Immunotherapy for Head and Neck Squamous Cell Carcinoma

David W. Schoppy, MD, PhD, John B. Sunwoo, MD*

KEYWORDS

• HNSCC • Immunotherapy • CTLA-4 • PD-1 • Cetuximab • Vaccine
• Chimeric antigen receptor

KEY POINTS

- Checkpoint blockade of the PD-1:PD-L1 axis has significant activity against head and neck squamous cell carcinoma (HNSCC).
- The mechanism of cetuximab is, at least in part, due antibody-induced cell-mediated cytotoxicity by immune effector cells, such as natural killer (NK) cells. This response by NK cells can be enhanced by additional immune-stimulatory mechanisms, such as activation of CD137.
- Vaccines can further augment recognition of tumor cells by the adaptive immune system, and a variety of approaches are being investigated for use against HNSCC. This strategy may ultimately be useful in combination with checkpoint blockade strategies.
- T cells engineered with chimeric antigen receptors (CARs) are being developed for use in HNSCC.

INTRODUCTION

Advanced head and neck squamous cell carcinoma (HNSCC) can involve multiple sites of the upper aerodigestive tract, often precluding surgical intervention with curative intent. Additionally, a substantial proportion of patients with HNSCC will progress despite traditional cytotoxic chemotherapy and radiation therapy, and locoregional recurrence following any initial treatment of advanced tumors is relatively common.[1–3] In concert with efforts to develop new chemotherapy regimens, radiation protocols, and surgical approaches, much work has been focused on understanding the immunobiology of HNSCC and on developing strategies to promote an antitumor immune response.[4]

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Division of Head and Neck Surgery, Department of Otolaryngology, Stanford University School of Medicine, Stanford, CA 94305, USA
* Corresponding author. 801 Welch Road, 2nd Floor, Stanford, CA 94305.
E-mail address: sunwoo@stanford.edu

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The idea that the immune system may be able to recognize and control cells undergoing malignant transformation has been around for more than a century.[5,6] Recent robust and durable clinical responses with immune checkpoint blocking antibodies have led to a resurgence in enthusiasm for this therapeutic strategy for solid malignancies.

IMMUNE CHECKPOINT BLOCKADE

Immune checkpoints are inhibitory pathways critical for self-tolerance under normal circumstances. It is now clear that tumors often co-opt these pathways by expressing cognate ligands for inhibitory checkpoint receptors and are thus able to induce immune tolerance and suppress responses by tumor-infiltrating lymphocytes (TIL), which would otherwise be activated in the tumor microenvironment. Antibodies that block the interaction between these immune checkpoint receptors and their ligands have demonstrated significant clinical efficacy in recent trials. The first of this class of drugs to be approved by the Food and Drug Administration (FDA) in 2011 was ipilimumab, an antibody to the cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4), designed for use in unresectable or metastatic melanoma. This came following the landmark phase III clinical trial, demonstrating a survival benefit with ipilimumab in this disease.[7] As a single agent, however, a role for anti–CTLA-4 antibodies has not yet been reported in HNSCC.

More recently, another checkpoint inhibitory receptor, the programmed cell death protein 1 (PD-1), has garnered significant interest as a therapeutic target. Expression of PD-1 is induced on activated T cells and, on binding its ligands, PD-L1 (also known as B7-H1 and CD274) or PD-L2 (also known as B7-DC and CD273), inhibits T-cell receptor–induced signaling. Although PD-L2 is primarily expressed on activated macrophages and dendritic cells, PD-L1 expression is induced on both hematopoietic and nonhematopoietic cells, including epithelial cells, both benign and malignant, of head and neck mucosa.[8] Inflammatory cytokines, particularly interferon-γ (IFNγ), upregulate PD-L1 expression on these cells, further promoting an immunosuppressive environment.

Phase I studies of blocking antibodies to either PD-1 or PD-L1 showed surprising responses in solid tumor malignancies, including melanoma, renal cell carcinoma, and traditionally nonimmunogenic cancers, such as non–small cell lung cancer (NSCLC).[9,10] In 2014, accelerated approval of pembrolizumab, an antibody that blocks PD-1, was granted by the FDA for advanced melanoma. This followed significant responses seen in an open-label, multicenter expansion cohort of a phase I trial (KEYNOTE-001), in which 173 patients with advanced melanoma, who were refractory to ipilimumab, were randomized to either 2 mg/kg or 10 mg/kg every 3 weeks.[11] At both dosing regimens, there was an objective response rate of 26%, and the toxicity profile was similar between the 2 arms, with the most common adverse reactions being fatigue, pruritus, and rash. More recently, a phase III study of patients with previously untreated BRAF wild-type advanced melanoma compared nivolumab (another antibody to PD-1) with dacarbazine. The patients receiving nivolumab had significantly greater overall (72.9%) and median progression-free (5.1 months) survival compared with those receiving dacarbazine (42.1% and 2.2 months).[12]

As part of the phase I KEYNOTE-001 trial previously mentioned, an expansion cohort of patients with NSCLC receiving pembrolizumab also was analyzed.[13] An objective response rate of 19.4% and a median duration of response of 12.5 months were observed. Of note, in this study, the proportion of tumor cells expressing PD-L1 correlated with improved efficacy of pembrolizumab. In a randomized phase III trial of