ORIGINAL ARTICLE

The Timing, Trajectory, and Incidence of Immune-Related Adverse Events in NSCLC Treated With Atezolizumab

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ABSTRACT

Introduction: Immune-related adverse events (irAEs) due to immune checkpoint inhibitors can have complicated clinical courses. We comprehensively evaluated the timing, trajectory, and incidence of both single and multiple irAEs for NSCLC treated with atezolizumab.

Methods: Data were pooled from 2457 patients who participated in the IMpower130, IMpower132, and IMpower150 clinical trials investigating the use of atezolizumab in metastatic NSCLC as part of a chemoimmunotherapy regimen. Longitudinal irAE data with landmark analysis, time-to-onset, changes in grading severity, and occurrence of multiple events were summarized.

Results: In general, 1557 patients were treated with atezolizumab and 900 patients were in the control groups. Median follow-up was 32.3 and 23.5 months, respectively. In the atezolizumab group, 753 patients (48.4%) experienced at least one irAE. In the control group, 289 patients (32.1%) experienced at least one nonimmune adverse event that was attributed to an irAE. In the atezolizumab group, the most common irAEs were rash, hepatitis, and hypothyroidism. Furthermore, 13% of the patients experienced two irAEs and 4% experienced three irAEs. Within 5 months of treatment, the cumulative incidence for any irAE was 39.2%. Median time-to-onset varied from 1 to 10 months based on the specific irAE. Grade 1 to 2 irAEs increased in severity for 33% of the patients.

Conclusions: We identified dynamic clinical patterns for irAEs in patients treated with atezolizumab, including variations in time-to-onset, incidence of multiple irAEs, and frequency of irAEs increasing in severity. These results can

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guide clinical management and future reporting of adverse events to enable comprehensive longitudinal analyses.

Keywords: Immune-related adverse events; Immune checkpoint inhibitors; Non–small cell lung cancer; Atezolizumab

Introduction

Immune checkpoint inhibitors (ICIs) have drastically changed the cancer therapy landscape since the approval of ipilimumab in 2011.[1] More than 40% of patients with cancer are eligible for treatment with an ICI, which will continue to increase over time as ICIs move to earlier treatment settings and as novel ICI therapies are developed.[1–3] ICIs target immune inhibitory receptors such as cytotoxic T-lymphocyte associated protein 4 (CTLA-4), programmed cell death protein-1 (PD-1), and programmed death-ligand 1 (PD-L1), resulting in improved T-cell recognition and clearance of tumor cells.[1,4] Toxicity from ICIs, also known as immune-related adverse events (irAEs), is due to loss of self-tolerance from immune checkpoint blockade leading to damage of normal tissues.[5] The development of self-tolerance and subsequent irAEs can occur owing to release of inhibitory T cells resulting in direct destruction of normal tissue and indirect epitope spreading, expansion of autoantibody-producing B cells, and ICI antibodies binding to off-target tissues.[5,6]

As ICI utilization continues to increase in clinical practice, it is imperative that clinicians are equipped with the knowledge to manage irAEs. These toxicities are documented for nearly every organ system with events ranging from mild dermatitis to devastating outcomes, such as severe neurologic or cardiopulmonary toxicities.[7] Compared with adverse events (AEs) from cytotoxic chemotherapy, which have predictable patterns based on the timing of drug administration, irAEs vary in the organ systems affected, time-to-onset, and time to resolution depending on the underlying disease and the medications administered.[8,9] Some studies have reported irAEs in up to 80% of patients receiving ICI monotherapy and up to 95% of those receiving combination ICI therapy.[10] Despite the negative impacts that irAEs can have on quality of life, low-grade (1–2) irAEs are associated with improved overall survival (OS).[11–13]

There have been substantial improvements in outcomes for metastatic NSCLC, in part due to the use of ICIs. Currently, all first-line treatment options for metastatic NSCLC without actionable driver mutations include ICI-based regimens.[14,15] Atezolizumab, a PD-L1 inhibitor, has been found to have safety and efficacy in multiple clinical trials for NSCLC. The phase 3 IMpower130 and IMpower132 trials evaluated atezolizumab plus chemotherapy for the first-line treatment of advanced NSCLC. IMpower150 evaluated atezolizumab plus chemotherapy with or without bevacizumab.[16–19] These three trials led to incorporation of atezolizumab into the treatment guidelines for NSCLC.[14]

