Radiotherapy and Immunotherapy for Head and Neck Cancer: Current Evidence and Challenges

Jack M. Qian1,2* and Jonathan D. Schoenfeld1

1 Department of Radiation Oncology, Dana-Farber/Brigham and Women’s Cancer Center, Harvard Medical School, Boston, MA, United States, 2 Harvard Radiation Oncology Program, Massachusetts General Hospital/Brigham and Women’s Hospital/Dana-Farber Cancer Institute, Boston, MA, United States

Immune checkpoint inhibitors (ICI) have revolutionized cancer treatment over the past decade. However, although the immune landscape suggests a strong rationale for the use of these agents in patients with head and neck squamous cell carcinoma, the available clinical evidence indicates that most patients currently do not respond to ICI monotherapy. Radiotherapy is a primary treatment modality for many patients with locally advanced head and neck cancer. While ionizing radiation traditionally has been thought to act in a purely cytotoxic fashion, a growing body of preclinical studies have demonstrated additional profound immunomodulatory effects. Consequently, there has been a surge of interest in the potential synergy between radiotherapy and immunotherapy, both the potential for radiotherapy to augment the systemic anti-tumor immune response and the potential for immunotherapy to improve in-field tumor response to radiation. In this review, we summarize the current preclinical and clinical evidence for radioimmunotherapy, with a particular focus on studies directly relevant to head and neck squamous cell carcinoma, as well as existing challenges and future directions for this emerging field.

Keywords: anti-PD-1, immunotherapy, radiation therapy, head and neck cancer, anti-PD-L1

INTRODUCTION

Head and neck cancers comprise a significant portion of the global cancer burden; when aggregating subsites, they are the 8th most common cancer worldwide by both incidence and mortality (1). Although the vast majority of head and neck cancers are squamous cell carcinomas (HNSCC) and have traditionally been associated with tobacco and alcohol use, HPV-associated oropharyngeal squamous cell carcinoma (SCC) has emerged as a new disease entity with markedly different biological behavior (2).

Ever since the foundational work of Henri Coutard, who was the first to use X-rays to treat laryngeal cancer almost 100 years ago (3), radiation therapy has played a key role in the treatment of HNSCC. Radiation continues to be used extensively both in the curative as well as palliative setting, although the distinction between the two is now sometimes blurred with growing recognition of the oligometastatic state, where patients with limited numbers of metastases can achieve prolonged survival, or even cure (4, 5). Technological advancements, both in imaging as well as treatment delivery, have enabled more precise radiation treatment that has reduced treatment-related...
morbidity and improved patient outcomes. However, even with the use of modern radiation techniques, there are still opportunities for further improvement (4).

The immune system has a critical role in tumor development, and the development of immune evasion by tumors is a key step in carcinogenesis (6, 7). Attempts to reinvigorate an anti-tumor immune response have been widely integrated into practice following the development of the immune checkpoint inhibitors (ICIs) targeted against the immune checkpoint receptors cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed cell death protein 1 (PD-1), and programmed death-ligand 1 (PD-L1). Since the initial FDA approval of ipilimumab (a CTLA-4 inhibitor) in 2011 for the treatment of metastatic melanoma based on a proven overall survival advantage (8), antibodies blocking CTLA-4 and PD-1/PD-L1 have been tested and approved across a wide spectrum of malignancies. In HNSCC, both pembrolizumab and nivolumab (PD-1 inhibitors) have gained FDA approval for use in recurrent/metastatic HNSCC after progression through platinum-based chemotherapy (9–11). Pembrolizumab additionally has been approved in the US for use in the first line setting in patients with recurrent/metastatic HNSCC, either in combination with chemotherapy or alone as monotherapy depending on tumor/tumor microenvironment PD-L1 expression (12).

Unfortunately, overall response rates to PD-1 inhibitors in unselected patients with HNSCC remain low at approximately 10–20% (9–12), although patients who do respond can have long-lasting, durable remissions, as has been the case with other solid tumor patients who respond to PD-1 blockade (13). The possibility of durable long-term response has been a driver of the rapid uptake in clinical practice and has invigorated efforts to develop predictive biomarkers. Tumor mutational burden, a potential surrogate for tumor neoantigens that can be recognized by the immune system, is one such biomarker, leading to the first ever histology-agnostic FDA approval of the PD-1 inhibitor pembrolizumab for mismatch repair deficient tumors of any histology (14, 15), though there is increasing recognition that the types and functional nature of mutations may be as important as the number of mutations present (16). PD-L1 expression on both tumor cells and infiltrated immune cells has also been explored as a biomarker across several histologies with varying results; in HNSCC, subgroup analyses of Checkmate 141, KEYNOTE-040, and KEYNOTE-048 all suggest that higher PD-L1 expression does correlate with the likelihood of survival benefit (10–12). It is less clear whether patients with low or no PD-L1 expression still benefit from PD-1 directed therapy; analyses of Checkmate 141 and KEYNOTE-048 show questionable benefit for the PD-L1 negative subgroup when comparing the treatment and control arms (11, 17).

Finally, for HNSCC patients, HPV-associated malignancies with relatively fewer tumor mutations as compared to tobacco-associated malignancies may also respond to immune checkpoint blockade as novel viral-associated neoantigens might be recognized by the immune system. Indeed, subgroup analyses of the Checkmate 141 and KEYNOTE-040 trials did not show any clear differences in response or clinical benefit based on p16 expression status (a surrogate for HPV-associated tumors) (10, 11).

In addition to better patient selection through the use of predictive biomarkers, augmenting the anti-tumor immune response with other therapies could also improve immunotherapy response rates. Radiation therapy increasingly has been recognized to have diverse immunomodulatory effects, and there has consequently been intense interest in possible synergism between radiation therapy and immunotherapy. In this review, we will summarize the preclinical data that illustrate the immune effects of radiation therapy, review the unique immune landscape of HNSCC, and finally discuss both current preclinical and clinical data relevant to the combination of radiation therapy and immunotherapy specifically in HNSCC (Figure 1).

