Immunotherapy for head and neck cancer : from recurrent/metastatic disease to (neo)adjuvant treatment in surgically resectable tumors

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Abstract

Purpose of review: We aim to summarize the current evidence on the role of immune checkpoint inhibitors in the (neo)adjuvant treatment of squamous cell carcinoma of the head and neck (HNSCC), with a particular focus on surgically treated patients.
Recent findings: Pembrolizumab +/- chemotherapy improves the outcome in patients with previously untreated recurrent/metastatic HNSCC. Nivolumab is superior to chemotherapy after platinum failure. The addition of avelumab to chemoradiation failed to improve the outcome in patients with locally advanced HNSCC.
Neoadjuvant pre-surgical PD-1 blockade is safe and is associated with encouraging overall response rate. KEYNOTE-689 randomizes patients with resectable stage III/IVA HNSCC to surgery and adjuvant standard of care +/- neoadjuvant and adjuvant pembrolizumab. ADHERE assigns surgically treated HNSCC at high risk of recurrence to CRT plus either durvalumab or placebo.
MK-3475-689 evaluates the role of pembrolizumab in patients with resectable HNSCC. NIVOPOSTOP evaluates the addition of nivolumab to CRT in patients with surgically treated pStage III/IV HNSCC or pT3N1/pT4N1 OPC with ≥20 packs/year at high risk of relapse.
Summary: Multiple trials are currently evaluating the role of immunotherapy in HNSCC amenable to surgery. Neoadjuvant pre-surgical PD-1 blockade is feasible and safe and is associated with an encouraging overall response rate.

Key words

Immune checkpoint inhibitors
Adjuvant
Neo-adjuvant
Surgery
Head and neck cancer

Introduction

The immune checkpoint inhibitors (ICI) were first evaluated in patients with recurrent/metastatic (R/M) disease. Pembrolizumab and nivolumab target the Programmed Cell Death 1 Receptor (PD-1) and were both approved by the United States Food and Drug Administration (FDA) and the European Medicines Agency for the treatment of R/M Squamous Cell Carcinoma of the Head and Neck (HNSCC)(1-3). More than 60% of patients with HNSCC present with stage III or IV disease (4). Despite multidisciplinary multimodal treatment, locally advanced disease carries a high risk of local recurrence (15 to 40%) and distant metastasis, with a poor prognosis (5-year overall survival, <50%), leaving ample room for improvement (4). The promising results with ICI in the R/M setting strongly support studies on the potential role of ICI earlier in the disease i.e. neoadjuvant or perioperative treatment, concurrent definitive treatment, or adjuvant therapy (4).

Immunotherapy in R/M HNSCC

In KEYNOTE-048, 882 patients with untreated locally incurable R/M HNSCC were stratified by Programmed death-ligand 1 (PD-L1) expression, p16 status, and performance status and randomly allocated (1:1:1) to pembrolizumab alone, pembrolizumab plus a platinum and 5-fluorouracil (pembrolizumab with chemotherapy), or cetuximab plus a platinum and 5-fluorouracil (cetuximab with chemotherapy)(5). The primary endpoints were overall survival (OS) and progression-free survival (PFS) in the intention-to-treat (ITT) population (5). The statistical plan was very complex and there were no less than 14 primary hypotheses: superiority of pembrolizumab alone and of pembrolizumab with chemotherapy versus cetuximab with chemotherapy for OS and PFS in the PD-L1 Combined Positive Score (CPS) of 20 or more, CPS of 1 or more, and total populations and non-inferiority (non-inferiority margin: 1.2) of pembrolizumab alone and pembrolizumab with chemotherapy versus cetuximab with chemotherapy for OS in the total population (5). The definitive findings for each hypothesis were obtained when statistical testing was completed for that hypothesis; this occurred at the second interim analysis for 11 hypotheses and at final analysis for three hypotheses (5). Seven hundred and fifty four patients (85%) had CPS of 1 or more and 381 (43%) had CPS of 20 or more. At the second interim analysis, pembrolizumab alone improved OS versus cetuximab with chemotherapy in the CPS of 20 or more population (median 14.9 months vs 10.7 months, hazard ratio [HR] 0.61 [95% confidence interval 0.45-0.83], p=0.0007) and CPS of 1 or more population (median 12.3 months vs 10.3 months, HR 0.78 [95 % CI 0.64-0.96], p=0.0086) and was non-inferior in the total population (median 11.6 months vs 10.7 months, HR 0.85 [95 % CI 0.71-1.03]). Pembrolizumab with chemotherapy improved OS versus cetuximab with chemotherapy in the total population (median 13.0 months vs 10.7 months, HR 0.77 [95% CI 0.63-0.93], p=0.0034) at the

second interim analysis and in the CPS of 20 or more population (median 14.7 months vs 11.0 months, HR 0.60 [95 % 0.45-0.82], p=0.0004) and CPS of 1 or more population (median 13.6 months vs 10.4 months, HR 0.65 [95 % CI 0.53-0.80], p<0.0001) at final analysis. Neither pembrolizumab alone nor pembrolizumab with chemotherapy improved PFS at the second interim analysis (5). At final analysis, grade 3 or worse all-cause adverse events (AEs) occurred in 55% of the patients in the pembrolizumab alone group, in 85% of the patients in the pembrolizumab with chemotherapy group, and in 83% of the patients in the cetuximab with chemotherapy group. Adverse events led to death in 8%, 12%, and 10 % of the patients, respectively (5).

