The most robust overall survival estimate was published by Jeremic et al where the 53 patients treated with carboplatin in combination with radiotherapy reported a median overall survival of 30 months.
- No studies were identified which had a greater loco regional control (months) or median overall survival reported, than found in the Bonner study[11] (49 months median overall survival).

### Carboplatin in combination with fluorouracil and radiotherapy

- Three studies reported median overall survival of around 20 months.
- No studies were identified which had a greater loco regional control or median overall survival reported than found in the Bonner study (49 months median overall survival).
- The phase III research of carboplatin in combination with fluorouracil and radiotherapy identified high rates of grade 3/4 mucositis/ stomatitis, radiation dermatitis/ skin problems, haematological toxicities and dysphagia.

## Appendix 1:

### Table A1: Subgroup analyses for patients younger than 65 years

| | | Subgroup <65 years | | | | |
|---|---|---|---|---|---|---|
| | | **KPS 60** | **KPS 70** | **KPS 80** | **KPS 90** | **KPS 100** |
| **Cost** | RT | £7,225 | £6,671 | £6,670 | £7,587 | £7,646 |
| | ERT | £11,033 | £12,535 | £12,211 | £14,756 | £13,766 |
| **QALYs** | RT | 2.6716 | 0.9928 | 1.8604 | 3.3577 | 3.6014 |
| | ERT | 3.5715 | 2.9404 | 2.4748 | 4.7773 | 3.9473 |
| **Life years** | RT | 5.1527 | 1.5160 | 2.4317 | 4.9377 | 4.9070 |
| | ERT | 4.2260 | 4.0271 | 3.0352 | 6.1225 | 5.5058 |
| **Cost per QALY gained** | | £4,232 | £3,011 | £9,020 | £5,050 | £17,695 |
| **Cost per Life year gained** | | -£4,110 | £2,335 | £9,181 | £6,051 | £10,221 |

### Table A2: Subgroup analyses for patients aged 65 years and older

| | | Subgroup >=65 years | | | | |
|---|---|---|---|---|---|---|
| | | **KPS 60** | **KPS 70** | **KPS 80** | **KPS 90** | **KPS 100** |
| **Cost** | RT | £5,549 | £6,673 | £6,988 | £7,010 | £7,109 |
| | ERT | £8,980 | £14,340 | £12,449 | £14,488 | £12,214 |
| **QALYs** | RT | 0.4196 | 2.1973 | 2.4156 | 2.6719 | 3.2999 |
| | ERT | 0.0211 | 0.5170 | 0.8414 | 4.9555 | 4.0286 |
| **Life years** | RT | 0.4645 | 3.2774 | 4.2478 | 3.5972 | 4.4099 |
| | ERT | 0.0891 | 0.8136 | 1.0717 | 5.9684 | 5.3950 |
| **Cost per QALY gained** | | -£8,608 | -£4,563 | -£3,469 | £3,275 | £7,006 |
| **Cost per Life year gained** | | -£9,140 | -£3,112 | -£1,719 | £3,154 | £5,182 |

