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# Immunotherapy for head and neck cancers: an update and future perspectives

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**“cancer therapy approaches are changing as immunotherapeutic agents make their way into curative treatment regimen and artificial intelligence is utilized in finding the optimal therapy for each individual patient.”**

For a long time, there have been no innovative therapies available for head and neck squamous cell carcinoma (HNSCC). This changed with the emerging immunotherapeutic approaches of PD-1 and PD-L1 blockade and the multitude of clinical trials, which are recruiting at the moment. The following article aims to give an overview about recent immunotherapeutic study results for the treatment of HNSCC and interesting running studies. Furthermore, the role of potential biomarkers is elucidated, and finally a look ahead into the future regarding machine learning is discussed.

## PD-1/PD-L1 axis

Based on the success of basic immunology and the increasing insights of tumor escape mechanisms during the past decade, new promising therapeutic agents were developed with the goal to restore immunity against cancer cells. These new therapeutics include checkpoint inhibitors, like blockers of the PD-1/PD-L1 interaction. At ESMO 2018, results of the Keynote-048 study were presented, showing a significant survival advantage for patients with recurrent and/or metastatic (R/M) HNSCC and a positive PD-L1 expression (combined positive score [CPS] score  $\geq 20$  and also  $\geq 1$ ) treated with pembrolizumab versus standard of care (SOC) first-line therapy (cisplatin, 5-FU and cetuximab = EXTREME). The CPS score is calculated by counting all PD-L1 positive cells (tumor and immune) in relation to living tumor cells multiplied by 100 (see ‘Biomarkers’ section below). Opposed to the lower overall response rate (ORR) of patients treated with pembrolizumab alone (23.3 vs 36.1% for EXTREME) stands the favorable safety profile compared with the EXTREME regimen. Only 16.7% of the patients experienced a grade 3–5 toxicity compared with 69% in the EXTREME arm. Therefore, the authors propose a pembrolizumab monotherapy as new first-line standard for R/M HNSCC with a CPS  $\geq 1$ . Patients with low or negative PD-L1 expression can be treated with a combination of cisplatin, 5-FU and pembrolizumab as even in this study group the overall survival was not diminished as compared with EXTREME at the same safety profile and ORR (35.6 vs 36.3%) [1]. When looking at the duration of response (DOR) another conclusion could be made. In the total population, DOR for pembrolizumab alone was 20.9%, for pembrolizumab and chemotherapy 6.7% and for EXTREME 4.3%. This shows that adding pembrolizumab to chemotherapy raises the DOR not as much as pembrolizumab alone. Additionally, the progression-free survival could not be significantly prolonged even in the CPS  $\geq 20$  cohort. Therefore, the real advantage of pembrolizumab may lie in the durable response and pembrolizumab alone could also be beneficial for PD-L1-negative patients.

The importance of these results also lies in the implementation of a possible biomarker for response prediction, which is desperately needed regarding the high costs of immunotherapeutic agents and the limited ORR [2,3].

Currently, most studies address possible combination therapies. To this end, immunotherapeutic agents, which are effective in palliative settings, are combined with SOC approaches or with other immunotherapeutic drugs.

One strategy persuaded within the SCORES study is the combination of durvalumab (anti-PD-L1) with so-called antisense oligonucleotides. In a previous Phase II study, an ORR of 9.2% (3.46–19.02%) for durvalumab monotherapy was observed with a limited toxicity profile in patients with PD-L1 low or negative R/M HNSCC [4]. To further increase the response rate, the combination of durvalumab and a STAT3 inhibitor and a CXCR2 inhibitor is being explored. These inhibitors are antisense oligonucleotids which are constructed to inhibit protein expression at the mRNA level. First results of the study show a promising ORR of 23% for the combination of durvalumab and danvatirsen (anti-Stat3) regardless of PD-L1 expression after first-line failure. Additionally, mechanistic observations of danvatirsen monotherapy revealed an increase of gene expression signatures associated with response to anti-PD-1 inhibitors and a decrease of immunosuppressive gene expression [5].

Another combination comprises pembrolizumab and the intratumoral injection of SD-101, a synthetic oligonucleotide, which has an agonistic effect on the Toll-like receptor 9 (TLR9) and so enhances antigen presentation by dendritic cells. In a Phase Ib/II study, 26 patients with R/M HNSCC were included. Patients with previous anti-PD-1/PD-L1 treatment were excluded. First results describe a good tolerability and an ORR of 30.4%, which is almost double when looking at the ORR of pembrolizumab monotherapy in a similar setting in Keynote-040 (14.6%) [6,7].

The next step, which is currently under investigation, integrates anti-PD-1 drugs in curative treatment plans. The first Phase III trial to mention is Keynote-412 (NCT03040999), which is approaching the final enrollment goal of 780 patients. It is a two-armed, randomized, triple-blind design with concomitant administration of pembrolizumab versus placebo in a primary chemoradiotherapy scheme for advanced head and neck carcinoma. The primary end point is event-free survival and stratification follows radiotherapy regimen, p16 status and disease stage [8]. A similar study (Javelin) is recruiting patients for investigating the anti-PD-L1 antibody avelumab (NCT02952586). Additionally, there is a multitude of investigator-initiated trials (IIT) evaluating all sorts of combinations with anti-PD-1/PD-L1 and SOC. In case of surgical treatment, checkpoint inhibitors are given in a neoadjuvant as well as an adjuvant setting. The IMSTAR HN trial (IIT, EudraCT 2016-004758-13) is currently recruiting patients with locally advanced HNSCC. The three-armed design allows for randomization in either neoadjuvant nivolumab, followed by surgery, adjuvant SOC and nivolumab or nivolumab and ipilimumab versus surgery and adjuvant SOC alone.

