

# TRIAL SUMMARY

## De-ESCALaTE HPV

<b>Title:</b>	<b>De-ESCALaTE HPV: Determination of Epidermal growth factor receptor-inhibitor (cetuximab) versus Standard Chemotherapy (cisplatin) early And Late Toxicity Events in Human Papillomavirus-positive oropharyngeal squamous cell carcinoma</b>
<b>Rationale:</b>	<p>Oropharyngeal squamous cell carcinoma (OPSCC) incidence is increasing rapidly in the developed world. This has been attributed to a rise in Human Papillomavirus (HPV) infection. HPV+OPSCC is considered a distinct disease entity, affecting younger patients and has a good prognosis following treatment. Subsequently, patients can live with the considerable side effects for several decades.</p> <p>Radiotherapy and cetuximab (Epidermal Growth Factor Receptor-inhibitor) have demonstrated similar efficacy to ‘platin’ chemoradiotherapy (current standard treatment containing platinum-based compounds) in head and neck cancer, but is potentially less toxic.</p> <p>Results of this trial will be used to determine the optimum treatment of this debilitating cancer, with the primary aim of decreasing toxicity and improving quality of life for HPV+OPSCC patients.</p>
<b>Eligibility Criteria:</b>	<ol style="list-style-type: none"> <li>1. AJCC TNM Stage III-IVa [T3N0-T4N0, and T1N1-T4N3] oropharyngeal SCC tumours</li> <li>2. Clinical multidisciplinary team decision to treat with primary curative chemoradiotherapy</li> <li>3. No previous treatment for the primary tumour, including surgery, neck dissection or tracheostomy [except node biopsies or diagnostic tonsillectomy]</li> <li>4. Medically fit (ECOG 0, 1 or 2)</li> <li>5. Adequate cardiovascular, haematological, renal and hepatic function</li> <li>6. Age <math>\geq</math> 18 years</li> <li>7. Written informed consent given</li> <li>8. Using adequate contraception [male and female participants]. Must take contraceptive measures during, and for at least six months after treatment.</li> </ol>
<b>Exclusion Criteria:</b>	<ol style="list-style-type: none"> <li>1. Distant metastasis (i.e. AJCC TNM stage IVc disease)</li> <li>2. AJCC TNM Stage T1-2N0 disease</li> <li>3. Treated with primary radical surgery to the primary site (e.g. resection)</li> <li>4. Concurrent use of CYP3A4 inducers or inhibitors. [A standard course of dexamethasone or aprepitant for the prevention of cisplatin-induced nausea and vomiting is permitted]</li> <li>5. Serious cardiac illness or other medical conditions precluding the use of cisplatin or cetuximab</li> <li>6. HPV+ patients who have p16+ tumours who also have N2b, N2c or N3 nodal disease <u>and</u> whose lifetime smoking history is also more than 10 pack years (i.e. have both risk factors)</li> <li>7. Pregnant or lactating</li> <li>8. Previous treatment for any other cancer with cytotoxics, radiotherapy or anti-EGFR therapies</li> <li>9. Inadequate renal, haematological or liver functions</li> <li>10. Patients with clinically significant hearing impairment</li> <li>11. Life expectancy less than 3 months</li> <li>12. Other malignancy within the past 3 years except basal cell skin cancer or pre-invasive carcinoma of the cervix</li> </ol>

<b>Objectives:</b>	For HPV+OPSCC compared to current standard treatment will cetuximab + radiotherapy result in: <ol style="list-style-type: none"> <li>1. Less morbidity (acute and late toxicity)?</li> <li>2. Better quality of life?</li> <li>3. Better cost effectiveness?</li> <li>4. Any significant differences of overall survival and locoregional recurrence between the two arms?</li> </ol>
<b>Trial Design:</b>	Pragmatic, randomised, international, multi-centre, open label, phase III clinical trial determining the optimum treatment for patients with HPV+OPSCC.
<b>Treatment:</b>	<b>Experimental arm:</b> Cetuximab: IV 400mg/m <sup>2</sup> dose 1 week before start of radiotherapy followed by a weekly IV infusion of 250mg/m <sup>2</sup> X 7 during radiotherapy <b>Control Arm:</b> Cisplatin: 3 doses of 100mg/m <sup>2</sup> given at days 1, 22 and 43 from start of radiotherapy
<b>No. patients:</b>	304
<b>Sample Collection:</b>	40mls bloods at baseline, 3 months & 12 months post treatment end. Also, at recurrence or progression for relevant patients.  Oral fluid at baseline, 3 months & 12 months post treatment end. Also, at recurrence or progression for relevant patients.  FFPE blocks of diagnostic biopsy specimens and, if applicable, post treatment biopsies and when neck dissection has been performed and biopsies at recurrence or progression. A subset of patients will have fresh frozen samples collected.
<b>Stratification:</b>	<ol style="list-style-type: none"> <li>1. Radiotherapy Treatment centre</li> <li>2. Tumour stage [T1-T2; T3-T4]</li> <li>3. Nodal stage [N0-N1; N2-N3]</li> <li>4. Radiotherapy [Unilateral; Bilateral]</li> <li>5. Planned PEG use before treatment [Yes; No]</li> </ol>
<b>Outcome measures:</b>	<b>Primary:</b> <ul style="list-style-type: none"> <li>• Severe (acute and late) toxicity (Grade 3-5), assessed by CTCAE version 4</li> </ul> <b>Secondary:</b> <ul style="list-style-type: none"> <li>• Acute severe toxicity</li> <li>• Late severe toxicity</li> <li>• Quality of Life (QoL) – assessed by EORTC QLQ C30 and HN35</li> <li>• Dysphagia – assessed by MDADI and by PEG utilisation rate at 1 and 2 years</li> <li>• Cost effectiveness – assessed by EuroQoL-5D</li> <li>• Overall survival, recurrence and metastasis</li> </ul>
<b>Analysis:</b>	Analyses will be performed on the intention to treat population. Comparison of numbers of late and acute events will be by the Mann-Whitney test; comparison of proportion of patients affected by toxicity by Pearson's chi-squared. A sensitivity analysis will be carried out using the TAME method of reporting toxicities. Overall survival will be compared using the log-rank test. Analysis of all other secondary endpoints will be carried out using appropriate tests.