Despite the increasing use of ICIs in clinical practice, there remains limited data exploring the dynamic clinical courses that can occur with irAEs. Most clinical trials report irAE frequency as single events, which does not accurately encompass the patient experience. Our study aimed to comprehensively evaluate irAEs in a large, pooled analysis of patients with NSCLC treated with atezolizumab in IMpower130, IMpower132, and IMpower150 to better characterize irAE patterns, including timing, severity, and incidence of multiple irAEs.

Materials and Methods

Patients

Data were pooled from patients who consented to participate in the IMpower130, IMpower132, and IMpower150 clinical trials. The individual trial designs are included in the Supplementary Materials (Supplementary Fig. 1). The analysis population included all patients who received any amount of study treatment.

Definitions

IrAEs were defined using the Medical Dictionary for Regulatory Activities (MDRA) preferred terms, which included diagnosed immune conditions, and signs and symptoms potentially representative of immune-related events, regardless of investigator-assessed causality. Events were summarized as medical concepts rather than single MDRA preferred terms. The term irAE was used to describe events in the control arm for ease of comparison to the known irAEs in patients treated with atezolizumab; however, we refer to these events as nonimmune AEs for clarity.

Statistical Analysis

Longitudinal irAE data with cumulative incidence rates at multiple landmarks, median time-to-onset, changes in grading severity, and multiple events were summarized. Cumulative incidence curves and rates at landmark time points were generated using Kaplan-Meier methodology. Upset plots were used to illustrate the incidences of single and multiple irAEs.

Table 1. Baseline Characteristics of Patients Treated in the Atezolizumab and Control Arms

Characteristic	Atezolizumab Arm (n = 1557)	Control Arm (n = 900)
Age, median (range)[a]	64.0 (18-89)	63.0 (31-90)
Male, n (%)	938 (60)	551 (61)
Female, n (%)	619 (40)	349 (39)
Race, n (%)		
White	1257 (81)	736 (82)
Asian	188 (12)	113 (13)
Black	31 (2)	24 (3)
Other	81 (5)	27 (3)
ECOG PS, n (%)	n = 1553	n = 897
0	664 (43)	377 (42)
1	889 (57)	520 (58)
EGFR mutation status, n (%)		
Positive	107 (7)	53 (6)
Negative	1433 (92)	841 (93)
Unknown	17 (1)	6 (1)
PD-L1 status per SP142, n (%)[b]	n = 1556	n = 900
TC3 or IC3 (high PD-L1)	257 (17)	132 (15)
TC1, 2, 3 or IC1, 2, 3 (any PD-L1)	738 (47)	393 (44)
TC0 and IC0 (PD-L1 negative)	702 (45)	395 (44)
Unknown	116 (8)	112 (12)

[a]Age in years.
[b]Categories are not mutually exclusive.
ECOG PS, Eastern Cooperative Oncology Group performance status; IC, immune cell; PD-L1, programmed death-ligand 1; TC, tumor cell.

Results

A total of 2457 patients were included in the pooled analysis. In general, 1557 patients received atezolizumab and 900 patients were in control groups. Median follow-up was 32.3 months in patients treated with atezolizumab and 23.5 months in the control group. Patient characteristics were similar between the two groups (Table 1). The median age was 64 years for the atezolizumab group and 63 years for the control group. Performance status was 0 to 1 based on the Eastern Cooperative Oncology Group Performance Status Scale. Most patients were EGFR negative (92% in the atezolizumab group and 93% in the control group). PD-L1 status was negative in 45% of patients on atezolizumab and 44% of control patients.

