CETUXIMAB in Metastatic or Recurrent SCC Head & Neck
(to be used in conjunction with “Cis100/5FU 1000 D1-4” up to 6 cycles)

Indication:
Treatment of metastatic and/or recurrent Squamous cell carcinoma of the Head & Neck
In combination with platinum based chemotherapy
(Cisplatin 100mg/m²/ 5FU 1000mg/m² days 1-4 or Carboplatin (AUC5)/5FU1000mg/m² days 1-4 for up to six cycles, Refer to separate treatment protocol for dosing and monitoring of platinum based chemotherapy)
Cetuximab then continues as single agent until disease progression.

LCNDG criteria to be met:
- Histologically or cytologically confirmed Squamous cell carcinoma of the Head & Neck
- Stage III/IV metastatic and/or recurrent disease
- Patient has not previously been treated with chemotherapy, except for multi-modal treatment for locally advanced disease, completed more than 6 months prior to treatment
- Karnofsky PS 70% or more

Ensure funding has been confirmed according local arrangements.

Drugs/ Dosage:

Cetuximab loading dose  400mg/m²  IV  D1(week 1)
Cetuximab maintenance dose  250mg/m²  IV  D8 (week 2)
and then onwards once a week, until progression
Cetuximab is administered one hour before starting concomitant platinum based chemotherapy.
Consider reloading with Cetuximab if treatment interrupted for more than 4 weeks

Administration:

Cetuximab loading dose  5mg/ml  IV over 120 minutes
Cetuximab maintenance dose  5mg/ml  IV over 60 minutes
Supplied neat in a sterilised 250ml empty infusion bag for infusion, or in a sterilised syringe for the syringe pump.
Cetuximab is administered intravenously with an infusion pump, gravity drip or a syringe pump. Maximum infusion rate must not exceed 10mg/min.
Availability of resuscitation equipment must be ensured, as anaphylactic reactions have been documented.
Patients should be observed during the infusion and at least 1 hour after the completion of the infusion for symptoms like fever and chills or other infusion-related symptoms (heart rate, blood pressure, temperature, respiration rate). Interruption and slowing down the infusion rate may help control such symptoms and infusion may be resumed when milder symptoms abate (see infusion related reactions- section below).

Frequency:
Loading dose, then weekly until progression

Main Toxicities:
Cetuximab: Infusion related symptoms (mild to moderate in severity): fever, chills, nausea, vomiting, headache, dizziness, dyspnoea (occur mainly soon after the first infusion). Serious infusion related reactions/ anaphylaxis, Skin reactions (acne-like
rash, dry skin, itching, nail changes), radiation dermatitis, mucositis, dry mouth, dysphagia, dyspnoea, hypomagnesaemia (very common) electrolyte disturbances, increased liver enzymes, weight loss, cardiovascular disorders

In combination with fluoropyrimidines, the frequency of cardiac ischaemia including myocardial infarction and congestive heart failure as well as the frequency of hand-foot syndrome (palmar-plantar erythrodysaesthesia) were increased compared to that with fluoropyrimidines alone.

**Anti-emetics:**
Low emetogenicity

**Supportive medication:**
Prophylactic chlorphenamine + corticosteroid to be given 30 minutes before cetuximab infusion to prevent infusion related side-effects. Loperamide tablets 4mg stat, then 2mg prn for diarrhoea

**Extravasation:**
Non-vesicant

**Regular investigations:**
- FBC  *D1
- U&Es  *D1
- LFTs  *D1
- Mg, Ca  Baseline and periodically until 8 weeks post therapy
- Disease assessments  weeks 4 and 8, 
  4 monthly for 2 years, Then 6 monthly

**Note:**
*FBC, U&Es & LFTs are not required when Cetuximab administered on days without platinum based chemotherapy.
When Cetuximab is given as a single agent until progression, the blood profile is recommended to be assessed 4 weekly

**Toxicities and Dose Modifications**

**Renal Impairment**
Before every cycle, calculate CrCl using Cockcroft and Gault. If borderline, an EDTA should be requested. Deteriorating organ function may be a sign of disease progression, therefore always discuss with the consultant. There is little experience of administering cetuximab in patients with renal insufficiency. No specific guidelines are available, however the major route of clearance is thought to be by internalisation & degradation of EGFR complex.

