HHS Public Access

Author manuscript

*Curr Treat Options Oncol*. Author manuscript; available in PMC 2023 April 04.

Published in final edited form as:

*Curr Treat Options Oncol*. ; 20(4): 31. doi:10.1007/s11864-019-0630-9.

# Immunotherapy Approaches Beyond PD-1 Inhibition: the Future of Cellular Therapy for Head and Neck Squamous Cell Carcinoma

**Hannan A. Qureshi, MD**[1], **Sylvia M. Lee, MD**[2,*]

[1]Department of Otolaryngology-Head and Neck Surgery, University of Washington, Seattle, WA, 98195, USA

[2]Division of Medical Oncology, Department of Medicine, University of Washington, 825 Eastlake Ave East, Mail Stop K2-231, Seattle, WA, 98109, USA

## Opinion statement

In a span of a few years, the surprising early successes of programmed cell death 1 (PD-1) inhibitors across a vast range of tumor types have transformed our understanding of cancer immunogenicity and provided proof of principle that T cells, if manipulated, can mediate meaningful tumor regression. In head and neck cancer, only a minority of patients respond to PD-1 therapy, but these small outcomes have fueled the enthusiasm for the next generation of immunotherapy—adoptive cell therapy—which employs recent advances in genetic engineering and cell culturing methods to generate T cells with enhanced anti-tumor efficacy for infusion back into the patient. Head and neck cancer is comprised of biologically distinct cancers, HPV-positive and HPV-negative, and the clinical responses to PD-1 inhibitors in both HPV-positive and HPV-negative head and neck patients have showcased better than any other cancer type that there are distinct pathways to immunogenicity that may lend themselves to different therapeutic approaches. Thus, head and neck cancer is uniquely poised to benefit from the personalized approach of adoptive cell therapy as well as provide a valuable platform to explore contrasting T cell modalities. In this article, we will review the growing portfolio of trials of adoptive cell therapies in head and neck cancer and discuss the future directions of this emerging new field.

### Keywords

Head and neck squamous cell carcinoma; Immunotherapy; Tumor-infiltrating lymphocytes; Chimeric antigen receptor; T cell receptor; Adoptive cellular therapy

* leesm@uw.edu .

Conflict of Interest

Hannan A. Qureshi declares that he has no conflict of interest. Sylvia M. Lee is supported by research funding (paid to her institution) by Juno Therapeutics and Iovance Biotherapeutics.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

## Introduction

The landscape of oncology has changed dramatically over the past few years with the advent of immune checkpoint inhibition. Until recently, immunotherapy was considered a niche field that carried benefit for only a handful of cancers; however, the surprising early successes of program death protein 1 (PD-1) inhibitors across a vast range of tumor types revealed that the immune system has a greater capacity to recognize cancers than previously imagined. By providing proof of principle that T cells, if manipulated, are able to mediate an anti-tumor response that can achieve clinical tumor regression in many solid cancers, PD-1 therapy has also fueled the enthusiasm and hopes for another niche therapeutic modality, adoptive cellular therapy. As one of the early beneficiaries of PD-1 immune checkpoint blockade, head and neck cancer has been a natural area of interest in the development of T cell therapies that will hopefully deliver greater precision and efficacy. The distinct pathways of oncogenesis seen in head and neck cancer lend itself particularly well to the exploration and development of multiple T cell strategies.

Head and neck squamous cell carcinoma (HNSCC) is the seventh leading cause of cancer-related mortality in the world [1] with an estimated 63,030 new cases and 13,360 deaths in 2017 in the USA alone [2]. In reality, it is comprised of two clinically and biologically distinct cancers: tobacco- and alcohol-induced HNSCC versus virally mediated HNSCC. Numerous studies have demonstrated that the risk of head and neck cancer increases in a dose-dependent manner from tobacco and alcohol consumption, with a fivefold to 25-fold increase among heavy smokers and a synergistic impact from concurrent alcohol use [3, 4]. While improved public education on the health risks of smoking has led to a decline in tobacco-associated HNSCC in the USA and other developed countries, this has been offset by a recent rise in human papillomavirus (HPV)–associated HNSCC which is expected to surpass the incidence of cervical cancer by 2020 [5–7]. Regardless of the type of HNSCC, the standard-of-care treatments have been chemotherapy, radiation therapy, and surgery. The historical 5-year overall survival rates with multimodality therapy approximate 50% among patients with locoregionally advanced disease [8]. The prognosis for patients with recurrent or metastatic HNSCC is especially poor with a median survival between 6 to 12 months [9], although superior outcomes have been seen in both the locally advanced and the recurrent metastatic setting for HPV-related oropharynx cancer [10, 11•]. HNSCC survivors often experience significant morbidity from aggressive treatment with surgery and radiation, including speech and swallowing dysfunction and physical disfigurement, which substantially lowers their daily quality of life. A great deal of hope has been placed on PD-1 therapy, with the recent approval of nivolumab and pembrolizumab in the USA for second-line therapy in HNSCC; however, the response rates remain less than 20% [12, 13]. Thus, there is a significant need for the development of alternative therapeutic modalities that can improve patient survival outcomes and limit the morbidity associated with treatment in HNSCC. This review will focus on the current developments in adoptive T cell therapy as a personalized immunotherapeutic approach for HNSCC.

## Background: HNSCC and the immune response

Initially posited by Paul Ehrlich more than a century ago, immune surveillance is now widely accepted to be an important mechanism by which the body's immune system continuously detects and eliminates malignant tumor cells [14]. Ultimately, an immune-mediated anti-tumor response relies on the ability of the T cell to recognize an antigen present on the cancer cell that is sufficiently different from the normal antigens expressed. Tumor outgrowth occurs when there is an acquisition of traits that allows cancer cells to evade the host immune response.

