Editorial Commentary

Long-term efficacy of immune checkpoint inhibitors with or without chemotherapy in recurrent or metastatic squamous cell carcinoma of the head and neck: a commentary on the 4-year follow-up of the KEYNOTE-048 trial

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Patients with recurrent or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN) has had a poor prognosis over a long period of time (1), however, the development of new and effective systemic therapies has improved the survival outcomes for many of these patients. In 2008, the EXTREME trial demonstrated that adding cetuximab to cisplatin/carboplatin and 5-fluorouracil (5-FU), as the standard first-line therapy (2), significantly prolonged overall survival (OS) (10.1 *vs.* 7.4 months) and progression-free survival (5.6 *vs.* 3.3 months) compared to cisplatin/carboplatin and 5-fluorouracil regimen, with a higher response rate (36% *vs.* 20%) in patients with R/M SCCHN (3). Based on the results of this trial, the EXTREME regimen has been recognized as the standard first-line treatment for patients with R/M SCCHN until recently. Meanwhile, over the last few years, the development of immunotherapy has revolutionized the treatment of R/M SCCHN.

SCCHN is a malignancy with suppressed immune surveillance mechanisms owing to a decline in the functioning of tumor-infiltrating lymphocyte (TIL), elevated regulatory T-cell (T-reg) activity, and an upregulation of cancer antigens (4). In addition, a high tumor mutational burden is frequently observed in SCCHN, similar to malignant melanoma (5) and lung cancer (6). Moreover, among head and neck cancers, virus-associated SCCHN, such as nasopharyngeal and oropharyngeal SCC, have been reported to evade tumor T-cell immune response due to persistent viral infection. Therefore, immune checkpoint inhibitors (ICIs) hold promise for the treatment of patients with R/M SCCHN (4).

In 2016, Ferris *et al.* reported the results of the Checkmate 141 trial, a randomized phase III trial that evaluated the efficacy of nivolumab, an anti-programmed cell death 1 (PD-1) antibody, in comparison to the investigator's choice of monotherapy (methotrexate, docetaxel, or cetuximab) in patients with platinum-refractory R/M SCCHN (7). This was the first trial demonstrating a survival benefit for patients with platinum-refractory disease of R/M SCCHN with poor prognosis and showed a significantly longer OS (7.5 *vs.* 5.1 months) and a higher response rate (13.3% *vs.* 5.8%) in the nivolumab arm compared to the control arm (7). The superiority of nivolumab treatment efficacy over the investigator's choice of monotherapy was also confirmed by

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the 2-year follow-up data (8).

The KEYNOTE-048 trial evaluated the efficacy of pembrolizumab, another anti-PD-1 monoclonal antibody, administrated as monotherapy or in combination with chemotherapy (cisplatin/carboplatin plus 5-FU) compared to the EXTREME regimen in patients with chemo-naïve R/M SCCHN (9). In this study, patients were categorized according to the PD-1 ligand 1 (PD-L1) combined positive score (CPS), defined as the number of PD-L1 positive cells (tumor cells as well as lymphocytes/macrophages) divided by the total number of tumor cells ×100 with a minimum of 100 viable tumor cells (9). Burtness *et al.* reported that pembrolizumab monotherapy significantly improved OS in patients with CPS ≥20 and ≥1 compared to the EXTREME regimen and was non-inferior in OS in the overall population, as described in detail below. Pembrolizumab in combination with chemotherapy also significantly prolonged OS compared to the EXTREME regimen in CPS ≥20, CPS ≥1, and the overall population. Based on these results, nivolumab has been approved for the treatment of patients with platinum-refractory R/M SCCHN, and pembrolizumab alone or in combination with chemotherapy has been approved for the treatment of patients with R/M SCCHN as first-line standard therapy in real-world clinical practice (10). However, regarding pembrolizumab, the median follow-up at the time of the final analysis in the KEYNOTE-048 study was only approximately 1 year; thus, the long-term impact of pembrolizumab therapy has not yet been well determined.

