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# Highlights from the 2025 American Society of Clinical Oncology Annual meeting: head-and-neck cancers


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## Introduction

Head and neck squamous cell carcinoma (HNSCC) represents a heterogenous group of diseases, and remains a major global health challenge, with survival rates for locally advanced disease showing limited improvement despite multimodal therapy strategies. The American Society of Clinical Oncology (ASCO) Annual Meeting is a premier global forum for presenting cutting-edge oncology research and clinical trials that shape future standards of care. The 2025 meeting highlighted pivotal phase III studies poised to redefine treatment paradigms in head and neck oncology. NIVOPOSTOP (GORTEC 2018-01) evaluated adjuvant nivolumab in resected high-risk HNSCC, while KEYNOTE-689 established the benefit of perioperative pembrolizumab. Updated results from KEYNOTE-412 assessed pembrolizumab combined with definitive chemoradiation in unresectable disease. Furthermore, the DIAMOND trial introduced a cisplatin-sparing immunotherapy regimen for nasopharyngeal carcinoma (NPC), aiming to maintain efficacy while reducing toxicity.

This review critically examines the latest phase III evidence supporting immune checkpoint inhibition in curative settings for HNSCC and emerging de-escalation approaches in NPC.

## HNSCC

The integration of immune checkpoint inhibitors into the management of HNSCC is well established in the recurrent/metastatic setting. In first line, for tumors with programmed death-ligand 1 (PD-L1) combined positive score (CPS) ≥ 1, this approach is supported by the results of the KEYNOTE-048 trial, which led to the approval of pembrolizumab based on improved overall survival[1-4]. Nivolumab has also been approved for platinum-resistant disease following the results of the CHECKMATE-141 trial[5]. However, translating these benefits to earlier-stage disease has been challenging. Several phase III trials have failed to demonstrate statistically significant improvements in their primary endpoints, tempering the initial optimism surrounding immunotherapy in the curative setting[6-8].

The integration of immunotherapy in curative-intent settings is supported by the immunomodulatory effects of radiotherapy (RT), which promotes immunogenic cell death and the release of damage-associated molecular patterns, modulation of the tumor microenvironment, enhancing antigen presentation and dendritic cells activation and maturation[9]. In some cases, RT may induce systemic antitumor effects (abscopal responses)[9].

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However, RT also triggers immunosuppressive mechanisms, including PD-L1 upregulation, Treg expansion, lymphopenia, and impaired immune priming due to lymph node irradiation[9]. These opposing effects highlight both the promise and complexity of combining RT with immune checkpoint blockade in curative settings.

## Resectable HNSCC

In resectable HNSCC, the standard adjuvant treatment–RT with or without cisplatin–has remained unchanged for over two decades[4,10]. This approach is based on a pooled analysis of two pivotal phase III trials (EORTC 22931 and RTOG 9501), which identified extracapsular extension (ECE) and positive margins as key pathological risk factors warranting the addition of high-dose cisplatin (100 mg/m$^2$ every 3 weeks) to RT[11].

### Nivopostop trial (Gortec 2018-01)[12]

Phase III trial that enrolled 680 patients with resected, high-risk locally advanced HNSCC, randomizing them to receive either standard adjuvant chemo RT (CRT) or CRT combined with nivolumab. Eligible patients had high-risk features, including ECE, positive/close margins, ≥ 4 involved lymph nodes (without ECE), or multiple perineural invasions. With median follow-up of 30.3 months, the trial met its primary endpoint, showing improved 3-year disease-free survival (63.1% vs. 52.5%, hazard ratio [HR] 0.76), driven mainly by reduced locoregional recurrence. Distant metastasis rates were similar between arms. Treatment compliance was high. Acute toxicity was comparable, though the nivolumab arm had a modest increase in grade 4 toxicities (mainly renal disorder and dysphagia) without increased mortality. Overall survival data remain immature but suggest a numerical benefit with nivolumab.

