

**NRG HN002: A RANDOMIZED PHASE II TRIAL FOR PATIENTS WITH p16 POSITIVE,
NON-SMOKING ASSOCIATED, LOCOREGIONALLY ADVANCED
OROPHARYNGEAL CANCER**

Fast Facts

Conditions for Patient Eligibility

For questions concerning eligibility, please contact the Biostatistical/Data Management Center (via the contact list on the NRG web site). For radiation therapy-related eligibility questions, please contact IROC Philadelphia RT (via the contact list on the NRG web site).

- Patients must have the psychological ability and general health that permits completion of the study requirements and required follow up.
- Women of childbearing potential and men who are sexually active should be willing and able to use medically acceptable forms of contraception throughout the treatment phase of the trial and until at least 60 days following the last study treatment.
- Submission of H&E and p16 slides to the NRG Oncology Biospecimen Bank for confirmation of positive immunohistochemical staining for p16 is required for all patients. Investigators should check with their site Pathology department regarding release of biospecimens before approaching patients about participation in the trial. (See Sections 10 and 11).

ELIGIBILITY CRITERIA

Step 1: Registration

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); cytologic diagnosis from a cervical lymph node is sufficient in the presence of clinical evidence of a primary tumor in the oropharynx. Clinical evidence should be documented, may consist of palpation, imaging, or endoscopic evaluation, and should be sufficient to estimate the size of the primary (for T stage).
2. 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.
3. Immunohistochemical staining for p16 must be performed on tissue, and this tissue must be submitted for central review. Fine needle aspiration (FNA) biopsy specimens may be used as the sole diagnostic tissue if formalin-fixed paraffin-embedded cell block material is available for p16 immunohistochemistry. FNA specimens prepared with adequate p16 testing in this manner are acceptable to submit for central review. If the p16 preparation is not adequate, additional specimens will be required to establish p16 status. Centers are encouraged to contact the pathology chairs for clarification.
4. Clinical stage T1-T2, N1-N2b or T3, N0-N2b (AJCC, 7th ed.) including no distant metastases based on the following diagnostic workup:
 - General history and physical examination within 56 days prior to registration;
 - Fiberoptic exam with laryngopharyngoscopy (mirror and/or fiberoptic and/or direct procedure) within 70 days prior to registration;
 - One of the following combinations of imaging is required within 56 days prior to registration:
 - a) A CT scan of the neck (with contrast) and a chest CT scan (with or without contrast);
 - b) **or** an MRI of the neck (with contrast) and a chest CT scan (with or without contrast);
 - c) **or** a CT scan of neck (with contrast) and a PET/CT of neck and chest (with or without contrast);
 - d) **or** an MRI of the neck (with contrast) and a PET/CT of neck and chest (with or without contrast).

Note: A CT scan of neck and/or a PET/CT performed for the purposes of radiation planning may serve as both staging and planning tools.

5. Patients must provide their personal smoking history prior to registration. The lifetime cumulative history cannot exceed 10 pack-years. The following formula is used to calculate the pack-years during the periods of smoking in the patient's life; the cumulative total of the number of pack-years during each period of active smoking is the lifetime cumulative history. Number of pack-years = [Frequency of smoking (number of cigarettes per day) × duration of cigarette smoking (years)] / 20

Note: Twenty cigarettes is considered equivalent to one pack. The effect of non-cigarette tobacco products on the survival of patients with p16-positive oropharyngeal cancers is undefined. While there are reportedly increased risks of head and neck cancer associated with sustained heavy cigar and pipe use (Wyss 2013), such sustained use of non-cigarette products is unusual and does not appear to convey added risk with synchronous cigarette smoking. Cigar and pipe tobacco consumption is therefore not included in calculating the lifetime pack-years. Marijuana consumption is likewise not considered in this calculation. There is no clear scientific evidence regarding the role of chewing tobacco-containing products in this disease, although this is possibly more concerning given the proximity of the oral cavity and oropharynx. In any case, investigators are discouraged from enrolling patients with a history of very sustained use (such as several years or more) of noncigarette tobacco products alone.

6. Zubrod Performance Status of 0-1 within 56 days prior to registration;
7. Age \geq 18;
8. The trial is open to both genders;
9. Adequate hematologic function within 14 days prior to registration, defined as follows:
- Absolute neutrophil count (ANC) \geq 1,500 cells/mm³;
 - Platelets \geq 100,000 cells/mm³;
 - Hemoglobin \geq 8.0 g/dl; Note: The use of transfusion or other intervention to achieve Hgb \geq 8.0 g/dl is acceptable.
10. Adequate renal function within 14 days prior to registration, defined as follows:
- Serum creatinine $<$ 1.5 mg/dl or creatinine clearance (CC) \geq 50 ml/min determined by 24-hour collection or estimated by Cockcroft-Gault formula:
- $$\text{CCr male} = \frac{[(140 - \text{age}) \times (\text{wt in kg})]}{[(\text{Serum Cr mg/dl}) \times (72)]}$$
- $$\text{CCr female} = 0.85 \times (\text{CrCl male})$$
11. Adequate hepatic function within 14 days prior to registration defined as follows:
- Bilirubin $<$ 2 mg/dl;
 - AST or ALT $<$ 3 x the upper limit of normal.
12. Negative serum pregnancy test within 14 days prior to registration for women of childbearing potential;
13. Patients who are HIV positive but have no prior AIDS-defining illness and have CD4 cells of at least 350/mm³ are eligible. HIV-positive patients must not have multi-drug resistant HIV infection or other concurrent AIDS-defining conditions. Patients must not be sero-positive for Hepatitis B (Hepatitis B surface antigen positive or antihepatitis 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).
14. The patient must provide study-specific informed consent prior to study entry, including consent for mandatory submission of tissue for required, central p16 review.

