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The promise of immunotherapy in head and neck squamous cell carcinoma: combinatorial immunotherapy approaches

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ABSTRACT
The immune system plays a fundamental role in preventing cancer development by recognising and eliminating tumour cells. The recent success in the field of immunotherapy has confirmed the potential to exploit the immune response as a cancer treatment. Head and neck squamous cell carcinoma (HNSCC) is a malignancy characterized by dismal prognosis and high mortality rate; low survival outcomes in combination with significant toxicity of current treatment strategies highlight the necessity for novel therapeutic modalities. HNSCC is a favourable disease for immunotherapy, as immune escape plays a key role in tumour initiation and progression. T-cell checkpoint inhibitors targeting programmed cell death protein-1 have emerged as novel immunotherapy agents showing remarkable efficacy in HNSCC. However, only a minority of patients derive benefit for single-agent immunotherapies. In this regard, combinatorial immunotherapy approaches represent an alternative strategy that might increase the number of patients who respond to immunotherapy. Focusing on HNSCC, this review will summarise novel combinations of immune checkpoint blockade with other immunotherapy treatment modalities.

INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common malignancy worldwide. HNSCC incidence trends have been strongly associated with patterns of tobacco use over time and across countries. While tobacco and alcohol use account for the vast majority of HNSCC, a substantial proportion of oropharynx cancers appears to be a sexually transmitted disease and is causally associated with high-risk human papillomaviruses (HPVs), especially type 16.[1 2] HPV-associated oropharynx cancer appears to be a distinct biological and clinical entity; it has a better prognosis than HPV-negative counterparts and may require less-intensive treatment. Despite advances in multimodality treatment, the 5-year progression-free survival (PFS) rates of patients with HPV-negative locally advanced disease do not exceed 40%–50% and survival rates in recurrent or metastatic (R/M) setting remain poor.[3]

Low survival outcomes in combination with substantial toxicities associated with current treatment strategies employed in HNSCC emphasize the necessity for novel treatment strategies. Immunotherapy has led to a paradigm shift in the treatment of several cancers, providing long-lasting, durable responses for patients with advanced cancers.[4–7] In July 2016, the Food and Drug Administration (FDA) has granted a priority review designation to nivolumab, an anti-programmed cell death protein-1 (anti-PD-1) monoclonal antibody (mAb) for the treatment of platinum-refractory recurrent and/or metastatic HNSCC based on a pivotal phase III clinical trial which demonstrated improved overall survival (OS) compared with treatment with the investigator's choice of weekly methotrexate, docetaxel or cetuximab.[8] The anti-PD-1 pembrolizumab was also recently approved by the US FDA for the treatment of platinum-refractory recurrent and/or metastatic HNSCC based on the demonstration of a durable objective response rate (ORR) in a subgroup of patients in an international, multicenter, non-randomized, open-label, multi-cohort study.[9] Building on initial hypotheses[10–12] that the host immune system plays a pivotal role in shaping HNSCC, the recent successes of immunotherapies have confirmed the potential to harness the immune system for the treatment of patients with HNSCC. In particular, T-cell checkpoint inhibitors targeting PD-1 have demonstrated efficacy in HNSCC.[8 9] As single agents, these therapies have response rates in the range of 14%–32% in second-line setting in R/M HNSCC, with responses characterized by a durability that is rarely, if ever, attained with other types of anticancer therapy. However, only a minority of patients derives benefit

from single-agent immunotherapies, with some patients not responding to treatment at all, and others attaining a limited response followed by tumour progression. One of the major challenges at present is the development of alternative treatment strategies that improve the subset of patients who may respond to immunotherapy. A better understanding of the mechanisms implicated in response to immune-based therapies may allow physicians to identify patients likely to benefit from these therapies and will potentially provide insight into how other therapies may be used in combination to increase the number of patients who benefit from immunotherapy. This review will focus on ongoing efforts to use T-cell checkpoint inhibitors in combination with other therapeutic approaches to address this challenge. The organisational framework for this review is structured around anti-PD-1/programmed death ligand-1 (PD-L1) therapies in combination with (1) other coinhibitory checkpoints, (2) costimulatory checkpoints and (3) other molecules in the tumour microenvironment.

