



ORIGINAL RESEARCH

A phase I/II trial of concurrent immunotherapy with chemoradiation in locally advanced larynx cancer

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Abstract

Objectives: Cisplatin-based chemoradiation is an established organ-preserving strategy for locally advanced laryngeal cancer, but long-term survival remains suboptimal. Immunotherapy has been studied in the metastatic and unresectable recurrent settings. However, additional data are needed to assess its role in organ preservation for locally advanced laryngeal cancer.

Methods: This trial was an open-label, single-arm, multi-institutional study with a Phase I run-in portion followed by a planned Phase II component, which closed early due to low accrual. Study patients had Stage III or IV (T2–3; N0–3; M0) laryngeal squamous cell carcinoma and were candidates for larynx preservation. Pembrolizumab was given 2–3 weeks prior to chemoradiation and then, q21 days concurrently with high-dose cisplatin and radiation prescribed to a total dose of 70 Gy. The primary endpoint of the trial was organ-preservation rate (OPR) at 18 months.

Results: A total of nine patients were enrolled with a median follow-up of 30.1 months. No patient required laryngectomy, resulting in 100% OPR at 18 months. The 12-month overall survival (OS) rate was 77.8% and the median duration of OS was not reached. All acute Grade 4 ($n = 3$) toxicities occurred in a single patient with poorly controlled diabetes at baseline. One patient had late Grade 4 laryngeal edema requiring tracheostomy 8 months after chemoradiation, which self-resolved.

Conclusion: UCCI-HN-15-02 demonstrated the safety of the addition of immunotherapy to definitive chemoradiation and the patient outcomes suggest the potential for improving long-term survival while minimizing negative impact from treatment. While results from this trial were promising, a randomized study with a larger number of patients and longer follow-up is warranted to verify this treatment approach prior to wider adoption. NCT #: NCT02759575.

Level of evidence: 2b

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KEYWORDS

chemotherapy, immunology, laryngeal cancer/vocal fold dysplasia, organ preservation, radiation therapy

1 | INTRODUCTION

Laryngeal cancer is a common head and neck cancer.¹ In 2018, there were projected to be 177,422 new cases with 94,771 deaths worldwide.² Smoking and alcohol use represent major risk factors.³ Given the critical functions of the larynx in vocalization, airway protection, and swallowing, cancer of the larynx can be life-altering, particularly in cases with locally advanced disease.

Prior to the 1990s, the standard of care for locally advanced laryngeal cancer was total laryngectomy. Following the Veteran's Affairs (VA) trial, the use of chemotherapy and radiation to preserve the larynx became feasible.⁴ Subsequently, the standard shifted from induction chemotherapy followed by radiation as per the VA trial to concurrent chemoradiation based upon RTOG 91-11, which demonstrated improved larynx preservation compared to either radiation alone or induction chemotherapy followed by radiation.⁵ Despite the success of concurrent chemoradiation, long-term overall survival (OS) remained suboptimal at 55% at 5 years and 28% at 10 years, potentially due to toxicity from treatment.⁶ Additionally, a national database study of Stage III and IV laryngeal cancer patients reported that organ preservation could come at the cost of decreased OS at 2 and 5 years compared to surgery (57% vs. 64% and 39 vs. 44%, respectively).⁷ Given these data, there is a need for an improved approach for larynx preservation.

Immunotherapy represents a modality to improve disease control whereas minimizing additional side effects. Pembrolizumab is a humanized monoclonal antibody and member of the checkpoint inhibitor family. It acts by inhibiting programmed cell death 1 (PD-1), a receptor which leads to decreased T-cell activation following interaction with programmed death ligand 1 (PD-L1).⁸ This ligand is overexpressed on some head and neck squamous cell carcinoma (HNSCC) cells.⁹ HNSCC has known immune escape mechanisms, making it a target for immunomodulation.¹⁰ Prior studies have demonstrated the tolerability of checkpoint inhibitors and efficacy has been demonstrated in the recurrent and metastatic setting for head and neck cancer leading to FDA approval.¹¹⁻¹⁶ More recent data have evaluated chemotherapy as a concurrent agent with checkpoint inhibitors based upon the potential for increased antigen shedding and rapid disease control. Positive results have been obtained and pembrolizumab in combination with platinum and fluorouracil in metastatic or unresectable recurrent HNSCC was FDA-approved in 2019.^{9,17} Radiation is known to have immune impacts based upon activation of inflammatory pathways and antigen release, leading to enhanced cross-presentation and T cell responses.¹⁸ However, limited clinical evidence exists to evaluate immune synergy with conventionally fractionated radiation to the head and neck and there are currently no published data assessing concurrent chemioimmunotherapy with radiation in the setting of organ preservation for locally advanced laryngeal cancer. The goal of UCCI-HN-15-02 was to assess the safety

