TURKISH JOURNAL of ONCOLOGY

Turk J Oncol 2021;36(4):519–28
doi: 10.5505/tjo.2021.2849

REVIEW

Systemic Therapy in Recurrent or Metastatic Squamous Cell Head and Neck Cancer

Ivane KILADZE,[1] Gökhan ÖZYİĞİT,[2] Pavol DUBINSKY,[3] Nenad FILIPOVIĆ,[4] Branislav JEREMIĆ[5]

[1]Department of Clinical Oncology, Caucasus Medical Center, Tbilisi-*Georgia*
[2]Department of Radiation Oncology, Hacettepe University, Ankara-*Turkey*
[3]Department of Radiation Oncology, East Slovakia Institute of Oncology, Kosice, *Slovakia*
[4]Department of Oncology, BioIRC, Center for Biomedical Engineering, Kragujevac-*Serbia*
[5]University of Kragujevac Faculty of Medicine, Kragujevac-*Serbia*

SUMMARY

Squamous cell head and neck cancer (SCHNC) is the seventh most common cancer worldwide. Most of SCHNC are locally advanced at diagnosis and are treated with combination of surgery and/or radiotherapy with chemotherapy. In spite of aggressive treatment, many patients relapse within the 3 years following the diagnosis. Those whose tumor cannot be resected or reirradiated are treated with a systemic treatment mostly in a palliative setting. They are identified as recurrent and/or metastatic SCHNC (R/M-SCHNC) patients. First-line treatment of R/M-SCHNC historically consisted of cytotoxic agents such as methotrexate, bleomycin, or platinum-based protocols until targeted biological therapies were introduced in the 2000's. The recent years witnessed a shift in systemic treatment toward the use of monoclonal antibodies and tyrosine kinase inhibitors, largely based on recent understanding of the role of immune dysfunction in SCHNC. Our review focuses on recent developments of molecular-targeted and immunotherapies in the treatment SCHNC, mostly focusing on R/M-SCHNC. It also highlights ongoing trials and discusses some promising novel targets in HNC, as well as clinical trial design challenges.

Keywords: Chemotherapy; head and neck cancer; immunotherapy; squamous cell; systemic therapy; targeted therapy.

Introduction

Head and neck cancer (HNC) is a heterogeneous disease of the upper aerodigestive tract, encompassing different anatomic sites and histologic types, including both human papilloma virus (HPV)-positive and HPV-negative cancers. Squamous cell HNC (SCHNC) is the seventh most common cancer worldwide with an annual incidence of approximately 700 000 and a mortality rate estimated at 350 000 in 2018.[1]

Most of SCHNC are locally advanced at diagnosis and are treated with combination of surgery and/or radiotherapy (RT) with chemotherapy (CHT).[2-4] In spite of aggressive treatments almost half of these patients relapse within 3 years of initial diagnosis. Those whose tumor is unresectable or cannot be reirradiated are treated with a systemic treatment mostly in a palliative setting. They are identified as recurrent and/or metastatic SCHNC (R/M-SCHNC) patients.

The treatment of unresectable R/M-SCHNC is generally dictated by patient's performance status (PS) and intent to treatment (palliative vs. curative). A vast majority of these patients, however, have unresectable disease and only qualify for palliative treatment with

Received: June 07, 2021
Accepted: August 25, 2021
Online: September 16, 2021

Accessible online at:
www.onkder.org

Dr. Branislav JEREMIĆ
University of Kragujevac Faculty of Medicine,
Kragujevac-Serbia
E-mail: nebareje@gmail.com

Turk J Oncol 2021;36(4):519–28
doi: 10.5505/tjo.2021.2849

systemic therapy. First-line treatment of R/M-SCHNC historically consisted of cytotoxic agents such as Methotrexate (MTX), Bleomycin, or platinum-based protocols until targeted biological therapies were introduced in the 2000's.[5] Despite considerable progress made in the use of CHT, RT, and targeted therapies, in majority of patients with R/M SCHNC the survival outcomes remain poor.[5]

The recent years witnessed a shift in systemic treatment toward the use of monoclonal antibodies and tyrosine kinase inhibitors, largely based on recent understanding of the role of immune dysfunction in SCHNC, including the observation that antagonizing the programmed cell death (PD-1) immune checkpoint can disable T-cell suppression by R/M-SCHNC cells for re-sensitization of the immune system to clear tumor cells.[6]

Indeed, HNC, like all other cancers, is a result of a stepwise accumulation of genomic instability, chromosomal aberrations, and genetic mutations,[7] with common features of HNCs also including tumor-mediated inhibition of antitumor immune responses and a high mutational burden. While the number of promising immune-based therapies continuously rises, efficiency of these is expected to rapidly improve with the possibility of patients' selection based on personal immunogenomic profiles. The emerging role of immunotherapy (IMT) as a potentially beneficial addition to standard treatments for R/M-SCHNC offers hope to the patients for whom no other therapeutic options exist.[8]

However, despite the optimism, the optimal regime is still unknown. Many recommendations are based on a single randomized controlled trial (RCT) results with current lack of efficacious treatment options available when FDA-approved 1st and 2nd line treatments are contraindicated.[9] The present manuscript reviews recent developments of molecular-targeted and immunotherapies in the treatment SCHNC, focusing on R/M-SCHNC. It also highlights ongoing trials and discusses some promising novel targets in HNC, as well as clinical trial design challenges.

