Multiorgan Immune-Related Adverse Events During Treatment With Atezolizumab

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ABSTRACT

Background: Immune-related adverse events (irAEs) are known to occur in patients with cancer who are treated with immune checkpoint inhibitors. However, limited literature exists on the incidence, time of onset, and risk factors for irAEs, particularly those affecting multiple organs, associated with anti–PD-L1 inhibitors. **Methods:** A post hoc pooled analysis was conducted using individual patient data from atezolizumab monotherapy arms of 4 non–small cell lung cancer clinical trials. Incidence, clinical patterns, outcomes, and risk factors were investigated of selected organ-specific and multiorgan irAEs during treatment using the anti–PD-L1 inhibitor atezolizumab. **Results:** From a total of 1,548 patients, 730 irAE episodes were reported in 424 patients (27%). Skin irAEs were the most common (42%), followed by laboratory abnormalities (27%) and endocrine (11.6%), neurologic (7.6%), and pulmonary (6.2%) irAEs. A total of 84 patients (5.4%) had multiorgan irAEs, 70 had 2, 13 had 3, and 1 had 4 different organs affected. "Skin plus" or "laboratory plus" were the most common irAE multiorgan clusters. Patients with multiorgan irAEs were more likely to be white and have a good performance status, a lower baseline neutrophil-lymphocyte ratio, and a good or intermediate lung immune prognostic index score. Multiorgan irAEs were also associated with improved overall survival (hazard ratio, 0.47; 95% CI, 0.28–0.78; P<.0001) but not with progression-free survival (hazard ratio, 0.92; 95% CI, 0.62–1.35; P=.74) compared with the cohort with no irAEs. **Conclusions:** Multiorgan irAEs occurred in 5.4% of patients treated with atezolizumab in non–small cell lung cancer trials. Future trials should consider routine reporting of data on multiorgan toxicities in addition to organ-specific toxicities.

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Background

Immune checkpoint inhibitors (ICIs) commonly target CTLA-4, PD-1, and PD-L1, which promote inhibitory signals on immune effector T cells against cancer cells.[1] Although ICIs have improved outcomes in several cancers, their use is also associated with significant adverse events (AEs), including death.[2]

In contrast to other anticancer therapies, ICIs cause heterogeneous toxicities through nonspecific immune activation affecting tissues and organs. Although guidelines exist for the diagnosis and treatment of ICI-related toxicities, there is no international consensus on the terminology used for their definition, diagnostic criteria, grading, and causal attribution, and little evidence supporting their management.[3–5] ESMO guidelines divide ICI-related AEs into infusion reactions and immune-related AEs (irAEs).[4] Other guidelines have used AEs of special interest or immune-mediated AEs interchangeably with irAEs.[6] Their pathophysiology is poorly understood, with several proposed mechanisms leading to organ damage.[7,8]

In addition, the reported incidence and time course of irAEs in clinical trials have varied based on the type of checkpoint being targeted. A recent network meta-analysis identified that atezolizumab, an anti–PD-L1 inhibitor, had the best safety profile.[9] Other analyses reported an incidence of up to 30% with PD-1/PD-L1 inhibitors,[10] 72% with ipilimumab,[11] and 88% with combined therapies.[12]

Although more than 1 autoimmune disease can occur in the same patient (polyautoimmunity),[13] it is unclear whether multiple-organ irAEs have occurred in the same patient with cancer, and when they occur, whether they have occurred simultaneously or serially. Moreover, the reported irAEs in clinical trials are often limited to single organs, preventing accurate information regarding the incidence and time course of multiple irAEs.[14] Such an occurrence of multiple irAEs in the same patient may influence their treatment decisions for both the AEs and the cancer. There are additional

complexities, such as the use of polypharmacy and the involvement of various specialties for the management of AEs. Hence, it is important to have a thorough understanding of multiorgan irAEs from ICIs. Using pooled data from 4 prospective clinical trials in patients with non–small cell lung cancer treated using atezolizumab monotherapy, we analyzed the incidence, severity, time course, treatment, outcomes, and risk factors of various organ-specific irAEs and their relationships with response rates/survival outcomes.

