

Therapeutic approaches for the treatment of head and neck squamous cell carcinoma—An update on clinical trials

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ABSTRACT

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common non-skin cancer with a tobacco consumption and infection with high-risk human papillomavirus (HPV) being major risk factors. Despite advances in numerous therapy modalities, survival rates for HNSCC have not improved considerably; a vast number of clinical outcomes have demonstrated that a combination strategy (the most well-known docetaxel, cisplatin, and 5-fluorouracil) is the most effective treatment choice. Immunotherapy that targets immunological checkpoints is being tested in a number of clinical trials, either alone or in conjunction with chemotherapeutic or targeted therapeutic drugs. Various monoclonal antibodies, such as cetuximab and bevacizumab, which target the EGFR and VEGFR, respectively, as well as other signaling pathway inhibitors, such as temsirolimus and rapamycin, are also being studied for the treatment of HNSCC. We have reviewed the primary targets in active clinical studies in this study, with a particular focus on the medications and drug targets used.

Introduction

Squamous cell carcinoma of the head and neck (HNSCC) is one of the most common malignancies in the world, accounting for over 90% of head and neck tumors in Asia and Europe [85]. Tobacco usage, alcohol consumption, and infection with high-risk Human Papillomaviruses (HPV) are the main risk factors for HNSCC [86]. Furthermore, hypercalcemia and comorbidities are associated with poor clinical outcomes, increased relapse rates, and shorter survival times [87]. HNSCC is a kind of human cancer that is responsive to treatment. Despite the use of numerous treatment techniques in HNSCC patients, such as chemo-radiotherapy, targeted therapy, and immunotherapy, overall clinical outcomes have not conclusively indicated a potential therapeutic

benefit.

Furthermore, individuals with metastasis are usually incurable, and only a few therapy approaches have been shown to improve overall survival (OS) or progression-free survival (PFS) [88]. Several factors other than treatment appear to influence OS and time to progression, according to multivariable study [1]. Chemotherapy is primarily assessed using several prognostic markers to determine the clinical result; however, prior treatment (chemo/radiotherapy, surgery, or other) and stage of cancer are the most important factors influencing the response [87]. Despite these restrictions, a number of pharmacological compounds, particularly monoclonal antibodies, have showed great promise in the treatment of HNSCC, and many are currently undergoing clinical studies [89].

Abbreviations: HNSCC, Head and Neck Squamous Cell Carcinoma; HPV, Human Papillomaviruses; OS, Overall Survival; PFS, Progression-Free Survival; 5-FU, Fluorouracil; R/M, Recurrent/Metastatic; EGFR, Epidermal growth factor receptor; TKI, Tyrosine kinase inhibitor; CRR, Complete response rate; VEGF, Vascular endothelial growth factor; PDGFR, Platelet-derived growth factor receptor; CDK, Cyclin dependent kinase; ALK1, Activin receptor-like kinase-1; STAT3, Signal transducer and activator of transcription 3; IDO-1, Indoleamine 2, 3-dioxygenase 1; PD-1, Programmed cell death protein 1; PDL-1, Programmed death-ligand 1; CTLA4, Cytotoxic T lymphocyte antigen 4; LAG-3, Lymphocyte activated gene-3; NK, Natural killer; APCs, Antigen presenting cells; TIM-3, T cell immunoglobulin mucin-3; VISTA, V-domain immunoglobulin suppressor of T cell activation.

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A large number of appropriately powered randomized and controlled clinical studies have established the therapeutic effects of numerous medications in various treatment cohorts such as chemotherapy, radiation, immunotherapy, and targeted therapy [90,91]. So far, the most promising treatment is a combination of docetaxel, cisplatin, and 5-FU. However, new advancements in immunotherapy and targeted therapy suggest that monoclonal antibody-based medicines such as nivolumab, pembrolizumab, cetuximab, panitumumab, zalutumumab, and nimotuzumab could be used in the future [89]. We provide a synopsis of the primary therapeutic techniques used in clinical trials around the world, as well as their application in the treatment of HNSCC.

Recent clinical trials of HNSCC

A large number of clinical trials in patients with HNSCC have been undertaken around the world. In the clinicaltrials.gov database, 1266 clinical studies with the condition/disease 'HNSCC' and a start date on or before 31 January 2022 have been found. A total of 393 studies were completed out of 1266 trials registered, while 590 studies were still recruiting with the following recruitment statuses: recruiting (387), active-not recruiting (157), not yet recruiting (42), and enrolling by invitation (4). (Fig. 1). Notably, the majority of completed clinical trials have yet to be published. Docetaxel, cisplatin, and 5-fluorouracil (5-FU) have been identified as the most often used medications in clinical trials around the world [89]. Furthermore, the thorough examination of completed trials led to a greater understanding of the numerous therapeutic agents employed in chemotherapy, immunotherapy, and targeted therapy. Table 1 summarizes the results of selected clinical trials examining the efficacy of immunotherapy and molecular targeted treatments.

Chemotherapy

Localized HNSCC is usually treated with surgery and/or chemoradiotherapy in a multidisciplinary manner [92]. Concomitant chemotherapy consists of regular docetaxel, cisplatin, and 5-FU treatment followed by radiation, which has been shown to enhance clinical outcomes in post-operative or inoperable situations. Cisplatin-based treatment enhanced OS in patients with localized HNSCC, according to a meta-analysis of 50 trials [93]. Furthermore, in high-risk patients, chemoradiotherapy with cisplatin in the post-operative environment resulted in a considerable benefit. Five-year PFS increased from 36 to 47 percent in a phase III trial with 334 patients, while five-year OS climbed

from 40 to 53 percent. However, cisplatin-treated patients had more adverse effects (hematologic toxicities, mucositis, and nausea/vomiting) than radiotherapy-only individuals [94].

Other platinum-based therapy schemes were developed due to toxicity concerns. Three cycles of carboplatin (70 mg/m²/day; 4d) and 5-FU (600 mg/m²/d; 4d) treatment in stage III/IV patients, for example, showed better 3-year PFS and OS. Mucositis of grade 3–4 looked to be a serious adverse occurrence once more [83]. Induction chemotherapy with cisplatin and 5-FU has been proven to be beneficial, as evidenced by a meta-analysis in the HNC cohort. In a phase III trial with 237 inoperable stage III/IV HNSCC patients, four rounds of cisplatin (100 mg/m² q3w) and 5-FU (1000 mg/m²/days; 5days; q3w) followed by radiation increased 5-year OS by 13% as compared to radiotherapy alone [84].

