Merck response to NICE ACD: Cetuximab in the treatment of LA SCCHN: 26th February 2007

NICE Single Technology Appraisal of cetuximab for the treatment of locally advanced squamous cell carcinoma of the head & neck

On behalf of Merck Pharmaceuticals, please find herewith, our response to the NICE ACD with regards to the NICE Single Technology Appraisal for cetuximab in the treatment of locally advanced squamous cell carcinoma of the head and neck (LA SCCHN). Our comments fall under points 1 and 3 of the general headings requested:

i) whether you consider that all of the relevant evidence has been taken into account;

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.

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:

1. The proposed patient population for the treatment with cetuximab plus radiotherapy:
    a) The definition of patient "fitness" described by NICE in the ACD and the relationship to Karnofsky Performance Status (KPS)
    b) NICE proposed alternative treatments for SCCHN: the licensing and contraindications associated with the use of cisplatin and carboplatin
    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
2. Radiotherapy treatment patterns for the treatment of LA SCCHN in the UK
3. Critique of the decision problem
    a) Medical ethics governing the choice of treatment with radiotherapy alone
    b) Clinical research timelines and the use of current standard treatment
    c) Implications for clinical research in the UK

In summary:

- 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.

- 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.

- 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 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.

- 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 al study which clearly demonstrates significant clinical benefit for cetuximab in this setting.

1a) The definition of patient "fitness" described by NICE in the ACD and the relationship to Karnofsky performance status

Section 4.8 of the ACD[1] states:

"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"

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.

Section 4.7 of the ACD [1] 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."

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].

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.

Reasons why a patient may be inappropriate for cisplatin based chemoradiotherapy treatment are presented below:

- **Comorbidity:**
  - Active peripheral, cerebral or coronary vascular disease
  - Any form of myelosuppression
- **Contraindication:**
  - Condition that may be exacerbated by the risks associated with thrombocytopenia
  - Impaired renal function
  - Impaired hearing
  - Peripheral neuropathy
- **Other reasons:**
  - Previous cisplatin therapy
  - Patient choice for treatment

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.

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.

The key demographic data from both "waves" are shown in table 1 below:

Table 1: Merck Pharmaceuticals A+A audit of SCCHN

Parameter collected	**Wave 1 (Nov '05)**	**Wave 2 (Nov '06 –Jan '07)**
Number of participating physicians	52	51
Number of patient records	405	412
Number of patients with locally advanced non-resectable disease	133 (33%)	154 (37%)
Patients who are LA & non resectable		
Who received RT alone	51 (38%)	32 (21%)
% patients with ECOG 0-1	84%	68%
Mean age	62 yrs	61.2yrs
Comorbidities prior to treatment	Information not collected	Observed in 17/22 pts. See Table 2 for details

Data presented in table 1 shows that this actual patient population compares well with those patients treated in the Bonner study.

The research conducted from November 2006 – January 2007[5] reflects how the treatment of SCCHN has developed in a one year time frame.

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.

Each physician provided data from case notes of their last 7-8 patient cases treated with radiotherapy and/or chemotherapy for SCCHN.

- In total, data from **412 patient cases** treated with radiotherapy and/or chemoradiotherapy were collected
- **154 patient cases (37%)** described the treatment of patients who were termed as locally advanced and non resectable
- **32 patient cases (21%)** described the treatment of patients who were termed as locally advanced and non resectable and treated with radiotherapy

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:

- Locally advanced SCCHN
- Non resectable
- Treated with radiotherapy
- Reporting an ECOG performance score of 0 or 1 (i.e. a high performance status)

This group consists of 22 patient cases which is 14% of the LA nopn resectable patients treated.

- The mean age of patients in this group was 71 years
- 7 (32%) of these patients were under the age of 65
- Tumour location:
    - Oral cavity: 3 14%
    - Nasopharynx: 1 5%
    - Oropharynx: 6 27%
    - Hypopharynx: 5 23%
    - Larynx: 7 32%

- A concomitant condition was found in 17 patients (77%). Further details of the concomitant conditions reported are detailed below in table 2.

Table 2: Concomitant conditions found in patients with LA SCCHN, non resectable and receiving radiotherapy treatment alone

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**

- 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) NICE proposed alternative treatments for SCCHN: the licensing and contraindications associated with the use of cisplatin and carboplatin

Section 4.3 of the ACD[1] 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 [1] 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."

