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Original Article

Immune-Related Adverse Events Are Associated With Improved Response, Progression-Free Survival, and Overall Survival for Patients With Head and Neck Cancer Receiving Immune Checkpoint Inhibitors

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BACKGROUND: The authors hypothesized that patients developing immune-related adverse events (irAEs) while receiving immune checkpoint inhibition (ICI) for recurrent/metastatic head and neck cancer (HNC) would have improved oncologic outcomes. **METHODS:** Patients with recurrent/metastatic HNC received ICI at 2 centers. Univariate and multivariate logistic regression, Kaplan-Meier methods, and Cox proportional hazards regression were used to associate the irAE status with the overall response rate (ORR), progression-free survival (PFS), and overall survival (OS) in cohort 1 (n = 108). These outcomes were also analyzed in an independent cohort of patients receiving ICI (cohort 2; 47 evaluable for irAEs). **RESULTS:** The median follow-up was 8.4 months for patients treated in cohort 1. Sixty irAEs occurred in 49 of 108 patients with 5 grade 3 or higher irAEs (10.2%). ORR was higher for irAE+ patients (30.6%) in comparison with irAE– patients (12.3%; *P* = .02). The median PFS was 6.9 months for irAE+ patients and 2.1 months for irAE– patients (*P* = .0004), and the median OS was 12.5 and 6.8 months, respectively (*P* = .007). Experiencing 1 or more irAEs remained associated with ORR (*P* = .03), PFS (*P* = .003), and OS (*P* = .004) in multivariate analyses. The association between development of irAEs and prolonged OS persisted in a 22-week landmark analysis (*P* = .049). The association between development of irAEs and favorable outcomes was verified in cohort 2. **CONCLUSIONS:** The development of irAEs was strongly associated with an ICI benefit, including overall response, PFS, and OS, in 2 separate cohorts of patients with recurrent/metastatic HNC. ***Cancer* 2021;0:1-9**. © *2021 American Cancer Society*.

KEYWORDS: immune checkpoint inhibitor, immunotherapy, metastasis, squamous cell carcinoma of head and neck, toxicity.

INTRODUCTION

Head and neck cancers (HNCs) represent a significant disease burden, with 66,000 new diagnoses and 15,000 cancer-related deaths expected in the United States in 2020,[1] and the increasing incidence of human papillomavirus (HPV)–associated oropharyngeal cancer[2-4] suggests that the prevalence of HNCs will continue to rise for the foreseeable future. Contemporary landmark trials[5-7] have prompted a paradigm shift toward immunotherapy as an attractive option for patients with recurrent or metastatic HNC, and it has moved to the first-line setting as standard of care on the basis of the positive results of KEYNOTE-048. Although the response to anti–programmed death 1 (PD-1) therapy in this setting appears to be enhanced with increased tumoral expression of programmed death ligand 1 (PD-L1),[5,7-9] PD-L1 remains an imperfect biomarker because tumoral expression is spatially and temporally heterogeneous, and an assessment of positivity requires an invasive biopsy.[10] Therefore, alternative biomarkers, including the tumor mutational burden, gene expression signatures, and blood-based markers, are being evaluated.[9]

Because of PD-L1's drawbacks as a biomarker for responses to immune checkpoint inhibition (ICI), alternative indicators of immune competence that identify patients most likely to benefit from ICI may be of greater clinical utility. The search for such optimal biomarkers would likely be most efficient when focused on target populations known to have favorable responses to ICI. Such biomarkers may indicate with a higher degree of immune competence. Specifically, the ability to develop immune-related adverse events (irAEs) has been correlated with improved antitumor responses in patients with various primary malignancies, and this suggests that it could be one such indicator.[11-25] Despite these prior

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associations between irAEs and improved outcomes with ICI, the relationship between irAEs and prognosis is less clear for patients with HNC. We hypothesized that experiencing irAEs would be associated with an improved overall response rate (ORR), improved progression-free survival (PFS), and improved overall survival (OS) for patients with recurrent or metastatic HNC and thereby could identify candidate patients with favorable immune competence for the investigation of meaningful pretreatment biomarkers.