First-line Treatment

In locally advanced but M0 SCHNC concurrent administration of RT and CHT is a standard of care in both HPV– and HPV+HNC.[10-13] Cisplatin (CDDP) is mostly used single-agent with radical RT (mostly 70 Gy in 35 daily fractions over 7 weeks) administered as three cycles of 100 mg/m^2 on days 1, 22, and 43 of the RT course. Due to a significant toxicity and frequent dose reduction and treatment interruptions of this approach, researchers attempted to offer an alternative schedule using mostly 40 mg/m^2 given weekly for 7 weeks. This was based on the assumption that it would lead to a lesser toxicity while, at the same time, offering better (more prolonged) radio sensitization due to a more frequent CDDP administration.[10,11] In HPV+SCHNC, majority occurring in oropharynx, current trends in clinical research focus on de-intensification of treatment approach as data shows higher radiosensitivity of HPV+SCHNC.[12]

Chemotherapy (CHT)

Various trials compared the activity of single cytotoxic agents. Response rates to single agent therapies range from 15% to 35%.[14-16] MTX was compared to taxane therapy and found objective response rate (ORR) favoring taxanes (OR=3.16, 95% CI: 1.26-7.97 p=0.01), without the difference in the overall survival (OS). Exception to this was increased progression-free survival (PFS) when Paclitaxel was given over 24 h but at the expense of higher toxicity. No other single agent increased ORR, PFS, and OS.[17-19] Two RCTs demonstrated a superior ORR of CDDP-5-Fluorouracil (5-FU) when compared to CDDP alone (OR=2.44, 95% CI: 1.50-3.95, p<0.0003), which did not lead to OS advantage for the combination regimen.[20,21]

Targeted Therapy (Epidermal Growth Factor Receptor [EGFR], EGFR Combination Therapy, PI3K Inhibitors, and VEGF Inhibitor)

EGFR expression is associated with poor prognosis and resistance to therapy and it occurs in up to 90% of SCHNC.[22] Vermorken et al.[23] tested single agent Cetuximab in a phase II trial enrolling 103 patients with R/M SCHNC who had progressed on platinum-based CHT. The ORR for Cetuximab alone was 13% and the stable disease rate was 33%. Median time to progression and median survival time (MST) were 2.3 and 6 months, respectively.

The phase III IMEX study compared an anti-EGFR agent Gefitinib with MTX in patients who had at least one prior therapy for R/M SCHNC and showed that Gefitinib was not superior to MTX in this setting.[24]

Combination therapy of Cetuximab, CDDP and 5-FU (the EXTREME regimen) became the standard for first-line treatment in 2008 based on its OS benefit when compared to CHT alone in this phase III RCT.[25] Cetuximab with platinum-based CHT significantly prolonged the MST from 7.4 months in the CHT-alone group to 10.1 months in CHT/Cetuximab

group (HR 0.80; 95% CI:, 0.64 to 0.99; p=0.04) as well as it prolonged median PFS (MPFS) from 3.3 to 5.6 months (HR for progression, 0.54; p<0.001).[25]

In multicenter open-label, randomized, phase 2 trial, six cycles of EXTREME regimen was compared to four cycles of TPEx regimen (CDDP, docetaxel, and cetuximab). In both arms in case of disease control after four cycles, cetuximab was continued as maintenance therapy until progression or unacceptable toxicity. Although the trial did not meet its primary endpoint (OS), with no significant improvement in OS with TPEx versus EXTREME, the TPEx regimen had a favorable safety profile. The TPEx regimen could provide an alternative to standard of care with the EXTREME regimen in the first-line treatment of patients with R/M HNSCC, especially for those who might not be good candidates for up-front pembrolizumab treatment.[26]

Panitumumab with platinum-combination shows increasing of ORR and PFS (HR 0·780, 95% CI: 0·659-0·922; p=0.0036) without prolongation of OS (HR=0.87, 95% CI: 0.72-1.04, p=0.1403).[27]

The addition of Bevacizumab to platinum-doublet CHT did not improve OS but improved the ORR and PFS with increased toxicities.[28]

Immunotherapy (IMT)

While the concept of the immune system being able to recognize and control cells undergoing malignant transformation exists for more than a century,[29] recent work focused on understanding the immunobiology of SCHNC and, consequently, on developing strategies to promote an antitumor immune response.[30] Introduction of immune checkpoint inhibitors (ICI) has significantly changed the therapeutic approach in HNC. SCHNC shows a high mutational burden and also present with a high infiltration of immune cells, demonstrating that they are immunogenic through the expression of epitopes, virus or not virus-related. While this may have an important implication in the future; however, the most important current limitation of potential biomarkers is the impossibility to identify responding patients. As a consequence, TMB testing in HNSCC is not yet recommended as a standard of care.[31]

For R/M-SCHNC, tumor programmed death-ligand 1 (PD-L1) expression should be evaluated and PD-L1 expression is assessed by two methods: The tumor proportion score (TPS), defined as the percentage of tumor cells with membranous PD-L1 staining, or by the combined positive score (CPS), defined as the number of PD-L1-positive cells (tumor cells, lymphocytes, and macrophages) divided by the total number of tumor cells multiplied by 100. The CPS can help to define the first-line treatment strategy for R/M-SCHNC.[32]

Pembrolizumab

In the Phase Ib Keynote-012 study, both treatment-naive and pretreated patients (n=60) with R/M SCHNC with ≥1% of PD-L1 expression were treated with Pembrolizumab. Among the heavily pretreated patients 70% were previously treated with ≥2 lines of CHT for R/M disease. Several non-progressing patients continued therapy beyond progression. Of these, 18% demonstrated an ORR while 51% experienced any reduction in tumor burden. Median time to response (MTTR) was 8 weeks and the median duration of response (MDR) was 53 weeks. MPFS and MST were 2 and 13 months, respectively. HPV status did not affect the effect of Pembrolizumab. PD-L1 expression levels were associated with ORR and PFS.[33] A larger expansion cohort of the Keynote-012 trial,[34] with 132 patients with unrestricted PD-L1 positivity level, confirmed the results with ORR of 18%, the MPFS and MST of 2 and 8 months, respectively. Response to Pembrolizumab was again unrelated to HPV status.