Immune checkpoints, such as program death protein 1 (PD-1), cytotoxic T lymphocyte–associated protein 4 (CTLA-4), T cell immunoglobulin and mucin-domain-containing 3 (TIM-3), and lymphocyte activation gene 3 (LAG-3), play a critical role in the immune escape mechanisms utilized by cancer cells to counter their own immunogenicity. Immune checkpoint blockade drugs targeting the T cell inhibitory receptors tip the balance of immune activation and inhibition in favor of activation. The most successful immune checkpoint inhibitors thus far, anti-PD1 anti-bodies, have demonstrated overall response rates of 16–18% and have produced durable clinical responses in the clinical trial setting (CHECK-MATE-141, KEYNOTE-012, KEYNOTE-040) in patients with recurrent/metastatic HNSCC [12, 15, 16]. This led to the FDA approvals in 2016 of pembrolizumab and nivolumab following progression on platinum-based chemotherapy. The ongoing examination of the mechanisms of response and resistance to immune checkpoint blockade is now guiding the first generation of adoptive T cell therapies that aim to target HNSCC.

Prior to the advent of PD-1 therapy, melanoma had long been considered one of the only truly immunogenic cancers, achieving responses to the older generation of immune therapies including IL-2 and adoptive cellular therapy with tumor-infiltrating lymphocytes (TIL) as well as the first immune checkpoint inhibitor, anti-CTLA-4 [17–19]. Only in recent years was it fully appreciated that melanoma also has the highest mutational burden among solid cancers—presumably due to years of exposure to an environmental mutagen, UV light—and these mutations, in turn, give rise to neoantigens on tumor cells that serve as potent stimulators of T cell–mediated anti-tumor responses within the host immune system [20].

With this understanding, efforts intensified towards developing immunotherapy against smoking-related cancers, including HNSCC. Like melanoma, HNSCC also arises after years of exposure to a mutagen in the form of tobacco, and sometimes alcohol, and has been found to have a relatively high mutational burden [20, 21]. The early finding that both lung cancer and head and neck cancer also experienced responses to PD-1 blockade further solidified the concept that mutational burden, regardless of etiology, is an important component of immunogenicity.

However, head and neck cancer also highlighted another important pathway to immunogenicity. The initial studies in PD-1 checkpoint blockade in HNSCC demonstrated responses not only in the heavy smokers but also slightly higher responses in the younger, non-smoking, HPV-positive patient population [22•]. Although the mutation rate of HPV-positive HNSCC is half that of HPV-negative HNSCC by whole-exome sequencing [21], the

HPV infection that leads to oncogenesis also provides the immune system with a convenient tag to distinguish between self and non-self through the novel expression of viral oncogenes. In fact, HPV-positive HNSCC has higher levels of T cell infiltration and overall immune cell infiltration [23] and is more sensitive to standard treatments compared to HPV-negative HNSCC. While there are other differences in tumor biology and contrasts in the patient populations, it is speculated that the increased T cell infiltration reflects the superior activity of the immune system against HPV-positive cancer cells and is one of the primary reasons why more favorable outcomes are seen in patients with HPV-positive HNSCC compared to smoking-related HNSCC.

## Adoptive T cell therapy

Adoptive T cell therapy involves the collection of T cells from a patient, followed by the ex vivo selection, manipulation, and expansion of the cells, for infusion back into a patient. One of the limitations of immune checkpoint blockade is that it relies on the presence of adequate endogenous tumor-reactive T cells to be unleashed by the removal of the checkpoint. However, some patients may not have enough naturally existing, tumor-reactive cells, or their cells may be exhausted or dysfunctional. The goal of adoptive cell therapy is to create a population of tumor-reactive T cells that will provide a therapeutic advantage either by the sheer number of expanded cells, or by an enhanced T cell specificity through genetic modification of a patient's T cells, or by additional activation of the T cell to carry superior functional capacity.

There are several critical components to an efficacious and safe adoptive T cell therapy, starting with target selection. The target peptide is ideally expressed by the majority of the cancer cells and intrinsic to cancer's survival and proliferative capacity; otherwise, downregulation of the target could be an easy mechanism of resistance [24]. The target peptide must also not be expressed on critical healthy tissues to avoid on-target, off-tumor toxicity.

Another important component of cellular therapy is a lymphodepleting chemotherapy regimen which is typically administered prior to the T cell infusion. Numerous studies have demonstrated improved expansion and persistence of the transferred T cells and superior efficacy when T cells are infused after a lymphodepleting regimen [25, 26]. It is believed that the creation of a lymphopenic environment prior to the T cell infusion reduces the competition for homeostatic cytokines, such as IL-7 and IL-15, leading to improved proliferation of the transferred T cells. In addition, the lymphodepleting chemotherapy reduces the numbers of immunosuppressive cells in the tumor microenvironment, such as regulatory T cells and myeloid-derived suppressor cells, which is thought to enhance T cell trafficking and activity.

After the T cell infusion, many adoptive cell therapy regimens incorporate a course of interleukin-2, a cytokine that enhances the anti-tumor efficacy and persistence of the transferred T cells [27, 28]. Both high-dose intravenous IL-2 and low-dose subcutaneous IL-2 are used in many regimens.

The three main modalities of adoptive cellular therapy under active development include tumor-infiltrating lymphocytes (TIL), T cells with genetically modified T cell receptors (TCR), and T cells inserted with chimeric antigen receptors (CAR). TIL therapy harnesses the endogenous anti-tumor T cells naturally residing in the patient and represents a heterogeneous population of cells with specificity against multiple targets, whereas TCR and CAR are typically clonal T cells that have been genetically engineered to target a specific antigen expressed by the cancer cells. Each of these types of adoptive T cell therapy is currently being investigated in head and neck cancers (Table 1).