COMBINATIONS OF COINHIBITORY CHECKPOINTS
Targeting cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) + PD-1/PD-L1

Although both CTLA-4 and PD-1 are inhibitory coreceptors expressed on T cells, they have distinct ligands and functions. After antigen-driven T-cell receptor (TCR)-mediated T-cell activation,[13] CTLA-4 binds to ligands cluster of differentiation 80 (CD80) and cluster of differentiation 86 (CD86)[14] and inhibits effector T-cell activation and proliferation[15–17] by competitively inhibiting binding of B7 ligands to the costimulatory receptor cluster of differentiation 28[18–21] and blockade of intracellular signaling pathways[22–24]; PD-1 is similarly located at the surface of effector T cell on activation,[25] where PD-1 binds to ligands PD-L1[26 27] and PD-L2[28] and prevents T-cell proliferation,[29] cytokine production[30 31] and survival,[32 33] which is typical of the state of T-cell exhaustion.[34 35] A recent study that evaluated blood and tissue specimens of patients undergoing monotherapy or combination therapies of anti-CTLA-4 and anti-PD-1 antibodies demonstrated that blockade of CTLA-4 induces a proliferative signature in a subset of memory T cells, whereas PD-1 blockade results in modification of genes that are involved in T-cell or natural killer (NK) functions.[36] Furthermore, anti-CTLA4 antibodies are more capable of inducing antibody-dependent cell-mediated cytotoxicity than PD-1 antibodies.[37]

In this context, CTLA-4 and PD-1 can produce complementary effects on effector T cells, including inhibitory effects on early activation and differentiation by CTLA-4 and modulation of effector function by PD-1.[38 39] Preclinical observations that mice deficient for CTLA-4[40 41] or PD-1[42–44] had different toxicity patterns further highlighted their distinct properties and inspired efforts to examine the effects of the combined blockade of these pathways. In melanoma mouse model, the combination of CTLA-4 and PD-1 blockade significantly enhanced

tumour rejection compared with either agent alone.[45] The first study testing the combination of T-cell checkpoint blockade was conducted in patients with advanced melanomas treated with the PD-1 inhibitor nivolumab and the CTLA-4 inhibitor ipilimumab.[46] Thirty-three of 86 patients enrolled in this phase I study had previously received ipilimumab within 12 weeks and were then treated sequentially with nivolumab monotherapy (sequential regimen); 53 patients were ipilimumab naive and received ipilimumab and nivolumab combined (concurrent regimen). In patients treated with the concurrent regimen, 40% had objective partial response, while 65% derived clinical benefit. In patients treated with the sequential regimen, the ORR was 20% and 43% had clinical benefit. Importantly, the majority of responses seen in the concurrent arm were fast, deep (one-third achieving 80% reduction in tumour burden) and durable (78% of patients alive at 2 years).[47] Notably, there were some substantial toxicities. In the concurrent regimen, treatment-related grade 3–4 elevated liver enzymes were seen in 15%, gastrointestinal toxicities reported in 9%, rash in 4%, and pneumonitis and endocrinopathy occurred in 2% each. Still, toxicity was manageable and nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks for four doses followed by nivolumab 3 mg/kg every 2 weeks was selected to be the optimal dosing regimen for further development.

A subsequent double-blind, phase II, randomised study of nivolumab plus ipilimumab compared with ipilimumab alone in advanced melanoma has confirmed the substantial activity of this combination.[48] Particularly, the ORR to nivolumab plus ipilimumab was 59%, versus 11% with ipilimumab alone. A more recent double-blind, phase III, randomized study of nivolumab plus ipilimumab versus nivolumab versus ipilimumab was performed in patients with treatment-naive advanced melanoma and confirmed the superiority of the combination versus ipilimumab or nivolumab alone (NCT01844505).