MATERIALS AND METHODS

Patient Population

The medical records of 114 patients (108 evaluable for their irAE status) with metastatic HNC consecutively receiving ICI at the University of Chicago from June 17, 2013, to September 29, 2017, were retrospectively reviewed in an institutional review board–approved study. The medical records of an external patient cohort (n = 47) with metastatic HNC consecutively treated with ICI from April 28, 2014, to April 12, 2018, at Providence Cancer Institute were also retrospectively reviewed with institutional review board approval. All patients underwent a complete history and physical as well as baseline diagnostic imaging and laboratory assessments confirming adequate organ and bone marrow function before they received ICI. Treatments before ICI was started were diverse and included combinations of surgery, radiation, chemoradiation, and/or systemic chemotherapy as deemed appropriate by the treating physician. Among patients with oropharyngeal cancer treated at the University of Chicago, 42 had a known HPV status determined by p16 immunohistochemistry and/or HPV polymerase chain reaction, whereas 17 patients with oropharyngeal primaries from Providence Cancer Institute had a known HPV status. Furthermore, 78 patients from the University of Chicago had tumor specimens subjected to tumor PD-L1 immunostaining using the E1L31 antibody (Cell Signaling, Danvers, Massachusetts). Tumor PD-L1 expression was assessed, and positivity was defined as expression in ≥1% of tumor cells. PD-L1 combined positivity scores were not assessed or available in either patient cohort, and the tumor PD-L1 status was not routinely assessed for patients at Providence Cancer Institute.

Treatment Details

All patients received ICI with anti-PD(L)1 therapy, and treatment was independent/unselected for tumor PD-L1 expression. Among University of Chicago patients, ICI included nivolumab for 31 patients, pembrolizumab for 75 patients, and durvalumab for 2 patients, whereas ICI consisted of nivolumab for 29 patients, pembrolizumab for 14 patients, durvalumab for 3 patients, and cemiplimab for 1 patient at Providence Cancer Institute. Patients were generally continued on immunotherapy until the development of dose-limiting toxicity or clinical/radiographic progression. While receiving ICI, patients routinely underwent follow-up, including a physical examination, a laboratory evaluation, and imaging, to assess for a clinical response as dictated by individual protocols or clinical judgment, with diagnostic imaging most often performed at a minimum interval of every 3 months. The best overall response was determined with the Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1) for both patient cohorts. Toxicities were prospectively graded for all patients according to the Common Terminology Criteria for Adverse Events (version 4.0).

Statistical Analyses

irAEs were considered to be any possibly immune-mediated adverse events as determined by physician review, regardless of grade or treatment attribution. The types, numbers, and grades of irAEs during the receipt of ICI were summarized with descriptive statistics. Comparisons of patient- and treatment-related variables were performed via χ^2 analysis for categorical variables or via univariate regression for continuous variables. The relationship between irAE positivity and a complete or partial response (eg, ORR) by RECIST (version 1.1) was assessed via univariate and multivariate logistic regression. Kaplan-Meier curves estimated PFS and OS as a function of the irAE status, with comparisons between groups performed with the log-rank test. Both PFS and OS were calculated from the start date of ICI. For multivariate analyses, Cox proportional hazards regression was used. Factors associated with PFS and OS ($P < .10$) in the univariate analysis were included in multivariate analyses.

To correct for a potential time-related bias, a landmark analysis using the Kaplan-Meier method at 22 weeks (5.5 months) was performed for OS. The 22-week landmark time was chosen in an attempt to balance the risks and benefits associated with a late landmark potentially lowering the sample size and an earlier landmark potentially misclassifying a larger number of patients experiencing irAEs in the analysis. Furthermore, this was close to the median duration of