## Appendix 2:

## Table A3: Carboplatin in combination with radiotherapy reported efficacy.

| Reference | Phase | Study name | N | Median LRC | Median RR (%) | Median OS (months) | 2,3,4,5 year OS rate (%) |
|---|---|---|---|---|---|---|---|
| Budach et al BMC cancer, 2006 (epub), vol. 6, p. 28 1471−2407. | Meta-analysis | A meta-analysis of hyperfractionated and accelerated radiotherapy and combined chemotherapy and radiotherapy regimens in unresected locally advanced squamous cell carcinoma of the head and neck | 10,225 (only approx 53 patients had carboplatin/ RT alone) | NR | NR | Increase of 6.7 months compared to RT alone. | NR |
| Sanghera et al Int−J−Radiat−Oncol −Biol−Phys}, 2007 vol. 67( 5) 1342−51, | Retrospective study | Hypofractionated accelerated radiotherapy with concurrent chemotherapy for locally advanced squamous cell carcinoma of the head and neck. | 81 | The results were not split out but combined methotrexate and carboplatin outcomes | | | |
| Pradier O et al. ORL 2004; 66(6): 325-331. | II | A long−term follow−up study after split−course irradiation with concurrent chemotherapy (carboplatin) for locally advanced head and neck cancer and a review of the literature | 66 | NR | NR | 14.3 months | 32% at yr 2<br>18% at yr 5 |
| Hosokawa−Y et al {lin−Oncol−R−Coll− Radiol 1995, vol. 7, no. 3, p. 168−72, | II | Simultaneous carboplatin and radiotherapy for all stages of head and neck squamous cell carcinoma. | 63 | NR | 72.2% | NR | 69.2% at yr 2 |
| Zamboglou N et al. Semin Oncol 1994 ; 21(5 suppl 12) : 45-53. | II | Carboplatin and radiotherapy in the treatment of head and neck cancer: six years' experience | 103 | NR | 99% | Approx 23 months | 53% at yr 2 |
| Jeremic B et al. Radiother Oncol 1997; 43(1): 29-37. | II/ III | Radiation therapy alone or with concurrent low−dose daily either cisplatin or carboplatin in locally advanced unresectable squamous cell carcinoma of the head and neck: a prospective randomized trial. | 159<br>(53 carboplatin) | NR | 85% | 30 months | 55% at yr 2<br>47% at yr 3<br>31% at yr 4<br>29% at yr 5 |

| Reference | Phase | Study name | N | Median LRC | Median RR (%) | Median OS (months) | 2,3,4,5 year OS rate (%) |
|---|---|---|---|---|---|---|---|
| Homma−Akihiro et al, Cancer journal 2004, vol. 10, no. 5, p. 326−32, 1528−9117. | II | Randomized Phase II Trial of Concomitant Chemoradiotherapy Using Weekly Carboplatin or Daily Low-Dose Cisplatin for Squamous Cell Carcinoma of the Head and Neck<br><br>(45% of patients had Stage II disease). | 119<br><br>(60 patients carboplatin) | 56.2% at yr 5 | NR | NR | 71.4% at yr 5 |
| Zamboglou N et al. Cancer Invest 1992; 10(5): 349-355. | II | Simultaneous radtiotherapy and chemotherapy with carboplatin in inoperable squamous cell carcinoma of the head and neck: a phase II study. | 56 | NR | 98% | NR | 53% at yr 2 |
| Jeremic B et al. J Chemother 1992; 4(3): 180-184. | II | Carboplatin and radiation therapy for stage IV carcinoma of the head and neck. Preliminary results of a phase II study. | 34 | NR | 74% | NR | NR |
| Mucke R et al. Strashlenther Onkol 1999; 175(5): 213-217. | Retrospecti ve study | Simultaneous radiochemotherapy with carboplatin in patients with inoperable advanced stage III and IV head and neck tumours (article in German/part English) | 92 | 18% at 5 years | 93% | NR | 24.3% at yr 5 |
| Maisano R et al. J Chemother 1995 ; 7(6) : 549-553. | II | Concurrent carboplatin and radiotherapy in the treatment of squamous cell carcinoma of the head and neck, stage IV. Preliminary data of a phase II study. | 14 | NR | 85.7% | NR | 44% at yr 3 |
| Fountzilas G et al. Tumori 1995; 81: 354-358. | II | Radiation and concurrent carboplatin administration in locally advanced head and neck cancer. A Hellenic Cooperative Oncology Group study. | 39 | NR | 85% | NR | NR |