The predictive value of PD-L1 expression on tumour cells, which has been postulated to be a predictor of response to anti-PD-1/PD-L1 therapy[6 49–52] was also evaluated. Responses to both combination therapy and nivolumab monotherapy were enriched in PD-L1-positive patients (72.1% and 57.5%, respectively, compared with 54.8% and 41.3% in PD-L1-negative patients). Among PD-L1-positive patients, PFS was relatively similar in patients who received either combination therapy or nivolumab monotherapy, but follow-up is still short and many patients remain on treatment. Further follow-up will determine whether PD-L1 is useful for patient selection (combination vs PD-1 blockade monotherapy).

Building on the remarkable activity seen in patients with melanoma, several studies have begun to explore the combination of PD-1/PD-L1 and anti-CTLA-4 in other diseases including HNSCC. In HNSCC, several trials are currently assessing the efficacy of durvalumab, a selective high-affinity engineered human IgG1 mAb that blocks binding of PD-L1 to PD-1 and CD80, in combination with anti-CTLA-4 mAb tremelimumab. Durvalumab

has yielded promising results (~14% response rate as per Response Evaluation Criteria in Solid Tumours (RECIST) criteria, with 24% response rate in PD-L1-positive patients) in a phase I trial.[53] A phase II study is currently evaluating the efficacy of durvalumab monotherapy in PD-L1-positive R/M HNSCC (NCT02207530). The phase I, open-label, dose-escalation and expansion study evaluating durvalumab and tremelimumab in advanced solid tumours showed a 27% response rate (95% CI 13 to 46) in PD-L1-negative patients, with a disease control rate of 48% (95% CI 31 to 66) at ≥16 weeks after therapy. Notably, anti–PD-1/PD-L1 monotherapy yields an approximately 5%–10% response rate in PD-L1-negative patients; therefore, the addition of low-dose anti-CTLA-4 therapy may benefit these patients. Durvalumab at 20 mg/kg every 4 weeks plus tremelimumab at 1 mg/kg every 4 weeks was the dose level chosen for phase III development, and at this dose level, toxicity leading to discontinuation was <10%, while lower tremelimumab dosing did not affect clinical efficacy. The regimen of durvalumab 20 mg/kg plus tremelimumab 1 mg/kg given together every 4 weeks has been chosen for further development.

The phase III KESTREL study (NCT02551159) compares durvalumab alone and durvalumab plus tremelimumab with EXTREME standard of care regimen for first-line treatment of R/M HNSCC. KESTREL is an open-label, multicenter, global study of patients with R/M (oral cavity, oropharynx, hypopharynx or larynx) who have received no prior systemic chemotherapy (unless part of multimodality treatment for locally advanced disease). Patients will be stratified by PD-L1 expression status, tobacco history, tumour location, and then HPV status (oropharyngeal cancer) and randomized (2:1:1) to receive flat doses of tremelimumab 75 mg every 4 weeks (maximum four doses) plus durvalumab 1500 mg every 4 weeks; durvalumab 1500 mg every 4 weeks or EXTREME regimen (carboplatin or cisplatin + 5-fluorouracil + cetuximab), all until disease progression. The combination will be assessed versus standard of care in terms of coprimary endpoints, PFS and OS. Durvalumab plus tremelimumab versus standard of care will be further assessed in terms of overall response rate, duration of response, proportion of patients alive and PFS at 12 months, OS at 24 months, secondary progression, safety and tolerability, pharmacokinetics, immunogenicity and HR quality of life. The efficacy of durvalumab monotherapy versus both durvalumab/tremelimumab and EXTREME will also be tested. Exploratory endpoints include blinded independent central review of antitumour activity (immune-related RECIST v1.1) and potential biomarkers of progression/response.

