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Research Article

Prognostic Impact of Immune-Related Adverse Events in Patients with Non–Small Cell Lung Cancer Treated with Second-Line Nivolumab: A Single-Center Real-World Experience

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Abstract

Objectives: Although nivolumab is a standard second-line option for advanced non–small cell lung cancer (NSCLC), treatment benefit differs substantially across patients in routine clinical practice. Biomarkers that may help explain this heterogeneity remain limited. Immune-related adverse events (irAEs) have been suggested as a potential clinical correlate of immune activation; however, their prognostic significance in real-world settings remains uncertain.

Methods: We retrospectively reviewed patients with NSCLC who received nivolumab as second-line therapy at a single institution between 2018 and 2024. Immune-related adverse events were identified through systematic evaluation of clinical records. Progression-free survival (PFS) and overall survival (OS) were analyzed using Kaplan–Meier estimates and Cox regression models.

Results: Among 230 patients, 78 (33.9%) developed at least one irAE during treatment. Dermatologic, endocrine, and pulmonary toxicities were the most frequently observed events. In univariable analyses, irAE occurrence was associated with longer PFS (5.8 vs. 3.2 months, p=0.003) and OS (13.7 vs. 8.4 months, p=0.001). However, after multivariable adjustment for clinical confounders, the association with overall survival did not retain statistical significance.

Conclusion: In this real-world cohort, the development of irAEs was associated with improved survival outcomes in unadjusted analyses, although this relationship was attenuated after adjustment. These findings suggest that irAEs may represent a clinical correlate of immune activation rather than an independent prognostic factor.

Keywords: Immune-Related Adverse Events; Non–Small Cell Lung Cancer; Nivolumab; Immunotherapy; Real-World Data

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Non–small cell lung cancer (NSCLC) remains a major global health burden despite ongoing advances in systemic anticancer therapies. A considerable proportion of patients are diagnosed with advanced-stage disease, while many others experience disease progression following first-line platinum-based chemotherapy. As a result, long-term survival outcomes remain limited, underscoring the continued need for effective treatment strategies beyond initial therapy.[1–3]

The therapeutic landscape of advanced NSCLC has been fundamentally reshaped by the introduction of immune checkpoint inhibitors targeting the programmed cell

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death-1 (PD-1) and programmed death-ligand 1 (PD-L1) pathway. These agents have altered treatment paradigms by offering durable clinical benefit in a subset of patients with previously treated disease.[4,5] Among PD-1 inhibitors, nivolumab—a fully human monoclonal antibody—demonstrated superior survival outcomes compared with docetaxel in patients with advanced NSCLC who had progressed after platinum-based chemotherapy, irrespective of histological subtype.[6,7] Findings from the CheckMate-017 and CheckMate-057 trials established nivolumab as a standard second-line treatment option and supported its widespread adoption in routine clinical practice.[6,7] In this context, increasing attention has shifted toward treatment-emergent clinical features that may reflect effective immune engagement and complement survival data derived from controlled clinical trials.

Immune checkpoint inhibition is associated with a distinct spectrum of immune-related adverse events (irAEs), which arise as a consequence of immune system activation. These events can involve multiple organ systems, with the skin, endocrine organs, gastrointestinal tract, and lungs being most commonly affected.[8,9] Although most irAEs are manageable with appropriate monitoring and timely intervention, some cases require treatment interruption or permanent discontinuation, highlighting their clinical relevance in daily practice.[10]

Beyond safety considerations, increasing attention has been directed toward the potential prognostic implications of irAEs during immune checkpoint inhibitor therapy. Several studies have suggested that the occurrence of immune-mediated toxicity may correlate with improved treatment efficacy, including prolonged progression-free and overall survival.[11–13] Real-world analyses and retrospective cohorts have further supported this association, raising the possibility that irAEs may reflect enhanced immune activation and antitumor response rather than representing isolated adverse effects.[14–16] However, available evidence remains heterogeneous, and the prognostic value of irAEs has not been definitively established, particularly outside the controlled environment of randomized clinical trials.[17]

In Türkiye, data examining the relationship between immune-related adverse events and survival outcomes in NSCLC patients treated with nivolumab in routine clinical practice are scarce. Differences in patient characteristics, treatment patterns, and follow-up strategies across regions may influence real-world outcomes. Against this background, we conducted a real-world analysis to explore whether treatment-emergent immune-related adverse events provide clinically meaningful prognostic information in patients receiving second-line nivolumab.

