Highlights in head and neck cancer

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Immunotherapy in squamous cell carcinoma of the head and neck (HNSCC)

Anti-PD1 and anti-PD-L1 monoclonal antibodies produce durable responses in patients with platinum-refractory recurrent/metastatic (R/M) Squamous Cell Carcinoma of the Head and Neck (HNSCC). Nivolumab is the first agent demonstrating overall survival (OS) benefit in this patient population.

In CheckMate 141, 361 patients with R/M HNSCC, whose disease had progressed within 6 months after platinum-based chemotherapy, were randomized to receive nivolumab at a dose of 3 mg/kg every 2 weeks or investigator's choice chemotherapy (weekly methotrexate, docetaxel, or cetuximab).[1] After a median follow-up for survival of 5.1 months (range 0-16.8), the OS (primary endpoint) was significantly longer with nivolumab than with standard therapy (hazard ratio [HR] 0.70; 97.73% confidence interval [CI] 0.51-0.96; p = 0.01). The median OS was 7.5 months (95%CI 5.5-9.1) in the nivolumab group *vs.* 5.1 months (95% CI 4.0-6.0) in the group that received standard therapy. The estimated 1-year OS rates were 36.0% and 16.6%, respectively. In the analysis of OS in the pre-specified subgroup of patients with a PD-L1 expression level of ≥1%, the HR among patients treated with nivolumab versus standard therapy was 0.55 (95%CI 0.36-0.83), whereas in the subgroup of patients with a PD-L1 expression level of < 1%, the HR was 0.89 (95%CI 0.54-1.45; p= 0.17 for interaction). Similar results were observed at a cut-off of 5%, or 10%. The median progression-free survival (PFS) was 2.0 months (95%CI 1.9-2.1) with nivolumab *vs.* 2.3 months (95%CI 1.9-3.1) with standard therapy (HR[95%CI]: 0.89[0.70 -1.13]; p= 0.32).

The PFS rate at 6 months was 19.7% with nivolumab *vs.* 9.9% with standard therapy. The overall response rate (ORR) was 13.3% in the nivolumab group *vs.* 5.8% in the standard-therapy group. Treatment-related adverse events of grade 3 or 4 occurred in 13.1% of the patients in the nivolumab group versus 35.1% of those in the standard-therapy group.

Harrington et al. presented the Patient Reported Outcome (PRO) data from the CheckMate 141 trial.[2] Patient-reported quality-of-life measures were similar at baseline among patients randomly assigned to the nivolumab group and those assigned to the standard-therapy group. Analyses were limited to data collected through week 15 as the number of responses to the questionnaires in the standard-therapy group were too low after that time point. Patients in the standard-therapy group reported clinically meaningful worsening of physical, role, and social functioning (as assessed by means of the QLQ-C30), as well as of pain, sensory problems, and social-contact problems (as assessed by means of the QLQ-H&N35). In contrast, among patients treated with nivolumab, these measures remained stable or showed slight improvements. Differences at 15 weeks were statistically significant and clinically meaningful for most comparisons.

In Keynote-055, patients with R/M HNSCC, resistant to platinum and cetuximab, receive pembrolizumab every 3 weeks.[3] The confirmed ORR was 15 % (95 % CI 10-21) with a median duration of response of 7 months (range 0-8+); the stable disease (SD) rate was 22% (95% CI 16-29). When unconfirmed and confirmed responses were evaluated, the ORR was 22% (95% CI 16-29) and the SD rate was 15% (95% CI 10-21).

