An Update on the Immunotherapy for Oropharyngeal Squamous Cell Carcinoma

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Oropharyngeal squamous cell carcinoma (OPSCC) is an uncommon malignancy worldwide. Remarkably, the rising incidence of OPSCC has been observed in many developed countries over the past few decades. On top of tobacco smoking and alcohol consumption, human papillomavirus (HPV) infection has become a major etiologic factor for OPSCC. The radiotherapy-based or surgery-based systemic therapies are recommended equally as first-line treatment, while chemotherapy-based strategy is applied to advanced diseases. Immunotherapy in head and neck squamous cell carcinoma (HNSCC) is currently under the spotlight, especially for patients with advanced diseases. Numerous researches on programmed death-1/programmed death-ligand 1 checkpoint inhibitors have proven beneficial to patients with metastatic HNSCC. In 2016, nivolumab and pembrolizumab were approved as the second-line treatment for advanced metastatic HNSCC by the USA Food and Drug Administration. Soon after, in 2019, the USA Food and Drug Administration approved pembrolizumab as the first-line treatment for patients with unresectable, recurrent, and metastatic HNSCC. It has been reported that HPV-positive HNSCC patients were associated with increased programmed death-ligand 1 expression; however, whether HPV status indicates different treatment outcomes among HNSCC patients treated with immunotherapy has contradicted. Notably, HPV-positive OPSCC exhibits a significantly better clinical response to primary treatment (i.e., radiotherapy, surgery, and chemotherapy) and a more desirable prognosis compared to the HPV-negative OPSCC. This review summarizes the current publications on immunotherapy in HNSCC/OPSCC patients and discusses the impact of HPV infection in immunotherapeutic efficacy, providing an update on the immune landscape and future perspectives in OPSCC.

Keywords: oropharyngeal squamous cell carcinoma (OPSCC), immunotherapy, immune checkpoint inhibitor, human papillomavirus infection, treatment outcome
1 INTRODUCTION

Oropharyngeal squamous cell carcinoma (OPSCC) is one of the head and neck squamous cell carcinoma (HNSCC), developing in the following areas: soft palate, base of the tongue, palatoglossal folds, palatine tonsils, valleculae, and posterior pharyngeal wall (1). According to the latest GLOBOCAN estimates, OPSCC is uncommon globally, with an estimated 98,412 new cases (0.5% of all cancers combined) and 48,143 deaths (0.5% of all cancers combined) in 2020 (2). Historically, tobacco smoking and alcohol consumption are considered the most common risk factors for HNSCC, including OPSCC (3, 4). Benefits from successfully controlling tobacco and alcohol use in the western world since a few decades ago, incident OPSCCs related to smoking and drinking have been declining (5–8). However, the overall incidence of OPSCC is still on the rise, along with an increasing subset of HPV-positive cases (5–7, 9).

The standard of care (SoC) for OPSCC, which includes surgery, radiotherapy, and chemotherapy, has continuously improved. However, the prognosis of OPSCC patients remains poor due to late diagnosis, high rates of primary-site recurrence, and lymphatic metastasis (10, 11). Recently, the use of immunotherapy in patients with HNSCC, including OPSCC, has become a hot spot (12–15). Among numerous immunomodulatory agents, programmed death-1 (PD-1)/programmed death-ligand 1 (PD-L1) checkpoint inhibitors have been proven effective in those patients with metastatic HNSCC (16–18). Nevertheless, the influence of the HPV status in OPSCC patients on the efficacy of immunotherapy, drug resistance, and heterogeneity on response remain unclear, which are under investigation (19, 20).

This review intends to update the current evidence in immunotherapy among OPSCC patients and the impact of HPV infection on the treatment efficacy of immunotherapy, providing future perspectives in OPSCC treatment.

2 HPV AND OPSCC

HPV is a small non-enveloped, circular, double-stranded DNA virus with epithelial tropism and commonly transmits by sexual contact. It has been reported that HPV infection was attributed to around 20% ~ 60% of OPSCC worldwide (9, 21). Among 200 identified genotypes of HPVs, genotype HPV-16 accounts for over 80% of HPV-positive OPSCC, followed by HPV-18, 31, 33, 35, which are well-known high-risk HPVs (9, 22). E6 and E7, two early viral proteins expressed by high-risk HPV, are mainly involved in developing and maintaining the transformed phenotype of HPV-induced cancers (23). Specifically, the oncoprotein E6 degrades the tumor suppressor p53 and helps escape cell death (21, 24). E7 binds to the retinoblastoma proteins (pRb), promoting the E2F/pRb complex dissociation and releasing E2F, which stimulates the cell re-entering S-phase, leading to escape from oncogene-induce senescence (21, 25). Besides, E6, E7, and E6/E7 contribute to the maintenance of cancer phenotype, epigenetic regulation, microRNAs, DNA damage response, genetic instability, angiogenesis, immune system modulation, telomerase activity via a variety of molecules/pathways (25). Although playing a less crucial role, other early proteins, including E1, E2, E4, and E5, participate in completing the viral cell cycle (9, 21).

