Immunotherapy Makes Inroads in Head and Neck Cancer Treatment

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Abstract

Immunotherapy has transformed the treatment landscape of metastatic head and neck squamous cell carcinoma (HNSCC), but its role in curative-intent settings remained elusive—until now. Recent data from two pivotal phase III trials, NIVOPOSTOP and KEYNOTE-689, mark a turning point by demonstrating statistically significant improvements in disease-free and event-free survival, respectively. However, the magnitude of benefit remains limited, subgroup efficacy is unclear, and overall survival data are immature. Given the logistical complexity and potential for overtreatment, these results warrant cautious interpretation. Future strategies must prioritize biomarker-driven selection, real-world feasibility, and long-term survival outcomes before immunotherapy can claim a definitive role in curative HNSCC.

Keywords
- head and neck cancer
- HNSCC
- immunotherapy
- neoadjuvant therapy

Introduction

Head and neck squamous cell carcinoma (HNSCC) represents one of the few areas in oncology where the accelerated advancements and accompanying disappointments associated with immunotherapy have been most striking. Despite its biological plausibility and success in the metastatic disease, the integration of immune checkpoint inhibitors (ICIs) into curative-intent strategies for locally advanced HNSCC has been a frustrating journey of failed promises. After years of negative trials, recent phase III data from NIVOPOSTOP[1] and KEYNOTE-689[2] offer new hope. But hope, as we have learned repeatedly, should not substitute for rigorous evidence.

This article examines whether these trials represent a genuine inflection point in the curative treatment of HNSCC or whether we are once again overestimating modest gains, especially in the absence of mature overall survival (OS) data and realistic global applicability.

A History of Missed Opportunities: A Trial Graveyard

For nearly a decade, trials attempting to incorporate ICIs into curative HNSCC therapy have been largely unsuccessful. JAVELIN Head & Neck 100,[3] arguably the most ambitious early effort, added avelumab to chemoradiotherapy (CRT) but failed to show benefit—a hazard ratio (HR) of 1.21 for progression-free survival was observed, pointing toward potential harm. KEYNOTE-412[4] fared little better: the addition of pembrolizumab to CRT showed a nonsignificant trend (HR 0.83), narrowly missing statistical significance and falling short of the prespecified threshold for success.

Several other trials underscored the same theme. In the REACH study,[5] the cisplatin-fit group paradoxically did worse with the ICI arm (HR 1.27). The PembroRad trial,[6] replacing cetuximab with pembrolizumab in patients unfit for cisplatin, showed an HR of 1.05. Simply put, these trials

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did not fail because of poor design alone—they failed because the approach itself may be biologically unsound.

Even in the adjuvant setting, where one might expect better immune reconstitution after surgery, the results were disappointing. IMvoke010[7] (atezolizumab postsurgery and radiotherapy [RT]) reported an HR of 0.94, essentially a null trial. The NRG-HN004[8] study of durvalumab in cisplatin-unfit patients showed an HR of 1.33—again suggesting that simply swapping chemotherapy for immunotherapy is not a viable shortcut ►**Table 1-2**.

So Why Did These Trials Fail?

Immunotherapy is Not Just Plug-and-Play

The key mistake was assuming that immunotherapy's success in lung cancer or melanoma could be imported wholesale into HNSCC. This disease is biologically distinct—characterized by intense stromal immunosuppression, T-cell exhaustion, and frequently human papillomavirus (HPV)-driven oncogenesis that does not necessarily correlate with immunogenicity.[9,10]

Moreover, the context of delivery matters. Combining ICIs with high-dose cisplatin and radiation—both profoundly immunosuppressive interventions—may neutralize the very immune activation ICIs require. Concurrent administration may have been the wrong strategy altogether.

Another cardinal flaw was the absence of biomarker-driven stratification. Across many clinical trials, programmed death-ligand 1 (PD-L1) combined positive score (CPS) or HPV/p16 status were often not recorded, not incorporated into therapeutic strategies, or lacked adequate power to determine benefit. Consequently, any potential advantage in a subset was diluted in the broader analysis.

The Turning Point? Dissecting NIVOPOSTOP and KEYNOTE-689

NIVOPOSTOP,[1] presented at ASCO 2025, was the first study to demonstrate a statistically significant improvement in disease-free survival (DFS) with adjuvant nivolumab after surgery and postoperative CRT in patients with high-risk HNSCC. The 3-year DFS was 63.1% with nivolumab versus 52.5% with CRT alone (HR 0.76; $p = 0.034$). Importantly, benefits were seen regardless of p16 or PD-L1 status, though subgroup sizes were small.