15. Patients who speak English (or read one of the languages for which a translation is available (see Section 10.2) must consent to complete the mandatory dysphagia-related patient reported instrument (MDADI). If the patient cannot understand spoken English and reads only languages not available in the MDADI translations, the patient can still participate in the trial, as this has been factored into the trial statistics. For all other patients, the MDADI is mandatory as it is included in the primary endpoint to be studied.

Step 2: Randomization

16. p16 positive by immunohistochemistry (defined as greater than 70% strong nuclear or nuclear and cytoplasmic staining of tumor cells, confirmed by central pathology review; (see Section 10.1 for details).

INELIGIBILITY CRITERIA

Step 1: Registration

1. Cancers considered to be from an oral cavity site (oral tongue, floor mouth, alveolar ridge, buccal or lip), or the nasopharynx, hypopharynx, or larynx, even if p16 positive;
2. Carcinoma of the neck of unknown primary site origin (even if p16 positive);
3. Radiographically matted nodes, defined as 3 abutting nodes with loss of the intervening fat plane;
4. Supraclavicular nodes, defined as nodes visualized on the same axial imaging slice as the clavicle;
5. Definitive clinical or radiologic evidence of metastatic disease or adenopathy below the clavicles;
6. Gross total excision of both primary and nodal disease with curative intent; this includes tonsillectomy, local excision of primary site, and nodal excision that removes all clinically and radiographically evident disease. In other words, to participate in this protocol, the patient must have clinically or radiographically evident gross disease for which disease response can be assessed.
7. Patients with simultaneous primary cancers or separate bilateral primary tumor sites are excluded with the exception of patients with bilateral tonsil cancers.
8. Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 1095 days (3 years) (for example, carcinoma in situ of the breast, oral cavity, or cervix are all permissible);
9. Prior systemic chemotherapy for the study cancer; note that prior chemotherapy for a different cancer is allowable;
10. Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields;
11. Severe, active co-morbidity defined as follows:
 - Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months;
 - Transmural myocardial infarction within the last 6 months;
 - 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 within 30 days of registration;
 - 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 other than those requested in Section 3.2.10.
 - 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 immuno-compromised patients.

12. Pregnancy; this exclusion is necessary because the treatment involved in this study may be significantly teratogenic.
13. Prior allergic reaction to cisplatin.

TREATMENT

Experimental: Arm I (IMRT, cisplatin)

- Patients undergo Intensity-Modulated Radiation Therapy (IMRT) QD five days a week for 6 weeks to a total dose of 60 Gy and receive cisplatin IV over 30-60 minutes weekly during radiation therapy for 6 doses in the absence of disease progression or unacceptable toxicity.

Experimental: Arm II (IMRT)

- Patients undergo Intensity-Modulated Radiation Therapy (IMRT) five days a week for 5 weeks to a total dose of 60 Gy in the absence of disease progression or unacceptable toxicity.

PRE-STUDY PARAMETERS (Section 4.0)

Prior to Registration – Step 1

1. History/physical with height & weight by Rad Onc and Med Onc
2. Fiberoptic exam with laryngopharyngoscopy
3. Imaging:
 - CT with contrast of neck and CT of chest +/- contrast;
 - Or MRI with contrast of neck and CT of chest +/- contrast;
 - Or CT with contrast of neck and PET/CT of neck and chest +/- contrast;
 - Or MRI with contrast of neck and PET/CT of neck and chest +/- contrast
4. Patient's smoking history
5. Zubrod Performance Status
6. CBC/differential
7. Bilirubin, AST or ALT, serum creatinine or creatinine clearance
8. Serum pregnancy test, if applicable

Prior to Treatment

1. Na, K, Cl, glucose, Ca, Mg, and albumin
2. Dental assessment
3. Audiogram
4. Swallowing assessment
5. MDADI, PSS-HN, CCI, and Work Status
6. EKG - Recommended for Arm 1
7. Whole body PET/CT - Recommended
8. Nutritional evaluation - Recommended
9. QOL
10. Biospecimen Collection for Central Review and for Banking
11. Modified Barium Swallow, if patient consents