

Rising to the therapeutic challenge of head and neck cancer

Jane de Lartigue, PhD

As a significant cause of cancer-related mortality, head and neck cancer presents an important therapeutic challenge that has proven relatively resistant to attempts to improve patient outcomes over the past several decades. In recent years, molecular profiling of head and neck cancers has provided greater insight into their significant genetic heterogeneity, creating potential opportunities for novel therapies. Here, we discuss the most promising advances.

Limited progress in HNSCC treatment

Cancers of the nasal cavity, sinuses, mouth, lips, salivary glands, throat, and larynx, collectively called head and neck cancers, are the sixth leading cause of cancer-related death worldwide. The majority of head and neck cancer arises in the epithelial cells that line the mucosal surfaces of the head and neck and is known as squamous cell carcinoma (HNSCC).

If caught in the early stages, HNSCC has a high cure rate with single-modality treatment with either surgery or radiation therapy (RT).¹ However, a substantial proportion of patients present with advanced disease that requires multimodality therapy and has significantly poorer outcomes. Locally advanced HNSCC is typically treated with various combinations of surgery, RT, and chemotherapy and survival rates for all patients at 5 years are 40%-60%, compared with 70%-90% for patients with early-stage disease.^{1,3} Up to half of locally advanced tumors relapse within the first 2 years after treatment. For patients with recurrent/metastatic disease, various chemotherapeutic regimens are available but median survival is typically less than a year.³⁻⁵

EGFR and beyond: novel targeted strategies

In recent years, the focus of research has shifted to the identification of molecularly targeted therapies as researchers have begun to unravel the mechanisms underlying the development of HNSCC. Epidermal growth factor receptor (EGFR) emerged as a promising target since the discovery of its upregulation in more than 90% of tumors and across all stages of disease.^{6,7} Intense research into EGFR-targeting

therapies culminated in the approval of the EGFR-targeting monoclonal antibody (mAb) cetuximab in 2006 for the treatment of locally advanced disease in combination with RT and platinum-based chemotherapy, and as monotherapy.⁸ Cetuximab is also often used in combination with platinum-based chemotherapy in patients with recurrent/metastatic disease after it was shown that the combination improved disease control rates and increased overall survival (OS).^{9,10} Despite these successes, only modest gains in survival have been achieved.

Numerous other agents targeting EGFR and other members of the EGFR family, including both mAbs and tyrosine kinase inhibitors, have been and continue to be evaluated in patients with HNSCC, with several in late-stage clinical testing (Table 1). The results of a phase 2 study of nimotuzumab administered concurrently with chemoradiation therapy (CRT) demonstrated that the combination is safe and effective and warrants further long-term study.¹¹ Meanwhile, promising results have also recently been reported from 2 trials of the irreversible EGFR-HER2 inhibitor afatinib.

In a phase 2 study, afatinib showed significant efficacy in patients with HNSCC following failure of platinum-based chemotherapy, particularly when used after cetuximab failure.¹² Results from the phase 3 LUX-Head & Neck 1 trial were reported at the 2014 European Society for Molecular Oncology meeting (ESMO) and showed that afatinib improved progression-free survival (PFS), with a 20% reduction in the risk of progression, and significantly delayed deterioration of global health status and worsening of pain compared with methotrexate in the recurrent/metastatic setting.¹³

To address the potential for development of resistance to EGFR-targeting therapies in HNSCC, which may partly explain the limited efficacy observed to date, other nodes of this signaling pathway are also being targeted. Agents under investigation include PI3K, Akt, and mTOR inhibitors, as well as multitargeted tyrosine kinase inhibitors that block multiple pathways simultaneously. Despite promising clinical trials, none of these agents has

