Highlights in head and neck cancer

P. Specenier, MD, PhD
Department of Oncology, University Hospital Antwerp, Edegem, Belgium

The 2018 annual meeting of the European Society for Medical Oncology (ESMO) turned out to be a grand cru for head and neck cancer, with two abstracts in this disease entity presented during the presidential sessions of the meeting. These two presentations, one on the use of immune checkpoint inhibition in the frontline treatment of recurrent/metastatic (R/M) Squamous Cell Carcinoma of the Head and Neck (HNSCC) and one evaluating treatment de-escalation in low-risk, p16-positive oropharyngeal cancer, form the lion's share of this report. In addition to this data were presented of clinical trials looking at the potential of durvalumab plus danvatirsen, M7824, tipifarnib and SD-101 in the treatment of R/M SCCHN.

RECURRENT/METASTATIC SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK: PEMBROLIZUMAB ADVANCES INTO FIRST LINE.

In KEYNOTE-048, 882 patients with previously untreated R/M HNSCC were randomly assigned (1:1:1) to receive pembrolizumab 200 mg every 3 weeks (Q3w), or 3-weekly cisplatin 100 mg/m² or carboplatin, at an area under the curve (AUC) of 5 mg/ml x min, followed by 5-FU 1000 mg/m²/day as a continuous infusion for 4 days plus either pembrolizumab 200 mg, or cetuximab (400 mg/m² loading dose followed by weekly 250 mg/m²) (EXTREME).[1]

Primary endpoints included progression-free survival (PFS) and overall survival (OS) for pembrolizumab *vs.* EXTREME and pembrolizumab plus chemotherapy *vs.* EXTREME in patients with a PD-L1 combined positive score (CPS) ≥20, ≥1, and in the total populations. The minimum follow-up at the time of data cut-off date was approximately 17 months. Pembrolizumab monotherapy proved to be superior to EXTREME for OS in the CPS ≥ 20 population (N= 255; median 14.9 *vs* 10.7 months; HR[95%CI]: 0.61[0.45-0.83]; p= 0.0007) (*Figure 1*) and in the subgroup of patients with a CPS ≥1 (N= 512; median 12.3 *vs.* 10.3 months; HR[95%CI]: 0.78[0.64-0.96]; p= 0.0086). Unfortunately, the authors did not provide data on the population with a CPS between 1 and 20. Therefore, we cannot exclude that the benefit in the CPS ≥1 population can be mainly attributed to the patients with a CPS ≥20, which constitutes ~50 % of the CPS ≥1 population. The OS with pembrolizumab was not inferior to EXTREME in the total population (N= 601). Pembrolizumab did not prolong PFS in the CPS ≥20 population (median 3.4 months with pembrolizumab *vs.* 5.0 months with EXTREME; HR[95%CI]: 0.99[0.75-1.29]; p= 0.5). The PFS curves initially favoured EXTREME but crossed at approximately 7 months. In the CPS ≥ 20 population, the confirmed overall response rate (ORR) was 23% with pembrolizumab *vs.* 36 % with EXTREME. Overall response rates were 19 % *vs.* 35 % and 17 % *vs.* 36 % in the CPS ≥1 population and in the total population, respectively. The ORR for the population with a CPS between 1 and 20 is not provided but can be calculated by subtracting the patient numbers of the CPS ≥1 population from the number of patients with a CPS ≥20 (13.5% *vs.* 36.3 %). The median duration of response (DoR) was 20.9 months with pembrolizumab as compared to 4.2 months with EXTREME in the CPS ≥20 group (20.9 months *vs.* 4.5 months, and 20.9 months *vs.* 4.5 months, in CPS ≥ 1 patients and in the total population, respectively). The OS with pembrolizumab plus chemotherapy was non-

Please send all correspondence to: P. Specenier, MD, PhD, Department of Oncology, University Hospital Antwerp, Wilrijkstraat 10, B-2650 Edegem, Tel: +32 (0)3 821 33 85, E-mail: Pol.Specenier@uza.be.

