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## Immunotherapy in head and neck squamous cell carcinoma: a narrative review

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### Abstract

**Objective:** Provide a narrative review of the literature describing immunological concepts and novel approaches in the treatment of head and neck squamous cell carcinoma.

**Background:** In 2016, two anti-PD1 antibodies, nivolumab and pembrolizumab, were shown to improve overall survival in patients with recurrent/metastatic HNSCC and were approved by the US Food and Drug Administration (FDA) for use in the second line, cisplatin-resistant setting, although the overall response rates were only about 15%. More recently, pembrolizumab was approved for use in the first-line R/M setting as monotherapy in patients with CPS >1 or in combination with chemotherapy regardless of PD-L1 expression. Interestingly, while response rates with combination therapy were increased compared to pembrolizumab alone, the duration of response was shorter than might be expected. Based on a growing amount of evidence in other types of cancer treated with various combinations of immunotherapy, similar concepts are being studied in HNSCC, both in pre-clinical models and in clinical trials.

**Methods:** A review of the literature was conducted using the Medline-PubMed and [ClinicalTrials.gov](https://clinicaltrials.gov) databases. Main topics were selected for review, including basic immunology background, checkpoint inhibition, neoadjuvant immunotherapy, the combination of immunotherapy with radiation therapy and chemotherapy, intratumoral immunotherapy, and future prospects.

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**Conclusions:** There is an ongoing effort, which is supported by an increasing body of evidence, to enhance response rates with combinations of immunotherapy with other immunotherapy agents, targeted small molecules, chemotherapy, radiation therapy, and surgery. The clinician and the scientist should be familiarized with basic immunologic concepts, key findings in recent clinical trials, and current indications for administering immunotherapy.

### Keywords

Head and neck; cancer; immunotherapy

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## Introduction

Head and neck squamous cell carcinoma (HNSCC) accounts for 600,000 new diagnosed cases worldwide each year (1), and approximately 60% of patients are expected to survive 5 years (2), a rate that has not changed significantly over the last decades. For many years, tobacco and alcohol consumption were regarded as the only known risk factors for the development of HNSCC, until more recently, when human papillomavirus (HPV) infection was also attributed as an independent risk factor for the development of oropharyngeal SCC. HPV-positive HNSCC is more prevalent among the young population (3), and its survival rate is 54% greater than its HPV-negative counterpart, which is generally caused by tobacco and alcohol consumption (4). The two conventional approaches to treat HNSCC are: (I) primary surgery followed by risk-adapted adjuvant radiation therapy (RT) or chemoradiotherapy (CRT); (II) definitive CRT. Treatment with either surgery and adjuvant therapy or definitive CRT achieves high rates of cure for HPV-positive HNSCC, while a high rate of therapeutic resistance characterizes HPV-negative tumors. Since HPV-positive patients are likely to live longer and experience the associated long-term toxicity of definitive CRT (5), there has been recent interest in radiation and/or chemotherapy de-intensification. Both surgical and non-surgical de-intensification strategies are actively pursued in numerous clinical trials (6–9). Retrospective studies of transoral surgery compared with definitive CRT suggest improved functional results in patients undergoing surgery with decreased gastrostomy tube dependency (6,10,11) whereas a recent prospective study (ORATOR) reported contrasting results at an early time point (12).

On the other hand, poor outcomes and little change in overall survival (OS) over the last 50 years suggest that novel approaches are necessary for patients with HPV-negative disease. Regardless of etiology, recurrent or metastatic (R/M) HNSCC poses an even greater challenge as only one-third of patients respond to treatment, and the median survival period is only 6–8 months (13). Immunotherapy has the potential to activate an immune response to target cancer cells by utilizing the function of the immune system to survey the body for abnormal cells and eliminate them continually. Numerous elements are engaged in the action of the immune system, but some of them have already been established as fundamental components of immunotherapy, such as programmed death receptor-1 (PD-1). Our review will describe recent advancements in treating HNSCC, focusing on the translation of immunological concepts into the standard of care. We will delineate key aspects of the immune response which are turning into “must-know” concepts in this world of personalized medicine. Next, we will review their implementation in various treatment modalities and

provide a scientific background that will allow both the clinician and the scientist to comprehend their potential to be translated into the standard of care today and in the future. We present the following article in accordance with the Narrative Review reporting checklist (available at <https://dx.doi.org/10.21037/fomm-21-48>).

## Methods

The relevant English literature was identified by searching [ClinicalTrials.gov](https://www.clinicaltrials.gov) and Medline via PubMed using the following search terms: Head and neck cancer, head and neck squamous cell carcinoma, immunotherapy, radiation in head and neck, radiotherapy, stereotactic radiation, intratumoral, intralesional, neoadjuvant, STING, microparticles, nanoparticles. To allow for a thorough review of immunology concepts, there was no limitation on the year of publication. However, novel approaches were reviewed with an emphasis on publications from recent years. The data was reviewed using original research papers and clinical trials, while reviews were used mainly for a scientific background.

## Immunology

### Immune response to cancer antigens

Immune cells react to the tumor microenvironment (TME) by differentiating and varying their gene expression, hence constitute a means for understanding tumor behavior (14). The T-cell-mediated immune response is elicited by antigens presented by target cells or antigen-presenting cells (APC), such as dendritic cells (DC). Depending on their exposure to cytokines during DC activation, CD4<sup>+</sup> T-cells may differentiate into two major subpopulations, T helper 1 (Th1) and T helper 2 (Th2). Broadly, Th1 differentiation drives cellular immunity against viruses and infections, while Th2 differentiation directs the immune response to control parasitic diseases. Production of IL-12 and interferon-gamma (IFN $\gamma$ ) by macrophages and natural killer cells, respectively, cause T-cells to differentiate into Th1 cells, while IL-4 may trigger Th2 cell differentiation. When stimulated in the presence of activated CD4<sup>+</sup> T-cells, CD8<sup>+</sup> T-cells expand into effector T-cells that can attack target cells. Following initial expansion, CD4<sup>+</sup> cells may also differentiate into regulatory T-cells (Treg's), which can suppress CD8<sup>+</sup> cells and anti-tumor immunity.