TABLE 1 EGFR-targeting agents evaluated in HNSCC

Drug	Manufacturer	Description	Status of ongoing clinical testing in head and neck cancer (clinicaltrials.gov identifier)
Cetuximab (Erbix)	Bristol-Myers Squibb/ Eli-Lilly	Chimeric monoclonal antibody targeting EGFR	FDA approved
Panitumumab (Vectibix)	Amgen	Fully human monoclonal antibody targeting EGFR	Phase 3 in combination with RT (NCT00820248) Various phase 2 (NCT00446446, NCT00798655, NCT01307956)
Zalutumumab	Genmab	Fully human monoclonal antibody targeting EGFR	Phase 3 in combination with CRT (NCT00496652)
Nimotuzumab	YM Biosciences	Chimeric monoclonal antibody targeting EGFR	Phase 3 CRT +/- nimotuzumab (NCT01345084) Phase 3 Post-op adjuvant concurrent CRT +/- nimotuzumab (NCT00957086) Various phase 2 (NCT01516996, NCT02041819, NCT02034968)
Erlotinib (Tarceva)	Genentech	Reversible tyrosine kinase inhibitor targeting EGFR	Phase 2 CT +/- erlotinib in resectable HNSCC (NCT01064479) Phase 2 in combination with IMRT and pemetrexed in secondary or primary disease (NCT00573989) Phase 2 in combination with carboplatin, paclitaxel and cetuximab in recurrent/metastatic disease (NCT01316757)
Gefitinib (Iressa)	AstraZeneca	Reversible tyrosine kinase inhibitor targeting EGFR	Numerous completed, none ongoing
Lapatinib (Tykerb)	GlaxoSmithKline	Dual tyrosine kinase inhibitor targeting EGFR and HER2/neu	Phase 2 RT and cisplatin +/- lapatinib (NCT01711658; TRYHARD) Phase 2 in combination with RT for stage III/IV patients who cannot tolerate concurrent chemotherapy (NCT00490061) Phase 2 in combination with cisplatin and RT in patients with unresected disease (NCT00387127)
Afatinib (Gilotrif)	Boehringer Ingelheim	Irreversible tyrosine kinase inhibitor targeting EGFR and HER2/neu	Phase 3 as maintenance therapy (NCT01427478) Phase 3 vs methotrexate in recurrent/metastatic disease after platinum chemotherapy (NCT01345682; LUX-Head&Neck 1) Phase 3 vs methotrexate in recurrent/metastatic disease after platinum chemotherapy (NCT01856478; LUX-Head&Neck 3) Phase 3 vs placebo as adjuvant therapy after CRT (NCT01345669; LUX-Head&Neck 2) Phase 3 vs placebo as adjuvant therapy after CRT (NCT02131155; LUX-Head&Neck 4)

CRT, chemoradiation therapy; EGFR, epidermal growth factor receptor; FDA, Food and Drug Administration; HER2/neu, human epidermal growth factor receptor 2; IMRT, intensity-modulated radiation therapy; RT, radiation therapy

been introduced into clinical practice as yet.

A range of other therapeutic strategies has been evaluated in HNSCC (Table 2, Figure 1). Mutations in the cyclin-dependent kinase gene, *CDKN2A*, are frequently detected in HNSCC. Loss of *CDKN2A* can drive overexpression of CDK4 and CDK6, which may make head and neck tumors sensitive to pharmacological inhibition of these proteins, thus several CDK inhibitors have been evaluated in HNSCC. Again there has been limited success, with only 1 agent currently being evaluated in clinical trials. The SPARK and MONARCH trials of P276-00 –

