Association between immune-related adverse events and therapeutic outcomes in patients with advanced non-small cell lung cancer treated with pembrolizumab: A retrospective study

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Abstract. Several studies have indicated that the emergence of immune-related adverse events (irAEs) in patients receiving immunotherapy is a positive prognostic indicator. The aim of the present study was to assess the influence of irAEs on the clinical outcomes of patients with advanced stage non-small cell lung cancer (NSCLC), particularly the prognostic importance of irAEs. For this purpose, 60 patients with NSCLC were enrolled retrospectively; the patients received immunotherapy between January, 2020 and April, 2022. Clinical outcomes and progression-free survival (PFS) were compared between individuals with irAEs and those without. Of note, more than half of the patients (55%) developed irAEs. The median PFS of the patients with irAEs was significantly longer than that of the patients without irAEs (12.19 vs. 5.48 months). Furthermore, as regards the clinical outcomes, the disease control rate was significantly increased in the group with irAEs (72.7 vs. to 27.3%; P=0.033). On the whole, the present study indicated that patients with advanced stage NSCLC who experienced irAEs exhibited improved clinical outcomes following immunotherapy compared to those without irAEs. This underscores the prospective application of the development of irAEs as a clinical biomarker for immunotherapy-treated advanced stage NSCLC.

Introduction

Worldwide, the incidence of cancer is increasing, with lung cancer representing the most commonly diagnosed type, accounting for 11.6% of the total number of cancer cases (1). Lung cancer continues to be the foremost cause of worldwide cancer-related mortality, accounting for 18.4% of overall cancer-related fatalities, resulting in considerable societal burden and economic detriment (1,2). The World Health Organization (WHO) states that there are two primary forms of lung cancer: Non-small cell lung cancer (NSCLC), which accounts for 80-85% of all lung cancer cases, and small cell lung cancer, which accounts for 15% of cases (3,4). Additional subtypes of non-small cell lung cancer include adenocarcinoma, squamous cell carcinoma and large cell carcinoma (5).

During the initial decade of the 21st century, the median overall survival (OS) rate of individuals diagnosed with stage IV NSCLC was 1 year. The identification of actionable genetic abnormalities and the advancement of targeted therapeutics resulted in the significant enhancement of OS rates in a specific group of patients with NSCLC. Patients with NSCLC who lack driver mutations do not derive advantages from targeted therapy (5,6). The prognosis of the majority of patients with NSCLC lacking an actionable genetic driver was restricted, and platinum-based chemotherapy constituted the primary first-line treatment for these individuals (7). The paradigm for treating lung cancer, particularly NSCLC, has markedly changed as a result of the discovery of immunological checkpoints and the subsequent development of immune checkpoint inhibitors (ICIs), which were awarded the Nobel Prize (8). Targeting the programmed cell death protein 1 (PD-1)/programmed death ligand 1 (PD-L1) axis, ICIs, such as PD-1 antibodies (pembrolizumab and nivolumab) and PD-L1 antibodies (atezolizumab) exhibit immense promise due to their potent antitumor effects, which include restoring T-cell function and stimulating immune responses against tumors (8,9). Immune checkpoint molecules provide inhibitory signals to T-cells, preventing the excessive activation of the immune system and maintaining immunological homeostasis (10-12). Consequently, by inhibiting immune checkpoint molecules, ICIs activate antitumor T-cell responses that subsequently eradicate cancer cells (13,14).

Unlike conventional chemotherapy and targeted therapies, the use of ICIs is associated with side-effects, termed immune-related adverse events (irAEs), due to increased T-cell activation. Pneumonitis, thyroid dysfunction, skin

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toxicity, hepatitis and colitis are common immune-related side-effects, while other anatomical regions may also be affected (15,16). Previous studies have investigated the prognostic determinants in patients with NSCLC treated with ICIs (17-19). Nonetheless, a dependable predictive biomarker is still lacking (20). Consequently, previous studies have assessed the association between the adverse events and clinical benefits in patients undergoing anti-PD-1 antibody therapy (14,15). In recent years, it has become increasingly evident that the adverse events may serve as predictive markers for patients who experience them; nevertheless, the patient features linked to responses to immunotherapy remain ambiguous (20).