Treg's are a subset of CD4<sup>+</sup> T-cells that possess a central role in adjusting the immune response and preventing autoimmunity. They secrete IL-10 and transforming growth factor beta (TGF $\beta$ ), which inhibit immune response; they consume IL-2 that is required to trigger the proliferation of antigen-activated T-cells; and they express FOXP3, which in turn inhibits the expression of IL-2 and stimulates the expression of CTLA-4 and CD25. Expression of CD25 causes consumption of IL-2, which is a vital component of the immune response (15). The amount of Treg's within a tumor and in the peripheral blood of cancer patients is high, and they are presumed to suppress the immune response against cancer (16).

Since the anti-cancer response is directed towards intracellular mutated peptides, Th1 type responses are optimal to help drive CD8<sup>+</sup> mediated cellular immunity against the tumor. The differentiation of CD4<sup>+</sup> cells into Th1 cells promotes CD8<sup>+</sup> T-cell-mediated adaptive immunity (17), and it has been associated with anti-cancer response and better clinical

outcomes (18). Conversely, serum analysis of HNSCC patients demonstrated elevated levels of Treg's (19) and Th2 cytokines, such as IL-4 and IL-10, compared to healthy individuals (20). Th2-associated cytokines have also been linked to a worse clinical outcome in cancer patients (21).

Mature DC are believed to play a central role by presenting tumor-specific antigens in the lymph nodes, thus priming and activating tumor-specific T-cells (22,23). On the other hand, immature DC are characteristic of a steady-state condition, in which low expression of major histocompatibility complex (MHC) and co-stimulatory molecules elicits immune tolerance towards the antigens that they present (23,24). Different subsets of DC populations possess variable capabilities for stimulating cytotoxic T-cells; some exist within the tumor, and their amount has been shown to predict tumor regression and clinical outcome (25).

Thus, as the HNSCC tumor progresses, the immune response shifts to suboptimal Th2 phenotypes and suppressive Treg populations (21), CD8<sup>+</sup> control of cancer cells becomes limited, and DC drive towards tolerance rather than prime new CD8<sup>+</sup> responses.

Since surgery plays a vital role in the treatment of most solid tumors, including HNSCC, its immunological effect on cancer cells is under investigation. Krall *et al.* demonstrated in the murine model that the systemic inflammatory response following surgery leads to reactivation of tumors, which correlated to earlier reports of the outgrowth of distant metastases in post-mastectomy cancer patients that underwent late breast reconstruction (26,27). The notion that the surgery itself is pro-metastatic suggests that perioperative approaches to overcoming postoperative immunosuppression may be warranted.

### Checkpoint inhibition

Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), PD-1, and programmed death-ligand 1 (PD-L1) are crucial components of the immune response being targeted by immunotherapy. CTLA-4 interferes with the interaction between APC, CD4<sup>+</sup>, and CD8<sup>+</sup>; blocking CTLA-4 allows this interaction to reform, and it also causes depletion of Treg's. PD-1 is a receptor expressed on activated T-cells, B-cells, and myeloid cells; it acts to downregulate immune response, and its ligands, PD-L1 and PD-L2, are expressed on both normal and cancerous cells (28). PD-L1 serves as a regulator of the inter-relationship between the tumor and the immune response and, as such, is suggested to play a prognostic role in the survival of HNSCC patients (29). PD-L1 is expressed in 50–60% of HNSCC and at a higher level in intra-tumoral Treg cells than peripheral Treg cells (30). Using the combined positive score (CPS), which takes both the tumor cells and the surrounding immune cells into account, the expression level reaches 85% (31,32). Immunotherapeutic drugs such as nivolumab and pembrolizumab act by blocking PD-1 and lead to improved survival in many solid tumor types, including HNSCC.

## Immunotherapy

### Immunotherapy in HNSCC

In 2016, the FDA approved nivolumab and pembrolizumab as a second-line treatment for R/M HNSCC, and in 2019 pembrolizumab, either alone or in combination with

chemotherapy, was approved as a first-line treatment, establishing a new standard of care. Prior to that, the only monoclonal antibody being used in HNSCC was the epidermal growth factor receptor (EGFR) inhibitor, cetuximab. It was approved by the FDA in 2006 for treating HNSCC in the definitive setting, and together with concurrent RT, it was considered a standard of care systemic option (33,34). Recently, however, the results of two large phase 3 trials, including RTOG 1016 and the De-ESCALaTE trial comparing cetuximab to cisplatin in the definitive treatment of patients with p16<sup>+</sup> HPV-related oropharynx cancer were reported: In both RTOG 1016 (a randomized, multi-center, non-inferiority trial; n=805) (35) and De-ESCALaTE (open-label, randomized controlled phase 3 trial, n=334) (36), cetuximab was inferior to cisplatin for OS and was more toxic.

