Checkpoint 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 6and12 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]

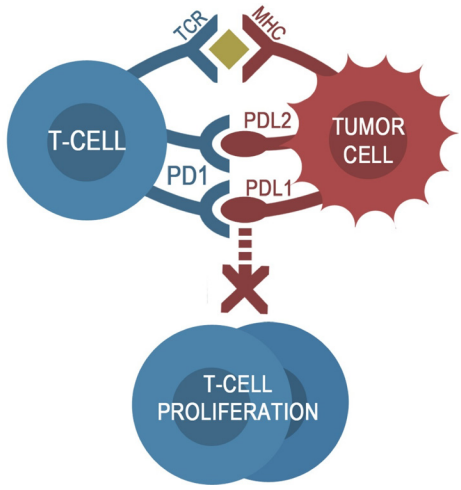

Figure 1 Programmed death-ligand 1 (PD-L1)/PD-L2 costimulatory pathway. Tumor cell expression of PD-L1/PD-L2 results in binding PD1 to PD-L1/PD-L2, inhibiting T-cell activation and proliferation. MHC, major histocompatibility complex; TCR, T-cell receptor.

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 effector 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.[12] 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.[13] PD-L1 and PD-L2 expressions are frequently elevated in HNSCC tumor and immune cells, particularly HPV-positive patients.[14]

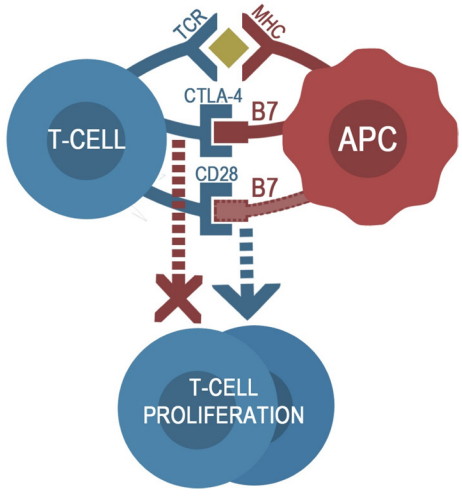

Figure 2 Cytotoxic T-lymphocyte antigen 4 (CTLA-4) costimulatory pathway. Normal B7-CD28 binding activates T-cell proliferation. CTLA-4 is a homolog to CD28, which competitively and preferentially binds to B7, preventing CD28 binding and T-cell activation. APC, antigen-presenting cells; MHC, major histocompatibility complex; TCR, T-cell receptor.

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.[15] 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,[16] 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.[17 18] Interestingly, the recently published phase III randomized trial failed to show superiority of pembrolizumab compared with chemotherapy.[19] 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).[20] 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.[17] 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.[18] 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 23] 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 I/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

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

Trial	Phase	Sample size	Setting	Arms	Primary end points	Major findings	Effect of HPV status	Effect of PD-L1 expression
KEYNOTE-012	Ib	132	Advanced solid tumors. Cohort B2: R/M HNSCC	Pembrolizumab 200 mg once every 3 weeks	Safety and efficacy	ORR 20% Overall, 6-month OS was 59%	6-month OS was 70% in HPV+ and 56% in HPV− patients	Higher OS for patients with PD-L1≥1% (303 vs 151 days)
KEYNOTE-055	II	171	R/M HNSCC refractory to platinum and cetuximab	Pembrolizumab 200 mg once every 3 weeks	ORR and safety	ORR 16% Median DoR 8 months Median OS 8 months	Similar ORR but higher OS for HPV+	Increased ORR without affecting OS or PFS
KEYNOTE-040	III	495	Platinum-refractory R/M HNSCC	Pembrolizumab 200 mg once every 3 weeks vs investigator choice of either methotrexate, docetaxel or cetuximab	OS	Non-statistically significant improvement in OS (8.4 vs 7.1 months, p=0.204)	Not reported	Increased OS with higher PD-L1 expression
CheckMate-141	III	361	Platinum-refractory R/M HNSCC	Nivolumab 3 mg/kg once every 2 weeks vs investigator choice of either methotrexate, docetaxel or cetuximab	OS	OS benefit for nivolumab: 7.5 vs. 5.1 months (HR=0.70, p=0.01)	Better OS benefit for P16+ disease	OS benefit in PD-L1>1%

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.

may have synergistic antitumor activity by potentiating the immune effect. This combination strategy has shown consistent efficacy in advanced melanoma[27] and metastatic renal cell carcinoma.[28] 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 HNSCC in two different settings (R/M and locoregional) are presented in table 2 and table 3, respectively.

