short review

memo (2019) 12:249–252
https://doi.org/10.1007/s12254-019-0511-8

memo
magazine of european medical oncology

# Checkpoint inhibitors in head and neck cancer

**Ilson Sepulveda · Rodrigo Ascui · A. Andrés Capizzano**

Received: 25 March 2019 / Accepted: 8 July 2019 / Published online: 17 July 2019


**Summary** Head and neck cancer (HNC) are aggressive cancers and represents the sixth leading cancer by incidence worldwide. This kind of cancer constitutes about 3% of all newly diagnosed malignant tumors in humans, and this percentage is likely to increase in the future. Most common available treatment methods which include surgery, radiotherapy, and chemotherapy are associated with low survival outcomes in combination with substantial toxicities emphasize the necessity for novel treatment strategies.The combination immunotherapies represent a fundamental step in the progress towards improving responses, and immune checkpoint inhibitors will likely become the immunotherapeutic backbone of future cancer treatments.

**Keywords** Head and neck · Cancer · Chemotherapy · Inmunotherapy

## Background

Head and neck cancer (HNC) are aggressive cancers and represent the sixth leading cancer by incidence worldwide. This kind of cancer constitutes about 3% of all newly diagnosed malignant tumors in humans, and this percentage is likely to increase in the future [1].

HNC comprises a heterogeneous group of tumors with different natural history that strictly depends on histology, anatomical site of origin and tumor biology.

Well-known risk factors are alcohol abuse, tobacco smoking, and human papillomavirus (HPV) infection [2]. HNC is the result of cumulative mutations that cause the activation of oncogenes and the inactivation of tumor suppressor genes in a clonal cell population [1].

Nearly all the cases of head and neck malignancies (95%) are represented by squamous cell carcinoma (HNSCC) arising in the oral cavity and pharynx [1]. Patients with HNSCC have altered lymphocyte homeostasis (mainly reduced levels of CD3+, CD4+, and CD8+ T cells) compared to healthy controls. This imbalance even remains 2 years after treatment with curative intent [3], whereby most patients present with locoregionally advanced disease, and more than 50% have recurrence within 3 years by immune evasion, which is mediated in part by expression of the programmed death ligands (PD-L1 and PD-L2) of the T-cell suppressive immune-checkpoint receptor programmed death 1 (PD-1) [4] The PD-1/PD-L1 immune checkpoints have important roles in the formation of "immune privilege" regions, viral persistence, tumor development and immune evasion resulting in a dysfunction of CD8 cytotoxic T cells (CTL) [5–7]. Additionally, HNSCC cells develop the ability to evade antitumor immune attacks by diminishing recognition of cancer-specific antigens by T cells via downregulating the antigen processing machinery (APM, [8]).

Dr. I. Sepulveda (✉)
Radiology Department, Finis Terrae University School of Dentistry, Santiago, Chile

ENT-Head and Neck Surgery Service, General Hospital of Concepcion, San Martin Av. 1436, Concepcion, Chile
isepulvedaa@uft.edu

R. Ascui
Oncology Service, General Hospital of Concepción, Concepción, Chile

A. A. Capizzano
Radiology Department, Division of Neuroradiology, University of Michigan Health System, Ann Arbor, MI, USA

## Single agent checkpoint inhibitor therapy in HNSCC

The use of immune check point inhibitors (CPI) that block the interaction between PD-1/PD-L1 are appealing treatment options for patients and clinicians for several reasons: first, they have broad activity, demonstrating response rates ranging from 15 to 90% in over 10 different cancer types. Second, they frequently induce durable disease control. Worldwide the PD-1 CPI nivolumab and pembrolizumab have been approved for the treatment of recurrent/metastatic (R/M) HNSCC.