Conflict of interest: The author has nothing to disclose and indicates no potential conflict of interest.

Key Words: head and neck, squamous cell, pembrolizumab, first-line, de-escalation, HPV, oropharyngeal, M7824, danvatirsen.

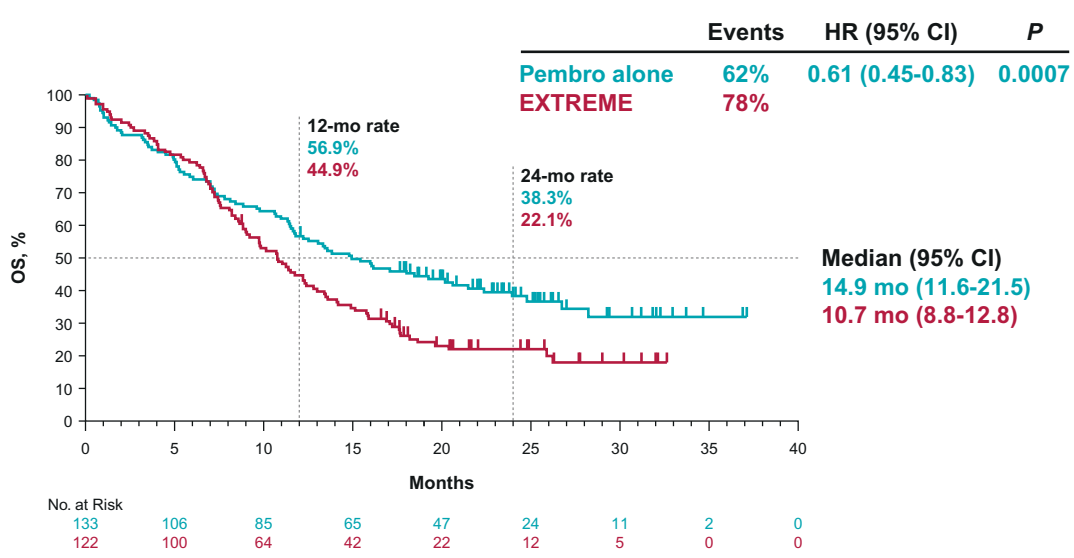

FIGURE 1. OS for pembrolizumab vs. EXTREME in patients with a CPS ≥20 in Keynote 048.[1]

inferior and superior to EXTREME in the total population (N = 559; median 13.0 *vs* 10.7 months; HR[95%CI]: 0.77[0.63-0.93]; p = 0.0034). In contrast, the OS was not prolonged with pembrolizumab plus chemotherapy compared to EXTREME. The confirmed ORR was 36% in both arms, with a median DoR of 6.7 months with pembrolizumab plus chemotherapy and 4.3 months with EXTREME.[1]

Cohen *et al.* presented updated ORR and DoR data of the phase 1b/2 SCORES trial in which 44 PD-L1-naïve R/M HNSCC patients received durvalumab (anti-PD-L1) in association with danvatirsen (an oral antisense oligonucleotide inhibitor of STAT3). The ORR was 23% with a complete response (CR) in 7% of the patients and a partial response (PR) in 16%.[2] This response rate compares favourably with the ORR with either durvalumab or danvatirsen as single agents and further supports the investigation of this combination. The median DoR with this combination was 11.1 months, ranging from 3 to 22 months.[2]

M7824 is a first-in-class bi-functional fusion protein composed of an anti–PD-L1 monoclonal antibody combined with the extracellular domain of TGF-βRII (a TGF- "trap"). Cho *et al.* reported results with M7824 in 32 patients with R/M SCCHN who received at least 1 prior treatment and progressed within 6 months after their last platinum dose. The ORR reported in this trial was 15.6 % in the overall population. Interestingly, two additional patients responded after initial disease progression. When these patients are considered as responders, the ORR increases to 21.9%. Four out of 8 patients with HPV-positive tumours responded. The 12-month OS rate with M7824 was 51.2%.[3]