## IMMUNE EFFECTS OF RADIATION THERAPY

Traditionally, the anti-tumor effects of radiation therapy have been attributed to direct cytotoxicity secondary to the induction of DNA damage, and while it was known over 40 years ago that radiation therapy also depends on an intact immune system to exert its full anti-tumor effect (18), the interaction between the immune system and radiation therapy has garnered more interest in the past two decades. It is now recognized that the immune effects of radiation may contribute significantly to an anti-tumor response; however, these immune effects are also quite complex and can be both immunostimulatory and immunosuppressive.

Radiation can induce immunogenic cell death, which gives rise to adaptive immune responses (19, 20). Many mechanisms can be involved in this process, and a full detailed review is beyond the scope of this discussion. However, recent studies have shown radiation can promote release of danger-associated molecular patterns such as calreticulin, ATP, and HMGB (20, 21). Radiation also induces release of cytosolic DNA, which triggers the cGAS/STING pathway to upregulate production of type-I interferon (22, 23). Type-I interferon is crucial for the activation of dendritic cells, which ultimately recruit and prime T-cells. These signals together are critical for the initial development of an immune response specific to tumor neoantigens.

Radiation can promote anti-tumor immunity through additional mechanisms. Radiation can diversify antigen presentation by tumor cells through promotion of intracellular peptide degradation as well as upregulation of MHC expression (24, 25). This ultimately can enhance recognition and tumor cell killing by cytotoxic T-cells (26). Radiation has also been associated with increased production of other immune stimulating cytokines and chemokines, which together can promote the infiltration of T-cells into tumors and modulate the function of these T-cells, as well as dendritic cells and macrophages (21).

Radiation also has immunosuppressive effects that could be detrimental to an anti-tumor immune response. Lymphocytes
are radiosensitive, with in vitro studies demonstrating that 3 Gy of radiation is enough to deplete 90% of human lymphocytes (27). This may be overly simplistic, however, as more recent work suggests differential radiosensitivity of T-cell subtypes. Pre-existing intra-tumoral T-cells in particular appear to be potentially more radioresistant than either circulating T-cells or lymphoid tissue T-cells. These intra-tumoral T cells survive even high doses (20 Gy) of radiation in preclinical studies and can develop a similar transcriptomic profile to tissue-resident memory T-cells, which are also thought to be radioresistant (28, 29). These intra-tumoral T-cells can mediate some of the anti-tumor immune effects of high dose radiation. Regardless, clinical data suggest that radiation-induced lymphopenia may be a negative prognostic factor in patients treated with PD-1 and CTLA-4 inhibitors (30).

Within the local tumor microenvironment, a variety of inhibitory immune cells, such as T-regulatory cells (Tregs), myeloid-derived suppressor cells (MDSCs), and tumor-associated macrophages (TAMs, and specifically M2 macrophages), are often already present. In several studies, radiation increases recruitment of these inhibitory immune cells and can also modulate their function towards an even more immunosuppressive phenotype (21). There may also be dose-dependent effects of radiation; for instance, Vanpouille-Box et al. demonstrated that as radiation doses were escalated to 12–18 Gy, there was induction of Trex1, a DNA exonuclease which degrades cytosolic DNA and thus prevents activation of the cGAS/STING pathway (23). The balance between competing activating and inhibitory immune responses, then, likely plays a key role in the probability of a successful anti-tumor immune response and provides opportunity for therapeutic intervention.

### IMMUNE LANDSCAPE OF HNSCC

Work over the past decade has helped characterize the immune landscape of HNSCC. As noted above, HPV-associated oropharyngeal SCC is a distinct disease entity from other non-HPV-driven, tobacco-associated HNSCC, with a distinct immune profile. Using data from The Cancer Genome Atlas, Mandal et al. showed that HPV-positive tumors were significantly more immune infiltrated than HPV-negative tumors (31). However, both HPV-positive and HPV-negative HNSCC had the highest rate of immunosuppressive Treg infiltration among 10 different cancer types. There was a correlation between the molecular smoking signature of HNSCC tumors and increased tumor mutational burden, but also conversely an inverse association between the molecular smoking signature and immune infiltration, despite this higher tumor mutation burden (and therefore presumably increased neoantigen load). This suggests that tobacco-associated tumors can still be immunologically cold despite their higher mutational load. Further work has demonstrated that HPV-positive tumors are associated with increased T-cell receptor diversity, higher levels of immune cytolytic activity, and an overall enriched inflammatory response (32, 33). The anatomic subsite where head and neck cancer develops likely plays a key role in tumor immunity as well; the oropharynx contains particularly lymphoid-rich tissue, and this unique immune environment may explain why the improved prognosis for HPV-driven HNSCC is largely limited to oropharyngeal tumors (34). Additional work on oropharyngeal SCC has confirmed a higher degree of infiltration of CD8+ T-cells in HPV-positive vs HPV-negative tumors (35). Overall, these studies suggest that the increased sensitivity of HPV-associated oropharyngeal SCC to chemotherapy and radiation therapy may
at least in part be mediated through immune mechanisms (36, 37), and that differing immunotherapeutic approaches may be optimal for HPV-positive and HPV-negative HNSCC.

HNSCC also appears to be uniquely associated with high levels of natural killer (NK) cell infiltration, even when compared to other highly-immune infiltrated cancer types (31, 35). Patients with high levels of NK cell infiltration were also found to have improved survival compared to those with low levels of infiltration (31). The potential anti-tumor effects of NK cells is an emerging area of research and has been reviewed elsewhere (38); currently, there is limited clinical data on their role in HNSCC, or whether opportunities for synergy between NK-directed therapies and radiation exist.