Initial evidence for the efficacy of nivolumab, a human IgG4 monoclonal antibody directed against PD-1 protein, came from metastatic melanoma trials. Nivolumab has been associated with a 34% 5-year overall survival (OS) rate in this setting, with similar durability observed in other cancers. However, the activity of CPI monotherapy in terms of response rate is limited in heavily pretreated R/M HNSCC patients compared to melanoma or non-small cell cancer patients, although early clinical trial results such as the KEYNOTE-012 or KEYNOTE-055 studies were encouraging. In the KEYNOTE-012 trial Chow et al. demonstrated an overall response rate (ORR) of 20% with the humanized monoclonal PD-1 antibody pembrolizumab [9]. In the larger phase 2 KEYNOTE-055 study including patients with platinum and cetuximab refractory R/M HNSCC Bauml et al. reported that pembrolizumab was an effective and well tolerated option. ORR was 16% and despite that 64% of patients experienced a treatment-related adverse event, the majority of which were grade 1 to 2 [10].

Since then, the results of two pivotal phase 3 studies with nivolumab and pembrolizumab monotherapy in platinum-resistant HNSCC have been published resulting in the approval of those compounds:

The randomized controlled phase 3 CheckMate 141 trial compared nivolumab to single-agent chemotherapy (methotrexate, docetaxel or cetuximab) revealing a longer OS (7.5 months vs. 5.1 months), a benefit in quality of life and a lower incidence of treatment-related adverse events over conventional cytotoxic drugs [2, 4]. Of note, only a minority of patients responded to nivolumab yielding an ORR of 13.3% vs. 5.8% in favor of nivolumab in the total population [4].

The second randomized controlled phase 3 study (KEYNOTE-040) evaluated the benefit of pembrolizumab compared with standard of care therapy (methotrexate, docetaxel, or cetuximab intravenously) in a very similar setting as CheckMate 141. Interestingly, the trial missed its primary OS endpoint in the initial analysis (OS 8.4 vs. 7.1 months; HR 0.81), although the clinical activity of pembrolizumab was obvious [11, 12]. Further subgroup analyses revealed that the OS benefit was more pronounced in patients with higher PD-L1 expression on their tumors or in the tumor microenvironment than in those without PD-L1 expression. ORR was 14.6%. Pembrolizumab had a better safety profile than standard of care, with overall profiles consistent with those previously observed and no new or unexpected toxicities were reported [11].

## Checkpoint inhibitor combinations

As outlined above the vast majority of R/M HNSCC patients experience primary or secondary disease progression following treatment with CPI monotherapy. In order to overcome resistance to CPI and enhance their efficacy multiple combination strategies have been developed. From a clinical perspective the most promising approaches include the combination with cytotoxic regimens such as radiation or chemotherapy or dual checkpoint blockade of a PD-1/PD-L1 plus cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitor. Both strategies have been investigated in HNSCC and are based on a sound scientific rationale.

Targeting CTLA-4 + PD-1/PD-L1 can produce complementary effects on effector T cells, leading to T cell activation by CTLA-4 in the priming phase of the immune cycle and modulation of effector function by PD-1 inhibition. Despite initial enthusiasm raised by early trial results evaluating the combination of the PD-L1 inhibitor durvalumab (D) plus the CTLA-4 inhibitor tremelimumab (T), larger studies reported only modest efficacy. The CONDOR phase 2 study in PD-L1 low/negative disease could not demonstrate superior efficacy of D + T compared to D [13]. More importantly the negative results of the EAGLE study have been released recently. EAGLE was a phase 3, randomised, open-label, multicenter trial evaluating D or D in combination with T versus standard of care chemotherapy in patients with R/M HNSCC who experienced disease progression following platinum-based chemotherapy, regardless of their PD-L1 status. D (OS 6.5 months) and D + T (OS 7.6 months) did not demonstrate a statistically significant improvement in OS compared to standard of care (OS 8.3 months) [14]. Although the results of the first line studies Checkmate 651 with nivolumab plus ipilimumab and the KESTREL study with D + T are still pending, the concept of CTLA-4/PD-1 inhibition in the absence of a suitable predictive biomarker remains challenging in R/M HNSCC.

