



## Head and neck cancer revisited

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Head and neck cancer (HNC) is a heterogenous disease involving multiple anatomical subsites such as the oral cavity, pharynx, and larynx. While incidence rates have been increasing during the last few decades, HNC remains the seventh most common cancer resulting in approximately 325,000 annual deaths globally [1]. Well-recognized risk factors for the development of HNC include alcohol consumption, smoking tobacco products, betel nut chewing, human papilloma virus (HPV), and Epstein–Barr virus (EBV) infections.

As for head and neck squamous cell carcinoma (HNSCC), the prognosis both in the locally advanced (LA) setting and at the recurrent/metastatic stage (R/M) is poor, although HPV-positive oropharyngeal carcinoma patients have a more favorable prognosis compared to patients with HPV-negative cancer [2].

Approximately 50% of the patients with HPV-negative stage III/IV LA-HNSCC experience long-term survival after curative intent multimodality treatment due to high recurrence rates (approximately 40–50%) and a constant rate of 2–3% per year of second primaries [3, 4].

Since immunotherapy with immune checkpoint inhibitors (CPI) has revolutionized cancer treatment during the last couple of years, it was obvious to investigate CPI in combination with standard of care chemoradiation (CRT) to improve outcomes for LA-HNSCC patients. However, the enthusiasm for immunotherapy plus radiotherapy concepts has been dampened, since the primary endpoints of multiple phase III studies comparing CRT to CRT plus CPI were

not met [5–7]. Studies such as the Keynote 412 study demonstrated an event-free survival rate at 24 months for CRT plus pembrolizumab of 63.2 vs. 56.2% for CRT (hazard ratio 0.83; 95% confidence interval 0.68–1.03;  $p=0.0429$ ), although subgroup analysis suggested a benefit in the combined positive score (CPS)  $\geq 1$  and CPS  $\geq 20$  subgroups [7].

In their article, Resl et al. [8] provide an overview about the most relevant strategies to overcome treatment failure in LA-HNSCC and reduce therapy-related toxicity from a radiation oncologist's point of view. Novel treatment de-intensification (for patients with a low-risk profile) and intensification approaches for high-risk HPV-negative HNSCC are outlined.

For R/M HNSCC, the prognosis is even worse and palliative system therapy is the mainstay of treatment in this setting for the majority of patients, since only a minority of patients are candidates for local salvage surgery options or re-irradiation.

Prior to the approval of CPI for the treatment of R/M HNSCC, the standard of care therapy consisted of a platinum-based doublet chemotherapy in combination with the epidermal growth factor receptor antibody cetuximab (EXTREME regimen) [9]. Long-term survival, however, was rarely achieved for patients treated with EXTREME.

In their manuscript Kocher et al. [10] outline the current standard of care options and developments for the first-line therapy of R/M HNSCC. Most notably, the authors suggest a treatment algorithm in this setting, which could support the clinical decision-making based on the approval status of immunotherapy in Europe. In addition, the authors discuss potential novel approaches such as the incorporation of taxanes into immunotherapy regimens and the limitations/recent trial results of dual checkpoint blockade strategies.

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Finally, this article series covers the most recent treatment recommendations for nasopharyngeal carcinoma (NPC). While NPC is an orphan disease in Western Europe/USA, it is endemic to southern China, southeast Asia and northern Africa [11]. Since phase III trials in non-endemic regions are hardly feasible to conduct, relevant data gaps exist for this patient population. The article by Fuereder [12] addresses this issue and reviews clinically relevant challenges such as the optimal treatment strategy for stage II disease, non-Epstein–Barr virus-associated NPC or the role of immunotherapy.

Overall, this head and neck cancer special issue provides an update on the current developments in the field and addresses the most relevant unresolved questions. We want to thank the experts for their valuable contributions.

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