Highlights in head and neck cancer

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IMMUNOTHERAPY

In Keynote-040, 495 recurrent/metastatic (R/M) Head and Neck Squamous Cell Carcinoma (HNSCC) patients progressing after a platinum-containing regimen for R/M disease or recurring or progressing within 3-6 months after multimodal platinum-containing therapy for local disease, were randomised to receive pembrolizumab 200 mg every 3 weeks for up to 2 years or standard of care (SoC) i.e. methotrexate 40 mg/m² or cetuximab 400/250 mg/m² administered weekly, or docetaxel 75 mg/m² administered every 3 weeks. In the intent to treat (ITT) population, the median overall survival (OS) (primary endpoint) was 8.4 months (95%CI: 6.5-9.4) with pembrolizumab and 7.1 months (95%CI 5.9-8.1) with SoC, representing a hazard ratio (HR) of 0.81 (95%CI: 0.66-0.99; p= 0.0204). However, the pre-specified efficacy boundary for statistical significance was not met (one-sided α= 0.0175, HR ~0.80). In patients with a Programmed Death-Ligand 1 (PD-L1) protein tumour proportion score (percentage of tumour cells with membranous PD-L1; TPS) ≥50%, the median OS was 11.6 months (95%CI 8.3-19.5) with pembrolizumab *vs.* 7.9 months (95%CI 4.8-9.3) with SOC representing a HR of 0.54 (95%CI: 0.35-0.82; p= 0.0017). In the ITT population, the overall response rate (ORR) with pembrolizumab was 14.6 % *vs.* 10.1 % with SoC (p= 0.0610). In the PD-L1 TPS ≥50% population, the ORR was 26.6 % with pembrolizumab as compared to 9.2 % with SoC (p= 0.0009). There was no difference in progression-free survival (PFS) between treatment arms in the ITT population (median 2.1 months [95%CI 2.1-2.3] *vs.* 2.3 months [95%CI 2.1-2.8]; HR[95%CI]: 0.95[0.79-1.16]; p= 0.3037). However, in the PD-L1 TPS ≥50% population, the PFS was significantly longer with pembrolizumab (median 3.5 months [95%CI 2.1-6.3] *vs.* 2.2 months [95%CI 2.0-2.5]; HR[95%CI]: 0.58[0.39-0.87]; p= 0.0034).[1]

In another study, 112 immunotherapy–naïve R/M HNSCC patients with PD-L1 protein expression in ≥25 % of tumour cells and disease progression during or after one platinum-based regimen were treated with durvalumab 10 mg/kg IV every 2 weeks up to 12 months in a single-arm phase II trial. The ORR in evaluable patients was 13.5% (95%CI 7.8-21.3) overall and 26.5% (95%CI 12.9-44.4) and 7.9% (95%CI 2.6-17.6) for Human Papilloma Virus (HPV)-positive and HPV-negative patients, respectively. The median PFS was reported to be 2.3 months (95%CI 1.9-3.7). The incidence of grade ≥3 treatment-related adverse events (TRAE) was 9.8 %, but no 5 TRAEs were reported.[2]

Treatment responses to immune checkpoint inhibitors may occur after initial radiologic evidence of progression. In CheckMate 141, a randomised phase III study in patients with R/M SCCHN, nivolumab significantly prolonged the OS *vs.* single-agent investigator's choice (IC) chemotherapy (HR[97.73%CI]: 0.70[0.51-0.96]). Treatment beyond first progression was permitted in the nivolumab arm for patients who met protocol defined criteria. Of 240 patients randomised to nivolumab, 146 (61%) experienced progression of whom 62 (42 %) received ≥1 dose of nivolumab after progression. The median OS reached 12.7 months (95%CI 9.7-14.6) in the treatment beyond progression (TBP) group. After initial progression, 15 (24%) patients in the TBP group had a reduction in the target leasion size. Of note, certain immune cell profiles in the TBP group appeared to be similar to those of responders.[3]