Table 4 below compares contraindications for cisplatin and carboplatin.

Table 4:An assessment of SPC contraindications and warnings for cisplatin and carboplatin

Reason why a patient may be medically inappropriate	Cisplatin[9]	Carboplatin
Active peripheral, cerebral or coronary vascular disease.	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)	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)
Impaired renal function (given the nephrotoxicity profile of cisplatin).	Section 4.3. Contraindication in renal impairment.	Section 4.3. Contraindication in severe renal impairment (CrCL <20ml/min).
Impaired hearing (given ototoxicity).	Section 4.3. Contraindication in ototoxicity	Section 4.8 Undesirable effects. Ear and Labyrinth disorders
Peripheral neuropathy.	Section 4.8 Undesirable effects. Neurotoxicity including peripheral neuropathy	Section 4.8 Undesirable effects. Mild peripheral neuropathy
Any form of myelosuppression.	Section 4.3 Contraindicated in myelosuppressed patients	Section 4.3 Contraindicated in severe myelosuppressed patients

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.

Furthermore with regards to patients who may be inappropriate for cisplatin based chemoradiotherapy, section 4.3 of the ACD[1] 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."

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.

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].

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>

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[2] are transferred to the naturalistic setting.

1. Patient is to receive a radiotherapy regimen:
2. The patient is of good performance status (KPS>80 or ECOG 0-1)
3. The patient is considered medically inappropriate to receive cisplatin based chemoradiotherapy or the patient's choice of treatment/ unwilling to receive chemoradiotherapy

Based upon input from UK oncologists, the following are reasons by which a patient may be considered medically inappropriate to receive cisplatin based chemoradiotherapy:

- Active peripheral, cerebral or coronary vascular disease
- Any condition that may be exacerbated by the risks of thrombocytopenia (commonly observed with high-dose cisplatin treatment)
- Impaired renal function (cisplatin can induce nephrotoxicity)
- Impaired hearing (cisplatin can induce ototoxicity)
- Peripheral neuropathy (cisplatin can induce neuropathy)
- Previous cisplatin therapy for any malignancy
- Any form of myelosuppression

2. Radiotherapy treatment patterns for the treatment of LA SCCHN in the UK

Section 3.6 of the ACD[1] states;

"Furthermore, there are differences between the radiotherapy regimens used predominantly in UK clinical practice and those that were used in the trial".

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.

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:

"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]".

However the reference for such a survey appears to be referenced incorrectly as:

"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."

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[4] and in the period of November 2006 to January 2007[5] validates this.

In Wave 1 of the audit conducted in November 2005[4], 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.

- The average total dose was 62 Gy (with 79% between 60 and 70)
- The average number of fractions planned was 29 (with 79% between 30 and 35)

In wave 2 of the audit, in the 35 patients with LA SCCHN non resectable disease that received radiotherapy a similar picture was observed:

- The average total dose was 65 Gy (with 79% between 65 and 70)
- The average number of fractions planned was 31 (with 79% between 30 and 35)

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:

> *"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)".*

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[2] due to differences in radiotherapy.

3. Critique of the decision problem

a) Medical ethics governing the choice of treatment with radiotherapy alone

b) Clinical research timelines and the use of current standard treatment

c) Implications for clinical research in the UK

a) Medical ethics governing the choice of treatment with radiotherapy alone

Section 3.6 of the ACD states;

"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."

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 medically unethical to give radiotherapy alone following the publication of the Bonner et al[2] study which clearly demonstrates significant clinical benefit as follows:

- Improved median duration of locoregional control by 9.5 months (from 14.9 months (RT) to 24.4 months (ERT) (p=0.005)).
- 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.
- 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).
- When used in combination with radiotherapy, cetuximab does not significantly exacerbate the toxicities associated with radiotherapy.

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.

b) Clinical research timelines and the use of current standard treatment

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.

c) Implications for clinical research in the UK

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.

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.

Merck response to NICE ACD: Cetuximab in the treatment of LA SCCHN: 26th February 2007

Appendix 1: SCCHN A+A audit: Wave 2 – Data collected January 2007

Background

Merck pharmaceuticals provided SCCHN A+A audit data to NICE as part of a submission for cetuximab in the treatment of LA SCCHN. This original data was from market research collected in November 2005. Since then Merck pharmaceuticals have conducted a further wave of research and this most recent data is presented below. This data reflects how the treatment of SCCHN has developed in a one year time frame.