**PRECLINICAL EVIDENCE FOR RADIOIMMUNOTHERAPY IN HNSCC MODELS**

**Augmenting Anti-tumor Cellular Immunity**

Preclinical work in HNSCC models has demonstrated synergy between radiation and immunotherapy. In a poorly immunogenic orthotopic HNSCC mouse model, Oweida et al. demonstrated effective tumor cell killing when both 10 Gy of radiation and an anti PD-L1 antibody were administered together, but not for either treatment individually (39). Tumor control was correlated with increased tumor T-cell infiltration and was abrogated when CD4+ and CD8+ T-cells were depleted. In addition, although much of research on anti-tumor immunity has focused on the role of T-cells, work from Kim et al. in a mouse model of HPV-associated HNSCC demonstrated synergy between radiation, and this effect was correlated with upregulation of interferon-stimulated genes and a significant increase in innate immune cell infiltration into the tumor microenvironment (40). Finally, there is growing interest in harnessing additional molecular pathways to promote anti-tumor immunity. For instance, in a mouse model of HPV-driven carcinoma, Dillen et al. demonstrated that inhibitors of ATR, a key protein in the DNA damage response pathway, significantly sensitized tumors to radiation, and this effect was correlated with upregulation of interferon-stimulated genes and a significant increase in innate immune cell infiltration into the tumor microenvironment (41). Xiao et al. showed that ASTX600, an inhibitor of IAP1/2 and XIAP, proteins that modulate apoptosis and the tumor necrosis factor signaling pathway, significantly enhanced T-cell mediated tumor cell killing when combined with radiation and PD-1 inhibition in a mouse model of oral cavity carcinoma (42).

**Decreasing an Immunosuppressive Microenvironment**

The immunosuppressive microenvironment remains a challenge even with combined radiation and immunotherapy. In a follow-up study, Oweida et al. demonstrated that the anti-tumor immune responses to combined radiation and PD-1 inhibition in their HNSCC mouse model were ultimately transient, as compensatory mechanisms of immune evasion were activated, including upregulation of another immune checkpoint, TIM-3, as well as increased tumor infiltration of Tregs (39, 43). Adding an anti-TIM-3 antibody further delayed tumor growth, but the response was still not durable; only targeted depletion of Tregs was able to induce durable immunologic memory. Another group has explored the use of cyclophosphamide and an inhibitor of inducible nitric oxide synthase (iNOS) as immunomodulatory agents in a mouse model of HPV-associated HNSCC. When combined with traditional chemoradiation, addition of these two agents increased the CD8+ T-cell/Treg ratio and decreased immunosuppression (44). In this particular model system the combination of radiation with PD-1 and CTLA-4 inhibition only minimally altered the immunologically cold tumor microenvironment, but the addition of cyclophosphamide and the iNOS inhibitor shifted the balance of infiltrated immune cells away from immunosuppressive types (such as MDSCs) to those more associated with anti-tumor immunity (such as dendritic cells and anti-tumor M1 macrophages). This led to an increased CD8+ T-cell-dependent response and complete tumor rejection in more than 70% of the treated mice (45). This is now being investigated in a clinical trial, NCT03844763, which explores the use of cyclophosphamide, avelumab (a PD-L1 inhibitor), and radiation therapy in the treatment of recurrent/metastatic HNSCC.

**Radiation Dose and Fractionation Effects**

Additional studies have demonstrated the importance of radiation dose and fractionation in generating an effective anti-tumor immune response. Consistent with work in other diseases (46), Morisada et al. showed in a syngeneic mouse oral cavity carcinoma model that hypofractionated radiation (16 Gy in two fractions) was associated with preservation of both peripheral and tumor-infiltrating lymphocytes, reduction of both peripheral and tumor-associated MDSCs, and increased expression of interferon genes, when compared to conventionally fractionated radiation (20 Gy in 10 fractions) (47). Moreover, analysis of the draining lymph nodes (which notably were included within the radiation fields) suggested that 20 Gy in 10 fractions suppressed local tumor-specific T-cell responses. Consequently, only 16 Gy in two fractions demonstrated synergy with an anti-PD-1 antibody in these mice. Additional work by this group suggests a dose-dependent effect of radiation on both antigen release and T-cell priming, with 8 Gy in a single fraction enhancing these pathways compared to 2 Gy in a single fraction, resulting in increased tumor cell susceptibility to T-cell mediated killing (48). However, the doses used in these preclinical models differ from those used in clinical practice, as do the size of the treated tumors, and so it is uncertain how these findings might translate to the treatment of patients.

**CLINICAL EVIDENCE FOR RADIOIMMUNOTHERAPY IN HNSCC**

**Recurrent/Metastatic Setting**

Despite the widespread use of ICIs in advanced malignancies, prospective clinical data on their combination with radiation...
therapy remain scarce, particularly in HNSCC. The unique immune-related adverse effects (irAEs) that have been observed with ICIs are now well established (49) and there have been concerns that the pro-inflammatory effects of radiation could enhance toxicities when combined with ICIs. Reassuringly, however, most of the available clinical data to date suggests that the combination of radiation and ICIs is generally well tolerated (50). For instance, in a cohort of 133 patients with metastatic melanoma, non-small cell lung cancer (NSCLC), or renal cell cancer who received palliative radiation to a wide range of anatomic sites, Bang et al. demonstrated numerically higher rates of irAEs when radiation was given within 14 days of immunotherapy, but the toxicities were generally mild with rates of grade 3+ toxicity less than 10% (51). Similarly, a prospective phase I trial of pembrolizumab and stereotactic body radiotherapy (SBRT) in patients with a variety of metastatic solid tumors also demonstrated a grade 3+ toxicity rate of less than 10% (52). Notably, this study did include four patients with HNSCC, and radiation was delivered to two distinct anatomic sites in more than 60% of the cohort. Finally, a phase 2 trial which randomized 62 patients with metastatic HNSCC to nivolumab with or without SBRT to a single metastatic site did not find a significant difference in either grade 3–5 adverse events (13% for nivolumab alone vs 10% for nivolumab with SBRT, p = 0.70) or any grade adverse events (70% for nivolumab alone vs 87% for nivolumab with SBRT, p = 0.12) with the addition of SBRT (53).

