Head and neck cancer (HNC) is the sixth most common malignancy worldwide; head and neck squamous cell carcinoma (HNSCC) account for the most cases of HNC. Past smoking and alcohol consumption are common risk factors of HNSCC; however, an increasing number of cases associated with human papillomavirus (HPV) infection have been reported in recent years. The treatment of HNSCC is integrated and multimodal including traditional surgery, radiotherapy, chemotherapy, and targeted therapy. Since pembrolizumab was approved in 2016, an increasing number of studies have focused on immunotherapy. However, not all of HNSCC patients have a better outcome on immunotherapy. Immunotherapy has been reported to be more effective in HPV-positive patients, but its molecular mechanism is still unclear. Some researchers have proposed that the high proportion of infiltrating immune cells in HPV-positive tumors and the difference in immune checkpoint expression level may be the reasons for their better response. As a result, a series of individualized immunotherapy trials have also been conducted in HPV-positive patients. This paper summarizes the current status of HNSCC immunotherapy, individualized immunotherapy in HPV-positive patients, and immune differences in HPV-positive tumors to provide new insights into HNSCC immunotherapy and try to identify patients who may benefit from immunotherapy.

Keywords: head and neck squamous cell carcinoma, immunotherapy, human papillomavirus, immune-checkpoint inhibitors, immune characteristics
INTRODUCTION

Head and neck cancer (HNC) is the sixth most common malignancy worldwide, with approximately 800,000 new cases and 400,000 deaths annually (1), of which head and neck squamous cell carcinoma (HNSCC) account for >90% cases. Past smoking and alcohol consumption are major risk factors of HNSCC. However, the incidence of human papillomavirus (HPV)-associated HNSCC has been increasing recently (2, 3), especially HPV-associated oropharyngeal squamous cell carcinoma (OPSCC) (4, 5). Of the >200 subtypes of HPV have been identified (6), HPV16 is the most closely related to the occurrence and development of HNSCC (7). The prevalence of HPV16 is >80% among HPV-infected OPSCC patients (4, 8). E6 and E7, the two major oncogenic proteins of HPV, can downregulate the tumor suppressor factors TP53 and RB (9, 10), thereby mediating the expression cytokines, leading to immune escape (11), downregulating the interferon pathway, and resulting in an immune-privileged tumor state (12). The above mechanism is the main mechanism underlying HPV-driven HNSCC. Although HPV-positive tumors are more advanced, have a greater burden of disease, but patients with such tumors generally have higher survival rates (13-15), possibly because they have a better treatment response (16).

The treatment of HNSCC is integrated and multimodal including surgery, radiotherapy, chemotherapy and so on (17-19). Patients with early-stage tumors are often considered curable. However, most patients have the advanced disease, often involving the lymph nodes (20, 21). The overall survival rates of patients with advanced disease remain low and most patients relapse within 3–5 years, despite the use of a platinum-based chemotherapy of treatments (22). Nevertheless, combination therapy has been the mainstay of treatment for decades until 2016, when a new immunotherapy was introduced, ushering a new era for HNSCC therapy. Programmed death receptor-1 (PD-1) inhibitors were approved in 2016 for recurrent/metastatic (R/M) HNSCC that progresses after chemotherapy failure. Subsequently, studies on immune-checkpoint inhibitors (ICs) against PD-1, programmed death receptor ligand-1 (PD-L1), and cytotoxic T lymphocyte-associated protein-4 (CTLA-4) were performed (23-25). To date, five PD-1 inhibitors for HNSCC have been developed to the second line of therapy, with the most comprehensive data available for pembrolizumab (KEYNOTE-012 trial) and nivolumab (CheckMate-141 trial) (26, 27). Currently, these two PD-1 inhibitors have been approved by the Food and Drug Administration (FDA) for the treatment of platinum-resistant HNSCC (26, 27). ICs have achieved good efficacy in some HNSCC, indicating that targeted immune system therapy can achieve clinical benefits in HNSCC patients (28, 29). However, most patients show primary resistance, and it is unclear which patients with HNSCC will benefit the most from immunotherapy (30). Studies have shown that immune differences in HPV-positive HNSCC patients may make immunotherapy more effective (29). Hence, studies on immunotherapy in HPV-positive HNSCC have also been conducted.

This article aimed to review the progress of immunotherapy for HNSCC, and to further elucidate the differences between HPV-positive and HPV-negative of immune levels, and the molecular mechanisms underlying the different immunotherapy effects.

IMMUNOTHERAPY IN HNSCC

The Cancer Genome Atlas (TCGA) data shows that HNSCC is the most immune-active tumor tissue after lung adenocarcinoma and renal cell carcinoma (31-33). The occurrence and progression of HNSCC is associated with serious immune deficiency, including immune cell dysfunction, decreased cytokine secretion, and antigen presentation defects (34, 35). Therefore, targeting the immune system is expected to become a new treatment strategy for HNSCC (36). The interactions between tumor cells and the immune system in HNSCC is shown in Figure 1. This study aimed to review immunotherapy for HNSCC from these aspects: immune checkpoint and immune microenvironment.

