



Combinations of immunotherapy and radiation therapy in head and neck squamous cell carcinoma: a narrative review

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Abstract: Radiation therapy and systemic therapy are the primary non-surgical treatment modalities for head and neck squamous cell carcinoma (HNSCC). Despite advances in our biologic understanding of this disease and the development of novel therapeutics, treatment resistance remains a significant problem. It has become increasingly evident that the innate and adaptive immune systems play a significant role in the modulation of anti-tumor responses to traditional cancer-directed therapies. By inducing DNA damage and cell death, radiation therapy appears to activate both innate and adaptive immune responses. Immunotherapies targeting programmed cell death protein 1 (PD-1) and programmed cell death ligand 1 (PD-L1) also have yielded promising results, particularly in the recurrent/metastatic setting. In this review, we will discuss the rationale for combining radiotherapy with immunotherapy to harness the immunomodulatory effects of radiation therapy on HNSCC, as well as biomarkers for immune response. We will also review recent preclinical and clinical data exploring these combinations in various contexts, including recurrent/metastatic and locally advanced disease. Among those with locally advanced HNSCC, we will discuss clinical trials employing immunotherapy either concurrently with radiation therapy or as maintenance following chemoradiation in both the definitive and postoperative settings, with or without the use of cisplatin-based or non-cisplatin-based chemotherapy.

Keywords: Radiation therapy (RT); immunotherapy; synergy; head and neck cancer; squamous cell

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Introduction

Radiation therapy (RT) combined with systemic therapy is the primary non-surgical definitive treatment option for locally advanced head and neck squamous cell carcinoma (HNSCC), which causes over 400,000 deaths annually worldwide (1). Despite treatment intensification, local recurrence occurs in up to 50% of patients with locally advanced disease. This has led to a concerted effort to

understand and exploit interactions of oncogenic signaling pathways with RT (2). Specifically, the epidermal growth factor receptor (EGFR) pathway has garnered interest both pre-clinically and clinically in HNSCC, especially after an overall survival (OS), progression-free survival (PFS), and locoregional control (LRC) benefit was shown with the addition of the EGFR-targeted monoclonal antibody cetuximab to RT compared with RT alone (3). However,

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when cetuximab-based chemoradiotherapy was compared with the combination of RT and cisplatin (a crosslinking cytotoxic chemotherapy), OS, PFS, and LRC were significantly worse in unselected patients with HPV-positive oropharyngeal cancer who received cetuximab rather than cisplatin (4,5). Furthermore, combining cetuximab and cisplatin together with RT failed to improve outcomes relative to cisplatin and RT (6). These data demonstrate the need to identify novel therapies to improve patient outcomes beyond those currently achievable with the combination of RT with standard cytotoxic and/or EGFR-targeted systemic therapy.

Over the past decade there has been increasing recognition of the immune system's importance in the regulation of oncogenesis and response to therapy. Numerous preclinical and clinical studies have shown that tumors are able to evade immune recognition via a variety of mechanisms leading to tumor progression and ultimately death (7,8). Specifically, two immune checkpoint pathways, cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death protein 1/programmed cell death ligand 1 (PD-1/PD-L1) have been the most well-studied targets for immunotherapy (9). CTLA-4 regulates the amplitude of early activation of naïve and memory T-cells via its binding to B7-1 or B7-2 molecules on the antigen presenting cells (APCs) (9). It inhibits or dampens T-cell function primarily by diminishing signaling through the costimulatory CD28 receptor by competing with CD28 for binding to B7-1 or B7-2. This prevents the necessary second signal that supports T-cell activation and stops a T-cell mediated sustained immune response (10). Whereas CTLA-4 is involved in the early immune response, PD-1/PD-L1 function primarily to constrain the activity of T-cells in the periphery to limit autoimmunity. The interaction of PD-L1 with PD-1 [present on most tumor-infiltrating lymphocytes (TILs)] lowers the threshold for lymphocyte apoptosis, leads to anergy by blunting T-cell receptor (TCR) signaling, and ultimately causes T-cell depletion and exhaustion (10,11).

Ipilimumab, an inhibitory monoclonal anti-CTLA-4 antibody, was the first immune checkpoint inhibitor (ICI) to be tested and approved for use in cancer therapy with large clinical trials showing improvements in OS, PFS, and response rates in melanoma and other malignancies; however, there is no clear evidence that CTLA-4-directed therapy is active in HNSCC (10). Drugs targeting PD-1 (e.g., nivolumab and pembrolizumab) and PD-L1 (e.g., atezolizumab and durvalumab) have been developed and approved for use in several malignancies, including

non-small cell lung cancer (NSCLC), melanoma, and HNSCC (nivolumab and pembrolizumab) (12). Despite their successes, responses as monotherapy have largely been limited to certain subsets of patients, suggesting highlighting the importance of combination therapy and development of biomarkers to predict response.

The rationale for the use of immunotherapy in HNSCC stems from several observations (13). First it has been shown that HNSCC has a relatively high tumor mutation burden (TMB) (14), with high TMB shown to be predictive for increased efficacy of ICIs (7,15). In human papillomavirus (HPV)-negative HNSCC, the carcinogen and tobacco mutagenesis signatures are thought to be associated with enhanced ICI response (13). Conversely, HPV-positive HNSCC are postulated to be rendered sensitive to ICIs secondary to APOBEC (apolipoprotein B mRNA editing catalytic polypeptide-like) proteins and their associated gene-editing function (16,17). Several APOBEC proteins have increased expression in HPV-positive HNSCC relative to HPV-negative disease, as they are viral response genes. APOBEC proteins lead to mutagenesis with these neo-peptides predicted to exhibit greater hydrophobicity and hence enhanced immunogenicity and correlation with increased ICI response (18). Additionally, HNSCC has been shown to be immunosuppressive with many patients with HNSCC showing impaired TILs, natural killer (NK) cells, and decreased antigen-presenting capacity (13). Furthermore, upregulation of PD-L1 in HNSCC and other tumor types lead to impaired T-cell function (8). Therefore, immunomodulatory therapies that can simultaneously reverse the immunosuppressive phenotype of HNSCC and take advantage of increased mutagenesis may have therapeutic significance for patients with HNSCC.