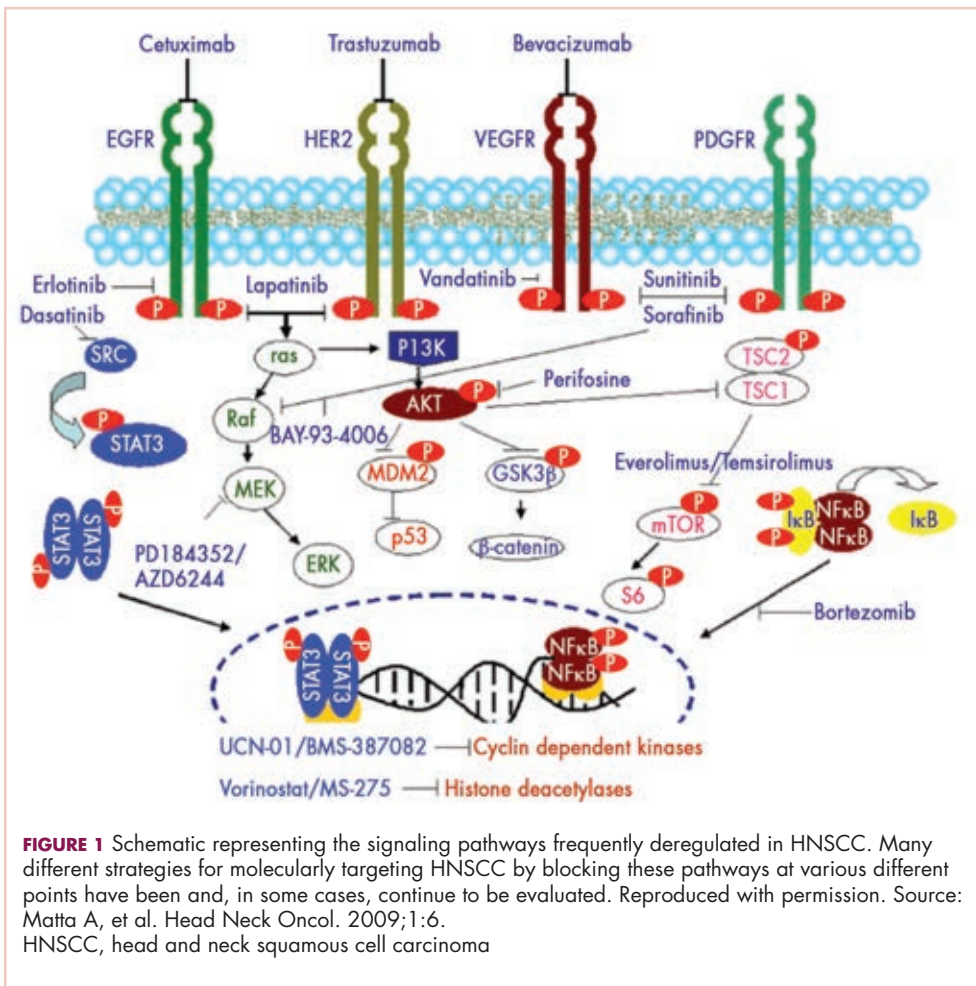
an inhibitor of CDK4, 1, and 9 – have been completed but the results have not yet been reported.

The vascular endothelial growth factor receptor (VEGFR) pathway, which plays a significant role in blood vessel formation (angiogenesis) and is often co-opted by tumors to enhance the tumor blood supply, has been reported to be upregulated in up to 40% of HNSCCs.¹⁴ The VEGF-targeting mAb bevacizumab is currently being evaluated in a variety of clinical trials in patients with HNSCC, including a phase 3 trial in combination with chemotherapy in recurrent/metastatic disease.