In the open-label, phase III, CheckMate 141 trial (6), 361 patients with R/M HNSCC whose disease had progressed within 6 months after platinum-based chemotherapy were randomly assigned in a 2:1 ratio to receive nivolumab (at a dose of 3 mg per kilogram of body weight) every 2 weeks or investigator's choice (IC) standard, single-agent systemic therapy (weekly methotrexate, docetaxel, or cetuximab)(6). The median OS (primary endpoint) was 7.5 months (95% CI 5.5-9.1) in the nivolumab group versus 5.1 months (95% CI 4.0-6.0) in the IC group. Overall survival was significantly longer with nivolumab than with IC (HR 0.70, 97.73% CI 0.51-0.96, p=0.01), and the estimates of the 1-year survival rate were 36.0% and 16.6% with nivolumab and I, respectively (6). Nivolumab appeared to improve efficacy versus IC regardless of prior cetuximab use (7). Nivolumab resulted in a higher survival versus IC in patients <65 and $\geq$65years, with a manageable safety profile in both age groups (8). The median PFS was 2.0 months (95% CI 1.9-2.1) with nivolumab versus 2.3 months (95% CI 1.9-3.1) with IC (HR 0.89, 95% CI 0.70-1.13, p=0.32). The rate of PFS at 6 months was 19.7% with nivolumab versus 9.9% with IC (6). The overall response rate (ORR) was 13.3% in the nivolumab group versus 5.8% in IC group. Treatment-related AEs (TRAEs) of grade $\geq$ 3 occurred in 13.1% of the patients in the nivolumab group versus 35.1% of those in IC group (6). Nivolumab delayed time to deterioration of patient-reported quality-of-life outcomes compared with IC (9). With 24.2 months' minimum follow-up, nivolumab continued to improve OS vs standard therapy with a HR of 0.68 (95% CI 0.54-0.86) (10). Nivolumab nearly tripled the estimated 24-month OS rate (16.9% vs 6.0%, and demonstrated OS benefit across patients with tumor PD-L1 expression $\geq$1% (HR 0.55, 95 % CI 0.39-0.78) and <1% (HR 0.73, 95 % CI 0.49-1.09), and regardless of tumor HPV status (10).

In KEYNOTE-040, 495 patients with HNSCC that progressed during or after platinum-containing treatment for recurrent or metastatic disease (or both), or whose disease recurred or progressed within 3-6 months of previous multimodal therapy containing platinum for locally advanced (LA) disease, were randomly assigned (1:1) to receive pembrolizumab 200 mg every 3 weeks (Q3W) or investigator's choice of standard doses of methotrexate, docetaxel, or cetuximab intravenously (standard-of-care group

[SoC])(11). Median OS in the ITT population (primary endpoint) was 8.4 months (95% CI 6.4-9.4) with pembrolizumab and 6.9 months (5.9-8.0) with SoC (HR 0.80, 95 % CI 0.65-0.98; nominal p=0.0161). Fewer patients treated with pembrolizumab than with SoC had grade $\geq$ 3 or worse TRAEs (13% vs 36%)(11). Global health status (GHS)/Quality of Life (QoL) was stable with pembrolizumab but declined with SoC at week 15 (12).

Median time to deterioration in GHS/QoL score was 4.8 months and 2.8 months, respectively (HR 0.79, 95% CI: 0.59-1.05). At week 15, GHS/QoL scores were stable for pembrolizumab (least squares mean [LSM] 0.39, 95% CI -3.00-3.78) but worsened for SoC (LSM -5.86, 95% CI -9.68--2.04); LSM between-group difference was 6.25 points (95% CI 1.32-11.18; nominal 2-sided p=.01). Greater difference in LSM score for GHS/QoL occurred with pembrolizumab versus docetaxel (10.23, 95% CI 3.15-17.30) compared with pembrolizumab versus methotrexate (6.21, 95% CI -4.57-16.99) or pembrolizumab versus cetuximab (-1.44, 95% CI -11.43-8.56) (12).

Dual blockade of PD-L1 and cytotoxic T-lymphocyte associated protein 4 (CTLA-4) might overcome immune checkpoint inhibition (13). Durvalumab and tremelimumab target PD-L1 and CTLA-4, respectively. CONDOR is a phase 2, randomized, open-label study of durvalumab, tremelimumab, and durvalumab in combination with tremelimumab in patients with R/M HNSCC (13). In total, 267 patients with PD-L1-low/negative disease that had progressed after 1 platinum-containing regimen in the R/M setting were randomized in a 2:1:1 ratio to receive durvalumab (20 mg/kg every 4 weeks [Q4W]) + tremelimumab (1 mg/kg Q4W) for 4 cycles, followed by durvalumab (10 mg/kg every 2 weeks [Q2W], or durvalumab (10 mg/kg Q2W) monotherapy, or tremelimumab (10 mg/kg Q4W for 7 doses then every 12 weeks for 2 doses) monotherapy. Grade 3/4 TRAEs occurred in 15.8%, 12.3%, and 16.9 % of the patients treated with durvalumab plus tremelimumab, durvalumab, and tremelimumab, respectively. Grade 3/4 immune-mediated adverse events (IRAEs) occurred in 6.0% of the patients in the combination arm only. Objective response rate was 7.8% (95 % CI 3.78-13.79) in the combination arm, 9.2% (95 % 3.46-19.02) for durvalumab monotherapy, and 1.6% (95 % CI 0.04-8.53) for tremelimumab monotherapy (13). Median OS for all patients treated was 7.6 months (95 % CI 4.9-10.6), 6.0 months (95 % CI 4.0-11.3), and 5.5 months (95 % CI 3.9-7.0), respectively (13). EAGLE is an open-label phase III study evaluating the efficacy of durvalumab or durvalumab plus tremelimumab versus SoC in R/M HNSCC patients (14). Patients were randomly assigned to receive 1:1:1 durvalumab (10 mg/kg Q2W), durvalumab plus tremelimumab (durvalumab 20 mg/kg Q4W plus tremelimumab 1 mg/kg Q4W, then durvalumab 10 mg/kg Q4W), or SoC (cetuximab, a taxane, methotrexate, or a fluoropyrimidine) (14). The primary endpoint was not met as no statistically significant improvements in OS were observed for durvalumab versus SoC

