TURKISH JOURNAL of ONCOLOGY

Turk J Oncol 2025;40(Supp 1):53–65
doi: 10.5505/tjo.2025.6

REVIEW

Radiotherapy and Immunotherapy Combinations in Head and Neck Cancers: Clinical Perspectives from Radiation Oncology

Pantea BAYATFARD,[1,2] Sümerya Duru BİRGİ[2]

[1]Department of Radiation Oncology, Onkomer Oncology Center, İzmir-*Türkiye*
[2]Department of Radiation Oncology, Ankara University Faculty of Medicine, Ankara-*Türkiye*

SUMMARY

Head and Neck Squamous Cell Carcinoma (HNSCC) is a significant global health concern, and while traditional treatments have advanced, prognosis for advanced-stage disease remains poor due to challenges like treatment resistance. Immunotherapy (IO), particularly immune checkpoint inhibitors (ICIs), has revolutionized cancer treatment, showing promising results, especially in recurrent/metastatic settings. Given that radiotherapy (RT) is a standard treatment for HNSCC, there is intense interest in combining RT with IO to enhance therapeutic efficacy and overcome resistance. This review offers a summary of current evidence regarding the integration of RT and IO in the management of HNSCC from radiation oncology perspective. It underscores the potential benefits of combining these modalities, including enhanced tumor response, improved survival outcomes, and the possibility of reduced treatment-related toxicity. In addition, the review addresses key challenges in redefining the standard of care, emphasizing the need for further research to optimize treatment sequencing, and identify the patient subgroups most likely to benefit from combined approaches.

Keywords: Head and neck cancers; immunotherapy; radiotherapy.

INTRODUCTION

Head and neck squamous cell carcinomas (HNSCC) remain a major global health burden, accounting for over 700,000 new diagnoses and approximately 350,000 deaths each year worldwide.[1] Historically, the management of HNSCC has involved various combinations of chemotherapy (ChT) and radiotherapy (RT), depending on disease stage and patient characteristics. For patients with locoregionally advanced HNSCC, the standard of care includes either definitive chemoradiotherapy (CRT) or surgical resection followed by adjuvant RT, with or without ChT.[2] Despite established treatment techniques approximately 50% of locally advanced HNSCC cases recur within the first two years.[3] However, in recurrent or metastatic settings, treatment strategies have expanded to include immunotherapy (IO) and other targeted approaches guided by prior therapies.

In recent decades, IO has emerged as a transformative approach in oncology by enhancing the immune system's ability to detect and eliminate cancer cells. Although tumor antigens can be recognized by immune cells, malignant cells often evade immune surveillance by creating an immunosuppressive tumor microenvironment (TME) that disrupts effective T-cell responses.[4]

IO primarily targets immune checkpoints such as the Programmed Cell Death Protein 1 (PD-1)/Programmed Cell Death Ligand-1 (PD-L1) axis and Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4). Blocking these checkpoints helps reverse immune suppression, allowing T

Accessible online at:
www.onkder.org

Dr. Sümerya Duru BİRGİ
Ankara Üniversitesi Tıp Fakültesi,
Radyasyon Onkolojisi Anabilim Dalı,
Ankara-Türkiye
E-mail: sumeryadurubirgi@gmail.com

Turk J Oncol 2025;40(Supp 1):53–65
doi: 10.5505/tjo.2025.6

cells to become active again and attack cancer cells more effectively. At the same time, RT has immune-related effects, including boosting the presentation of tumor antigens and increasing the infiltration of immune cells into the tumor.[5] Given this interplay there is growing interest in combining RT with IO to overcome the immunosuppressive TME and enhance treatment response. Therefore, understanding these effects is essential to elucidate the TME and synergistic potential of combining RT and IO in the treatment of HNSCC.

TUMOR MICROENVIRONMENT OF HNSCC

The TME of HNSCC is a complex network that promotes tumor growth and evasion from immune surveillance. It consists of both cellular and non-cellular components, encompassing tumor cells, normal stromal tissue, and various immune cell populations within the surrounding milieu. Tumor cells utilize multiple mechanisms to escape the immune system, including defects in antigen presentation, downregulation of the Class I Human Leukocyte Antigen (HLA) system, or the inactivation of antigen processing.[6] In addition, the TME can strongly suppress the immune system by attracting immune-suppressive cells like regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), and M2 macrophages. These cells can induce T-cell apoptosis, impair T-cell function, and support tumor growth.[7]

Tumors also undergo a process known as immunoediting, through which less immunogenic cancer cell clones are selected over time, helping the tumor escape immune reaction. Furthermore, low levels of lymphocytes, weak natural killer (NK) cell activity, and poor function of tumor-infiltrating lymphocytes (TIL) can also contribute to disease progression and reduce patient survival.[8]

A classification system of the tumor immune microenvironment has been proposed to better predict treatment response, categorizing tumors as 'hot' or 'cold' based on the presence of tumor-associated antigens and the degree of TIL.[9] 'Hot' tumors are characterized by high levels of TIL, but these T cells are often functionally exhausted due to chronic antigen exposure and increased expression of inhibitory receptors such as PD-1. IO can help restore T-cell activity by blocking these inhibitory pathways, thereby reactivating the anti-tumor immune response. In contrast, 'cold' tumors exhibit poor TIL and an immunosuppressive TME, enriched with MDSCs and Tregs, which hinder T-cell entry and suppress immune function. Notably, RT has been shown to reprogram cold tumors into hot ones by promoting antigen release, altering the cytokine environment, and enhancing immune cell recruitment thereby potentially increasing the effectiveness of IO.[10]

The immune landscape of HNSCC is further shaped by human papillomavirus (HPV) status. HPV-positive oropharyngeal cancers generally exhibit a more immunogenic phenotype, characterized by higher CD8+ T-cell infiltration and elevated PD-L1 expression. Conversely, HPV-negative tumors, often associated with tobacco and alcohol use, tend to have a more immunosuppressive TME and may exhibit poorer responses to both RT and IO.[11]

The local cytokine environment also influences immune dynamics; immunosuppressive cytokines such as IL-10 and TGF-β are prevalent in HNSCC and can enhance Treg function, suppress antigen presentation, and inhibit effector T-cell activity.[12] Together, these factors underscore the complexity of the HNSCC immune microenvironment and the importance of integrating immune-modulatory strategies such as RT and IO for improved therapeutic outcomes.