Immune checkpoints are part of the protein-ligand receptor system that controls T cell activation. Therefore, the application of ICs to block the role of immune checkpoints can promote the release of T cells, increase the antitumor response, and, thus, enhance tumor cell clearance and immune monitoring. PD-1 is a transmembrane protein of the CD28 family of T cell costimulatory receptors, which is expressed in a variety of immune cells, especially in cytotoxic T cells (37, 38). PD-L1 binds to its ligands (PD-L1 and PD-L2), reducing T cell activity and maintaining immune tolerance (39). Therefore, the binding of monoclonal antibodies to PD-1 or PD-L1 can block the inhibitory function of immune checkpoints on T cells to restore the T cell immune response. Pembrolizumab (KEYNOTE-012 trial), the first reported PD-1 inhibitor for R/M HNSCC, had a response rate of 18% (26). This trial supported further study of pembrolizumab as anticancer therapy for HNSCC. Subsequently, the KEYNOTE-055 trial also confirmed this finding (40). Based on these findings, pembrolizumab received accelerated FDA approval in 2016 for the treatment of HNSCC. The KEYNOTE-040 was the randomized, open-label, phase III study, which included 495 patients with refractory HNSCC. The results showed that the median survival time in the pembrolizumab and standard treatment groups was 8.4 and 6.9 months, respectively. In addition, pembrolizumab group had fewer treatment-related adverse events of grade 3 and worse than standard treatment group (30). The results suggest that pembrolizumab may be monotherapy and a part of combination therapy for HNSCC. Subsequently, a clinical trial using pembrolizumab in combination with chemotherapy was conducted. The KEYNOTE-048 trial compared the effectiveness of pembrolizumab alone and pembrolizumab combined with chemotherapy to traditional chemotherapy in patients who relapsed 6 months after standard treatment, which results showed pembrolizumab with chemotherapy improved overall survival versus chemotherapy (13 months vs. 10.7 months, HR 0.77, p=0.0034) (28). Thus, pembrolizumab alone and pembrolizumab in combination with platinum and 5-fluorouracil can be used as an appropriate first-line treatment for R/M HNSCC. In view of this, more clinical
trials are currently underway, including a comparison of pembrolizumab plus radiotherapy with chemotherapy (NCT02641093). In addition, studies have compared the efficacy of pembrolizumab and the oncolytic virus Talimogene laherparepvec (NCT02626000) and the use of pembrolizumab in combination with other agents such as colony-stimulating factor receptor kinase inhibitors (NCT02452424) and histone deacetylase inhibitors (NCT02538510).

CheckMate 141 was the first reported phase III clinical trial of a PD-1 inhibitor, which was designed to compare the efficacy of nivolumab to that of the conventional regimen in R/M HNSCC (27). The results showed that nivolumab was significantly better than traditional chemotherapy, with an increased median survival time of 2.4 months (7.5 months vs. 5.1 months), a 20% higher 1-year survival rate (36% vs. 16%), and a significantly reduced risk of severe adverse reactions (27). Hence, FDA approved nivolumab as a second-line treatment for R/M HNSCC in 2016. In addition, nivolumab in combination with lirilumab, an NK cell-targeted antibody, showed an objective response rate of 24%, and a tumor load reduction of 80% in patients with HNSCC (41, 42). In NCT02426892, nivolumab in combination with the HPV vaccine (ISA101) showed significant activation of T cells and better anti-tumor response in patients with OPSCC (43). In addition, ongoing clinical studies have been assessing the effectiveness of nivolumab in combination with other regimens, such as nivolumab combined with stereotactic radiotherapy (SBRT) (NCT02684253).

Clinical trials of PD-L1 antibodies are also widely underway, such as durvalumab, atezolizumab, and avelumab. A phase II clinical study showed a 16% response rate and a 33% 1-year survival rate for 100 patients administered durvalumab (44). In addition, several clinical studies of durvalumab monotherapy are ongoing (such as NCT02207530 and NCT02827838). The phase I clinical study of atezolizumab showed an effective rate of 22% (45). The phase I clinical trial that evaluate the efficacy of avelumab and CD137 agonists (NCT02554812) is underway.

In addition to PD-1 and PD-L1 inhibitors being applied on HNSCC, CTLA-4 is also an important immune checkpoint. Tremelimumab is an antibody to CTLA-4, CONDOR and EAGLE trial concluded that durvalumab alone or in combination with tremelimumab in patients with R/M HNSCC does not show a significant difference in efficacy (46, 47). Ipilimumab is also a monoclonal antibody against CTLA-4. Clinical trials of ipilimumab and cetuximab combined with IMRT in patients with advanced HNSCC are ongoing (NCT01860430 and NCT01935921). In addition, clinical trials of CD276 and OX40 as new immunotherapeutic targets are also being carried out widely, such as NCT02381314, NCT02274155, etc.

