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New Therapies in Head and Neck Cancer

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Abstract

Head and neck squamous cell carcinoma (HNSCC) is a common malignancy with high rates of mortality and morbidity. Beginning with cetuximab, investigators continue to optimize antibody technology to target cell surface receptors that promote HNSCC growth. Small molecules and oligonucleotides have also emerged as therapeutic inhibitors of key receptor-mediated signaling pathways. Although many such therapies have been disappointing in clinical trials as single agents, they continue to be studied in combination with standard therapies. Approvals of pembrolizumab and nivolumab opened a new era of immunotherapy that aims to stimulate anti-tumor immunity in the tumor microenvironment. Immunotherapies are being intensively investigated in new HNSCC clinical trials, with the goal of optimizing the therapeutic potential of this new class of anti-cancer agent.

Keywords

Head; neck; cancer; squamous cell; immunotherapy

Therapeutic Potentials for a Devastating Disease

Head and neck squamous cell carcinoma (HNSCC) is a common epithelial malignancy of the oral cavity, oropharynx, larynx or hypopharynx. Worldwide, HNSCC is the 6th leading cancer and accounts for over 600,000 new cancer cases and 350,000 deaths each year [1,2]. Approximately half of newly diagnosed patients will not survive beyond five years. At diagnosis, 45% of patients already have regional lymph node metastasis. Moreover, the rate of second primary tumor development in HNSCC patients is exceptionally high [3].

In addition to surgery, treatment of HNSCC had long consisted of cytotoxic chemotherapy and radiation. The monoclonal antibody (mAb) platform signaled the beginning of targeted cancer therapy, and in 2006 the anti-EGFR mAb cetuximab was approved for HNSCC. In addition to induction of cytotoxicity, the small molecule paradigm widened to include

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interruption of oncogenic signaling. Further drug approvals in 2016 ushered in a new era of immunotherapy and unleashed the potential for synergistic combination therapies. Table 1 outlines therapies that will be discussed in this review.

Epidermal Growth Factor Receptor

The epidermal growth factor receptor (EGFR) is a member of the ErbB family of receptor tyrosine kinases and is abnormally activated in many epithelial cancers, including HNSCC [4]. EGFR activation leads to downstream tumor-promoting activities, and overexpression of EGFR in human tumors correlates with more aggressive disease [5]. Radiation therapy increases EGFR expression; therefore, blockade of signaling emanating from EGFR can sensitize cells to radiation [6,7].

Current Therapies

Cetuximab, a chimeric IgG1 mAb directed against EGFR, was approved in 2006 for use in combination with radiation therapy to treat locally or regionally advanced HNSCC. Findings from a Phase III clinical trial showed statistically significant improvement in locoregional control (24.4 months vs. 14.9 months), median overall survival (OS; 49.0 months vs. 29.3 months), and progression-free survival (PFS) when comparing radiation plus cetuximab to radiation alone [8]. In a single-arm study of patients with platinum-resistant, recurrent or metastatic HNSCC, cetuximab monotherapy showed a response rate of 13% [9]. This led to approval of cetuximab for single-agent use in this population. In 2011, cetuximab in combination with platinum-based therapy plus 5-fluorouracil (5-FU) was approved as first-line treatment for patients with recurrent locoregional and/or metastatic disease. Adding cetuximab to platinum/5-FU therapy prolonged median OS from 7.4 to 10.1 months and prolonged median PFS from 3.3 to 5.6 months [10]. Although these findings indicate a positive benefit of cetuximab treatment, relatively rapid development of resistance is seen in patients with recurrent or metastatic disease. To date, there are no predictive biomarkers for cetuximab response.

In addition to blocking the EGFR pathway and, thereby, inhibiting growth, cetuximab has been shown to induce antibody-dependent cell-mediated cytotoxicity (ADCC) *in vitro* (Figure 1) [11]. Moreover, cetuximab can activate T-cells by increasing dendritic cell cross-presentation [12].

Although the addition of cetuximab to therapeutic regimens represents a significant advance in the treatment of HNSCC, the low response rate to cetuximab monotherapy and eventual treatment failure when combined with other modalities highlight the limitations imposed by high rates of intrinsic and acquired resistance. As described below, other therapies targeting the EGFR pathway are currently under investigation.