IMMUNOMODULATORY AND IMMUNOSUPPRESSIVE EFFECT OF RADIOTHERAPY

The mechanisms underlying RT's immunomodulatory effects are diverse. First, RT-induced DNA damage can trigger both adaptive and innate immune signaling pathways. This DNA damage enhances the release and presentation of tumor antigens and promoting the activation of immune cells. Second, RT can trigger immunogenic cell death, causing the release of damage-associated molecular patterns (DAMPs), which act as 'danger signals' to the immune system and help initiate an anti-tumor response. Key DAMPs released following RT include HMGB1, ATP, and calreticulin which are proinflammatory agents that enhance the effects of both IO and RT within the TME.[13] Third, RT associated vascular damage and upregulated adhesion molecules increase lymphocyte infiltration in TME.[14] Lastly, RT can increase the expression of MHC class 1 molecules which facilitates the recognition of tumor cells by CD8+ T cells.[15] As a result, RT can enhance the effect of IO not only in irradiated site but in distant regions as well.

Despite activating the immune system, RT alone is not a sufficient treatment modality. One of the main reasons is its partially immunosuppressive effect on the TME, including the upregulation of PD-L1 expression. Although this process can weaken CD8+ T cells and

help tumors resist cell death, combining it with PD-1/PD-L1 inhibitors may turn this into an advantage by boosting the immune system's ability to kill cancer cells.[16] To optimize the immune effects of RT, factors such as dose per fraction, timing, and the choice of irradiated sites must be carefully considered. A preclinical study showed that delivering 6–12 Gy per fraction, either concurrently with PD-1/PD-L1 inhibitors or starting RT with the second cycle, resulted in the most effective tumor responses.[17]

Moreover, in the definitive treatment of HNSCC, regional lymphatic areas are routinely included in the RT field. While this approach is essential for eradicating potential micrometastatic disease, it presents an immunologic challenge, as circulating T cells are highly radiosensitive. In contrast, tumor-infiltrating T cells exhibit greater radioresistance. This disparity introduces a key concern which irradiation of elective lymphatic regions may lead to a significant depletion of functional circulating T cells, thereby diminishing the efficacy of concurrent IO and limiting the potential for a robust systemic anti-tumor immune response.[18]

Considering all these immunological mechanisms the combination of RT and IO has been actively investigated in recent years. It is first evaluated in metastatic disease and widen to neoadjuvant, definitive and adjuvant settings.

NEOADJUVANT IMMUNOTHERAPY BEFORE SURGERY OR DEFINITIVE RADIOTHERAPY

Neoadjuvant IO, which is administered before primary treatment like surgery or RT, represents a significant area of investigation in the management of HNSCC. The rationale behind this approach is having the advantage of treating the tumor when it is still intact, allowing it to prime a more robust anti-tumor immune response.[19] Preclinical models also support that neoadjuvant IO is more effective in inducing anti-tumor immunologic memory responses compared to postoperative IO.[20] This approach can lead to pathologic responses within the tumor area, including tumor necrosis, and can result in clinical to pathological downstaging of the malignancy. By achieving significant tumor regression, neoadjuvant IO may potentially allow for less extensive surgery and de-escalation or even omission of subsequent adjuvant therapies like RT or CRT, thereby reducing morbidity and improving quality of life.[21] Remarkable trials evaluating neoadjuvant IO use are summarized in Table 1.

Anti-PD-1 antibodies such as nivolumab and pembrolizumab are central to these investigations. Initial phase II trials with neoadjuvant pembrolizumab have shown promising results in resectable HNSCC, demonstrating pathologic responses and clinical downstaging with a good safety profile and no delays to planned surgery.[22] Pathologic complete response (pCR) rates with monotherapy have been modest and major pathologic response (mPR) rates range from 6% to 17%.[22,23] In contrast, combination regimens involving dual IO agents have yielded higher mPR rates. [20–25%) compared to monotherapy.[24,25] Building in this concept, the phase II trial by Zinner et al.,[26] patients with resectable HNSCC received neoadjuvant nivolumab plus weekly carboplatin and paclitaxel. Although adjuvant RT or CRT was recommended, 25% of patients did not receive it. The study reported a 73% mPR and 45% pCR at the primary site which is higher compared to monotherapy. An unplanned analysis revealed that those patients who skipped RT/CRT had poorer OS and PFS, indicating, the need for further trials to de-escalate RT in adjuvant setting.

Since the main reason of combining IO in neoadjuvant setting is immune priming, stereotactic body radiation therapy (SBRT) doses (≥6 Gy per fraction) are known to be more effective than conventional doses (1.8 Gy-2 Gy). The Neoadjuvant Immuno-Radiotherapy Trial (NIRT-HNC; NCT03247712) is a phase Ib study that investigated neoadjuvant SBRT delivered to the gross tumor volume in combination with nivolumab prior to surgery. This trial was well-tolerated, resulted in a high rate of mPR (86%) and pCR (67%), and achieved clinical to pathological downstaging in 90% of patients without delaying surgery. The modest grade 3 toxicity observed in NIRT compared to conventional CRT suggests a potential for improved quality of life. [27] Another phase Ib/II trial on HPV+ oropharyngeal cancer investigated neoadjuvant durvalumab and tremelimumab with concurrent SBRT to the primary tumor and involved nodes only, followed by transoral robotic surgery (TORS) and adjuvant durvalumab.[28] In this cohort, surgery was performed a median of 46 days after SBRT. Clinical-to-pathologic downstaging was observed in 95%, with a 47% pCR. Among non-pCR cases, 80% showed treatment effect, and 5% had occult nodal disease undetected preoperatively.

Studies on neoadjuvant IO use have shown a correlation between PD-L1 expression/CPS scores with pathological treatment response.[22,28] However, research on combining RT with IO has generally not found a significant correlation between baseline tu-

Turk J Oncol 2025;40(Supp 1):53–65
doi: 10.5505/tjo.2025.6

Table 1 Summary of trials designed to combine IO in neoadjuvant setting

Trial	Phase	Year	Patient number	Intervention	Primary outcome	Outcomes
NIRT-HNC (NCT03247712) [27]	Ib	2020	21	SBRT (40 Gy/5 fx or 24 Gy/3 fx) ± nivo 5 weeks later → surgery+ adjuvant nivo	pCR	Well-tolerated, 86% mPR, 67% pCR, 90% downstaging
Uppaluri et al.[22]	II	2021	36	Pembro x 1-2 → 2-3 weeks later → surgery + adjuvant RT ± cis	pCR (defined as ≥50% tumor necrosis)	22% pCR, 16.7% 1-year relapse rates in high risk patients
IMCISION trial (NCT03003637) [25]	Ib/II	2020	32	Nivo ± ipili before surgery	Feasibility to resect no later than week 6 & pCR	No delay to surgery, 33% Grade 3-4 irAEs in nivo mono, 38% Grade 3-4 irAE in combo, 35% mPR with combo, 0% pCR in mono, 4% pCR with combo, no recurrence at 24 mo
Schoenfeld et al.[24]	II	2020	29 oral cavity SCC patients	Nivo vs nivo + ipi → surgery after cycle 2	mPR	No surgical delay, 14% grade 3-4 irAE in nivo mono, 33% grade 3-4 irAE in combo, 20% mPR in combo 8% mPR in mono
Ma et al.[28] (NCT03618134)	Ib/II	2022	19 HPV+ oropharyngeal patients	Durva ± tremelimumab + SBRT → TORS + neck dissection + adjuvant durva	Safety/efficacy for the phase Ib, 2-year PFS for the phase II portion	95% downstaging, 47% pCR 26% locoregional recurrence