In contrast, more promising results were reported in clinical trials studying the safety and efficacy of nivolumab and pembrolizumab, including overall response rate (ORR), OS, progression-free survival (PFS), and adverse events. Among these studies, CHECKMATE-141 was a phase 3 randomized trial conducted on 361 heavily pretreated R/M HNSCC patients that showed longer OS in the nivolumab group (7.5 months, 95% CI: 5.5–9.1) than standard chemotherapy regimens (5.1 months, 95% CI: 4.0–6.0), with OS hazard ratio for death 0.70 (37). This trend was also apparent after 24 months of follow-up, exhibiting OS of 16.9% (95% CI: 12.4–22.0%) vs. 6.0% (95% CI: 2.7–11.3%), and median survival of 7.7 (95% CI: 5.7–8.8) months vs. 5.1 (95% CI: 4.0–6.2) months, nivolumab vs. investigator's choice, respectively (38). These results were confirmed at ASCO 2019, showing similar OS rates among patients older or younger than 70 years (39). Pembrolizumab and investigator's choice were compared in KEYNOTE-040 (a randomized, open-label, phase 3 trial, n=495) and, while pembrolizumab was found to be clinically beneficial, the survival endpoints in the study were not met 8.4 (95% CI: 6.4–9.4) vs. 6.9 (95% CI: 5.9–8.0) months, presumably because of cross-over in the study group (40). However, a phase 3 clinical trial in the first-line R/M setting, KEYNOTE-048 (a randomized, open-label, phase 3 trial, n=882), recently showed that pembrolizumab alone improved survival compared to cetuximab with chemotherapy in PD-1 positive HNSCC patients (CPS >20 14.9 vs. 10.7 months, HR 0.61, 95% CI: 0.45–0.83, P=0.0007; CPS >1 12.3 vs. 10.3 months, HR 0.78, 95% CI: 0.64–0.96, P=0.0086), and pembrolizumab with chemotherapy improved survival compared to cetuximab with chemotherapy regardless of PD-1 status (13.0 vs. 10.7 months, HR 0.77, 95% CI: 0.63–0.93, P=0.0034) (41).

Adverse events following treatment of HNSCC with pembrolizumab appeared in 62–64% of patients and consisted of fatigue, decreased appetite, nausea, pruritus, rash, and hypothyroidism. Grade 3–4 adverse events included hyponatremia, elevated alanine aminotransferase and aspartate aminotransferase, atrial fibrillation, congestive heart failure, and pneumonitis, which had also led to the death of a single patient during the KEYNOTE-055 trial (42–44). Grade 3 and above adverse events were evident in 13% of patients treated with pembrolizumab vs. 36% among patients administered with investigator's choice in KEYNOTE-040 trial (40), and similar values were also reported in CHECKMATE-141 trial (15.3% vs. 36.9%, nivolumab and investigator's choice, respectively) (38). The relatively low rate of adverse events underlines the potential of immunotherapy as an alternative to the current standard of care treatment, which is often not well tolerated. This benefit was especially evident in the final analysis of KEYNOTE-048

trial, which demonstrated a significantly lower rate of grade three and above adverse events among the pembrolizumab alone group (55%) than in the chemotherapy combination groups (83% for chemotherapy and pembrolizumab, 85% for chemotherapy and cetuximab) (41). Incorporating immunotherapy into the treatment regimen of R/M HNSCC patients can also address the unmet need for improving quality of life (QOL). Analysis of questionnaires given to patients enrolled in KEYNOTE-040 demonstrated a stable QOL in pembrolizumab-treated patients, contrasting a decline in QOL among patients treated with standard of care (methotrexate, docetaxel, or cetuximab) (45).

In recent years, the number of immunotherapy trials for HNSCC has increased substantially, and since immunotherapy as a single modality treatment has yielded low response rates in the R/M setting, trials are concentrating on the combination of immunotherapeutic agents, concurrent immunotherapy and chemotherapy, and concurrent immunotherapy and RT. Table 1 summarizes selected combination immunotherapy clinical trials in HNSCC.

### Neoadjuvant immunotherapy

The propagation of immunotherapy into the neoadjuvant realm can prime both local and systemic immunity by targeting cancer cells and counteract immunosuppression at an early stage, tackling the potential suppression imposed by the surgery itself. It has also facilitated the study of resected specimens to evaluate responders vs. non-responders on a cellular level (46,47) and to examine the response to treatment and adjust it accordingly. While data regarding a possible link between pathological features and regression of HNSCC is still limited, data from other solid tumors demonstrated a correlation between several pathologic features and tumor regression: In a study of twenty cases of non-small-cell lung carcinoma (NSCLC) that received neoadjuvant nivolumab followed by surgical resection, tumor's regression was correlated with a dense population of tumor-infiltrating lymphocytes (TIL) and macrophages; tertiary lymphoid structures; cholesterol clefts; neovascularization and proliferative fibrosis (48). Accumulation of TIL was also associated with pathologic response in high-risk resectable stage 3–4 melanoma patients treated with a single dose of anti-PD-1, which likewise was associated with a clinical benefit (47). These data emphasize the potential of neoadjuvant therapy, not only for better loco-regional and systemic control of the disease but also as a method for further understanding the underlining pathology and for tailoring the treatment to the individual.

Pembrolizumab has been tested in the neoadjuvant setting prior to surgery in HPV-negative HNSCC (NCT02296684), with results recently published (49). In this trial, pathologic tumor response (pTR) was quantified as the proportion of the resection bed with tumor necrosis, keratinous debris, and giant cells/histiocytes: pTR-0 (<10%), pTR-1 (10–49%), and pTR-2 (50%) in 36 patients. While there were no complete pathologic responses (pCR) observed after neoadjuvant pembrolizumab, pTR-2 occurred in the surgical specimens of 8 patients (22%), and pTR-1 occurred in 8 additional patients (22%). Overall, pTR of >10% was observed in 16 of 36 patients (44%). Down-staging of cancer (defined as pathologic stage lower than clinical stage) after neoadjuvant pembrolizumab occurred in 7 patients (19%), but only one patient had what would be considered a major pathologic response (MPR). These data provided the rationale for KN689, the ongoing phase 3 registrational