EAGLE is a phase III trial designed to evaluate durvalumab alone or in conjunction with tremelimumab versus standard of care (cetuximab, taxane, methotrexate or fluoropyrimidine) in platinum-refractory HNSCC (EAGLE-NCT02369874). CONDOR trial randomised patients to durvalumab alone, tremelimumab alone or the combination in patients with PD-L1-negative platinum refractory disease (NCT02319044).

Of note, US FDA has placed a clinical hold on the enrolment of new patients in clinical trials with durvalumab monotherapy or durvalumab and tremelimumab combination due to safety concerns (haemorrhagic complications). All trials are continuing with existing patients.

CheckMate 651 (NCT02741570) which recently opened to accrual is a phase III study of nivolumab in combination with ipilimumab compared with the standard of care (Extreme regimen) as first-line treatment in patients with R/M HNSCC.

Targeting lymphocyte activation group-3 or killer-cell immunoglobulin-like receptors + PD-1/PD-L1 or CTLA-4

Another category of receptors with a modulating effect on immune cells includes other checkpoint receptors such as lymphocyte activation group-3 (LAG-3) or the killer-cell immunoglobulin-like receptors (KIRs).[54] They regulate immune response via interaction with major histocompatibility complex I molecules. Most of the receptors suppress cytotoxicity, mainly by turning off NK cells when human leukocyte antigen (HLA) is expressed on tumour cells. In combination with PD-1 blockade, murine data are suggestive of significant synergistic potential. Ongoing trials are testing an anti-KIR mAb in combination with ipilimumab (NCT01750580) or nivolumab (NCT01714739). A phase I trial is evaluating the efficacy of nivolumab in combination with anti-LAG-3 antibody BMS-986016 in advanced solid tumours including HNSCC (NCT01968109).

Targeting T-cell immunoglobulin and mucin domain 3 + PD-1/PD-L1

T-cell immunoglobulin and mucin domain 3 (TIM-3) is a coinhibitory receptor expressed by interferon gamma (IFN-γ) secreting CD4 + helper T cells and cluster of differentiation 8 (CD8) + cytotoxic T cells.[55] High TIM-3 expression is a marker of T-cell exhaustion which is manifested by decreased T-cell proliferation, decreased IFN-γ, tumour necrosis factor-α (TNF-α) and interleukin-2 (IL-2) secretion, and increased IL-10 secretion.[56–59] In preclinical models, blockade of TIM-3 can enhance cytokine-producing, tumour-specific T cells and potentiate antitumour activity in combination with PD-L1 blockade.[59 60] A phase I study of TSR-022, an anti-TIM-3 mAb, in patients with advanced solid tumours is ongoing (NCT02817633).

COMBINATIONS WITH COSTIMULATORY CHECKPOINTS
Targeting glucocorticoid-induced TNF receptor + PD-1/PD-L1

Glucocorticoid-induced TNF receptor (GITR)/GITR ligand axis is a pathway that functions by inhibiting T regulatory cells (Treg) function while activating CD8þ T effector cells.[61] Murine models have shown that GITR stimulation (with an agonist antibody or with cognate ligand) promotes effector T-cell proliferation, cytokine

production,[62][63] resistance to Treg suppression[64–66] and inhibition of Treg suppressive function.[67] In in vivo models, administration of a GITR agonist antibody is associated with reduction of intratumoural Treg accumulation and potentiation of antitumour CD8+ effector T-cell function,[64][65][68] as well as antitumour activity.[64][68][69] When given in combination with PD-1 blockade, increased activity was also seen. For example, when anti-GITR and anti-PD-1 administered to mice with ID8 ovarian cancer, 20% of mice were tumour-free after 90 days while either anti-PD-1 or anti-GITR antibody alone exhibited little antitumour effect.[70] Anti-GITR antibodies in clinical development (TRX518, MK4166) are being tested in solid tumours as single agents (NCT01239134) and in combination with PD-1 blockade (NCT02740270).