SBRT: Stereotactic body radiotherapy; fx: Fraction; nivo: Nivolumab; pCR: Pathologic complete response; mPR: Major pathologic response; Pembro: Pembrolizumab; RT: Radiotherapy; cis: Cisplatin; ipi: Ipilimumab; irAEs: Immune related adverse effects; mo: Months; durva: Durvalumab

mor PD-L1 levels or CPS and pCR or tumor recurrence. Highlighting the potentially reduced importance of PD-L1 levels when IO is administering prior to RT. In light of all these studies, the use of neoadjuvant IO is one of the approaches that has not yet gained standardization but continues to be investigated. Several ongoing clinical trials are investigating novel IO and combined modality treatments in neoadjuvant setting. Phase III studies such as KEYNOTE-689 (NCT03765918) and IMSTAR-HN (NCT03700905) evaluate neoadjuvant pembrolizumab or nivolumab combined with surgery and standard CRT, focusing on endpoints like mPR, event -free survival (EFS), and disease-free survival (DFS). Multiple Phase II trials are assessing the safety and efficacy of IO (e.g., pembrolizumab, nivolumab, atezolizumab, cemiplimab, camrelizumab) alone or with RT, often exploring biomarker-guided approaches and deintensification strategies.

COMBINATION OF IMMUNOTHERAPY WITH DEFINITIVE CHEMORADIOTHERAPY

In definitive treatment of locally advanced HNSCC, concomitant CRT is the mainstay treatment modality. Cisplatin, administered either as 100 mg/m² every three weeks or 40 mg/m² weekly, remains the primary concurrent agent. For patients ineligible for cisplatin, alternatives such as carboplatin with or without 5-fluorouracil, paclitaxel, or cetuximab are commonly used.[29] The addition of IO to definitive CRT has produced mixed and often disappointing outcomes in large-scale clinical trials. Several phase III studies evaluating the concurrent use of IO with standard CRT in this setting have demonstrated limited or no clinical benefit.[30] Remarkable studies evaluating the addition of IO are summarized in Table 2 briefly.

Previous historical trials have showed that concomitant cetuximab with RT was inferior compared to concomitant cisplatin.[31] As a result, IO agents like durvalumab and pembrolizumab were tested with RT in patients ineligible for cisplatin, hoping for better outcomes than cetuximab. However, none outperformed it—even the combination of cetuximab and avelumab failed to show improvement in survival parameters.[32–34]

Table 2 Summary of trial designed in definitive setting

Trial	Phase	Year	Patient number	Population	Intervention	Primary outcome	Outcomes	Serious irAEs
JAVELIN HN 100 [35]	III	2016–2019	697	Previously untreated, locally advanced squamous cell carcinoma of the oropharynx, hypopharynx, larynx, or oral cavity	Avel + SOC vs Placebo + SOC	PFS	Avel (NR; 95% CI=16.9 mos.: NR) vs. Placebo (NR; 95% CI=23 mos.: NR); HR=1.21; p=0.92	Avel (36%) Placebo (32%)
KEYNOTE-412 [36]	III	2017–2019	804	Previously untreated, locally advanced squamous cell carcinoma of the oropharynx, hypopharynx, larynx, or oral cavity	Pembro + SOC vs Placebo + SOC	EFS (months)	Pembro (NR; 95% CI=44.7-NR) vs. Placebo (46.6; 95% CI=27.5-NR); HR=0.83; p=0.0429 (significance threshold p≤0.024)	Pembro (92.2%) Placebo (88.4%)
REACH [32]	III	2017–2018	82	Previously untreated, locally advanced squamous cell carcinoma of the oropharynx, hypopharynx, larynx, or oral cavity	Cisplatin Eligible: Avel + Cetux + RT vs Cis + RT Cisplatin Ineligible: Avel + Cetux + RT vs Cetux + RT	2 year PFS	Cisplatin Ineligible: Avel + Cetux + RT (44%; 95% CI=35-53%) vs. Cetux + RT (31%; 95% CI=23-40%); HR=0.83; p=0.34	N/A
PEMBRORAD [33]	II	2016–2017	133	Previously untreated, locally advanced squamous cell carcinoma of the oropharynx, hypopharynx, larynx, or oral cavity	Cetux+RT vs Pembro+RT	15-month LRC	Cetux+RT (59%; CI=45-72%) vs. Pembro+RT (60%; 95% CI=46-72%); p=0.91	Cetux (92%) Pembro (74%)
NRG-HN004 [34]	II/III	2019–2021	186	Previously untreated, locally advanced squamous cell carcinoma of the oropharynx, hypopharynx, larynx, or oral cavity	Durva+RT vs Cetux+RT	2 year PFS	Durva+RT (50.6%; 95% CI=41.5-59.8%) vs. Cetux+RT (63.7%; 95% CI=51.3-76.1%); HR=1.33; p=0.89	Durva (69%) Cetux (79%)
CONTINUUM [46]	III	2018–2020	425	Locally advanced nasopharyngeal carcinoma (Stage III/IVA)	Induction Gem + Cis → Cis + RT vs Gem + Cis + Sint → Cis + Sint + RT → Sint	36 month EFS	Gem + Cis → Cis + RT (76%;95% CI=70-81%) vs.Gem + Cis + Sint → Cis + Sint + RT → Sint (86%; 95% CI=81-90%); HR=0.59 (0.39-0.92); p=0.019	65%
NRG-HN005 [47]	II/III	2019–2023	382	Non-Smoking p16+ Oropharyngeal Cancer (T1-2N1M0 or T3N0-N1M0)	Cis+RT vs Cis + Dose Reduced RT (60 Gy) vs Nivo + Dose Reduced RT (60 Gy)	2 year PFS	Cis+RT (98.1%; 95% CI=95.4-100%) vs. Cis+Dose Reduced RT (88.6%; 95% CI=82.4-94.7%) vs. Dose Reduced RT + Nivo (90.3%; CI=84.5-96.1%); HR=4.34 and 5.51 for arm two and three, respectively	N/A

