HHS Public Access

Author manuscript

Curr Cancer Rep. Author manuscript; available in PMC 2024 October 11.

Published in final edited form as:

Curr Cancer Rep. 2024 February 20; 5(1): 168–180. doi:10.25082/ccr.2023.01.004.

Risk of severe immune-related adverse events in cancer patients with pre-existing autoimmunity receiving immune checkpoint inhibitor therapy

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Abstract

Purpose: To evaluate the frequency and severity of irAEs in patients with pre-existing autoimmunity, including irAE-related morbidity and mortality, irAE-related management and resolution, and outcome of ICI rechallenge, to better understand the treatment options for this vulnerable patient population.

Methods: We designed a retrospective, single-center, case-control study at a large, academic medical center to evaluate the incidence and severity of irAEs in patients with pre-existing autoimmunity compared to controls. Controls were matched 2:1 for age, sex, cancer histology, and ICI class. Patients were identified with ICD 9 and 10 codes followed by manual chart extraction. Cases were defined as patients with pre-existing, systemic autoimmunity. The primary outcome was severe irAE (Grade 3 or higher by Common Terminology Criteria for Adverse Events) within 6 months of ICI therapy. Secondary outcomes included response to ICIs, resolution of the irAE, ICI rechallenge success, and survival. Statistical analyses were performed by Chi-square, Fishers exact, Mann-Whitney, and Log-rank tests.

Results: Of 3,130 patients treated with ICIs from 2015–2021, 28 cases with pre-existing autoimmune disease were identified and were matched with 56 controls. Pre-existing autoimmune conditions included antiphospholipid syndrome, inflammatory polyarthritis, juvenile rheumatoid arthritis, multiple sclerosis, psoriatic arthritis, rheumatoid arthritis, and type I diabetes. Multiple cancer histologies, including genitourinary, gynecologic, head & neck, hepatobiliary, lung,

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Conflicts of Interest

The authors declare that they have no conflict of interest.

melanoma, and pancreatic, were represented. Six of 28 cases (21.4%) experienced severe irAEs compared to 9/56 (16.1%) controls; the odds of developing a severe irAE were not significantly different (OR 0.43, 95% CI 0.083–2.33, $p = 0.627$, ns). Moreover, there were no significant differences in overall survival or tumor response between the two groups. The majority of irAEs resolved without long-term sequelae (66.7% of cases, 55.6% of controls). The majority of patients who were rechallenged with ICIs were successful in continuing therapy (66.7% of cases, 100% of controls).

Conclusion: Our study suggests that patients with pre-existing autoimmune disease can be treated with ICI cancer therapies and experience rates of severe irAEs and overall survival that are similar to those of the general population. These data can aid oncologists in discussing risks and benefits of ICIs when treating patients with pre-existing autoimmunity and solid tumors.

Keywords

immune checkpoint inhibitor; autoimmunity; immune related adverse events; cancer

1 Introduction

Immune checkpoint inhibitors (ICIs) are a type of cancer immunotherapy used to treat an expanding group of solid and hematologic malignancies. These agents block regulatory molecules on T cells, such as cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death protein-1 (PD-1)/programmed death ligand-1 (PD-L1), thereby increasing immune activation and anti-tumor immune responses [1]. These agents have revolutionized the field of oncology since the initial approval of ipilimumab in 2011, and now include multiple single agent and combination regimens, including atezolizumab, avelumab, cemiplimab, dostarlimab, durvalumab, nivolumab, pembrolizumab, relatlimab, and tremelimumab [1, 2].