Therapies in Development

Panitumumab is a fully human IgG2 mAb that shares an overlapping epitope on EGFR with cetuximab. Like cetuximab, panitumumab also functions to prevent ligand binding [13]. In a Phase III study of patients receiving cisplatin and fluorouracil, the addition of panitumumab was shown to increase PFS, while having no effect on OS [14]. In a Phase II trial of patients

with locally advanced HNSCC, there was no benefit associated with the addition of panitumumab to standard fractionation radiotherapy and cisplatin (CONCERT 1) [15]. Substitution of cisplatin with panitumumab in combined treatment with radiotherapy for unresected stage III-IVb HNSCC resulted in reduced locoregional control (CONCERT-2) [16]. This unremarkable clinical data may be due to panitumumab's inability to induce ADCC, owing to its IgG2 subclass [17]. Like cetuximab, zalutumumab is an IgG1 mAb that can block ligand binding and EGFR dimerization as well as induce ADCC [17,18]. A Phase III study showed that zalutumumab did not increase OS in patients with recurrent or metastatic disease after failure of platinum-based therapy [19]. Unlike the above anti-EGFR mAbs, nimotuzumab blocks ligand binding while still allowing EGFR dimerization and therefore basal activation [20]. Nivolumab is already approved in Cuba for the treatment of advanced, nonoperable HNSCC, and is currently undergoing Phase II testing in conjunction with chemoradiation for locally advanced disease (NCT00702481[i]) [21].

In an attempt to mimic the ADCC properties of cetuximab, imgatuzumab was introduced as a glycoengineered mAb for ADCC. The carbohydrate-containing Fc region of this molecule binds avidly to the FcγRIIIα receptor, which is expressed on immune effector cells [22]. In addition to demonstrating clinical activity in *KRAS*-mutated colorectal cancer patients, an exploratory study in HNSCC patients showed that imgatuzumab treatment resulted in increased tumor immune infiltration [23,24]. Sym004 is a mixture of two mAbs that bind to two different epitopes in the extracellular region of EGFR. Sym004 not only blocks ligand binding but also induces internalization and degradation of the receptor. In a trial of patients with cetuximab-resistant HNSCC, nearly half of patients treated with Sym004 experienced a modest tumor response. However, only 12% of Sym004-treated patients were alive without disease progression at 6 months [25,26]. ABBV-221 is an antibody-drug conjugate that utilizes a mAb linked to the antineoplastic agent, monomethyl auristatin E, in order to deliver a toxic payload directly to the tumor site. A Phase I study showed stable disease following ABBV-221 treatment in 38% (16/42) of patients with various EGFR-dependent cancers [27].

Unlike mAbs that are targeted to the extracellular domain of EGFR, a number of small molecule tyrosine kinase inhibitors (TKIs) have been developed that bind to the EGFR intracellular domain and inhibit the intrinsic tyrosine kinase activity (Figure 1). The most studied TKI in HNSCC clinical trials is erlotinib, which binds reversibly. As a single agent in refractory, recurrent and/or metastatic HNSCC, erlotinib has shown only a 4% response rate, which is worse than cytotoxic therapy, and a median survival and 1-year survival comparable to palliative care [28]. In patients with locoregional disease, erlotinib did not increase PFS when added to cisplatin and radiation [29]. An ongoing Phase II study is examining the benefit of adding erlotinib to standard cytotoxic therapy and cetuximab in patients with recurrent or metastatic disease (NCT01316757[ii]). Another well-studied reversible TKI, gefitinib, did not improve outcomes in recurrent/metastatic disease in a Phase III trial. Dacomitinib is an irreversible TKI that not only targets EGFR (HER1), but also other ErbB family members, including ErbB2 (HER2) and ErbB4 (HER 4). As a single

[i] https://clinicaltrials.gov/ct2/show/NCT00702481
[ii] https://clinicaltrials.gov/ct2/show/NCT01316757

agent, dacomitinib has shown similar response rates compared to cetuximab in recurrent/metastatic disease [30,31]. Afatinib, an irreversible EGFR and HER2 inhibitor, has shown promise as a second line agent in metastatic disease compared to methotrexate, especially in patients with tumor biomarkers: p16-negative, EGFR-amplified, HER3-low, and PTEN-high [32].

