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# Incidence, Risk Factors, and Effect on Survival of Immune-related Adverse Events in Patients With Non–Small-cell Lung Cancer

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## Abstract

**Immunotherapy is a mainstay of treatment for non–small-cell lung cancer. Serious immune-related adverse events (irAEs) occur; however, their effect on survival is unclear, and no defined risks factors have been elucidated. In the present study, we found no significant effect of irAE on survival in a landmark analysis, and no increased risk of pneumonitis in patients with previous radiation.**

**Background:** The risk factors for immune-related adverse events (irAEs) remain undefined. Recently, a correlation between irAEs and clinical benefit was suggested. We examined the risk factors for irAEs and their effect on survival in patients with non–small-cell lung cancer (NSCLC) who had received immunotherapy. **Patients and Methods:** We performed a retrospective review of patients with NSCLC treated with single-agent immunotherapy at our institution. irAEs were determined by treating physician diagnosis. A landmark analysis was performed at 3 months using log-rank tests and the Bonferroni method. **Results:** irAEs occurred in 27 of 91 patients (30%). The median overall survival (OS) for patients with irAEs was longer than that for patients without (24.3 vs. 5.3 months; hazard ratio, 2.75; 95% confidence interval, 1.54–4.92;  $P < .001$ ). However, a landmark analysis of patients after 3 months of treatment revealed no difference in OS between patients with and without irAEs. No increased risk of pneumonitis was seen in patients with previous thoracic radiotherapy, although these patients had shorter survival (4.2 vs. 9.7 months;  $P = .004$ ). Radiotherapy after the initiation of immunotherapy ( $n = 15$ ) did not increase the risk of irAEs or pneumonitis; however, these patients had improved OS (17.3 vs. 6.0 months;  $P = .016$ ). **Conclusion:** The development of irAEs did not significantly correlate with survival when controlling for the duration of therapy in a landmark analysis. We found no increased risk of pneumonitis or irAEs in patients who had received radiotherapy. Radiotherapy before immunotherapy was associated with shorter survival, and radiotherapy after immunotherapy was associated with improved survival.

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**Keywords:** Immune checkpoint inhibitor, Immunotherapy, irAEs, NSCLC, Toxicity

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## Introduction

Recent studies of immune checkpoint inhibitors (ICIs) have demonstrated dramatic improvement in outcomes for select patients with metastatic non–small-cell lung cancer (NSCLC).<sup>1–3</sup> Overall, these treatments have been well tolerated; however, serious immune-related adverse events (irAEs) can occur,<sup>4</sup> including pneumonitis, colitis, and hepatitis. The reported incidence of irAEs in clinical trials has been relatively low; however, rare fatal events have been reported.<sup>5,6</sup>

The effect of irAEs on survival of patients with NSCLC is uncertain. In melanoma, irAEs appear to be more likely in patients who will derive clinical benefit from treatment with ICIs.<sup>7,8</sup> Recent

# Effect on Survival of irAEs in NSCLC

data have emerged for NSCLC; however, the findings have not been uniform. One retrospective study of 71 patients with NSCLC reported an association between overall response rate and irAEs ( $P = .007$ ) but not OS ( $P = .827$ ).<sup>9</sup> Another report of 51 patients treated with pembrolizumab in the KEYNOTE-001 trial [study of pembrolizumab (MK-3475) in participants with progressive locally advanced or metastatic carcinoma, melanoma, or non-small cell lung carcinoma (P07990/MK-3475-001/KEYNOTE-001)] found that thyroid dysfunction occurring during treatment was associated with improvement in OS (hazard ratio, 0.29; 95% confidence interval [CI], 0.09-0.94;  $P = .04$ ) but not progression-free survival (PFS).<sup>10</sup> A multi-institution retrospective study of 134 patients with NSCLC found an association at 6 weeks between the occurrence of irAEs and both PFS and OS in a landmark analysis.<sup>11</sup> A prospective study of 43 patients found that the early occurrence of irAEs was associated with a better disease control rate and PFS but not the response rate or OS.<sup>12</sup> These discrepant results between the development of irAEs and the effect on the disease response rate, PFS, and OS warrant further investigation.

