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# The effects of checkpoint inhibition on head and neck squamous cell carcinoma: A systematic review

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ABSTRACT

*Background:* Head and neck squamous cell carcinoma (HNSCC) is the sixth most frequent malignancy worldwide. Immunotherapy with checkpoint inhibitors such as anti-CTLA-4 anti-PD-l and anti-PD-L1 has shown promising results in treating patients with recurrent/metastatic HNSCC. We aimed to systematically review the literature on immunotherapy with checkpoint inhibitors as treatment for advanced HNSCC.

*Methods:* PubMed, EMBASE, Google Scholar, and the Cochrane Library were systematically searched with the purpose of identifying all studies addressing the effects of checkpoint inhibitors as treatment for HNSCC in human clinical trials. We assessed effects of the treatment with checkpoint inhibitors on overall survival (OS), progression-free survival (PFS), HPV-status, PD-L1-status, and adverse events.

*Results:* We identified eight studies (n = 1431 patients) with an OS ranging from 7.5 to 14.9 months in PD-1 checkpoint inhibition. Two studies (n = 541 patients) observed a significantly (p = 0.01) and (p = 0.007) longer OS with checkpoint inhibition compared to standard-treatment, platinum-based chemotherapy (7.5 versus 5.1 months and 14.9 months versus 10.7 months). Two studies (n = 411 patients) found an increased OS associated with PD-L1-postive patients compared to PD-L1-negative patients. The eight studies have heterogenous design with only three being randomized.

*Conclusion:* Few clinical trials have investigated the treatment with checkpoint inhibition for HNSCC. Solely, two randomized studies comprising 240 patients treated with nivolumab (anti-PD-L) and 301 patients treated with pembrolizumab (anti-PD-L) showed a significantly prolonged survival in patients with recurrent/metastatic HNSCC compared with standard-treatment. There is a further need for randomized clinical trials investigating a putative role of checkpoint inhibition in the treatment of advanced HNSCC.

## Introduction

Head and neck cancer is the sixth most frequent malignancy worldwide, with more than 650,000 reported cases annually [1] and with a continued increase in incidence [2]. The far majority of head and neck cancers are squamous cell carcinomas (HNSCC) accounting for more than 90% of the cancers located in the upper aerodigestive tract [3]. Several standard treatment modalities for HNSCC exist including surgery, chemotherapy, radiation-therapy, and epidermal growth factor receptor inhibitor (Cetuximab) [4]. Despite the development in chemotherapy, targeted radiotherapy, and surgery the estimated 5-year survival of HNSCC remains approximately 50% [5]. A potentially new therapeutic option in the treatment of HNSCC is immunotherapy targeting checkpoint inhibitors, such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) or programmed cell death protein 1 (PD-1) [6]. The basic principle of immunotherapy is to activate and allow the endogenous immune system to attack the tumor cells.

PD-1 and CTLA-4 downregulate and inhibit T-cells by binding with its ligands programmed death-ligand 1 (PD-L1)/programmed death-ligand 2 (PD-L2) or CD80/CD86. Unlike the ligands of CTLA-4, which are only expressed on antigen presenting cell (APC), PD-1's ligands are more widely expressed on leukocytes, nonlymphoid tissues, and some tumors including HNSCC [7]. Under normal conditions the immune system uses the inhibitory checkpoint pathways with CTLA-4 and PD-1 to regulate targeted activation and immune response against pathogens, while preventing the immune system from attacking itself and inducing autoimmune activity. Tumor cells take advantage of these pathways to create an immunosuppressive microenvironment in which they can hide themselves from the immune system [8]. Some tumors including HNSCC have showed an increased expression of PD-L1, the ligands for PD-1, which is thought to help create the immunosuppressive microenvironment around the tumor [9]. Blockage of the immunosuppressive

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effect of PD-1, PD-L1, and CTLA-4 has shown promising results as antitumor immunity, allowing T-cells to be upregulated and attack tumor cells, leading to a potentially reduction of the tumor. This has been seen in the treatment of solid tumors including HNSCC [10].

This study systematically evaluated the literature on the effects of checkpoint inhibitors on HNSCC patients. We aimed to clarify the potential benefits and harms in the use of immunotherapy targeting checkpoint inhibitors in patients with advanced HNSCC.