Methods

Study Population
Individual patient data from the OAK (ClinicalTrials.gov identifier: NCT02008227),[15] POPLAR (NCT01903993),[16] BIRCH (NCT02031458),[17] and FIR (NCT01846416)[18] clinical trials were analyzed via established protocols for clinical data-sharing.[19] This secondary analysis of trial data was exempted from review by the local ethics committee. Only atezolizumab-treated cohorts were included in the analysis.

Definition of AEs
AEs for which the investigator attributed causality to atezolizumab and that occurred while patients were on atezolizumab or within 30 days after the last dose were adjudicated as treatment-related AEs (trAEs). irAEs were defined as per prespecified study protocols (ie, AEs of special interest as conditions suggestive of an autoimmune disorder resulting from atezolizumab use). These events were organ-specific and included endocrine, ocular, gastrointestinal, hepatobiliary and pancreatic, neurologic, pulmonary, rheumatologic, skin, laboratory abnormalities, and other miscellaneous organ-specific irAEs. Definition terms for each organ-specific irAE are summarized in Table 1. The single-organ irAE cohort was defined as patients with 1 organ system affected, and the multiorgan irAE cohort was defined as patients with >1 organ system involved. Concurrent multiorgan irAE was defined as the onset of irAEs within 7 days of each other, and sequential multiorgan irAEs as onset >7 days between each. An irAE "episode" was recorded at the time of reporting and when the grade (ie, the severity) increased, decreased, or resolved. An irAE that had not resolved or changed grade was counted as a single episode. AEs were graded using NCI CTCAE version 4.0, with grades 3–5 considered severe irAEs.

Outcomes
Primary objectives were the incidence, grades, and time course of irAEs resulting from atezolizumab. Secondary objectives were the incidence and grades of trAEs, progression-free survival (PFS), and overall survival (OS). PFS was assessed using RECIST (version 1.1) or a modified RECIST. Exploratory analyses investigated risk factors for irAEs and the relationship between irAEs and survival outcomes.

Baseline age, sex, race, tumor characteristics, serum lactate dehydrogenase and C-reactive protein (CRP) levels, lung immune prognostic index (LIPI), neutrophil-to-lymphocyte ratio, and various subpopulations of white cells were evaluated for associations with incidence of irAEs.

Statistical Analysiss
Two-sided statistical tests were conducted using R version 3.4.3 (R Foundation for Statistical Computing), and $P<.05$ was considered statistically significant. The Fisher exact test for categorical data and the Wilcoxon test for continuous data were used for the association between baseline characteristics and irAEs. Timing of onset of

Table 1. Medical Dictionary for Regulatory Activities Terms Used to Identify Organ-Specific irAEs

Organ-Specific irAE	Reported Terms
Skin	Rash, maculopapular rash, macular rash, popular rash, erythematous rash, dermatitis, psoriasis, eczema, lichen planus, generalized rash, pruritic rash, vitiligo, dermatomyositis, or pemphigoid
Endocrine	Hypothyroidism, hyperthyroidism, adrenal insufficiency, thyroiditis, hypophysitis, adrenal insufficiency, type 1 diabetes mellitus, and increased or decreased thyroid stimulating hormone
Gastrointestinal	Colitis or duodenitis
Neurologic	Peripheral neuropathy, polyneuropathy, or Guillain-Barré syndrome
Pulmonary	Pneumonitis, interstitial pneumonitis, or organizing pneumonia
Hepatobiliary and pancreatic	Cholangitis, hepatitis, or pancreatitis
Ocular	Episcleritis, uveitis, optic neuritis, or endocrine ophthalmopathy
Rheumatologic	Rheumatoid arthritis, polyarthritis, rheumatic disorder, or autoimmune arthritis
Laboratory irAEs	Elevated serum liver enzymes or bilirubin, lipase, or amylase level
Miscellaneous	Those which did not fit under the above organs, such as cardiovascular system, kidneys, and pericardium

Abbreviation: irAE, immune-related adverse event.

irAEs was visually displayed using a Swimmer plot. Logistic regression analysis was performed to investigate the association between irAEs and best overall response. Simple Cox and time-dependent Cox proportional hazards regression were used to model the association between the irAE cohorts and survival outcomes (OS and PFS) and reported as hazard ratios (HRs) with 95% confidence intervals. Survival curves were estimated using Kaplan-Meier analysis.