trial sponsored by Merck (NCT03765918). Pathological response was also reported in a phase 2 clinical trial that included 29 oral cavity SCC patients treated with neoadjuvant nivolumab vs. a combination of nivolumab and ipilimumab. Clinical staging at diagnosis was T2 for twenty patients and T3–4 for the remaining nine. Pathologic response was as high as 54% and 73%, pathologic downstaging of 53% and 69%, RECIST response of 13% and 38%, and 1-year PFS of 85% and 89% (95% CI, 72.4–99.7%; 78.3–100%), nivolumab vs. nivolumab+ipilimumab, respectively. Four patients demonstrated major or complete response, and the individual description of these patients is of particular interest: Following one cycle of neoadjuvant nivolumab, a cT4aN2b patient was treated with definitive CRT due to the extent of the disease, which resulted in complete metabolic response and remaining disease-free at 34 months. Another patient demonstrated 70% pathologic response at the primary tumor site but developed distant metastases, which were treated with adjuvant nivolumab and resulted in a complete metabolic response (50). Although the amount of patients in these trials is relatively small, and complete response is evident only in a limited set of patients, the potential of neoadjuvant immunotherapy to improve survival is substantial. Moreover, it allows for the study of response while administering treatment and adjusting it accordingly. Numerous trials are ongoing (Table 2).

### The immunogenic radiation

RT is an essential component of treating many types of cancer, and for many years, it was generally regarded as immunosuppressive, mostly due to its cytotoxic effect on leukocytes, leading to lymphopenia and impaired leukocyte function (51,52). However, more recent studies demonstrated a synergy between RT and the immune system that under certain circumstances may induce the immune response (53). This synergy can be subclassified into two types: In the first type, RT functions as an *in situ* vaccine that has the potential to boost immune control of distant disease (30,54). In the second type of synergy, RT promotes a distinctive mechanism of immunogenic cell death, characterized by the release of activating signals that initiate the attraction of DC into the tumor and phagocytosis of irradiated tumor cells (52,55,56). Induction of vascular density and leakiness by the tumor is counteracted by combined RT and immunotherapy, leading to more significant infiltration of CD8<sup>+</sup> T-cells and induction of migration and extravasation of leukocytes into the tumor (52,57). Importantly, RT alone may lead to immunosuppression by the accumulation of Treg cells inside the tumor due to their radio-resistance; however, this process can be inhibited by administering concurrent immunotherapy (52,58). These data demonstrate the potential of combining RT and immunotherapy to improve response rates and has led to a growing interest in this combination (59).

### SBRT and hypo-fractionated radiation therapy

The conventional RT that most patients undergo is protracted fractionation RT, during which small doses of radiation (around 2 Gy per fraction) are delivered daily. This method presumably allows for normal tissue to undergo repair better than tumor tissue (60), therefore targeting the radiation effect at cancer cells more than at their surrounding healthy counterparts. A different approach for administering RT is stereotactic body radiation therapy (SBRT) which is, in essence, a precise delivery of high dose hypo-fractionated radiation to a target of either a single dose or a limited number of doses. This method

enables a high dose of radiation to be focused on a specific location while maintaining a steep dose gradient beyond (61). For a group of medically unfit patients, administering primary hypo-fractionated RT has already proved to be a viable treatment alternative, minimizing the related toxicities and yielding impressive local control (LC) and OS rates (n=24 lesions in 21 patients, 25% complete response, 67% partial response) (62) (n=55 lesions in 44 patients, tumor control at one year 83.3% and 60.6%, primary and recurrent groups, respectively) (63). SBRT is also being employed to treat oligometastatic disease, a state defined in 1995 by Hellman and Weichselbaum as an intermediate condition on a spectrum extending from localized disease to a rapidly advancing systemic disease. According to this notion, a disease that has spread to the lymph nodes is considered aggressive, and the involved nodes also serve as a nexus for seeding cancer (64). On the other hand, the oligometastatic state might signify an advanced disease that has not yet evolved into a systemic state; hence, it can be potentially cured. Various attempts are being made to treat oligometastatic disease, including surgical resection of metastases (metastasectomy) and SBRT. Interestingly, metastasectomy was proven beneficial for lung metastases, prolonging life, and even potentially curative in a selected group of patients (65). Metastases are also managed non-surgically, utilizing SBRT to target a specific focus while minimizing the undesirable peripheral effect. Although SBRT can be seen, like surgery, as an opportunity for annulling a cancer site, the effect of SBRT on metastases is also hypothesized to be inherently immunogenic by turning the irradiated site into a vaccine that primes the immune response both locally and systemically (66,67). The effect of hypo-fractionated RT on the immune response is investigated in both pre-clinical models and clinical trials. In HNSCC models, Morisada *et al.* irradiated mouse oral cancer cells with 2 and 8 Gy, both *in vitro* and *in vivo*, and demonstrated dose-dependent antigen release, antigen-specific T-cells activation, and cytotoxic targeting of cells in both models. Importantly, the effect that followed 8 Gy was greater than the effect achieved after administering 2 Gy (68). The same group also combined PD-1 blockade with hypo-fractionated RT given in two doses; two fractions of 8 Gy and ten fractions of 2 Gy. The hypo-fractionated high dose preserved and even enhanced anti-tumor immunity, and when it was combined with PD-1 blockade, better control of primary and distant tumors was achieved (69). It has also been shown that PD-L1 upregulation following radiation can limit local control of tumors in murine models and that blockade of the PD-1/PD-L1 axis concurrently with radiation results in enhanced tumor control (70). These and other pre-clinical studies have provided a rationale for investigating the combination of RT and immunotherapy in human clinical trials.

