Notably Off Key: Questioning the Clinical Benefit of Perioperative Immunotherapy for Resectable Head and Neck Squamous Cell Carcinoma After KEYNOTE-689

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After decades of minimal progress in the treatment of human papillomavirus (HPV)–negative head and neck squamous cell carcinoma (HNSCC), the recent publication of KEYNOTE-689 has led many to conclude that perioperative pembrolizumab is a clinical breakthrough and a new standard of-care for patients with resectable stage III-IV HNSCC.[1] Briefly, this randomized phase III trial demonstrated an event-free survival (EFS) benefit to neoadjuvant pembrolizumab followed by surgery, risk-adapted (chemo)radiation based on pathologic risk factors and almost 1 year of adjuvant pembrolizumab when compared with standard-of-care up-front surgery followed by risk-adapted (chemo)radiation. Furthermore, a planned subgroup analysis of enrolled patients with a combined positive score (CPS) ≥10 demonstrated a trend toward an overall survival (OS) benefit with perioperative pembrolizumab, although there been an insufficient number of events to trigger the final analysis for this end point. Regardless, these results have led to a change in National Comprehensive Cancer Network guidelines, such that perioperative pembrolizumab is considered standard of care for all stage III-IV patients with a CPS ≥1 treated with primary surgery. Although we applaud a completed study of any novel paradigm, especially one with a disease-control benefit, the true clinical impact of these results should be carefully interrogated. After careful examination of the study details and outcomes, we believe that up-front surgery should remain the standard of care in most clinical scenarios, while reserving perioperative pembrolizumab for carefully selected patients.

Although the authors of KEYNOTE-689 recommend perioperative pembrolizumab for all patients with a CPS ≥1 based on their analysis, there are obvious signals that the benefit resides in patients with a CPS ≥10. Briefly, CPS has been predictive of response to PD-1 therapy in HNSCC and other cancers and is calculated by measuring the total number of PD-L1–positive cells in a tumor (including tumor cells, lymphocytes, and macrophages), dividing by the total number of tumor cells and multiplying by 100. To examine the benefit of pembrolizumab in patients with a CPS between 1 and 9 on KEYNOTE-689, we separated the number of major pathologic responses that were seen by CPS category. Only 1.8% (2/113) of patients with CPS between 1 and 9 showed a major pathologic response compared with 13.7% (32/234) of patients with CPS ≥10. Similar differential responses by CPS score have also been seen on the KEYNOTE-048 trial, which tested pembrolizumab in the recurrent/metastatic setting. In the CPS 1-19 population, response rates were only 14.5% compared with 23.3% in the CPS ≥20 population.[2] Diminishing returns with pembrolizumab at lower CPS scores echo across multiple phase III HNSCC trials, raising the question of whether patients with a CPS <10 truly benefit from immunotherapy.

Even for patients with a CPS ≥10, there are potential disadvantages to perioperative pembrolizumab. Disease progression in nonresponders could result in increased morbidity and extent of surgery. Critically, on KEYNOTE-689, only progression to inoperability was considered an event, and no reporting on any clinical tumor progression during the neoadjuvant pembrolizumab phase was done in the primary study. In fact, according to the supplementary appendix accompanying the publication of KEYNOTE-689, there were 45 progressions in the pembrolizumab arm by the end of the surgery phase, in contrast to only eight in the surgery-alone arm. Furthermore, data from a separate phase II trial of perioperative pembrolizumab demonstrate that clinical progression can happen even in a narrow perioperative window with 3 of 19 evaluable patients demonstrating progression by RECIST criteria after only one cycle of

pembrolizumab.[3] Although two of these three patients ultimately showed some measure of pathologic response, pseudoprogression could still affect surgical extent. Combining these data and the fact that 10% of patients on KEYNOTE-689 did not undergo resection after neoadjuvant therapy in the experimental arm, raises legitimate concerns that neoadjuvant pembrolizumab may result in more extensive surgeries or omission of surgery.