Results

Overall Incidence and Severity of AEs
The analysis included 1,548 patients who received at least 1 dose of atezolizumab. One or more trAEs occurred in 1,000 patients (65%), with grade 3–5 trAEs in 13% of patients across the trials. A total of 730 irAE episodes were reported across 424 patients (27%) who had ≥1 irAEs. Median time of onset was 49 days (interquartile range, 21–130 days).

Baseline Characteristics of Patients Who Developed irAEs
Tables 2 and 3 present the characteristics of patients with irAEs. Twelve percent of irAEs occurred within the first 42 days of atezolizumab use. Patients with irAEs were more likely to be Asian and have good performance status, lower CRP levels, differential changes in subpopulations of white cells, a good LIPI score, and a lower neutrophil-to-lymphocyte ratio score. Details of organ-specific irAEs are described in Table 4. Figure 1 shows selected single-organ irAEs and their time of onset. Skin irAEs were the most common single-organ irAE, followed by laboratory abnormalities and other organs. Notably, there were no reported myocarditis or severe cutaneous reactions, such as bullous pemphigoid. The investigators did not consider anemia (36 episodes), thrombocytopenia (7 episodes), neutropenia (5 episodes), and lymphopenia (3 episodes) to be irAEs.

Treatment of irAEs and Their Outcomes
Overall, 7.5% of the 730 episodes of irAEs resulted in hospitalization, which was required in almost half of grade 3 or 4 events and in 5.7% of grade 1 or 2 events. A total of 109 (15%) irAE episodes were treated with systemic corticosteroids, of which 31 episodes (30%) were grade 1 or 2 and the rest were grade ≥3, including 1 grade 5 event (1 death). Atezolizumab was interrupted in 14% (102/730) of all episodes and was permanently discontinued in 2.5% (18/730). At the time of last follow-up, most irAE episodes (n=438; 60%) were resolved and 28% (n=204) had ongoing irAEs. Nine episodes resulted in sequelae despite resolution of the irAE, and the remainder (11%) were resolving at last follow-up. Only 1 death from irAEs (pneumonitis) was reported.

Second-Line Treatment for irAEs
Second-line immunosuppressants for the treatment of irAEs, after systemic corticosteroid failure, was required in 5 patients. One patient received infliximab for colitis and experienced complete resolution, 1 required oral mycophenolate mofetil for hepatitis, 1 received anakinra for arthritis, and 2 had topical cyclosporine A for ocular irAEs. Atezolizumab was discontinued permanently in the patient with hepatitis. All other patients requiring second-line immunosuppressants received further atezolizumab.

Multiorgan irAEs
Of the 424 patients with irAEs, 340 had 1 organ-specific irAE (see Tables 2 and 3). The remainder (n=84; 5.4% [84/1,548] of all atezolizumab-treated patients and 19.8% [84/424] of all patients with irAEs) had multiorgan irAEs. Among those who had multiorgan irAEs, 70 patients (83.3%) had 2 organ systems affected by irAEs, 13 (15.5%) had 3, and 1 had 4 (Figure 2); 12 had concurrent-onset irAEs and the remainder (n=72) had sequential onset. Those who had multiorgan irAEs were more likely to be white and have an ECOG performance status of 0 and a lower baseline CRP level and neutrophil-lymphocyte ratio than those who developed single-organ irAEs.

The combinations of organs affected by irAEs were "skin irAE plus," "laboratory irAE plus without skin," or "other combinations without skin or laboratory irAE." A total of 60 patients were in the skin irAE plus cluster, 9 were in the laboratory irAE plus without skin cluster, and the remaining 15 had other combinations.