Secondly and more successfully, modalities that result in cell death, such as radiotherapy and chemotherapy in combination with CPI have been investigated in HNSCC.

Different chemotherapeutic drugs—apart from their cytotoxic effect—modulate the immune microenvironment via various mechanisms [15] including:

- Increased immunogenicity due to tumor cell apoptosis (anthracyclines, 5-fluorouracil [5-FU] or oxaliplatin).

- Direct immunostimulation activating immune effector cells (gemcitabine, paclitaxel and pemetrexed)
- Indirect immunostimulation inhibiting immunosuppressive cells such as regulatory T cells or myeloid derived suppressor cells (5-FU, cyclophosphamide and oxaliplatin)

Very recently, a phase 3 study showed that chemotherapy plus CPI is a valuable strategy for the treatment of R/M HNSCC.

The KEYNOTE-048 study, was a randomized, phase 3 open-label trial of pembrolizumab, or pembrolizumab plus platinum plus 5-FU chemotherapies versus standard of care platinum plus 5-FU plus cetuximab in first line R/M HNSCC. The final results, which were recently presented at ASCO 2019, showed that compared with standard of care pembrolizumab/chemotherapy had superior OS in the total population (13.0 months vs. 10.7 months) and PD-L1 positive subgroups and pembrolizumab monotherapy was superior in PD-L1 positive subgroups as well compared to standard of care [16]. Based on these results the FDA approved pembrolizumab in this setting in the United States of America.

Besides cytotoxic chemotherapy, radiotherapy can also influence the tumor immune response. Tumor cell death from irradiation can enhance the antitumor immunity by inducing antigen expression on tumor cells and activating lymphocytes [17, 18], and by generating a potential so-called abscopal effect [19], although this has not been reproducibly shown in HNSCC.

Finally, it has to be noted that targeted therapies such cetuximab, an approved anti-Epidermal Growth Factor Receptor (Anti-EGFR) monoclonal antibody, displays immunomodulatory effects as well via antigen dependent cytotoxicity (ADCC) and should not be abandoned as an immunotherapeutic agent [20]. While its efficacy is modest, when administered as a monotherapy, novel combination strategies such as with pembrolizumab or the angiogenesis inhibitor pazopanib warrant further investigation. Pembrolizumab plus cetuximab showed a promising ORR of 42.8% in a small cohort of platinum refractory HNSCC as recently reported [21]. On the other hand cetuximab plus pazopanib demonstrated substantial anti-tumor activity in both cetuximab-naive cetuximab-resistant HNSCC [22].

## Perspectives and conclusion

The management of both locally advanced and R/M HNSCC remains a clinical challenge, since current treatment options are still unsatisfactory. Conventional therapeutic approaches including surgery, radiotherapy and systemic therapy are associated with suboptimal survival outcomes in combination with substantial toxicities and the necessity for novel treatment strategies is obvious. While the introduction of CPI therapy into the clinical routine resulted in unprecedented long-term survival, these therapies fail in the majority of cases. Therefore, not only novel combination strategies with cytotoxic therapies, radiation, and other CPI or oncolytic viruses have to be developed, but also predictive biomarkers and the optimal time point (neo-adjuvant, locally advanced, R/M) for the use of these compounds have to be identified. However, there is hope that immunotherapy will be ready for prime time in the near future facilitating long-term survival in the majority of HNSCC patients.