NR: Not reached; SOC: Standard of care; HR: Hazard ratio; PFS: Progression-Free Survival; LRC: Locoregional control; EFS: Event-Free Survival; irAEs: Immune-related adverse events; CI: Confidence interval; Gem: Gemcitabine; Cis: Cisplatin; Sint: Sintilimab; Pembro: Pembrolizumab; Avel: Avelumab; Cetux: Cetuximab; RT: Radiotherapy; Durva: Durvalumab; Nivo: Nivolumab; N/A: not achieved

Turk J Oncol 2025;40(Supp 1):53–65
doi: 10.5505/tjo.2025.6

JAVELIN HN 100 is one of the major trials conducted to evaluate the addition of Avelumab, a novel PDL1 blockade.[35] Patients were randomly assigned in a 1:1 ratio with stratification based on HPV status, tumor stage, and nodal stage. Patients received either 10 mg/kg of avelumab intravenously every two weeks in combination with CRT (consisting of 100 mg/m² cisplatin every three weeks and RT delivering 70 Gy in 35 fractions over 7 weeks) or placebo alongside the same CRT regimen. Treatment began with a dose of avelumab, or placebo (10 mg/kg) administered 7 days prior to CRT, followed by maintenance therapy with avelumab or placebo every two weeks for up to 12 months. The study was terminated prematurely due to futility, as it failed to demonstrate an improvement in PFS over placebo arm. A non-significant trend towards improved outcomes was observed in patients with ≥25% PD-L1 expression. No statistically significant differences were observed in the incidence of grade 3–5 treatment-related adverse events between the avelumab and placebo arms.

A second attempt to push the boundaries came with the KEYNOTE-412 trial, testing pembrolizumab in high risk locally advanced HNSCC alongside standard treatment—mirroring the JAVELIN design accept pembrolizumab initiated concomitant with CRT. While it hinted at better EFS (HR 0.83, p=0.0429), the trial missed its primary endpoint. Adverse events were comparable between arms, and 3-year OS was nearly the same (72% vs. 70%). Subgroup analyses, including CPS ≥20, showed encouraging trends in EFS (12.6% improvement) and OS (10.2% improvement), but none reached significance marking another negative but promising trial.[36]

In summary, IO has not improved outcomes when added to standard treatments whether RT alone, with cisplatin, or with cetuximab. Despite being well tolerated and not disrupting curative therapy, the reasons behind these negative results remain unclear. One key limitation is the irradiation of elective lymphatic regions, which leads to lymphopenia and may counteract the immune system's effectiveness.[37] Moreover, the timing and sequencing of RT and IO, variations in RT dose and fractionation, and inadequate patient selection without evaluating PD-L1 status might be possible factors contributing to the negative outcomes.[30]

ADJUVANT IMMUNOTHERAPY FOLLOWING CURATIVE RADIOTHERAPY OR SURGERY

The use of IO in the adjuvant setting is also rationalized by their potential to improve distant control of the disease. However, a significant consideration in the postoperative adjuvant setting is that the removal of regional lymph nodes in surgery. This could potentially hinder the efficacy of immunoradiotherapy.[30]

Some remarkable trials are summarized in Table 3 as well. Early-phase trials of neoadjuvant and concurrent pembrolizumab regimens showed encouraging pathological responses with acceptable safety profiles. Nonetheless, recent phase III trials in the adjuvant setting have produced negative or inconclusive outcomes.[38] One such study is the phase III, double-blind, randomized IMvoke010 trial, which is evaluating adjuvant atezolizumab in patients with locally advanced HNSCC following definitive local treatment. In this study patients in stage III HPV-positive or stage IVa/IVb HPV-negative disease were randomized to receive atezolizumab or placebo for 12 months. Preliminary results have shown only modest differences in EFS between groups (67.4% vs. 63.8%) but definitive conclusions await full data maturity.

Recently, the phase III NIVOPOSTOP trial was the first study in over 20 years to show superiority over CRT alone in this setting. Here, the addition of nivolumab to CRT in resected, high-risk locally advanced HNSCC have been evaluated. Patients received either standard CRT (66 Gy RT and 3 cycles of cisplatin) or CRT plus nivolumab. With a median follow-up of 30.3 months, adjuvant nivolumab significantly improved 3-year disease-free survival (63.1% vs. 52.5%; HR 0.76; p=0.034). CRT compliance was similar in both groups, though grade 4 side effects were more common with nivolumab (13.1% vs. 5.6%). Overall survival data are still pending.[39]

IMMUNOTHERAPY IN METASTATIC AND RECURRENT DISEASE

First attempts for combining IO with RT in HNSCC have begun with recurrent/metastatic stage. The prognosis for recurrent/metastatic HNSCC has remained poor, with median OS ranging from 7 to 10 months, and second-line treatment options typically yielding response rates under 20%.[19] KEYNOTE-040 and CheckMate 141 trials are key studies on IO in recurrent/metastatic HNSCC.[40,41] KEYNOTE-040 showed pembrolizumab improved median OS to 8.4 months versus 6.9 months with standard therapy, with a higher response rate (14.6% vs. 10.1%) and lower grade ≥3 toxicity (13% vs. 36%). CheckMate 141 demonstrated nivolumab increased median survival to 7.5 months versus 5.1 months and reduced grade 3/4 adverse events (16.3% vs. 36%). These results supported FDA approval of pembrolizumab and

Table 3 Summary of trials evaluated using IO in adjuvant setting

Trial	Phase	Year	Patient number	Population	Intervention	Primary outcome	Outcomes
Wise-Draper et al.[23]	II	2016–2020	92	High-risk HPV-negative locally advanced HNSCC	Neoadjuvant/adjuvant pembro (single dose before surgery + adjuvant RT or CRT)	1year DFS and pathological response	1-year DFS 97% in the intermediate-risk group and 66% in the high-risk group; Pathological response in 47%; Acceptable safety
NRG-HN003 [38]	I	2021	34	Resected HPV-negative HNSCC with positive margins or ENE	Pembro q3w x8 starting before adjuvant CRT	Defining dose limiting toxicities	Rare irAE
HNSCC 15-132 [48]	II	2016–2021	80	Curative CRT candidates	Seq vs. concurrent pembro + CRT	1-year LRC>40%, PFS ≥60%, Dose limiting toxicity rate ≤20% and OS	LRC: Seq (96%) vs. Concurrent (64%) HR=0.11 (95% CI, 0.01 to 0.89); p=0.012) PFS: Seq (69%) vs. concurrent (49%) HR=0.55 (95% CI, 0.25 to 1.22); p=0.132 OS: Seq (83%) vs. Concurrent (71%) HR=0.51 (95% CI, 0.19 to 1.37); p=0.17
IMvoke010 [49]	III	2018–2020	406	Post-surgery and/or CRT in locally advanced HNSCC	Adjuvant atezo vs placebo	EFS	No statistical difference in EFS or OS; TRAE: 27.2% vs 21.2%

