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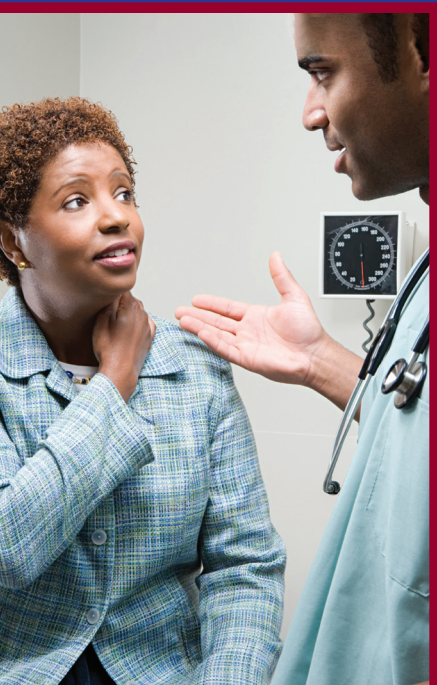

A Phase II Randomized Trial of Adjuvant Therapy with Pembrolizumab after Resection of Recurrent/Second Primary Head and Neck Squamous Cell Carcinoma (HNSCC) with High Risk Features

Study Schema

Locally Recurrent/Second Primary HNSCC s/p Surgical Resection with High Risk Features*

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 thereapy: Yes vs. No

RANDOMIZATION†

Arm B
Reirradiation 2 Gy once daily x 30 fractions for a total of 60 Gy
Cistplatin 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

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.

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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-LI 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

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