RT remains a critical modality for both definitive and palliative treatments in HNSCC. The immunomodulatory effects of RT have been recognized for decades, given that the toxicities of RT are often immunologically-mediated (e.g., fibrosis, necrosis, and acute inflammation) (19). Furthermore, preclinical and clinical data have characterized the immunomodulatory effects of radiation, leading to significant interest in combining ICIs and other immunotherapies with RT. In this review, we highlight the relevant studies that have examined combinations of ICIs and RT for HNSCC, as well as future possible combinations with immunotherapies beyond ICIs.

We present the following article in accordance with the NARRATIVE REVIEW Reporting Checklist (available at <http://dx.doi.org/10.21037/tcr-20-2096>).

Effects of HPV status on immune microenvironment in HNSCC

HPV status of HNSCC is strongly prognostic and predictive with regards to outcomes and treatment response (20,21). Furthermore, the tumor microenvironment and associated mutational profiles of HPV-positive and carcinogen-related (HPV-negative) HNSCC are starkly different. It has also been shown that HPV-positive HNSCC is associated with increased immune infiltrate and inflammatory cytokines (9,13). Despite these features, immune evasion and tumor progression can still occur.

HPV infection and associated immune evasion are hallmark features of HPV-positive HNSCC that allow for tumor progression and therapeutic resistance (9,22,23). Interference with interferon (IFN) signaling by HPV itself blunts both the innate and adaptive immune response pathways. Under normal circumstances, IFNs link the innate and adaptive immune responses via the activation of dendritic cells (DCs) and CD8 T-cells, leading to the production of virus-specific antibodies. In the antiviral response, IFNs are produced by virally infected cells, leading to inhibition of viral protein expression, NK-cell stimulation, leukocyte migration, increased antigen presentation and ultimately viral clearance (9). HPV can additionally interact with the antigen-presenting machinery via suppression of STAT1, leading to impaired expression of the tumor human leukocyte antigen (HLA) class I molecules (8,23,24). Furthermore, HPV-infected cells might avoid immune recognition by the production of immunosuppressive cytokines such as IL-10 or TGF β (25,26). It has been shown that levels of IL-10 and TGF β are higher in HPV-positive HNSCC than in normal individuals, with the viral E6 protein stimulating IL-10 production (25,27). Lastly, activation of the PD-1/PD-L1 axis may play an important role in HPV-associated tumorigenesis and progression. PD-1 positive regulatory T-cells infiltrate HPV-positive HNSCC more commonly than HPV-negative tumors and HPV-positive HNSCC tumors show higher levels of PD-L1 protein expression when compared to HPV-negative tumors (9,28). However, it is worth noting that despite this association, the prognostic significance of PD-L1 expression in p16-positive (HPV-positive) tumors remains unclear and is not associated with changes in OS (29).

As mentioned above, there is a suggestion of improved response to ICIs with tobacco exposure in HPV-negative HNSCC. It is tempting to speculate that this may hold

true in HPV-positive HNSCC as well, and suggests that having higher-risk HPV-positive disease (e.g., >10 pack year smoking history) may inform response to ICIs, but this deserves further evaluation.

Altogether, these data suggest that HPV infection may lead to an immunosuppressive phenotype permitting oncogenesis and tumor progression. However, this understanding also suggests potential areas of therapeutic intervention to eliminate this virally driven immune suppression.

Recurrent/metastatic HNSCC and ICIs

The initial clinical data that established the efficacy of immunotherapy in HNSCC were generated from studies in the recurrent and metastatic HNSCC setting. Prior to the use of ICIs patients with platinum-refractory recurrent/metastatic HNSCC, second-line treatment included cetuximab and methotrexate or taxane-based chemotherapy regimens, with response rates typically less than 20% and median PFS <5 months (30,31). The KEYNOTE-012 trial was a phase Ib trial that first demonstrated durable response with pembrolizumab treatment in platinum-refractory HNSCC with PD-L1 $\geq 1\%$ and an overall response rate of 16% (32,33).

Shortly thereafter came the publication of the CheckMate 141 trial, a randomized phase III trial comparing nivolumab with standard-of-care single-agent systemic therapy (i.e., cetuximab, docetaxel or cetuximab) in recurrent platinum-refractory HNSCC (29). This landmark trial showed improved OS [1-year 36.0% *vs.* 16.6%, median 7.5 *vs.* 5.1 months, hazard ratio (HR) 0.70, 97.73% confidence interval (CI), 0.51–0.96], response rate (13.3% *vs.* 5.8%), and quality of life (QOL) with nivolumab. On exploratory subgroup analysis, patients with p16-positive tumors had a statistically significant improvement in OS with nivolumab (median 9.1 *vs.* 4.4 months, HR 0.56, 95% CI, 0.32–0.99), whereas those with p16-negative tumors did not (median 7.5 *vs.* 5.8 months, HR 0.73, 95% CI, 0.42–1.25). Furthermore, patients with PD-L1 $\geq 1\%$ tumors had a statistically significant improvement in OS with nivolumab (median 8.7 *vs.* 4.6 months, HR 0.55, 95% CI, 0.36–0.83), but not for those with PD-L1 <1% (median 5.7 *vs.* 5.8 months, HR 0.89, 95% CI, 0.54–1.45).

KEYNOTE-040, a phase III randomized control trial, included 495 patients with platinum-refractory recurrent or metastatic HNSCC who were randomized to either pembrolizumab or standard-of-care chemotherapy (34). Pembrolizumab improved median OS to 8.4 months from

6.9 months with standard of care chemotherapy (HR 0.80, 95% CI, 0.65–0.98) with lower grade 3 or greater toxicity (13% *vs.* 36%). Together, these data led to the Food and Drug Administration's (FDA) approval of pembrolizumab and nivolumab in 2016.