Targeting OX40 + CTLA-4 or PD-1/PD-L1

OX40 (CD134) and its binding partner, OX40L (CD252), are members of the TNF receptor/TNF superfamily. OX40 is a costimulatory immune checkpoint molecule that is expressed on activated CD4 and CD8 T cells.[71] Costimulatory signals from OX40 lead to division and survival of T cells, enhancing the clonal evolution of effector and memory populations.[72] OX40 is also a regulator of Treg function.[73] In preclinical mouse models, agonist targeting OX40 can augment T-cell effector responses.[74] There is substantial preclinical evidence that anti-OX40 synergizes with immune checkpoint inhibitors and other immunotherapies.[75–77] In an ovarian cancer murine model, although treatment with either anti-OX40 or anti-PD-1 was ineffective, the combination of anti-OX40 and anti-PD-1 antibodies resulted in successful tumour growth inhibition.[78] Similarly, anti-OX40 and anti-PDL-1 antibodies have a synergistic effect in preclinical models.[79] In HNSCC patient samples, OX40 and CTLA-4 molecules have been shown to be expressed in tumour-infiltrating lymphocytes.[80] In a phase I study in patients with treatment refractory solid tumours, agonistic anti-OX40 antibody 9B12 showed mild toxicity and good tumour control in 18/30 of patients treated.[81] A phase I study with anti-OX40 antibody MEDI6469 administered prior to surgical resection in patients with locally advanced HNSCC is currently recruiting patients (NCT02274155). Anti-OX40 antibodies (MOXR0916, MEDI6383) are currently being tested in combination with anti-PD-1/anti-PDL-1 agents in metastatic solid tumours (NCT02410512, NCT02221960).

Targeting 4-1BB (CD137) + CTLA-4 or PD-1/PD-L1

4-1BB is a costimulatory receptor that belongs to the TNF receptor family and is upregulated on CD8 T cells following activation. It is also expressed on CD4 T cells, NK cells and Tregs.[82] 4-1BB signalling enhances T-cell activation, provokes T-cell proliferation[83] and upregulates the expression of antiapoptotic molecules,[84] facilitating the formation of immunological memory. In preclinical models, anti-41BB agonistic antibodies have shown efficacy in combination with immune checkpoint inhibitors. In a melanoma murine model, concurrent administration of anti-41BB and anti-CTLA-4 antibodies resulted in

prolonged survival.[85] In a phase I clinical trial, urelumab, a 4-1BB antibody, was evaluated in 83 patients with melanoma, renal cell carcinoma, ovarian and prostate cancer. Patients with melanoma showed good clinical response (three had partial responses and four stable disease) albeit with significant liver toxicity. 4-1BB has been found to be expressed in lower levels on CD4 T cells of patients with HNSCC.[86] Urelumab is being evaluated in combination with cetuximab (NCT02110082) and nivolumab (NCT02253992) in advanced solid tumours including HNSCC. Anti-41BB antibody PF-05082566 is being tested in combination with anti-OX40 antibody PF-04518600 in advanced solid tumours including HNSCC (NCT02315066).

COMBINATIONS WITH OTHER MOLECULES IN THE TUMOUR MICROENVIRONMENT
Targeting indoleamine 2,3-dioxygenase + CTLA-4 or PD-1/PD-L1

Indoleamine 2,3-dioxygenase (IDO) is a haeme-containing enzyme involved in tryptophan catabolism, catalysing the degradation of amino acid L-tryptophan into kynurenine.[87] It is expressed in both tumour cells and infiltrating myeloid cells. IDO is an immunomodulatory enzyme that produces immunosuppressive effects, such as inhibition of T-cell activation and proliferation and decrease of TCR expression.[88] In preclinical models, IDO has been shown to inhibit immune responses through the depletion of L-tryptophan that is critical for anabolic functions in lymphocytes or through the synthesis of specific ligands for cytosolic receptors that can alter lymphocyte functions.[89] In IDO knockout mice with melanomas, anti-CTLA4 targeting resulted in inhibition of tumour growth marked with increased infiltration of effector T cells.[90]