In addition, other immunotherapy drugs have been studied successively, such as the indoleamine 2,3-dioxygenase 1 (IDO1) inhibitors navoximod and epacadostat. IDO1, a rate-limiting enzyme converted to kynurenine by tryptophan, plays an immunosuppressive role in tumor immune microenvironments (48, 49). In previous studies, upregulation of IDO1 inhibited the function of antitumor T cells (50) and high IDO1 expression was associated with poor prognosis (51). IDO1 inhibitor can restore T lymphocyte function, resulting in tumor microenvironment immunogenicity (52). In a phase I clinical trial, navoximod
showed good efficacy in 36% patients (53). KEYNOTE-037 has also reported that epacadostat combined with pembrolizumab has good antitumor effects (54).

Research on immunotherapy for small molecule receptor agonists such as immunoglobulin 2 (IgG2) CD137 agonists, and toll-like receptor 8 (TLR8) agonists are underway. Such as, IgG2 CD137 agonists combined with nivolumab for patients with advanced HNSCC (e.g., NCT02253992). TLR8 agonists stimulate the immune system, further blocking tumor cell survival. NCT01334177 was a phase Ib clinical study designed to evaluate the efficacy of the TLR8 agonist VTX-2337 combined with cetuximab in the treatment of R/M HNSCC. The results showed an objective response rate of 15% and a disease control rate of 54%, with no serious toxicity or deaths; thus, the TLR8 agonist combined with cetuximab was proved to be safe and effective. In NCT01836029, a phase II clinical study, patients with HNSCC also showed good tolerance to VTX-2337 combined with standard chemotherapy; however, significant differences were observed in the overall and progression-free survival (55). A further phase II clinical study of VTX-2337 in combination with nivolumab is ongoing (NCT02124850). In addition, research is being conducted on antitumor vaccines. NCT01998542, a phase II clinical trial completed in 2020, has compared the efficacy and safety of the personalized antitumor vaccine AlloVax (PA) for the treatment of R/M HNSCC; the results are awaited. All of ongoing and completed immunotherapy trials are summarized in Tables 1 and 2, respectively.

The number of immunotherapy trials for R/M HNSCC has been increasing. Different ICs act on different immune checkpoints; these are summarized in Figure 2. Great advances have been made in immunotherapy, bringing new hope for R/M HNSCC treatment. The ongoing and completed clinical trials for different drugs and targets are summarized in Figure 3. However, the benefits of immunotherapy are limited to a small proportion of patients with HNSCC. Therefore, it is important to identify markers that respond well to immunotherapy and further screen appropriate populations for immunotherapy (56, 57). PD-L1 has been studied as a potential biomarker in CheckMate 141, KEYNOTE 040, KEYNOTE 048 (28, 30, 58). PD-L2 has also been studied as another ligand of PD-1 (59, 60). In addition, HPV infection may be a new target to improve the efficacy of HNSCC immunotherapy.

## IMMUNOTHERAPY FOR HPV-ASSOCIATED HNSCC

In HPV-positive tumors, HPV infection leads to an increase in CRT response (61), which activates the immune response and leads to a high proportion of immune cell infiltration, thus exerting a better antitumor response (62). Conversely, HPV-negative tumors are presumed to have a relatively lower immune response. Therefore, the impact of HPV infection on the immunotherapeutic efficacy for HNSCC may be critical (63, 64).

In the KEYNOTE trials, a subset of HPV-positive patients administered pembrolizumab was evaluated to examine the relationship between HPV infection and immunotherapy. In the KEYNOTE-012, HPV-positive HNSCC patients showed a higher response rate with pembrolizumab, a higher progression-free survival for phase I HPV-positive tumors (4 months vs. 2 months), and higher objective response rate (ORR) (32% vs. 14%) (26, 65, 66). Similar results were also confirmed in KEYNOTE-055, although ORR and progression-free survival were similar between the two groups, overall survival in HPV-positive patients showed some advantage, even if it was not statistically significant (40). In addition, in CheckMate 141, nivolumab group showed better overall survival in HPV-positive tumors (27). A 2020 meta-analysis of 11 studies showed that HPV-positive HNSCC patients were 1.29 times more likely to respond to immunotherapy than HPV-negative HNSCC patients (risk ratio 1.29; 95% CI = 0.85-1.96; I² = 0), and have a two-fold higher overall survival rate (11.5 months vs. 6.3 months) (29). In conclusion, the better prognosis of HPV-related HNSCC may be associated with better immunotherapy efficacy.

Given the good efficacy of immunotherapy for HPV-positive patients, a large number of immunotherapy studies targeting HPV-positive HNSCC have been conducted. Several therapeutic vaccine strategies are being studied (67). NCT00257738 is a phase I clinical trial in which patients with R/M HNSCC were administered two peptide vaccines—GL-0810 (HPV16 vaccine) and GL-0817 (MAGE-A3)—to observe their safety and immune response. The results showed that both vaccines were well tolerated and able to activate the antibody response. However, not all clinical trials have reported similar results. A phase I clinical trial using low-dose cyclophosphamide combined with the E7DNA vaccine was halted prematurely (NCT01493154).

