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Review

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ABSTRACT

Head and neck cancer (HNC) is the sixth most common cancer type, accounting for approximately 277,597 deaths worldwide. Recently, the Food and Drug Administration (FDA) has approved immune checkpoint blockade (ICB) agents targeting programmed death-1 (PD-1) and programmed death-ligand 1 (PD-L1) as a treatment regimen for head and neck squamous cell carcinomas (HNSCC). Studies have reported the role of immune checkpoint inhibitors as targeted therapeutic regimens that unleash the immune response against HNSCC tumors. However, the overall response rates to immunotherapy vary between 14–32% in recurrent or metastatic HNSCC, with clinical response and treatment success being unpredictable. Keeping this perspective in mind, it is imperative to understand the role of T cells, natural killer cells, and antigen-presenting cells in modulating the immune response to immunotherapy. In lieu of this, these immune molecules could serve as prognostic and predictive biomarkers to facilitate longitudinal monitoring and understanding of treatment dynamics. These immune biomarkers could pave the path for personalized monitoring and management of HNSCC.

Abbreviations: HNC, Head and neck cancer; ICB, immune checkpoint blockade; FDA, Food and Drug Administration; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; HNSCC, head and neck squamous cell carcinoma; CD, cluster of differentiation; NKG2D, natural killer group 2 member D; TNFRSF4, tumor necrosis factor receptor superfamily member 4; TIM-3, T cell immunoglobulin and mucin domain 3; CTLA-4, cytotoxic Tlymphocyte–associated antigen 4; LAG-3, lymphocyte-activation gene 3; IDO, indoleamine-pyrrole 2,3-dioxygenase; BTLA, B and T lymphocyte attenuator; APC, antigen-presenting cells; NK, natural killer; IL, interleukin; IFN, interferon; MHC, major histocompatibility complex; NF-κB, nuclear factor kappa B; PI3K, phosphatidylinositol 3-kinase; NPC, nasopharyngeal carcinoma; Tregs, regulatory T cells; CT, computed tomography; EBV, Epstein-Barr virus; UNPC, undifferentiated NPC; CAR, chimeric antigen receptor; DC, dendritic cells; TRAF, tumor necrosis factor receptor-associated factor; MAPK, mitogen-activated protein kinase; HPV+, human papillomavirus positive; mAb, monoclonal antibody; iPSC, pluripotent stem cell; TNFR, Tumor necrosis factor receptor; TIL, tumor-infiltrating lymphocytes; DAMP, damage-associated molecular pattern; TLR, toll-like receptors; RAGE, receptors for advanced glycation; OSCC, Oral squamous cell carcinoma; Ig, immunoglobulin; IgV, immunoglobulin variable–type; HPV, human papillomavirus; TAMs, tumor-associated macrophages; PKD2, protein kinase D isoform 2; CMTM6, CKLF Like, MARVEL Transmembrane Domain Containing 6; ADCC, antibody-dependent NK-mediated cytotoxicity; sPD-L1, soluble form of PD-L1; HAVCR2, hepatitis A virus cellular receptor 2; Gal-9, galectin-9; PS, phosphatidylserine; HMGB1, high-mobility group protein B1; CEACAM-1, carcinoembryonic antigen cell adhesion molecule 1; Th1, T helper 1; PtdSer, phosphatidylserine.; TCR, T cell receptor; TDLNs, tumor-draining lymph nodes; s-LAG-3, soluble LAG-3; OS, overall survival; PFS, progression-free survival; TNF- α, tumor necrosis factor-α; PBMCs, peripheral blood mononuclear cells; cDC1, type 1 conventional dendritic cells; TA, tumor antigen.

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In this review, we aim to provide updated immunological insight on the mechanism of action, expression, and the clinical application of immune cells' stimulatory and inhibitory molecules as prognostic and predictive biomarkers in HNC. The review is focused mainly on CD27 and CD137 (members of the TNF-receptor superfamily), natural killer group 2 member D (NKG2D), tumor necrosis factor receptor superfamily member 4 (TNFRSF4 or OX40), S100 proteins, PD-1, PD-L1, PD-L2, T cell immunoglobulin and mucin domain 3 (TIM-3), cytotoxic T lymphocyte–associated antigen 4 (CTLA-4), lymphocyte-activation gene 3 (LAG-3), indoleamine-pyrrole 2,3-dioxygenase (IDO), B and T lymphocyte attenuator (BTLA). It also highlights the importance of T, natural killer, and antigen-presenting cells as robust biomarker tools for understanding immune checkpoint inhibitor-based treatment dynamics. Though a comprehensive review, all aspects of the immune molecules could not be covered as they were beyond the scope of the review; Further review articles can cover other aspects to bridge the knowledge gap.

1. Background

Head and neck cancer (HNC) is the sixth most common cancer in the world, with a five-year survival rate of less than 60%. In 2020, an estimated 562,328 people were diagnosed with HNC, and a mortality rate of approximately 277,597 was observed [1]. HNC is a profoundly immunosuppressive disease characterized by abnormal secretion of proinflammatory cytokines and dysfunction of immune effector cells. Keeping this in perspective, the role of immune checkpoint inhibitors, targeting immune suppressive mediators such as PD-1 and PD-L1, can unleash the immune cells, allowing tumor regression and robust therapeutic responses [2]. In lieu of this, FDA has recently approved anti-PD-1

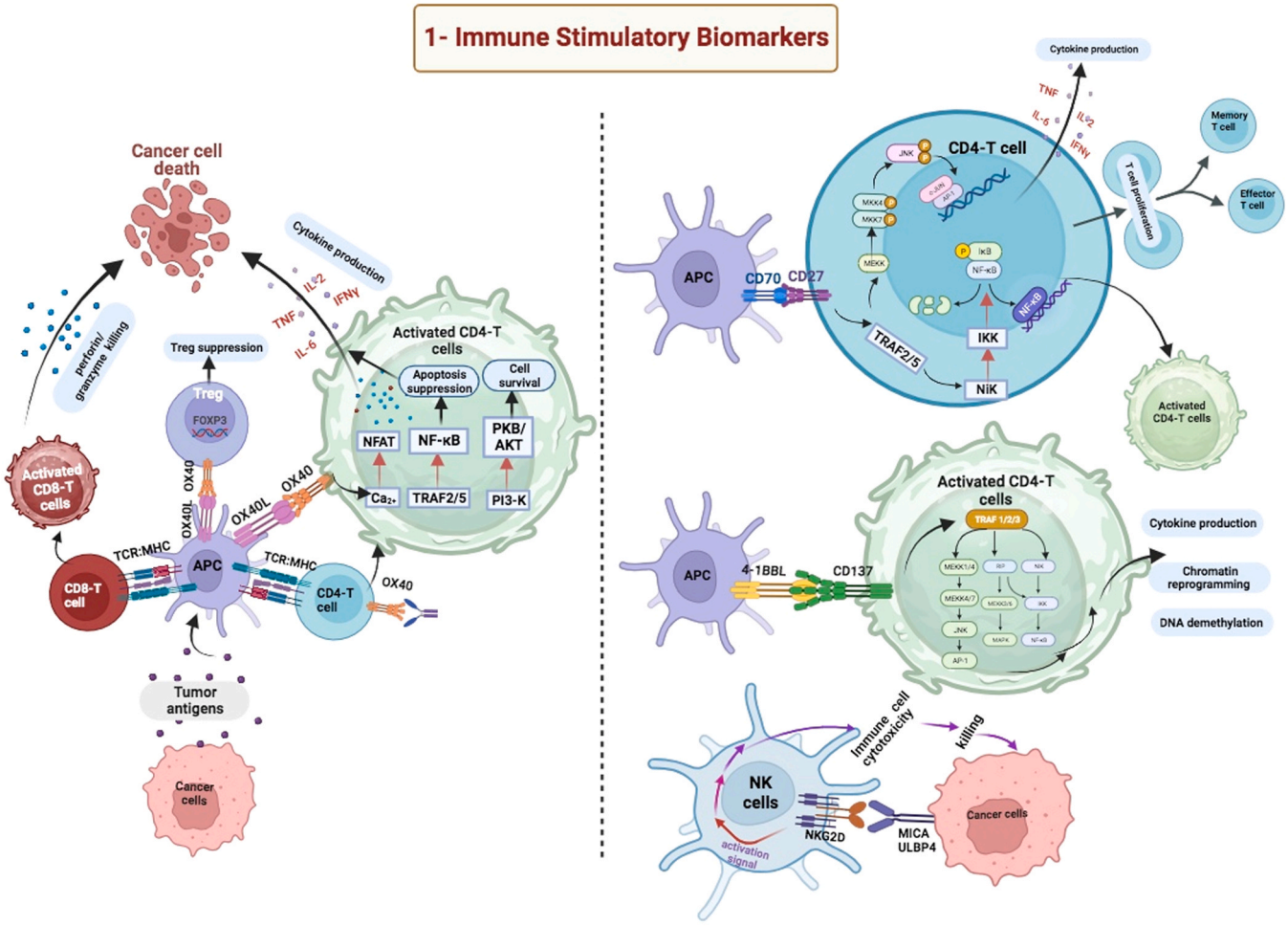

Fig. 1. Immune stimulatory biomarkers in head and neck squamous cell carcinoma (HNSCC). The main immune stimulatory pathways involved in boosting the antitumor immune responses of HNSCC are elucidated: CD27, CD137, NKG2D and OX40. The OX40/OX40L interaction activates TNFR-associated factor (TRAF2/5) in T cells, which subsequently activates a signaling cascade inducing nuclear factor κB (NF-κB) activation that increases the expression of apoptosis-suppressing proteins. Also, the ligand binding activates T-cell nuclear factor (NFAT) pathway that leads to an increase in the synthesis of cytokines such as IL-2, IL-6, TNF, and IFN-γ. Additionally, OX40 enhances the PI3 K/PKB and NFAT pathways downstream of the TCR, which has implications for long-term survival, proliferation, and cytokine generation. Costimulation of OX40 inhibits the FOXP3 transcription factor, impairing the Treg function and diminishing the tumor immunosuppression. Similar to OX40/OX40L, the CD27/CD70 pathway also triggers TRAF2/5 in T cells, which enhances MEKK-JNK-AP-1 and NiK-IKK-NF-κB pathways that augment T cell differentiation to effector and memory T cells, cytokine production, and the survival of T lymphocytes. Upon ligation of CD137 with its ligand on APC, activated TRAF1/2/3 in T cells, which subsequently activates a signaling cascade MEKK1/4-AP-1, RIP-MAPK, and NiK-NF-κB that leads to an increase in the synthesis of cytokines, chromatin reprogramming, and DNA demethylation.

and anti-PD-L1 for HNSCC as first-line treatment in a recurrent/metastatic setting [3].