In the subsequent nonrandomized Phase II study (Keynote-055),[35] 171 patients with R/M SCHNC resistant to both platinum and Cetuximab were treated with pembrolizumab 200 mg/3 weeks. ORR was 16% with a MTTR of 2 months, and MDR of 8 months. MPFS and MST were 2.1 months and 8 months, respectively, with no influence of HPV status on clinical activity.

In a randomized phase 3 study (KEYNOTE-048), 882 patients with untreated locally incurable R/M-SCHNC were stratified by PS, p16 status, and PD-L1 expression and randomly allocated (1:1:1) to Pembrolizumab alone, Pembrolizumab plus a platinum and 5-FU (Pembrolizumab with CHT), or Cetuximab plus a platinum and 5-FU (Cetuximab with CHT). Of these, 754 (85%) had CPS of ≥1 and 381 (43%) had CPS of ≥20. At the final analysis, Pembrolizumab with CHT improved OS versus Cetuximab with CHT in both total population (13.0 months vs. 10.7 months, HR 0.77 [95% CI: 0.63-0.93], p=0.0034), in the CPS of ≥20 population (14.7 vs. 11.0, HR, 0.60 [95% CI: 0.45-0.82]; p=0.0004) as well as in the CPS of ≥1 population (13.6 vs. 10.4, HR, 0·65; [95% CI: 0.53-0.80], p<0.0001). Neither Pembrolizumab alone nor Pembrolizumab with CHT improved PFS at the second interim analysis. Grade ≥3 all-cause adverse events were less frequent (55%) in the Pembrolizumab alone group, than in the Pem-

Turk J Oncol 2021;36(4):519–28
doi: 10.5505/tjo.2021.2849

brolizumab with CHT group (85%), or Cetuximab with CHT group (83%). Based on the observed efficacy and safety, Pembrolizumab with CHT seemed an appropriate first-line treatment for R/M-SCHNC while single agent Pembrolizumab seemed an appropriate first-line treatment for PD-L1-positive R/M-SCHNC.[36]

However, in a subgroup analysis, no survival benefit was found in patients presenting with local or regional recurrence only, irrespective of the CPS or assigned IMT arm (monotherapy or combination treatment), indicating that patients with a substantial locoregional disease burden represent a particularly challenging group. Indeed, the rates of progressive disease in patients receiving Pembrolizumab alone as first-line treatment in KEYNOTE-048 was quite disappointing (32-41%). Although being substantially lower for Pembrolizumab plus CHT (15-17%), they still remain numerically higher than in the CHT arm (8-12%) irrespective of CPS. Furthermore, some patients might experience an accelerated tumor growth known as hyperprogression. Caution must be advocated when treating patients with high locoregional disease burden, in particular when it concerns single agent Pembrolizumab. Here, the risk of progression should be weighed against the reduced morbidity with IMT and warrants individual decision making.[37] Finally, current evidence does not point to platinum/5-FU/Pembrolizumab improving survival compared with platinum/5-FU/Cetuximab in patients with SCHNC not expressing PD-L1. The impact of Pembrolizumab on survival in patients with SCHNC and a CPS between 1 and 19 also calls for further investigation.

The phase 3 randomized, KEYNOTE-040 trial, in which patients who failed prior platinum-based CHT failed were included, compared Pembrolizumab 200 mg/3 weeks to the drug of investigator choice. Randomization ratio was 1:1 and stratification by ECOG PS (0 vs. 1), p16 status for oropharyngeal tumors (positive vs. negative) and PD-L1 TPS (TPS >50 vs. <50%). The primary endpoint, the MST, was 8.4 months in the Pembrolizumab arm versus 6.9 months in the investigator choice arm (95% CI: 0.65-0.98; nominal p=0.0161). In the subgroup of patients with a TPS ≥50%, the MST was 11.6 months with Pembrolizumab and 6.6 months with standard of care (HR 0.53, p=0.0014). In the subgroup of patients with TPS <50%, the MST was 6.5 months with Pembrolizumab and 7.1 months with standard of care. Grade ≥3 toxicity was rare (13%).[38]

Nivolumab

In randomized phase III (CHECKMATE-141) study[39] 361 SCHNC patients with tumor progression or recurrence within 6 months after the last dose of platinum-containing CHT were treated with Nivolumab 3 mg/kg every 3 weeks versus investigator's single agent CHT choice (MTX, Docetaxel or Cetuximab). The MST was 7.5 months in the Nivolumab group versus 5.1 months in the control group, with no difference in PFS (2 vs. 2.3 months). The ORR and duration of response were higher for Nivolumab-treated patients (13.3 vs. 5.8%). The safety profile was also in favor of the Nivolumab with less frequent grade 3-4 AEs (13.1 vs. 35.1%) as well as the quality of life.[40] A 2-year update confirmed the benefit for survival (2-year OS rate: 16.9 vs. 6.0%) and safety (grade 3-4 AEs: 15.3 vs. 36.9%) of Nivolumab on investigator choice.[40]

Durvalumab

In the 1108 study, 62 pretreated R/M SCHNC patients received Durvalumab monotherapy, obtaining seven responses, with six patients showing response duration of >12 months. MPFS and MST were 1.4 months and 8.4 months, respectively. OS was 62% at 6 months and 38% at 12 months (42% for PD-L1 ≥25%, 36% for <25%).[41]