Tipifarnib is a potent and highly selective inhibitor of farnesyltransferase, a critical enzyme required for the proper function of HRAS, a proto-oncogene overexpressed and mutated in HNSCC. Encouraging activity of tipifarnib was observed in an ongoing phase 2 trial enrolling patients with *HRAS* mutant HNSCC.[4]

Study DV3-MEL-01 (SYNERGY-001) assesses safety and preliminary efficacy of SD-101, in combination with pembrolizumab in patients with recurrent or metastatic HNSCC.[5] SD-101 is a synthetic CpG-ODN agonist of TLR9 that stimulates dendritic cells to release IFN-α and mature into antigen presenting cells to activate T cell anti-tumour responses. In a phase 2 expansion cohort for anti-PD-1/PD-L1 treatment naïve R/M HNSCC patients, SD-101 was injected in a single tumour lesion (four weekly doses followed by seven 3-weekly doses) at 8 mg in combination with pembrolizumab 200 mg administered IV Q3W. The ORR in 26 patients enrolled to date is 30.4 % (all PR). Tumour shrinkage was observed both in injected and non-injected lesions.[5]

LOCO-REGIONALLY ADVANCED DISEASE: DE-ESCALATION FAILS IN HPV-POSITIVE OROPHARYNGEAL CANCER

Human papilloma virus (HPV)-associated oropharyngeal cancer carries a favourable prognosis when compared to HPV-negative tumours. Treatment de-intensification in these patients aims to spare toxicity while preserving efficacy. A strategy pursued in this context is the substitution of cisplatin by cetuximab in association with radiotherapy.

Mehanna *et al.* presented the results of De-ESCALaTE HPV,

KEY MESSAGES FOR CLINICAL PRACTICE

1. **Pembrolizumab advances into the first-line treatment of R/M SCCHN**
2. **Promising data were presented with durvalumab plus danvatirsen, M7824, tipifarnib and SD-101 in R/M SCCHN**
3. **Treatment de-escalation in HPV-positive oropharyngeal cancer should not be introduced in the absence of phase III data.**

in which 334 patients were randomised to receive irradiation (70 Gy in 35 fractions over 7 weeks) with either 3 cycles of cisplatin 100 mg/m² on days 1, 22, and 43, or weekly cetuximab. Eligible were patients with low-risk p16-positive oropharyngeal cancer (< 10 pack years), stage III or IV according to AJCC 7th edition (T3N0-T4N0 and T1N1-T4N3). The primary endpoint was overall acute and late CTCAEv4 grade 3-5 toxicity. The trial was designed to detect a >25 % reduction in overall toxicity with a 90 % power and a 2-sided 5% level of significance, allowing for a 10% dropout assuming an average of 2.5 events per patient. In total, 79% of the patients received 8 doses of cetuximab (median dose 2150 mg/m²) and 96 % received ≥70 Gy. Four percent of the patients received between 65 and 70 Gy and modifications of the radiotherapy was required in 8 %. Total cumulative dose of cisplatin was >200 mg/m² in 84 % of the patients with 38% receiving 3 doses and 51% receiving 2 doses.[6]

The rates of acute, late, and overall toxicities of grade 3-5 and any grade was similar between the two treatment arms. On average 4.81 grade 3-5 events occurred with cisplatin as compared to 4.82 with cetuximab (p= 0.98). OS was one of the secondary endpoints of this study. The 2-year OS rate was 97.5% with cisplatin as compared to 89.4% with cetuximab (HR[95%CI]: 4.99[1.7-14.67]; adjusted HR[95%CI]: 5.94[1.98-17.79]; p= 0.001). The 2-year relapse rate was 6.0 % and 16.1 %, respectively (HR[95%CI]: 3.39[1.61-7.19]; p= 0.0007).[6] There were more locoregional (3 % *vs.* 12 %; p = 0.003) and distant relapses (3 % *vs.* 9 %; p = 0.009).