HPV-positive OPSCC represents distinct prognostic characteristics and genomic patterns compared to HPV-negative disease. Numerous studies have revealed that HPV-positive OPSCCs exhibited better disease-free survival after primary treatment (26–30). A large-scale retrospective analysis has confirmed the prognostic value of HPV status with a remarkable result: HPV-positive OPSCC patients (63.8%, 206 in 323) represented a better 3-year rates of overall survival (82.4%, vs. 57.1% in HPV-negative OPSCC patients; P<0.001) (31). Besides, the comprehensive genomic landscape in HPV-positive HNSCC is remarkably different from smoking-related HNSCC (32–34). In general, HPV-positive HNSCCs exhibited a relatively low mutational burden (2.28 mutations per Mb vs. 4.83 mutations per Mb in HPV-negative cases) (32), a high proliferative index, a frequent alteration in the PIK3CA pathway, compared to HPV-negative HNSCCs (35). A recent study reported that the most frequent mutation exhibited in an OPSCC cohort with 948 subjects was TP53 (33%), followed by PIK3CA (17%) and KMT2D (10.6%); and TP53 was more commonly mutated in the HPV-negative group (mutation rate: 49% vs. 10%, P < 0.0005) (36).

The 7th edition of the Union for International Cancer Control and American Joint Committee on Cancer (UICC/AJCC) staging system failed to differentiate the impact of HPV infection on survival (hazard consistency) between stages and lost the capability in predicting features of any stage (37). Hence, the latest released 8th edition has introduced apparent modifications in a new staging algorithm to categorize OPSCC patients into two different systems regarding HPV status. We summarize the difference between the 7th and 8th edition of UICC/AJCC staging systems of OPSCC in the Supplementary Table. The College of American Pathologist Guidelines recommended that p16 expression tested by immunohistochemistry is a feasible and reliable surrogate marker for diagnosing HPV-positive OPSCC (38, 39). It is worth noting that discordance between p16 staining and HPV status (e.g., patients with p16INK4a-positive/HPV DNA-negative) has been observed and related to differentiated survival (40, 41). Therefore, we shall be aware that p16INK4a alone may not be the best biomarker for prognosis prediction. Alternative and/or complementary biomarker, such as DNA and RNA in situ hybridization and other molecular HPV tests, is urgently needed (37, 42).

3 IMMUNOTHERAPY

A significant breakthrough has been achieved in cancer immunotherapy, making it an important weapon in fighting cancer (43–46). According to the Cancer-Immunity Cycle proposed by Chen et al., cancer cells can be effectively eradicated by the immune cells via a stepwise process which
starts with a successful initiation of cancer immune recognition and accumulation of adaptive immune responses, to cancer cell elimination eventually (47). Nevertheless, the Cancer-Immunity Cycle does not always work desirably in cancer patients; for instance, T-cell-mediated attack might fail to activate due to the suppression by some factors in the tumor microenvironment (48). Each step in the Cycle acts as a potential strategy for cancer immune escape and an eligible target for treatment (49). Among those steps, PD-1/PD-L1 checkpoint axis is most widely studied, which prevents the over-activation of T cells from damaging normal tissues and leads to the potential of tumor immune escape (12). In the past decade, blocking the PD-1/PD-L1 axis by monoclonal antibodies to overcome the immune suppressive signals in cancer patients and promote the reactivation of antitumor response has been well-established as an efficient treatment in a broad range of cancer types (including but not limited to lung cancer, breast cancer, head and neck cancer, pancreatic cancer, and prostate cancer) (50–54).

4 IMMUNOTHERAPY IN HNSCC/OPSCC

4.1 Clinical Application of Immunotherapy in HNSCC/OPSCC

4.1.1 PD-1/PD-L1 in HNSCC/OPSCC

In the past decade, dozens of clinical trials have demonstrated the superiority of immunotherapy over chemotherapy in prolonging patients’ survival with advanced HNSCC, including patients with OPSCC. Recent clinical practice in immunotherapy is summarized in Table 1.