Although immunotherapy aims to benefit HNSCC patients, in real-world clinical settings, the overall response rates vary between 14–32% with unpredictable clinical response and treatment success [4]. Therefore, there is a need for the identification of robust immune-specific biomarkers that can ultimately optimize treatment strategies, conferring superior clinical outcomes. Several pre-clinical studies and clinical trials focus on identifying predictive and prognostic biomarkers for HNC [5–8]. Some of these biomarkers include antigen-presenting cells (APC), T cells, natural killer (NK) cells, immune stimulatory and inhibitory markers that can serve as potential predictive and prognostic biomarkers [9–11]. Briefly, the main mechanism of action of immune stimulatory markers is to activate the T cells with the help of "co-stimulatory molecules". These co-stimulatory molecules result in the release of immune-activating inflammatory cytokines [12, 13]. In contrast, the immune inhibitory molecules prevent T cell activation by expressing immune suppressive receptors such as PD-1, CTLA-4, etc., leading to the expression of anti-inflammatory cytokines that suppress the immune response [14]. In HNC, the immune cells are manipulated to subvert the immune response toward a suppressive environment [15]. One of the mechanisms to counter this strategy is to unleash the immune response through immunotherapy. However, the dilemma of limited response rates in patients receiving immune checkpoint inhibitors (ICIs) fuels the need to understand the dynamic immunosuppressive network within the tumor microenvironment. In this context, an insight into the role of T, NK, and APC is required for a to better understand the immune modulation (Figures 1 and 2). Given this understanding, the utility of these mediators as prognostic and predictive biomarkers can be ascertained for diagnostics and therapeutic monitoring of HNSCC. We aim to provide novel insight into the role of APC, T, and NK cells with respect to their role as predictive and

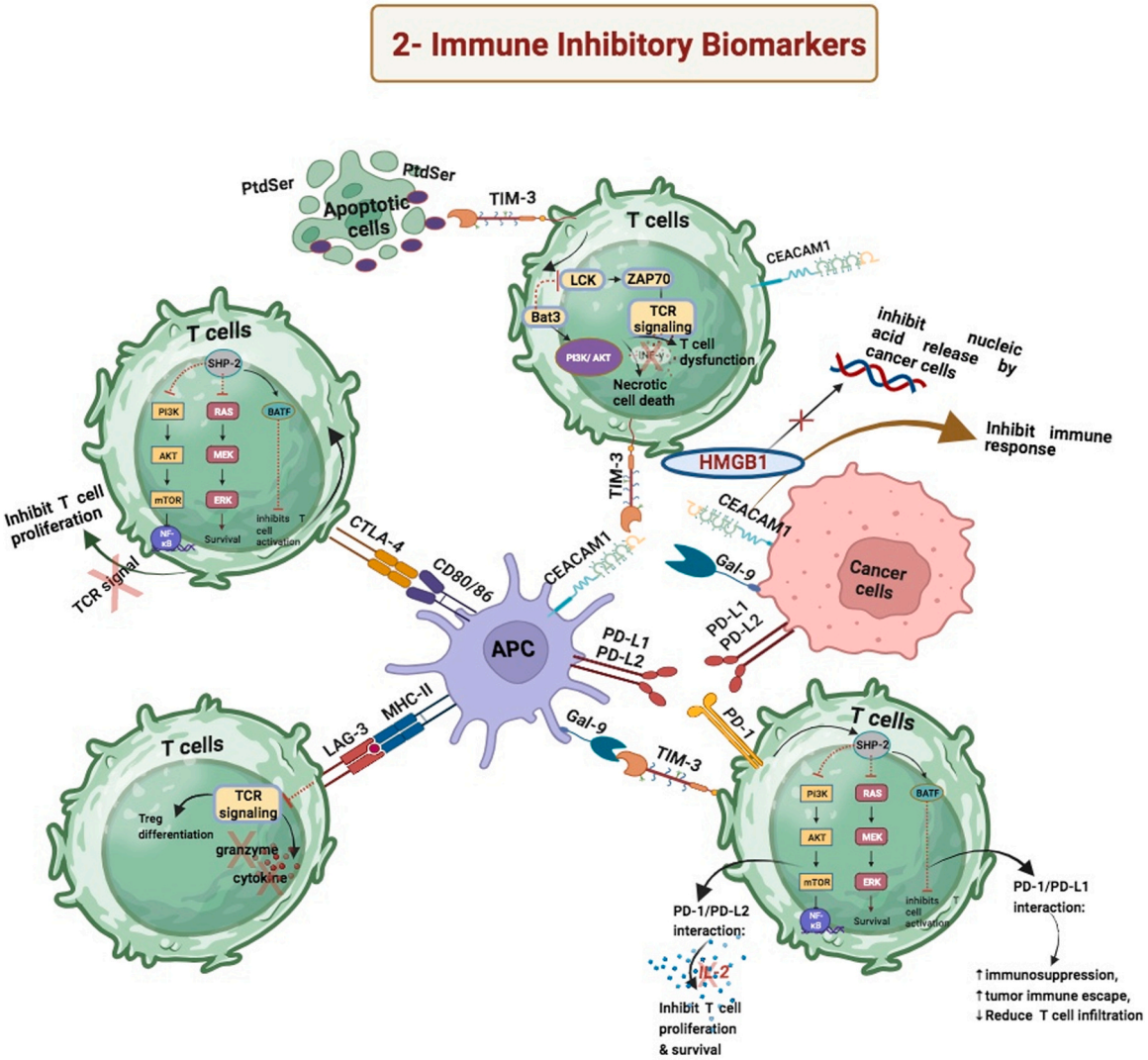

Fig. 2. Immune inhibitory biomarkers in head and neck squamous cell carcinoma (HNSCC). The main immune inhibitory pathways involved in HNSCC immune escape are elucidated: PD-1/PD-L1/PD-L2, CTLA-4, TIM-3, and LAG-3. Immunoreceptor tyrosine-based switch motif residue sites are phosphorylated upon engagement of PD-1 and CTL4 with their ligands on T cells. This phosphorylation attracts phosphatases such as SHP-2 (Src homology region 2 domain-containing phosphatase-2). Recruited SHP2 directly downregulates T cell receptor (TCR) signaling via dephosphorylation of proximal signaling elements, including PI3K, RAS, and PKC, leading to decreased activation, proliferation, cytokine production, and survival of T cells. Furthermore, PD-1 and CTL4 signaling increase the expression of the basic leucine zipper transcriptional factor ATF-like factor (BATF), which affects the differentiation of immune cells. Moreover, TIM-3 ligation by ligand displaces Bat-3 (HLA-B-associated transcript) from the TIM-3 tail. This causes tyrosine phosphatases to be recruited, which in turn dephosphorylate Lck, downregulate Zeta-chain-associated protein kinase ZAP70/TCR signaling, and suppress T-cell survival and proliferation. Additionally, ligand binding to LAG3 induces inhibition in the early steps of the TCR pathway in a manner dependent onLAG3′s cytoplasmic domain. It also leads to reduced cytokine and granzyme production and encourages Treg cell differentiation.

prognostic biomarkers of response in HNC treated with ICIs.

2. Immune Stimulatory Biomarkers

2.1. CD27

CD27 is a member of the tumor necrosis factor receptor superfamily that is expressed on both naive $CD4^+$ and $CD8^+$ T cells, NK cells, and B cells. It plays a crucial role in T and B cell activation and co-stimulation with the help of its ligand CD70 [16,17]. Mainly, the CD27/CD70 signaling axis enhances the proliferation of T cells and their differentiation into effector and memory T cells [18], as well as cell division, cell survival, and cytokine production [19]. In addition, it can promote cytotoxic activity of immune cells by activating nuclear factor kappa B (NF-κB) and phosphatidylinositol 3-kinase (PI3K) pathways [19,20]. Furthermore, T cells expressing CD27/CD70 are key players in plasma cell differentiation and the regulation of immunoglobin synthesis [21–23].

2.1.1. The role of CD27/CD70 signalling in HNC

Although a few studies elucidated the role of the CD27/CD70 signaling axis in the pathogenesis of cancers [24,25], there are new insights on its significance in immune regulation in HNC. For example, upregulated expression of CD70 was observed in nasopharyngeal carcinoma (NPC) and HNSCC [26–30]. The tumoral expression of CD70 was reported in 69% of HNSCC patients' samples and was strongly associated with tumor progression and staging [30]. Increased interaction between CD27 and CD70 has been observed as a transient, natural-response element of the immune system [31]. In contrast, prolonged expression of CD70 on tumor cells has been linked to enhanced proliferation and recruitment of regulatory T cells (Tregs), inducing T cell exhaustion and apoptotic markers. This, in turn contributes to the development of an immunosuppressive tumor microenvironment that facilitates tumor survival and progression [30, 32–34]. Wang et al. applied computed tomography (CT)-based radiomics technology to predict CD27 expression and clinical prognosis in HNSCC. The expression levels of CD27 in HNSCC significantly influenced the prognosis of patients and correlated with HNSCC immune-cell infiltration [35].

Infectious agents like the Epstein-Barr virus (EBV) are known to be commonly linked to the pathogenesis of HNC [36]. Indeed, EBV-associated undifferentiated NPC (UNPC), is often highly invasive and metastatic [37]. CD70 expression has been reported in 80% of the tumor samples from patients with UNPC which were all associated with the presence of EBV infection and CD27 expression in the infiltrating lymphoid cells [38]. Interestingly, immuno-deficiencies in CD27 and its ligand CD70 were found to promote the pathogenesis of EBV infection [39]. Additionally, the depletion of CD27, and blocking its interaction with CD70 can lead to uncontrolled EBV infection [39].

2.1.2. Clinical and research-based application of CD27 in HNC

The strategic positioning of the CD27/CD70 axis as dual markers for normal immune processing, as well as for malignant pathogenesis (in the case of chronic CD70 expression), has highlighted its importance as a target for therapeutic development. Targeting CD27 with agonistic antibodies has been shown to promote adaptive immunity in several tumor models and was linked to an increase in NK and T cell frequencies and function enhancement [40–44]. Varlilumab, a fully human anti-CD27 agonist antibody, has been recently tested in combination with nivolumab (anti-PD-1) in phase I/II clinical trials in advanced refractory solid tumors, including HNSCC (NCT02335918). Varlilumab was reported to be well-tolerated in this trial [45]. The combination of varlilumab with nivolumab in advanced solid tumors, including HNC, showed clinical activity in patients that are typically refractory to anti-PD-1 therapy [45]. Currently, another phase I clinical trial is being conducted to determine the safety, tolerability, and activity of a PD-L1xCD27 Bispecific Antibody (CDX-527) in HNC patients (NCT04440943). Preliminary results showed that the treatment of eight patients with different doses of CDX-527 (ranging from 0.03 mg/kg to 1 mg/kg) has been well tolerated [46]. Moreover, cusatuzumab (ARGX-110), a CD70-targeting monoclonal antibody, was found to be capable of inducing cytotoxicity against CD70-expressing tumor cells via a variety of effector functions, as well as enhancing the anti-tumor immune response through the inhibition of Tregs accumulation and activation [47]. The combination of this drug with radiotherapy and/or chemotherapy was evaluated in NPC patients as a phase I clinical trial. It showed that patients who received combinational therapy had longer progression-free survival [48]. Furthermore, a recent pre-clinical study showed that CD70-specific chimeric antigen receptor (CAR) T cells efficiently recognize and kill CD70-positive HNSCC cells but not CD70-negative cancer cells [49]. This study formed the basis for further investigation of the clinical response of NHC patients to CD70-specific CAR-T cell treatment.

2.2. CD137

CD137 (4–1BB) is a surface glycoprotein that belongs to the tumor necrosis factor receptor superfamily. It functions as a co-stimulatory molecule on the surface of activated T and NK cells [50]. CD137 often cooperates with its natural ligand TNFSF9 (4–1BBL), which is superficially expressed on APC such as activated B-cells, macrophages, and mature dendritic cells (DC) [51]. To date, no enzymatic activity has been attributed to the intracellular domain of CD137 [52], although it has been reported to function through the recruitment of adaptor proteins called tumor necrosis factor receptor-associated factor (TRAF), such as TRAF1, TRAF2, and TRAF3 [52]. Moreover, CD137 activates the NF-κB and mitogen-activated protein kinase (MAPK) signaling pathways via its trimerization and subsequent receptor clustering [53]. Other studies have reported that CD137 co-stimulation improves memory and effector T cell differentiation [53,54], regulates mitochondrial metabolism to enhance respiratory capacities of T cells [55], shields T cells from apoptosis [56], and induces chromatin reprogramming and DNA demethylation [57], in addition to effector cytokine production [58].

