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Review Paper
Head and Neck Oncology

Clinical immunotherapeutic approaches for the treatment of head and neck cancer

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Abstract. Head and neck squamous cell carcinoma (HNSCC) is the sixth most common malignancy worldwide, accounting for more than 550,000 cases and 380,000 deaths annually. The primary risk factors associated with HNSCC are tobacco use and alcohol consumption; nevertheless genetic predisposition and oncogenic viruses also play important roles in the development of these malignancies. The current treatments for HNSCC patients include surgery, chemotherapy, radiotherapy, and cetuximab, and combinations of these. However, these treatments are associated with significant toxicity, and many patients are either refractory to the treatment or relapse after a short period. Despite improvements in the treatment of patients with HNSCC, the clinical outcomes of those who have been treated with standard therapies have remained unchanged for over three decades and the 5-year overall survival rate in these patients remains around 40–50%. Therefore, more specific and less toxic therapies are needed in order to improve patient outcomes. The tumour microenvironment of HNSCC is immunosuppressive; therefore immunotherapy strategies that can overcome the immunosuppressive environment and produce long-term tumour immunosurveillance will have a significant therapeutic impact in these patients. This review focuses on the current immunological treatment options under investigation or available for clinical use in patients with HNSCC.

Key words: head and neck cancer; immunotherapy; biomarkers; PD-L1; PD-1; HPV; EGFR; tumour microenvironment.

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Head and neck squamous cell carcinoma (HNSCC) is the sixth most common malignancy worldwide[1], and accounts for an annual incidence of more than 550,000 cases and 300,000 deaths[2]. Alcohol consumption and tobacco use are the predominant risk factors for HNSCC; however, studies have shown the involvement of genetic variations, as well as human papillomavirus (HPV) and Epstein–Barr virus (EBV) infections in the development of HNSCC[3]. The current treatments for HNSCC patients include surgery, chemotherapy (CT), radiotherapy (RT), and the epidermal growth factor receptor (EGFR) inhibitor cetuximab, and combinations of these. Treatment is based on the patient's status, primary tumour site, stage of the disease, and prior therapies. However, most patients still do not respond to the treatment or develop acquired resistance. Additionally, the conventional treatments are associated with severe long-term side effects. Despite recent advances in the

treatment of patients with HNSCC, such as transoral robotic surgery, precise intensity-modulated radiotherapy (IMRT), multi-agent CT regimens, and the development of targeted therapies, the 5-year overall survival (OS) rate has remained 40–50% over the last three to four decades[1]. Therefore, there is a need for novel treatment strategies that are less toxic and able to extend survival rates and improve patient quality of life.

The immune system plays a major role in the development and progression of HNSCC[4], and numerous immunological alterations occur that allow the tumours to escape immunosurveillance. To this end, various immunological strategies have been proposed in recent years in order to restore the function of the host's immune system and induce anti-tumour immune responses in HNSCC. This review summarizes the immunotherapeutic approaches that are currently undergoing clinical investigation in HNSCC.

Monoclonal antibodies

EGFR inhibitors

EGFR is a member of the ErbB receptor tyrosine kinases family and its overexpression has been observed in about 90% of HNSCC[5]. EGFR overexpression is known to be associated with advanced clinical stage, poor patient prognosis, and resistance to CT and RT[6]. Therefore, EGFR is a major therapeutic target in HNSCC, and several inhibitors against EGFR have been developed in recent years.

Cetuximab

Cetuximab (Erbitux) is a recombinant human/mouse chimeric IgG1 monoclonal antibody (mAb) against EGFR and it is the first and the only targeted therapy for HNSCC patients[7]. In March 2006, the US Food and Drug Administration (FDA) approved cetuximab for use in combination with RT for the treatment of locally advanced HNSCC as first-line therapy and as a single agent for the treatment of patients with recurrent or metastatic (R/M) HNSCC for whom prior platinum-based therapy has failed. In November 2011, the US FDA approved cetuximab as first-line treatment for R/M HNSCC in combination with platinum-based therapy plus 5-florouracil (5-FU). To date, 253 clinical studies have been conducted to evaluate cetuximab alone or in combination with other drugs for the treatment of HNSCC.

Panitumumab

Panitumumab (Vectibix) is a fully human IgG2 mAb against EGFR that has received approval from the US FDA for the treatment of metastatic colorectal cancer[8]. In HNSCC, panitumumab has been studied widely in the clinical setting. In a phase II S10PANI01 trial (NCT02643056), panitumumab did not induce tumour shrinkage in platinum-resistant advanced HNSCC, but did improve the disease control rate[9]. In a phase II PARTNER trial (NCT00454779) in patients with R/M HNSCC, panitumumab plus docetaxel/cisplatin improved progression-free survival (PFS) and the response rate compared to CT alone, but no survival benefit was observed, and the regimen was associated with an increased frequency of grade 3/4 adverse events (AEs)[10]. In another phase II trial (NCT00756444) in R/M HNSCC patients, panitumumab plus cisplatin and 5-FU decreased disease progression when compared to the CT alone arm; however, the combination treatment was associated with an increase in serious AEs. The same regimen also increased grade 3/4 AEs and treatment-related deaths in a phase III SPECTRUM trial (NCT00460265) and did not improve the median OS significantly, but it prolonged median PFS by 1.2 months when compared to the CT alone arm[11]. In locally advanced HNSCC, the combination of panitumumab with chemoradiotherapy (CRT) was associated with a partial response in all 19 participants in a phase I study (NCT00513383)[12]; however, in the phase II CONCERT-1 trial (NCT00500760), this combination did not produce any survival benefit compared to the CRT group and was associated with increased toxicity[13]. In the CONCERT-2 phase II trial (NCT00547157), panitumumab plus RT was compared with CRT in patients with locally advanced HNSCC. The PFS and OS results favoured the CRT arm, and grade 3+ AEs were higher in the panitumumab plus RT arm[14]. There are currently three ongoing panitumumab trials in HNSCC: second-line panitumumab monotherapy (PRISM/NCT00446446), panitumumab plus RT versus CRT (NCT00820248), and postoperative panitumumab plus CRT (NCT00798655).

Zalutumumab

Zalutumumab is a novel high-affinity fully human IgG1 mAb against EGFR and has shown promise for the treatment of HNSCC[15]. In a phase I/II study (NCT00093041), zalutumumab was found to be well tolerated up to the highest tested dose of 8 mg/kg in patients with advanced HNSCC[16], and in a phase II trial (NCT00542308), it showed reasonable efficacy in patients with platinum-refractory R/M HNSCC[17]. In a phase III trial (NCT00382031), R/M HNSCC patients with disease progression within 6 months of platinum-based CT received either zalutumumab plus best supportive care or best supportive care with optional methotrexate. Although zalutumumab did not improve the OS, it extended PFS[18]. Results from a phase III trial (DAHANCA 19-NCT00496652) in which HNSCC patients received either RT or CRT with or without zalutumumab, showed that zalutumumab did not increase loco-regional control, disease-specific survival, or OS[19].

Nimotuzumab

Nimotuzumab (h-R3) is a humanized IgG1 anti-EGFR mAb with anti-proliferative, anti-angiogenic, and pro-apoptotic activity in EGFR overexpressing tumours[20]. In a prospective phase II study (NCT00910117), induction CT plus nimotuzumab was very effective in locally advanced HNSCC[21]. In another phase II study (NCT01616849), nimotuzumab plus CT showed encouraging efficacy in untreated metastatic nasopharyngeal carcinoma[22]. Studies have also shown that concurrent use of nimotuzumab with RT/CRT was well tolerated and improved patient survival[23–31]. Clinical studies are currently underway to evaluate nimotuzumab alone (NCT02293356) or in combination with RT (NCT03025958) or CRT (NCT00702481, NCT00957086, NCT01516996, NCT02012062).

ABT-806

ABT-806 is a humanized IgG1 mAb raised against a truncated version of EGFR (EGFR vIII). However, ABT-806 has also been shown to bind to wild-type EGFR on the cell surface of the cells that have EGFR gene amplification[32]. In a phase I clinical trial, 26 patients with advanced solid tumours including HNSCC were treated with ABT-806. Two HNSCC patients, two colorectal cancer patients, and one lung cancer patient achieved stable disease (>8 weeks) and one HNSCC patient with EGFR amplification had stable disease for 23 weeks[33].

MEHD7945A

MEHD7945A is a novel dual-target human IgG1 mAb against EGFR and human

epidermal growth factor receptor-3 (HER-3)[34]. In a phase I trial, the safety and tolerability of MEHD7945A were assessed in 36 patients with refractory/recurrent epithelial tumours (10 HNSCC, nine non-small-cell lung cancer (NSCLC), 12 colorectal cancer, and five pancreatic cancer). Two patients (HNSCC) had a partial response and six patients (four with colorectal cancer and two with NSCLC) had stable disease for at least 8 weeks[35]. In a phase II study (NCT01577173), MEHD7945A did not improve R/M HNSCC patient outcomes in comparison to cetuximab[36]. A phase I study is currently evaluating the safety and pharmacokinetics of MEHD7945A in patients with incurable, locally advanced, or metastatic epithelial cancers (NCT01207323).