The single-arm, phase II HAWK study evaluated Durvalumab monotherapy, in IMT -naïve patients with platinum-refractory R/M SCHNC having high PD-L1 (TC≥25%). Among 111 evaluable patients, ORR was 16.2% (95% CI: 9.9-24.4). MPFS and MST were 2.1 months and 7.1 months, respectively, while PFS and OS at 12 months were 14.6% (95% CI: 8.5-22.1) and 33.6% (95% CI: 24.8-42.7), respectively. Grade ≥3 AEs were 8.0%, and none led to death. These results supported its ongoing evaluation in phase III trials in first- and second-line setting. In an ad hoc analysis, HPV-positive patients had a numerically higher response rate and survival than HPV-negative patients.[42]

Atezolizumab

Another anti-PD-L1 agent, Atezolizumab showed in all patients, regardless of PD-L1 expression, the confirmed ORR of 22%, MPFS of 2.6 months and MST of 6.0 months, seemingly comparable to the results other ICIs achieved. In this phase I trial, after the first ten patients were non-selectively enrolled, identification of PD-L1 as a potential biomarker led to subsequent enrolment based on PD-L1 status of >5% expression on immune cells. Among 32 treated patients, a slightly higher ORR was observed in case of high PD-L1 expression (24%) than in those with low or no expression of PD-L1 (14%).[43]

Combination IMT

The phase 3 EAGLE trial compared Durvalumab monotherapy (A) or Durvalumab in combination with Tremelimumab (B), an anti-CTLA4 antibody versus standard CHT (C) regardless of the PD-L1 status. No statistically significant improvements in OS were observed for A versus C (HR: 0.88; 95% CI: 0.72-1.08; p=0.20) or B versus C (HR: 1.04; 95% CI: 0.85-1.26; p=0.76). One-year survivals were 37.0%, 30.4%, and 30.5% for A, B, and C, respectively. Grade ≥3 AE rates were 10.1%, 16.3%, and 24.2% for A, B, and C, respectively. In spite of no significant difference in OS for A or B versus C, authors suggested clinical activity for Durvalumab due to its higher survival rates at 12-24 months and higher response rates.[44]

A phase 2, randomized, open-label study (CONDOR) included patients with disease progression or recurrence during or after treatment with only 1 platinum containing regimen for R/M disease. Patients were stratified by HPV and smoking status and then randomized 2:1:1 to treatment with (A) Durvalumab and Tremelimumab for four cycles, followed by Durvalumab, (B) Durvalumab monotherapy, or (C) Tremelimumab monotherapy for up to 12 months. ORR for the three groups was 7.8%, 9.2%, and 1.6%, respectively, while the MST for the three groups was 7.6 (95% CI: 4.9-10.6), 6.0 (95% CI: 4.0-11.3), and 5.5 (95% CI: 3.9-7.0) months, respectively. This study showed that Durvalumab monotherapy had a manageable toxicity profile and clinical benefit for patients with R/M SCHNC and low or no PD-L1 TC expression, while Durvalumab + Tremelimumab demonstrated similar efficacy to Durvalumab monotherapy.[45]

According to updated efficacy and safety findings from a Phase II study dual CTLA-4/PD-1 blockade with Ipilimumab plus Nivolumab provided durable responses in 40 patients with R/M nasopharyngeal carcinoma (NPC) who have received no more than one prior line of CHT. Nivolumab was given at 3 mg/kg/ 2 weeks and ipilimumab at 1 mg/kg/6 weeks. The best overall response was partial response, achieved in 14 (35%) patients (95% CI: 20.6-51.7%). Responding patients showed a MDR of 5.9 months (95% CI: 3.95-8.97), MPFS of 5.3 months (95% CI: 3.0-6.4 months), and MST 17.6 months (95% CI: 13.1-30.0). Treatment-related AEs occurred in 34 (85%) patients and four (10%) patients had grade 3/4 serious AEs including hypocortisolism, pneumonia, myasthenia gravis, and increased lipase. No relationship was observed between response and either tumor mutation burden or PD-1 expression. This combination treatment was proven active based on durable responses and PFS data as well as safe in patients with NPC.[46]

Toll-like Receptor (TLR) Agonists, Other Agents and Vaccines

Therapeutic antibodies against the TLRs are immunomodulatory oligonucleotides with an agonistic effect. The TLR-9 agonist EMD1201081 has been compared with Cetuximab in a randomized Phase II trial involving R/M SCHNC patients after failure of one CHT regimen. It showed a good tolerance but no therapeutic improvement over Cetuximab.[47]

The preliminary results of a phase I/II study with 13 SCHNC patients receiving the TLR-8 agonist Motolimod showed disease control rate in 54% of patients when Motolimod was combined with Cetuximab.[48] Although Motolimod added to the EXTREME regimen did not offer an improvement in either PFS or OS it provided significant improvement in both PFS and OS in patients with HPV positive oropharyngeal cancer.[49]

When Paclitaxel was combined with PI3K inhibitor Buparlisib modest but promising response rates were observed.[50] Other agents from the same category demonstrated different activity: While mTOR inhibitor Everolimus failed in two consecutive phase II trials,[51,52] Temsirolimus showed meaningful efficacy in another Phase II trial.[53]

Due to ability of oncolytic therapy to selectively replicate in tumor cells causing direct cytotoxicity and inducing specific immune response against the tumor, several oncolytic viruses were tested in clinical trials. They have demonstrated safety and potential local tumor control in SCHNC due to both facility of intratumoral injection and importance of locoregional control in this disease. Current trials are ongoing in combination with PD-1 inhibitors.[54]

Second-line Treatment (Targeted Therapy, IMT, TLR-Agonists)

Unfortunately, many patients with R/M SCHNC further relapse despite treatment. In second-line treatments no consensus exists on the optimal therapies. Participation in clinical trials represents preferred and recommended t option in many situations.