The success of ICIs in the second-line recurrent/metastatic setting spurred significant interest in moving these agents into the first-line setting. KEYNOTE-048 was a phase III trial that randomized 882 patients with previously untreated locally incurable or metastatic HNSCC to pembrolizumab alone, pembrolizumab plus a platinum and 5-fluorouracil, or cetuximab plus a platinum and 5-fluorouracil (EXTREME regimen) (35). Randomization was prospectively stratified by percentage of PD-L1 expressing tumor cells ($\geq 50\%$ *vs.* $< 50\%$) and combined positive score (CPS) (sum of PD-L1 stained tumor cells and surrounding lymphocytes and macrophages divided by total viable number of tumor cells multiplied by 100). The primary outcomes were OS and PFS in patients with CPS ≥ 20 , CPS ≥ 1 , and the total population. Pembrolizumab alone compared with EXTREME improved OS in patients with CPS ≥ 20 (median OS 14.9 *vs.* 10.7 months, HR 0.61, 95% CI, 0.45–0.83) and CPS ≥ 1 (median OS 12.3 *vs.* 10.3 months, HR 0.78, 95% CI, 0.64–0.96), and was non-inferior in the overall cohort (median 11.6 *vs.* 10.7 months, HR 0.85, 95% CI, 0.71–1.03). Pembrolizumab plus chemotherapy improved OS over EXTREME among all three PD-L1 CPS subgroups. Interestingly, in the second interim analysis (final analysis), PFS was not improved for either pembrolizumab alone or pembrolizumab and chemotherapy compared to EXTREME among patients with CPS ≥ 20 . In this subgroup, response rate was 23% for pembrolizumab alone *vs.* 36% for EXTREME, but the median duration of response was 22.6 months for pembrolizumab alone *vs.* 4.2 months for EXTREME. These data suggest that a long duration of response may improve OS in the first-line recurrent/metastatic HNSCC setting.

Taken together, data from these clinical trials set the stage for the use of ICIs as a standard treatment modality in HNSCC. Given the still relatively low response rates, however, combination therapies with other agents like RT may be necessary to improve outcomes with HNSCC.

Biomarkers of immunotherapy response in HNSCC

Biomarkers of response to immunotherapy will be critical

in determining which patients will optimally benefit. As discussed above, PD-L1 expression $\geq 1\%$ appeared to be predictive of an improved response to nivolumab in the recurrent/metastatic setting in the KEYNOTE-040 trial. It has been noted that approximately 50% of HNSCC tumor cells express PD-L1, and when analyzed in combination with the infiltrating immune cells, this percentage increases to 85% (composite PD-L1 score as defined in KEYNOTE-048) (13,28). When the CPS is used rather than tumor PD-L1 expression, the predictive value of PD-L1 expression is enhanced. The KEYNOTE-012 trial demonstrated response rates of 21% with PD-L1 positive *vs.* 6% in PD-L1 negative disease using CPS, as compared with 18% in PD-L1 positive *vs.* 19% in PD-L1 negative tumors using tumor expression alone (33).

However, there are still responses that occur in patients despite having negative PD-L1 expression. Therefore, additional biomarkers of response have been proposed for ICI response. One such biomarker is PD-L2, the other known ligand for PD-1. Retrospective analysis of clinical samples from the KEYNOTE-012 trial showed response rates of 27% in PD-L2 positive tumors *vs.* 5% in PD-L2 negative tumors (36). Beyond the PD-1/PD-L1 axis, other biomarkers currently under study include TILs, TMB, mismatch repair deficiency (MMRD), neoantigen frequency, and signatures of T-cell dysfunction and exclusion—each of which may further our understanding and assist future patient selection and utilization of ICIs for this cohort (7,21).

As a less invasive approach to biomarker and response-driven therapy, analysis of circulating tumor cells (CTC) and circulating tumor DNA (ctDNA) has gained significant interest (37,38). Tumor-specific somatic mutations visualized in ctDNA allow for the quantitation of tumor burden and may serve as a more sensitive marker of response to therapy than traditional imaging based techniques (39). Additionally, via analysis of CTC surface markers personalized treatment approaches may be obtained in a minimally invasive manner. In HNSCC CTCs, PD-L1 mRNA expression was evaluated in a cohort of HNSCC patients (40). CTCs overexpressing PD-L1 at the end of treatment predicted for worse PFS and OS ($P=0.0001$ and $P<0.001$, respectively). Similar reports suggesting PD-L1 positive CTCs predict for worse PFS have also been reported (37,38). These data suggest that further evaluation of PD-L1 expression on CTCs in HNSCC as a prognostic biomarker deserves consideration. Additionally, whether CTC PD-L1 expression is predictive of response to ICIs remains unknown.

RT and immunotherapy in recurrent/metastatic HNSCC

RT has been shown to modulate the immune system in a complex manner, both stimulating and repressing its activity. There has been significant preclinical and clinical investigation into harnessing the immunomodulatory effects of radiation, typically through combinations of ICIs and RT (13). Specifically, in the metastatic setting there has been interest in eliciting the “abscopal response”. The abscopal response is a phenomenon by which local RT elicits distant tumor regression and may be potentiated by combining it with ICIs (41). Various cases of the abscopal response have been reported in the literature, including a *New England Journal of Medicine* report in 2012 regarding a case of a 33-year-old female with metastatic melanoma who experienced systemic tumor progression on ipilimumab and subsequently underwent palliative RT to a paraspinal mass (42). Following RT, she surprisingly experienced tumor regression at both the primary irradiated site and at distant sites as well.