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.[29] 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.[30] 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),[31] or by inducing apoptosis in immunosuppressive Tregs (cyclophosphamide).[32] 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.[33] 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 2 Select ongoing trials for checkpoint inhibitors in R/M HNSCC

Immune checkpoint inhibitor	Trial/identifier	Phase	Setting	Intervention/drug	Primary end point
Pembrolizumab	NCT02358031 (KEYNOTE-048)	III	R/M HNSCC first line, or >6 months after last therapy for locally advanced disease	Pembrolizumab vs pembrolizumab+platinum/5-FU vs cetuximab+platinum/5-FU	PFS and OS
Pembrolizumab	NCT03082534	II	R/M HNSCC	Pembrolizumab+cetuximab	ORR
Pembrolizumab	NCT02454179	II	Platinum-refractory R/M or unresectable HNSCC	Pembrolizumab±acalabrutinib	ORR
Pembrolizumab	NCT02892201	II	HNSCC with residual disease after definitive RT (±chemo)	Pembrolizumab	ORR
Pembrolizumab	NCT02626000 (MASTERKEY 232/KEYNOTE-137)	Ib/III	R/M HNSCC	Pembrolizumab+talimogene laherparepvec	DLT
Nivolumab	NCT02741570 (CheckMate 651)	III	R/M HNSCC, first-line therapy	Nivolumab+ipilomumab vs SOC (cetuximab+cisplatin/carboplatin+5-FU)	OS and PFS
Nivolumab	NCT02823574 (CheckMate 714)	II	R/M HNSCC	Nivolumab+ipilimumab vs nivolumab alone	ORR and DoR in platinum-refractory subgroup
Durvalumab	NCT02207530	II	PD-L1-positive, platinum-refractory R/M HNSCC	Durvalumab	ORR
Durvalumab	NCT02551159 (KESTREL)	III	R/M HNSCC, first-line therapy	Durvalumab±tremelimumab vs SOC (EXTREME regimen)	PSF and OS
Durvalumab	NCT02369874	III	R/M HNSCC, first-line therapy	Durvalumab±tremelimumab vs SOC	PFS and OS
Durvalumab	NCT02499328	Ib/II	R/M HNSCC, second-line therapy	AZD9150 and AZD5069—both as monotherapy and in combination with durvalumab	MTD, safety and tolerability and ORR
Durvalumab	NCT03162224	Ib/II	HPV-associated R/M HNSCC	Durvalumab+MEDI0457 (INO-3112), which is an HPV DNA vaccine	Safety and efficacy
Avelumab	NCT01772004 (JAVELIN solid tumor)	I	Metastatic or locally advanced solid tumors	Avelumab	DLT and confirmed best overall response
Avelumab	NCT03260023	Ib/II	HPV 16 positive R/M cancers and expansion cohort to OPC	Avelumab+TG4001	Safety and tolerability
Ipilimumab	NCT01935921	I	Previously untreated stage III/IV HNSCC	Ipilimumab+cetuximab+IMRT	DLT

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 remove 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,

Table 3 Select ongoing trials for checkpoint inhibitors in locally advanced or high-risk HNSCC (non-recurrent, non-metastatic)

Immune checkpoint inhibitor	Trial/identifier	Phase	Setting	Intervention/drug	Primary end point
Pembrolizumab	NCT03040999 (KEYNOTE-412)	III	Locally advanced HNSCC	Pembrolizumab or placebo, concomitantly and as maintenance+chemoRT (cisplatin once every 3 weeks)	EFS
Pembrolizumab	NCT02289209	II	Locoregional inoperable recurrence/second primary	Reirradiation+pembrolizumab	PFS
Pembrolizumab	NCT02609503	II	Locally advanced HNSCC, not cisplatin eligible	Pembrolizumab+IMRT	PFS at 20 weeks
Pembrolizumab	NCT02759575	I/II	Locally advanced HNSCC	Pembrolizumab+cisplatin (once every 3 weeks)+RT	AEs and laryngectomy-free survival
Pembrolizumab	NCT02841748 (PATHWay study)	II	HNSCC at high risk of recurrence	Adjuvant pembrolizumab vs placebo	PFS (at 2 years)
Pembrolizumab	NCT02777385	II	Intermediate or high-risk locally advanced HNSCC	Concurrent or sequential pembrolizumab in combination with cisplatin+IMRT	1-year PFS and acute toxicity
Pembrolizumab	NCT03057613	II	High-risk resected cutaneous HNSCC	Pembrolizumab+postoperative radiation	DLT and PFS (at 1 year)
Pembrolizumab	NCT02586207	Ib	Locally advanced HNSCC	Pembrolizumab+weekly cisplatin+RT	AEs
Nivolumab	NCT02764593	I	Intermediate and high-risk locoregionally advanced HNSCC	Addition of nivolumab to either cisplatin-based chemoRT, or cetuximab+RT or IMRT	DLT
Durvalumab	NCT02997332 (MEDINDUCTION)	I	Locally advanced HNSCC	Durvalumab+docetaxel+ cisplatin+5-FU	Recommended phase II dose, DLT
Avelumab	NCT02952586 (JAVELIN head and neck 100)	III	Locally advanced HNSCC	Avelumab+SOC chemoRT vs SOC chemoRT	PSF and OS

