Checkpoints inhibitors in head and neck cancer: current knowledge and perspectives

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ABSTRACT
The emergence of immunotherapy has provided significant clinical improvements in the treatment of metastatic solid tumors. Recurrent/metastatic head and neck squamous cell carcinoma (HNSCC) has dismal prognosis with median survival ranging between 6 and 12 months. Our aim is to review the current knowledge on the role of the immune system and immune checkpoint inhibitors in HNSCC. We will focus on the landmark trials that led to the regulatory approvals of pembrolizumab and nivolumab, and discuss a few promising contenders in clinical development and highlight the need to identify better biomarkers other than programmed death-ligand 1 to improve patient selection and help predict response.

INTRODUCTION
Head and neck squamous cell carcinomas (HNSCC) are cancers that comprise the oral cavity, pharynx and larynx, and account for >90% of histological subtypes. According to the Surveillance, Epidemiology, and End Results (SEER) data, fewer than two-thirds of patients remain alive at 5 years.1 Tobacco has been identified as the most important risk factor, followed by human papilloma virus (HPV), which is primarily seen in oropharyngeal cancers (tonsils and base of the tongue). HPV-associated HNSCC occurs mainly in younger patients, and is associated with longer survival and better treatment outcomes. Current treatment is different depending on stage, goals of care, patient’s comorbidities and performance status. In general, patients with localized disease (stage I and II) are treated with single modality local therapy with either surgery or radiation therapy (RT). Patients with locally advanced, non-metastatic disease are typically treated with a multimodality approach with chemotherapy and RT (as organ preservation is preferred) with or without surgery (which can also be done as salvage in recurrent/persistent localized disease). Despite an aggressive multidisciplinary approach, up to 30% of patients relapse in distant sites, and up to 60% have local recurrence.2 Platinum-based combination chemotherapy with or without cetuximab remains the standard of care (SOC) for relapsed/recurrent and metastatic (R/M) disease based on the Cetuximab in First-Line Treatment of Head and Neck Cancer (EXTREME) trial, which showed the addition of cetuximab to platinum/5-fluorouracil (5-FU) chemotherapy improved overall survival (OS) from 7.1 to 10.1 months.3 However, toxicity with this regimen is significant, and responses are short. Unfortunately, disease progression, which occurs in many of these patients, seldom responds to further chemotherapy, thus highlighting the need for novel therapies. Multiple factors support the use of immunotherapy in HNSCC, which have prompted the development of clinical studies of immune checkpoint inhibitors (ICI) in HNSCC. We review the rationale for ICI in HNSCC and review the landmark trials that led to regulatory approvals of pembrolizumab and nivolumab, and how to manage their unique toxicities. We also provide an overview of current trials in clinical development and we highlight the need for predictors of response to these novel agents.

THE ROLE OF IMMUNE SYSTEM AND CHECKPOINT PATHWAY IN HNSCC
HNSCC is characterized by immune evasion strategies in an immunosuppressive microenvironment and leads to tumor progression unchecked by the immune system.4 Tumor evasion and immune dysfunction have been associated with several mechanisms and are well described in the literature.5 6 FoxP3+ T regulatory (Treg) cells are known to have an immunoregulatory effect through interleukin-10 and transforming growth factor-β, causing suppression and downregulation of proliferation of CD4+ and CD8+ T cells, as well as inducing apoptosis. Treg cells are found in high levels in HNSCC, which downregulate cytokine expression and may be responsible for antitumor response.7 8 Tumor cells also appear to have decreased HLA class I expression with tumor-associated antigens, which allows for evasion of the adaptive immune system and T cells.9 10 Other mechanisms act to alter the tumor microenvironment by favoring immunosuppressive cells including myeloid-derived suppressive cells (MDSC) and tumor-associated macrophages. These cells cause an increase in pro-inflammatory cytokines and subsequent activation of signal transducer and activator of transcription 3 pathway, ultimately promoting tumor growth.11

A relatively newer therapeutic target involves the immune checkpoint inhibitors. Programmed death-ligand 1 (PD-L1) and cytotoxic T-lymphocyte antigen 4 (CTLA-4) normally regulate immune responses by effecting T cells to prevent autodamage. Levels of PD-L1 and CTLA-4 are found to be increased in HNSCC, thus providing an additional pathway for immune evasion by inactivation of T cells, even when presented with tumor-associated antigen. PD-1 binding suppresses T-cell receptor (TCR) signals and induces T-cell inactivation by preventing phosphorylation of TCR signaling intermediates. Prolonged T-cell activation, such as what is seen in chronic HPV infections, can cause upregulation of PD-1 expression contributing to the ‘exhausted’ phenotype of inactive T cells. PD-L1 and PD-L2 expressions are frequently elevated in HNSCC tumor and immune cells, particularly HPV-positive patients.