Multi-combinatorial therapy have also been found to be extremely beneficial, as evidenced by the results of multiple clinical trials. In comparison to the cisplatin-5-FU combination, adding docetaxel to the above-mentioned cisplatin and 5-FU combination followed with chemoradiotherapy (weekly carboplatin) increased 3-year OS [95]. Only grade 3/4 neutropenia was frequently reported as an adverse occurrence [95]. Patients who received docetaxel, cisplatin, and 5-FU (DCF) followed by chemotherapy/radiotherapy or cetuximab/radiotherapy significantly improved their PFS or OS in previous trials [96,97]. DCF toxicity, on the other hand, remained a worry, accounting for 25.8% of grade 3–4 neutropenia and, more crucially, 7% of treatment-related death [96]. Other similar trials, on the other hand, found no significant changes in PFS and OS [98,99]. Furthermore, when compared to regular DCF, patients treated with modified DCF (leucovorin as an adjuvant) had a greater response and tolerability. Chemotherapy-induced toxicity appears to be a key issue in HNSCC treatment, highlighting the need for less toxic therapeutic options [100]. To date, no standard radiation regimen for post-induction chemotherapy has been created. To obtain a conclusion, experiments are being done employing cisplatin and/or cetuximab [101,102].

Molecular targeted therapy

Despite advances in traditional therapies such as surgery, chemotherapy, and radiotherapy, HNSCC patients' overall survival has not improved considerably. Molecular targeted treatments have showed potential in HNSCC in the current scenario [89]. Several molecular targets have been implicated in the treatment of HNSCC, including epidermal growth factor receptor (EGFR), Vascular endothelial growth

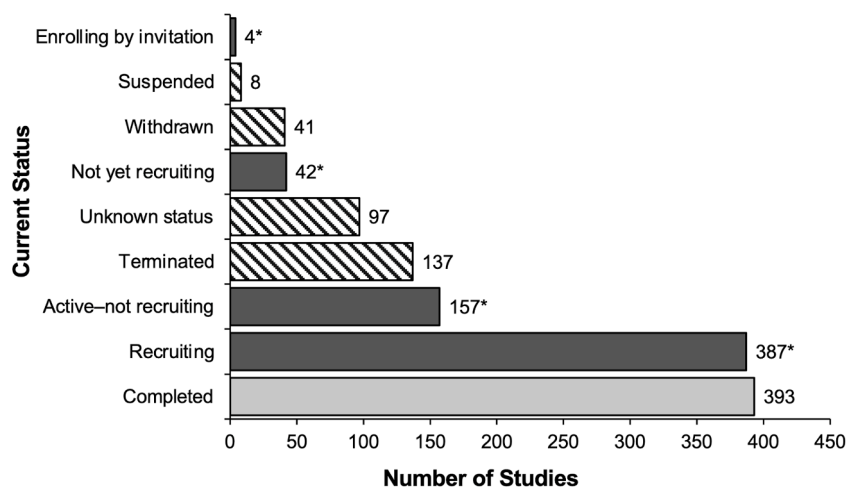


Fig. 1. Number of HNSCC clinical studies in different stages as on 31 January 2022, searched with the term 'HNSCC' on <https://clinicaltrials.gov/>. Numbers marked with asterisks represent the studies which are currently active. Studies with "Unknown status" have passed their completion date but the status has not been verified within the past 2 years.

Table 1
Selected clinical trials of immune checkpoint inhibitors and molecular targeted therapies in HNSCC.

Target	Drug	Comparison treatment	Clinicaltrials.gov Identifier	Phase	Status	Treatment setting
PD-1	Nivolumab	Therapy of investigator's choice (cetuximab, methotrexate, docetaxel)	NCT02105636 (CheckMate 141)	3	Active, not recruiting	As monotherapy in R/M platinum-refractory HNSCC
	Pembrolizumab	–	NCT01848834 (KEYNOTE-012)	1	Completed	Monotherapy for the treatment of advanced solid tumors
	Sintilimab, nimotuzumab (anti-EGFR) combined with chemotherapy	–	NCT04882462	2	Not yet recruiting	R/M HNSCC
CTLA-4	Nivolumab, ipilimumab	Extreme study regimen (cetuximab + cisplatin/ carboplatin + fluorouracil)	NCT02741570 (CheckMate 651)	3	Active, not recruiting	First line therapy of R/M HNSCC
	Nivolumab alone or in combination with ipilimumab	Surgical resection + adjuvant radio(-chemo) therapy	NCT03700905 (IMSTAR-HN)	3	Recruiting	In surgical resectable HNSCC after adjuvant therapy
LAG-3	Relatlimab (BMS-986016) alone and in combination with anti-PD-1 monoclonal antibody nivolumab (BMS-936558)	–	NCT01968109	1/2a	Recruiting	Solid tumors that have spread and/or cannot be removed by surgery
	INCAGN02385	–	NCT03538028	1	Completed	Select advanced malignancies
	XmAb®22841 monotherapy & in combination with pembrolizumab	–	NCT03849469 (DUET-4)	1	Recruiting	Subjects with selected advanced solid tumors
TIM-3	TSR-022	–	NCT02817633 (AMBER)	1	Recruiting	As a single agent and combination therapy in advanced solid tumors
Siglec-15	NC318	–	NCT03665285	1/2	Recruiting	Advanced or metastatic solid tumors
VISTA	JNJ-61610588	–	NCT02671955	1	Terminated	Advanced cancer
	CI-8993	–	NCT04475523	1	Recruiting	Advanced solid tumor malignancies
STAT-3	Durvalumab (MEDI4736, PD-L1 inhibitor) in combination with AZD9150 (STAT3 inhibitor) or AZD5069 (CXCR2 inhibitor)	–	NCT02499328	1b/2	Active, not recruiting	In patients with advanced solid malignancies and subsequently comparing AZD9150 and AZD5069 both as monotherapy and in combination with MEDI4736 as second line treatment in patients with R/M HNSCC
	TTI-101	–	NCT03195699	1	Recruiting	Advanced cancers
IDO-1	Pembrolizumab (MK-3475) in combination with INCB024360 (IDO-1 inhibitor)	–	NCT02178722 (ECHO-202/ KEYNOTE-037)	1/2	Active, not recruiting	In participants with selected cancers
	Pembrolizumab plus epacadostat, pembrolizumab monotherapy	EXTREME Regimen	NCT03358472 (KEYNOTE-669/ ECHO-304)	3	Active, not recruiting	As first line treatment for R/M HNSCC
	combination of GDC-0919 and atezolizumab	–	NCT02471846	1	Completed	In participants with locally advanced or metastatic solid tumors that has progressed after available standard therapy or for which standard therapy is ineffective, intolerable, or inappropriate
EGFR	BMS-986205 In combination with nivolumab	Nivolumab	NCT03854032	2	Recruiting	In treating patients with stage II-IV squamous cell cancer of the head and neck
	Cetuximab	Radiotherapy	NCT00004227	3	Terminated	In treating patients with stage III or stage IV cancer of the oropharynx, hypopharynx, or larynx
	Erlotinib in combination with chemoradiotherapy	Chemo-radiotherapy	NCT00410826	2	Completed	In patients with stage III and IV squamous cell carcinoma of the head and neck
	Afatinib	Placebo	NCT01345669	3	Terminated	As adjuvant therapy after chemo-radiotherapy in primary unresected patients with stage III, IVa, or IVb loco-regionally advanced HNSCC
	EGFR antisense DNA in combination with radiation and cetuximab	–	NCT01592721	1/2	Active, not recruiting	In patients with locally advanced HNSCC
	BB-401	–	NCT03433027	2	Completed	In patients with R/M HNSCC who have failed all available standard therapies
	MRG003	–	NCT04868162	2	Recruiting	R/M HNSCC
VEGF	Dacomitinib	–	NCT04946968	2	Recruiting	Patients With EGFR-driven advanced solid tumours with low EGFR-AS1 lncRNA Expr or other novel emerging biomarkers
	Bevacizumab and erlotinib	–	NCT00055913	1/2	Completed	R/M HNSCC
	Pemetrexed and bevacizumab	–	NCT00222729	2	Completed	R/M HNSCC
	Cetuximab and bevacizumab	–	NCT00409565	2	Completed	R/M HNSCC
mTOR	Cetuximab with or without sorafenib	–	NCT00939627	2	Completed	R/M HNSCC
	Temsirolimus	–	NCT01172769 (TEMHEAD)	2	Completed	In Patients With relapsed/recurrent HNSCC
	Temsirolimus	–	NCT01016769	1/2	Completed	In combination with weekly paclitaxel and carboplatin for R/M HNSCC
CDK	Everolimus (RAD001)	–	NCT01051791	2	Terminated	Refractory, recurrent, locally advanced squamous cell carcinoma of the head and neck
	Palbociclib (PD 0,332,991)	–	NCT02101034	1/2		