The most serious adverse effect from ICI therapy is autoimmune destruction of healthy tissues, termed immune-related Adverse Events (irAEs). The incidence of irAEs varies depending on ICI regimen with a wide range reported in the literature, between 10–80% [3, 4]. In general, irAEs occur more frequently with anti-CTLA-4 monotherapy compared with anti-PD-1/PD-L1 monotherapy, 72% and 66%, respectively [5–7]. Combination ICI therapy leads to even higher rates of irAEs, with reported rates over 90% [8]. IrAEs can affect nearly any tissue in the body, including the skin, gut, liver, endocrine organs, lungs, joints, nervous system, kidney, eye, heart, and blood [7]. The NIH Common Terminology Criteria for Adverse Events (CTCAEs) grade irAEs from 1–5, with Grade 1 as the least severe and Grade 5 as resulting in death [9, 10]. Grade 3 or higher irAEs signify severe symptoms requiring hospitalization and/or other emergent measures, and have been reported in 2.5–18% of patients [3]. The most fatal irAEs reported in the literature are colitis, hepatitis, neurotoxicity, and myocarditis [7].

Administering ICIs to patients with pre-existing autoimmune disease presents a dilemma for oncologists. Not treating a potentially fatal disease like cancer due to the fear of toxicity in these patients has been very unsettling. These patients have historically been excluded from clinical trials of ICI therapy due to concerns of inducing severe irAEs in patients whose

immune systems are already overactive, including potential flares of underlying autoimmune disease. As a result, little is known about the safety and efficacy of ICIs in this population [11]. Several retrospective studies have sought to evaluate the risk of irAEs and exacerbation of autoimmune disease in patients with pre-existing autoimmunity by evaluation of this subgroup within larger cohorts. A systematic review by Abdel-Wahab et al. identified 123 cases with pre-existing autoimmunity from 49 retrospective studies, including case reports, case series, and observational studies. This report found that 92/123 patients (75%) experienced an autoimmune exacerbation and/or de-novo irAE, which resulted in 21 patients (17.1%) permanently discontinuing ICI therapy and 5 patient deaths (4.1%) [12]. On the other hand, more than half of the irAEs in patients with pre-existing autoimmunity resolved and did not require discontinuing ICI therapy [12]. In another review of the topic, Tison and colleagues evaluated 24 studies of patients receiving ICIs, with a focus on patients with pre-existing rheumatologic diseases [2]. They reported that 6–83% of study participants experienced flares of their autoimmune disease and that 16–90% of patients experienced irAEs involving other organs, although fewer than 35% of patients experienced severe (Grade ≥ 3) irAEs [2]. Similarly, another literature review by Wu et al. reinforced the notion that irAEs in patients with pre-existing autoimmunity are manageable [13].

These studies were limited by the use of International Classification of Diseases (ICD) codes for the identification of pre-existing autoimmunity, inclusion of autoimmune diseases with only limited systemic manifestations (such as vitiligo and Hashimoto's thyroiditis), and the absence of matched control groups for comparison [2, 12, 13]. Given the increasing recognition of irAEs in clinical practice, more indications for ICI use as cancer therapy, varying irAE incidence across regimens, and evolving approaches to treatment of irAEs, a control group is crucial to accurately evaluate the frequency of irAEs in this vulnerable population. Placais et al. recently published a case-control study of patients with autoimmune disease and melanoma, but excluded other cancer histologies [14]. Similarly, we previously studied the use of ICIs in patients with autoimmune diseases and genitourinary cancers in addition to patients with pre-existing type 1 diabetes mellitus [15, 16]. However, given the limited data, there remains clinical uncertainty about the safety of ICI therapy in patients with pre-existing systemic autoimmunity.

The purpose of this study was to evaluate the frequency and severity of irAEs in patients with pre-existing autoimmunity, including irAE-related morbidity and mortality, irAE-related management and resolution, and outcome of ICI rechallenge, to better understand the treatment options for this vulnerable patient population.

2 Methods

2.1 Study Design & Patient Selection

This is a retrospective nested case-control study conducted at a single academic center. Our patient population encompassed 3,130 adult patients (age ≥ 18 years) who received one or more FDA-approved ICIs for treatment of a solid malignancy from 2015–2021 within this health system.