Sym004

Sym004 is a mixture of two anti-EGFR mAbs that target distinct non-overlapping epitopes in the extracellular domain III of the EGFR[37]. In a phase II trial (NCT01417936), the efficacy and safety of Sym004 were evaluated in 26 HNSCC patients who had failed other anti-EGFR-based therapies. Twelve percent of patients were alive without disease progression at 6 months and the median PFS was 82 days. Fifty percent of patients had stable disease, and tumour shrinkage was observed in 8/19 evaluable patients[38].

VEGFR inhibitors

Vascular endothelial growth factor (VEGF) and its receptors (VEGFR) are involved in blood vessel formation and growth in normal tissues. They are the key regulators in tumour angiogenesis and therefore are associated with increased tumour invasion and metastasis. A correlation between high levels of VEGF and a poor prognosis has been shown in patients with various types of tumours[39], including head and neck cancer (HNC)[40]. Therefore, inhibition of the VEGFR pathway has been suggested as a potential therapy in these patients.

Bevacizumab (Avastin) is a US FDA-approved anti-VEGF IgG1 mAb for the treatment of metastatic colorectal cancer, NSCLC, platinum-resistant ovarian cancer, advanced cervical cancer, metastatic renal cell carcinoma, and recurrent glioblastoma. In R/M HNSCC patients, bevacizumab with pemetrexed showed encouraging efficacy; however, bleeding complications were reported in 15% of patients (NCT00222729)[41]. In locally advanced HNSCC, bevacizumab plus CRT was effective (NCT00281840)[42] and had the potential to delay the development of distant metastasis (NCT00408694)[43]. Bevacizumab in combination with cetuximab was well tolerated and yielded promising anti-tumour activity in R/M HNSCC (NCT00409565)[44]. In locally advanced HNSCC bevacizumab ± cetuximab, pemetrexed, and RT produced a high level of toxicity and failed to improve the outcome (NCT00703976)[45]. Encouraging efficacy was reported in patients with stage III/IVB HNSCC who were treated with bevacizumab plus high-dose cisplatin and IMRT (NCT00423930)[46] or bevacizumab plus cetuximab and high-dose cisplatin given concurrently with IMRT (NCT00968435)[47]. The combination of bevacizumab with erlotinib (EGFR tyrosine kinase inhibitor) (NCT00055913) or erlotinib with concurrent CRT (NCT00140556) was found to be tolerable in HNSCC[48,49]. In a phase II study, neoadjuvant CT combined with bevacizumab followed by concurrent CT, bevacizumab, erlotinib, and RT in locally advanced HNSCC (NCT00392704) was feasible and yielded a high level of efficacy[50]. There are currently ongoing trials investigating bevacizumab in combination with CT (NCT00588770, NCT02250599), CRT (NCT02047487), cetuximab plus CRT (NCT01588431), and in combination with other immune-modulating therapies (NCT03169764, NCT03074513, NCT02174172) in HNSCC.

HGF inhibitors

Hepatocyte growth factor (HGF) is a potent angiogenic factor that plays an important role in tumour invasion and metastasis through activation of its transmembrane receptor tyrosine kinase, mesenchymal epithelial transition factor (MET/c-MET)[51–53]. Alterations in c-MET have been reported in various types of malignancy, including HNC. While c-MET gene mutation, amplification, and high copy number are rare in HNSCC, overexpression of c-MET has been observed in more than 80% of HNSCC[54]. c-MET overexpression has been shown to be associated with reduced disease-free survival and OS[55,56], and it is believed to be responsible for resistance to radiation, cisplatin, and cetuximab[57–59]. Therefore the HGF/c-MET signalling pathway is considered to be an important potential therapeutic target.

Ficlatuzumab (AV-299) is currently the only anti-HGF mAb undergoing clinical development in HNSCC. An ongoing phase I trial is evaluating the combination of cetuximab and ficlatuzumab in patients with R/M HNSCC (NCT02277197). A phase II study is currently recruiting patients with cetuximab-resistant R/M HNSCC to assess the efficacy of ficlatuzumab, with or without concurrent cetuximab (NCT03422536).

Immune checkpoint inhibitors

Immune checkpoints are regulatory pathways in the immune system that are crucial in maintaining immunological homeostasis and self-tolerance. In the context of cancer immunotherapy, cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1) as well as its ligand, programmed cell death ligand 1 (PD-L1), are the most critical immune checkpoints. Several preclinical studies have shown that the inhibition of CTLA-4 and PD-1/PD-L1 can restore anti-tumour immune responses[60]. These promising results have led to the development of immunological checkpoint blockades for the treatment of cancer.

CTLA-4 inhibitors

Among the CTLA-4 inhibitors, two blocking antibodies have been tested in advanced clinical trials. Ipilimumab (YERVOY) and tremelimumab are humanized anti-CTLA-4 mAbs that bind to CTLA-4 and block its interaction with ligands CD80 (B7-1) and CD86 (B7-2). This eventually induces T-cell activation and proliferation. Ipilimumab is the first immune checkpoint inhibitor to be approved for the treatment of cancer patients[61]. In 2011, the US FDA approved ipilimumab for the treatment of unresectable or metastatic melanoma and it is currently undergoing 17 clinical trials for HNSSC (Table 1). Tremelimumab has not yet been approved by the US FDA for the treatment of cancer patients, but it is under clinical investigation for various types of malignancies. Ongoing clinical trials with tremelimumab in HNSSC are listed in Table 1.

PD-1 inhibitors

Nivolumab (Opdivo, BMS-936558, MDX-1106) is a human IgG4 mAb against PD-1 that has US FDA approval for the treatment of patients with advanced NSCLC, metastatic melanoma, advanced renal cell carcinoma, advanced liver cancer, advanced urothelial carcinoma, classical Hodgkin lymphoma, and DNA mismatch repair–deficient (dMMR)/mi-

Table 1. Ongoing clinical trials evaluating cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) inhibitors in HNSCC as of July 2018.

Study design	Population	Phase	Status	ID
Ipilimumab				
Intra-tumoural ipilimumab	HNSCC	I	Recruiting	NCT02812524
Ipilimumab + cetuximab + IMRT	Locally advanced HNSCC	Ib	Active, not recruiting	NCT01860430
Ipilimumab + cetuximab + IMRT	Previously untreated stage III–IVB HNSCC	Ib	Active, not recruiting	NCT01935921
Ipilimumab ± nivolumab	SCC of oral cavity	II	Recruiting	NCT02919683
Ipilimumab ± nivolumab	Advanced or recurrent HNSCC	Ib/II	Recruiting	NCT03003637
Ipilimumab + nivolumab	Recurrent/metastatic salivary gland cancer	II	Recruiting	NCT03172624
Ipilimumab + nivolumab	Recurrent/metastatic salivary gland cancer	II	Recruiting	NCT03146650
Ipilimumab + nivolumab	Advanced nasopharyngeal carcinoma	II	Recruiting	NCT03097939
Ipilimumab + nivolumab	Rare tumours	II	Recruiting	NCT02834013
Ipilimumab + nivolumab	HNSCC	II	Not yet recruiting	NCT03406247
Ipilimumab + nivolumab + RT	Stage IVA–B HNC	Early-I	Active, not recruiting	NCT03162731
Ipilimumab + nivolumab vs. extreme regimen (cetuximab + cisplatin/ carboplatin + fluorouracil)	Recurrent/metastatic HNSCC	III	Recruiting	NCT02741570
Ipilimumab + nivolumab vs. ipilimumab-placebo + nivolumab	Recurrent/metastatic HNSCC	II	Active, not recruiting	NCT02823574
Ipilimumab or pembrolizumab + LTX-315 vs. LTX-315 (synthetic oncolytic peptide-based immunotherapy)	Patients with transdermally accessible tumours	I	Active, not recruiting	NCT01986426
Ipilimumab + nivolumab + INCAGN01876 (anti-GITR antibody) vs. ipilimumab + INCAGN01876 vs. nivolumab + INCAGN01876	Advanced or metastatic malignancies	I/II	Recruiting	NCT03126110
Ipilimumab + evofosfamide	Advanced solid malignancies including HPV-negative HNSCC	I	Recruiting	NCT03098160
Combination of immune-modulating therapies	Locally advanced or metastatic solid tumours	I	Active, not recruiting	NCT02174172
Tremelimumab				
Tremelimumab ± durvalumab	Malignant oropharynx carcinoma	Early-I	Recruiting	NCT03144778
Tremelimumab ± durvalumab	Advanced solid tumours	I	Active, not recruiting	NCT01938612
Tremelimumab vs. durvalumab vs. tremelimumab + durvalumab	Recurrent/metastatic HNSCC	II	Active, not recruiting	NCT02319044
Tremelimumab + durvalumab + RT	Locally advanced HNSCC	II	Not yet recruiting	NCT03426657
Tremelimumab + durvalumab + stereotactic body RT	Metastatic HNSCC	I/II	Not yet recruiting	NCT03283605
Tremelimumab + durvalumab + stereotactic body RT	Metastatic HNSCC, lung, oesophagus	I/II	Recruiting	NCT03212469
Tremelimumab + durvalumab + stereotactic body RT	Recurrent/metastatic HNSCC	I/II	Recruiting	NCT03522584
Tremelimumab + durvalumab + proton therapy	Recurrent/metastatic HNSCC	II	Not yet recruiting	NCT03450967
Tremelimumab + durvalumab + IMRT	Intermediate risk HNSCC	I	Not yet recruiting	NCT03529422
Tremelimumab + durvalumab + first-line CT	Advanced solid tumours	I	Recruiting	NCT02658214
Tremelimumab + durvalumab + metronomic vinorelbine	Advanced solid tumours	I/II	Not yet recruiting	NCT03518606
Tremelimumab + durvalumab + IRX-2 regimen	Incurable HNSCC	I/II	Not yet recruiting	NCT03381183
Tremelimumab ± durvalumab + CRT	Advanced solid tumours	I	Recruiting	NCT03509012
Tremelimumab + durvalumab vs. durvalumab vs. standard of care	Recurrent/metastatic HNSCC	III	Active, not recruiting	NCT02551159
Tremelimumab + durvalumab vs. durvalumab vs. standard of care	Recurrent/metastatic HNSCC	III	Active, not recruiting	NCT02369874
Tremelimumab + durvalumab + azacitidine	Recurrent/metastatic HNSCC	Ib/II	Recruiting	NCT03019003
Tremelimumab + durvalumab + AZD9150 (STAT3 inhibitor)/AZD5069 (chemokine receptor 2 antagonist)	Advanced solid tumours and relapsed metastatic HNSCC	I/II	Recruiting	NCT02499328
Tremelimumab ± durvalumab vs. BYL719 (PI3K inhibitor) vs. poziotinib (EGFR/HER2 inhibitor) vs. nintedanib (FGFR inhibitor) vs. abemaciclib (CDK4/6 inhibitor)	HNSCC and oesophageal cancer	II	Recruiting	NCT03292250
Tremelimumab + durvalumab + Toll-like receptor agonist poly ICLC	Advanced, measurable, biopsy-accessible cancers	I/II	Recruiting	NCT02643303
Tremelimumab + durvalumab + selumetinib (AZD6244 hyd-sulfate) vs. durvalumab + selumetinib	Advanced solid tumours	I	Active, not recruiting	NCT02586987