(HR 0.88, 95 % CI 0.72-1.08; p=0.20) or durvalumab plus tremelimumab versus SoC (HR 1.04, 95% CI 0.85-1.26, p=0.76). The 12-month survival rates were 37.0% (95 % CI 30.9-43.1), 30.4% (95 % CI 24.7-36.3), and 30.5% (95 % CI 24.7-36.4) for durvalumab, durvalumab plus tremelimumab, and SoC, respectively (14).

Stereotactic Body Radiotherapy (SBRT) aims at ablating metastatic lesions and may play a synergistic role with immunotherapy (15). Bahig et al are conducting a phase I/II single arm trial evaluating the safety of durvalumab (1500 mg IV Q4W) and tremelimumab (75 mg Q4W) for a total of 4 doses in combination with SBRT to 2-5 metastases administered between cycles 2 and 3 of immunotherapy (15).

Immunotherapy with (C)RT in LA HNSCC

Chemoradiotherapy (CRT) is the standard of care for LA HNSCC not amenable to surgery (14). Prospective studies incorporating ICs in the definitive management of poor prognosis, non-metastatic, LA HNSCC are ongoing (14). Weiss et al (16) enrolled 29 cisplatin-ineligible stage III-IV HNSCC patients in a phase II trial. Reasons for cisplatin ineligibility included otopathy (69.0%), nephropathy (20.7%), and neuropathy (6.9%). Patients received radiotherapy (RT) concurrently with three cycles of pembrolizumab 200 mg Q3W followed by three adjuvant cycles. The primary endpoint was a PFS of $\geq$16 months. With median follow-up of 21 months, estimated 24-month PFS and OS rates were 71% (95% CI 49-84) and 75% (95 % CI 51-88), respectively. The primary PFS endpoint has exceeded the hypothesis and its median has not been reached (16).
The JAVELIN Head and Neck 100 study is a multinational, phase III, double-blind, placebo-controlled, randomized clinical trial assessing the efficacy of the PD-L1 inhibitor avelumab in combination with CRT compared with placebo in combination with CRT for high-risk HNSCC (14). In total, 697 previously untreated LA SCCHN of the oropharynx, hypopharynx, larynx, or oral cavity, stage III, IVa, or IVb disease per American Joint Committee on Cancer (AJCC) (7^{th} edition) except for Human Papillomavirus (HPV) positive (+) oropharyngeal cancer (OPC) patients, for whom only T4 or N2c or N3 status was allowed, eligible for definitive CRT with curative intent were randomized 1:1 to receive avelumab 10 mg/kg Q2W plus CRT (cisplatin 100 mg/m² Q3W + standard fractionation RT [70 Gy in 35 fractions over 7 weeks] or placebo + CRT. This was preceded by a lead-in dose and followed by avelumab or placebo maintenance therapy for up to 1 year (17). Grade ≥3 AEs were more frequent with avelumab + CRT vs placebo + CRT (88% vs 82%); fatal AEs occurred in 6% and 5% of patients, respectively. Rates of AEs leading to discontinuation of any study drug were similar in

both arms (33% vs 32% in the avelumab vs placebo arms). The addition of avelumab failed to improve the outcome.

At interim analysis, the HRs for PFS per modified RECIST v1.1 (primary endpoint) and overall survival were 1.21 (95% CI 0.93-1.5, p=0.920) and 1.31 (95% CI 0.93-1.85, p=0.937), respectively, both in favor of placebo + CRT (17).

The avelumab-cetuximab-RT combination is safe in patients with LA HNSCC (18).

GORTEC 2017-01 (REACH) is a phase III trial in patients with LA HNSCC deemed fit to receive cisplatin (100 mg/m² Q3W) (cohort 1) or unfit to cisplatin (cohort 2). Standard of care is Intensity Modulated Radiation Therapy (IMRT) with cisplatin in cohort 1 (arm A) and with weekly cetuximab in cohort 2 (arm D) (18). In both cohorts, experimental arms (arms B and C) were IMRT with cetuximab and avelumab (10 mg/kg day 7 Q2W) followed by avelumab Q2W for 12 months. Tao et al reported the data of the safety phase which was conducted among the first 41 patients in experimental arms by monitoring grade ≥4 adverse events (AEs) with a pre-defined unacceptability rate of 35% (18). All patients of experimental arms except one (arm C) received RT as planned. Most common grade ≥3 AEs were mucositis, radio-dermatitis, and dysphagia. Grade ≥4 AEs occurred in 5/41 (12%) patients, all in arm C (no grade 5). In the SoC arms, grade ≥4 AEs occurred in 3/21 patients (14%) in arm A and 2/20 (10%) in arm D. One grade 5 hemorrhage occurred in arm A (18).