## Tumor-infiltrating lymphocytes

TIL are comprised of a heterogeneous population of T cells that are present within a tumor's microenvironment. These T cells are thought to have infiltrated the tumor as a response to neoantigen exposure, but due to complex mechanisms are ineffective at eradicating the tumor. These mechanisms include expression of immune checkpoint ligands by tumor cells and other cells in the tumor microenvironment, inhibition of inflammatory cytokines and transcription factors, development of T cell tolerance to overexpressed/mutated antigens, and downregulation or mutation of HLA class I and antigen-processing machinery components [40]. The anti-tumor response from infiltrating T cells can be enhanced by removing these cells from the immunosuppressive tumor microenvironment to a setting where they can be preferentially expanded and activated in vitro and then infused back into the patient in high enough numbers to overcome many of the inhibitory factors in the tumor microenvironment and eliminate tumor cells [19].

The use of TIL to induce tumor regression was first carried out in a murine model at the Surgery Branch of the NIH in 1986 by Rosenberg and colleagues, who showed that a combination of autologous TIL and cyclophosphamide could induce regression of metastases [41]. They then pioneered and published the first human study in 1988 using autologous TIL to treat patients with metastatic melanoma and cause regression of cancer [42]. Thus far, TIL therapy has demonstrated consistent success in treating metastatic melanoma, with response rates greater than 50% and durable complete response rates of over 20% [17], and has fueled the interest in the development of similar adoptive T cell strategies in cancers such as head and neck. The standard regimen of TIL therapy includes nonmyeloablative lymphodepletion with cyclophosphamide and fludarabine, followed by the TIL infusion (comprised mostly of CD8+ and CD4+ T cells), followed by an abbreviated course of high-dose IL-2 (e.g., up to six doses), which is a potent cytokine growth factor that aids in the proliferation of the TIL.

In HNSCC, higher numbers of TIL are shown to be a significant independent prognostic factor in the overall survival of patients, in both HPV-positive and HPV-negative disease [43, 44], and higher levels of infiltrating T cells also predict a more favorable clinical outcome after adjuvant chemoradiation [23, 45–47]. Specifically, increased cytotoxic T cells (CD8+) and helper T cells (CD4+) are most commonly associated with improved prognosis [23, 48]. There is also a strong infiltration of regulatory T cells (Treg; FoxP3+), but the impact of these T cells on prognosis is unclear as they have been associated with improved or worse outcomes [23, 48, 49]. Lechner et al. studied the composition of TIL in HNSCC by

flow cytometry and found that they are mainly composed of an effector memory phenotype (CD45RA−, CCR7−) [50].

In a recent study by the National Cancer Institute (NCI), TIL therapy in HPV-related cancers showed a partial response in 2 out of 11 patients (18.2%) with non-cervical HPV-related cancer, one of which was a patient with oropharyngeal cancer with six prior lines of treatment, who experienced a response lasting 5 months (NCT01585428) [29]. The patients in this trial received a nonmyeloablative, lymphocyte-depleting preparative regimen consisting of cyclophosphamide and fludarabine, followed by the TIL infusion, followed by high-dose IV aldesleukin (IL-2), which has been the standard treatment regimen for TIL established by the NCI. Serious adverse events occurred in 2 of 11 non-cervical cancer patients, which included lymphopenia, febrile neutropenia, dysphagia, and syncope.

Currently, there is an ongoing phase II prospective, multicenter, single-arm clinical trial that is sponsored by Iovance Biotherapeutics, Inc. utilizing a single autologous TIL infusion (LN-145) as a treatment for recurrent and/or metastatic, previously treated HNSCC (NCT03083873). The primary endpoint is the objective response rate per RECIST v1.1, and secondary endpoints include an assessment of safety and other efficacy parameters such as progression-free and overall survival [30]. A second Iovance phase II trial has recently opened as well, examining a combination approach of TIL therapy plus PD-1 inhibitor pembrolizumab with a cohort dedicated to PD-1-naïve HNSCC patients (NCT03645928). There is also a phase II trial studying the safety and efficacy of cisplatin concurrent chemoradiotherapy plus TIL versus cisplatin concurrent chemoradiotherapy only with IMRT in patients with locoregionally advanced high-risk nasopharyngeal carcinoma centered in China (NCT02421640). The results of these ongoing trials will further elucidate the potential benefits of TIL therapy for patients with HNSCC.

## T cell receptor–engineered T cells

T cell receptor (TCR)–engineered T cells leverage the ability of clonal T cell populations to recognize given tumor-associated antigens and eradicate tumor cells via HLA-dependent mechanisms. These cells are engineered to express TCR α and β heterodimers that assemble into a TCR-CD3 signaling complex, with specificity for a target antigen [51]. A TCR may recognize either intracellular or extracellular antigens in the context of the major histocompatibility complex (MHC). Once the target antigen is selected, then the TCR can be genetically engineered to optimize the affinity for the specified antigen, assembled in gene transfer vectors, and introduced into T cells from a patient of the appropriate MHC type to deliver tumor specificity.