### Combination of radiation therapy with immunotherapy

Although immunotherapy with checkpoint inhibitors targeting PD-1 has been shown to improve OS in patients with R/M HNSCC, response rates to monotherapy are only 13–17% (37,41–43). To improve immunotherapy response rates, there has recently been a surge of interest in combining checkpoint inhibitors with radiation (59). The rationale for these studies is that the addition of radiation will incrementally improve the systemic response seen with PD-1 blockade via a radiation *in situ* vaccination effect that will propagate via epitope spread, or other means, to ultimately drive a systemic anti-tumor immune response beyond the locally irradiated field. To date, evidence of such effect in R/M HNSCC or



other solid tumors is lacking, and a recently reported phase 2 randomized clinical trial failed to show any difference in response rate between patients treated with anti-PD-1 vs. those treated with anti-PD-1 and SBRT (n=62, objective response rate 34.5% vs. 29.0%, 95% CI: 19.9–52.7%, 16.1–46.6%, respectively) (71). An alternative but an equally plausible hypothesis is that notwithstanding a weak *in situ* vaccine effect, the addition of PD-1 blockade to RT will modulate the TME and exert a far greater influence on the local response via blockade of upregulated PD-L1 in tumor following RT, leading to enhanced immune-mediated tumor killing. It has been shown that PD-L1 upregulation following radiation can limit local control of tumors in murine models and that blockade of the PD-1/PD-L1 axis concurrent with RT results in enhanced tumor control (70). The addition of avelumab (PD-1 inhibitor) to CRT in unresected locally advanced HNSCC was assessed in a randomized, double-blind, placebo-controlled phase 3 clinical trial. Median PFS was not reached in the avelumab group (n=350, 95% CI, 16.9 months) or in the placebo group (n=347, 23.0 months), with a stratified HR of 1.21 in favor of placebo (95% CI, 0.93–1.57) (72). These data suggest that the addition of PD-1 inhibitor may lead to a different outcome in primary vs. locally advanced HNSCC and if combined with surgery vs. definitive CRT.

Ongoing trials aim to combine SBRT and PD-1 blockade in the adjuvant and neoadjuvant settings. Study [NCT03247712](#) has completed the recruitment of twenty-one primary HNSCC patients to receive three doses of nivolumab and 3 or 5 fractions of 8 Gy prior to restaging and surgical resection. Following surgery, the patients received three additional doses of nivolumab. Outcome measures include an unplanned delay to surgery (safety and tolerability of neoadjuvant treatment), reduced tumor size, and reduction in lymph nodes size. The results of this study were recently published, demonstrating 86% MPR and 67% pCR (73). Study [NCT03618134](#) by UCLA, Jonsson Comprehensive Cancer Center, is recruiting primary HPV-positive oropharyngeal SCC patients to receive durvalumab (with or without tremelimumab) and undergo SBRT. Between weeks 6–8, patients will undergo transoral robotic surgery and neck dissection, and on week 12, they will be administered with durvalumab every four weeks up to 4 doses. Study [NCT03635164](#) by the University of Colorado, Denver recruited primary HPV-negative HNSCC patients to receive one dose of neoadjuvant durvalumab approximately 3–6 weeks prior to standard-of-care surgery. It is given concurrently with the first dose of radiation, which includes two fractions of 6 Gy and, if possible, three fractions of 6 Gy. Patients receive up to 6 doses of durvalumab and undergo radiation postoperatively.

### Combination therapies—immunotherapy and chemotherapy

A combined effect of chemotherapy and immunotherapy is evident while treating various kinds of cancer. Mapping the tumoral environment of breast cancer and colorectal cancer patients who responded to chemotherapy reveals many T-cells and a shift towards cytotoxic CD8<sup>+</sup> T-cells over Treg cells (74,75). The underlying mechanism is assumed to be chemotherapy-driven tumor cell death, which leads to the activation of T-cells and antigen presentation by DC. A fundamental concept in this process is defining tumor stress and tumor death as immunogenic (76). Several studies have demonstrated the crucial role of a competent immune response as a prerequisite for successful CRT. Among these are pre-clinical models in which chemotherapy was administered in parallel to immunogenic

cell death induction but yielded optimal response only in immunocompetent mice (76–78). Clinical trials in NSCLC (79,80) and triple-negative breast cancer (81) have resulted in encouraging results and are pointing to the interdependency of chemotherapy and immunotherapy and the therapeutic effect exerted by this synergy. In the phase 3 study [NCT02358031](#), R/M HNSCC patients (n=882) were randomly allocated into three groups: Pembrolizumab alone, pembrolizumab plus a platinum, and 5-FU, or cetuximab plus a platinum and 5-FU (EXTREME). Benefit in OS was demonstrated for the combination of pembrolizumab plus a platinum and 5-FU over EXTREME for the entire population (13.0 vs. 10.7 months, HR 0.77, 95% CI: 0.63–0.93, P=0.0034), and for pembrolizumab alone over EXTREME for patients with a combined positive score of PD-L1 expression (CPS)  $\geq 1$  (12.3 vs. 10.3 months, HR 0.78, 95% CI: 0.64–0.96, P=0.0086) (41). This has led to the FDA approval for pembrolizumab alone as first-line therapy for patients with CPS  $\geq 1$  and for pembrolizumab plus a platinum and 5-FU for the entire population, regardless of CPS. Importantly, this study demonstrated the added value for each treatment modality: Pembrolizumab increased OS as long as CPS  $\geq 1$ , it has led to a lower rate of adverse events, and its response rate was more durable with a median duration of 22.6 months compared to 4.5 with EXTREME. However, the response rate to EXTREME was superior to that of pembrolizumab alone (36% vs. 17%, respectively), and the rate of progressive disease was better in EXTREME compared to pembrolizumab alone (12% vs. 41%, respectively) (41). These data demonstrate the diversity among patients and the substantial effect of the TME on the outcome of a given treatment. Accordingly, combining pembrolizumab and chemotherapy may be more appropriate for patients with lower CPS scores and a need for a rapid response rate, while pembrolizumab alone may be preferred for a less symptomatic state of disease and a high CPS score (32). Providing the appropriate combination for each patient and unveiling the factors that determine a successful outcome is essential in the studies that should follow.