Multiorgan irAEs and Cancer Outcomes
The development of multiorgan irAEs was associated with improved response rates, PFS, and OS. The best overall response (combined complete and partial response) was significantly higher among those who developed multiorgan irAE than those with single-organ irAEs or without irAEs (42%, 23%, and 12%, respectively), with an odds ratio of 2.18 (95% CI, 1.5–2.9) for single-organ irAEs (vs no irAEs) and 5.32 (95% CI, 3.3–8.5) for multiorgan irAEs (vs no irAEs) (P<.0001). Median PFS using a simple Cox model was significantly improved with multiorgan irAEs (7.2 months; 95% CI, 5.4–12.4) vs single-organ irAEs (4.2 months; 95% CI, 3.9–5.5) and no irAEs (2.7 months; 95% CI, 2.5–2.8; P≤.001) (Figure 3A). Similarly, median OS measured with a simple Cox model was significantly improved in patients with multiorgan irAEs (not reached; 95% CI, 23.5–not reached) versus those with single-organ irAEs (20.1 months; 95% CI, 16.0–23.3) and no irAEs (10.3 months; 95% CI, 9.5–11.4; P<.001) (Figure 3B). HRs calculated using a time-dependent Cox regression model for OS was 0.47 (95% CI, 0.28–0.78) for multiorgan irAEs (vs no irAEs) and 0.69 (95% CI, 0.57–0.85)

Table 2. Baseline Clinical Characteristics and Outcomes of Atezolizumab-Treated Patients

	Patients n (%)	irAEs n (%)	Single-Organ irAEs n (%)	Multiorgan irAEs n (%)	P Value[a]
Total, N	1,548	1,124	340	84	
Study					.61
BIRCH[17]	659 (43%)	487 (43%)	138 (41%)	34 (40%)	
FIR[18]	138 (9%)	108 (10%)	24 (7%)	6 (7%)	
OAK[15]	609 (39%)	428 (38%)	145 (43%)	36 (43%)	
POPLAR[16]	142 (9%)	101 (10%)	33 (10%)	8 (10%)	
Age, y	64 (57–70)	63 (56–70)	66 (58–72)	62 (57–68)	.14
Sex					.75
Male	936 (60%)	673 (60%)	211 (62%)	52 (62%)	
Female	612 (40%)	451 (40%)	129 (38%)	32 (38%)	
Race					.008
White	1,216 (79%)	901 (80%)	245 (72%)	70 (83%)	
Asian	231 (15%)	149 (13%)	70 (21%)	12 (4%)	
Other	66 (4%)	48 (4%)	17 (5%)	1 (1%)	
Missing	35 (2%)	26 (2%)	8 (2%)	1 (1%)	
ECOG performance status					.031
0	535 (35%)	366 (33%)	131 (39%)	38 (45%)	
1	1,002 (65%)	749 (67%)	208 (61%)	45 (54%)	
2	8 (1%)	6 (1%)	1 (<1%)	1 (1%)	
Missing	3 (<1%)	3 (<1%)	0 (0%)	0 (0%)	
Histology					.20
Nonsquamous	1,155 (72%)	797 (71%)	258 (76%)	60 (71%)	
Squamous	403 (28%)	327 (29%)	82 (24%)	24 (29%)	
Prior treatments[b]					.067
0	170 (11%)	133 (12%)	31 (9%)	6 (7%)	
1	929 (60%)	661 (59%)	206 (72%)	62 (74%)	
2	449 (29%)	330 (29%)	34 (10%)	16 (19%)	
Smoking history					.055
Never	270 (17%)	201 (18%)	61 (18%)	8 (10%)	
Previous	1,081 (70%)	777 (69%)	245 (72%)	59 (70%)	
Current	197 (13%)	146 (13%)	34 (10%)	17 (20%)	
Missing	1 (0.1%)	1 (0.1%)	0 (0%)	0 (0%)	

Abbreviation: irAE, immune-related adverse event.
[a]P values per Fisher exact test for categorical data and Wilcoxon test for continuous data.
[b]Number of prior treatments in the locally advanced or metastatic setting.

for single-organ irAEs (vs no irAEs) ($P<.0001$). However, the occurrence of multiorgan irAEs was not associated with an improved PFS in the time-dependent Cox model (HR, 0.92; 95% CI, 0.62–1.35), nor was the occurrence of single-organ irAEs (HR, 0.95; 95% CI, 0.81–1.11; $P=.74$).