### Keynote-689[13]

This phase III trial investigated perioperative pembrolizumab in 714 patients with resectable, locally advanced HNSCC. Patients were randomized to standard of care (SOC) surgery followed by risk-adapted adjuvant RT ± high-dose cisplatin, or an experimental arm receiving two cycles of neoadjuvant pembrolizumab, surgery, then three cycles of adjuvant pembrolizumab with RT ± cisplatin (according to pathological risk-factors), followed by up to 12 maintenance pembrolizumab cycles. At a median follow-up of 38.3 months, the primary endpoint of event-free survival (EFS) was significantly improved in the pembrolizumab arm (modified EFS [mEFS] 51.8 vs. 30.4 months, HR 0.73). Subgroup analyses showed consistent benefits in PD-L1 CPS ≥ 10 (mEFS 59.7 vs. 26.9 months, HR 0.66) and CPS ≥1 (mEFS 59.7 vs. 29.6 months, HR 0.70). Major pathologic response rates with pembrolizumab were 9.4% overall and 13.7% in patients with CPS ≥ 10. Pathologic complete response rates were 3.0% and 4.3%, respectively. Distant metastasis free survival (DMFS) favored the pembrolizumab arm (metastatic DMFS [mDMFS] 51.8 vs. 35.7 months, HR 0.71), while locoregional failure rates were similar.

### Discussion and clinical impact

The 2025 ASCO Annual Meeting spotlighted the evolving role of immunotherapy in resectable, locally advanced HNSCC, with pivotal data from the NIVOPOSTOP and KEYNOTE-689 trials. Despite differences in trial design, both studies were positive and demonstrated meaningful improvements in recurrence outcomes beyond standard trimodal therapy (Table 1).

In KEYNOTE-689, neoadjuvant pembrolizumab may raise concerns about pre-operative disease progression (12.4% vs. 1.2%) and surgical timing. Although surgery and adjuvant therapy completion rates were comparable, the longer neoadjuvant interval may pose risks for rapidly growing tumors. NIVOPOSTOP, in contrast, focused only on adjuvant nivolumab post-CRT, showing reduced locoregional recurrence, possibly favoring tumors with aggressive local behavior. Biomarker analyses revealed limited pathologic responses in PD-L1-negative tumors, casting doubt on the predictive value of CPS < 1 in the early-stage setting, although this group is underrepresented in KYENOTE-689 (3.8%) and NIVOPOSTOP (3.5%). Notably, pembrolizumab reduced the proportion of patients with high-risk pathology (11.9% lower in the pembrolizumab group) and subsequent adjuvant cisplatin use (11.6% fewer patients receiving adjuvant cisplatin), hinting at possible risk de-escalation benefits, though the long-term impact remains unproven. Overall, these findings support integrating immunotherapy into curative-intent strategies as new SOC, though optimal timing, patient selection, and long-term efficacy continue to warrant investigation.

**Table 1.** Trial characteristics

| Trial | Combination | Treatment | Eligibility criteria | Risk population | Efficacy results |
|---|---|---|---|---|---|
| NIVOPOSTOP[12] (n = 680) Primary endpoint: DFS | Adjuvant | Nivolumab 1 cycle<br>Nivolumab 3/3 w 3 cycles + cisplatin + RT 66 Gy<br>Nivolumab 4/4 w 6 cycles | Larynx/hypopharynx/ oropharynx/oral cavity with:<br>Complete ressection<br>pStage III or IVA (II if HPV + oropharynx + T3/T4 + ≥ 20 UMA)<br>High-risk pathological features of relapse<br>Extracapsular extension<br>Positive margins (R1 or close margins ≤ M1 mm)<br>≥ 4 positive cervical nodal involvements (without ECE)<br>Multiple peri-neural invasion | High pathological risk.<br>Intermedial pathological risk (10.5%) | ITT<br>3-year DFS 63.1% versus 52.5% (HR 0.76)<br>PD-L1 CPS not strongly correlated with DFS, but most patients CPS > 1 (82%)<br>Decrease the locoregional recurrence (39% vs. 61%, HR 0.63)<br>Similar distant recurrence |
| Keynote-689[13] (n = 714) Primary endpoint: EFS | Neoadjuvant + adjuvant | Pembrolizumab 2 cycles<br>Surgery<br>High risk: Pembrolizumab 3/3 w 3 cycles + cisplatin + RT 66 Gy//Low risk:_ Pembrolizumab 3/3 w 3 cycles + RT 66 Gy<br>Pembrolizumab 3/3 w 12 cycles | Ressectable locally advanced<br>Larynx/hypopharynx/oral cavity III/IVA<br>Oropharyngeal p16 - III/ IVA<br>Oropharyngeal p16 + T4 N0-2 | High and intermedial clinical risk | mEFS<br>ITT - 51.8 versus 30.4 m (HR 0.73)<br>PD-L1 CPS ≥ 10 (65% of the ITT) – 59.7 versus 26.9 m (HR 0.66)<br>PD-L1 CPS ≥ 1 (96% of the ITT) – 59.7 versus 29.6 m (HR 0.70)<br>Decrease the distant recurrence (35.7 vs. 51.8 months, HR 0.71)<br>Similar locoregional recurrence. |