Among the patients treated with atezolizumab, 753 (48.4%) experienced at least one irAE compared with 289 patients (32.1%) in the control arm who experienced at least one nonimmune AE. The most common irAEs in patients who received atezolizumab were rash (28%), hepatitis (15%), hypothyroidism (12%), and pneumonitis (6%) (Table 2). In addition, 13% of patients treated with atezolizumab experienced at least two irAEs, most frequently rash and hepatitis (4%), followed by rash and hypothyroidism (3%). The median duration between the first and second irAEs was 2.6 months (0–28.1 mo). Furthermore, 4% of patients treated with atezolizumab experienced three irAEs (Fig. 1*A*). The most common nonimmune AE in patients from the control group was rash (18%) and hepatitis (10%) (Table 2). Of the patients in the control arm, 5% had two AEs with a median duration of 1.5 months (0–19.6 mo) between the first and second events (Fig. 1*B*).

Most irAEs in patients treated with atezolizumab were of grade 1 or 2. Grade 3 to 5 events occurred in 23% (174 of 753) of patients with irAEs or 11% (174 of 1557) of all patients treated with atezolizumab. There were four grade 5 irAEs observed, including one case of hepatitis and pneumonitis at 1 month and two cases of pneumonitis at 6 months. Within 5 months of treatment, the cumulative incidence for all irAEs was 39.2% for patients treated with atezolizumab and 28% in the control groups (Fig. 2*A*). Figure 2*B* illustrates cumulative incidences for rash, hypothyroidism, hyperthyroidism, and colitis. Among the patients in the atezolizumab-containing treatment arms who experienced any irAE, the median time to onset varied from 1 to 10 months based on the specific irAE. For example, the median time to onset for rash was 1.1 months, pneumonitis was 4.5 months, hypothyroidism was 5.5 months, and adrenal insufficiency was 10.4 months (Table 2).

For patients who had an initial grade 1 to 2 irAE, 33% in the atezolizumab group experienced a subsequent higher grade irAE, compared with 20% of patients in the control group (Fig. 3*A* and *B*). The irAEs that were initially scored as grade 1 increased to greater than or equal to grade 3 in 13.4% of the patients, and the irAEs that were initially scored as grade 2 increased to greater than or equal to grade 3 in 20.1% of the patients (Fig. 3*A*).

Table 2. Summary of Immune-Related Adverse Events and Median Time-to-Onset in Months

Treatment Group	Atezolizumab (n = 1557)			Control (n = 900)		
IrAEs,[a] n (%)	Any Grade (%)	Grades 3-5 (%)	Median Time-to-Onset Any Grade[b] [Range]	Any Grade (%)	Grades 3-5 (%)	Median Time-to-Onset Any Grade[a] [Range]
Any irAE	753 (48)	174 (11)	1.68 [0.03-34.66]	289 (32)	45 (5)	1.38 [0.03-17.25]
Rash	435 (28)	38 (2)	1.12 [0.03-35.06]	160 (18)	11 (1)	0.92 [0.03-16.85]
Hepatitis	226 (15)	73 (5)	1.63 [0.03-34.66]	92 (10)	17 (2)	2.07 [0.03-12.42]
Hypothyroidism	192 (12)	6 (<1)	5.55 [0.10-31.64]	33 (4)	0	3.98 [0.03-24.15]
Hyperthyroidism	59 (4)	3 (<1)	4.14 [0.26-31.54]	14 (2)	0	5.93 [0.36-13.01]
Adrenal insufficiency	19 (1)	3 (<1)	10.41 [0.66-30.36]	3 (<1)	1 (<1)	3.68 [1.84-7.36]
Hypophysitis	6 (<1)	2 (<1)	5.85 [5.03-8.84]	0	0	-
Colitis	26 (2)	17 (1)	3.37 [0.23-39.13]	3 (<1)	2 (<1)	0.59 [0.10-3.98]
Pneumonitis	88 (6)	25 (2)	4.47 [0.26-30.78]	17 (2)	8 (1)	4.86 [0.72-16.49]
Myocarditis	1 (<1)	1 (<1)	1.38 [-]	0	0	-
Nephritis	11 (<1)	7 (<1)	5.82 [2.33-17.94]	1 (<1)	0	0.72 [-]

[a]IrAEs were defined using the MDRA preferred terms, which included diagnosed immune conditions and signs and symptoms potentially representative of immune-related events, regardless of investigator-assessed causality.
[b]Measured in months.
irAE, immune-related adverse event; MDRA, Medical Dictionary for Regulatory Activities.