Nevertheless, a few key issues must be considered when interpreting these and other safety data. Just as dose and fractionation likely affect potential anti-tumor immunity induced by radiation (as demonstrated in preclinical work), it is probable that these parameters influence potential toxicities when combined with ICIs. The relative timing of radiation and immunotherapy is likely to be important as well; notably, radiation recall, a relatively rare, unpredictable, and poorly understood phenomenon wherein an inflammatory reaction can develop in previously irradiated tissue following administration of a new systemic agent (54), has now been reported following ICI administration (55, 56). Additionally, the anatomic site treated with radiation could influence the side effect profile of combination treatment; for instance, the landmark PACIFIC trial, which demonstrated a significant overall survival benefit to adjuvant durvalumab (an anti-PD-L1 antibody) after definitive chemoradiation for stage III NSCLC, also showed an increase in any-grade pneumonitis with the addition of durvalumab (although rates of clinically relevant pneumonitis, i.e. grade 3+, were similar between treatment groups and low overall) (57). Within the brain, there is a potential increased risk of developing radiation necrosis after treatment of brain metastases with combined ICIs and radiation (58, 59). Finally, as discussed earlier, in certain settings radiation can induce lymphopenia, which could ultimately interfere with the efficacy of ICIs (30). These data highlight the importance of collecting robust radiation treatment and toxicity data to facilitate future analyses as we study combination radiation and immunotherapy treatments.

There are very few efficacy data relevant to the addition of radiation to ICIs in patients with recurrent or metastatic HNSCC. In general, the primary rationale for radiation in this setting is to help stimulate a systemic anti-tumor immune response, or abscopal effect. This is particularly difficult to study retrospectively, as disentangling a true abscopal effect from a delayed response to immunotherapy is challenging (60). The only available prospective data for HNSCC comes from the randomized phase 2 trial noted above, in which 62 patients with metastatic HNSCC were randomized to nivolumab with or without SBRT to a single metastatic site (9 Gy ×3 fractions, between the first and second doses of nivolumab). Ultimately, there was no improvement in overall response rate (34.5% for nivolumab alone vs 29.0% for nivolumab with SBRT, p = 0.86) (53). In NSCLC, a similarly designed phase 2 trial of pembrolizumab with or without SBRT to a single metastatic site in patients with advanced NSCLC also failed to meet its primary endpoint, although it did demonstrate a doubling of overall response rate with the addition of SBRT that was not statistically significant (18% for pembrolizumab alone vs 36% for pembrolizumab with SBRT, p = 0.07) (61). Differences between the designs of these two studies include the anti-PD-1 agent used (nivolumab vs pembrolizumab), the type of cancer (HNSCC vs NSCLC), timing of SBRT (between first and second dose of nivolumab vs prior to starting pembrolizumab), and dose of SBRT (9 Gy ×3 fractions vs 8 Gy ×3 fractions). Given the results of these trials, further research is clearly needed; Table 1 summarizes ongoing trials that will help address these questions specifically in patients with recurrent/metastatic HNSCC. Notably, however, only a few of these studies are randomized, and so any efficacy data will require confirmation in larger, phase 3 trials.