| Reference | Phase | Study name | N | Median LRC | Median RR (%) | Median OS (months) | 2,3,4,5 year OS rate (%) |
|---|---|---|---|---|---|---|---|
| Porceddu SV et al. Int J Radiat Oncol Biol Phys 2004 ; 60(2) : 365-373. | II | Postoperative chemoradiotherapy for high-risk head-and-neck squamous cell carcinoma.<br><br>Note that this is an adjuvant study therefore in a different setting to the majority of others which inoperable patients. | 47 (20 with carboplatin) | The results were pooled for cisplatin and carboplatin therefore no carboplatin specific results were available | | | |
| Benazzo M et al. Eur Arch Otorhinolaryngol 2000; 257(5): 279-282. | II | Induction chemotherapy by superselective intra-arterial high-dose carboplatin infusion for head and neck cancer. | 40 | NR | 90% | 21 mths | NR |
| Ackland SP et al. Clin Oncol (R Coll Radiol) 1993; 5(3): 133-138. | I/ II | Phase I/II study of concurrent weekly carboplatin and radiation therapy in advanced head and neck cancer. | 32 | Approx 13 months | 75% | NR | NR |
| Jacobs MC et al. Int J Radiat Oncol Biol Phys 1989; 17(2): 361-363. | I/ II | Carboplatin (CBDCA) and radiotherapy for stage IV carcinoma of the head and neck: a phase I-II study. | 26 | NR | 76% | Approx 10.8 months | NR |
| Volling P et al. Semin Oncol 1992; 19(1 suppl 2): 66-71.<br>and neck. | I/ II | Phase I/II study of simultaneous carboplatin and radiotherapy in unresectable squamous cell carcinoma of the head | 36 | NR | 97% | NR | NR |
| Zamboglou N et al. Stahlenther Onkol 1989; 165(9): 647-651. | Retrospecti ve review | Combined radiotherapy with cis- or carboplatin in advanced head and neck tumors<br><br>(article in German). | 30 | NR | 100% | Further text is reported in German. | |

| Reference | Phase | Study name | N | Median LRC | Median RR (%) | Median OS (months) | 2,3,4,5 year OS rate (%) |
|---|---|---|---|---|---|---|---|
| Fuwa N et al. Cancer 2000; 89(10): 2099-2105. | I/ II | A combination therapy of continuous superselective intraarterial carboplatin infusion and radiation therapy for locally advanced head and neck carcinoma. | 35 | No overall figure given for LRC | 97% | 36.2 months | 73% at yr 2<br>63% at yr 3<br>NR<br>59% at yr 5 |
| Osoba D et al. Head Neck 1991; 13(3): 217-222. | I | Phase I study of concurrent carboplatin and radiotherapy in previously untreated patients with stage III and IV head and neck cancer. | 22 | NR | 91% | NR | NR |
| Ausili-Cefaro G et al. Am J Clin Oncol 1995; 18(3) : 273-276. | I | Prolonged continous infusion of carboplatin and concomitant radiotherapy in advanced head and neck cancer. A phase I study. | 21 | NR | 88% | NR | NR |
| Madhava−K et al. Clin Oncol (R Coll Radiol) 2006; 18(1): 77-81. | I | Carboplatin and hypofractionated accelerated radiotherapy: dose escalation for squamous cell carcinoma of the head and neck. | 19 | 75% 2 year LRC | 89% | NR | 66% at yr 2 |
| | | | | | | | |
| *Bonner J et al. New Engl J Med 2006; 354(6): 354-356.* | III | Radiotherapy plus Cetuximab for squamous-cell carcinoma of the head and neck. | 424<br><br>(211 pts in the cetuximab/ RT arm) | 24.4 | 74% | 49.0 | 62% at yr 2<br>55% at yr 3 |

## Appendix 3:

## Table A4: Carboplatin reported Tolerability. Grade 3 or 4 acute side effects unless stated otherwise

| Reference | n | Mucositis/ Stomatitis | Radiation dermatitis/ Skin | Haematological toxicities* | Dysphagia | Fatigue | Xerostomia |
|---|---|---|---|---|---|---|---|
| Budach et al BMC cancer, 2006 (epub), vol. 6, p. 28 1471−2407. | 10,225 (276 carboplatin +5FU) | Toxicities Not reported | | | | | |
| Sanghera et al Int−J−Radiat−Oncol−Biol−Phys}, 2007 vol. 67( 5) 1342−51. | 81 | Toxicities for carboplatin/ RT alone not reported | | | | | |
| Pradier O et al. ORL 2004; 66(6): 325-331. | 66 | 26% grade 3 | 19% grade 3 | 53% grade 3 | NR | NR | 23% |
| Homma−Akihiro et al, Cancer journal 2004, vol. 10, no. 5, p. 326−32, 1528−9117. | 60 | 3% | 17% | 13% | NR | NR | NR |
| Jeremic B et al. Radiother Oncol 1997; 43(1): 29-37. | 159 (53 patients on carboplatin alone) | 13% | NR | 19% | NR | NR | 2% |
| Hosokawa−Y et al Iin−Oncol−R−Coll−Radiol 1995, vol. 7, no. 3, p. 168−72, | 61 | NR | NR | NR | NR | NR | NR |
| Zamboglou N et al. Semin Oncol 1994; 21(5 suppl 12): 45-53. | 103 | 14% G3/G4 | NR | 22% | NR | NR | NR |
| Zamboglou N et al. Cancer Invest 1992; 10(5): 349-355. | 56 | 21% | NR | 33% | NR | NR | NR |
| Jeremic B et al. J Chemother 1992; 4(3): 180-184. | 34 | 9% | NR | 29% | NR | NR | NR |
| Mucke R et al. Strashlenther Onkol 1999; 175(5): 213-217. | 93 | 10% | NR | 14% | NR | NR | NR |
| Maisano R et al. J Chemother 1995; 7(6): 549-553. | 14 | 43% | NR | NR | NR | NR | NR |