Harrington *et al.* reported the results of the post hoc analysis of the KEYNOTE-048 trial with an approximate 4-year follow-up of treatment efficacy and progression-free survival on subsequent therapy (PFS2) in late 2022 (11). In the original report, 882 patients with R/M SCCHN were randomly allocated to receive pembrolizumab alone (n=301), pembrolizumab plus chemotherapy (n=281), and the EXTREME regimen (n=300). In the second interim analysis, pembrolizumab alone significantly prolonged OS compared to the EXTREME regimen, cetuximab with chemotherapy in the CPS ≥20 [median 14.9 *vs.* 10.7 months; hazard ratio (HR) 0.61, 95% confidence interval (CI): 0.45–0.83, P=0.0007], and CPS ≥1 populations [12.3 *vs.* 10.3 months; HR, 0.78 (0.64–0.96), P=0.0086], and was non-inferior in the overall population [11.6 *vs.* 10.7 months; HR, 0.85 (0.71–1.03)]. Furthermore, pembrolizumab plus chemotherapy significantly prolonged OS compared to the EXTREME regimen in the overall population (13.0 *vs.* 10.7 months; HR 0.77, 95% CI: 0.63–0.93, P=0.0034) at the second interim analysis, and also significantly prolonged OS compared to the control in CPS ≥20 [14.7 *vs.* 11.0 months; HR, 0.60 (0.45–0.82), P=0.0004] and CPS ≥1 [13.6 *vs.* 10.8 months; HR, 0.65 (0.53–0.80), P<0.0001] populations in the final analysis. In the post hoc analysis, the median observation period was 45.0 months (interquartile range, 41.0–49.2; n=882). Pembrolizumab monotherapy continued to show significantly prolonged OS compared to the EXTREME regimen in the CPS ≥20 [median 14.9 *vs.* 10.8 months; HR, 0.61 (95% CI: 0.46–0.81), nominal one-sided P=0.00034] and CPS ≥1 [12.3 *vs.* 10.8 months; HR, 0.74 (0.61–0.89), nominal one-sided P=0.00080] populations, and was still non-inferior in the overall population [11.5 *vs.* 10.7 months; HR, 0.81 (0.68–0.97), nominal one-sided P=0.00994]. Furthermore, pembrolizumab plus chemotherapy also continued to show significantly prolonged OS compared to the EXTREME regimen in the CPS ≥20 [median 14.7 *vs.* 11.1 months; HR, 0.62 (95% CI: 0.46–0.84), nominal one-sided P=0.00082], CPS ≥1 [13.6 *vs.* 10.6 months; HR, 0.64 (0.53–0.78), nominal one-sided P=0.0008], and the overall [13.0 *vs.* 10.7 months; HR, 0.71 (0.59–0.85), nominal one-sided P=0.00008] populations. The safety profiles of the treatments in the post hoc analysis did not differ significantly from those of the original report.

Only a small number of patients received a second course of pembrolizumab therapy (six patients received pembrolizumab monotherapy and five patients received pembrolizumab plus chemotherapy) in the post hoc analysis. Of these patients, 3 (27.3%) achieved partial or complete responses, suggesting that retreatment with pembrolizumab therapy may be beneficial in some patients. The results are similar to those of the subgroup analysis of the CheckMate trial 141, which evaluated the efficacy of nivolumab monotherapy beyond the Response Evaluation Criteria in Solid Tumors (RECIST)-defined progression, demonstrating a 16% objective response rate (ORR) in patients with platinum-refractory R/M SCCHN (12). For subsequent therapy after pembrolizumab treatment in the post hoc analysis in the intention-to-treat (ITT) population, 150 (49.8%) patients in the pembrolizumab-alone group and 161 (53.7%) in the EXTREME regimen group received ≥1 subsequent therapies. Pembrolizumab alone significantly prolonged PFS2 compared to the EXTREME regimen in the CPS ≥20 [median 11.7 *vs.* 9.4 months; HR, 0.64 (95% CI: 0.48–0.84), nominal one-sided P=0.00069] and CPS ≥1 [10.3 *vs.* 9.0 months; HR, 0.66 (95% CI: 0.55–0.81), nominal one-sided P=0.00002] populations.