The proportion of T cells in patients is closely related to the antitumor immune response (68). Therefore, antigen-specific T cells have become a promising immunotherapeutic strategy. An ongoing phase II clinical trial (NCT01585428II) is examining the efficacy of autologous T cell transfusion after genetic modification for the treatment of HPV-positive tumors (38). Meanwhile, A phase II clinical trial that observing the prognosis of patients with HPV-positive tumors treated with tumor-infiltrating lymphocyte (TIL) infusion was conducted (NCT01585428). MED10457 is a synthetic plasmid targeting the HPV E6/E7 antigen. Aggarwal et al. (69) found that T cells produced a large amount of HPV-specific interferon and increased antigen-specific T cell infiltration with no serious adverse reactions in HPV-positive HNSCC patients administered MED10457 (NCT02163057). In addition, flow cytometry showed HPV-specific PD-1-positive T cells (0% vs. 1.8%) after using MED1047. The results showed that MED10547 can activate the tumor immune response and generate HPV-specific T cells, which has achieved some efficacy in antitumor therapy and may be used as a supplementary treatment strategy for PD-1 inhibitors. Table 3 summarizes ongoing clinical trials for HPV-positive HNSCC patients.

In conclusion, immunotherapy for HPV-positive tumors may have better effect. Next, we will further review the molecular mechanisms by which HPV-related HNSCC has a better immunotherapeutic effect.
| ID          | Phase | N   | Inclusion criteria                                      | Interventions                                                                 | Immunotherapy targets                  | Primary Outcome |
|------------|-------|-----|---------------------------------------------------------|-------------------------------------------------------------------------------|----------------------------------------|-----------------|
| NCT030406247 | II    | 140 | R/M HNSCC                                               | Nivolumab vs Nivolumab + Ipilimumab                                          | PD-1, CTLA-4                            | 2-years DFS     |
| NCT044228151 | II    | 40  | R/M HNSCC                                               | Nivolumab + Relitormab vs Nivolumab + Ipilimumab                             | PD-1, LAG-3, CTLA-4                    | ORR             |
| NCT022966884 | II    | 66  | Locoregionally Advanced, Resectable HNSCC              | Lenvatinib + Pembrolizumab vs Chemotherapy + Lenvatinib                        | PD-1                                    | ORR             |
| NCT03283605  | II    | 45  | Metastatic HNSCC                                        | Nivolumab vs Adjuvant Pembrolizum vs Adjuvant Pembrolizum                    | PD-1                                    | LRR, Distant failure rate |
| NCT03098160  | II    | 400 | R/M HNSCC                                               | Lenvatinib + Pembrolizum vs Docetaxel                                         | PD-1, CTLA-4                            | Acute toxicities, PFS |
| NCT03131804  | II    | 57  | Advanced, Metastatic HNSCC                              | Nivolumab OR Pembrolizum OR Atezolizumab + RT                                 | PD-1, PD-1, PD-L1                      | PFS             |
| NCT01149902  | I     | 10  | Relapsed, Refractory HNSCC                              | cyclophosphamide, docetaxol, OK-43                                           | Vaccine                                | Safety and Feasibility |
| NCT03341936  | II    | 58  | Relapsed, Resectable HNSCC                              | Neodjuviant Nivolumab, Lirilmab + Surgery + Adjuvant Nivolumab, Lirilmab     | PD-1, KIR                               | DFS             |
| NCT03098160  | I     | 69  | Metastatic, Locally Advanced, HPV- HNSCC                | Evofosfinamide, Iplimumab                                                    | CTLA-4                                  | RP2D            |
| NCT03317327  | II    | 20  | Recurrent, secondary primary HNSCC                      | Nivolumab + RT                                                               | PD-1                                    | Incidence, Nature, and Severity of AE |
| NCT03098160  | I     | 69  | Metastatic, Locally Advanced, HPV- HNSCC                | Evofosfinamide, Ipilimumab                                                   | RP2D                                    | OS              |
| NCT03317327  | II    | 58  | Advanced, Metastatic HNSCC                              | Nivolumab OR Pembrolizum OR Atezolizumab + RT                                 | PD-1, PD-1, PD-L1                      | PFS             |
| NCT02999646  | II    | 41  | Stage III/IV, R/M HNSCC                                | M7824 vs M7824 + TriAd vaccine vs M7824 + TriAd vaccine + N-803               | PD-L1, Vaccine                          | pCR             |
| NCT03695510  | I     | 29  | R/M HNSCC                                               | Atevatinib + Pembrolizum                                                      | PD-1                                    | ORR             |
| NCT03552718  | I     | 16  | HNSCC                                                   | YE-NEO-001                                                                  | Vaccine                                | Incidence of AE, RP2D |
| NCT03088039  | I     | 340 | R/M HNSCC                                               | Atevatinib, Palbociclib, Niraparib, BAY1163877, IPH2201, Durvalumab baseline + Nivolumab, Pembrolizum | NKG2A, PD-L1                           | PFS, ORR        |