and efficacy of the addition of pembrolizumab to conventional chemoradiation for locally advanced laryngeal cancer.

2 | MATERIALS AND METHODS

2.1 | Study design

UCCI-HN-15-02 (NCT02759575) was an open-label, single-arm study that enrolled patients from two academic centers. The study was designed with two parts: a Phase I run-in portion to assess the safety of the studied treatment approach and a planned re-opening for a Phase II component following the safety assessment. The study proceeded to Phase II, but was terminated early due to low accrual and the data were allowed to mature prior to survival analysis. The trial was approved by the University of Cincinnati Institutional Review Board (Approval # 2015-8190) after independent review and followed the principles outlined by the Declaration of Helsinki including obtaining written informed consent from patients at the time of enrollment. The trial was financially supported by Merck Sharp & Dohme Corp., but was conducted and analyzed independently by the authors.

2.2 | Patients

Inclusion criteria were biopsy-proven, previously untreated Stage III-IVb (T2-3; N0-3; M0) laryngeal squamous cell carcinoma; eligibility for curative treatment with chemoradiation; age \geq 18; ECOG performance status of 0 or 1; anticipated survival of at least 12 months; the presence of measurable disease based on RECIST 1.1; and the absence of other active primary malignancies within 5 years of enrollment except for basal cell carcinoma or in situ cervical cancer. Assessment of PD-L1 expression was not required prior to enrollment. Exclusion criteria included a T1 primary tumor; a T4 primary tumor causing baseline laryngeal dysfunction; prior radiation to the larynx or involved neck; prior complications such as radiation pneumonitis deemed to increase the risk of toxicity with anti-PD-1 therapy; immunodeficiency or the receipt of immunosuppressive therapy; a history of active TB; prior receipt of anti-PD-1, anti-PD-L1, or anti-PD-L2 agents; history of human immunodeficiency virus infection; and active Hepatitis B or C infection.

2.3 | Treatment

All patients in this trial were treated with concurrent pembrolizumab, cisplatin, and radiation following a complete history and physical and radiologic assessment of disease. Pembrolizumab was given as a

200 mg flat dose intravenously (IV) 2–3 weeks prior to the start of chemoradiation and then, concurrently with chemoradiation q21 days until the completion of radiation for a total of four doses. Cisplatin was given IV at a dose of 100 mg/m² q21 days during radiation.

Radiation delivered using megavoltage photons was prescribed to a total dose of 70 Gy in 35 fractions using intensity-modulated radiation therapy with 95% of the planning target volume (PTV) receiving at least 95% of the prescribed dose. All patients underwent CT simulation with a thermoplastic mask for immobilization. Treatment targets included a gross target volume (GTV70) encompassing gross tumor based upon physical exam and imaging and a clinical target volume (CTV70) defined as a 1.0 cm expansion of the GTV70 with subsequent modification for anatomic barriers to spread. Regions at risk of microscopic tumor presence (i.e., elective cervical nodal volumes) were delineated with separate CTVs and prescribed a dose of 56 Gy at 1.6 Gy/fraction with an optional intermediate 63 Gy volume (1.8 Gy/fraction) at the discretion of the treating radiation oncologist; all CTVs underwent a 3 mm expansion to form the individual PTVs and these volumes were treated concurrently with the PTV70 in a simultaneous integrated boost approach. Dose constraints for radiation planning followed standard of practice with no adjustments for the concurrent use of pembrolizumab.