Cases and controls were stratified by the presence or absence of a pre-existing autoimmune condition. Cases were defined as patients with pre-existing autoimmunity with one of the following conditions: antiphospholipid syndrome (ICD 9 714; ICD 10 M05, M06.9), chronic inflammatory demyelinating polyneuropathy (ICD 9 357.81; ICD 10 G61.81), dermatomyositis (ICD 9 710.3; ICD 10 M33), diffuse connective tissue disease (ICD 9 710.9, ICD 10 M35.9), inflammatory polyarthritis (ICD 9 714.9; ICD 10 M06.4), juvenile arthritis (ICD 9 714.3; ICD 10 M08), multiple sclerosis (ICD 9 340; ICD 10 G35), psoriatic arthritis (ICD 9 696; ICD 10 L40), rheumatoid arthritis (ICD 9 714; ICD 10 M05, M06.9), systemic lupus erythematosus (ICD 9 710; ICD 10 M32), systemic sclerosis (ICD 9 710.0; ICD 10 M34), or type I diabetes (ICD 9 250.03 and 205.010; ICD 10 E10.9, E10.65) [17]. Controls were patients without any of the aforementioned autoimmune conditions and were selected in a 2:1 ratio to cases. Controls were matched for sex, age, organ of tumor origin, and ICI class (anti-PD1 or PDL1 monotherapy, or combination anti-CTLA4 with anti-PD1 or PDL1). Patients who were pregnant or had a history of stem cell and/or solid organ transplant were excluded.

2.2 Data Collection

Cases were first ascertained using ICD 9 and 10 codes for the autoimmune diseases listed above. The autoimmune diagnosis was confirmed via manual chart review of the electronic medical record. Data including age at cancer diagnosis, gender, Eastern Cooperative Oncology Group (ECOG) performance status prior to immunotherapy, cancer diagnosis, cancer staging, and ICI type(s) were obtained by manual chart review [18]. The primary outcome was the development of severe irAEs within six months of ICI exposure, with severe defined as Grade 3 or higher by CTCAE criteria [10]. Secondary outcomes included response to ICI, resolution of the irAE, ICI rechallenge success, and survival.

2.3 Statistical Analyses

Statistical analyses were performed using Prism software (v9.4, GraphPad Software, Boston, Massachusetts USA, www.graphpad.com). Baseline characteristics were reported with descriptive statistics. Mann-Whitney testing was used for comparisons between non-parametric variables. Chi-square or Fisher's exact test was used to compare differences between proportions and categorical variables, and odds ratios (OR) were determined using the Baptista-Pike method. Conditions for performing Chi-square calculations were not met in all subgroup analyses; therefore, qualitative analysis was performed for age, gender, ECOG score, and baseline disease burden (metastatic or non-metastatic on presentation). Survival was compared between cases and controls by Log-Rank testing. Significance for all statistical tests was defined as alpha = 0.05, with correction for multiple comparisons.

3 Results

3.1 Patient Characteristics

Of 3,130 adult cancer patients who received treatment with an FDA-approved ICI within the UCLA Health system between 2015 and 2021, we identified 28 cases with pre-existing systemic, chronic autoimmune disease: 1/28 (3.6%) with antiphospholipid syndrome, 3/28 (10.7%) with inflammatory polyarthritis, 1/28 (3.6%) with juvenile rheumatoid arthritis,

3/28 (10.7%) with multiple sclerosis, 3/28 (10.7%) with psoriatic arthritis, 14/28 (50.0%) with rheumatoid arthritis, and 3/28 (10.7%) with type I diabetes mellitus (Table 1). Controls matched for sex, age within 10 years, ICI regimen, and cancer type were selected in a 2:1 ratio with cases (Table 1).

The median age at cancer diagnosis of the cases was 65.5 years (IQR 60.3–74.8) and the median age at cancer diagnosis of the controls was 65.0 years (IQR 59.3–73.8). Thirteen of the 28 cases (46.4%) were female, and 26/56 controls were female (46.4%). The majority of cases (21/28, 75.0%) had an ECOG score of 0–1 prior to treatment with ICIs, 4/28 (14.2%) had an ECOG score of 2 or higher, and 3/28 (10.7%) had an ECOG score that was not reported in the medical record. In the control group, 50/56 (89.3%) had an ECOG score of 0–1, and 3/56 (5.4%) had an ECOG score of 2 or higher. Three of 56 (5.4%) controls had an ECOG score that was not reported in the medical record. Most patients with pre-existing autoimmune disease who were treated with ICI therapy had metastatic disease [22/28 (78.6%)], as did the controls (Table 1).