Finally, as noted above, there is growing recognition of an oligometastatic disease state. Contrary to previous conceptualization of metastatic disease as inevitably widespread and thus incurable, the oligometastatic hypothesis suggests that there is a wide range of metastatic potential that varies among different cancers and from patient to patient, and that an intermediate state likely exists between purely localized disease and widely metastatic disease, wherein a limited number of metastases might develop with limited further metastatic potential (62). Aggressive local treatment of patients with limited metastases would thus potentially offer a significant survival benefit. Results from several randomized phase 2 trials have supported this hypothesis (though notably HNSCC was not represented in any of these studies) (63–67). Consequently, there is interest in the addition of ICIs to radiation in this population of patients to improve outcomes (68). In this setting, radiation would be administered at ablative doses to all metastatic sites, and so the addition of ICIs would also be intended to augment the local effects of radiation at each treatment site. To our knowledge, no prospective clinical data has yet been published on the combination of radiation and ICIs in patients with oligometastatic HNSCC, though there is at least one ongoing clinical trial (NCT03283605, which examines the use of durvalumab, tremelimumab [a CTLA-4 inhibitor], and SBRT in patients with HNSCC with fewer than 10 metastases).
| NCT#          | Title                                                                 | Inclusion criteria                                                                 | Treatment arms                                                                                       | Timing  | Phase |
|--------------|----------------------------------------------------------------------|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|---------|-------|
| NCT03539198 | Study of Proton SBRT and Immunotherapy for Recurrent/Progressive Locoregional or Metastatic Head and Neck Cancer | Recurrent/metastatic HNSCC, ≥2 metastatic sites                                      | 1: nivolumab given every 2 weeks, with proton SBRT to one metastatic site administered with cycle 3 | concurrent | n/a   |
| NCT03389209 | Immunotherapy and SBRT for Metastatic Head and Neck Carcinomas       | Metastatic HNSCC, ≥2 metastatic sites                                              | 1: durvalumab + tremelimumab for four cycles (4 weeks each), SBRT between cycles 2 and 3           | concurrent | 1/2   |
| NCT03844763 | CONFRONT: Targeting the Tumor Microenvironment in R/M SCCHN          | Recurrent/metastatic HNSCC                                                          | 1: avelumab, cyclophosphamide, and radiation (8 Gy/1 fx) to a single site 1 week after first dose of avelumab | concurrent | 1/2   |
| NCT03522584 | Durvalumab, Tremelimumab and Hypofractionated Radiation Therapy in Treating Patients With Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma | Recurrent/metastatic HNSCC, progression through prior PD-1/PD-L1 inhibitor         | 1: durvalumab + tremelimumab for four cycles (4 weeks each) followed by durvalumab alone for nine cycles; SBRT during week 3 in three fractions, every other day | concurrent | 1/2   |
| NCT03474497 | UCDCC#272: IL-2, Radiotherapy, and Pembrolizumab in Patients Refractory to Checkpoint Blockade | Recurrent/metastatic HNSCC, progression through prior PD-1/PD-L1 inhibitor         | 1: one cycle of pembrolizumab, then SBRT (24 Gy/3 fx) and intratumoral injection of interleukin-2 during cycle 2, then additional pembrolizumab | concurrent | 1/2   |
| NCT03317327 | REPORT: REirradiation and Programmed Cell Death Protein 1 (PD-1) Blockade on Recurrent Squamous Cell Head and Neck Tumors | Recurrent HNSCC after prior radiation or second primary HNSCC                       | 1: nivolumab with re-irradiation to 60 Gy (in 1.5 Gy bid fx), followed by nivolumab for up to 12 months | concurrent | 1/2   |
| NCT04340258 | Trial Combining Pembrolizumab and Cesium 131 Brachytherapy With Salvage Surgery in HNSCC | Resectable recurrent HNSCC after prior surgery or radiation                      | 1: one dose of pembrolizumab, then salvage surgery with implantation of Cesium-131 brachytherapy seeds (60–70 Gy), followed by adjuvant pembrolizumab for 6 months | concurrent | 1/2   |
| NCT04454489 | Quad Shot Radiotherapy in Combination With Immune Checkpoint Inhibition | Recurrent/metastatic HNSCC                                                          | 1: pembrolizumab given every 3 weeks; quad-shot radiation (14.8 Gy in 4 bid fx) between cycles 2 and 3 | concurrent | 2     |
| NCT03313804 | Priming Immunotherapy in Advanced Disease With Radiation              | Recurrent/metastatic HNSCC                                                          | 1: nivolumab, pembrolizumab, or atezolizumab, with either SBRT (BED > 100 Gy) or 30 Gy fractionated RT | concurrent | 2     |
| NCT03386357 | Radiotherapy With Pembrolizumab in Metastatic HNSCC                   | Recurrent/metastatic HNSCC, ≥2 metastatic sites, progression through platinum-based therapy | 1: radiation to 1–3 metastases (36 Gy/12 fx), with pembrolizumab starting between fraction 3 and 4; 2: pembrolizumab alone | concurrent | 2     |
| NCT03511391 | CHEERS: CHEKpoint Inhibition in Combination With an Immunoboost of External Body Radiotherapy in Solid Tumors | Recurrent/metastatic HNSCC, progression through platinum-based therapy             | 1: 2 cycles of nivolumab, then SBRT to 1–3 metastases (24 Gy/3 fx) prior to cycle 3; 2: nivolumab alone | concurrent | 2     |
| NCT03085719 | Targeting PD-1 Therapy Resistance With Focused High or High and Low Dose Radiation in SCCHN | Metastatic HNSCC, progression through prior PD-1 inhibition, ≥3 metastatic sites | 1: pembrolizumab and high dose SBRT (3 fx) to one metastatic site; 2: pembrolizumab and high dose SBRT (3 fx) to one metastatic site, and low dose radiation (2 fx) to another site | concurrent | 2     |
| NCT03546582 | KEYSTROKE: SBRT +/- Pembrolizumab in Patients With Local-Regionally Recurrent or Second Primary Head and Neck Carcinoma | Recurrent HNSCC after prior radiation or second primary HNSCC                       | 1: reirradiation with SBRT over 2 weeks, then pembrolizumab every 3 weeks for up to 2 years; 2: reirradiation with SBRT over 2 weeks | sequential | 2     |
| NCT03521570 | Intensity-Modulated Radiation Therapy & Nivolumab for Recurrent or Second Primary Head & Neck Squamous Cell Cancer | Recurrent HNSCC after prior radiation or second primary HNSCC                       | 1: one dose of nivolumab, then radiation with concurrent nivolumab, then adjuvant nivolumab for 5 months | concurrent | sequential  |
| NCT02289209 | Reirradiation With Pembrolizumab in Locoregional Inoperable Recurrence or Second Primary Squamous Cell CA of the Head and Neck | Unresectable recurrent HNSCC after prior radiation or second primary HNSCC          | 1: pembrolizumab with re-irradiation to 60 Gy (in 1.2 Gy bid fx), followed by pembrolizumab for 3 months | concurrent | sequential  |
| NCT02684253 | Screening Trial of Nivolumab With Image Guided, Stereotactic Body Radiotherapy (SBRT) Versus Nivolumab Alone in Patients With Metastatic Head and Neck Squamous Cell Carcinoma (HNSCC) | Metastatic HNSCC, ≥2 metastatic sites                                              | 1: one cycle of nivolumab, then SBRT (27 Gy/3 fx) with the 2nd cycle, followed by additional nivolumab; 2: nivolumab alone | concurrent | 2     |

**BED**, biologically effective dose; **bid**, twice a day; **fx**, fraction; **HNSCC**, head and neck squamous cell carcinoma; **ICIs**, immune checkpoint inhibitors; **SBRT**, stereotactic body radiotherapy.
Related to the overall concept of oligometastases is oligoprogression, or the development of a limited number of progressive metastatic lesions after a period of stability on systemic therapy (69). In the context of ICIs, oligoprogression may herald general immune escape in patients who had previously been responding to treatment. However, in certain cases oligoprogression may develop as the result of resistant tumor clones that lack particular tumor antigens or antigen presentation, or because of differences in the underlying immune microenvironment of the anatomic site that permit localized immune escape (e.g. brain) (70, 71). If this is the case, local treatment such as radiation to these oligoprogressive sites may enable the patient to continue to derive benefit from ICIs (72–74). This paradigm is being tested prospectively in SCCHN (NCT03085719).

**Locally Advanced/Definitive Setting**

ICIs are being investigated in the setting of curative treatment of earlier stages of disease across all cancer types, including HNSCC. Addition of ICIs to radiation in this setting would be intended to potentially augment the local effects of radiation (i.e. as a radiosensitizer) and address micrometastatic disease. Several possible combinations are under investigation—immunotherapy added to a chemoradiation regimen to intensify therapy (for patients with currently poor outcomes), immunotherapy given concurrently with radiation instead of chemotherapy or with a lower dose of radiation (potentially as a way to reduce treatment morbidity while maintaining overall efficacy), or immunotherapy administered adjuvantly and/or as induction (i.e. sequential therapy). To date adjuvant immunotherapy has proven successful in NSCLC; as noted earlier, the PACIFIC trial demonstrated a significant and meaningful overall survival benefit for adjuvant durvalumab starting within 6 weeks of completing standard chemoradiation for unresectable stage III NSCLC, with an increase in 2-year overall survival from 55.6 to 66.3% (75). Of note, the magnitude of benefit was greater patients who were randomized within 2 weeks of completing chemoradiation. Adjuvant immunotherapy also has newly demonstrated success in esophageal cancer; Checkmate-577 demonstrated improved disease-free survival with the administration of adjuvant nivolumab following neoadjuvant chemoradiation and surgical resection in patients with esophageal and gastroesophageal cancer, though full trial results have yet to be presented (76).

