Evolving Role of Immunotherapy in Recurrent Metastatic Head and Neck Cancer

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ABSTRACT

Immunotherapy has revolutionized cancer treatment in the past 2 decades, mostly with immune checkpoint blockade approaches. In squamous cell carcinoma of the head and neck (SCCHN), the initial efficacy of immunotherapy was observed in patients with recurrent or metastatic (R/M) disease who received other prior systemic treatment. As monotherapy, anti–PD-1 therapies induce responses in 13% to 18% of patients. More recently, immunotherapy in combination with cytotoxic chemotherapy demonstrated greater safety and efficacy as first-line systemic treatment compared with chemotherapy alone. In R/M SCCHN, the most important benefit of immunotherapy is the significantly improved overall survival, especially in patients with PD-L1-positive tumors. As of 2019, immunotherapy can be used as first-line or subsequent treatment of R/M SCCHN. Many ongoing trials are evaluating immunotherapy combinations or novel immunotherapy strategies, aiming to improve response rate and overall survival. As new targets are identified and new approaches are leveraged, the role of immunotherapy in R/M SCCHN continues to evolve.


Head and Neck Cancers

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These cancers arise primarily from the mucosal surfaces lining the paranasal sinuses, nasal cavity, oral cavity, oropharynx, larynx, and hypopharynx, or from the major and minor salivary glands. Cancers may have a variety of histopathologic types, such as adenocarcinoma, adenoid cystic carcinoma, neuroendocrine carcinoma, or nonkeratinizing (eg, lymphoepithelioma) carcinoma. However, squamous cell carcinoma is the most common pathologic type.2

Squamous cell carcinoma of the head and neck (SCCHN) can be largely divided into 2 groups: those associated with carcinogens (eg, tobacco and alcohol) or with HPV infection.3 Most oral cavity, larynx, and hypopharynx cancers are tobacco- and alcohol-related. In contrast, most HPV-positive cancers arise from the oropharynx.3,4 HPV-positive cancers usually demonstrate high p16 expression by immunohistochemistry, which serves as a surrogate for HPV infection.5 Due to strong birth cohort effects, patients with HPV-positive cancer were on average younger than those with HPV-negative cancer, but the age difference is decreasing over time.6 Although oropharynx cancers in nonsmokers are attributable to HPV infection, most patients with HPV-positive oropharynx in the United States have a history of tobacco exposure,7,8 and response to therapy among this “intermediate-risk” group is less favorable compared with never-smokers.8 In both the United States and Europe, the incidence of HPV-associated SCCHN has been increasing, whereas the tobacco- and alcohol-related SCCHN has been decreasing.4,9,10 In Asian countries, cases of tobacco- and alcohol-related SCCHN and Epstein-Barr virus–associated nasopharyngeal cancer remain dominant.

Recurrent or Metastatic SCCHN

Most patients with SCCHN have locoregionally limited disease at diagnosis, with only 10% of patients presenting with distant metastasis.11 Primary surgery followed by risk-adapted radiation with or without chemotherapy or with definitive concurrent chemoradiation are the
principal treatment strategies for locoregionally advanced disease. Even with recent advances in surgery and radiation, however, a subset of patients will eventually experience disease progression. For example, locoregional or distant failure occurs in approximately 40% and 20%, respectively, of patients with locoregionally advanced, HPV-negative SCCHN treated with cisplatin-based chemoradiotherapy. Recurrent disease is often complex, requiring multidisciplinary care to select the optimal combination and sequence of treatment. When disease recurrence is limited to local or regional failures, treatment with curative-intent surgical salvage may be possible. Patients who are not candidates for salvage surgery may be candidates for curative-intent radiation or reirradiation with or without chemotherapy, depending on the time since prior treatment and previous treatment-related toxicity. Palliative systemic therapy is indicated in patients diagnosed with recurrent or metastatic (R/M) SCCHN not amenable to the locally curative options mentioned earlier.

