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Immunotherapy: Who is Eligible?

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Synopsis

Recurrent and/or metastatic head and neck cancer portends a poor prognosis with traditional treatments, but current immunotherapy with immune checkpoint inhibitors has the potential to improve these clinical outcomes. This review focuses on the major breakthroughs that have led to our current understanding of immunotherapy in head and neck cancer as well as the future direction of the field. Ultimately, this understanding will guide clinicians on the selection of head and neck cancer patients and practical considerations prior to starting immunotherapy.

Keywords

Immunotherapy; Recurrent metastatic head & neck Carcinoma; checkpoint inhibitors; PD-1/PD-L1 blocking antibodies; nivolumab; pembrolizumab

Introduction

An important paradigm shift in oncology in the past several years has been the adoption of immunotherapy for recurrent and/or metastatic cancer. While cancer immunotherapy using anti-tumor T-cells and interleukins have been used for melanoma previously, clinical trials for various forms of immunotherapy for epithelial cancers had not shown any clinical efficacy. Immune checkpoint inhibitors (PD-1/PD-L1/CTLA-4), however, have altered the oncologic landscape such that many of the near future clinical trials may be based primarily on immuno-oncologic platforms. Head and neck carcinomas have not been immune from this revolution, and we review the historical and immunological basis of immunotherapy for head and neck squamous cell carcinoma.

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Historical Perspective of Recurrent and/or Metastatic Head and Neck Squamous Cell Carcinoma

Recurrent and/or metastatic head and neck squamous cell carcinoma (R/M HNSCC) remains a disease with poor morbidity and mortality. Traditional cytotoxic chemotherapy agents have been the only systemic treatment option until recently. Both single agents and two combination agents ("doublets") have demonstrated modest response rates with no survival advantage noted for combinations of drugs over single agents in the recurrent/metastatic (R/M) setting. (1–8) The introduction of cetuximab, (an IgG1 chimeric monoclonal antibody to the epidermal growth factor receptor (EGFR)), to the armamentarium of agents for R/M HNSCC represented an important step away from dependence on traditional cytotoxic agents as the only systemic option for R/M disease. Clinical studies revealed that EGFR was overexpressed in >90% of human HNSCC tissue samples and associated with poorer clinical outcomes.(9, 10) In an ECOG Phase Ⅲ randomized trial of cisplatin plus placebo compared with cisplatin plus cetuximab in R/M HNSCC, the combination of cisplatin plus cetuximab (26% v 10%, p=0.03) compared to cisplatin alone, with trends toward PFS and OS as the study was not powered for survival.(11) The landmark EXTREME phase 3 trial randomized patients to platinum and fluorouracil based therapy with or without cetuximab and demonstrated a survival benefit in R/M HNSCC since the approval of cisplatin in the 1980s. (12) The addition of cetuximab to a platinum doublet chemotherapy improved median OS to 10.1 months and median PFS to 5.6 months (HR 0.8, 95% CI 0.64 – 0.99, p=0.04). Currently, cetuximab is approved in first-line treatment (for non-salvageable recurrent/ metastatic settings) when combined with platinum/FU and in platinum-refractory treatment as monotherapy. Further investigations in other EGFR inhibitors such as monoclonal antibodies (panitumumab and zalatumumab) and tyroskine kinase inhibitors (gefitinib, erlotinib, and lapatinib) have not demonstrated any significant benefits. Afatinib, an irreversible pan-ErbB inhibitor to EGFR, HER2, and HER4, initially demonstrated comparable activity to cetuximab, especially in the setting of cetuximab failure. However, LUX-Head & Neck 1, a phase 3 trial in R/M HNSCC, which compared afatinib to methotrexate in the second-line setting failed to demonstrate a significant OS benefit.(13) Thus, prior to immunotherapy, oncologists were presented with a therapeutic challenge for patients who failed first -line treatment as second-line regimens had no significant proven efficacy.