## Materials and methods

This systematic review was conducted with reference to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [11].

### *Systematic literature search and eligibility criteria*

One author (MG) systematically searched PubMed, Clinicaltrials.gov, Cochrane Library, Embase, and Google Scholar for articles in English published between 1980 and 2018. The search was updated on May the 25th 2018, with a final revision on December the 15th 2018.

We included studies assessing the effect of checkpoint inhibitors as immunotherapy treatment for HNSCC in human clinical trials, regardless of the publication date. We included studies using the checkpoint inhibitors anti-CTLA-4, anti-PD-1, and anti-PD-L1 as treatment for squamous cell carcinoma located in the upper aerodigestive tract including the oral cavity, oropharynx, nasopharynx, hypopharynx, sinonasal cavity and larynx. Studies assessing the effect of immunotherapy with checkpoint inhibitors in combinations with either radiation therapy or chemotherapy were excluded.

The following keywords were used when searching PubMed and Embase: Immunotherapy and Head and neck cancer or HNC or head and neck squamous cell carcinoma or HNSCC or squamous cell carcinoma or SCC or SCCHN and oral cavity or nasal cavity or pharynx or nasopharynx or oropharynx or hypopharynx or sinonasal and CTLA-4 or PD-1 or PD-L1 or checkpoint inhibitors or checkpoint blockade or checkpoint molecules or Nivolumab or Pembrolizumab or Ipilimumab or Durvalumab or Atezolizumab. In Cochrane Library keywords searched were: Head and Neck cancer and Immunotherapy or CTLA-4 or PD-1. In Google Scholar keywords searched were: Head and neck cancer and PD-1 or CTLA-4 or PD-L1. In Clinicaltrials.org the search was performed with the keywords: “Head and neck cancer and PD-1” and “head and neck cancer and CTLA-4”

The following data were extracted from the included studies: Study design, study participants, focus of interest, statistic test, median age of participants, pretreatment, drug, antibody, dose, adverse events, death related to treatment, overall response rate (ORR), overall survival (OS), progression-free survival (PFS), HPV-Status, OS or PFS stratified on HPV-status, PD-L1- Status, OS or PFS stratified on PD-L1-status and cancer locations.

## Results

The electronic literature search generated 670 potentially eligible studies of which four studies met the inclusion criteria. Four additional study was found through reference list (Fig. 1).

Eight clinical trials (n = 1431 patients) evaluated the safety and effects of checkpoint inhibitors as a treatment for HNSCC (Table 1 and 2). All clinical trials included patients that had been diagnosed with recurrent HNSCC and whose previous standard treatment had failed, or primary HNSCC with metastatic spreading expect one trial using checkpoint inhibitors as a first-line systemic therapy for HNSCC [12]. Cancers were located in the oral cavity, oropharynx, hypopharynx, larynx, pharynx, or other regions in the head and neck (Table 3).

Six studies [12–17] evaluated the use of PD-1 antibodies, one study, Hanna G. et al. [18] included patients treated with both anti-PD-1 and anti-PD-L1 and Siu L. et al. evaluated PD-L1 and CTL-4 antibodies in a combination arm and as monotherapy arms (Table 4).

In three of eight studies the design comprised a prospective, single-arm, multicenter, open-label, clinical trials [13,15,16]. One study was conducted as a 3-year retrospective observational cohort study [18]. The remaining studies were prospective randomized clinical trials [12,14,17,19].

### *PFS and OS after checkpoint inhibition of HNSCC*

Six of the included studies (n = 737 patients) evaluated the PFS in patients treated with a PD-1 antibody [13–17]. The PFS measured in the studies ranged from 2.0 months [14,15,17] to 2.1 months [13,16]. Siu LL. et al. also evaluated the PFS of an PD-L1, CLTA-4 antibody and a combination of PD-L1/CTLA-4 with a PFS of 1.9 months, 1.9 months and 2.0 months, respectively [19].

