

Combining radiotherapy and immunotherapy in definitive treatment of head and neck squamous cell carcinoma: review of current clinical trials

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Background. Head and neck squamous cell carcinoma (HNSCC) presents as locally advanced disease in a majority of patients and is prone to relapse despite aggressive treatment. Since immune checkpoint inhibitors (ICI) have shown clinically significant efficacy in patients with recurrent/metastatic HNSCC (R/M HNSCC), a plethora of trials are investigating their role in earlier stages of disease. At the same time, preclinical data showed the synergistic role of concurrently administered radiotherapy and ICIs (immunoradiotherapy) and explained several mechanisms behind it. Therefore, this approach is prospectively tested in a neoadjuvant, definitive, or adjuvant setting in non-R/M HNSCC patients. Due to the intricate relationship between host, immunotherapy, chemotherapy, and radiotherapy, each of these approaches has its advantages and disadvantages. In this narrative review we present the biological background of immunoradiotherapy, as well as a rationale for, and possible flaws of, each treatment approach, and provide readers with a critical summary of completed and ongoing trials.

Conclusions. While immunotherapy with ICIs has already become a standard part of treatment in patients with R/M HNSCC, its efficacy in a non-R/M HNSCC setting is still the subject of extensive clinical testing. Irradiation can overcome some of the cancer's immune evasive manoeuvres and can lead to a synergistic effect with ICIs, with possible additional benefits of concurrent platinum-based chemotherapy. However, the efficacy of this combination is not robust and details in trial design and treatment delivery seem to be of unprecedented importance.

Key words: head and neck neoplasms; immunoradiotherapy; radiotherapy; immunotherapy

Introduction

Head and neck squamous cell carcinoma (HNSCC) accounts for more than 800,000 new cancer cases and over 400,000 deaths each year worldwide.¹ Despite aggressive therapeutic approaches the outcomes are still highly dependent on disease burden. Five-year disease control ranges from almost 100% in patients with T1a glottic carcinoma to below 30% in patients with locally-advanced hypopharyngeal cancer.^{2,3} More than 60% of all cases are locally-advanced at diagnosis with a 50% rate

of relapse in the first two years, despite the use of multimodal state-of-the-art treatment.⁴ Therefore, while treatment-related toxicity is now of primary concern in early stage HNSCC and low-risk human papilloma virus (HPV) mediated oropharyngeal carcinomas, with 3-year overall survival rates in excess of 90%^{5,6}, in other patients the focus of research is on treatment intensification and/or modification.

After intrinsic tumour suppressor mechanisms fail, further tumour progression is the result of an inefficient elimination phase or equilibrium phase

of the extrinsic tumour suppression by the immune system.⁷ Genetically unstable cancer cells under constant immune selection pressure evade immune recognition and destruction. Thus, they become invisible to immune cells by reducing the presentation of tumour antigens, decreasing their sensitivity to the cytotoxic effects of immune cells, and rendering their microenvironment immunosuppressive.⁷ In the fight against the latter, immune checkpoint inhibitors (ICI) targeting immune checkpoint programmed cell death protein 1 (anti-PD-1) are now considered standard care in recurrent and metastatic HNSCC (R/M HNSCC).^{8,9} Because of their proven efficacy and significantly improved toxicity profile as well as positive effect on quality of life as compared to standard chemotherapy regimens, an increasing number of trials are testing ICIs in the earlier stages of HNSCC.¹⁰⁻¹²

Besides a well-known immunosuppressive effect of radiotherapy (RT), it can also lead to positive alterations in innate and adaptive immunity.¹³ The same is true for the positive effects of the immune system on radiation efficacy, as a tumoricidal effect of RT is dependent on functional T cells, even at ablative doses.¹⁴ Furthermore, RT induces programmed death-ligand 1 (PD-L1) expression in dendritic cells (DCs) and cancer cells which contributes to acquired cancer radioresistance, which could be overcome by concurrent anti-PD-1/L1.¹⁵ These intricate interactions form the basis for combined treatment with RT and ICIs (immunoradiotherapy). This combination was shown to cause similar toxicity compared to either RT or ICI alone across different cancer types.¹⁶ Encouraging efficacy of this treatment combination has also been shown in early prospective trials in metastatic malignant melanoma and non-small cell lung cancer.¹⁷⁻²¹ The first results of trials using immunoradiotherapy in non-R/M HNSCC are now also available and many are underway. In this review we presented a biological rationale for the combination of RT and anti-PD-1/L1 and performed a systematic search for, and critical assessment of, completed and ongoing trials using a combination in non-R/M HNSCC.

Role of anti-PD-1 and radiotherapy in immune rejection of HNSCC

The efficacy of anti-PD1 therapy in HNSCC is poor with less than 20% of responding patients.^{8,22,23} These high rates of primary or acquired resistance

in R/M HNSCC to anti-PD1 agents are a result of absent antigenic proteins, defective antigen presentation, T cell exhaustion/absence, insensibility of tumours to T cells, presence of immunosuppressive cells, and/or presence of other inhibitory immune checkpoints.²⁴

For the immune system to exert its cytotoxic function, mutant peptides, also known as tumour neoantigens (TNA) or ectopically expressed antigens, must be presented to antigen-presenting cells by cancer cells on major histocompatibility complex I (MHC I).²⁵ Even though the tumour mutation burden in HNSCC is rather high with 5 mutations per million base pairs, a proper presentation is needed for them to elicit an immune response.^{26,27} A vital role of antigen processing machinery in this step is evident by the absence of CD8⁺ T cell recognition of HNSCC in the case of defective antigen processing machinery (defect present in 20–80% of HNSCCs).²⁸⁻³⁰ The next step is presentation of the TNA by MHC I. The complete loss of MHC I results in natural killer (NK) cells' activation, while aberrant expression is beneficial for cancer cells and is present in up to 60% of HNSCCs.³¹⁻³³ Up to 80% of HNSCC patients overexpress the epidermal growth factor receptor (EGFR), which also down-regulates MHC I.³⁴ Treatment with anti-PD-1 was shown to be less efficient in cancers with aberrant MHC I.^{35,36}

Yet tumour antigenicity is not enough to elicit immune response by itself. TNA presentation must be put in context by accompanying adjuvants in the form of danger-associated molecular patterns (DAMP) which are recognised by pattern recognition receptors on the cells of innate immunity. Different types of DAMPs are exposed by different modes of cell death and even by stressed cancer cells.³⁷ These include membrane-bound calreticulin, emitted ATP, and passively released nuclear high-mobility group box protein 1 (HMGB1). This leads to the recruitment and activation of dendritic (DCs) and other mononuclear cells.^{38,39} DCs cross-present antigens to naïve CD8⁺ T and by co-stimulatory signals (ligands and cytokines provided by DCs upon stimulation by DAMPs and type I interferons [IFNs]) prime these cytotoxic T lymphocytes in regional lymph nodes.⁴⁰ Type I IFN is produced by cancer cells as a result of a stimulator of interferon genes (STING) responding to DNA in the cytosol of cancer cell, which is a consequence of cancer's unstable genome.^{41,42}