TABLE 1. Patient- and Treatment-Related Characteristics

Characteristic	Entire Cohort (n = 108)	Immune AE (n = 49)	No Immune AE (n = 59)	P^a
Age, median (range), y	60 (25-85)	61 (33-85)	59 (25-83)	.19
Disease site, No. (%)				.66
Hypopharynx	5 (4.6)	4 (8.2)	1 (1.7)	
Larynx	10 (9.3)	6 (12.2)	4 (6.8)	
Oral cavity	29 (26.9)	13 (26.5)	16 (27.1)	
Oropharynx	47 (43.5)	19 (38.8)	28 (47.5)	
Nasal cavity	5 (4.6)	2 (4.1)	3 (5.1)	
Unknown primary	4 (3.7)	2 (4.1)	2 (3.3)	
Other or multiple sites	8 (7.4)	3 (6.1)	5 (8.5)	
Sex, No. (%)				.72
Male	82 (75.9)	38 (77.6)	44 (74.6)	
Female	26 (24.1)	11 (22.4)	15 (25.4)	
Ethnicity, No. (%)				.61
White	89 (82.4)	39 (79.6)	50 (84.7)	
African American	11 (10.2)	7 (14.3)	4 (6.8)	
Asian/Mideast Indian	5 (4.6)	2 (4.1)	3 (5.1)	
Other	3 (2.8)	1 (2.0)	2 (3.3)	
HPV status (oropharynx only), No. (%)				.51
Positive	33 (30.6)	15 (78.9)	18 (64.3)	
Negative	9 (8.3)	3 (15.8)	6 (21.4)	
Unknown	5 (4.6)	1 (5.3)	4 (14.3)	
No. of prior treatments, median (range)	2 (0-6)	2 (0-5)	2 (0-6)	.97
Tobacco use, No. (%)				.65
Yes	70 (64.8)	33 (67.3)	37 (62.7)	
No	33 (30.6)	14 (28.6)	19 (32.2)	
Unknown	5 (4.6)	2 (4.1)	3 (5.1)	
PD-L1 status, No. (%)				.76
Positive	55 (51.0)	26 (53.1)	29 (49.2)	
Negative	23 (21.3)	10 (20.4)	13 (22.0)	
Unknown	30 (27.8)	13 (26.5)	17 (28.8)	

Abbreviations: AE, adverse event; HPV, human papillomavirus; PD-L1, programmed death ligand 1.
[a]Comparing those with immune AEs and those with no immune AEs.

ICI therapy among irAE+ patients, and previous reports documenting long-term outcomes for patients receiving ICI have demonstrated that treatment-related adverse events are stable after a median time on treatment of 22 weeks.[26] A landmark analysis was not performed for the cohort of patients treated at Providence Cancer Institute because the small sample size limited statistical inference. All analyses were performed with JMP Statistical Software (version 13.0; SAS Institute, Cary, North Carolina).

RESULTS

Patient and irAE Characteristics

The baseline characteristics for all University of Chicago patients and for irAE+ and irAE− subsets are displayed in Table 1. A large proportion of the patients were male (82 of 108 [75.9%]) with a median age of 60 years (range, 25-85 years) and with primary lesions of the oropharynx (47 of 108 [43.5%]). Most of the patients with oropharyngeal disease and a known HPV status (n = 42) had HPV-associated tumors (33 of 42 [78.6%]), and these individuals were similarly distributed in the irAE+/− groups ($P = .51$). Furthermore, 78 patients had a known tumor PD-L1 status, with 55 (70.5%) being positive for PD-L1 (47 of 55 with tumor PD-L1 expression of 1%-49% and 8 of 55 with tumor PD-L1 expression ≥ 50%). The proportions of patients with known PD-L1–positive tumors were similar in the irAE+ and irAE− cohorts (26 of 36 [72.2%] for irAE+ vs 29 of 42 [69.0%] for irAE−; $P = .76$). Patients were heavily pretreated with a median of 2 prior lines of systemic therapy (range, 0-6) with or without concurrent radiation in the definitive or palliative setting. The median duration of ICI therapy was 23 weeks among irAE+ patients and 12 weeks among irAE− patients ($P = .0006$).

Among patients treated at the University of Chicago, there were a total of 60 irAEs occurring in 49 of 108 patients (45.4%), with 8 of the 49 patients (16.3%) experiencing more than 1 irAE. irAE types and severities are displayed in Table 2, and the median time to irAE incidence in the irAE+ group was 42 days (interquartile range, 19-84 days), with 2 patients developing irAEs beyond 22 weeks. The majority of irAEs were dermatologic (21 of 60 [35.0%]), endocrine (14 of 60 [23.3%]), or musculoskeletal (15 of 60 [25.0%]). Low-grade irAEs were common, with grade 1 and 2 events

TABLE 2. Characteristics of Immune Adverse Events

Characteristic	No. (% of Events)
Type of immune adverse event	
Dermatologic	21 (35.0)
Pulmonary	1 (1.7)
Gastrointestinal	1 (1.7)
Endocrinopathy	14 (23.3)
Musculoskeletal	15 (25.0)
Ophthalmologic	2 (3.3)
Transaminitis	6 (10.0)
Type of immune adverse event by grade	
1	41 (68.3)
Dermatologic	16 (26.7)
Pulmonary	0 (0)
Gastrointestinal	0 (0)
Endocrinopathy	10 (16.7)
Musculoskeletal	13 (21.7)
Ophthalmologic	0 (0)
Transaminitis	2 (3.3)
2	14 (23.3)
Dermatologic	4 (6.7)
Pulmonary	0 (0)
Gastrointestinal	0 (0)
Endocrinopathy	4 (6.7)
Musculoskeletal	1 (1.7)
Ophthalmologic	1 (1.7)
Transaminitis	4 (6.7)
3	5 (8.3)
Dermatologic	1 (1.7)
Pulmonary	1 (1.7)
Gastrointestinal	1 (1.7)
Endocrinopathy	0 (0)
Musculoskeletal	1 (1.7)
Ophthalmologic	1 (1.7)
Transaminitis	0 (0)