2.2.1. CD137 expression and its role in the diagnosis and prognosis of HNC

CD137 is identified as a key modulator of various malignancies. According to certain studies, CD137 can promote T cell proliferation through the activation of DCs, leading to the subsequent secretion of IL-2 and IL-6 [59]. However, the activated DCs can also activate cytotoxic lymphocytes leading to the secretion of IFN-γ, thereby improving anti-tumor effects [60]. Interestingly, a recent study demonstrated that the quantification of soluble CD137 in plasma and the CD137 surface expression could be used as a dynamic biomarker that reflects the therapeutic co-stimulatory activity induced by CD137 immunotherapies [61].

2.2.2. Clinical and research-based application of CD137 in HNC

A considerable number of clinical research have been focused on the CD137/4–1BBL axis as a promising target for enhancing anti-tumor immune responses in HNC. Currently, two new bi or tri-specific antibodies (Inbrx-105 and NM21–1480, respectively) targeting PD-L1/PD-1 signaling axis and CD137 are under investigation. These antibodies act simultaneously as CD137 agonists to induce the T cell co-stimulation and as PD-1/PD-L1 inhibitors, thus promoting the anti-tumor activity [62]. The combination of inbrx-105 with the anti-PD-1 pembrolizumab is under investigation in a phase II clinical trial for HNC patients (NCT03809624) to determine the safety profile and identify the maximum tolerated dose and/or recommended phase II dose. In addition, NM21–1480 is currently being tested in a phase I/II clinical trial (NCT04442126) in HNC patients to evaluate its safety and immunogenicity, and to determine its maximal tolerated dose and recommended phase II dose. In the context of human papillomavirus-positive (HPV+) HNSCC, it has been shown in a mouse model that systemic activation of

CD137 (via anti-CD137 antibody) synergizes tumor inhibition by cisplatin/radiotherapy [63]. Indeed, the overexpression of the CD137L on the tumor cells significantly enhances tumor clearance with cisplatin and radiation therapy via the activation of the CD137/4–1BBL axis [63].

Two CD137 monoclonal antibody (mAb) agonists, urelumab (BMS-663513) and utomilumab (PF-05082566), have been developed for clinical use [64–66]. Utomilumab can enhance the efficiency of other immunotherapies in HNC patients [67]. Primary reports on CD137 mAb in murine and human cells showed that the binding to CD137 amplified the co-stimulatory signals in T cells and increased their IL-2 and IFN-γ synthesis and proliferation [68]. CD137 immunotherapy largely decreased tumor growth and survival and led to the stabilization of body weight over time in a murine model for HNC [69]. Moreover, CD137 agonists promoted DC maturation and improved the cross-presentation function of NK cells and DC to HNSCC antigens [70].

2.3. NKG2D

NKG2D is an NK cell receptor that belongs to the class of C-type lectin-like protein receptors of the CD94/NKG2 superfamily [71]. This co-stimulatory receptor is also expressed on the surface of NKT cells, $CD8^+$ T cells, γδ T cells, and particular subsets of $CD4^+$ T cells [71]. The interaction between NKG2D and its ligands on the surface of tumor cells (including MICA/B, ULBP1/2/3, and Rae-1, which are preferentially overexpressed on tumor cells) enhances the immune cells cytotoxicity and anti-tumor activity [72]. However, tumor cells developed mechanisms to escape the NKG2D-mediated immune surveillance through a cell-contact-dependent mechanism via the upregulation of immunosuppressive factors and shedding soluble NKG2D ligands [73]. Hence, the NKG2D receptor or its ligands might be an attractive target for immunotherapy.

2.3.1. NKG2D expression and its role in the diagnosis and prognosis of HNC

NKG2D receptor expression on NK cells and several T cell subsets play an important role in the immunosurveillance of HNC. Indeed, Xu et al. showed that NPC patients had decreased expression of NKG2D on $CD8^+$ T cells compared to healthy individuals [74]. This study suggested that tumor cells release soluble ligands that bind to NKG2D, further reducing its expression on $CD8^+$ T cells and impairing T cell activation. Consequently, the decreased expression of NKG2D on $CD8^+$ T cells could serve as a biomarker for immune evasion in NPC patients [75]. An in vitro study showed that the NKG2D induction on $CD8^+$ T cell plays an important role in their cytolytic activity against tumor cells [76]. In addition, elevated plasma levels of soluble MHC class I chain-related protein A (MICA) and transforming growth factor beta-1 (TGFb1) were associated with a significant decrease in NKG2D-dependent NK cell activation and cytotoxicity against cancer cells, leading to tumoral progression in HNSCC patients [77]. Another study revealed that the concentration of soluble NKG2D ligands (sNKG2D-L) in the bloodstream is directly proportional to the amount of tumor present, and the extent of tumor load determines the highest level of plasma sNKG2D-L [78]. A recent meta-analysis indicated that the elevation of sNKG2D-L levels correlated to indications of worse prognosis in HNC patients [79]. On the other hand, decreased expression of the NKG2D ligand, ULBP4, on cancer cells may indicate poor prognosis in patients with NPC [74].

2.3.2. Clinical and research-based application of NKG2D receptor and its ligands in HNC

The frequent and high expression of NKG2D ligands by tumor cells in different types of human cancers, along with the strong anti-tumor effects of the NKG2D/NKG2D-L pathway, are well-established. Consequently, there is considerable interest in cancer therapies that aim to enhance or restore NK and T cell responses by either activating the NKG2D pathway or inhibiting NKG2D ligand shedding using NKG2D ligand inhibitors. Monoclonal antibodies targeting NKG2D-L showed insufficient efficiency against solid tumors in vivo, which prompted the development of other immunotherapy-based strategies [80]. Recently, Goulding et al. developed a novel CAR targeting the conserved α3 domain of MICA/B (3MICA/B CAR) and incorporated it into induced pluripotent stem cell (iPSC)-derived NK cells (3MICA/B CAR iNK) [81]. These engineered NK cells expressed a shedding-resistant form of the CD16 Fc receptor, enabling the recognition of tumors through two major targeting receptors. The 3MICA/B CAR iNK effectively reduced MICA/B shedding and inhibition by soluble MICA/B while exhibiting antigen-specific anti-tumor activity against a wide range of human cancer cell lines [81]. In pre-clinical assessments, 3MICA/B CAR iNK cells demonstrated potent antigen-specific cytolytic activity in both solid and blood cancer xenografts [81]. A phase I clinical trial (NCT05395052) is still ongoing to evaluate the safety and tolerability of FT536, a CAR-NK product targeting a conserved domain of MICA/B, as a monotherapy and in combination with mAb therapies to determine the recommended phase II dose in solid tumor patients including HNC [82]. Moreover, the safety and efficacy of CAR T NKR-2 modified T cells targeting NKG2D-ligands are currently being tested in many clinical trials for solid and hematological malignancies [83].

2.4. OX40

OX40 (CD134) is a member of the tumor necrosis factor receptor (TNFR) superfamily. This co-stimulatory receptor is a type I transmembrane glycoprotein primarily expressed on activated $CD4^+$ and $CD8^+$ T cells and has also been found on several immune cells, including neutrophils and NK cells [84,85]. The binding of OX40 to its only known ligand OX40L (CD252), which is expressed on the surface of activated APCs, leads to the recruitment of adaptor proteins called TNF-associated factors and triggers the OX40 signaling pathway resulting in T cell activation, T cells survival enhancement, memory $CD8^+$ T cells maintenance, $CD4^+$ T cells differentiation, Tregs suppression, and cytokine production [86,87].

2.4.1. OX40 expression and its role in the diagnosis and prognosis of HNC

The surface T cell expression of OX40 has been reported in several solid tumors, including HNC. Vetto et al. were the first to discover the expression of OX40 on T cell surface in the tumors of HNSCC patients [88]. A study by Ryan et al. reported that OX40 expression was significantly higher inHNC patients' tumors than in T cells isolated from peripheral blood. They also found that tumor-infiltrating lymphocytes (TIL)-Tregs showed higher expression of OX40, PD-1, and CTLA-4 compared to Tregs isolated from peripheral blood [89]. Several studies have demonstrated that OX40 expression is elevated in HNC tissue samples compared to normal tissue samples, suggesting it as a potential diagnostic biomarker for this type of cancer. Lacerf et al. found that OX40 mRNA was overexpressed in HNSCC tissues compared to normal tissues, and this high level was associated with poor prognosis and a high probability of recurrence [90]. Furthermore, OX40 levels were higher in HNSCC patients with advanced stages, suggesting that OX40 is a promising biomarker for tumor severity. Consequently, OX40 agonists could be the future promising therapy for such patients [91].

2.4.2. Clinical and research-based application of OX40 and its ligands in HNC

OX40 has been identified as a potential therapeutic target in HNC. In pre-clinical studies, targeting OX40 with agonistic antibodies has enhanced anti-tumor immunity and improved response to therapy [92]. A study by Duhen et al. reported an elevation of $CD4^+$ and $CD8^+$ T cell stimulation and proliferation in HNSCC patients treated with anti-OX40 antibodies prior to tumor resection [93]. Currently, five OX40 agonists (MEDI6469, MEDI0562, INBRX-106, PF-04518600, and BGB-A445) alone or in combination with other immunotherapies are under investigation in phase I clinical trials for HNC patients (NCT02274155, NCT03336606, NCT04198766, NCT02315066, and NCT04215978

respectively). Phase I clinical trial (NCT02315066) of ivuxolimab (PF-04518600) alone showed that the drug was generally well tolerated and exhibited immune activation and anti-tumor activities in patients with locally advanced or metastatic cancers, including HNSCC [94]. Moreover, the safety and tolerability of ivuxolimab and 4–1BB antibodies (utomilumab) combination therapy have recently been tested in advanced solid tumor patients, including HNSCC (NCT02315066). This combination therapy was well tolerated and induced an anti-tumor activity in HNSCC patients [67].

2.5. S100

The S100 proteins family consists of calcium-binding proteins involved in different intracellular and/or extracellular functions [95]. This allows them to participate in a broad range of functions through distinct signaling pathways. To date, 25 members of the S100 proteins family have been identified in humans [95]. Despite their similar structures, the S100 family members are involved in different intracellular processes such as proliferation, apoptosis, migration, differentiation, and cell growth [96]. In addition, S100 can function as damage-associated molecular pattern (DAMP) molecules, which are released during cell stress or damage or activation of immune cells. Once released into the extracellular compartment, they bind to the toll-like receptors (TLR) or receptors for advanced glycation (RAGE) to activate immune and endothelial cells [97,98].

The S100 proteins are expressed in granulocytes, macrophages, monocytes, and neutrophils [99]. They have been reported to be dysregulated in many cancers [100]. The upregulation of the S100 protein expression has previously been observed in HNSCC and NPC patients and was involved in the invasion and migration of tumor cells as well as the downregulating tumor suppressors [101,102]. However, reports on the expression profiles of S100 proteins in oral squamous cell carcinoma (OSCC) have been conflicting [103]. Hu et al. found that high expression of S100A8 and S100A9 proteins was associated with poor prognosis of NPC [104]. Another study revealed a significant correlation between S100 protein expression and the clinical staging of NPC type III [105]. Recently, Bai et al. explored the effect of the S100 expression on the survival of HNSCC patients [106]. This study reported that the upregulation of S100A10 and S100A13 expression and the downregulation of S100A4 expression were associated with poor overall survival, disease-free survival, and tumor-infiltrating immune cell enrichment [106]. Moreover, S100A2, S100A7, S100A9, S100A12, S100A14, S100A16, and S100A7A were identified as biomarkers of tumor progression, invasion, and metastasis [106]. The role of S100 proteins in HNC progression can make them potential therapeutic targets for cancer therapy through small molecule inhibitors and mAbs. To our knowledge, these approaches have not yet been applied to HNC.