To prevent unnecessary damage to surrounding tissue in their fight against viruses, CD8⁺ T lymphocytes also express inhibitory receptors, such

as PD-1, with its ligand PD-L1 on host tissue and immune cells.⁴³ The same PD-L1 expression is exploited by cancer cells to escape immune surveillance.⁴⁴ An active PD-1/PD-L1 pathway in tumour microenvironment (TME) also promotes T cell exhaustion and differentiation of regulatory T cells (Treg).⁴⁵ Primed tumour-infiltrating lymphocytes (TILs) that are suppressed due to PD-1/PD-L1 interaction are vital for anti-PD-1 efficacy, which also tips the balance from differentiation of exhausted T cells and Tregs towards generation of effector T cells.^{45,46}

Immunostimulatory effect of RT depends a great deal on inducing the above-described immunogenic cell death, with dose-dependent (from 2 to 20 Gy) increase in concentrations of DAMPs calreticulin, HMGB1, and ATP.⁴⁷ RT also produces free cytosolic DNA which is more pronounced in cancers with a loss of p53 function, as is the case in the majority of HNSCC.^{48,49} Cytosolic DNA is sensed by various pattern recognition receptors with STING being a central connecting protein. Activation of the cyclic GMP-AMP synthase-STING (cGAS-STING) pathway by free cytosolic DNA leads to type I IFN production in cancer and DCs.^{41,50} Regarding antigenicity, RT increases MHC I expression and diversifies the tumour-infiltrating T cell receptor repertoire which is a positive predictor of response to anti-PD-1/L1.⁵¹⁻⁵³ Previously silent mutated genes can be expressed by RT, thus leading to presentation of these TNAs by MHC I.^{54,55} RT also induces some constituents of antigen processing machinery by enhancing degradation of proteins into peptides.⁵¹ The positive effects of RT are also apparent in TME. By reducing tumour hypoxia and consequently reducing the expression of vascular endothelial growth factor, SBRT can inhibit mobilisation of myeloid-derived suppressor cells (MDSC).⁵⁶ Some authors also observed an enhanced recruitment of T cells into TME after RT.⁵⁷ RT-enhanced death receptor Fas expression further promotes the antitumour activity of recruited T cells.^{58,59} Furthermore, RT promotes the function and differentiation of cytotoxic T cells by inducing interleukin-1B, tumour necrosis factor- α , and interleukin-6.¹³ Considering vasculature, low dose RT increases the ratio of antitumoural macrophages type 1 and tumour-promoting macrophages type 2, which leads to vascular normalisation and T cell recruitment.⁶⁰ Besides, low dose RT also appears to decrease TME's immunosuppressive cells such as Tregs and MDSCs.⁶¹ Another beneficial vasculature-related effect of RT is induction of cell adhesion molecules, for example Intercellular Adhesion

Molecule 1 and E-selectin, that help leukocytes extravasate to TME.⁶²

Importantly, as a part of standard treatment in HNSCC, concurrent platinum-based chemoradiotherapy (CRT) was also shown to induce immunogenic cell death.⁴⁷ In the *in vitro* model, antigen presentation and T cell cytotoxicity were enhanced by moderate doses of cisplatin. In the *in vivo* mouse model synergism of cisplatin and anti-PD-1 was observed.⁶³ However, cisplatin also resulted in PD-L1 upregulation on cancer cells and higher doses were immunosuppressive. Nevertheless, Luo *et al.* showed on murine cancer models that cisplatin combined with anti-PD-1 treatment enhances RT-induced abscopal effect in non-irradiated nodes.⁶⁴

It should be noted that all the above-mentioned effects of RT were observed in preclinical studies and are not universally beneficial, as was shown in clinical setting. Release of DAMPs HMGB1 and ATP, which is degraded into extracellular adenosine, can have many immunosuppressive effects.⁶⁵⁻⁷⁰ Activation of cGAS-STING can lead to increased concentrations of MDSC in TME and even increase cancer aggressiveness.^{71,72} STING activation can also lead to depletion of tryptophan in TME via upregulation of Indoleamine 2,3-dioxygenase, resulting in reduced T cell cytotoxicity and increased tumour-associated macrophages and MDSCs.^{73,74} Even sustained type I IFN signalling is detrimental as it results in increased Treg and MDSC concentrations in TME and enhanced expression of PD-1.⁷⁵ Besides, RT increases tumour growth factor beta concentration which was shown to promote tumour-promoting macrophages type 2 differentiation and inhibit DCs and cytotoxic T cells.¹³ In addition, RT was shown to even upregulate hypoxia inducible factor-1 α , leading to eventual Treg and MDSC accumulation and DC and T cell inhibition via vascular endothelial growth factor.⁷⁶⁻⁸⁰

Methods

We searched PubMed and Clinicaltrials.gov databases with search terms ((immunoradiotherapy OR radioimmunotherapy) OR ((head and neck) OR (oral cavity) OR (oropharyngeal) OR (oropharynx) OR (larynx) OR (laryngeal) OR (hypopharynx) OR (hypopharyngeal)) AND (immunotherapy OR checkpoint OR pembrolizumab OR avelumab OR atezolizumab OR camrelizumab OR durvalumab OR nivolumab OR toripalimab OR PD-1 OR PD-L1 OR tremelimumab OR CTLA-4)

TABLE 1. Neoadjuvant immunoradiotherapy trials

| Trial, start year | Phase | N | Subsite and subtype | Basic scheme | Immunotherapy details | RT details | Main results |
|---|-------|-------------|---|--|---|---|---|
| NIRT-HNC, NCT03247712, ⁸⁹ 2018 | I | 10 | HPV+ resectable HNSCC stage I-III or CUP with clinical indications for adj. RT or TORS ineligible | NIVO+SBRT 5 weeks before surgery, followed by NIVO | 3x NIVO neoadj. and 3x adj. NIVO starting 4 weeks postop. | SBRT to GTV+3mm; 5pts: 5x8Gy daily (A), and 5 pts: 3x8Gy (B) every other day; delivered between 1st and 2nd NIVO cycle | no surgical delays; G3 postop. toxicity higher in cohort A; pCR: 100% in cohort A, and 80% in cohort B. |
| | II | 11, ongoing | cohort C: same as phase I, cohort D: stage III-IV HPV- resectable HNSCC | cohort C: SBRT alone 5 weeks before surgery, followed by NIVO, cohort D: same as phase I | cohort C: only adj. NIVO, same as in phase I cohort D: same as phase I | cohort C (6pts): SBRT 3 x 8 Gy cohort D (5 pts): SBRT 3 x 8 Gy | no G3-4 toxicity; major pathologic response in majority of pts |
| NCT03635164, ⁹¹ 2018 | I | 18 | HPV- resectable LAHNSCC | DURVA+SBRT 3-6 weeks before surgery, followed by DURVA | DURVA neoadj. with the first SBRT fraction and up to 6x DURVA postop. | SBRT to gross disease only, starting dose of 2x6Gy (planned increase to 3x6Gy, cohort size of 3 patients) every other day, starting concurrently with DURVA | NA |
| NCT03618134, ⁹² 2018 | I/II | 82 | TORS eligible HPV+ oropharyngeal HNSCC | DURVA+SBRT+/- tremelimumab 5-7 weeks before TORS, followed by DURVA | DURVA+/- tremelimumab neoadj. with the first SBRT fraction and on day 27, followed by up to 4x adj. DURVA | SBRT in 5fx, starting concurrently with DURVA+/- tremelimumab | NA |