CDK4/6, cyclin-dependent kinase 4 and 6; CRT, chemoradiotherapy; CT, chemotherapy; EGFR, epidermal growth factor receptor; FGFR, fibroblast growth factor receptor; GITR, glucocorticoid-induced tumour necrosis factor receptor-related protein; HER-2, human epidermal growth factor receptor 2; HNC, head and neck cancer; HNSCC, head and neck squamous cell carcinoma; HPV, human papillomavirus; IMRT, intensity-modulated radiotherapy; PI3K, phosphoinositide 3-kinase; RT, radiotherapy; SCC, squamous cell carcinoma; STAT3, signal transducer and activator of transcription 3.

crosatellite instability–high (MSI-H) metastatic colorectal cancer[62]. In 2016, nivolumab received USA FDA approval for the treatment of patients with R/M HNSCC with disease progression on or after a platinum-based CT. This approval was based on data from the CheckMate 14 trial, which showed a statistically significant improvement in OS in patients who were treated with nivolumab[63]. Clinical studies are currently evaluating nivolumab monotherapy/combination therapy in HNSCC, as listed in Table 2.

Pembrolizumab (Keytruda, MK-3475), a humanized anti-PD-1 mAb, is an approved treatment for patients with advanced NSCLC, advanced melanoma, classical Hodgkin lymphoma, primary mediastinal B-cell lymphoma, advanced urothelial carcinoma, advanced gastric cancer, advanced cervical cancer, and MSI-H or dMMR solid tumours[64,65]. The US FDA approved pembrolizumab in 2016 for the treatment of patients with R/M HNSCC who have disease progression on or after platinum-based CT. This approval was based on results from the KEYNOTE-012 phase Ib study (NCT01848834) in which pembrolizumab showed an overall response rate of 17.7% and stable disease rate of 17%. In this subgroup, the median PFS and OS were 2 months and 8.5 months, respectively[66]. In the phase II trial of pembrolizumab, KEYNOTE-055 (NCT02255097), the overall response rate was 16% and median PFS and OS were 2.1 months and 8 months, respectively[67]. Table 2 summarizes the studies that are currently assessing pembrolizumab in the clinical setting in HNSCC patients.

PDR001 is a humanized anti-PD-1 IgG4 antibody that binds to PD-1 with high affinity and prevents the binding of PD-1 receptor to its ligands, PD-L1 and PD-L2. Preliminary data from a phase I/II study (NCT02404441) in patients with advanced solid tumours showed that PDR001 was safe and well tolerated[68]. Investigators are currently evaluating the safety and efficacy of PDR001 vs. CT in patients with R/M nasopharyngeal carcinoma (NCT02605967). Studies are also evaluating PDR001 in combination with FAZ053 anti-PD-L1 antibody (NCT02936102), LGK974 (porcupine inhibitor) (NCT01351103), NIR 178 (adenosine receptor antagonist) (NCT03207867), NIZ985 (interleukin (IL)-15 agonist) (NCT02452268), BLZ945 (selective inhibitor of the colony stimulating factor 1 receptor) (NCT02829723), MBG453 (anti-T-cell immunoglobulin and mucin domain 3 checkpoint inhibitor) (NCT02608268), MIW 815 (ADU-S100) (stimulator of interferon genes agonist) (NCT03172936), LHC165 (toll-like receptor 7 agonist) (NCT03301896), and GWN323 (anti-human glucocorticoid-induced tumour necrosis factor receptor mAb) (NCT02740270) in solid tumours.

PD-L1 inhibitors

To date, three PD-L1 inhibitors have received US FDA approval for the treatment of cancer patients. Atezolizumab (TECENTRIQ/MPDL3280A), avelumab (BAVENCIO/MSB0010718C), and durvalumab (MEDI4736, Imfinzi) are fully human IgG mAbs that target PD-L1[69].

Atezolizumab received US FDA accelerated approval in May 2016 for the treatment of patients with locally advanced or metastatic urothelial carcinoma in whom prior platinum-based therapy has failed. In October 2016, the US FDA approved atezolizumab for the treatment of patients with metastatic NSCLC whose disease has progressed during or following platinum-containing CT. In 2017, avelumab received US FDA accelerated approval for the treatment of patients with urothelial carcinoma in whom disease has progressed after platinum-based CT (May) and for patients with metastatic Merkel cell carcinoma (March). Durvalumab has demonstrated clinical activity in a phase I/II study (NCT01693562) in patients with advanced solid tumours, including HNSCC[70]. In May 2017, the US FDA granted accelerated approval to durvalumab for platinum-refractory locally advanced or metastatic urothelial carcinoma, and in February 2018 approved durvalumab for patients with unresectable stage III NSCLC whose disease has not progressed following CRT. Several clinical trials are currently assessing PD-L1 inhibitors in HNSCC, as listed in Table 3.

Cytokine-based immunotherapy

Cytokines are mediators of the immune responses in maintaining homeostasis and immune tolerance[71]. To date, two cytokines have achieved US FDA approval: interferon alpha (IFN-α) for advanced melanoma and interleukin 2 (IL-2) for metastatic melanoma and renal cell carcinoma[71]. In the context of HNSCC, a large number of cytokines have been explored in the clinical setting. The 5-year PFS and OS rates were 80% and 81.3%, respectively, when patients were treated with the combination of IFN-α with isotretinoin and vitamin E (NCT00054561)[72]. The combination of IFN-α with recombinant IL-2 was also associated with an 18% response rate in advanced HNSCC[73]. Recombinant IL-2 produced a significant improvement in disease-free survival and OS in HNSCC patients[74], and recombinant human IFN-γ resulted in tumour regression and disease stabilization in 3/8 and 4/8 patients, respectively[75]. Results from a phase I study (CITN11-02-NCT01727076) also indicated that recombinant human IL-15 is safe and can induce the expansion of peripheral blood CD56 + natural killer (NK) cells in advanced cancers including HNSCC[76]. Table 4 summarizes ongoing cytokine-based immunotherapy trials in HNSCC.

CD antigen inhibitors

Cluster of differentiation (CD) antigens are membrane proteins that are predominantly expressed on the leukocyte surface. CD antigens are considered excellent targets for therapeutic antibodies for the treatment of autoimmune disease and multiple types of cancers, such as HNSCC, lymphoma, leukaemia, colorectal cancer, lung cancer, and breast cancer[77]. To date, several inhibitors have been designed to target cells that have a particular type of CD marker. A list of CD agonists that are under clinical investigation in HNSCC is given in Table 5.