The development of predictive biomarkers for serious irAEs would aid patient selection for treatment plans that minimize the risk of toxicities. Cancer-associated inflammation has long been recognized as having a profound effect on survival,<sup>13</sup> and markers of systemic inflammation such as the neutrophil/lymphocyte ratio (NLR) have been found to be prognostic in large meta-analyses of all cancers<sup>14</sup> and NSCLC.<sup>15,16</sup> However, the ability of baseline markers of systemic inflammation, including the NLR, platelet/lymphocyte ratio (PLR),<sup>17,18</sup> and advanced lung cancer inflammation index (ALI),<sup>19,20</sup> to predict irAEs has not been assessed.

In the present study, we report the outcomes of 91 patients treated with ICIs for NSCLC, with a specific focus on the development of irAEs, their correlation with survival, an assessment of the risk factors for irAEs, and the predictors of benefit from treatment with ICIs.

## Patients and Methods

A retrospective review of patients with NSCLC treated with a single-agent ICI from September 2014 to June 2016 was performed at The Ohio State University Comprehensive Cancer Center. Consecutive patients with metastatic NSCLC who received treatment either in clinical trial or with standard of care at our institution were included in the present study. The baseline patient characteristics were assessed from the physician clinical care documentation and the electronic medical records. irAEs were identified by diagnosis, attribution, and clinical intervention (requiring either withholding treatment or new treatment, whether topical or systemic, for the irAE). The irAEs were graded using the Common Terminology Criteria for Adverse Events, version 4.0. OS was calculated from the date of the initiation of the ICI to death from any cause or the date of the last follow-up examination. Patients with active malignancies other than NSCLC were excluded. Patients who had received an ICI in combination with either other immunotherapy or chemotherapy were also excluded from the present analysis. The institutional review board of The Ohio State University Medical Center approved the present study.

## Statistical Analysis

The patient demographic data and characteristics were summarized using descriptive statistics (median and range for continuous outcomes and frequency for discrete outcomes). OS was calculated from the date of treatment initiation to death from any cause. Patients who were still alive were censored at the last follow-up examination. Survival curves were estimated using the Kaplan-Meier method. OS was compared between patients with and without serious irAEs using the log-rank test. The estimated median with 95% CIs are reported in tabular format. OS was also compared with the other patient demographic data and tumor characteristics using a log-rank test or Cox regression model. In a landmark analysis, patients were categorized into 4 groups according to whether they had received ICI for > 3 months and whether they had experienced irAEs. OS was compared among the groups using log-rank tests, and the Bonferroni method was used to adjust for multiple comparisons. The association of the incidence of irAEs and pneumonitis with the patient and tumor characteristics has been studied using the  $\chi^2$  test or Fisher's exact test for categorical characteristics and the logistic regression model for continuous characteristics. The  $P$  values were adjusted for multiple comparisons using the Bonferroni method, as needed.  $P$  values < .05 were considered to indicate statistical significance. All analyses were conducted using SAS, version 9.4 (SAS Institute, Cary, NC).

## Inflammatory Markers

The NLR was calculated at baseline as the ratio of absolute neutrophils to lymphocytes. An elevated NLR was defined as  $\geq 5$ , as previously described.<sup>14,15,21</sup> The ALI was calculated as described previously (body mass index  $\times$  serum albumin/NLR), and values of  $\geq 18$  were considered elevated.<sup>20</sup> The PLR was calculated as the ratio of platelets to absolute lymphocytes and was considered elevated if > 237 (median PLR).<sup>17,18</sup> Tumor mutation data were obtained as the routine standard of care at our Clinical Laboratory Improvement Amendments-certified molecular pathology laboratory.

## Results

### Patient Characteristics

The characteristics of the 91 included patients are listed in Table 1. The median patient age at immunotherapy was 67 years (range, 40-87 years). The gender was relatively evenly split between male and female (52% women). Nearly all patients received nivolumab ( $n = 88$ ; 97%). The median line of therapy was 2 (range, 1-8). Of the 91 patients, 26 (29%) had been treated in the setting of a clinical trial.