Prospective data in this setting in HNSCC are relatively sparse, other than a phase II randomized trial combining stereotactic body radiotherapy (SBRT) and ICIs in metastatic HNSCC at Memorial Sloan Kettering Cancer Center (NCT02684253) (43). Fifty-three patients with at least two measurable lesions were randomized to nivolumab with SBRT *vs.* nivolumab alone. The primary endpoint was objective response rate (ORR) in non-irradiated lesions with secondary endpoints of OS, PFS, and duration of response. ORRs were not improved with the addition of SBRT to nivolumab (26.9%, 95% CI, 13.7–46.1%) when compared to nivolumab alone (22.2%, 95% CI, 10.6–40.8%). Median duration of response was not reached in the nivolumab arm and was 9.3 months in the SBRT plus nivolumab arm ($P=0.21$). OS at 1 year was not significantly different between the two treatment arms [64% (95% CI, 47–88%) without SBRT *vs.* 53% (95% CI, 36–79%) with SBRT ($P=0.79$)]. Median PFS was also not improved with the addition of SBRT [1.9 months (95% CI, 1.78–not reached) without SBRT *vs.* 2.4 months (95% CI, 1.0–11.4) with SBRT ($P=0.8$)]. Grade 3 or greater adverse events (AE) were similar between treatment arms (15% without SBRT *vs.* 11% with SBRT). These data suggest that combination of SBRT plus nivolumab is safe, but failed to demonstrate abscopal responses in this patient cohort. However, given the safety of SBRT and improved understanding of the biology underlying the HNSCC immune response this

continues to be an area of active investigation.

RT and immunotherapy in locally advanced HNSCC

At the time of this review, no formally published studies exist on the combination of ICIs with RT in the definitive or postoperative setting for locally advanced HNSCC. However, several abstracts have been reported and are reviewed below. These data have led to the launch of several phase III trials that have not yet reported results (*Table 1*).

Definitive chemoradiation with concurrent ICI in platinum-eligible patients

The incorporation of ICIs into standard-of-care concurrent chemoradiation with cisplatin requires extensive safety analysis given potential for increased toxicity from multiagent therapy. A phase I study reported by Powell *et al.* (NCT02586207) examined the tolerability of pembrolizumab with cisplatin-based chemoradiation in 27 patients with stage III–IVB HNSCC (44). Pembrolizumab was given 200 mg IV 4–7 days prior to initiation of chemoradiation and then every 3 weeks for a total of 8 doses. Cisplatin was dosed 40 mg/m² on a weekly basis for 6 doses. Safety was determined by the occurrence of treatment-related dose-limiting AEs and immune-related AEs (irAEs), whereas efficacy was determined as complete response on imaging or with salvage surgery at 100 days following completion of chemoradiation. Twenty-one patients (78%) completed all planned doses of pembrolizumab, with 3 discontinuing due to irAEs and 3 discontinuing due to protocol reasons (2 with early neck dissections and 1 with prolonged hospitalization). All patients completed the full dose of RT without >5-day delay, and 85% received the target dose of cisplatin. There was a patient death due to concurrent illness unrelated to treatment. These data have led to reopening of the study with expansion cohorts of 34 HPV-positive and 23 HPV-negative patients to evaluate efficacy. These data indicate that the addition of pembrolizumab to concurrent cisplatin and RT appears safe and does not impair the ability of patients to complete definitive chemoradiation.

RTOG 3504 was a phase I trial also designed to address the safety of the addition of nivolumab with concomitant cisplatin or cetuximab-RT for intermediate-risk (IR) or high-risk HNSCC (45). The primary endpoint of this trial was dose-limiting toxicity (DLT), defined as nivolumab-

Table 1 Phase III trials examining the addition of immune checkpoint inhibitors to radiotherapy for locally advanced head and neck squamous cell carcinoma

Trial name and ID	Standard arm	Study arm	Estimated accrual	Trial status
Definitive chemoradiation with concurrent ICI				
GORTEC 2017-01/REACH (NCT02999087)	Radiotherapy + concurrent cisplatin or cetuximab (if cisplatin-ineligible)	Radiotherapy + concurrent cetuximab with avelumab	688	Recruiting
The JAVELIN Head and Neck 100 study (NCT02952586)	Radiotherapy + concurrent cisplatin	Radiotherapy and concurrent cisplatin with avelumab	697	Terminated
KEYNOTE-412 (NCT03040999)	Radiotherapy + concurrent cisplatin	Radiotherapy + concurrent cisplatin with pembrolizumab	780	Active, not recruiting
NRG-HN004 (NCT03258554)	Radiotherapy + concurrent cetuximab (cisplatin-ineligible)	Radiotherapy + concurrent durvalumab	523	Recruiting
Definitive chemoradiation with maintenance ICI				
IMvoka010 (NCT03452137)	Definitive local therapy	Definitive local therapy + maintenance atezolizumab	400	Recruiting
ECOG-ACRIN EA3161 (NCT03811015)	Radiotherapy + concurrent cisplatin	Radiotherapy + concurrent cisplatin + maintenance nivolumab	744	Recruiting
Definitive radiation with concurrent ICI vs. cisplatin (even if cisplatin-eligible)				
NRG-HN005 (NCT03952585)	Radiotherapy (standard-dose or reduced-dose) + concurrent cisplatin	Reduced-dose accelerated radiotherapy + concurrent nivolumab	711	Recruiting
Postoperative chemoradiation with concurrent ICI				
MK-3475-689 (NCT03765918)	Surgery + adjuvant (chemo) radiotherapy	Surgery + adjuvant (chemo) radiotherapy and concurrent pembrolizumab	704	Recruiting
NIVOPOSTOP (GORTEC 2018-01; NCT03576417)	Surgery + adjuvant radiotherapy and concurrent cisplatin	Surgery + adjuvant radiotherapy and concurrent cisplatin with nivolumab	680	Recruiting
Postoperative chemoradiation with maintenance cisplatin				
EORTC ADHERE (NCT03673735)	Surgery + adjuvant radiotherapy and concurrent cisplatin	Surgery + adjuvant radiotherapy and concurrent cisplatin + maintenance durvalumab	650	Not yet recruiting

ICI, immune checkpoint inhibitor.

related grade ≥ 3 AE unresolved to grade ≤ 1 in 28 days. Only data from the ten patients (8 ultimately evaluable) enrolled to the nivolumab and cetuximab arm were reported. One DLT was observed (mucositis) with 1 other grade 3 AE (lipase elevation) that was not a DLT. Seven/8 patients completed RT, 7/8 completed cetuximab, and 5/8 completed 10 concurrent doses of nivolumab. The authors concluded that nivolumab is safe to administer with concurrent cetuximab with newly diagnosed IR/high-risk HNSCC.