As of April 29, 2016, 62 R/M HNSCC patients who had received a median of 3 prior systemic treatments have been included in an ongoing phase I/II, multicenter,

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Table 1. Tumor response to durvalumab in the study 1108, a dose escalation and dose expansion study in patients with R/M HNSCC.[4]

	All patients	PD-L1 high	PD-L1 low/negative	HPV+	HPV-
RECIST response (ORR), n/N (%) 95% CI	**7/62 (11) 4.7-21.9**	**4/22 (18) 5.2-40.3**	**3/37 (8) 1.7-21.9**	**1/25 (4) 0.1-20.4**	**4/25 (16) 4.5-36.1**
DCR 12 weeks, n/N (%) 95% CI	18/62 (29) 18.2-41.9	7/22 (32) 13.9-54.9	10/37 (27) 13.8 44.1	6/25 (24) 9.4-45.1	6/25 (24) 9.4-45.1
Range of ongoing DoR, weeks	59.1 +-85.1 +	85.1+	59.1 +-70.3+	59.1+	70.3+-85.1+
Ongoing responders, n/N (%)	3/7 (43)	1/4 (25)	2/3 (67)	1/1 (100)	2/4 (50)

open-label study of the human lgG1 PD-L1 blocking monoclonal antibody durvalumab (MEDI4736).[4] In this study, durvalumab was given every 2 weeks IV at 10 mg/kg for 12 months. Retreatment is permitted upon progression after 12 months. Median duration of follow-up was 25.0 months (range 1.4-31.6). The most frequent drug-related adverse events were fatigue (18%), diarrhea (8%), and nausea (8%). Eight percent of patients had grade ≥3 adverse events. There were no drug-related adverse events leading to death. Among seven responders (ORR 11 %), six patients had a duration of response of >12 months (reponse outcomes, summarized in *table-1*). Six- and 12-month OS rates were 62% (95% CI 48-74) and 42% (95% CI 27-55), respectively.[4] CheckMate-651 is an ongoing randomized, open-label, phase 3 study comparing the combination of nivolumab and ipilimumab with the EXTREME regimen as fist-line treatment in patients with R/M HNSCC.[5] CheckMate-714 is a double-blind, two-arm, phase 2 study of nivolumab in combination with ipilimumab *vs.* ipilimumab-placebo as first-line therapy in patients with R/M HNSCC.[6]

Cetuximab with chemotherapy or RT in R/M HNSCC

SOCCER is a prospective, non-interventional study evaluating symptom control in patients with R/M HNSCC treated with cetuximab in combination with either platinum-based chemotherapy or RT (RT). Response data from 103 patients were available for the interim analysis.[7] The ORR and disease control rate (DCR) were 70% in the RT group, 76% in the cisplatin group, and 71% in the carboplatin group, respectively. The median OS (8.8 months) and median PFS (5.0 months) reported here are comparabe to the results of the pivotal phase III, EXTREME Trial.

Cisplatin schedule

A study presented by *Lan et al.* compared the outcomes of 1,582 patients with stage II-IVb nasopharyngeal carcinoma treated with concomitant chemoradiation (CCRT) between January 2007 and December 2011 and identified 802 patients treated with triweekly cisplatin (80-100 mg/m^2 every three weeks, two to three cycles) and 780 patients treated with weekly cisplatin (30-40 mg/m^2/week, 5 cycles).[8] After a median follow-up of 64 months (range 4–194), the HR for distant metastasis risk was 0.70 (95%CI 0.49-0.99) for the triweekly group *vs.* the weekly group. Subgroup analyses revealed that, for patients treated with intensity-modulated RT (IMRT), triweekly cisplatin was associated with a better 5-year distant metastasis-free survival (DMFS) (92.6% *vs.* 85.8%, p< 0.001) and disease-free survival (DFS) (82.6% *vs.* 77.6%, p= 0.016). The 5-year DMFS rates were significantly better with triweekly cisplatin in patients with N3 (HR[95%CI]: 0.37[0.14-0.94]) and stage IV disease (HR[95%CI]: 0.52[0.29-0.93]). Grade 3-4 acute toxicities were similar in two groups.