### Occurrence of irAEs

Twenty-seven patients (30%) developed  $\geq 1$  irAE. The details of the individual irAEs are listed in Table 2. The median time to onset of irAEs was 3 months (range, 0.4-41.9 months; Figure 1). Patients treated in a clinical trial had a greater rate of irAEs (53.9% vs. 20%;  $P = .001$ ). For patients with immune-related pneumonitis ( $n = 9$ ; 10%), the median time to onset was 1.6 months (range, 0.4-11.4 months). Eight of these patients were treated with steroids, and only 1 patient was rechallenged with ICI. Three patients (3%) developed

**Table 1** Patient Characteristics

Characteristic	n (%)
Age, y	
Median	67
Range	40-87
Female gender	52 (57)
Smoking status	
Current/former	81 (89)
Never	10 (11)
Histologic type	
Nonsquamous cell carcinoma	58 (64)
Squamous cell carcinoma	33 (36)
Therapy line	
Median	2
Range	1-8
Immunotherapy agent	
Nivolumab	88 (97)
Pembrolizumab	1
Atezolizumab	2
ECOG performance status	
0	11 (12)
1	56 (62)
2	20 (22)
> 2	2 (2)
Missing	2 (2)
Mutation	
KRAS	26 (29)
TP53	37 (41)
KRAS and TP53	11 (12)
EGFR	5 (5)
SMAD	5 (5)
STK11	4 (4)
MET	3 (3)
ALK	2 (2)

Data presented as n (%).  
Abbreviation: ECOG = Eastern Cooperative Oncology Group.

colitis; all required steroids. Three patients experienced multiple irAEs. The other irAEs included dermatologic events (n = 6), thyroid dysfunction (hypothyroidism, n = 6; thyrotoxicosis, n = 1), autoimmune insulin-dependent diabetes mellitus (n = 1), hepatitis (n = 1), and pancreatic insufficiency (n = 1).

### Risk Factors for Development of irAEs

Data from the patient and tumor characteristics were assessed to identify potential risk factors for the occurrence of irAEs overall (Table 3) and for pneumonitis specifically (Table 4). A positive smoking history was not associated with an increased risk of irAEs in general ( $P = 1.00$ ) or pneumonitis specifically ( $P = 1.00$ ). The histologic type (squamous vs. nonsquamous) also was not associated with an increased risk of irAEs ( $P = 1.00$ ). The incidence of irAEs was not affected by age ( $P = .71$ ). The Eastern Cooperative Oncology Group performance status at treatment was also not associated with the development of irAEs ( $P = .25$ ).

Data from tumor mutation analysis were available for 72 patients (55 with nonsquamous, 14 with squamous, and 3 with adenocarcinoma). The most commonly identified alteration was *TP53* (n = 37; 41%), followed by *KRAS* mutations (n = 26; 29%; Table 1). Although not statistically significant, fewer irAEs developed in patients with *KRAS*-mutated tumors than in those with *KRAS* wild-type tumors ( $P = .059$ ). A similar trend was observed in patients with tumors harboring *TP53* mutations ( $P = .063$ ).

All patients had undergone baseline laboratory testing before starting treatment with immunotherapy, and the NLR, PLR, and ALI were calculated to determine whether these indexes of inflammation correlated with an increased risk of irAEs. An  $NLR \geq 5$  was not associated with an increase in irAEs overall ( $P = .94$ ) or pneumonitis specifically ( $P = .18$ ). An elevated PLR also did not correlate with the occurrence of irAEs ( $P = .45$ ) or pneumonitis ( $P = .74$ ), and an elevated ALI also was not associated with irAEs ( $P = .80$ ) or pneumonitis ( $P = .17$ ).

### Radiotherapy, irAEs, and Survival

Of the 91 patients, 28 (31%) had received previous chest radiotherapy (RT) or thoracic RT (TRT) before receiving immunotherapy. The median time between TRT completion and ICI therapy was 8.7 months (range, 0.4-34.7 months). Overall, no increased risk of irAEs ( $P = .81$ ) or pneumonitis ( $P = .13$ ) was found in patients who had received previous TRT, and the timing of