3. Inhibitory markers

3.1. PD-1, PD-L1 and PD-L2

One of the hallmarks of cancer development and progression is to escape the anti-tumor T cell activity [107]. T cells orchestrate cell-mediated immunity through multiple receptor molecules that can convey activating or inhibitory signals. These inhibitory receptors are known as checkpoint molecules, among them the PD-1/PD-L1/PD-L2 axis [108].

PD-1, known as CD279, is a CD28 immunoglobulin superfamily encoded by the *PDCD1* gene [108,109]. PD-1 is a co-inhibitory receptor expressed on the cell surface of activated T and B cells, NK cells, macrophages, DCs, and monocytes [110]. PD-1 receptor is composed of the extracellular, cytoplasmic, and transmembrane domains. The tyrosine residues in the cytoplasmic domain are involved in forming immunoreceptor tyrosine-based switch motifs. These motifs are responsible for PD-1 signal transduction and are closely related to the response activity of effector T cells [109,111,112]. In addition, PD-1 is the crucial immune checkpoint regulating the cellular function of T and B cells in response to antigens [113]. PD-1 has two identified ligands, PD-L1 (known as B7-H1/CD274) and PD-L2 (known as B7-DC/CD273) [114].

PD-L1 is mainly expressed in APCs and tumor cells. The interaction of PD-1 with PD-L1 on cancer cells or APCs provokes an immunosuppressive reaction that includes successive metabolic reprogramming in T cells, reduced effector T cells as well as memory T cells, and shattered T cell profusion [115]. Therefore, any upregulation of PD-L1 in tumor and immune cells will promote immune escape. PD-L1 expression can be regulated through two different mechanisms: the persistent mechanism is through proliferative oncogenic signals of the cancer cells (such as EGFR, ALK/STAT3, and PI3K-AKT) [116,117]. The non-persistent mechanism is controlled by the inflammatory signals (such as IFN-γ) produced during the immune response process, preventing the body from immune damage caused by infection-induced inflammation [118].

PD-L2 is mainly present in various types of immune cells such as macrophages, bone marrow-derived mast cells, peritoneal B1 lymphocytes [119], intestinal stromal cells [120], and in many solid malignancies, including HNSCC [121]. Structurally, like PD-1 and PD-L1, PD-L2 is also a type I transmembrane glycoprotein, consisting of an extracellular domain containing an immunoglobulin (Ig) variable–-type (IgV), a transmembrane region, and a cytoplasmic tail [6]. PD-L1 and PD-L2 show about 40% of amino acid similarity [122]. PD-L2 shows a higher binding affinity (2–6 folds) to PD-1 than PD-L1. The higher PD-1/PD-L2 binding can be explained by the presence of a tryptophan residue at W110 in PD-L2 [123]. PD-1/PD-L2 interaction interferes with the early T cell receptor (TCR)/CD28 signaling, inhibiting IL-2 production, T cells proliferation, T cells effector functions, and T cells survival. The inhibition of the proliferation and the impairment of effector T cell function lead to adverse effects on anti-tumor immunity [124].

3.1.1. PD-1, PD-L1, and PD-L2 expression in HNC

HNSCC is divided into two major groups based on human papillomavirus (HPV) infection: HPV-positive, classified by p16 protein expression, and HPV-negative [124]. The clinical trials established by Chen and his colleagues determined a direct correlation between the expression level of p16 protein and PD-1/ PD-L1 in HNSCC samples. The same study showed that HNSCC patients with positive PD-1/PD-L1 expression tend to have a better prognosis and lower susceptibility to recurrence, thus indicating a better tumor response to anti-PD-1/PD-L1 drugs [124,125]. Furthermore, several studies correlated PD-L1 expression with HPV positivity [126–128]. On the other hand, Yu et al. showed that the proportion of myeloid-derived suppressor cells (MDSCs) and tumor-associated macrophages (TAMs) were significantly correlated with the expression levels of PD-1 and PD-L1 in human HNSCC tissue samples via the CD47/SIRPα pathway [129]. Other studies demonstrated that IFN-γ upregulated PD-L1 expression in OSCC either directly or through protein kinase D isoform 2 (PKD2) and its downstream targets [130,131]. Furthermore, the expression of PD-L1 in HNSCC was induced by CKLF Like MARVEL Transmembrane Domain Containing 6 (CMTM6), which reduced $CD8^+$ and $CD4^+$ T cell infiltration [132]. In addition, IFN-γ enhances the upregulation of PD-L1 expression on HNSCC through the IFNAR1/STAT1 pathway, thus promoting the cancer cells' immune escape [126].

It has been reported that the PD-1 expression on NK cells in the tumor microenvironment and peripheral blood constitutes an activation phenotype of the NK cells in HNSCC patients. However, this activation status is inhibited once it binds to PD-L1. Accordingly, PD-1 blockade could enhance the NK cell activation and their antibody-dependent NK-mediated cytotoxicity (ADCC), resulting in HNSCC cell lysis [133]. Interestingly, a soluble form of PD-L1 (sPD-L1) was found in the patient's plasma with HNSCC [134]. Several studies demonstrated that sPD-L1 could be a promising prognostic and recurrence-predictive biomarker in HNC [135–137]. Moreover, PD-L1 positive exosomes were narrated to HNSCC activity, grading, lymph node levels,

andsuppressed $CD8^+$ T cell activity, thus acting as a prognostic marker for HNSCC and NPC patients [134,138]. Furthermore, Fu et al. showed that $CD4^+$ TILs and PD-L1 act as prognostic markers for HNSCC in a cohort study of 63 patients. The same study reported that HNSCC patients with high levels of PD-L1 showed unfavorable overall survival and disease-free survival [139].

The degree of PD-L1 expression in HNSCC tissues varies across different studies due to different intratumor heterogeneity, different staining protocols, and inconsistent cut-off values for positivity, among others [140]. Similarly, several studies revealed that PD-L2 expression varied significantly among tumor types [6]. Half of the HNSCC samples showed expression of PD-L2, while it was not seen in any of the renal cell carcinoma samples and was present in a minority of melanoma samples [6]. Yu Qiao et al. reported that PD-L2 was positively stained in 62.7% of HNC tumors, in which 61.4% of patients were found to be PD-L1-negative [141]. It has been reported recently that high expression of PD-L2 was an independent predictor biomarker of poor prognosis and overall survival (OS) in OSCC and HNSCC patients [141,142]. Additionally, PD-L2 tissue expression in OSCC patients could be used as a diagnostic biomarker for malignancy [143]. Elevated expression of PD-L2 was also reported in HPV-positive head and neck squamous cell cancer. This elevated expression is due to the hypo methylation of specific CpG- islands of the promoter region of the PD-L2 gene [144].

3.1.2. Clinical and research-based application of PD-1, PD-L1, and PD-L2 in HNC

The first immunecheckpoint inhibitors approved for HNSCC recurrent/metastatic are nivolumab and pembrolizumab (anti-PD-1) [145, 146]. These drugs act by inhibiting the suppressive signals through the PD-1/PD-L1 axis, thus enhancing the immune response to eradicate HNSCC [147,148]. Recently, PD-L1 was used as a novel diagnostic marker for the prognosis of advanced-stage HNSCC. This study showed a significantly higher expression level of PD-L1 in metastatic HNSCC that could be associated with a poor prognosis [149]. Indeed, the PD-L1 combined positive score is the only accepted biomarker for selecting recurrent/metastatic HNSCC patients for immunotherapy [146]. Despite the relevant expression of PD-1 in $CD8^+$, $CD4^+$, and $FoxP3^+$ TILs in HNSCC [150], and the growing evidence about PD-1-based immune checkpoint therapy that is being tested in HNSCC [146], to date, the role of PD-1 as a potential prognostic and diagnostic marker remains to be elucidated. Table 1 summarizes the recent clinical and randomized controlled trials based on the evaluation of PD-1/ PD-L1 expression as prognostic and diagnostic biomarkers in HNC.

Tumor-associated PD-L1 expression is a predictive marker for response to anti-PD-1 axis targeted therapies. However, PD-L1–negative patients also respond to anti-PD-1 axis targeted therapies [151]. This suggests that PD-1 interactions with PD-L2 could also be involved in predicting patient responses. Recent results of the PD-L2 expression in pembrolizumab-treated patients indicate that the presence or absence of PD-L2 may also play a role in response to PD-1 axis targeted therapies [141]. Clinical response to the anti–PD–1 (pembrolizumab) in recurrent or metastatic head and neck squamous cell carcinoma patients have been partially linked to the blockade of the PD-1/PD-L2 pathway [152]. PD-L2 expression detected on stromal, immune, and tumor cells was associated with a better survival outcome [153]. Interestingly, anti-PD-1 axis targeted therapies show more significant responses in patients positive for both PD-L1 and PD-L2 (27.5%) as compared to those positive for PD-L1 only (11.4%) [154]. Immunotherapies targeting PD-L2 have also been developed to expand the anti-tumor therapeutic possibilities. Small molecules specifically targeting PD-L2, mAbs blocking the PD-1/PD-L2 pathway, and novel PD-L2–based vaccines, alone or in combination with other immune checkpoint blockade agents, are at various stages of development [6].

3.2. TIM-3

TIM-3, also called hepatitis A virus cellular receptor 2 (HAVCR2), was first described in 2002 [155]. TIM-3 is a member of the TIM gene family, which includes TIM-1, TIM-3, and TIM-4, and is located in syntenic chromosomal regions on chromosome 5q33.2 [156,157]. TIM-3 is a type I transmembrane glycoprotein with 302 amino acid residues. It comprises an extracellular N-terminal immunoglobulin variable domain and a mucin domain, followed by a single transmembrane domain and a C-terminal cytoplasmic tail [158,159]. TIM-3 plays different roles in several diseases, such as chronic infections, auto-immune disorders, and various malignancies. The underlying mechanisms of TIM-3 effects have not yet been thoroughlyinvestigated, but it has been shown that specific ligands will interact with TIM-3 to initiate different signal transduction mechanisms. Indeed, four ligands have been identified for TIM-3: carbohydrate-binding protein galectin-9 (Gal-9), phosphatidylserine (PS), high-mobility group protein B1 (HMGB1), and carcinoembryonic antigen cell adhesion molecule 1 (CEACAM-1) [160]. TIM-3 is known as an immune checkpoint molecule involved in regulating of the innate and adaptive immune response [158, 161–164]. In fact, TIM-3 is expressed in different types of immune cells, including T helper 1 (Th1) T cells, cytotoxic T cells, Tregs, DCs, B cells, macrophages, NK cells, and mast cells [158, 162–164]. Interestingly, TIM-3 was also detected on leukemic stem cells but not on normal hematopoietic progenitors [165].