Methods

Study Design and Patient Population

This study was designed as a retrospective, single-center, real-world observational analysis conducted at a tertiary oncology center. The study period spanned from January 2018 to December 2024. The analysis included patients with histologically confirmed non–small cell lung cancer (NSCLC) who received nivolumab as second-line systemic therapy following failure of platinum-based chemotherapy.

Patients were eligible if they were adults (≥18 years) and had received at least one cycle of nivolumab in the second-line setting. Patients treated with nivolumab outside the second-line setting, those enrolled in prospective interventional clinical trials, and individuals with insufficient clinical or follow-up data were excluded. Based on these criteria, a total of 230 patients were included in the final analysis.

Treatment and Follow-up

Nivolumab was administered intravenously according to dosing schedules routinely applied in daily clinical practice during the study period. Treatment continuation was determined by disease status, treatment tolerability, patient preference, and physician discretion, and therapy was discontinued in the event of radiologically confirmed disease progression or unacceptable toxicity.

Patients underwent routine clinical evaluation, laboratory testing, and radiological assessment in accordance with institutional practice. Tumor response and disease progression were evaluated based on radiological findings documented in the medical records.

Assessment of Immune-Related Adverse Events

Immune-related adverse events (irAEs) were identified through systematic review of electronic medical records, including outpatient documentation, inpatient reports, laboratory findings, and imaging results. An irAE was defined as an adverse event temporally associated with nivolumab exposure and considered consistent with the known toxicity profile of PD-1 inhibition that required clinical assessment or intervention.

To reduce the risk of misclassification inherent to retrospective analyses, alternative etiologies such as infectious, metabolic, medication-related, or disease-related causes were systematically evaluated and excluded based on available clinical, laboratory, and radiological data. For example, suspected pneumonitis cases were assessed in conjunction with imaging findings to differentiate immune-mediated inflammation from infection or tumor progression. Endocrine events were classified as immune-related when no alternative endocrine disorder or medication-related cause was identified.

Event severity was graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.[18] Information regarding event grade, need for treatment interruption, corticosteroid administration, and permanent discontinuation of nivolumab was recorded when applicable. Final attribution of immune-related toxicity was based on the treating medical oncologist's documented clinical judgment within routine practice, acknowledging the inherent limitations of retrospective assessment.

Study Endpoints

The primary endpoints of the study were progression-free survival (PFS) and overall survival (OS). PFS was defined as the interval from the initiation of nivolumab therapy to radiologically confirmed disease progression or death from any cause, whichever occurred first. OS was defined as the time from nivolumab initiation to death from any cause.

Radiological tumor response and disease progression were evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, based on radiology reports documented in the medical records in accordance with routine clinical practice. Patients without documented events were censored at the time of last follow-up.

Secondary analyses included the occurrence and distribution of immune-related adverse events, the incidence of grade ≥3 toxicities, and objective response rates. Objective response was defined as complete or partial response according to RECIST version 1.1 criteria.

Statistical Analysis

Baseline characteristics and adverse events were summarized using descriptive statistics. Continuous variables were reported as median (range) and compared using the Mann–Whitney U test, while categorical variables were summarized as frequencies and percentages and compared using the Chi-square test.

Survival outcomes were estimated using the Kaplan–Meier method, with group comparisons performed using the log-rank test. The association between immune-related adverse events and survival outcomes was initially evaluated using univariable Cox proportional hazards regression models.

Multivariable Cox proportional hazards regression models were subsequently constructed to adjust for potential confounders, including ECOG performance status, brain metastases, liver metastases, metastatic burden (≥2 sites), objective response status, and the number of nivolumab cycles received. The number of nivolumab cycles was modeled as a continuous variable to account for potential exposure-related bias.