Landmark trials have demonstrated the efficacy of immunotherapy in patients with HNC (including OPSCC). The phase Ib trial published in 2016, KEYNOTE-012 (NCT01848834), was the first study investigating PD-1 blockade therapy in 104 recurrent/metastasis (R/M) HNSCC patients expressing PD-L1 (38% were HPV-positive and 62% were HPV-negative) (70). The overall response rate (ORR) reached 18% (95% CI, 8.3–32%), and median overall survival (OS) was 13 months. CheckMate 141, a phase III trial, revealed that nivolumab was superior to standard, single-agent therapy (cetuximab, methotrexate, or docetaxel) among 361 patients with platinum-refractory HNSCC (p16-positive/negative were 25.5% and 23.8%, respectively) (43–45). The response rate (RR) in the nivolumab group was 13.3% (95% CI, 9.3 to 18.3) versus 5.8% (95% CI, 2.4 to 11.6) in the standard group; and the OS was significantly longer in the nivolumab group than the standard, single-agent group (hazard ratio for death, 0.70; 97.73% CI, 0.51 to 0.96; P=0.01). Based on these two landmark trials, the FDA approved pembrolizumab and nivolumab as the second-line treatment for R/M HNSCC in 2016. Soon after, the phase II, single-arm study, KEYNOTE-055, demonstrated that 16% (95% CI, 11% to 23%) of the 171 R/M HNSCC patients (22% were HPV+ and 77% were HPV-) refractory to platinum and cetuximab who received pembrolizumab achieved confirmed response, with 8 months median duration of response (range, 2+ to 12+ months) (43–45). Around 64% of all patients treated with pembrolizumab experienced different levels of treatment-related adverse events (trAEs) which was deemed acceptable safety. KEYNOTE-040 (NCT02358031) was a globally randomized, phase III study involving 495 R/M HNSCC patients after platinum-based chemotherapy (24.0% were HPV+ and 76.0% were HPV-) (43–45). In 2019, it proved the superiority of pembrolizumab to chemotherapy in the R/M HNSCC patients [median OS: 8.4 months (95% CI 6.4–9.4) in the pembrolizumab group versus 6.9 months (5.9–8.0) in the standard-of-care (SoC) group, the HR was 0.80 (0.65–0.98)]. In addition, fewer patients treated with pembrolizumab exhibited severe trAEs (grade 3 or worse) (43–45). Meanwhile, KEYNOTE-048, a randomized, phase III study, stated that pembrolizumab with chemotherapy (platinum and 5-fluorouracil) was effective and safe as a first-line treatment for R/M HNSCC patients (43% were HPV+), and pembrolizumab alone was an appropriate first-line therapy for PD-L1 positive patients (71). Patients treated with pembrolizumab with chemotherapy had better overall survival than those exposed to cetuximab with chemotherapy in the total population [13.0 months vs 10.7 months, HR 0.77 (95% CI 0.63–0.93), P=0.0034]. Hence, the FDA had taken one big step forward.

**TABLE 1 | Clinical practice in immunotherapy among OPSCC patients.**

| Immunotherapy                          | Effect                                      | Drug                          | Ref. |
|----------------------------------------|---------------------------------------------|-------------------------------|------|
| Monoclonal antibody (mAbs)             | Targeting molecular involving in tumor-genesis | Cetuximab                     | (55) |
| Tumor antigen–targeted mAbs            | EGFR antagonist                             | Ipilimumab and Tremelimumab   |      |
| Immune checkpoint–targeted mAbs        | CTLA4                                       | Pembrolizumab and Nivolumab   |      |
| Cancer vaccines                        | PD-1                                        | Darvalumab                    |      |
| Tumor system modulators                | Activating tumor-antigen presentation by APC to T cells | Vaccinia-based E6/E7 vaccines |      |
| Stimulatory receptor agonists           | Enhancing immune cell activation and expansion | Agonists for CD40             | (56–58) |
| T-cell transfer therapy                | Transfer of ex vivo expanded/modulated tumor-reactive T cells into patients. | Agonists for tol-like receptor | (69) |
|                                        |                                             | Tumor-infiltrating lymphocytes (TIL) therapy, Chimeric antigen receptor(CAR) T-cell therapy | (60, 61) |

*mAbs, Monoclonal antibody; EGFR, epidermal growth factor receptor; CTLA4, Cytotoxic T-Lymphocyte Associated Protein 4; APC, antigen-presenting cell (62–69).*
to approve pembrolizumab as the first-line treatment for patients with R/M HNC in 2019 (43–45).

4.1.2 Immunotherapy-Combined Treatments in HNSCC/OPSCC
SoC of HNSCC, including surgery, radiotherapy, chemotherapy, and targeted therapy, have been well-studied and widely applied in clinics with a proven impact (72). Nevertheless, the efficacy of SoC has reached a plateau, and a novel therapeutic modality is urgently needed. After the notable success of PD-1/PD-L1 achieved in treating advanced HNSCC, researchers have devoted their passion to explore the potential of immunotherapy-combined treatments.

Lenvatinib is a tyrosine kinase inhibitor of several VEGF receptors and could modulate immune suppression in the tumor micro-environment by angiogenesis inhibition. The effectiveness of pembrolizumab in combination with lenvatinib in patients with HNSCC has been supported by a phase II trial (NCT02501096) (72) towards 137 patients with various advanced solid tumors. The ORR at week 24 at the recommended dose (lenvatinib 20 mg/d, pembrolizumab 200 mg every 3 weeks) of HNSCC patients was 36% (8/22; 95% CI, 17.2% to 59.3%). Large-scale studies are needed to evaluate the long-term safety and efficacy of this combination.

Besides, the impact of ICI therapy combined with chemotherapy was investigated in a wide range of solid tumors. Some of these trials (KEYNOTE-189, 355, 361, 407, 590, 826) observe statistically significant survival benefits (longer PFS, higher estimated rate of overall survival at 12 months) in patients with corresponding cancers (73–78), suggesting adding pembrolizumab to standard chemotherapy for cancer treatment. As described above, the KEYNOTE-048 trial reported that pembrolizumab plus chemotherapy improved HNSCC patients’ OS versus cetuximab with chemotherapy (13.0 vs. 10.7 months, P = 0.0034), while pembrolizumab monotherapy was non-inferior to cetuximab with chemotherapy (11.6 vs. 10.7 months). When stratifying the patient population with CPS score, both arms show survival benefits compared to cetuximab with chemotherapy. However, 85% of the R/M HNSCC patients in the pembrolizumab with chemotherapy group suffered grade 3 or worse all-cause adverse events (AEs), while 55% of the patients in the pembrolizumab monotherapy group endured AEs. It indicates that when clinicians decide on monotherapy or combined therapy, the toxicity should be considered in the clinical settings.