During 2008 through 2019, cetuximab and platinum-5-FU, also known as the EXTREME regimen, was the first-line systemic therapy of choice for R/M SCCHN based on results of a phase III trial. The addition of cetuximab to the platinum doublet significantly improved overall survival (OS) and progression-free survival (PFS) and yielded an objective response rate (ORR) of 36%. This regimen, however, is associated with an 82% rate of grade 3/4 toxicities and a 20% treatment discontinuation rate. In clinical practice, a taxane is frequently substituted for 5-FU and administered with or without cetuximab. Until 2016, the second-line options after platinum-containing regimen were limited to monotherapy, including a taxane, methotrexate, or cetuximab.

Initial Success of Anti–PD-1 Therapy in R/M SCCHN

Immunotherapy with immune checkpoint blockade was initially evaluated in clinical trials in patients with treatment-refractory melanoma (ClinicalTrials.gov identifier: NCT00289627, a single-arm ipilimumab trial). Subsequently, immune checkpoint blockade has demonstrated clinical benefit in a number of solid tumors. PD-1 is a “death receptor” that causes apoptosis in T cells to regulate the immune response and prevent autoimmunity. Many tumors express the PD-L1 ligand, which upon binding to the PD-1 receptor results in apoptosis of T cells and thus immune evasion. These discoveries led to the development of monoclonal antibodies to the PD-1 receptor, such as pembrolizumab and nivolumab, both of which were FDA approved for platinum-refractory R/M SCCHN in 2016.

The first anti–PD-1 therapeutic trial in R/M SCCHN was KEYNOTE-012 (NCT01848834), a phase I/II single-arm trial investigating the safety, tolerability, and antitumor activity of pembrolizumab (a humanized IgG4 antibody of PD-1) in a variety of solid tumors, including advanced head and neck cancer (cohorts B and B2). Patients were heavily pretreated with chemotherapy, because many had received 4 previous lines of systemic therapy. In cohort B (n = 60), all tumors had PD-L1 expression (immunohistochemistry [IHC] antibody clone 22C3) of at least 1%, whereas tumors in cohort B2 (n = 132) were not required to have PD-L1 expression. In this trial, the ORR in all patients was 18%, with 4% complete response, and median PFS was 2.1 months. ORR in HPV-positive tumors was 24% (95% CI, 13%–40%) versus 16% (95% CI, 10%–23%) in HPV-negative tumors (a nonsignificant difference, due to overlapping 95% CI in the 2 groups).

KEYNOTE-055 (NCT02255097) was designed to evaluate the ORR with pembrolizumab in patients with R/M SCCHN who were platinum- and cetuximab-refractory. Among 171 patients treated, the ORR was 16% (95% CI, 11%–23%) and PFS was 2.1 months. In this study, 82% of tumors were PD-L1–positive (based on combined positive score [CPS]), and the ORR was 18% versus 12% in PD-L1–negative tumors. Response rates were similar regardless of HPV status: 16% (95% CI, 6%–32%) in HPV-positive patients and 15% (95% CI, 10%–23%) in HPV-negative patients.