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Table 1 (continued)

Target	Drug	Comparison treatment	Clinicaltrials.gov Identifier	Phase	Status	Treatment setting
	Palbociclib	Cetuximab	NCT02499120	2	Active, not recruiting Active, not recruiting	With cetuximab in patients with incurable SCCHN With cetuximab, in HPV negative, cetuximab naïve patients with R/M HNSCC after failure of one prior platinum containing chemotherapy regimen
	P276-00	-	NCT00899054 (SPARK)	1/2	Completed	In combination with radiation, in patients with recurrent and/or locally advanced HNSCC
	P276-00	-	NCT00824343 (MONARCH)	2	Completed	In Indian patients with recurrent, metastatic or unresectable locally advanced HNSCC
	Flavopiridol	-	NCT00020189	2	Completed	R/M HNSCC
ALK1	Dalantercept	-	NCT01458392	2	Completed	R/M HNSCC

factor (VEGF) and phosphatidylinositol 3-kinase (PI3K). Concurrent chemoradiotherapy has been linked to a slew of hazardous side effects in HNSCC patients, suggesting that exploring targeted therapies could be a good strategy in this cohort [89].

Epidermal growth factor receptor (EGFR)

EGFR is a well-known cancer drug target as it influences cell proliferation, apoptosis, angiogenesis, and metastasis of cancer cells. EGFR is a transmembrane protein, and after binding to the ligand (EGF and TGF- α), it forms a homo- or heterodimer with other Erb family proteins (ErbB2, ErbB3, ErbB4) and activates the downstream signaling through the mitogen-activated protein kinase (MAPK) cascades and PI3K/AKT/mTOR pathway. This signaling cascade leads to the activation of certain genes in the nucleus, which promotes tumorigenesis and metastases (Fig. 2) [1,2]. EGFR overexpression is a negative prognostic factor that can be seen in about 90% of the HNSCC cases [3]. Furthermore, its overexpression has been positively correlated with earlier relapse, reduced disease-free survival and OS. Considering the abovementioned facts, inhibition of EGFR was targeted in HNSCC therapy. For EGFR inhibition, drug molecules either bind to the extracellular domain of EGFR, disrupting the link between ligands, or the cytoplasmic region of

EGFR and inhibit the EGFR autophosphorylation by competing with ATP and thus interfere with the downstream cell signaling cascade [4].

Monoclonal antibodies

Monoclonal antibodies form a major subset of the current EGFR targeted therapy regimen and have demonstrated significant clinical benefits. Cetuximab is a chimeric monoclonal antibody that binds to domain III of the extracellular region of EGFR, and its anti-cancer effects are based on apoptosis induction and inhibition of cancer proliferation and angiogenesis [5]. Cetuximab also inhibits the phosphorylation of EGFR and prevents signals from being transmitted to the cell [6]. Several clinical trials have demonstrated that cetuximab in combination with radiotherapy increased the median OS and PFS [7,8]. In 2006, after promising application of cetuximab in combination with radiotherapy, USFDA approved its use for HNSCC therapy (Table 2). Panitumumab [9], zalutumumab [10], and nimotuzumab [11] are other promising human EGFR monoclonal antibodies which have shown favorable but limited effects in HNSCC patients. Other investigational EGFR monoclonal antibodies are being evaluated as monotherapy as well as combination therapy in several phase 1/2 clinical trials (NCT02277197, NCT03491709, and NCT03744208) (Fig. 2).

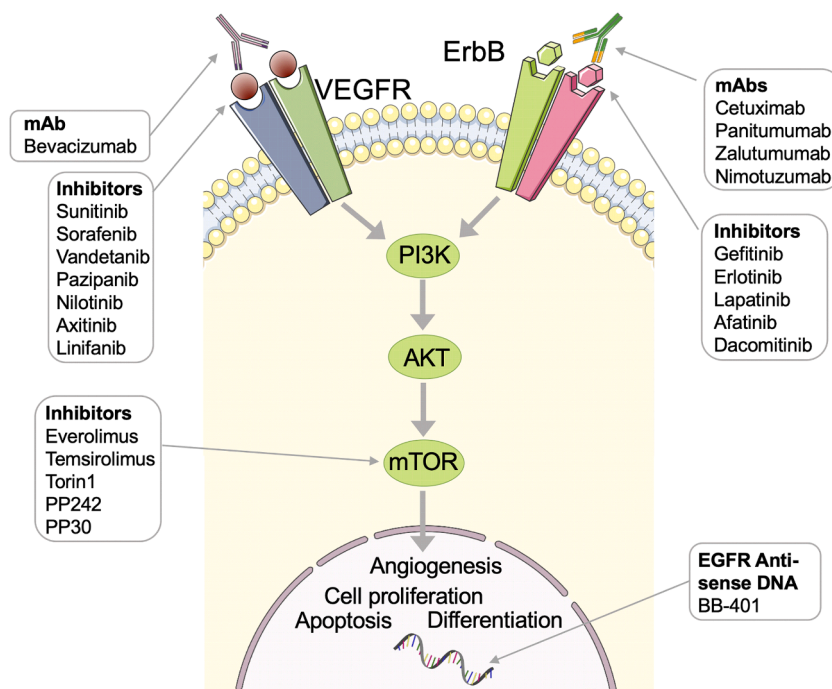


Fig. 2. Inhibitors and monoclonal antibodies targeting various molecules in EGFR and VEGFR pathways being utilized in clinical trials of HNSCC.