Phosphoinositide 3-kinase/Mechanistic Target of Rapamycin

Once activated, receptor tyrosine kinases initiate several signal transduction cascades, including activation of the phosphoinositide 3-kinase (PI3K) pathway. PI3K phosphorylates phosphatidylinositol 4,5-bisphosphate (PIP_2) to generate phosphatidylinositol 3,4,5-trisphosphate (PIP_3), which in turn activates PDK1 and AKT (Figure 1). Activated AKT phosphorylates the mechanistic target of rapamycin (mTOR), leading to cell cycle progression, proliferation, and cell survival. Aberrant hyperactivation of the PI3K pathway has been observed in half of HNSCC cases. The PI3K enzyme is comprised of multiple catalytic and regulatory isoforms, but mutations in *PIK3CA*, the gene encoding p110α catalytic subunit, have been detected in 35% of HNSCC tumors [33]. *In vivo* studies have shown that patient-derived xenograft tumors harboring these mutations are sensitive to a PI3K inhibitor, suggesting opportunities for future clinical investigations [34]. Downstream of PI3K, mTOR has been shown to be activated in >70% of HNSCC specimens and therefore presents another favorable target for therapy [35].

Therapies in Development

When added to paclitaxel, the pan-PI3K inhibitor, buparlisib, demonstrated increased PFS in patients with platinum-pretreated recurrent/metastatic HNSCC [36]. Buparlisib is also being studied in combination with cetuximab in recurrent/metastatic disease and as monotherapy in patients with platinum- and cetuximab-refractory disease (NCT01816984[iii], NCT01737450[iv]). To increase delivery to target sites, the pan-PI3K inhibitor SF1126 includes a peptide sequence that binds to integrins (αvβ3/α5β1) expressed on the surface of endothelial and tumor cells [37]. Also in clinical trials are the isoform-specific PI3K inhibitors, alpelisib (anti-p110α), INCB050465 (anti-p110δ), and copanlisib (anti-p110α and anti-p110δ), which have been developed in an attempt to minimize the adverse effects observed with less specific inhibitors (NCT02145312[v], NCT02822482[vi]). Another isoform, p110γ, is the target of IPI-549. Unlike the above-mentioned targets, the p110γ isoform is highly expressed in myeloid cells. p110γ inhibition switches activation of macrophages from the immunosuppressive M2 subtype to the proinflammatory M1 subtype [38]. Therefore, IPI-549 has the potential to work synergistically with established immunotherapies to overcome resistance.

Everolimus and temsirolimus are mTOR inhibitors that are also being studied to disrupt PI3K pathway signaling. Everolimus as monotherapy did not show clinical activity in

[iii] https://clinicaltrials.gov/ct2/show/NCT01816984
[iv] https://clinicaltrials.gov/ct2/show/NCT01737450
[v] https://clinicaltrials.gov/ct2/show/NCT02145312
[vi] https://clinicaltrials.gov/ct2/show/NCT02822482

patients with recurrent/metastatic disease nor did everolimus with erlotinib produce a significant benefit for patients with platinum-resistant disease [39,40]. Everolimus is currently being studied in induction and adjuvant therapy in locally advanced disease (NCT01133678[vii], NCT01111058[viii]). Temsirolimus in combination with carboplatin and paclitaxel in patients with recurrent/metastatic disease resulted in a 41.7% objective response [41].

The modest clinical effects of PI3K/mTOR inhibitor monotherapy may be due to feedback activation of several receptor tyrosine kinases [42]. Combination therapy and pre-selection of patients with relevant PI3K/mTOR mutations may maximize the efficacy of these inhibitors [43].

Signal Transducer and Activator of Transcription

The ultimate target site of most signal transduction cascades is gene expression in the nucleus, where transcription factors can drive oncogenic signaling. The signal transducer and activator of transcription (STAT) family of proteins mediate various cellular functions related to oncogenesis (Figure 1). Increased activation of STAT3 in particular has been observed in many cancers and is a well-validated target for therapeutics [44]. Activation of STAT3 is associated with negative prognoses in many malignancies including colorectal, cervical, and gastric cancers [45–47]. Unlike enzymatic targets (egg. kinases), however, transcription factors like STAT3 lack the catalytic pockets amenable to small-molecule inhibition. Moreover, their intracellular localization makes them difficult to target with mAbs.

Therapies in Development

By harnessing the DNA binding activity of STAT3, an oligonucleotide “decoy” inhibitor was developed. This decoy consists of a 15-bp double-stranded oligonucleotide that is derived from a STAT3 response element in the *c-fos* promoter. The STAT3 decoy competitively inhibits STAT3 binding to genomic DNA and inhibits target gene expression in preclinical models [48]. In the first clinical trial involving a STAT3-specific inhibitor, the decoy was injected into patient tumors prior to resection. Compared to tumors injected with saline, specimens from decoy-injected tumors showed reduced expression of the STAT3 target genes encoding cyclin D1 and Bcl-X_L. Subsequent cyclization of the decoy molecule has allowed for effective systemic administration and anti-tumor activity in preclinical models [49]. Only one small molecule STAT3 inhibitor, C188-9, is currently being evaluated in clinical trials (NCT03195699[ix]). C188-9 targets a peptide-binding site within the STAT3 Src homology 2 (SH2) domain, which is necessary for dimerization and activation of STAT3 [50].