Elbers et al (19) conducted a phase-I feasibility trial of conventional cetuximab-RT with avelumab (concurrent 10 mg/kg Q2W + 4 months maintenance) for advanced-stage HNSCC patients unfit for cisplatin treatment (19). One of ten included patients experienced grade 2 cetuximab-related infusion reaction and withdrew from the study before avelumab was administered. One patient discontinued treatment after 2 courses of avelumab and 12×2 Gy RT for personal reasons. In 2/8 remaining patients, avelumab was stopped after 4 and 8 courses because of toxicity and tumor progression, respectively (19). There was no grade $\geq$ 4 toxicity. Grade 3 immune-related toxicity was manageable and occurred in 4 patients. Seven patients experienced grade 3 RT-related toxicity with no severe specific cetuximab-related toxicity (19).

KEYNOTE-412 is an ongoing randomized, double-blind, phase III trial investigating pembrolizumab or placebo administered concurrently with CRT and as maintenance treatment in patients with LA HNSCC (20).

DUCRO is an open label, multi-center, single-arm, phase I/II study, enrolling patients with high-risk ($\geq$N2a or $\geq$T3 any N) laryngeal cancer, hypopharyngeal cancer and HPV negative (-) OPC or HPV+ OPC ($\geq$T2, $\geq$N2b, $\geq$10pack/years)(21).

Patients receive RT (69.9Gy in 33 fractions of 2.12Gy) with concurrent cetuximab (400mg/m² 1 week before RT followed by 250 mg/m² weekly) and durvalumab (1500

mg Q4W starting from RT week 1) followed by adjuvant durvalumab (to a maximum of 6 months after completion of RT)(21). Primary endpoint of the study is 2-year PFS (21).

Immunotherapy with induction chemotherapy

In CheckRad-CD8 patients received a single cycle of cisplatin 30 mg/m² on days 1-3 and docetaxel 75 mg/m² on day 1 combined with durvalumab 1500 mg and tremelimumab 75 mg on day 5 (22). Patients with pCR in the re-biopsy after induction treatment or at least 20% increase of intra-tumoral CD8+ cell density in the re-biopsy compared with baseline entered radio-immunotherapy with concomitant durvalumab/tremelimumab. The objective of the interim analysis reported by Hecht et al was to analyze safety and efficacy of the chemo-immunotherapy induction treatment before radio-immunotherapy. A total of 57 patients were enrolled. Single cycle induction treatment with cisplatin/docetaxel and durvalumab/tremelimumab is feasible and achieves a high biopsy-proven pCR rate (22). After induction treatment, 27 patients (48%) had a pCR in the re-biopsy and further 25 patients (45%) had a relevant increase of intra-tumoral CD8(+) cells (median increase by a factor of 3.0). Grade 3-4 AEs occurred in 38 patients (68%) and mainly consisted of leukopenia (43%) and infections (29%). Six patients (11%) developed grade 3-4 immune-related AEs. On multivariable analysis, intra-tumoral CD8+ cell density predicted pCR independently. In peripheral blood CD8(+) cells, the co-expression of PD-1otein 1 significantly increased especially in patients with pCR (22).

MEDINDUCTION is a phase I trial evaluating the safety of 3 cycles of durvalumab 1120 mg Q3W in combination with docetaxel 75 mg/m², cisplatin 75 mg/m² and 5-FU 750 mg/m²/day from day 2 to day 6 Q3W as induction therapy for LA HNSCC (23). The trial was stopped early due to toxicity. Only nine of fourteen treated patients completed the 3 cycles of induction and six patients experienced dose limiting toxicities (23).

DEPEND is a phase II trial of carboplatin, paclitaxel, and nivolumab induction therapy followed by response-stratified locoregional therapy for patients LA HPV- HNSCC (24). The primary endpoint is the deep response rate defined as $\geq$ 50 % to induction therapy based on RECIST criteria. The objective is to intensify induction chemotherapy with the addition of an immune checkpoint inhibitor aiming to increase the proportion of patients achieving a deep tumor response in order to subsequently allow risk-adapted definitive CRT (24).

Immunotherapy in surgically treated HNSCC

Multiple trials are currently evaluating the role of immunotherapy in HNSCC amenable to surgery.