The histologic types of cancers in our cases included 8/28 (28.6%) genitourinary, 4/28 (14.3%) gynecologic, 1/28 (3.6%) head and neck, 3/28 (10.7%) hepatobiliary, 7/28 (25.0%) lung, 4/28 (14.3%) melanoma, and 1/28 (3.6%) pancreatic. In controls, 16/56 (28.6%) had genitourinary malignancies, 8/56 (14.3%) gynecologic 2/56 (3.6%) head & neck, 6/56 (10.7%) hepatobiliary, 14/56 (25.0%) lung, 8/56 (14.3%) melanoma, and 2/56 (3.6%) pancreatic. Most cases received PD-1 or PD-L1 monotherapy [23/28 (82.1%)], while 5/28 (17.9%) received combination therapy of CTLA-4 and PD-1 inhibitors. Similarly, 44/56 (78.6%) of controls received PD-1 or PD-L1 monotherapy and 11/56 (19.6%) received combination therapy of CTLA-4 and PD-1 inhibitors, while 1 (1.8%) received PD1 and PDL1 inhibitors (Table 1).

3.2 IRAE Incidence and Outcomes

The incidence of all-grade irAEs in the total population encompassing cases and controls was 37/84 (44.0%).

3.2.1 All Cases—Four of 28 (14.2%) cases experienced Grade 1–2 irAEs, of whom 3 (3/28, 10.7%) had received PD-1 or PD-L1 monotherapy and 1 (1/28, 3.6%) had received combination therapy. These irAEs included maculopapular rash (n = 1), arthralgias (n=1), adrenal insufficiency (n = 1), and myositis (n = 1). Only one of these irAEs was an autoimmune disease flare; a patient with a history of rheumatoid arthritis experienced Grade 1 arthritis after 1 cycle of nivolumab. Six of 28 (21.4%) cases experienced Grade ≥ 3 irAEs, of whom 3 (3/28, 10.7%) had received PD-1 or PD-L1 monotherapy and 3 (3/28, 10.7%) received combination therapy. These irAEs included hyperglycemia (n = 1), bullous dermatitis (n = 1), colitis (n = 1), transaminitis (n = 2), and arthritis (n = 1) (Table 2, Figure 1). Only one of these irAEs was an autoimmune disease flare (case #5); this patient had a history of juvenile rheumatoid arthritis and received 9 cycles of nivolumab (Table 2). The other irAEs involved tissues unrelated to patients' autoimmune diseases.

3.2.2 All Controls—Eighteen of 56 (32.1%) controls experienced Grade 1–2 irAEs, of whom 14 (14/56, 25%) had received PD-1 or PD-L1 monotherapy and 4 (4/56, 7.1%)

had received combination therapy. IrAEs included hypothyroidism (n = 7), pneumonitis (n = 3), maculopapular rash (n = 3), bullous dermatitis (n = 2), hyperbilirubinemia (n=1), arthritis (n = 1), and pruritus (n = 1). Nine of 56 (16.1%) controls experienced Grade ≥ 3 irAEs, of whom 6 (6/56, 10.7%) had PD-1 or PD-L1 monotherapy and 3 (3/56, 5.4%) received combination therapy. These irAEs included hyponatremia (n = 1), nephritis (n = 1), arthritis (n = 2), hepatitis (n = 3), colitis (n = 1), and anemia (n = 1) (Table 3, Figure 1). Three controls had pre-existing autoimmune conditions that were not included in our search, including hypothyroidism (n = 2) and immune thrombocytopenic purpura (n = 1); none of these patients developed Grade ≥ 3 irAEs.