2.4 | Study endpoints

The primary objective of the Phase I portion of the study was to determine the safety of pembrolizumab in conjunction with standard of care chemoradiation and included the first six enrolled patients. These patients were evaluated for dose-limiting toxicities (DLTs) from the time of study initiation to the start of cycle 2 of concurrent cisplatin, pembrolizumab, and radiation. DLTs were defined as side effects during treatment that were sufficiently severe to prevent further treatment. All toxicities were graded as per the National Cancer Institute (NCI) CTCAE Version 4.0 criteria. DLTs included Grade 3 or 4 pneumonitis, diarrhea/colitis, hyperglycemia, hypophysitis, thyroid dysfunction, and hepatic failure as well as any Grade 5 toxicity. Adverse events typically attributable to cisplatin or radiation such as renal impairment, neurotoxicity, mucositis, and myelosuppression were not categorized as DLTs unless they developed after the first dose of pembrolizumab and before the start of chemoradiation.

The primary outcome of interest in the Phase II portion was 18-month organ preservation rate (OPR). OPR was defined as freedom from laryngectomy alone and did not include death as an event of interest. Secondary objectives included 12-month OPR, OS, laryngectomy-free survival (LFS), oncologic event-free survival (EFS), and progression-free survival (PFS) rates. LFS was defined as freedom from death or laryngectomy. Oncologic EFS focused upon progressive malignant disease as an event of interest and did not include death, as this outcome was included in the determination of PFS. Events included for the calculation of PFS were death; persistent or progressive disease; and laryngectomy. All survival endpoints were calculated from the date of trial enrollment. Acute toxicities were also recorded for each patient until 30 days following completion of therapy.

2.5 | Statistical analysis

Assuming an OPR rate of ~70% for standard of care treatment, the trial hypothesized an improvement of the primary endpoint of 18-month OPR to 85% with the addition of pembrolizumab. The initial goal was to enroll 47 patients to test this hypothesis. Due to lower than expected accrual, OPR was estimated using the Kaplan–Meier method without formal statistical comparisons to historical controls. Secondary endpoints including 12-month OPR, OS, oncologic EFS, and PFS were also estimated using the Kaplan–Meier method. Statistical analyses were performed using IBM SPSS (version 27).

2.6 | Role of funding source

The funder of this study (Merck Sharp & Dohme Corp.) subsidized the study drug and reviewed the final manuscript, but did not participate in data collection, analysis, or interpretation; the composition of the manuscript; or the decision to submit for publication.

3 | RESULTS

From 2017 to 2018, a total of six patients were enrolled for the Phase I portion of the trial. An additional three patients were enrolled through 2019 for the Phase II component following the demonstration of safety in Phase I, resulting in a total of nine patients accrued prior to trial closure (Figure 1). Demographic characteristics are listed

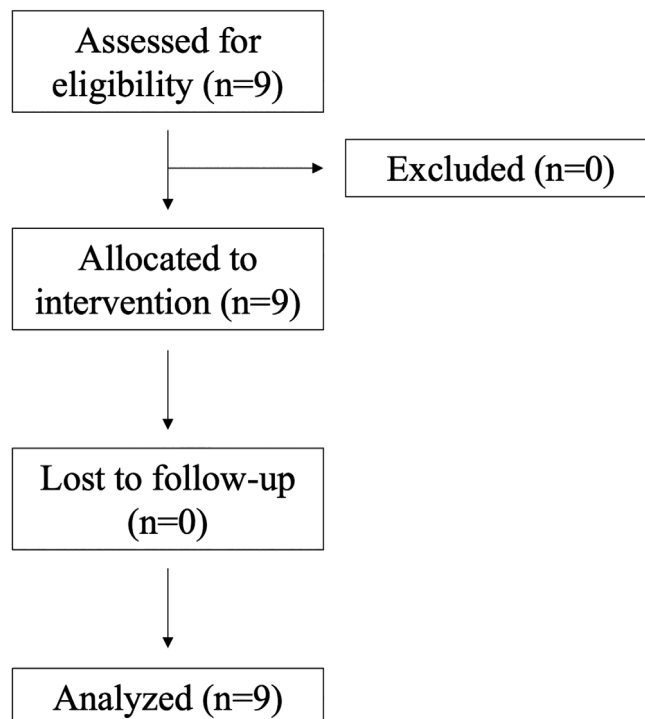


FIGURE 1 Eligibility, allocation, and analysis. A total of nine patients were screened, treated as per protocol, and analyzed