4.1.3 Dual Immune Checkpoint Blockade Therapy in HNSCC/OPSCC
The desirable effect of single-agent immunotherapy sparks research into the combination of anti-CTLA-4 and anti-PD-1 therapies (79). Ipilimumab, a monoclonal antibody medication targeting CTLA-4, has been approved for application in melanoma, advanced high-risk renal cell carcinoma, colorectal cancer (80–82). A phase II, open-label, randomized clinical trial (NCT02919683) evaluating the effect of nivolumab (N arm) or nivolumab-ipilimumab (N+I arm) in HNSCC patients before surgical resection showed that both arms had a favorable response, whereas RR in the N+I arm was better in the RECIST manner (N+I arm: 38%, N arm: 13%) (83).

In addition, a phase III trial, EAGLE (NCT02369874), aimed to assess the combination of durvalumab plus tremelimumab (anti-CTLA4 mAb, approved by the FDA to treat malignant mesothelioma) (84). This trial investigated the efficacy of durvalumab +/- tremelimumab versus SoC (e.g., cetuximab, taxane, methotrexate, or fluoropyrimidine) towards 736 R/M HNSCC patients (37.2% with primary OPSCC). Neither in durvalumab arm (D arm) nor in durvalumab plus tremelimumab arm (D+T arm) reported significant survival difference when compared to SoC group (OS: D arm vs. SoC arm, P = 0.20; D+T arm vs. SoC arm, P = 0.76). Further research is needed to investigate dual ICI therapy’s efficacy in HNSCC, especially OPSCC patients (85).

4.1.4 Novel Immunotherapy in HNSCC/OPSCC
Apart from immune-combined therapy and a combination of anti-CTLA4 and anti-PD-1/PD-L1 therapy, there are other immunotherapies toward HNSCCs using anti-PD-L1 drugs (e.g., avelumab and atezolizumab) (86, 87). Besides, other immunotherapies targeting additional immune checkpoints (e.g., LAG-3, TIM-3, TIGIT, and VISTA) are under investigation (88).

Among these novel therapies, researchers in the field of HNSCC, including OPSCC, start to explore the effect of IDO1 inhibition therapy and toll-like receptor 8 (TLR8) agonists therapy through clinical trials. The results of the phase Ib study (NCT02471846) were disappointing that the combination of navoximod (IDO1 inhibitors) and atezolizumab (anti-PD-L1 agent) failed to improve clinical benefit among patients with various solid tumors, including HNSCC (89). However, the results of the Active8 study were encouraging that TLR8 agonists might prolong survival among HPV-positive HNSCC patients compared to HPV-negative patients (PFS: 7.8 versus 5.9 months; HR, 0.58; P = 0.046; OS: 15.2 versus 12.6 months; HR:0.41; P = 0.03) (59).

In all, immunotherapy provides a promising future, but the application in the treatment of OPSCC is still lacking. Researchers should take steps to discover more information in this field.

4.2 Immunotherapy in OPSCC Regarding the HPV Status
4.2.1 Immunotherapy in HPV-Positive OPSCC
HPV is a solid causative agent in the formation and progression of OPSCCs, making viral neoantigens an attractive target for therapeutic immunization. Tumor vaccine aims to reduce tumor burden and control tumor recurrence by stimulating both humoral and cellular immune response, offering an immune activation strategy (90). Current HPV-positive therapeutic vaccines are depicted in Figure 1.

Given the essential roles E6 and E7 play in HPV-positive cancers, they are usually selected as targets for a therapeutic
A phase I study (ACTRN12618000140257) assessed the safety, tolerability, and immunogenicity of an HPV E6/E7 vaccine (AMV002) in patients with HPV-positive OPSCC (91). The vaccine-induced RR was 83.3% (10 of 12). In addition, a phase Ib/II trial (NCT03162224) evaluating the safety and efficacy of MEDI0457 (DNA vaccine targeting HPV-16/18 E6/E7 antigens accompanied with an IL-12 adjuvant) plus durvalumab in HPV-positive R/M HNSCC patients is underway (92).

On top of various vaccines, Ramireddy et al. showed that tumor membrane vesicle (TMV) vaccine comprises glycolipid-anchored immuno-stimulatory molecules GPI-B7-1 and GPI-IL-12, magnified the efficacy of anti-PD1 antibodies and inhibited tumor growth, and thus improved the survival of mice with stage VII SCC (93). In addition, the early expressed HPV E5 protein has gained attention recently (94). By amplifying EGFR, HPV E5 protein promoted cell proliferation and invasion through Ras-ERK1/2, PI3K-AKT, and COX-2 pathways (95). As more signaling pathways are involved in understanding tumor-related events, new target sites are under active investigation.