Discussion

Our pooled analysis of 2457 patients with metastatic NSCLC from IMpower130, IMpower132, and IMpower150 revealed that 48% of the patients treated with atezolizumab experienced irAEs, with 77% of all irAEs being low-grade (1–2) events. Rash, hepatitis, and hypothyroidism were the most common irAEs. Rash had the fastest median time to onset at 1.1 months and adrenal insufficiency had the longest median time to onset at 10.4 months (Table 2). In addition to reporting single events, we evaluated the incidence of multiple irAEs and changes in grading over time, which further showcases the potential complexity in irAE courses.

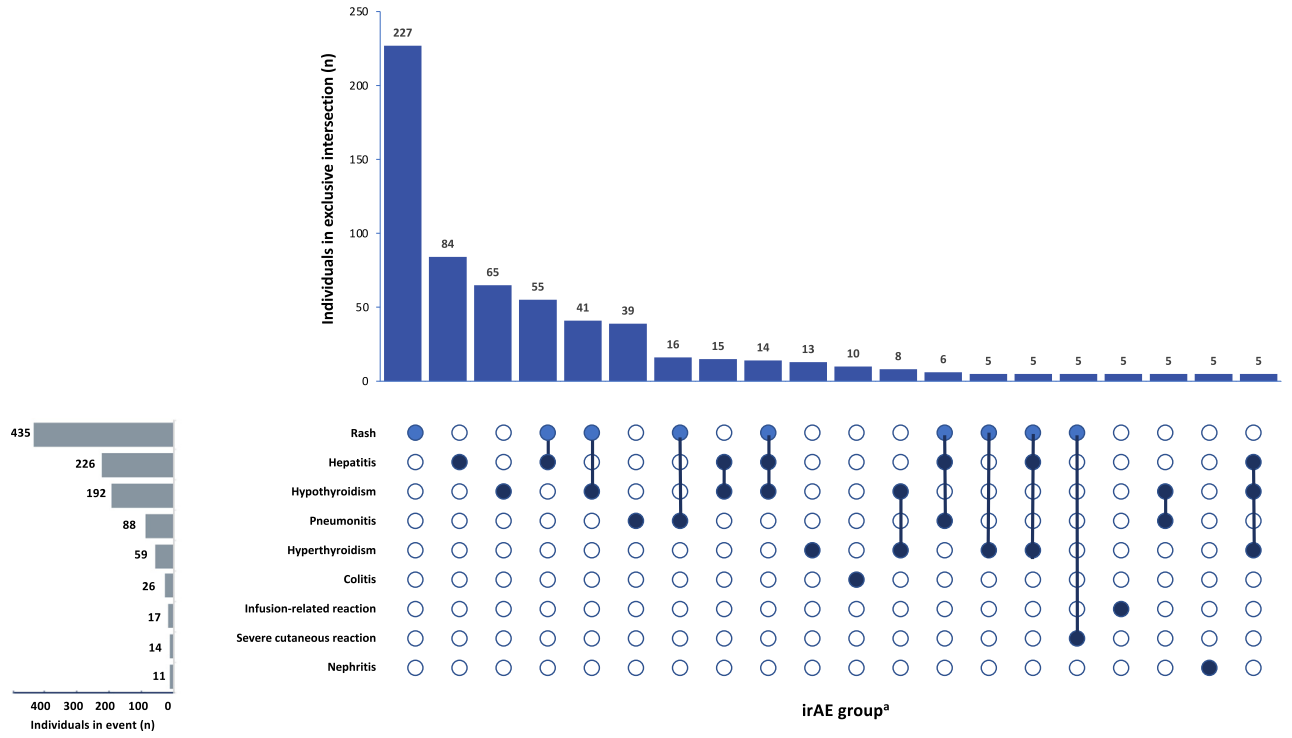
A recent analysis of ipilimumab plus nivolumab in NSCLC pooled from CheckMate 227, CheckMate 568, and CheckMate 817 also found that most irAEs were of low grade (1–2). Similar to our study, rash was the most frequent event at a median time to onset of 1.5 months.[20] Nevertheless, this study differs from our study in that they found a higher incidence of colitis, more frequent grade 3 or higher events (34% versus 11%), and earlier onset for several irAEs with the combined CTLA-4 and PD-1 blockade. The comparison between our study and the pooled analysis of ipilimumab and nivolumab from Paz-Ares et al.[20] highlights that there can be differences in irAE patterns based on treatment regimens. Further support for this concept is found in a systematic analysis across 48 trials (6938 patients) revealing that CTLA-4 inhibitors were associated with more colitis and hypophysitis compared with PD-1 and PD-L1 inhibitors, potentially linked to variances in checkpoint expression on different organ systems.[21]