3.2.3 Comparison—4/28 (14.2%) of cases developed a low-grade (1–2) irAE compared to 18/56 (32.1%) of controls. 6/28 (21.4%) of cases developed a high-grade (≥ 3) irAE compared to 9/56 (16.1%) of controls. Therefore, cases and controls demonstrated a similar odds of developing a low-grade irAE compared to a high-grade irAE [OR 0.33, 95% CI 0.091 to 1.38, $p = 0.258$, not significant (ns), Figure 2]. Subgroup analysis of 23 cases and 44 controls treated with anti-PD1/PD-L1 monotherapy found that 6/23 (26.0%) cases experienced all-grade irAEs and 20/44 (45.4%) controls experienced all-grade irAEs. There was no significant difference in the odds of developing a severe irAE between cases and controls (OR 0.43, 95% CI 0.083–2.33, $p = 0.627$, ns, Figure 3).

3.3 Cases with Severe IRAES (Grade 3–5)

3.3.1 Baseline Characteristics—Half (3/6, 50%) of cases who experienced severe irAEs were female. The median age at time of cancer diagnosis was 57.5 years (IQR 45.8–69.0). The cases' pre-existing autoimmune diseases included multiple sclerosis (n = 2) and multiple types of arthritis (n = 4) (Table 2).

Case #2 and Case #3 were both taking immunosuppressants at baseline (glatiramer acetate for multiple sclerosis and methotrexate for rheumatoid arthritis, respectively); others remained controlled off immunosuppressants (Table 2). Cancer histologies included gynecologic (n = 2), genitourinary (n = 2), and melanoma (n = 2) (Table 2). All cases except for one (Case #6) had metastatic disease prior to ICI therapy (Table 2).

3.3.2 Outcomes—We evaluated patient response to ICI therapy using Response Evaluation Criteria in Solid Tumors (RECIST) [19]. Cancer outcomes of cases who had severe irAEs included 3/6 (50.0%) with progression of disease (PD), 1/6 (16.7%) with stable disease (SD), and 2/6 (33.3%) with a partial response (PR). None of the cases had a complete response to ICIs (Table 2, Figure 4).

Two of the three (66.7%) cases with PD were taking autoimmune agents at baseline (Case #2 and Case #3, Table 2). Case #2 was taking glatiramer acetate for multiple sclerosis and had progression of his renal cell carcinoma after two cycles of ipilimumab and six cycles of nivolumab. Case #3 was taking methotrexate for rheumatoid arthritis and had progression of his melanoma after 4 cycles of ipilimumab and 22 cycles of nivolumab. Case #3 then experienced Grade 5 diarrhea, thought to be ICI colitis from combination therapy superimposed on the patient's history of microscopic colitis. Upon further chart review, the patient declined to take antidiarrheal agents and preferred not to present to the

hospital for intravenous hydration, so this death may have been preventable under different circumstances.

Only 1 case developed a long term irAE; Case #1 developed insulin-dependent diabetes mellitus after experiencing irAE hyperglycemia. This patient had a history of multiple sclerosis controlled off medications and received 46 cycles of pembrolizumab for endometrial cancer. The remaining 4/6 (66.7%) cases, excluding Case #3 who died, did not experience long-term sequelae of the irAEs. Their irAEs resolved with supportive measures and/or immunosuppressants.

Overall, 5/6 (83.3%) cases with Grade ≥ 3 irAEs survived. Moreover, 2/3 (66.7%) cases (Case #5 and Case #6) were successfully rechallenged with ICIs without further irAEs. Case #5 had a history of polyarthritis, recovered from nivolumab-induced transaminitis, and was able to continue nivolumab for her urothelial cell carcinoma. Similarly, case #6 had a history of juvenile rheumatoid arthritis, recovered from nivolumab-induced Grade 3 arthralgias, and was able to continue nivolumab for ovarian cancer. Case #4 had a history of rheumatoid arthritis and recovered from Grade 4 transaminitis after combined ipilimumab/nivolumab for melanoma. However, when she was rechallenged with ipilimumab alone she developed recurrent Grade 4 transaminitis. Although she recovered uneventfully from the transaminitis, ICI therapy was permanently discontinued. Case #1 declined ICI rechallenge due to personal preference and case #2 was offered ICI rechallenge but was lost to follow-up.