Table 2
Monoclonal antibodies approved for the treatment of HNSCC.

S. No.	Drug	Mechanism of action	Year	Disease conditions	Clinical trial	Ref.
1.	Cetuximab	EGFR inhibitor	2006	HNSCC after platinum-based therapy (in combination with radiotherapy)	NCT00004227	[8]
			2009	R/M HNSCC (in combination with platinum-fluorouracil chemotherapy)	NCT00122460	[68]
2.	Pembrolizumab	PD-1 inhibitor	2016	HNSCC after platinum-based chemotherapy	NCT01848834	[66]
			2019	Metastatic or unresectable recurrent HNSCC (in combination with platinum and fluorouracil (FU) for all patients and as a single agent for patients whose tumors express PD-L1)	NCT02358031	[71]
3.	Nivolumab	PD-1 inhibitor	2016	R/M HNSCC with disease progression on or after a platinum-based therapy	NCT02105636	[65]

Tyrosine kinase inhibitors (TKIs)

Drugs of this class are under investigation in several early and late phase clinical trials. Gefitinib and erlotinib are the popular inhibitors which have shown potential for the treatment of HNSCC (Fig. 2) [12]. In a phase II study (NCT00410826), erlotinib in combination with cisplatin and radiotherapy was reported to improve complete response rate (CRR) as compared to the control group (only cisplatin and radiotherapy) but that was not significant [13]. Lapatinib is another TKI that inhibits EGFR (ErbB1) and HER2 (ErbB2) receptors by binding to the intracellular phosphorylation domain (ATP-binding pocket) preventing their self-phosphorylation and subsequent signaling activation [14]. Combinatorial therapy of lapatinib and capecitabine has been found effective and well-tolerated in HNSCC patients [15]. Afatinib, an irreversible ErbB family blocker, showed anti-proliferative and antitumor activity in *in-vitro* studies, which was further explored in clinical trials [16]. Efficacy of afatinib has been found comparable to cetuximab as evidenced by a phase II trial in recurrent HNSCC treated previously with platinum-based chemotherapy [17]. The utility of afatinib as an adjuvant has also been evaluated in a phase III trial (LUX-Head & Neck 2, NCT01345669) following chemoradiotherapy in the advanced stage of HNSCC [18]. Similarly, dacomitinib, an oral pan-EGFR inhibitor, has also shown clinical potential during the first line treatment of R/M HNSCC, warranting further studies as a part of combination therapy in advanced disease conditions (Fig. 2) [19].

EGFR anti-sense DNA

EGFR anti-sense DNA is a synthetic DNA sequence designed as an antisense to the DNA sequence of *EGFR* gene (Fig. 2). It inhibits the EGFR expression by tumor cells and thus inhibits tumor growth. Antisense therapy tends to be more effective due to the specificity and flexibility. Another advantage of this therapy is the ability to overcome drug resistance, since, the sequence of antisense DNA can be altered according to the genetic mutations of the targeted genes [20]. EGFR antisense DNA has been shown to reduce HNSCC proliferation and viability in preclinical studies [20,21]. Intratumoral EGFR antisense DNA has been evaluated in two phase 1/2 studies (NCT00903461 and NCT01592721), in combination with cetuximab and radiotherapy, in patients with locally advanced HNSCC and was well tolerated [22]. Intratumoral EGFR antisense DNA (BB-401) has completed a phase 2 trial (NCT03433027) evaluating the safety, tolerability, and efficacy in patients with R/M HNSCC who have failed all available standard therapies, and results have not been published yet.

Vascular endothelial growth factor (VEGF)

VEGF is a crucial signaling protein that stimulates angiogenesis and is responsible for the formation of new blood vessels [23]. Over-expression of VEGF has been positively correlated in majority of HNSCC cases and favors tumor growth, cell migration and metastases. Activated angiogenesis by tumor cells reduce the sensitivity to radiation in the patients undergoing radiotherapy treatment [24]. There are several clinical trials focused on VEGF, where targeted therapies have helped inhibiting the angiogenesis. The most commonly used molecules in targeted therapies are bevacizumab, sunitinib, sorafenib and vandetanib (Fig. 2). [25]. Bevacizumab is USFDA approved monoclonal antibody

and employed in the treatment of several cancer types including colon cancer, kidney cancer and cervical cancer. Although underlying mechanism remains unclear, pre-clinical studies have confirmed the ability of bevacizumab to improve the HNSCC sensitivity towards radiotherapy [26]. In a phase 1/2 trial (NCT00055913), bevacizumab in combination with erlotinib was well tolerated with four patients (out of 48) having a complete response. Median time of OS and PFS were 7.1 and 4.1 months [27]. Another phase 2 study (NCT00222729) investigating combinatorial therapy of bevacizumab and pemetrexed also has shown favorable outcomes [28]. Cetuximab (anti-EGFR) and bevacizumab (anti-VEGF) were evaluated in preclinical as well as phase 2 clinical study (NCT00409565). The combination enhanced growth inhibition both *in-vitro* and *in-vivo*, and also reduced tumor vascularization. Clinically, 16% of objective response rate (ORR) and 73% of disease control rate (DCR) were observed [29]. Furthermore, in a phase II trial, bevacizumab in combination with high doses of cisplatin and intensity-modulated radiation therapy (IMRT) delivered favorable clinical outcomes in advanced stage HNSCC [30]. It is worth adding that IMRT minimizes the radiation exposure to healthy area by a planned and focused photon irradiation to the tumor confined area [31].