Adoptive cell therapy

Adoptive cell therapy (ACT) makes use of either naturally occurring autologous/allogeneic or genetically modified immune cells to treat cancer patients. For this purpose, different sources of cells such as lymphokine activated killer (LAK) cells, tumour-infiltrating lymphocytes (TILs), T-cells, and NK cells have been tested for their safety and efficacy. Treatment with LAK cells in conjunction with IL-2 has shown a promising clinical response in advanced HNC patients[78,79], and treatment with TILs has been shown to mediate objective tumour regression in patients with metastatic melanoma[80]. A phase II study (NCT03083873) is currently investigating ACT with autologous TILs (LN-145) for the treatment of patients with R/M HNSCC. Genetically engineered T-cells have been successfully applied for the treatment of melanoma and haematological malignancies, but they have limited application for the treatment of solid tumours and have only shown promising results in the virally mediated HNSCC. In R/M EBV-associated nasopharyngeal cancer, treatment with ex vivo expanded autologous T-cells by means of

Table 2. Ongoing clinical trials evaluating programmed cell death protein 1 (PD-1) inhibitors in HNSCC as of July 2018.

Study design	Population	Phase	Status	ID
Nivolumab				
Nivolumab	HNSCC	II	Recruiting	NCT03355560
Nivolumab	Locally advanced oral cavity SCC	II	Recruiting	NCT03021993
Nivolumab	Locally advanced or metastatic rare cancers	II	Recruiting	NCT03012581
Nivolumab	Recurrent and/or metastatic salivary glands carcinoma	II	Recruiting	NCT03132038
Nivolumab + RT	HNSCC	I/II	Recruiting	NCT03247712
Nivolumab + RT	Recurrent HNSCC	I/II	Recruiting	NCT03317327
Nivolumab + IMRT	Recurrent HNSCC	II	Recruiting	NCT03521570
Nivolumab + stereotactic body RT	HNSCC	II	Recruiting	NCT02684253
Nivolumab or pembrolizumab + stereotactic body RT	Solid tumours	II	Recruiting	NCT03511391
Nivolumab + carboplatin + paclitaxel	Stage III–IV HNSCC	II	Recruiting	NCT03342911
Nivolumab + nab-paclitaxel/carboplatin induction CT followed by response-stratified loco-regional therapy	Loco-regionally advanced HPV-related oropharyngeal cancer	II	Recruiting	NCT03107182
Nivolumab + CRT	HNSCC	III	Not yet recruiting	NCT03576417
Nivolumab vs. cetuximab/methotrexate/docetaxel	Recurrent/metastatic HNSCC	III	Active, not recruiting	NCT02105636
Nivolumab + cetuximab	Recurrent/metastatic HNSCC	I/II	Recruiting	NCT03370276
Nivolumab + cisplatin vs. nivolumab + cetuximab vs. nivolumab + IMRT	Intermediate and high-risk local-regionally advanced HNSCC	I	Recruiting	NCT02764593
Nivolumab + RT vs. cetuximab + RT or nivolumab + RT + cisplatin vs. RT + cisplatin + placebo	Locally advanced HNSCC	III	Recruiting	NCT03349710
Nivolumab + cetuximab + motolimod (Toll-like receptor 8 agonist) vs. cetuximab + motolimod	HNSCC	Ib	Recruiting	NCT02124850
Nivolumab ± ipilimumab	SCC of oral cavity	II	Recruiting	NCT02919683
Nivolumab ± ipilimumab	Advanced or recurrent HNSCC	Ib/II	Recruiting	NCT03003637
Nivolumab + ipilimumab	Recurrent/metastatic salivary gland cancer	II	Recruiting	NCT03172624
Nivolumab + ipilimumab	Rare tumours	II	Recruiting	NCT02834013
Nivolumab + ipilimumab	Recurrent/metastatic salivary gland cancer	II	Recruiting	NCT03146650
Nivolumab + ipilimumab	Advanced nasopharyngeal carcinoma	II	Recruiting	NCT03097939
Nivolumab + ipilimumab	HNSCC	II	Not yet recruiting	NCT03406247
Nivolumab + ipilimumab vs. nivolumab + ipilimumab-placebo	Recurrent/metastatic HNSCC	II	Active, not recruiting	NCT02823574
Nivolumab + ipilimumab + RT	Stage IVA–B HNC	Early-I	Active, not recruiting	NCT03162731
Nivolumab + ipilimumab vs. extreme regimen (cetuximab + cisplatin/carboplatin + fluorouracil	Recurrent/metastatic HNSCC	III	Recruiting	NCT02741570
Nivolumab + ipilimumab + INCAGN01876 vs. nivolumab + INCAGN01876 vs. ipilimumab + INCAGN01876	Advanced or metastatic malignancies	I/II	Recruiting	NCT03126110
Nivolumab + adenoviral p53 vs. nivolumab	Recurrent HNSCC	II	Recruiting	NCT03544723
Nivolumab + adenoviral p53 vs. pembrolizumab + adenoviral p53 vs. capecitabine + adenoviral p53	Recurrent HNSCC, metastatic solid tumour	I/II	Not yet recruiting	NCT02842125
Nivolumab + lirilumab (anti-killer cell immunoglobulin-like receptors mAb)	HNSCC	II	Recruiting	NCT03341936
Nivolumab + sitravatinib (tyrosine kinase inhibitor)	SCC of oral cavity	Early-I	Not yet recruiting	NCT03575598
Nivolumab + enadenotucirev (oncolytic virus)	Metastatic or advanced epithelial tumours	I	Recruiting	NCT02636036
Nivolumab + IPI-549 (PI3K gamma inhibitor)	Advanced solid tumours	I	Recruiting	NCT02637531
Nivolumab + FPA008	Advanced cancers	I	Active, not recruiting	NCT02526017
Nivolumab + DSP-7888 vs. atezolizumab + DSP-7888	Advanced solid tumours	I	Recruiting	NCT03311334
Nivolumab ± tadalafil	HNSCC	Early-I	Recruiting	NCT03238365
Nivolumab or pembrolizumab or atezolizumab + RT	Advanced HNSCC, NSCLC	II	Recruiting	NCT03313804
Nivolumab + pembrolizumab	HNSCC	I	Recruiting	NCT03129061
Nivolumab + varlilumab (anti-CD27 mAb)	Advanced refractory solid tumours	I/II	Active, not recruiting	NCT02335918

Table 2 (*Continued*)

Study design	Population	Phase	Status	ID
Nivolumab + epacadostat (inhibitor of indoleamine 2,3-dioxygenase-1) vs. nivolumab + epacadostat + CT	Advanced solid tumours and lymphomas	I/II	Active, not recruiting	NCT02327078
Nivolumab + TAK-659 (inhibitor of spleen tyrosine kinase)	Advanced solid tumours	I	Recruiting	NCT02834247
Combination immunotherapy	HNSCC patients who progressed on or after CT and anti-PD-1/PD-L1 therapy	Ib/II	Not yet recruiting	NCT03169764
Pembrolizumab				
Pembrolizumab	Advanced solid tumours	I	Active, not recruiting	NCT01848834
Pembrolizumab	Recurrent or metastatic HNSCC who have failed platinum and cetuximab	II	Active, not recruiting	NCT02255097
Pembrolizumab	Locally advanced HNSCC	II	Recruiting	NCT02296684
Pembrolizumab	Advanced solid tumours	II	Active, not recruiting	NCT02644369
Pembrolizumab	HNSCC with residual disease after RT	II	Recruiting	NCT02892201
Pembrolizumab vs. placebo	HNSCC	II	Recruiting	NCT02841748
Pembrolizumab + placebo	Relapsed, locally recurrent HNSCC	II	Recruiting	NCT02769520
Pembrolizumab + RT	Metastatic HNSCC	II	Recruiting	NCT03386357
Pembrolizumab + RT	HNSCC	II	Recruiting	NCT03085719
Pembrolizumab + RT	Loco-regional inoperable recurrence or second primary HNSCC	II	Recruiting	NCT02289209
Pembrolizumab + RT	HNSCC	II	Recruiting	NCT03057613
Pembrolizumab + RT	Recurrent/metastatic HNSCC, renal cell cancer, lung cancer and melanoma	I	Active, not recruiting	NCT02318771
Pembrolizumab + stereotactic body RT	Loco-regionally recurrent or second primary HNSCC	II	Not yet recruiting	NCT03546582
Pembrolizumab + IMRT	Cisplatin-ineligible HNSCC	II	Recruiting	NCT02609503
Pembrolizumab or cetuximab + RT	Locally advanced HNSCC	II	Active, not recruiting	NCT02707588
Pembrolizumab + RT vs. CRT	Patients with advanced/intermediate-risk p16+ HNSCC	II	Not yet recruiting	NCT03383094
Pembrolizumab vs. methotrexate	Cisplatin-ineligible HNSCC	II	Recruiting	NCT03193931
Pembrolizumab + docetaxel	Recurrent/metastatic HNSCC	I/II	Recruiting	NCT02718820
Pembrolizumab + induction CT	Locally advanced untreated, unresectable HNSCC	II	Not yet recruiting	NCT03114280
Pembrolizumab + CRT	HNSCC	II	Recruiting	NCT02641093
Pembrolizumab + CRT	Locally advanced laryngeal SCC	I/II	Recruiting	NCT02759575
Pembrolizumab + CRT	Locally advanced HNC	II	Not yet recruiting	NCT03532737
Pembrolizumab + CRT	Locally advanced HNSCC	II	Not yet recruiting	NCT03480672
Pembrolizumab + CRT	HNSCC	I	Not yet recruiting	NCT02819752
Pembrolizumab + CRT	Locally advanced HNSCC	I	Recruiting	NCT02586207
Pembrolizumab + CRT vs. placebo + CRT	Locally advanced HNSCC	III	Recruiting	NCT03040999
Pembrolizumab + cisplatin + IMRT	HNSCC	II	Recruiting	NCT02777385
Pembrolizumab + cetuximab	Recurrent/metastatic HNSCC	II	Recruiting	NCT03082534
Pembrolizumab vs. standard treatment (methotrexate, docetaxel or cetuximab)	Recurrent/metastatic HNSCC	III	Active, not recruiting	NCT02252042
Pembrolizumab vs. pembrolizumab + cisplatin or carboplatin + 5-FU vs. cetuximab + cisplatin or carboplatin + 5-FU	Recurrent/metastatic HNSCC	III	Active, not recruiting	NCT02358031
Pembrolizumab + epacadostat	HNC patients who failed prior PD-1/PD-L1 therapy	II	Recruiting	NCT03463161
Pembrolizumab + epacadostat	Selected cancers including HNC	I/II	Active, not recruiting	NCT02178722
Pembrolizumab + epacadostat	HNSCC	II	Not yet recruiting	NCT03325465
Pembrolizumab + epacadostat + INCAGN01876	Advanced or metastatic malignancies	I/II	Active, not recruiting	NCT03277352
Pembrolizumab + epacadostat + CT	Advanced or metastatic solid tumours	I/II	Recruiting	NCT03085914
Pembrolizumab vs. pembrolizumab + epacadostat vs. extreme regimen (cetuximab + cisplatin or carboplatin + 5-FU)	Recurrent/metastatic HNSCC	III	Active, not recruiting	NCT03358472