Objective of research

- To determine how patients with SCCHN are treated in the UK.
- To assess treatment patterns in SCCHN (Chemotherapy / Radiotherapy).
- Assess treatment patterns in different stages of SCCHN:
    - Early stage.
    - Locally advanced and resectable.
    - Locally advanced and not resectable.
    - Recurrent or Metastatic.

Information presented here will focus upon those patients who are termed as locally advanced and non resectable (this consists of patients who are locally advanced who are not resected and for whom resection is not planned).

Method

- Data was collected from 51 physicians between November 2006 and January 2007.
- Each physician provided data from the case notes from their last 7-8 patient cases treated with Radiotherapy and/or Chemotherapy for SCCHN.

- The 51 oncologists with a stated interest in SCCHN as detailed in the Cancer Care Directory 2005 were enrolled from different areas of the UK based upon the number of Cancer Networks to take into account geographical representation:
    - *Scotland and Ireland : 4 cancer networks = 6 doctors*
    - *North : 8 cancer networks = 7 doctors*
    - *Eastern and Midlands : 14 cancer networks = 16 doctors*
    - *South : 9 cancer networks = 6 doctors*
    - *Wales : 3 cancer networks = 2 doctors*
    - *London : 5 cancer networks = 14 doctors*

- Of physicians included in the January 2007 audit, 57% completed the original audit in November 2005.
- In total, data from **412 patient cases** treated with RT and/or CRT were collected.
- Of this data, **154 patient cases** described the treatment of patients who were termed as locally advanced and non resectable.

Description of physicians who completed research

Presented below in Table 1 is a description of the sample of physicians who provided information for this research.

Table 1: Description of physicians who completed research

	Number	%
Regional distribution		
Scotland & N. Ireland	6	12%
North	7	14%
Eastern and Midland	16	31%
Southern Region	6	12%
Wales	2	4%
London	14	27%
Hospital type		
Cancer centre	47	92%
Cancer unit	4	8%
Other	-	-
Teaching NHS hospitals	44	86%
District General hospitals	6	12%
Specialist: Non private hospitals	1	2%
Doctor Grade		
SPR	34	67%
Consultant	15	29%
Other	2	4%
Clinical Specialty		
Clinical oncologists	49	96%
Medical oncologists	2	4%
ENTs	-	-

Results presented

Results presented are strictly descriptive and the application of statistical tests would not be appropriate for this type of data. Of the 412 total patient records assessed, **154 patient cases** described the treatment of patients who were termed as **locally advanced and non resectable**. Analysis was carried out on the total locally advanced and non resectable population and in two subgroups as follows:

1. Those patients for whom radiotherapy was prescribed.
2. Those patients for whom radiotherapy was prescribed and the patient had an ECOG status of 0 or 1.

1. Overall population of locally advanced and non resectable patients

- **154 patient cases** described the treatment of patients who were termed as locally advanced and non resectable.
- The mean age of patients in this group was 61.2 years.
- 95 of these patients were under the age of 65 (62%).
- 75% of patients were male.

- Tumour location:
  - Oral cavity: 19 12%
  - Nasopharynx: 24 16%
  - Oropharynx: 55 36%
  - Hypopharynx: 26 17%
  - Larynx: 30 19%

- ECOG status:
  - 0 41 27%
  - 1 97 63%
  - >2 15 10%
  - Missing ECOG status 1 1%

- A concomitant condition was found in 61 patients (40%). Further details of the concomitant conditions reported are detailed below in table 2.

Table 2: Concomitant conditions found in patients with LA SCCHN and non resectable

Concomitant conditions	Number	%
Coronary arterial disease	11	7.1
Coronary arterial disease / Other CV disease	2	1.3
Coronary arterial disease / Other CV disease / Other	1	0.6
Coronary arterial disease / Other CV disease / Renal impairment	3	1.9
Coronary arterial disease / Renal impairment	3	1.9
Coronary arterial disease / Renal impairment / Pulmonary disease	1	0.6
Other	5	3.2
Other CV disease	8	5.2
Other CV disease / Pulmonary disease	1	0.6
Peripheral vascular disease	7	4.5
Peripheral vascular disease / Coronary arterial disease	4	2.6
Peripheral vascular disease / Other CV disease	1	0.6
Peripheral vascular disease / Other CV disease / Other	1	0.6
Peripheral vascular disease / Renal impairment	1	0.6
Pulmonary disease	10	6.5
Renal impairment	1	0.6
Renal impairment / Other	1	0.6
Total	**61**	**40**