As shown in Table 2, ongoing trials are evaluating various combinations of radiation and ICIs for HNSCC in the definitive setting, and several have now reported safety data. In general, combinations of PD-1/PD-L1 inhibitors with definitive radiation appear well tolerated with no unexpected toxicities. KEYCHAIN is a randomized phase 2 study of radiation combined with concurrent and adjuvant pembrolizumab compared with radiation and concurrent cisplatin in intermediate-risk p16-positive HNSCC; the safety lead-in phase of the study found only one dose-limiting toxicity (grade 4 adrenal insufficiency) among eight patients in the pembrolizumab arm, and so the trial has proceeded to its phase 2 component (77). A single arm phase 2 trial of radiation administered with concurrent and adjuvant pembrolizumab in cisplatin-ineligible patients with locally advanced HNSCC similarly demonstrated relatively low toxicity in the first 12 enrolled patients, and 11 of 12 patients received all planned cycles of pembrolizumab (78). Finally, PembroRad is a randomized phase 2 trial of radiation combined with concurrent pembrolizumab versus radiation combined with concurrent cetuximab, again in cisplatin-ineligible patients with locally advanced HNSCC. There have been 133 patients randomized in a 1:1 fashion, and the pembrolizumab arm was found to have significantly less mucositis or dermatitis within the radiation field than the cetuximab arm (79).

Early results also suggest that intensification of existing chemoradiation regimens with the addition of ICIs is reasonably safe. In a small phase 1 trial of concurrent and adjuvant avelumab added to standard cetuximab/radiation in 10 cisplatin-ineligible patients with locally advanced HNSCC, no grade 4–5 toxicities were observed, and only one of eight evaluable patients discontinued avelumab for toxicity (80). REACH is a phase 3 trial that is also comparing concurrent avelumab, cetuximab, and radiation, followed by 12 months of adjuvant avelumab, against either standard bolus cisplatin with radiation or cetuximab with radiation (depending on if the patient is judged to be fit for cisplatin or not) in patients with locally advanced HNSCC; results for the 82 patients randomized during the safety phase of the trial suggested that addition of avelumab was tolerable, with 88% of patients completing concurrent avelumab as per protocol, and rates of grade 4+ events similar between control and experimental arms (81).

Similarly, a single arm phase 1b study of the addition of concurrent and adjuvant pembrolizumab to standard radiation and weekly cisplatin in patients with locally advanced HNSCC demonstrated in 59 patients that concurrent pembrolizumab did not prevent patients from completing chemoradiation, and only 5 of 59 patients ultimately discontinued treatment because of irAEs (82). Finally, RTOG 3504 is a four-arm phase 1 trial in patients with intermediate or high risk HNSCC that is examining the addition of concurrent and adjuvant nivolumab to either radiation alone or radiation with weekly cisplatin, bolus cisplatin, or cetuximab; safety results from the latter three arms again demonstrated that nivolumab did not prevent timely completion of chemoradiation, and rates of dose-limiting toxicities were low (83).

Efficacy data, however, have not yet been reported from most of these or other ongoing trials. One of the single arm phase 2 trials noted above (78) of radiation with concurrent and adjuvant pembrolizumab in cisplatin-ineligible patients with locally advanced HNSCC ultimately enrolled 29 patients, and reported 1-yr progression-free survival and overall survival of 76 and 86%, respectively (84). Notably, the phase 3 Javelin 100 study is a double-blind, placebo-controlled trial that randomized 697 patients with locally advanced HNSCC to standard of care cisplatin-based chemoradiation with or without concurrent and adjuvant (for 12 months) avelumab, with progression-free survival as the primary endpoint. Unfortunately, this trial was recently terminated for likely futility after a preplanned interim
### TABLE 2 | Ongoing trials evaluating combinations of ICIs and radiation in the definitive management of locally advanced HNSCC.