Table 2 (*Continued*)

Study design	Population	Phase	Status	ID
Pembrolizumab + anti-platelet therapy	Recurrent/metastatic HNSCC	I	Recruiting	NCT03245489
Pembrolizumab + vorinostat (histone deacetylase inhibitor)	Recurrent HNSCC or salivary gland cancers that are metastatic and/or cannot be removed by surgery	I/II	Active, not recruiting	NCT02538510
Pembrolizumab + SD-101 (TLR9 agonist)	Recurrent/metastatic HNSCC or metastatic melanoma	Ib/II	Recruiting	NCT02521870
Pembrolizumab + enoblituzumab (MGA271)	Patients with B7-H3-expressing HNSCC, NSCLC, melanoma, and other B7-H3 expressing cancers	I	Recruiting	NCT02475213
Pembrolizumab + galectin inhibitor (GR-MD-02)	Advanced HNSCC, NSCLC, melanoma	Ib	Recruiting	NCT02575404
Pembrolizumab + recombinant EphB4-HSA fusion protein	HNSCC and NSCLC	II	Recruiting	NCT03049618
Pembrolizumab + L-NMMA (pan-nitric oxide synthase inhibitor)	HNSCC, NSCLC, melanoma, classical Hodgkin lymphoma, urothelial carcinoma, microsatellite instability-high/mismatch repair deficient cancer	I	Recruiting	NCT03236935
Pembrolizumab + T-Vec	Recurrent/metastatic HNSCC	I	Active, not recruiting	NCT02626000
Pembrolizumab + AGI-134 (synthetic αGal immunotherapy) vs. AGI-134	Unresectable metastatic solid tumours	I/II	Not yet recruiting	NCT03593226
Pembrolizumab + cabozantinib (tyrosine kinase inhibitor)	Recurrent/metastatic HNSCC who have failed platinum based therapy	II	Not yet recruiting	NCT03468218
Pembrolizumab + acalabrutinib (Bruton's tyrosine kinase inhibitor)	Advanced HNSCC	II	Active, not recruiting	NCT02454179
Pembrolizumab + PLX3397 (CSF1R inhibitor)	Advanced solid tumours	I/II	Active, not recruiting	NCT02452424
Pembrolizumab + nivolumab	HNSCC	I	Recruiting	NCT03129061
Pembrolizumab or nivolumab + stereotactic body RT	Solid tumours	II	Recruiting	NCT03511391
Pembrolizumab or nivolumab or atezolizumab + RT	Advanced HNSCC, NSCLC	II	Recruiting	NCT03313804
Pembrolizumab + INCB001158 (arginase inhibitor) vs. INCB001158	Advanced/metastatic solid tumours	I/II	Recruiting	NCT02903914
Pembrolizumab + SEA-CD40 vs. SEA-CD40	Advanced malignancies	I	Recruiting	NCT02376699
Pembrolizumab or ipilimumab + LTX-315 vs. LTX-315 (synthetic oncolytic peptide-based immunotherapy)	Patients with transdermally accessible tumours	I	Active, not recruiting	NCT01986426
Pembrolizumab + itacitinib (Janus-associated kinase 1 inhibitor) and/or pembrolizumab + INCB050465 (PI3Kδ inhibitor)	Advanced solid tumours	I	Recruiting	NCT02646748
Pembrolizumab + p53-MVA vaccine	Patients with solid tumours that have failed prior therapy	I	Active, not recruiting	NCT02432963
Pembrolizumab + adenoviral p53 vs. nivolumab + adenoviral p53 vs. capecitabine + adenoviral p53	Recurrent HNSCC and metastatic solid tumour	I/II	Not yet recruiting	NCT02842125

CRT, chemoradiotherapy; CSF1R, colony stimulating factor 1 receptor; CT, chemotherapy; 5-FU, 5-fluorouracil; HNC, head and neck cancer; HNSCC, head and neck squamous cell carcinoma; HPV, human papillomavirus; IMRT, intensity-modulated radiotherapy; mAb, monoclonal antibodies; NSCLC, non-small-cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; PI3K, phosphoinositide 3-kinase; RT, radiotherapy; SCC, squamous cell carcinoma; TLR9, Toll-like receptor 9.

Table 3. Ongoing clinical trials evaluating programmed cell death ligand 1 (PD-L1) inhibitors in HNSCC as of July 2018.