Seven studies (n = 1164 patients) [12–18] investigated the OS after treatment with PD-1 checkpoint inhibitors, the OS varied from 7.5 months to 14.9 months [12,14]. One study evaluated the OS of an PD-L1, CLTA-4 antibody, and a combination of PD-L1/CTLA-4 with a OS of 6.0 months, 5.5 months and 7.6 months, respectively [19].

One of the randomized studies [14] with 240 patients, found no significant difference ($p = 0.32$) regarding PFS between the group (n = 240) of patients treated with checkpoint inhibitors and the group receiving standard treatment. However, a significantly ($p = 0.01$) longer OS was observed in the checkpoint inhibitor group with an OS of 7.5 months, versus the standard-treatment group with an OS of 5.1 months [14]. Burtness B. et al. also found a significant difference in the OS ($p = 0.0007$) between checkpoint inhibition (14.9 months) and standard-treatment (10.7 months) [12].

### *The effects of checkpoint inhibition regarding HPV- and PD-L1 status*

Five studies (n = 837 patients) analyzed the OS or the PFS stratified according to HPV-status [13–15,17,18]. Three of the five studies included more HPV-negative patients (n = 244) compared to HPV-positive patients (n = 110) [13,15,18]. Two (n = 366 patients) of the five studies demonstrated a higher OS in HPV-positive patients compared to HPV-negative patients ($p = 0.02$), with an OS of 9.1 months [14] and 11.0 months [18] in the HPV-positive group versus an OS in the HPV-negative group of respectively 7.5 months [14] and 7.0 months [18]. Ferris R. et al.’s two year update reported an OS of 9.1 months in the HPV-positive versus 7.7 months in HPV-negative patients [17]. Seiwert T. et al. [15] did not examine the OS in HPV- positive patients, but found an OS of 8.0 months in HPV-negative patients. Furthermore, Seiwert T. et al. [15] reported that HPV-positive patients had a two months longer PFS compared to HPV-negative patients (4 months in HPV-positive patients versus 2 months in HPV-negative patients). One study [13] found no difference in OS and PFS between the two HPV subgroups (OS = 8.0 months and PFS = 2.1 months regardless of HPV-status).

Five studies (n = 978 patients) analyzed the OS or PFS of the PD-L1 subgroups [13–15,17,19] (Table 2). Three studies, Bauml J. et al. [13] and Ferris et al. [14,17], found an increased OS in PD-L1-positive patients compared to PD-L1-negative. Bauml J. et al. reported a 4% greater 6-months PFS in PD-L1-positive patients compared to PD-L1-negative patients [13].

### *Adverse events related to checkpoint inhibitor treatment*

All eight studies investigated the safety of their clinical trials regarding adverse events related to treatment. In six studies (n = 1004 patients) [13–17,19] the most common grade of adverse events were graded as 1 and 2 assessed according to the Common Terminology Criteria for Adverse Events, version 4.0 [21]. Ferris R. et al. ’s. two year update (n = 240 patients) found a higher reported treatment related