| NCT03129061  | I     | 24  | Unresectable, Metastatic HNSCC                          | M7824 + TriAd vaccine                                                        | PD-L1, Vaccine, pCR                     | T cell activation |
| NCT03522584  | II    | 20  | R/M HNSCC                                               | Tremelimumab, Durvalumab, HigRT, SBRT                                       | CTLA-4                                  | Incidence of AE  |
| NCT04220775  | I     | 21  | Local-regional Recurrent HNSCC                          | M7824, SBRT                                                                | PD-L1, Vaccine                          | PFS             |
| NCT03975270  | II    | 41  | R/M HNSCC                                               | Sinitilmab + Nabi-pacitaxine                                                  | PD-1                                    | ORR             |
| NCT04133057  | I     | 9   | EBV + R/M HNSCC, EBV-specific TCR-T cells              | EBV-specific TCR-T cells                                                     | PD-1, Engineered T cells                | MTD             |
| NCT04193293  | II    | 30  | R/M HNSCC                                               | Duvelisib + Pembrolizum                                                      | PD-1                                    | Rate of DLT, AE, ORR |
| NCT03823131  | I     | 68  | Unresectable, R/M HNSCC                                | Tavo-EP, Pembrolizum, Epacadostat                                            | PD-1, IDO1                              | ORR             |
| NCT02997332  | I     | 36  | Locally Advanced, untreated HNSCC                       | Durvalumab, Docetaxel, Cisplatin, 5-FU                                        | PD-L1,                                  | PR2D, Number of DLT |
| NCT03546582  | I     | 102 | Locoregionally Recurrent or Second Primary HNSCC        | Pembrolizum + SBRT vs SBRT                                                   | PD-1                                    | PFS             |
| NCT03565783  | II    | 44  | Advanced-Stage, Resectable HNSCC                        | Cemiplimab                                                                  | PD-1                                    | Overall response rate |
| NCT03548467  | I     | 65  | Locally advanced, Metastatic HNSCC                      | VB10.NEO + Bempegadesleukin                                                  | Vaccine                                | Rate of AE      |
| NCT03245499  | I     | 20  | R/M HNSCC                                               | Pembrolizum + Clopidogrel + Acetylsalicylic acid vs Pembrolizum               | PD-1                                    | Effect on major cellular parameters |
| NCT04282109  | II    | 141 | R/M HNSCC                                               | Nivolumab + Paclitaxel vs Cetuximab + Paclitaxel                             | PD-1                                    | OS              |
| NCT03426657  | II    | 120 | Locally Advanced HNSCC                                  | Durvalumab + Tremelimumab + RT                                              | PD-1, CTLA-4                            | PFS             |
| NCT03529422  | II    | 33  | Intermediate Risk HNSCC                                 | Durvalumab + IMRT                                                           | PD-1                                    | DFS             |
| NCT04585782  | I     | 111 | R/M HNSCC                                               | Pembrolizum + Vorinostat                                                     | PD-1                                    | ORR             |
| NCT03629756  | I     | 44  | Advanced, Recurrent HNSCC                               | AB928, AB122                                                               | PD-1                                    | Rate of AE and DLT |
| NCT02812524  | II    | 18  | HNSCC                                                   | Intratumoral ipilimumab                                                     | CTLA-4                                  | Surgery delay rate |
| NCT02764593  | I     | 40  | Intermediate/High-Risk Local-Regionally Advanced HNSCC  | Nivolumab + Cisplatin, Nivolumab + High-dose Cisplatin, Nivolumab + Cetuximab, Nivolumab + IMRT | PD-1                                    | DLT             |
| ID                | Phase | N       | Inclusion Criteria | Interventions                                                                 | Immunotherapy Targets | Primary Outcome                  |
|------------------|-------|---------|--------------------|-------------------------------------------------------------------------------|-----------------------|----------------------------------|
| NCT03226756      | II    | 351     | R/M HNSCC          | Nivolumab                                                                     | PD-1                  | Incidence for AEI                |
| NCT04107103      | II    | 20      | Recurrence HNSCC   | Nivolumab + Pemetrexed                                                         | PD-1                  | Feasibility, Safety/ tolerability |
| NCT03085719      | II    | 26      | R/M HNSCC          | BMS986205 + Nivolumab vs Nivolumab High Dose Radiation + Pembrolizumab         | PD-1                  | Overall Response Rate            |