VEGFR and platelet-derived growth factor receptor (PDGFR) inhibition

Several preclinical and clinical trials have indicated the importance of small molecules capable of modulating the signaling pathways acting through VEGFR and PDGFR [32]. Sorafenib is USFDA approved serine/threonine protein kinase inhibitor that targets VEGFR and inhibits tumor growth by inhibiting cell proliferation, cell migration, cell invasion (Fig. 2) [33] and inducing autophagy [34]. Furthermore, Sorafenib sensitizes the HNSCC to radiotherapy by its ability of double-stranded DNA break repair inhibition [35]. Sunitinib is another FDA approved oral kinase inhibitor that targets VEGFR, PDGFR and c-kit, however its activity is not explored much in HNSCC cases. During clinical trials, Sunitinib showed poor activity alone, but in combination with cetuximab, it showed significant synergic effects, and addition of radiotherapy completely abolished tumor growth [36]. Vandetanib is also a potential oral kinase inhibitor targeting EGFR, VEGFR, and RET-tyrosine kinase [37]. Pazopanib, nilotinib, axitinib and linifanib are other VEGF inhibitors which are under investigation in various clinical trials of HNSCC [32] (Fig. 2).

PI3K/AKT/mTOR pathway

The PI3K/AKT/mTOR pathway is an intracellular signaling pathway and serves a crucial role in the regulation of cell cycle [38]. Activation of this pathway leads to reduced apoptosis and increased cell proliferation in tumor. mTOR is a serine threonine kinase which has been found activated in HNSCC and thus a potential therapeutic target [39]. Primarily there are two types of mTOR inhibitors. First generation inhibitors are derived from rapamycin (antibiotic) while second generation is ATP competitive such as Torin1, PP242 and PP30. For mTOR inhibition in clinical trials, rapamycin analogues have been used including temsirolimus and everolimus (Fig. 2) [40]. Pre-clinical studies and patient derived xenograft models indicates that temsirolimus and everolimus is effective in inhibiting cell proliferation in HNC [41,42].

Several mTOR inhibitors are being evaluated alone or in

combination therapies (with chemo/radiotherapy) in several phase 1/2 clinical trials. Temsirolimus has been evaluated in a phase 2 study (NCT01172769) in platin- and cetuximab refractory R/M HNSCC patients and has shown tumor shrinking properties with clinical efficacy. However, the incidence of mutations (KRAS, BRAF, and PI3KCA) were lower than anticipated and showed no association with clinical outcome [43]. A combination therapy consisting of temsirolimus along with low-dose weekly carboplatin and paclitaxel was evaluated in a phase 2 study (NCT01016769) in R/M HNSCC patients and showed efficacy comparable to that of standard high-dose chemotherapy regimens and was well tolerated as well [44]. Everolimus failed to show efficacy as monotherapy in a phase 2 trial in previously treated R/M HNSCC patients (NCT01051791) [45]. Metformin, widely used drug for the treatment of type-2 diabetes worldwide, has shown to inhibit mTORC1 activity by both AMPK dependent and independent mechanisms and reduced the growth of HNSCC cells in *in-vitro* and *in-vivo* models [46,47]. Based on these studies, metformin is being evaluated in several phase 1/2 clinical trials alone and in combination with chemo/radiotherapy and immunotherapies [48].

Cyclin dependent kinases (CDK)

Cyclin dependent kinases play crucial roles in the cell-cycle regulation and are also involved in the pathogenesis of several diseases including cancer. USFDA approval of three CDK 4/6 inhibitors viz., palbociclib, ribociclib, and abemaciclib for the treatment of advanced and metastatic breast cancer has already proven the efficacy of this class of molecules as potential anticancer drugs (Fig. 3) [49]. Several CDK inhibitors have been evaluated in preclinical as well as clinical studies for the treatment of HNSCC. Ribociclib (LEE011), a CDK 4/6 inhibitor, has shown cytostatic effects in human papillomavirus (HPV) negative HNSCC models [50]. In another study, ribociclib was shown to induce cell-cycle arrest in HNSCC cell lines and also exhibited radiosensitization effects, suggesting that a combination of CDK 4/6 inhibitors with radiotherapy could be a promising option for the treatment of HNSCC [51].

Clinically, palbociclib, in combination with cetuximab, was

evaluated in a phase 2 study (NCT02101034) in platinum-resistant and cetuximab-resistant HPV unrelated HNSCC patients. An objective response rate of 39% and 19% was observed in platinum-resistant and cetuximab-resistant groups, respectively, warranting further studies of CDK 4/6 inhibitors [52]. The same combination was investigated in another phase 2 study (PALATINUS, NCT02499120) in platinum-resistant, cetuximab-naive, HPV-unrelated HNSCC patients. Median OS was reported to be 9.7 months in palbociclib plus cetuximab group and 7.8 months in cetuximab group, showing a prolongation of median OS in combination group compared to cetuximab alone [53]. Riviciclib (P276-00), a novel inhibitor of CDK 1/4/9 [49], has been tested in two clinical studies (NCT00899054 and NCT00824343) in advanced HNSCC patients, and results are forthcoming. Flavopiridol, a CDK 4/9 inhibitor, has also completed a phase 2 trial (NCT00020189) focussed on the effectiveness in R/M HNSCC patients. Additional clinical trials investigating CDK inhibitors to treat HNSCC are ongoing (Fig. 3).

Activin receptor-like kinase-1 (ALK1)

The activin receptor-like kinase-1 (ALK1) belongs to TGF-β class and plays crucial role in modulating angiogenesis and vasculature development [54]. Dalantercept, an anti-angiogenic compound, has shown a significant potential as an ALK1 inhibitor in patients suffering from advanced solid tumors including HNSCC in a phase 2 clinical trial (NCT01458392) (Fig. 3) [55]. Apart from this several other line of targeted drugs such as proteasome inhibitors (e.g. bortezomib) and Notch inhibitors has also been explored [56–58], however an extensive clinical investigation is required in further studies.

Signal transducer and activator of transcription 3 (STAT3)

STAT3 is a transcriptional factor involved in various cellular processes including cell proliferation, survival, differentiation, and angiogenesis. In tumor cells, STAT3 becomes hyperactivated decreasing the expression of immunity factors like interferons, pro-inflammatory cytokines, and chemokines, while increasing the expression of growth factors [59]. STAT3 has also been found to be involved in the increased expression of various checkpoint molecules (PD-1, CTLA-4), the combination of STAT3 inhibitors with checkpoint inhibition therapy has shown encouraging results by increasing the therapeutic potential of checkpoint inhibitors and decreasing the resistance against them [59]. Various clinical studies are ongoing evaluating the potential of combination immunotherapy for the cancer treatment. A combination therapy of durvalumab (MEDI4736, PD-L1 inhibitor) and danvatirsen (AZD9150, STAT3 inhibitor) or AZD5069 (CXCR2 inhibitor) has been evaluated in a phase 1b/2 study (NCT02499328) in patients with advanced solid malignancies and HNSCC. This study showed improved anticancer activity as a result of combining PD-L1 inhibitor with STAT3 inhibitor as compared to PD-L1 monotherapy [60]. Further, enhanced activity was reported by the combination of PD-L1 inhibitor with STAT3 inhibitor compared to CXCR2 inhibitor plus PD-L1 inhibitor or PD-L1 monotherapy and warrants further investigation. Another STAT3 inhibitor, TTI-101, is undergoing a phase 1 evaluation in patients with advanced cancers including HNSCC (NCT03195699).