The promise of immunotherapy

Cancer immunotherapy was first introduced in the 1890s, by Dr. William B. Coley, who demonstrated anti-tumor responses in sarcoma patients who received "toxins" consisting of killed bacteria.(14) Despite such anecdotal reports, immunotherapeutic modalities were not developed as a significant component of cancer therapy until more recently in the form of immune checkpoint inhibitors. From preclinical models and the infectious disease processes, T-cell responses were thought to be activated based on a "two-signal" model requiring engagement of T-cell receptor (TCR) - major histocompatibility complex (MHC) class molecules ('signal 1') and co-stimulatory molecules, B7 and CD28 ('signal 2'). However, the discovery of negative regulators of T-cell activation in the form of checkpoint inhibitors

in the 1990s changed this paradigm. Cancer research shifted from enhancing anti-tumor T cell response to removing the negative regulators of anti-tumor T cell response. The scientific basis for these novel therapies originated from the discovery of the first checkpoint, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and the clinical development of ipilimumab (the monoclonal IgG1 antibody that blocks CTLA-4's activity), which showed remarkable improvements in survival for metastatic melanoma.(15) However, this success came with a unique and significant safety profile (up to 30% of patients with significant adverse events - SAE) defined by immune related adverse events (irAEs). These irAEs are common among immune checkpoint inhibitors (ICI) and are characterized by various forms and degrees of autoimmunity mediated damage by T cells to normal tissue. The clinical manifestations can range from manageable arthritis, dermatitis, and endocrinopathies to life threatening colitis, pneumonitis, hepatitis and endocrinopathies.

Anti-PD-1 therapy

In parallel to the research and development of ipilimumab, Honjo and others who studied other regulators of T-cell activation discovered that programmed death 1 (PD-1) and ligand, PD-L1 can also inhibit this anti-tumor process through multiple, non-redundant regulatory pathways.(16–18) Pre-clinical models revealed that the blockade of this PD-1/PD-L1 interaction led to activation of T-cells and development of anti-tumor responses.(16, 19) These led to the development of nivolumab, a fully human IgG4 anti-PD-1 monoclonal antibody, and pembrolizumab, a humanized monoclonal IgG4-kappa isotype antibody against PD-1. Various trials found these anti-PD-1 therapies improved clinical outcomes in many epithelial cancers and had a significantly better tolerated safety profile as compared to ipilimumab.(20, 21) As of 2016, anti-PD-1 therapies have been approved for melanoma, lung cancer, kidney cancer, and Hodgkin's lymphoma. (20–26) (Table 1)

Anti-PD-1 therapy has been investigated in R/M HNSCC with both pembrolizumab and nivolumab. Pembrolizumab was first investigated in a phase 1b trial (KEYNOTE-012) as second line therapy in R/M HNSCC.(27) Patients with at least 1% of PD-L1 expression received pembrolizumab at 10 mg/kg IV every 2 weeks. Of the 60 patients treated, only 17% had any grade 3–4 drug-related adverse events. In terms of efficacy, 18% (8/45 evaluable patients) had an objective response (OR) among all patients. Notably, there was a higher response rate in HPV-positive patients (25%) as compared to the HPV-negative (14%) patients. An expansion cohort of 132 patients regardless of PD-L1 expression was also studied with pembrolizumab at 200 mg IV every 3 weeks.(28) Central imaging vendor review and investigator review revealed an ORR of 18% and 20%, respectively and a median OS of 8 months. These results were encouraging as they were comparable to contemporary treatments, while maintaining a better tolerated safety profile.(12, 13, 29). The preliminary results from the non-randomized phase 2 trial (KEYNOTE-055 with pembrolizumab confirmed these results with an ORR of 18%.(30) The phase 3 trial with pembrolizumab is on-going. In CheckMate 141, a phase 3 clinical trial, nivolumab (3 mg/kg every 2 weeks) was compared to standard therapy (single-agent methotrexate, docetaxel, or cetuximab) in patients with platinum-refractory R/M HNSCC.(31) The study demonstrated superior efficacy in nivolumab based on overall survival (HR 0.70, 97.73% CI 0.51 to 0.96, P=0.01), median OS (7.5 v 5.1 months), and 1-year survival (36% v 16.6%). In terms of safety, only

13.1% of patients developed serious grade 3–4 treatment-related adverse events with nivolumab as compared to 35.1% in those that received standard therapy. Based on the evidence from these clinical trials, pembrolizumab and nivolumab have been FDA approved in 2016 for the use in second-line therapy in R/M HNSCC.

