

RTOG 1016 - Phase III Trial of Radiotherapy Plus Cetuximab Versus Chemoradiotherapy in HPV-Associated Oropharynx Cancer

Fast Facts

AJCC Staging 7th ed; CTCAE v.4;

Patient Eligibility

1. Pathologically (histologically or cytologically) proven diagnosis of squamous cell carcinoma (including the histological variants papillary squamous cell carcinoma and basaloid squamous cell carcinoma) of the oropharynx (tonsil, base of tongue, soft palate, or oropharyngeal walls);
 Note: Paraffin-embedded cytology specimens are acceptable for p16 evaluation, but cytology smears are not. Patients with a diagnosis based upon cytopathology alone may require biopsy of the primary tumor for eligibility determination.
2. **Patients must be positive for p16, determined by OSU Innovation Center CLIA lab prior to Step 2 registration (randomization)**; see 10.2 for details of tissue submission;
3. Patients must have clinically or radiographically evident measurable disease at the primary site or at nodal stations. Tonsillectomy or local excision of the primary without removal of nodal disease is permitted, as is excision removing gross nodal disease but with intact primary site. Limited neck dissections retrieving ≤ 4 nodes are permitted and considered as non-therapeutic nodal excisions. Fine needle aspirations of the neck are insufficient due to limited tissue for retrospective central review. Biopsy specimens from the primary or nodes measuring at least 3- 5 mm are required.
4. Clinical stage T1-2, N2a-N3 or T3-4, any N (AJCC, 7th ed.; see Appendix IV), including no distant metastases, based upon the following minimum diagnostic workup:
 - a. General history and physical examination by a radiation oncologist and medical oncologist within 8 weeks prior to registration;
 - b. Examination by an ENT or head and neck surgeon, including laryngopharyngoscopy (mirror and/or fiberoptic and/or direct procedure) within 8 weeks prior to registration;
 - c. A CT scan of the neck (with contrast) and a chest CT scan (with or without contrast); or an MRI of the neck and a chest CT scan (with or without contrast); or a CT scan of neck and a PET/CT of neck and chest within 8 weeks prior to registration; Note: A CT scan of neck and/or a PET/CT performed for radiation planning may serve as both staging and planning tools.
5. Zubrod Performance Status 0-1 within 2 weeks prior to registration
6. Age ≥ 18 ;
7. CBC/differential obtained within 2 weeks prior to registration on study, with adequate bone marrow function, defined as follows:
 - a. Absolute neutrophil count (ANC) $\geq 1,500$ cells/mm³;
 - b. Platelets $\geq 100,000$ cells/mm³;
 - c. Hemoglobin ≥ 8.0 g/dl; Note: The use of transfusion or other intervention to achieve Hgb > 8.0 g/dl is acceptable.
8. Adequate hepatic function, defined as follows:
 - a. Bilirubin ≤ 2 mg/dl within 2 weeks prior to registration;
 - b. AST or ALT ≤ 3 x the upper limit of normal within 2 weeks prior to registration;
9. Adequate renal function, defined as follows:
 - a. Serum creatinine ≤ 1.5 mg/dl 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
10. Patients must provide their smoking history (for stratification) via the computer-assisted self interview (CASI) head and neck risk factor survey tool.
11. Negative serum pregnancy test within 2 weeks prior to registration for women of childbearing potential;
12. Women of childbearing potential and male participants must agree to use a medically effective means of birth control throughout their participation in the treatment phase of the study and until at least 60 days following the last study treatment.
13. Patients who are HIV positive but have no prior AIDS-defining illness and have CD4 cells of at least 350/mm³ are eligible. Patient HIV status must be known prior to registration. Patients must not be sero-positive for Hepatitis B (Hepatitis B surface antigen positive or anti-hepatitis B core antigen positive) or sero-positive for Hepatitis C (anti-Hepatitis C antibody positive). However, patients who are immune to hepatitis B (anti-Hepatitis B surface antibody positive) are eligible (e.g. patients immunized against hepatitis B). HIV-positive patients must not have multi-drug resistant HIV infection or other concurrent AIDS-defining conditions.
14. Patient must provide study specific informed consent prior to study entry, including consent for mandatory submission of tissue for required, central p16 review and consent to participate in the computer-assisted self interview (CASI) survey questions regarding smoking history.

Patient Ineligibility

1. Cancers considered to be from an oral cavity site (oral tongue, floor mouth, alveolar ridge, buccal or lip), nasopharynx, hypopharynx, or larynx, even if p16 positive, are excluded. Carcinoma of the neck of unknown primary site origin (even if p16 positive) are excluded from participation.
2. Stage T1-2, N0-1;
3. Distant metastasis or adenopathy below the clavicles;
4. Gross total excision of both primary and nodal disease; this includes tonsillectomy, local excision of primary site, and nodal excision that removes all clinically and radiographically evident disease.
5. Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 3 years (For example, carcinoma in situ of the breast, oral cavity, or cervix are all permissible);
6. Prior systemic chemotherapy for the study cancer; note that prior chemotherapy for a different cancer is allowable;
7. Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields;
8. Severe, active co-morbidity, defined as follows:
 - a. Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months;
 - b. Transmural myocardial infarction within the last 6 months;
 - c. Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration;
 - d. Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy within 30 days of registration;
 - e. Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects; note, however, that laboratory tests for liver function and coagulation parameters are not required for entry into this protocol.
 - f. Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition with immune compromise greater than that noted in Section 3.1.13; note, however, that 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 immunocompromised patients.
9. 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.
10. Prior allergic reaction to cisplatin or cetuximab;
11. Prior cetuximab or other anti-EGFR therapy.

Pre-Study Parameters

1. History; Exam by the following: Radiation Oncology, Medical Oncology and ENT or Head and Neck Surgeon; performance status, adverse event evaluation
2. Labs including CBC with differential, ANC, CMP, Mg, HCO₃, serum pregnancy test if applicable
3. Chest imaging, Neck imaging; Whole Body PET/CT recommended
4. EKG recommended
5. Swallowing evaluation, Dental assessment, Audiogram, Nutrition/feeding tube evaluation recommended

Treatment (See section 7 for complete details of chemotherapy planning)

			T Stage		
R		S	1. T1-2	R	
E		T	2. T3-4	A	Arm 1 (Control):
G	Mandatory p16 analysis	R	N Stage	N	Accelerated IMRT, 70 Gy for 6 weeks
I		A	1. N0-2a	D	+ high dose DDP (100 mg/m ²) Days 1 and 22
S		T	2. N2b-3	O	(Total: 200 mg/m ²)
T		I	Zubrod	M	
E		F	Performance Status	I	Arm 2: Accelerated IMRT, 70 Gy for 6 weeks
R		Y	1. 0	Z	+ 8 doses of cetuximab (400 mg/m ²) loading dose
			2. 1	E	pre-IMRT, 250 mg/m ² weekly during IMRT,
			Smoking History		and for 1 week after IMRT)
			1. ≤ 10 pack-years		
			2. > 10 pack-years		