representing 68.3% (41 of 60) and 23.3% (14 of 60) of all irAEs, respectively. Grade 3 irAEs occurred in 10.2% of the patients (5 of 49) and included arthralgias in bilateral shoulders (n = 1), uveitis (n = 1), macular rash (n = 1), pneumonitis (n = 1), and colitis (n = 1). No grade 4 or higher irAEs occurred in the University of Chicago cohort.

Treatment Response

The results of univariate and multivariate analyses investigating factors associated with RECIST (version 1.1) responses for University of Chicago patients are displayed in Table 3. The number of prior treatments (odds ratio [OR], 0.52, 95% confidence interval [CI], 0.31-0.87; $P = .01$), age (OR, 1.04; 95% CI, 1.00-1.10; $P = .06$), and irAE positivity (OR, 3.15; 95% CI, 1.16-8.54; $P = .02$) were associated with the likelihood of experiencing at least a partial response in the univariate analysis. Specifically, patients in the irAE+ group had an ORR of 30.6%, whereas it was 12.3% for irAE− patients. In the multivariate analysis, irAE positivity continued to be independently associated with a likelihood of response to ICI (OR, 3.23; 95% CI, 1.12-9.29; $P = .03$).

TABLE 3. Regression Analysis for Any Response

Covariate	Odds Ratio	95% Confidence Interval	*P*
Univariate			
Age	1.04	1.00-1.10	.06
Disease site			
Other	1.00 (reference)		
Oropharynx	1.11	0.43-2.86	.83
Sex			
Male	1.00 (reference)		
Female	1.2	0.41-3.48	.74
Ethnicity			
White	1.00 (reference)		
Non-White	0.39	0.08-1.85	.24
HPV-positive	0.98	0.17-5.82	.98
No. of prior treatments	0.52	0.31-0.87	.01
Tobacco use	1.63	0.54-4.93	.39
PD-L1–positive	1.11	0.36-3.41	.85
Immune adverse event–positive	3.15	1.16-8.54	.02
Multivariate			
Age	1.04	0.99-1.09	.09
No. of prior treatments	0.49	0.28-0.85	.01
Immune adverse event–positive	3.23	1.12-9.29	.03

Abbreviations: HPV, human papillomavirus; PD-L1, programmed death ligand 1.

Survival Outcomes

The median follow-up for all surviving University of Chicago patients was 8.4 months (interquartile range, 4.7-24.0 months). Table 4 displays factors associated with PFS. In the univariate analysis, age (hazard ratio [HR], 0.97; 95% CI, 0.96-0.99; $P = .008$), number of prior treatments (HR, 1.20; 95% CI, 1.01-1.41; $P = .03$), and irAE status (HR, 0.45; 95% CI, 0.28-0.70; $P = .0005$) were associated with PFS, whereas tumor PD-L1 positivity was not ($P = .63$). Notably, experiencing 1 or more irAEs was associated with a median PFS of 6.9 months in contrast to 2.1 months for irAE− patients, as displayed in Figure 1. Additionally, a multivariate analysis including variables significantly associated with PFS in the univariate analysis found irAE positivity to be independently associated with improved PFS (HR, 0.49; 95% CI, 0.30-0.78; $P = .003$).

Among University of Chicago patients, factors associated with OS are displayed in Table 5. Disease site (oropharynx vs other, HR, 0.63; 95% CI, 0.39-0.99; $P = .05$), number of prior treatments (HR, 1.21; 95% CI, 1.01-1.43; $P = .03$), and irAE status (HR, 0.53; 95% CI, 0.33-0.85; $P = .008$) were associated with OS in the univariate analysis, whereas PD-L1 positivity was not ($P = .58$). Notably, irAE+ patients experienced a median OS 5.7 months longer than that of