Hazard ratios (HRs) were reported with 95% confidence intervals (CIs). A two-sided p value <0.05 was considered statistically significant for all analyses.

Ethics Approval and Consent to Participate

Ethical approval for the study was obtained (Decision No: 2025/010.99/15/9, dated 30 April 2025). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Artificial intelligence–assisted tools were not used for data analysis, interpretation, or generation of scientific content.

Results

Patient Characteristics

A total of 230 patients with non–small cell lung cancer who received nivolumab as second-line therapy were included in the analysis. According to the occurrence of immune-related adverse events during treatment, 78 patients were classified as irAE-positive and 152 as irAE-negative. The median follow-up duration was 23.4 months (range: 2.1–71.6). Baseline demographic and clinical characteristics of the study population are presented in Table 1.

Across the two groups, baseline demographic and clinical characteristics showed a largely similar distribution. Median age, sex, histological subtype, ECOG performance status, smoking history, metastatic burden, and prior lines of systemic therapy were comparable between patients with and without irAEs. The extent of metastatic disease, including the presence of brain and liver metastases, was also similar between groups. However, patients who developed irAEs received a significantly higher number of nivolumab cycles compared with those who did not (median 11 vs. 6 cycles, p<0.001).

Immune-Related Adverse Events

Immune-related adverse events were documented in 78 patients, corresponding to 33.9% of the overall cohort. Dermatologic and endocrine toxicities constituted the most frequently observed events, with skin rash reported in 18% of patients and thyroid dysfunction in 15%. Fatigue (12%) and pneumonitis (8%) were also commonly encountered, whereas gastrointestinal and hepatic toxicities occurred less frequently.

Severe immune-related adverse events (grade ≥3) were observed in 9 patients (3.9% of the overall cohort), corresponding to 11.5% of patients who developed irAEs. In most cases, irAEs were successfully managed with standard supportive approaches, including temporary treatment interruption and corticosteroid therapy when required. Permanent discontinuation due to immune-related toxicity occurred infrequently. A detailed summary of the spectrum and severity of immune-related adverse events is provided in Table 2.

Table 1. Baseline demographic and clinical characteristics according to immune-related adverse event status

Characteristic	Total (n=230)	irAE (+) (n=78)	irAE (–) (n=152)	p
Age, median (range), years	62 (38–81)	60 (39–79)	63 (38–81)	0.10
Sex, n (%)				
Male	178 (77.4)	58 (74.4)	120 (78.9)	0.45
Female	52 (22.6)	20 (25.6)	32 (21.1)	
Histology, n (%)				0.80
Adenocarcinoma	142 (61.7)	50 (64.1)	92 (60.5)	
Squamous cell carcinoma	78 (33.9)	25 (32.1)	53 (34.9)	
Other	10 (4.4)	3 (3.8)	7 (4.6)	
ECOG performance status, n (%)				0.16
0–1	182 (79.1)	66 (84.6)	116 (76.3)	
≥2	48 (20.9)	12 (15.4)	36 (23.7)	
Smoking status, n (%)				0.62
Current / former smoker	201 (87.4)	67 (85.9)	134 (88.2)	
Never smoker	29 (12.6)	11 (14.1)	18 (11.8)	
Disease status at nivolumab initiation, n (%)				
Metastatic disease	230 (100)	78 (100)	152 (100)	
Brain metastases, n (%)	52 (22.6)	16 (20.5)	36 (23.7)	0.59
Liver metastases, n (%)	39 (17.0)	11 (14.1)	28 (18.4)	0.44
Number of metastatic sites ≥2, n (%)	121 (52.6)	38 (48.7)	83 (54.6)	0.40
Prior lines of systemic therapy, median (range)	1 (1–2)	1 (1–2)	1 (1–2)	0.90
Median number of nivolumab cycles (range)	8 (2–38)	11 (3–38)	6 (2–24)	<0.001

Percentages are calculated based on column totals. ECOG: Eastern Cooperative Oncology Group; irAE: immune-related adverse event. Comparisons between groups were performed using the Chi-square test for categorical variables and the Mann–Whitney U test for continuous variables.