**Conflict of interest** I. Sepulveda, R. Ascui, and A. A. Capizzano declare that they have no competing interests.

## References


1. Guidi A, Codecà C, Ferrar D. Chemotherapy and immunotherapy for recurrent and metastatic head and neck cancer: a systematic review. Med Oncol. 2018;35(3):37.
2. Cavalieri S, Rivoltini L, Bergamini C, Locati LD, Licitra L, Bossi P. Immuno-oncology in head and neck squamous cell cancers: News from clinical trials, emerging predictive factors and unmet needs. Cancer Treat Rev. 2018;65:78–86.
3. Fuereder T. Immunotherapy for head and neck squamous cell carcinoma. Memo. 2016;9:66–9.
4. Ferris RL, Blumenschein G Jr., Fayette J, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. N Engl J Med. 2016;375:1856–67.
5. Dorsey K, Agulnik M. Promising new molecular targeted therapies in head and neck cancer. Drugs. 2013;73(4):315–25.
6. Pai SI, Zandberg DP, Strome SE. The role of antagonists of the PD-1:PD-L1/PD-L2 axis in head and neck cancer treatment. Oral Oncol. 2016;61:152–8.
7. Pai SI. Adaptive immune resistance in HPV-associated head and neck squamous cell carcinoma. Oncoimmunology. 2013;2(5):e24065.
8. Moskovitz J, Moy J, Ferris RL. Immunotherapy for Head and Neck Squamous Cell Carcinoma. Curr Oncol Rep. 2018;20:22. https://doi.org/10.1007/s11912-018-0654-5
9. Chow LQM, Haddad R, Gupta S, 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.
10. Bauml J, Seiwert TY, Gilbert J, Pfister DG, Worden F, Liu SV, et al. Pembrolizumab for platinum- and cetuximab-refractory head and neck cancer: results from a single-arm, phase II study. J Clin Oncol. 2017;35:1542–9.
11. Cohen EEW, Soulières D, Le Tourneau C, 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. Jan.
12. Cohen, ESMO 2017; September, 11; Madrid, Spain, Oral Presentation. 2017
13. Siu LL, Even C, Mesía R, et al. Safety and Efficacy of Durvalumab With or Without Tremelimumab in Patients With PD-L1–Low/Negative Recurrent or Metastatic HNSCC: The Phase 2 CONDOR Randomized Clinical Trial. JAMA Oncol. 2018;5(2):195–203. https://doi.org/10.1001/jamaoncol.2018.4628

14. Licitra LF, Haddad RI, Even C, et al. EAGLE: A phase 3, randomized, open-label study of durvalumab (D) with or without tremelimumab (T) in patients (pts) with recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC). J Clin Oncol. 2019;37(15):6012–6012.
15. Galluzzi L, Zitvogel L, Kroemer G. Immunological mechanisms underneath the efficacy of cancer therapy. Cancer Immunol Res. 2016;4:895–902.
16. Burtness B, Harrington KJ, Greil R, et al. KEYNOTE-048: Fase III study of first line pembroluzimab (P) for recurrent/metastasic head and neck squamous cell carcinoma (R/M HNSCC). ASCO. 2019;The ASCO Post
17. Teng F, Kong L, Meng X, Yang J, Yu J. Radiotherapy combined with immune checkpoint blockade immunotherapy: achievements and challenges. Cancer Lett. 2015;365:23–9.
18. Kalbasi A, June CH, Haas N, Vapiwala N. Radiation and immunotherapy: a synergistic combination. J Clin Invest. 2013;123:2756–63.
19. Park B, Yee C, Lee KM. The effect of radiation on the immune response to cancers. Int J Mol Sci. 2014;15:927–43.
20. Ferris RL, et al. Rationale for combination of therapeutic antibodies targeting tumor cells and immune checkpoint receptors: Harnessing innate and adaptive immunity through IgG1 isotype immune effector stimulation. Cancer Treat Rev. 2018;63:48–60. https://doi.org/10.1016/j.ctrv.2017.11.008
21. Sacco AG, Chen R, Ghosh D, et al. An open label, non-randomized, multi-arm, phase II trial evaluating pembrolizumab combined with cetuximab in patients with recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC): Results of cohort 1 interim analysis. J Clin Oncol. 2019;37(suppl):Abstr 6033
22. Adkins D, et al. Pazopanib plus cetuximab in recurrent or metastatic head and neck squamous cell carcinoma: an open-label, phase 1b and expansion study. Lancet Oncol. 2018;19:1082–93.