However, those HPV therapeutic vaccines were neither successful in achieving desired clinical outcomes nor applied to human study. Researchers put forward that one reason might be that patients obtained immune tolerance to antigens due to chronic exposure to the virus for years (96). Therefore, we suggest that improving the immunogenicity of several types of vaccines and ensuring safety and tolerability warrant more future efforts.

4.2.2 Immunotherapy in HPV-Negative OPSCC
Currently, there are few studies on immunotherapy towards HPV-negative OPSCC. DURTRERAD is a randomized phase II trial evaluating feasibility and efficacy of durvalumab (D arm) versus durvalumab and tremelimumab (DT arm) in combination with radiotherapy as primary treatment for locally advanced HPV-negative HNSCC, more than a half being OPSCC (97). In this trial, the DT arm was halted due to increased toxicity. Five among six patients in the DT arm suffered varying degrees of trAEs, with one quitting the cohort because of grade 5 trAE. However, detailed analysis has not been fully reported (97).

4.2.3 Survival Benefits of Immunotherapy in Relation to HPV Status
As mentioned above, the prognosis of OPSCC patients is closely associated with HPV status in the setting of SoC. Nevertheless, HPV status seems to be limited in predicting the prognosis of

**FIGURE 1** | Different Types of Therapeutic Vaccines against HPV-positive Tumors. CD4+ T Cell, Cluster of differentiation 4-positive thymus cell; CD8+ T Cell, Cluster of differentiation 8-positive thymus cell; Fas, Factor associated suicide; FasL, Factor associated suicide ligand. (Figure was created with BioRender.com.)
immunotherapies towards OPSCC patients. A systematic review of clinical trials using immunotherapy, mainly ICIs in HNSCC, did not report any statistically significant difference concerning ORR, stable disease (SD), progressive disease (PD), or OS when patients were classified by HPV status. However, ORR was approaching significance in HPV-positive patients compared to HPV-negative ones (21.2% vs. 15.0%, $P = 0.06$) (7).

It should be pointed out that the accuracy of existing detection methods would influence the result of these trials. A study held by Miren Taberna et al. Proves that the ICON-S model in 8th AJCC predicts overall survival assessment better in HPV-related OPC patients when using at least two biomarkers to define HPV-causality (HPV-DNA and (p16INK4a or HPV-mRNA) or double positivity for HPV-DNA/p16INK4a) (98). These results call for a clear definition of HPV status in future studies, and competent biomarkers to identify the beneficiaries from immunotherapies.

4.3 Biomarkers for Immunotherapy in OPSCC
Cancer biomarkers help evaluate treatment effects, monitor tumor recurrence and predict survival. The application of biomarkers will influence patient outcomes; hence, exploring and discovering novel biomarkers have significant research value.

The prediction value of PD-(L)1 expression measured by immunohistochemistry for prognosis in patients with HNSCC was analytically validated (99). Previous studies evaluating durvalumab treatment effect demonstrated a better anti-tumor response in R/M HNSCC patients with high PD-L1 expression versus those with low or no PD-L1 expression (median OS: 7.1 vs 6.0 months, ORR: 16.2% vs 9.2%) (100). Nevertheless, the cut-off value varies from trials to trials, and researchers need more trials to define a uniform standard when using PD-(L)1 expression as a prognostic marker (100).

Recent efforts to excavate molecular biomarkers through next-generation sequencing provided deeper and broader insights. Genetic and epidemic alterations are involved in the initiation of HNSCC formation. Genetic alterations include the classic mutations in TP53 and CDKN2A and the newly discovered mutations in FBXW7, TP63, IRF6, and NOTCH1 (32). NOTCH signaling pathways were associated with the development of multiple types of tumors, such as hepatocellular carcinoma, T cell leukemias, myeloid leukemia (101–103). Gianluigi Grilli et al. reported that the activation of the NOTCH pathway improved prognosis in HPV-negative HNSCC patients and suggested that NOTCH1 expression might be a predictive marker for survival in HPV-negative HNSCC (104). Besides, Esposti et al. identified a unique epigenetic feature: hypomethylation in NCAN, NMX1, COL19A1, SYCP2, RPA2, and SMCL1, related to HPV infection among HNSCCs regardless of the anatomic site (105). Moreover, differentially expressed small non-coding RNA molecules (miRNAs) may also predict survival. Expression of miR-21 was associated with poor cancer-specific survival in HPV-negative tumors (106).