3.2.1. TIM-3 expression in HNC

TIM-3 overexpression was linked to advanced disease and poor prognosis in cancer, where it emerged as a negative regulator of antitumor immunity [166–170]. Therefore, targeting TIM-3 has emerged as a promising immunotherapeutic strategy for both hematological malignancies and solid tumors [156, 171–174]. TIM-3 was initially reported as a negative regulator of T helper 1 (Th1) activity [175,176]. In 2005, Zhu et al. identified the TIM-3 ligand Gal-9 and described the effect of the TIM-3-Gal-9 pathway on Th1 cell function. Indeed, the interaction between these two molecules selectively dampens Th1 immunity by inducing both apoptotic and necrotic cell death, eliminating IFN-γ-producing Th1 cells, and mediating T cell exhaustion and dysfunction [175]. Moreover, Yan et al. showed that the $TIM\text{-}3^+$ Tregs population accumulates in the human tumor tissues in close contact with Gal-9 and suggested that the TIM-3-Gal-9 pathway promotes the suppressive tumor microenvironment in human cancers [177]. Huang et al. demonstrated that the interaction between CEACAM1 and TIM-3, both expressed on activated T cells, is associated with TIM-3-induced immune tolerance and T cell exhaustion in cancer and chronic infections [178]. In colorectal cancer patients, the co-expression of CEACAM1 and TIM-3 was linked to T cell exhaustion, and the blockade of both pathways couldreinvigorate the anti-tumor immune response [178,179]. Therefore, CEACAM1 plays an important role in mediating TIM-3-T cell's suppressive function [157]. Additionally, it has been demonstrated that the expression of CEACAM1 in HNSCC was increased in poorly differentiated tumors compared to well-differentiated ones where the expression of membranous CEACAM1 could function as a tumor suppressor and correlates with poor prognosis [180].

TIM-3 ligand Phosphatidylserine (PtdSer) is expressed in apoptotic cells. The interaction between the two molecules will trigger a signal for macrophage recognition, promoting apoptotic cell phagocytosis [157]. The clearance of dying cells will promote cross-antigen presentation, which will play a crucial role in the regulation of immune cell activities and pathogenic pathways [157,181,182].

It has been demonstrated that TIM-3 expression on tumor-infiltrating DCs is associated with suppression of the innate immune response. Interestingly, it has been shown that TIM-3 expression was higher on tumor microenvironment DCs compared to normal tissue DCs. Therefore, in the tumor microenvironment, TIM-3 binding to HMGB1 will prevent the HMGB1-mediated activation of nucleic acids released by

Table 1
Ongoing clinical trials testing the effectiveness of anti-PD-1/anti-PD-L1 antibodies alone or in combination with various immune checkpoint inhibitors and/or other therapies such as chemotherapy, radiotherapy, and surgery (2022–2023).

Clinical trial identifier	Status	Phase	Interventions	Target tested	Disease/Tumor type	Primary outcome measures	Enrollment
NCT03143153	Active, not recruiting	III	Nivolumab, Ipilimumab, Cisplatin, Fluorouacil	PD-L1	Advanced esophageal squamous-cell carcinoma	OS in Participants with Tumor Cell PD-L1. PFS as Assessed by BICR in Participants with Tumor Cell PD-L1.	970
NCT03000257	Completed	I	Venetoclax, Budigalimab, Rovalpituzumab Tesirine	PD-1, PD-L1	Advanced Solid Tumors, Recurrent/ metastatic HNSCC	RPTD, MTD, Cmax, Tmax, AUCt and t1/2 of Budigalimab. RP2D and Schedule for Budigalimab and Rovalpituzumab Tesirine Combination as well as Budigalimab and Venetoclax Combination. Cmax, AUC (0-24), Tmax of Venetoclax. Number of Participants with Adverse Events.	182
NCT03341936	Active, not recruiting	II	Nivolumab, Lirilumab	PD-1, KIR	Squamous Cell Carcinoma of the Head and Neck	Year Disease-Free Survival Percentage.	29
NCT03238365	Completed	I	Nivolumab, Tadalafil, Surgery	PD-1, PDE5 inhibitor	Squamous Cell Carcinoma of the Head and Neck	Change in immune cell polarization (Th1/Th2; M1/M2) in peripheral blood and tumor specimens.	50
NCT03019003	Active, not recruiting	I/II	Decitabine, Durvalumab	PD-1, PD-L1, CTLA-4	Recurrent and/or metastatic squamous cell carcinoma of the head and neck	BED and PFS of oral decitabine, changes in HLA Class I and tumor antigen expression.	13
NCT04338399	Recruiting	III	Buparlisib & Paclitaxel	PD-1, PD-L1	Recurrent and/or metastatic squamous cell carcinoma of the head and neck	OS will be measured from time of randomization until death from any cause.	483
NCT03946358	Active, not recruiting	II	Atezolizumab, UCPVax Vaccine	PD-1, PD-L1	Squamous Cell Carcinoma of the Head and Neck Anal-Canal Cancer Cervical Cancer	OR rate at 4 months	47
NCT04601402	Recruiting	I	GEN-001, Avelumab	PD-1, PD-L1	Solid Tumor Non Small Cell Lung Cancer Squamous Cell Carcinoma of Head and Neck Urothelial Carcinoma	Incidence of adverse events, laboratory abnormalities, DLT and OR	93
NCT02358031	Active, not recruiting	III	Cisplatin, Carboplatin, 5-FU, Cetuximab	PD-L1	Recurrent and/or metastatic squamous cell carcinoma of the head and neck	PFS, BICR and OS in All Participants	882
NCT03347838	Recruiting	II	Nivolumab	PD-1	Bronchial dysplasia Tobacco smoking Non-Small cell lung cancer Head and neck cancer	Improvement in endobronchial histology	42
NCT02644369	Active, not recruiting	II	Pembrolizumab	PD-L1	Squamous Cell carcinoma of head and neck, Triple negative breast cancer, Epithelial ovarian cancer Malignant melanoma, Advanced solid tumors	Changes in genomic and immune biomarkers that will be measured in blood and tumor pre-treatment, on-treatment and at progression	100
NCT03082534	Active, not recruiting	II	Pembrolizumab, Cetuximab	PD-1, PD-L1	Lip SCC, Oral cavity cancer Oropharynx cancer, Larynx cancer Hypopharynx cancer, Nasopharynx cancer, Sinonasal carcinoma, Cutaneous squamous cell carcinoma, Head and neck neoplasm, Head and neck squamous cell carcinoma	Overall Response Rate	78
NCT03132038	Completed	II	Nivolumab	PD-1	Salivary gland carcinoma Metastatic cancer Recurrent cancer	The proportion of patients with CR or PR or SD after 6 months of treatment.	98
NCT03765918	Recruiting	III	Pembrolizumab, Radiation, Cisplatin	PD-1, PD-L1	Head and neck neoplasms	mPR and EFS	704
NCT03040999	Active, not recruiting	III	Pembrolizumab, Cisplatin, Radiation	PD-1, PD-L1	Head and neck neoplasms	EFS	804
NCT05760196	Recruiting	II	GM-CSF	PD-1, PD-L1	Recurrent metastatic head and neck tumors	Objective tumor response, including CR and PR	56
NCT03881488	Recruiting	I	CTX-471, pembrolizumab	PD-1, PD-L1	Locally advanced solid tumor Metastatic cancer Non-small cell lung cancer Small cell lung cancer	Number of participants with DLTs, TEAEs, and/or changes in clinical laboratory abnormalities	157

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Table 1 (*continued*)

Clinical trial identifier	Status	Phase	Interventions	Target tested	Disease/Tumor type	Primary outcome measures	Enrollment
					Mesothelioma melanoma Head and neck cancer		
NCT05431270	Recruiting	I	PT199 (anti-CD73 mAb), Anti-**PD-1** mAb	PD-1, CD73	Advanced solid tumor, Metastatic cancer, Refractory cancer Non-small cell lung cancer Pancreatic adenocarcinoma, Pancreatic neoplasms, Gastric adenocarcinoma, Gastric cancer Esophageal cancer, Hepatic carcinoma Ovarian cancer, Head and neck squamous cell carcinoma Colorectal cancer, Colon adenocarcinoma, Breast adenocarcinoma, Triple negative breast cancer, Thyroid cancer Lung cancer	MTD	41
NCT05777824	Recruiting	II	anti-PD-1 or PD-L1 antibody	PD-1, PD-L1	Head and neck cancer	Disease-free survival	84
NCT04795713	Recruiting	I	MT-6402	PD-L1	Advanced solid tumor Non-small cell lung cancer Squamous cell carcinoma of head and neck	Estimate MTD, RP2D and OR rate	138
NCT03162224	Completed	I/II	MEDI0457, CELLECTRA®5 P device, Durvalumab	PD-1, PD-L1, CD80	Head and neck cancer Human papilloma virus	Number of participants with TEAEs, TESAEs, abnormal electrocardiogram and abnormal laboratory parameters	35
NCT03952065	Recruiting	III	PD-1/PD-L1 inhibitor	PD-1, PD-L1	Head and neck cancer	Overall survival	100
NCT02955290	Recruiting	I/II	Nivolumab, Pembrolizumab, Recombinant Human EGF-rP64K/Montanide ISA 51 Vaccine	PD-1, PD-L1	Advanced head and neck squamous cell carcinoma, Lung non-small cell carcinoma, Metastatic lung non-small cell carcinoma, PD-L1 positive Recurrent head and neck squamous cell carcinoma Stage III cutaneous squamous cell carcinoma of the head and neck AJCC v8 Stage III lung cancer AJCC v8 Stage IIIA lung cancer AJCC v8 Stage IIIB lung cancer AJCC v8 Stage IIIC lung cancer AJCC v8 Stage IV cutaneous squamous cell carcinoma of the head and neck AJCC v8 Stage IV lung cancer AJCC v8 Stage IVAlung cancer AJCC v8 Stage IVB lung cancer AJCC v8 Unresectable lung non-small cell carcinoma	DLT and OS	193
NCT03818061	Active, not recruiting	II	Atezolizumab, Bevacizumab	PD-L1, VEGF-A	Head and neck neoplasms	OS rate	33
NCT05287113	Recruiting	II	Retifanlimab, INCAGN02385, INCAGN02390	PD-1, PD-L1	Recurrent and/or metastatic squamous cell carcinoma of the head and neck	PFS	162
NCT05187338,	Recruiting	I/II	Ipilimumab, Pembrolizumab, Durvalumab	PD-1, PD-L1, CTLA-4	Lung cancer, Liver cancer, Colorectal cancer, Pancreas cancer Ovary cancer, Head and neck cancer Breast cancer, Gastric cancer Cervical cancer, Esophageal cancer Sarcoma	PFS, Disease control rate (OR+ SDR) and DOR	100
NCT04096638	Recruiting	I	SB 11285, Atezolizumab	PD-L1	Melanoma Head and neck squamous cell carcinoma Solid tumor	MTD, RP2D and incidence of adverse events	146
NCT03212404	Recruiting	I	CK-301 (cosibelimab)	PD-L1, PD-1	Lung neoplasms, Carcinoma, non-small-cell lung, Head and neck cancer Melanoma, Merkel cell carcinoma Renal cell carcinoma, Urothelial carcinoma, Classical hodgkin lymphoma, Cutaneous squamous cell carcinoma, Non hodgkin lymphoma Endometrial cancer	DLT, OR rate and TEAEs	500

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Table 1 (*continued*)

Clinical trial identifier	Status	Phase	Interventions	Target tested	Disease/Tumor type	Primary outcome measures	Enrollment
NCT05144698	Recruiting	I/II	RAPA-201 Rapamycin Resistant T Cells, Chemotherapy Prior to RAPA-201 Therapy	PD-1, PD-L1, CTLA4, TIM-3, LAG3, LAIR1	Solid tumor, Breast cancer Small cell and non-small cell lung cancer, Triple negative breast cancer, Gastric cancer Esophageal adenocarcinoma Gastric junction adenocarcinoma Esophageal squamous cell carcinoma Head and neck cancers, Squamous cell carcinoma of oral cavity Squamous cell carcinoma of larynx Squamous cell carcinoma of nasopharynx, Bladder cancer Malignant melanoma	Safety of RAPA-201 Cell Therapy	22
NCT04633278	Active, not recruiting	II	CMP-001, Pembrolizumab	PD-1, PD-L1,	Squamous cell carcinoma of the head and neck	OR rate	24
NCT04128696	Active, not recruiting	II/III	Feladilimab, Pembrolizumab	PD-1, PD-L1,	Recurrent and/or metastatic squamous cell carcinoma of the head and neck	OS and PRS rate	315
NCT05838729	Recruiting	I/II	RiMO-301	PD-1	Head neck cancer Intratumoral injection	DLT and OR rate	16

PFS, Progression-free Survival; OS, Overall Survival; BICR, Blinded Independent Central Review; RP2D, Recommended Phase 2 Dose; MTD, Maximum tolerated dose; Cmax, Maximum Observed Serum Concentration; Tmax, Time to Cmax; AUCt, Area Under the Serum Concentration Time Curve from Time 0 to Last Measurable Concentration; AUC (0-24), Area Under the Serum Concentration Time Curve from Time 0 to 24 Hours Post-dose; t1/2, Terminal Half-life; PDE-5, phosphodiesterase-5; KIR, killer-cell immunoglobulin-like receptors; BED, Biologically Effective Dose; DLT, dose-limiting toxicity; OR, objective response; CR, complete response; PR, partial response; SD, stable disease; mPR, major pathological response; EFS, Event-free Survival; DLTs, dose-limiting toxicities; TEAEs, treatment-emergent adverse events; TESAEs, treatment-emergent serious adverse events; SDR, steady disease rate; DOR, Duration of remission;

tumor cells, thereby restraining these nucleic acids from entering endosomes to stimulate the innate immune response [157,183].