| NCT#          | Title                                                                 | Inclusion criteria                                                                 | Treatment arms                                                                                             | Timing          | Phase |
|---------------|------------------------------------------------------------------------|------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------|-----------------|-------|
| NCT02819752   | Pembrolizumab Combined With Chemoradiotherapy in Squamous Cell Carcinoma of the Head and Neck (PEACH) | LA HNSCC                                                                          | 1: pembrolizumab added to standard chemoradiation, three doses concurrently, four doses adjuvantly          | concurrent + sequential | 1     |
| NCT04477759   | Dose-Escalated Hypofractionated Adaptive Radiotherapy for Head and Neck Cancer (DEHART) | LA HNSCC, cisplatin-ineligible, or primary metastatic HNSCC                       | 1: MR-guided hypofractionated radiation (50–60 Gy/15 fx), atezolizumab given with fraction 1 and 11 of radiation, then every 4 weeks for up to 1 year | concurrent + sequential | 1     |
| NCT03509012   | CLOVER: Immunotherapy in Combination With Chemoradiotherapy in Patients With Advanced Solid Tumors | LA HNSCC                                                                          | 1: durvalumab concurrent with standard radiation and cisplatin                                               | concurrent      | 1     |
| NCT02764593   | RTOG 3504: Safety Testing of Adding Nivolumab to Chemotherapy in Patients With Intermediate and High-Risk Local-Regionally Advanced Head and Neck Cancer | LA HNSCC, intermediate or high risk                                              | 1: one dose of nivolumab as induction, then radiation (70 Gy/35 fx) and nivolumab with weekly cisplatin, then adjuvant nivolumab for seven doses | concurrent + sequential | 1     |
| NCT03051906   | DUCRO-HN: Durvalumab, Cetuximab and Radiotherapy in Head Neck Cancer   | LA HNSCC                                                                          | 1: durvalumab every 4 weeks, cetuximab weekly, and radiation to 69.96 Gy/33 fx, followed by adjuvant durvalumab for 6 months | concurrent + sequential | 1/2    |
| NCT03247712   | Neoadjuvant Immunoradiotherapy in Head & Neck Cancer                   | Resectable LA HNSCC                                                              | 1: neoadjuvant SBRT (24–40 Gy/3–5 fx) and nivolumab, followed by surgery, followed by adjuvant nivolumab | concurrent + sequential | 1/2    |
| NCT02966684   | Immunotherapy With MK-3475 in Surgically Resectable Head and Neck Squamous Cell Carcinoma | Resectable LA HNSCC, except p16-positive oropharyngeal SCC | 1: two doses of pembrolizumab neoadjuvantly followed by surgery and standard risk-adapted adjuvant (chemo)radiation | sequential       | 2     |
| NCT03894891   | Induction TPN Followed by Nivolumab With Radiation in Locoregionally Advanced Laryngeal and Hypopharyngeal Cancer | LA p16-negative SCC of larynx or hypopharynx                                    | 1: induction cisplatin, docetaxel, and nivolumab, followed by concurrent radiation and nivolumab       | concurrent + sequential | 2     |
| NCT03708224   | Phase II Study of Perioperative Immunotherapy in Patients With Advanced Non-Virally Associated Squamous Cell Carcinoma | Resectable LA HNSCC, except p16-positive oropharyngeal SCC | 1: one dose of atezolizumab neoadjuvantly, followed by surgery and standard risk-adapted adjuvant (chemo)radiation, followed by atezolizumab every 3 weeks for up to 12 cycles | sequential       | 2     |
| NCT03426657   | Radiotherapy With Double Checkpoint Blockade of Locally Advanced HNSCC  | LA HNSCC                                                                          | 1: one cycle of induction cisplatin, docetaxel, durvalumab, and tremelimumab; patients with increased CD8+ T-cell infiltration on interval biopsy then receive durvalumab, tremelimumab, and radiation, followed by adjuvant durvalumab for 8 months | concurrent + sequential | 2     |
| NCT03532737   | Concomitant Immune Check Point Inhibitor With Radiochemotherapy in Head And Neck Cancer | LA HNSCC, non-nasopharynx                                                       | 1: pembrolizumab for six cycles (3 weeks each), and chemoradiation starting with cycle 2, with either bolus cisplatin or cetuximab, and radiation to 66–70 Gy/30–35 fx | concurrent + sequential | 2     |
| NCT02892201   | Pembrolizumab in HNSCC With Residual Disease After Radiation          | LA HNSCC with residual disease after definitive radiation                          | 1: pembrolizumab for four cycles, followed by evaluation for salvage surgery; unresectable patients continue pembrolizumab for up to 1 year | sequential       | 2     |
| NCT03721757   | CA209-891: Neoadjuvant and Adjuvant Nivolumab as Immune Checkpoint Inhibition in Oral Cavity Cancer (NICO) | LA oral cavity SCC                                                               | 1: one dose of neoadjuvant nivolumab followed by surgery, then one dose of nivolumab, then standard post-operative radiation | sequential       | 2     |

(Continued)
| NCT#          | Title                                                                 | Inclusion criteria                                                                 | Treatment arms                                                                 | Timing          | Phase |
|--------------|-----------------------------------------------------------------------|------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|----------------|-------|
| NCT03944915  | De-Escalation Therapy for Human Papillomavirus Negative Disease (DEPEND) | LA p16-negative HNSCC                                                             | chemoradiation (60 Gy/30 fx), then 6 months of adjuvant nivolumab              | sequential     | 2     |
| NCT04405154  | A Study of Concomitant Camrelizumab With Chemoradiation for Locally Advanced Head and Neck Cancer | LA HNSCC                                                                           | 1: induction carboplatin, paclitaxel, and nivolumab, followed by response-adapted chemoradiation (66–75 Gy) | concurrent + sequential | 2     |
| NCT02777385  | Pembrolizumab in Combination With Cisplatin and Intensity Modulated Radiotherapy (IMRT) in Head and Neck Cancer | LA HNSCC, intermediate or high risk                                                | 1: pembrolizumab for one initial dose, then concurrent with radiation and weekly cisplatin, then adjuvant pembrolizumab for a total of eight doses | concurrent + sequential | 2     |
| NCT03383094  | KEYCHAIN: Chemoradiation vs Immunotherapy and Radiation for Head and Neck Cancer | LA HNSCC, p16-positive, intermediate risk                                         | 1: pembrolizumab and standard radiation to 70 Gy/33–35 fx, followed by adjuvant pembrolizumab for up to 20 cycles (3 weeks each) | concurrent     | 2     |
| NCT02707588  | PembrolRad: Tolerance and Efficacy of Pembrolizumab or Cetuximab Combined With RT in Patients With Locally Advanced HNSCC | LA HNSCC                                                                           | 1: radiation (69.96 Gy/33 fx) with concurrent pembrolizumab                   | concurrent     | 2     |
| NCT02609503  | Pembrolizumab + Radiation for Locally Adv SCC of the Head and Neck (SCHN) Not Eligible Cisplatin | LA HNSCC, cisplatin-ineligible                                                   | 1: radiation (70 Gy/35 fx) with three concurrent cycles of pembrolizumab, then three adjuvant cycles | concurrent + sequential | 2     |
| NCT03258554  | NRG-HN004: Radiation Therapy With Durvalumab or Cetuximab in Treating Patients With Locoregionally Advanced Head and Neck Cancer Who Cannot Take Cisplatin | LA HNSCC, cisplatin-ineligible                                                   | 1: durvalumab for seven cycles (4 weeks each); radiation to 70 Gy/35 fx starting week 2 | concurrent + sequential | 2/3   |
| NCT01810913  | RTOG 1216: Testing Docetaxel-Cetuximab or the Addition of an Immunotherapy Drug, Atezolizumab, to the Usual Chemotherapy and Radiation Therapy in High-Risk Head and Neck Cancer | Resected LA HNSCC, except p16-positive oropharyngeal SCC, with pathologic ENE or positive margins | 1: atezolizumab for eight cycles (3 weeks each) following surgery, with standard chemoradiation (to 60 Gy/30 fx with weekly cisplatin) starting week 2 | concurrent + sequential | 2/3   |
| NCT03811015  | E3A161: Testing Immunotherapy Versus Observation in Patients With HPV Throat Cancer | LA HNSCC                                                                           | 1: radiation (70 Gy/35 fx) and concurrent weekly cisplatin, then adjuvant nivolumab for 12 months | sequential     | 2/3   |
| NCT03452137  | IMv002101: A Study of Atezolizumab (Anti-Pd-L1 Antibody) as Adjuvant Therapy After Definitive Local Therapy in Patients With High-Risk Locally Advanced Squamous Cell Carcinoma of the Head and Neck | LA HNSCC after definitive local therapy (chemoradiation or surgery + [chemo] radiation) | 1: adjuvant atezolizumab for one year                                        | sequential     | 3     |
| NCT03576417  | NIVOPOST: A Trial Evaluating the Addition of Nivolumab to Cisplatin-RT for Treatment of Cancers of the Head and Neck | Resected LA HNSCC, with ENE, positive margins, or multiple positive nodes          | 1: one dose of nivolumab, then nivolumab concurrent with radiation (66 Gy/33 fx) and bolus cisplatin | concurrent + sequential | 3     |
| NCT03673735  | Maintenance Immune Check-point Inhibitor Following Post-operative Chemo-radiation in Subjects With HPV-negative HNSCC (ADHERE) | Surgically resected p16-negative HNSCC with pathologic ENE or positive margins    | 1: one dose of induction durvalumab followed by standard chemoradiation (bolus cisplatin and radiation (66 Gy/33 fx), followed by 6 months of adjuvant durvalumab | sequential     | 3     |
| NCT03700905  | IMSTAR-HN: Study of Nivolumab Alone or in Combination With Ipilimumab as Immunotherapy vs Standard Follow-up in Surgical Resectable HNSCC After Adjuvant Therapy | Resectable LA HNSCC, except p16-positive oropharyngeal SCC                          | 1: one dose of adjuvant nivolumab followed by surgery, followed by standard risk adapted adjuvant (chemo)radiation, followed by either adjuvant nivolumab or adjuvant nivolumab+ ipilimumab for 6 months | sequential     | 3     |
analysis performed by their independent data monitoring committee (85).