Another approach being used to downregulate STAT3 signaling in cancer cells involves the use of antisense. AZD9150 is a STAT3 antisense oligonucleotide that has been shown to

[vii] https://clinicaltrials.gov/ct2/show/NCT01133678
[viii] https://clinicaltrials.gov/ct2/show/NCT01111058
[ix] https://clinicaltrials.gov/ct2/show/NCT03195699

decrease STAT3 mRNA and protein levels and inhibit the growth of xenograft tumors in preclinical models. A Phase I clinical trial of AZD9150 showed antitumor activity in patients with treatment-refractory lymphoma and non-small cell lung cancer. These results have led to an ongoing Phase II trial of AZD9150 in advanced solid tumors including HNSCC (NCT02499328[x]) [51].

Immunotherapy

The immunotherapeutic landscape for HNSCC encompasses a variety of targets that suppress or stimulate the immune system's ability to eliminate neoplastic cells. Activation of checkpoint receptors, such as programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated protein (CTLA-4), causes T cell suppression. In contrast, activation of co-stimulatory receptors, such as CD40, glucocorticoid-induced tumor necrosis factor receptor (GITR), and toll-like receptors (TLRs), causes immune system stimulation. In addition to receptor signaling, certain enzymes, such as indoleamine 2,3-dioxygenase (IDO) and arginase 1 (Arg1), modify the tumor microenvironment by depleting nutrients essential for T cell proliferation while other enzymes, such as inducible nitric oxide synthase (NOS2), produce toxins that inhibit T cell proliferation.

A functioning immune system with the capacity to eliminate neoplastic cells is dependent on T cell recognition of antigens along with co-stimulatory and inhibitory signals. Co-stimulatory signals contribute to the defense against pathogens while inhibitory signals prevent autoimmunity. Cancer cells have been shown to express ligands that lead to inhibitory signaling in order to evade elimination by T cells [52]. These ligands bind to receptors, often called checkpoint receptor proteins, on the surface of T cells, resulting in T cell suppression (Figure 2). One such inhibitory receptor is PD-1, which is expressed on activated T cells. PD-1 expression and engagement has been shown to inhibit immune-modulated tissue damage as well as lead to suppression of T cell proliferation during chronic infections [53]. The expression of checkpoint ligands such as PD-L1 and PD-L2 by tumors leads to evasion of the anti-tumor immune response. Efforts to prevent this mechanism of immune evasion have led to the development and approval of the two newest therapies for HNSCC. Combinations of immune and antineoplastic therapies are being studied to maximize immunostimulatory effects.

Current Therapies

Pembrolizumab is a mAb directed against PD-1 and was first approved for use in metastatic melanoma. In August 2016, it was granted accelerated approval as a single agent in patients with recurrent/metastatic HNSCC with disease progression on or after platinum chemotherapy. Approval was based on the results of a Phase Ib trial that showed an overall response rate of 18% in this population. Moreover, median duration of response (time from initial disease response to disease progression) for pembrolizumab was 53 weeks compared to 4 months for cetuximab [54]. A Phase III study comparing pembrolizumab with standard of care (SOC) in patients with recurrent or platinum-resistant disease showed an increase in

[x]https://clinicaltrials.gov/ct2/show/NCT02499328

OS from 7.1 months in the SOC group to 8.4 in the pembrolizumab group. This result of unstratified data was not statistically significant but alluded to the presence of prolonged stable disease. In fact, in patients harboring tumors with PD-L1 expression in >50% of their cancer cells, OS improved to 11.6 in the pembrolizumab group vs. 7.9 months in the SOC group [55].

This study also suggests that pembrolizumab may be a better treatment option in this population due to its favorable toxicity profile compared to SOC. In addition, results from a study of patients with recurrent/metastatic disease refractory to both platinum and cetuximab show an overall response rate of 16% [56]. An ongoing Phase III study in patients with recurrent/metastatic HNSCC is evaluating pembrolizumab alone or in combination with cisplatin and 5-FU versus cetuximab in combination with cisplatin and 5-FU (NCT02358031[xi]).