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Estimates of median OS, 12-months, and 18-months OS rates in CheckMate-141 favoured nivolumab versus IC in complete response (CR), partial response (PR), and stable disease (SD) groups.[4]

Bahleda et al. reported the safety and efficacy data from 32 patients enrolled in a phase Ib trial with atezolizumab 15 or 20 mg/kg or 1200 mg fixed dose administered every 3 weeks. A confirmed ORR of 22% was reported with a median PFS of 2.6 months (range 0.5-48.4) and a median OS of 6.0 months (range 0.5-51.6). There was no association between HPV status and outcome. The ORR was 14% in patients with PD-L1 expression ≤5% on immunohistochemistry *vs.* 24 % in patients with PD-L1 >5%.[5]

BGB-A317 is a humanised IgG4 anti-PD-1 monoclonal antibody that blocks PD-L1/Program Death-Ligand 2 (PD-L2) binding to Programmed Cell Death Protein 1 (PD-1) restoring T-cell mediated tumour response. The Fc-hinge region has been engineered to preclude FccR1 mediated binding to macrophages/myeloid derived suppressor cells, a potential mechanism of PD-1 bound T-cell clearance. Eighteen patients with R/M HNSCC were enrolled in a phase I, open-label, multi-centre, dose-escalation/expansion study evaluating the safety, tolerability, and anti-tumour activity of BGB-A317 in patients with advanced solid tumours. Eleven unique grade ≥3 TRAEs were reported in 7 patients. A partial response has been confirmed in 1 patient, and 8 patients have SD, including 2 unconfirmed PRs. The DCR in this study, defined as the proportion of patients who have achieved CR, PR and SD was 50%.[6]

Conflicting data were presented on the prognostic role of PD-L1 expression in HNSCC. In a retrospective study, *Pai et al.* investigated tumour PD-L1 expression as a prognostic biomarker in 412 R/M HNSCC patients treated with SoC therapy between March 2011 and June 2015 at 19 institutions in 7 countries. In this analysis, tumour PD-L1 expression proved not to be associated with improved OS or PFS following 1st line SoC chemotherapy. However, there was a trend for an improved PFS after 2nd line SoC chemotherapy.[7]

In a retrospective analysis of 214 HNSCC patients treated between 1989 en 2015, PD-L1 high expression based on a tumour cell (TC) ≥1 % was associated with an improved OS.[8]

In another study PD-L1 expression in tumour and immune cells was also demonstrated to be a favourable prognostic factor in 60 Oral Cavity Squamous Cell Carcinomas (OCSCC).[9] In contrast, PD-L1 overexpression predicted a poor prognosis and a high risk of recurrence in tonsillar Squamous Cell Carcinoma (TSCC), particularly in HPV-positive tumours.[10]

Hyperprogression is a pattern of accelerated tumour growth with ECOG deterioration that has been described in patients with solid tumours within the first weeks of immunotherapy. In a cohort of 69 HNSCC patients treated with immunotherapy, *Ortego Franco et al.* did not detect hyperprogression defined by a twofold increase in tumour growth rate.[11]

CheckMate 358 is an ongoing phase I/II study in patients with virus-associated cancers. *Ferris et al.* reported safety and efficacy data on a cohort of 29 patients with previously untreated, resectable HPV-positive or HPV-negative HNSCC that were treated with nivolumab 240 mg on days 1 and 15 followed by surgery on day 29. Treatment-related AEs did not result in any protocol-defined surgery delay. As of database lock, presurgery tumour reduction per CT scan was observed in 11 of 23 (48%) evaluable patients (5/10 HPV-positive and 6/13 HPV-negative). In 3 patients, a tumour reduction of 40% or more was reported (largest reduction 75%).[12]

Multiple randomised phase III trials are assessing the efficacy and safety of immunotherapy agents in combination with concurrent chemoradiation (CCRT), bio radiation or induction chemotherapy for patients with locally advanced (LA) HNSCC. In a phase I trial, ipilimumab was safely combined with cetuximab and Intensity Modulated Radiotherapy (IMRT) in previously untreated LA-HNSCC. The recommended phase II dose for ipilimumab plus cetuximab and IMRT was set at 1 mg/kg at week 5, 8, 11, and 14.[13]