**Table 2** Incidence and Severity of Immune-related Adverse Events

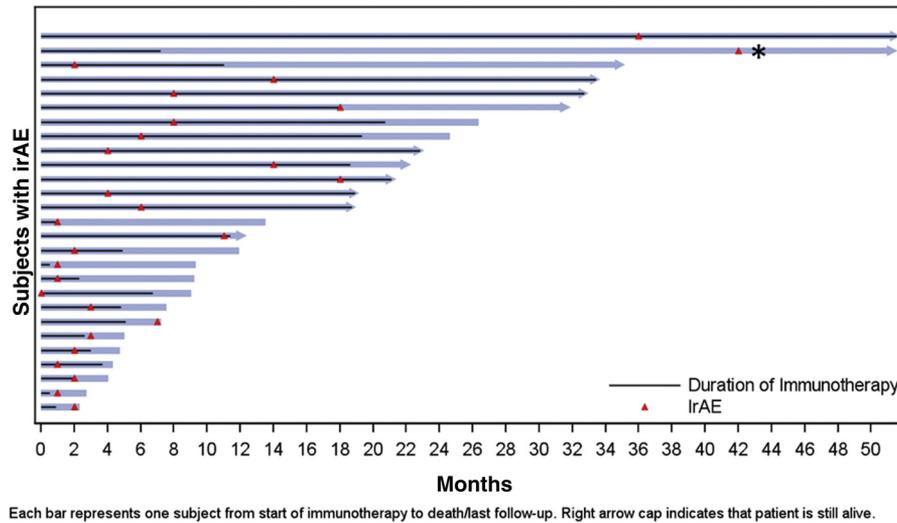
Toxicity	All Grades (n, %)	Grade 1-2	Grade $\geq 3$	Rechallenge	Systemic Steroid Use
Any irAE	27 (30)	21 (23)	6 (7)	16 (60)	13 (48)
Pneumonitis	9 (10)	5 (6)	4 (4) <sup>a</sup>	1 (11)	8 (89)
Dermatologic <sup>b</sup>	6 (7)	6 (7)	0 (0)	6 (100)	0 (0)
Endocrine <sup>c</sup>	7 (8)	6 (7)	1 (1)	5 (83)	0 (0)
Colitis	3 (3)	2 (2)	1 (1)	2 (67)	3 (100)
Hepatitis	1 (1)	0 (0)	1 (1)	1 (100)	1 (100)
Pancreatic insufficiency	1 (1)	1 (1)	0 (0)	1 (100)	0 (0)

<sup>a</sup>One possible grade 5 pneumonitis developed in 1 patient with underlying lung disease with previous pneumonectomy, concern for pneumonia (sputum culture positive for *Serratia marcescens* and *Candida*) or aspiration; the patient was transitioned to comfort care after no improvement with steroids, broad-spectrum antibiotics, and noninvasive positive-pressure ventilator support.

<sup>b</sup>Included 1 case of palmar-plantar erythrodysesthesia syndrome.

<sup>c</sup>Included 6 cases of hypothyroid and 1 case of Graves thyroiditis treated with methimazole.

**Figure 1** Swimmer's Plot of Time to Immune-related Adverse Event (irAE), Duration of Treatment, and Outcome. Patients Who Developed irAEs > 3 Months Had Improved Overall Survival (OS) Compared With Those Who Had Developed irAEs Within the First 3 Months ( $P < .001$  With Bonferroni Correction). However, a Landmark Analysis of Patients Still Receiving Treatment at 3 Months Revealed No Differences in Overall Survival Between Patients With and Without irAEs. One Patient (Asterisk) Was Administered a Different Immunotherapy Treatment (Programmed Cell Death-1) After Stopping Initially and Developed an irAE



**Table 3** Clinical and Laboratory Risk Factors for Development of Immune-related Adverse Events

Risk Factor	irAE, n (%)		P Value
	Yes	No	
All patients	27 (30)	64 (70)	
Histologic type (nonsquamous, n = 58)	16 (28)	42 (72)	1.00 <sup>a</sup>
Previous TRT or chest wall RT (n = 28)	8 (29)	20 (71)	.806 <sup>a</sup>
RT after ICI	8 (53)	7 (47)	.059 <sup>b</sup>
Smoking history			1.00 <sup>b</sup>
Current/former smoker	24 (30)	57 (70)	
Nonsmoker	3 (30)	7 (70.00)	
Gender			.260 <sup>a</sup>
Male	14 (36)	25 (64)	
Female	13 (25)	39 (75)	
Inflammatory biomarkers			.804 <sup>a</sup>
ALI ≥ 18	13 (31)	20 (69)	.260 <sup>a</sup>
NLR ≥ 5	15 (30)	35 (70)	.939 <sup>a</sup>
PLR ≥ 237	12 (26)	34 (74)	.449 <sup>a</sup>
KRAS mutation (n = 26)	4 (15)	22 (85)	.059 <sup>a</sup>
TP53 mutation (n = 37)	7 (19)	30 (81)	.063 <sup>a</sup>

Abbreviations: ALI = advanced lung cancer inflammation index; ICI = immune checkpoint inhibitor; irAE = immune-related adverse event; NLR = neutrophil/lymphocyte ratio; PLR = platelet/lymphocyte ratio; RT = radiotherapy; TRT = thoracic RT.