These data have begun to demonstrate that the combination of RT and immunotherapy in HNSCC

appears to be well-tolerated with some signal of treatment efficacy. Due to these data, several phase III trials testing the addition of ICIs to standard-of-care curative-intent therapy in HNSCC are ongoing. For example, GORTEC 2017-01/REACH (NCT02999087) is a phase III open-label, multicenter, randomized trial for patients with locally advanced HNSCC (46). This trial has two cohorts: those eligible for cisplatin and those ineligible for cisplatin. Those not eligible for cisplatin received cetuximab with RT. Cisplatin was given 100 mg/m² every 3 weeks concurrently with RT. The experimental arm for both cohorts consists

of avelumab with concurrent cetuximab and RT. Avelumab (10 mg/kg) started 7 days prior to RT (with cetuximab loading dose) and was given every 2 weeks during the course of RT and for an additional 12 months following RT. The primary endpoint was PFS with secondary endpoints of OS and AEs. The safety analysis of the first 29 patients with stage III–IV HNSCC (including 14 in the experimental arms) reported that all patients completed RT as prescribed, but 6 of 14 in the experimental arm did not receive the entire systemic therapy regimen. Three patients (21.4%) developed grade 4 AEs (1 dermatitis, 1 lymphopenia, and 1 mucositis). Based upon these results the trial was continued and is actively recruiting towards its estimated enrollment of 688 participants.

The JAVELIN Head and Neck 100 study (NCT02952586) is a multinational, phase III, double-blinded, placebo-controlled, randomized clinical trial that examines the efficacy of avelumab *vs.* placebo in combination with definitive chemoradiation (47). Cisplatin was 100 mg/m² (for three doses). Avelumab (10 mg/kg) was given in 3 phases: lead-in (single dose), concurrent (concurrent avelumab at days 8, 25 and 39 with chemoradiation) and maintenance (avelumab every 2 weeks for 12 months) with the rationale of inducing an immune response during lead-in and chemoradiation phases that is sustained during the maintenance phase. The primary endpoint is PFS with secondary endpoints of OS, ORR, LRC, distant metastatic failure, and duration of response. While formal results have not released, it has been stated in a March 2020 press release by EMD Serono and Pfizer that the study has been terminated as a preplanned interim analysis has shown that the study is unlikely to show a statistically significant improvement in the primary endpoint of PFS (48). Formal publication and analysis of results are expected.

KEYNOTE-412 (NCT03040999) is a phase III randomized, placebo-controlled, double-blinded clinical trial that seeks to evaluate the addition of pembrolizumab to cisplatin-based chemoradiation (49). Pembrolizumab or placebo (every 3 weeks) was given 1 week prior to chemoradiation, followed by 2 doses during chemoradiation and an additional 14 doses after the completion of chemoradiation. Cisplatin was given every 3 weeks (2–3 doses) concurrently with RT. Patients were eligible with locally advanced, previously untreated HNSCC. Primary endpoint is event-free survival (EFS) with secondary endpoints of OS, safety and patient-reported outcomes. The study has completed accrual (estimated enrollment of 780 patients) and formal results are pending.

Definitive chemoradiation with concurrent ICI in platinum-ineligible patients

Unfortunately, not all patients with HNSCC are eligible to receive a platinum-based agent due to medical comorbidities that may include renal or hearing dysfunction. A single-arm, multi-institution, phase II study (NCT02609503) included 29 platinum-ineligible patients with locally advanced HNSCC (AJCC 7th stage III–IV) who received RT with concurrent and adjuvant pembrolizumab (50,51). Pembrolizumab was delivered 200 mg/m² q3 weeks followed by 3 adjuvant cycles. The primary endpoint was PFS, with secondary endpoints including common terminology criteria for adverse events (CTCAE) toxicity, OS, QOL, and several correlative translational endpoints. One-year PFS and OS were noted to be 76% (95% CI, 56–88%) and 86% (95% CI, 67–95%), respectively. At a median follow-up of 21 months, median PFS and median OS had not yet been reached (this noted to exceed their pre-specified PFS endpoint of 16 months). Typical RT side effects were noted, with the exception of high rates of grade 3/4 lymphopenia (58.6%). Correlative studies revealed decreases in CD4 positive T-cells and B-cells but not CD8 positive cells with treatment. Patients who were noted to have progression had greater percentages of baseline naïve B cells and fewer marginal zone B cells. These phase II clinical trial data suggest that the combination of ICI and RT appear to be relatively well tolerated with promising OS and PFS, warranting further evaluation in a randomized setting.

The GORTEC 2015-01/PembroRad trial was designed as a phase II randomized trial comparing standard-of-care RT with concurrent cetuximab *vs.* RT and concurrent pembrolizumab for platinum-ineligible patients with locally advanced stage III–IVB HNSCC (52). One hundred and thirty-three patients were ultimately randomized to the two treatment arms with evaluation of LRC at 15 months as the primary endpoint. At least one grade 3 AE was noted in 94% of cetuximab patients and 78% of pembrolizumab patients. Compliance with RT was not significantly different between either arm with 86% and 88% of patients completing their full RT course with cetuximab and pembrolizumab. Patients receiving cetuximab had significantly more grade 3 or greater mucositis than those receiving pembrolizumab (57% *vs.* 24%; P=0.004) as well as dermatitis (49% *vs.* 17%; P=0.0003), but without differences in dysphagia (34% *vs.* 39%). These data suggest that pembrolizumab in combination with RT compares favorably with cetuximab.