TABLE 4. Regression Analysis for Progression-Free Survival

Covariate	Hazard Ratio	95% Confidence Interval	*P*
Univariate			
Age	0.97	0.96-0.99	.008
Disease site			
Other	1.00 (reference)		
Oropharynx	1.07	0.69-1.65	.76
Sex			
Male	1.00 (reference)		
Female	1.10	0.65-1.79	.71
Race/ethnicity			
White	1.00 (reference)		.99
African American	0.95	0.44-1.80	
Asian/Mideast Indian	1.09	0.27-2.95	
Hispanic/Latino	1.16	0.19-3.73	
HPV-positive	0.80	0.37-2.01	.61
No. of prior treatments	1.20	1.01-1.41	.03
Tobacco use	0.68	0.43-1.10	.11
PD-L1–positive	1.14	0.67-2.02	.63
Immune adverse event–positive	0.45	0.28-0.70	.0005
Multivariate			
Age	0.98	0.96-1.00	.04
No. of prior treatments	1.23	1.03-1.44	.02
Immune adverse event–positive	0.49	0.30-0.78	.003

Abbreviations: HPV, human papillomavirus; PD-L1, programmed death ligand 1.

irAE− patients (median, 12.5 months for irAE+ patients vs 6.8 months for irAE− patients) and continued to experience significantly improved OS in the 22-week landmark analysis (median, 25.3 months for irAE+ patients [n = 20] vs 13.4 months for irAE− patients [n = 14]; $P = .047$), as displayed in Figure 1. Moreover, experiencing 1 or more irAEs remained independently associated with OS (HR, 0.49; 95% CI, 0.30-0.79; $P = .004$) in a multivariate analysis.

Analyses investigating the association between irAE type and grade and OS for University of Chicago patients are displayed in Supporting Tables 1 and 2, respectively. In a univariate Cox proportional hazards regression, only dermatologic irAEs (HR, 0.38; 95% CI, 0.19-0.76; $P = .002$), pulmonary irAEs (HR, 11.0; 95% CI, 0.60-58.7; $P = .09$), and endocrine-related irAEs (HR, 0.47; 95% CI, 0.22-0.90; $P = .02$) were associated with OS. Both dermatologic irAEs (HR, 0.42; 95% CI, 0.21-0.84; $P = .007$) and endocrine-related irAEs (HR, 0.49; 95% CI, 0.24-0.99; $P = .03$) remained associated with OS in a multivariate analysis when dermatologic, endocrine-related, and pulmonary