adj. = adjuvant; CUP = cancer of unknown primary; DURVA = durvalumab; fx = fraction; GTV = gross tumour volume; G3 = grade 3; HNSCC = head and neck squamous cell carcinoma; HPV- = human papilloma virus negative cancer; HPV+ = human papilloma virus associated cancer; LAHNSCC = locally advanced HNSCC; N = planned number of enrolled patients, NA = not available; neoadj. = neoadjuvantly, NIVO = nivolumab; pCR = pathological complete response; postop. = postoperatively; pts = patients; RT = radiotherapy, SBRT = stereotactic body RT; TORS = transoral robotic surgery

AND (radiotherapy OR SBRT OR RT OR SABR OR irradiation) and with the start date of the studies from 15th July 2013 to 15th July 2020. In total, 39 completed or ongoing trials were found, using concurrent (chemo)radiotherapy and ICIs in primary definitive treatment of non-R/M HNSCC (non-nasopharyngeal).

Trials using anti-PD-1/L1 and radiotherapy combination in HNSCC: different approaches

In completed and ongoing trials, concurrent anti-PD-1/L1 and RT was delivered either before or after surgery, or as a sole definitive treatment. Few delivered anti-PD-1/L1 also as an extended consolidative treatment. Taking the intricate relationship between the immune system and therapy into account, attention to the below-described caveats should help shed light on the pros and cons of these research approaches.

Neoadjuvant immunoradiotherapy

Except for the earliest stages of HNSCC, elective neck treatment either by lymphadenectomy or irradiation is part of the standard treatment.⁸¹ Lymph nodes are also one of the places where DCs cross-prime CD8⁺ T lymphocytes.⁸² Even though the immediate treatment effect of concurrent anti-PD-1 and RT depends primarily on TILs already present in the primary tumour, T cells from lymph nodes are responsible for long-lasting tumour control.^{83,84} Preclinical studies in murine cancer models clearly showed the vital role of functioning draining lymph nodes for RT efficacy with or without concurrent ICI.^{85,86} Removal of draining lymph nodes or elective nodal irradiation led to reduced tumour-specific TILs.^{85,86} Furthermore, clinical data show reduced efficacy of anti-PD-1 in previously treated patients with HNSCC.⁸⁷ This speaks strongly in favour of using an immunoradiotherapy combination before surgery as compared to its postoperative application.

Neoadjuvant RT is not considered a standard of care in HNSCC, therefore these “window of opportunity trials” serve mostly to advance our understanding of the underlying mechanisms and to lay the ground for further studies.⁸⁸ Special attention must be therefore given to patient safety. In the, so far only, immunoradiotherapy “window of opportunity” trial that reported results, no surgical delays were noted.⁸⁹ The possibility of anti-PD-1 induced hyperprogression must nevertheless be kept in mind as it was reported in up to 29% of patients with R/M HNSCC.⁹⁰

The ongoing trials are presented in detail in Table 1. Leidner *et al.* completed phase I of their phase I/II trial and already provided intriguing results.⁸⁹ In the first phase, 10 patients with stage I-III HPV associated HNSCC or cancer of unknown primary with clinical indications for adjuvant RT or who were ineligible for transoral robotic surgery were accrued. Two cohorts were formed of which five patients received neoadjuvant SBRT with 5x8 Gy (A cohort), and another five patients had SBRT with 3x8 Gy (B cohort), both with concurrent nivolumab. No grade 4 toxicity was observed, with somewhat higher grade 3 toxicity in the A cohort. Notably, grade 2 renal insufficiency was observed in 50% of patients. Both fractionation regimens were shown to be effective with 100% and 80% complete pathological responses in the A and B cohort, respectively. However, on presurgical imaging evaluated by RECIST criteria, no complete responses were found. Recently, preliminary results of their phase II cohort expansion were also presented.⁹¹ Only the SBRT fractionation of the B cohort was further pursued. In cohort C inclusion criteria were the same as in cohorts A and B, while these six patients were treated with only neoadjuvant SBRT, followed by surgery and adjuvant nivolumab. Cohort D included only patients with HPV-negative HNSCC, and these five patients were treated the same as those in cohort B (SBRT with 3x8 Gy concurrently with nivolumab). Results were so far only vaguely described: there was no limiting toxicity, but the complete pathological response rate was somewhat lower than in cohorts A and B. In-detail results are awaited.

The approach to treatment was similar in HPV-negative HNSCC patients in the NCT03635164 trial, with the difference that anti-PD-L1 agent durvalumab was used instead of nivolumab.⁹¹ The third ongoing trial (NCT03618134) with a similar approach is testing whether the addition of tremelimumab, an anti-cytotoxic T-lymphocyte-associated protein 4 (anti-CTLA-4), to durvalumab

can improve the outcome in HPV-positive HNSCC patients.⁹² These two ICIs provide complementary effects, albeit at the expense of increased toxicity.^{93,94}

Definitive immunoradiotherapy

Considering only non-cancer/TME-related factors, synergism between anti-PD-1 and RT is probably most pronounced when these two treatment modalities are delivered concurrently in previously untreated patients with intact draining lymph nodes and no lymphopenia.^{85-87,95-98} Definitive immunoradiotherapy as a sole treatment fulfils these criteria, except for nodal irradiation. If, in a neoadjuvant setting, elective nodal irradiation is not mandatory, its omission would be ill-advised in a definitive (chemo)radiotherapy setting based on our current knowledge.⁸¹ However, advancement in diagnostic imaging and treatment (e.g. sentinel lymph node biopsy) provides the basis for ongoing trials testing reduced dose and/or volume of elective nodal irradiation which would be welcomed in immunoradiotherapy as well.⁹⁹

Preclinical studies also provide rather strong support for greater efficacy of hypofractionated RT compared to conventionally fractionated RT.^{56,100,101} In contrast to all the above-listed trials with immunotherapy in the neoadjuvant setting, however, the definitive setting immunoradiotherapy trials mostly utilise conventionally fractionated RT courses as compared to hypofractionated SBRT. This could be an important outcome-defining factor.