5 LIMITATIONS AND PROSPECTS

5.1 Resistance to Immune Checkpoint Blockade
Most clinical trials evaluating the RR to ICIs in OPSCC patients indicate that less than 15% of patients receiving ICI therapy could achieve durable responses (14, 15, 107). Evidence supports that failure of immune sensing might contribute to compromised immune function. Two dysfunctional oncogenic pathways, the SOX2-mediated suppression of the IFN-I signaling pathway and the PI3K-mTOR pathway, deprive extracellular glucose and thus exhaust cytotoxic T lymphocytes (CTLs) (108). Pervasive immune suppression is the primary barrier, contributing to the limited beneficial effects of ICIs in OPSCC. Researchers proposed that targeting the IFN-I signaling pathway through IFN-I agonists (e.g., cGAMP), inducing DNA damage by RT or DNA-damage inducing agents (e.g., cisplatin and 5-fluorouracil), and is revitalizing CTLs (e.g., rebuilding a pH-neutralized environment to provide nutrition) might be effective (109–112). In addition, Zhou L. et al. suggest that epigenetic targeting drugs such as DNA methyltransferase inhibitors, histone deacetylase, and methyltransferase inhibitors may potentially reverse immune suppression in various cancer models (113).

5.2 Difficulty in Personalized Immunotherapy Strategy
In the clinical practice of immunotherapy, evaluating patients’ immune status could be challenging. As discussed above, feasible biomarkers could guide researchers to identify potential beneficial patients and monitor adverse events. However, it is insufficient to select patients for ICI immunotherapy based on a single parameter without considering other factors given the highly heterogeneous microenvironment in OPSCC. An ex vivo platform, CANscript system, has been proven helpful to for profiling the response of immunotherapy combining chemotherapy (114). Besides, researchers have established several prognosis risk models to indicate immunosuppression state and predict survival in patients based on a set of immune checkpoint-related genes (115, 116). It is a pity that, however, existing predictive models lack validation upon large sample size.

6 CONCLUSION
In summary, classified by HPV status, OPSCC is a heterogeneous disease. The unique TME shaping by HPV status calls for distinct therapeutic approaches. Immunotherapy offers a wide range of therapeutic strategies which will be especially useful in meeting this need. Monotherapy of novel agents has proved effective, while combinations of immunotherapy with conventional therapies and dual immunotherapy are undergoing clinical investigation. Notably, there is an urgent need for a feasible treatment stratification by HPV status. Immunosuppression and lack of desirable biomarkers for personalized therapy are the two significant issues in immunotherapy. More clinical trials are warranted to assess the efficacy of novel immunotherapies based on HPV status.
REFERENCES

1. Chi AC, Day TA, Neville BW. Oral Cavity and Oropharyngeal Squamous Cell Carcinoma—an Update. CA Cancer J Clin (2015) 65(4):401–21. doi: 10.3322/caac.21292

2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin (2021) 71(3):209–49. doi: 10.3322/caac.21660

3. Retting EM, D’Souza G. Epidemiology of Head and Neck Cancer. Surg Oncol Clin N Am (2015) 24(3):379–96. doi: 10.1016/j.soc.2015.03.001

4. Hashibe M, Brennan P, Benhamou S, Castellague X, Chen C, Curado MP, et al. Alcohol Drinking in Never Users of Tobacco, Cigarette Smoking in Never Drinkers, and the Risk of Head and Neck Cancer: Pooled Analysis in the International Head and Neck Cancer Epidemiology Consortium. J Natl Cancer Inst (2007) 99(10):777–89. doi: 10.1093/jnci/djk179

5. D’Souza G, Kreimer AR, Viscidi R, Pavlita M, Fakhry C, Koch WM, et al. Case-Control Study of Human Papillomavirus and Oropharyngeal Cancer. N Engl J Med (2007) 356(19):1944–56. doi: 10.1056/NEJMoa065497

6. Gillison ML, Castellsague X, Chaturvedi A, Goodman MT, Snijders P, Tommasino M, et al. Erythropoietin: Comparative Epidemiology of HPV Infection and Associated Cancers of the Head and Neck and Cervix. Int J Cancer (2014) 134(3):497–507. doi: 10.1002/ijc.28201

7. Patel JJ, Levy DA, Nguyen SA, Knochelmann HM, Day TA. Impact of PD-L1 Expression and Human Papillomavirus Status in Anti-PD1/PD-L1 Immunotherapy for Head and Neck Squamous Cell Carcinoma: Systematic Review and Meta-Analysis. Head Neck (2020) 42(4):774–86. doi: 10.1002/hed.26036

8. van Monsjou HS, Balm AJ, van den Brekel MM, Wreessman VB. Oropharyngeal Squamous Cell Carcinoma: A Unique Disease on the Rise? Oral Oncol (2010) 46(11):780–5. doi: 10.1016/j.joraloncology.2010.08.011

9. Taberna M, Mena M, Pavón MA, Alemany L, Gillison ML, Mesia R. Human Papillomavirus-Related Oropharyngeal Cancer. Ann Oncol (2017) 28(10):2386–98. doi: 10.1093/annonc/mdx304

10. Liebertz DJ, Lechner MG, Masood R, Sinha UK, Han J, Puri RK, et al. Establishment and Characterization of a Novel Head and Neck Squamous Cell Carcinoma Cell Line USC-Hn1. Head Neck Oncol (2010) 2.5. doi: 10.1186/1284-3284-2-5

11. Warnaakulasuriya S. Global Epidemiology of Oral and Oropharyngeal Cancer. Oral Oncol (2009) 45(4-5):309–16. doi: 10.1016/j.joraloncology.2008.06.002