Discussion

We comprehensively assessed multiorgan irAEs associated with ICIs using a large dataset from clinical trials. One-fifth of patients treated using atezolizumab developed at least 1 irAE, whereas 5.4% had multiorgan irAEs. Mortality from irAEs and irAEs leading to permanent discontinuation of atezolizumab was uncommon, with most patients recovering without sequelae. Any irAEs, including multiorgan irAEs, were significantly associated with better tumor response and survival outcomes.

Although the occurrence of polyautoimmunity is well-known in the rheumatologic literature, there has been little information on the occurrence of multisystem

Table 3. Baseline Laboratory Characteristics of Atezolizumab-Treated Patients

	Patients n (%)	No irAEs n (%)	Single-Organ irAEs n (%)	Multiorgan irAEs n (%)	P Value[a]
Total, N	1,548	1,124	340	84	
PD-L1 expression					.69
Negative	528 (34%)	383 (34%)	119 (35%)	26 (31%)	
Positive	1,015 (65%)	737 (65%)	220 (64%)	58 (69%)	
Missing	5 (<1%)	4 (<1%)	1 (<1%)	0 (0%)	
Lactate dehydrogenase					.23
≤ULN	913 (59%)	649 (58%)	211 (62%)	53 (63%)	
>ULN	584 (38%)	439 (39%)	116 (34%)	29 (35%)	
Missing	51 (3%)	36 (3%)	13 (4%)	2 (2%)	
Neutrophil count (10^9/L)					.002
Median (IQR)	5 (3.7–6.7)	5.1 (3.8–7.0)	4.7 (3.7–6.0)	4.9 (3.5–6.3)	
Missing	28 (1.8%)	23 (2%)	5 (1.5%)	0 (0%)	
Lymphocyte count (10^9/L)					.28
Median (IQR)	1.3 (0.9–1.8)	1.3 (0.9–1.8)	1.3 (1.0–1.8)	1.5 (1.1–2.0)	
Missing	90 (5.8%)	67 (6%)	18 (5.3%)	5 (6%)	
Basophil count (10^9/L)					.14
Median (IQR)	0.02 (0–0.05)	0.02 (0–0.05)	0.03 (0–0.06)	0.03 (0–0.06)	
Missing	124 (8%)	93 (8.2%)	26 (7.6%)	5 (5.9%)	
Eosinophil count (10^9/L)					.12
Median (IQR)	0.14 (0.09–0.24)	0.14 (0.09–0.23)	0.15 (0.10–0.29)	0.15 (0.10–0.30)	
Missing	108 (6.9%)	79 (7%)	24 (7%)	5 (5.9%)	
Monocyte count (10^9/L)					.28
Median (IQR)	0.61 (0.48–0.84)	0.63 (0.48–0.85)	0.60 (0.48–0.80)	0.60 (0.48–0.80)	
Missing	96 (6.2%)	72 (6.4%)	19 (5.6%)	5 (5.9%)	
CD3 count (10^9/L)					.30
Median (IQR)	834 (561–1,193)	812 (540–1,182)	868 (600–1,210)	952 (630–1,297)	
Missing	75 (5%)	56 (5%)	15 (4%)	4 (5%)	
CD4 count (10^9/L)					.13
Median (IQR)	486 (321–732)	470 (306–717)	510 (343–763)	559 (370–791)	
Missing	75 (5%)	56 (5%)	15 (4%)	4 (5%)	
CD8 count (10^9/L)					.78
Median (IQR)	293 (177–455)	291 (175–450)	292 (184–446)	313 (218–468)	
Missing	75 (5%)	56 (5%)	15 (4%)	4 (5%)	
Neutrophil-to-lymphocyte ratio					.007
Median (IQR)	2.2 (1.6–3.2)	2.3 (1.7–3.3)	2.1 (1.6–2.8)	2.0 (1.4–2.8)	
Missing	29 (1.9%)	23 (2%)	6 (1.8%)	0 (0%)	
C-reactive protein (mg/L)					<.001
Median (IQR)	14 (4–42)	15 (4–48)	13 (5–45)	11 (4–32)	
Missing	43 (3%)	26 (4%)	9 (2%)	8 (3%)	
Lung immune prognostic index					.010
0	678 (44%)	464 (41%)	172 (51%)	42 (50%)	
1	631 (41%)	472 (42%)	125 (37%)	34 (40%)	
2	180 (12%)	145 (13%)	29 (9%)	6 (7%)	
Missing	59 (4%)	43 (4%)	14 (4%)	2 (2%)	