**Table 1**
Overview of studies: checkpoint inhibition in HNSCC.

| Author (Year) [Reference] | Patients, N (median age) | Lines of prior therapy | Drug (Antibody) | Study design | Focus of interest | Statistic test |
|---|---|---|---|---|---|---|
| Bauml J. et al. (2017) [13] | N = 171 (61) | 39% of patients had one line of prior systemic therapy and 76% of patients had two or more lines of systemic therapy | Pembrolizumab (Anti-PD-1) | Prospective, single-arm multicenter, phase II - study | Primary: Efficacy of ORR and safety. Secondary: PFS, OS, duration of response, and ORR in HPV-positive/negative patients | One-sided p value with binomial methods and Kaplan-Meier statistics was applied for PFS and OS |
| Ferris R. et al. (2016) [14] | N = 240 (59) | 44.2% of patients had one line of prior systemic therapy and 55.8% of patients had two or more lines of systemic therapy | Nivolumab (Anti-PD-1) | Prospective, randomized, open-label, phase III- study | Primary: OS.<br>Secondary: PFS, time to response, associations between PD-L1 and HPV-status, response rate, safety and quality-of-life assessments | Overall survival and<br>progression-free survival were estimated by the<br>Kaplan–Meier method and compared by means<br>of log-rank tests stratified according to previous<br>receipt of cetuximab |
| Seiwert T. et al. (2016) [15] | N = 60 (63) | 15% of patients had one line of prior systemic therapy and 70% of patients had two or more lines of systemic therapy | Pembrolizumab (Anti-PD-1) | Prospective, single-arm, multicenter, open-label, phase Ib - study | Primary: the safety of Pembrolizumab and the overall response. Secondary: overall response in HPV-positive and PSF + OS in the total patient population | Statistical tests were done at the<br>α = 0·05 (two-sided) level, and<br>Kaplan-Meier statistics was applied |
| Tahara M. et al. (2018) [16] | N = 26 (62) | 23% of patients had one line of prior therapy and 61% had two or more lines of prior therapy | Pembrolizumab (Anti-PD-1) | Prospective, single-arm, multicenter, non-randomized, multi-cohort, phase Ib - study | Primary: Safety and ORR Secondary: ORR by investigator assessment and PSF, OS | Kaplan-Meier were used to analyze PFS, OS, DOR and binomial para-meters were used to deter-mine ORR |
| Hanna G. et al. (2018) [18] | N = 126 (57) | Percentage of prior lines of therapy was not disclosed, but 75% of patients were treated with combination of radiation and chemotherapy | (Anti-PD-1 or Anti-PD-L1) | Retrospective,<br>3-year observational cohort - study | Presenting a clinically annotated cohort of HNSCC patients treated with checkpoint inhibitor therapies and massively parallel sequencing and tumor immune profiling results were analyzed to further nominate predictors of checkpoint inhibitor response | Pearson's χ2 test, Binary logistic regression analysis, Spearman's ρ and Kaplan-Meier statistics were applied using log-rank testing to evaluate outcome data |
| Ferris R. et al. (2018) [17] | N = 240 (59) | 44.2% of patients had one line of prior systemic therapy and 55.8% of patients had two or more lines of systemic therapy | Nivolumab (Anti-PD-1) | Prospective,<br>randomized, open-label, phase III- study | Primary: OS<br>Secondary: PFS, ORR, associations between PD-L1 and HPV-status, and safety | OS and PFS were assessed using the Kaplan-Meier method, HRs and corresponding 2-sided 95% CIs were estimated using a Cox proportional<br>hazards model |
| Burtness B. et al. (2018) [12] | N = 301 | No lines of prior therapy | Pembrolizumab (Anti-PD-1) | Prospective,<br>randomized, phase III, open-label - study | Primary end points PFS and OS in pembrolizumab vs cetuxmab and Pembrolizumab + cisplatin vs cetuxmab | Not disclosed |
| Siu L. et al. (2018) [19] | N = 133<br>(62) combination arm.<br>N = 67<br>(62) Durvalumab.<br>N = 67<br>(61)<br>Tremelimumab<br>N = 267<br>(61) Total | 45.3% of patients had one line of prior systemic therapy and 54.3% of patients had two or more lines of systemic therapy | Durvalumab (Anti-PD-L1), Tremelimumab (Anti- CTLA-4) | Prospective, randomized, open-label, phase II – study | Primary end points were ORR of<br>durvalumab + tremelimumab. Secondary end points were ORR in monotherapy arms, duration of response, best objective response, disease control rate, PFS, OS and safety in all arms | Kaplan-Meier plots and median values of PFS and OS determined and presented using a 95% CI and 2-sided p value. Statistical analyses were performed using SAS software |