Other immune checkpoint inhibitors

Other than nivolumab and pembrolizumab, other immune checkpoints that target the PD-1:PD-L1 pathway have been investigated in HNSCC clinical trials. These include PDR001, PF-06801591, and REGN-2810 to name a few, which have been developed by other pharmaceutical companies. Most of these have gone into patients already, and their phase I clinical trials have either closed or ongoing. There are also several anti-PD-L1 blocking antibodies – atezolizumab (Genentech) and durvalumab (AZ-Medimmune) – which h ave treated HNSCC patients in various ongoing clinical trials as well. There are no clear consensus that one of these PD-1:PD-L1 blocking agents are better for HNSCC patients, and, unfortunately, there are no trials that will compare them in a head-to-head manner. Outside of these PD-1:PD-L1 targeting agents, CTLA-4 is the other immune checkpoint inhibitor that has been used to treat HNSCC patients.

Ipilimumab (Merck) and tremelimumab (AZ) are the two well characterized CTLA-4 blocking agents, and there are ongoing clinical trials for these two agents in the HNSCC space. The mmuno-oncologic field has rapidly expanded recently to develop other immunomodulatory agents that targets other “druggable” cell surface molecules on the immune cells. Typically, these antibodies target other immune checkpoint inhibitors or co-activators that can either “release the brake” or “push the gas” on the cytoly tic activity of the tumor specific T-cells, respectively. Anti-LAG-3 (BMS-986916), anti-TIM-3 (TSR-022), and anti-KIR (BMS-986015) are examples of such other immune checkpoint inhibitors while, anti-4–1BB (PF-05082566) and anti-OX40 (PF-04518600, MEDI6469) are examples of the immune co-activators. Preliminary results from many of these agents are promising, and the investigators have been actively pursuing optimal combinations of these agents for recurrent and metastatic cancer.

Considerations prior to institution of anti-PD-1 therapy in R/M HNSCC

There are many factors to consider when selecting candidates for ICI therapy in R/M HNSCC. In essence, immune checkpoint inhibitors induce some degree of autoimmunity in the context of recurrent/metastatic cancer. Attendant side effects that range from tolerable inflammation such as arthritis and dermatitis to life threatening pulmonary pneumonitis are possible sequelae that must be discussed with the patients. First, patients and clinicians must both understand that due to their mechanism of action, the safety profile of ICIs differs significantly to traditional systemic chemotherapies and the consequences of irAEs needed to be thoroughly discussed with patients with pre-existing co-morbidities including advanced age, autoimmune disease and baseline organ dysfunction. Advanced age has been associated with immunosenescence, but retrospective studies have shown no significant difference with efficacy or safety profile with ICIs in the elderly population.(32, 33) Conversely, a rare pattern of hyper-progression of the tumor has been observed

retrospectively in patients on anti-PD-1/L-1 therapy that has been observed more frequently in elderly patients.(34) There are no clinical or molecular biomarkers to segregate these patients who can potentially hyper-progress. While patients with pre-existing autoimmune conditions were excluded from clinical trials, retrospective studies in patients with autoimmune conditions and melanoma have shown that irAEs were relatively more frequent, but mild and manageable, while still providing clinical responses.(35) Additionally, a retrospective cohort study of patients with baseline organ dysfunction on anti-PD-1 therapy did not reveal significant worsening of organ function or irAEs, while still inducing clinical response in some patients.(36) All these findings were retrospective and more research is needed to address some of these questions. Second, there are no available standardized biomarkers on tissue or blood now to predict response with anti-PD-1 therapy. While, there has been suggestions from clinical trials in other tumor types that higher PD-L1 expression on tumor correlates with improved response, even patients with no PD-L1 expression can achieve a clinical response.(37) Additionally, issues with heterogeneity of samples, lack of standardization among PD-L1 assays, and an unclear definition of PD-L1 positivity limits the utility of PD-L1 expression. Further efforts are needed to evaluate other predictive biomarkers with anti-PD-1 therapy to select candidates for ICIs. Finally, while HPV status in oropharyngeal HNSCC predicts improved survival with chemotherapy, the role of HPV status with ICI is currently unknown.(38) Early studies have suggested a trend towards improved survival with HPV positivity but larger prospective studies are needed.(31)

Candidacy for anti-PD-1 therapy

PD-1 blocking antibodies – either nivolumab or pemb rolizumab – are approved as second line agents for patients with R/M HNSCC that progress on or after a platinum-based therapy, based on the results from CheckMate 141 and KEYNOTE-012, respectively. As expected, study criteria for both trials included patients that were healthy with ECOG performance status of 0–1 and adequate organ function. Both studies excluded patients with CNS metastasis, autoimmune diseases, or systemic immunosuppression. Unlike CheckMate 141, KEYNOTE-12 also required patients to have at least 1% of PD-L1 tumor expression. However, there are no predicative biomarkers, including PD-L1 expression, to assist in selecting patients currently. Future clinical and correlative studies will help to inform the generalizability of these results in other clinically relevalant populations stratified by HPV status, bulky disease, or anatomic site as well as the development of clinical and molecular criteria to determine the appropriate candidates for therapy.