TABLE 2 Selection of targeted therapies evaluated in HNSCC

Drug	Manufacturer	Description	Status of ongoing clinical testing in head and neck cancer (clinicaltrials.gov identifier)
P276-00	Piramal Enterprises	CDK inhibitor	Phase 2 MONARCH trial in recurrent/metastatic disease completed (NCT00824343) – no results reported yet Phase 1/2 SPARK trial in combination with RT completed (NCT00899054) – no results reported yet
Bevacizumab (Avastin)	Genentech	Humanized monoclonal antibody targeting VEGF-A	Phase 3 in combination with chemotherapy in recurrent/metastatic disease (NCT00588770) Various phase 2 (NCT00703976, NCT01588431, NCT00423930)
Sorafenib (Nexavar)	Bayer Healthcare/ Onyx Pharmaceuticals	Multitargeted tyrosine kinase inhibitor	Phase 2 in combination with carboplatin and paclitaxel (NCT00494182) Phase 1/2 in combination with cisplatin and docetaxel (NCT02035527)
Sunitinib (Sutent)	Pfizer	Multitargeted tyrosine kinase inhibitor	Phase 2 alternating with cisplatin and gemcitabine as induction therapy for locally advanced nasopharyngeal carcinoma (NCT01309633) Phase 1b in combination with RT in patients with cancer, including head and neck cancer (NCT00437372)
Vandetanib (Vactima)	AstraZeneca	Tyrosine kinase inhibitor targeting VEGFR, EGFR, and RET kinases	Phase 2 in preventing cancer in patients with precancerous head and neck lesions (NCT01414426)
Pazopanib (Votrient)	GlaxoSmithKline	Tyrosine kinase inhibitor targeting VEGFR, PDGFR, and c-KIT	Phase 1 in combination with cetuximab for incurable disease (NCT01716416)
Axitinib (Inlyta)	Pfizer	Tyrosine kinase inhibitor targeting VEGFR, PDGFR, and c-Kit	Phase 2 in unresectable, recurrent/metastatic disease (NCT01469546)
Nilotinib (Tasigna)	Novartis	Multi-targeted tyrosine kinase inhibitor	Phase 1 in combination with cetuximab in solid tumors including head and neck (NCT01871311)
Trametinib	GlaxoSmithKline	MEK inhibitor	Phase 2 in surgically resectable oral cavity squamous cell carcinoma (NCT01553851)
PX866	Oncothyreon	PI3K inhibitor	Phase 1/2 in combination with cetuximab (NCT01252628) Phase 1/2 in combination with docetaxel (NCT01204099)
BKM120 (Buparlisib)	Novartis	PI3K inhibitor	Phase 2 in combination with paclitaxel in recurrent/metastatic disease treated with platinum-based chemotherapy (NCT01852292) Phase 1/2 in combination with cetuximab (NCT01816984)
BYL719	Novartis	PI3K inhibitor	Phase 2 in recurrent/metastatic patients who failed platinum-based chemotherapy (NCT02145312) Phase 1/2 in combination with cetuximab in recurrent/metastatic disease (NCT01602315)
MK2206	Merck	Akt inhibitor	Phase 2 in recurrent nasopharyngeal carcinoma (NCT01370070)
Everolimus (Afinitor)	Novartis	mTOR inhibitor	Phase 2 (NCT01111058) Phase 2 in locally advanced disease (NCT01133678)
Temsirolimus (Torisel)	Pfizer	mTOR inhibitor	Phase 1 in combination with cetuximab in advanced solid tumors including head and neck (NCT02215720)
LY2801653	Eli Lilly	MET inhibitor	Phase 1 (NCT01285037)
AZD1775	AstraZeneca	Wee1 kinase inhibitor	Phase 1 in refractory solid tumors including head and neck (NCT01748825) Phase 2 in combination with cisplatin in recurrent/metastatic disease (NCT02196168)

CDK, cyclin-dependent kinase; VEGF-A, vascular endothelial growth factor-A; VEGFR, vascular endothelial growth factor receptor; EGFR, epidermal growth factor receptor; PDGFR, platelet-derived growth factor receptor; PI3K, phosphatidylinositol 3-kinase; mTOR, mammalian target of rapamycin; RT, radiation therapy



Challenges of molecular targeting in HNSCC

The development of molecularly targeted therapies in HNSCC have thus far been tempered by a poor understanding of the complex genetic background of this disease. More recently, advances in high throughput genome sequencing technology have allowed researchers to more thoroughly profile the genomic landscape of HNSCC and to identify potential novel therapeutic targets. Several key sequencing studies have been performed and are summarized in Table 3. From these studies it has become clear that HNSCCs are highly heterogeneous; characterized by a paucity of readily targetable driver mutations and frequent loss of tumor suppressor genes, which are significantly more difficult to target pharmacologically.