Nivolumab is another mAb targeting PD-1 and was approved in November 2016 for use as a single agent in patients with recurrent/metastatic HNSCC with disease progression on or after platinum chemotherapy. This approval was based on results from a Phase III study comparing nivolumab to standard, single-agent therapies of methotrexate, docetaxel, or cetuximab. Compared to standard therapy, nivolumab showed improvement in median OS from 5.1 months to 7.5 months and an increase in the estimated 1-year survival rate from 16.6% to 36.0%. In addition, the response rate in the nivolumab group was 13.3% compared to 5.8% in the standard therapy group [57].

Although the response rates of pembrolizumab and nivolumab in HNSCC remain below 20%, the dramatic improvements in OS compared to SOC suggest prolonged stable disease. Checkpoint inhibition offers tremendous promise, and there is a high level of interest in this therapeutic approach. Pembrolizumab and nivolumab are involved in 47 and 25 active clinical trials, respectively. In addition to being studied in the neoadjuvant setting and in combination with radiotherapy, PD-1 inhibitors are being studied with other chemotherapeutic modalities in hopes of maximizing the potential of immunotherapy.

Therapies in Development

Like PD-1, CTLA-4 is also a checkpoint receptor protein that inhibits T cell activation (Figure 2). T cell inhibition mediated by PD-1 and CTLA-4, however, occurs via distinct intracellular mechanisms [58]. In addition, CTLA-4 can cause further immunosuppression via its constitutive expression on regulatory T cells (Tregs), which results in competitive binding to B7. The co-inhibitory CTLA-4 receptor is a homologue of the co-stimulatory CD28 receptor, and both bind the B7 ligand. The binding of B7 to CTLA-4 is thought to down-regulate cell surface expression of B7 on antigen presenting cells, leading to reduced CD28-B7 co-stimulation [59]. In a HNSCC patient cohort, CTLA-4-positive Tregs were enriched in tumor infiltrating lymphocytes and were the suspected cause of the observed dysfunction of the neighboring effector cells [60]. Moreover, in a study of cetuximab-treated HNSCC patients, those with increased frequency of circulating CTLA-4 had worse clinical outcomes [61]. Ipilimumab is a mAb directed against CTLA-4 and is approved for treatment

[xi] https://clinicaltrials.gov/ct2/show/NCT02358031

of metastatic melanoma. Ipilimumab is undergoing trials both as a single-agent and in combination with nivolumab in recurrent/metastatic HNSCC. The differing mechanisms of action of CTLA-4 and PD-1 offer potential for synergistic activity. A Phase III study in untreated metastatic melanoma showed improved PFS with the combination of nivolumab and ipilimumab versus treatment with either agent alone [62].

In contrast to antagonizing co-inhibitory receptors, other therapeutic approaches seek to stimulate co-stimulatory proteins. CD40 is a co-stimulatory receptor expressed on antigen-presenting cells (APCs) and binds to its ligand on activated T cells in order to initiate adaptive immunity (Figure 2). SEA-CD40 is a mAb that promotes APC maturation, up-regulation of co-stimulatory receptors, and production of pro-inflammatory cytokines *in vitro.* Moreover, like imgatuzumab described above, SEA-CD40 is also designed to bind to FcγRIIIα with high affinity in order to induce ADCC [63]. SEA-CD40 is currently being evaluated in a Phase I trial as monotherapy and in combination with pembrolizumab in HNSCC (NCT02376699[xii]). ABBV-927 is another agonistic mAb directed against CD40 and is in Phase I trials as monotherapy and in combination with nivolumab (NCT02988960[xiii]).

GITR is another co-stimulatory protein that can be targeted to promote antitumor immune response (Figure 2). In mouse models, GITR co-stimulation led to proliferation of $CD8^+$ and $CD4^+$ peripheral T cell populations. Treg proliferation was also triggered, but with a corresponding loss of the anergic phenotype [64]. INCAGN01876 is an agonistic mAb directed against GITR and is undergoing Phase I trials in combination with pembrolizumab and nivolumab in patients with various metastatic cancers, including HNSCC (NCT03126110[xiv]).

Like CD40 and GITR, TLRs can also be targeted with agonists (Figure 2). Part of the innate immune system, TLRs recognize conserved microbial products, such as bacterial lipopolysaccharides, and transduce signals that lead to host defense [65]. SD-101 is a novel oligonucleotide therapeutic agent that binds to TLR9. Intratumoral injection of SD-101 in combination with pembrolizumab is being studied in patients with recurrent/metastatic HNSCC (NCT02521870[xv]). The small molecule TLR8 agonist, motolimod, is being studied in the neoadjuvant setting in combination with cetuximab and nivolumab in patients with resectable tumors (NCT02124850[xvi]).