| Reference | n | Mucositis/ Stomatitis | Radiation dermatitis/ Skin | Haematological toxicities* | Dysphagia | Fatigue | Xerostomia |
|---|---|---|---|---|---|---|---|
| Porceddu SV et al. Int J Radiat Oncol Biol Phys 2004 ; 60(2) : 365-373. | 20 (carbo) | 40% (results pooled for carboplatin and cisplatin) | 15% (results pooled for carboplatin and cisplatin) | 25% | NR | NR | NR |
| Benazzo M et al. Eur Arch Otorhinolaryngol 2000; 257(5): 279-282. | 40 | 3% | 3% Skin erythema | No G3 or G4 observed | NR | NR | NR |
| Fountzilas G et al. Tumori 1995; 81: 354-358. | 39 | 13% | NR | 60% | 5% | NR | NR |
| Ackland SP et al. Clin Oncol (R Coll Radiol) 1993; 5(3): 133-138. | 32 | 25% | None observed | 34% | NR | NR | NR |
| Jacobs MC et al. Int J Radiat Oncol Biol Phys 1989; 17(2): 361-363. | 26 | 81% developed mucositis but 40% had moderate to severe | NR | NR according to WHO or NCI criteria | NR | NR | NR |
| Volling P et al. Semin Oncol 1992; 19(1 suppl 2): 66-71. | 36 | 33% | | Approx 14% | NR | NR | NR |
| Zamboglou N et al. Stahlenther Onkol 1989; 165(9): 647-651. | 30 | Myelotoxicities were dose-limiting- further text is in German | | | | | |
| Fuwa N et al. Cancer 2000; 89(10): 2099-2105. carcinoma. | 35 | None were observed | 11% | None were observed | | | |
| Osoba D et al. Head Neck 1991; 13(3): 217-222. | 22 | 41% | 18% | None observed | NR | NR | 27% |
| Ausili-Cefaro G et al. Am J Clin Oncol 1995; 18(3) : 273-276. | 21 | 38% | None observed | leucopenia 57%<br>neutropenia 57%<br>Thrombocytopenia 29%<br>Anaemia 5% | NR | NR | NR |
| Madhava−K et al. Clin Oncol (R Coll Radiol) 2006; 18(1): 77-81. | 19 | 84% | 26% | 16% | NR | NR | NR |
| | | | | | | | |
| *Bonner J et al. New Engl J Med 2006; 354(6): 354-356.* | 424 (211 pts in the cetuximab/ RT arm) | 56% grade 3-5 | 23% radiation dermatitis, 17% acneiform rash grade 3-5 | 1% anaemia grade 3-5 | 26% grade 3-5 | NR | 5% grade 3-5 |

* Haematological toxicities consist of leucopenia, thrombocytopenia, anaemia and neutropenia