The tumor suppressor gene *TP53* is particularly frequently associated with HNSCC and makes it substantially more difficult to treat. The p53 protein is a transcription factor that regulates the expression of a host of target genes and, as its moniker “guardian of the genome” sug-

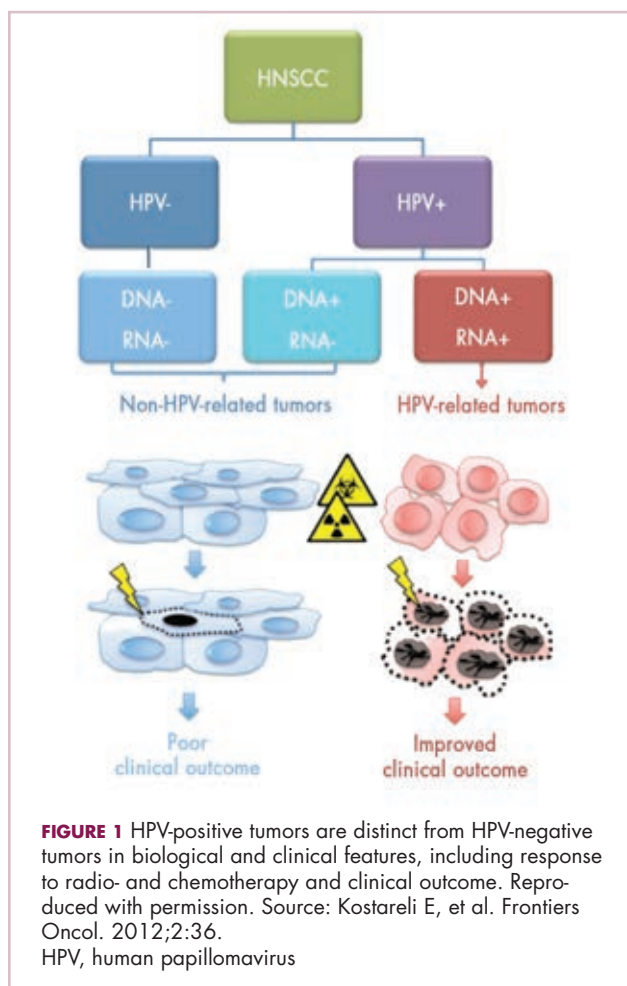
FIGURE 1 Schematic representing the signaling pathways frequently deregulated in HNSCC. Many different strategies for molecularly targeting HNSCC by blocking these pathways at various different points have been and, in some cases, continue to be evaluated. Reproduced with permission. Source: Matta A, et al. *Head Neck Oncol.* 2009;1:6. HNSCC, head and neck squamous cell carcinoma

TABLE 3 Major sequencing studies of HNSCC

Study	No. of patients	% smokers	% HPV-positive	Significantly mutated genes identified (%)	Mutations per MB (HPV-positive/-negative)
Stransky ¹	74	89	14	<i>TP53</i> (62), <i>CDKN2A</i> (12), <i>FAT1</i> (12), <i>NOTCH1</i> (14)	2.28/4.83
Agrawal ²	32	75	25	<i>TP53</i> (47), <i>CDKN2A</i> (9.2), <i>NOTCH1</i> (15)	4.8/20.6
Pickering ³	40	78.6	2.5	<i>TP53</i> (66), <i>CASP8</i> (10), <i>FAT1</i> (28), <i>PIK3CA</i> (11)	Not reported
India ICGC ⁴	50	96	26	<i>TP53</i> (62), <i>CASP8</i> (34), <i>FAT1</i> (40), <i>NOTCH1</i> (16), <i>HRAS</i> (12)	4.07/3.36
Seiwert ⁵	120	55	42.5	HPV-negative tumors: <i>TP53</i> (81), <i>CDKN2A</i> (21), <i>MLL2</i> (18), <i>CUL3</i> (10), <i>NSDI</i> (10), <i>PIK3CA</i> (13), <i>NOTCH1</i> (16) HPV-positive tumors: <i>PIK3CA</i> (22), <i>FGFR</i> (14), <i>NOTCH1</i> (12), <i>MLL2</i> (10), <i>DDX3X</i> (8), <i>CYLD</i> (6)	2.46/2.22

Adapted from Riaz N. *Genes Dis.* 2014;1:75.

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gests, functions primarily to maintain the integrity of the genome. Since p53 has proven difficult to target directly researchers have turned to seeking out other genes that are specifically required for the survival of cancerous cells that contain p53 mutations so that they might indirectly target p53-mutant cancers like HNSCC.