3.2.2. Clinical and research-based application of TIM-3 in HNC

In a cohort of HNSCC patients, TIM-3 expression was higher on intratumoral Tregs compared to circulating Tregs, indicating a more suppressive phenotype of TILs Tregs [184]. The same study showed that TIM-3 expression was linked to $CD8^+$ T cells and MDSCs and reported that TIM-3 expression in human HNSCC correlated with recurrent disease and was upregulated in patients who received radiotherapy or chemotherapy. Further, the blockade of TIM-3 in an HNSCC mouse model restored the immune response, decreased the immunosuppressive MDSCs, and inhibited tumor growth [185]. Another study showed that TIM-3 was highly expressed on intratumoral and/or stromal TILs in HNSCC cells in 91.3% of cases [180]. Furthermore, the expression of TIM-3 + TILs correlated with tumor size, lymph node metastasis, and TNM stage. The same study reported that HNSCC patients with low expression $TIM\text{-}3^+$ TILs had significantly improved survival and prognosis compared to patients with high $TIM\text{-}3^+$ TILs expression [180].

Several ongoing pre-clinical and clinical trials evaluate the efficacy of various TIM-3 antibodies as monotherapy or in combination with other ICIs in various types of cancer [171,186]. Preliminary clinical data have been revealed for three major anti-TIM-3 agents: TSR-022 (Tesaro), LY3321367 (Eli Lily and Company), and sabatolimab or MBG453 (Novartis Pharmaceuticals). However, the efficacy of these drugs has not been tested in HNC. Currently, two anti-TIM-3 mAbs are being tested in HNC (INCAGN02390 and INCAGN02385). Phase I clinical trial testing the safety, tolerability, and preliminary efficacy of INCAGN02390 in participants with selected advanced malignancies has been completed (NCT03652077). Another phase II clinical trial is still in progress to evaluate the safety and efficacy of retifanlimab plus INCAGN02385 and retifanlimab plus INCAGN02385 and INCAGN02390 compared with retifanlimab alone as first-line treatment in PD-L1-positive and systemic therapy-naive recurrent/metastatic HNSCC (NCT05287113).

To this end, TIM-3 is emerging as an important regulator of the anti-tumor immune response, and targeting this immune checkpoint inhibitor is a promising immunotherapeutic strategy to enhance the clinical response and overcome resistance to standard immunotherapy and chemotherapy in patients with both solid tumors and hematological malignancies. However, current clinical data is still scarce, and the efficacy of TIM-3 blocking agents needs to be validated with more robust clinical studies.

3.3. CTLA-4

CTLA-4, one of the most important immunosuppressive proteins targeted in clinical settings, is mainly expressed by T cells [187]. It is also present on Tregs and produces the immunosuppressive molecule transforming growth factor-β (TGF-β) when activated by CD28 [187]. CTLA-4 binds to its ligands CD80 and CD86 on the APCs, leading to repression of T cell proliferation and activation by inhibiting signaling through the TCR [188]. Generally, CTLA-4 plays a role in stimulating the immune response effectively while minimizing damage to healthy tissues [189]. However, in cancer, the TGF-β secreted by cancer cells can promote the expression of CTLA-4, resulting in T cell exhaustion and immune escape [189]. Therefore, antibodies targeting CTLA-4 could be used as an immune modulatory strategy in various cancer types, aiming to hinder the suppressive impact of CTLA-4 on T cells.

3.3.1. CTLA-4 expression and its role in the diagnosis and prognosis of HNC

It has been demonstrated that laryngeal squamous cell carcinoma patients have higher intracellular and surface CTLA-4 expression in $CD8^+$ T cells compared to control subjects [190]. In fact, Koike et al. showed that OSCC patients exhibiting a low presence of $CTLA\text{-}4^+$ cells at the invasive front of the tumor had better outcomes in terms of recurrence-free survival and metastasis-free survival [191]. Another study showed that NPC patients with lower tumor CTLA-4 expression displayed higher 3-year OS, failure-free survival, and distant failure-free survival rates compared to their counterparts with high tumor CTLA-4 expression [192]. A multicolor flow cytometry characterization of OSCC patients' tumor samples showed that $CTLA\text{-}4^+$ and $PD\text{-}1^+$ Treg accumulation in tumor-draining lymph nodes (TDLNs) was associated with lymph node involvement, indicating their potential role in disease spread. This finding suggests that the heightened infiltration of Tregs in TDLNs may contribute to the development of an immune-suppressed environment that promotes the progression of cancer [193]. Another study demonstrated that the ratio of $CD8^+$/CTLA4 could be used as a

clinical prognostic indicator for HNSCC [194]. Furthermore, soluble CTLA-4 could serve as a biomarker for predicting disease progression and determining the appropriate stratification of patients for targeted therapies in HNC [195]. These findings indicate that targeting CTLA-4 could serve as a promising and efficient therapeutic strategy for HNC patients.

3.3.2. Clinical and research-based application of CTLA-4 in HNC

Pre-clinical studies demonstrated that CTLA-4 mAbs trigger tumor regression and induce durable anti-tumor immunity in animal models [196]. Currently, there are no approved immunotherapies targeting CTLA-4 for the treatment of HNSCC. Nevertheless, numerous clinical trials are underway to assess the potential of combining anti-CTLA-4 antibodies with other immunotherapies or the standard of care treatments for HNSCC. The hypothesis being tested is that combining these therapies may lead to improved clinical outcomes, a concept that has shown promising results in other cancer types. The ongoing clinical trials testing the effectiveness of combining anti-CTLA-4 antibodies with various ICIs and/or additional treatments, such as chemoradiotherapy and radiotherapy, are summarized in Table 2.

3.4. LAG-3

LAG-3 is a type I transmembrane protein that belongs to the immunoglobulin superfamily members and binds to MHC class II molecules [197]. It is expressed on the surface of activated T cells as well as DC, NK, and B cells [198,199]. The interaction between LAG-3 and MHC-II on APC blocks the interaction between the T cell receptor and MHC-II, leading to reduced cytokine and granzyme production and encouraging Tregs differentiation [197]. LAG-3 plays an important role in infection, auto-immune disease, and cancer [200]. Importantly, LAG-3 is involved in the immune escape mechanism of tumors and plays an immunosuppressive effect by maintaining immune homeostasis, which is expressed on various types of lymphocytes by cooperation with other immune checkpoint molecules, especially with PD-1 [201]. Deng et al. found that LAG-3 was highly expressed on TILs and correlated with poor prognosis in human primary HNSCC patients with negative lymph node status [202]. Using the HNSCC mouse model, tumor growth was delayed by LAG-3 inhibitors (along-3) [202]. Recently, Botticelli et al. showed that increased levels of soluble LAG-3 (s-LAG-3) were associated with poor prognosis in HNSCC patients with significantly shorter progression-free survival (PFS) and OS regardless of disease stage and treatment. [203]. Thus, LAG-3 could be an excellent prognostic and predictive biomarker for HNC. Currently, five types of LAG-3 inhibitors are being tested in clinical trials alone or combined with ICIs in HNC patients (Table 3).

3.5. IDO

IDO is an intracellular cytosolic enzyme involved in the tryptophan degradation to kynurenine [204]. Kynurenine is considered an immunosuppressive metabolite in different malignancies [205]. The accumulation of kynurenine and its downstream derivative metabolites in the tumor micro-environment triggers the activation and the recruitment of immunosuppressed immune cells such as Tregs, MDSCs, and M2-like macrophages, in addition to the inhibition of the effector T cell activity [206]. Therefore, the IDO enzymes play an important role in immune escape and inflammatory immune responses [207,208]. A meta-analysis studied the prognostic value of IDO1 checkpoint molecules, including 52 studies with a total of 7127 patients. The results indicated that higher IDO expression predicted a poorer prognosis in HNC patients [209]. Similarly, other studies also confirmed that high IDO expression was correlated with a poor prognosis in patients with breast and melanoma cancer [210,211]. Two IDO enzymes have been described in the literature: IDO1 and IDO2. IDO1 has been studied more but both convert tryptophan to kynurenine with different activity rates [212]. Although its expression is restricted to some normal tissues, the IDO1 expression also has been detected in malignant cells [213,214]. Interestingly, it has been reported that IDO1 expression could also be induced in the intratumoral cells, including DCs, macrophages, endothelial cells, cancer-associated fibroblasts, mesenchymal stem cells, and cancer cells via different inflammatory cytokines such as IFN-γ, IL-6, tumor necrosis factor-α (TNF-α) and IL-32 [215–223].

3.5.1. IDO1 expression and its role in the diagnosis and prognosis of HNC

Economopoulou et al. recently demonstrated that post-treatment IDO1 expression in circulating tumor cells correlated with a poor prognosis and OS in HNSCC treated with cisplatin chemoradiation [224]. Another study showed that the elevated expression of IDO1 in tumor-infiltrating immune cells, especially macrophages, is an indicator of the advanced tumor stage of OSCC and reduced PFS [225]. The same study observed a higher expression of IDO1 in peripheral blood mononuclear cells (PBMCs) of OSCC metastatic patients compared to healthy controls [225].

3.5.2. Clinical and research-based application of IDO1 in HNC

The exact mechanism of IDO-driven immune modulation in HNC is poorly understood. Therefore, more pre-clinical and clinical studies are needed to explore the biology and immune-regulatory role of IDO1 and IDO2 and their expression modulation through HNC treatment in order to achieve better prognosis and treatment response. The combination of IDO1 inhibitors (BMS-986205, IO102-IO103, and epacadostat) with PD-1 inhibitors (Pembrolizumab or nivolumab) is currently being tested for HNC patients' treatment. These phase II/III clinical trials are registered under the following numbers (NCT03854032, NCT05280314, NCT03358472).