<sup>a</sup>Association between categorical variables compared using  $\chi^2$  test.

<sup>b</sup>Association between categorical variables compared using Fisher's exact test.

previous TRT did not affect the occurrence of irAEs overall ( $P = .252$ ) or pneumonitis, in particular ( $P = .321$ ). Thirty-six patients had received non-central nervous system RT (including TRT) before ICI treatment (median, 5.7 months; range, 0.2-47.3 months), and 15 patients had received RT after beginning ICI therapy (median, 3.9 months; range, 1-18.8 months). RT before immunotherapy was not associated with an increased risk of irAEs ( $P = .54$ ) or pneumonitis ( $P = .48$ ). Also, RT after the initiation of immunotherapy was not associated with a significantly increased risk of irAEs ( $P = .059$ ) or pneumonitis ( $P = .17$ ). However, given these small numbers, this finding should be interpreted with caution. The timing of RT after ICI therapy was not significantly associated with OS ( $P = .120$ ; Cox regression model). Unlike previous studies, patients who received RT before ICI therapy had shorter OS (median, 4.2 months; 95% CI, 2.4-8.1 months) than that of the patients without previous RT (median, 9.7 months; 95% CI, 6.5-19.4 months;  $P = .004$ ). However, the 15 patients who had received RT after the initiation of immunotherapy had improved OS (median, 17.3 months; 95% CI, 6.5 months to not reached [NR]) compared with those without RT after the initiation of immunotherapy (median, 6.0 months; 95% CI, 4.0-8.9;  $P = .016$ ).

### Effect on OS

The median OS for the entire cohort was 7.7 months (95% CI, 4.7-10.6 months). The median OS for the 27 patients who developed any irAEs was 24.3 months (95% CI, 7.2 months to NR) compared with 5.3 months (95% CI, 3.1-8.3 months) for the 64 patients without irAEs (hazard ratio, 2.75; 95% CI, 1.54-4.92;  $P < .001$ ; Figure 2). Patients with irAEs treated with steroids had a

**Table 4** Clinical and Laboratory Risk Factors for Development of Pneumonitis

Risk Factor	Pneumonitis		P Value <sup>a</sup>
	Yes	No	
RT history			.133
Previous TRT/chest wall RT	5 (18)	23 (82)	
No previous TRT	4 (7)	57 (93)	
Non-CNS radiation after ICI	3 (20)	12 (80)	.165
Heavy smoking history (>50 PYH)	5 (22)	18 (78)	1.00
Inflammatory biomarkers			
ALI ≥ 18	2 (5)	40 (95)	.170
NLR ≥ 5	7 (14)	43 (86)	.178
PLR ≥ 237	4 (9)	42 (91)	.739

Abbreviations: ALI = advanced lung cancer inflammation index; CNS = central nervous system; ICI = immune checkpoint inhibitor; NLR = neutrophil/lymphocyte ratio; PLR = platelet/lymphocyte ratio; PYH = pack-year history; RT = radiotherapy; TRT = thoracic RT.  
<sup>a</sup>Association between categorical variables compared using Fisher's exact test.

median OS of 10.3 months (95% CI, 3.7-26.0 months) from the initiation of ICI therapy, which was not significantly different from that of those not treated with steroids (median NR; 95% CI, 7.2 months to NR;  $P = .072$ ). Patients with irAEs who had received steroids had a significantly shorter OS from the development of irAEs (median, 8.3 months; 95% CI, 1.2-18.2 months) compared with those patients who had not received steroids (median, NR; 95% CI, 4.3 months to NR;  $P = .028$ ). The development of pneumonitis in 9 patients did not affect OS ( $P = .34$ ), nor did the development of colitis ( $P = .14$ ). In the 7 patients who developed autoimmune thyroid dysfunction, the median OS was NR (95% CI, 7.2 months to NR) compared with 6.5 months for patients without thyroid irAEs (95% CI, 4.4-9.5 months;  $P = .018$ ; Figure 2B). The patients' performance status was associated with OS ( $P = .018$ ).