The choice of second line therapy was initially poorly defined until PD-1 inhibitors Nivolumab and Pembrolizumab became FDA- licensed for second-line treatment of R/M SCHNC for patients who had disease progression on or after platinum-based therapy.[55,56]

Turk J Oncol 2021;36(4):519–28
doi: 10.5505/tjo.2021.2849

Table 1 Ongoing clinical trials in SCHNC

Study name	Phase	NCT	Treatment regimen
INTERLINK-1	3	NCT04590963	Monalizumab+Cetuximab versus Placebo+Cetuximab
INDUCE-4	3	NCT04428333	Feladilimab+Pembrolizumab+5-FU/platinum versus Placebo+Pembrolizumab + 5-FU/platinum
LEAP-10	3	NCT04199104	Pembrolizumab+Lenvatinib versus Placebo + Pembrolizumab
	3	NCT03855384	TQB2450+Cisplatin or Carboplatin+5-FU versus Placebo+Cisplatin or Carboplatin+5-FU
	3	NCT03358472	Pembrolizumab + Epacadostat versus Pembrolizumab versus EXTREME Regimen (Cetuximab+Cisplatin/Carboplatin+FU)
CheckMate 651	3	NCT02741570	Nivolumab+Ipilimumab versus EXTREME Regimen
CheckMate 141	3	NCT02105636	Nivolumab versus Cetuximab/Methotrexate/Docetaxel
LUX-Head and Neck 3	3	NCT01856478	Afatinib versusMethotrexate
	3	NCT00588770	Bevacizumab+Docetaxel+Cisplatin versus Docetaxel+Cisplatin
	1/2	NCT03650764	Pembrolizumab+Ramucirumab
	2	NCT04220866	Intratumoral MK-1454+Pembrolizumab versus Pembrolizumab
	1b/2	NCT04193293	Duvelisib+Pembrolizumab

Source: https://clinicaltrials.gov. SCHNC: Squamous cell head and neck cancer; FU: Fluorouracil

In second-line therapy none of single CHT agents demonstrated a superior clinical benefit over their control arms.[57-60] Cetuximab at escalating doses did not impact ORR, PFS, and OS.[61] Cixutuxumab with or without Cetuximab demonstrated limited benefit to PFS and OS despite the increased ORR observed with Cixutuxumab and Cetuximab combination.[62] When Gefitinib was added to Docetaxel, only a limited activity without improvements in ORR, PFS, and OS was observed.[63]

Two studies assessed PI3K inhibitors.[64,65] PX-866 added to Cetuximab failed to improve ORR, PFS, and OS over Cetuximab alone. Although ORR reached borderline significance (OR=3.88, 95% CI: 1.91-7.86, p=0.05), when PI3K inhibitor was added to taxane therapy,[50,64] PFS (HR=0.74, 95% CI: 0.55-1.00, p=0.183), and OS (HR=0.86, 95% CI: 0.69-1.06, p=0.16) did not improve.

In the network meta-analysis by Jin et al.,[66] 12 trials including a total of 10 and 12 second-line treatments were available for PFS and OS analysis, respectively. Nivolumab was the highest-ranked treatment for prolonging OS (0.95), while Buparlisib plus Paclitaxel was the highest-ranked treatment for PFS (0.94). This identified Nivolumab as the treatment of choice for overall R/M SCHNC patients due to its most remarkable OS benefit (HR 0.68, 95% CI: 0.58-0.80) and lower AEs ≥grade 3 (OR 0.37, 95% CI: 0.11-1.22). Nivolumab was also significantly associated with improvement of OS in patients with high PD-L1 expression (HR 0.55, 0.43-0.70), but was similar to conventional CHT for those with low PD-L1 expression. Buparlisib plus Paclitaxel showed the best OS benefit in subgroups of patients with HPV-negative status.[66]

New Targets and Ongoing Trials

The frequent RAS-RAF family pathway activation[67] in SCHNC has made it an appealing conceptual target, although mostly unsuccessful in clinical scenario until recently. The RAS family is composed of three distinct genes (HRAS, KRAS, and NRAS), which can be pathologically activated by a series of mutations, some of whose sites are shared between the genes. HRAS is mutated in approximately 6% of SCHNC cases and overexpressed in higher proportions.[68]

Ho et al.[69] described promising results of a single-arm, open-label Phase II study when treating HRAS-mutated R/M SCCHN using the farnesyltransferase (FT) inhibitor Tipifarnib, which prevents FT from prenylating the HRAS protein CAAX tail motif. Inhibiting this prenylation prevents HRAS membrane binding and thereby renders it inactive. Of the 22 patients with variant allele frequency (VAF) >20% (high VAF), 20 were evaluable for response. Objective RR for evaluable patients with high-VAF SCCHN was 55% (95% CI: 31.5-76.9). MPFS on Tipifarnib was 5.6 months (95% CI: 3.6-16.4) versus 3.6 months (95% CI: 1.3-5.2) on last prior therapy. The MST was 15.4 months (95% CI: 7.0-29.7). The most frequent treatment-emergent AEs were anemia (37%) and lymphopenia (13%). The safety profile of Tipifarnib was tolerable and manageable in this Phase II trial. The

study population had significant prior treatment with a median of two prior lines of therapy and the majority of patients had received IMT. These results represent potentially impactful change in clinical SCHNC research and successful targeting of HRAS would mark a significant step forward for precision oncology care in SCHNC.[70] Unfortunately, a lot of patients with R/M SCHNC have no response to IMT, or initial responses are followed by disease progression. To improve response rates and survival, ongoing trials are evaluating various combinations of novel drugs including ICIs, therapeutic vaccines, and cytotoxic agents. Selected ongoing studies continue recruitment and further results are eagerly awaited (Table 1).