TABLE 1 Baseline characteristics of enrolled patients ($n = 9$)

Characteristic	Patients (% of total)
Median age (range)	54 (37–69)
Gender	
Male	8 (89%)
Female	1 (11%)
Race	
Caucasian	8 (89%)
African-American	1 (11%)
Primary site	
Supraglottis	8 (89%)
Glottis	1 (11%)
Overall Stage per AJCC-8	
III	3 (33%)
IVA	6 (67%)
T Stage per AJCC-8	
2	2 (22%)
3	7 (78%)
N Stage per AJCC-8	
0	3 (33%)
1	0 (0%)
2a	1 (11%)
2b	2 (22%)
2c	3 (33%)

in Table 1. Eight patients were enrolled at the University of Cincinnati and one patient was enrolled at University of Washington. The median age of enrolled patients was 54 (range, 37–69). Eight of the patients were male and eight patients were Caucasian (89% for each). Eight patients had supraglottic primary tumors and one patient had a glottic primary. The majority of patients had Stage IVA ($n = 6$) disease with the remaining three patients categorized as Stage III per AJCC-8.

All patients completed the planned course of radiation therapy except for one patient who received 66 Gy before being admitted for diabetic ketoacidosis (DKA) unrelated to study treatment. The majority of patients ($n = 6$) received all three planned doses of cisplatin at 100 mg/m²; the remaining three patients received two doses of cisplatin, which was allowable per protocol. No patients received cisplatin at a reduced dose. All patients received the planned four doses of pembrolizumab. Data from all nine enrolled patients were evaluable with a median follow-up time of 30.1 months from the date of trial enrollment.

3.1 | Laryngeal preservation

No enrolled patients required laryngectomy, resulting in 100% organ preservation at the primary timepoint of 18 months as well as the secondary timepoint of 12 months (Figure 2). The median duration of organ preservation was not reached. Of note, three patients died prior to the 18-month timepoint but did not undergo laryngectomy and were not counted for this outcome as a result.