KEYNOTE-412 is a phase III, randomised, placebo-controlled, double blind trial enrolling subjects with newly diagnosed, treatment-naive, oropharyngeal p16 positive (any T4 or any N3), oropharyngeal p16 negative (any T3-T4, or N2a-N3), or larynx/hypopharynx/oral cavity (any T3-T4, any N2a-N3) Squamous Cell Carcinoma (SCC). Approximately 780 subjects will be randomly assigned (1:1) to receive pembrolizumab plus cisplatin-based CCRT or placebo plus cisplatin-based CCRT. Treatment with pembrolizumab 200 mg Q3W or placebo Q3W will continue up to 1 year (maximum 17 doses).[14]

Finally, MEDINDUCTION is a phase I trial evaluating the safety of durvalumab in combination with Docetaxel, Cisplatin and 5-FU (DCF) as induction chemotherapy for LA-HNSCC.[15]

CONCURRENT CHEMORADIATION

Chemoradiation, including three cycles of cisplatin 100 mg/m², is considered to be the SoC for patients with LA-HNSCC. However, a substantial fraction of patients is unable to tolerate this regimen. For these patients, carboplatin-5-fluorouracil (5-FU) can be used as an alternative. *Hanemaaijer et al.* retrospectively compared the tolerability and efficacy of CCRT with either cisplatin or carboplatin-5-FU in LA-HNSCC treated at

2 large Dutch cancer centres.[16] One centere routinely administered carboplatin 300-350 mg/m² at day 1, 22 and 43 followed by 5-FU 600 mg/m²/day for 96 hours. The other centre used cisplatin 100 mg/m² at day 1, 22 and 43. In the carboplatin-5FU cohort, 61.6% of patients completed chemotherapy (primary endpoint of the analysis) compared to 76.7% (p= 0.001) of the patients in the cisplatin cohort. Patients in the cisplatin cohort were more likely to have an unplanned admission (OR[95%CI]: 2.96[2.21-4.27]). The risk of death was higher in the carboplatin-5FU cohort (HR[95%CI]: 1.50[1.06-2.12], p=0.02) with a three-year OS of 64.6% compared to 76.6% in the cisplatin cohort.[16]

Bauml et al. compared the outcomes of patients treated weekly high- (HDC) and low-dose cisplatin (LDC) within the Veteran's Administration Corporate Data Warehouse (CDW). A total of 2,820 patients stage III-IVB HNSCC treated non-surgically from 2002 to 2014 with radiotherapy with LDC or HDC were identified of whom 69.7 % received HDC. The mean initial dose was 96 mg/m² and 30 mg/m² in the HDC and LDC group, respectively. Patients treated with HDC were significantly younger and had a significantly lower creatinine level and a lower incidence of baseline neuropathy. After adjustment for performance status (PS), the difference in OS between HDC and LDC was no longer statistically significant (p= 0.06) for the overall population. A subgroup analysis considering the primary site, showed that HDC provided a benefit only for oropharyngeal primaries (OP). When adjusting for PS, HDC was associated with more renal failure (OR[95%CI]: 2.2[1.6-3]), more neutropenia (OR[95%CI]: 2[1.1-3.5]), more dehydration/electrolyte disturbance (OR[95%CI]: 1.3[1.04-1.6]) and an increased rate of hearing loss (OR[95%-CI]: 1.6[1.3-2]).[17]