Indoleamine 2, 3-dioxygenase 1 (IDO-1)

IDO-1 is a tryptophan catabolizing enzyme that is expressed by the cancer cells and cancer-associated cells. It exerts immunosuppressive effects by suppressing activity of T-cells and NK cells, and activation of regulatory T-cells. Further, IDO-1 is involved in the development of resistance against checkpoint inhibitors. Combination of IDO-1 inhibitor with checkpoint inhibitors could be an alternative therapy for the cancer treatment. Several IDO-1 inhibitors are in currently clinical development.

Epacadostat is an investigational oral IDO-1 inhibitor; in a

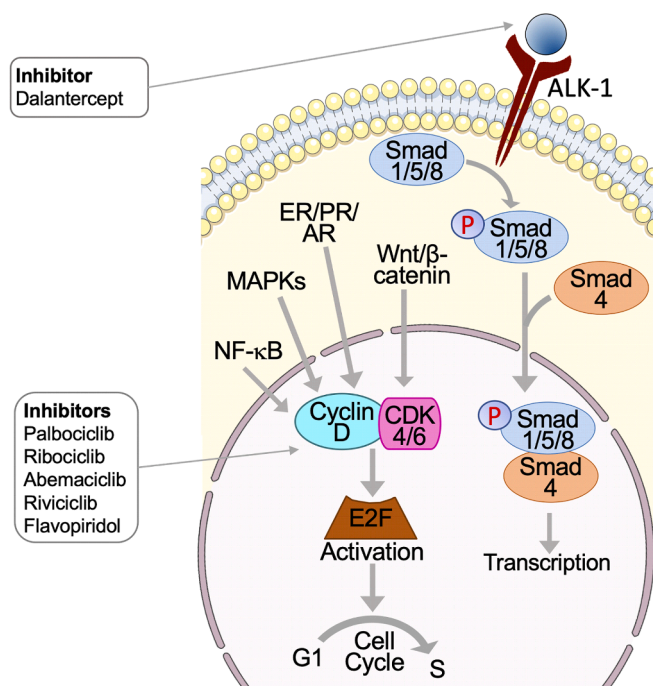


Fig. 3. Inhibitors and monoclonal antibodies targeting ALK1 and cyclin-D pathways.

preliminary phase 1/2 study (ECHO-202/KEYNOTE-037, NCT02178722) Epcadostat in combination with pembrolizumab showed tolerable safety profile and encouraging antitumor activity in multiple advanced solid tumors [61]. A phase 3 clinical study (KEYNOTE-669/ECHO-304, NCT03358472) is evaluating the efficacy and safety of pembrolizumab and epacadostat combination therapy, pembrolizumab monotherapy, and the EXTREME regimen (cetuximab + cisplatin/carboplatin + 5-FU) as first-line treatment for R/M HNSCC. Another IDO-1 inhibitor, Navoximod (GDC-0919), has been studied in combination with a PD-L1 inhibitor atezolizumab in a phase 1 study (NCT02471846) in patients with advanced solid tumors, but failed to show additional benefit of combination [62]. BMS-986205 (linrodostat) is a selective and irreversible IDO-1 inhibitor that is being evaluated in a phase 2 clinical trial (NCT03854032) in combination with nivolumab in treating patients with stage II-IV HNSCC. Another phase 3 clinical study (NCT03386838) evaluating BMS-986205 plus nivolumab vs. standard of care EXTREME regimen in first line R/M HNSCC has been withdrawn.

Immunotherapy

Surgery and radiotherapy, with or without conventional chemotherapy, are the existing mainstays of advanced head and neck squamous cell carcinoma (HNSCC) treatment. Advanced human papillomavirus (HPV)-negative HNSCC has a dismal prognosis despite this multi-modality treatment. Treatment intensification with molecular targeted therapies is not enough to appreciably improve overall survival. Immunotherapy for head and neck cancer offers patients, particularly those with HPV-related malignancies, interesting new treatment options without the potentially fatal side effects of traditional treatments.

It is now widely accepted that a properly functioning immune system may effectively resist tumor cell effects. Blocking negative signaling pathways in effector cells (e.g., CTLA-4, PD-1/PD-L1) or inducing co-

stimulatory signals could thus be used to boost host immunity. Agonistic monoclonal antibodies like MEDI0562 (against OX-40), urelumab and utomiliumab (against CD137), and motolimod (toll-like receptor-8 agonist) have been studied in multiple clinical studies in the co-stimulatory cohort [103]. It's worth noting that, in addition to cytotoxic effects, chemotherapy can also cause immunogenic changes that can stimulate the immune system. Cisplatin, for example, upregulates immunosuppressive signaling in the tumor microenvironment by activating the expression of major histocompatibility complex I and promoting the lytic activity of effector cells [104]. These findings suggest that immunotherapy could be combined with chemoradiotherapy to improve clinical outcomes in HNSCC. Immunotherapies are being tested on a variety of patient subgroups, including HPV-positive and HPV-negative subtypes. As indicated by multiple clinical trials [103], immunotherapy in HPV positive cases targets different non-host virus-specific tumor antigens E6 and E7. Recent clinical evidence from immunotherapy trials suggests that using the right checkpoint inhibitors can increase survival by many times.

Programmed cell death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1)

Programmed death-1 (PD-1) is an immunoreceptor which is expressed on T and B lymphocytes, as well as on monocytes and dendritic cells (Fig. 4) [63]. PD-1 is activated through binding of its ligands: PD-L1 and PD-L2, and as a result, suppress inflammatory response. Both PD-1 and PD-L1 have been found to be overexpressed in cancer cases, including head and neck, lung, colon, melanoma, breast, and kidney. In fact, overexpression of these receptors and ligands results in dysfunction of anti-cancer signaling, which allows tumor cells to escape from immune surveillance [64]. Thus PD-1 receptor and its ligands (PD-L1 and PD-L2) are attractive targets for various cancers, including HNSCC.