Despite the encouraging antitumor effects of ICIs in patients with NSCLC, a thorough understanding of immunotherapy and the improvement of treatment outcomes are hampered by the paucity of literature detailing the safety and effectiveness of both licensed and emergent ICIs for first-line NSCLC treatment. Thus, the present study aimed to investigate the therapeutic relevance of irAEs as a prognostic indicator in patients with NSCLC treated with pembrolizumab.

Patients and methods

Patient selection. The Research Ethics Committee of Mustansiriyah University, Baghdad, Iraq reviewed and approved the study (approval no. BCSMU/1024/0050Z). All data were retrospectively obtained from medical records in compliance with the principles of the Declaration of Helsinki. From January, 2020 and April, 2022, the present study included patients with stage IV NSCLC who had received a minimum of one dose of pembrolizumab at the Oncology Teaching Hospital/Medical City, in Baghdad, Iraq. All patients included were aged ≥18 years, and had received at least one dose of pembrolizumab, had previously untreated stage IV NSCLC, and a PD-L1 tumor proportion score (TPS) of at least 50%, measurable disease by irRECIST v1.1 (21), and an Eastern Cooperative Oncology Group performance status of 0 or 1. Patients received 200 mg intravenous pembrolizumab monotherapy once every 3 weeks for up to 45 cycles. Treatment was continued for the specified number of cycles until progressive disease, as per the irRECIST v1.1, adverse events (AEs) of unacceptable severity, or patient withdrawal. The exclusion criteria encompassed individuals who were administered pembrolizumab alongside other ICIs or therapeutic drugs, including standard chemotherapeutics and targeted therapies, as well as patients who did not have a follow-up visit following treatment with a single dose of pembrolizumab. Patients with sensitizing EGFR or ALK alterations, untreated brain metastases, or active autoimmune disease requiring systemic treatment or receiving systemic glucocorticoids or immunosuppressive therapy were also excluded. Patient-specific information was safeguarded and remains undisclosed. Data were retrospectively collected from January 1, 2024 to May 1, 2024.

Data collection and variables. Data were gathered from the initiation of pembrolizumab treatment until the transition to an alternative medicine, the occurrence of mortality, or the conclusion of the study period by retrospective medical record analysis. Upon initiating treatment with pembrolizumab, demographic information, such as sex, age and tobacco use was obtained. Additional obtained data encompassed the specifics of pembrolizumab medication (e.g., cycle), irAEs (e.g., occurrence, degree, type, treatment and progression). irAEs, including thyroiditis, hepatitis and renal insufficiency, were documented during each cycle. Thyroid function was also documented at each treatment cycle. Objective tumor response was evaluated every four to six cycles via PET or CT scans, in accordance with the irRECIST, version 1.1 (21). AEs were graded using the Common Terminology Criteria for Adverse Events version 4.0 (22). The grading of irAEs was determined by treating physicians (hematologists and oncologists). The present retrospective study was designed and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. All retrospectively collected data were stored using Microsoft Office Excel software on a computer belonging to the Oncology Teaching Hospital (Medical City Center, Ministry of Health, Baghdad, Iraq). The data was password-protected. For the purpose of the present study, no identifying information was collected. Instead, all patients recruited for the study were allocated study codes, beginning from 0001, representing the first observed patient.

Data analysis. The objective response rate (ORR) was established as the sum of the complete response (CR) rate and the partial response (PR) rate. The disease control rate (DCR) was defined as the ORR plus the stable disease rate. Progression-free survival (PFS) was defined as the interval from the initiation of immunotherapy to the onset of progressive illness. PFS was examined between individuals with irAEs and those without such events. PFS was also examined between patients with early- and late-onset irAEs. For retrospective analysis, pre-existing PD-L1 expression data were compared between patients who developed irAEs and those who did not.