3.6. BTLA

BTLA is an important co-inhibitory receptor that is highly expressed on naïve $CD4^+$ and T $CD8^+$ T cells, resting Vγ9Vδ2 cells, and type 1 conventional DC (cDC1), which play an important role in Tregs induction [226]. The BTLA ligand, HVEM, is an immunomodulatory receptor marker that can act either as a proinflammatory or inhibitory maker. HVEM is also expressed in mesenchymal, epithelial, and immune cells, including resting T and B cells, NK cells, Tregs, monocytes, and DCs [227]. HVEM overexpression was reported in different malignancies [226]. BTLA signal transduction leads to the repression of T cell proliferation and function [228]. It has been reported that the depletion of BTLA expression in T cells increased TCR-induced proliferation compared to their counterpart [228].

The overexpression of BTLA on tumor antigen (TA) specific $CD8^+$ T cells and its ligand HVEM on cancer cells is a defense mechanism developed by cancer cells to evade immune response [229]. Studies have revealed that cancer cells evade the immune system through the inhibitory pathway mediated by BTLA-HVEM interaction [229]. Recently, three BTLA gene variants were identified as promising biomarkers for OSCC early diagnosis and treatment response [230,231]. BTLA and HVEM DNA methylation profiles have been studied in HNSCC. Vogt et al. found that the methylation pattern of BTLA is lower in HNC. mRNA levels for BTLA were higher and positively associated with better survival [232]. Interestingly, Yu et al. reported that BTLA expression positively correlated with PD-L1 expression in OSCC [233]. The same study demonstrated that high expression of BTLA predicted a poor prognosis in OSCC [233]. Moreover, another study revealed that circulating soluble BTLA levels significantly correlated with the frequency of $CD3^+$ $CD8^+$ $BTLA^+$ T cells in peripheral blood, therefore promoting it as a non-invasive biomarker of ICIs therapy outcome prediction and patient stratification in solid malignancies [234]. Inhibitors against BTLA are under development as a potential target therapy for HNSCC. The safety and efficacy of a combination therapy of two monoclonal antibodies targeting BTLA and PD-1 is currently being

Table 2
Ongoing clinical trials testing the effectiveness of combining anti-CTLA-4 antibodies with various immune checkpoint inhibitors and/or other therapies such as chemotherapy, radiotherapy, and surgery.

Clinical trial identifier	Status	Phase	Interventions	Target tested	Disease/Tumor type	Primary outcome measures	Enrollment
NCT04080804	Recruiting	II	Nivolumab, Relatlimab, Ipilimumab	PD-1, LAG3, CTLA-4	Squamous Cell Carcinoma	Adverse events, Radiographic response, Levels of TIL and PBL, Effector CD4 and CD8 Tumor mutational burden, Gene expression signature, Single-cell RNAseq pathways	60
NCT02551159	Completed	III	Durvalumab, Tremelimumab, Cetuximab, 5-fluorouracil, Cisplatin, Carboplatin	PD-L1, CTLA-4	Squamous Cell Carcinoma of the Head and Neck	OR, PFS, ORR, DOR, Percentage of patients alive	823
NCT03518606	Active, not recruiting	I/II	Durvalumab, Tremelimumab, metronomic Vinorelbine	PD-L1, CTLA-4	Advanced Solid Tumors,Breast Cancer,Head and Neck Cancer, Cervix Cancer,Prostate Cancer,	Maximum Tolerated Dose, phase II recommended dose, CBR-24week	150
NCT05187338	Recruiting	I/II	Ipilimumab, Pembrolizumab, Durvalumab	CTLA-4, PD-1, PD-L1	Lung Cancer, Liver Cancer, Colorectal Cancer, Pancreas Cancer, Ovary Cancer, Head and Neck Cancer, Breast Cancer, Gastric Cancer, Cervical Cancer, Esophageal Cancer, Sarcoma	Safety, PFS, DCR, DOR	100
NCT03058289	Completed	I/II	INT230-6, Ipilimumab, Pembrolizumab	CTLA-4, PD-1	Breast Cancer, Head and Neck Cancer, Squamous Cell Carcinoma, Lymphoma, Pancreatic Cancer, Liver Cancer, Colon Cancer, Lung Cancer, Bile Duct Cancer, Chordoma of Sacrum Sarcoma	Adverse events, Efficacy, Pharmacokinetic parameter Peak Plasma of INT230-6 components, key pharmacokinetic parameter of INT230-6 components, Biomarkers, OR	110
NCT04290546	Recruiting	I	Interleukin-15 superagonist, CIML NK cell Infusion, Ipilimumab, Cetuximab	CTLA-4	Recurrent Head and Neck Squamous Cell Carcinoma	Rate of dose-limiting toxicity, ORR, DCR, PFS, OS	12
NCT03690986	Recruiting	I	VX15/2503, Ipilimumab, Nivolumab	PD-1, CTLA-4	Squamous Cell Carcinoma of the Head and Neck	Adverse events, Changes in immune profile in the tumor microenvironment, Change in circulating percentage of immune suppressor subsets in peripheral blood, Phenotypic shifts in T lymphocyte subsets in peripheral blood	50
NCT01935921	Active, not recruiting	I	Cetuximab, Radiation Therapy, Ipilimumab	CTLA-4	Stage III Hypopharyngeal Squamous Cell Carcinoma, Stage III Laryngeal Squamous Cell Carcinoma, Stage III Oropharyngeal Squamous Cell Carcinoma, Stage IVA Hypopharyngeal Squamous Cell Carcinoma, Stage IVA Laryngeal Squamous Cell Carcinoma, Stage IVA Oropharyngeal Squamous Cell Carcinoma, Stage IVB Hypopharyngeal Squamous Cell Carcinoma, Stage IVB Laryngeal Squamous Cell Carcinoma, Stage IVB Oropharyngeal Squamous Cell Carcinoma	The proportion of dose-limiting toxicities, Clinical response, T cell phenotypes, T regulatory and Myeloid-derived suppressor cell counts, HPV status, Serum factors and tumor infiltrates	19
NCT03755739	Recruiting	II/III	Pembrolizumab, Ipilimumab, chemotherapy	PD-1, CTLA-4	Hepatocarcinoma, Lung Cancer, Melanoma, Renal Cancer, Head and Neck Cancer, Pancreas Cancer, Ovarian Cancer, Colo-rectal Cancer, Cervical Cancer, Breast Cancer	OS, CR, PFS, DOR, DCR, COD	200
NCT03292250	Completed	II	BYL719, Poziotinib, Nintedanib, Abemaciclib, Durvalumab, Tremelimumab	PD-L1, CTLA-4	Head and Neck Squamous Cell carcinoma Head and Neck Neoplasms	DCR, RR, ORR, PFS, OS, TTP, Quality of life, Duration of response, Toxicity, Biomarkers	180
NCT03162731	Completed	I	Nivolumab, Ipilimumab, Radiation	PD-1, CTLA-4	Stage IVA-B Head and Neck Cancer: Larynx, Lip, Oral Cavity and Pharynx	Safety, PFS, OR, Biomarkers	24
NCT03212469	Active, not recruiting	I/II	Durvalumab, Tremelimumab, Radiation	PD-L1, CTLA-4	Head and Neck Squamous Cell Carcinoma, Lung Cancer, Oesophageal Cancer	Dose Limiting Toxicity	54
NCT04954599	Recruiting	I/II	CP-506, Carboplatin, Immune checkpoint inhibitors	PD-1, PD-L1, CTLA-4	Solid tumor including head and neck cancer	Adverse events, CP-506 levels in plasma, Minimal biological effective dose, Change in tumor size, ORR	126

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Table 2 (*continued*)

Clinical trial identifier	Status	Phase	Interventions	Target tested	Disease/Tumor type	Primary outcome measures	Enrollment
NCT02643303	Completed	I/II	Durvalumab, Tremelimumab, Poly-ICLC	PD-L1, CTLA-4	Head and Neck Squamous Cell Carcinoma, Breast Cancer, Sarcoma, Merkel Cell Carcinoma, Cutaneous T-Cell Lymphoma, Melanoma, Renal Cancer, Bladder Cancer, Prostate Cancer, Testicular Cancer, Solid Tumor	Adverse events, Immune-related Response Evaluation, PFS, ODC, OS, OR	58
NCT02919683	Active, not recruiting	II	Nivolumab, Ipilimumab, Surgery	PD-1, CTLA-4	Head and Neck Cancer	Percentage of participants with a volumetric response rate to treatment, Safety and tolerability of protocol treatment, Percentage of participants demonstrating objective response, Percentage of participants demonstrating pathological Response, PFS, OS	30
NCT03700905	Active, not recruiting	III	Surgery, radio/chemo therapy, Nivolumab, Ipilimumab	PD-1, CTLA-4	Head and Neck Cancer	DFS, LRC, DMFS, OS, Acute toxicity and late morbidity, QOL, Survival depending on PD-L1 status	276
NCT02741570	Completed	III	Nivolumab, Ipilimumab, Cetuximab/Erbitux, Cisplatin/Platinol, Carboplatin/Paraplatin Fluorouracil/Adrucil	PD-1, CTLA-4	Head and Neck Cancer	OS, PFS, ORR, DOR	947
NCT02823574	Completed	II	Nivolumab, Ipilimumab	PD-1, CTLA-4	Head and Neck Cancer	ORR, DOR, TTR, PFS, OS	425
NCT01986426	Completed	I	LTX-315, Ipilimumab, Pembrolizumab	PD-1, CTLA-4	Cancer Melanoma, Breast Cancer, Head and Neck Cancer, Lymphoma, Triple-Negative Breast Cancer	Dose-limiting toxicity, Anti-tumor activity, Complete response and partial response rate, PFS, OR, DCR, Pharmacokinetic profile of LTX-315	80
NCT03003637	Completed	I/II	Nivolumab, Ipilimumab	PD-1, CTLA-4	Head and Neck Neoplasms	The number of patients that will not endure a delay in surgery, Tumor response to neoadjuvant, The potential impact of local tumor hypoxia on tumor T-cell abundance and capacity before and after neo-adjuvant immunotherapy	33
NCT03752398	Recruiting	I	XmAb®23104, Ipilimumab	PD-1 ICOS CTLA-4	Melanoma, Cervical Carcinoma, Pancreatic Carcinoma, Breast Carcinoma, Hepatocellular Carcinoma, Urothelial Carcinoma, Squamous Cell Carcinoma of the Head and Neck, Nasopharyngeal Carcinoma, Renal Cell Carcinoma, Colorectal Carcinoma, Endometrial Carcinoma, Non-small Cell Lung Carcinoma, Small Cell Lung Cancer, Gastric or Gastroesophageal Junction, Adenocarcinoma, Advanced Solid Tumors, Undifferentiated Pleomorphic Sarcoma	Adverse events	300
NCT03098160	Unknown	I	Evofosfamide, Ipilimumab	CTLA-4	Pancreatic Cancer, Melanoma, Squamous Cell Carcinoma of the Head and Neck, Prostate Cancer	Recommended phase 2 dose, Maximum tolerated dose, Adverse events, Change from tumor diameter baseline	69
NCT03645928	Recruiting	II	Lifileucel, Pembrolizumab, Ipilimumab, Nivolumab	PD-1, CTLA-4	Metastatic Melanoma, Squamous Cell Carcinoma of the Head and Neck, Non-small Cell Lung Cancer	Objective Response Rate, Safety profile, Complete Response Rate, Duration of Response, DCR, PFS, OS	178
NCT04074967	Recruiting	I/II	ARRY-614, Nivolumab, Ipilimumab	PD-1, CTLA-4	Renal Cell Carcinoma, Melanoma, Solid Tumor, Non-small Cell Lung Cancer, Head and Neck Squamous Cell Carcinoma	Adverse events, OS, PRS, Duration of response, Immune-related response, Pharmacokinetic profile of ARRY-614, Pharmacodynamic profile of ARRY-614	144
NCT05176483	Recruiting	I	XL092, Nivolumab, Ipilimumab, Relatlimab	PD-1, CTLA-4, LAG-3	Renal Cell Carcinoma, Metastatic Castration-resistant, Prostate Cancer, Urothelial Carcinoma, Solid Tumor, Hepatocellular Carcinoma, Non-small Cell, Lung Cancer, Colorectal Cancer, Head and Neck Squamous Cell Carcinoma	Adverse events, ORR, PFS, OS	1078
NCT03737968	Active, not recruiting	II	Durvalumab, Tremelimumab	PD-L1, CTLA-4	Stage II-IVB Operable HNSCC: Oral Cavity, Hypopharynx, Oropharynx Larynx	locoregional relapse rate, Distant metastatic rate, Distant metastases free survival, locoregional control, Progression-free survival	48