Immunotherapy prior to surgery

Neoadjuvant pre-surgical PD-1 blockade is feasible and safe and is associated with an encouraging ORR. Horton et al (25) conducted a phase II clinical trial in patients with stage II-IVA OCSCC with a preplanned analysis after completion of stage one. The first stage included 9 patients who received 3-4 biweekly doses of 3mg/kg nivolumab followed by definitive surgical resection. Pre-surgical nivolumab therapy resulted in an overall response rate of 44% (95% CI 14-79%) with four patients having >30% reduction in tumor size consistent with partial response. An additional patient had stable disease while the remaining four patients progressed through treatment. Neoadjuvant nivolumab was not associated with delays in definitive surgical treatment. There were no grade 3-4 adverse events and no treatment interruptions. In OPC, high CD8-positive [CD8(+)] tumor-infiltrating lymphocyte (TIL) density confers improved prognosis (26). Ferrarotto et al (26) compared neoadjuvant durvalumab with durvalumab + tremelimumab in terms of impact on CD8(+)TIL density, safety, and efficacy in patients with newly diagnosed stage II-IVA OPC or locoregionally recurrent OPC amenable to resection. Twenty-eight eligible patients were randomized to two cycles of durvalumab or durvalumab + tremelimumab before surgery. Twenty patients had newly diagnosed OPC, and 24 were p16-positive. The post-treatment to pre-treatment median CD8+TIL density ratio (primary endpoint) was 1.31 for durvalumab and 1.15 for combination treatment ($p = 0.97$, 95% CI: -1.07-2.28). In each group, 6 patients (43%, 95% CI 17.66-71.14) had a response. Eight patients (29%) had a major pathologic response (MPR; $\leq$10% viable tumor cells) at the primary tumor and/or nodal metastases. Neither baseline CD8(+) TIL density nor PD-L1 expression level correlated with ORR, but a trend toward greater CD8+TIL change in patients with a MPR was seen ($p = 0.059$, 95% CI -0.33-3.46). Four patients (14%) had grade $\geq$3 AEs (26).

Knochelmann et al demonstrated that TIL can be reliably expanded from oral cavity squamous cell carcinoma (OCSCC) patients on neoadjuvant nivolumab. TILs from responders expressed higher CD26 and Tim3 (27). Nivolumab caused opposing effects on CD4(+) and CD8(+) cell populations, with CD4(+) cell levels declining and CD8(+) cells increasing (28).

The IMCISION trial is a Ib/II study in which 32 stage II-IVB HNSCC patients indicated for curative (salvage) surgery were treated with nivolumab 240 mg in weeks 1 and 3 or nivolumab 240 mg in weeks 1 and 3 and ipilimumab 1 mg/kg in week 1 prior to surgery in week 5 (29). Surgery was not postponed in any patient. (Near)-pCR in the primary tumor was seen in 9/29 evaluable patients (31%). Another 31% of patients had a 20-89% pathological tumor response (pTR) (29).

In a randomized phase II trial conducted at Dana-Farber Cancer Institute, 29 patients with untreated OCSCC ($\geq$T2, or clinically node positive) were randomized to receive nivolumab, 3 mg/kg, weeks 1 and 3, or nivolumab 3 mg/kg, weeks 1 and 3, and

ipilimumab 1 mg/kg, given week 1 only prior to surgery 3 to 7 days following cycle 2 (30). There were no surgical delays. There were toxic effects at least possibly related to study treatment in 21 patients, including grade $\geq$ 3 events in 2 patients treated with nivolumab and 5 patients treated with nivolumab and ipilimumab. There was evidence of response in both treatment arms (30).

In a phase II trial conducted by Wise-Draper et al, 28 of 80 planned patients with clinically high risk (T3/4 and/or ≥2 positive lymph nodes) HNSCC received pembrolizumab 200 mg 1-3 weeks before resection (31). Adjuvant concurrent pembrolizumab (Q3W x 6 doses) and RT (60-66Gy) were administered, along with weekly cisplatin (40mg/m²) for those with high risk features. A pCR (> 10 % tumor effect) was observed in 9 of 19 (47 %) of evaluable patients with 6 (32%) major responses (> 70 % tumor effect) and 1 pCR after one dose. Pathological response was associated with robust immune cell infiltration, increased PD-L1 and PD-L2 (31).

Uppaluri et al (32) conducted a multicenter phase II trial to determine if pembrolizumab would be safe, result in pTR, and lower the relapse rate in patients with resectable HPV-HNSCC. Neoadjuvant pembrolizumab 200 mg was administered 2-3 weeks prior to surgery. Postoperative (C)RT was planned. Patients with high-risk pathology (positive margins and/or extranodal extension [ENE]) received adjuvant pembrolizumab. Pathological tumor response was quantified as the proportion of the resection bed with tumor necrosis, keratinous debris, and giant cells/histiocytes: pTR-0 (<10%), pTR-1 (10%-49%), and pTR-2 ($\geq$50%). Co-primary endpoints were pTR-2 among all patients and 1-year relapse rate in patients with high-risk pathology. Thirty-six patients were enrolled. Pembrolizumab was safe as grades 3-4 AEs and unexpected surgical delays/complications did not occur (32). After neoadjuvant pembrolizumab, pTR-2 occurred in eight patients (22%), and pTR-1 in eight other patients (22%). There were no pCR. One-year relapse rate among 18 patients with high-risk pathology was 16.7% (95% CI 3.6-41.4), which is lower than historical (35 %). Pathological tumor response $\geq$10% correlated with baseline tumor PD-L1, immune infiltrate, and interferon gamma (IFN γ) activity (32).