**Table 2**
Study results of the effects of checkpoint inhibition in HNSCC.

| Author (Year) [Reference] | Adverse events (Most common side effect) {Number of deaths related to treatment} | | Overall response rate to treatment | Overall Survival, median | Progression free survival, median | HPV-Status | | HPV-survival, OS or PFS in Months | | PD-L1 Status | | PD-L1 survival, OS or PFS in Months | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Grade < 2 | Grade > 2 | | | | Pos | Neg | Pos | Neg | Pos | Neg | Pos | Neg |
| Bauml J. et al. (2017) [13] | (Fatigue, hypothyroidism, nausea)<br>{n = 0}<br>N = 83 | N = 26 | N = 28 (16.4%) | 8.0 months | 2.1 months | N = 37 | N = 131 | OS = 8.0<br>PFS = 2.1 | OS = 8.0<br>PFS = 2.1 | N = 140 | N = 26 | 6-months OS = 59% 6-months PFS = 24% | 6-months OS = 56% 6-months PFS = 20% |
| Ferris R. et al. (2016) [14] | (Fatigue, nausea, rash)<br>{n = 2}<br>N = 108 | N = 31 | N = 32 (13.3%) | 7.5 months | 2.0 months | N = 63 | N = 50 | OS = 9.1 | OS = 7.5 | N = 88 | N = 73 | OS = 8.7 | OS = 5.7 |
| Seiwert T. et al. (2016) [15] | (Fatigue, pruritus, rash)<br>{n = 0}<br>N = 28 | N = 10 | N = 8 (13.3%) | 13.0 months | 2.0 months | N = 23 | N = 37 | OS = Not researched,<br>PFS = 4 months | OS = 8.0 months,<br>PFS = 2 months | N = 60 | N = 0 | All patients were PD-1 pos.<br>OS = 13 months | |
| Tahara M. et al. (2018) [16] | (Fatigue, decreased appetite, hypothyroidism)<br>{n = 0}<br>N = 14 | N = 2 | N = 5 (19.2%) | 11. 6 months | 2.1 months | N = 2 | N = 24 | No data | | N = 22 | N = 4 | No data | |
| Hanna G. et al. (2018) [18] | (gastrointestinal, hepatic, or pancreatic inflammation, acute cervical neck or facial edema, pneumonitis)<br>{n = 0}<br>Not disclosed | N = 12 | N = 17 (13.5%) | 9.0 months | No data | N = 50 | N = 76 | OS = 11.0 | OS = 7.0 | N = 29 of 41 tested | N = 12 of 41 tested | No data | |
| Ferris R. et al. (2018) [17] | (Fatigue, nausea, anemia)<br>{n = 2}<br>N = 146 | N = 36 | N = 32 (13.3%) | 7.7 months | 2.0 months | N = 64 | N = 56 | OS = 9.1 | OS = 7.7 | N = 96 | N = 76 | OS = 8.2 | OS = 6.5 |
| Burtness B. et al. (2018) [12] | Not disclosed<br>No data | 17%[a] | 23%[a] | 14.9 months | Not disclosed | No data | | No data | | No data | | do data | |
| Siu L. et al. (2018) [19] | (Diarrhea, fatigue, asthenia)<br>{N = 1, combination arm}<br>N = 56 combination arm.<br>N = 33 Durvalumab.<br>N = 25 Tremelimumab. | N = 21 combination arm.<br>N = 8 Durvalumab.<br>N = 11 Tremelimumab. | N = 10 (7.8%) combination arm.<br>N = 9 (9.2%) Durvalumab.<br>N = 1 (1.6%) Tremelimumab. | 7.6 months combination arm<br>6.0 months Durvalumab<br>5.5 months Tremelimumab | 2.0 months combination arm<br>1.9 months Durvalumab<br>1.9 months Tremelimumab | N = 75 | N = 192 | No data | | N = 0 | N = 267 | All patients were PD-1 neg/low.<br>OS = 7.6 months combination arm<br>6.0 months Durvalumab<br>5.5 months Tremelimumab | |

Abbreviation: OS: Overall Survival, PFS: Progression Free Survival, ORR: Overall Response Rate, HPV: Human Papillomavirus, PD-1: Programmed cell death protein 1, PD-L1: Programmed death-ligand 1 and N: Number of patients.

[a] Data was only disclosed in percentage.