Conclusion

SCHNC represents a diverse group of diseases. The outcome for R/M SCHNC remains poor for most patients. Currently approved immunotherapies have shown some promise but unfortunately only a small fraction of patients benefit. Appropriate selection of patients including identification of predictive markers of sensitivity and/or resistance to treatment remains of paramount importance. Investigational strategies using IMT, vaccines, cellular therapy, and optimization of incorporation of biomarkers promise to further advance the field. Many promising studies are ongoing and the next several years will be exciting as the results of these studies become available.

Peer-review: Externally peer-reviewed.

Conflict of Interest: I have no conflict of interest.

Financial Support: I have no financial support.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68(6):394–424.
2. Pignon JP, le Maître A, Maillard E, Bourhis J, MACH-NC Collaborative Group. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 93 randomised trials and 17,346 patients. Radiother Oncol 2009;92(1):4–14.
3. Bernier J, Domenge C, Ozsahin M, Matuszewska K, Lefebrve JL, Greiner RH, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med 2004;350(19):1945–52.
4. Cooper JS, Pajak TF, Forastiere AA, Jacobs J, Campbell BH, Saxman SB, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med 2004;350(19):1937–44.
5. Sacco AG, Cohen EE. Current treatment options for recurrent or metastatic head and neck squamous cell carcinoma. J Clin Oncol 2015;33(29):3305–13.
6. Ling DC, Bakkenist CJ, Ferris RL, Clump DA. Role of immunotherapy in head and neck cancer. Semin Radiat Oncol 2018;28(1):12–6.
7. Vogelstein B, Kinzler KW. Cancer genes and the pathways they control. Nat Med 2004;10(8):789–99.
8. Whiteside TL. Head and neck carcinoma immunotherapy: Facts and hopes. Clin Cancer Res 2018;24(1):6–13.
9. Lau A, Yang WF, Li KY, Su YX. Systemic therapy in recurrent or metastatic head and neck squamous cell carcinoma a systematic review and meta-analysis. Crit Rev Oncol Hematol 2020;153:102984.
10. Jeremic B, Dubinsky P, Jeremic M, Kiladze I, Ozyigit G. Optimal dose of cisplatin (CDDP) given concurrently with radiotherapy (RT) in locally advanced squamous cell head and neck cancer (SQC HNC). Turk J Oncol 2020;35:237–41.
11. Jeremic B, Dubinsky P, Filipovic N, Ozyigit G. Optimal administration frequency of cisplatin concurrently with radical radiotherapy in the definitive treatment of locally advanced, inoperable squamous cell carcinoma of the head and neck. Still obscured by clouds? Turk J Oncol 2019;34:133–6.
12. Jeremic B, Ozyigit G, Dubinsky P, Filipovic N. Importance of HPV positivity in squamous cell head and neck cancer. Turk J Oncol 2019;34(3):204–14.
13. Jeremic B, Ozyigit G, Jeremic M, Dubinsky P. Impact of radiotherapy fractionation on outcome in squamous cell head and neck cancer (SQC HNC). Turk J Oncol 2020;35(3):356–62.
14. Molin Y, Fayette J. Current chemotherapies for recurrent/metastatic head and neck cancer. Anticancer Drugs 2011;22(7):621–5.
15. Hoffmann TK. Systemic therapy strategies for head--neck carcinomas: Current status. GMS Curr Top Otorhinolaryngol Head Neck Surg 2012;11:Doc03.
16. Price KA, Cohen EE. Current treatment options for metastatic head and neck cancer. Curr Treat Options Oncol 2012;13(1):35–46.
17. Guardiola E, Peyrade F, Chaigneau L, Cupissol D, Tchiknavorian X, Bompas E, et al. Results of a randomised phase II study comparing docetaxel with

Turk J Oncol 2021;36(4):519–28
doi: 10.5505/tjo.2021.2849

methotrexate in patients with recurrent head and neck cancer. Eur J Cancer 2004;40(14):2071–6.