Possible reasons for the failure of Javelin 100 to achieve its primary endpoint may be revealed when more complete data are available. However, in the interim, it is interesting to highlight distinctions from the successful incorporation of PD-L1 blockade into the treatment of locally advanced NSCLC as evidenced by the PACIFIC study. A predominant mode of failure in locally advanced HNSCC is locoregional recurrence (4), whereas distant metastases are more common in locally advanced NSCLC (86). Thus, examining patterns of failure in the Javelin 100 study and comparing these to patterns of failure in the PACIFIC study may inform whether ICIs in this setting are mainly eradicating systemic micrometastatic disease versus also providing further support for the importance of the draining lymph nodes; following initiation of neoadjuvant ICIs, there was a high rate of increased fluorodeoxyglucose (FDG) uptake in the draining cervical lymph nodes on an interval PET-CT, which ultimately on surgical pathology demonstrated only reactive changes. This observed increase in FDG uptake may therefore represent radiographic evidence of a mounting immune response (88). Given the radiosensitivity of lymphocytes, then, it seems possible that radiation (particularly longer conventionally fractionated regimens) that electively treats the draining lymph nodes following the receipt of ICI could actually hinder T-cell priming. Indeed, as noted above, there is some preclinical data to support this, as Morisada et al. demonstrated in an syngeneic mouse model of oral cavity cancer that 20 Gy in 10 fractions compared to 16 Gy in 2 fractions to both the primary tumor and the draining lymph nodes blunted tumor-specific CD8+ T-cell responses within those draining lymph nodes (although notably tumors were implanted in the mice legs and thus this is not a perfect model for head and neck lymphatics) (47). The phase 2 trial.
reported by Weiss et al. also noted a rate of grade 3+ lymphopenia of 58.6% (84). Another notable issue is that the design of Javelin 100, as well as many of the other trials described above, incorporated both concurrent and adjuvant ICIs in the experimental arm, whereas PACIFIC (and Checkmate-577) only tested the value of adjuvant immunotherapy. Timing and sequencing of ICIs and radiation remains a critical issue that requires further study, although the concerns regarding radiation-induced T-cell death may be particularly problematic when ICI is administered concurrently as compared with sequentially (89). Finally, as demonstrated in the preclinical work above, radiation dose and fractionation are also likely critical to successful synergy between radiation and ICIs; however, the hypofractionated regimens that appear to have the greatest immunologic potential in preclinical models differ tremendously from the long conventionally fractionated regimens (1.8–2 Gy/fraction) used in the current standard management of HNSCC. PACIFIC did also employ conventional fractionation, though standard total doses for NSCLC are somewhat lower than for HNSCC (54–66 Gy versus 70 Gy). Overall, given the years of experience supporting the current standard radiation regimen and fields used in the definitive management of HNSCC, careful studies will be required to determine what kinds of modifications to elective nodal irradiation, timing/sequencing, dose, and/or fractionation are required to maximize synergy with ICIs and ultimately improve patient outcomes. There is already significant heterogeneity amongst the ongoing trials in Tables 1 and 2 with regard to these parameters, and so examining the results collectively will hopefully be informative.

CONCLUSIONS/FUTURE DIRECTIONS

There remains excitement for the possibility of combining radiation therapy and immunotherapy to improve outcomes for patients with HNSCC. Ongoing trials will help advance this emerging field, and the developing paradigm of oligometastatic disease provides further opportunity to integrate improving systemic and local therapies. Biomarker studies conducted in parallel will also inform optimal patient selection for combined treatment approaches. Moreover, while this review has largely focused on ICIs (and PD-1/PD-L1 targeted therapies in particular) given their widespread use, immunotherapeutic agents targeting other checkpoints and pathways are in development as well (90), as are trials testing their combination with radiation (e.g. NCT04220775). Nevertheless, significant work remains to be done in both the preclinical and clinical space to determine the dose, fractionation, timing, target, and field size of radiation that will be the most synergistic with immunotherapies. Finding the optimal balance between the immunostimulatory and immunosuppressive effects of radiation is key and hopefully will herald continued improvement in outcomes for patients with HNSCC.

AUTHOR CONTRIBUTIONS

JQ: conceptualization; writing, original draft; writing, review and editing. JS: conceptualization; writing, review and editing. All authors contributed to the article and approved the submitted version.

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