Statistical analysis. All statistical analyses were carried out using the Statistical Package for Social Sciences (IBM Corp.) software version 25. Categoric variables are expressed as frequency and percentage. Comparisons between groups were performed using the Chi-squared test. Fisher's exact test was applied when expected value in a cell was <5. Sample normality was tested using the Shapiro-Wilk test and a visual inspection of their histograms and normal Q-Q plots and box blots revealed that PD-L1 data were not normally distributed. Comparisons between groups were conducted using the Mann-Whitney U test. PFS was assessed using Kaplan-Meier curves, and comparisons between different groups were performed using the log-rank test. P-values <0.05 were considered to indicate statistically significant differences.

Results

A total of 60 patients considered eligible were recruited in the present study (Fig. 1). The mean age of the patients was 64±11.9 years. Males constituted the majority of this

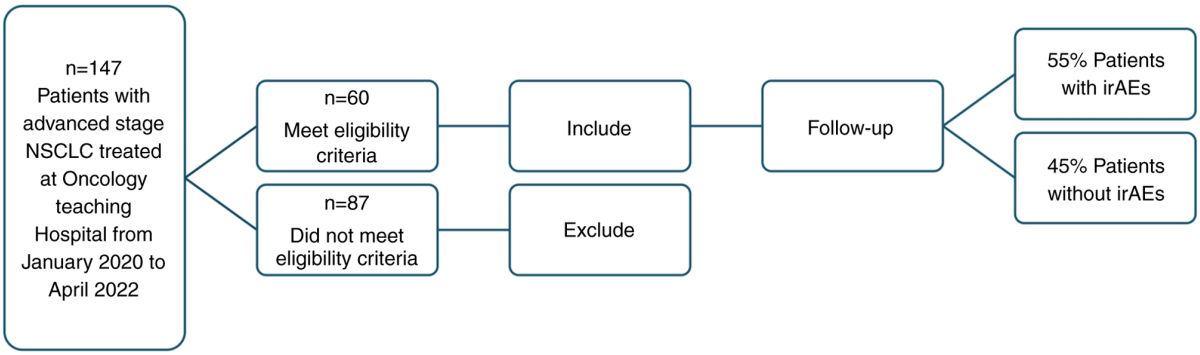

Figure 1. Flowchart summarizing the number of patients included in the present study. NSCLC, non-small cell lung cancer; irAEs, immune-related adverse events.

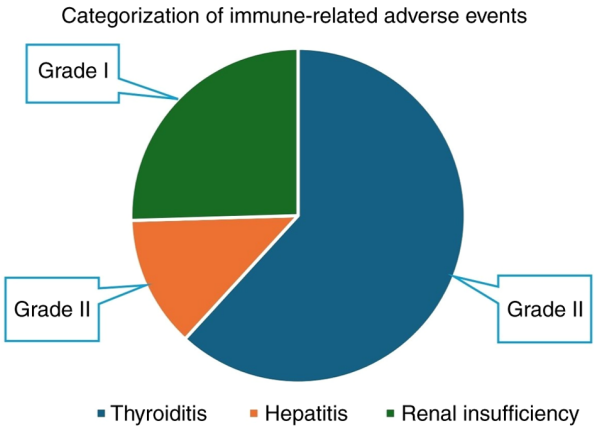

Figure 2. Categorization of immune-related adverse events.

cohort. Never smokers represented (23.4%) of all patients. Adenocarcinoma was the main histopathological type (70.0%); the remaining patients had squamous cell carcinoma. The patient characteristics are presented in Table I.