In contrast to PD-L1 pathway, which occurs in the tumor microenvironment, CTLA-4 regulation occurs primarily in lymphoid tissue. CTLA-4 is expressed on activated T cells and binds to CD80 and CD86 on antigen-presenting cells (APC). TCR binding to major histocompatibility complex (MHC) on APCs provide T-cell activation but requires costimulatory signals provided by B7 on APCs and CD28 on T cells. CTLA-4 is a homolog to CD28 and binds to B7 with higher affinity than CD28. When CTLA-4 binds to B7 and prevents B7 binding to CD28, there is insufficient costimulatory signal and the T cell is not activated. These findings prompted the development of clinical studies of ICI in HNSCC. Figures 1 and 2 illustrate PD-L1 and CTLA-4 pathways, respectively.

**IMMUNE CHECKPOINT INHIBITORS**

The past 2 years have witnessed the approvals of nivolumab and pembrolizumab in patients with HNSCC who have progressed on, or following, platinum-based chemotherapy. Nivolumab has increased OS compared with chemotherapy, and has a category 1 recommendation from the National Cancer Committee Network based on high level of evidence, whereas pembrolizumab has a category 2a recommendation based on non-randomized trials.

Interestingly, the recently published phase III randomized trial failed to show superiority of pembrolizumab compared with chemotherapy. Despite the variable utility of PD-L1 status as a biomarker of response across trials, a higher PD-L1 expression seems to be associated with greater survival benefit with nivolumab and increased responses and perhaps survival with pembrolizumab. Finding a better/more reliable biomarker remains an unmet goal in order to improve patient selection, maximize efficacy and predict response.

**Pembrolizumab**

Pembrolizumab (MK-3475) is a humanized IgG4 monoclonal antibody against PD-1. The safety and efficacy of pembrolizumab was initially assessed in the HNSCC cohort of the phase Ib open-label trial KEYNOTE-012 (which included patients with different advanced refractory solid tumors). Clinical and durable antitumor activity was shown in PD-L1-positive patients at the dose of 10 mg/kg every 2 weeks. PD-L1 positivity was defined by both tumor and immune cell expression ≥1%. Thereafter, a fixed dose of 200 mg every 3 weeks was studied in the expansion cohort of 132 patients with R/M HNSCC irrespective of biomarker or HPV status. The fixed and less frequent dose regimen conferred multiple advantages including safety, convenience, reduction of waste and adherence. Most patients were heavily pretreated (57% had at least two prior therapies) and 78% of patients were PD-L1 positive. The overall objective response rate (ORR) was 20% and the 6-month OS rate was 59%. Pembrolizumab was well tolerated with the majority of adverse events (AE) reported as grade 1/2 (59.8%); fatigue being the most common. Grade 3/4 immune-related AEs, especially pneumonitis, were relatively infrequent (<4%). Based on these findings, the Food and Drug Administration (FDA) granted pembrolizumab...
accelerated approval in August 2016 for patients with R/M HNSCC with disease progression on, or after, platinum-containing chemotherapy. Recently, KEYNOTE-055, a phase II single-arm study, evaluated pembrolizumab in 171 patients with R/M HNSCC refractory to platinum and cetuximab.\(^{16}\) Median age was 61 and three-quarters of patients had received at least two prior therapies. Eighty-two per cent of patients were PD-L1-positive, and 22% were HPV-positive. ORR, comprising complete response (CR) and partial response (PR), was 16%, all of which but one were PR. Stable disease (SD) was achieved in 19%. Responses were similar regardless of HPV or PD-L1 status (16% in HPV-positive vs 15% in HPV-negative disease, and 18% in PD-L1-positive vs 12% in PD-L1-negative patients). Median duration of response (DoR) was 8 months overall and significantly longer in HPV-positive responders compared with HPV-negative responders (not reached vs 7 months). Median progression-free survival (PFS) and OS were 2.1 and 8 months, respectively, with no significant difference between all PD-L1 and HPV subgroups. The majority of AEs were of grade 1 and 2. Grade 3 or more AEs occurred in 15%, and led to discontinuation of treatment in 4% of patients. One patient died of immune-mediated pneumonitis. The most common immune-mediated AEs included hypothyroidism (16%), pneumonitis (4%) and hyperthyroidism (2%). Based on the acceptable toxicity and significant efficacy in the two trials above, a randomized controlled phase III trial was conducted to compare pembrolizumab with standard chemotherapy in R/M HNSCC after failure of platinum-based chemotherapy (KEYNOTE-040). The results were presented at the European Society of Medical Oncology (ESMO) 2017 Congress.\(^{21}\) Four hundred ninety-five patients were equally randomized to either pembrolizumab or standard chemotherapy (investigator choice of methotrexate, docetaxel or cetuximab). Pembrolizumab failed to meet the primary end point of OS (8.4 vs 7.1 months, HR 0.81, p=0.0204). However, subset analysis showed more significant benefit with increased PD-L1 expression (see ‘predictive biomarkers of response’ section for further details). The safety profile favored pembrolizumab in all subgroups except hypothyroidism, which occurred in 13% with pembrolizumab vs 1% in chemotherapy arm.