Compliance was excellent: 91% completed RT, $>80\%$ received adequate cisplatin doses, and 75% of patients belonging to the nivolumab arm completed at least 10 cycles. Fewer grade ≥ 3 treatment-related adverse events were observed in the nivolumab group (39%) compared with the control group (49%), referring to overall grade ≥ 3 adverse events (AEs), not immune-related ones. OS data remain immature.

What makes NIVOPOSTOP[1] noteworthy is not just the positive result but that it learned from prior failures. It avoided concurrent administration of ICIs with CRT and instead placed immunotherapy in the adjuvant slot—a setting where the immune system may be less suppressed and more responsive.

KEYNOTE-689,[2] now published in *New England Journal of Medicine* (June 2025), assessed the use of pembrolizumab in both the neoadjuvant and adjuvant settings for resectable, locally advanced HNSCC. At a median follow-up of 38.3 months, patients treated with pembrolizumab achieved a 3-year event-free survival (EFS) of 59.8%, whereas the control arm reported 45.9% (HR 0.73; 95% confidence interval, 0.58–0.92). Notably, the benefit was even more pronounced in biomarker-enriched subgroups: CPS ≥ 10 (HR 0.60), CPS ≥ 1 (HR 0.70).

Surgery completion rates were similar between the two arms ($\sim$88%), alleviating prior concerns about neoadjuvant ICI interfering with operability. In the pembrolizumab arm, 24.5% of patients experienced grade 3 AEs, compared with 22.5% in the control arm. This robust benefit led to Food and Drug Administration approval on June 12, 2025, for perioperative pembrolizumab in CPS ≥ 1 resectable HNSCC.[11]

Should We Be Celebrating Yet? Let's Pause and Reflect

Despite the excitement surrounding NIVOPOSTOP[1] and KEYNOTE-689,[2] several cautionary issues need to be addressed before calling this a paradigm shift.

Surrogate Endpoints

Neither NIVOPOSTOP[1] nor KEYNOTE-689[2] reported mature OS data. We are again anchoring major practice changes on DFS or EFS—surrogate endpoints that often fail to predict survival in HNSCC. A 10 to 15% EFS improvement may not translate into a meaningful OS benefit, especially in a disease where salvage treatments are possible and quality of life matters.

Subgroup Ambiguity

Benefit in PD-L1–negative or HPV-positive subgroups remains unclear. These are substantial populations. Approving and funding treatment across the board risks overtreatment in many and benefit for few.

No Clarity on Timing

In KEYNOTE-689,[2] is the benefit coming from the neoadjuvant part, the adjuvant part, or both? While the trial succeeded overall, the individual contributions remain undefined, limiting the ability to streamline protocols.

Feasibility in the Real World

Weekly cisplatin, multiple infusions of ICI, and real-time PD-L1 testing—all increase complexity. In low- and middle-income countries, where most HNSCC cases occur, such logistics are often prohibitive. Unless simplified, these regimens will remain a luxury for the few.

No Quality-of-Life Data

Functional outcomes—swallowing, speech, and nutrition—are crucial in HNSCC, especially after multimodal treatment. None of these trials report validated quality-of-life

Table 1 Comparison of major phase III immunotherapy trials in curative-intent HNSCC

Feature	JAVELIN 100 (Avelumab)[3]	KEYNOTE-412 (Pembrolizumab)[4]	KEYNOTE-689 (Pembrolizumab)[2]	NIVOPOSTOP (Nivolumab)[1]
Phase	Phase 3	Phase 3	Phase 3	Phase 3
Setting	Locally advanced, resectable HNSCC	Locally advanced, resectable HNSCC	Locally advanced, resectable HNSCC	Resected, high-risk HNSCC
Control arm	CRT (cisplatin + RT)	CRT (cisplatin + RT)	Surgery → adjuvant RT ± cisplatin	Surgery → CRT (cisplatin + RT)
Experimental arm	CRT + avelumab (before, during, after)	CRT + pembrolizumab (during, after)	Neoadjuvant pembrolizumab → surgery → adjuvant pembrolizumab + RT ± cisplatin	CRT → adjuvant nivolumab
IO start timing	Lead-in before CRT → concurrent CRT	Start with CRT	Neoadjuvant before surgery	Adjuvant after CRT
Primary endpoint	PFS	EFS	EFS	DFS
Primary HR (95% CI)	0.81 (0.62–1.06)	0.83 (0.68–1.03)	0.73 (0.58–0.92)	0.76 (0.60–0.98)
Primary result	Did not meet primary endpoint	Did not meet primary endpoint	Met primary endpoint	Met primary endpoint
OS HR (95% CI)	0.90 (NS)	Trend favorable (immature)	0.72 (0.52–0.98)	Immature, trend favors NIVO
PD-L1 subgroup	PFS HR 0.59 (0.34–1.02)	EFS HR 0.67 (CPS $\geq$ 20)	13.7% mPR improvement (CPS $\geq$ 10)	No clear differential by CPS
Biomarker enrichment	No	No	Stratified CPS $\geq$ 10	No
Safety	Higher immune AEs	Higher immune AEs	Manageable, consistent	Favorable, fewer grade $\geq$ 3 TRAEs
Trial status	Stopped early (futility)	Completed (failed)	Completed (positive)	Completed (positive)
Publication year	2021	2023	2025	2025
Main summary	Poor timing, no biomarker	Tight alpha, poor timing	Smarter timing, EFS success	First positive adjuvant IO trial in HNSCC