**Table 3**
Overview of cancer types included in the studies.

| Author (Year) [Reference] | Oropharynx cancer | Hypopharynx cancer | Oral cavity cancer | Larynx cancer | Pharynx cancer | Other cancers[a] |
|---|---|---|---|---|---|---|
| Bauml J. et al. (2017) [13] | N = 100 | N = 7 | N = 28 | N = 30 | N = 1 | N = 4 |
| Ferris R. et al. (2016) [14] | No data | No data | N = 108 | N = 34 | N = 92 | N = 6 |
| Seiwert T. et al. (2016) [15] | N = 16 | N = 1 | N = 11 | N = 2 | No data | N = 30 |
| Tahara M. et al. (2018) [16] | N = 4 | N = 9 | N = 5 | N = 4 | No data | N = 4 |
| Hanna G. et al. (2018) [18] | N = 56 | No data | N = 26 | N = 14 | No data | N = 28 |
| Ferris R. et al. (2018) [17] | No data | No data | N = 108 | N = 34 | N = 92 | N = 6 |
| Burtness B. et al. (2018) [12] | No data | No data | No data | No data | No data | No data |
| Siu L. et al. (2018) [19] | N = 107 | N = 42 | N = =54 | N = 60 | No data | N = 3 |

[a] Other cancer is a group we made which includes all other cancer locations.

adverse events of grade 1 or 2 with 146 patients compared to 36 patients of grade 3 or higher [17]. Two studies (n = 427 patients) only presented the number of patients with adverse events graded 3 or higher [12,18]. The most common adverse event in six of the included studies (n = 1004 patients) was fatigue (14.05%) followed by nausea (6.57%) [13–17,19]. The most common adverse events grade 3 or higher reported by Hanna G. et al. [18] were gastrointestinal, hepatic or pancreatic inflammation.

Four studies (n = 524 patients) had patients drop-out due to treatment-related adverse events, with a 4% (n = 7 patients) dropout in [13], 8.3% (n = 5 patients) in [15], 3.8% (n = 1) in [16], and 4.8% (n = 12 patients) in [19].

One study (n = 240 patients) [14] compared the adverse events found in a group of patients treated with checkpoint inhibitor to a standard treatment group. The study found that the rates of treatment-related adverse events of any grade were similar in the two groups. However, the checkpoint inhibitor group had fewer reported cases of grade 3 and 4 adverse events compared to the standard-treatment group, with 13.1% of patients in the checkpoint inhibitor group versus 35.1% of patients in the standard treatment group. The two-year update from Ferris R. et al. reported a larger amount of patients experiencing adverse events of grade 3 and 4 in to the standard-treatment group with 36.9% compared to checkpoint inhibitor group with 15.3% [17].

Three studies reported treatment-related deaths; in Bauml et al. one patient died of treatment-related pneumonitis [13], in Siu LL. et al. one patient died of treatment-related grade 3 acute respiratory failure [19], and Ferris. R et al. reported two treatment-related deaths caused by pneumonitis and hypercalcemia [14,17].

## Discussion

This study is the first systematic review to evaluate the effect of immunotherapy with checkpoint inhibitors for HNSCC.

We found that treating recurrent/metastatic HNSCC patients with PD-1 checkpoint inhibitors resulted in an OS ranging from 7.5 months to 14.9 months. There is a clear interval-difference of 7.4 months between the highest reported OS and the lowest. Furthermore, in patients treated with a combination of PD-L1/CTLA-4 checkpoint inhibitors resulted in an OS of 7.6 months. PD-L1 and CTLA-4 checkpoint inhibitors as separate monotherapy resulted in OS of 6.0 months and 5.5 months respectively. These differences in the results between the studies could have been caused by the variations in treatment regimen, drug, dose, and selection-bias. The study with the highest OS (14.9 months) used a dose of 200 mg anti-PD-1(pembrolizumab) every 3 weeks [12], while the study with the lowest OS (7.5 months) used a dose of 3 mg/kg anti-PD-1 (Nivolumab) every 2 weeks [14].

Ferris R. et al. [14] randomized trial found that the OS was significantly (p = 0.01) prolonged in patients treated with checkpoint inhibitors compared to standard treatment in recurrent/metastatic HNSCC patients. This is support by the two-year update from the same group [17]. Similar results were found by the largest randomized trial by Burtness B et al. [12] as the study reported a significantly (p = 0.0007) prolonged OS in treated with checkpoint inhibitor compared to standard treatment. It should be noted the study included patients with no prior line of therapy [12].