The discussant (*A. Psyrri*) heavily criticised the study mainly for the choice of the primary endpoint and for statistical reasons. She pointed out that, although the trial failed to demonstrate a difference in severe adverse events rate, only 38% of the patients received the planned 3 cycles of cisplatin.

However, the outcome of De-ESCALaTE is supported by the more mature NRG-RTOG 1016, which was presented virtually simultaneously by Trotti *et al.* at the Annual Meeting of ASTRO and which failed to demonstrate non-inferiority of cetuximab *vs.* cisplatin. The primary endpoint in NRG-RTOG was OS. In total, 849 patients were randomised (1:1) to accelerated radiotherapy (70 Gy in 6 weeks, 6 fractions/week) with either 2 cycles of cisplatin 100 mg/m² every 3 weeks or weekly cetuximab. Eligibility criteria included diagnosis of p16-positive squamous cell carcinoma of the oropharynx and clinical stage T1-2, N2a-N3, or T3-4, any N, according to AJCC 7th edition. Patients were stratified by T-stage, N-stage, Zubrod performance status, and smoking history. At final analysis, non-inferiority would be concluded if the HR (cetuximab/cisplatin) for OS upper confidence bound was ≤1.45. The HR for OS was 1.45 (95%CI 1.03-2.05). Estimated 5-year OS rates were 84.6% (95%CI: 80.6-88.6) with cisplatin as compared to 77.9% (95%CI: 73.4-82.5) with cetuximab. The PFS was significantly worse with cetuximab compared to cisplatin (HR[95%CI]: 1.72[1.29-2.29]; one-sided log-rank p= 0.0001) with 5-year estimates of 78.4% (95%CI: 73.8-83.0) with cisplatin and 67.3% (95%CI: 62.4-72.2) with cetuximab. Estimated 5-year local-regional failure rates were 9.9% with cisplatin and 17.3% with cetuximab. Estimated 5-year distant metastases rates were 8.6% and 11.7% with cisplatin and cetuximab, respectively. Acute grade 3-4 adverse events occurred in 82% and 77 % of the patients with cisplatin and cetuximab, respectively. Fatal adverse events occurred in 0.8% and 1.3% of the patients, respectively.[7]

Both trials combined underscore that treatment de-escalation in HPV-positive oropharyngeal cancer should not be introduced in the absence of phase III data.

REFERENCES

1. B. Burtness, et al. KEYNOTE-048: Phase 3 study of first-line pembrolizumab (P) for recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC). Presented at ESMO 2018; Abstract LBA8_PR.

2. Cohen E, et al. A phase 1b/2 study (SCORES) of durvalumab (D) plus danvatirsen (DAN; AZD9150) or AZD5069 (CX2i) in advanced solid malignancies and recurrent/metastatic head and neck squamous cell carcinoma (RM-HNSCC): Updated results. Presented at ESMO 2018; Abstract 1044O.

3. Cho B, et al. M7824 (MSB0011359C), a bifunctional fusion protein targeting PD-L1 and TGF-_, in patients (pts) with advanced SCCHN: results from a phase

1 cohort. Presented at ESMO 2018; Abstract 1048O.

4. Ho L, et al. Preliminary results from a phase 2 trial of tipifarnib in Squamous Cell Carcinomas (SCCs) with HRAS mutations. Presented at ESMO 2018; Abstract 1046O.

5. Cohen E, et al. Phase 1b/2, open label, multicenter study of intratumoral SD-101 in combination with pembrolizumab in anti-PD-1 treatment naïve patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC). Presented at ESMO 2018; Abstract 1050PD.

6. Mehanna H, et al. Cetuximab versus cisplatin in patients with HPV-positive, low risk oropharyngeal cancer, receiving radical radiotherapy. Presented at ESMO 2018; Abstract LBA9_PR.

7. Trotti A, et al. NRG-RTOG 1016: Phase III Trial Comparing Radiation/Cetuximab to Radiation/Cisplatin in HPV-related Cancer of the Oropharynx. Presented at ASTRO 2018; Abstract LBA-4.