The mean follow-up period was 26±3.3036 months. During this period, more than half of the patients (55%) experienced irAEs. Thyroid-related irAEs accounted for 34%, followed by renal insufficiency 14% and hepatitis (7%). Hypothyroidism was the most frequently reported form of thyroiditis, accounting for 70% of cases, while hyperthyroidism accounted for 30% of all thyroiditis cases. All thyroiditis and hepatitis cases were grade II, while renal insufficiency cases were grade I (Fig. 2). There were no treatment-related deaths. irAEs were significantly more frequent after the tenth cycle, observed in 91.7% of the patients (P=0.003); however, early occurrence in the first five cycles was also observed (Table II). The median PD-L1 expression in the tumors of patients who experienced irAEs was 70% compared to 55% in those who did not have irAEs (Fig. 3). The ORR was 60.0%, with 53.3% of patients demonstrating a PR and 6.7% of patients exhibiting a CR (Table I). When all irAEs were considered, the DCR was significantly higher in the group with irAEs (72.7 vs. 27.3%; P=0.033) compared with the group with no irAEs. No significant difference was observed when early-onset irAEs (after the second cycle) and late-onset irAEs (after the sixth cycle) were analyzed separately (Table III).

Table I. Characteristics of the patients in the present study (n=60).

Characteristic	No	%
Age, years		
≤50	14	23.3
>50	46	76.7
Sex		
Female	16	26.7
Male	44	73.3
Smoking status		
Never smoker	14	23.4
Ex-smoker	26	43.3
Current smoker	20	33.3
Subtype		
Adenocarcinoma	42	70.0
Squamous cell carcinoma	18	30.0
No. of pembrolizumab cycles		
2-5	18	30.0
6-10	20	33.3
11-18	22	36.7
Response		
Stable	8	13.3
Partial response	32	53.3
Complete response	4	6.7
Progressive disease	16	26.7

Out of the 60 patients who received the treatment, 26.7% developed progressive disease. The mean PFS rate of the patients with irAEs was 12.19 months, while that of patients without irAEs was markedly shorter at 5.48 months, with the difference being statistically significant (P=0.013). This significant difference was maintained when the patients with irAEs were stratified to late-onset (P=0.026; Fig. 4). While the Kaplan-Meier analysis focused on the 13-month where progressions occurred, the mean follow-up of 26 months reflects the complete monitoring period including censored patients with prolonged surveillance.

Table II. Patient characteristics in the presence and absence of irAEs.

Characteristic	Total no.	No irAEs		With irAEs		P-value
		No.	%	No.	%	
Age groups						
≤50	14	2	14.3	12	85.7	0.354
>50	46	22	47.8	24	52.2	
Sex						
Female	16	6	37.5	10	62.5	0.999
Male	44	19	43.2	25	56.8	
Smoking status						
Never smoker	14	7	50.0	7	50.0	0.999
Ex-smoker	26	10	38.5	16	61.5	
Current smoker	20	8	40.0	12	60.0	
Subtype						
Adenocarcinoma	42	17	40.5	25	59.5	0.999
Squamous cell carcinoma	18	8	44.4	10	55.6	
No. of pembrolizumab cycles						
2-5	16	14	87.5	2	12.5	0.003
6-10	20	8	40.0	12	60.0	
11-18	24	2	8.3	22	91.7	

irAEs, immune-related adverse events.

Table III. Response to treatment in the two study groups (with and without irAEs).

	No irAEs, n (%)	irAEs, n (%)	P-value
All irAEs			
ORR	10 of 36 (27.8)	26 of 36 (72.2)	0.148
DCR	12 of 44 (27.3)	32 of 44 (72.7)	0.033
Early-onset irAEs			
ORR	24 of 36 (66.7)	12 of 36 (33.3)	0.999
DCR	26 of 44 (59.1)	18 of 44 (40.9)	0.371
Late-onset irAEs			
ORR	14 of 36 (38.9)	22 of 36 (61.1)	0.44
DCR	16 of 44 (36.4)	28 of 44 (63.6)	0.077

irAEs, immune-related adverse events; ORR, objective response rate; DCR, disease control rate.

Discussion

The present study demonstrated the predictive value of irAEs in patients with NSCLC treated with pembrolizumab. irAEs manifested in 55% of patients, with the prevalence in observed being parallel to that observed in clinical trials (23). The incidence of irAEs induced by pembrolizumab was associated with a clinical advantage in patients with NSCLC. This aligns with the findings of other retrospective studies that demonstrated an association between the incidence of irAEs and the clinical efficacy of ICIs (13,17).