- Noticeably from table 2, coronary artery disease (25 (16%)), renal impairment (10 (6%)), and peripheral cardiovascular disease (14 (9%)) are the primary concomitant conditions in patients who were diagnosed with non resectable LA SCCHN. This particular data was calculated by simple addition of reference to a particular concomitant condition, e.g. the phrase, “Coronary artery disease”, appears 25 times either in isolation or with other concomitant conditions.

- The following treatments were prescribed to this population of patients
    - 103 (67%) patients received chemoradiotherapy
    - 32 (21%) patients received radiotherapy alone
    - 17 (11%) patients received chemotherapy alone

- 32 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	5.8
Patient is not compliant	1	0.6
Patient performance status/general state does not allow to prescribe CT	9	5.8
Patient performance status/general state does not allow to prescribe CT / Patient is not compliant / Toxicity of CT would be too great	2	1.3
Patient performance status/general state does not allow to prescribe CT /Toxicity of CT would be too great	7	4.5
Toxicity of CT would be too great	4	2.6
Total	**32**	**20.8**

- Of the reasons for not prescribing chemoradiotherapy, patient state / fitness / toxicity was stated in 22 patients (14%) who were diagnosed with non resectable LA SCCHN.

1. Locally advanced and non resectable patients who were treated with radiotherapy

- **32 patient cases** described the treatment of patients who were termed as locally advanced and non resectable and treated with radiotherapy. This is 21% of the locally advanced and non resectable population of patients.
- The mean age of patients in this group was 71.7 years
- 8 of these patients under the age of 65 (25%).

- Tumour location:
  - Oral cavity: 7 22%
  - Nasopharynx: 1 3%
  - Oropharynx: 10 31%
  - Hypopharynx: 7 22%
  - Larynx: 7 22%

- ECOG status:
  - 0 3 9%
  - 1 19 59%
  - >2 10 31%
  - Missing ECOG status 0 0%

- A concomitant condition was found in 27 patients (84%) of those receiving radiotherapy. Further details of the concomitant conditions reported are detailed below in table 4.

Table 4: Concomitant conditions found in patients with LA SCCHN, non resectable and receiving radiotherapy treatment

Concomitant conditions	Number	%
Coronary arterial disease	4	12.5
Coronary arterial disease / Other CV disease	2	6.3
Coronary arterial disease / Other CV disease / Other		0.0
Coronary arterial disease / Other CV disease / Renal impairment	3	9.4
Coronary arterial disease / Renal impairment	2	6.3
Coronary arterial disease / Renal impairment / Pulmonary disease	1	3.1
Other	1	3.1
Other CV disease	2	6.3
Other CV disease / Pulmonary disease	1	3.1
Peripheral vascular disease	4	12.5
Peripheral vascular disease / Coronary arterial disease	1	3.1
Peripheral vascular disease / Other CV disease		0.0
Peripheral vascular disease / Other CV disease / Other		0.0
Peripheral vascular disease / Renal impairment	1	3.1
Pulmonary disease	3	9.4
Renal impairment	1	3.1
Renal impairment / Other	1	3.1
Total	**27**	**84.4**

- Noticeably from table 4, coronary artery disease (13 (41%)), renal impairment (9 (28%)), and peripheral cardiovascular disease (6 (19%)) was a concomitant condition in patients treated with radiotherapy diagnosed with non resectable LA SCCHN. This particular data was calculated by simple addition of reference to a particular concomitant condition.

- 32 patients received radiotherapy alone. Of these patients the rationale for not prescribing chemoradiotherapy is presented in table 5 below.

Table 5: Rationale not to prescribe any chemotherapy to this patient?

Rationale	Number	%
No indication	9	28.1
Patient performance status/general state does not allow to prescribe CT / Toxicity of CT would be too great	1	3.1
Patient is not compliant	1	3.1
Patient performance status/general state does not allow to prescribe CT	17	53.1
Toxicity of CT would be too great	4	12.5
Total	**32**	**100.0**

- Of the reasons for not prescribing chemoradiotherapy, patient state / fitness / toxicity was stated in 22 patients (72%) treated with radiotherapy and diagnosed with non resectable LA SCCHN.