## Appendix 4

## Table A5: Carboplatin in combination with fluorouracil (and radiotherapy) reported efficacy.

| Reference | Phase | Study name | N | Median LRC | Median RR (%) | Median OS (months) | 2,3,4,5 year OS rate (%) |
|---|---|---|---|---|---|---|---|
| Denis et al J Clin Oncol 22:69-76. (2004) | III | Final Results of the 94-01 French Head and Neck Oncology and Radiotherapy Group Randomized Trial Comparing Radiotherapy Alone With Concomitant Radiochemotherapy in Advanced-Stage Oropharynx Carcinoma | 226 (109 carboplatin/ 5FU) | 47.6% | NR | 20 months | 22% at yr 5 |
| Staar S et al Int J Radiat Oncol Biol Phys. 2001 Aug 1;50(5):1161-71. | III | Intensified hyperfractionated accelerated radiotherapy limits the additional benefit of simultaneous chemotherapy—results of a multicentric randomized german trial in advanced head-and-neck cancer | 240 (113 carboplatin/5FU) | 69% at 1 year 2 years 51% | 92.4% | Approx 23 months | 48% at yr 2 |
| Fallai et al Tumori. 2006 Jan-Feb;92(1):41-54. Efficacy also reported in Olmi P et al Int J Rad Oncol Biol Phys 2003. 55; (1) 78-92. | III | Long-term results of conventional radiotherapy versus accelerated hyperfractionated radiotherapy versus concomitant radiotherapy and chemotherapy in locoregionally advanced carcinoma of the oropharynx. | 192 (64 carboplatin/ 5FU) | Approx 13 mths | NR | 19 mths | 51% at yr 2 40% at yr 5 |
| Krengli M et al. Tumori 2001; 87: 312-316. | II | Concurrent chemotherapy with carboplatin + 5-fluorouracil and radiotherapy in advanced squamous cell head and neck carcinoma : a retrospective single institution's study. | 58 | NR | 93.1 | 23 months recurrence-free | 52% at yr 3 |
| Tejador M et al. Am J Clin Oncol (CCT) 1992; 15(5): 417-421. | II | Induction chemotherapy with carboplatin and ftorafur in advanced head and neck cancer. | 36 | NR | 68.5% after chemotherapy, and 100% after radiotherapy | NR | 54% DFS at yr 2 48% DFS at yr 3 48% DFS at yr 4 |

| Reference | Phase | Study name | N | Median LRC | Median RR (%) | Median OS (months) | 2,3,4,5 year OS rate (%) |
|---|---|---|---|---|---|---|---|
| Tepmongkol P et al. J Med Assoc Thailand 1991; 74(12): 658-668. | II | Neoadjuvant carboplatin & 5 fluorouracil combination and radiotherapy in the treatment of locally advanced head and neck cancer: primary report. | 53 | NR | 85% after neoadjuvant chemotherapy, & 96% after postradiation chemotherapy | NR | NR |
| Segura-Huerta A et al. Clin Transl Oncol 2005; 7(1): 23-28. | II | Carboplatin and tegafur-uracil concomitant with standard radiotherapy in the management of locally advanced head and neck cancer. | 58 | NR | 74% | 18.4% | NR |
| Gregoire V et al. J Clin Oncol 1991 ; 9(8) : 1385-1392. | I/II | A Phase I-II trial of induction chemotherapy with carboplatin and fluorouracil in locally advanced head and neck squamous cell carcinoma: a report from the UCL-Oncology Group, Belgium.<br><br>Note this is an induction chemotherapy | 83 | NR | 57% | NR | NR |
| Taguchi T et al. Anticancer Res 2003 ; 23 (1B) : 713-717. | I | Combined radiotherapy and chemotherapy with carboplatin and UFT for head and neck squamous cell carcinoma. | 27 | NR | 75% | NR | NR |
| | | | | | | | |
| *Bonner J et al. New Engl J Med 2006; 354(6): 354-356.* | *III* | Radiotherapy plus Cetuximab for squamous-cell carcinoma of the head and neck. | 211 | 24.4 | 74% | 49.0 | 62% at yr 2<br>55% at yr 3<br>NR<br>NR |

## Appendix 5

## Table A6: Carboplatin in combination with fluorouracil and radiotherapy reported tolerability. (acute toxicities Grade 3 or 4 where reported)