TCR-engineered T cells have been an attractive strategy for virally induced HNSCC given the potent immunogenicity of associated viral antigens. A preliminary study has shown the feasibility of expanding HPV-16 E6/E7–specific T cells from 33 of 52 oropharyngeal cancer patients [52]. The NCI conducted a phase I/II clinical trial (NCT02280811) of genetically engineered TCR T cells that target an HLA-A*02:01-restricted epitope of E6 in patients with metastatic HPV-16+ carcinoma, including HPV-associated oropharyngeal cancer [31, 32]. Only one of the 12 patients in this trial had oropharyngeal cancer and the

two partial responders had anal cancer; nevertheless, this trial validated that TCR T cell therapy can mediate HPV-associated epithelial cancer regression [31, 32]. More recently, the NCI reported encouraging results from another phase 1 clinical trial (NCT02858310) using TCR T cells targeting HPV16 E7 in HLA-A0201 patients who had progressed on multiple prior lines of treatment [33]. Of 12 patients, four of whom had oropharyngeal cancer, they observed four confirmed responses, which included 1 patient with oropharyngeal cancer.

There are several other ongoing studies that are exploring the use of HPV-specific TCRs. A trial at Baylor College of Medicine (NCT02379520) is investigating HPV-16/18 E6/E7–specific T cells engineered to be TGF-beta resistant to assess the safety of this therapy in patients with relapsed HPV-associated cancer. If the TCRs meet safety requirements, an additional study arm will then explore the combination of nivolumab plus the HPV-specific T cells following a lymphodepleting chemotherapy regimen. In China, a single-arm clinical trial is planned to open to determine the safety and efficacy of E6-specific TCR T cells for patients with HPV-16+ HNSCC and cervical cancer (NCT03578406).

TCR T cells specific for other non-viral antigens found on HNSCC are under active investigation as well. A phase 1 collaboration between Immatics and MD Anderson explores a personalized strategy of TCR generation through the use of a high-throughput cancer peptide discovery platform (XPRESIDENT®) to identify cancer cell targets from a patient's tumor to which exogenous TCRs are then generated and engineered into autologous T cells for infusion back into the patient (NCT03247309). This study is evaluating the safety and clinical activity of this custom-designed TCR T cell (IMA201) in recurrent or refractory HNSCC in addition to squamous non-small cell lung cancer [34]. A phase I clinical trial explores the safety of MAGE-A10$^{c796}$ T cells directed against cancer/testis antigen MAGE-A10, which is expressed in 17% of HNSCC (NCT02989064) [53]. The latter trial also includes patients with melanoma and bladder cancer, and early data from 8 patients treated with a dosage of $0.1 \times 10^9$ cells showed no evidence of on-target or off-target toxicity and supported continued investigation at higher doses [35].

## Chimeric antigen receptor T cells

Chimeric antigen receptors (CAR) confer enhanced T cell specificity and function by combining antibody-binding domains with T cell signaling and costimulatory domains [51, 54]. A CAR is commonly composed of a specificity-conferring extracellular antibody single-chain variable fragment (scFV), a CD3$\zeta$ domain, and one or more intracellular costimulatory domains. CAR allow for highly specific targeting of a cell surface antigen in an MHC-independent fashion. Compared to TCRs, a primary limitation of CAR T cells in head and neck cancer is they cannot recognize intracellular peptide targets (such as the viral oncoproteins E6 and E7). However, one of the benefits is that CAR T cells do not require patients to have a matched HLA type to be treated. Also, CAR are less vulnerable to the tumor escape mechanisms of acquired impairment in tumor antigen presentation machinery or HLA expression [55].

Data on the efficacy of CAR T cells to treat HNSCC is limited to in vitro and pre-clinical studies. Targets that have been tested in these models for HNSCC have included chondroitin

sulfate proteoglycan-4 (CSPG4), HER2, and ErbB [56–58]. Of these targets, there is an active phase I clinical trial evaluating the safety of intratumoral delivered CAR T cells targeting the ErbB receptor family (NCT01818323). Intratumoral delivery of CAR T cells is a relatively novel approach aimed at avoiding associated toxicities, such as cytokine release syndrome and neurologic dysfunction [59]. Most recent data on the dose escalation in 13 patients displayed no dose-limiting toxicities with an overall disease control rate of 69% using RECIST 1.1 criteria despite rapidly progressing tumors on trial entry [36]. Given the accessibility of disease sites in head and neck cancer in the oropharynx and cervical neck nodes, HNSCC is ideal cancer to investigate the intratumoral delivery of T cells.

## T cell approaches for EBV+ head and neck cancer

Nasopharyngeal cancer is a unique subset of head and neck cancer, which is endemic in Southern China, Southeast Asia, and North Africa, and is characterized by the presence of intratumoral Epstein-Barr virus DNA [60]. As in HPV-positive oropharyngeal cancer, EBV infection leads to the incorporation of foreign oncogenes that can then serve as a potent immunogenic target. In the 1990s, the exploration of T cell strategies against EBV antigens had an early start through the investigation of the adoptively transferred EBV-specific cytotoxic T cells for EBV-associated lymphoproliferative disease in transplant recipients. Straathof et al. showed safety and feasibility of EBV-specific T cells in 10 patients with nasopharyngeal cancer, including 6 patients who had disease refractory to intensive chemotherapy and radiation, and achieved complete or partial responses in 3 of the 6 patients with relapsed disease [37]. Comoli et al. similarly studied the use of EBV-specific T cells in patients with stage IV EBV–related nasopharyngeal cancer refractory to conventional therapy and observed disease control in six of 10 patients (two with partial response and four with stable disease) [38]. Smith et al. investigated the use of T cells specific for EBV latent membrane proteins LMP1 and LMP2 in 24 patients with recurrent and metastatic nasopharyngeal carcinoma and demonstrated an increase in median overall survival to 17 months, from 7 months in patients who did not receive these T cells [39]. There is an ongoing phase I clinical trial of TGF-beta resistant, EBV-specific T cells for the treatment of EBV-positive nasopharyngeal carcinoma (NCT02065362).