Preliminary results from a phase I/II study (NCT02178722) of IDO inhibitor epacadostat (INCB024360) with permbrolizumab in a variety of human malignancies including HNSCC were recently reported.[91] The combination of two immunotherapies showed an overall response rate of 53% and disease control rate of 74%; efficacy was greater in patients with melanoma. Toxicity was tolerable with very few patients experiencing grade 3/4 events. In one evaluable patient with HNSCC, a partial response was noted. A phase I/II study in which evaluated the combination of IDO inhibitor INCB024360 with ipilimumab in patients with melanoma showed a disease control rate of 755 in eight evaluable patients.[92] Notably, patients had significant increase of liver function tests when treated with high doses of INCB024360.[92]

OTHER ANTICANCER TREATMENT MODALITIES IN COMBINATION WITH T-CELL CHECKPOINT BLOCKADE
Oncolytic viruses

Oncolytic viruses are natural or genetically altered viruses that preferentially infect and replicate in tumour cells and lead to immunogenic tumour cell death. Apart from direct tumour killing, oncolytic viruses promote

the induction of antitumour T cells by the release of danger signals and tumour antigens following oncolysis.[93] Talimogene laherparepvec (TVEC) is an oncolytic immunotherapy that is furthest along in clinical development. It is derived from herpes simplex virus type-1 that has been engineered to selectively replicate within tumours and to produce granulocyte-macrophage colony stimulation factor (GM-CSF) to enhance systemic antitumour immune responses. In a randomized phase III clinical trial in patients with advanced melanoma, TVEC demonstrated statistically significant superior overall response rate compared with GM-CSF (26% vs 6%).[94]

TVEC is currently being tested in combination with immune checkpoint inhibitors. In a phase Ib trial, TVEC in combination with ipilimumab showed promising results (overall response rate 56%) in patients with melanoma, with tolerable toxicity. Another phase Ib/II is assessing the safety and efficacy of TVEC in combination with pembrolizumab versus permbrolizumab monotherapy in patients with stage IIIB/IV unresectable melanoma (NCT02263508).

In patients with HNSCC, TVEC was evaluated in a phase I/II study in combination with standard cisplatin and radiation for patients with locally advanced disease. All patients had post-treatment neck dissections. Median follow-up was 29 months with 100% patient free of locoregional disease and a disease-specific survival of 82.4% and overall survival rate of 70.5%. Pathological complete response in the neck dissections were 100%.[95] TVEC is currently being tested in combination with pemrolizumab in patients with R/M HNSCC in the phase Ib/III MASTERKEY232/KEYNOTE-034 study (NCT02626000). Other oncolytic viruses, such as oncolytic reovirus and oncolytic adenoviruses H101 and Onyx 015 have been evaluated in advanced HNSCC as monotherapies or in combination with chemotherapy.[96 97] Recombinant vaccinia virus Pexa-Vec and recombinant avian fowlpox virus TRICOM are currently being assessed as monotherapies in HNSCC in phase I trials (NCT00625456 and NCT00021424).

Vaccines

Anticancer vaccine therapies include generating an antitumour immune response by presenting a tumour-associated antigen (TAA) plus an immunostimulatory adjuvant, resulting in immune sensitisation to tumour antigens. Several vaccination strategies have been evaluated, including the transfection of TAA expression plasmids into patient tissues (DNA vaccines), the administration of TAA peptides (peptide vaccines) and the use of cultured human or microbial cells to generate an antitumour immune response.[98]

In HNSCC, several vaccines, such as DNA vaccine INO-3112 and peptide vaccines Mucin-1 and Allo-Vax are currently under investigation in phase I/II clinical trials. In a phase I trial, five patients with advanced HNSCC were treated with peptide vaccines composed of HLA-I and HLA-II restricted melanoma antigen E-A3 or HPV-16 derived peptides, provoking a measurable immune response and acceptable toxicity.[99] Furthermore, a phase II trial evaluating the efficacy of HPV16 E6 and E7 peptide vaccines in patients with HPV-related tumours including HNSCC has been completed and results are expected shortly (NCT00019110).