| NCT03854032      | II    | 48      | Stage II-IV HNSCC  | Cisplatin + IMRT vs Cetuximab + Avelumab + IMRT vs Cetuximab + IMRT           | IDO1, PD-1            | ORR                              |
| NCT02999087      | II    | 688     | Locally Advanced HNSCC | Nivolumab                                                                     | PD-L1                 | PFS                              |
| NCT02274155      | I     | 17      | Locally Advanced HNSCC | MEDI6469                                                                      |OX40                   | Safety and Feasibility           |
| NCT04080804      | II    | 60      | Locally Advanced, Recurrent HNSCC | Nivolumab + Relatlimab vs Nivolumab + Ipilimumab vs Nivolumab                      | PD-1, LAG-3, CTLA-4 | Number of AE                      |
| NCT02955290      | I/II  | 181     | Advanced HNSCC     | CIMAvax, + Nivolumab vs CIMAvax + Pembrolizumab                               | PD-1                  | DLT, OS                          |
| NCT03509012      | II    | 360     | Advanced HNSCC     | Durvalumab + Cisplatin + RT                                                    | PD-L1                 | Rate of DLT and AEs              |
| NCT03336606      | II    | 35      | Advanced, Resectable HNSCC | MEDIO6562 + Surgery                                                             |OX40                   | Activation of immune response     |
| NCT04348916      | I     | 71      | Refractory, Ineligible, Relapsed HNSCC | ONCR-177 vs ONCR-177 + Pembrolizumab                                            |          | Rate of DLT and AE               |
| NCT04129320      | II/III| 750     | R/M HNSCC          | Pembrolizumab + Chemotherapy, Enoblituzumab + MGA012, Enoblituzumab + MGA012 + Chemotherapy | PD-1, B7-H3, PD-1     | Overall Response Rate, Incidence of AE, OS |
| NCT02575404      | I     | 22      | HNSCC with progression | GR-MD-02, Pembrolizumab                                                         | PD-1                  | Rate of AE                        |
| NCT03247712      | II    | 28      | HNSCC planned for surgery | Nivolumab + RT                                                                  | PD-1                  | Rate to Delay to Surgery          |
| NCT04007744      | I     | 45      | R/M HNSCC          | Sonidegib + Pembrolizumab                                                       | PD-1                  | MTD, Response rate               |
| NCT03258554      | II/III| 523     | Locoregionally Advanced HNSCC | Durvalumab + RT vs Cetuximab + RT                                              | PD-L1                 | DLT, PFS, OS                      |
| NCT03083873      | I     | 55      | R/M HNSCC          | LN-145/LN-145-S1                                                               | Cell transfer therapy | ORR                              |
| NCT03051906      | I/II  | 69      | Locally Advanced HNSCC | Durvalumab + Cetuximab + Radiotherapy                                          | PD-L1                 | 2-year PFS                       |
| NCT02892201      | II    | 9       | HNSCC with Residual Disease | Pembrolizumab                                                                 | PD-1                  | Overall response rate            |
| NCT03993333      | I     | 30      | R/M HNSCC          | Tadalafil + Pembrolizumab                                                       | PDE-5, PD-1           | Rate of DLT, OS                  |
| NCT03665285      | I/II  | 143     | Advanced, metastatic HNSCC | NC3118                                                                        | PDE-5, PD-1           | MTD, PAD                         |
| NCT03818061      | I     | 110     | R/M HNSCC          | Atezolizumab + Bevacizumab                                                      | PD-L1                 | Overall response rate            |
| NCT03228667      | II/III| 611     | HNSCC with progression | Durvalumab + RT vs Cetuximab + RT                                              | PD-1, PD-1            | ORR                              |
| NCT03319459      | I     | 100     | Advanced HNSCC     | FATE-NK100                                                                     | NK cell product       | Incidence of DLT                 |
| NCT03631110      | I/II  | 99      | HNSCC              | GEN-009 Adjuvanted Vaccine + Nivolumab, Pembrolizumab                          | Vaccine, PD-1         | Incidence of AE, T-cell responses |
| NCT02376699      | I     | 135     | Advanced HNSCC     | Intravenous (IV) SEA-CD40, Pembrolizumab, Subcutaneous (SC) SEA-CD40, Gemcitabine, Nabi-paclitaxel | CD40, PD-1            | Incidence of AE, ORR             |
| NCT02827838      | II    | 20      | OSCC, OPSCC        | Durvalumab                                                                     | PD-L1                 | Immune effector                   |
| NCT04393506      | I     | 20      | Locally Advanced and Resectable OSCC | Carmelizumab, Apatinib                                                        | PD-1                  | Major pathologic response         |
| NCT03673735      | II    | 650     | HPV-negative HNSCC  | Durvalumab + RT + Cisplatin vs Placebo + RT + Cisplatin                        | PD-L1                 | DFS                              |
| NCT03841110      | I     | 76      | Advanced, HNSCC    | FT500                                                                           | NK cell product       | Rate of DLT                      |