Concurrent chemoradiotherapy with cisplatin causes severe radiomucositis (grade 3–4) in around 40% of HNSCC patients.^{102,103} Even though anti-PD-1/L1 induced oral mucositis or stomatitis occurs in less than 3% of patients and is usually mild, it can nevertheless occasionally be severe.¹⁰⁴ Special attention should be paid to this when using an approach with combined CRT and anti-PD-1/L1, despite the fact that pertinent trials have so far not reported exacerbated toxicity in oral mucosa (see below). Another important aspect of concurrent CRT and immunotherapy is the effect of chemotherapy on immunotherapy's efficacy which seems to be beneficial in low doses, whereas high-dose chemotherapy is known to cause myelosuppression and could be detrimental to the efficacy of immunotherapy.^{63,64} Several trials use ICI combined with cetuximab, an anti-EGFR agent. Cetuximab is a mouse/human chimeric monoclonal IgG1 antibody.¹⁰⁵ Besides acting through targeting EGFR and dysregulating its signaling pathway, it also stimulates NK cells anti-

tumour activity, activates DCs, and recruits cytotoxic CD8⁺ T cells.¹⁰⁵ Cetuximab's ability to prime adaptive and innate immunity is met with regulatory immunosuppressive mechanisms. Targeting these immunosuppressive mechanisms (induction of Tregs, MDSC, PD-1, PD-L1, CTLA-4) by immunotherapy such as ICI has great potential and is still being tested in several trials.¹⁰⁶ A prospective trial using anti-PD-1 combined with cetuximab in 33 patients with platinum-refractory/ineligible R/M HNSCC showed a 41% response rate. About a third of patients experienced treatment-related grade 3 toxicity.¹⁰⁷ Furthermore, retrospectively gathered data on a triple combination of cetuximab, chemotherapy and anti-PD-1 used in 15 patients with R/M HNSCC was presented in 2018 by Lin *et al.*¹⁰⁸ The combination seemed effective with 58% partial responses and acceptable toxicity.

Completed and ongoing trials treating patients with non-R/M HNSCC with a definitive immunoradiotherapy combination are presented in Table 2, while important details are presented below.

JAVELIN Head and Neck 100 (NCT02952586) is the first randomised phase III trial combining CRT with concomitant ICI in patients with LAHNSCC to be terminated due to inefficiency.¹⁰⁹ Concurrent administration of a PD-L1 inhibitor avelumab and standard CRT (70 Gy and high-dose cisplatin) followed by maintenance avelumab for 12 months was compared to a placebo arm receiving the same CRT but with placebo instead of avelumab in 697 high-risk LAHNSCC patients.¹¹⁰ A pre-planned interim analysis showed that this combination is unlikely to show a significant improvement in progression-free survival and the trial was therefore terminated. Detailed study findings are awaited.

In a GORTEC 2017-01 REACH trial (NCT02999087), two standard arms (CRT with a three-weekly high-dose cisplatin in a cohort of patients fit for high-dose cisplatin, and RT with concurrent cetuximab in a cohort of patients unfit for high-dose cisplatin) were compared to experimental arms with the same RT regimen and concurrent avelumab and cetuximab (preliminary results, Table 2).^{111,112} All patients completed RT except for one cisplatin-ineligible patient receiving RT concurrently with avelumab and cetuximab. 88% and 76% of patients received all planned doses of avelumab and cetuximab, respectively. A grade ≥ 4 adverse effect occurred in 5/41 (12%) patients in experimental arms (all in the cohort of patients ineligible for high-dose cisplatin), and in 5/41 (12%) patients in standard arms (14% in high-dose cisplatin eligible and 10% in high-dose cisplatin ineli-

gible patients) where one grade 5 toxicity was also observed. The trial continues.

In 2019, results of the lead-in phase of randomised phase II/III trial NRG-HN004 (NCT03258554) were presented. Ten out of a planned 523 cisplatin-ineligible patients received durvalumab concomitantly with RT and all completed RT as planned, while 8/10 patients received all the planned durvalumab cycles. Randomisation will continue to either RT with durvalumab or RT with cetuximab.¹¹³

The GORTEC 2015-01 PembroRad randomised phase II trial's safety-related results were presented in 2018.¹¹⁴ In 133 cisplatin ineligible patients with LAHNSCC cetuximab or pembrolizumab were added to conventional RT, which resulted in a similar completion rate of RT (86 vs. 88%) and dysphagia (34 vs. 39%). However, mucositis was more prevalent in the cetuximab arm and the same goes for dermatitis (49 vs. 17%) (Table 2). Final results are still awaited.

The results of the first 16 randomised patients of the planned 120 patients with HPV- LAHNSCC in a DURTRE-RAD trial (NCT03624231) were recently presented.¹¹⁵ Among the first six patients treated with a combination of RT, durvalumab and tremelimumab (arm A), five patients (83%) stopped treatment due to immune-related adverse effects (irAE), of which one was grade 5. This arm was terminated due to excessive toxicity. Arm B with only durvalumab added to RT, which resulted in only 1/10 patients stopping treatment due to irAE, is continuing to enrol.

Weiss *et al.* (NCT02609503) presented the results of their phase II trial after a median follow-up of 21 months.¹¹⁶ In 29 cisplatin ineligible patients with LAHNSCC pembrolizumab was given concurrently with definitive RT and for an additional three adjuvant cycles (Table 2). The estimated two-year overall and progression-free survival was 75% and 71% respectively. RT was delivered in full in 28/29 patients, and 25/29 patients received all pembrolizumab doses. Toxicities were mild with a major exception being grade 3–4 lymphopenia, which occurred in 59% of patients, however, absolute lymphopenia did not predict for progression. Further characterisation of this unexpected lymphopenia showed declines in blood concentrations of B cells and CD4⁺ T cells, whereas CD8⁺ T cells were relatively preserved.¹¹⁶

Powel *et al.* presented results from their phase I trial (NCT02586207), testing pembrolizumab with chemoradiotherapy in 59 patients with LAHNSCC.¹¹⁷ Pembrolizumab was discontinued due to irAE in 9% during CRT and for non-irAE