Perioperative pembrolizumab on KEYNOTE-689 also increased toxicity compared with the control arm, with a significant risk (10%) of developing grade 3 or higher immune-related toxicities. A similar finding was seen on the recently published NIVOPOST-OP[4] trial, with nearly 19% of patients developing grade 3 or higher immunotherapy-related adverse events with 6 months of adjuvant nivolumab. Immune-mediated toxicities may be lifelong. Furthermore, these numbers do not consider the nontrivial financial toxicities resulting from 6 months to 1 year of additional immunotherapy.

Some may counter that perioperative pembrolizumab on KEYNOTE-689 reduced high-risk pathologic features by approximately 12% compared with control arm, thus reducing the number of patients requiring concurrent chemotherapy with adjuvant radiation. However, this reduction in high-risk features did not substantially reduce grade 3+ stomatitis (11.6% *v* 13.3%) as would be expected from a reduction in chemotherapy usage, suggesting that perioperative pembrolizumab itself may result in increased stomatitis compared with radiation alone.

The recently published results of the NIVOPOST-OP trial also raise questions about the utility of a perioperative approach for all patients versus a more selective use of immunotherapy in a higher-risk population.[4] NIVOPOST-OP tested the addition of postoperative nivolumab to adjuvant chemoradiation in patients with resected HNSCC with high-risk pathologic features. Despite a similar 10% EFS benefit, failure patterns were different between trials: In NIVOPOST-OP the EFS benefit was driven by a reduction in locoregional relapse, whereas in KEYNOTE-689, the EFS benefit was a result of fewer distant metastases. Unlike KEYNOTE-689, all patients on NIVOPOST-OP were restaged before adjuvant therapy, effectively ruling out the presence of both locoregional recurrence and distant metastases developing in the postsurgical window. As there was no restaging before adjuvant therapy on KEYNOTE-689, distant metastases may have developed in the postsurgical window. These metastases were potentially undetected for nearly 6 months after surgery in the control arm resulting in a large lead-time phenomenon. As pembrolizumab improves OS in recurrent/metastatic HNSCC, we are concerned this lead-time difference could result in a survival difference between arms. This is magnified by the fact that there was no mandated crossover on KEYNOTE-689, and the published manuscript

TABLE 1. Randomized Trials of Perioperative Immunotherapy in Resectable HNSCC

Study	Patient Population	Stratification Factors	Percent Oral Cavity Patients	Percent p16+ Oropharynx Patients	Treatment Arms	Adjuvant Local Therapy	Results
KEYNOTE-689	Stage III-IV HNSCC planned for surgical resection: p16+ oropharynx patients must have had T4a N0-N2 disease to be eligible	Primary tumor site (oropharynx or oral cavity *v* larynx *v* hypopharynx) Tumor stage (III *v* IV) PD-L1 status (TPS[a] ≥50% *v* <50%)	60.5%	3.8%	Up-front surgery Perioperative pembrolizumab for up to 1 year (2 neoadjuvant cycles and 15 adjuvant cycles)	Radiation to 60-66 Gy with concurrent cisplatin if positive margins (<1 mm) or extranodal extension	Perioperative pembrolizumab: Improved EFS (HR, 0.73, 3-year EFS: 57.6% *v* 46.4%, *P* = .008) Improved major pathologic response (13.7% *v* 0.0%) Reduced the rate of high-risk pathologic features (32.5% *v* 44.4%) Primary end point driven by decrease in distant metastases OS results remain immature
NIVOPOST-OP	High-risk resected HNSCC having at least one of: Positive margins (R1 or ≤1 mm) Extranodal extension 4+ involved nodes Multiple perineural invasions	p16 status	58%	5%	Observation Adjuvant nivolumab for up to 6 months	Radiation to 66 Gy with concurrent cisplatin	Adjuvant nivolumab: Improved DFS (HR, 0.76, 3-year DFS: 63.1% *v* 52.5%, *P* = .034) Primary end point driven by increased locoregional control (HR, 0.63 [95% CI, 0.42 to 0.94]) Blinded independent central review and sensitivity analyses did not confirm DFS benefit (HR, 0.81 [95% CI, 0.63 to 1.03]) OS results remain immature