This table contains only ongoing clinical trials registered on the ClinicalTrials.gov, not including terminations or completed trials.

DFS, Disease Free Survival; R/M, Recurrence/metastasis; HNSCC, Head and neck squamous cell carcinoma; ORR, Objective Response Rate; LRR, Locoregional recurrence rates; RT, Radiation therapy; PFS, Progression-free survival; SBRT, Stereotactic Body Radiotherapy; KIR, Killer cell immunoglobulin receptor(NK cell); RP2D, Recommended phase 2 dose; OS, Overall survival; pCR, Pathologic complete response; HOGRT, Hypofractionated Image-Guided Radiation Therapy; MTD, Maximum Tolerated Dose; DLTs, dose-limiting toxicities; DLT, Dose Limiting Toxicity; AE, Adverse Events; AEI, adverse events of interest; PAD, pharmacologically active dose; OSCC, Oral Squamous Cell Carcinoma; HPV., Human papillomavirus.
FIGURE 2 | To summarize the existing immune checkpoint inhibitors for HNSCC patients. Immunotherapy drugs combine with immune checkpoints to block the inhibitory effect of immune checkpoints on cytotoxic T lymphocytes, and then activate the proliferation and infiltration of T cells.

TABLE 2 | Summary of clinical trials that have been completed.

| ID          | Phase | N   | Inclusion criteria                          | Interventions                     | Immunotherapy targets | Primary Outcome                  | State       |
|-------------|-------|-----|---------------------------------------------|-----------------------------------|-----------------------|----------------------------------|-------------|
| NCT02163057| I/II  | 22  | HPV+ HNSCC                                  | NO-3112+EP                        | Vaccine               | Safety and Tolerability          | Completed   |
| NCT02577738| I     | 17  | MAGE-A3+, HPV16+, R/M HNSCC                 | MAGE-A3, HPV16 Vaccine            | Vaccine               | Toxicity                         | Completed   |
| NCT0021424 | I     | 20  | Stage I HNSCC                               | Foxpox-TRICOM vaccine             | Vaccine               | Effectiveness and MTD            | Completed   |
| NCT01998542| II    | 12  | R/M HNSCC                                   | Cancer Vaccine (AlloxA/TM)         | Vaccine               | Progression and MTD, Toxicities  | Completed   |
| NCT01334177| I     | 13  | Locally Advanced, R/M HNSCC                | VTX-2337 + Cetuximab              | TLR8                  | Safety and Efficacy               | Completed   |
| NCT0050388 | II    | 35  | Stage I, II, Resectable HNSCC              | Taladafil                         | PDE-5                 | Ratio of MDSC, T-reg              | Completed   |
| NCT00643635 | –    | 35  | Resectable HNSCC                           |                                   |                       |                                  |             |
| NCT01848834| I     | 297 | R/M HNSCC                                   | Pembrolizumab                      | PD-1                  | OR, OS, Rate of AE               | Completed   |
| NCT02105636| II    | 506 | R/M HNSCC                                   | Nivolumab, Cetuximab, Methotrexate, Docetaxel | PD-1                  | OS, PFS, ORR                     | Completed   |
| NCT02255097| I     | 172 | R/M HNSCC                                   | Pembrolizumab                      | PD-1                  | ORR, Number of AE                | Completed   |
| NCT01375842| I     | 661 | Locally Advanced, Metastatic HNSCC         | Atezolizumab                      | PD-L1                 | Number of DLTs, MTD, RP2D, Rate of AE | Completed   |
| NCT01836029| II    | 195 | R/M HNSCC                                   | Chemotherapy + Cetuximab + VTX-2337 vs Chemotherapy + Cetuximab + placebo | TLR8                  | PFS, OS, AE                      | Completed   |
| NCT02023550| II    | 140 | R/M HNSCC                                   | Nivolumab + Cetuximab             | NKG2A                 | DLTs, ORR                        | Completed   |
| NCT02207530| I     | 112 | R/M HNSCC                                   | Durvalumab                        | PD-L1                 | ORR                              | Completed   |
| NCT02426898| II    | 34  | HPV16+, Incurable HNSCC                    | ISA101 + Nivolumab                | Vaccine, PD-1         | ORR                              | Completed   |
| NCT02525042| II    | 495 | R/M HNSCC                                   | Pembrolizumab vs Active Comparator | PD-1                  | OS, PFS                          | Completed   |
| NCT02319044| II    | 267 | R/M HNSCC                                   | Durvalumab, Tremelimumab,         | PD-L1, CTLA-4         | ORR                              | Completed   |

This table contains only completed clinical trials registered on the ClinicalTrials.gov. R/M, Recurrence/metastasis; HNSCC, Head and neck squamous cell carcinoma; ORR, Objective Response Rate; PFS, Progression-free survival; RP2D, Recommended phase 2 dose; OS, Overall survival; MTD, Maximum Tolerated Dose; DLTs, Dose Limiting Toxicities; DLT, Dose Limiting Toxicity; AE, Adverse Events; HPV, Human papillomavirus; OR, Overall response.
IMMUNE CHARACTERISTICS OF HPV-POSITIVE TUMORS

The differences in the efficacy of immunotherapy are mainly related to the intrinsic characteristics of HPV-positive tumors, including tumor immunogenicity, immune cell infiltration, and IC expression (70).

In 2013, differences in immune cell infiltration between HPV-positive and HPV-negative HNSCC were reported for the first time; higher proportions of B cell infiltration were noted in HPV-positive tissues (71). Subsequent research by Wood et al. confirmed this finding (72). Studies have confirmed a larger proportion of CD8+T cell infiltration in HPV-positive HNSCC (31, 73, 74), which is strongly associated with improved prognosis of HPV-positive tumors (75, 76). TILs are often present in tumor tissues and represent an adaptive host antitumor response. Chakravarthy et al. (77) measured CD4 and CD8 mRNA abundance to compare TIL levels between HPV-positive and HPV-negative tumors, showing higher TIL levels in the HPV-positive group. Significant increases in multiple T cell markers were also found, indicating that lymphocyte infiltration may be a key factor leading to survival differences in HPV-positive HNSCC (77). Subsequently, in a 2014 study (78), patients were divided into high-risk and low-risk groups based on TIL levels. The results showed a significantly higher 3-year survival rate in the high-TIL group than in the low-TIL group. Similar results were reported in two studies by King and Nasman (79, 80). Therefore, a high proportion of TILs may play an antitumor role through adaptive host immune response, which may contribute to increased survival of HPV-positive patients (81, 82).