<table>
<thead>
<tr>
<th>CrCl (ml/min)</th>
<th>Cetuximab Dose</th>
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</thead>
<tbody>
<tr>
<td>&gt; 30</td>
<td>100% dose</td>
</tr>
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</table>

**Hepatic Impairment**
Deteriorating organ function may be a sign of disease progression, and require cessation of, or change in, treatment, therefore always discuss with the consultant. There is little experience of administering cetuximab in patients with hepatic insufficiency. No specific guidelines are available, however the major route of clearance is thought to be by internalisation & degradation of EGFR complex.

<table>
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<tr>
<th>Liver Function</th>
<th>Cetuximab Dose</th>
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<tbody>
<tr>
<td>Bili &lt; 3 x ULN and/or ALT/AST &lt; 2.5 x ULN</td>
<td>100% dose</td>
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Haematological Toxicity
Cetuximab has not been studied in patients with pre-existing haematological disorders. Generally Cetuximab is not myelosuppressive and the treatment may continue during periods of mild myelosuppression. Discuss with consultant if concerned.
In combination with platinum-based chemotherapy, the frequency of severe leukopenia or severe neutropenia may be increased, and thus may lead to a higher rate of infectious complications such as febrile neutropenia, pneumonia and sepsis compared to platinum-based chemotherapy alone.

Severe skin reactions:
Acneiform/ papulopustular rash occurs in over 70% of patients. Usually occurs on the face, upper chest & back with multiple follicles & pustules. Onset is usually within the first 3 weeks.

Cetuximab dosing after severe skin reaction:
Interrupt Cetuximab in severe skin reactions (grade 3 or more skin rash). Discontinue cetuximab in the event of 3 consecutive weeks of non-resolving grade 3 toxicity.

<table>
<thead>
<tr>
<th>Grade 3 or more skin rash</th>
<th>Cetuximab continuation dose after resolving to grade 2.</th>
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<tbody>
<tr>
<td>First occurrence</td>
<td>100% previous dose</td>
</tr>
<tr>
<td>2nd occurrence</td>
<td>reduce from 250mg/m² to 200mg/m²</td>
</tr>
<tr>
<td>3rd occurrence</td>
<td>reduce from 200mg/m² to 150mg/m²</td>
</tr>
<tr>
<td>4th occurrence</td>
<td>Discontinue Cetuximab permanently</td>
</tr>
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Management recommendations for skin toxicities:

<table>
<thead>
<tr>
<th>Mild (grade 1) localised reaction with no associated physical symptoms</th>
<th>Moderate (grade 2) more disseminated reaction, can include tenderness and/or pruritus</th>
<th>Severe (grade 3) major symptoms affecting activities of daily living, intolerable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continue Cetuximab</td>
<td>Continue Cetuximab, consider dermatology advice</td>
<td>Hold Cetuximab (see above), refer to the dermatology for advice/management</td>
</tr>
<tr>
<td>Topical low/medium potency corticosteroids (hydrocortisone 1%) as pulsed therapy, or</td>
<td>Topical low/medium potency corticosteroids (hydrocortisone 1% or 2.5%) and/ or</td>
<td>Topical low/medium potency corticosteroids (hydrocortisone 1% or 2.5%) and</td>
</tr>
<tr>
<td>Topical antibacterial (clindamycin 1%)</td>
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</tr>
<tr>
<td>Consider course of oral tetracyclines (doxycycline 100mg od)</td>
<td>4 weeks course of oral tetracyclines (doxycycline 100mg od-bd)</td>
<td>4 weeks course of oral tetracyclines (doxycycline 100mg od-bd)</td>
</tr>
<tr>
<td>Assess 2 weekly, if worsens or does not improve, proceed to next step</td>
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<td>Consider additional short course of oral corticosteroid (empirical)</td>
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If pruritus occurs an oral antihistamine is advised. Dry skin often occurs (and may contribute to pruritus) general advice on replacing soap with oil for washing, avoidance of hot water for baths or showers and regular use of emollient creams are beneficial. Cetuximab causes sun-sensitivity that may exacerbate skin reactions. Protect from sun. Advise use of sunscreens with SPF ≥ 15.
Avoid over-the-counter acne medications, as these may worsen the rash.
Infusion related reactions