Similarly, 119 (42.3%) patients in the pembrolizumab plus chemotherapy group and 147 (52.9%) patients in the EXTREME regimen group received ≥1 subsequent therapies. The pembrolizumab plus chemotherapy group also demonstrated significantly prolonged PFS2 compared to that in the EXTREME regimen group in the CPS ≥20 [median 11.3 *vs.* 9.8 months; HR, 0.64 (95% CI: 0.48–0.86), nominal one-sided P=0.00123], CPS ≥1 [9.4 *vs.* 8.9 months; HR, 0.79 (0.66–0.95), nominal one-sided P=0.00680] and the overall [10.3 *vs.* 9.0 months; HR, 0.73 (0.61–0.88), nominal one-sided P=0.00030] populations. This subgroup analysis showed that second-line treatment with taxane-containing chemotherapy had a similar treatment efficacy compared to pembrolizumab monotherapy and the EXTREME regimen, with significantly prolonged PFS2 in the pembrolizumab plus chemotherapy group compared to the EXTREME regimen group. Thus, the results suggest that patients who initially receive pembrolizumab-based therapy may benefit from treatment with taxane-based chemotherapy as subsequent therapy.

The results of this updated analysis are noteworthy in several aspects. First, first-line pembrolizumab monotherapy and pembrolizumab plus chemotherapy in chemotherapy-naïve R/M HNSCC demonstrated a durable survival benefit compared to the EXTREME regimen in long-term follow-up. Of note, this post hoc analysis with long-term observation showed that at least 20% of patients who received pembrolizumab as first-line therapy achieved a long-term response, presenting a plateau in the survival curve around the 4-year landmark. Furthermore, the proportion of patients achieving this long-term response was as high as approximately 30% in the PD-L1 CPS ≥20 population of patients receiving pembrolizumab plus chemotherapy. Second, this post hoc analysis showed that the response to salvage chemotherapy after progression on the pembrolizumab regimen as first-line therapy was very high, particularly when second-line treatment with taxane-containing chemotherapy was administered to patients who received pembrolizumab plus chemotherapy as first-line therapy. This high therapeutic efficacy of salvage chemotherapy after progression on the first-line ICI regimen compared to that of second-line therapy in R/M SCCHN in previous clinical trials (13,14) is consistent with the results of several retrospective studies presenting the outcomes of cytotoxic or biological agents after ICI administration for patients with R/M SCCHN (15-17). Several possible mechanisms may explain the high therapeutic efficacy of cytotoxic or biological agents after ICI administration, including the restoration of chemosensitivity due to changes in the tumor microenvironment caused by ICI administration, the elimination of bone marrow-derived suppressor cells and regulatory T cells by chemotherapy agents, and a temporary combined chemotherapeutic/immunotherapeutic effect due to the long half-life of the ICI agent (15,18). However, the significance of retreatment with pembrolizumab is difficult to determine in this analysis since very few patients received the second-course pembrolizumab regimen.

These results suggest that many patients with R/M HNSCC may benefit from pembrolizumab or pembrolizumab chemotherapy as first-line therapy; however, we should consider that neither the original report nor this post hoc analysis shows any results for patients with CPS <1. The subgroup analyses by CPS in the European Medicines Agency's (EMA) Assessment report for the KEYNOTE-048 study (19) revealed that the CPS <1 population in the pembrolizumab-alone group had inferior OS (HR, 1.51; 95% CI: 0.96–2.37), PFS (HR, 4.31; 95% CI: 2.63–7.08), and ORR (5% *vs.* 42%) compared to those in the EXTREME group. Although these results were based on an exploratory subgroup analysis, the EMA and U.S. Food and Drug Administration restrict pembrolizumab monotherapy to patients with CPS-positive R/M SCCHN (20); that is, pembrolizumab monotherapy is not recommended for patients with CPS-negative R/M SCCHN. The subgroup analyses by CPS in the EMA's Assessment report for the KEYNOTE-048 study (19) also revealed that pembrolizumab combined chemotherapy was not superior to the EXTREME regimen for OS (HR, 1.21; 95% CI: 0.76–1.94), PFS (HR, 1.46; 95% CI: 0.93–2.30), and ORR (31% *vs.* 40%) in the CPS <1 population. Therefore, the EMA still recommends the EXTREME regimen as the first choice as first-line therapy for patients with PD-L1 CPS-negative R/M SCCHN (20). Thus, it is essential for physicians to select the appropriate treatment for patients with R/M SCCHN, particularly based on CPS-negative/positive results, as well as patient characteristics, such as the Eastern Cooperative Oncology Group performance status, the presence of previous chemotherapy, and the progress of recurrent lesions.

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Footnote

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