Anti–PD-1 Therapy Established as Second-Line Treatment

CheckMate 141 was a large randomized phase III study in patients with platinum-refractory R/M SCCHN designed to evaluate a principal outcome of OS with nivolumab (a fully human IgG4 anti–PD-1 antibody) versus single-agent chemotherapy of investigator’s choice. Eligible patients included those with disease progression within 6 months of receipt of cisplatin in the primary treatment setting (eg, as induction, concurrent, or adjuvant therapy) or for R/M disease. Patients were randomized 2:1 to nivolumab versus standard monotherapy (eg, cetuximab, methotrexate, docetaxel). A total of 347 patients received at least one dose of assigned therapy (236 in the nivolumab group and 111 in the standard therapy group). The ORR in the nivolumab was 13.3% versus 5.8% in the standard-therapy group (P < .01), and median OS was significantly longer (7.7 vs 5.1 months with standard therapy; HR, 0.68; P < .01). With long-term follow-up at 24 months, the estimated 24-month OS rate was nearly tripled with nivolumab compared with standard-of-care therapy (16.9% vs 6.0%). Median PFS in the 2 groups was similar. The magnitude of benefit of nivolumab over standard therapy appeared stronger at a median follow-up of 5.1 months for patients who were PD-L1–positive (≥1% by IHC PD-L1 antibody clone 28-8) or had p16-positive tumors, but was similar after a
minimum 24-month follow-up. Of note, nivolumab improved OS in the subset of patients (21.6%) treated in the first-line (hazard ratio [HR], 0.56; 95% CI, 0.33–0.95), leading to a 1-year OS rate of 39.2% versus 15.4% with single-agent chemotherapy.26 The nivolumab arm also demonstrated less frequent treatment-related adverse events (trAEs) compared with standard-of-care therapy (all-grade trAEs: 58.9% vs 77.5%; grade 3–4 trAEs: 13.1% vs 35.1%).24

Similar to CheckMate 141, KEYNOTE-040 was a randomized phase III study comparing pembrolizumab versus standard-therapy (eg, cetuximab, methotrexate, or docetaxel) with a total of 395 patients enrolled. Response rates were 14.6% in the pembrolizumab group and 10.1% in the standard therapy group, and median OS was 8.4 months versus 6.9 months, respectively (HR, 0.80; 95% CI, 0.65–0.98; \( P = .016 \)). Patients with at least 1% PD-L1 (IHC antibody clone 22C3) in the tumor (78% of all patients) benefited more from pembrolizumab (HR, 0.74; 95% CI, 0.58–0.93; \( P < .01 \)).27

In summary, for patients with R/M SCCHN who have received prior platinum-based therapies, anti–PD-1 monotherapy induces ORRs ranging from 13.3% to 18%. These results were superior to those for the standard second-line therapy options. Most importantly, both of these large randomized phase III studies showed that immunotherapy conferred a survival benefit. In the biomarker analysis, PD-L1 positivity was associated with improved benefits with anti–PD-1 therapy. However, patients with PD-L1 0% tumors still may benefit from immunotherapy, although with a lower response rate. Based on these data, the FDA approved both pembrolizumab (August 2016) and nivolumab (November 2016) for treatment of patients with R/M SCCHN who experience disease progression on or after platinum-based therapy. It should be noted, however, that nivolumab is also approved for in the first-line setting if disease progresses within 6 months of platinum therapy in the primary treatment setting.26

Combination of Chemoimmunotherapy in R/M SCCHN

KEYNOTE-048 was designed to evaluate single-agent pembrolizumab or combination pembrolizumab + chemotherapy as first-line therapy for R/M SCCHN. In this large phase III study, 882 patients with newly diagnosed R/M SCCHN were randomized to 3 treatment groups: pembrolizumab alone versus pembrolizumab/cisplatin/5-FU versus cetuximab/cisplatin/5-FU. Pembrolizumab or cetuximab maintenance was allowed. In this 3-arm study, pembrolizumab alone was noninferior in the total population when compared with cetuximab chemotherapy, and was associated with improved OS in patients with R/M SCCHN.

PD-L1–Based Biomarkers in SCCHN

As data have accumulated, use of immunotherapy based on tumor PD-L1 testing has evolved (Table 1). In the biomarker analysis of KEYNOTE-012, PD-L1 expression was scored using 2 methods: the tumor proportion score (TPS) and the CPS. TPS was defined as the percentage of tumor cells with membranous PD-L1 expression and tumor-associated immune cells that express PD-L1. Both scores range from 0% to 100%. With a cutpoint of CPS ≥1, response rates were higher in patients with positive versus negative (CPS <1) tumors (21% vs 6%; \( P = .023 \)) but were not different based on the same TPS cutpoints. In subsequent studies, PD-L1 CPS ≥1 was used as a biomarker cutpoint in pembrolizumab trials.

