## Patient Population

**Step 1 Registration:**
- ≥ 18 years of age, ECOG PS 0-1, adequate lab values
- Must have biopsy-proven metastatic squamous cell carcinoma, originating in the oral cavity, larynx, oropharynx or hypopharynx, with active disease present in both the head and neck (H&N) and distant sites
  - Note: the tumor from an oropharynx primary site must have known p16 status; p16 positive cancer of unknown primary is allowed provided the disease presentation is consistent with a H&N primary
- Can have prior surgical resection of a primary cancer in the H&N at any previous time; however, residual/recurrent disease in the H&N must be present on baseline imaging; no prior H&N radiotherapy
- Must have 4 or fewer metastatic sites prior to starting any treatment, with thoracic nodal disease considered a single site if encompassable in a tolerable radiotherapy hypofractionated field (i.e., 15 fractions or less; see protocol)
- Must have measurable disease defined per protocol
- HIV, HBV, and HCV patients are permitted per protocol
- Arm S: must have received chemoimmunotherapy consistent with protocol section 5.1
- Patients with a prior/concurrent malignancy whose natural history/treatment does not have the potential to interfere with safety/efficacy are eligible
- No active autoimmune disease that has required systemic treatment in the past 2 years (see protocol)

**Step 2 Randomization:**
- ECOG PS 0-2; must have completed 3 cycles of initial systemic chemotherapy
- Arm S: must have at least stable disease after completing 3 cycles of pembrolizumab + chemotherapy (defined per protocol section 5.1)
- Must have no signs of progression (CR/PR/SD) on restaging imaging (consisting of neck, chest, and abdomen CT), done after initial Step 1 therapy and within 7 days prior to Step 2 randomization

## Treatment Plan

**Step 1 – Arms S and T (pembro + chemotherapy):**
- Cycle = 21 days; patients to continue with the same regimen until 3 cycles are completed (note: if dose modifications are not sufficient, patients may switch regimens per the investigator’s discretion)
  - **Option 1:** pembro 200 mg IV day 1 of each cycle; carboplatin AUG 5 day 1; paclitaxel per protocol
  - **Option 2:** pembro 200 mg IV day 1 of each cycle; cisplatin 100 mg/m² IV day 1 of each cycle; 5-FU 1000 mg/m² IV per day on continuous infusion days 1-4 of each cycle
  - **Option 3:** pembro 200 mg IV day 1 of each cycle; carboplatin AUG 5 day 1; 5-FU 1000 mg/m² IV per day on days 1-4 of each cycle
- Restaging imaging; patients without progression will be randomized to Arms A or B

**Step 2 – Arm A (consolidative radiotherapy with pembrolizumab):**
- All patients will receive a 4th cycle of initial systemic therapy before consolidation
  - Radiation therapy per protocol Section 5.2 (once daily x 30 fractions for a total of 66 Gy)
  - Pembrol 200 mg IV day 1 of each cycle until progression or a total of 2 years from the start of chemoimmunotherapy (note: pembrol 400 mg IV every 6 weeks may be used after radiation ends)

**Step 2 – Arm B (pembro monotherapy):**
- All patients will receive a 4th cycle of initial systemic therapy before consolidation
  - Pembrol 200 mg IV day 1 of each 21-day cycle for 6 cycles followed by pembrol 400 mg IV day 1 of each 42-day cycle until progression or a total of 2 years from the start of chemoimmunotherapy

Note: post-progression therapy is at the discretion of the treating oncologist

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**Study Chair:**
David J. Sher, MD, MPH

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

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

Please Enroll Your Eligible Patients!
The image contains a flowchart with various steps and decision points. The diagram is not fully transcribed here, but it appears to outline a process involving decision-making and progression through different phases. The text is not legible due to the image quality, but it seems to involve steps labeled 'Step 1', 'Step 2', 'Step 3', etc., and includes terms like 'Normal Tallassemia', 'Normal Carriage', and 'Family History'. The diagram is likely intended to represent a medical or genetic counseling process.

Unfortunately, the specific details of the text are not readable in the image provided. If you need further assistance or have specific questions about the diagram, please let me know!