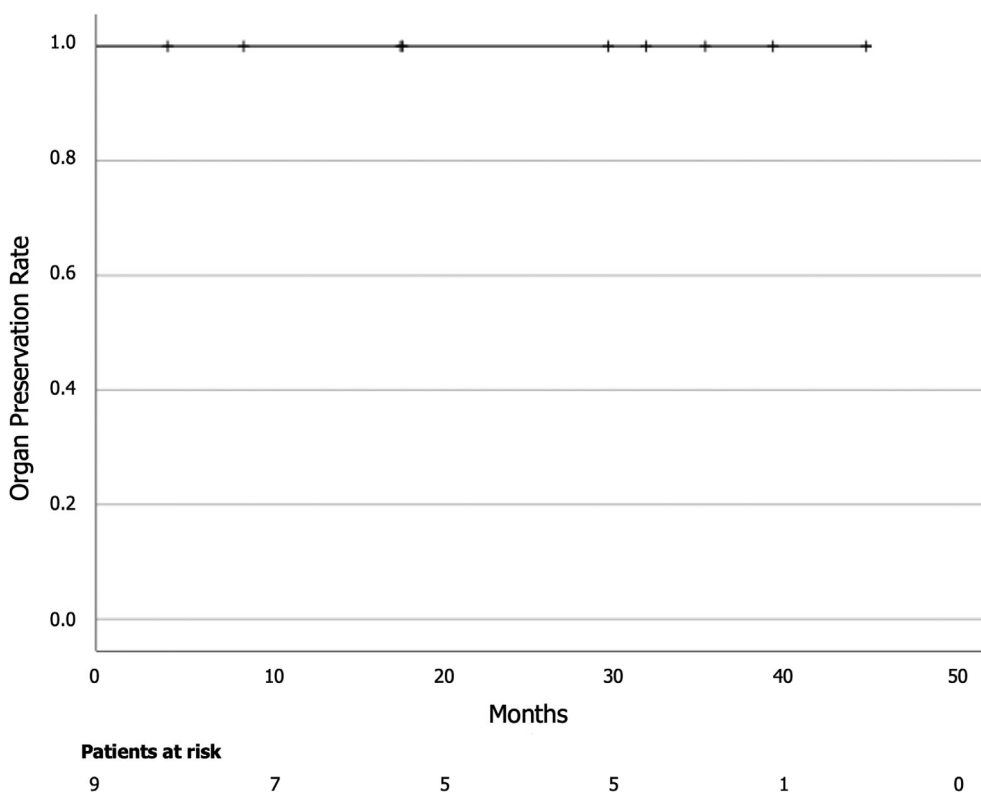
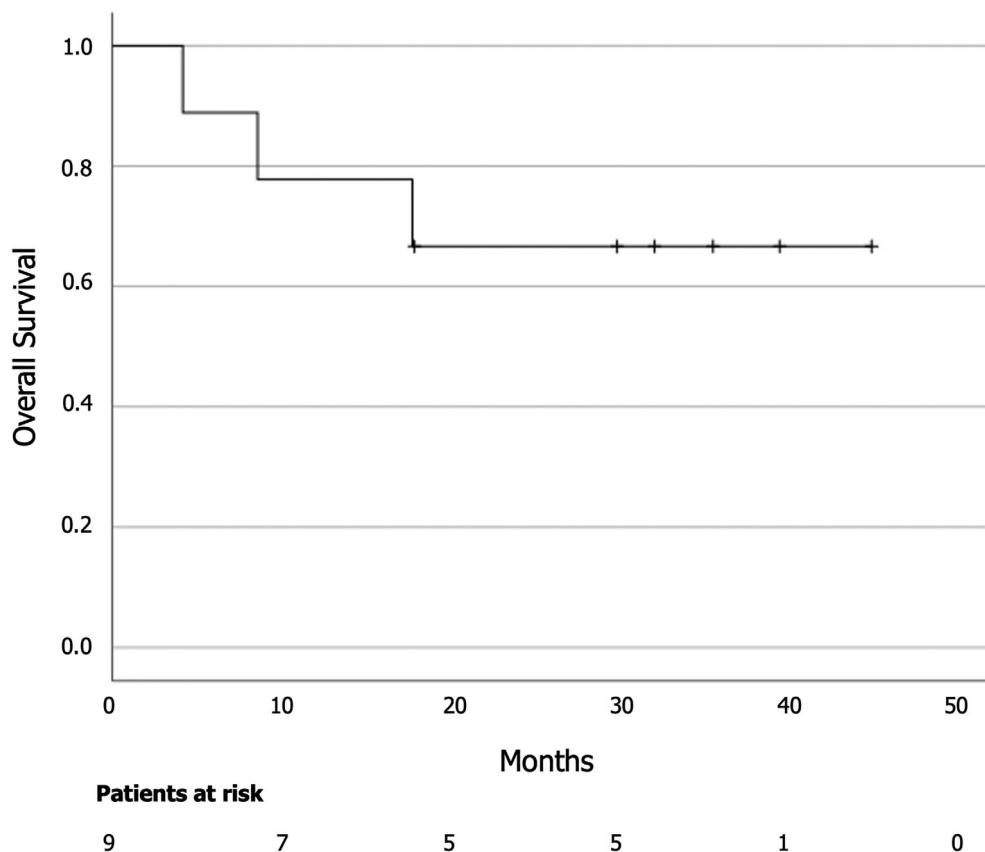


FIGURE 2 Kaplan–Meier curve for OPR. No patient in the trial cohort required laryngectomy, leading to 100% OPR at a median follow-up interval of 30.1 months

FIGURE 3 Kaplan–Meier curve for OS. The secondary endpoint of 12-month OS was 77.8% and median OS was not reached. Six of the nine patients on the trial were alive at time of last follow-up and two of the patient deaths were due to co-morbid conditions rather than malignancy