(*continued on next page*)

Table 2 (*continued*)

Clinical trial identifier	Status	Phase	Interventions	Target tested	Disease/Tumor type	Primary outcome measures	Enrollment
NCT02369874	Completed	III	Durvalumab, Tremelimumab	PD-L1, CTLA-4	Recurrent or Metastatic PD-L1-positive or -Negative Squamous Cell Carcinoma of the Head and Neck	OS, ORR, DOR, DCR, Percentage of participants alive, Progression-free percentage of participants alive, Number of participants reporting one or more adverse events	736
NCT02319044	Completed	II	Durvalumab, Tremelimumab	PD-L1, CTLA-4	Recurrent/Metastatic Squamous Cell Carcinoma of Head & Neck	Objective response rate, Time to response, DCR, PFS, OS, Duration of response, Quality of life	267
NCT02499328	Active, not recruiting	I/II	AZD9150, Durvalumab, AZD5069, Tremelimumab	PD-L1, CTLA-4	Advanced Solid Tumors & Metastatic Squamous Cell Carcinoma of the Head and Neck	Adverse events, ORR, DCR, Duration of overall response, OR, PFS, Immunogenicity, Antitumor activity, Evaluation of AZD9150 pharmacodynamics and PD-L1 expression	340

DCR, disease control rate; DFS, disease-free survival; DOR, duration of response; DRR, durable response rate; ICI, immune checkpoint inhibitors; ORR, objective response rate; OS, overall survival; PBLs, Peripheral Blood Lymphocytes; PFS, progression-free survival; QOL, quality of life; TIL, Tumor Infiltrating Lymphocyte.

Table 3
Ongoing clinical trials testing the effectiveness of combining anti-LAG-3 antibodies with various immune checkpoint inhibitors.

Clinical trial identifier	Status	Phase	Interventions	Target tested	Disease/Tumor type	Primary outcome measures	Enrollment
NCT04080804	Recruiting	II	Nivolumab, Relatlimab, Ipilimumab	PD-1, LAG3, CTLA-4	Head and Neck Squamous Cell Carcinoma	Adverse events, Radiographic response, Levels of TIL and PBL, Effector CD4 and CD8 Tumor mutational burden, Gene expression signature, Single-cell RNAseq pathways	60
NCT05287113	Recruiting	II	Retifanlimab INCAGN02385 INCAGN02390	PD-1, LAG3, TIM-3	Recurrent/metastatic squamous cell carcinoma of the head and neck	Adverse events, PFS, ORR, DOR, DCR, OR	162
NCT03625323	Active, not recruiting	II	LAG-3 Fusion Protein Eftilagimod Alpha (MP321), Pembrolizumab	PD-1, LAG3	Non-small cell lung carcinoma Head and neck carcinoma patients	Adverse events, Time to response, Duration of response, Response rate, DCR, PFS, OS, Occurrence of eftilagimod alpha-specific antibodies, Plasma concentration-time profile of eftilagimod alpha	189
NCT03440437	Recruiting	I/II	FS118 (anti-LAG-3/PD-L1 Bispecific Antibody)	PD-L1, LAG3	Head and Neck Squamous Cell Carcinoma	The safety, tolerability, pharmacokinetics, and activity of FS118	80
NCT03849469	Completed	I	XmAb22841 (anti-CTLA-4/LAG-3 bispecific antibody) Pembrolizumab	PD-1, LAG3, CTLA-4	Melanoma Cervical Carcinoma Pancreatic Carcinoma Triple Negative Breast Cancer Hepatocellular Carcinoma Urothelial Carcinoma Squamous Cell Carcinoma of the Head and Neck Nasopharyngeal Carcinoma Renal Cell Carcinoma Non-small Cell Lung Carcinoma Small Cell Lung Carcinoma Gastric or Gastroesophageal Junction Adenocarcinoma Advanced or Metastatic Solid Tumors Prostate Carcinoma Epithelial Ovarian Cancer Fallopian Tube Cancer Primary Peritoneal Carcinoma Intrahepatic Cholangiocarcinoma Squamous Cell Anal Cancer Squamous Cell Penile Carcinoma Squamous Cell Vulvar Carcinoma Colorectal Carcinoma Endometrial Carcinoma	Safety and tolerability	78

DCR, disease control rate; DFS, disease-free survival; DOR, duration of response; DRR, durable response rate; ICI, immune checkpoint inhibitors; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TIL, Tumor Infiltrating Lymphocyte.

tested in NPC and OSCC patients (NCT04929080).

4. Discussion

Immunotherapy using ICIs (such as PD-1, PD-L1, and CTLA-4 mAbs) has revolutionized the treatment of multiple solid tumors, including HNC [235]. However, the percentage of patients who respond to such treatment is still unsatisfactory [236]. The resistance to ICIs could be attributed to the heterogeneity of the tumor microenvironment (TME) and the complex communications between its different components [11]. In the tumor microenvironment, cancer cells could evade the immune response through several mechanisms, such as reducing the tumor immunogenicity, expression of multiple inhibitory immune receptors, and altering the expression of co-stimulatory immune receptors, resulting in the induction of immunosuppressive pathways [237,238]. In this review, we mainly discussed the diversity of immune checkpoint molecules expressed on T, NK, and APC cells and their modulatory role in the response to ICIs (Figures 1 and 2). In the past few years, research has mainly focused on finding novel drugs targeting T cell immune checkpoint molecules that can effectively restore their functions. However, the immune checkpoints expressed on the NK and APC are much less explored.

To overcome the resistance to ICIs, many ongoing clinical trials evaluate the safety and efficacy of combination strategies with other immunotherapies, chemotherapy, and radiotherapy in HNSCC patients (Tables 2 and 3) to improve the response rate and prolong the response duration. Indeed, ICIs could improve the therapeutic effect by reversing the inhibitory immune microenvironment and enhancing the anti-tumor response. Combining the anti-CTLA-4 antibody tremelimumab with the anti-PD-L1 antibody durvalumab demonstrated a higher rate of disease control than monotherapy in HNSCC patients [239]. Interestingly, the efficacy of durvalumab plus tremelimumab was also tested in metastatic/recurrent HNSCC patients and was associated with higher survival and response rates at 12 to 24 months [240,241]. Importantly, it has been reported that PD-1 and CTLA-4 receptors downregulate T cells by distinct mechanisms [242]. Therefore, this synergistic effect of durvalumab plus tremelimumab results from blocking the CTLA-4 and PD-1/PD-L1 pathways, and enhancing T cell activity. Therefore, this combination approach could be beneficial not only to newly diagnosed HNSCC but also to metastatic and recurrent patients. The phase III KEYNOTE-048 trial demonstrated that adding of pembrolizumab to chemotherapy significantly improved OS in the total recurrent/metastatic HNSCC [243]. This study supported the use of pembrolizumab with cetuximab-chemotherapy as first-line standard therapy for recurrent/metastatic HNSCC. Interestingly, Harrington et al. reported that these patients continued to demonstrate survival benefits after four years [244]. The phase III KEYNOTE-412 trial enrolled 804 locally advanced HNSCC patients to determine the efficacy of adding Pembrolizumab to cisplatin-based chemoradiation therapy (CRT) versus placebo. The results showed that the combination therapy improved the event-free survival versus placebo but did not reach statistical significance (63.2% versus 56.2%) [245]. In contrast, another phase II trial examined whether stereotactic body radiotherapy (SBRT) may act synergistically with anti-PD-1 therapy to improve response in metastatic/recurrent HNSCC patients. The results showed no improvement in ORR, OS, and PFS with the addition of SBRT to nivolumab in such patients [246]. Together, these findings show that certain combinations may have remarkable clinical efficiency in HNSCC treatment. Moreover, drugs targeting other immune checkpoints molecules including CD27, CD137, IDO1, LAG-3, TIM-3, S100, NKG2D etc… are still under clinical evaluation. Importantly, these novel drugs could be tested in combination with other anti-cancer therapies for the treatment of HNSCC in the future. Given the low response rates to ICIs and the high risk of recurrence associated with HNSCC [236], the identification of novel predictive biomarkers is urgently needed to determine the HNC patients' outcomes before the initiation of proposed therapy and to detect recurrence before overt relapse. These biomarkers should indicate whether a patient would benefit from a particular checkpoint monotherapy or if there is a need for combination therapy. In this review, we gave a novel insight into how the immune checkpoint molecules (immune stimulatory and inhibitory) could serve as potential predictive and prognostic biomarkers for the treatment of ICIs. Currently, many candidate biomarkers with promising results are undergoing investigations, including PD-L1 [247–249], PD-L2 [6], HPV [250], TIL [251], clonal tumor mutational burden [252], and peripheral blood indicators [253–256]. However, all these markers impede their validation for use in clinical practice mainly due to their dynamic variations between HNSCC patients. Consequently, the combination of several markers represents a promising method that might offer a more effective, robust, and reliable selection of patients who may benefit from ICIs and to select the proper treatment strategy. The association between biomarkers was recently evaluated [257–260] and showed encouraging results for classifying patients into subtypes. Upon validation, this approach could provide the basis for developing precision medicine in HNSCC.

5. Conclusion and future perspectives

HNC is a profoundly immunosuppressive disease. The dysregulation of immune checkpoint molecules expressed on immune cells was associated with tumor evasion, resistance to anti-cancer therapies, and tumor progression. Therefore, these molecules have been of great interest in developing novel immunotherapeutic strategies targeting these co-stimulatory and inhibitory molecules. Numerous ongoing clinical trials evaluate the potential clinical benefit of these immunotherapeutic therapies alone or in combination with other agents. Furthermore, ongoing efforts are focused on the development of novel, effective, predictive and prognostic biomarkers of response to ICIs. In this regard, we discussed using immune checkpoint molecules as promising biomarkers of response to ICIs in HNC and their future clinical applications.

Consent statement/ethical approval

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CRediT authorship contribution statement

Zar Gul Abdul Rehman: Conceptualization, Writing – review & editing. **Khan Shahab:** Writing – original draft, Writing – review & editing. **Anwar Shaheena:** Writing – original draft. **Assami Laila:** Writing – original draft. **Inchakalody Varghese:** Writing – original draft. **Akbar Shayista:** Writing – original draft. **Almoghrabi Salam:** Writing – original draft. **Dermime Said:** Conceptualization, Writing – original draft, Writing – review & editing. **Bedhiafi Takwa:** Writing – original draft. **Raza Afsheen:** Conceptualization, Writing – original draft, Writing – review & editing. **Fernandes Queenie:** Writing – original draft. **Merhi Maysaloun:** Writing – original draft, Writing – review & editing. **Abo El-Ella Dina Moustafa:** Conceptualization, Writing – original draft. **Al-Muftah Mariam:** Writing – original draft, Writing – review & editing. **Mestiri Sarra:** Conceptualization, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial

interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

No data was used for the research described in the article.

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