## Future directions

The advent of adoptive T cell strategies for HNSCC is still in its infancy; however, there is growing interest and hope for their potential to improve the poor prognosis associated with recurrent and metastatic HNSCC. Challenges that need to be overcome to increase treatment responses include identifying target peptides with higher specificity on HNSCC cells. Initiatives, such as The Cancer Genome Atlas (TCGA), and efforts at other institutions to further identify and profile genes expressed in tumor cells as well as intracellular and extracellular neoantigens in HNSCC would aid in the discovery of new potential targets for TCR and CAR T cell therapy. TIL therapy has already demonstrated itself to be not only a therapeutic end but also a simultaneous platform for further antigen discovery through the interrogation of TIL populations that successfully mediate tumor regression [61]. Further optimization of the design of receptor constructs for TCR-engineered T cells to minimize auto-immunity and the design of CAR T cells to enhance T cell signaling and persistence, as

well as identification of the ideal T cell subsets for genetic modification, is an active area of research.

HNSCC is an immunosuppressive malignancy with lower absolute numbers of circulating T cell lymphocytes, higher levels of immunosuppressive cytokines, and higher numbers of immunosuppressive regulatory T cells compared to healthy subjects [40]. A greater understanding of the immune suppressive entities specific to the HNSCC tumor microenvironment is also needed to develop other strategies to diminish its intrinsic immunosuppressive nature, optimize T cell trafficking to tumor sites, and help potentiate overall responses to adoptive T cell strategies as well as other immunotherapy approaches. Lastly, combination approaches of adoptive T cell therapy with other cancer treatments for HNSCC, such as immune checkpoint inhibitors, are starting to be explored in the next wave of trials and may achieve higher and/or more durable responses than either treatment alone.

## Conclusions

HNSCC is a heterogeneous disease group with distinct pathways of oncogenesis and immunogenicity. The emerging understanding of antigenicity combined with the early successes of PD-1 therapy has positioned HNSCC in a historically new light, as cancer that can be recognized by endogenous immune responses in a significant number of patients and a promising target for the next wave of T cell–based strategies. All three of the major modalities of T cell therapy—TIL, TCR, and CAR—are actively being investigated in HNSCC. In turn, the diversity of HNSCC provides a unique platform to improve our understanding of the factors influencing the efficacy of different T cell approaches and ultimately inform the development of cellular therapy in other cancers as well. Many challenges remain in identifying effective target antigens, optimizing T cell design for improved efficacy and persistence, identifying biomarkers to predict treatment response, and ultimately, developing a cost-effective and scalable manufacturing process to ensure the accessibility of effective T cell therapy to patients. In the coming years, adoptive cell therapy will hopefully usher in a new era of personalized treatment, with greater precision, decreased morbidity, and more lasting responses, and in doing so transform the prognosis of HNSCC along the way.

## References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

• Of importance

1. Fitzmaurice C, Allen C, Barber RM, Barregard L, Bhutta ZA, Brenner H, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 Cancer groups, 1990 to 2015: a systematic analysis for the global burden of disease study. JAMA Oncol. 2017;3(4):524–48. [PubMed: 27918777]
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin. 2017;67(1):7–30. [PubMed: 28055103]
3. Blot WJ, McLaughlin JK, Winn DM, Austin DF, Greenberg RS, Preston-Martin S, et al. Smoking and drinking in relation to oral and pharyngeal cancer. Cancer Res. 1988;48(11):3282–7. [PubMed: 3365707]

4. Wyss A, Hashibe M, Chuang SC, Lee YC, Zhang ZF, Yu GP, et al. Cigarette, cigar, and pipe smoking and the risk of head and neck cancers: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. Am J Epidemiol. 2013;178(5):679–90. [PubMed: 23817919]

5. Chaturvedi AK, Engels EA, Pfeiffer RM, Hernandez BY, Xiao W, Kim E, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. J Clin Oncol. 2011;29(32):4294–301. [PubMed: 21969503]

6. Ramqvist T, Dalianis T. An epidemic of oropharyngeal squamous cell carcinoma (OSCC) due to human papillomavirus (HPV) infection and aspects of treatment and prevention. Anticancer Res. 2011;31(5):1515–9. [PubMed: 21617204]

7. Sturgis EM, Cinciripini PM. Trends in head and neck cancer incidence in relation to smoking prevalence: an emerging epidemic of human papillomavirus-associated cancers? Cancer. 2007;110(7):1429–35. [PubMed: 17724670]

8. Tao Y, Auperin A, Sire C, Martin L, Khoury C, Maingon P, et al. Improved outcome by adding concurrent chemotherapy to cetuximab and radiotherapy for locally advanced head and neck carcinomas: results of the GORTEC 2007–01 phase III randomized trial. J Clin Oncol. 2018;2018:JCO2017762518.

9. Vermorken JB, Mesia R, Rivera F, Remenar E, Kawecki A, Rottey S, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med. 2008;359(11):1116–27. [PubMed: 18784101]

10. Ang KK, Harris J, Wheeler R, Weber R, Rosenthal DI, Nguyen-Tân PF, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med. 2010;363(1):24–35. [PubMed: 20530316]

11•. Fakhry C, Zhang Q, Nguyen-Tan PF, Rosenthal D, El-Naggar A, Garden AS, et al. Human papillomavirus and overall survival after progression of oropharyngeal squamous cell carcinoma. J Clin Oncol. 2014;32(30):3365–7. [PubMed: 24958820] This randomized, phase 3 trial provided definitive evidence that T cell enhancement, using nivolumab, can achieve an overall survival benefit in HNSCC, providing proof of principle for the ongoing investigation of adoptive T cell strategies in HNSCC.