In addition to receptor targeting, modification of the tumor microenvironment can also be exploited to promote antitumor immune responses (Figure 2). IDO catalyzes the initial rate-limiting step in tryptophan catabolism, and IDO expression in various tumor types correlates with poor prognoses [66–68]. Tryptophan-deficient conditions lead to T cell cycle arrest *in vitro*, and IDO inhibition exhibits antitumor effects *in vivo*, suggesting a role for IDO in tumor immune escape [69,70]. The small molecule IDO inhibitor, epacadostat, is being

[xii] https://clinicaltrials.gov/ct2/show/NCT02376699
[xiii] https://clinicaltrials.gov/ct2/show/NCT02988960
[xiv] https://clinicaltrials.gov/ct2/show/NCT03126110
[xv] https://clinicaltrials.gov/ct2/show/NCT02521870
[xvi] https://clinicaltrials.gov/ct2/show/NCT02124850

investigated in combination with pembrolizumab in the neoadjuvant setting in patients with resectable HNSCC and with nivolumab in advanced HNSCC (NCT03325465[xvii], NCT02327078[xviii]).

Another approach for modifying the tumor microenvironment involves interfering with the function of myeloid-derived suppressor cells (MDSCs). MDSCs exert their immunomodulating effects through diverse mechanisms, including Arg1-mediated depletion of L-arginine and production of nitric oxide (NO) via NOS2 [71]. Similar to the effects of IDO on local tryptophan concentrations, Arg1 acts to starve the tumor microenvironment of L-arginine, thus limiting T cell proliferation. INCB001158 is a small molecule arginase inhibitor that is being studied in clinical trials both as monotherapy and in combination with pembrolizumab (NCT02903914[xix]). In addition to L-arginine depletion, NO production also transforms the tumor microenvironment to promote immune escape. Short-term NO exposure reversibly inhibits T cells, and sustained exposure leads to T cell apoptosis [72]. L-NMMA is a small molecule pan nitric oxide synthase inhibitor that is being investigated in combination with pembrolizumab (NCT03236935[xx]). Interestingly, inhibition of phosphodiesterase 5 (PDE5) leads to increased cGMP within MSDCs, resulting in reduced expression of Arg1 and NOS2 [73]. Treatment of HNSCC patients with the PDE5 inhibitor tadalafil led to decreased circulating and tumor MSDCs and Tregs, and elevated levels of circulating $CD8^+$ T cells [74]. Tadalafil is currently being studied in combination with nivolumab (NCT03238365[xxi]).

Concluding Remarks

Targeted therapy in HNSCC began with molecules directed against the extracellular region of EGFR, evolved to interrupt downstream components of receptor-mediated intracellular signaling, and now involves activation of anti-tumor immunity. Existing targets will continue to be pursued using new technology platforms like antibody-drug conjugates and oligonucleotides (see Outstanding Questions). In addition to systemic administration of emerging therapies, there is also potential for their use in the perioperative setting to decrease tumor burden and in combination with radiation to promote chemosensitization. Because of the vast number of therapies being studied, reliable biomarkers should be developed to identify patients most likely to benefit. In metastatic non-small cell lung cancer (NSCLC), for example, testing for PD-L1 expression guides first-line treatment of TKIs versus pembrolizumab. The potential of combination regimens using emerging therapies is both promising and resource-prohibitive. In view of the large number of potential combinations to be tested, prioritization criteria should be established to yield the most effective treatments in a timely manner. In addition to target identification, the next decade in HNSCC therapy research is poised to focus on new drug technology platform development, utilization of other treatment modalities, and optimization of combination regimens. Realization of this research, along with the results of ongoing clinical trials, is

[xvii] https://clinicaltrials.gov/ct2/show/NCT03325465
xviii: https://clinicaltrials.gov/ct2/show/NCT02327078
[xix] https://clinicaltrials.gov/ct2/show/NCT02903914
[xx] https://clinicaltrials.gov/ct2/show/NCT03236935
[xxi] https://clinicaltrials.gov/ct2/show/NCT03238365

critical to moving beyond incremental improvement of patient prognoses and achieving curative results in this devastating disease.