In a clinical trial (CheckMate 141, NCT02105636), an anti-PD-1

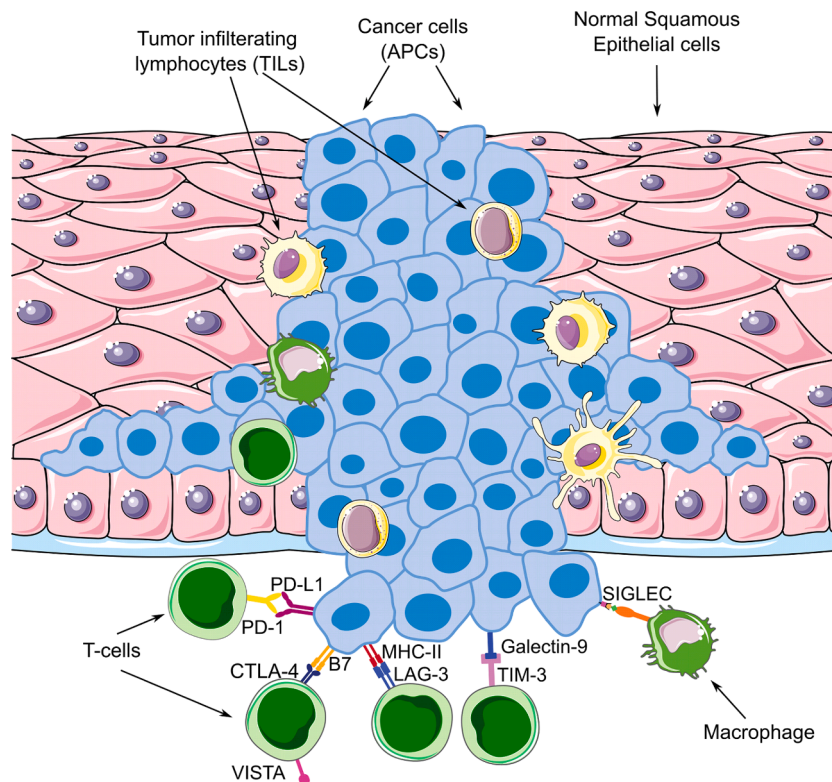


Fig. 4. Interaction between various co-inhibitory molecules expressed on cancer cells (APCs) and various immune cells infiltrated in tumor microenvironment (TME). APC, antigen-presenting cells; CTLA-4, cytotoxic T lymphocyte antigen 4; LAG-3, lymphocyte activation gene 3; MHC, major histocompatibility complex; PD-1, Programmed death 1; PDL-1, Programmed death-ligand 1; TIM-3, T-cell immunoglobulin mucin protein 3; VISTA, V-domain Ig suppressor of T cell activation.

antibody nivolumab was evaluated in recurrent/metastatic (R/M) HNSCC patients at an intravenous dose of 3 mg/kg every 2 weeks and compared with weekly single agent intravenous chemotherapy using methotrexate (40–60 mg/m²), docetaxel (30–40 mg/m²) or cetuximab (first dose at 400 mg/m² then 250 mg/m²). The group treated with nivolumab showed less adverse effects and increased OS as compared to other groups [65]. In another prospective trial (KEYNOTE-012, NCT01848834) with an anti-PD-1 antibody pembrolizumab (10 mg/kg every 2 weeks), clinical outcomes in terms of efficacy and toxicity were found similar to nivolumab [66]. Furthermore, an expanded study in similar cohort of R/M HNSCC patients at a fixed intravenous doses of 200 mg/kg every 3 weeks also showed promising clinical outcome in line with the nivolumab trial [67]. It is worth adding that several factors need to be determined before interpreting or comparing the results of different trials, as the inclusion criteria of trials may vary to a significant extent, which may affect the outcome across the trials. For example, pre-treatment status and age range of participants, randomized or non-randomized trials, drug doses, and treatment duration are major factors that directly impact final clinical outcomes. To date, cetuximab as an adjunct to platinum/5-FU, and, nivolumab monotherapy have responded to achieve significantly longer OS as compared to their respective control arms [68]. Immune checkpoint inhibitors usually elicit a delayed but a unique long-term off-treatment survival response than that of other targeted therapies (e.g., EGFR inhibitors) and conventional chemotherapies [69,70]. Both nivolumab and pembrolizumab are well tolerated and have gained FDA approval to be used as new care options for the treatment of HNSCC (Table 2) [32].

Cytotoxic T lymphocyte antigen 4 (CTLA4)

CTLA-4 is a receptor present on the surface of activated T-lymphocytes (Fig. 4), it competes with CD28 receptors to bind with B7 ligands present on the antigen presenting cells (APCs, tumor cells), inhibiting the activation signal required for T-cells. CTLA-4 has also been reported to inhibit IL-2 production, T-cell proliferation, and induce cell-cycle arrest [72]. Blocking CTLA-4 receptors can result in T-cell activation and immune response in the host cells. To date, only one CTLA-4 inhibitor, ipilimumab (Yervoy), has been approved for the treatment of unresectable or metastatic late-stage melanoma as well as adjuvant to surgery for high-risk stage III melanoma patients [73,74]. Recently, USFDA has approved the combination of ipilimumab and nivolumab as first-line treatment of metastatic non-small cell lung cancer (PD-L1 tumor expression ≥1%) after an investigation in a randomized, open-label, phase-3 clinical trial, CHECKMATE-227 (NCT02477826) [75].

CTLA-4 inhibitors are being evaluated in several clinical studies for the treatment of HNSCC. The combination of ipilimumab and nivolumab is undergoing a randomized, open-label phase 3 clinical trial as first-line treatment of R/M HNSCC compared to standard of care (CheckMate 651, NCT02741570). Another phase 3 clinical study, IMSTAR-HN (NCT03700905) is evaluating the potential of nivolumab, alone or in combination with ipilimumab, as immunotherapy vs standard follow up in surgical resectable HNSCC after adjuvant radio(-chemo)therapy [76].

Lymphocyte activated gene-3 (LAG-3)

LAG-3 is present on the surface of activated T-cells as well as natural killer (NK) cells, B cells, and dendritic cells (Fig. 4). It binds to MHC-II present on APCs inhibiting the interaction of T-cell receptors with MHC-II. Crosslinking of LAG-3 and T-cell receptors can impair cytokine production and T-cell proliferation [77]. Thus, LAG-3 interferes T-cell signaling in immune response. LAG-3 blockers can inhibit the binding of LAG-3 to MHC-II and provoke an immune response to the APCs. Anti-LAG-3 antibody relatlimab (BMS-986016) is being evaluated in a phase 1/2 study to assess the safety, tolerability, and effectiveness alone or in combination with anti-PD-1 nivolumab for the treatment of solid

tumors (NCT01968109). INCAGN02385, an Fc-engineered IgG1κ antibody having high affinity to LAG-3, is being evaluated against advanced malignancies including HNSCC in a phase 1 study (NCT03538028). A bispecific antibody, XmAb®22841, targeting CTLA-4 and LAG-3 simultaneously has been developed and is being tested as monotherapy and in combination with pembrolizumab in patients with advanced solid tumors in an ongoing trial (DUET-4, NCT03849469). More clinical trials are undergoing to assess anti-LAG-3 antibodies alone or in combination with other drugs (nivolumab, relatlimab, ipilimumab; NCT04326257).