CPS: combined positive score; DFS: disease free survival; ECE: extracapsular extension; EFS: event-free survival; HR: hazard ratio; ITT: intention to treat population; n: number; RT: radiotherapy; w: week, mEFS: modified event-free survival; PD-L1: programmed death-ligand 1.

## *Unresectable HNSCC*

For the past two decades, definitive CRT with high-dose cisplatin has remained the SOC for patients with unresectable, locally advanced HNSCC[4,10,14]. Despite its curative intent, long-term outcomes remain suboptimal: up to 50% of patients experience locoregional recurrence, approximately 30% develop distant metastases, and 5-year overall survival hovers around 60%. These figures underscore the urgent need for novel strategies to improve durable disease control and survival in this population.

### *Keynote-412[15]*

Phase III trial evaluating the addition of pembrolizumab to definitive CRT in 804 patients with locally advanced, high-risk, unresectable HNSCC. Patients received pembrolizumab, starting one cycle before CRT, continuing during CRT, and up to 14 maintenance cycles post-CRT, or placebo. Initial 4-year analysis showed no significant benefit[8]. However, updated data with 74.4 months median follow-up revealed a significant improvement in EFS (mEFS 71.8 vs. 49.8 months, HR 0.79). The primary benefit was in DMFS (mDMFS NR vs. 64.3 months, HR 0.80). Median OS was not reached (NR) in either arm, with curve separation after year 3 (60-month OS 64.4% vs. 59.8%). Subgroup analyses showed greater benefit in PD-L1 positive tumors: for CPS ≥ 1, mEFS 70.9 versus 48.3 months (HR 0.80), mOS NR versus NR (HR 0.84); for CPS ≥ 20, mEFS NR versus 65.9 months (HR 0.70), mOS NR versus NR (HR 0.73).

### *Discussion and clinical impact*

Although early analyses were negative, the extended data suggests a clinically meaningful long-term benefit, with an absolute improvement of 7.5% in 5-year EFS, along with improved DMFS in the pembrolizumab arm, supporting a role in enhanced systemic disease

**Table 2.** Summary of phase III clinical trials investigating the addition of immunotherapy to locally advanced NPC treatment

| Trial | Combination | Experimental arm | Eligibility criteria | Primary endpoint | Preliminary results |
|---|---|---|---|---|---|
| Beacon[19] (n = 450) | Induction + adjuvant | Tislelizumab + IC 3 cycles CCRT Tislelizumab 8 cycles | III-VA (except T3N0, or T3N1 with retropharyngeal positive lymph nodes) | CCR after induction therapy 3-year PFS | CCR 30.5% versus 16.7% (p < 0.001) ORR 93.3% versus 90.7% |
| Dipper[20] (n = 450) | Adjuvant | CCRT -> camrelizumab 12 cycles | III-IVA (T4N1 or T1-4N2-3) | 3-year EFS | 3-year EFS: 86.9% versus 77.4% (HR 0.61) |
| Continuum[18] (n = 425) | Full course | Sintilimab + IC 3 cycles -> Sintilimab 3 cycles + CCRT Sintilimab 6 cycles | III-IVA (except T3-4N0 or T3N1) | 3-years EFS | 3-year EFS: 86.1% versus 76.0% (HR 0.59) 3-year OS: 92.8% versus 92.9% (HR 0.95) |