While any organ system may be affected, irAEs primarily affect the gastrointestinal tract, hormonal glands, the skin and liver (24,25). The predominant irAEs in NSCLC linked to the use of pembrolizumab are thyroid-related toxicities (26). In the present study, thyroid-related irAEs accounted for 34%, renal insufficiency for 14% and hepatitis accounted for 7%. Hypothyroidism was the most frequently reported form of thyroiditis, accounting for 70%, while hyperthyroidism accounted for ~30% of all thyroiditis cases; this finding is consistent with the findings of previous studies (27,28). In the present study, all

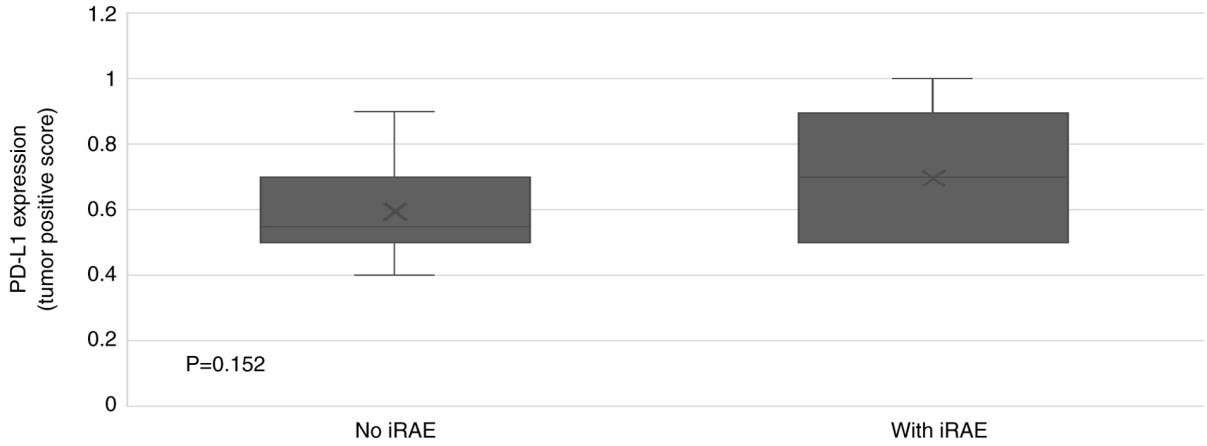

Figure 3. PD-L1 expression (tumor positive score) in patients with and without irAEs. PD-L1, programmed death ligand 1; irAEs, immune-related adverse events.