Abbreviations: AE, adverse event; CI, confidence interval; CPS, combined positive score; CRT, chemoradiotherapy; DFS, disease-free survival; EFS, event-free survival; HNSCC, head and neck squamous cell carcinoma; HR, hazard ratio; IO, immuno-oncology; mPR, major pathologic response; NS, not significant; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; RT, radiotherapy; TRAE, treatment-related adverse event.

Table 2 Failed immunotherapy trials in curative HNSCC

Trial name	*N* (patients)	Arms	EFS/DFS/PFS	OS	Remarks
REACH (cisplatin-fit group)[5]	~300	CRT + durvalumab vs. CRT alone	HR 1.27 (PFS)	Not reported	Durvalumab added to CRT in cisplatin-fit patients showed worse outcomes (HR 1.27), raising concerns about ICI synergy with concurrent chemoradiation
PembroRad[6]	133	RT + pembrolizumab vs. RT + cetuximab	HR 1.05 (PFS)	Not reported	Replacing cetuximab with pembrolizumab in RT for cisplatin-ineligible patients did not improve outcomes, highlighting limited efficacy of ICIs in this context
IMvoke010[7]	682	Postop RT + atezolizumab vs. RT alone	HR 0.94 (DFS)	Not reported	Adjuvant atezolizumab post-surgery and RT did not improve DFS. The trial failed to demonstrate added benefit in a setting theoretically favorable for immunotherapy
NRG-HN004[8]	251	RT + durvalumab vs. RT alone (cis-unfit)	HR 1.33 (PFS)	Not reported	Durvalumab added to RT in cisplatin-unfit patients resulted in worse outcomes (HR 1.33), reinforcing the challenge of integrating ICIs in frail populations

Abbreviations: CRT, chemoradiotherapy; DFS, disease-free survival; EFS, event-free survival; HNSCC, head and neck squamous cell carcinoma; HR, hazard ratio; ICI, immune checkpoint inhibitor; OS, overall survival; PFS, progression-free survival; RT, radiotherapy.

outcomes, which undermines the relevance of their clinical gains.

The Way Forward—Smarter, not Just More Trials

As we plan the next wave of studies, we must prioritize strategic designs over sheer enthusiasm. The following principles should guide future research:

- Biomarker-driven design: Trials must prospectively stratify by PD-L1 CPS, HPV status, and ideally, immune gene signatures or circulating tumor deoxyribonucleic acid.
- Minimal residual disease (MRD): Leveraging MRD or pathologic response to guide adjuvant ICI could help limit overtreatment. Adaptive trial designs are sorely needed.[12]
- Deescalation and organ preservation: Could ICIs allow for reduced radiation fields or avoidance of mutilating surgery in responders? Trials must test this explicitly.

Conclusion

After a long and disappointing journey, immunotherapy has finally shown signs of life in curative HNSCC. But let us be clear: these are small, cautious steps forward—not a revolution.

The survival benefits, while statistically significant, are modest and built on surrogate endpoints. The subgroups that benefit remain murky. The real-world feasibility is questionable, particularly in resource-limited settings. And the long-term impact on quality of life—perhaps the most important outcome in this disease—is still unknown.

If we are to move forward, let it be with scientific humility and practical wisdom. Let us resist the urge to rubber-stamp another expensive, complex treatment protocol based on short-term gains. Instead, we should demand clarity on who benefits, how much, and at what cost.

Immunotherapy in curative HNSCC has earned a seat at the table. But it will take more than two trials to justify putting it at the head.

Patient's Consent

Patient consent is not required.

Conflict of Interest

None declared.

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