Tringale KR. and Carroll KT. et al. [22] published a study on the cost-effectiveness of checkpoint inhibition compared to standard treatment in HNSCC patients. This study showed that the overall cost of treatment increased with $117 800 (from $57 000 with standard treatment to $174 800 with checkpoint inhibition) and concluded that checkpoint inhibition at its current cost was not a cost-effective treatment compared to standard therapy, even if it has an improved OS in patients with recurrent/metastatic HNSCC.

Ferris R. et al. [14] and Hanna G. et al.'s [18] studies showed a significantly improved OS based on nivolumab [14] and anti-PD-L/anti-PD-L1 [18] in HPV-positive patients versus HPV-negative (p = 0.02). The improved OS in HPV-positive patients was not reported in all of the included studies. Based on the published outcome, it is difficult to conclude whether an association between HPV-positivity and better OS exists, and if HPV-status can be used as a biomarker for the efficacy of checkpoint inhibitors on HNSCC patients. There is a need for additional clinical trials investigating the subject.

Most of the studies, investigating OS or PFS stratified on PD-L1-status, found that HNSCC patients with PD-L1-postive tumors

**Table 4**
Overview of ongoing trials using checkpoint inhibitors on HNSCC with/without combining treatments.[a]

| Title | Estimated Enrollment | Phase | Drug/antibody | Status | Estimated Study Completion Date | Id-number |
|---|---|---|---|---|---|---|
| Phase III Open Label Study of MEDI 4736 With/Without Tremelimumab Versus Standard of Care (SOC) in Recurrent/Metastatic Head and Neck Cancer | N = 823 | 3 | MEDI 4736 (Durvalumab), Tremelimumab | Active, not recruiting | December 31, 2018 | NCT02551159 |
| Safety and Efficacy of MEDI0457 and Durvalumab in Patients With HPV Associated Recurrent/Metastatic Head and Neck Cancer | N = 50 | 1/2 | Durvalumab, MEDI0457 | Recruiting | August 10, 2020 | NCT03162224 |
| CHEckpoint Inhibition in Combination With an Immunoboost of External Body Radiotherapy in Solid Tumors (CHEERS) | N = 97 | 2 | Pembrolizumab, Nivolumab | Recruiting | August 14, 2022 | NCT03511391 |
| Pembrolizumab Plus Docetaxel for the Treatment of Recurrent or Metastatic Head and Neck Cancer | N = 22 | 1/2 | Docetaxel, Pembrolizumab | Recruiting | August 2020 | NCT02718820 |
| Metronomic Oral Vinorelbine Plus Anti-PD-L1/Anti-CTLA4 ImmunothErapy in Patients With Advanced Solid Tumours (MOVIE) | N = 150 | 1/2 | Durvalumab + Tremelimumab + Metronomic Vinorelbine | Recruiting | August 30, 2023 | NCT03518606 |
| Azacitidine, Durvalumab, and Tremelimumab in Recurrent and/or Metastatic Head and Neck Cancer Patients | N = 59 | 1/2 | Azacitidine, Durvalumab, Tremelimumab | Recruiting | | NCT03019003 |
| A Phase 1/2 Study of In Situ Vaccination With Tremelimumab and IV Durvalumab Plus PolyICLC in Subjects With Advanced, Measurable, Biopsy-accessible Cancers | N = 102 | 1/2 | Durvalumab, Tremelimumab, Poly ICLC | Recruiting | August 2022 | NCT02643303 |
| GSK3359609 Plus Tremelimumab for the Treatment of Advanced Solid Tumors | N = 115 | 1/2 | GSK3359609, Tremelimumab | Recruiting | June 16, 2022 | NCT03693612 |

[a] This information is from clinicaltrials.gov.

responded with greater antitumor activity compared to PD-L1- negative tumors. PD-L1-positive HNSCC patients have an increased expression of PD-L1 compared to PD-L1 negative patients, which could be an explanation as to why PD-L1-positive tumors respond with greater antitumor activity when treated with checkpoint inhibitors targeting PD-1. When dealing with HNSCC, PD-L1-status could potentially function as a biomarker, indicating which patients would have the best response to immunotherapy-treatment with checkpoint inhibitors.

