Association of pathological response to neoadjuvant pembrolizumab with tumor PD-L1 expression and high disease-free survival (DFS) in patients with resectable, local-regionally advanced, head and neck squamous cell carcinoma (HNSCC).

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Background: Patients with resected HNSCC, with high-risk (positive margins, extracapsular spread [ECE]) or intermediate-risk pathological features have an estimated 1-year DFS of 65% and 69%, respectively. Immune checkpoint blockade improved survival of patients with recurrent/metastatic HNSCC, and preclinical models indicate radiotherapy (RT) synergizes with anti-PD-1. Therefore, we administered the PD-1 inhibitor pembrolizumab (pembro) pre- and post-surgery with adjuvant RT +/- cisplatin in patients with resectable, locoregionally advanced (clinical T3/4 and/or ≥2 nodal metastases) HNSCC (NCT02641093).

Methods: Eligible patients received pembro (200 mg I.V. x 1) 1-3 weeks before resection. Adjuvant pembro (q3 wks x 6 doses) was administered with RT (60-66Gy) with or without weekly cisplatin (40mg/m2 X 6) for patients with high-risk and intermediate-risk features, respectively. The primary endpoint was 1-year DFS estimated by Kaplan Meier curves. Safety was evaluated by CTCAE v5.0. Pathological response (PR) to neoadjuvant pembro was evaluated by comparing pre- and post-surgical tumor specimens for treatment effect (TE), defined as tumor necrosis and/or histiocytic inflammation and giant cell reaction to keratinaceous debris. PR was classified as no (NPR, < 20%), partial (PPR, 20% and < 90%) and major (MPR, ≥90%). Tumor PD-L1 immunohistochemistry was performed with 22c3 antibody and reported as combined positive score (CPS).

Results: Ninety-two patients were enrolled. Seventy-six patients received adjuvant pembro and were evaluable for DFS. Patient characteristics included: median age 58 (range 27 – 80) years; 32% female; 88% oral cavity, 8% larynx, and 3% human papillomavirus negative oropharynx; 86% clinical T3/4 and 65% ≥2N; 49 (53%) high-risk (positive margins, 45%; ECE, 78%; 64% (44/69 available) had PD-L1 CPS ≥1. At a median follow-up of 20 months, 1-year DFS was 67% (95%CI 0.52-0.85) in the high-risk group and 93% (95%CI 0.64-1) in the intermediate-risk group. Among 80 patients evaluable for PR, TE scoring resulted in 48 NPR, 26 PPR and 6 MPR. Patients with PPR/MPR had significantly improved 1-year DFS when compared with those with NPR (100% versus 68%, p = 0.01; HR = 0.23). PD-L1 CPS ≥1 was not independently associated with 1-year DFS, but was highly associated with MPR/PPR (p = 0.0007). PPR/MPR in PD-L1 CPS < 1, ≥1 and ≥20, were estimated as 20, 55 and 90%, respectively. Grade ≥ 3 adverse events occurred in 62% patients with most common including dysphagia (15%), neutropenia (15%), skin/wound infections (10%), and mucositis (9%). Conclusions: PR to neoadjuvant pembro is associated with PD-L1 CPS≥1 and high DFS in patients with resectable, local-regionally advanced, HNSCC. Clinical trial information: NCT02641093. Research Sponsor: Merck & Co., Startup funds, internal pilot grants.