**Nivolumab**

Nivolumab is a fully human IgG4 monoclonal antibody against PD-1. In two pivotal phase I trials in advanced solid tumors, nivolumab showed significant clinical antitumor activity and was relatively well tolerated at an escalated dose of 10 mg/kg once every 2 weeks.\(^{22}\) This led to a randomized phase III trial of nivolumab in platinum-refractory R/M HNSCC (CheckMate-141).\(^{16}\) Three hundred sixty-one patients were assigned in a 2:1 ratio to either nivolumab (at a dose of 3 mg/kg of body weight once every 2 weeks) or investigator’s choice of single agent standard chemotherapy (methotrexate, docetaxel or cetuximab); 54.6% of patients had at least two prior lines of systemic therapy. PD-L1 expression was evaluated by immunohistochemistry by a rabbit antihuman PD-L1 antibody and was scored at prespecified expression levels (≥1%, ≥5% and ≥10% in a minimum of 100 tumor cells that could be evaluated). The trial was terminated early after meeting its primary end point. Median OS was superior in the nivolumab group (7.5 vs 5.1 months (HR=0.70, p=0.01) and was more than double at 1 year (36% vs 16.6%). ORR was also superior with nivolumab (13.3% vs 5.8%). Median PFS was similar in both groups (2 vs 2.3 months). However, PFS was interestingly higher at 6 months for nivolumab (19.7% vs 9.9%) based on the late separation of the PFS curves, which likely reflects the longer DoR seen with nivolumab. Regarding safety profile, nivolumab was better tolerated than chemotherapy with grade 3 or higher AEs reported in 13.1% vs 35.1%, respectively. Most common AEs were fatigue (14.0%), nausea (8.5%) and rash (7.6%); the most common grade 3 or 4 events were fatigue (2.1%) and anemia (1.3%). Furthermore, an exploratory analysis proved that nivolumab was superior in terms of health-related quality of life.\(^{24}\) This trial has led to the FDA approval of nivolumab in November 2016 for the treatment of patients with R/M HNSCC with disease progression on, or after, a platinum-based therapy. Table 1 summarizes the findings of completed trials for both pembrolizumab and nivolumab in HNSCC.

**Other agents**

Alternative targets for immune checkpoint inhibition exist in PD-L1 and CTLA-4 axis. Durvalumab (MEDI4736) is an IgG1 antibody against PD-L1 on tumor cells and seems to have similar efficacy and toxicity to the previously mentioned agents. In an open-label phase II trial including multiple advanced solid malignancies (NCT01693562), 62 patients with R/M HNSCC received durvalumab every 2 weeks intravenously at 10 mg/kg for 12 months. Preliminary results were reported at the ESMO 2016 Congress.\(^{25}\) Six-month and 12-month OS were 62% and 42%, respectively, and responses were durable (>12 months in 6/7 responders). Although ORR was higher in PD-L1-positive patients (25% vs 12% overall), no significant difference in OS was seen by PD-L1 status. Fatigue was the most common AE (18%), and grade ≥3 AEs occurred in only 8%. Additionally, durvalumab is being evaluated as monotherapy in platinum-refractory, PD-L1-positive R/M HNSCC in phase II trial (HAWK; NCT02207530). Preliminary results for 111 evaluated patients were recently presented at the ESMO 2017 Congress.\(^{26}\) PD-L1 positivity was different than for other ICI and was defined by the staining of at least 25% of tumor cells. ORR was 16.2% but higher in HPV-positive patients compared with HPV-negative counterparts (29.4% vs 10.8%). The disease control rate at 24 weeks (CR+PR+SD) was 23.4%. Overall, median PFS was 2.1 months, median OS was 7.1 months and the 12-month survival rate was 33.6%. Grade 3 or more AEs occurred in only 8% and there was no death due to treatment-related AEs.

