

Study: A Phase III Study of Postoperative Radiation Therapy (IMRT) +/- Cetuximab for Locally-Advanced Head and Neck Cancer

Schema:

					Arm 1: Radiation Therapy Alone
R	For all	S	EGFR Expression	R	RT, 2 Gy/day, in 30 fractions
E	patients:	T	1. High (\geq 80% of cells	A	for a total of 60 Gy ^A
G	Mandatory	R	staining positive for EGFR)	N	
I	submission	A	2. Low (< 80% of cells	D	Arm 2: Radiation Therapy + Cetuximab
S	of tissue for	T	staining positive for EGFR)	O	At least 5 days prior to RT:
T	EGFR ^B	I	3. Not evaluable	M	cetuximab: Initial dose, 400 mg/m ²
E		F		I	
R	For	Y	Primary Site	Z	RT, 2 Gy/day in 30 fractions for a total of 60 Gy ^A
	oropharyngeal		1. Oral cavity	E	plus cetuximab: 250 mg/m ² /week x 6 weeks
	cancer		2. Larynx		
	patients:		3. Oropharynx p16+		plus
	Mandatory		4. Oropharynx p16-		cetuximab: 250 mg/m ² /week
	analysis for		5. Oropharynx p16 not		x 4 weeks post-RT
	HPV ^B		evaluable		
					(cetuximab: 1 initial dose + 10 maintenance
			Use of IGRT		doses, a total of 11 doses)
			1. No		
			2. Yes		

Required Sample Size: 700

Inclusion Criteria:

- Pathologically (histologically) proven diagnosis of squamous cell carcinoma of the head/neck (oral cavity, oropharynx or larynx); **Note:** Hypopharynx primaries are excluded because these patients have both a poor prognosis and high likelihood of post-radiation complications.
- Clinical stage T1, N1-2 or T2-3 or T2-3,N0-2, M0 including no distant metastases, based upon the following minimum diagnostic workup:
 - General history and physical examination by a Radiation Oncologist and/or Medical Oncologist within 8 weeks prior to registration;
 - Examination by an ENT or Head & Neck Surgeon, laryngopharyngoscopy (mirror and/or fiberoptic and/or direct procedure), within 8 weeks prior to registration;
 - Chest x-ray (at a minimum) or chest CT scan (with or without contrast) or CT/PET of chest (with or without contrast) within 8 weeks prior to registration
- Gross total resection of the primary tumor with curative intent must be completed within 7 weeks of registration with surgical pathology demonstrating one or more of the following "intermediate" risk factors:
 - Perineural invasion;
 - Lymphovascular invasion;
 - Single lymph node > 3 cm or 2 lymph nodes (all < 6 cm) [no extracapsular extension];
 - Close margin(s) of resection, defined as cancer extending to within 5 mm of a surgical margin;
 - T3 or microscopic T4a primary tumor (**Note:** Gross T4a or T4b is ineligible);
 - T2 oral cavity cancer with > 5 mm depth of invasion.
- Zubrod Performance Status of 0-1 within 2 weeks prior to registration
- Age 18;

- CBC/differential obtained within 4 weeks prior to registration on study, with adequate bone marrow function defined as follows:
 - Absolute granulocyte count (AGC) 1,500 cells/mm³;
 - Platelets 100,000 cells/mm³;
 - Hemoglobin 8.0 g/dl (**Note:** The use of transfusion or other intervention to achieve Hgb 8.0 g/dl is acceptable).
- Total bilirubin < 2 x institutional ULN within 2 weeks prior to registration;
- AST or ALT < 3 x institutional ULN within 2 weeks prior to registration.
- Adequate renal function, defined as follows:
 - Serum creatinine < 2 x institutional ULN within 2 weeks prior to registration or; creatinine clearance (CC) 50 ml/min within 2 weeks prior to registration determined by 24-hour collection or estimated by Cockcroft-Gault formula:

$$CC_{\text{male}} = \frac{[(140 - \text{age}) \times (\text{wt in kg})]}{[(\text{Serum Cr mg/dl}) \times (72)]}$$

$$CC_{\text{female}} = 0.85 \times (CrCl \text{ male})$$
- Negative serum pregnancy test within 2 weeks prior to registration for women of childbearing potential
- The following assessments are required within 2 weeks prior to the start of registration: Na, K, Cl, glucose, Ca, Mg, and albumin. Note: Patients with an initial magnesium < 0.5 mmol/L (1.2 mg/dl) may receive corrective magnesium supplementation but should continue to receive either prophylactic weekly infusion of magnesium and/or oral magnesium supplementation (e.g., magnesium oxide) at the investigator's discretion.
- Women of childbearing potential and male participants who are sexually active must agree to use a medically effective means of birth control;
- Patients must provide study specific informed consent prior to study entry, including consent for mandatory tissue submission for EGFR and for oropharyngeal patients, HPV analyses.

Exclusion Criteria

- Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 3 years; noninvasive cancers (For example, carcinoma *in situ* of the breast, oral cavity, or cervix are all permissible) are permitted even if diagnosed and treated < 3 years ago. Patients with simultaneous primaries or bilateral tumors are excluded.
- Per the operative report, positive margin(s) [defined as tumor present at the cut or inked edge of the tumor], nodal extracapsular extension, and/or gross residual disease after surgery;
- Prior systemic chemotherapy or anti-EGF therapy for the study cancer; **note:** prior chemotherapy or anti-EGF therapy for a different cancer is allowable.
- Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields;
- Severe, active co-morbidity, defined as follows:
 - Unstable angina and/or congestive heart failure requiring hospitalization within 6 months prior to registration;
 - Transmural myocardial infarction within 6 months prior to registration
 - Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration;
 - Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration;
 - Idiopathic pulmonary fibrosis or other severe interstitial lung disease that requires oxygen therapy or is thought to require oxygen therapy within 1 year prior to registration;

- Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects; note, however that laboratory tests for coagulation parameters are not required for entry into this protocol.
- Acquired Immune Deficiency syndrome (AIDS) based upon current CDC definition; **note:** HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive. Protocol-specific requirements may also exclude immuno-compromised patients.
- Grade 3-4 electrolyte abnormalities (CTCAE, v. 4.0):
 - Serum calcium (ionized or adjusted for albumin) < 7 mg/dl (1.75 mmol/L) or > 12.5 mg/dl (> 3.1 mmol/L) despite intervention to normalize levels;
 - Glucose < 40 mg/dl (< 2.2 mmol/L) or > 250 mg/dl (> 14mmol/L);
 - Magnesium < 0.9 mg/dl (< 0.4 mmol/L) or > 3 mg/dl (> 1.23 mmol/L) despite intervention to normalize levels;
 - Potassium < 3.5 mmol/L or > 6 mmol/L despite intervention to normalize levels;
 - Sodium < 130 mmol/L or > 155 mmol/L despite intervention to normalize levels.
- Pregnancy or women of childbearing potential and men who are sexually active and not willing/able to use medically acceptable forms of contraception; this exclusion is necessary because the treatment involved in this study may be significantly teratogenic.
- Prior allergic reaction to cetuximab
- Eligibility for an RTOG "high risk" head and neck cancer protocol (e.g., RTOG 0619).