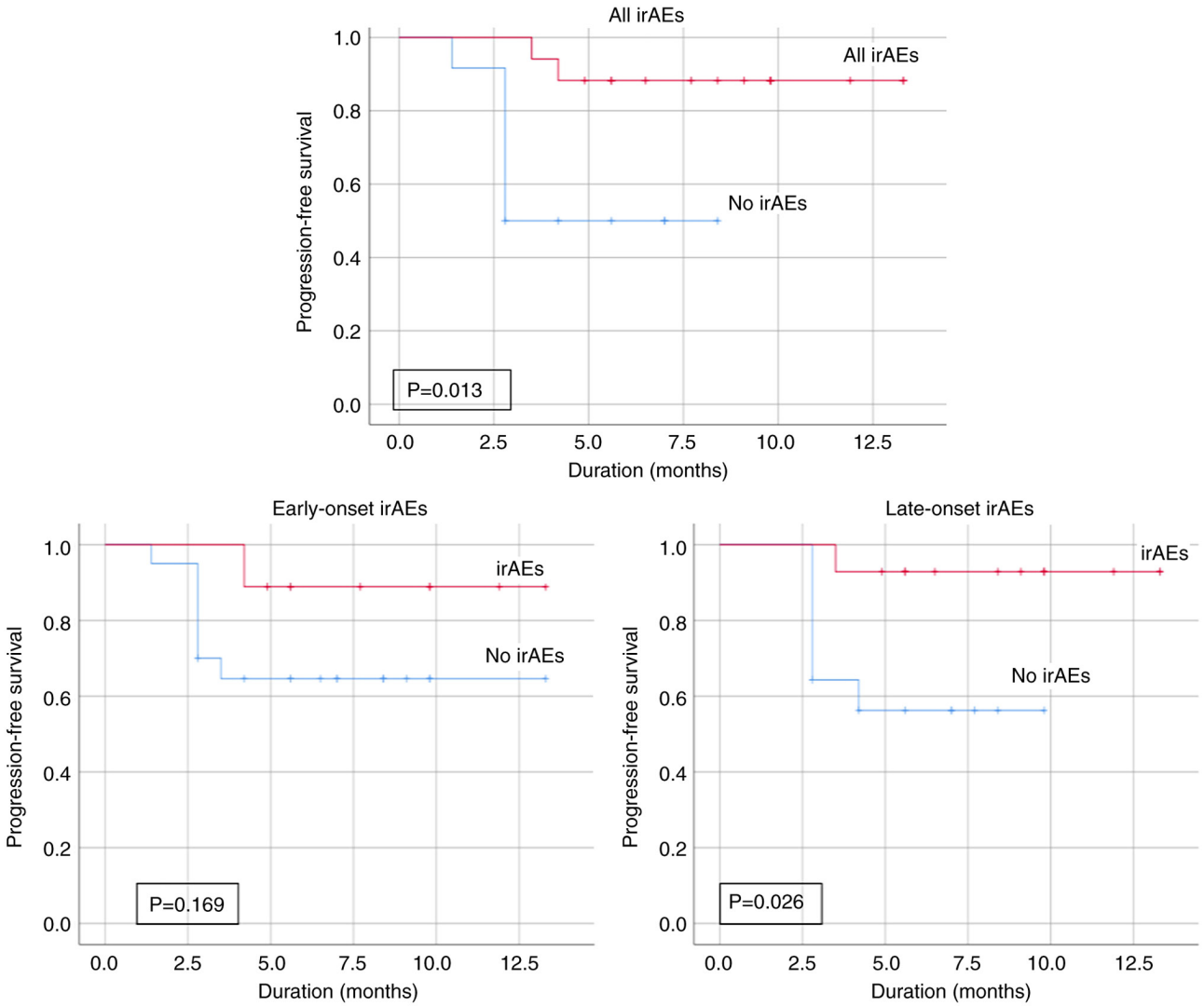

Figure 4. Kaplan-Meier curves for progression-free survival. (Top panel) All irAEs included; (bottom left panel) only early-onset irAEs included; (bottom right panel) only late-onset irAEs included. irAEs, immune-related adverse events.

thyroiditis and hepatitis cases were grade II, while the renal insufficiency cases were grade I. The patients received appropriate treatment tailored to each of the mentioned conditions. During this period, there were no interruptions to the administration schedule of the immunotherapy. There were no treatment-related deaths.

Nevertheless, the mechanisms behind the development of irAEs remain to be fully elucidated. The function of immunological checkpoints in preserving immunological homeostasis is considered to be connected to irAEs. Increased T-cell activity against antigens found in tumors and healthy tissue, elevated levels of pre-existing autoantibodies, elevated levels of inflammatory cytokines (such as interleukin-17), and enhanced complement-mediated inflammation as a result of direct antibody binding against cytotoxic T-lymphocyte antigen 4 are some possible mechanisms that may be linked to the occurrence of irAEs (29). The activation of the 'ideal immune system' must equilibrate the immunological response to the tumor with the self-immune response. However, the precise pathophysiology underlying irAEs warrants further investigation. The severity of the irAE, the affected system or organ, and the number of sites involved determine the equilibrium between its advantages and disadvantages (30). Additionally, as irAEs frequently manifest suddenly and can even result in fatal toxicities, it is critical that clinicians identify and treat the events as soon as possible (31).