Combination of vaccine therapy with immune checkpoint inhibitors is currently being assessed in a number of clinical trials. In a phase I trial in patients with advanced solid tumours including patients with HNSCC, a combination of pembrolizumab and modified vaccinia virus Ankara vaccine expressing p53 is being evaluated (NCT02432963). A phase I/II study of a live attenuated *Listeria monocytogenes* immunotherapy bioengineered to secrete an HPV-E7 tumour antigen as a truncated ListerioLysin O–E7 fusion protein in cells capable of presenting antigen (ADXSII-001) is being tested alone or in combination with MEDI4736 in patients with R/M cervical or HPV+ HNSCC in a phase I/II study (NCT02291055). Ipilimumab is being evaluated in combination with vaccines in advanced pancreatic cancer and melanoma in ongoing clinical trials (NCT00836407, NCT01810016).

Combinatorial immunotherapy approaches in HNSCC are summarised in table 1.

CONCLUSIONS

Immunotherapy has been introduced as a strategy for the treatment of cancer more than 100 years ago,[10] and it is currently established that malignant cells develop multiple mechanisms to escape immune detection, such as induction of immune tolerance, repression of immune response and disruption of T-cell signalling.[100] During the last decade, further investigation on the mechanistic basis of the immune system has led to the development of breakthrough immunotherapies, mainly through checkpoint inhibition.[101] Immune checkpoints, such as CTLA-4 and PD-1, are normal immunoregulatory pathways that have a major role in maintaining self-tolerance and modulating immune response in normal human peripheral tissues.[89] Hence, T-cell checkpoint inhibitors targeting CTLA-4 and PD-1 block these inhibitory pathways enhance immune surveillance against tumour cells, therefore harnessing the immune system in favour of patients with cancer.

Anti-CTLA-4 and anti-PD-1 antibodies have demonstrated substantial clinical activity in a variety of cancer types,[4–7 102] including HNSCC. However, though monotherapy regimens for HNSCC have yielded some success, there are significant limitations with regard to response rates and duration of therapy. Indeed, monotherapies are unlikely to overcome the major mechanisms that impede antitumour immunity in patients because the induction, capacity and persistence of host immune responses reflect the complex interplay of different immune cell populations with progressive tumours. Combination immunotherapies represent a fundamental step in the progress towards improving responses, and immune checkpoint inhibitors will likely become the