3.4 Controls with Severe IRAES (Grade 3–5)

3.4.1 Baseline Characteristics—7/9 (77.8%) controls with severe irAEs were female. The median age of the control group at cancer diagnosis was 62.0 years (IQR 46.0–71.0). The cancer histologies included lung (n = 2), urothelial (n = 2), cervical (n = 3), hepatobiliary (n = 1), and melanoma (n = 1). All (100%) had metastatic disease prior to ICI therapy (Table 1).

3.4.2 Outcomes—Of the 9 controls with severe irAEs, 4 (44.4%) had stable disease or a positive clinical response by RECIST [19]. Five of 9 (55.6%) had PD, 3/9 (33.3%) had SD, none (0.0%) had PR, and 1/9 (11.1%) achieved a CR (Figure 4).

Three of the 9 (33.3%) controls with severe irAEs developed long-term sequalae. Control #3 developed chronic arthritis requiring weekly methotrexate after receiving 3 cycles of combined ipilimumab and nivolumab for urothelial cell carcinoma. Control #4 developed chronic arthritis requiring the use of daily non-steroidal anti-inflammatories after receiving 9 cycles of pembrolizumab for cervical cancer. Lastly, control #6 developed chronic transfusion-dependent anemia after receiving 6 cycles of pembrolizumab for cervical cancer (Table 3).

Overall, 8/9 (88.9%) controls with Grade ≥ 3 irAEs survived the irAE. Control #5 received one cycle of nivolumab for cervical cancer and died from ICI hepatitis. Five of 5 (100%) controls who were rechallenged with ICI monotherapy were successful. Two of 9 (22.2%) controls (Control #1 and Control #9) were offered rechallenge but declined due to personal preference (Table 3).

3.5 ICI Cessation

The most common reason for discontinuation of ICI therapy was disease progression (17/28 cases, 60.7%). Other reasons were therapy completion in 6/28 cases (21.4%), immunotoxicity in 3/28 cases (10.7%), and patient preference or relocation reasons in 2/28 cases (7.1%). ICI therapy was discontinued due to disease progression in 31/56 controls (55.4%), therapy completion in 17/56 controls (30.4%), immunotoxicity in 4/56 controls (7.1%), and other reasons in 4/56 controls (7.1%). Other reasons included patient preference, relocation, and transition to hospice.

3.6 Clinical Response & Survival Analysis

The median follow-up time among cases was 12.8 months (IQR 5.8–35.7 months). The median follow-up time among controls was 10.4 months (IQR 4.1–39.9 months). There was no significant difference in the median follow-up time between cases and controls (Mann-Whitney U = 766, $p = 0.867$, ns).

The clinical responses to ICI therapy did not differ significantly between cases and controls $X^2(3.0, 84) = 0.26$, $p = 0.967$, ns, Figure 5). Among cases, 13/28 (46.4%) had PD, 6/28 (21.4%) had SD, 6/28 (21.4%) had PR, and 3/28 (10.7%) had CR. Among controls, 29/56 (51.8%) had PD, 11/56 had SD (19.6%), 10/56 (17.9%) had PR, and 6/56 (10.7%) had CR.

Overall survival did not differ between cases and controls (Figure 6, Log-Rank $p = 0.998$, ns).

4 Discussion

Given the unknown safety profile of ICIs in patients with pre-existing autoimmune conditions, we evaluated irAE incidence and severity in this population. Specifically, our study focused on individuals with pre-existing systemic, chronic autoimmune disease with detailed evaluation of clinical outcomes for both irAEs and cancer treatment. In this cohort, patients with pre-existing autoimmunity experienced irAEs at similar rates to patients without pre-existing autoimmunity when matched for sex, age, cancer type, and ICI regimen. Patients with pre-existing autoimmunity also experienced severe irAEs (Grade ≥ 3) at similar rates to patients without pre-existing autoimmunity. Importantly, cases and controls demonstrated similar overall survival and tumor response.