T cell immunoglobulin mucin-3 (TIM-3)

TIM-3 is an inhibitory protein expressed by CD4⁺ and CD8⁺ T-cells, and other immune cells including regulatory T-cells, mast cells, natural killer cells and dendritic cells (Fig. 4). Galectin-9 act as major ligand for TIM-3, and is produced by the APCs (tumor cells). Upon binding, galectin-9-TIM-3 complex suppresses immune responses by disrupting the formation of immune synapse, phosphatase recruitment, and ultimately, cell becomes anergic [78]. Blocking the interaction of galectin-9 and TIM-3 by anti-TIM-3 antibodies may facilitate the immune response against cancer, inhibiting tumor growth. In a preclinical study, PD-1 and TIM-3 have been reported to be co-expressed on T-cells of mice bearing solid tumors; and combined targeting both targets was highly effective in inhibiting tumor growth and restoring T-cell functions [79]. TIM-3 is also being targeted in multiple clinical trials for the treatment of various types of cancer. An anti-TIM-3 antibody TSR-022 is being evaluated in a phase 1 dose escalation and dose expansion in patients with advanced solid tumors (AMBER, NCT02817633). In another phase 1 clinical study, INCAGN02390 is undergoing safety, tolerability and preliminary effectiveness evaluation as a monotherapy in patients with advanced malignancies including HNSCC.

Siglec-15

Siglec-15 is an immunosuppressive protein expressed on tumor cells and/or tumor-associated macrophages (Fig. 4). It has been shown to suppress T-cell proliferation and activation *in-vitro* as well as *in-vivo*. On the other hand, siglec-15 deficiency has been shown to promote T-cell responses, and control tumor growth. Also, siglec-15 targeting with monoclonal antibody in murine model inhibited tumor growth by reversing T-cell suppression [80]. Thus, targeting siglec-15 by specific monoclonal antibodies can be a therapeutic option for cancer treatment, or it can provide additional support to the existing anti-cancer immunotherapy. Currently, anti-siglec-15 monoclonal antibody, NC318, is being evaluated in a phase 1/2 dose-escalation, safety and tolerability study, in patients with advanced or metastatic solid tumors including HNSCC cohort (NCT03665285).

V-domain immunoglobulin suppressor of T cell activation (VISTA)

VISTA is a negative checkpoint regulator, expressed on hematopoietic cells, mainly tumor infiltrating myeloid cells. It has been shown to inhibit T-cell proliferation and cytokine production *in vitro*. The same study highlighted that anti-VISTA mAb enhanced T-cell responses [81]. Another preclinical study demonstrated that VISTA mAb administration enhanced T-cell proliferation and function, as well as, suppressed tumor growth in transplantable and inducible tumor models [82]. Thus, VISTA could be an important target for the cancer therapeutics, either as a monotherapy or in combination with other therapies. To date, there has been two clinical studies utilizing anti-VISTA antibodies in subjects with advanced cancer, of which, a phase 1 study of monoclonal antibody JNJ-61610588 has been terminated (NCT02671955). Another phase 1 clinical trial evaluating the safety, tolerability, pharmacokinetics, pharmacodynamics, and anti-cancer activity of CI-8993, anti-VISTA antibody, in patients with advanced solid tumor malignancies is currently in the recruiting stage (NCT04475523).

Conclusion

Despite the fact that a variety of therapeutic techniques are being used to improve the prognosis of HNSCC patients, the treatment has yet to be revolutionized due to the disease's complexity and heterogeneity. Several medications have been studied in clinical trials around the world as monotherapies or in combination with other drugs. Chemotherapy, chemoradiotherapy, targeted therapy, and immunotherapy have all shown varying results depending on a variety of parameters such as the stage of HNSCC, comorbidities, age, and past treatment. Because of the critical involvement of the immune system in carcinogenesis, immunotherapy has emerged as a promising treatment option in recent years. The development of targeted therapeutics is based on a molecular understanding of the underlying biology of cancer progression, however the response is limited because to the complicated interplay of numerous cell-signaling cascades. To ensure their significance in diverse cohorts and stages of HNSCC, more clinical trials are needed. Docetaxel, cisplatin, and 5-FU were the most commonly used medications in the prospective and conventional treatment of HNSCC. Apart from these medications, the USFDA has only approved three others: cetuximab, pembrolizumab, and nivolumab. Furthermore, there is still room for advancement in immunotherapy and the addition of appropriate prognostic biomarkers for better therapeutic options in HNSCC patients. Biomarkers may play a crucial role in onco-immunotherapy, according to the suggestions of a research committee from the National Cancer Institute. For example, tumor-related biomarkers (e.g., interferon, PD-1/PD-L1, and CTLA-4 expression), peripheral blood mononuclear cell-related biomarkers (e.g., MDSCs and regulatory T lymphocytes, HPV virus peptides), serum biomarkers (e.g., cytokines, antibodies, and growth factors), bio-imaging (e.g., computed tomography and/or positron emission) Although these biomarkers are not routinely used before and after diagnosis, they must be prospectively validated in well-designed controlled clinical trials. The direct link between exosomes, metabolomics, and the aggressiveness of HNSCC has become a hot area of research in recent years. Exosomes as HNSCC biomarkers, therapeutic targets, and drug carriers for HNSCC treatments require more research, and metabolomics must overcome a number of challenges before it can be extensively employed in clinical research and practice.

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CRedit authorship contribution statement

Bharat Goel: Conceptualization, Methodology, Writing – original draft. **Anoop Kumar Tiwari:** Data curation, Writing – review & editing. **Rajeev Kumar Pandey:** Writing – review & editing. **Akhand Pratap Singh:** Conceptualization, Methodology, Writing – original draft. **Sujeet Kumar:** Writing – review & editing. **Abhishek Sinha:** Writing – review & editing. **Shreyans K. Jain:** Supervision, Writing – review & editing. **Arun Khattri:** Conceptualization, Methodology, Investigation, Supervision, Writing – review & editing, Project administration, Funding acquisition.

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.

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