Avelumab is a fully human monoclonal anti-PD-L1 antibody characterized by an antibody-dependent cell-mediated cytotoxicity. Avelumab is being evaluated either as monotherapy or in combination with other therapies in locally advanced and metastatic HNSCC.

Ipilimumab is a monoclonal antibody against CTLA-4. To date, no results have been reported for ipilimumab in HSNCC. Targeting both PD-L1 and CTLA-4 pathways...
may have synergistic antitumor activity by potentiating the immune effect. This combination strategy has shown consistent efficacy in advanced melanoma and metastatic renal cell carcinoma. CheckMate 651 is a phase III trial comparing nivolumab and ipilimumab combination with standard chemotherapy (cetuximab+cisplatin/carboplatin+5-FU) as first-line treatment in R/M HNSCC. CheckMate 741 is a phase II trial comparing nivolumab monotherapy with nivolumab+ipilimumab.

Tremelimumab is a selective human IgG2 monoclonal antibody of CTLA-4. Given the promising results from a pivotal phase I trial in non-small lung cancer where the combination of durvalumab and tremelimumab showed tolerable and meaningful clinical efficacy, this combination is also being explored in HNSCC. Two phase III studies are currently evaluating durvalumab with and without tremelimumab compared with SOC chemotherapy as first-line therapy in R/M HNSCC (EAGLE NCT02369874 and KESTREL NCT02551159). Select ongoing trials of ICI in R/M HNSCC (EAGLE NCT02369874 and EXTREME NCT02551159) may have synergistic antitumor activity by potentiating the immune effect. This combination strategy has shown consistent efficacy in advanced melanoma and metastatic renal cell carcinoma. CheckMate 651 is a phase III trial comparing nivolumab and ipilimumab combination with standard chemotherapy (cetuximab+cisplatin/carboplatin+5-FU) as first-line treatment in R/M HNSCC. CheckMate 741 is a phase II trial comparing nivolumab monotherapy with nivolumab+ipilimumab.

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### COMBINATION THERAPY

While the use of cytotoxic and targeted agents can alter the expression of checkpoint receptors, their effects on the immune system and HNSCC tumor cells remain complex and poorly understood. For instance, cetuximab has been shown to increase CTLA-4 Foxp3+ Treg suppressor cells in the circulation and in the microenvironment, suggesting that the addition of ipilimumab may eliminate this suppressive effect and promote antitumor immunity. Similarly, in HPV-positive oropharyngeal squamous cell carcinoma, chemoradiation has been shown to upregulate PD-1 expression on CD4+ T cells and to increase peripheral MDSC, antagonizing antitumor and anti-HPV immunity, and suggesting that PD-1 blockade can have a positive effect. Conversely, cetuximab can exert a positive antitumor immunogenic response by promoting dendritic cell maturation and cytotoxic T-cell priming, which would enhance adaptive immune responses. In addition, select chemotherapy agents can potentiate T-cell-dependent antitumor immunity by inducing apoptosis in MDSCs (5-FU), or by inducing apoptosis in immunosuppressive Tregs (cyclophosphamide). Therefore, the interactions between therapeutic agents and tumor microenvironment are far from being fully delineated. Nonetheless, they provide a rationale for combining checkpoint inhibitors with conventional treatments. Targeting CTLA-4 and PD-1/ PD-L1 axis in this setting allows for lifting of inhibitory signals on effector T lymphocytes in the tumor microenvironment, which then allows therapeutic synergy with cytotoxic or targeted agents. In the R/M setting, pembrolizumab alone or in combination with fluorouracil/platinum versus the SOC, that is, EXTREME trial regimen (cetuximab+platinum+5-FU) is currently being investigated in a phase III trial (NCT02358031) and results are eagerly awaited. Furthermore, synergy between ICI and RT, both inside and outside of the radiation field (known as an abscopal effect) has been documented in different tumors in both mouse models and in humans. Exposure of cancer cell neoantigens following radiation-induced cell death leads to priming of T cells, which can in turn cause tumor regression in distant sites outside of radiation field, potentiated by the action of checkpoint inhibitors. Another therapeutic combination strategy involves the use of HPV vaccines with checkpoint inhibitors. Preclinical models