Study design	Population	Phase	Status	ID
Atezolizumab				
Atezolizumab	Locally advanced or metastatic solid tumours or haematological malignancies	I	Active, not recruiting	NCT01375842
Atezolizumab	Locally advanced HNSCC	III	Recruiting	NCT03452137
Atezolizumab + bevacizumab	Rare solid tumour	II	Recruiting	NCT03074513
Atezolizumab + RO7198457 (personalized cancer vaccine) vs. RO7198457	Locally advanced or metastatic tumours	I	Recruiting	NCT03289962
Atezolizumab + DSP-7888 vs. nivolumab + DSP-7888	Advanced solid tumours	I	Recruiting	NCT03311334
Atezolizumab or nivolumab or pembrolizumab + RT	Advanced HNSCC, NSCLC	II	Recruiting	NCT03313804
Combination of immune-modulating therapies	Locally advanced or metastatic solid tumour	I	Active, not recruiting	NCT02174172
Avelumab				
Avelumab	Metastatic or locally advanced solid tumours	I	Active, not recruiting	NCT01772004
Avelumab	Recurrent/metastatic nasopharyngeal cancer	II	Active, not recruiting	NCT02875613
Avelumab + standard of care CRT vs. placebo + standard of care CRT	HNSCC	III	Recruiting	NCT02952586
Avelumab + cetuximab	HNSCC	II	Recruiting	NCT03494322
Avelumab + cetuximab + RT	Locally advanced HNSCC	Ib	Recruiting	NCT02938273
Avelumab + cetuximab + RT vs. standard of care	Locally advanced HNSCC	III	Recruiting	NCT02999087
Avelumab + cetuximab + palbociclib (Ibrance)	HNSCC	I	Not yet recruiting	NCT03498378
Avelumab + TG4001 (investigational viral-based therapeutic vaccine)	HPV-16-positive recurrent/metastatic oropharyngeal SCC and other advanced HPV-related malignancies	Ib/II	Recruiting	NCT03260023
Avelumab + PT-112 (platinum-pyrophosphate agent)	Advanced solid tumours	I/II	Recruiting	NCT03409458
Avelumab + utomilumab (4-1BB/CD137 agonist) + PF-04518600 (CD134 agonist) + CRT	Advanced malignancies	I/II	Recruiting	NCT03217747
Avelumab + other cancer immunotherapies	Advanced malignancies	Ib/II	Recruiting	NCT02554812
Combination immunotherapy	HNSCC patients who progressed on or after CT and anti PD-1/PD-L1 therapy	Ib/II	Not yet recruiting	NCT03169764
Durvalumab				
Durvalumab	Recurrent/metastatic PD-L1-positive HNSCC	II	Active, not recruiting	NCT02207530
Durvalumab	Oral cavity or oropharynx cancer	II	Recruiting	NCT02827838
Durvalumab ± tremelimumab	Advanced solid tumours	I	Active, not recruiting	NCT01938612
Durvalumab ± tremelimumab	Malignant oropharynx carcinoma	Early-I	Recruiting	NCT03144778
Durvalumab vs. tremelimumab vs. durvalumab + tremelimumab	Recurrent/metastatic HNSCC	II	Active, not recruiting	NCT02319044
Durvalumab + tremelimumab + RT	Locally advanced HNSCC	II	Not yet recruiting	NCT03426657
Durvalumab + tremelimumab + proton therapy	Recurrent/metastatic HNSCC	II	Not yet recruiting	NCT03450967
Durvalumab + tremelimumab + stereotactic body RT	Recurrent/metastatic HNSCC	I/II	Recruiting	NCT03522584
Durvalumab + tremelimumab + stereotactic body RT	Metastatic HNSCC	I/II	Not yet recruiting	NCT03283605
Durvalumab + tremelimumab + stereotactic body RT	Metastatic HNSCC, lung, oesophagus	I/II	Recruiting	NCT03212469
Durvalumab + tremelimumab + IMRT	Intermediate risk HNSCC	I	Not yet recruiting	NCT03529422
Durvalumab + cetuximab + IMRT	Locally advanced HNSCC	I/II	Not yet recruiting	NCT03051906
Durvalumab + CT	Locally advanced HNSCC	I	Recruiting	NCT02997332
Durvalumab + carboplatin + nab-paclitaxel (induction and adjuvant therapy)	Locally advanced HNSCC	II	Recruiting	NCT03174275
Durvalumab + tremelimumab + first line CT	Advanced solid tumours	I	Recruiting	NCT02658214
Durvalumab + tremelimumab + metronomic vinorelbine	Advanced solid tumours	I/II	Not yet recruiting	NCT03518606
Durvalumab ± tremelimumab + CRT	Advanced solid tumours	I	Recruiting	NCT03509012
Durvalumab vs. durvalumab + tremelimumab vs. standard of care	Recurrent/metastatic HNSCC	III	Active, not recruiting	NCT02369874
Durvalumab + tremelimumab vs. durvalumab vs. standard of care	Recurrent/metastatic HNSCC	III	Active, not recruiting	NCT02551159
Durvalumab + tremelimumab + IRX-2 regimen	Incurable HNSCC	I/II	Not yet recruiting	NCT03381183
Durvalumab + AZD9150 or AZD5069	Advanced solid tumours and metastatic HNSCC	I/II	Recruiting	NCT02499328

Table 3 (*Continued*)

Study design	Population	Phase	Status	ID
Durvalumab + tremelimumab + AZD9150/AZD5069	Advanced solid tumours and relapsed metastatic HNSCC	I/II	Recruiting	NCT02499328
Durvalumab + tremelimumab + azacitidine	Recurrent/metastatic HNSCC	Ib/II	Recruiting	NCT03019003
Durvalumab ± tremelimumab vs. BYL719 vs. poziotinib vs. nintedanib vs. abemaciclib	HNSCC and oesophageal cancer	II	Recruiting	NCT03292250
Durvalumab + tremelimumab + selumetinib vs. durvalumab + selumetinib	Advanced solid tumours	I	Active, not recruiting	NCT02586987
Durvalumab + tremelimumab + Toll-like receptor agonist poly ICLC	Advanced, measurable, biopsy-accessible cancers	I/II	Recruiting	NCT02643303
Durvalumab + MEDI6383 (anti-OX40 (CD134) mAb) vs. MEDI6383	Recurrent/metastatic solid tumours	I	Active, not recruiting	NCT02221960
Durvalumab + MEDI0457 (therapeutic cancer vaccine)	Recurrent/metastatic HPV-associated HNC	I/II	Recruiting	NCT03162224
Durvalumab + epacadostat	Advanced HNC, NSCLC, urothelial cancer	I/II	Recruiting	NCT02318277

CRT, chemoradiotherapy; CT, chemotherapy; HNC, head and neck cancer; HNSCC, head and neck squamous cell carcinoma; HPV, human papillomavirus; IMRT, intensity-modulated radiotherapy; NSCLC, non-small-cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; RT, radiotherapy; SCC, squamous cell carcinoma.

Table 4. Ongoing clinical trials evaluating cytokine-based immunotherapy in HNSCC as of July 2018.

Agent	Study design	Population	Phase	Status	ID
Interleukin					
IL-2	PD-1 knockout EBV-CTL + IL-2	Advanced EBV-positive malignancies	I/II	Recruiting	NCT03044743
	IMA201 T-cells + recombinant human IL-2	HNSCC, NSCLC	I	Recruiting	NCT03247309
IL-12	Cetuximab + recombinant IL-2	Unresectable primary or recurrent HNSCC	I/II	Active, not recruiting	NCT01468896
	INO-9012 (IL-12) + INO-1400 (hTERT) + INO-1401 (SynCon TERT)	Solid tumours	I	Active, not recruiting	NCT02960594
IL-15	ALT-803 (recombinant IL-15)	Advanced solid tumours	I	Active, not recruiting	NCT01946789
	ALT–803 + other immune modulating therapies	HNSCC patients who progressed on or after CT and anti PD-1/PD-L1 therapy	Ib/II	Not yet recruiting	NCT03169764
	ALT–803 + ETBX-011 vaccine	Carcinoembryonic antigen expressing cancers	Ib/II	Active, not recruiting	NCT03127098
	Heterodimeric IL-15 (NIZ985) + PDR001	Metastatic cancers	I	Recruiting	NCT02452268
Colony stimulating factor (CSF)					
G-CSF	Platinum and cetuximab + docetaxel or 5FU + G-CSF	Recurrent/metastatic HNSCC	II	Active, not recruiting	NCT02268695
FPA008 (CSF1R Ab)	FPA008 + nivolumab	Advanced cancers	I	Active, not recruiting	NCT02526017
IRX-2 (multiple active cytokine components)	IRX-2 + cyclophosphamide + indomethacin	Newly diagnosed stage II, III, or IVA SCC of the oral cavity	II	Active, not recruiting	NCT02609386
Pegfilgrastim (PEGylated form of the recombinant human G-CSF analogue filgrastim)	Pegfilgrastim + mitomycin C	Incurable p16+ oropharyngeal and p16− HNSCC resistant to cetuximab, 5-FU, platin, taxane	II	Recruiting	NCT02369458
PLX3397 (CSF1R inhibitor)	PLX3397 + pembrolizumab	Advanced solid tumours	I/II	Active, not recruiting	NCT02452424

Ab, antibody; CSF1R, colony stimulating factor 1 receptor; CT, chemotherapy; CTL, cytotoxic T-lymphocyte; EBV, Epstein–Barr virus; 5-FU, 5-fluorouracil; G-CSF, granulocyte colony stimulating factor; HNSCC, head and neck squamous cell carcinoma; hTERT, human telomerase reverse transcriptase; IL, interleukin; NSCLC, non-small-cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; SCC, squamous cell carcinoma.

Table 5. Ongoing clinical trials evaluating cluster of differentiation (CD) agonists in HNSCC as of July 2018.

Target	Study design	Population	Phase	Status	ID
CD27	Varlilumab + nivolumab	Advanced refractory solid tumours	I/II	Active, not recruiting	NCT02335918
CD40	CDX-1140 monotherapy	Advanced solid tumours	I	Recruiting	NCT03329950
	APX005M monotherapy	Solid tumours	I	Active, not recruiting	NCT02482168
	SEA-CD40 vs. SEA-CD40 + pembrolizumab	Advanced malignancies	I	Recruiting	NCT02376699
CD70	ARGX-110	Nasopharyngeal carcinoma	I	Active, not recruiting	NCT02759250
CD134 (Ox40)	MEDI6469 monotherapy	HNSCC	I	Active, not recruiting	NCT02274155
	MEDI6383 vs. MEDI6383 + durvalumab	Recurrent/metastatic solid tumours	I	Active, not recruiting	NCT02221960
	MOXR0916 + atezolizumab	Locally advanced or metastatic solid tumours	I	Active, not recruiting	NCT02410512
	MEDI0562 monotherapy	Advanced solid tumours	I	Active, not recruiting	NCT02318394
	MEDI0562 + durvalumab vs. MEDI0562 + tremelimumab	Advanced solid tumours	I	Recruiting	NCT02705482
	MOXR0916 monotherapy	Locally advanced or metastatic solid tumours	I	Active, not recruiting	NCT02219724
	GSK3174998 ± pembrolizumab	Advanced solid tumours	I	Recruiting	NCT02528357
	INCAGN01949 monotherapy	Advanced or metastatic cancers	I/II	Recruiting	NCT02923349
	INCAGN01949 + ipilimumab vs. INCAGN01949 + nivolumab vs. INCAGN01949 + nivolumab + ipilimumab	Advanced or metastatic cancers	I/II	Recruiting	NCT03241173
CD134 and CD137	PF-04518600 (CD134 agonist) vs. PF–04518600 + PF-05082566 (CD137 agonist)	Locally advanced or metastatic cancers	I	Recruiting	NCT02315066
	PF–04518600 + PF–05082566 + avelumab + CRT	Advanced malignancies	I/II	Recruiting	NCT03217747
	PF–04518600 + avelumab vs. PF–05082566 + avelumab vs. PD 0360324 (anti-CSF1 mAb) + avelumab vs. PF–04518600 + PF–05082566 + avelumab	Advanced malignancies	Ib/II	Recruiting	NCT02554812
CD137	PF-05082566 vs. PF–05082566 + ISA101b vaccine	HPV-16-positive incurable oropharyngeal SCC	II	Recruiting	NCT03258008
	PF–05082566 ± rituximab	Advanced cancer or CD20+ non-Hodgkin lymphoma	I	Active, not recruiting	NCT01307267
CD166	CX-2009 monotherapy	Solid tumours	I/II	Recruiting	NCT03149549
CD27(B7-H3)	Enoblituzumab monotherapy	Refractory cancer	I	Active, not recruiting	NCT01391143
	Enoblituzumab + pembrolizumab	Patients with B7-H3 expressing cancers	I	Recruiting	NCT02475213
CD276 (B7-H3) and CD3	MGD009	Unresectable or metastatic B7-H3 expressing tumours	I	Recruiting	NCT02628535