Survival Outcomes

Treatment outcomes according to immune-related adverse event status are summarized in Table 3.

Differences in time-to-event outcomes were observed according to the occurrence of immune-related adverse events during nivolumab therapy. Patients who experienced irAEs had longer progression-free survival compared with those without immune-mediated toxicity. Median PFS was 5.8 months in the irAE-positive group and 3.2 months in the irAE-negative group (p=0.003). In univariable analysis, the risk of disease progression or death was lower among patients who developed irAEs (HR: 0.68, 95% CI: 0.52–0.89). Kaplan–Meier curves showed separation between groups throughout follow-up (Fig. 1).

In multivariable analysis adjusting for ECOG performance status, brain metastases, liver metastases, metastatic burden (≥2 sites), objective response status, and number of nivolumab cycles, the association between irAE occurrence and progression-free survival was attenuated and did not retain statistical significance.

Table 2. Immune-related adverse events profile

Immune-related adverse event	Any grade, n (%)	Grade ≥3, n (%)
Skin rash	41 (18.0)	2 (0.9)
Thyroid dysfunction	35 (15.0)	1 (0.4)
Fatigue	28 (12.0)	1 (0.4)
Pneumonitis	18 (8.0)	5 (2.2)
Gastrointestinal toxicity	12 (5.2)	0
Hepatic toxicity	9 (3.9)	0
Any irAE	78 (33.9)	9 (3.9)

Immune-related adverse events were graded according to CTCAE v5.0. Percentages are calculated based on the total study population (n=230). Patients could experience more than one immune-related adverse event.

Overall survival analysis yielded similar findings. Median OS was 13.7 months in patients with irAEs compared with 8.4 months in those without irAEs (p=0.001). In univariable analysis, irAE occurrence was associated with a reduced risk of death (HR: 0.62, 95% CI: 0.45–0.85), with survival curves favoring the irAE-positive group (Fig. 2).

Table 3. Treatment outcomes according to immune-related adverse event status

Outcome	irAE (+) (n=78)	irAE (–) (n=152)	p
Objective response rate, n (%)	23 (29.5)	27 (17.8)	0.041*
Median PFS, months (95% CI)	5.8 (4.9–6.7)	3.2 (2.7–3.8)	0.003**
Median OS, months (95% CI)	13.7 (11.2–16.1)	8.4 (7.1–9.6)	0.001**
HR for progression (95% CI)	0.68 (0.52–0.89)	—	—
HR for death (95% CI)	0.62 (0.45–0.85)	—	—

irAE: Immune-related adverse events; PFS: Progression-free survival; OS: Overall survival; HR: Hazard ratios. Hazard ratios (HRs) were estimated using Cox proportional hazards regression models. P values for categorical variables were derived from the Chi-square test (*) and for survival outcomes from the log-rank test (**).

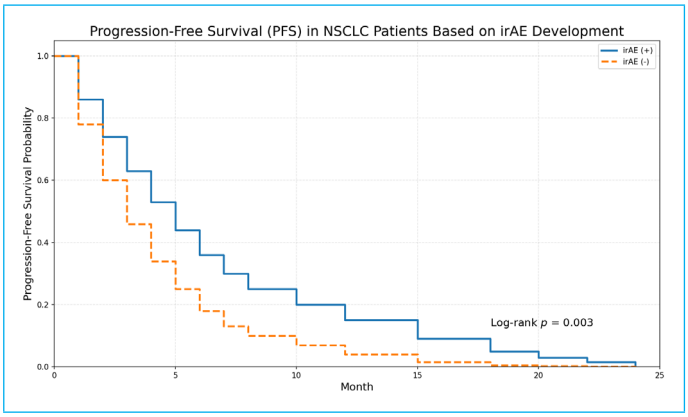

Figure 1. Progression-free survival (PFS) in NSCLC patients based on irAE development.