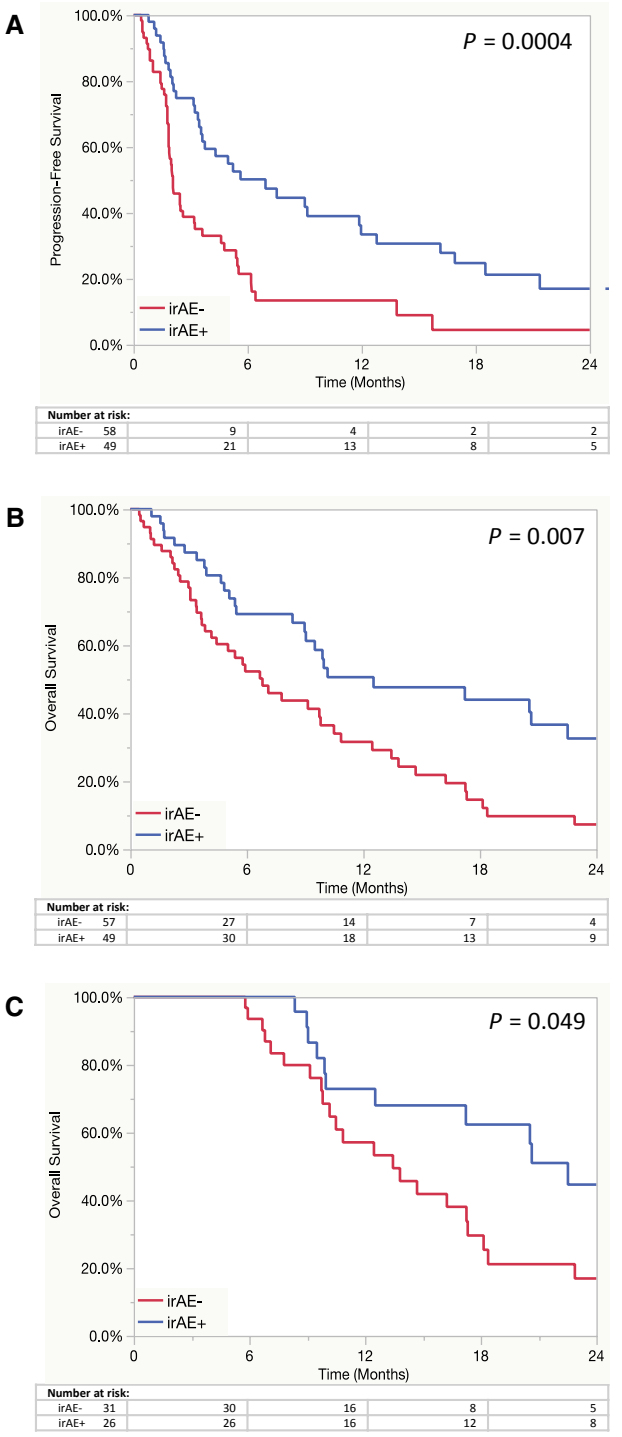

Figure 1. (A) Progression-free survival as a function of the irAE status. (B) Overall survival as a function of the irAE status. (C) Landmark analysis 22 weeks after the initiation of anti–PD-1 therapy for overall survival as a function of the irAE status. irAE indicates immune-related adverse event; PD-1, programmed death 1.

TABLE 5. Regression Analysis for Overall Survival

Covariate	Hazard Ratio	95% Confidence Interval	*P*
Univariate			
Age	0.98	0.97-1.00	.13
Disease site			
Other	1.00 (reference)		
Oropharynx	0.63	0.39-0.99	.05
Sex			
Male	1.00 (reference)		
Female	1.03	0.57-1.75	.93
Race/ethnicity			
White	1.00 (reference)		.11
African American	0.26	0.06-0.70	
Asian/Mideast Indian	1.17	0.19-3.81	
Hispanic/Latino	2.43	0.13-12.06	
HPV-positive	1.01	0.37-3.51	.99
No. of prior treatments	1.21	1.01-1.43	.03
Tobacco use	0.68	0.41-1.13	.13
PD-L1–positive	1.18	0.67-2.16	.58
Immune adverse event–positive	0.53	0.33-0.85	.008
Multivariate			
Disease site			
Other	1.00 (reference)		
Oropharynx	0.57	0.36-0.91	.02
No. of prior treatments	1.21	1.01-1.43	.04
Immune adverse event–positive	0.49	0.30-0.79	.004

Abbreviations: HPV, human papillomavirus; PD-L1, programmed death ligand 1.

irAEs were included as covariates. Furthermore, there was a significant association between grade 1 (HR, 0.46; 95% CI, 0.23-0.86; $P = .01$) and grade 2 irAEs (HR, 0.52; 95% CI, 0.27-0.93; $P = .03$) and OS, but there was no significant association for grade 3 irAEs (HR, 1.02; 95% CI, 0.31-2.53; $P = .97$). Rapid development of an irAE ≤2 weeks from the initiation of ICI was not statistically significantly associated with OS.

External Patient Cohort Results

Among the 47 patients receiving ICI at Providence Cancer Institute, with a median follow-up of 14.9 months (interquartile range, 10.4-27.4 months) for surviving patients, the median age was 60 years, with 85.1% being male, as displayed in Supporting Table 3. Within this cohort, 19 irAEs occurred in 17 patients, with most being dermatologic (5 of 19 irAEs [26.3%]) or pulmonary (3 of 19 irAEs [15.8%]) and low grade (12 of 17 patients with the worst irAE grade ≤ 2 [70.6%]), as detailed in Supporting Table 4. Experiencing 1 or more irAEs was significantly associated with PFS (median PFS, 9.2 months for irAE+ vs 3.6 months for irAE−; $P = .0002$) and OS (median OS, 36.4 months for irAE+ vs 8.2 months for irAE−; $P = .001$), as displayed in Figure 2A,B, respectively. Moreover, developing 1 or more irAEs remained independently associated with PFS (HR, 0.29; 95% CI, 0.13-0.59; $P = .001$) and OS (HR, 0.20; 95% CI, 0.07-0.50; $P = .002$) in multivariate survival analyses, as displayed in Supporting Tables 5 and 6, respectively. Finally, Supporting Table 7 demonstrates that the irAE status was significantly associated with response in both univariate (OR, 12.86; 95% CI, 2.77-59.66; $P = .001$) and multivariate analyses (OR, 30.90; 95% CI, 3.08-309.65; $P = .004$).