NRG-HN004 (NCT03258554) was designed as a phase II/III trial with a lead-in component to evaluate the safety and efficacy of concurrent and adjuvant durvalumab with RT as compared to cetuximab and RT for platinum-ineligible HNSCC patients (53). The safety data for the ten patients on the lead-in portion of the trial have been reported at the American Society of Clinical Oncology (ASCO) 2019. Durvalumab was given every 2 weeks for 7 cycles starting 2 weeks prior to RT. The primary endpoint of the lead-in component was DLT, defined as a high-grade AE linked to durvalumab treatment. In the ten patients enrolled on the lead-in portion of this study, all 10 completed RT and 8 received all 7 doses of durvalumab. No DLTs or grade 4–5 AEs were observed. The authors concluded that it is safe and feasible to administer durvalumab concurrently with RT for patients with HNSCC with a contraindication to cisplatin. The trial remains open and is actively recruiting for the phase II/III component with primary endpoints of PFS (phase II component) and OS (phase III component).

Definitive chemoradiation with maintenance ICI

Whereas the previous trials focused on the use of concurrent immunotherapy with definitive RT, the IMvoke010 study (NCT03452137), a global, double-blind, placebo-controlled, randomized phase III trial, studies the addition of adjuvant atezolizumab after definitive chemoradiation for locally advanced HNSCC (54). Approximately 400 patients with stage III–IVB HNSCC who complete definitive locoregional therapy will be randomized to complete 16 doses of q3 week atezolizumab (1,200 mg). Primary endpoints are EFS and OS. Secondary endpoints are AEs, serum concentrations of atezolizumab and patient-reported outcomes/QOL. The trial is actively recruiting.

The ECOG-ACRIN EA3161 trial (NCT03811015) is a phase II/III randomized study evaluating the addition of maintenance nivolumab *vs.* observation following definitive treatment with radiation and concurrent weekly cisplatin (40 mg/m²) in patients with IR, HPV-positive, locally advanced oropharyngeal HNSCC (54). Maintenance nivolumab (480 mg every 4 weeks for 12 months) is initiated 4 weeks after completion of concurrent chemoradiation. Patients who were randomized to observation are given the option to cross over to maintenance nivolumab with documented progression of disease. Primary endpoints are PFS, OS, and response assessment with 12-week positron emission tomography-computed tomography (PET-CT) scan. Secondary endpoints are prognostic effects of baseline

PD-L1 expression, plasma/saliva HPV status following completion of therapy, and several PET-based response assessments. This trial is actively recruiting towards its estimated final enrollment of 744 patients.

Definitive radiation with concurrent ICI vs. cisplatin

While cisplatin remains the standard-of-care for concurrent chemoradiotherapy, there been interest in de-escalating systemic therapy for HPV-positive patients (even if platinum-eligible) by replacing cisplatin with ICI. KEYCHAIN (NCT03383094) is a phase II randomized, multi-institutional trial designed to compare the efficacy and safety of standard cisplatin-based chemoradiation with pembrolizumab (ever 3 weeks for up to 20 cycles) given concurrently and adjuvantly with RT in intermediate- to high-risk p16-positive locoregionally advanced HNSCC (54). The primary endpoint is PFS with secondary endpoints of OS, toxicity, and patterns of failure. The trial is actively recruiting and with an estimated final enrollment of 114 patients.

NRG-HN005 (NCT03952585) is a phase II/III trial that seeks to determine whether the use of immunotherapy will allow for deintensification of therapy for HPV-positive HNSCC (54). Patients with low-risk stage I–II p16-positive oropharyngeal cancer were randomized to 3 treatment arms. Arm 1 is standard-of-care accelerated RT (70 Gy in 6 weeks) with concurrent cisplatin, Arm 2 is reduced-dose RT (60 Gy in 6 weeks) with concurrent cisplatin, and Arm 3 is reduced-dose, accelerated RT (60 Gy in 5 weeks) with concurrent and adjuvant nivolumab (every 2 weeks up to 6 cycles). It is worth noting that while Arm 3 has a reduced dose overall, treatment acceleration improves the time-corrected biologically effective dose close to that of non-accelerated standard-dose RT. The phase II component seeks to demonstrate non-inferiority in terms of PFS for concurrent cisplatin or nivolumab with reduced-dose RT compared with standard-of-care (Arm 1). The phase III portion of the trial focuses on the co-primary endpoints of non-inferiority of PFS and superiority of QOL (as measured by the MD Anderson dysphagia index) between the winner of Arms 2 and 3 compared to Arm 1. Secondary endpoints are locoregional failure, distant failure, and AEs. The study is actively recruiting with an estimated total enrollment of 711 participants.

Postoperative chemoradiation with concurrent ICI

In the postoperative setting, chemoradiation is often

necessary for high-risk indications like positive margins or extranodal extension. Despite trimodality therapy, outcomes are still suboptimal for these patients. NRG-HN003 (NCT02775812) was a phase I and expansion cohort trial that sought to determine the recommended phase II schedule (RP2S) for the combination of pembrolizumab and standard adjuvant cisplatin-RT in high-risk HPV-negative HNSCC given relatively high rates of local recurrence despite adjuvant therapy (55). High-risk disease was defined as positive margins or extranodal extension. Thirty-four patients were enrolled from 22 NRG institutions. The RP2S was determined to be pembrolizumab 200 mg IV q3 weeks for 8 doses starting the week before adjuvant chemoradiation with only one initial DLT from the initial cohort (grade 3 fever) and 3 additional DLTs noted during the expansion. No DLT unacceptably delayed RT. Eighty-two percent of patients received at least 5 doses of pembrolizumab with 50% receiving all 8 planned doses. OS and PFS data have not been reported to date. These data demonstrate a well-tolerated regimen combining standard platinum-based chemoradiation and immunotherapy in high-risk HNSCC and suggest that efficacy testing in a phase II/III clinical trial may be reasonable.