3.2 | Survival outcomes

At 12 months, there were two deaths among the enrolled patients. One of these patients had multiple admissions for DKA prior to and during treatment that were deemed to be a result of poor home glucose monitoring, which ultimately resulted in DKA as the cause of death ~1 month after completing chemoradiation. The second patient died from progression of malignancy at ~5 months following completion of radiation; persistent uptake at the initially treated site and metastatic disease were noted at 3-month post-treatment PET imaging. The 12-month OS rate was 77.8% (Figure 3). At ~15 months post-treatment, an additional patient died from acute aortic occlusion. This patient had severe peripheral vascular disease and there was no evidence of malignant disease at the time of death. The estimated median OS was not reached. As no laryngectomy events occurred, LFS was equivalent to OS at all-time points.

Oncologic EFS at 12 months was 87.5%. The patient described above died from progression of disease at ~5 months post-treatment. A second patient was treated empirically with radiation for a pulmonary nodule at 16 months following the completion of treatment. This patient had an ~60-pack-year history of smoking. On evaluation by Thoracic Surgery, the nodule was felt to be most consistent with a primary lung cancer, but metastasis from laryngeal cancer could not be excluded and the case was recorded as a progression event. This patient remains alive as of final analysis in February 2021. At the 12-month post-treatment timepoint, PFS was 77.8%.

TABLE 2 Acute Grade 3+ adverse events observed

Grade	Total events	Attribution to treatment (% per Grade)		
		Cisplatin	Radiation	Pembrolizumab
3	23	12 (52%)	7 (30%)	1 (4%)
4	3	2 (67%)	0 (0%)	0 (0%)
5	0	0 (0%)	0 (0%)	0 (0%)

Note: One Grade 3 (colitis) was classified as a late event and was attributed to pembrolizumab. One late Grade 4 event (laryngeal edema) was categorized as possibly related to pembrolizumab.

3.3 | Toxic effects

There were a total of 26 Grade 3 or greater acute toxicities reported, 23 of which were Grade 3 (Table 2). Most adverse events were attributable to chemoradiation (54% cisplatin, 27% radiation). One acute Grade 3 toxicity (sore throat) and one late Grade 3 toxicity (colitis, 77 days after completing treatment) were attributed to pembrolizumab. All acute Grade 4 ($n = 3$) toxicities occurred in a single patient with poorly controlled diabetes at baseline. This patient died shortly after treatment due to DKA that was not attributable to treatment. One patient experienced late Grade 4 laryngeal edema, which required tracheostomy ~8 months following chemoradiation. The edema resolved without intervention and the tracheostomy was reversed at 15 months after placement.

4 | DISCUSSION

In this trial, the use of concurrent pembrolizumab with chemoradiation for locally advanced larynx cancer was well-tolerated overall with the majority of Grade 3+ acute toxicities attributable to chemoradiation rather than pembrolizumab. Among the nine patients included in this study, laryngeal preservation was achieved in all cases at a median follow up of 30.1 months. Although the follow-up in our study was shorter than that of RTOG 91-11, 80% of salvage laryngectomies in this historical study occurred during the first 2 years after treatment and no laryngectomies were performed in the median follow-up of 30.1 months in our trial.⁶ Despite the lower than expected accrual, this finding is significant and novel as there are little data for the concurrent use of immunotherapy with standard of care cisplatin-based chemotherapy and radiation for head and neck cancer. Although there are ongoing trials with combination approaches using immunotherapy, the vast majority of them use immunotherapy in combination with chemotherapy in the metastatic setting or after chemoradiation in the adjuvant setting. The recent JAVELIN Head and Neck 100 and GORTEC-REACH trials investigated avelumab with chemoradiation in locally advanced HNSCC, but failed to meet their primary PFS endpoints.¹⁹⁻²¹ However, the majority of patients in each study had oropharyngeal cancer, which could have masked the benefit of concurrent immunotherapy given the more favorable prognosis at this subsite.