| Reference | n | Mucositis/ Stomatitis | Radiation dermatitis/ Skin | Haematological toxicities* | Dysphagia | Fatigue | Xerostomia |
|---|---|---|---|---|---|---|---|
| Denis et al J Clin Oncol 22:69-76. (2004) | 226 (109 carboplatin/ 5FU) | Late toxicities only reported | | | | | |
| Staar S Int J Radiat Oncol Biol Phys. 2001 Aug 1;50(5):1161-71. | 240 (113 carboplatin/ 5FU) | 68% | 30% | 23% | 51% all grades | NR | NR |
| Fallai et al Tumori. 2006 Jan-Feb; 92(1):41-54.<br><br>Safety also reported in Olmi P et al Int J Rad Oncol Biol Phys 2003. 55; (1) 78-92 | 192 (64 carboplatin with 5FU) | 48% | 16% | 29.5% | NR | NR | None observed |
| Gregoire V et al. J Clin Oncol 1991 ; 9(8) : 1385-1392. | 83 | 12% with more than grade 1 mucosal toxicity | NR | 17% neutropenia<br><br>28-50% thrombocytopenia | NR | NR | NR |
| Krengli M et al. Tumori 2001; 87: 312-316. | 58 | 60.3% grade 2-3 | 32.7% cutaneous reaction (grade 2-3) | 55.1% leucopenia<br><br>55.1% neutropenia | 32.7% grade 2-3 | NR | 48.2% grade 2-3 |
| Tejador M et al. Am J Clin Oncol (CCT) 1992; 15(5): 417-421. | 36 | 5.5% grade 1-2 | | 5.5% leucopenia,<br><br>11% anaemia,<br><br>22% thrombocytopenia (grade 1-2) | NR | NR | NR |
| Tepmongkol P et al. J Med Assoc Thailand 1991; 74(12): 658-668. | 53 | 15% grade 2 | NR | 4% grade 2 myelosuppression | NR | NR | NR |
| Segura-Huerta A et al. Clin Transl Oncol 2005; 7(1): 23-28. | 58 | 47% grade 3-4 | NR | 17% leucopenia & 9% anaemia | NR | NR | NR |
| | | | | | | | |
| *Bonner J et al. New Engl J Med 2006; 354(6): 354-356.* | 211 | 56% grade 3-5 | 23% radiation dermatitis, 17% acneiform rash grade 3-5 | 1% anaemia grade 3-5 | 26% grade 3-5 | NR | 5% grade 3-5 |

* Haematological toxicities consist of leucopenia, thrombocytopenia, anaemia and neutropenia

[1] Erbitux Summary of Product Characteristics (SmPC)

last updated Wednesday 21st March 2007 available from the electronic medicines compendium at http://emc.medicines.org.uk/emc/assets/c/html/DisplayDoc.asp?DocumentID=14625

[2] A review of UK health research funding. Sir David Cooksey, December 2006: hm-treasury.gov.uk; Crown copyright 2006.

[3] Budach et al; A meta−analysis of hyperfractionated and accelerated radiotherapy and combined chemotherapy and radiotherapy regimens in unresected locally advanced squamous cell carcinoma of the head and neck.

BMC cancer, 2006 (epub), vol. 6, p. 28 1471−2407.

[4] Jeremic B et al; Radiation therapy with or without concurrent low-dose daily chemotherapy in locally advanced, nonmetastatic squamous cell carcinoma of the head and neck.

J Clin Oncol 2004; 22(17): 3540-3548.

[5] Fuwa N et al ; combination therapy of continuous superselective intraarterial carboplatin infusion and radiation therapy for locally advanced head and neck carcinoma. Cancer 2000; 89(10): 2099-2105.

[6] Jacobs MC et al. Carboplatin (CBDCA) and radiotherapy for stage IV carcinoma of the head and neck: a phase I-II study. Int J Radiat Oncol Biol Phys 1989; 17(2): 361-363.

[7] Bourhis et al. Update of MACH-NC (Meta-Analysis of Chemotherapy in Head & Neck Cancer) database focused on concomitant chemoradiotherapy. Journal of Clinical Oncology, 2004 ASCO Annual Meeting Proceedings (Post-Meeting Edition). Vol 22, No 14S (July 15 Supplement), 2004: 5505 plus presentation at the meeting. www.asco.org

[8] Fallai C et al. Conventional radiotherapy versus accelerated hyperfractionated radiotherapy versus concomitant radiotherapy and chemotherapy in locoregionally advanced carcinoma of the oropharynx. Tumori, 2006, vol. 92(1) , p. 41−54.

[9] Denis F et al. Final results of the 94-01 French Head and Neck Oncology and Radiotherapy Group randomized trialcomparing radiotherapy alone iwth concomitant radiochemotherapy in advanced-stage oropharynx carcinoma. J Clin Oncol 2004 ; 22(1) : 69-76.

[10] Staar S. Int J Radiat Oncol Biol Phys. 2001 Aug 1;50(5):1161-71.

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