### Table 1 Completed trials for pembrolizumab and nivolumab in R/M HNSCC and their major findings

<table>
<thead>
<tr>
<th>Trial</th>
<th>Phase</th>
<th>Sample size</th>
<th>Setting</th>
<th>Arms</th>
<th>Primary end points</th>
<th>Major findings</th>
<th>Effect of HPV status</th>
<th>Effect of PD-L1 expression</th>
</tr>
</thead>
<tbody>
<tr>
<td>KEYNOTE-012</td>
<td>I</td>
<td>132</td>
<td>Advanced solid tumors</td>
<td>Pembrolizumab 200 mg once every 3 weeks</td>
<td>Safety and efficacy</td>
<td>ORR 20% Overall, 6-month OS was 39%</td>
<td>6-month OS was 70% in HPV+ patients</td>
<td>Higher OS for patients with PD-L1≥1% (803 vs 151 days)</td>
</tr>
<tr>
<td>KEYNOTE-055</td>
<td>II</td>
<td>171</td>
<td>R/M HNSCC</td>
<td>Pembrolizumab 200 mg once every 3 weeks</td>
<td>ORR and safety</td>
<td>ORR 16% Median DoR 8 months Median OS 8 months</td>
<td>Similar ORR but higher OS for HPV+</td>
<td>Increased ORR without affecting OS or PFS</td>
</tr>
<tr>
<td>KEYNOTE-040</td>
<td>III</td>
<td>495</td>
<td>Platinum-refractory R/M</td>
<td>Pembrolizumab 200 mg once every 3 weeks</td>
<td>OS</td>
<td>Non-statistically significant improvement in OS (8.4 vs 7.1 months, p=0.204)</td>
<td>Not reported</td>
<td>Increased OS with higher PD-L1 expression</td>
</tr>
<tr>
<td>CheckMate-141</td>
<td>III</td>
<td>361</td>
<td>Platinum-refractory R/M</td>
<td>Nivolumab 3 mg/kg once every 2 weeks</td>
<td>OS</td>
<td>OS benefit for nivolumab: 7.5 vs 5.1 months (HR=0.70, p=0.01)</td>
<td>Better OS benefit for P16+ disease</td>
<td>OS benefit in PD-L1&gt;1%</td>
</tr>
</tbody>
</table>

ORR, overall response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; R/M HNSCC, recurrent/metastatic head and neck squamous cell carcinoma.
Table 2  Select ongoing trials for checkpoint inhibitors in R/M HNSCC