12. Chow LQM, Haddad R, Gupta S, Mahipal A, Mehra R, Tahara M, et al. Antitumor activity of pembrolizumab in biomarker-unselected patients with recurrent and/or metastatic head and neck squamous cell carcinoma: results from the phase Ib KEYNOTE-012 expansion cohort. J Clin Oncol. 2016;34(32):3838–45. [PubMed: 27646946]

13. Ferris RL, Blumenschein G, Fayette J, Guigay J, Colevas AD, Licitra L, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. N Engl J Med. 2016;375(19):1856–67. [PubMed: 27718784]

14. Ehrlich P Über den jetzigen Stand der Karzinomforschung. Ned Tijdschr Geneeskd. 1909;5:273–90.

15. Ferris RL, Blumenschein G, Fayette J, Guigay J, Colevas AD, Licitra L, et al. Nivolumab vs investigator's choice in recurrent or metastatic squamous cell carcinoma of the head and neck: 2-year long-term survival update of CheckMate 141 with analyses by tumor PD-L1 expression. Oral Oncol. 2018;81:45–51. [PubMed: 29884413]

16. Cohen EEW, Soulières D, Le Tourneau C, Dinis J, Licitra L, Ahn MJ, et al. Pembrolizumab versus methotrexate, docetaxel, or cetuximab for recurrent or metastatic head-and-neck squamous cell carcinoma (KEYNOTE-040): a randomised, open-label, phase 3 study. Lancet. 2019;393(10167):156–67. [PubMed: 30509740]

17. Rosenberg SA, Yang JC, Sherry RM, Kammula US, Hughes MS, Phan GQ, et al. Durable complete responses in heavily pretreated patients with metastatic melanoma using T-cell transfer immunotherapy. Clin Cancer Res. 2011;17(13):4550–7. [PubMed: 21498393]

18. Callahan MK, Kluger H, Postow MA, Segal NH, Lesokhin A, Atkins MB, et al. Nivolumab plus ipilimumab in patients with advanced melanoma: updated survival, response, and safety data in a phase I dose-escalation study. J Clin Oncol. 2018;36(4):391–8. [PubMed: 29040030]

19. Lee S, Margolin K. Tumor-infiltrating lymphocytes in melanoma. Curr Oncol Rep. 2012;14(5):468–74. [PubMed: 22878966]

20. Alexandrov LB, Nik-Zainal S, Wedge DC, Aparicio SA, Behjati S, Biankin AV, et al. Signatures of mutational processes in human cancer. Nature. 2013;500(7463):415–21. [PubMed: 23945592]
21. Stransky N, Egloff AM, Tward AD, Kostic AD, Cibulskis K, Sivachenko A, et al. The mutational landscape of head and neck squamous cell carcinoma. Science. 2011;333(6046):1157–60. [PubMed: 21798893]
22•. Seiwert TY, Burtness B, Mehra R, Weiss J, Berger R, Eder JP, et al. Safety and clinical activity of pembrolizumab for treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-012): an open-label, multicentre, phase 1b trial. Lancet Oncol. 2016;17(7):956–6. [PubMed: 27247226] This study demonstrated the clinical impact of HPV status in HNSCC on the endogenous T cell response following immune checkpoint blockade, providing guidance for future immuno-therapeutic strategies.
23. Mandal R, Şenbabaoğlu Y, Desrichard A, Havel JJ, Dalin MG, Riaz N, et al. The head and neck cancer immune landscape and its immunotherapeutic implications. JCI Insight. 2016;1(17):e89829. [PubMed: 27777979]
24. Debets R, Donnadieu E, Chouaib S, Coukos G. TCR-engineered T cells to treat tumors: seeing but not touching? Semin Immunol. 2016;28(1):10–21. [PubMed: 26997556]
25. Dudley ME, Yang JC, Sherry R, Hughes MS, Royal R, Kammula U, et al. Adoptive cell therapy for patients with metastatic melanoma: evaluation of intensive myeloablative chemoradiation preparative regimens. J Clin Oncol. 2008;26(32):5233–9. [PubMed: 18809613]
26. Turtle C, Hanafi L, Berger C, Sommermeyer D, Pender B, Robinson E, et al. Addition of fludarabine to cyclophosphamide lymphodepletion improves in vivo expansion of CD19 chimeric antigen receptor-modified T cells and clinical outcome in adults with B cell acute lymphoblastic leukemia. Blood. 2015;126(23):3773.
27. Donohue JH, Rosenstein M, Chang AE, Lotze MT, Robb RJ, Rosenberg SA. The systemic administration of purified interleukin 2 enhances the ability of sensitized murine lymphocytes to cure a disseminated syngeneic lymphoma. J Immunol. 1984;132(4):2123–8. [PubMed: 6607956]
28. Yee C, Thompson JA, Byrd D, Riddell SR, Roche P, Celis E, et al. Adoptive T cell therapy using antigen-specific CD8+ T cell clones for the treatment of patients with metastatic melanoma: in vivo persistence, migration, and antitumor effect of transferred T cells. Proc Natl Acad Sci U S A. 2002;99(25):16168–73. [PubMed: 12427970]
29. Stevanovic S, Helman SR, Wunderlich JR, Langhan MM, Doran SL, Kwong MM, et al. Treatment of meta-static human papillomavirus-associated epithelial cancers with adoptive transfer of tumor-infiltrating T cells. J Clin Oncol. 2018;36(suppl)abstr):3004.
30. Leidner RS, Sukari A, Chung CH, Ohr J, Haigentz M, Cohen EE, et al. A phase 2, multicenter study to evaluate the efficacy and safety of autologous tumor infiltrating lymphocytes (LN-145) for the treatment of patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck (HNSCC). J Clin Oncol. 2018;36(suppl). abstr):TPS6096.
31. Doran SL, Stevanovic S, Adhikary S, Gartner JJ, Jia L, Kwong MM, et al. Genetically engineered T-cell therapy for HPV-associated epithelial cancers: a first in human, phase I/II clinical trial. J Clin Oncol. 2018;36(suppl)abstr):3019.
32. Hinrichs CS, Doran SL, Stevanovic S, Adhikary S, Mojadidi M, Kwong ME, et al. A phase I/II clinical trial of E6 T-cell receptor gene therapy for human papillomavirus (HPV)-associated epithelial cancers. J Clin Oncol. 2017;35(suppl)abstr):3009.
33. Norberg SM, Nagarsheth N, Doran S, Kanakry JA, Adhikary S, Schweitzer C, et al. Regression of epithelial cancers following T cell receptor gene therapy targeting human papillomavirus-16 E7. Blood, 132(Suppl 1), 492. [PubMed: 29866811]
34. Blumenschein GR, Bourgogne A, Reinhardt C, Ma H, Walter S, Weinschenk T, et al. Phase I trial evaluating genetically modified autologous T cells (ACTengine IMA201) expressing a T-cell receptor recognizing a cancer/germline antigen in patients with squamous NSCLC or HNSCC. J Clin Oncol. 2018;36(suppl 5S). abstr):TPS78.
35. Lam VK, Hong DS, Heymach J, Blumenschein GR, Creelan BC, Bradbury PA, et al. Initial safety assessment of MAGE-A10 c796 TCR T-cells in two clinical trials. J Clin Oncol. 2018;36(suppl)abstr):3056. [PubMed: 30183464]