CRT, chemoradiotherapy; CSF1, colony stimulating factor 1; HNSCC, head and neck squamous cell carcinoma; HPV, human papillomavirus; mAb, monoclonal antibodies; SCC, squamous cell carcinoma.

ADE1-LMPpoly adenoviral vector, resulted in significantly longer OS compared with patients who did not receive T-cells (NCT00779337)[81], and treatment by EBV-specific cytotoxic T-lymphocytes (CTLs) in combination with CT produced a response rate of 71.4% with three complete responses and 22 partial responses[82]. Autologous T-cells transduced with an E6 T-cell receptor also led to tumour regression in 2/12 patients with metastatic HPV-16-positive tumours including oropharyngeal cancer (NCT02280811)[83]. Further study of adoptive T-cell therapy is underway, as listed in Table 6. To date, ACT using NK cells has produced promising clinical improvements in haematological malignancies and solid tumours[84–87]. In HNSCC, the NKEXPHNC trial is currently evaluating the combination of NK cells with cetuximab for the treatment of refractory, EGFR- positive patients (NCT02507154).

Cancer vaccine

Anti-cancer vaccine therapy aims to induce an anti-tumour immune response by means of tumour-specific or tumour-associated antigens[88]. For this purpose, various cancer vaccination strategies have been developed. This review focuses on therapeutic vaccines that are now at the clinical stage.

Peptide vaccines

GL-0817 and GL-0810

GL-0817 and GL-0810 are cancer therapeutic vaccines directed against melanoma-associated antigen 3 (MAGE-A3) and HPV-16 epitopes, respectively[89]. An ongoing phase I trial is evaluating the safety and immunological response to GL-0817 and GL-0810 in combination with the adjuvants Montanide and granulocyte–macrophage colony-stimulating factor (GM-CSF) in MAGE-A3-positive and HPV-16-positive R/M HNSCC patients, respectively (NCT00257738). A phase II study is also evaluating the safety and efficacy of GL-0817 in HLA-A2-positive patients with squamous cell carcinoma (SCC) of the oral cavity who are at high risk of disease recurrence following surgery and CRT (NCT02873819).

VicOryx

VicOryx (P16_37-63) is a synthetic $p16^{INK44a}$ (human cyclin-dependent kinase inhibitor) peptide, emulsified with an adjuvant, Montanide ISA-51 VG[90]. VicOryx has been designed for the treatment of $p16^{INK44a}$ overexpressing HPV-positive cancer patients. Results from a phase I/IIa study have suggested that vaccination with P16_37-63 peptide is safe and can induce immune responses against $p16^{INK44a}$ in patients with advanced HPV-associated cervical, vulvar, vaginal, penile, anal, or HNC (NCT01462838)[90]. In an additional phase I study (VICORYX-2 trial), concurrent cisplatin-based CT combined with P16_37-63 peptide is being investigated in patients with HPV and $p16^{INK44a}$-positive anogenital cancers or HNC (NCT02526316).

ISA101/ISA101b

ISA101 is a synthetic HPV-16 E6 and E7 long peptides vaccine with incomplete Freund's adjuvant (solution of antigen emulsified in oil) that is under clinical investigation for the treatment of HPV-16-induced tumours[91]. In an ongoing phase II clinical study, researchers are investigating the safety and efficacy of combining ISA101 with nivolumab for the control of HPV-16-positive incurable solid tumours (including oropharyngeal SCC) that have spread (NCT02426892). Another phase II trial is also evaluating ISA101b plus utomilumab in patients with HPV-16-positive incurable oropharyngeal cancer (NCT03258008).

ISA201 (HESPECTA)

ISA201 is a second-generation therapeutic peptide vaccine based on ISA101. ISA201 is made up of two HPV-16 E6 synthetic long peptides (E6 71–95 and E6 127–158) conjugated to AMPLIVANT (a synthetic Toll-like receptor 1/2 ligand)[92]. A phase I trial is currently recruiting participants to investigate the safety and biological activity of ISA201 in patients with HPV-16-positive head and neck tumours or malignant lesions (NCT02821494).

DPX-E7

DepoVax (DPX) is a novel lipid-based vaccine platform designed to raise sustained antigen-specific immune responses. DPX-based vaccines have demonstrated safety, tolerability, and immunogenicity in clinical cancer trials[93]. DPX-E7 is an investigational DPX-based cancer vaccine and is made of a synthetic peptide consisting of amino acids 11–19 of HPV-16 E7. DPX-E7 is intended to treat HPV-related tumours[94]. The safety and efficacy of the DPX-E7 vaccine in combination with low-dose metronomic oral cyclophosphamide is currently being investigated in a phase Ib/II

Table 6. Ongoing clinical trials evaluating adoptive T-cell therapy in HNSCC as of July 2018.

Design	Population	Phase	Status	ID
4ab T1E28z positive T-cells	HNSCC	I	Recruiting	NCT01818323
MAGE $A10^{c}$ ^{9} ^{6} T-cells	HNC, urinary bladder cancer, melanoma	I	Recruiting	NCT02989064
MAGE-$A4^{c1032}$ T-cells	HLA-A2+ patients with MAGE-A4-positive locally advanced inoperable or metastatic cancers	I	Recruiting	NCT03132922
IMA101 T-cells	Solid tumours	I	Recruiting	NCT02876510
IMA201 T-cells + recombinant human IL-2	HNSCC, NSCLC	I	Recruiting	NCT03247309
EBV-specific CTL	Advanced nasopharyngeal carcinoma	III	Recruiting	NCT02578641
TBI-1301 (NY-ESO-1-specific TCR gene transduced T-cells)	Solid tumours	I	Recruiting	NCT02366546
TBI-1201 (MAGE-A4-specific TCR gene transduced T-cells)	Solid tumours	I	Recruiting	NCT02096614
PD-1 knockout EBV-CTL + IL-2	Advanced stage EBV-positive malignancies	I/II	Recruiting	NCT03044743
LMP-specific T-cells	Patients with relapsed EBV-associated diseases	I	Active, not recruiting	NCT01447056

CTL, cytotoxic T-lymphocyte; EBV, Epstein–Barr virus; HNC, head and neck cancer; HNSCC, head and neck squamous cell carcinoma; IL, interleukin; LMP, latent membrane protein; NSCLC, non-small-cell lung cancer; PD-1, programmed cell death protein 1.

trial in HLA-A*02-positive patients with incurable HPV-16-related oropharyngeal, cervical, and anal cancers (NCT02865135).

MUC1 vaccine

Mucin 1 (MUC1) is a membrane-bound glycoprotein that belongs to the mucin family. Overexpression of the hypoglycosylated form of MUC1 has been observed in various epithelial malignancies and it has been shown to promote tumour growth, metastasis, and resistance to cancer therapy[95]. In recent years, researchers have been investigating the safety, immunogenicity, and anti-tumour activity of MUC1-based immunotherapy approaches such as anti-MUC1 vaccines in various forms of malignancies, and a phase I/II trial for HNSCC is currently underway (NCT02544880).

AlloVax

AlloVax is a personalized, therapeutic anti-cancer vaccine consisting of chaperone-rich cell lysate, isolated from the patient's tumour, combined with AlloStim, a bioengineered living cell allograft, as an adjuvant[96]. AlloVax is currently undergoing two clinical investigations in HNSCC. A phase I/II study is currently evaluating the safety and tolerability of AlloVax in R/M HNSCC patients who cannot be treated with surgery, CT, or RT (NCT01998542). A phase II study is now underway in order to compare AlloVax to cisplatin-based CT in R/M HNSCC patients (NCT02624999).