A multivariable Cox proportional hazards model was constructed adjusting for ECOG performance status, brain metastases, liver metastases, metastatic burden (≥2 sites), objective response status, and number of nivolumab cycles. After adjustment, the association between irAE occurrence and overall survival was attenuated and did not retain statistical significance (HR: 0.84, 95% CI: 0.61–1.15, p = 0.27). Although the direction of effect remained consistent, statistical significance was not maintained. Cycles were modeled as a continuous variable to account for potential exposure-related bias.

Tumor Response

Tumor response was assessable in the majority of patients included in the analysis. Objective responses were more frequently observed among patients who developed immune-related adverse events compared with those who did not (29% vs. 18%). A higher rate of disease control was also observed in the irAE-positive group, consistent with the unadjusted survival findings.

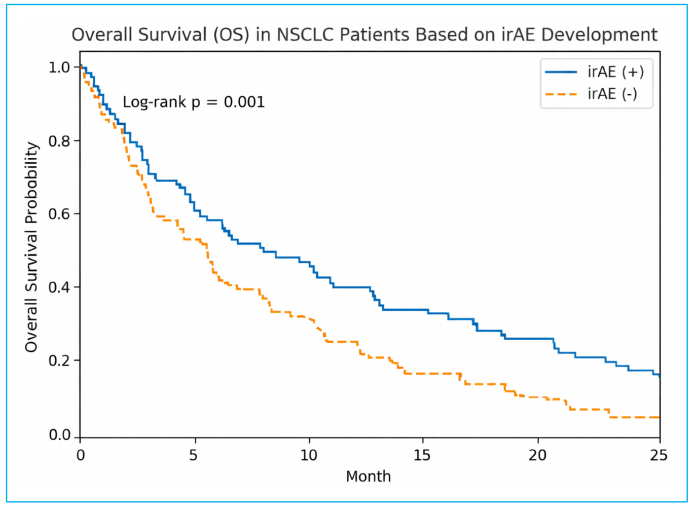

Figure 2. Overall survival (OS) in NSCLC patients based on irAE development.

Discussion

Our findings suggest that treatment-emergent immune-related adverse events are associated with a clinically distinct subgroup of patients receiving second-line nivolumab, characterized by more sustained disease control and longer survival in unadjusted analyses within routine practice.

The survival differences observed in patients with irAEs are consistent with the established activity of nivolumab in previously treated NSCLC. Pivotal randomized trials such as CheckMate-017 and CheckMate-057 demonstrated superior survival outcomes with nivolumab compared with docetaxel across histological subtypes, leading to its adoption as a standard second-line option.[6,7] Subsequent long-term follow-up and real-world studies have confirmed the durability of benefit achieved with PD-1 inhibition outside the controlled setting of clinical trials.[19,20] However, these landmark studies were not primarily designed to explore the prognostic implications of immune-related toxicity, underscoring the need for real-world analyses addressing this specific question.

Growing evidence from retrospective cohorts supports an association between irAE development and favorable treatment outcomes in NSCLC. Haratani et al.[12] reported prolonged survival among patients treated with nivolumab who developed immune-related adverse events, while Ricciuti and colleagues similarly observed improved overall survival in patients experiencing immune-mediated toxicity during PD-1 inhibitor therapy.[15] In addition, meta-analyses encompassing multiple tumor types, including lung cancer, have demonstrated a consistent relationship

between irAE occurrence and improved survival metrics.[21,22] The results of the present study are aligned with these observations. However, in our adjusted multivariable analysis, the association between irAE occurrence and overall survival did not retain statistical significance, suggesting that the observed survival differences may be influenced by clinical confounders and treatment exposure.

Given that patients who developed irAEs received a higher number of nivolumab cycles, the possibility of reverse causality and exposure-related bias should be considered when interpreting the survival advantage observed in univariable analyses. Although treatment exposure was accounted for in multivariable modeling, residual confounding related to time-dependent factors cannot be completely excluded.