We found that most adverse events due to treatment with checkpoint inhibitors were graded as 1 or 2 (n = 493 patients; 77.2%) indifferent of drug or combination-therapy. When compared to standard treatment Ferris R. et al. studies support that checkpoint inhibition is associated with fewer toxic effects of grade 3 or 4 [14,17]. Furthermore, long term survivors treated with checkpoint inhibitors reported better quality of life in contrary to patients who received other palliative treatment including cetuximab and chemotherapy [14].

In conclusion, data on checkpoint inhibition on HNSCC is still very sparse. Checkpoint inhibition has showed antitumor activity. However, only two randomized studies comprising 240 patients and 301 patients, respectively, found a significantly prolonged survival in recurrent or metastatic HNSCC [12,14]. The present literature suggests that checkpoint inhibition showed greater antitumor activity in PD-L1-positive HNSCC patients and resulted in fewer toxic adverse events when compared with standard-treatment. There is especially a need for achieving a higher level of evidence based on randomized clinical trials to investigate the safety and efficiency of checkpoint inhibition as a novel treatment modality for patients suffering from advanced or recurrent HNSCC.

## Conflicts of interest

The authors declare no conflicts of interest.

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None.

## Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oraloncology.2019.01.018.

## References


[1] Ferlay J, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136(5):E359–86.

[2] Jakobsen KK, et al. Increasing incidence and survival of head and neck cancers in Denmark: a nation-wide study from 1980 to 2014. Acta Oncol (Madr) 2018:1–9.

[3] Lambert R, Sauvaget C, de Camargo Cancela M, Sankaranarayanan R. Epidemiology of cancer from the oral cavity and oropharynx. Eur J Gastroenterol Hepatol 2011;23(8):633–41.

[4] Pezzuto F, et al. Update on head and neck cancer: current knowledge on epidemiology, risk factors, molecular features and novel therapies. Oncology 2015;89(3):125–36.

[5] Warnakulasuriya S. Global epidemiology of oral and oropharyngeal cancer. Oral Oncol 2009;45(4–5):309–16.

[6] Strome SE, et al. B7-H1 blockade augments adoptive T-cell immunotherapy for squamous cell carcinoma. Cancer Res 2003;63(19):6501–5.

[7] Parry RV, et al. CTLA-4 and PD-1 receptors inhibit T-cell activation by distinct mechanisms. Mol Cell Biol 2005;25(21):9543–53.

[8] Dong H, et al. Tumor-associated B7–H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. Nat Med 2002;8(8):793–800.

[9] 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; 2016.

[10] Seiwert T. Inflamed-phenotype gene expression signatures to predict benefit from the anti-PD-1 antibody pembrolizumab in PD-L1 + head and neck cancer patients. J Clin Oncol 2015.

[11] Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009;151(4):264–9. W64.

[12] Burtness B, et al. KEYNOTE-048: Phase III study of first-line pembrolizumab (P) for recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC). Ann

Oncol 2018;29(suppl_8).

[13] Bauml J, 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(14):1542–9.

[14] Ferris RL, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. N Engl J Med 2016;375(19):1856–67.

[15] Seiwert TY, 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. LancetOncol 2016;17(7):956–65.

[16] Tahara M, et al. Pembrolizumab in Asia-Pacific patients with advanced head and neck squamous cell carcinoma: analyses from KEYNOTE-012. Cancer Sci 2018;109(3):771–6.

[17] Ferris RL, 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.

[18] Hanna GJ, et al. Frameshift events predict anti–PD-1/L1 response in head and neck cancer. JCI Insight 2018;3(4).

[19] Siu LL, et al. Safety and efficacy of durvalumab with or without tremelimumab in patients with PD-L1–low/negative recurrent or metastatic HNSCC. JAMA Oncol 2018.

[21] Chen AP, et al. Grading dermatologic adverse events of cancer treatments: the common terminology criteria for adverse events version 4.0. J Am Acad Dermatol 2012;67(5):1025–39.

[22] Tringale KR, Carroll KT, Zakeri K, Sacco AG, Barnachea L, Murphy JD. Cost-effectiveness analysis of nivolumab for treatment of platinum-resistant recurrent or metastatic squamous cell carcinoma of the head and neck. JNCI J Natl Cancer Inst 2018;110(5):479–85.