The median OS for the patients who developed irAEs > 3 months after starting ICI therapy was NR (95% CI, 24.3 months to NR) compared with 8.0 months (95% CI, 2.4-11.6 months) for those patients in whom irAEs occurred within the first 3 months ( $P < .001$ ). Patients who developed irAEs had received ICI treatment longer than had those who had not developed irAEs (7.2 vs. 1.9 months;  $P < .001$ ). In a landmark analysis, OS was not significantly different for the patients who had received ICI for > 3 months without an irAE compared with either the patients receiving an ICI for > 3 months with an early irAEs (occurring within 3 months;  $P = 1.00$ , with Bonferroni correction) or patients receiving treatment for > 3 months with late irAEs (occurring after 3 months;  $P = 1.00$ , with Bonferroni correction). For the patients receiving treatment for < 3 months, the median survival for the 41 patients without irAEs was 2.5 months (95% CI, 1.8-3.6 months) compared with 6.4 months for the 6 patients with irAEs ( $P < .001$ , with Bonferroni correction). In the same landmark analysis, OS was significantly longer for the patients receiving treatment for > 3 months who developed thyroid irAEs (median OS, NR; 95% CI, 7.2 months to NR) compared with the patients without thyroid irAEs (median OS, 16.2 months; 95% CI, 9.5-28.8 months;  $P = .0296$ ).

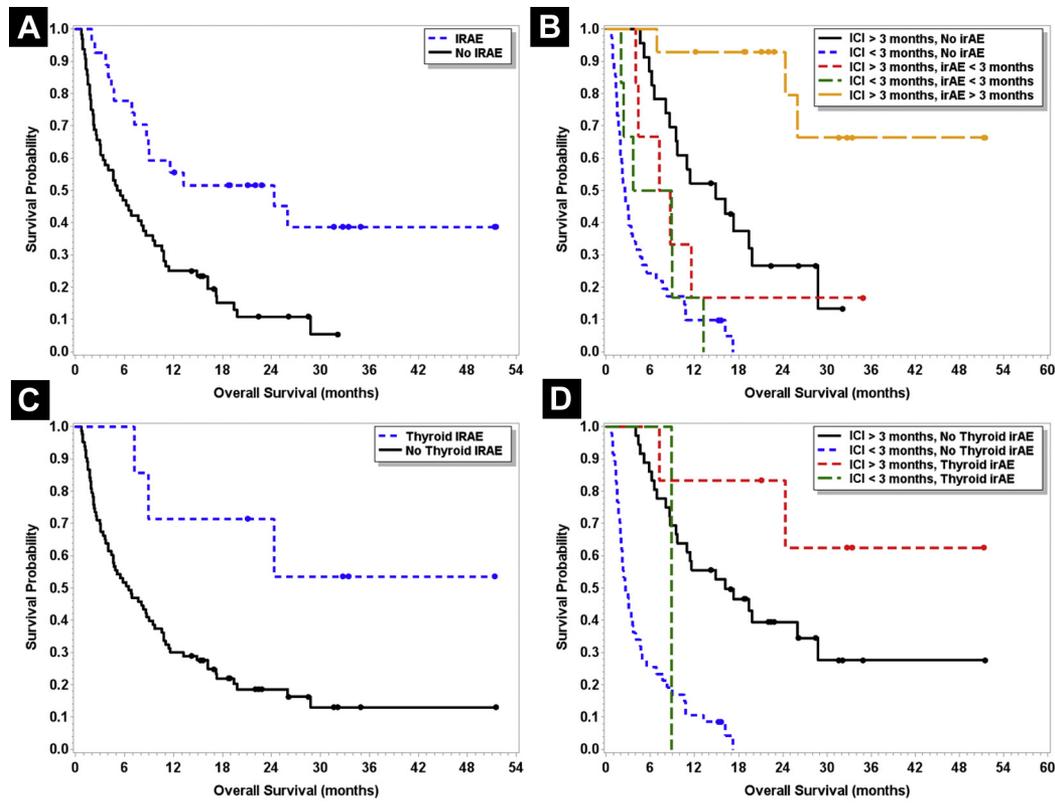
Markers of systemic inflammation, including NLR, PLR, and ALI, were assessed for any association with OS. Patients with an elevated ALI at treatment initiation had longer median OS (median, 14.9 months; 95% CI, 9.0-19.8 months) compared with patients with a lower ALI (median, 4.0 months; 95% CI, 2.3-5.5 months;  $P < .001$ ). Patients with a baseline elevated NLR (> 5) had a shorter median OS (median, 4.0 months; 95% CI, 2.3-6.9 months) compared with those with a lower NLR (median, 11.4 months; 95% CI, 8.7-19.4 months;  $P = .002$ ). Patients with a lower PLR (less than the median of 237 in this cohort) had a median OS of 8.9 months (95% CI, 5.1-17.2 months) compared with 5.2 months (95% CI, 2.6-9.5 months;  $P = .182$ ) for those with an elevated PLR at baseline.

