EA3191

**A Phase II Randomized Trial of Adjuvant Therapy with Pembrolizumab after Resection of Recurrent/Second Primary Head and Neck Squamous Cell Carcinoma (HNSCC) with High Risk Features**

### Study Schema

| Arm B | Reirradiation 2 Gy once daily x 30 fractions for a total of 60 Gy
|       | Cisplatin 40 mg/m² IV weekly x 6 cycles
|       | OR
|       | Carboplatin AUC 2 IV weekly x 6 cycles

| Arm C | Pembrolizumab 400 mg IV q 6 weeks x 9 cycles

### Stratification Factors:
- HPV status oropharynx only (p16 positive vs. negative by local testing)
- PD-L1 by Combined Positive Score (1–19 vs. ≥ 20)
- Received prior anti-PD-1/PD-L1 as part of curative intent therapy: Yes vs. No

| Accrual goal = 188 patients
| High risk features include Positive Margins and/or Extranodal Extension.
| Randomization is 1:1 across all arms.
| Carboplatin will be given for patients who are ineligible for cisplatin.

*Enrollment to Arm A (reirradiation + pembrolizumab) closed effective with protocol version 06/16/23 (Addendum #7) activation. All patients already randomized to Arm A at the time of Add. #7 activation can continue on study per protocol.*
Study Objectives

Primary Objective
• To evaluate overall survival of adjuvant pembrolizumab for 12 months compared to adjuvant reirradiation plus concurrent platinum chemotherapy

Secondary Objectives
• To evaluate the following endpoints in both arms: disease-free survival, locoregional control, rates of distant metastasis, toxicity
• To evaluate whether high PD-L1 expression (defined as Combined Positive Score [CPS] ≥ 20) is predictive of increased efficacy in the experimental group compared to control

Eligibility Criteria*

Main Inclusion Criteria
• Between 18 and 79 years of age, ECOG PS 0-1, adequate organ and marrow function defined per protocol
• Locoregionally recurrent or second primary HNSCC (oral cavity, oropharynx, larynx, hypopharynx) in previously radiated field
• Had surgery with gross total resection (must be randomized within 8 weeks of surgery)

• High risk disease defined as positive margins and/or extra nodal extension (ENE)
  – Positive margins = malignancy at or within 1 mm of the margin
  – High grade dysplasia (i.e., carcinoma in situ) at the margin is also considered positive
  – ENE may be gross or microscopic
• PD-L1 CPS ≥ 1 in a CLIA certified laboratory

*When evaluating patients for this study, please refer to the full protocol for complete list of eligibility criteria.
• Had prior radiation to the area of recurrent or second primary tumor (defined as > 50% of the pre-surgical tumor volume having previously received a dose of > 45 Gy)
  – Must have completed prior radiation a minimum of 6 months prior to randomization

Main Exclusion Criteria
• Evidence of distant disease based on baseline imaging done within 28 days prior to randomization
• Received anti-PD-1/PD-L1 therapy for recurrent disease; if anti-PD-1/PD-L1 was received as part of the initial upfront curative intent treatment, the last dose must have been given greater than 1 year prior to randomization
• Current active infection that requires systemic treatment at time of randomization
• History of non-infectious pneumonitis requiring steroids within 3 years prior to randomization
• History of solid organ transplant or stem cell transplant
• New York Heart Association Class III or IV heart failure
• Hypersensitivity (≥ Grade 3) to pembrolizumab and/or any of its excipients
• Active autoimmune disease that required systemic treatment in the past 2 years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs; note that replacement therapy is not considered systemic treatment and is allowed)
• Known history of Hepatitis B (HBsAg reactive) or known active Hepatitis C virus (HCV RNA [qualitative detected] infection)