HPV: human papilloma virus; HNSCC: head and neck squamous cell carcinoma; Pembro: Pembrolizumab; TIL:tumor infiltrating lymphocyte; riAE: immune related adverse effect; ENE: extranodal extension; CRT: chemoradiotherapy; Atezo: atezolizumab; Seq: sequential; OS: overall survival; LRC: Locoregional control; EFS: Event-Free Survival

nivolumab in 2016. While the response rates for these IO remain moderate, they have demonstrated an ability to improve OS up to15 months compared to standard therapies.[42]

There are several trails investigating the IO and ChT combinations in recurrent/metastatic stages but data about effectiveness of combining RT remains limited. A phase II trial in metastatic HNSCC comparing nivolumab alone with nivolumab plus SBRT indicated no clinical benefit in the group receiving both IO and RT, with the highest objective response rate observed in the IO-alone group. This specific trial did not demonstrate a clear benefit from adding SBRT in the recurrent/metastatic setting.[43] However, in this trial SBRT was applied to only one metastatic lesion and aimed to perform an abscopal effect with SBRT and did not show any benefit. But as shown previously, treating all metastatic sites improves PFS and OS in patients with 1–5 metastatic lesions.[44] In the light of this trial, PembroMetaRT (NCT04747054) phase III trial has designed and investigating the addition of SBRT (54 Gy/8 fractions) to first-line pembrolizumab (with or without ChT) in recurrent/metastatic HNSCC. Further trials are waited for scrutinizing the effect of combined therapies.

TOXICITY OF IMMUNOTHERAPY AND RADIOTHERAPY COMBINATIONS

Common immune-related adverse events (irAEs) in HNSCC include mucositis, dermatitis, pneumonitis and thyroid dysfunction. The incidence of irAEs is generally higher in combination therapies compared to monotherapy. Many published trials combining RT and IO have not reported substantially increased normal tissue toxicity. However, caution must be taken for severe irAEs, particularly when RT is delivered to near organs like bladder, bowel, or in the lung. Grade 3–4 lymphopenia has been a notable adverse event in

Turk J Oncol 2025;40(Supp 1):53–65
doi: 10.5505/tjo.2025.6

Table 4 Ongoing clinical trials for HNSCC combining IO

Trial neoadjuvant and adjuvant settings	Phase	Intervention	Primary endpoint	Status	Estimated completion
KEYNOTE-689 (NCT03765918)	III	Neoadjuvant pembro x2+ surgical resection + SOC adjuvant RT ± cis + adjuvant pembro x15 vs. Surgical resection + SOC adjuvant RT ± cis	mPR, EFS	Recruiting	7/2026
IMSTAR-HN (NCT03700905)	III	Neoadjuvant nivo x1 + surgery + PO(C)RT+ adjuvant nivo (6 months) ± vs. surgical resection + PO(C)RT only	DFS	Patient enrollment completedresults awaited	5/2024
NIVOSTOP (NCT03576417)	III	Surgical resection → PO(C)RT + concurrent and adjuvant nivo vs. Surgical resection → PO(C)RT (cisplatin) only	DFS	Recruiting	9/2027
NCT02841748 (PATHWay)	II	Adjuvant pembro vs. placebo	PFS	Recruiting	Not specified
NCT03708224	II	Neoadjuvant atezo x1 ± tocilizumab, followed by surgery + risk-adapted PO(C)RT, followed by adjuvant atezo x12	Complete resection rate; Proportion of subjects with ≥40% increase of CD3+ T cells	Active, recruiting	Not specified
NCT04405154	II	Standard-of-care chemoradiation therapy + neoadjuvant and concomitant camrelizumab x8	Objective response rate	Not yet recruiting	Not specified
IMMUNEBOOST (NCT03838263)	II	Induction nivo + SOC (IMRT + cisplatin) vs. SOC	Feasibility (primary endpoint not reached due to toxicity); PFS and OS results pending	Ongoing	Not specified
MINIMA (NCT04988074)	II	Neoadjuvant cemiplimab ± carboplatin/paclitaxel→2-armed biomarker-guided deintensification treatment strategy + adjuvant cemiplimab		Ongoing	Not specified
Definitive Treatment (Concurrent, Sequential, and Maintenance)					
NCT03349710	Not specified	Cohort 1: Nivo + RT vs. Cetux + RT (cis unfit); Cohort 2: Nivo + cis + RT vs. cis + RT (cisplatin eligible)	Effectiveness of nivo combination	Under study	Not specified
DUCRO-HN (NCT03051906)	I/II	Durva 4-weekly concurrent with weekly cetux and RT; adjuvant durva for 6 months	Two-year PFS	Ongoing (not yet recruiting)	Not specified
NCT03799445	II	Nivo + ipi+ concomitant low-dose RT in low-intermediate volume HPV+ OPC	Not specified	Under study	Not specified
eVOLVE-HNSCC (NCT06129864)	III	Observation vs. volrustomig as sequential therapy	Not specified	Ongoing	2029
JADE	III	Observation vs. PD-1 inhibitor dostarlimab	Not specified	Ongoing	Not specified

Table 4 Cont.