A multi-site phase II trial (NCT02641093) was completed examining the addition of neoadjuvant pembrolizumab followed by surgical resection and adjuvant concurrent RT and pembrolizumab, with or without cisplatin (56). In this trial, clinically high-risk (T3–4 and/or ≥ 2 positive lymph nodes) received 200 mg pembrolizumab 1–3 weeks prior to surgery. Adjuvant concurrent pembrolizumab was delivered every 3 weeks for 6 doses with RT. Concurrent weekly cisplatin (40 mg/m²) was administered for high-risk features (extranodal extension and/or positive margins). Pre- and post-surgical specimens were evaluated for treatment effect. At the time of abstract publication, 28 out of the 80 planned patients were enrolled with 23 evaluable for efficacy. No DLTs were appreciated in the lead-in safety period. Nine/19 patients (47%) demonstrated a pathologic response ($>10\%$ tumor effect) and 6/19 achieved a major pathologic response ($>70\%$ tumor effect), one of whom had a complete pathologic response after one dose. Pathologic response was associated with robust immune cell infiltration and increased PD-L1/2. Two patients, neither of whom achieved a pathologic response, had subsequent recurrence. These data suggest that a single neoadjuvant dose of pembrolizumab produces tumor responses with an association between increased

tumor immune cell infiltration and pathologic response, and that adjuvant combined pembrolizumab with RT appears to have an acceptable safety profile. Final safety and efficacy data for the full cohort are still awaited.

Given the promising data from these early-phase studies in the postoperative setting, a phase III randomized, open-label clinical trial (NCT03765918) has opened for patients with stage III–IVA resectable HNSCC evaluating the addition of pembrolizumab to surgery and adjuvant RT (with or without concurrent and adjuvant cisplatin) (54). Patients receive 200 mg of pembrolizumab every 3 weeks for 2 doses prior to surgical resection. Following surgical resection, patients receive pembrolizumab every 3 weeks for 15 doses concurrently with RT. High-risk patients also receive concurrent cisplatin with RT (100 mg/m²) every 3 weeks for three doses. The primary endpoints of the trial are EFS and major pathologic response at the time of definitive surgery. The trial is actively recruiting with an estimated enrollment of 704 patients.

The NIVOPOSTOP (GORTEC 2018-01; NCT03576417) study is phase III, open-label, randomized multicenter trial that examines the addition of adjuvant nivolumab to adjuvant chemoradiation in high-risk resected locally advanced HNSCC (54). Concurrent cisplatin was dosed at 100 mg/m² every 3 weeks for 3 cycles. Three hundred and sixty mg of nivolumab was given every 3 weeks (starting 3 weeks prior to chemoradiation) for a total of four doses. The primary outcome is DFS, with secondary outcomes of OS and toxicity. The study is actively recruiting with an estimated enrollment of 680 patients.

Postoperative chemoradiation with maintenance ICI

A similar concept involves ICI following postoperative chemoradiation following surgical resection for high-risk resected locally advanced HNSCC (50). The EORTC ADHERE trial (NCT03673735) is planned as a phase III randomized study examining the utility of adding one dose of durvalumab 1,500 mg/m² within 1 week before postoperative chemoradiation and 6 monthly doses of adjuvant durvalumab after postoperative chemoradiation. Concurrent cisplatin was dosed at 100 mg/m² every 3 weeks for 3 cycles, with adjuvant RT delivered to 66 Gy. The primary outcome is DFS, with secondary outcomes of OS, toxicities, health-related QOL, and incidence of distant metastases, locoregional recurrence, and second cancers. The study is not yet recruiting but has an estimated

enrollment of 650 patients.

For a summary of all randomized phase III studies studying the addition of ICI to RT for locally advanced HNSCC, please see *Table 1*.

Nasopharyngeal carcinoma (NPC)

NPC represents a unique subset of HNSCC with distinct molecular underpinnings and regional predilection (38). NPC is endemic to parts of Asia and North Africa and as opposed to oropharyngeal carcinoma it is typically associated with Epstein-Barr virus (EBV) rather than HPV (38). EBV-associated malignancies have been shown to be associated with PD-L1 expression on both tumor cells and tumor-infiltrating macrophages (57). Specifically, PD-L1 expression has been positively associated with EBV infection in NPC, with 89–95% of NPC tumors expressing PD-L1 (57,58). EBV has been shown to drive PD-L1 expression through the viral protein latent membrane protein 1 (LMP1) in combination with IFN gamma activation (59). NPCs with increased PD-L1 expression are associated with worse clinical outcomes in patients who received RT (58). As such there has been interest in the use of ICIs in NPC.

The KEYNOTE-028 study was a nonrandomized, multicohort, phase Ib trial of pembrolizumab in patients with PD-L1-positive advanced solid tumors (60). This included an NPC cohort, with unresectable or metastatic disease with failure of prior standard therapy and PD-L1 expression of 1% or more on tumor cells or TILs. A total of 27 patients received pembrolizumab every 2 weeks for up to 2 years, disease progression, or unacceptable toxicity. The primary endpoint was ORR. An ORR of 25.9% (95% CI, 11.1–46.3%) was observed over a median follow up of 20 months. Grade 3 or greater toxicity occurred in 8 patients (29.6%) with one drug-related death (sepsis). This led the authors to conclude that pembrolizumab demonstrated antitumor activity with a manageable safety profile in patients with recurrent/metastatic NPC.

In the NCI-9742, a phase II multinational study, patients with pre-treated recurrent or metastatic NPC were treated with nivolumab until disease progression (61). The primary endpoint was ORR and secondary endpoints were OS and toxicity. PD-L1 and HLA A and B expression as well as plasma clearance of EBV DNA were correlated with ORR and OS. At total of 44 patients were evaluated with an overall ORR of 20.5%. The 1-year OS was 59% (95% CI, 44.3–78.5%) and 1-year PFS was 19.3% (95% CI, 10.1–

37.2%). There was no statistically significant correlation between ORR and the biomarkers; however, descriptive analysis showed that 33% of patients with PD-L1 positive tumors responded compared to only 13% with PD-L1 negative tumors. These results compared well to historic controls and suggest that further evaluation in a randomized setting is warranted.