Table 1 Combinatorial immunotherapy approaches in HNSCC

Combination immunotherapy	Mechanisms of action	Stage of clinical development	Study design	Setting
Nivolumab + ipilimumab	Anti-PD-1 + anti-CTLA-4	Phase III (NCT02741570, Checkmate 651)	Nivolumab + ipilimumab vs EXTREME regimen	First-line R/M HNSCC
Durvalumab + tremelimumab	Anti-PD-L1 + anti-CTLA-4	Phase III (NCT02551159, KESTREL)	Durvalumab vs durvalumab + tremelimumab vs EXTREME regimen	First-line R/M HNSCC
Durvalumab + tremelimumab	Anti-PD-L1 + anti-CTLA-4	Phase III (NCT02369874, EAGLE)	Durvalumab vs durvalumab + tremelimumab vs EXTREME regimen	Platinum refractory R/M HNSCC
Durvalumab + tremelimumab	Anti-PD-L1 + anti-CTLA-4	Phase II (NCT02319044, CONDOR)	Durvalumab vs tremelimumab vs durvalumab + tremelimumab	PD-L1-negative, platinum-refractory R/M HNSCC
Nivolumab + BMS-986016	Anti-PD-1 + anti-LAG-3	Phase I (NCT01968109)	Nivolumab + BMS-986016 vs BMS-986016	Advanced solid tumours including HNSCC naive to immuno-oncology agents
Nivolumab + lirilumab	Anti-PD-1 + anti-KIR	Phase I (NCT01714739)	Nivolumab + lirilumab	Advanced solid tumours that have progressed to at least one standard regimen
Anti-PD-1 + TSR-022	Anti-PD-1 + anti-TM-3	Phase I (NCT02817633)	Expansion cohort Anti-PD-1 + TSR-022 vs TSR-022	Advanced refractory solid tumours
PDR001 + GWN323	Anti-PD-1 + anti-GITR	Phase I (NCT02740270)	Expansion cohort PDR001+ GWN323 vs GWN323	Advanced solid tumours and lymphomas
Atezolizumab + MOXR0916	Anti-PD-L1 + anti-OX40	Phase I (NCT02410512)	Atezolizumab + MOXR0916 vs atezolizumab + MOXR0916 + bevacizumab	Advanced refractory solid tumours
Durvalumab + MEDI6383	Anti-PD-L1 + anti-OX40	Phase I (NCT02221960)	Durvalumab + MEDI6383 vs MEDI6383	Advanced refractory solid tumours
Urelumab + cetuximab	Anti-4-1BB + anti-EGFR	Phase I (NCT02110082)	Urelumab + cetuximab	Advanced refractory HNSCC and colorectal cancer
Nivolumab + urelumab	Anti-PD-1 + anti-4-1BB	Phase I (NCT02253992)	Nivolumab + urelumab	Advanced refractory solid tumours/ lymphomas
PF-05082566 + PF-04518600	Anti-4-1BB + anti-OX40	Phase I (NCT02315066)	PF-05082566 + PF-04518600 vs PF-04518600	Advanced solid tumours including HNSCC
Pembrolizumab + epacadostat	Anti-PD-1 + IDO inhibitor	Phase I/II (NCT02178722)	Pembrolizumab + epacadostat	Advanced solid tumours including HNSCC
Pembrolizumab + TVEC	Anti-PD-1 + oncolytic virus	Phase Ib/ III (NCT02626000, MASTERKEY232/ KEYNOTE-034)	Pembrolizumab + TVEC	R/M HNSCC not amenable to curative surgery/radiation
Pembrolizumab + p53MVA vaccine	Anti-PD-1 + vaccine	Phase I (NCT02432963)	Pembrolizumab + p53MVA vaccine	Advanced solid tumours including HNSCC that have progressed to at least one standard regimen
Durvalumab + ADXS11-001	Anti-PD-1 + vaccine	Phase I (NCT02291055)	Durvalumab + ADXS11-001 vs ADXS11-001 vs durvalumab	Previously treated LA/metastatic HPV+ HNSCC or cervical cancer

CTLA-4, cytotoxic T-lymphocyte-associated protein 4; EGFR, epidermal growth factor receptor; EXTREME regimen, platinum/5-fluorouracil + cetuximab; GITR, glucocorticoid-induced tumour necrosis factor receptor; HNSCC, head and neck squamous cell carcinoma; HPV, human papillomavirus; IDO, indoleamine 2,3-dioxygenase; KIR, killer-cell immunoglobulin-like receptor; LA, locally advanced; LAG-3, lymphocyte activation gene 3; PD-1, programmed cell death protein-1; PD-L1, programmed death ligand-1; p53MVA, modified vaccinia virus Ankara vaccine expressing p53; R/M, recurrent/metastatic; TIM-3, T-cell immunoglobulin and mucin domain 3; TVEC, talimogene laherparepvec.

immunotherapeutic backbone of future cancer treatments. Importantly, combinatorial immunotherapy approaches should be designed rationally and safely. Future research should focus on the selection of optimal immunotherapeutic combinations and identification of appropriate biomarkers with the view to improve patient outcomes.

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