DISCUSSION

Within 2 separate cohorts of patients with recurrent/metastatic HNC receiving ICI, experiencing 1 or more irAEs was associated with significantly improved clinical outcomes, including response, PFS, and OS. IrAEs were common and occurred in 45.4% of patients (49 of 108) treated at the University of Chicago and in 36.2% of patients (17 of 47) treated at Providence Cancer Institute. Despite this high incidence, the vast majority of irAEs were low grade, with grade 3 or higher irAEs occurring in just 10 of 66 patients (15.2%) treated at both sites. Furthermore, the most common irAEs were dermatologic, musculoskeletal, or endocrine-related, with dermatologic and endocrine-related irAEs having the strongest association with OS among University of Chicago patients. Importantly, the association between irAE status and OS persisted in a 22-week landmark analysis for patients treated at the University of Chicago, and this mitigates the likelihood that this association is confounded by differences in the duration of ICI according to the irAE status. Similar statistical results between groups of patients receiving ICI at a different clinical facility strengthen the conclusion that experiencing 1 or more irAEs in this setting is associated with favorable oncologic outcomes.

The association between 1 or more irAEs during the receipt of ICI and improved oncologic outcomes likely stems from the role of the PD-1/PD-L1 axis in the maintenance of self-tolerance for normal tissues[27] and the potential for cross-reactivity among antigens on the surface of tumor and nontumor cells.[28] Importantly, the development of irAEs is a potential surrogate for baseline immune competence because both antitumor response and the primarily T cell–driven pathogenesis of irAEs[29] require a functional baseline endogenous immune response. Despite the postulated importance of baseline immune competence for generating a successful antitumor response on ICI, barriers to an optimally functional endogenous immune system in patients with HNC include

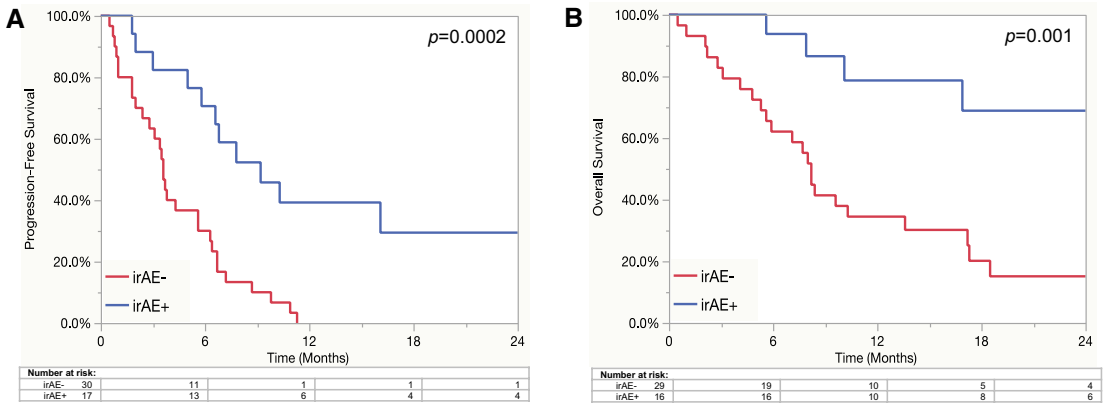

Figure 2. (A) Progression-free survival as a function of the irAE status for patients treated at Providence Cancer Institute. (B) Overall survival as a function of the irAE status for patients treated at Providence Cancer Institute. irAE indicates immune-related adverse event.

immunosuppression attributed to cancer itself and imparted by standard treatments such as cytotoxic chemotherapy/radiation.[30] Although the importance of baseline immune competence is just beginning to be understood and predictive biomarkers are being explored,[31] irAEs appear to preferentially develop in patients who have a systemic and intratumoral immunologic milieu primed for a strong response to ICI as evidenced by the impressive prolongation of OS in irAE+ patients in this report. As such, irAE+ patients may be an ideal candidate population for the identification of novel, measurable pretreatment biomarkers of immune competence that could inform clinical trials investigating the role of immunomodulatory agents in cancer care.