DSP-7888

DSP-7888 is an investigational therapeutic cancer vaccine comprised of peptides derived from the Wilms' tumour gene 1 (WT1) protein. DSP-7888 is expected to induce a specific CTL and helper T-cell response against WT1-expressing cancerous cells, which are found in various types of haematological and solid cancers[97,98]. DSP-7888 is now being investigated in a phase I clinical trial in advanced malignancies (NCT02498665). An additional phase I study is currently investigating DSP-7888 in combination with nivolumab or atezolizumab in patients with advanced solid tumours including HNSCC (NCT03311334).

DNA-based vaccines

INO-1400/INO-1401/INO-9012

INO-1400 and INO-1401 are synthetic DNA plasmids against human telomerase reverse transcriptase (hTERT), which is upregulated in various forms of malignancies and plays a key role in tumour invasion and metastasis[99]. INO-1400 and INO-1401 are expected to generate hTERT-specific IFN-γ-secreting T-cells[100]. A phase I trial is currently recruiting patients to evaluate the safety, tolerability, and immunogenicity of INO-1400 and INO-1401 alone or in combination with INO-9012 (dual promoter plasmid encoding human IL-12 subunits p35 and p40) in patients with solid tumours who are at high risk of relapse (NCT02960594).

INO-3112

INO-3112 (MEDI0457) is a combination of two previously developed DNA vaccines, VGX-3100 and INO-9012. INO-3112 has been designed to generate HPV-specific CD8+ T-cells to target tumours caused by HPV types 16 and 18[100]. INO-3112 is now in clinical development for the treatment of HPV-associated cervical cancer and HNC. Based on interim data from a phase I/IIa trial (NCT02163057), INO-3112 can produce HPV-16/18-specific CD8 T-cell immunity in HPV-associated HNSCC patients[101]. A phase I/II trial is now recruiting HPV-associated R/M HNSCC patients to evaluate INO-3112 plus durvalumab (NCT03162224).

Cell-based vaccines

Tumour cell vaccine

Tumour cell vaccines are made from autologous or allogeneic cancer cells. These cells are manipulated ex vivo, infected with a replication-defective adenoviral vector, and transferred into patients to stimulate a cytotoxic immune response. MVX-ONCO-1 is the first personalized tumour cell vaccine and is now being investigated in a phase I trial for solid cancers (NCT02193503). This trial has been assessing the safety and tolerability of MVX-ONCO-1 in patients with progressing solid tumours who have failed all standard therapies. Preliminary results from this study demonstrated that MVX-ONCO-1 was safe and well tolerated, with no serious AEs[102]. An ongoing study is currently investigating the efficacy of MVX-ONCO-1 in patients with advanced HNSCC (NCT02999646).

Dendritic cell vaccine

As the most potent antigen-presenting cells in the immune system, dendritic cells (DCs) play crucial roles in the initiation of tumour antigen-specific immune responses in tumours[103]. Due to their ability in promoting adaptive and innate immunity, DCs have gained lots of attention as a new therapeutic strategy in several types of cancers. The first therapeutic DC vaccine approved by the US FDA is Provenge (sipuleucel-T), which is used for the treatment of asymptomatic or minimally symptomatic metastatic hormone-refractory prostate cancer. In a phase I study (NCT00404339), adjuvant p53 peptide loaded DC vaccine increased the p53-specific T-cell frequency in 69% of HNSCC patients[104]. In another study, all 30 patients with stage III/IV HNSCC who were treated with DC-based autologous tumour vaccine survived disease-free for the long-term[105].

Biological vaccines

ADXS11-001 is a bioengineered strain of living *Listeria monocytogenes* that encodes HPV-16 E7 fusion protein. ADXS11-001 targets HPV-transformed cells and induces anti-tumour T-cell immunity[106]. Several studies have been conducted to assess the effect of ADXS11-001 in patients with HPV-associated tumours. A phase II trial is currently investigating the effect of ADXS11-001 on anti-tumour immunity in peripheral blood and the tumour immune microenvironment in patients with HPV-positive oropharyngeal SCC before they undergo robotic surgery (NCT02002182). Preliminary results from this ongoing study have shown increased E6 or E7-specific IFN-γ responses in 5/8 patients[107].

Recombinant viral vaccines

TG4001

TG4001 is an investigational viral-based therapeutic vaccine that consists of attenuated recombinant modified vaccinia Ankara (MVA) encoding HPV-16 E6/E7 and IL-2. TG4001 has demonstrated promising preclinical and clinical efficacy in terms of HPV viral clearance[108]. A phase Ib/II trial is now recruiting patients with HPV-16-positive R/M oropharyngeal SCC and other advanced HPV-related malignancies to evaluate the safety, tolerability, and efficacy of TG4001 in combination with avelumab (NCT03260023).

MVA-EL

MVA-EL is a recombinant vaccinia virus that encodes the EBV viral tumour anti-

gens EB nuclear antigen 1 (EBNA1) and latent membrane protein 2 (LMP2) and has been designed to boost T-cell immunity against the virus[109]. Results from a phase I study of MVA-EL in nasopharyngeal carcinoma patients suggested that this vaccine is safe and immunogenic[109]. Results from this study led to two subsequent clinical trials: a phase Ib trial to evaluate the safety and immunogenicity of extended schedule vaccination in EBV-positive nasopharyngeal carcinoma (NCT01800071) and a phase II study to further evaluate its efficacy in persistent, R/M nasopharyngeal carcinoma patients (NCT01094405).

ETBX

Etubics is developing multiple types of adenovirus-based vaccines for the treatment of cancers. These immunotherapeutic vaccines have been designed to target carcinoembryonic antigen (ETBX-011), HER-2/Neu (ETBX-021), HER-3 (ETBX-031), HPV (ETBX-041), brachyury (ETBX-051), MUC1 (ETBX-061), or prostate-specific antigen (PSA) (ETBX-071)[110]. The phase Ib/II QUILT-3.047 trial (NCT03169764) is now investigating ETBX vaccines (ETBX-011, ETBX-021, ETBX-051, and ETBX-061) in combination with other immune-modulating therapies in HNSCC patients who have progressed on or after CT and PD-1/PD-L1 therapy.

TRICOM

The TRICOM cancer vaccine platform consists of a single recombinant vaccinia virus (rV-) prime vaccination followed by multiple boosts with a replication defective fowlpox (rF-) vector. To date two TRICOM vaccine platforms have been developed: PROSTVAC, which expresses PSA (rV, rF-PSA-TRICOM), and PANVAC, which expresses two pan-carcinoma transgenes, MUC-1 and carcinoembryonic antigen (rV, rF-CEA-MUC1-TRICOM). TRICOM-based vaccines have been investigated in the clinical setting and have demonstrated limited toxicity in a range of human carcinomas[111]. TRICOM has been assessed as monotherapy in two phase I trials in HNSCC (NCT00021424) and in advanced/metastatic cancers including HNC (NCT00027534), but results are not yet available.

Oncolytic virus therapies

Oncolytic viruses (OVs) are native or genetically modified viruses that selectively replicate within malignant cells, kill the cells, and eventually initiate systemic anti-tumour immunity[112,113]. In recent years, several viruses have been tested as oncolytic agents for the treatment of cancer. However, the only US FDA approved OV is talimogene laherparepvec (T-VEC), which is used to treat melanoma lesions that cannot be entirely removed by surgery[114]. T-VEC is a modified herpes simplex virus type 1 (HSV-1) that lacks the herpes virus ICP34.5 and ICP47 genes and encodes GM-CSF[115]. A phase Ib/III trial (MASTERKEY-232) is now recruiting participants to assess T-VEC plus pembrolizumab in R/M HNSCC (NCT02626000). Vaccinia virus Pexa-Vec (JX-594) (NCT02977156), vaccinia virus GL-ONC1 (NCT02714374), oncolytic measles virus (MV-NIS) (NCT01846091), and recombinant oncolytic vesicular stomatitis virus expressing the human IFN-β gene (VSV-hIFNβ-NIS) (NCT02923466) are also in clinical trials for HNSCC.

In conclusion, it is well-established that immune system dysfunction is a key feature in HNSCC. The immune suppressive tumour microenvironment, together with moderate to high mutation load in HNSCC, suggest that immunotherapy is an attractive treatment option for improving the survival rate and reducing toxic side effects of current treatment modalities. Recent advances in our understanding of the mechanisms of immune escape have led to the development of novel immunotherapies that have shown, initial, encouraging results in many solid tumours including HNSCC. In recent years, a number of promising immunotherapy approaches have been developed, including targeted monoclonal antibodies and checkpoint inhibitors, as well as systemic cell-mediated immunotherapy. These novel treatment modalities, either as monotherapy or combined with conventional or other targeted therapies, exemplify the possible future directions in the treatment of HNSCC. Although HNSCCs remain difficult to treat, it is hoped that immunotherapy will provide new insights into and opportunities for the treatment of HNSCC with the aim of improving clinical outcomes.

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Competing interests

There is no conflict of interest.

Ethical approval

Not required.

Patient consent

Not required.

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