

FAST FACTS

NRG-HN005 - A RANDOMIZED PHASE II/III TRIAL OF DE-INTENSIFIED RADIATION THERAPY FOR PATIENTS WITH EARLY-STAGE, P16-POSITIVE, NON-SMOKING ASSOCIATED OROPHARYNGEAL CANCER

Eligibility Criteria

1. Pathologically (histologically or cytologically) proven diagnosis of squamous cell carcinoma (including the histological variants papillary squamous cell carcinoma and basaloid squamous cell carcinoma but not neuroendocrine phenotype) 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. Simple 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. P16-positive based on local site immunohistochemical tissue staining (defined as greater than 70% strong diffuse nuclear or nuclear and cytoplasmic staining of tumor cells). Fine needle aspiration (FNA) biopsy specimens may be used as the sole diagnostic tissue. Centers are encouraged to contact the pathology chair for clarification.
Note: Institutions must screen patients, whose tumors must be p16-positive by immunohistochemistry (IHC) in order to be eligible for the trial using a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory. A rigorous laboratory accreditation process similar to the U.S. CLIA certification, such as the provincial accreditation status offered by the Ontario Laboratory Accreditation (OLA) Program in Canada, the College of American Pathologists (CAP), or an equivalent accreditation in other countries, is acceptable. The p16-positive results must be reported on the pathology report being submitted.
4. Clinical stage T1-2, N1, M0 (AJCC, 8th ed.) or T3, N0-N1, M0 (AJCC, 8th ed.) including no distant metastases based on the following diagnostic workup:
 - General history and physical examination within 56 days prior to registration;
 - Exam with laryngopharyngoscopy (mirror or in office direct procedure acceptable) within 70 days prior to registration;
 - One of the following imaging studies is required within 56 days prior to registration:
 - FDG-PET/CT of the neck and chest (with or without contrast); FDG-PET/CT scan is strongly preferred and highly recommended to be used for eligibility
 - OR**
 - Chest CT (with or without contrast)
 - One of the following imaging studies is required within 28 days prior to registration:
 - A diagnostic CT scan of neck (with contrast and of diagnostic quality)
 - OR**
 - an MRI of the neck (with contrast and of diagnostic quality)**Note:** A diagnostic quality CT or MRI with contrast or FDG-PET/CT scan of neck 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 non-cigarette tobacco products alone.

6. Zubrod Performance Status of 0-1 within 14 days prior to registration.
7. Age \geq 18.
8. Normal organ and marrow function within 14 days prior to registration defined as follows:
 - Absolute neutrophil count \geq 1,500/mcL
 - Platelets \geq 100,000/mcL
 - Hemoglobin \geq 8.0 g/dL (Note: use of transfusion or other intervention to achieve Hgb \geq 8.0 g/dL is acceptable)
 - Total bilirubin \leq 1.5× institutional upper limit of normal (ULN)
 - AST(SGOT) or ALT(SGPT) \leq 3.0 × institutional ULN
 - Serum creatinine \leq 1.5× ULNOR
 - Creatinine clearance (CrCl) \geq 50 mL/min (if using the Cockcroft-Gault formula below):
Female CrCl = $\frac{(140 - \text{age in years}) \times \text{weight in kg} \times 0.85}{72 \times \text{serum creatinine in mg/dL}}$
Male CrCl = $\frac{(140 - \text{age in years}) \times \text{weight in kg} \times 1.00}{72 \times \text{serum creatinine in mg/dL}}$
9. Human immunodeficiency virus (HIV)-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.
10. For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.

Note: Known positive test for hepatitis B virus surface antigen (HBV sAg) indicating acute or chronic infection would make the patient ineligible unless the viral load becomes undetectable on suppressive therapy. Patients who are immune to hepatitis B (anti- Hepatitis B surface antibody positive) are eligible (e.g. patients immunized against hepatitis B).
11. Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment for the hepatitis, they are eligible if they have an undetectable HCV viral load.

Note: Known positive test for hepatitis C virus ribonucleic acid (HCV RNA) indicating acute or chronic infection would make the patient ineligible unless the viral load becomes undetectable on suppressive therapy.
12. For women of childbearing potential (WOCBP), negative serum or urine pregnancy test within 24 hours prior to registration.
 - Women of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) or who is not postmenopausal. Menopause is defined clinically as 12 months of amenorrhea in a woman over 45 in the absence of other biological or physiological causes. In addition, women under the age of 55 must have a documented serum follicle stimulating hormone (FSH) level less than 40 mIU/mL.
13. Women of childbearing potential (WOCBP) and men who are sexually active with WOCBP must be willing to use an adequate method of contraception during and after treatment (see Section 9.0).

14. The patient or a legally authorized representative must provide study-specific informed consent prior to study entry.
15. Only English, Spanish, or French speaking patients are eligible to participate as these are the only languages for which the mandatory dysphagia-related patient reported instrument (MDADI) is available.