### Intratumoral immunotherapy

Over the years, therapeutic agents were introduced into tumors using variable techniques and substances to achieve several potential advantages. First, focusing the desired effect at the target area while limiting unwanted impact at other sites; second, using a reduced amount of medication for each patient while maintaining a high concentration at the tumor site; and third, maximizing the immune response by utilizing the direct interaction between the agent and the TME (82). Intratumoral and intertumoral heterogeneity pose a significant challenge for treatment, as it necessitates the targeting of different antigens throughout the tumor and across remote sites. Introducing an immune-stimulator directly into the tumor may overcome this major obstacle by utilizing the specific TME and the host's immune system, potentially negating the need for antigen isolation and exogenous treatment personalization (82). Over the years, several techniques were developed and tested for the delivery of various agents to induce an anti-tumoral immune response. The delivery methods include direct injection, image-guided injection, electroporation, and nano/micro-delivery. The therapeutic agents are divided into bacteria-derived agents, oncolytic viruses, immune-modulators, cytokines, and chemotherapeutic agents. Methods that are relevant to HNSCC will be described next.

## Cytokines

Since cytokines are vital components of the immune response, they form a natural target for cancer therapy. Interleukin 2 (IL-2) is synthesized by CD4<sup>+</sup> T-cells, and it constitutes a key factor for the maintenance of Treg's and the differentiation of effector T-cells following antigen-mediated activation (83). Manipulation of IL-2 may stimulate an immune response by induction of CD8<sup>+</sup> T-cells or suppressing it by expanding Treg's (83). Systemic treatment with high-dose IL-2 (aldesleukin) to melanoma and renal cancer patients has evolved over the years, being integrated with adoptive cell transfer, non-myeloablative chemotherapy, and total body irradiation demonstrating a continually improving response rate (84). However, this treatment has been associated with severe toxicities to the heart, lungs, kidneys, and central nervous system (85). To minimize systemic adverse effects, IL-2 was injected intralesionally to 48 patients with advanced melanoma metastases; the results showed an impressive complete response rate of more than 60% while limiting toxicities to grade 1 and 2 (86). Several trials have focused on HNSCC patients undergoing perilymphatic injections of IL-2 with contradictory results. Earlier studies resulted in a temporary partial or complete response followed by a relapse in inoperable cases (87), a low ORR in advanced HNSCC (88), and no benefit in clinical outcome when combined with surgery and RT (89). In contrast, later studies demonstrated prolonged disease-free survival (DFS) and OS following neoadjuvant IL-2 perilymphatic injection prior to surgery and RT (n=201, 5 years OS 73%, 55%, DFS 64%, 51%, IL-2 vs. control, respectively) (90). Studies also focus on a mixture of several cytokines, as in the case of IRX-2, a human donor-derived mix containing IL-1 $\beta$ , IL-2, IL-6, IL-8, IFN $\gamma$ , TNF $\alpha$ , and GM-CSF (91). Prolonged survival and delay in recurrence were demonstrated following neoadjuvant perilymphatic injections of IRX-2 before surgery and RT according to the standard of care (92). INSPIRE is an ongoing phase 2 study of neoadjuvant and adjuvant IRX-2 in patients with newly diagnosed stage II-IVa oral SCC ([NCT02609386](https://clinicaltrials.gov/ct2/show/study/NCT02609386)).

TNFerade Biologic is an adenoviral vector inserted with a human TNF $\alpha$  gene that is constructed to be induced by radiation. In a phase 1 escalation study conducted on 14 recurrent HNSCC patients, TNFerade Biologic was injected into the tumor concurrently with CRT. The study met its safety and dosage outcomes with a response rate of 83.3% and a median survival rate of 9.6 months (93).

Increased level of IL-12 is among the causes for differentiation of T-cells into Th1 cells, which consequently leads to CD8<sup>+</sup> T-cell-mediated adaptive immunity (17), and its level has been associated with improved clinical outcomes (18). Tavokinogene Telseplasmid is a DNA plasmid that encodes for p35 and p40 subunits of IL-12, and it is administered intratumorally followed by electroporation. This protocol was studied in a phase 1 trial conducted on 19 advanced melanoma patients, and results showed complete regression in two patients and partial response or disease stabilization in eight patients (94). Importantly, unlike the systemic administration of IL-12, the intratumoral administration was well tolerated, and additional clinical trials in melanoma patients are ongoing (95). Study [NCT03823131](https://clinicaltrials.gov/ct2/show/study/NCT03823131) by UCSF Medical Center-Mount Zion, San Francisco, will recruit R/M HNSCC patients to receive intratumoral Tavokinogene Telseplasmid by electroporation,

together with pembrolizumab and epacadostat (inhibitor of Indoleamine 2,3 dioxygenase, a negative regulator of immune responses) (96).

## STING

STING (STimulator of INterferon Genes) is a critical component of the innate immune response in detecting certain viruses and intracellular DNA and induction of type I interferon production as part of cellular host defense (97,98). To harness this mechanism to induce an anti-tumoral immune response, STING agonists were injected into an established murine B16 melanoma tumor, 4T-1 colon tumor, and CT26 mammary tumor, leading to a durable regression and a potent anti-tumor T-cell response that was mainly dependent upon CD8<sup>+</sup> cells (99). Interestingly, the anti-tumoral effect included the rejection of non-injected tumors (abscopal effect), clearance of metastases, and successful immune response to autologous tumor rechallenge (99).