12. Carlisle JW, Steuer CE, Ovonikoko TK, Saba NF. An Update on the Immune Landscape in Lung and Head and Neck Cancers. CA Cancer J Clin (2020) 70(6):505–17. doi: 10.3322/caac.21630

13. Bauml J, Seiwert TY, Pfister DG, Worden F, Liu SV, Gilbert J, et al. Pembrolizumab for Platinum- and Cetuximab-Refractory Head and Neck Cancer: Results From a Single-Arm, Phase II Study. J Clin Oncol (2017) 35(14):1542–9. doi: 10.1200/JCO.2016.70.1524

14. Ferris RL, Blumenschein G Jr., Fayette J, Guigay J, Colevas AD, Licitra L, et al. Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck. N Engl J Med (2016) 375(19):1856–67. doi: 10.1056/NEJMoa1602252

15. Cohen EEW, Soulères D, Le Tourneau C, Dinis J, Licitra L, Ahn MJ, et al. Pembrolizumab Versus Methotrexate, Docetaxel, or Cetuximab for Recurrent or Metastatic Head-and-Neck Squamous Cell Carcinoma (KEYNOTE-040): A Randomised, Open-Label, Phase 3 Study. Lancet Oncol (2019) 20(13):1913–23. doi: 10.1016/S1470-2045(19)30247-1

16. Mehra R, Seiwert TY, Gupta S, Jeck I, Eder JP, et al. Efficacy and Safety of Pembrolizumab in Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma: Pooled Analyses After Long-Term Follow-Up in KEYNOTE-012. Br J Cancer (2018) 119(2):153–9. doi: 10.1038/s41416-018-0131-9

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.800315/full#supplementary-material
73. Gandhi L, Rodriguez-Leon J, Blankenstein T, et al. Pembrolizumab Plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. *JAMA Oncol* (2020) 6(10):1563–70. doi: 10.1001/jamaoncol.2020.2955

74. Ferris RL, Haddad R, Even C, Tahara M, Dvorakin M, Ciuleanu TE, et al. Durvalumab With or Without Tremelimumab in Patients With Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma: EAGLE, a Randomized, Open-Label Phase III Study. *Ann Oncol* (2020) 31(7):942–50. doi: 10.1016/j.annonc.2020.04.001

75. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Durvalumab After Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. *N Engl J Med* (2017) 377(20):1919–29. doi: 10.1056/NEJMoa1709937

76. Paz-Ares L, Vicente D, Tafreshi A, Robinson A, Soto Parra H, Mazières J, et al. Pembrolizumab Plus Standard-of-Care Chemoradiotherapy Versus Chemoradiotherapy Alone in Patients With Locally Advanced Squamous Cell Carcinoma of the Head and Neck: A Randomised, Double-Blind, Placebo-Controlled, Multicentre, Phase 3 Trial. *Lancet Oncol* (2021) 22 (4):450–62. doi: 10.1016/S1470-2045(20)30737-3

77. Colevas AD, Bahlada R, Brateh F, Balmanoukian A, Brana I, Chau NG, et al. Safety and Clinical Activity of Atezolizumab in Head and Neck Cancer: Results From a Phase 1 Trial. *Ann Oncol* (2018) 29(11):2247–53. doi: 10.1093/annonc/mdy111

78. Qin S, Xu L, Yi M, Su W, Su K, Luo S, Novel Immune Checkpoint Targets: Moving Beyond PD-1 and CTLA-4. *Mol Cancer* (2019) 18(1):155. doi: 10.1186/s12934-019-1091-2

79. Sailer V, Sailer U, Baden GW, Zarlø R, Wiek C, Vogt TJ, et al. DNA Methylation of Indoleamine 2,3-Dioxygenase 1 (IDO1) in Head and Neck Squamous Cell Carcinomas Correlates With IDO1 Expression, HPV Status, Patients' Survival, Immune Cell Infiltrates, Mutational Load, and Interferon γ Signature. *ElBioMedicine* (2019) 48:341–52. doi: 10.1016/j.ebio.2019.09.038

80. Sahin U, Türeci Ö. Personalized Vaccines for Cancer Immunotherapy. *Science* (2018) 359(6382):1355–60. doi: 10.1126/science.aar7112

81. Bommireddy R, Munoz LE, Kumari A, Huang L, Fan Y, Monteroza L, et al. Tumor Membrane Vesicle Vaccine Augments the Efficacy of Anti-PD1 Antibody in Immune Checkpoint Inhibitor-Resistant Squamous Cell Carcinoma Models of Head and Neck Cancer. *Vaccines (Basel)* (2020) 8(2):182. doi: 10.3390/vaccines8020182

82. Aggarwal C, Cohen RR, Morrow MP, Krynisky KA, Sylvester AJ, Knoblock DM, et al. Immunotherapy Targeting HPV16/18 Generates Potent Immune Responses in HPV-Associated Head and Neck Cancer. *Clin Cancer Res* (2019) 25(1):114–20. doi: 10.1158/1078-0433.CCR-18-1763