36. Papa S, Adami A, Metoudi M, Achkova D, van Schalkwyk M, Pereira AP, et al. A phase I trial of T4 CAR T-cell immunotherapy in head and neck squamous cancer (HNSCC). J Clin Oncol. 2018;36(suppl):abstr):3046.
37. Straathof KC, Bollard CM, Popat U, Huls MH, Lopez T, Morriss MC, et al. Treatment of nasopharyngeal carcinoma with Epstein-Barr virus-specific T lymphocytes. Blood. 2005;105(5):1898–904. [PubMed: 15542583]
38. Comoli P, Pedrazzoli P, Maccario R, Basso S, Carminati O, Labirio M, et al. Cell therapy of stage IV nasopharyngeal carcinoma with autologous Epstein-Barr virus-targeted cytotoxic T lymphocytes. J Clin Oncol. 2005;23(35):8942–9. [PubMed: 16204009]
39. Smith C, Tsang J, Beagley L, Chua D, Lee V, Li V, et al. Effective treatment of metastatic forms of Epstein-Barr virus-associated nasopharyngeal carcinoma with a novel adenovirus-based adoptive immunotherapy. Cancer Res. 2012;72(5):1116–25. [PubMed: 22282657]
40. Ferris RL. Immunology and immunotherapy of head and neck cancer. J Clin Oncol. 2015;33(29):3293–304. [PubMed: 26351330]
41. Rosenberg SA, Spiess P, Lafreniere R. A new approach to the adoptive immunotherapy of cancer with tumor-infiltrating lymphocytes. Science. 1986;233(4770):1318–21. [PubMed: 3489291]
42. Rosenberg SA, Packard BS, Aebersold PM, Solomon D, Topalian SL, Toy ST, et al. Use of tumor-infiltrating lymphocytes and interleukin-2 in the immunotherapy of patients with metastatic melanoma. A preliminary report. N Engl J Med. 1988;319(25):1676–80. [PubMed: 3264384]
43. Kong CS, Narasimhan B, Cao H, Kwok S, Erickson JP, Koong A, et al. The relationship between human papillomavirus status and other molecular prognostic markers in head and neck squamous cell carcinomas. Int J Radiat Oncol Biol Phys. 2009;74(2):553–61. [PubMed: 19427557]
44. Ward MJ, Thirdborough SM, Mellows T, Riley C, Harris S, Suchak K, et al. Tumour-infiltrating lymphocytes predict for outcome in HPV-positive oropharyngeal cancer. Br J Cancer. 2014;110(2):489–500. [PubMed: 24169344]
45. Badoual C, Hans S, Merillon N, Van Ryswick C, Ravel P, Benhamouda N, et al. PD-1-expressing tumor-infiltrating T cells are a favorable prognostic biomarker in HPV-associated head and neck cancer. Cancer Res. 2013;73(1):128–38. [PubMed: 23135914]
46. Balermpas P, Michel Y, Wagenblast J, Seitz O, Weiss C, Rödel F, et al. Tumour-infiltrating lymphocytes predict response to definitive chemoradiotherapy in head and neck cancer. Br J Cancer. 2014;110(2):501–9. [PubMed: 24129245]
47. Bann DV, Deschler DG, Goyal N. Novel immunotherapeutic approaches for head and neck squamous cell carcinoma. Cancers (Basel). 2016;8(10):E87.
48. Nguyen N, Bellile E, Thomas D, McHugh J, Rozek L, Virani S, et al. Tumor infiltrating lymphocytes and survival in patients with head and neck squamous cell carcinoma. Head Neck. 2016;38(7):1074–84. [PubMed: 26879675]
49. deLeeuw RJ, Kost SE, Kakal JA, Nelson BH. The prognostic value of FoxP3+ tumor-infiltrating lymphocytes in cancer: a critical review of the literature. Clin Cancer Res. 2012;18(11):3022–9. [PubMed: 22510350]
50. Lechner A, Schlößer H, Rothschild SI, Thelen M, Reuter S, Zentis P, et al. Characterization of tumor-associated T-lymphocyte subsets and immune checkpoint molecules in head and neck squamous cell carcinoma. Oncotarget. 2017;8(27):44418–33. [PubMed: 28574843]
51. Sadelain M, Rivière I, Riddell S. Therapeutic T cell engineering. Nature. 2017;545(7655):423–31. [PubMed: 28541315]
52. Ramos CA, Narala N, Vyas GM, Leen AM, Gerdemann U, Sturgis EM, et al. Human papillomavirus type 16 E6/E7-specific cytotoxic T lymphocytes for adoptive immunotherapy of HPV-associated malignancies. J Immunother. 2013;36(1):66–76. [PubMed: 23211628]
53. Hong DS, Butler MO, Sullivan RJ, Erickson-Miller CL, Trivedi T, Chagin K, et al. A phase I single arm, open label clinical trial evaluating safety of MAGE-A10c796T in subjects with advanced or metastatic head and neck, melanoma, or urothelial tumors (NCT02989064). J Clin Oncol. 2017;35(suppl). abstr):TPS3098.
54. June CH, Riddell SR, Schumacher TN. Adoptive cellular therapy: a race to the finish line. Sci Transl Med. 2015;7(280):280ps7.