In KEYNOTE-055, 82% of tumors had CPS ≥1 (PD-L1–positive). ORRs were 18% (95% CI, 12%–25%) in PD-L1–positive patients versus 12% (95% CI, 2%–30%) in PD-L1–negative patients, indicating similar benefit. Exploration of a different cutpoint of CPS ≥50 observed in 29% of tumors demonstrated an ORR of 27% (95% CI, 15%–42%). The confidence bounds overlapped with groups defined by CPS <1 and ≥1.

In KEYNOTE-040, 79% of tumors in the pembrolizumab-alone group had CPS ≥1 and 26% had CPS ≥50. Patients with CPS ≥1 tumors had improved OS compared with those treated with standard-of-care chemotherapy (HR, 0.74; 95% CI, 0.58–0.93; \( P < .001 \)), and the benefit was stronger in the TPS ≥50 group in the pembrolizumab-alone group (HR, 0.53; 95% CI, 0.35–0.81; \( P < .001 \)). In contrast, pembrolizumab did not benefit
patients with CPS <1 tumors (HR, 1.28; 95% CI, 0.80–2.07; \( P = .84 \)).

The CheckMate 141 biomarker analysis used PD-L1 TPS with a different antibody (clone 28-8). However, in the Blueprint PD-L1 IHC Assay Comparison Project for lung cancer, tumor and immune cell scoring by pathologists was comparable for clones 28-8 and 22C3. In CheckMate 141, tumor TPS cutpoints of \( 1, 5, \) and \( 10 \) were evaluated. Among 260 evaluable tumors, 57% had PD-L1 TPS \( \geq 1 \), with an HR for death of 0.55 (95% CI, 0.36–0.83). Analogous to KEYNOTE-040, the group with tumor PD-L1 TPS \( < 1 \) did not experience significant benefit from immunotherapy.

In KEYNOTE-048, further stratification of tumor PD-L1 CPS was performed at cutpoints of \( \geq 1 \) and \( \geq 20 \), representing 85% and 43% of patients, respectively. As discussed in the previous session, pembrolizumab alone prolonged OS in the CPS \( \geq 20 \) and CPS \( \geq 1 \) groups. For patients with CPS \( \geq 20 \), the 12-month OS rate with pembrolizumab alone was 23%.

In conclusion, biomarker analyses have established that PD-L1 is a reasonable biomarker for enrichment of survival benefit from anti–PD-1/L1 immunotherapy in the first and subsequent line for R/M SCCHN (Table 1). Most patients have PD-L1–positive tumors (57%–82%). Ongoing trials with additional anti–PD-1/L1 agents, such as atezolizumab (NCT03818061), will provide additional analyses.

## Clinical Practice After the Addition of Immunotherapy

When incorporating clinical trial evidence into general oncology practice, some practical aspects must be taken into consideration, such as the need for immediate symptom relief, short- versus long-term benefit from the therapy, toxicity, quality of life, logistical convenience of treatment administration, and financial burden. One major challenge to implementing the KEYNOTE-048 platinum + 5-FU/pembrolizumab combination is 5-FU–associated toxicity and the need for central venous access for continuous infusion.

At the annual ASCO 2019 meeting, results from the randomized phase III TPEx trial were reported. This trial of 539 patients with newly diagnosed R/M SCCHN was designed to evaluate the noninferiority of cisplatin/docetaxel/cetuximab for 4 cycles versus cetuximab/cisplatin/5-FU for 6 cycles (also known as the EXTREME regimen). The cisplatin/docetaxel/cetuximab arm was shown to be noninferior to the EXTREME regimen with regard to OS, and neither PFS nor ORR showed any statistical