Several research groups are taking this concept a step further and performing “functional kinomics” to identify genes that encode kinases because these are so readily druggable. Researchers have recently reported the results of such a screen in which they identified 38 candidate kinases that had an impact on the survival of p53-mutant HNSCC cell lines. Among the kinases was Wee1, which regulates the G2/M transition in the cell cycle. Because p53 plays an important role in the G1 checkpoint, p53-mutant cancer cells may be more dependent on a functioning G2 checkpoint, thus they may be exquisitely sensitive to inhibitors of proteins like Wee1. Drugs targeting this kinase are already under development, including AZD1775. In preclinical mouse models, it inhibited the growth of p53-mutant HNSCC tumors by more than 60% and up to 80%

when combined with cisplatin.¹⁵ The results of a phase 1 trial of AZD1775 in patients with refractory solid tumors was reported at the 2014 American Society of Clinical Oncology meeting. There was evidence of significant anti-tumor efficacy in HNSCC patients with *BRCA* mutations and accrual is ongoing in *BRCA*-positive patients.¹⁶ A phase 2 trial of AZD1775 in combination with cisplatin in patients with recurrent/metastatic HNSCC is currently enrolling patients (Table 2).

HPV – more than a prognostic indicator

The most significant risk factors for HNSCC are heavy exposure to alcohol, tobacco, and high-risk human papillomavirus (HPV) infection, mainly HPV-16. In recent years, the epidemiology of HNSCC has shifted considerably as a result of a reduction in tobacco consumption and a notable increase in HPV infection, such that although the overall incidence of HNSCC has decreased in developed countries over the last 30 years, the incidence of oropharyngeal cancers related to HPV infection has increased significantly.¹⁷⁻¹⁹

Currently, HPV-negative and HPV-positive tumors are treated in the same way. However, HPV-positive patients typically have a more favorable prognosis than do their HPV-negative counterparts – they have been shown to have a better 3-year OS rate and a more than 50% reduction in the risk of death.²⁰ HPV E6 and E7 serology in combination with HPV-16 is most directly correlated with prognosis.²¹ Patients with HPV-positive tumors have also been reported to have significantly improved outcomes when treated with CRT (Figure 2).

In addition to these biological and clinical differences, a recent sequencing study highlighted the substantial genetic diversity between HPV-negative and HPV-positive tumors. Seiwert and colleagues analyzed mutations and copy number variations in 617 cancer-associated genes in 120 tumor-normal pairs from HNSCC patients. Although previous sequencing studies have been dominated by HPV-negative tumor samples, HPV-positive tumors represented almost half of the total tumor samples in this study. There was no significant difference in the frequency of mutations in patients with HPV-negative compared with HPV-positive tumors, but there were very different types of genetic alterations (Table 3). HPV-negative tumors had a mutation spectrum that was similar to squamous cell lung carcinoma, with frequent mutations in *TP53* and *CDKN2A*, whereas HPV-positive tumors had a unique mutation profile, including mutations that were previously thought to be rare in HNSCC.²² Further characterization of the distinct mutation profiles of HPV-positive and HPV-negative tumors will be extremely important to assist in the development of targeted therapies and HPV status may become an important biomarker of treatment response.