AE, adverse events; DLT, dose limiting toxicity; DoR, duration of response; EFS, event free survival; HPV, Human papilloma virus; IMRT, intensity-modulated radiotherapy; ORR, overall response rate; OPC, oropharyngeal cancer; OS, overall survival; PFS, progression-free survival; RT, radiation therapy; R/M HNSCC, recurrent/metastatic head and neck squamous cell carcinoma; SOC, standard of care.

cetuximab and vorinostat (histone deacetylases inhibitor of the Fas/FasL-dependent activation-induced death of T cells).[39]

PREDICTIVE BIOMARKERS OF RESPONSE

Despite the positive results for ICI compared with chemotherapy, responses are seen in 30% overall at best. Identifying the ideal biomarkers is crucial for optimizing and personalizing immunotherapy and remains an active area under investigation. The utility of PD-L1 expression as a biomarker has been variable across trials. Preliminary data have shown promise for alternative biomarkers such as high tumor mutation burden, which may explain the responses seen in PD-L1-negative patients. HPV-related patients with HNSCC have significantly longer survival than HPV-negative tumors[40–43]; however, the reasons for such outcome remain largely unknown. Nonetheless, it is known that HPV-associated HNSCC respond better to chemotherapy and radiotherapy and have better prognosis with surgery alone.[44 45] It is estimated that 50%–60% of human head and neck cancers express PD-L1.[40 46] It has also been reported that HPV-positive HNSCC are more heavily infiltrated by Treg cells and PD-1-positive T cells, and that these PD-1 expressing tumor infiltrating T cells correlate with better OS in HPV-associated head and neck cancer.[40] In the phase Ib KEYNOTE-012 trial of pembrolizumab in R/M HNSCC, ORR and median OS were higher for PD-L1-positive patients (22% vs 4% and 303 vs 151 days, respectively).[17] Of note, PD-L1 positivity was defined by both tumor and immune cell expression ≥1%. The 6-month OS rate was also higher for HPV-positive (70% vs 56%). In the phase II KEYNOTE-055 trial evaluating pembrolizumab in R/M HNSCC refractory to platinum and cetuximab, response rates were similar irrespective of HPV status (16%) but OS at 6 months was higher in HPV-associated disease (72% vs 55% in HPV-negative disease).[18] On the other hand, responses were higher based on PD-L1 status (18% in PD-L1≥1%, 12% in PD-L1<1% and 27% in PD-L1≥50%). However, this did not translate into significant difference in PFS or OS. Although the phase III KEYNOTE-040 trial showed no benefit for pembrolizumab over chemotherapy in the intent-to-treat analysis, subgroup analysis showed superiority with increased PD-L1 expression.[21] For instance, among PD-L1≥1% group, OS was 8.7 vs 7.1 months with chemotherapy (HR=0.75; p=0.0078), whereas for PD-L1 expression ≥50% (which accounted for only 26% of patients), OS was 11.6 vs 7.9 months, respectively (HR 0.54; 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).[21] Median OS was 8.7 vs 4.6 months among patients with PD-L≥1% (HR=0.55) and 5.7 vs 5.8 months (HR=0.89, p=0.17) among those with PD-L1<1% for nivolumab and chemotherapy respectively. On the other hand, 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) for 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 HSNCC.