Although only singular irAEs are usually reported in ICI trials, patients can have multisystem irAEs.[22] In our cohort, 13% of patients were diagnosed with two irAEs and 4% with three irAEs. IMpower130, 132, and 150 all excluded patients with preexisting autoimmune conditions, so the incidence of multiple irAEs was not due to a prior chronic condition. We found that the most common irAE combinations were rash and hepatitis followed by rash and hypothyroidism, rash and pneumonitis, and hepatitis and hypothyroidism (Fig. 1). To help visualize this concept, we used upset plots to clearly illustrate the incidence for both single and multiple irAEs.

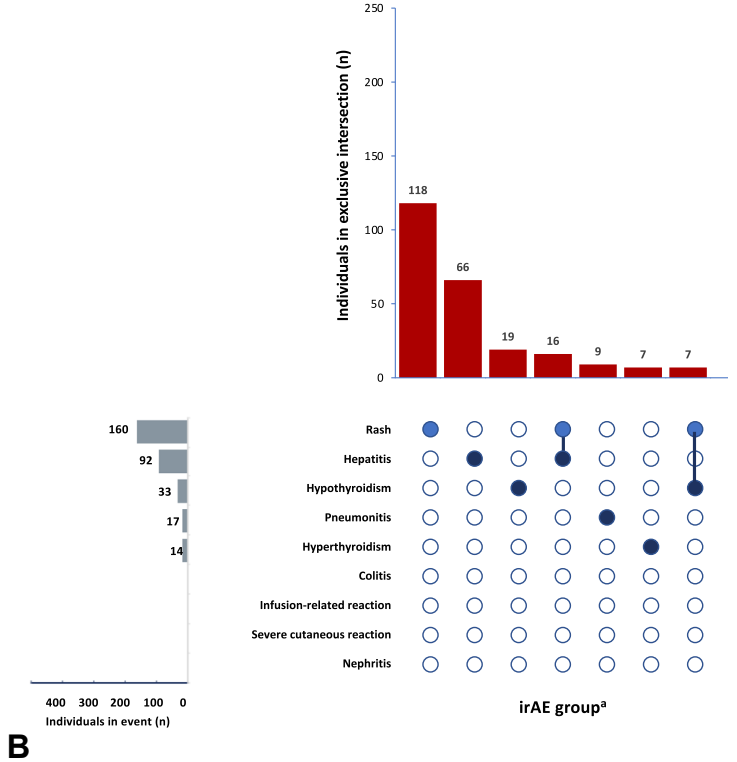
Another variable to consider is the time to onset for irAEs. For our study, the median time to onset ranged from 1.1 to 10.4 months (Table 2 and Fig. 2). Understanding the median time to onset can help clinicians know whether a symptom is more or less likely to be an irAE, which is otherwise more challenging to predict compared with adverse events from cytotoxic chemotherapy.[23] Although reporting irAE time to onset is not yet routine, some studies have started to incorporate this important data point.[11,20]

After a patient is diagnosed with an irAE, the severity may fluctuate over time. Our study found that the irAE grade increased in 33% of patients who initially presented with grade 1 to 2 irAEs. From a clinical perspective, this is relevant because worsening severity leads to increased doses of steroids or the need for an alternative immunosuppressive medications; however, changes in irAE grading are not usually included in AE reporting.[7,24,25]

Although there are challenges with diagnosing and managing irAEs, patients who experience mild to moderate irAEs often have improved clinical outcomes.[11–13,26] A prior analysis was conducted for our cohort of patients



A



B

Black circles indicate the presence of a specific irAE and black lines link irAEs that co-occurred in patients (after applying cutoff).
[a] After applying cutoff, events not observed in any intersection are not shown.