Future direction with combination therapy

With the success with anti-PD-1 therapy in HNSCC, combination therapies with anti-PD-1 agents are currently being studied. These combinations include ICI, targeted therapy, chemotherapy, and radiation. Success with dual blockade of PD-1 and CTLA-4, with nivolumab and ipilimumab, has already been shown in metastatic melanoma with a superior efficacy in the combination arm over both monotherapy arms (ORR 58% in combination vs 44% with nivolumab and 19% with ipilimumab).(39) This combination has been open in a clinical trial as first line therapy for R/M HNSCC (CheckMate 651, NCT 027414570). Further combinations are being explored in other immunomodulatory agents such as anti-

LAG3, anti-TIM3, anti-KIR, anti-41BB and anti-OXO40 therapies as noted previously above. Given the multi-modal nature of HNSCC therapy including targeted therapy, chemotherapy and radiotherapy; multiple studies are exploring such modalities in various combinations with anti-PD-1 therapy. Current on-going trials include studies with pembrolizumab, cetuximab, and chemotherapy (NCT 02358031), nivolumab, cetuximab and motolomid (NCT 02124850), pembrolizumab and radiation (NCT 02318771), and nivolumab and SBRT (NCT 02684253). (Table 1)

References:

1. Sullivan RD, Miller E, Sikes MP. Antimetabolite-metabolite combination cancer chemotherapy. Effects of intraarterial methotrexate-intramuscular Citrovorum factor therapy in human cancer. Cancer 1959;12:1248–62. [PubMed: 13835650]
2. Wittes RE, Cvitkovic E, Shah J, Gerold FP, Strong EW. CIS-Dichlorodiammineplatinum(II) in the treatment of epidermoid carcinoma of the head and neck. Cancer Treat Rep 1977;61(3):359–66. [PubMed: 872136]
3. Jacobs C, Lyman G, Velez-Garcia E, Sridhar KS, Knight W, Hochster H, et al. A phase III randomized study comparing cisplatin and fluorouracil as single agents and in combination for advanced squamous cell carcinoma of the head and neck. J Clin Oncol 1992;10(2):257–63. [PubMed: 1732427]
4. Forastiere AA, Metch B, Schuller DE, Ensley JF, Hutchins LF, Triozzi P, et al. Randomized comparison of cisplatin plus fluorouracil and carboplatin plus fluorouracil versus methotrexate in advanced squamous-cell carcinoma of the head and neck: a Southwest Oncology Group study. J Clin Oncol 1992;10(8):1245–51. [PubMed: 1634913]
5. Clavel M, Vermorken JB, Cognetti F, Cappelaere P, de Mulder PH, Schornagel JH, et al. Randomized comparison of cisplatin, methotrexate, bleomycin and vincristine (CABO) versus cisplatin and 5-fluorouracil (CF) versus cisplatin (C) in recurrent or metastatic squamous cell carcinoma of the head and neck. A phase III study of the EORTC Head and Neck Cancer Cooperative Group. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO 1994;5(6):521–6.
6. Gibson MK, Li Y, Murphy B, Hussain MH, DeConti RC, Ensley J, et al. Randomized phase III evaluation of cisplatin plus fluorouracil versus cisplatin plus paclitaxel in advanced head and neck cancer (E1395): an intergroup trial of the Eastern Cooperative Oncology Group. J Clin Oncol 2005;23(15):3562–7. [PubMed: 15908667]
7. Posner MR, Hershock DM, Blajman CR, Mickiewicz E, Winquist E, Gorbounova V, et al. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. The New England journal of medicine 2007;357(17):1705–15. [PubMed: 17960013]
8. Vermorken JB, Remenar E, van Herpen C, Gorlia T, Mesia R, Degardin M, et al. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. The New England journal of medicine 2007;357(17):1695–704. [PubMed: 17960012]
9. Dassonville O, Formento JL, Francoual M, Ramaioli A, Santini J, Schneider M, et al. Expression of epidermal growth factor receptor and survival in upper aerodigestive tract cancer. J Clin Oncol 1993;11(10):1873–8. [PubMed: 8410112]
10. Rubin Grandis J, Melhem MF, Gooding WE, Day R, Holst VA, Wagener MM, et al. Levels of TGF-alpha and EGFR protein in head and neck squamous cell carcinoma and patient survival. J Natl Cancer Inst 1998;90(11):824–32. [PubMed: 9625170]
11. Burtness B, Goldwasser MA, Flood W, Mattar B, Forastiere AA, Eastern Cooperative Oncology G. Phase III randomized trial of cisplatin plus placebo compared with cisplatin plus cetuximab in metastatic/recurrent head and neck cancer: an Eastern Cooperative Oncology Group study. J Clin Oncol 2005;23(34):8646–54. [PubMed: 16314626]
12. Vermorken JB, Mesia R, Rivera F, Remenar E, Kawecki A, Rottey S, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. The New England journal of medicine 2008;359(11):1116–27. [PubMed: 18784101]