### Table 1. PD-L1–Based Biomarkers in R/M SCCHN Trials

<table>
<thead>
<tr>
<th>Trials</th>
<th>PD-L1 Staining Cells</th>
<th>Eligibility PD-L1 Required</th>
<th>Antibody Used</th>
<th>Population Defined</th>
<th>Response in Total Population</th>
<th>Response by PD-L1 Subgroups</th>
</tr>
</thead>
<tbody>
<tr>
<td>KEYNOTE-012, cohort B21,22</td>
<td>Tumor cells (TPS) Yes, ( \geq 1 % )</td>
<td>22C3</td>
<td>NA</td>
<td>18%</td>
<td>ORR, 21% in CPS ( \geq 1 ) vs 6% in CPS ( &lt; 1 )</td>
<td></td>
</tr>
<tr>
<td>KEYNOTE-012, cohort B21,22</td>
<td>Tumor cells (TPS) No</td>
<td>22C3</td>
<td>82% CPS ( \geq 1 )</td>
<td>16%</td>
<td>ORR, 18% in CPS ( \geq 1 ) vs 12% in CPS ( &lt; 1 ); ORR, 27% in CPS ( \geq 50 ) group</td>
<td></td>
</tr>
<tr>
<td>KEYNOTE-05523</td>
<td>CPS No</td>
<td>22C3</td>
<td>79% CPS ( \geq 1 ) 26% TPS ( \geq 50 )</td>
<td>14.6% with immunotherapy</td>
<td>HR, 0.74 (95% CI, 0.58–0.93) for survival in CPS ( \geq 1 ); HR, 0.53 (95% CI, 0.35–0.81) for survival in TPS ( \geq 50 )</td>
<td></td>
</tr>
<tr>
<td>CheckMate 14124,26</td>
<td>Tumor cells No</td>
<td>28-8</td>
<td>57% PD-L1 ( \geq 1 )</td>
<td>13.3% with immunotherapy</td>
<td>HR, 0.55 (95% CI, 0.36–0.83) for survival in PD-L1 ( \geq 1 )</td>
<td></td>
</tr>
<tr>
<td>KEYNOTE-04828</td>
<td>CPS No</td>
<td>22C3</td>
<td>85% CPS ( \geq 1 ) 43% CPS ( \geq 20 )</td>
<td>16.9% with immunotherapy</td>
<td>12-month survival CPS ( \geq 20 ): 23% (pembrolizumab) 24% (pembrolizumab + chemotherapy) 11%–12% (EXTREME) 12-month survival CPS ( \geq 1 ): 20% (pembrolizumab) 19% (pembrolizumab + chemotherapy) 11%–12% (EXTREME) 12-month survival total: 17% (pembrolizumab) 17% (pembrolizumab + chemotherapy) 12%–14% (EXTREME)</td>
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</tr>
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Abbreviations: CPS, combined positive score; HR, hazard ratio; NA, not applicable; ORR, overall response rate; R/M, recurrent or metastatic; SCCHN, squamous cell carcinoma of the head and neck; TPS, tumor proportion score.

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difference. However, grade ≥4 toxicity with taxane was significantly less compared with 5-FU (34% vs 50%; P<.001). Due to the manageable toxicity profile and the convenience of same-day administration, docetaxel is viewed as a reasonable replacement for 5-FU, although the platinum/taxane/pembrolizumab combination has not been formally evaluated.

Although pembrolizumab + chemotherapy was FDA approved for first-line therapy for all patients with R/M SCCHN, pembrolizumab alone or cetuximab + chemotherapy may be preferred in some cases. In the KEYNOTE-048 trial, pembrolizumab + chemotherapy was associated with improved OS in the PD-L1 CPS ≥1 population when compared with cetuximab + chemotherapy, but there was no subgroup analysis for patients whose tumors had 0% CPS (15% of patients). Furthermore, in the PD-L1–unselected population, pembrolizumab alone did not demonstrate a survival benefit compared with the EXTREME regimen or pembrolizumab + chemotherapy.28 Therefore, we recommend careful selection of therapy for patients with tumors of CPS <1. For patients with large disease burden and positive CPS ≥1, who are otherwise healthy with excellent functional status to tolerate platinum doublet/pembrolizumab, the combination is the most appropriate first-line therapy.

