Accrual goal = 744 patients.
Cycle = 28 days.

*Submit tissue for PD-L1 testing.
†Patients 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 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.

Cisplatin 40 mg/m² weekly during radiation for 7 weeks
Radiation therapy 70.0 Gy once daily

Nivolumab 480 mg IV q4 weeks for 12 cycles
LTFU

Observation
Progression

Nivolumab 480 mg IV q4 weeks for 12 cycles
LTFU

Eligibility
• p16+ by IHC
• Smoking status: ≥ 10 pack-years, stage T1-2N2-3 or T3-4N0-3
or < 10 pack-years, stage T4N0-3 or T1-3N2-3

Stratification
• Smoking history: ≥ 10 pack-years vs < 10 pack-years
• T stage: T4 vs T1-3
• Nodal stage: N0-2 vs N3
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 cancer (OPCA)

Study Objectives

Primary Objective
• Phase II: Assess efficacy of concurrent definitive therapy followed by nivolumab compared with concurrent definitive therapy followed by observation in terms of progression-free survival (PFS)
• Phase III: 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
• Further assess efficacy of nivolumab compared with observation in terms of the following:
  – Assess the relationship of baseline programmed-death ligand 1 (PD-L1) expression to clinical outcome
  – Evaluate the predictive value of HPV16 E6 and E7 DNA in saliva and plasma at baseline, 12 weeks, and 9 months after completion of radiation on PFS and OS
  – Evaluate tumor mutation burden by whole exome sequencing of the initial pretreatment tissue sample as well as samples obtained at the time of progression
  – Evaluate the association of 12-week posttherapy FDG PET/CT with PFS and OS
  – Establish the prognostic value of maximum standardized uptake value (SUV\text{max}) of primary tumor or neck nodal metastasis of baseline FDG PET/CT for OS (and/or PFS)
  – Correlate SUV\text{max} of primary tumor or nodal metastasis of baseline FDG PET/CT with PD-L1 expression (positive vs negative)
  – Correlate posttherapy (cisplatin + radiation therapy) FDG PET/CT with saliva or plasma levels of HPV DNA collected at time of standard 3-month PET/CT scan and 6 months later (ie, 9 mo after therapy)
  – 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**

**Step 1: Randomization**
- ≥ 18 years of age with oropharynx cancer that is p16-positive by immunohistochemistry with smoking status ≥ 10 pack-years and stage T1-2N2-3 or T3-4N0-3 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
- ECOG performance status 0 or 1
- Adequate marrow, renal, and hepatic function, obtained ≤ 2 weeks prior to randomization
- Use of effective contraception or abstinence

**Step 2: Registration**
- Progression per RECIST criteria and tissue-proven progression on arm B treatment within 12 months after completion of radiation therapy
- Adequate marrow, renal, and hepatic function, obtained ≤ 2 weeks prior to registration
- 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 2 registration

**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 or radiation treatment for p16-positive oropharyngeal squamous cell carcinoma
- Received previous irradiation for head and neck, skull base, or brain tumor
- Received investigational agents within 4 weeks of enrollment or at any time while on study
- Evidence of distant metastases or leptomeningeal disease

*When evaluating patients for this study, please refer to the full protocol for the complete list of eligibility criteria.
- Uncontrolled intercurrent illnesses that in the investigator’s opinion will interfere with the ability to undergo therapy, including chemotherapy
- History of a different malignancy, unless the disease has not progressed for ≥ 2 years
- Pregnancy or breastfeeding