In terms of the timeline of occurrence, the time of onset of irAEs is also a critical element in determining the association between irAEs and the clinical results of ICI treatment. Previous studies have indicated that the majority of irAEs occur early, typically within the first 6 months of treatment (32,33). The majority of irAEs occur within the first 6 months of treatment, according to another retrospective cohort study that included a large number of hospitalized patients with irAEs (34). However, a consensus on whether irAEs, their timing, or specific types are indicative of positive therapeutic outcomes is still lacking (35). In the present study, irAEs were significantly more frequent after the tenth cycle, observed in ~91.7% of patients (P=0.003); however, early occurrence in the first five cycles was also observed; this result is consistent with the aforementioned previous studies.

In patients with NSCLC receiving ICI therapy, the incidence of irAEs and the timing of the events are key indicators of prognosis (35). The present study defined early-onset irAEs (after the second cycle, 1.4 months) and late-onset irAEs (after the sixth cycle, 4.2 months) based on the observed patterns within the study cohort. These cut-offs reflect marked changes in the frequency and timing of irAE occurrences. These intervals also align with common practices in similar studies, ensuring consistency and comparability in the analysis. Some studies have reported that early-onset irAEs are associated with improved outcomes following immunotherapy (36,37). However, in another study on 154 patients with NSCLC receiving ICI therapy, those who encountered later irAEs (defined as occurring after 3 months of commencing ICI medication) had a significantly longer OS and PFS than those who suffered irAEs at an early stage (38). Furthermore, Cortellini *et al* (30) revealed that patients who acquire irAEs are those who undergo prolonged therapy with ICIs and consequently exhibit a more favorable prognosis than those who do not. One possible confounding issue is that patients with late-onset irAE may have optimal outcomes as they have lived long enough to develop them. In the present study, there was no significant difference between early- and late-onset irAE; this may be attributed to the small sample size and the short follow-up period. The observed differences between the findings of the present study and those of previous studies further highlight the need for additional research to explore this topic in depth and understand the underlying factors contributing to these variations.

Consistent with the available data (39,40), the observations of the present study suggest a connection between the clinical benefits of anti-PD-1 immunotherapy and the development of irAEs. In the present study, DCR was significantly higher in the group with irAEs (72.7 vs. 27.3%, P=0.033). Moreover, the patients with irAEs were divided into two groups according to the timeline of occurrence; the early-onset irAEs group (after the second cycle) and late-onset irAEs group (after the sixth cycle). The DCR was higher in late-onset group (63.6 vs. 36.4; P-value 0.077). Recent studies have indicated that patients exhibit improved prognosis when they encounter irAEs during ICI therapy (41). In the present study, the non-highly significant results may be attributed to the investigation of a small number of patients.

The findings of the present study suggest an association between the development of irAEs and improved clinical outcomes in patients with advanced stage NSCLC treated with pembrolizumab. The occurrence of irAEs was substantially associated with an extended PFS. In the present study, the median PFS rate of patients with irAEs was 12.19 months, whereas for those without irAEs, this was markedly lower at 5.48 months, with a statistically significant difference (P=0.013). This is consistent with the findings of several recent retrospective studies. For example, Chen *et al* (42) and Chen *et al* (43) indicated that the incidence of irAEs was associated with an improvement in PFS, but not in OS. In particular, Boulhel *et al* (44) and Ricciuti *et al* (45) confirmed that patients who encountered irAEs exhibited a higher significant survival advantage than those without irAEs, further indicating a causal association between irAEs and the efficacy of immunotherapy. The findings of these investigations contribute to the expanding comprehension that irAEs enhance patient PFS rates and validate the observation observed herein that the occurrence of irAEs in patients with NSCLC is associated with a heightened responsiveness to immunotherapy and an extended PFS. While the present study focused on pembrolizumab, its efficacy is often compared with other ICIs, such as nivolumab (another PD-1 inhibitor) and atezolizumab (a PD-L1 inhibitor) within previous studies. A recent study indicated that pembrolizumab may be associated with a higher ORR compared to nivolumab, particularly in first-line therapy for advanced stage NSCLC (10). Moreover, in a small cohort study, the median PFS was 9.6 months for atezolizumab, 12.6 months for nivolumab and 8.5 months for pembrolizumab; however, the differences were not statistically significant, and survival outcomes were influenced by the patient performance status (46). Furthermore, other studies have also indicated that there is no significantly different between pembrolizumab and nivolumab across advanced stage NSCLC, by reporting a similar median PFS (10,47).