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Highlights

- Prior to cetuximab approval in 2006, treatment for head and neck cancer consisted of cytotoxic chemotherapy and radiation.
- Patients with recurrent and metastatic disease rapidly develop resistance to cetuximab, so novel EGFR-targeting therapies, such as antibody drug conjugates and glycoengineered immunostimulatory mAbs, are being studied.
- Small molecules and oligonucleotides are being developed to inhibit the downstream components of receptor signaling cascades including intracellular tyrosine kinases, PI3K, and STAT3.
- Approval of pembrolizumab and nivolumab in 2016 ushered in a new era of immunotherapy for HNSCC and unleashed the potential for synergistic combination therapies.
- Immunotherapeutic strategies include promotion of immunostimulatory signaling and inhibition of immunosuppresive signaling.

- With the vast number of therapies in development, can biomarkers be developed to guide targeted treatment in head and neck cancer, as is the case with PD-L1 expression in NSCLC?
- Is there a way to prioritize combination regimens in clinical trials, particularly those incorporating immunotherapy?
- Can targeted therapies be optimized with other modalities like radiation and surgery?
- Are there expanded opportunities for novel therapeutic agents such as oligonucleotides? Can they be developed for safe and effective systemic administration?

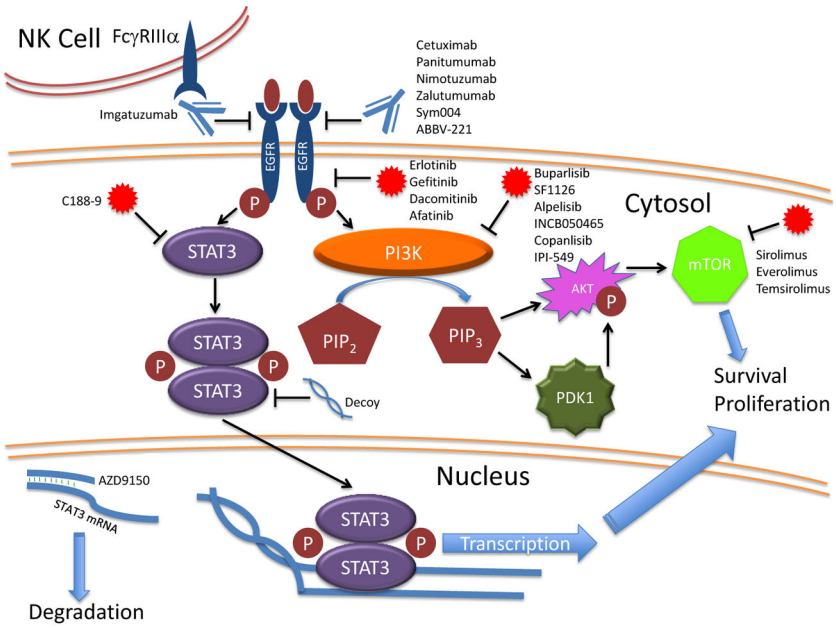

Figure 1. Stimulation of the EGFR Pathway Drives Survival and Proliferation of Tumor Cells

The epidermal growth factor receptor (EGFR) transduces extracellular signals by activating phosphoinositide 3-kinase (PI3K), which in turn facilitates the conversion of phosphatidylinositol 4,5-bisphosphate (PIP_2) to phosphatidylinositol 3,4,5-trisphosphate (PIP_3). Presence of PIP_3 ultimately results in cell survival and proliferation via several downstream mediators, notably the mechanistic target of rapamycin (mTOR). EGFR can also activate the signal transducer and activator of transcription 3 (STAT3), which is a transcription factor for genes involved in cell survival and proliferation. Monoclonal antibody-based therapeutics include cetuximab, panitumumab, nimotuzumab, zalutumumab, Sym004, ABBV-221, and imgatuzumab, which all target the EGFR extracellular domain. Erlotinib, gefitinib, dacomitinib, and afatinib are small molecule tyrosine kinase inhibitors that are directed toward the EGFR intracellular domain. PI3K is targeted by small molecules that include buparlisib, SF1126, alpelisib, INCB050465, copanlisib, and IPI-549. Sirolimus, everolimus, and temsirolimus are related compounds that inhibit mTOR. In addition to small molecule inhibition, therapeutic oligonucleotide decoys can bind to STAT3, and antisense oligonucleotides like AZD9150 can silence STAT3 mRNA.