Trial neoadjuvant and adjuvant settings	Phase	Intervention	Primary endpoint	Status	Estimated completion
ECOG-ACRIN 3161 (EA3161) (NCT03811015)	II/III	CRT (weekly cis) + adjuvant nivo (12 months) vs. CRT (weekly cis)	OS	Active, recruiting	01/2027
CompARE (NCT04116047)	III	CRT vs. induction durva + CRT + adjuvant durva	EFS, OS	Recruiting	12/2026
DEHART (NCT04477759)	I	MR-guided hypofractionated radiotherapy (50–60 Gy in 15 fractions); atezo at fractions 1 and 11 of RT and 4-weekly up to 1 year	Safety	Active, not recruiting	Not specified
NCT03894891	II	Induction DC+nivo → CRT+Nivo in larynx and hypopharynx	Laryngectomy-free survival	Active, recruiting	Not specified
RTOG 1216 (NCT01810913)	II/III	Concurrent and sequential atezo x8 with PO(C) RT in resected LA-HNSCC with ENE or positive margin	DFS and OS	Active, recruiting	1/2027
NCT02777385	II	CRT+pembro vs. CRT → pembro	Compare concurrent vs. sequential application	Planning to randomize (implies ongoing/recruiting)	Not specified
REWRITe (NCT03726775)	II	Durva + RT (primary tumour and immediately adjacent lymph nodes only) + 6 months maintenance durva	Not specified	Ongoing	Not specified
Recurrent/metastatic (R/M) settings					
NCT04340258	I/II	Perioperative pembro and Cesium-131 BRT + salvage surgery	Not specified	Ongoing	Not specified
NCT03618134	I	Neoadjuvant durva + tremelimumab + SBRT + TORS + ipsilateral modified neck dissection + adjuvant durva in HPV+ OPC	Not specified	Ongoing	Not specified
NCT04830267	II	Camrelizumab + SBRT and camrelizumab alone	Not specified	Ongoing	Not specified
NCT04454489	Not specified	Quad Shot RT + IO	Not specified	Ongoing	Not specified
CONFRONT (NCT03844763)	I/II	Avelumab+ cyclophosphamide+RT (8 Gy single fx)	Exploring abscopal effect	Ongoing	Not specified
NCT03474497	I/II	Pembrolizumab, intralesional IL-2, and RT (8 Gy ×3 fx)	Exploring abscopal effect	Ongoing	Not specified
Keynote-717 (NCT03386357)	II	Pembrolizumab ± RT (12 × 3 Gy) of 1, 2, or 3 metastases	Exploring relationship between predictive biomarkers (PD-L1 and TIL) and abscopal effect	Ongoing	Not specified
NCT03283605	I/II	Durva/tremelimumab and SBRT followed by durva alone	Exploring benefit from dual IO (anti-PD-L1 and anti-CTLA-4)	Ongoing	Not specified
NCT05930938	III	Induction xevinapant (or placebo) + cetux and RT	Potential to add xevinapant to SOC cetux/RT	Ongoing	Not specified

Turk J Oncol 2025;40(Supp 1):53–65
doi: 10.5505/tjo.2025.6

Table 4 Cont.

Trial neoadjuvant and adjuvant settings	Phase	Intervention	Primary endpoint	Status	Estimated completion
XRAY VISION (NCT05386550)	III	Induction xevinapant (or placebo) + IMRT (66 Gy/2 fx)	Potential to add xevinapant to SOC RT	Ongoing	Not specified
TrilynX (NCT04459715)	III	Induction xevinapant (or placebo) + cis and IMRT (70 Gy/35 fx)	Potential to add xevinapant to SOC CRT	Ongoing	Not specified

mPR: Major pathological response; EFS: Event-free survival; Pembro: pembrolizumab; SOC: standard of care; RT: Radiotherapy; cis: cisplatin; Nivo: nivolumab; PO(C)RT: postoperative radiotherapy with or without chemotherapy; ipi: ipilimumab; DFS: disease free survival; PFS: progression free survival; Atezo: atezolizumab; IMRT: intensity modulated radiotherapy; cetux: cetuximab; Durva: durvalumab; OPC: oropharyngeal carcinoma; DC: docetaxel and cisplatin; BRT: brachytherapy; SBRT: stereotactic body radiotherapy; TORS: transoral robotic surgery; HPV: human papillomavirus; IO: immunotherapy; fx: fraction; TIL: tumor infiltrating lymphocyte

concurrent RT+IO trials. To avoid these irAEs, timing of SBRT application and duration of IO is important. The recommendations are generally based on the half-lives of commonly used IO which are relatively long, such as 26 days for nivolumab and pembrolizumab. There is a consensus against administering SBRT on the same day as certain IOs, for instance anti-VEGF, anti-EGFR antibodies, nivolumab, ipilimumab, BRAF and MEK inhibitors, multi-kinase inhibitors and PARP inhibitors.[45]

FUTURE DIRECTIONS

Unfortunately, curative RT-IO combination has not shown promising results so far. This may be partly due to the lack of patient selection based on PD-L1 status and the irradiation of elective nodal regions, which could have impaired the intended immune activation. In contrast, neoadjuvant IO administered before surgery has shown encouraging pathological responses that may translate into better disease-specific outcomes. In such cases, addition of SBRT alongside with IO may improve pathological response and locoregional control by stimulating immune system while gross tumor is viable. Ongoing trials which evaluating various combinations, sequencing and RT fractionation are summarized in Table 4.

Furthermore, another emerging biomarker with potential to enhance the screening and diagnosis of HNSCC is circulating tumor DNA (ctDNA) and may also aid in identifying candidates for IO. Several innovative therapies, including T cell transfer and tumor vaccines, are under investigation for recurrent/metastatic HNSCC, supported by encouraging early-phase data. Should these approaches demonstrate efficacy in the advanced disease setting, they may offer additional immunotherapy options to be integrated with curative RT in the definitive treatment context.

Additionally, novel RT modalities like proton therapy and FLASH RT are gaining attention in the field of radiation oncology. However, their effects on immune modulation remain poorly understood, and widespread clinical implementation of combination with IO will likely require further investigation.

CONCLUSION

In conclusion, the combination of RT and IO represents a promising therapeutic strategy for patients with HNSCC. While IO have demonstrated substantial benefits in the recurrent/metastatic setting, their integration into the curative setting—particularly when administered concurrently with definitive radiotherapy in unselected patients—has not yet translated into improved outcomes. Ongoing efforts aim to optimize treatment approaches, including hypofractionation, SBRT, and de-escalation strategies, as well as to identify biomarkers that help maintain tumor control while minimizing toxicity. Long-term follow-up data will be essential to assess the durability of response and late toxicities associated with radioimmunotherapy. As research advances and therapeutic approaches are optimized, radioimmunotherapy holds considerable potential to improve clinical outcomes and quality of life for patients with HNSCC.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Funding: The authors declared that this study received no financial support.

Use of AI for Writing Assistance: No AI technologies utilized.

Author Contributions: Concept – S.D.B.; Design – S.D.B., P.B.; Supervision – S.D.B.; Literature search – P.B., S.D.B.; Writing – P.B., S.D.B.; Critical review – S.D.B.