Interestingly, we found that dermatologic and endocrine-related irAEs were most strongly associated with improved OS among patients treated at the University of Chicago, and this suggests that the irAE type may modulate the prognostic association with OS. Dermatologic irAEs have similarly been associated with improved OS for patients with non–small cell lung cancer receiving nivolumab; however, a favorable association with OS was not observed for endocrine-related irAEs in the same cohort.[15] Although this is contradictory to our results, our ability to detect such an association between OS and endocrine-related irAEs was likely markedly enhanced because of our higher relative number of patients with this type of irAE in an HNC population (14 of 49 [28.6%] vs 11 of 134 [8%]). Additionally, specific types of irAEs may be more or less prognostically useful in patients with different primary malignancies. For instance, vitiligo and rash appear to be most prognostic for patients receiving ICI for melanoma.[11,17]

Just as the irAE type may influence the prognosis with immunomodulatory therapy, low-grade irAEs but not high-grade ones were associated with improved OS in patients treated at the University of Chicago. Although prior reports have suggested that grade 3 or higher irAEs are prognostically favorable for a response and the median time to progression,[12] the relatively low number of patients in the University of Chicago cohort experiencing grade 3 or higher irAEs (5 of 49) may have limited our ability to find a similar favorable prognostic relationship with OS. Furthermore, it is reasonable to hypothesize that a low-level breach of self-tolerance induced in immunocompetent individuals receiving ICI may strike the optimal balance between an enhanced antitumor effect and increased competing mortality risks associated with higher grade irAEs.

Our data add to the growing body of literature reporting the safety and efficacy of ICI in current clinical practice. The rate of irAEs in patients treated at 2 separate clinical facilities for HNC is somewhat lower than previously reported rates of approximately 70% for mixed solid malignancies receiving immune checkpoint blockade with anti–PD-1 or anti–PD-L1 agents.[32] Specific subsets of irAEs, including dermatologic (21 of 60 [35.0%]) and endocrine-related irAEs (14 of 60 [23.3%]) at the University of Chicago, occurred somewhat more frequently than has been previously reported in Checkmate 141 patients (15.7% for dermatologic ones and 7.6% for endocrine-related ones)[6] or pooled KEYNOTE-012 patients (9% for rash and 10% for hypothyroidism).[33] One possible explanation for the higher reported rate of any-grade endocrine-related irAEs, including primarily thyroid dysfunction, may

be the high proportion of patients in the University of Chicago group receiving previous radiation (100 of 108 [92.6%]) in comparison with KEYNOTE-012 (146 of 196 [74%])[33] because radiation to the thyroid gland for primary HNC may predispose patients to this adverse event.

Limitations to our study include its retrospective nature and inclusion of patients with diverse characteristics primarily treated on protocol before the use of ICI as standard of care in the setting of metastatic HNC. Additionally, there is no consensus definition for irAEs, and this makes comparisons of our experience with prior reports difficult. Finally, we were unable to evaluate the impact of irAE treatment with corticosteroids because data related to corticosteroid use were not available. Nevertheless, previous reports suggest that corticosteroid use in patients receiving ICI may not affect the prognostic significance of the irAE status[13] or adversely affect OS or the time to treatment failure.[34] Taken together, these findings suggest that the prompt treatment of severe irAEs with corticosteroids is safe, the treatment benefit is robust, and corticosteroid use does not negate the highly favorable association between the development of irAEs and outcomes.

Overall, low-grade irAEs were common for patients unselected for their PD-L1 status who were receiving ICI for recurrent/metastatic HNC. Low-grade irAEs and, in particular, dermatologic and endocrine-related irAEs were most strongly associated with improved OS. Furthermore, experiencing 1 or more irAEs of any grade was associated with superior responses, PFS, and OS in 2 separate patient cohorts. The development of irAEs has a positive prognostic association when patients are receiving ICI for recurrent/metastatic HNC and as such likely reflects immune competence. Future investigations should focus on measurements of baseline immune competence and strategies to modulate immune competence over time. Also, research analyzing the likely complex relationship between irAE management and prognosis is warranted because the majority of patients receiving ICI will experience 1 or more irAEs.

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AUTHOR CONTRIBUTIONS

Corey C. Foster: Conceptualization, data curation, formal analysis, investigation, methodology, writing–original draft, and writing–review and editing. **Marcus A. Couey:** Data curation, investigation, methodology, validation, and writing–review and editing. **Sara E. Kochanny:** Data curation, investigation, and writing–review and editing. **Arun Khattri:** Data curation, investigation, and writing–review and editing. **Rajesh K. Acharya:** Data curation, investigation, and writing–review and editing. **Yi-Hung Carol Tan:** Data curation, investigation, and writing–review and editing. **Ryan J. Brisson:** Data curation and writing–review and editing. **Rom S. Leidner:** Data curation and writing–review and editing. **Tanguy Y. Seiwert:** Conceptualization, data curation, investigation, methodology, project administration, resources, supervision, validation, and writing–review and editing.

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