83. Schoenfeld JD, Hanna GI, Jo VY, Rawal B, Chen YH, Catalano PS, et al. Neoadjuvant Nivolumab or Nivolumab Plus Ipilimumab in Untreated Oral Cavity Squamous Cell Carcinoma: A Phase 2 Open-Label Randomized Clinical Trial. *JAMA Oncol* (2020) 6(10):1563–70. doi: 10.1001/jamaoncol.2020.2955
Patient do Impact on TNM Classification and Patients’ Survival. PloS One (2018) 13(4):e0194107. doi: 10.1371/journal.pone.0194107

99. Chen SW, Li SH, Shi DB, Jiang WM, Song M, Yang AK, et al. Expression of PD-L1/PD-L1 in Head and Neck Squamous Cell Carcinoma and its Clinical Significance. Int J Biol Markers (2019) 34(4):398–405. doi: 10.1177/1724600819848722

100. Zandberg DP, Algazi AP, Jimeno A, Good JS, Fayette J, Bouganim N, et al. STINGel: Controlled Release of a Cyclic Dinucleotide for Enhanced Cancer Immunotherapy. Biomaterials (2018) 163:87–75. doi: 10.1016/j.biomaterials.2018.01.035

101. Hato SV, Khong A, de Vries JJ, Lesterhuis WJ. Molecular Pathways: The Immunogenic Effects of Platinum-Based Chemotherapeutics. Clin Cancer Res (2014) 20(11):2831–7. doi: 10.1186/1078-0432.CCR-13-3141

102. Ying L, Cao X, Yang M, Xu Q, Burnette B, Arina A, et al. STING-Dependent Cytosolic DNA Sensing Promotes Radiation-Induced Type I Interferon-Dependent Antitumor Immunity in Immunogenic Tumors. Immunity (2014) 41(5):843–52. doi: 10.1016/j.immuni.2014.10.019

103. Pilon-Thomas S, Kodumudi KN, El-Kenawi AE, Russell S, Weber AM, Luddy K, et al. Neutralization of Tumor Acidity Improves Antitumor Responses to Immunotherapy. Cancer Res (2016) 76(6):1381–90. doi: 10.1158/0008-5472.CAN-15-1743

104. Sont D, Tian J, Han X, Li X. A Model of Seven Immune Checkpoint-Related Genes Predicting Overall Survival for Head and Neck Squamous Cell Carcinoma. Eur J Cancer (2014) 41(5):843–52. doi: 10.1016/j.ejca.2013.11.015

105. Sharma A, Seow JJW, Dutertre CA, Pai R, Blieriot C, Mishra A, et al. Onco-Fetal Reprogramming of Endothelial Cells Drives Immunosuppressive Macrophages in Hepatocellular Carcinoma. Cell (2020) 183(2):377–394.e21. doi: 10.1016/j.cell.2020.08.040

106. Sanchez-Martinez M, Ferrando A. The NOTCH1-MYC Highway Toward T-Cell Acute Lymphoblastic Leukemia. Blood (2017) 129(9):1124–33. doi: 10.1182/blood-2016-09-692582

107. Ko YH, Won HS, Sun DS, An HJ, Jeon EK, Kim MS, et al. A Novel Tumour-Suppressor Function for the Notch Pathway in Myeloid Leukaemia. Nature (2011) 473(7346):230–3. doi: 10.1038/nature09999

108. Ferris RL, Blumenschein GJr., Fayette J, Colevas AD, Licitra L, et al. Impact of Notch Signaling on the Prognosis of Patients With Head and Neck Squamous Cell Carcinoma. Oral Oncol (2020) 110:105003. doi: 10.1016/j.oraloncology.2020.105003

109. Ko YH, Won HS, Sun DS, An HJ, Jeon EK, Kim MS, et al. Unique DNA Methylation Signature in HPV-Positive Head and Neck Squamous Cell Carcinomas. Genome Med (2017) 9(1):33. doi: 10.1186/s13073-017-0419-z

110. Ko YH, Won HS, Sun DS, An HJ, Jeon EK, Kim MS, et al. Human Papillomavirus-Stratified Analysis of the Prognostic Role of miR-21 in Oral Cancer and Oropharyngeal Squamous Cell Carcinoma. Pathol Int (2014) 64(10):499–507. doi: 10.1111/pin.12201

111. Heath BR, Michmerhuizen NL, Donnelly CR, Sansanaphongpricha K, Sun D, Brenner JC, et al. Head and Neck Cancer Immunotherapy Beyond the Checkpoint Blockade. J Dent Res (2019) 98(10):1073–80. doi: 10.1177/0022034519846112

112. Ferris RL, Blumenschein GJr., Fayette J, Guagay J, Colevas AD, Licitra L, et al. Nivolubam vs Investigator’s Choice in Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck: 2-Year Long-Term Survival Update of CheckMate 141 With Analyses by Tumor PD-L1 Expression. Oral Oncol (2018) 81:45–51. doi: 10.1016/j.oraloncology.2018.04.008

113. Zhang H, Lan H, Zhang F, Xiao H, Huang Y. Impact of Notch Signaling on the Expression and Patients–Cancer Immunotherapy. J Cancer (2020) 11:105003. doi: 10.1016/j.ejca.2018.11.015