TABLE 2. Definitive immunoradiotherapy trials

| Trial, start year | Phase | N | Subsite and subtype | Basic scheme | Immunotherapy details | RT details | Main results |
|---|------------|------|---|--|--|---|--|
| NCT02586207, ¹¹⁷ 2015 | I | 59 | LAHNSCC eligible for CRT (34 pts HPV + and 23 pts HPV-) | PEMBRO + CRT, followed by PEMBRO | PEMBRO on days -7 (before CRT), 15 and 36 (conc. with CRT), and adj. for 5 cycles | starting on day 1: CRT with IMRT 70 Gy (2Gy/tx) and LD-CDDP for 6 cycles | HPV + : 85% CR 12 weeks after CRT; HPV-: 78% CR 12 weeks after CRT; HPV + : 2-year OS 97% and PFS 93%; HPV-: 1-year OS 87% and PFS 73% |
| GORTEC 2015-01 "PembroRad" (NCT02707588), ¹¹⁴ 2016 | II, rand. | 133 | LAHNSCC ineligible for CDDP | arm A: CETUX + RT; arm B: PEMBRO + RT | arm A: CETUX during RT; arm B: PEMBRO during RT | IMRT (69.99Gy/33fx) | arm A: 94% grade 3 toxicity, 57% grade 3 mucositis, 86% received full RT; arm B: 78% grade 3 toxicity, 24% grade 3 mucositis, 88% received full RT |
| KEYNOTE-412 (NCT03040999), ¹²⁴ 2017 | III, rand. | 780 | LAHNSCC eligible for CRT | arm A: PEMBRO + CRT, followed by PEMBRO; arm B: placebo + CRT, followed by placebo | arm A: priming dose of PEMBRO followed by 2x PEMBRO + CRT, followed by 14x maint. PEMBRO; arm B: placebo instead of PEMBRO | CRT (70Gy/35fx) and HD-CDDP | NA |
| NCT02759575, ¹³¹ 2016 | I/II | 47 | LAHNSCC of larynx | PEMBRO + CRT | PEMBRO starting 3 weeks before CRT, maximum 4x | CRT (70Gy/35fx) and HD-CDDP | NA |
| NCT02609503, ¹¹⁶ 2016 | II | 29 | LAHNSCC ineligible for CDDP | PEMBRO + RT, followed by PEMBRO | PEMBRO conc. with RT and 3 adj. cycles | IMRT (70Gy/35fx) | 2-year OS 75% and PFS 71%; 59% grade 3-4 lymphopenia |
| NCT02777385, ¹³⁰ 2016 | II, rand. | 90 | LAHNSCC | arm A: PEMBRO + CRT; arm B: CRT followed by PEMBRO | arm A: 8x PEMBRO 1 week prior to RT; arm B: 8x PEMBRO beginning in week 10 | CRT with IMRT (70Gy/35fx) and LD-CDDP | NA |
| NCT03532737, ¹³² 2018 | II | 50 | LAHNSCC | PEMBRO + CRT or PEMBRO + CETUX + RT | PEMBRO starting 3 weeks before (C)RT and during CRT or during RT + CETUX | CRT with IMRT (66-70Gy/30-35fx) and HD-CDDP or conc. CETUX | NA |
| KEYCHAIN (NCT03383094), ¹³³ 2018 | II, rand. | 114 | HPV + LAHNSCC | arm A: PEMBRO + RT; arm B: CRT | arm A: conc. and adj. PEMBRO for 20 cycles; arm B: CDDP-based CRT | IMRT (70Gy/33-35fx) (arm A) and HD-CDDP in arm B | NA |
| PEACH (NCT02819752), ¹³⁴ 2017 | I | 36 | LAHNSCC | PEMBRO + CRT, followed by PEMBRO | pre-loading dose of PEMBRO (dose-escalation trial, 100-200mg) and conc. CRT and PEMBRO and 4x adj. PEMBRO | standard CRT | NA |
| NCT04369937, ¹²⁷ 2020 | II | 50 | IR HPV + HNSCC | HPV-16 vaccination (ISA101b) + PEMBRO + CRT | 3x ISA101b starting 1 week prior to PEMBRO and two weeks prior to CRT | CRT with IMRT (70Gy/35fx) and HD-CDDP | NA |
| RTOG 3504 (NCT02764593), ¹²⁰ 2016 | I | 40 | IR-HR LAHNSCC | conc. and adj. NIVO added to each of 4 (C)RT cohorts | conc. NIVO starting 2 weeks before (C)RT and adj. NIVO starting 3 months after CRT | all cohorts: IMRT (70Gy/35fx); cohort 1: CRT with LD-CDDP; cohort 2: CRT with HD-CDDP; cohort 3: RT + CETUX; cohort 4: RT | adj. NIVO infeasible after HD-CDDP or in CDDP-ineligible pts; low rates of NIVO DLT |
| NCT03349710, ¹²⁵ 2017 | III, rand. | 1046 | LAHNSCC | NIVO + RT vs. CETUX + RT vs. NIVO + CRT vs. CRT | Closed due to slow accrual | | |

| Trial, start year | Phase | N | Subsite and subtype | Basic scheme | Immunotherapy details | RT details | Main results |
|---|---------------|-----|---|---|--|--|---|
| NCT03162731, ¹²¹ 2017 | I | 24 | HR LAHNSCC | NIVO + ipilimumab + RT | 17x NIVO and 6x ipilimumab, both starting 2 weeks before RT | IMRT (70Gy/35fx) | first 12 pts: grade 3 in-RT-field toxicity in 50% of pts, 3 pts discontinued therapy >3 months post-RT, 1 grade 3 colitis, 1 grade 5 bleeding, irAE in 50% of pts |
| NCT03894891, ¹³⁵ 2019 | II | 70 | LAHNSCC of larynx and hypopharynx | induction docetaxel + CDDP + NIVO, followed by NIVO + RT | standard institutional dosing | standard institutional dosing | NA |
| NCT03829722, ¹³⁶ 2019 | II | 40 | HR HPV + OP cancer | NIVO + CRT, followed by adj. NIVO | 4x NIVO before and conc. with CRT, followed by 4x NIVO | CRT (70Gy/35fx) and carboplatin + paclitaxel combination once per week | NA (temporarily suspended due to COVID-19) |
| NRG-HN005 (NCT03952585), ¹²⁶ 2019 | II/III, rand. | 711 | early-stage HPV + OP cancer | arm A: NIVO + deescalated RT; arm B: CRT arm C: deescalated CRT | 6x NIVO, starting 1 week prior to RT | IMRT, CRT with HD-CDDP | NA |
| NCT03799445, ¹³⁷ 2019 | II | 180 | low-intermediate volume HPV + OP cancer | NIVO + ipilimumab + RT | NIVO on days 1, 15, 29, and ipilimumab on day 1; for 2 cycles | IMRT 50–66Gy starting on day 1 of 2. cycle of NIVO + ipilimumab | NA |
| GORTEC 2017-01 "REACH" (NCT02999087), ¹³⁸ 2017 | III, rand. | 688 | LAHNSCC | Cohort 1 (fit for CDDP): CRT with CDDP (arm 1A), RT + AVEL + CETUX (arm 1B); Cohort 2 (unfit for CDDP): RT + CETUX (arm 2A), RT + AVEL + CETUX (arm 2B) | AVEL and CETUX starting 1 week prior to RT, followed by AVEL maint. for 12 months | IMRT 69.96Gy with either HD-CDDP or CETUX | first 82 pts: thresholds of the safety monitoring rule not crossed; trial continues |
| JAVELIN HEAD AND NECK 100 (NCT02952586), ¹¹⁰ 2016 | III, rand. | 697 | LAHNSCC | arm A: AVEL + CRT; arm B: placebo + CRT | AVEL starting 1 week prior to CRT, followed by maint. AVEL for 12 months | CRT with IMRT (70Gy/35fx) and HD-CDDP | preplanned interim analysis: unlikely to show improvement, terminated |
| NCT02938273, ¹²² 2017 | I | 10 | LAHNSCC ineligible for CDDP | AVEL + CETUX + RT | AVEL starting 1 week prior to RT, followed by maint. AVEL for 4 months; CETUX conc. | VMAT (70Gy/35fx) | tumour recurrence in 50% after a median follow up of 12months; transient and manageable irAE |
| DUCRO-HN (NCT03051906), ¹³⁹ 2018 | I/II | 69 | LAHNSCC | DURVA + CETUX + RT | DURVA and CETUX, both conc. with RT, followed by adj. DURVA for 6 months | IMRT (69.9Gy/33fx) | NA |
| DURTRE-RAD (NCT03624231), ¹¹⁵ 2018 | II, rand. | 120 | HPV-LAHNSCC | arm A: DURVA + TREM + RT; arm B: DURVA + RT | DURVA started 2 weeks prior to RT and TREM started with RT, followed by DURVA for up to 9 cycles | RT (70Gy/35fx) | first 16 patients: in arm A 5/6 stopped treatment due to toxicity -> terminated; in arm B 1/10 patients stopped treatment |
| CheckRad-CD8 (NCT03426657), ¹²³ 2018 | II | 120 | LAHNSCC | induction DURVA + TREM + CDDP + docetaxel and in case of increased CD8 + TILs compared to pre-treatment Bx -> DURVA + TREM + RT | after induction: DURVA with RT and TREM with RT, followed by DURVA for up to 12 cycles | RT (70Gy/35fx) | first 10pts after induction (re-biopsies): pCR in 8/10pts, 2 grade 3 + toxicities |