Although larynx preservation with chemoradiation was shown to be a viable approach in RTOG 91-11, long-term survival outcomes remain suboptimal for larynx cancer and efforts at treatment intensification are limited by the toxicity of existing approaches. The 12-month OS was 77.8% in this study and the median OS was not reached; of note, six of nine patients remained alive at the time of last follow up. Two of the patients who died during the follow-up period had existing comorbidities that led to death from causes not related to malignancy or treatment. Oncologic EFS at 12 months was similarly favorable at 87.5%.

Several studies have shown a possible increase in efficacy of immunotherapy with higher levels of tumor PD-L1 expression,²² but the data on this topic are mixed.¹³ Although our trial demonstrated a good response without stratification by PD-L1 expression or other markers, this represents a future direction that could result in further treatment de-intensification. Patients who cannot receive cisplatin are another potential group for whom the reliable prediction of immunotherapy effect is important. An example of this approach is seen in the NRG-HN004 trial assessing durvalumab versus cetuximab as single agents in combination with definitive radiation in locoregionally advanced head and neck cancer patients ineligible for cisplatin.²³ Of note, NRG-HN004 is currently on hold for interim analysis and its ultimate clinical impact will be highly dependent upon whether it is completed as planned after this assessment.

One patient in this trial experienced late Grade 4 laryngeal edema at 8 months after chemoradiation and required tracheostomy. This toxicity resolved without intervention and the tracheostomy was reversed. Of note, this patient had mild laryngeal edema present on video stroboscopy in the immediate post-treatment period. It has been previously shown that significant laryngeal edema (RTOG Grade

2+) occurred in up to 44% of patients treated with radiation with or without chemotherapy for laryngohypopharyngeal squamous cell carcinoma and that the relative risk of this complication was 5.07 in T2-4 versus T1 tumors.²⁴ Given the locally advanced stage of patients in our trial, it is possible that the observed late Grade 4 laryngeal edema event was due to chemoradiation. However, the time of progression of edema to the point of requiring intervention was later than expected, leading to the possibility that the pro-inflammatory effect of immunotherapy contributed to this toxicity. A similar event occurred in a patient treated with combined nivolumab and ipilimumab immunotherapy with concurrent chemoradiation at another institution, further supporting this theory.²⁵ Although additional evidence beyond the aforementioned two cases is needed to better establish the potential risk of laryngeal edema, it represents an important consideration in future trials assessing the optimal timing of combinations of chemoradiation and immunotherapy.

This study had several limitations. Due to slow accrual, the trial was closed in 2019 after accruing nine patients. The primary challenge with accrual was felt to be the relatively limited pool of patients with locally advanced disease who were eligible for high-dose cisplatin and candidates for organ preservation. The small sample size of this trial and the lack of randomization limit the strength of its results and the ability to compare outcomes to historical trials as well as to definitively assess the contribution of pembrolizumab to acute toxicities. Although the trial was multi-institutional, another limitation is that the majority of enrolled patients were from a single institution. Larger randomized studies would be warranted prior to widespread adoption of the study regimen. However, given its combined Phase I and II intent and the lack of other published studies using immunotherapy in the upfront treatment of laryngeal cancer, this trial provides a foundation for future study.

5 | CONCLUSION

The treatment of locally advanced laryngeal cancer has evolved from routine use of total laryngectomy to the adoption of chemoradiation as a larynx-preserving approach. Despite its success in terms of organ preservation, survival outcomes are suboptimal and treatment intensification is limited by toxicity. UCCI-HN-15-02 demonstrated the safety of adding immunotherapy to definitive chemoradiation and the patient outcomes suggest the potential for improving long-term survival while minimizing negative impact from treatment. Although results from this trial were promising, a randomized study with a larger number of patients and longer follow-up is warranted to verify this treatment approach prior to wider adoption.

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CONFLICT OF INTEREST

Andrew J. Frankart was supported by the ASTRO-AstraZeneca Radiation Oncology Research Training Fellowship. Nooshin Hashemi Sadraei is currently employed by Amgen Inc. Trisha Wise-Draper has a separate clinical trial with support from Merck (NCT 02641093). For the remaining authors, no conflicts of interest were declared.

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