The biological mechanisms linking immune-related adverse events with enhanced treatment efficacy remain incompletely elucidated. A commonly proposed explanation is that irAEs may represent a surrogate marker of heightened systemic immune activation, which could simultaneously augment antitumor immunity.[16,23,24] Potential mechanisms include shared antigenic determinants between tumor and normal tissues, expansion of activated effector T-cell populations, and engagement of overlapping immune signaling pathways.[25] Importantly, irAEs should be regarded as indicators of immune engagement rather than direct mediators of clinical benefit, as their apparent prognostic impact may be influenced by factors such as timing, affected organ systems, severity, and treatment duration.[17,26]

In the current cohort, the distribution of immune-related adverse events was consistent with the known safety profile of nivolumab. Dermatologic and endocrine toxicities were most frequently observed, whereas pneumonitis, although less common, remained clinically significant due to its potential severity and need for prompt intervention.[8,9] High-grade immune-related toxicities were relatively infrequent and were generally manageable with established supportive strategies, including temporary treatment interruption and corticosteroid therapy, supporting the feasibility of nivolumab administration in real-world oncology practice.

Several limitations of this study merit consideration. The retrospective design and single-center setting may introduce selection bias and limit the generalizability of the findings. Because immune-related adverse events typically develop after a period of treatment exposure, the possibility of time-dependent bias cannot be fully excluded. Accordingly, the observed association between irAE occurrence and improved survival should be interpreted as associative rather than causal. Although treatment exposure was modeled as a continuous covariate in the multivariable analysis, this approach does not fully eliminate the potential for immortal time bias. The absence of formal time-dependent Cox modeling may therefore limit causal interpretation, and the findings should be interpreted with appropriate caution. Additionally, the lack of comprehensive immunological or molecular data limited the ability to explore potential biological mechanisms linking toxicity with treatment outcomes. Variations in clinical management following irAE onset, including treatment interruption or continuation decisions, may also have influenced outcomes in real-world practice.

Another limitation is the absence of PD-L1 expression data. During the study period, nivolumab was administered in the second-line setting irrespective of PD-L1 status, and PD-L1 testing was not routinely performed in our institution. Nevertheless, PD-L1 expression may influence survival outcomes and could potentially be associated with immune-related adverse events; therefore, residual confounding related to PD-L1 status cannot be entirely excluded.

Beyond its potential prognostic implications, the association between immune-related adverse events and improved outcomes may have practical relevance for treatment decisions in daily oncology practice. In real-world settings, the development of manageable irAEs often raises questions regarding treatment continuation, dose scheduling, or supportive interventions. The present findings suggest that, when appropriately monitored and managed, immune-related toxicity does not necessarily indicate treatment failure and may coexist with sustained clinical benefit. From a clinical perspective, these observations may help inform patient counseling, reinforce adherence to immunotherapy, and support individualized decision-making during PD-1 inhibitor treatment.

Overall, this real-world analysis indicates an association between immune-related adverse events and favorable clinical outcomes in patients with non–small cell lung cancer treated with second-line nivolumab. Prospective studies incorporating time-dependent modeling and biomarker integration are warranted to clarify whether irAEs represent an independent prognostic factor or primarily reflect treatment exposure and immune activation dynamics.

Conclusion

In conclusion, the development of immune-related adverse events during second-line nivolumab therapy was associated with longer survival outcomes in this real-world cohort of patients with non–small cell lung cancer. However, this association did not retain statistical significance after multivariable adjustment, suggesting that treatment exposure and clinical confounders may partly contribute

to the observed differences. These findings support the hypothesis that irAEs may reflect immune activation dynamics rather than representing a direct causal determinant of improved survival. Careful monitoring and appropriate management of irAEs remain essential to maintain treatment continuity and optimize clinical outcomes in routine oncology practice.

Disclosure

Ethics Committee Approval: Ethical approval for the study was obtained from the Istanbul Kartal Lutfi Kirdar City Hospital Ethics Committee (Decision No: 2025/010.99/15/9, dated 30 April 2025). The study was conducted in accordance with the principles of the Declaration of Helsinki.

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Author contribution's: Concept – UÖ, SÖ; Design – UÖ, SA; Supervision – SA; Findings – UÖ, SÖ; Materials – UÖ, SÖ; Data Collection and/or Processing – UÖ, SÖ; Analysis and/or Interpretation – UÖ; Literature Review – UÖ; Writing – UÖ; Critical Review – UÖ, SA.

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