Abbreviations: EFS, event-free survival; HNSCC, head and neck squamous cell carcinoma; OS, overall survival; TPS, tumor-positive score.
[a]TPS (number of tumor cells positive for PD-L1/number of tumor cells × 100).

does not report on the receipt of salvage therapy. This contrasts with NIVOPOSTOP, for which salvage immunotherapy was delivered in nearly 60% (70/123) of patients with disease recurrence on the control arm. If no OS benefit is seen on NIVOPOSTOP, this would suggest that patients would be salvageable by immunotherapy at recurrence.

Owing to these concerns, we advocate a more restricted and nuanced approach for perioperative pembrolizumab in patients with resectable, locally advanced, and/or node-positive HPV-negative HNSCC. Given the possibility of progression during neoadjuvant therapy, marginally resectable patients or those patients for whom progression would render greater surgical morbidity (ie, high likelihood of transition from a hemiglossectomy to a total glossectomy) should not be given perioperative immunotherapy alone because of the risk of omitting surgery or worsening quality of life. Furthermore, as oral cavity cancer was disproportionately represented on KEYNOTE-689 (nearly 60% of patients), the broad applicability of this approach to other primary sites such as the larynx and hypopharynx may be limited, where disease progression could result in imminent airway compromise. For marginally resectable patients who still desire neoadjuvant immunotherapy, emerging cytotoxic approaches such as combining immunotherapy with chemotherapy or stereotactic body radiotherapy,[5] may be reasonable in the setting of a clinical trial. Finally, on the basis of the clear difference in major pathologic response as a function of CPS, we would only consider perioperative pembrolizumab monotherapy in patients with a high CPS score (≥10) as they are most likely to garner benefit from therapy.

The implications of routinely exposing the entire population of eligible patients to immunotherapy are profound in terms of medical, financial, and time toxicity, which raises the standards by which we should judge the intervention. OS has long been the *de facto* gold standard for changing the standard of care in oncology for a reason, and we eagerly await the OS results for both KEYNOTE-689 and NIVOPOSTOP to properly interpret the EFS benefit (Table 1). We congratulate the investigators and patients who successfully executed both trials, but we firmly believe our considerations should influence how the use of immunotherapy in resected HNSCC is implemented in common practice and look forward to additional trials in this space.

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REFERENCES

1. Uppaluri R, Haddad RI, Tao Y, et al: Neoadjuvant and adjuvant pembrolizumab in locally advanced head and neck cancer. N Engl J Med 393:37-50, 2025
2. Burtness B, Rischin D, Greil R, et al: Pembrolizumab alone or with chemotherapy for recurrent/metastatic head and neck squamous cell carcinoma in KEYNOTE-048: Subgroup analysis by programmed death ligand-1 combined positive score. J Clin Oncol 40:2321-2332, 2022
3. Uppaluri R, Campbell KM, Egloff AM, et al: Neoadjuvant and adjuvant pembrolizumab in resectable locally advanced, human papillomavirus-unrelated head and neck cancer: A multicenter, phase II trial. Clin Cancer Res 26:5140-5152, 2020
4. Bourhis J, Auperin A, Borel C, et al: Nivolumab added to cisplatin and radiotherapy versus cisplatin and radiotherapy alone after surgery for people with squamous cell carcinoma of the head and neck at a high risk of relapse (GORTEC 2018-01 NIVOPOST-OP): A randomised, open-label, phase 3 trial. Lancet 407:363-374, 2026
5. Leidner R, Crittenden M, Young K, et al: Neoadjuvant immunoradiotherapy results in high rate of complete pathological response and clinical to pathological downstaging in locally advanced head and neck squamous cell carcinoma. J Immunother Cancer 9:e002485, 2021

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