TABLE 4 Promising immunotherapeutic agents being evaluated in HNSCC

Drug	Manufacturer	Description	Status of ongoing clinical testing in head and neck cancer (clinicaltrials.gov identifier)
ADXS 11-001	Advaxis	Live attenuated <i>Listeria</i> vaccine that targets the HPV oncoprotein E7	Phase 2 (NCT02002182)
Allovax	Immunovative Therapies	Combines Allostim (immune cells conjugated with monoclonal antibody-coated microparticles) and vaccine formulation containing chaperone proteins isolated from the patient's tumor	Phase 1/2 (NCT01998542)
INO-3112	Inovio Pharmaceuticals	Combines the DNA vaccine VGX-3100 with a DNA-based IL-12 immune activator (INO-9012)	Phase 1/2a (NCT02163057)
Multikine	CEL-SCI	Combination immunotherapy consisting of a mixture of cytokines including interleukins, interferons, chemokines and colony stimulating factors, giving it both active and passive immune activity	Phase 3 in advanced disease (NCT01265849; IT-MATTERS)
Ipilimumab (Yervoy)	Bristol-Myers Squibb	Immune checkpoint inhibitor; monoclonal antibody targeting CTLA-4	Phase 1 in combination with cetuximab and IMRT in locally advanced disease (NCT01860430) Phase 1 in combination with cetuximab and IMRT in previously untreated stage III/IVB disease (NCT01935921)
Pembrolizumab (Keytruda)	Merck	Immune checkpoint inhibitor; monoclonal antibody targeting PD-1	Phase 3 in metastatic/recurrent disease (NCT02252042; KEYNOTE-040) Phase 2 in metastatic/recurrent disease after treatment with platinum-based chemotherapy and cetuximab (NCT02255097; KEYNOTE-055) Phase 2 in combination with reirradiation in locoregional inoperable recurrent or second primary disease (NCT02289209) Phase 2 in surgically resectable disease (NCT02296684) Various phase 1
Nivolumab	Bristol-Myers Squibb	Immune checkpoint inhibitor; monoclonal antibody targeting PD-1	Phase 3 in recurrent/metastatic disease (NCT02105636; CheckMate041) Phase 1/2 in combination with the IDO inhibitor INCB24360 in advanced solid cancers, including head and neck (NCT02327078)
MPDL3280A	Roche	Immune checkpoint inhibitor; monoclonal antibody targeting PD-L1	Phase 1 in advanced/metastatic solid tumors, including head and neck (NCT01375842)

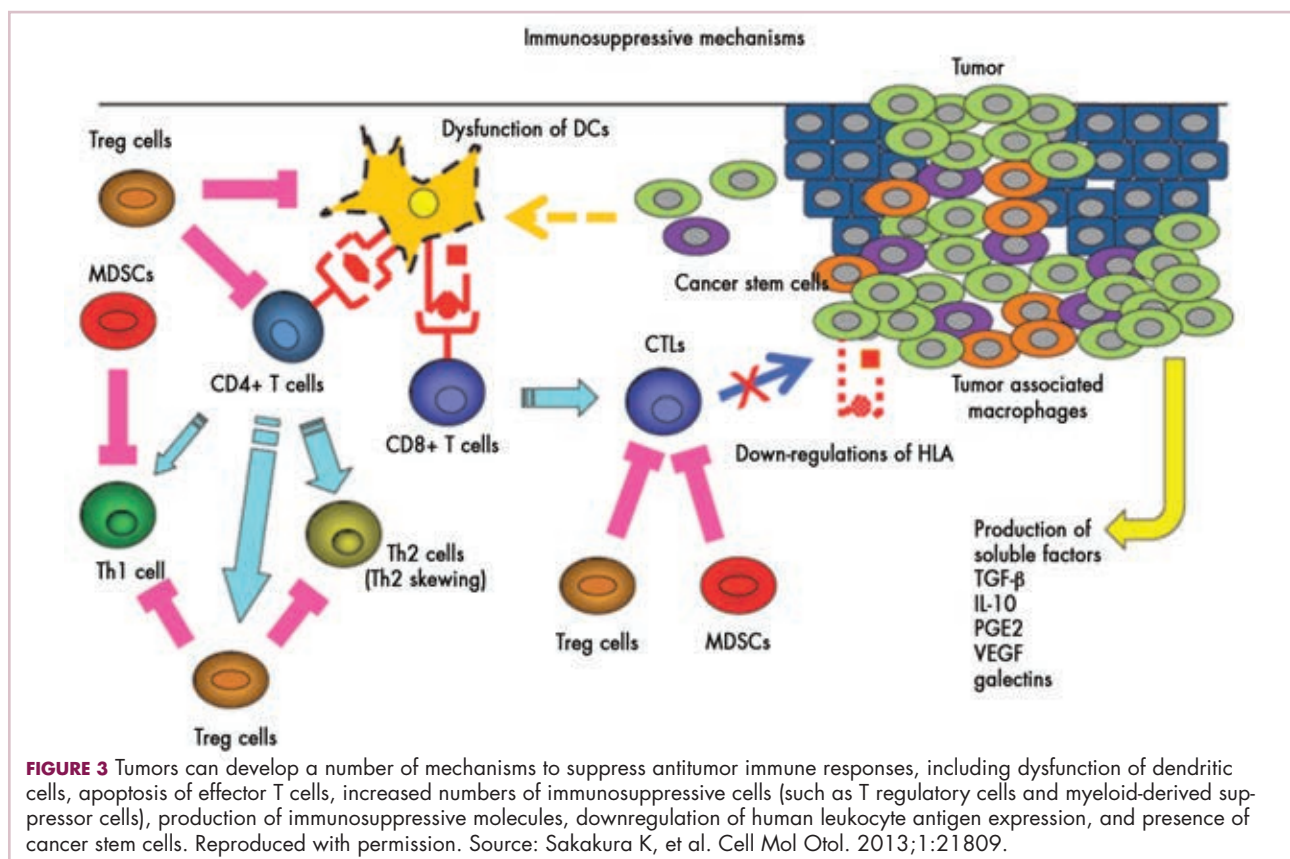
CTLA-4, cytotoxic T lymphocyte antigen 4; IDO, indoleamine 2,3-dioxygenase; IMRT, intensity modulated radiation therapy; PD-1: programmed cell death receptor 1; PD-L1: programmed cell death ligand 1

