**Comment/Response on ACD/Evaluation Report from Dr N J Slevin**
**12 February 2007**

I welcome the opportunity to comment on the Evaluation Report and Appraisal Consultation Document (ACD) for Cetuximab in locally advanced head and neck cancer.

The simple logic adopted in the ACD seems to be that patients considered unfit for the "standard" of chemoradiotherapy were not 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 has not taken into account all of the relevant evidence.

Radiotherapy Fractionation

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.

Variations in Chemoradiotherapy Practice

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).

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).

What then happens if synchronous chemotherapy is added to a modestly accelerated concomitant boost radiotherapy schedule?

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.

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).

Treatment Toxicity

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).

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).

Bonner Study

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.

In the absence of a randomised trial of a direct comparison between Cetuximab and Cisplatin:

| | | Benefit in LRC |
|---|---|---|
| (i) | Conventional fractionation (CF) v concomitant boost (CB) | 8.5% (RTOG Study) |
| (ii) | CF v CF + Cisplatin<br>(update of IGR meta analysis/Forastiere study) | approx 15% - 20% |
| (iii) | RTOG CB + Cisplatin | too toxic for routine use<br>(Ang study) |
| (iv) | RTOG CB v CB + Cetuximab (Bonner Study) | 13% |
| (v) | Variations in concomitant boost + chemo | 13% (Budach/Starr studies) |

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)

Recommendation to do Clinical Trial

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:

Option A

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.

Option B

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).

Option C

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.

How do we choose which Stage 3/4 patients should have Cetuximab?

1. A 75 year old KP 60 patient alcoholic smoker
   Is likely to struggle even with conventional RT alone.
   No evidence for benefit from modified fractionation, chemotherapy nor indeed Cetuximab.

2. A 50 year old KP 90 patient with myocardial infarct 6 months ago.
   Should not have Cisplatin with its recognised vasculopathic toxicity.
   Would be suitable for Cetuximab.

3. A 50 year old KP 90 patient with hypertension and GFR of 50.
   Should be considered for Cetuximab accepting that renal function and general toxicities should be closely monitored.

4. A 30 year old KP 100 patient having significant RT dose to the inner ear (with resultant risk of sensorineural deafness/tinnitus).
   Should have Cetuximab rather than Cisplatin (recognised ototoxicity).

5. A 50 year old depressed KP 90 patient living alone with poor nutrition/prior weight loss.
   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.
   Would be suitable for Cetuximab.

6. A 50 year old KP 100 patient with N2/N3 disease.
   Use adjuvant chemotherapy on account of significant risk of systemic metastases; no evidence that Cetuximab reduces metastatic disease.

7. A 50 year old KP 100 patient, NICE Committee Chair, with T2pN1 tonsil cancer.
   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, the patient opts for accelerated RT + Cetuximab.

Patients 1, 2, 3, 4, 5 and 7 are "UNSUITABLE" for Cisplatin chemotherapy.
Patient 1 is unsuitable for chemoradiotherapy and Cetuximab.
Patient 6 is better treated with adjuvant chemotherapy.
Patients 2, 3, 4, 5 and 7 are better treated with Cetuximab.

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.

Conclusion

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).

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.

POST SCRIPT

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).