<table>
<thead>
<tr>
<th>Immune checkpoint inhibitor</th>
<th>Trial/identifier</th>
<th>Phase</th>
<th>Setting</th>
<th>Intervention/drug</th>
<th>Primary end point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>NCT02358031 (KEYNOTE-048)</td>
<td>III</td>
<td>R/M HNSCC first line, or &gt;6 months after last therapy for locally advanced disease</td>
<td>Pembrolizumab vs pembrolizumab+platinum/5-FU vs cetuximab+platinum/5-FU</td>
<td>PFS and OS</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>NCT03082534</td>
<td>II</td>
<td>R/M HNSCC</td>
<td>Pembrolizumab+cetuximab</td>
<td>ORR</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>NCT02454179</td>
<td>II</td>
<td>Platinum-refractory R/M or unresectable HNSCC</td>
<td>Pembrolizumab+sacalabrutinib</td>
<td>ORR</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>NCT02892201</td>
<td>II</td>
<td>HNSCC with residual disease after definitive RT (chemo)</td>
<td>Pembrolizumab</td>
<td>ORR</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>NCT02626000 (MASTERKEY 222/KEYNOTE-137)</td>
<td>I/iII</td>
<td>R/M HNSCC</td>
<td>Pembrolizumab+talimogene laherparepvec</td>
<td>DLT</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>NCT02741570 (CheckMate 651)</td>
<td>III</td>
<td>R/M HNSCC, first-line therapy</td>
<td>Nivolumab+ipilimumab vs SOC (cetuximab+cisplatin/carboplatin+5-FU)</td>
<td>OS and PFS</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>NCT02823574 (CheckMate 714)</td>
<td>II</td>
<td>R/M HNSCC</td>
<td>Nivolumab+ipilimumab vs nivolumab alone</td>
<td>ORR and DoR in platinum-refractory subgroup</td>
</tr>
<tr>
<td>Durvalumab</td>
<td>NCT02207530</td>
<td>II</td>
<td>PD-L1-positive, platinum-refractory R/M HNSCC</td>
<td>Durvalumab</td>
<td>ORR</td>
</tr>
<tr>
<td>Durvalumab</td>
<td>NCT02551159 (KESTREL)</td>
<td>III</td>
<td>R/M HNSCC, first-line therapy</td>
<td>Durvalumab+tremelimumab vs SOC (EXTREME regimen)</td>
<td>PSF and OS</td>
</tr>
<tr>
<td>Durvalumab</td>
<td>NCT02369874</td>
<td>III</td>
<td>R/M HNSCC, first-line therapy</td>
<td>Durvalumab+tremelimumab vs SOC</td>
<td>PSF and OS</td>
</tr>
<tr>
<td>Durvalumab</td>
<td>NCT02499328</td>
<td>I/iII</td>
<td>R/M HNSCC, second-line therapy</td>
<td>AZD9150 and AZD5069—both as monotherapy and in combination with durvalumab</td>
<td>MTD, safety and tolerability and ORR</td>
</tr>
<tr>
<td>Durvalumab</td>
<td>NCT03162224</td>
<td>I/iII</td>
<td>HPV-associated R/M HNSCC</td>
<td>Durvalumab+MEDI0457 (INO-3112), which is an HPV DNA vaccine</td>
<td>Safety and efficacy</td>
</tr>
<tr>
<td>Avelumab</td>
<td>NCT015772004 (JAVELIN solid tumor)</td>
<td>I</td>
<td>Metastatic or locally advanced solid tumors</td>
<td>Avelumab</td>
<td>DLT and confirmed best overall response</td>
</tr>
<tr>
<td>Avelumab</td>
<td>NCT03260023</td>
<td>I/iII</td>
<td>HPV 16 positive R/M cancers and expansion cohort to OPC</td>
<td>Avelumab+TG4001</td>
<td>Safety and tolerability</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>NCT01935921</td>
<td>I</td>
<td>Previously untreated stage III/IV HNSCC</td>
<td>Ipilimumab+cetuximab+IMRT</td>
<td>DLT</td>
</tr>
</tbody>
</table>

DLT, dose-limiting toxicity; DoR, duration of response; HPV, human papilloma virus; IMRT, intensity-modulated radiotherapy; OS, overall survival; PD-L1, programmed death-ligand 1; ORR, overall response rate; PFS, progression-free survival; OPC, oropharyngeal cancer; SOC, standard of care; RT, radiation therapy; R/M HNSCC, recurrent/metastatic head and neck squamous cell carcinoma; 5-FU, 5-fluorouracil.

have shown more potent antitumor responses when anti-PD-1 therapy was combined with vaccines against HPV-specific antigens.34 Multiple trials are currently underway combining ICI with different HPV vaccines (ISA101/adjuvant montanide, MEDI0457, ADXS11-011 and TG4001). In locally advanced and untreated intermediate-risk to high-risk HNSCC, trials are incorporating ICI in cetuximab/radiotherapy protocols or platinum-based chemoradiation protocols (table 3). These trials will evaluate combination therapies in both upfront and adjuvant settings, and will compare the sequencing of checkpoint inhibitors in relation to radiation therapy. Killer-cell immunoglobulin-like receptors (KIR) are other checkpoint receptors that suppress cytotoxic effects of natural killer (NK) cells on HLA-expressing tumor cells. Inhibition of these receptors could reduce inhibitory signals on NK cells and further assist with antitumor immunogenic response.