Treg cells are a subset of T cells with immunosuppressive effects.
which inhibit the immune responses of other cells through Foxp3, CD25, and other transfer factors. Treg cells are usually associated with poor prognosis. However, recent findings in HPV-positive HNSCC show the opposite (72). NK cells are an important part of innate immunity. In HPV-positive tumors, NK cells also have higher levels of infiltration (83) and are associated with better prognosis (31, 72). Therefore, in HPV-positive tumor tissues, the high proportions of TILs infiltration, CD8+ T cells, Treg cells, NK cells, and other immune cells may explain the better prognosis (84–86).

In addition, in an analysis of TCGA Database, Marij et al. (87) found that HPV-specific T cells are present in HPV-positive tumors and that their presence is associated with better survival. Studies have also confirmed the presence of HPV-specific T lymphocytes in the peripheral blood of HPV-positive HNSCC patients in vitro (88). A recent study compared the immune spectra of HPV-positive and HPV-negative tumors by single-cell RNA and multispectral immunofluorescence analysis, reporting the presence of germinal center B cells in HPV-positive TILs and low percentages of B cells in HPV-negative HNSCC, with most in a non-germinal center state (89). Therefore, differences in immune cell infiltration may be one of the reasons for the good prognosis in HPV-positive HNSCC.

Through gene expression analysis, Wood et al. confirmed increased expressions of PD1, CTLA-4, and T-cell immunoglobulin and mucin-domain containing-3 (TIM-3) in HPV-positive HNSCC (72, 90). With the discovery of PD-L1 in head and neck tissue, higher PD-L1 expression and activity have been found in HPV-driven HNSCC (91, 92), which was associated with a good prognosis (93). PD1+ TILs were present in HPV-positive HNSCC, suggesting that PD-1 may play an important role in HPV-positive HNSCC (91). Some studies also speculated that TILs promote PD-L1 expression in HPV-positive HNSCC tumor cells through the secretion of pheromone -γ (81) to explain the expression levels exceeding 70% (91, 94). The higher expression level of CTLA-4 may be related to the higher proportion of T cells expressing CTLA-4 (31). During HPV infection, high levels and activity of PD-1, PD-L1, and CTLA-4 may contribute to the good effects of ICs in HPV-positive HNSCC patients.

**CONCLUSION**

After surgery, radiotherapy, chemotherapy, and targeted therapy, the emergence of immunotherapy has ushered in a new era in the treatment of HNSCC. Inhibitors based on immune checkpoints such as PD-1, PD-L1 have achieved good clinical efficacy, and clinical studies on multitarget combined immunotherapy, immunotherapy combined with traditional radiotherapy, chemotherapy, and IC combined with small molecular agonists are also being performed. The development of immunotherapy brings hope of new treatment options and survival for advanced HNSCC patients. However, their efficiency is only about 20%. Therefore, patient selection and the discovery of effective biomarkers for immunotherapy are important.

HPV infection is a newly discovered risk factor of HNSCC. Patients with HPV-positive tumors have better prognosis than HPV-negative tumors, which may be related to better treatment outcomes. Subgroup analysis of the KEYNOTE-012, 055 trials showed better responses in HPV-positive patients using pembrolizumab. Subsequently, trials on immunotherapy for HPV-positive HNSCC patients were gradually performed, including those for a immunomodulatory vaccine for HPVE6/E7 and auto-specific T-cell transfusion. HPV-positive patients have become a special group for immunotherapy. However, some studies have suggested that there is no significant advantage in immunotherapy for patients with HPV-positive HNSCC (95). So further research is needed to determine if immunotherapy can achieve better clinical benefits in these patients.

Studies have confirmed higher immune cell infiltration and expression levels of PD-1, PD-L1, and other immune checkpoints in HPV-positive tumors, which may be the key factor for better efficacy of immunotherapy. Further research on the immune system and immune microenvironment of HPV-positive tumors will provide a new theoretical basis for individual immunotherapy of HPV-
positive patients and lay a foundation for screening suitable populations for immunotherapy. In addition, further in vitro and in vivo studies of HPV-positive tumors related to the immune system and further exploration of potential immune-related targets in HPV-positive cells are essential to improve the immunotherapeutic efficacy of immune-tolerant HNSCC.

AUTHOR CONTRIBUTIONS

Conceptualization, XJ and YX. Software, investigation, HW, QZhang, YYZ, ZZ, and ZL. Resources, YX. Writing-original draft preparation, HW, QZhao, SL, ZL, and XJ. Writing-review and editing, LM, YX, and XJ. Funding acquisition, XJ. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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