18. Pivot X, Awada A, Gedouin D, Kerger J, Rolland F, Cupissol D, et al. Results of randomised phase II studies comparing S16020 with methotrexate in patients with recurrent head and neck cancer. Ann Oncol 2003;14(3):373–7.
19. Vermorken JB. Randomized phase II trial of weekly methotrexate versus two schedules of three-weekly paclitaxel (Taxol®) in patients with metastatic or recurrent squamous cell carcinoma of the head and neck. Proc Am Soc Clin Oncol 1999;18:395a.
20. 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. J Clin Oncol 1994;5(6):521–6.
21. Jacobs C, Lyman G, Velez-Garcai 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.
22. Ang KK, Berkey BA, Tu X, Zhang HZ, Katz R, Hammond EH, et al. Impact of epidermal growth factor receptor expression on survival and pattern of relapse in patients with advanced head and neck carcinoma. Cancer Res 2002;62(24):7350–6.
23. 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.
24. Stewart JS, Cohen EE, Licitra L, Van Herpen CM, Khorprasert C, Soulieres D, et al. Phase III study of gefitinib compared with intravenous methotrexate for recurrent squamous cell carcinoma of the head and neck. J Clin Oncol 2009;27(11):1864–71.
25. Vermorken JB, Mesia R, Rivera F, Remenar E, Kawecki A, Rottey S, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med 2008;359(11):1116–27.
26. Guigay J, Aupérin A, Fayette J, Saada-Bouzid E, Lafond C, Taberna M, et al. Cetuximab, docetaxel, and cisplatin versus platinum, fluorouracil, and cetuximab as first-line treatment in patients with recurrent or metastatic head and neck squamous-cell carcinoma (GORTEC 2014-01 TPExtreme): A multicentre, open-label, randomised, phase 2 trial. Lancet Oncol 2021;22(4):463–75.
27. Vermorken JB, Stöhlmacher-Williams J, Davidenko I, Licitra L, Winquist E, et al. SPECTRUM investigators. Cisplatin and fluorouracil with or without panitumumab in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck (SPECTRUM): An open-label phase 3 randomised trial. Lancet Oncol 2013;14(8):697–710.
28. Argiris A, Li S, Savvides P, Ohr JP, Gilbert J, Levine MA, et al. Phase III randomized trial of chemotherapy with or without bevacizumab in patients with recurrent or metastatic head and neck cancer. J Clin Oncol 2019;37(34):3266–74.
29. Ehrlich P. Uber den jetzigen Stand der Karzinomforschung. Ned Tijdschr Geneeskd 1909;5(2):273–90.
30. Galluzzi L, Vacchelli E, Bravo-San Pedro JM, Buqué A, Senovilla L, Baracco EE, et al. Classification of current anticancer immunotherapies. Oncotarget 2014;5(24):12472–508.
31. Tosoni A, Franceschi E, Pasquini E, Lanese A, Donini E, Foschini MP, et al. Immunotherapy in head and neck cancer: evidence and perspectives. Immunotherapy 2017;9(16):1351–8.
32. Machiels JP, Leemans CR, Golusinski W, Grau C, Licitra L, Gregoire V, et al. Squamous cell carcinoma of the oral cavity, larynx, oropharynx and hypopharynx: EHNS-ESMO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2020;31(11):1462–75.
33. 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. Lancet Oncol 2016;17(7):956–65.
34. 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;34(32):3838–45.
35. Bauml J, Seiwert TY, Pfister DG, Worden F, Liu SV, Gilbert 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.
36. Burtness B, Harrington KJ, Greil R, Soulières D, Tahara M, de Castro G Jr., et al. KEYNOTE-048 Investigators. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or

metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): A randomised, open-label, phase 3 study. Lancet 2019;394(10212):1915–28.
37. Szturz P, Vermorken JB. Further clinical interpretation and implications of KEYNOTE-048 findings. Lancet 2020;396(10248):378–9.
38. Cohen EE, Soulières D, Le Tourneau C, Dinis J, Licitra L, Ahn MJ, 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.
39. 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. N Engl J Med 2016;375(19):1856–67.
40. Ferris RL, Blumenschein G Jr., Fayette J, Guigay J, Colevas AD, Licitra L, 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.
41. Segal NH, Ou SI, Balmanoukian A, Fury MG, Massarelli E, Brahmer JR, et al. Safety and efficacy of durvalumab in patients with head and neck squamous cell carcinoma: Results from a phase I/II expansion cohort. Eur J Cancer 2019;109:54–161.
42. Zandberg DP, Algazi AP, Jimeno A, Good JS, Fayette J, Bouganim N, et al. Durvalumab for recurrent or metastatic head and neck squamous cell carcinoma: Results from a single-arm, phase II study in patients with ≥25% tumour cell PD-L1 expression who have progressed on platinum-based chemotherapy. Eur J Cancer 2019;107:142–52.
43. Colevas AD, Bahleda R, Braiteh F, Balmanoukian A, Brana I, Chau NG, et al. Safety and clinical activity of atezolizumab in head and neck cancer: Results from a phase I trial. Ann Oncol 2018;29(11):2247–53.
44. Ferris RL, Haddad R, Even C, Tahara M, Dvorkin M, Ciuleanu TE, et al. Durvalumab with or without tremelimumab in patients with recurrent or metastatic head and neck squamous cell carcinoma: EAGLE, a randomized, open-label phase III study. Ann Oncol 2020;31(7):942–50.
45. Siu LL, Even C, Mesía R, Remenar E, Daste A, Delord JP, 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 2019;5(2):195–203.
46. Kao HF, Ang MK, Ng QS, Tan DS, Tan W, Rajasekaran T, et al. Combination Ipilimumab and Nivolumab in Recurrent/Metastatic Nasopharyngeal Carcinoma (R/M NPC) Updated Efficacy and Safety Analysis of NCT03097939. ESMO Asia Virtual Congress; 2020.
47. Ruzsa A, Sen M, Evans M, Lee LW, Hideghety K, Rottey KS, et al. Phase 2, open-label, 1:1 Randomized controlled trial exploring the efficacy of EMD 1201081 in combination with cetuximab in second-line cetuximab-naïve patients with recurrent or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN). Invest New Drugs 2014;32(6):1278–84.
48. Chow LQ, Morishima C, Eaton KD, Baik CS, Goulart BH, Anderson LN, et al. Phase Ib trial of the toll-like receptor 8 agonist, motolimod (VTX-2337), combined with cetuximab in patients with recurrent or metastatic SCCHN. Clin Cancer Res 2016;23(10):2442–50.
49. Ferris RL, Saba NF, Gitlitz BJ, Haddad R, Sukari A, Neupane P, et al. Effect of adding motolimod to standard combination chemotherapy and cetuximab treatment of patients with squamous cell carcinoma of the head and neck: The active 8 randomized clinical trial. JAMA Oncol 2018;4(11):1583–8.
50. Soulières D, Faivre S, Mesía R, Remenár É, Li SH, Karpenko A, et al. Buparlisib and paclitaxel in patients with platinum-pretreated recurrent or metastatic squamous cell carcinoma of the head and neck (BERIL-1): A randomised, double blind, placebo-controlled phase 2 trial. Lancet. Oncol 2017;18(3):323–35.
51. Massarelli E, Lin H, Ginsberg LE, Tran HT, Lee JJ, Canales JR, et al. Phase II trial of everolimus and erlotinib in patients with platinumresistant recurrent and/or metastatic head and neck squamous cell carcinoma. Ann Oncol 2015;26(7):1476–80.
52. Geiger JL, Bauman JE, Gibson MK, Gooding WE, Varadarajan P, Kotsakis A, et al. Phase II trial of everolimus in patients with previously treated recurrent or metastatic head and neck squamous cell carcinoma. Head Neck 2016;38(12):1759–64.
53. Dunn LA, Fury MG, Xiao H, Baxi SS, Sherman EJ, Korte S, et al. A phase II study of temsirolimus added to low-dose weekly carboplatin and paclitaxel for patients with recurrent and/or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC). Ann Oncol 2017;28(10):2533–8.
54. Malhotra A, Sendilnathan A, Old MO, Wise-Draper TM. Oncolytic virotherapy for head and neck cancer: Current research and future developments. Oncolytic Virotherapy 2015;4:83–93.
55. Blasco M, Svider P, Raza S, Jacobs JR, Folbe AJ, Saraf P, et al. Systemic therapy for head and neck squamous cell carcinoma: Historical perspectives and recent breakthroughs. Laryngoscope 2017;127(11):2565–9.
56. Brockstein B, Vokes E. Treatment of Metastatic and