## Discussion

Although the results of our initial analysis suggested a survival benefit for patients treated with an ICI who developed irAEs (Figure 2A), this survival difference was not observed when controlling for the duration of therapy in a landmark analysis at 3 months (Figure 2B). The timing of performing the landmark analysis at 3 months was chosen because this was the median time of irAE development. A correlation between clinical benefit and the development of irAEs has been reported previously. However, the data have been conflicting regarding the association with OS.<sup>9,10,12</sup> We also found that the ALI, NLR, and PLR were not predictive of the development of irAEs. However, they were of prognostic value in NSCLC patients who received immunotherapy. We observed an increase in survival for the patients undergoing RT after beginning treatment with an ICI. In contrast, patients who had undergone RT before the initiation of immunotherapy had worse outcomes. Overall, the irAE rate of 30% was in line with that from previous studies, and the 10% rate of pneumonitis was slightly greater than previously reported. Uncommon irAEs, including new-onset autoimmune diabetes mellitus, thyrotoxicosis, and pancreatic insufficiency, also occurred. We found no difference in the incidence of irAEs when stratified by patient gender, age, smoking history, or tumor histologic type. The greater rate of irAEs in patients treated in the clinical study might have resulted from the closer monitoring for, and attribution of, immune toxicities in these patients. We found that patients who had developed thyroid toxicity during therapy with an ICI had longer OS than that of patients who had not, as reported previously.<sup>10</sup>

We did not observe an increase in either irAEs or pneumonitis in patients who had received previous RT. The risk factors for radiation pneumonitis have been reported to include the timing and schedule of RT sessions, the mean lung dose, the target volume and dose, pre-existing lung disease, and circulating cytokines.<sup>22-24</sup> The risk factors for immunotherapy-related pneumonitis have not been defined; however, suggestions have included active smoking, which we were unable to confirm in our study.<sup>25</sup> Little is known about which risk factors increase the likelihood of irAEs overall and pneumonitis in particular, and what effect irAEs might have on survival. Case reports have suggested an increased risk of pneumonitis in patients who had previously received TRT<sup>26,27</sup>; however, the recent PACIFIC trial (a global study to assess the effects of MEDI4736 following concurrent chemoradiation in patients with stage III unresectable non-small cell lung cancer) did not show a

**Figure 2** Kaplan-Meier Curves for (A) Survival of Patients Who Had Developed Immunotherapy-related Adverse Event(s) (irAE) ( $P < .001$ ), Including Specifically Thyroid irAE (C;  $P = .018$ ). In a Landmark Analysis Controlling for Duration of Therapy, Overall Survival Was Not Significantly Different in Patients Who Had Received an Immune Checkpoint Inhibitor (ICI) for > 3 Months With or Without irAEs Overall (B;  $P = 1.00$ , With Bonferroni Correction); However, Thyroid irAEs Remained Significantly Associated With Survival (D;  $P = .0296$ )



significant increase in severe pneumonitis in patients treated with durvalumab after concurrent chemoradiation.<sup>28</sup> Previous work had suggested that patients receiving RT before ICI had better outcomes.<sup>29</sup> Evidence has shown a synergistic effect of RT with immunotherapy, with 1 retrospective analysis from a prospective study demonstrating an improvement in progression-free survival and OS in patients treated with pembrolizumab for NSCLC who had previously received RT.<sup>29</sup> However, in our study, previous RT was associated with worse survival, despite timing between RT and ICI similar to that in previous studies. This might reflect different patient populations, because the previous study included patients in a phase I trial, or might have resulted from the smaller number of patients with previous RT in our study (28 of 91 patients in our study compared with 42 of 97 in previous study). Finally, the improvement in OS seen for patients who had received RT after starting ICI therapy is interesting; however, the finding should be interpreted with caution, given the small number of patients ( $n = 15$ ) and that patients receiving an ICI who had also received RT were likely to be those with acceptable performance status or who had experienced a response to treatment. Preclinical data are available supporting the role of immunotherapy and RT in shaping the repertoire of tumor-infiltrating lymphocytes.<sup>30</sup> Also, the role of

RT with ICI therapy is being evaluated in NSCLC patients in several ongoing studies (eg, ClinicalTrials.gov identifier, NCT02888743).