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REFERENCES

1 Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. *CA Cancer J Clin* 2017;67:7–30.
2 Sacco AG, Cohen EE. Current Treatment Options for Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma. *J Clin Oncol* 2015;33:3305–13.
3 Vermorken JB, Mesia R, Rivera F, *et al*. Platinum-based chemotherapy plus cetuximab in head and neck cancer. *N Engl J Med* 2008;359:1116–27.
4 Tong CC, Kao J, Sikora AG. Recognizing and reversing the immunosuppressive tumor microenvironment of head and neck cancer. *Immunol Res* 2012;54(1-3):266–74.
5 Dunn GP, Old LJ, Schreiber RD. The immunobiology of cancer immunosurveillance and immunoediting. *Immunity* 2004;21:137–48.
6 Vesely MD, Kershaw MH, Schreiber RD, *et al*. Natural innate and adaptive immunity to cancer. *Annu Rev Immunol* 2011;29:235–71.
7 Strauss L, Bergmann C, Gooding W, *et al*. The frequency and suppressor function of CD4+CD25highFoxp3+ T cells in the circulation of patients with squamous cell carcinoma of the head and neck. *Clin Cancer Res* 2007;13:6301–11.
8 Chikamatsu K, Sakakura K, Whiteside TL, *et al*. Relationships between regulatory T cells and CD8+ effector populations in patients with squamous cell carcinoma of the head and neck. *Head Neck* 2007;29:120–7.
9 Ferris RL, Hunt JL, Ferrone S, antigen Hleukocyte. Human leukocyte antigen (HLA) class I defects in head and neck cancer: molecular mechanisms and clinical significance. *Immunol Res* 2005;33:113–34.
10 Ferris RL, Whiteside TL, Ferrone S. Immune escape associated with functional defects in antigen-processing machinery in head and neck cancer. *Clin Cancer Res* 2006;12:3890–5.
11 Ferris RL. Immunology and Immunotherapy of Head and Neck Cancer. *J Clin Oncol* 2015;33:3293–304.
12 Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer* 2012;12:252–64.
13 Zandberg DP, Strome SE. The role of the PD-L1:PD-1 pathway in squamous cell carcinoma of the head and neck. *Oral Oncol* 2014;50:627–32.
14 Lyford-Pike S, Peng S, Young GD, *et al*. Evidence for a role of the PD-1:PD-L1 pathway in immune resistance of HPV-associated head and neck squamous cell carcinoma. *Cancer Res* 2013;73:1733–41.
15 McCoy KD, Le Gros G. The role of CTLA-4 in the regulation of T cell immune responses. *Immunol Cell Biol* 1999;77:1–10.
16 Ferris RL, Blumenschein G, Fayette J, *et al*. Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck. *N Engl J Med* 2016;375:1856–67.
17 Chow LQM, Haddad R, Gupta S, *et al*. Antitumor Activity of Pembrolizumab in Biomarker-Unselected Patients With Recurrent and/or Metastatic Head and Neck Squamous Cell Carcinoma: Results From the Phase Ib KEYNOTE-012 Expansion Cohort. *J Clin Oncol* 2016;34:3838–45.
18 Bauml J, Seiwert TY, Pfister DG, *et al*. Pembrolizumab for Platinum- and Cetuximab-Refractory Head and Neck Cancer: Results From a Single-Arm, Phase II Study. *J Clin Oncol* 2017;35:1542–9.
19 Bauman JE, Cohen E, Ferris RL, *et al*. Immunotherapy of head and neck cancer: Emerging clinical trials from a National Cancer Institute Head and Neck Cancer Steering Committee Planning Meeting. *Cancer* 2016.
20 Seiwert TY, Burtness B, Mehra R, *et al*. Safety and clinical activity of pembrolizumab for treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-012): an open-label, multicentre, phase 1b trial. *Lancet Oncol* 2016;17:956–65.
21 Pembrolizumab CEE. pembro) vs standard of care (SOC) for recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC): Phase 3 KEYNOTE-040 trial. *ESMO Congress; Madrid, Spain* 2017.
22 Brahmer JR, Drake CG, Wollner I, *et al*. Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. *J Clin Oncol* 2010;28:3167–75.
23 Topalian SL, Hodi FS, Brahmer JR, *et al*. Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer. *N Engl J Med Overseas Ed* 2012;366:2443–54.
24 Harrington KJ, Ferris RL, Blumenschein G, *et al*. Nivolumab versus standard, single-agent therapy of investigator's choice in recurrent or metastatic