Peer-review: Externally peer-reviewed.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021;71(3):209–49.
2. Bernier J, Cooper JS, Pajak TF, van Glabbeke M, Bourhis J, Forastiere A, et al. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). Head Neck 2005;27(10):843–50.
3. Nissi L, Suilamo S, Kytö E, Vaittinen S, Irjala H, Minn H. Recurrence of head and neck squamous cell carcinoma in relation to high-risk treatment volume. Clin Transl Radiat Oncol 2021;27:139–46.
4. Seliger B, Massa C, Yang B, Bethmann D, Kappler M, Eckert AW, et al. Immune escape mechanisms and their clinical relevance in head and neck squamous cell carcinoma. Int J Mol Sci 2020;21(19):7032.
5. Seidel JA, Otsuka A, Kabashima K. Anti-PD-1 and anti-CTLA-4 therapies in cancer: mechanisms of action, efficacy, and limitations. Front Oncol 2018;8:86.
6. Chen F, Zhuang X, Lin L, Yu P, Wang Y, Shi Y, et al. New horizons in tumor microenvironment biology: challenges and opportunities. BMC Med 2015;13:45.
7. Economopoulou P, Kotsantis I, Psyrri A. tumor microenvironment and immunotherapy response in head and neck cancer. Cancers 2020;12(11):3377.
8. Kuss I, Hathaway B, Ferris RL, Gooding W, Whiteside TL. Decreased absolute counts of T lymphocyte subsets and their relation to disease in squamous cell carcinoma of the head and neck. Clin Cancer Res 2004;10(11):3755–62.
9. Galon J, Bruni D. Approaches to treat immune hot, altered and cold tumours with combination immunotherapies. Nat Rev Drug Discov 2019;18(3):197–218.
10. Liu YT, Sun ZJ. Turning cold tumors into hot tumors by improving T-cell infiltration. Theranostics 2021;11(11):5365–86.
11. Welters MJP, Santegoets SJ, van der Burg SH. The tumor microenvironment and immunotherapy of oropharyngeal squamous cell carcinoma. Front Oncol 2020;10:545385.
12. Abdul-Rahman T, Ghosh S, Badar SM, Nazir A, Bamigbade GB, Aji N, et al. The paradoxical role of cytokines and chemokines at the tumor microenvironment: A comprehensive review. Eur J Med Res 2024;29(1):124.
13. Gong T, Liu L, Jiang W, Zhou R. DAMP-sensing receptors in sterile inflammation and inflammatory diseases. Nat Rev Immunol 2020;20(2):95–112.
14. Zhang Z, Liu X, Chen D, Yu J. Radiotherapy combined with immunotherapy: The dawn of cancer treatment. Signal Transduct Target Ther 2022;7(1):258.
15. Lind HT, Hall SC, Strait AA, Goon JB, Aleman JD, Chen SMY, et al. MHC class I upregulation contributes to the therapeutic response to radiotherapy in combination with anti-PD-L1/anti-TGF-β in squamous cell carcinomas with enhanced CD8 T cell memory-driven response. Cancer Lett 2025;608:217347.
16. Wakabayashi G, Lee YC, Luh F, Kuo CN, Chang WC, Yen Y. Development and clinical applications of cancer immunotherapy against PD-1 signaling pathway. J Biomed Sci 2019;26(1):96.
17. Dovedi SJ, Adlard AL, Lipowska-Bhalla G, McKenna C, Jones S, Cheadle EJ, et al. Acquired resistance to fractionated radiotherapy can be overcome by concurrent PD-L1 blockade. Cancer Res 2014;74(19):5458–68.
18. Wild AT, Herman JM, Dholakia AS, Moningi S, Lu Y, Rosati LM, et al. Lymphocyte-sparing effect of stereotactic body radiation therapy in patients with unresectable pancreatic cancer. Int J Radiat Oncol Biol Phys 2016;94(3):571–9.
19. Nenclares P, Rullan A, Tam K, Dunn LA, St. John M, Harrington KJ. Introducing checkpoint inhibitors into the curative setting of head and neck cancers: Lessons learned, future considerations. Am Soc Clin Oncol Educ 2022;42:511–26.
20. Liu J, O'Donnell JS, Yan J, Madore J, Allen S, Smyth MJ, et al. Timing of neoadjuvant immunotherapy in relation to surgery is crucial for outcome. Oncoimmunology 2019;8(5):e1581530.
21. Robert LF, William CS, Rom L, Anthony G, Uwe MM, Chrisann K, et al. Neoadjuvant nivolumab for patients with resectable HPV-positive and HPV-negative squamous cell carcinomas of the head and neck in the CheckMate 358 trial. J ImmunoTher Cancer. 2021;9(6):e002568.
22. Uppaluri R, Campbell KM, Egloff AM, Zolkind P, Skidmore ZL, Nussenbaum B, 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 2020;26(19):5140–52.