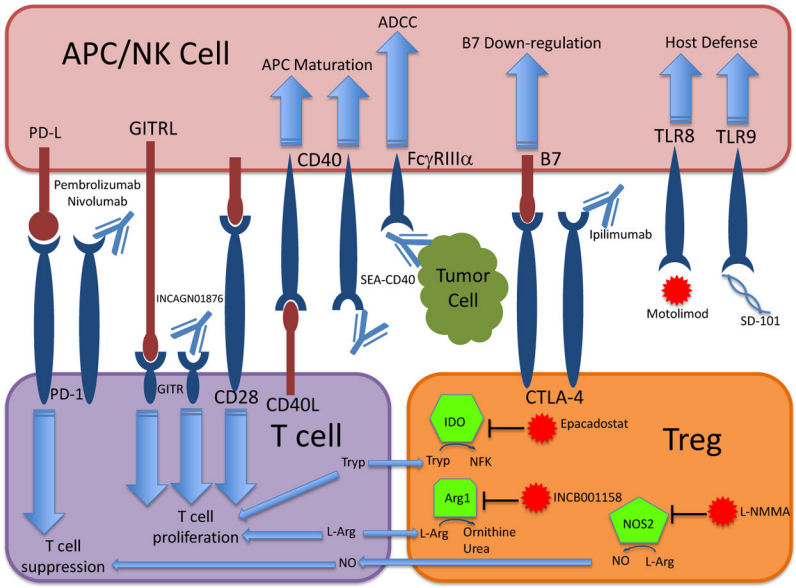

Figure 2. Immunotherapy Landscape in Head and Neck Cancer

Binding of programmed cell death protein 1 (PD-1) to its ligand, PD-L, causes T cell suppression. Pembrolizumab and nivolumab are mAbs that bind to PD-1 and antagonize its immunosuppressive effects. Activation of cytotoxic T-lymphocyte-associated protein (CTLA-4) also causes T cell suppression. Moreover, binding of CTLA-4 to B7 causes B7 downregulation, which is also immunosuppressive. Ipilimumab prevents ligand binding to CTLA-4, thereby antagonizing this immunosuppression. Activation of co-stimulatory receptors, such as CD40, glucocorticoid-induced tumor necrosis factor receptor (GITR), and toll-like receptors (TLRs), causes immune system stimulation. Binding of mAb SEA-CD40 to CD40 causes antigen presenting cell (APC) maturation and can also induce antibody-dependent cell-mediated cytotoxicity (ADCC) by binding the FcγRIIIα receptor. The mAb INCAGN01876 binds GITR and ultimately leads to T cell proliferation. The small molecule motolimod, and oligonucleotide SD-101 bind TLRs on APCs, thereby stimulating host defense. Indoleamine 2,3-dioxygenase (IDO) and arginase 1 (Arg1) deplete tryptophan and L-arginine, respectively. Both amino acids are essential for T cell proliferation. Epacadostat inhibits IDO while INCB001158 inhibits Arg1. Inducible nitric oxide synthase (NOS2) produces nitric oxide (NO), which causes T cell suppression. L-NMMA is a NOS2 inhibitor.

Table 1

Therapies in Development for Head and Neck Cancer

Target	Name	Class
Epidermal growth factor receptor (EGFR), extracellular	Cetuximab	Monoclonal antibody
	Panitumumab	
	Nimotuzumab	
	Zalutumumab	
	Sym004	
	ABBV-221	
Epidermal growth factor receptor (EGFR), tyrosine kinase	Erlotinib	Small molecule
	Gefitinib	
	Dacomitinib	
	Afatinib	
Phosphoinositide 3-kinase (PI3K)	Buparlisib	Small molecule
	SF1126	
	Alpelisib	
	INCB050465	
	Copanlisib	
	IPI-549	
Mechanistic target of rapamycin (mTOR)	Sirolimus	Small molecule
	Everolimus	
	Temsirolimus	
Signal transducer and activator of transcription 3 (STAT3)	C188-9	Small molecule
	Decoy	Oligonucleotide
	AZD9150	
Programmed cell death protein 1 (PD-1)	Pembrolizumab	Monoclonal antibody
	Nivolumab	
Cytotoxic T-lymphocyte-associated protein (CTLA-4)	Ipilimumab	
CD40	SEA-CD40	
Glucocorticoid-induced tumor necrosis factor receptor (GITR)	INCAGN01876	
Toll-like receptor (TLR)	Motolimod	Small molecule
	SD-101	Oligonucleotide
Indoleamine 2,3-dioxygenase (IDO)	Epacadostat	Small molecule
Arginase 1 (Arg1)	INCB001158	
Inducible nitric oxide synthase (NOS2)	L-NMMA	