**Novel Combinations and Strategies**

Despite the exciting progress with anti–PD-1 therapy with or without chemotherapy in patients with R/M SCCHN, response rates remain discouraging. When used as a single agent, anti–PD-1 therapies only achieve response in <20% of patients regardless of the lines of therapy (ORRs of 18% in KEYNOTE-01221; 14.6% in KEYNOTE-04027; 16% in KEYNOTE-05522; 13.3% in CheckMate 14124; and 16.9% in KEYNOTE-04828). Chemoimmunotherapy combinations used in the first-line setting have increased this response rate, but novel therapy combinations or novel immunotherapy strategies are desperately needed.

Many immunotherapy combinations have been tested in R/M SCCHN to evaluate whether adding a second or third immune checkpoint blockade can enhance anti–PD-1/L1 efficacy. For example, CTLA-4 is another immune checkpoint protein that is expressed on T cells (mostly T-regulatory cells) to downregulate immune responses and mediates tumor immune escape.32–34 Furthermore, anti–CTLA-4 in addition to anti–PD-1/L1 has been shown to improve response in patients with melanoma35,36 and possibly those with NSCLC.37,38 But anti–CTLA-4 plus anti–PD-L1 combinations reported to date have not shown additional benefit in R/M SCCHN. In the phase II randomized CONDOR study, the addition of tremelimumab (a human IgG2 antibody for CTLA-4) to durvalumab (a human IgG1 antibody for PD-L1) was safe and tolerable but did not add significant benefit regarding response or survival in patients whose tumors had low or zero PD-L1 expression (<25% tumor cells expressing PD-L1 by SP263 assay).39 Similar results were reported from the phase III EAGLE trial, in which durvalumab was given with or without tremelimumab and compared with standard-of-care second-line therapies in patients with R/M SCCHN. The primary endpoint was not met, because the addition of tremelimumab did not improve OS. Response rates were not different among all 3 groups.40 It was reported that IDO expression was associated with poor prognosis in SCCHN, and other cancer types, likely due to the inhibitory effect of IDO on T cells.41 Although inhibition of IDO in combination with pembrolizumab initially showed promising results in a phase I study (ECHO-202/KEYNOTE-037), including an ORR of 34% (13/38) in patients with SCCHN,42 subsequent studies in melanoma (ECHO-301/KEYNOTE-252) failed to confirm the efficacy43 and the SCCHN trial was halted. Additional immune checkpoints, for example, TIM-3 (NCT03652077 and NCT03307785), LAG3 (NCT04080804 and NCT03538028), and TIGIT (NCT04047862 and NCT02913313), are now being tested in early-phase clinical trials.

In addition to immune checkpoint inhibition, therapies targeting key cytokines and their pathways to induce immune modulation is another area of active immunotherapy research. The TGF-β pathway represents a promising immune modulation target in HPV-associated diseases.44 Phase I trials (NCT02517398 and NCT02699515) evaluated M7824, a bifunctional fusion protein composed of 2 extracellular domains of TGF-βRII (a TGF-β “trap”) fused with a human IgG1 monoclonal antibody against PD-L1,45 in HPV-associated solid tumors. Response rates ranged between 28% to 37% in HPV-associated cases.46,47 Confirmative studies are ongoing. VEGF-A and VEGF receptor pathway inhibition has shown efficacy in combination with immune checkpoint blockade in other solid tumors. The combination of lenvatinib with pembrolizumab has demonstrated some initial promise in SCCHN. Lenvatinib is a multikinase inhibitor of vascular endothelial growth factor receptor (VEGFR) 1–3, fibroblast growth factor receptor (FGFR) 1–4, platelet-derived growth factor receptor (PDGFR) α, RET, and KIT. A phase II trial in R/M SCCHN cancer reported a 36% ORR in 22 patients.48 Based on these data, an ongoing randomized placebo-controlled phase III trial (LEAP 010) is comparing this combination versus pembrolizumab alone. Additional combinations aiming to favorably modulate the tumor immune environment are in early-phase clinical trials, including combinations with anti–STAT3 (NCT03153982), PARP inhibitors, and cetuximab (NCT03082534 and NCT03691714).