It is unknown whether there is a link between PD-L1 expression and the development of IrAEs (48). Additionally, a previous clinical study found no significant link between PD-L1 expression and the development of irAEs (49). Moreover, in the BIRCH trial (50), which examined the effects of ICI, there was no significant association between

a high expression of PD-L1 and the development of irAEs. Additionally, a previous multicenter retrospective analysis of pembrolizumab monotherapy first-line treatment revealed no statistically significant difference in the incidence of adverse events (irAEs) between the TPS >90% and TPS 50-89% groups (51). This is consistent with the findings of the present study. Other research, however, has demonstrated that TPS ≥90% was only significantly linked to the likelihood of developing irAEs in patients undergoing ICIs as first-line treatment (52). In the present study, the median PD-L1 expression ratio in tumors of patients who developed irAEs was 70% compared to 55% in those who did not have irAEs; however, statistically, this was not significant. The lack of a significant impact of this result may be attributed to the limited sample size and the brief follow-up duration. For an understanding of the possible prognostic significance of PD-L1 expression, further research is warranted.

In several malignancies, ICIs are being used in addition to, or in place of front-line therapy due to their long-lasting antitumoral effect. As a result, diagnosing and treating irAEs presents clinicians with increasing difficulties in the treatment of patients. To solve these issues, basic, translational and clinical studies are required to elucidate the complex mechanisms of irAEs and identify biomarkers derived from these mechanisms (53). However, identifying broadly applicable biomarkers remains difficult due to the complexity of irAEs and their varied presentations across organs (54,55). Furthermore, given the possible link between irAEs and tumor response, efforts to prevent irAEs before they affect the immune system changes required for a prolonged survival time may deny patients the potential long-term and hidden advantages (56). Even in the absence of irAEs, efforts should be directed towards modifying the immune response in order to improve the survival rates (56). The future objectives of the field are not limited to strategies to increase efficacy. As aforementioned, separating effectiveness from irAEs requires immense efforts. In particular, further knowledge needs to be obtained about the parameters predicting the occurrence of irAEs (57). In order to provide a comprehensive understanding of the relative advantages and disadvantages of ICI therapy, it is necessary to continuously synthesize data from a variety of sources, including recent clinical trials and review articles. These initiatives would fill in the current gaps in the evidence and guide medical decisions in this area.

In conclusion, the present retrospective study indicated that irAEs may positively influence the therapeutic outcomes of patients with NSCLC undergoing immunotherapy. This underscores the prospective application of irAEs as a clinical indicator for survival in patients with advanced stage NSCLC treated with ICIs. Although a priori statistical power analysis was performed to determine the sample size needed to detect clinically significant differences, the timeframe of the study limited the authors' ability to include the optimal number of participants. This may have affected the statistical power to detect significant differences between the groups. While the generalizability of the results may be attributed to the aforementioned point, the strength of the observed discrepancies highlights the robustness and usefulness of the results of the study. Additional research is necessary to enhance the prediction of which individuals will experience irAEs and to determine optimal management strategies for their occurrence.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

TJT contributed to the conception and design of the study, and wrote and edited the manuscript. SMJ collected and analyzed data. FAAS reviewed and edited the manuscript, and was also involved in data curation, and supervised the study All authors have read and approved the final manuscript. TJT and SMJ confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The present study was reviewed and approved by the Research Ethics Committee of Mustansiriyah University (approval No. 1024/0050Z). and subsequently authorized by Oncology Teaching Hospital/Medical City administration per standard institutional collaboration procedures. All data were retrospectively extracted from medical records in accordance with the principles of the Declaration of Helsinki. All patients who participated in this study provided written informed consent for the publication of their data.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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