55. Turtle CJ, Hudecek M, Jensen MC, Riddell SR. Engineered T cells for anti-cancer therapy. Curr Opin Immunol. 2012;24(5):633–9. [PubMed: 22818942]

56. Rosewell Shaw A, Porter CE, Watanabe N, Tanoue K, Sikora A, Gottschalk S, et al. Adenovirotherapy delivering cytokine and checkpoint inhibitor augments CAR T cells against metastatic head and neck cancer. Mol Ther. 2017;25(11):2440–51. [PubMed: 28974431]

57. Davies DM, Foster J, Van Der Stegen SJ, Parente-Pereira AC, Chiapero-Stanke L, Delinassios GJ, et al. Flexible targeting of ErbB dimers that drive tumorigenesis by using genetically engineered T cells. Mol Med. 2012;18:565–76. [PubMed: 22354215]

58. Geldres C, Savoldo B, Hoyos V, Caruana I, Zhang M, Yvon E, et al. T lymphocytes redirected against the chondroitin sulfate proteoglycan-4 control the growth of multiple solid tumors both in vitro and in vivo. Clin Cancer Res. 2014;20(4):962–71. [PubMed: 24334762]

59. Papa S, Adami A, Metoudi M, Achkova D, van Schalkwyk M, Pereira AP, et al. T4 immunotherapy of head and neck squamous cell carcinoma using pan-ErbB targeted CAR T-cells. Cancer Res. 2017;77(13 Suppl). Abstract):CT118.

60. Chang ET, Adami HO. The enigmatic epidemiology of nasopharyngeal carcinoma. Cancer Epidemiol Biomark Prev. 2006;15(10):1765–77.

61. Stevanović S, Pasetto A, Helman SR, Gartner JJ, Prickett TD, Howie B, et al. Landscape of immunogenic tumor antigens in successful immunotherapy of virally induced epithelial cancer. Science. 2017;356(6334):200–5. [PubMed: 28408606]

**Table 1.**

Adoptive T cell therapy clinical trials for head and neck squamous cell carcinoma

| Therapy type | Target | Stage | Number enrolled | Results | Clinical trial number | Reference |
|---|---|---|---|---|---|---|
| TIL | HPV-assodated tumors | Phase II | 11 | Partial response in 2/11 non-cervical cancer patients | NCT01585428 | Stevanovic et al. [29] |
| TIL | Recurrent and/or metastatic HNSCC | Phase II | 47 | Pending | NCT03083873 | Leidneretal. [30] |
| TIL | Nasopharyngeal carcinoma | Phase II | 116 | Pending | NCT02421640 | |
| TCR | HLA-A*02:01-restricted epitope of HPV E6 | Phase I/II | 12 | Partial response in 2 patients with anal cancer but not oropharyngeal cancer | NCT02280811 | Doran et al. [31], Hinrichs etal. [32] |
| TCR | HPV-16/18 E6 and E7 | Phase I | 9 | Pending (trial not yet accruing) | NCT03578406 | |
| TCR | HPV-16 E6 | PhaseI | 32 | Pending | NCT02379520 | |
| TCR | HPV-16 E7 | Phase I | 12 | Four confirmed responses, one of which had oropharyngeal cancer | NCT02858310 | Norberg et al. [33] |
| TCR | Patient-derived cancer-germline peptides | Phase I | 16 | Pending | NCT03247309 | Blumenschein etal. [34] |
| TCR | MAG E-A10 | Phase I | 22 | Pending | NCT02989064 | Lam et al. [35] |
| CAR T cell | ErbB receptor family | Phase I | 30 | Overall disease control rate of 9/13 using RECIST 1.1 | NCT01818323 | Papa et al. [36] |
| TCR | EBV | Phase I | 14 | Pending | NCT02065362 | |
| TCR | EBV LMP2 | Phase I | 10 | Complete or partial responses in 3 of the 6 patients with refractory disease | NCT00609219 | Straathof et al. [37] |
| TCR | EBV LMP2 | Phase I/II | 10 | Control of disease progression in 6/10 patients | | Comoli etal. [38] |
| TCR | EBV LMP1 and LMP2 | Phase I | 24 | Increased progression-free survival but no partial or complete responses | ACTRN12609000675224 | Smith et al. [39] |