



KEYNOTE-689 and the Perioperative Paradigm: A Critical Appraisal of Design-Driven Success

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The recently presented KEYNOTE-689 trial has reignited interest in perioperative immunotherapy for resectable head and neck squamous cell carcinoma (HNSCC). This study explored the addition of pembrolizumab to definitive surgery and adjuvant radiotherapy with or without chemotherapy, marking a pivotal shift in the management paradigm. KEYNOTE-689 advances perioperative immunotherapy in resectable HNSCC, but key limitations warrant scrutiny.

Previous trials investigating immune checkpoint blockade (ICB) in the curative-intent setting—namely, KEYNOTE-412 and JAVELIN HN100, failed to demonstrate statistically significant benefit. In KEYNOTE-412, which evaluated concurrent chemoradiotherapy (CRT) with pembrolizumab, the hazard ratio (HR) for event-free survival (EFS) was 0.83 (95% confidence interval [CI], 0.68–1.03), narrowly missing significance level.¹ Similarly, JAVELIN HN100, which examined avelumab with CRT, reported an HR for progression-free survival of 1.21 (95% CI, 0.93–1.57), suggesting possible antagonism between ICB and CRT when administered concurrently.² This may reflect impaired immune priming due to lymphodepletion during the intensive CRT window.

Furthermore, IMvoker010, an adjuvant trial administering atezolizumab after completion of surgery and CRT, failed to improve EFS (HR 0.94; 95% CI, 0.70–1.26).^{3,4} Delayed initiation of ICB, after the window of maximal antigen release, may have contributed to suboptimal immune engagement.

KEYNOTE-689 attempted to optimize timing by integrating neoadjuvant and adjuvant pembrolizumab. However, the trial design raises several concerns. As emphasized in the simultaneous editorial by Rosenberg and Vokes, an important unresolved question is which component of immunotherapy, neoadjuvant priming, adjuvant consolidation, or cumulative exposure was primarily responsible for the observed benefit.⁵ This distinction is especially relevant in resource-constrained settings, where limited perioperative

dosing may be more pragmatic, and parallel observations from lung cancer trials in which short-course nivolumab exposure was associated with meaningful clinical benefit.⁶

Notably, crossover to ICB in the control arm was not permitted, despite robust evidence of benefit in the recurrent/metastatic setting from KEYNOTE-048 (HR for overall survival 0.61 with pembrolizumab vs. EXTREME regimen) and CheckMate-141. This limitation compromises the equipoise of the study and potentially inflates the perceived benefit of perioperative immunotherapy.

Moreover, approximately 10% of patients in the control arm, around 35 individuals, did not receive the assigned adjuvant treatment but were nonetheless included in the intention-to-treat analysis. The absence of detailed reasons for this omission whether due to disease progression, treatment-related toxicity, or patient withdrawal raises concerns about missed curative opportunities and the potential for analytic bias.

Subgroup analyses are also notably incomplete. Despite human papillomavirus (HPV)-positive oropharyngeal cancer comprising up to 26% of global HNSCC incidence, efficacy outcomes for this biologically distinct subgroup were not reported. Given the divergent prognosis and treatment responsiveness of HPV-associated disease, omission of this data limits the generalizability of the findings.

Similar underrepresentation of HPV-positive disease and resultant selection bias have been observed in other perioperative and definitive-intent trials, limiting extrapolation to this subgroup.⁷ The low representation of HPV-positive patients raises concerns regarding selection bias, a limitation similarly observed in other perioperative and definitive-intent trials, and restricts the generalizability of the findings.

Finally, and perhaps most critically, no health-related quality-of-life (HRQoL) outcomes were reported. A triphasic immunotherapy regimen spanning neoadjuvant, concurrent,

and adjuvant phases entails a substantial treatment burden, particularly in a population where functional preservation and long-term survivorship are paramount. The absence of HRQoL data hinders a balanced risk–benefit assessment of this intensive approach.

In conclusion, while KEYNOTE-689 advances the promise of perioperative immunotherapy in resectable HNSCC, its findings must be interpreted in the context of prior trial failures, design limitations, and missing data. A cautious, evidence-based integration into practice awaits further peer-reviewed results and longer-term follow-up.

Conflict of Interest

None declared.

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