Sitravatinib (receptor TKI against TYRO3, AXL, MERTK and VEGF family of receptors) is predicted to increase M1-type tumor-associated macrophages (TAMs) and decrease MDSCs in the tumor microenvironment (33). SNOW is a window-of-opportunity study evaluating the immunogenic and antitumor effects of preoperative sitravatinib and nivolumab in patients with OCSCC. As of January 31st, 2020, 10 out of 12 planned patients with untreated T2-4a, N0-2 or T1>1cm-N2 OCSCC received oral sitravatinib 120 mg daily from day 1 up to 48 hours and 1 dose of Nivolumab 240mg on day 15 prior to surgery, which was planned between day 23 and day 30. The study treatment was well-tolerated. All patients had tumor reduction, 9/10 had pathological downstaging, including

1 complete response. Lower percentage of MDSCs and increased percentage of M1-TAMs and M1:M2 ratio trend was seen at day 15 and pre-surgery, with stronger effect in major responders. Best responders had higher percentage of PD-L1+ TAMs at baseline (33). Zinner et al (34) hypothesized that the addition of nivolumab to weekly carboplatin and paclitaxel will increase the pathological complete response (pCR) rate at the primary site compared to historical controls. Twenty-seven patients with newly diagnosed stage III-IV HPV- OCSCC, OPC, hypopharyngeal carcinoma, or laryngeal carcinoma or stage II-III HPV+ OPC without distant metastasis, who are surgical candidates received neoadjuvant six weekly administrations of carboplatin area under the curve (AUC) 2 mg/mL•min and paclitaxel 100 mg/m² plus three biweekly administrations of nivolumab 240 mg. At surgery, which was planned at week 8, a pCR at primary site was observed in 11 of 26 patients (42 %) with known primary tumor. The combination was safe and the primary endpoint (pCR at the primary site > 11/37) was met with the 27th patient (34).

Planned trials

Phase III trials

IMvoke010 is a global, double-blind, placebo-controlled, randomized phase III trial enrolling 400 patients who have completed definitive local/regional therapy for stage III HPV+ OPC or stage IVA or IVB HPV-negative SCCHN involving the oral cavity, oropharynx, larynx or hypopharynx and are at high risk for disease recurrence or progression (35). Patients who have received surgery alone or radiotherapy alone as definitive local therapy are excluded. Patients are randomized 1:1 to receive placebo or atezolizumab 1200 mg Q3W for up to a year (16 cycles) or until unacceptable toxicity, disease recurrence or progression. Primary endpoints are independent review assessed event-free survival (EFS) and overall survival (35) .

KEYNOTE-689 is a randomized, open-label phase III trial in which patients with previously untreated, resectable stage III/IVA HNSCC will be randomly assigned 1:1 to two treatment arms (36). Patients in arm A will receive neoadjuvant pembrolizumab (200 mg Q3W for two cycles) followed by surgical resection followed by SoC plus adjuvant pembrolizumab (15 cycles). Patients in arm B will immediately proceed to surgical resection followed by adjuvant SoC. Randomization will be stratified by primary tumor site (oropharynx/oral cavity vs larynx vs hypopharynx), tumor stage (III vs IVA), and HPV p16 status (oropharynx p16 positive vs oropharynx p16 negative or larynx/hypopharynx/oral cavity). Treatment will continue until disease progression, unacceptable toxicity, or decision to withdraw. Patients in arm A will undergo the first radiologic imaging assessment after two cycles of neoadjuvant pembrolizumab and before surgery. Dual primary end points

are major pathological response, defined as ≤10% invasive squamous cell carcinoma within resected primary tumor and sampled regional lymph nodes per blinded central pathology, and EFS (36).

ADHERE is a phase III randomized blind placebo-controlled study conducted by EORTC. Eligible are patients with surgically treated SCC of the oral cavity (excluding lip), larynx, hypopharynx or p16-negative oropharynx at high risk of locoregional recurrence based on extranodal extension (ENE) and/or R1 resection margin < 1 mm. In total, 650 patients will be randomized 1:1 to receive either durvalumab or placebo (one dose) before CRT and for 6 months Q4W after CRT. The primary endpoint is DFS (37).

MK-3475-689 is a phase III, randomized, open-label study to evaluate pembrolizumab as neoadjuvant therapy and in combination with SoC as adjuvant therapy for stage III-IVA resectable LA HNSCC. The trial will enroll 704 patients with newly diagnosed resectable, non-metastatic, SCC of the oropharynx (stage III HPV positive [T4N0-2] or stage III or IVA HPV negative) or larynx, hypopharynx, or oral cavity (stage III or IVA) (38). Patients in the control arm receive no neoadjuvant therapy prior to surgery. Following surgical resection, high risk participants receive SoC RT plus cisplatin 100 mg/m² Q3W for 3 cycles. Low risk participants receive SoC RT as adjuvant therapy (38). Patients in the experimental arm receive pembrolizumab 200 mg Q3W for 2 cycles as a neoadjuvant prior to surgery. Following surgical resection, patient receive adjuvant pembrolizumab 200 mg Q3W for 15 cycles plus either SoC of care cisplatin-based CRT for high risk patients or SoC RT for low risk patients (38).

NIVOPOSTOP is an open label phase III trial evaluating the addition of nivolumab to CRT in patients with surgically treated pStage III or IV SCC of the oral cavity, oropharynx, hypopharynx, or larynx (39). Patients with pStage II, pT3N1 or pT4N1 OPC with ≥20 packs/year are also eligible. Eligible are patients carrying a high risk of relapse (ENE, multiple peri-neural invasion, ≥ 4 nodes, and/or R1 or close margin ≤ 1 mm). Six hundred and eighty patients will be randomly assigned 1:1 to receive standard CRT with 3 cycles of cisplatin 100 mg/m² or standard CRT plus nivolumab followed by nivolumab maintenance. Primary endpoint is DFS (39).