Beyond immune checkpoint blockade and immune modulation, novel immune therapy strategies, such as vaccines, intratumor immunotherapy, and
cellular therapy, have also been explored. Because the unique oncogenesis of HPV-associated SCCHN, targeting HPV16 (the most prevalent viral genotype) oncoproteins using a therapeutic vaccine approach has a solid biologic foundation and has achieved initial success. One example is the ISA101 vaccine, which is a synthetic long peptide HPV16 vaccine consisting of 13 overlapping peptides from the HPV16 oncoproteins E6 and E7. It has demonstrated an ORR of 36% (8/22) when combined with nivolumab in patients with oropharyngeal cancers. A randomized trial is ongoing to confirm the observed efficacy (NCT03669718). Other vaccines targeting either HPV oncoprotein or patient-specific neoantigens after whole-exon sequencing (GEN-009 trial; NCT03633110) are under active clinical investigation.

Intratumor injection of novel immunotherapies is especially appealing for SCCHN because of the technical feasibility of accessing the primary tumor or lymph nodes, especially for patients with locoregionally R/M SCCHN. Intratumor administration of antitumor agents can be used with or without combinations of systemic immune checkpoint blockade or cytotoxic chemotherapies. With this strategy, an experienced head and neck surgical team, as well as an interventional radiology team, begins to play an increasingly important multidisciplinary role in palliative therapy for R/M SCCHN. Ongoing trials are evaluating the use of those agents in newly diagnosed patients (such as CTLA-4), but other combinations demonstrated promising preliminary efficacy (such as VEGF/PDGFR inhibitor or TGF-β inhibitor). Novel immune therapy strategies, such as therapeutic vaccines or cellular therapy, might also yield great efficacy, especially for HPV-associated SCCHN. Moreover, numerous ongoing trials are evaluating the use of those agents in newly diagnosed SCCHN in earlier stages. We expect to continue learning how to best use immunotherapies to benefit patients through more trials and clinical experience.

Conclusions
Anti–PD-1 immune checkpoint blockade therapy has demonstrated efficacy in R/M SCCHN by inducing responses in 13% to 18% of patients and prolonging OS. PD-L1–based biomarkers have shown utility in guiding selection of treatment options, which is especially useful for first-line therapy. Current NCCN Guidelines for Head and Neck Cancers recommend immunotherapy with or without chemotherapy for patients with R/M SCCHN. In the first-line setting, platinum with 5-FU + pembrolizumab is a reasonable choice for all patients, and pembrolizumab is recommended as monotherapy for patients whose tumor have CPS ≥1 or ≥20. In the subsequent-line setting, nivolumab or pembrolizumab is recommended if disease progression occurs during or after platinum therapy.

Much effort is now focusing on designing immune therapy combinations to further improve response and duration of response in patients. Some clinical trials have shown that certain combinations did not yield expected benefit (such as CTLA-4), but other combinations demonstrated promising preliminary efficacy (such as VEGF/PDGFR inhibitor or TGF-β inhibitor). Novel immune therapy strategies, such as therapeutic vaccines or cellular therapy, might also yield great efficacy, especially for HPV-associated SCCHN. Moreover, numerous ongoing trials are evaluating the use of those agents in newly diagnosed SCCHN in earlier stages. We expect to continue learning how to best use immunotherapies to benefit patients through more trials and clinical experience.

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