Targeting the immunosuppressive environment

Head and neck tumors express many unique antigens that make them highly immunogenic, thus immunotherapy is a promising therapeutic strategy. A number of immunotherapies have been tested in HNSCC, including immune stimulants such as interleukins (eg, IL-2 and IL-12) and interferons (eg, IFN γ), and a range of different vaccines, including dendritic cell-based vaccines, peptide-based vaccines, whole tumor vaccines, and therapeutic HPV vac-

cines. Although clinical trials of several vaccines and novel immune stimulants (Table 4), are still ongoing, for the most part immunotherapy has met with disappointing results.²³

More recently, our understanding of the complex interaction between the immune system and cancer has led to the discovery of numerous mechanisms of immune suppression and avoidance that are used by tumors to overcome the antitumor immune response (Figure 3). HNSCC is no exception, and these mechanisms of immune evasion



may partly explain the poor clinical activity of immunotherapies to date.

The fact that HNSCCs are highly immunosuppressive provides a strong rationale for testing a new class of immunotherapy – checkpoint inhibitors. These drugs are designed to inhibit the cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death receptor 1 (PD-1) proteins that govern several inhibitory signaling networks, which switch off activated T cells at the appropriate time to maintain self-tolerance and limit collateral damage to healthy tissue. These pathways are hijacked by tumors as a means of dampening down the antitumor immune response and numerous cancer types have been shown to overexpress the PD-1 ligand PD-L1, which often correlates with poorer prognosis. Various checkpoint inhibitors are being evaluated in HNSCC patients (Table 4) and several are in late-stage clinical development.

The results of a phase 1b study of pembrolizumab were presented at the 2014 ESMO meeting. In that study, pembrolizumab was tested in 61 HPV-positive and -negative HNSCC patients who expressed PD-L1. The investigators reported an overall response rate of 26%, a response duration ranging from 8+ to 41+ weeks, and a response rate that was highly correlated with PD-L1 expression. The response rate was similar in HPV-negative and -positive patients,

but PFS and OS were longer in HPV-positive patients.²⁴

Treatment of advanced head and neck cancer remains a significant challenge, with poor response rates and substantial systemic toxicity associated with current standard of care. The search for more effective targeted therapies has proven disappointing to date, with still only a single targeted therapy approved by the US Food and Drug Administration. Improvements in sequencing technology are advancing our understanding of the significant genetic complexity and heterogeneity underlying this disease and may lead us to improvements in the HNSCC armamentarium in the near future.

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