Abbreviations: IQR, interquartile ratio; irAE, immune-related adverse event; ULN, upper limit of normal.
[a]P values per Fisher exact test for categorical data and Wilcoxon test for continuous data.

Table 4. Details of Organ-Specific irAEs

Organ-Specific irAE	Unique Episodes of irAEs, n	Type of irAE (%)	Grade (%)	
			1/2	≥3
Skin	306	Skin rash (89%), eczema (4.6%), psoriasis (2.3%), lichen planus (1%), dermatomyositis, vitiligo, and bullous pemphigoid (<1% each)	86	14
Laboratory	197	Liver enzyme abnormalities were the majority followed by increased bilirubin, lipase, or amylase	80	20
Endocrine	85	Thyroid gland–related (hyperthyroidism or hypothyroidism, 92.5%), adrenal gland–related (4.7%), type 1 diabetes mellitus (2.4%), hypophysitis (1.2%)	95.3	4.7
Neurologic	56	Peripheral neuropathy (84%), polyneuropathy (9%), Guillain-Barré syndrome (7%)	66	7
Pulmonary	45	Pneumonitis (95%) and organizing pneumonia (5%)	57.8	42.2[a]
Gastrointestinal	15	Colitis (93.3%) and duodenitis (6.7%)	66.7	33.3
Ocular	9	Uveitis and optic neuritis (33.3% each), endocrine ophthalmopathy (22.2%), episcleritis (11.1%)	88.8	11.2
Rheumatologic	8	Rheumatoid arthritis and polymyalgia rheumatica (37.5% each), polyarthritis and rheumatic disorder (12.5% each)	100	0
Miscellaneous	5	Pericarditis (40%) and cytokine release syndrome, Henoch-Schönlein purpuric nephritis, and vasculitis (20% each)	60	40
Hepatobiliary and pancreatic	4	Pancreatitis (75%) and cholangitis (25%)	100	0

Abbreviation: irAE, immune-related adverse event.
[a]Includes 1 death.

irAEs until recently, likely because of underrecognition and lack of routine reporting. Shankar et al[20] recently reported an incidence of 5% for multisystem irAEs among 319 patients with lung cancer treated using anti–PD-1/PD-L1 therapies, similar to our findings. However, in contrast to our study, pneumonitis was the dominant irAE, with pneumonitis/dermatitis as the most common multiorgan irAEs. In the current study, skin plus or laboratory plus clusters were the most dominant. Furthermore, our study included patients with lung cancer treated with a single drug (atezolizumab) in clinical trials, in contrast to the Shankar et al[20] study in which several types of ICIs were given to patients in a real-world setting.

The differences in the incidence of organ-specific irAEs between studies may be related to the lack of uniform definitions of organ-specific irAEs across trials. Maughan et al[14] previously identified important differences in the definition of irAEs between atezolizumab, nivolumab, and pembrolizumab trials and recommended standardized definitions. For the current analysis, irAEs were defined according to trial protocols as autoimmune conditions based on known mechanisms of ICIs.
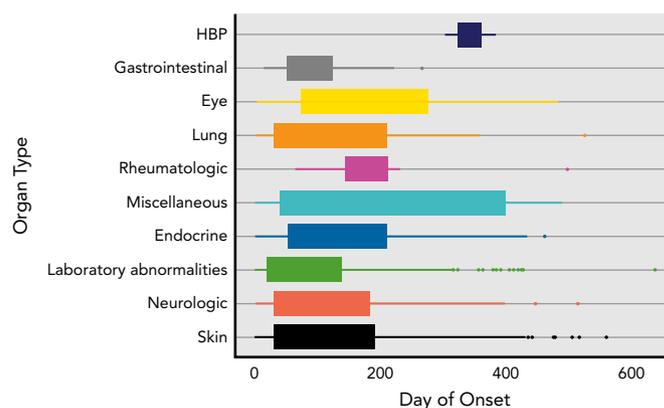
Figure 1. Time of onset of organ-specific immune-related adverse events.
Abbreviation: HBP, hepatobiliary and pancreatic.

