**Patient Population**

**Eligibility Criteria for Step 1:**
- Age ≥ 18 years, ECOG PS 0-1, adequate lab values
- Must have oropharynx cancer that is p16-positive by immunohistochemistry with smoking status ≥ 10 pack-years, stage T1-2N2-N3 or T3-4N0-3 OR < 10 pack-years, stage T4N0-N3 or T1-3N2-3
- Must not have known hypersensitivity to nivolumab or compounds of similar chemical/biological composition
- No history of allergic reactions attributed to platinum-based chemotherapy agents
- Must not have had prior systemic therapy/radiation treatment for p16 positive OPSCC
- Must not have received previous radiation for head and neck tumor, skull base, or brain tumors
- Must not receive investigational agents within 4 wks of enrollment/while on study
- Patients with evidence of distant metastases/leptomeningeal disease are excluded
- No patients with uncontrolled inter-current illness that would interfere with the ability to undergo therapy
- Patients with a history of a different malignancy are excluded, unless the disease has not progressed for ≥ 2 yrs
- Must not be pregnant/breast feeding
- Must have measurable disease, defined per protocol
- Must have tumor measurements with CT of neck and CT of chest (or CT of neck and FDG PET/CT if standard of care) within 4 wks prior to step 1 randomization

**Eligibility Criteria for Step 2:**
- Must have progression (RECIST) and tissue-proven progression on Arm B treatment within 12 mos after completion of radiation therapy
- Must not have received non-protocol anti-cancer therapy after completion of radiation and chemotherapy
- ECOG PS 0-1 and adequate lab values
- Tumor measurements with CT of neck and CT of chest (or CT of neck and FDG PET/CT if standard of care) within 4 weeks prior to step 2 randomization

**Treatment Plan**

**Arm A:**
- Cisplatin 40 mg/m2 weekly during a 5 days/wk radiation schedule with 70 Gy of radiation administered once daily, 7 weeks
- Maintenance therapy with nivolumab will initiate within 4 weeks after completion of concurrent therapy of cisplatin/RT
  - Nivolumab administered at 480 mg IV q4 wks for 12 mos (thus completing 1 yr maintenance therapy provided there is no evidence of disease progression/other reason for discontinuation, i.e., toxicity)

**Arm B:**
- Cisplatin 40 mg/m2 weekly during a 5 days/wk radiation schedule with 70 Gy of radiation administered once daily, 7 weeks
- Following the completion of the 7 weeks of concurrent therapy of cisplatin/RT, the patient will go on to observation

**Arm C:**
- Patients who were randomized to observation will be offered the option to cross over if they have clearly documented progression per protocol
- After progression and registration to Step 2, Nivolumab will be administered at 480 mg IV q4 wks for 12 mos starting within 2 wks of Step 2 registration
- Patients will complete a total of 1 yr of therapy provided there is no evidence of disease progression/other reason for discontinuation, i.e., toxicity

Notes:
- See protocol for hydration and antiemetic details
- IMRT and IGRT are required; proton therapy is not permitted
- At least 4 MV shall be used; cyberknife treatment is not allowed
- CT stimulation is required for all patients
- See protocol for RT credentialing requirements

**Patient Enrollment**

All Sites: Oncology Patient Enrollment Network (OPEN) [https://open.ctsu.org](https://open.ctsu.org)

**Protocol Information**

ECOG-ACRIN Operations-Boston: 857-504-2900, [http://ecog-acrin.org](http://ecog-acrin.org) (Member Login)

Please Enroll Your Eligible Patients!