Ineligibility Criteria

1. Clinical stages T0; T4; T1-2, N0; or any N2 (AJCC, 8th ed);
2. Recurrent disease.
3. Definitive clinical or radiologic evidence of metastatic disease or adenopathy below the clavicles.
4. 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, or histologies of adenosquamous, verrucous, or spindle cell carcinomas.
5. Carcinoma of the neck of unknown primary site origin (T0 is ineligible, even if p16- positive).
6. Radiographically matted nodes, defined as 3 abutting nodes with loss of the intervening fat plane.
7. Supraclavicular nodes, defined as nodes centered below the level of the cricoid cartilage.
8. 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. 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.
9. Patients with simultaneous primary cancers or separate bilateral primary tumor sites are excluded with the exception of patients with bilateral tonsil cancers.
10. Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 1095 days (3 years) (of note, the exclusion applies only for invasive cancers such that carcinoma in situ of the breast, oral cavity, or cervix are all permissible);
11. Prior systemic chemotherapy for the study cancer; note that prior chemotherapy for a different cancer is allowable.
12. Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields.
13. Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways.
14. History of severe hypersensitivity reaction to any monoclonal antibody.
15. 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.
 - Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition with immune compromise greater than that noted in Section 3.2.9; 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.
 - Condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of registration. Inhaled or topical steroids and adrenal replacement doses < 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.
 - Patients with active autoimmune disease requiring systemic treatment (i.e. disease modifying agents, corticosteroids, or immunosuppressive drugs) should be excluded. These include but are not limited to patients with a history of immune related neurologic disease, multiple sclerosis, autoimmune (demyelinating) neuropathy, Guillain-Barre syndrome, myasthenia gravis; systemic autoimmune disease such as SLE, rheumatoid arthritis, connective tissue diseases, scleroderma, inflammatory bowel disease (IBD), Crohn's, ulcerative colitis, hepatitis; and patients with a history of toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome, or phospholipid syndrome should be excluded because of the risk of recurrence or exacerbation of disease.

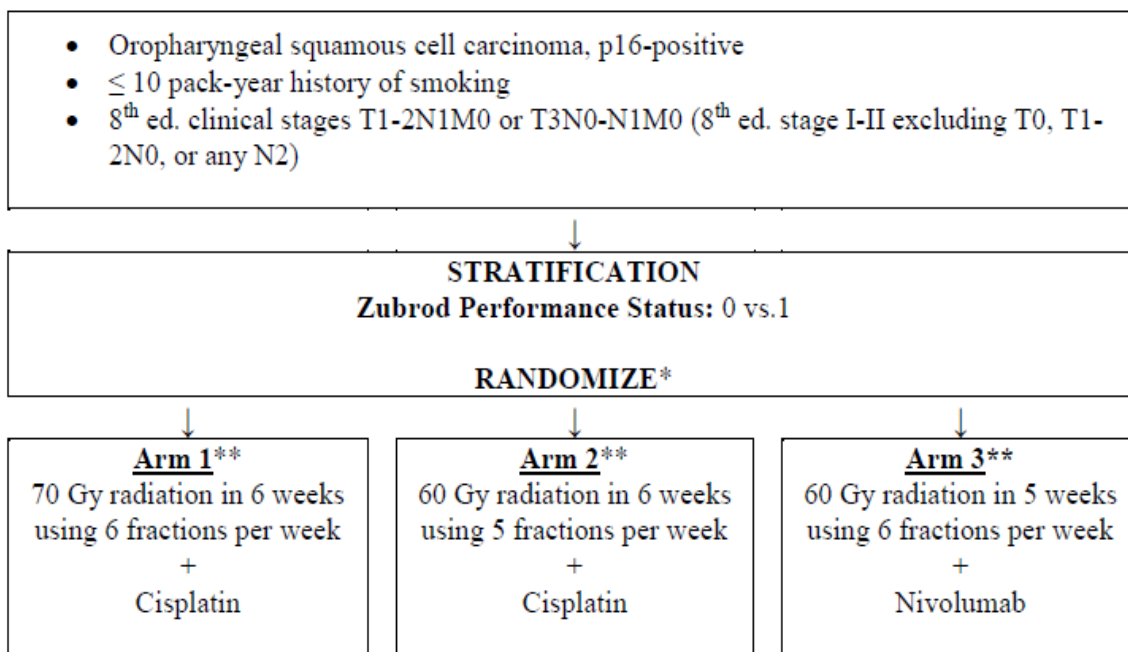
Note: Patients are permitted to enroll if they have vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger (precipitating event).

16. Patients who are pregnant, nursing, or expecting to conceive or father children (see Section 9.0).

17. Prior allergic reaction to cisplatin.

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PHASE II SCHEMA



*Randomization is 1:1:1.

**See Section 5 for radiation and systemic therapy treatment details.