In the field of HNSCC, the murine immunogenic MOC1 and non-immunogenic MOC2 models were used to study the effect of intratumoral injection of cyclic dinucleotide (CDN), a STING pathway activator. While the injection of CDN to MOC1 established tumors resulted in a complete regression rate of 50% and growth inhibition of the remaining tumors, only a slight delay in tumor growth was observed in the MOC2 group. Treating MOC1 in STING-deficient mice and CD8<sup>+</sup> depleted mice eliminated the anti-tumor response, while the addition of systemic PD-L1 antibody treatment to the intratumoral injection increased the complete regression rate to 90% (100). This study underlines the critical role of CD8<sup>+</sup> cells in the immune response to STING activation and the potential of incorporating intratumoral priming of immune response into existing checkpoint inhibition regimens.

Baird *et al.* performed subtotal tumor resection in several different murine HNSCC models, followed by intratumoral administration of STING ligand incorporated into Matrigel hydrogel. This treatment resulted in a cure of the residual tumor while all the control group members recurred (101). These data demonstrate that STING ligands act as potent local immunotherapy that controls residual tumors following surgical resection in HNSCC pre-clinical models and suggests a role for implantable immune-modulating interventions to improve loco-regional control in human patients.

## Future prospects

### Vaccines

Vaccine therapy aims at creating a durable immune response that will outlast the tumor cells and carcinogenesis. HPV is a principal target for vaccine therapy, and significant resources are being put into its continuing development and application. The causal effect of HPV on the development of HNSCC was described for the first time in 2000, after identifying its surrogate marker p16 in 25% of HNSCC specimens (102). It is known today that the combined expression of p16 (tumor suppressor gene) and HPV DNA in a specimen constitutes a favorable prognostic factor of HNSCC (14). Evaluation of the TME reveals a higher level of TIL in HPV-positive than in HPV-negative HNSCC specimens, indicating a more robust activation of the anti-tumoral immune response in HPV-positive HNSCC

(103,104). Moreover, HPV-positive HNSCC tumors are more radiosensitive as compared to HPV-negative tumors (105). These data underline the importance of designing different approaches for treating HNSCC patients based on their HPV status.

Of particular interest is the potential link between the HPV vaccine and oropharyngeal cancer. HPV vaccines were reported in phase 3 trials as preventing persistent genital lesions and premalignant genital lesions (106). The causal effect of the HPV vaccine and oropharyngeal cancer has not been identified to date, but a few trials have already begun to study this possible link. Phase 1 dose-escalation trial concentrated on HPV16 and MAGE-A3 vaccines given in four doses subcutaneously to R/M HNSCC patients who are positive for HPV16 and MAGE-A3, respectively. T-cell and antibody responses were observed, and the vaccines were reported to be well tolerated (107).

DC-based vaccines are mainly used in other types of cancer and, to a lesser degree, also in HNSCC. A phase 1 clinical trial focused on p53 as a target for a DC-based vaccine delivered into inguinal lymph nodes of sixteen HNSCC patients at three different time points. Results showed an elevated frequency of p53-specific T-cells, improved phenotype and function of DC, and a favorable two-year survival rate of 88% (108). In another study, autologous DC loaded with apoptotic tumor cells were used to formulate a vaccine from HNSCC resected tumors. Among the thirty patients initially enrolled in this study, only four were eventually administered with the vaccine due to a small number of cases in which the pre-vaccination criteria were met. Although all four patients benefited from the vaccine, the authors concluded that this vaccine type would only be relevant for a small number of patients that exhibit delayed-type hypersensitivity and only if a sufficient amount of sterile tumor cells has been produced (109).

The quantity of studies in which neoadjuvant vaccines are administered to HNSCC patients remains small. As studies ensue, the benefit from vaccinating the general population and HNSCC patients against HPV remains to be seen.

### **Microparticles and nanoparticles**

While surgery is considered the standard of care for most solid tumors, it does not necessarily eliminate the tumor in its entirety; thus, effective adjuvant therapy to counteract residual disease is required. Novel drug delivery technologies are constantly evolving, and significant progress is seen in post-surgical adjuvant treatment. Translation of these technologies to the clinical setting can transform the field of surgical oncology by reducing recurrence rates and metastasis, shifting treatment paradigms, and improving survival rates (110). To deliver immunotherapeutic agents directly into the TME over a more extended period, PD-1 and CTLA-4 inhibitors were encapsulated in dextran nanoparticles integrated with hyaluronic acid and introduced into a transdermal microneedle patch that was applied onto melanoma-bearing mice. Based on a preliminary *in vitro* assay that showed a sustained release period of three days, the authors showed a benefit in survival and a synergistic effect of this combination (111). The same group has also succeeded in conjugating PD-1 inhibitor onto platelets for its delivery into the TME, utilizing the natural migration of platelets to the tumor site. Following resection of the majority of melanoma and triple-negative mammary carcinoma, intentionally leaving behind residual tumor, mice were treated with intravenous

platelets conjugated with a PD-1 inhibitor. The circulating half-life of this construct proved to be over six times longer than the unconjugated PD-1 inhibitor, and it has led to an increased amount of TIL (112). These novel delivery methods demonstrate the potential of local delivery of immunomodulating agents using sustained-release methods that prime the immune response locally and systemically.