Turk J Oncol 2025;40(Supp 1):53–65
doi: 10.5505/tjo.2025.6

23. Wise-Draper TM, Gulati S, Palackdharry S, Hinrichs BH, Worden FP, Old MO, et al. Phase II clinical trial of neoadjuvant and adjuvant pembrolizumab in resectable local–regionally advanced head and neck squamous cell carcinoma. Clin Cancer Res 2022;28(7):1345–52.
24. Schoenfeld JD, Hanna GJ, Jo VY, Rawal B, Chen YH, Catalano PS, et al. Neoadjuvant nivolumab or nivolumab plus ipilimumab in untreated oral cavity squamous cell carcinoma: A phase 2 open-label randomized clinical trial. JAMA 2020;6(10):1563–70.
25. Vos JL, Elbers JBW, Krijgsman O, Traets JJH, Qiao X, van der Leun AM, et al. Neoadjuvant immunotherapy with nivolumab and ipilimumab induces major pathological responses in patients with head and neck squamous cell carcinoma. Nat Commun 2021;12(1):7348.
26. Zinner R, Johnson JM, Tuluc M, Curry JM, Luginbuhl A, Fundakowski CC, et al. Neoadjuvant nivolumab (N) plus weekly carboplatin (C) and paclitaxel (P) in resectable locally advanced head and neck cancer. J Clin Oncol 2024;38(15_Suppl):6583.
27. Leidner R, Crittenden M, Young K, Xiao H, Wu Y, Couey MA, 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. 2021;9(5):e002485.
28. Ma TM, Wong DJ, Chai-Ho W, Mendelsohn A, St John M, Abemayor E, et al. High recurrence for hpv-positive oropharyngeal cancer with neoadjuvant radiation therapy to gross disease plus immunotherapy: Analysis from a prospective phase Ib/II clinical trial. Int J Radiat Oncol Biol Phys 2023;117(2):348–54.
29. Colevas AD, Cmelak AJ, Pfister DG, Spencer S, Adkins D, Birkeland AC, et al. NCCN Guidelines® insights: Head and neck cancers, version 2.2025: Featured updates to the NCCN guidelines. J Natl Compr Cancer Network. 2025;23(2):2–11.
30. Plavc G, Strojan P. Combining radiotherapy and immunotherapy in definitive treatment of head and neck squamous cell carcinoma: Review of current clinical trials. Radiol Oncol 2020;54(4):377–93.
31. Sun L, Candelieri-Surette D, Anglin-Foote T, Lynch JA, Maxwell KN, D'Avella C, et al. Cetuximab-based vs carboplatin-based chemoradiotherapy for patients with head and neck cancer. JAMA Otolaryngol Head Neck Surg 2022;148(11):1022–8.
32. Tao Y, Aupérin A, Sun X, Sire C, Martin L, Coutte A, et al. Avelumab-cetuximab-radiotherapy versus standards of care in locally advanced squamous-cell carcinoma of the head and neck: The safety phase of a randomised phase III trial GORTEC 2017-01 (REACH). Eur J Cancer 2020;141:21–9.
33. Tao Y, Biau J, Sun XS, Sire C, Martin L, Alfonsi M, et al. Pembrolizumab versus cetuximab concurrent with radiotherapy in patients with locally advanced squamous cell carcinoma of head and neck unfit for cisplatin (GORTEC 2015-01 PembroRad): A multicenter, randomized, phase II trial. Ann Oncol 2023;34(1):101–10.
34. Mell LK, Torres-Saavedra PA, Wong SJ, Kish JA, Chang SS, Jordan RC, et al. Radiotherapy with cetuximab or durvalumab for locoregionally advanced head and neck cancer in patients with a contraindication to cisplatin (NRG-HN004): An open-label, multicentre, parallel-group, randomised, phase 2/3 trial. Lancet Oncol 2024;25(12):1576–88.
35. Lee NY, Ferris RL, Psyrri A, Haddad RI, Tahara M, Bourhis J, et al. Avelumab plus standard-of-care chemoradiotherapy versus chemoradiotherapy alone in patients with locally advanced squamous cell carcinoma of the head and neck: A randomised, double-blind, placebo-controlled, multicentre, phase 3 trial. Lancet Oncol 2021;22(4):450–62.
36. Machiels JP, Tao Y, Licitra L, Burtness B, Tahara M, Rischin D, et al. Pembrolizumab plus concurrent chemoradiotherapy versus placebo plus concurrent chemoradiotherapy in patients with locally advanced squamous cell carcinoma of the head and neck (KEYNOTE-412): A randomised, double-blind, phase 3 trial. Lancet Oncol 2024;25(5):572–87.
37. Safavi AH, Lee NY, Tsai CJ. Principles and paradigms of de-escalated elective nodal irradiation: Boldly going towards an inflection point in head and neck radiotherapy. Seminar Rad Oncol 2025;35(2):143–56.
38. Bauman JE, Harris J, Uppaluri R, Yao M, Ferris RL, Chen J, et al. NRG-HN003: Phase I and expansion cohort study of adjuvant pembrolizumab, cisplatin and radiation therapy in pathologically high-risk head and neck cancer. Cancers 2021;13(12):2882.
39. Bourhis J, Auperin A, Borel C, Lefebvre G, Racadot S, Geoffrois L, et al. NIVOPOSTOP (GORTEC 2018-01): A phase III randomized trial of adjuvant nivolumab added to radio-chemotherapy in patients with resected head and neck squamous cell carcinoma at high risk of relapse. J Clin Oncol 2025;43(17_suppl):LBA2–LBA.
40. Ferris RL, Blumenschein G Jr, Fayette J, Guigay J, Colevas AD, Licitra L, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. N Engl J Med 2016;375(19):1856–67.
41. Cohen EEW, Soulières D, Le Tourneau C, Dinis J, Licitra L, Ahn MJ, et al. Pembrolizumab versus methotrexate, docetaxel, or cetuximab for recurrent or metastatic head-and-neck squamous cell carcinoma (KEYNOTE-040): A randomised, open-label, phase 3 study. Lancet 2019;393(10167):156–67.

42. Harrington KJ, Burtness B, Greil R, Soulières D, Tahara M, de Castro G Jr, et al. Pembrolizumab with or without chemotherapy in recurrent or metastatic head and neck squamous cell carcinoma: Updated results of the phase III KEYNOTE-048 study. J Clin Oncol 2023;41(4):790–802.
43. McBride S, Sherman E, Tsai CJ, Baxi S, Aghalar J, Eng J, et al. Randomized phase II trial of nivolumab with stereotactic body radiotherapy versus nivolumab alone in metastatic head and neck squamous cell carcinoma. J Clin Oncol 2021;39(1):30–7.
44. Palma DA, Olson R, Harrow S, Gaede S, Louie AV, Haasbeek C, et al. Stereotactic ablative radiotherapy for the comprehensive treatment of oligometastatic cancers: Long-term results of the SABR-COMET phase II randomized trial. J Clin Oncol 2020;38(25):2830–8.
45. Kroeze SGC, Pavic M, Stellamans K, Lievens Y, Becherini C, Scorsetti M, et al. Metastases-directed stereotactic body radiotherapy in combination with targeted therapy or immunotherapy: Systematic review and consensus recommendations by the EORTC-ESTRO OligoCare consortium. Lancet Oncol 2023;24(3):e121–e32.
46. Liu X, Zhang Y, Yang KY, Zhang N, Jin F, Zou GR, et al. Induction-concurrent chemoradiotherapy with or without sintilimab in patients with locoregionally advanced nasopharyngeal carcinoma in China (CONTINUUM): A multicentre, open-label, parallel-group, randomised, controlled, phase 3 trial. Lancet 2024;403(10445):2720–31.
47. Yom SS, Harris J, Caudell JJ, Geiger JL, Waldron J, Gillison M, et al. Interim futility results of NRG-HN005, a randomized, phase II/III non-inferiority trial for non-smoking p16+ oropharyngeal cancer patients. Int J Rad Oncol Biol Phys 2024;120(2):S2–S3.
48. Zandberg DP, Vujanovic L, Clump DA, Isett BP, Wang H, Sica G, et al. Randomized phase II study of concurrent versus sequential pembrolizumab in combination with chemoradiation in locally advanced head and neck cancer. J Clin Oncol 2025;43:2572–82.
49. Haddad R, Fayette J, Teixeira M, Prabhash K, Mesia R, Kawecki A, et al. Atezolizumab in high-risk locally advanced squamous cell carcinoma of the head and neck: A randomized clinical trial. JAMA 2025;333(18):1599–607.