| Trial, start year | Phase | N | Subsite and subtype | Basic scheme | Immunotherapy details | RT details | Main results |
|--|---------------|-----|--|--|---|--|---|
| NRG-HN004 (NCT03258554), ¹¹³ 2017 | II/III, rand. | 523 | LAHNSCC ineligible for CDDP | arm A: DURVA + RT; arm B: CETUX + RT | DURVA started 2 weeks prior to RT for 7 cycles; CETUX conc. | RT (70Gy/35fx) | lead-in trial, 10 pts: all received arm A treatment, all completed RT, 8/10 received all doses of DURVA |
| CITHARE (NCT03623646), ¹⁴⁰ 2019 | II, rand. | 66 | early-stage HPV + OP cancer | arm A: DURVA + RT; arm B: CRT | DURVA conc. with RT | RT 70Gy with CDDP in arm B | NA |
| REWRITE (NCT03726775), ¹²⁹ 2018 | II | 73 | HNSCC T1-2 or HNSCC T3-4 and not eligible for CRT/CETUX + RT | DURVA + RT, followed by additional 6 months of DURVA | DURVA conc. with RT, followed by 6 months of DURVA | RT to only primary tumour and immediately adjacent nodal level without extended neck irradiation | NA |
| NCT04405154, ¹⁴¹ 2020 | II | 32 | LAHNSCC | CRT + camrelizumab | camrelizumab conc. with CRT and after for total of 8 cycles | CRT with IMRT/VMAT (66–70Gy/33–35fx) and HD-CDDP | NA |

adj. = adjuvantly; AVEL = avelumab; CETUX = cetuximab; ; CDDP = cisplatin; conc. = concurrently; CR = complete response; CRT = chemoradiotherapy; DLT = dose-limiting toxicity; DURVA = durvalumab; , fx = fractions; HD-CDDP = high dose cisplatin 100 mg/m² every three weeks during RT; HR = high-risk; HPV+ = human papilloma virus associated cancer; HPV- = human papilloma virus negative cancer; IMRT = intensity modulated RT; IR = intermediate-risk; irAE = immune-related adverse effects; LAHNSCC = locally advanced head and neck squamous cell carcinoma; LD-CDDP = low dose cisplatin 40 mg/m² every week during RT; maint. = maintenance; N = planned enrolment; NA = not available; NIVO = nivolumab; OP = oropharyngeal; OS = overall survival; PEMBRO = pembrolizumab; PFS = progression-free survival; RT = radiotherapy, TILs = tumour infiltrating lymphocytes; TREM = tremelimumab; VMAT = volumetric modulated arc therapy

related causes in 12% after CRT. The goal cisplatin dose of 200 mg/m² or more was received by 88% of patients and 98% of patients received all 70 Gy of RT. 76% of patients received all eight planned pembrolizumab cycles. Grade 4 toxicities were solely hematologic and electrolyte abnormalities. Outcomes are described in Table 2.

In the RTOG 3504, a phase I trial enrolling 40 patients with intermediate risk (HPV-associated oropharyngeal HNSCC, T1-2N2b-N3/T3-4N0-3, >10 pack-years or T4N0-N3, T1-3N3 ≤10 pack-years) or high-risk LAHNSCC (oral cavity, laryngeal, hypopharyngeal, or HPV-negative oropharyngeal HNSCC, T1-2N2a-N3 or T3-4N0-3), nivolumab was added to each of four (C)RT cohorts in a concurrent and adjuvant setting.^{118–120} RT was delivered with either a weekly low-dose or three-weekly high-dose cisplatin, with cetuximab, or as monotherapy (Table 2). The addition of nivolumab concurrently to all four (C)RT regimens was found safe. Levels of dose-limiting toxicity were acceptable and after 17, 16, 10, and 6 months of median follow-up in each of the four RT cohorts there were 0/10 (RT plus weekly cisplatin), 1/9 (RT plus three-weekly cisplatin), 1/10 (RT plus cetuximab), and 3/10 (RT only) events (i.e. death or disease progression), respectively. However, adjuvant administration of nivolumab was infeasible after (C)RT in cisplatin-ineligible patients or in those who received high-dose three-weekly concurrent cisplatin.

Data from the first 12 patients (planning to enrol 24 patients) from the NCT03162731 phase I trial, adding nivolumab and ipilimumab to standard RT in high-risk LAHNSCC, were also presented.¹²¹ After a follow-up of 7.2–18.4 months, 10 of the 12 patients are alive with no evidence of disease. Major toxicities are presented in Table 2.

Elbers *et al.* recently reported results from their phase I trial (NCT02938273) in 10 cisplatin ineligible patients with LAHNSCC that received avelumab and cetuximab in conjunction with RT, followed by avelumab as a maintenance therapy for an additional four months (Table 2).¹²² After a median follow-up of 12 months disease recurred in 50% of the patients. The majority of adverse effects were related to RT and cetuximab; grade 3 irAE occurred in four patients and were successfully managed.

An innovative approach is used in the CheckRad-CD8 phase II trial (NCT03426657) in which 120 patients with LAHNSCC have a second biopsy after induction durvalumab, tremelimumab, cisplatin, and docetaxel therapy. In the case of increased CD8⁺ TILs compared to pre-treatment biopsy, patients receive concurrent durvalumab, tremelimumab, and RT. Non-responders continue with standard therapy outside of the trial. The interim analysis for the first 10 patients was presented in 2019. After induction therapy re-biopsies showed a complete pathological response in 8/10 patients with another two patients showing an in-

crease in CD8⁺ TILs. There were two cases of grade III-IV toxicity: hepatitis and infectious diarrhoea.¹²³ Further results are awaited.