In IMSTAR-HN, 276 patients with treatment-naive LA HNSCC (oral cavity, oropharynx p16-, hypopharynx, and larynx), will be randomized (2:1) into 2 arms (40;41). Standard of care (arm II) consists of surgical resection followed by risk-adapted adjuvant (C)RT. In arm I, standard treatment is preceded by neoadjuvant nivolumab 3 mg/kg within 2 weeks prior to surgery. After surgery and risk adapted (C)RT, second randomization will be performed: in arm Ia, nivolumab 3mg/kg will be given Q2W until progression or up to 6 months. In arm Ib, ipilimumab 1mg/kg will be applied additionally every 6 weeks also

until progression or up to 6 months. Primary endpoints is disease free survival (DFS) in arms I and II (40;41).

Phase I/II trials

NeoNivo explores the safety of neoadjuvant nivolumab in patients with LA resectable OCSCC and studies the potential role of [18F]BMS-986192 / [18F]-FDG PET imaging and immunomonitoring for response prediction (42). NCT03635164 is a phase I/Ib trial aiming to establish the maximum tolerated dose (MTD) and dose limiting toxicities of RT in combination with durvalumab pior to surgery for HPV- HNSCC (43).
In NCT03618134, 82 patients with T0-3 N0-2b HPV+ OPC with all gross disease amenable to R0 resection and eligible for transoral robotic surgery (TORS) undergo SBRT, 5 days a week for 1 week and durvalumab with or wituout tremelimumab on days 0 and 27 followed by TORS and modified radical neck dissection (mRND) in week 6-8, followed by 4 cycles of adjuvant durvalumab Q4W starting in week 12 (44).
NCT03708224 is a phase II study of perioperative immunotherapy in patients with advanced non-virally associated stage III/IV HNSCC amenable to surgical resection with curative intent. Patients must agree to undergo post-surgery adjuvant radiation therapy with or without concurrent, weekly cisplatin at 40 mg/m² (as clinically indicated)(45). Patients receive atezolizumab Q3W +/- other immune-modulating agent yet to be determined for 1-2 courses prior to standard surgery and RT radiation. Sixteen weeks post-surgery, patients receive 12 courses of atezolizumab Q3W (45).
Primary objectives are to determine the effect of neoadjuvant atezolizumab alone or in combination with other immune modulating agents on T-cell infiltration and to determine the impact of neo-adjuvant immunotherapy on surgical outcomes (45).
The PATHWay study is a randomized, double-blind phase II study of adjuvant pembrolizumab versus placebo in head and neck cancers at high risk for recurrence (46). In total, 100 patients with head and neck cancer (squamous cell histology as well as HPV+ and/or EBV+ head and neck tumors) who, after prior curative intent treatment, have an estimated risk of recurrence ≥ 40-50%, will be randomized to receive either pembrolizumab 200 mg or placebo Q3W for 1 year (46).

Indoleamine 2,3-dioxygenase (IDO1) catabolizes tryptophan to kynurenine and is highly expressed in multiple malignancies including SCCHN (47). Luginbuhl designed a window-of-opportunity trial to test whether the IDO inhibitor BMS-986205 improves treatment responses and T cell function in SCCHN patients treated with nivolumab (47). Patients with previously untreated, resectable, pathologically confirmed SCCHN are eligible (47). Primaries of the oral cavity, oropharynx, larynx, hypopharynx, or nasal cavity/paranasal sinuses must be AJCC 8th edition stage II or higher (M0)(47). Stage I OPC cancers with

lymphadenopathy are also eligible. Forty-eight patients will be randomized 3:1 to receive either A) nivolumab 480 mg IV x 1 plus BMS-986205 100 mg orally (PO) daily starting a week prior to nivolumab and continuing for 4 more weeks for a total of 5 weeks or B) nivolumab 480 mg IV alone for 4 weeks. At the 5th week of treatment patients are assessed for response. If there is $\geq$ 10% reduction in volume of either primary tumor or lymph node metastases, patients will be considered responders and receive another cycle of their originally assigned treatment, i.e. nivolumab 480 mg IV for a second dose +/- BMS-986205 100 mg PO daily for an additional 4 weeks followed by surgery in week 9. If tumor volume is stable or progression is noted in either the primary site or lymph nodes, patients are considered non-responders and definitive surgery is performed in week 5 (47). The primary endpoint of this study is the ORR after cycle 1.

NICO is planned to enroll 120 patients with T1-4 N1-3 or any T3-T4 N0 OCSCC. Patients will be treated with a single dose of nivolumab 240mg flat dose, followed by surgery within 1-2 weeks (48). Based on pathological risk factors determined following surgery, patients will be assigned to undergo adjuvant RT or CRT. A single dose of nivolumab 240mg will be given between surgery and commencement of (C)RT. Within 1-2 following completion of (C)RT, patients will commence adjuvant nivolumab, for a total of 6 doses 480 mg Q4W (48).