CCR: clinical complete response; CCRT: concomitant chemoradiotherapy; EFS: event free survival; HR: hazard ratio; IC: induction chemotherapy; N: number; ORR: overall response rate; PFS: progression free survival; OS: overall survival.

control. Notably, OS curves separated late, potentially due to the high proportion of human papillomavirus -positive tumors (26.5%) and stage III disease (34.5%), both associated with more favorable prognoses. The benefit was more pronounced in patients with higher PD-L1 expression, especially those with a CPS ≥ 20. These findings reinforce the relevance of PD-L1 as a potential predictive biomarker and underscore the importance of long-term follow-up to fully capture the therapeutic impact of immunotherapy in this setting.

## NPC

The SOC for locally advanced NPC in Western guidelines involves induction chemotherapy with gemcitabine and cisplatin, followed by high-dose cisplatin-based concurrent CRT, but this regimen is associated with considerable toxicity[10,16,17]. In endemic regions, emerging phase III data support integrating immunotherapy into the treatment paradigm. Three recent trials in China demonstrated improved 3-year EFS (from 76% to 86% in CONTINUUM trial[18]) and increased complete response rates (from 17% to 31% in BEACON trial[19]) with the addition of immune checkpoint inhibitors, irrespective of PD-L1 expression[18-20]. This shift is biologically supported, as NPC is highly immunogenic, Epstein-Barr virus (EBV)-associated, and shows high PD-L1 expression. De-escalation strategies are also under investigation. The phase II PLATINUM trial evaluated nivolumab with gemcitabine–cisplatin induction followed by RT without concurrent cisplatin, yielding 88.5% 3-year failure-free survival (FFS) with reduced grade 3-4 toxicities, highlighting a potential safer alternative[21].

### DIAMOND[22]

A phase III trial investigating a cisplatin-free strategy in locally advanced NPC, randomizing 532 patients to receive toripalimab plus induction chemotherapy (gemcitabine/cisplatin) followed by RT alone (experimental arm) or standard induction chemotherapy followed by concurrent high-dose cisplatin-based CRT (SOC arm). Toripalimab was given for 17 cycles in both arms. The trial had two co-primary endpoints: FFS (FFS; tested for non-inferiority) and the incidence of any-grade vomiting (tested for superiority). At a median follow-up of 36 months, 3-year FFS was 88.3% in the experimental arm versus 87.6% in the SOC arm, meeting the non-inferiority criterion. Vomiting of any grade was significantly lower in the experimental arm (25.6% vs. 69.0%). Grade 3-4 adverse events (AEs) (52.3% vs. 63.6%) and immune-related AEs (5.0% vs. 8.4%) were also reduced. Patient-reported quality of life was better across multiple domains, supporting this cisplatin-free approach as a less toxic alternative without compromising efficacy.

## Discussion and clinical impact

NPC is rare in Europe, with only 4,500 cases annually, representing 3.7% of global incidence, compared to over 80% of cases occurring in Asia[23]. Most phase III trials, including DIAMOND, focus on endemic populations. NPC in non-endemic regions shows greater biological heterogeneity and worse prognosis[24], raising questions about applying DIAMOND's cisplatin-free immunotherapy results to Western patients. Despite this, most tumors in Europe are EBV-positive

and exhibit high PD-L1 expression along with prominent lymphocytic infiltration, supporting the use of immunotherapy[25]. DIAMOND suggests a promising, less toxic treatment approach, but longer follow-up and validation, ideally in non-endemic settings, are needed before broader European adoption.

## Conclusion

The 2025 ASCO Annual Meeting marked a pivotal moment in head and neck oncology, reinforcing the expanding role of immunotherapy in curative-intent treatment. Phase III data support the integration of immune checkpoint inhibitors in resectable HNSCC–and potentially in unresectable cases–with sustained benefits. In NPC, immunotherapy-based de-escalation strategies show promise in preserving efficacy while minimizing treatment-related toxicity. Collectively, these findings reflect a move toward more personalized and less toxic curative approaches, highlighting the need for continued research and thoughtful clinical implementation.

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