Majority occur during the first infusion. Mild or moderate symptoms may resolve following interruption of the infusion or increasing the infusion time. Maintain the lower infusion rate in all subsequent infusions (see below). More severe infusion-related symptoms have also been reported, usually during the first infusion. The reactions may occur after several hours from administration (rare). Occurrence of a severe infusion related reaction requires immediate and permanent discontinuation of Cetuximab therapy and may necessitate emergency treatment (see below).

<table>
<thead>
<tr>
<th>CTC Grade</th>
<th>Allergic/hypersensitivity reaction</th>
<th>Treatment</th>
</tr>
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<tbody>
<tr>
<td>Grade 1</td>
<td>Transient flushing or rash, drug fever &lt;38ºC</td>
<td>Decrease the cetuximab infusion rate by 50% and monitor closely for any worsening. The total infusion time for cetuximab should not exceed 240 minutes.</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Rash; flushing; urticaria; dyspnea; drug fever ≥ 38ºC</td>
<td>Stop cetuximab infusion. Administer bronchodilators, oxygen etc. as medically indicated. Resume infusion at 50% of previous rate once allergic/hypersensitivity reaction has resolved or decreased to grade 1 in severity, and monitor closely for any worsening.</td>
</tr>
<tr>
<td>Grade 3 or Grade 4</td>
<td>Grade 3: Symptomatic bronchospasm, with or without urticaria; parenteral medication(s) indicated; allergy-related oedema/angioedema; hypotension Grade 4: Anaphylaxis</td>
<td>Stop cetuximab infusion immediately and disconnect infusion tubing from the patient. Administer adrenaline, bronchodilators, antihistamines, glucocorticoids, intravenous fluids, vasopressor agents, oxygen etc., as medically indicated. Patients have to be withdrawn immediately from treatment and must not receive any further cetuximab.</td>
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Other non-Haematological Toxicities

Consider dose reducing cetuximab to 200mg/m² if symptoms persist. Cetuximab is recommended to be discontinued in grade 3 or 4 hypersensitivity reactions.

Hypomagnesaemia is very common. Fatigue, malaise, tremor, ataxia, carpopedal spasm, hyperreflexia, confusion, hallucinations, convulsions and arrhythmias may occur. ECG changes include prolonged QT interval and broad flattened T waves. Patients with marked hypomagnesemia (Mg less than 0.4mmol/L) require ECG and intravenous administration of magnesium. Secondary hypokalaemia & hypocalcaemia may also occur. Hypomagnesaemia should be corrected by intravenous supplementation if grade 3 (<0.4mmol/L) or if symptomatic. If lesser degrees of hypomagnesemia are detected, oral supplementation may be considered. A suitable preparation is magnesium glycerophosphate (unlicensed).

If Magnesium fails to rectify on magnesium supplementation, it may also be necessary to supplement calcium.
Respiratory disorders
Dyspnoea may occur as an immediate infusion related reaction, but has also been reported after several weeks of therapy. Advanced age, impaired performance status, and underlying cardiac/ pulmonary disorders may increase the risk of severe/ long-standing dyspnoea. Discontinue Cetuximab if interstitial lung disease is diagnosed.

Nail toxicities occur in 8% of patients characterised by a paronychial inflammation with associated swelling of the lateral skin folds of toes and fingers, especially great toes and thumbs, which may be painful. It may persist for up to three months after cessation of cetuximab therapy. Dermatological advice should be sought.

References:
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www.micromedex.com
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Vermocken et al. NEJM (2008); 359:1116-27
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Melosky et al. Current oncology, BCCA practise guideline series (2009);16(1)
Perez-Soler et al. The Oncologist (2005);10:345-356