In NCT03715946, 135 patients with newly diagnosed with resectable, HPV-16 positive squamous cell carcinoma (SCC) or undifferentiated carcinoma of the oropharynx will undergo transoral surgery followed by de-intensified adjuvant RT plus nivolumab (49). Nivolumab will be administered at a dose of 240 mg Q2W during RT, and at 480 mg Q4W for 6 doses after RT. Primary endpoints are PFS and percutaneous gastronomy dependence 1-year post-surgery (49).

NCT03341936 enrolls patients with histologically or cytologically confirmed locoregionally recurrent HNSCC including any primary site, eligible for salvage surgery. Lirilumab is a monoclonal antibody designed to block the interaction between KIR2DL-1,-2,-3 inhibitory receptors and their ligands. A single dose of nivolumab and lirilumab is administered prior to salvage surgical resection which is followed by adjuvant nivolumab and lirilumab for 6 months (50).

In NCT02827838, patients receive durvalumab Q2W for up to 2 courses. Within 3-17 days after the last dose administration of durvalumab, patients undergo surgery (51). NCT03174275 aims to estimate the pCR rate after induction chemotherapy with carboplatin, nab-paclitaxel, and durvalumab in previously untreated stage III and IV SCCHN amenable to surgical resection (52).

The German Interdisciplinary Study Group of German Cancer Society (IAG KHT) is conducting a randomized phase II trial in patients who underwent a macroscopically complete resection of a newly diagnosed stage III or IVA/B HNSCC arising in the

oral cavity, oropharynx, larynx, or hypopharynx. Two hundred and forty patients will be randomized to receive either cisplatin-based adjuvant CRT or cisplatin-based adjuvant CRT plus pembrolizumab 200 mg Q3W for 12 months (53).
NCT04671667 is a randomized phase II trial, which will enroll 282 patients with a locoregionally recurrent or second primary HNSCC (oral cavity, oropharynx, larynx, hypopharynx) in a previously radiated field (54). Patient must have undergone surgery with gross total resection and must have high risk disease defined as positive margins and/or extra nodal extension (ENE). Patients will receive IMRT or PBRT plus either six weekly cycles of cisplatin/carboplatin or 9 cycles of pembrolizumab Q6W (54).
GORTEC 2015-01 PembroRad is a phase II randomized trial, in patients with non operated stage III-IVa-b SCC of oral cavity, oropharynx, hypopharynx and larynx and unfit for receiving high dose of cisplatin. Patients received once-daily IMRT up to 69,96 Gy concomitant with cetuximab (Cetux-RT arm: 400 mg/m2 loading dose and 250 mg/m2 weekly) or pembrolizumab (Pembro-RT arm: 200 mg Q3W during RT) (55). Between May 2016 and October 2017, 131 patients were randomized. Acute toxicity was lower in the pembro-RT arm than cetux-RT arm (74% vs 92% patients with at least one grade ≥ 3 acute adverse events [p=0.006], mainly due to dermatitis in radiation field, mucositis and cutaneous rash. Locoregional control rate (LRC) at 15 months (primary endpoint) was not significantly different (OR=1.05; 95%CI: 0.43-2.59, p=0.91)(55).

Conclusions

The ICIs were first evaluated in patients with R/M HNSCC. Pembrolizumab either alone or in association with a platinum and 5-fluorouracil were compared to cetuximab plus a platinum and 5-fluorouracil in patients who received no prior treatment for R/M disease. Pembrolizumab alone improved OS in the CPS of 20 or more population and CPS of 1 or more population and was non-inferior in the total population. Pembrolizumab with chemotherapy improved OS in the total population, in the CPS of 20 or more population, and in the CPS of 1 or more population (5). In patients who progressed within 6 months after platinum-based chemotherapy, nivolumab prolonged OS when compared to SoC chemotherapy (6;10).
In the JAVELIN Head and Neck 100 study, the addition of avelumab to definitive CRT in patients with LA HNSCC failed to improve the outcome (17).
Neoadjuvant PD-1 blockade prior to surgery is feasible and safe and is associated with encouraging ORR.
Ongoing phase III trials evaluating the role of immunotherapy in HNSCC amenable to surgery include KEYNOTE-689, ADHERE and MK-3475-68 (36-38). KEYNOTE-689 is a randomized, open-label phase III trial in which patients with previously

untreated, resectable stage III/IVA HNSCC will be randomly assigned 1:1 to either neoadjuvant pembrolizumab followed by surgical resection followed by SoC plus adjuvant pembrolizumab or to immediate surgical resection followed by adjuvant SoC (36). ADHERE is a phase III randomized blind placebo-controlled study in patients with surgically treated SCC of the oral cavity (37). Patients will be randomized to receive either durvalumab or placebo (one dose) before CRT and for 6 months Q4W after CRT. MK-3475-689 is a phase III, randomized, open-label study designed to evaluate pembrolizumab as neoadjuvant therapy and in combination with SoC as adjuvant therapy for stage III-IVA resectable LA HNSCC (38).

Key points

- Pembrolizumab +/- chemotherapy improves the outcome in patients with previously untreated recurrent/metastatic (R/M) disease.
- Nivolumab is superior to chemotherapy after platinum failure.
- Neoadjuvant pre-surgical PD-1 blockade is feasible and safe and is associated with an encouraging overall response rate (ORR).
- Multiple trials are currently evaluating the role of immunotherapy in HNSCC amenable to surgery i.e. IMvoke010, KEYNOTE-689, ADHERE, MK-3475-689, NIVOPOSTOP, IMSTAR-HN.

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