2. <u>Locally advanced and non resectable patients who were treated with radiotherapy and reported an ECOG of 0 or 1</u>

- **<u>22 patient cases</u>** described the treatment of patients who were termed as locally advanced and non resectable, treated with radiotherapy alone with an ECOG status of 0 or 1. This is 14% of the locally advanced and non resectable population of patients.
- The mean age of patients in this group was 70.81 years
- 7 (32%) of these patients were under the age of 65.

- Tumour location:
  - Oral cavity: 3 14%
  - Nasopharynx: 1 5%
  - Oropharynx: 6 27%
  - Hypopharynx: 5 23%
  - Larynx: 7 32%

- ECOG status:
  - 0 3 14%
  - 1 19 86%

- A concomitant condition was found in 17 patients (77%). Further detail of the concomitant conditions reported are detailed below in table 6.

Table 6: Concomitant conditions found in patients with LA SCCHN, non resectable and receiving radiotherapy treatment

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**

- From table 6, coronary artery disease (9 (28%)), renal impairment (6 (19%)), and peripheral cardiovascular disease (3 (9%)) was a concomitant condition in patients treated with radiotherapy diagnosed with non resectable LA SCCHN and an ECOG of 0 or 1. This particular data was calculated by simple addition of reference to a particular concomitant condition.

- 22 patients received radiotherapy alone. Of these patients the rationale for not prescribing chemoradiotherapy is presented in table 7 below.

Table 7: 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**	**100.0**

- Of the reasons for not prescribing chemoradiotherapy, patient state / fitness / toxicity was stated in 12 patients (59%) treated with radiotherapy and diagnosed with non resectable LA SCCHN and an ECOG of 0 or 1.

Appendix 2: External opinion of SCCHN A+A audit: Wave 2 – Data collected January 2007

Dr Chris Gaffney, (Velindre Hospital, Cardiff):

"I have reviewed the latest data collected between November 2006 and January 2007 which clearly indicates a high level of comordities in this group of patients with unresectable locally advanced head and neck cancer. In particular there are a significant number of cases with coronary artery, vascular and pulmonary disease as well as a few with renal impairment which is exactly what I would expect from my own experience of treating head and neck cancer as a Consultant Clinical Oncologist over the last 18 years. I'm sure the data is representative of UK patients as a whole and indicates that there are a significant number of patients who would be regarded as good performance status by standard criteria but who are not deemed to be fit enough for chemoradiotherapy because of comorbidity".

In addition, the following Doctors reinforced this view that this data was representative; Dr C Baughan (Southampton General Hospital), Dr Mererid Evans (Velindre Hospital, Cardiff), Dr L Moss (Velindre Hopsital) Dr A Sykes (Christie Hospital, Manchester)

Dr Andrew Hartley, (Queen Elizabeth Hospital, Birmingham):

"In this survey of UK clinical oncologists 61/154 patients (40%) had significant co-morbidities. 32/61 were given RT alone. In 2/3 of cases the reason is clearly documented that the clinician felt that the patient would not tolerate chemoradiotherapy but would tolerate radiotherapy alone. An explanation as to why only 32 patients received radiotherapy alone is the ignorance of cisplatin mediated vascular events. The most significant feature about this audit is 68% of patients who received radiotherapy alone had a performance status of 0-1 which would be equivalent to the majority of patients in the Bonner study. 40% of patients who had significant co-morbidity is very similar to that seen in my West Midlands practice. In the last year I've had 14 patients who are not fit for chemoradiation but I considered fit for cetuximab +radiotherapy when compared with approx 20 patients in whom I administered chemoradiation".

Dr M Rolles, (Singleton hospital, Swansea):

"The patients that you describe are well represented in my practice. That is a fair representation of the patients who present with SCCH&N. The proportion of patients with locally advanced SCCH&N of good performance status in whom I do not prescribe concurrent chemoradiotherapy because of comorbid conditions is probably around 20-25%. That is about 3 patients per month, which is not an insignificant number. In my view, the Bonner study provides clear evidence that these patients would benefit from combined radical radiotherapy-Cetuximab over radical radiotherapy alone".

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.

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

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

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

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/

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

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

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)

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

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