13. Machiels JP, Haddad RI, Fayette J, Licitra LF, Tahara M, Vermorken JB, et al. Afatinib versus methotrexate as second-line treatment in patients with recurrent or metastatic squamous- cell carcinoma of the head and neck progressing on or after platinum-based therapy (LUX-Head & Neck 1): an open-label, randomised phase 3 trial. The Lancet Oncology 2015;16(5):583–94. [PubMed: 25892145]
14. Coley WB. The treatment of malignant tumors by repeated inoculations of erysipelas. With a report of ten original cases. 1893 Clin Orthop Relat Res 1991(262):3–11.
15. Leach DR, Krummel MF, Allison JP. Enhancement of antitumor immunity by CTLA-4 blockade. Science 1996;271(5256):1734–6. [PubMed: 8596936]
16. Freeman GJ, Long AJ, Iwai Y, Bourque K, Chernova T, Nishimura H, et al. Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. The Journal of experimental medicine 2000;192(7):1027–34 [PubMed: 11015443]
17. Strome SE, Dong H, Tamura H, Voss SG, Flies DB, Tamada K, et al. B7-H1 blockade augments adoptive T-cell immunotherapy for squamous cell carcinoma. Cancer Res 2003;63(19):6501–5. [PubMed: 14559843]
18. Iwai Y, Ishida M, Tanaka Y, Okazaki T, Honjo T, Minato N. Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. Proceedings of the National Academy of Sciences of the United States of America 2002;99(19): 12293–7. [PubMed: 12218188]
19. Hirano F, Kaneko K, Tamura H, Dong H, Wang S, Ichikawa M, et al. Blockade of B7-H1 and PD-1 by monoclonal antibodies potentiates cancer therapeutic immunity. Cancer Res 2005;65(3):1089–96. [PubMed: 15705911]
20. Robert C, Long GV, Brady B, Dutriaux C, Maio M, Mortier L, et al. Nivolumab in previously untreated melanoma without BRAF mutation. The New England journal of medicine 2015;372(4): 320–30. [PubMed: 25399552]
21. Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L, et al. Pembrolizumab versus Ipilimumab in Advanced Melanoma. The New England journal of medicine 2015;372(26):2521–32. [PubMed: 25891173]
22. Motzer RJ, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S, et al. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. New England Journal of Medicine 2015;373(19):1803–13. [PubMed: 26406148]
23. Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Csoszi T, Fulop A, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. The New England journal of medicine 2016.
24. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. The New England journal of medicine 2015;373(17):1627–39. [PubMed: 26412456]
25. Brahmer J, Reckamp KL, Baas P, Crino L, Eberhardt WE, Poddubskaya E, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. The New England journal of medicine 2015;373(2):123–35. [PubMed: 26028407]
26. Ansell SM, Lesokhin AM, Borrello I, Halwani A, Scott EC, Gutierrez M, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. The New England journal of medicine 2015;372(4):311–9. [PubMed: 25482239]
27. 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. The Lancet Oncology 2016;17(7):956–65. [PubMed: 27247226]
28. Chow LQ, 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.
29. Vermorken JB, Trigo J, Hitt R, Koralewski P, Diaz-Rubio E, Rolland F, et al. Open-label, uncontrolled, multicenter phase II study to evaluate the efficacy and toxicity of cetuximab as a

single agent in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck who failed to respond to platinum-based therapy. J Clin Oncol 2007;25(16):2171–7. [PubMed: 17538161]