### Adoptive T-cell therapy

To harness the potential of specific cell populations to target a patient's tumor, two adoptive T-cell therapy (ACT) methods were developed: (I) TIL are isolated from surgically resected specimens; (II) T-cells are derived from the peripheral blood and genetically modified *ex vivo* to target tumor cells. In both techniques, cells are expanded *ex vivo* and reinfused to the patient (113). Initially tested in metastatic melanoma in 1988 (114), ACT was further developed and produced objective clinical response rates of 42–51% among refractory metastatic melanoma patients (115–118). Utilizing a similar methodology, TIL were successfully expanded from HNSCC specimens by Junker *et al.* in 2011 (119), later evolving into clinical trials of ACT in HNSCC. Studies [NCT03083873](#) and [NCT03645928](#) by Iovance Biotherapeutics, Inc. are currently evaluating TIL infusion (LN-145/LN-145-S1) to R/M HNSCC patients.

### Conclusions

Cancer immunotherapy is a validated and transformational approach for treating patients with HNSCC. However, predictably modulating the immune response to overcome existing cancer and its future spread poses a significant challenge in pre-clinical models and patients. Despite the successful application of immunotherapy across multiple tumor types, durable response and cure remain elusive. Successful immunologic elimination of cancer is complex and challenged by a series of biological steps to dampen the immune response, with multiple negative feedback loops and checkpoints that enable control of anti-tumor immunity. Adding to this complexity is that the cancer itself is heterogeneous and the product of genetic mutations can, on one hand, lead to cancer progression, but on the other hand can serve as an important antigenic target of immune response. Large scale efforts are underway to test novel combinations of immunotherapy with other immunotherapy agents, targeted small molecules, chemotherapy, RT and surgery. Future success will be dependent upon better understanding of the synergies between therapies and the effect on anti-cancer immune response.

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Table 1

Selected combination immunotherapy clinical trials in head and neck cancer

Study	NCT ID	Phase	Drugs and treatment	HNSCC population
CHECKMATE-651	NCT02741570	3	Nivolumab + ipilimumab vs. extreme	R/M
CHECKMATE-714	NCT02823574	2	Nivolumab + ipilimumab vs. nivolumab + placebo	R/M
IMSTAR-HN	NCT03700905	3	Surgical resection + neoadjuvant/adjuvant nivolumab and ipilimumab followed by adjuvant CRT vs. surgical resection followed by adjuvant standard-of-care CRT	Primary
KRESTREL	NCT02551159	3	MEDI4736 (anti-PD-L1) +/- tremelimumab (anti-CTLA-4) vs. standard-of-care chemotherapy	R/M
CONDOR (c)	NCT02319044	2		
EAGLE (c)	NCT02369874	3		
INDUCE-3	NCT04128696	2/3	Pembrolizumab + feladilimab (ICOS inhibitor) vs. pembrolizumab + placebo	R/M
INDUCE 4	NCT04428333	3	Pembrolizumab + 5FU + feladilimab (ICOS inhibitor) vs. pembrolizumab + 5FU + placebo	R/M
LEAP-010	NCT04199104	3	Pembrolizumab + lenvatinib vs. pembrolizumab + placebo	R/M
KEYSTROKE	NCT03546582	2	Pembrolizumab + SBRT	R/M or 2 <sup>nd</sup> primary
Keynote-717	NCT03386357	2	Pembrolizumab + RT vs. pembrolizumab alone	R/M
	NCT03521570	2	Nivolumab + RT	R/M or 2 <sup>nd</sup> primary
	NCT02289209	2	Pembrolizumab + re-irradiation	Inoperable or 2 <sup>nd</sup> primary

RT, radiation therapy; SBRT, stereotactic body radiation therapy; CRT, chemoradiotherapy; R/M, recurrent or metastatic.

Table 2

Selected neoadjuvant immunotherapy trials in head and neck cancer

NCT ID	Phase	Neoadjuvant drug	Additional treatment
NCT03144778	1	Durvalumab +/- tremelimumab	S
NCT03003637	1/2	Nivolumab, Ipilimumab	S, CRT
NCT03247712	2	Nivolumab	S, RT
NCT03765918	3	Pembrolizumab	S, RT
NCT03708224	2	Atezolizumab, Tocilizumab, Tiragolumab	S
NCT02296684	2	Pembrolizumab	S, RT
NCT04681469	2	Dostarlimab, Niraparib	S, RT
NCT03174275	2	Durvalumab	S, RT
NCT03878979	2	Nivolumab	S
NCT03721757	2	Nivolumab	S, CRT
NCT03700905	2	Nivolumab	S, CRT
NCT02609386	2	IRX-2	S, CRT
NCT03635164	1	Durvalumab	S, SBRT
NCT02641093	2	Pembrolizumab	S, CRT
NCT03721757	2	Nivolumab	S, CRT
NCT03129061	1	Standard of care anti-PD1	S, CRT
NCT03021993	2	Nivolumab	S
NCT03737968	2	Durvalumab +/- tremelimumab	S, CRT
NCT03944915	2	Nivolumab+CT	S
NCT03843515	1	Nivolumab	S
NCT02827838	2	Durvalumab	S
NCT02274155	1	OX-40	S
NCT03336606	1	MEDI0562 (OX-40 agonist)	S
NCT02919683	2	Nivolumab, Ipilimumab	S
NCT03129061	1	Nivolumab, Pembrolizumab	S, RT
NCT03575598	1	Nivolumab, Sitravatinib	S
NCT03238365	1	Nivolumab, Tadalafil	S
NCT03854032	2	Nivolumab, anti-IDO	S

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NCT ID	Phase	Neoadjuvant drug	Additional treatment
<a href="#">NCT03341936</a>	2	Nivolumab, Liriumab	S

S, surgery; CRT, chemoradiotherapy; RT, radiation therapy; CT, chemotherapy; SBRT, stereotactic body radiation therapy.