Turk J Oncol 2021;36(4):519–28
doi: 10.5505/tjo.2021.2849

Recurrent Head and Neck Cancer. In: UpToDate [Database on the Internet]. Altham, MA: UpToDate; 2020.

57. Burtness BA, Manola J, Axelrod R, Argiris A, Forastiere AA, Eastern Cooperative Oncology Group. A randomized phase II study of ixabepilone (BMS-247550) given daily 3 5 days every 3 weeks or weekly in patients with metastatic or recurrent squamous cell cancer of the head and neck: An Eastern cooperative oncology group study. Ann Oncol 2008;19(5):977–83.
58. Joshi A, Patil V, Noronha V, Dhumal S, Pande N, Chandrasekharan A, et al. Results of a phase II randomized controlled clinical trial comparing efficacy of cabazitaxel versus docetaxel as second-line or above therapy in recurrent head and neck cancer. Oral Oncol 2017;75:54–60.
59. Machiels JP, Van Maanen A, Vandenbulcke JM, Filleul B, Seront E, Henry S, et al. Randomized phase II study of cabazitaxel versus methotrexate in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck previously treated with platinum-based therapy. Oncologist 2016;21(12):e1416–7.
60. Pivot X, Wadler S, Kelly C, Ruxer R, Tortochaux J, Stern J, et al. Result of two randomized trials comparing nolatrexed (Thymitaq™) versus methotrexate in patients with recurrent head and neck cancer. Ann Oncol 2001;12(11):1595–9.
61. Fury M, Sherman E, Lisa D, Agarwal N, Algazy K, Brockstein B, et al. A randomized phase II study of cetuximab every 2 weeks at either 500 or 750 mg/m^2 for patients with recurrent or metastatic head and neck squamous cell cancer. J Natl Compr Canc Netw 2012;10(11):1391–8.
62. Ferrarotto R, William W, Tseng J, Marur S, Shin DM, Murphy B, et al. Randomized phase II trial of cixutumumab alone or with cetuximab for refractory recurrent/metastatic head and neck squamous cell carcinoma. Oral Oncol 2018;82:83–90.
63. Argiris A, Ghebremichael M, Gilbert J, Lee JW, Sachidanandam K, Kolesar JM, et al. Phase III randomized, placebo-controlled trial of docetaxel with or without gefitinib in recurrent or metastatic head and neck cancer: An Eastern cooperative oncology group trial. J Clin Oncol 2013;31(11):1405–14.
64. Jimeno A, Bauman JE, Weissman C, Adkins D, Schnadig I, Beauregard P, et al. A randomized, phase 2 trial of docetaxel with or without PX-866, an irreversible oral phosphatidylinositol 3-kinase inhibitor, in patients with relapsed or metastatic head and neck squamous cell cancer. Oral Oncol 2015;51(4):383–8.
65. Jimeno A, Shirai K, Choi M, Laskin J, Kochenderfer M, Spira A, et al. A randomized, phase II trial of cetuximab with or without PX-866, an irreversible oral phosphatidylinositol 3-kinase inhibitor, in patients with relapsed or metastatic head and neck squamous cell cancer. Ann Oncol 2015;26(3):556–61.
66. Jin Z, Zhang B, Zhang L, Huang W, Mo X, Chen Q, et al. Immune-checkpoint inhibitor plus chemotherapy versus conventional chemotherapy for treatment of recurrent or metastatic head and neck squamous cell carcinoma: A systematic review and network meta-analysis. Ther Adv Med Oncol 2020;12:1758835920983717.
67. Cancer Genome Atlas Network. Comprehensive genomic characterization of head and neck squamous cell carcinomas. Nature 2015;517(7536):576–82.
68. Kiaris H, Spandidos DA, Jones AS, Vaughan ED, Field JK. Mutations, expression and genomic instability of the H-ras proto-oncogene in squamous cell carcinomas of the head and neck. Br J Cancer 1995;72(1):123–8.
69. Ho AL, Brana I, Haddad R, Bauman J, Bible K, Oosting S, et al. Tipifarnib in head and neck squamous cell carcinoma with HRAS mutations. J Clin Oncol 2021;39(17):1856–64.
70. Cox AD, Der CJ, Philips MR. Targeting RAS membrane association: Back to the future for anti-RAS drug discovery? Clin Cancer Res 2015;21(8):1819–27.