30. Bauml J, Seiwert TY, Pfister DG, Worden FP, Liu SV, Gilbert J, et al. Preliminary results from KEYNOTE-055: Pembrolizumab after platinum and cetuximab failure in head and neck squamous cell carcinoma (HNSCC). J Clin Oncol 2016;34(Suppl; abstr 6011).
31. Ferris RL, Blumenschein G, Jr., Fayette J, Guigay J, Colevas AD, Licitra L, et al. Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck. The New England journal of medicine 2016.
32. Tokarova B, Amirtaev KG, Krasavin EA, Kozubek S. [Role of the genotype in the mutagenic action of radiation with different LET on cells of Escherichia coli]. Radiobiologiia 1989;29(6): 754–9. [PubMed: 2694217]
33. Elias R, Morales J, Rehman Y, Khurshid H. Immune Checkpoint Inhibitors in Older Adults. Curr Oncol Rep 2016;18(8):47. [PubMed: 27287329]
34. Champiat S, Dercle L, Ammari S, Massard C, Hollebecque A, Postel-Vinay S, et al. Hyperprogressive disease (HPD) is a new pattern of progression in cancer patients treated by anti-PD-1/PD-L1. Clinical cancer research : an official journal of the American Association for Cancer Research 2016.
35. Menzies AM, Johnson DB, Ramanujam S, Atkinson VG, Wong AN, Park JJ, et al. Anti-PD-1 therapy in patients with advanced melanoma and preexisting autoimmune disorders or major toxicity with ipilimumab. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO 2016.
36. Kanz BA, Pollack MH, Johnpulle R, Puzanov I, Horn L, Morgans A, et al. Safety and efficacy of anti-PD-1 in patients with baseline cardiac, renal, or hepatic dysfunction. Journal for immunotherapy of cancer 2016;4:60. [PubMed: 27777770]
37. Daud AI, Wolchok JD, Robert C, Hwu WJ, Weber JS, Ribas A, et al. Programmed Death-Ligand 1 Expression and Response to the Anti-Programmed Death 1 Antibody Pembrolizumab in Melanoma. J Clin Oncol 2016;34(34):4102–9. [PubMed: 27863197]
38. Ang KK, Harris J, Wheeler R, Weber R, Rosenthal DI, Nguyen-Tân PF, et al. Human Papillomavirus and Survival of Patients with Oropharyngeal Cancer. New England Journal of Medicine 2010;363(1):24–35. [PubMed: 20530316]
39. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. The New England journal of medicine 2015;373(1):23–34. [PubMed: 26027431]

Key Points:

1. Immunotherapy with checkpoint inhibitors are now FDA approved for recurrent and/or metastatic head and neck carcinoma.
2. Cancer immunotherapy has distinct adverse events that are related to an induction of autoimmunity.
3. Predictive biomarker analysis for head and neck immunotherapy is ongoing.
4. Combinatorial trials for head and neck carcinoma is an active area of clinical research to improve the clinical efficacy of immunotherapy.

Table 1.

Summary of approved immune checkpoint inhibitors and combination therapies

Agent	Class	Tumor Types	Approval Date	Combo HNSCC trials	NCT trial No.
Ipilimumab	Anti-CTLA4	Melanoma	3/28/2011	Enoblituzumab	NCT02381314
				Cetuximab/Radiation	NCT01860430
Nivolumab	Anti-PD-1	Melanoma	12/22/2014	Ipilimumab	NCT02741570
		NSCLC	3/4/2015	Varlilumab	NCT02335918
		RCC	11/23/2015	Epacadostat	NCT02327078
		Hodgkin	5/17/2016	Motolimod	NCT02124850
		HNSCC	11/10/2016	Radiation	NCT02684253
				Chemotherapy	NCT02764593
Pembrolizumab	Anti-PD-1	Melanoma	9/4/2014	Epacadostat	NCT02178722
		NSCLC	10/2/2015	Vorinostat	NCT02538510
		HNSCC	8/5/2016	Chemoradiation	Multiple
				T-VEC	NCT02626000
				Cetuximab/Chemo	NCT02358031
Nivolumab and Ipilimumab	Anti-PD-1 Anti-CTLA-4	Melanoma	1/23/2016		
Atezolizumab	Anti-PD-L1	Bladder	5/18/2016	Alone	NCT01375842
		NSCLC	10/18/2016	Varlilumab	NCT02543645