Figure 1. Upset plots illustrating the occurrence of single and multiple irAEs among (*A*) patients who received atezolizumab and the (*B*) control group. (*A*) Upset plot for patients treated with atezolizumab who experienced an irAE. Black circles indicate the presence of a specific irAE and black lines link irAEs that co-occurred in patients (after applying a cutoff of $\geq$5 individuals per intersection). Of the patients, 13% (204 of 1557) experienced two irAEs, most frequently rash and hepatitis (4%; 55 of 1557) and followed by rash and hypothyroidism (3%, 41 of 1557). Of the patients treated with atezolizumab, 4% (66 of 1557) experienced three irAEs. (*B*) Upset plot for patients in the control group who experienced a nonimmune AE. In this group, 5% (47 of 900) of patients experienced two events, most frequently rash and hepatitis (2%; 16 of 900), followed by rash and hypothyroidism (1%; seven of 900), and 1% (five of 900) experienced three AEs. AE, adverse event; irAE, immune-related adverse event.

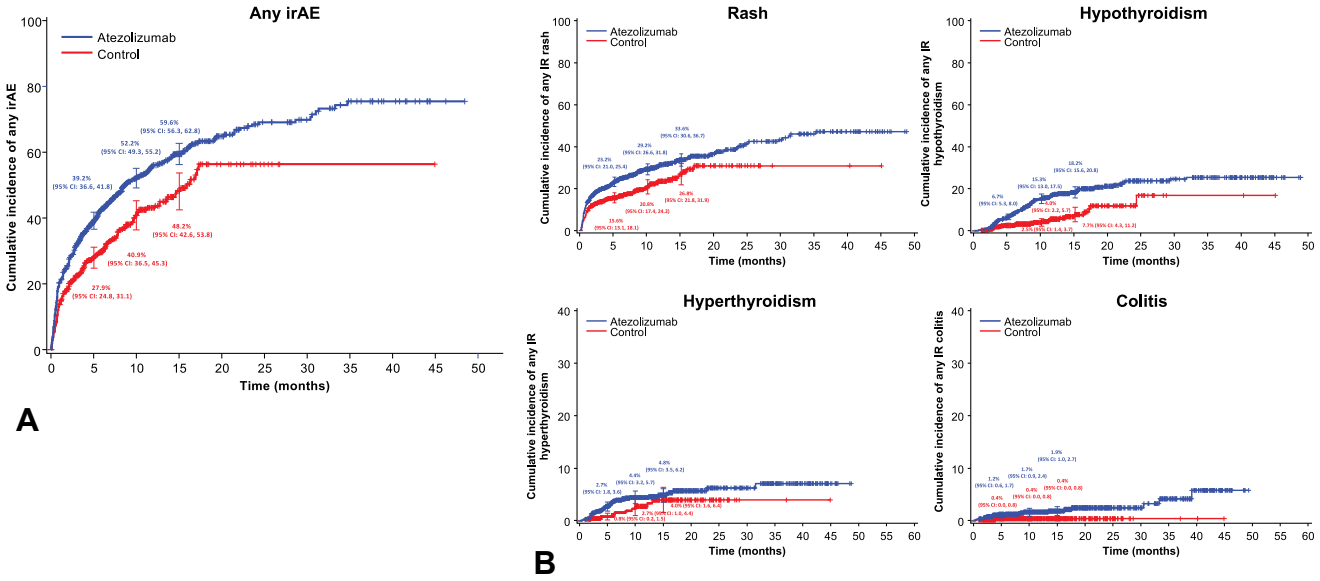


Figure 2. Cumulative incidence curves for (*A*) any and (*B*) selected irAEs. (*A*) The cumulative incidence for all irAEs at 5 months was 39% among patients treated with atezolizumab and 28% in the control group. At 10 months, the cumulative incidence for all irAEs was 52% and 41%, respectively. At 15 months, the cumulative incidence for all irAEs was 60% and 48%, respectively. (*B*) For rash in patients treated with atezolizumab, the cumulative incidence at 5 months was 23%, at 10 months was 29%, and at 15 months was 34%. For hypothyroidism in patients treated with atezolizumab, the cumulative incidence at 5 months was 7%, at 10 months was 15%, and 15 months was 18%. For hyperthyroidism in patients treated with atezolizumab, the cumulative incidence at 5 months was 3%, at 10 months was 4%, and 15 months was 5%. For colitis in patients treated with atezolizumab, the cumulative incidence at 5 months was 1%, at 10 months was 2%, and at 15 months was 2%. irAE, immune-related adverse event.

treated on IMpower130, 132, and 150, which found longer OS for patients with grade 1 to 2 irAEs compared with patients with grade 3 to 5 irAEs and patients without irAEs.[11] Pooled analyses of patients with NSCLC treated with either atezolizumab or nivolumab have also revealed improvements in OS for the patients diagnosed with an irAE. This survival benefit is still found with late-onset irAEs (>3 mo after ICI initiation) and multisystem irAEs.[11–13,26]