Rotschild et al. compared the cumulative dose that was reached and the associated toxicity of 3-weekly and weekly cisplatin regimens with concurrent radiotherapy in a multicentre, retrospective analysis of all patients with LA-SCCHN treated at 3 Swiss centres between 06/2008 and 12/2015. In total, 314 eligible patients were identified of whom 127 (40.4%) received 3-weekly cisplatin and 187 patients (59.6%) received weekly cisplatin. The median cumulative dose was 200 mg/m² (IQR 150-300) in patients who received 3-weekly cisplatin and 160 mg/m² (IQR 120-240) in patients who received weekly cisplatin. More patients treated with a 3-weekly schedule reached a cumulative dose >200 mg/m² (75.6% versus 47.1%, p< 0.001), even after adjustment for age and sex (OR[95%CI]: 3.46[2.1-5.7]). The 3-weekly regimen led to a higher rate of renal toxicity (33.1% *vs.* 20.9%; p= 0.022), while ototoxicity was similar between groups (15% *vs.* 12.8%). A landmark analysis could not confirm that a cisplatin dose >200mg/m² was associated with a better OS (HR[95%CI]: 1.3[0.8 -1.9]).[18]

SALIVARY GLAND TUMOURS

Salivary duct carcinoma (SDC) is a rare and aggressive subtype of salivary gland cancer (SGC). In a retrospective study, data from 18 patients with surgically resected, high-risk androgen receptor (AR)-positive, stage IVa/b SDC cancer who received adjuvant androgen deprivation therapy (ADT) at the Radboud UMC (Nijmegen, the Netherlands) or Istituto Nazionale dei Tumori (Milan, Italy) were collected and compared to a control group. This control group consisted of surgically resected patients diagnosed with stage IVa/b SDC between 1990 and 2014, who did not receive adjuvant ADT, collected by a search of the Dutch pathology database (PALGA). Although the number of treated patients in this analysis was low, ADT was not associated with an improved disease-free survival (DFS) or OS.[19]

Cellular MET (c-MET) was expressed in 54 of 136 SDCs collected by a retrospective search of PALGA. MET-overexpression is not a prognostic factor for OS. Membranous MET staining and HER2-positivity occurred more frequently in SDC ex pleomorphic adenoma than in the '*de novo*' SDC.[20]

Recently, a new subtype of SGC, mammary analogue secretory carcinoma (MASC), has been defined. It is characterized by the presence of the *ETV6-NTRK3* fusion gene. Previously, MASC was mixed up with acinic cell carcinoma (AciCC), polymorphous low grade adenocarcinoma and (cyst)adenocarcinoma. The clinical course of MASC seems to be favourable with a very low rate of recurrences and an excellent survival.[21]

Salivary Gland Cancers are rare and heterogeneous tumours (<1% of all malignancies in Europe) including more than 20 histotypes. Therefore, enrollment in clinical trials of patients with SGCs is highly recommended. EORTC HNCG/UKCRN 1206 is an ongoing randomised phase II study evaluating the efficacy and safety of chemotherapy versus ADT in patients with R/M AR-positive SGC.[22] NCT02867852 is a phase II trial evaluating the activity of abiraterone acetate in castration resistant AR-positive SGCs.[23] Finally, GORTEC 2016-02 is a multicentre, phase III randomised, open-label study evaluating the impact of the post-surgery addition after of cisplatin 100 mg/m² (every 3 weeks; 3 cycles) to radiotherapy in patients with salivary glands and nasal tumours who are at a high risk of locoregional relapse after surgery.[24]

FIRST LINE RECURRENT/METASTATIC SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK

In a phase IIB study, 200 R/M HNSCC patients were randomised to receive cisplatin and cetuximab with or without paclitaxel with maintenance cetuximab after 6 cycles. The inferiority hypothesis was rejected (upper limit of one-sided

90%CI of PFS HR < 1.4). The median PFS (primary endpoint) was 6 months (95%CI 5-7) with the 2-drug combination versus 7 months (95%CI 6-8) with the 3-drug combination as compared to (p not significant). The median OS was 13 months (95% 10-16) and 11 months (95% CI 9-14) with the 2 and 3 drug combination, respectively (p not significant). The ORR was 42% with the 2 drugs and 52% when using the 3-drug combination (p not significant). The rate of grade ≥3 AEs was 76% and 73% for the 2-drug versus the 3-drug regimen, respectively.[25]

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