Figure 2. Swimmer plot showing time of onset of multiple irAEs and deaths from all causes in 84 patients. Each bar indicates duration of atezolizumab treatment.

Abbreviation: irAE, immune-related adverse event.

The type of single-organ irAE in our study was dominated by cutaneous irAEs, followed by laboratory abnormalities and endocrine irAEs. This contrasts with a previous analysis of anti–PD-1/PD-L1 drugs, in which any grade of endocrine irAE was the most common organ system affected, followed by pneumonitis.[21] Of interest, neurologic irAEs, especially neuropathy, emerged as important irAEs in our analysis. The reason for the relatively high incidence of neuropathy as an irAE from atezolizumab is unknown. It is also unclear whether the incidence of neurologic irAEs is similar with other ICIs or whether they were underrecognized or underreported in previous trials. Future studies should consider a prospective evaluation of neuropathy during treatment.

Among the baseline characteristics associated with the development of irAEs, Asian race and a good LIPI score were statistically significant. Prior studies have similarly reported associations with Asian race[22]; however, the association with a good LIPI score has not been previously reported.

Prior studies have suggested a relationship between the occurrence of irAEs and tumor response and survival with ICIs for various cancers.[23,24] Presence of a generalized immunogenic state during ICI treatment may contribute toward better cancer control along with damage to normal organs that manifests as irAEs. We identified a similar association between the occurrence of irAEs and best overall response, PFS, and OS. Moreover, the occurrence of multiorgan irAEs was strongly associated with improved OS but not PFS, with time-dependent Cox models indicating a possible immortal time bias, confounding the results in the simple Cox model.

In addition, the definition of abnormal blood results and their attribution to organ-specific damage needs further consideration. Whether laboratory abnormalities alone constitute irAEs requires international consensus. None of the available guidelines provide definitions for organ-specific irAEs. We believe that our understanding of the pathophysiology, incidence, and management of irAEs can only be improved by using uniform definitions for the development of evidence-based guidance.

Although the diagnosis and characterization of irAEs remain inconsistent and challenging,[25] the expert consensus–based Trial Reporting of Immuno-Oncology (TRIO) recommendations are likely to improve the reporting of ICIs in clinical trials. However, the TRIO guidance does not recognize or mandate reporting on multiorgan irAEs.[25] As described in our analysis, multiorgan toxicities occur in a significant proportion of patients treated with ICIs, and these may have associations with treatment response and outcomes. Hence, their recognition and reporting should become part of published manuscripts and the routine care of patients undergoing with ICI treatment.

Polyautoimmunity phenotypes often occur because of common genetic factors, immune pathogenic mechanisms, and an established set of risk factors, such as female predominance, family history, smoking history, and Native American race; it is unclear whether multiorgan irAEs have any risk factors.[26] In the current study, white race and good ECOG performance status were associated with multiorgan irAEs. In contrast to the polyautoimmunity phenotype, sex and smoking history were not associated with multiorgan irAEs. Further studies should evaluate any underlying genetic risk factors that may predispose certain individuals who receive ICIs to multiorgan irAEs, using data through international collaboration.[27]