Our findings highlight that irAE clinical courses can be complex and dynamic. Comprehensive and standardized irAE reporting is needed, yet there is substantial variability in which safety parameters are reported, how they are reported, and the terminology used across clinical trials, publications, and clinicaltrial.gov data.[27,28] The Society for Immunotherapy of Cancer has recently published guidelines on standardizing the vocabulary surrounding irAEs, which is a step in the right direction.[29] Without standardized language, pooled analyses such this one are difficult to conduct. There is also increasing interest in implementing more intuitive data visualizations to illustrate irAE complexities.[30] In our study, we used novel AE reporting modalities not previously found in the irAE literature with upset plots to reveal the incidence of single and multiple irAEs concurrently, and cumulative incidence curves to show the timing of cumulative and select irAEs. Although our study has started to address the challenges surrounding irAE reporting, it is inherently limited in that it is a post hoc analysis. The inclusion of additional variables not reported here, such as duration of ICI treatment, percentage of patients who discontinued treatments, and details on immunosuppressive treatments, should be considered in future irAE analyses.

In conclusion, our large, pooled analysis of patients with metastatic NSCLC treated with atezolizumab-containing regimens comprehensively evaluated irAE courses for this population, including the incidence for both single and multiple irAEs, median time to onset, and the frequency at which irAE grading changes. Although most patients treated with atezolizumab were diagnosed with only one low-grade irAE that did not change increase in severity over time, it is important to recognize that patients can have a dynamic trajectory. We hope that future studies will begin incorporating more details regarding irAE patterns so that irAE recognition and management can continue to improve.

CRediT Authorship Contribution Statement

Katherine Smith: Conceptualization, Writing—original draft, Writing—review and editing.