The association of thyroid dysfunction during immunotherapy for NSCLC has been described in a previous study, although the mechanism is not well understood.<sup>10</sup> The study investigators hypothesized that thyroid toxicity during programmed cell death 1/programmed cell death ligand 1 therapy might occur as a result of either humoral immunity or an exacerbation of low-level autoimmunity. Decreased levels of cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)-expressing T cells have been reported in pediatric patients with chronic autoimmune thyroiditis.<sup>31</sup> Also, polymorphisms in CTLA-4 have been associated with autoimmune thyroid disease.<sup>32</sup> Whether any relation exists between T-cell CTLA-4 expression and the development of thyroid dysfunction during immunotherapy is unknown.

The use of systemic markers of inflammation derived from routine blood tests to determine prognosis has been well studied.<sup>14,16-18,20,21</sup> One retrospective study of 175 patients found that an elevated pretreatment NLR was associated with worse survival in patients with NSCLC treated with nivolumab.<sup>21</sup> Additional hematologic markers of systemic inflammation include the PLR<sup>17,18</sup>

and the ALI.<sup>19,20</sup> A recent retrospective study of 101 patients with melanoma treated with nivolumab reported that an increased total white blood cell count and decreased lymphocyte count were associated with irAEs.<sup>33</sup> However, the ability of these tests to predict the occurrence of irAEs is unknown. In our study, baseline NLR, ALI, and PLR were not associated with an increased risk of irAE or pneumonitis. The prognostic value of both NLR and ALI was confirmed in our study. Although data are available supporting the use of NLR as a prognostic marker in patients with NSCLC treated with nivolumab, we are unaware of any data supporting the ALI as a prognostic biomarker in this patient population.

Our study had several limitations. The sample size was among the largest in retrospective analyses that have found a clinical benefit in this patient population. However, our study sample was still sufficiently small that significant findings could have been missed. Also, our definition of irAEs requiring intervention discounted subclinical changes that might be useful in predicting the response. More reliable methods of determining irAEs are needed to better diagnose and document these events. The outcomes of patients treated with steroids for irAEs might have been because more severe irAEs (ie, pneumonitis, colitis, hepatitis) are commonly treated with steroids and others are often treated without steroids (ie, thyroid replacement for hypothyroidism). Given the small number of patients in the present study, the implication of this finding is unclear and should not affect the decision to treat irAEs with steroids. The presence of thyroid dysfunction as an early indicator of benefit is attractive because of its objectivity<sup>10</sup> and has been supported by the clinical benefit seen in patients who developed thyroid dysfunction in our study. Because most patients were treated with second-line nivolumab, programmed cell death ligand 1 testing was not routinely performed and, therefore, was not included in the present analysis. These findings might not be applicable for patients receiving first-line or combination immunotherapy.

## Conclusion

The present study has added to the current knowledge regarding the incidence, risk factors, and effect on survival of irAEs in NSCLC patients. No association between irAEs and survival was observed in our landmark analysis, although longer OS was observed in patients with thyroid irAEs, which is encouraging owing to its objectivity. No clear risk factors for irAEs were identified, and no increased risk of irAEs was observed in patients who had received RT. The demonstration of a survival benefit for patients who had received RT after ICI is encouraging; however, given the small number of patients and retrospective nature of the study, this finding should be investigated further in larger prospective clinical trials.

## Clinical Practice Points

- Immunotherapy has transformed the treatment of patients with NSCLC; in general, these treatments have been well tolerated.
- However, irAEs occur and can be serious and even fatal.
- Understanding the incidence, severity, and risk factors for irAEs will allow for better clinical decisions and management of NSCLC in patients treated with these agents.
- We have reported that irAEs occurred in 30% of patients treated with single-agent immunotherapy at our institution.

- These irAEs included well-known toxicities such as pneumonitis and colitis and more uncommon toxicities such as pancreatic insufficiency and insulin-dependent diabetes.
- No clear risk factors for irAEs were identified, including previous RT, tumor histologic type, mutational status, smoking history, and routine blood test results.
- In our study, previous RT was associated with worse clinical outcome, and RT after immunotherapy was associated with improved survival.
- The possible benefit of RT after the initiation of immunotherapy is being evaluated in several ongoing clinical studies.
- Given the lack of clearly identifiable risk factors for irAEs at baseline, clinical vigilance and education are of utmost importance to identify and treat patients who develop irAEs.

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## Disclosure

The authors declare that they have no competing interests.

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