Two trials are investigating the combination of ipilimumab (NCT01750580) or nivolumab (NCT01714739) with anti-KIR antibody. Additionally, CD137 and OX40 are costimulatory tumor necrosis factor superfamily receptors primarily expressed on activated T cells, with OX40 also present on dendritic and activated NK cells. They both stimulate T-cell proliferation and enhance antitumor eradication.35 36 Therefore, stimulation of these receptors with monoclonal antibodies represents a future therapeutic target (with anti-OX40 and anti-CD137 agonists) in HNSCC.37 Lymphocyte activation gene-3 (LAG-3) is another immune checkpoint protein that negatively regulates T cells and immune response by binding to MHC class II molecules, and has been found to be overexpressed in HNSCC.38 Monoclonal antibodies against LAG-3 are also being explored in multiple trials in HNSCC. Other trials include combinations of PD-1 inhibitors with CTLA-4 inhibitors,
human head and neck cancers express PD-L1. It has been observed that HPV-negative tumors show lower survival rates compared to HPV-positive tumors. However, the reasons for this difference remain largely unknown. Nonetheless, it is known that HPV-associated head and neck squamous cell carcinoma (HNSCC) has significantly longer survival rates than HPV-negative disease for nivolumab and chemotherapy, with median OS of 9.1 vs 4.4 months (HR=0.56) in HPV-positive disease and 6.6 vs 4.4 months (HR=0.65) in HPV-negative disease. Moreover, responses were higher based on PD-L1 expression, with 50% vs 30% ORR in PD-L1-positive patients (HR=0.55; p=0.0017). Similarly, extrapolated analysis of the CheckMate-141 phase III trial suggested higher benefit for nivolumab in patients with PD-L1 and HPV positive (which comprised 57% and 25% of the patients, respectively). Median OS was 8.7 vs 4.6 months among patients with PD-L1≥1% (HR=0.55; p=0.0017). Comparatively, median OS was 9.1 vs 4.4 months (HR=0.56) in HPV-positive and 7.5 vs 5.8 months (HR=0.73, p=0.55) in HPV-negative disease for nivolumab and chemotherapy, respectively. Table 1 summarizes the effect of HPV and PD-L1 status on response to ICI in the four published trials.
TOXICITY
As shown across the trials above, the side-effect profile of ICI is significantly more favorable than traditional cytotoxic chemotherapy and is similar to what is seen with their use in other indications. They are generally well tolerated with fatigue (−20%) and nausea (9%) being the most common AEs. However, given their unique mechanism of action, severe immune-mediated reactions can occur and include but are not limited to: thyroiditis, pneumonitis, hepatitis, colitis, nephritis, hypophysitis, myocarditis, myositis, neuritis, adrenal insufficiency, rash and neurological toxicities. Immune-mediated thyroiditis is the most commonly seen (15%), whereas the others occur in <5% of cases. Most of these reactions are transient and minor (grade 1 and 2). Nonetheless, grade 3/4 can still occur in −1%−2% of the cases and may be fatal in some of them. As future combinations with PD-1 and CTLA-4 inhibitors are being explored in HNSCC, additive toxicity is expected, in keeping with what has been reported in other solid tumors such as melanoma. Management depends on the type and severity of the immune-mediated reaction, but generally involves holding or discontinuing the immunotherapy and administering high-dose steroids with a slow taper over weeks to months until the toxicity decreases to grade 1 or completely resolves. Some cases require more potent immunosuppressants such as mycophenolate mofetil and infliximab (although the latter is contraindicated in immune-mediated hepatitis). Clear guidelines on the management of ICI toxicities have now been published by many oncological societies (American Society of Clinical Oncology and Society for Immuno-Therapy of Cancer).

CONCLUSION
These are exciting times for immunotherapy in oncology. Immune checkpoint inhibitors continue to garner new indications in different malignancies and various treatment settings. R/M HNSCC has dismal prognosis with median survival ranging between 6 and 12 months. Over the last decade, there has been minimal therapeutic advancement until the recent approvals of pembrolizumab and nivolumab beyond first-line chemotherapy. These novel therapies are of unique mechanism of action and thus also have unique adverse effects. They can in some cases, provide durable responses that we have never seen with standard chemotherapy and are generally well tolerated with the caveat of minimal risk of life-threatening immune reactions. Unfortunately, only –20% of the patients respond, highlighting the need to identify more reliable biomarkers than PD-L1 that can improve patient selection and help predict response. Trials of ICI in first line, adjuvant and in combination with other therapeutic modalities (chemotherapy, radiotherapy) are also under investigation and results have yet to determine the role ICI may play in treatment of HNSCC.

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