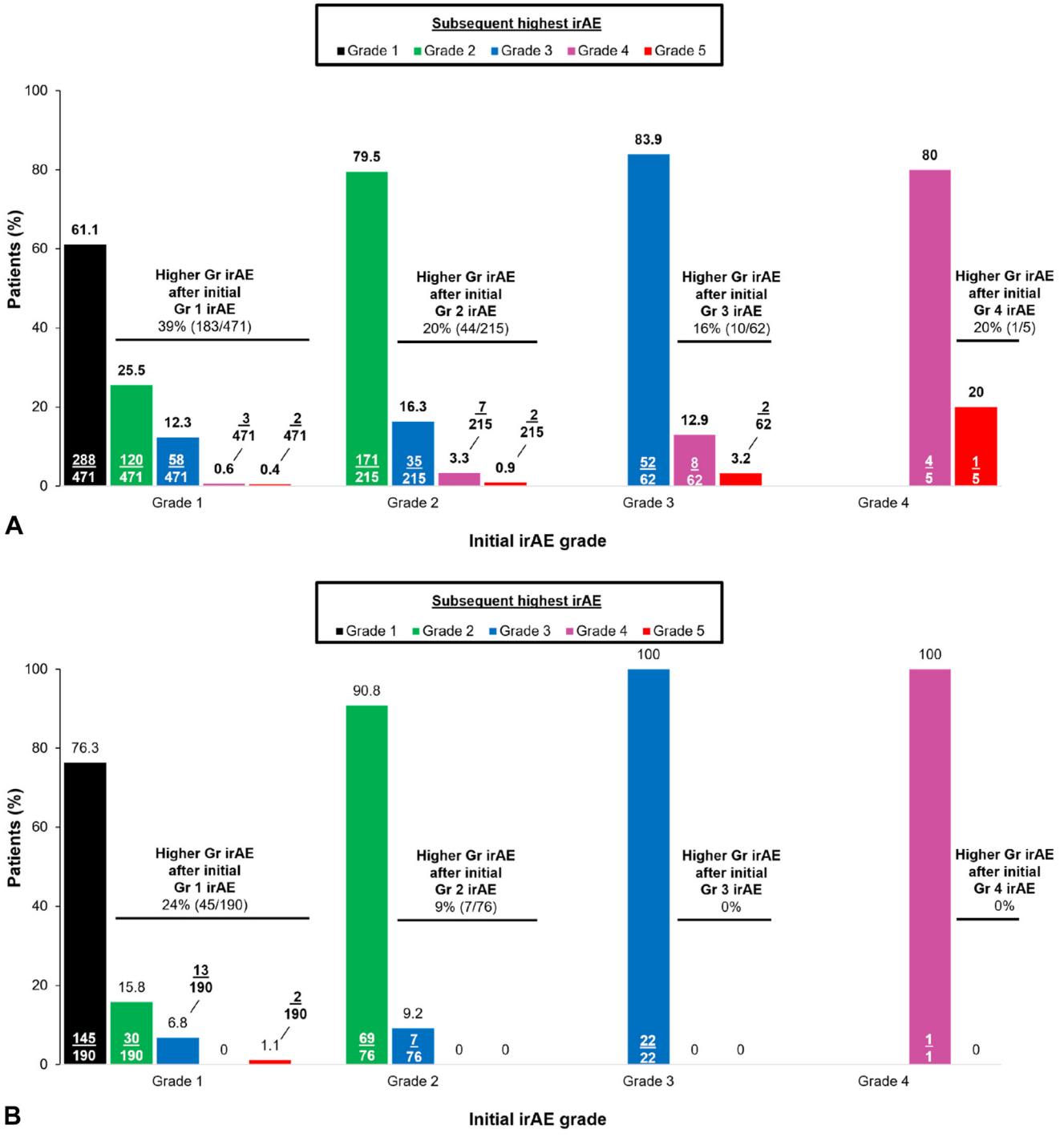


Figure 3. Changes in grading severity for the (*A*) atezolizumab group and (*B*) control group. (*A*) In patients treated with atezolizumab who had an initial grade 1 to 2 irAE, 33% (227 of 686) experienced a subsequent higher grade irAE. Of the patients with an initial grade 1 irAE, 13.4% increased to greater than or equal to grade 3, and of the patients with an initial grade 2 irAE, 20.1% increased to greater than or equal to grade 3. (*B*) In patients in the control arm, 20% (52 of 266) who had an initial grade 1 to 2 nonimmune AE later increased in severity. AE, adverse event; irAE, immune-related adverse event.

Stephanie Pritzl: Conceptualization, Writing—original draft, Writing—review and editing.

Wei Yu: Conceptualization, Methodology, Formal analysis, Writing—review and editing.

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Gita Thanarajasingam: Conceptualization, Writing—review and editing.

Monika D. Kaul: Conceptualization, Writing—review and editing.

Kirstin A. Williams: Conceptualization, Writing—review and editing.

Amylou C. Dueck: Conceptualization, Writing—review and editing.

Aaron Mansfield: Conceptualization, Writing—original draft, Writing—review and editing, Supervision.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2023.100611.

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