There are an additional 16 ongoing trials employing a combination of RT and ICIs that have not presented their results yet. Two of these are randomized phase III studies. The first one, KEYNOTE-412, will hopefully provide robust data to clarify the role of anti-PD-1 agent pembrolizumab given concomitantly with CRT and as a maintenance therapy in patients with locally advanced HNSCC.¹²⁴ The interpretation of the results could be hindered by the inability to discern the distinct effects of the priming, concurrent, and maintenance applications of pembrolizumab. Notably, a similar international phase III trial has previously been terminated due to slow accrual, and another similar trial, JAVELIN Head and Neck 100, testing the addition of anti-PD-L1 agent to CRT in LAHNSCC was terminated due to inefficiency.^{109,125} An additional phase III trial, NRG-HN005, is a non-inferiority trial, testing treatment de-escalation in patients with early stage HPV-positive oropharyngeal carcinoma.¹²⁶ A reduced dose RT, concurrently with either cisplatin or nivolumab, will be compared to standard CRT with cisplatin. The results will add valuable information to expanding pool of knowledge from the de-escalation trials in patients with HPV-positive HNSCC.

A somewhat different approach will be examined in the NCT04369937.¹²⁷ HPV-16 E6/E7-specific therapeutic vaccination (ISA101b) will be administered to 50 patients with intermediate risk of HPV+ HNSCC one week prior to the start of pembrolizumab and two weeks prior to the start of CRT with cisplatin (Table 2). The combination of ISA101 and nivolumab was already examined in a single-arm phase II trial where 24 patients with incurable HPV-positive cancers (22 oropharyngeal and one cervical and one anal cancer) were enrolled. An overall response rate of 33% with a median duration of response of 10.3 months and a median overall survival of 17.5 months seemed promising.¹²⁸

REWRITE (NCT03726775), a phase II trial that started in 2018, follows the recommendations from preclinical studies about omitting extended elective nodal irradiation when combining RT with immunotherapy. In this trial, patients with early stage T1–2 HNSCC or those with T3–4 disease and who are ineligible for cisplatin or cetuximab concurrently with RT will simultaneously receive durvalumab and RT to the primary tumour and immediately adjacent lymph nodes only. This will be followed by six months of maintenance durvalumab.¹²⁹

NCT02777385 is a phase II trial, planning to randomise 90 patients with LAHNSCC to either concurrent CRT with cisplatin and pembrolizumab or to CRT followed by pembrolizumab (Table 2).¹³⁰ It will hopefully help to answer if concurrent application is better than sequential or vice versa.

Adjuvant (postoperative) immunoradiotherapy

Testing novel treatments in an adjuvant setting offers a unique opportunity to stratify operated patients by risk of recurrence based on a detailed histopathological report, and therefore to avoid overtreatment. However, one should be aware of the above-described disadvantages when using immunotherapy with or without concurrent radiotherapy in patients with resected draining lymph nodes or after intensive treatment.

Two trials testing the potentials of adjuvant immunoradiotherapy reported early results. Wise-Draper *et al.* presented results of the lead-in stage of their phase II trial (NCT02641093). One to three weeks before planned surgery, patients who were clinically at high risk (cT3/4 stage and/or ≥ 2 +LNs) had one priming application of pembrolizumab followed by risk adjusted administration of adjuvant pembrolizumab in combination with RT or CRT. The pathological response to priming application of pembrolizumab was seen in 47% and was correlated with increased TILs. Adjuvant combination treatment with pembrolizumab and RT/CRT has an acceptable safety profile (Table 3).¹⁴² The other trial is a phase I NRG-HN003 trial that was conducted with the aim of determining a schedule for a phase II study. The tested regimen consisted of pembrolizumab added to adjuvant RT in patients with previously resected HPV-negative HNSCC with microscopically positive margins or an extracapsular extension of nodal metastases.¹⁴³ Pembrolizumab administered every three weeks in a dose of 200 mg for eight doses, starting the week before adjuvant CRT, was declared as worth pursuing. irAE were rare and non-significant (Table 3).

Beside these, there are six more ongoing trials registered in the international databases delivering different concurrent immunoradiotherapy combinations in an adjuvant setting and three of them are randomised phase 3 trials. The experimental arm in KEYNOTE-689 (NCT03765918) is similar to the one in trial by Wise-Draper *et al.*, except that two cycles of neoadjuvant pembrolizumab will be administered and longer maintenance therapy with pembrolizumab is planned. This will be com-

TABLE 3. Trials utilizing adjuvant immunoradiotherapy

| Trial, start year | Phase | N | Subsite and subtype | Basic scheme | Immunotherapy details | RT details | Main results |
|--|------------|-----|---|--|--|--|---|
| NCT02641093, ¹⁴² 2016 | II | 80 | LAHNSCC | neoadj. PEMBRO followed by resection, followed by PEMBRO + (C)RT | PEMBRO 1 week prior to surgery and conc. with RT for total of 7 doses | IMRT (60–66Gy/30fx) + /- LD-CDDP (if ECE + /R1) | first 23 pts (lead-in phase): 47% pathological response, no DLT, 2 pts recurred |
| NRG-HN003 (NCT02775812), ¹⁴³ 2016 | I | 34 | resected R1/ECE + HPV- HNSCC | adj. PEMBRO + CRT | 3 different schedules aimed to determine phase II schedule | CRT with IMRT (60Gy/30fx) and LD-CDDP | No irAE unacceptably delayed RT, 50% got all 8 doses of PEMBRO |
| KEYNOTE-689 (NCT03765918), ^{144,145} 2018 | III, rand. | 600 | resected LAHNSCC | arm A: neoadj. PEMBRO followed by resection then PEMBRO + (C)RT; arm B: resection then (C)RT | arm A: 2x neoadj. PEMBRO and PEMBRO conc. with adj. (C) RT, followed by PEMBRO for up to 15 cycles | (C)RT 60–70Gy/30–35fx + /- HD-CDDP depending on risk factors | NA |
| GORTEC 2018-01 "NIVOPOSTOP" (NCT03576417), ¹⁴⁶ 2018 | III, rand. | 680 | resected R1/ECE + LAHNSCC | arm A: adj. NIVO + CRT; arm B: adj. CRT | NIVO starting 3 weeks before CRT for total of 4 doses | CRT with IMRT (66Gy/33fx) and HD-CDDP | NA |
| ADHERE (NCT03673735), ¹⁴⁷ 2019 | III, rand. | 650 | resected HR HPV- HNSCC | arm A: adj. DURVA + CRT; arm B: adj. CRT | 1 dose of DURVA 1 week prior to CRT and maint. DURVA for 6 doses | CRT 66Gy/33fx and HD-CDDP | NA |
| ADRISK (NCT03480672), ¹⁴⁹ 2018 | II, rand. | 240 | resected LAHNSCC with >1LN/ECE + /R1 | arm A: adj. PEMBRO + CRT; arm B: adj. CRT | PEMBRO conc. with RT and for up to 12 months | CRT with CDDP | NA |
| NCT03715946, ¹⁵⁰ 2018 | II | 135 | resected IR-HR HPV + oropharyngeal cancer | adj. NIVO + deescalated RT | NIVO conc. with RT and for additional 6 doses after RT | RT (45–50Gy/25fx) | NA |
| NCT03529422, ¹⁵¹ 2019 | II | 33 | resected IR HNSCC | adj. DURVA + RT | DURVA starting conc. with RT for total of 6 cycles | IMRT (60Gy/30fx) | NA |