Prior reports on polyautoimmunity also identified that the treatment of multiple conditions adds complexity to their care.[13,26,28] Similarly, treatment of patients with multiorgan irAEs poses other challenges, such as need for endocrine replacement therapies, use of immunosuppressants at the same time, possible need for second-line immunosuppressants, and secondary
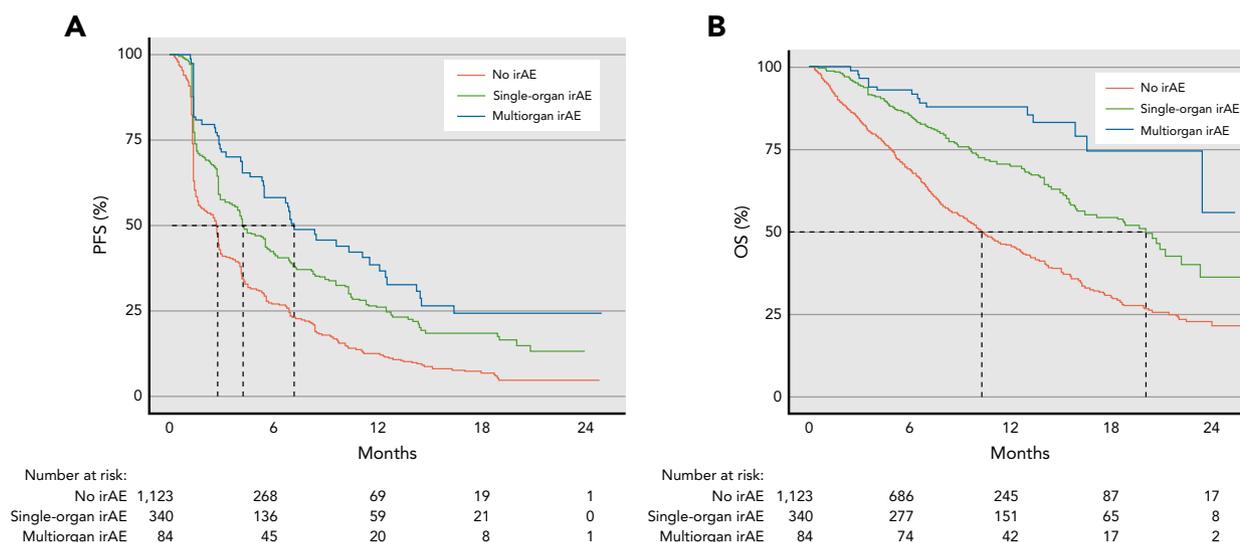
Figure 3. Simple Cox model showing association between irAEs and (A) PFS and (B) OS outcomes.
Abbreviations: irAE, immune-related adverse event; OS, overall survival; PFS, progression-free survival.

complications, such as high blood glucose levels and infections from corticosteroids. In the current study, because of the limited number of patients, it was unclear whether those with multiorgan irAEs had an increased need for second-line immunosuppressants.

Strengths

This study highlights a previously underrecognized issue of multiorgan irAEs arising from ICIs. This is the largest analysis of uniformly treated patients with non–small cell lung cancer who developed multiorgan irAEs from an anti–PD-L1 inhibitor. Data were collected prospectively through multicenter international clinical trials, thereby improving the accuracy of the information. Moreover, the association between the occurrence of irAEs and survival outcomes was evaluated using time-dependent Cox models to avoid bias from different treatment durations.[29]

Limitations

Our study has several limitations. First, the analysis is a post hoc exploratory analysis and therefore should be considered hypothesis-generating and confirmed in other studies. Second, the data were from lung cancer trials of atezolizumab; it is unclear whether a similar pattern of multiorgan irAEs occurs with other cancer types or ICIs. Third, the data had investigator-reported AEs and there was no external validation/confirmation of AEs. Finally, the irAEs analyzed were organ-specific, and did not include constitutional symptoms such as fatigue and fever, which could be related to cytokines released by activated immune cells. These toxicities are not traditionally regarded as irAEs, although they may have

immune etiology. Despite these study limitations, we have shown that multiorgan irAEs need appropriate recognition and evaluation.

Conclusions

Multiorgan irAEs were reported in 5.4% of patients treated with atezolizumab in lung cancer trials. Health professionals involved in the care of patients undergoing ICI therapies should recognize that irAEs can manifest as multiple organ system damage. Future trial reporting should consider the incorporation of data on multiorgan toxicities in addition to single-organ–specific toxicities.

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