The CONDOR study is a Dutch randomized phase II study, investigating the feasibility of docetaxel/cisplatin/5-fluorouracil (TPF) followed by conventional RT with cisplatin 100 mg/m^2 on days 1, 22, 43, or by accelerated RT with cisplatin weekly 40 mg/m^2 in patients with locally advanced (LA) HNSCC.[9] The conclusion of the trial was that neither regimen was feasible. *Driessen et al.* reported the effect of the two regimens on ototoxicity. Compliance to audiometry was low. Hearing deterioration over time was gradually for the weekly regimen and abrupt for the triweekly regimen. Patients treated with triweekly cisplatin suffered significantly more hearing loss at 8 kHz and 4 kHz.[10]

Biomarkers

Naghavi et al. identified a number of genes with alteration in expression, which may be associated with resistance to radiotherapy in HNSCC.[11] *Lourenço et al*. assessed whether single nucleotide polymorphisms (SNPs) of the mismatch repair (MMR) pathway, alters the outcome of in HNSCC patients treated with cisplatin and RT.[12] The risk of nephrotoxicity and ototoxicity was vastly increased in patients with the MSH3 c.3133GG genotype and GG or GA genotype. The EXO1 c.1765GA or AA genotype conferred an increased chance of achieving partial response (PR) or SD. Patients with the EXO1 c.2270CC genotype presented an increased risk of nephrotoxicity and the GT and AC haplotypes of EXO1 c.1765G > A and c.2270C >T SNPs were associated with an increased risk of ototoxicity, and a better chance of achieving PR or SD.

High levels of calreticulin were associated with a worse OS in a cohort of patients with Squamous Cell Carcinoma (SCC) of the Oral Cavity.[13] Preliminary evidence suggest that inherited abnormalities in FASL c.-844C > T and FAS c.-671A > G SNPs are determinants of overall HNSCC risk and risk of SCC of oral cavity, pharynx and larynx, particularly among smokers.[14]

Meta-analysis of chemotherapy

An update of the meta-analysis of chemotherapy in head and neck cancer (MACH-NC) involving 100 randomized trials and 19,248 patients confirms the superiority of CCRT over induction chemotherapy (IC) in LA-HNSCC.[15]

Fifteen new trials (2,574 patients) were included and updated data were obtained for 11 additional trials. Chemotherapy improved the OS with a HR of 0.89 (95% CI 0.86-0.92, $p < 0.0001$). There was a significant interaction between treatment effect and the timing of chemotherapy, the benefit being limited to CCRT ($p < 0.0001$), with a HR of 0.83 (95 % CI 0.79-0.87, $p < 0.0001$) translating into a 5- and 10-year absolute OS benefit of 6.5 % and 3.4%, respectively. In contrast, the addition of IC did not increase OS (HR 0.97 [95% CI 0.91-1.03]). An interaction test performed in recent concomitant trials revealed a trend towards decreased efficacy with increasing age (p for trend of 0.06; HR 1.00 [95 % 0.81-1.23] for age ≥ 70) or performance status (p for trend of 0.07, HR 0.93 [95 % 0.73-1.19] for PS ≥ 2. The analysis of 8 trials (1,214 patients) comparing IC + RT to CCRT confirmed the superiority of CCRT on OS (HR 0.84 [95 % CI 0.74-0.95], $p = 0.007$) and PFS (HR 0.85 [95 % CI 0.75- 0.96], $p = 0.008$).

Of note, in an analysis reported by *Rotolo et al*, PFS and DMFS are strongly associated with OS and can be considered valid surrogate endpoints for OS in LA nasopharyngeal carcinoma.

PET-CT

A prospective, randomized, controlled trial, *Mehana et al* assessed the non-inferiority of positron-emission tomography-computed tomography (PET-CT)-guided surveillance (performed 12 weeks after the end of chemoradiation, with neck dissection performed only if PET-CT showed an incomplete or equivocal response) to planned neck dissection in patients with stage N2 or N3 HNSCC. Survival was similar among patients who underwent PET-CT-guided surveillance and those who underwent planned neck dissection and surveillance resulted in considerably fewer operations and in short-term savings of £1,492 (approximately $2,190 in U.S. dollars) per person over the duration of the trial.[17] PET-CT surveillance results in a lifetime cost saving of £1,485 (95%CI 2,815-159) and health gain of 0.13 quality-adjusted life-years (QALYs) (95%CI -0.49-+0.79) per patient. The intervention therefore dominates standard care, being more effective and less costly.[18]

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