### Other immune checkpoint targets

Monalizumab is a blocking antibody for the checkpoint receptor NKG2A, which is expressed on natural killer cells and CD8<sup>+</sup> T cells and is responsible for inhibiting the function of these cells by binding to its ligand, HLA-E. On human tumors, HLA-E is strongly expressed on HNSCC, which represents a suitable target for this kind of immunotherapy. Moreover, a combination of monalizumab and other checkpoint inhibitors as well as cetuximab was seen to increase effectiveness of the treatment in preclinical models [9]. This led to a Phase II study for R/M HNSCC. Patients received 10 mg/kg monalizumab biweekly and cetuximab in standard dosing weekly. The ORR was 27.5% with a median overall survival of 10.3 months. One patient even had a complete response, whereas 25% had a partial response and 55% resulted in stable disease. The combination was well tolerated without any multiplication of cetuximab-related adverse events. Of special value is the pretreatment of the patients in this study, because almost half had received anti-PD-1 treatment beforehand [10].

OX-40 is a costimulatory receptor on B and T cells and its activation can lead to autoimmunity but also to a better immune response toward cancer cells [11]. However, there are only very few studies recruiting patients at the moment. In a neoadjuvant approach, before surgery, an anti-OX-40 antibody (MEDI6469) was tested in a Phase Ib study and first results were presented at ASCO 2018 [12]. Patients received the drug by infusion on day 1, days 3–4 and days 5–6 and underwent surgery either 2 days, 1 or 2 weeks after the last dose of anti-OX-40. The highest activation of T cells could be found after 2 weeks from the last dose. The administration was well tolerated with no grade 3 or 4 adverse events. No pathological response could be observed. Therefore, the same authors are recruiting for a similar study with another anti-OX-40 antibody (MEDI0562). In this study, all patients received surgery after 2 weeks from the last anti-OX-40 infusion but in two different administration plans (NCT03336606). Results are expected no earlier as 2022.

Another costimulatory receptor is CD137 or 4-1BB, which is mainly found on activated CD8<sup>+</sup> T cells. Despite its downregulation in HNSCC patients [13], synergistic effects of anti-CD137 antibody and cisplatin-based chemoradiotherapy in a HNSCC mouse model have been observed [14]. These data and promising results of a Phase I study with a combination of the 4-1BB agonist utomilumab and pembrolizumab with an ORR of 26.1%

including a partial response of a HNSCC patient lead to the design of a Phase II study for incurable HPV<sup>+</sup> oropharyngeal squamous cell carcinoma (NCT03258008) [15]. In this study, utomilumab is combined with a subcutaneous injection of ISA101b, an E6/E7 vaccine with promising results in a combination with nivolumab for HPV<sup>+</sup> cancers of all locations (ORR: 33%) [16].

## Biomarkers

The search for suitable biomarkers has been one of the central issues in the research community and a variety of approaches have been published. For anti-PD-1 and anti PD-L1 treatment, the analysis of PD-L1 expression is the only approach which has made it into the routine diagnostic. For pembrolizumab, the determination of PD-L1 expression is compulsory before clinical application. For the determination of PD-L1 expression, two algorithms have been suggested so far: the CPS calculates all PD-L1 positive cells relatively to living tumor cells. The tumor positive score is easier to assess and describes the percentage of all viable tumor cells with positive PD-L1 membrane staining. The CPS, however, is more precise as it includes patients with low PD-L1 expression on tumor cells but a relevant expression on antigen-presenting cells. PD-L1 expression on this immune cell subset was found to be the major predictor of anti-PD1/PD-L1 therapy in a mouse model and human study of ovarian cancer and melanoma [17]. However, the used antibodies are different to the ones used in the large clinical trials and a recent comparison of different PD-L1 antibodies and evaluation algorithms shows huge differences. Four, in clinical studies commonly used, immunohistochemistry antibodies were tested: VENTANA PD-L1 (SP263), VENTANA PD-L1 (SP142), PD-L1 IHC pharmDx 22C3 (Agilent) and PD-L1 IHC pharmDx 28-8 (Agilent). All stainings were evaluated using tumor cell, immune cell and CPS scoring methods. The authors found great differences in identifying PD-L1 positive patients when using other evaluation algorithms as the corresponding method for each assay and conclude that these assays should not be interchanged. Additionally, one should be careful in interpreting effectiveness measurements for one or the other anti-PD-1/PD-L1 treatment when patient groups are stratified by a specific PD-L1 assay and its corresponding scoring algorithm [18]. This might be very challenging for pathologists as they have to invest in a new staining system, if the antibody is restricted to a particular one, and learn to use the different algorithms depending on the suggested anti-PD1/PD-L1 drug for the patient. Therefore, harmonizing projects for PD-L1 testing are desirable.

In the future, the impact of machine learning or artificial intelligence will not be neglectable. There are already algorithms under development that help to immunoprofile tumors by analyzing known parameters, but also by discovering new prognostic and predictive parameters [19]. In this context, the project BD2Decide for a personalized head and neck cancer decision support has to be mentioned. The aim is to establish big data models in a joint venture of 12 European institutions [20]. These developments show that cancer therapy approaches are changing as immunotherapeutic agents make their way into curative treatment regimen and artificial intelligence is utilized in finding the optimal therapy for each individual patient.

## Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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## Conflict of interest

S Laban advisory board for Astra-Zeneca (AZ), Merck Sharp & Dohme (MSD); S Laban and PJ Schuler speaking fees from Bristol-Myers Squibb (BMS), Merck Serono, MSD; PJ Schuler advisory board for BMS; TK Hoffmann advisory board for BMS, MSD and Merck.

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