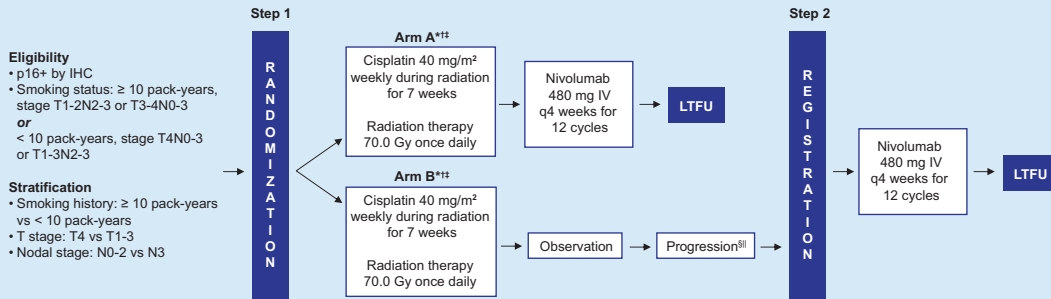


A Phase III Randomized Study of Maintenance Nivolumab Versus Observation in Patients With Locally Advanced, Intermediate Risk HPV Positive OPSCC



Study Schema



Accrual goal = 636 patients.

Cycle = 28 days.

*Submit tissue for PD-L1 testing.

†Patients on both arm A and B who have residual tumor or neck nodes following concurrent cisplatin/radiation therapy will be considered for salvage surgery. Nivolumab will be resumed no later than 6 weeks following surgical resection and will continue for a total of 12 treatments for patients randomized to arm A. Patients randomized to observation (arm B) who have salvage surgery at 12 weeks will continue observation and not cross over. Only when RECIST progression is documented following salvage surgery will these patients be offered crossover to arm C.

‡Intensity-modulated radiation therapy (IMRT) and image-guided radiation therapy (IGRT) are required for this study; proton therapy is not permitted.

§Patients who were randomized to observation (arm B) will be offered the option to cross over if they have clearly documented progression by the RECIST criteria and tissue-proven progression within 12 months from the end of cisplatin/radiation therapy.

¶Evidence of residual disease at 12 weeks that is salvageable by surgery does not count as tumor progression.

IHC = immunohistochemistry; LTFU = long-term follow-up; PD-L1 = programmed-death ligand 1.

Overall EA3161 Study Objective

To determine whether chemoradiation followed by maintenance therapy of nivolumab compared to observation can provide a survival benefit in patients with intermediate risk human papillomavirus (HPV) positive oropharyngeal squamous cell carcinoma (OPSCC)

Study Objectives

Primary Objective

- Assess efficacy of concurrent definitive therapy followed by nivolumab compared with concurrent definitive therapy followed by observation in terms of overall survival (OS)

Secondary Objectives

- Assess efficacy of concurrent definitive therapy followed by nivolumab in terms of progression-free survival (PFS)
- Assess efficacy of nivolumab compared with observation:
 - Evaluate the treatment effect within the subset of patients tested as PD-L1+
 - Evaluate the prognostic effect of (1) baseline saliva and/or plasma HPV status, (2) mutation burden among patients on the nivolumab arm
 - Evaluate the association of 12-week posttherapy FDG PET/CT OS and PFS

- Establish the prognostic value of maximum standardized uptake value (SUV_{max}) of primary tumor or neck nodal metastasis of baseline FDG PET/CT for OS (and/or PFS)
- Correlate SUV_{max} of primary tumor or nodal metastasis of baseline FDG PET/CT with PD-L1 expression (positive vs negative)
- Compare PET-based therapy response assessment (Hopkins criteria) to the RECIST 1.1 assessment at 12 weeks after chemoradiation therapy, for patients who have a PET/CT scan at 12 weeks

Eligibility Criteria*

Main Inclusion Criteria

- ≥ 18 years of age with oropharynx cancer (AJCC 8) that is p16-positive by immunohistochemistry *or* p16 equivocal by IHC and HPV positive by in situ hybridization with the following criteria:
 - ≥ 10 pack-years and stage T1-2N2-3 or T3-4N0-3 (less than 10 pack-years is considered a non-smoker) *or*
 - < 10 pack-years and stage T4N0-3 or T1-3N2-3
- Measurable disease

- Tumor measurements with CT of neck and chest (or CT of neck and FDG PET/CT if standard of care) within 4 weeks prior to step 1 randomization/step 2 registration
- ECOG performance status 0 or 1
- Adequate marrow, renal, and hepatic function, obtained ≤ 2 weeks prior to randomization/registration
- Step 2 registration: Progression per RECIST criteria *and* tissue-proven progression on arm B treatment within 12 months after completion of radiation therapy

Main Exclusion Criteria

- Known hypersensitivity to nivolumab or compounds of similar chemical or biological composition
- History of allergic reactions attributed to platinum-based chemotherapy agents
- Prior systemic therapy, radiation treatment or surgery for p16-positive OPSCC (note: patients with resection of T1/T2 carcinoma with no radiation or chemotherapy are eligible if surgery was done 5 years prior to enrollment)
- Received previous irradiation for head and neck, skull base, or brain tumor

(Continued)

*When evaluating patients for this study, please refer to the full protocol for the complete list of eligibility criteria.

Main Exclusion Criteria (cont)

- Received investigational agents within 4 weeks of enrollment or at any time while on study
- Evidence of distant metastases or leptomeningeal disease
- Uncontrolled intercurrent illnesses that will interfere with the ability to undergo therapy, i.e., chemotherapy
- History of a prior or second malignancy, with the exception of curatively treated non-melanoma skin cancer/cervical cancer; patients curatively treated for malignancy who remain disease-free at > 2 years of follow-up are not excluded
- Pregnancy or breastfeeding
- Active autoimmune disease or history of autoimmune disease that might recur, which may affect vital organ function or require immune suppressive treatment (see protocol for details)
- Patients with evidence of chronic hepatitis B virus infection, or history of hepatitis C infection may be eligible (see protocol for details)
- Baseline clinically significant hearing loss