squamous cell carcinoma of the head and neck (CheckMate 141): health-related quality-of-life results from a randomised, phase 3 trial. *Lancet Oncol* 2017;18:1104–15.
25 Segal SIO NH, Balmanoukian AS, Massarelli E, *et al*. Clinical activity and safety of MEDI4736, an anti-PD-L1 antibody, In Head and neck cancer. *ESMO* 2016. Congress.
26 Zandberg. Durvalumab for recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC): preliminary results from a single-arm, phase 2 study. *ESMO* 2017. Congress.
27 Wolchok JD, Rollin L, Larkin J. Nivolumab and Ipilimumab in Advanced Melanoma. *New Engl J Med* 2017;377:2503–4.
28 Motzer RJ, Tannir NM, McDermott DF, *et al*. Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. *N Engl J Med Overseas Ed* 2018;378:1277–90.
29 Jie HB, Schuler PJ, Lee SC, *et al*. CTLA-4(+) Regulatory T Cells Increased in Cetuximab-Treated Head and Neck Cancer Patients Suppress NK Cell Cytotoxicity and Correlate with Poor Prognosis. *Cancer Res* 2015;75:2200–10.
30 Parikh F, Duluc D, Imai N, *et al*. Chemoradiotherapy-induced upregulation of PD-1 antagonizes immunity to HPV-related oropharyngeal cancer. *Cancer Res* 2014;74:7205–16.
31 Vincent J, Mignot G, Chalmin F, *et al*. 5-Fluorouracil selectively kills tumor-associated myeloid-derived suppressor cells resulting in enhanced T cell-dependent antitumor immunity. *Cancer Res* 2010;70:3052–61.
32 Ghiringhelli F, Larmonier N, Schmitt E, *et al*. CD4+CD25+ regulatory T cells suppress tumor immunity but are sensitive to cyclophosphamide which allows immunotherapy of established tumors to be curative. *Eur J Immunol* 2004;34:336–44.
33 Brix N, Tiefenthaller A, Anders H, *et al*. Abscopal, immunological effects of radiotherapy: Narrowing the gap between clinical and preclinical experiences. *Immunol Rev* 2017;280:249–79.
34 Rice AE, Latchman YE, Balint JP, *et al*. An HPV-E6/E7 immunotherapy plus PD-1 checkpoint inhibition results in tumor regression and reduction in PD-L1 expression. *Cancer Gene Ther* 2015;22:454–62.
35 Lynch DH. The promise of 4-1BB (CD137)-mediated immunomodulation and the immunotherapy of cancer. *Immunol Rev* 2008;222:277–86.
36 Weinberg AD, Rivera MM, Prell R, *et al*. Engagement of the OX-40 receptor in vivo enhances antitumor immunity. *J Immunol* 2000;164:2160–9.
37 Bell RB, Leidner RS, Crittenden MR, *et al*. OX40 signaling in head and neck squamous cell carcinoma: Overcoming immunosuppression in the tumor microenvironment. *Oral Oncol* 2016;52:1–10.
38 Deng WW, Mao L, Yu GT, *et al*. LAG-3 confers poor prognosis and its blockade reshapes antitumor response in head and neck squamous cell carcinoma. *Oncoimmunology* 2016;5:e1239005.
39 Gillenwater AM, Zhong M, Lotan R. Histone deacetylase inhibitor suberoylanilide hydroxamic acid induces apoptosis through both mitochondrial and Fas (Cd95) signaling in head and neck squamous carcinoma cells. *Mol Cancer Ther* 2007;6:2967–75.
40 Badoual C, Hans S, Merillon N, *et al*. PD-1-expressing tumor-infiltrating T cells are a favorable prognostic biomarker in HPV-associated head and neck cancer. *Cancer Res* 2013;73:128–38.
41 Ang KK, Harris J, Wheeler R, *et al*. Human Papillomavirus and Survival of Patients with Oropharyngeal Cancer. *N Engl J Med Overseas Ed* 2010;363:24–35.
42 Marur S, D'Souza G, Westra WH, *et al*. HPV-associated head and neck cancer: a virus-related cancer epidemic. *Lancet Oncol* 2010;11:781–9.
43 Fakhry C, Westra WH, Li S, *et al*. Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. *J Natl Cancer Inst* 2008;100:261–9.
44 Chung CH, Gillison ML. Human papillomavirus in head and neck cancer: its role in pathogenesis and clinical implications. *Clin Cancer Res* 2009;15:6758–62.
45 Fisher JW, Thompson BM, Garcia AD. Integrative clinical experience: an innovative program to prepare for internship. *Teach Learn Med* 2007;19:302–7.
46 Strome SE, Dong H, Tamura H, *et al*. B7-H1 blockade augments adoptive T-cell immunotherapy for squamous cell carcinoma. *Cancer Res* 2003;63:6501–5.