adj. = adjuvant; CDDP = cisplatin; conc. = concurrent; CRT = chemoradiotherapy; DLT = dose-limiting toxicity; DURVA = durvalumab; ECE+ = extracapsular extension of metastasis in lymph node; fx = fractions; HD-CDDP = high dose cisplatin 100 mg/m² every three weeks during RT; HPV+ = human papilloma virus associated cancer; HPV- = human papilloma virus negative cancer; HR = high-risk; IMRT = intensity modulated RT; IR = intermediate-risk; irAE = immune-related adverse effects; LAHNSCC = locally advanced head and neck squamous cell carcinoma; LD-CDDP = low dose cisplatin 40 mg/m² every week during RT; N = planned enrolment; neoadj. = neoadjuvant; NIVO = nivolumab; PEMBRO = pembrolizumab; RT = radiotherapy; R1 = microscopically positive resection margin, LN = lymph node; NA = not available

pared to standard adjuvant CRT in LAHNSCC patients with either more than one pathological lymph node, microscopically positive margins or an extracapsular extension of nodal metastases.^{144,145} The two other randomised phase III trials, GORTEC 2018-01 (NCT03576417, also known as NIVOPOSTOP)¹⁴⁶ and ADHERE (NCT03673735)¹⁴⁷, will both enrol patients with resected high-risk HNSCC and randomise them to either adjuvant CRT with concurrent nivolumab (NIVOPOSTOP)/durvalumab (ADHERE), or to standard of care adjuvant CRT. These three phase III trials could set ground for the new era in the setting of adjuvant treatment of a high-risk HNSCC based on pathological data (microscopically positive margins or extracapsular extension of nodal metastases). Currently, with adjuvant CRT locoregional relapse rates as well as distant metastases rates at five years are around 20% in these patients.^{102,148} Based

on the preclinical data described above, it would be reasonable to expect a synergistic locoregional activity of radioimmunotherapy. A major drawback of adding immunotherapeutics to RT in postoperative setting could be the absence of regional lymph nodes that could hinder the efficacy of this combination. Nevertheless, ICIs will be delivered in doses that were shown to be effective systemically, therefore, it is justified to expect improved distant control of the disease.^{8,10}

The other three phase I and phase II trials are presented in Table 3.

Adjuvant/maintenance therapy with immune checkpoint inhibitor

In several of the above-described trials anti-PD-1/L1 therapy is also applied as a prolonged adjuvant or maintenance therapy. Support for this approach

comes from two other tumour types. In patients with unresectable locally-advanced non-squamous cell carcinoma lung cancer (NSCLC) without progression after definitive CRT, consolidation durvalumab was shown to prolong survival.¹⁵² Also, after a complete resection of stage III melanoma, adjuvant ipilimumab prolonged overall survival compared to placebo, while adjuvant nivolumab compared head-to-head to adjuvant ipilimumab showed better relapse-free survival and less toxicity. Long-term data of the latter study are not yet available.^{153,154} Besides differences in tumour-intrinsic factors and the composition of their TME, another important aspect to consider is the different recurrence pattern of these tumours. While melanoma and NSCLC are prone to dissemination, HNSCC tends to recur more often locoregionally in previously treated tissue. After resection alone, stage III melanoma spreads to distant sites in more than 60% of cases, and stage III NSCLC relapses distantly after CRT alone in up to 50% of cases.^{154,155} On the other hand, the risk of distant metastases is around 15% in HNSCC, whereas isolated locoregional relapses are much more common.^{4,156} Whether consolidation anti-PD-1/L1 agents can decrease rates of distant metastases as well as locoregional relapses in HNSCC is still to be determined.

Another important consideration in prolonged treatment with anti-PD-1/L1 agents is toxicity. Even though the overall effect on the quality of life with anti-PD-1 agents in R/M HNSCC was found to be positive and there were fewer adverse effects compared to standard chemotherapy, irAE nevertheless occurred in around 60% of patients with 17% of them experiencing a grade 3 or higher toxic event.^{22,157} Prolonged treatment with anti-PD-1/L1 agents should therefore be approached carefully and weighted against its toxicity. It should not be ignored that there is also financial toxicity associated with these treatments. It was estimated that in CheckMate 141 the incremental cost-effectiveness ratio per quality-adjusted life year for nivolumab was around 90,000 euros.¹⁵⁸ Even if the methods used in such calculations had some flaws, the financial burden of these new drugs is obvious and therefore special attention should already be paid in trial design.¹⁵⁸ Importantly, with the above-described trials it will be hard to discern the benefit of concurrent immunoradiotherapy from the benefit of maintenance immunotherapy as none of these trials compares this extended adjuvant treatment to a comparator arm without it. In either case, careful patient selection for immunotherapy, probably biomarker driven, will help to prevent unneces-

sary additional toxicity and the financial burden of this treatment. Potential biomarkers for immunotherapy in HNSCC have recently been extensively reviewed by Gavrielatou *et al.*¹⁵⁹

Conclusions

Researchers pursue different strategies in using a RT-ICI combination in a non-R/M HNSCC setting and the first results are already available. Window of opportunity trials are most welcomed since biological mechanisms behind the synergistic effect of combined immunoradiotherapy are not fully understood and reliable criteria for patient selection are lacking. The first results of these trials that use immunoradiotherapy neoadjuvantly are encouraging. In a definitive setting results are more varied. A large phase III trial employing concurrent and maintenance avelumab for 12 months post-chemoradiotherapy was terminated because of inefficacy. Prolonged RT courses with large treatment fields and high doses of concomitant chemotherapy agents could be detrimental to the success of immunotherapy. In an adjuvant setting it is hard to overlook factors such as a changed anatomy of lymphatics and a changed microenvironment of possible remaining cancer cells due to previous surgery, which could both adversely affect the effectiveness of immunoradiotherapy. Additionally, many of these trials administer anti-PD-1/L1 agents not only concurrently with RT but also as prolonged adjuvant treatment, without a comparator arm for proper evaluation of this approach. However, immunoradiotherapy is evolving rapidly in HNSCC and final results of the herein presented ongoing trials are eagerly awaited.

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