Novel immunotherapies

A large proportion of the clinical trial efforts in the immunotherapy space in HNSCC have focused on ICIs due to promising preclinical and clinical results in HNSCC and other disease sites as well as the availability of FDA-approved therapeutics engaging these pathways. However, extrapolating from early clinical data in HNSCC and other disease sites, it is likely that there will be a significant proportion of patients who will not derive benefit from these therapies. While an exhaustive discussion of novel and emerging immunotherapies is beyond the scope of this manuscript, we will briefly discuss two in the context of HNSCC.

The canonical cyclic guanosine monophosphate (GMP)-adenosine monophosphate synthase-stimulator of IFN genes (cGAS/STING) signaling pathway has been implicated in regulating the response to DNA-damaging agents including RT (62). This involves the recognition of treatment-induced cytosolic DNA by cGAS, leading to production of 2'-3'-cyclic GMP-AMP (cGAMP), and activation of STING leading to the transcription of type I IFNs and other cytokines ultimately leading to the activation of the adaptive immune system and CD8⁺ T-cell mediated tumor cell death (63–65). In HNSCC syngeneic mouse models the use of intratumoral STING agonists have shown promising results as monotherapy with considerable tumor responses (66,67). These responses have been shown to be due to activation of the adaptive immune machinery, and specifically upon CD8⁺ T-cells (66,68). However, interim phase I clinical data in patients with advanced solid tumors showed that MK-1454 (an intratumoral STING agonist) was unable to achieve responses as a monotherapy (69). When delivered in combination with pembrolizumab, 24% of the cohort achieved partial responses. While these results in combination with pembrolizumab are promising, these response rates remain relatively low, suggesting that other treatment combinations may be needed. The interaction of the cGAS/STING signaling pathway and DNA damage is an area of active investigation with promising preclinical results. Animal models have suggested that the effects of

RT are in part dependent upon STING-mediated cytokine expression (e.g., type I IFNs), activation of DCs and subsequent downstream adaptive immune responses (63,64). Given this reported dependence of the radiation response on activation of the cGAS/STING signaling, it is tempting to speculate that a combination of a STING agonist and RT may further potentiate the efficacy of RT. In preclinical immunocompetent mouse models combinations of STING agonists (RR-CDG of cGAMP) with RT show that addition to a STING agonist to RT significantly enhances the immune-mediated anti-tumor effects of radiation (64,70). These preclinical data suggest that combinations of STING agonists with RT may be beneficial in patients with HNSCC undergoing RT and deserve clinical trial evaluation. However, it is worth noting that there are paradoxical effects of chronic cGAS/STING signaling when compared with short-term activation. It has been shown that chronic STING pathway activation leads to pro-tumorigenic effects by establishing an immunosuppressive microenvironment, thereby promoting therapy resistance and metastasis (71-73). Careful design of the clinical evaluation of STING agonists and radiation will need to be implemented to ensure that the immunosuppressive effects of chronic cGAS/STING activation are minimized, perhaps through short-term, intermittent STING agonist dosing.

A significant proportion of HNSCC are related to HPV infection. Since the E6 and E7 viral proteins are critical for HPV-associated oncogenesis, they are logical targets for a therapeutic cancer vaccination (25). Furthermore, while there exists a benefit to immunotherapy as a monotherapy in incurable HNSCC, the response rates are still relatively low, suggesting that augmentation of this response is necessary to improve treatment outcomes. An HPV vaccine, ISA101, consists of several E6 and E7 peptides covering the complete sequences of E6 and E7 proteins (74). These peptides deliver antigens to DCs, inducing a CD4 and CD8 T-cell response. A single-arm phase II clinical trial evaluating the combination of ISA101 and nivolumab in incurable HPV-positive HNSCC was designed as a means to increase the HPV-specific T-cell population, which could increase response to ICIs (74). Twenty-four patients were ultimately enrolled on the trial. The primary endpoint of ORR was 33% (8 patients; 90% CI, 19–50%) with a median duration of response of 10.3 months (95% CI, 10.3 months to inestimable). These data appear favorable compared with KEYNOTE-012, KEYNOTE-055 and CheckMate 141 historical controls with ORRs of 16–22%. Five of 8 patients continued to have a response at the time of publication.

Median PFS was 2.7 months (95% CI, 2.5–9.4 months) and median OS was 17.5 months (95% CI, 17.5 months to inestimable). Furthermore, the authors note that the median OS was approximately double that of KEYNOTE-055 and CheckMate 141. The treatment was well-tolerated, with only 2 grade 3–4 toxicity events (asymptomatic transaminase elevation in one patient and a grade 4 lipase elevation in one patient) that required discontinuation of nivolumab. The ORR was 43% in PD-L1 positive tumors as compared with 18% in PD-L1 negative tumors. These data are promising and suggest evaluation in a phase III trial in order to augment the immunogenic effects of radiation in combination with an ICI.

Conclusions

Significant effort has been made examining the role of immunotherapy in combination with RT in HNSCC. Early-phase clinical trial data are beginning to emerge and suggest that combinations of various ICIs and RT in the curative-intent setting appears to be safe, tolerable, and possibly efficacious. Final results from a number of these phase I/II trials are awaited. Because of the demonstrated safety and tolerability noted in those trials so far, multiple phase III trials are actively accruing to determine the efficacy of combining ICIs with RT. Caution should be taken when interpreting interim analyses using a PFS endpoint, since improving OS will be the standard by which ICI will enter the standard of care in the locally advanced setting, as it has in the recurrent/metastatic setting. While these results are eagerly awaited, it is likely that unselected patients may not routinely benefit from the addition of ICIs to definitive RT. Therefore, translational and biomarker data from these trials and preclinical studies are going to be paramount in advancing patient outcomes. Finally, adding novel immunotherapies like STING agonists or HPV vaccines in combination with definitive RT and ICIs may yield improved results beyond what is currently achievable. However, there must be a clear preclinical and translational rationale to guide these novel combinations.

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