Our study's overall irAE incidence (44%) and severe irAE incidence (17.9%) are within the range of those previously reported in the literature (10–80% and 2.5–18%, respectively) [3, 4]. We matched cases 2:1 for sex, age, organ of tumor origin, and ICI class for a variety of cancer histologies and autoimmune diseases. Furthermore, all patients were treated at the same academic medical center, reducing the likelihood of significant differences in irAE recognition between groups. Thus, our study provides an important benchmark for the relative risk of all grade and severe irAEs in patients with pre-existing systemic, chronic autoimmune conditions, a population for which the use of ICI therapies has historically not been used due to irAE concerns. Prior studies, including the largest authored by Tison et al. and Pizuorno Machado et al., utilized a case series design and lacked a comparator group [20, 21]. Placais et al. recently published a similar case-control study but only in patients

with melanoma [14]. Our data found no difference in the frequency of irAEs or severe irAEs and can inform discussions between providers and their patients in considering initiation of ICI cancer treatments.

Regarding ICI rechallenge success, the patients in our study were more successful in continuing ICI therapy compared to patients in prior studies. After experiencing a Grade 3–4 irAE, the majority of patients who were rechallenged with ICIs were successful in continuing therapy (66.7% of cases, 100% of controls). In other words, the irAE recurrence rate was 33.3% for cases and 0% for controls who had experienced severe irAEs. The case who was not successful in rechallenge experienced Grade 4 transaminitis, recovering with steroids. In the literature, the irAE recurrence rate after ICI rechallenge has been reported to be 18–42% [22–26]. One of the largest studies on this topic was a cross-sectional study conducted by Dolladille et al., which analyzed 24,079 irAEs and found an irAE recurrence rate of 28.8% [27]. Notably, prior studies included all-grade irAEs, while we analyzed irAE recurrence in patients with severe (Grade 3–4) irAEs. Our data support consideration of ICI rechallenge with clinically appropriate monitoring and follow-up, even in patients who have experienced Grade 3 irAEs. The 2021 American Society of Clinical Oncology guidelines recommend permanent discontinuation of ICIs in patients who have experienced Grade 4 irAEs, which align with our results [28].

One of the major strengths of our study was the variety of autoimmune conditions, cancer histologic types, and ICI therapies represented in our cases and controls. We had a variety of autoimmune conditions represented in our patient population (12 different autoimmune diseases included in our search, with seven different autoimmune diseases in cases), compared to prior studies which evaluated only one or a few autoimmune conditions [29, 30]. Rheumatoid arthritis is frequently studied [2]. Additionally, we selected patients with autoimmune diseases that have multiple systemic manifestations rather than patients with singular organ involvement, such as thyroiditis. Moreover, we had patients with a variety of cancer histologies, compared to other studies that administered ICIs primarily to patients with melanoma or NSCLC [14, 20, 31–33]. These histologies were likely selected because of the initial approval of ICI in this population, whereas ICI indications have now expanded to many cancer histologies. Therefore, as ICI indications continue to expand, evaluation of the safety of ICI in patients with autoimmune diseases and multiple cancer histologies is paramount. Lastly, we included patients receiving PD1/PD-L1 monotherapy and patients receiving combination therapy with anti-CTLA4 therapy, whereas other studies have only included patients receiving one or the other [29, 31, 33].

Another strength of our study includes automated data extraction from electronic medical records in tandem with manual chart review by physicians. ICD codes alone could only identify patients treated with ICIs. Thus, physician interpretation of oncology clinic, specialty clinic, and hospitalization records was critical in identifying specific details regarding autoimmune disease and irAEs. For example, an irAE may ultimately be ambiguous given that it is a diagnosis of exclusion based on clinical history and diagnostics. We adopted a conservative approach by having a low threshold to diagnose an irAE if it fit the clinical picture instead of requiring an irAE diagnosis to appear in oncology

documentation. This was especially pertinent if patients experienced mortality or were lost to follow up, as they were not seen again by their oncologists.

We found that patients generally did not experience irAEs in the same organ affected by their autoimmune disease, which is an area of uncertainty in the literature. Studies by Pizuorno Machado et al. and Richter et al. had similar findings to ours, whereas Labadzhyan et al. found that serum endocrine-specific antibodies were found in patients with endocrine irAEs [21,34,35]. We also describe the cancer outcomes of our cases and controls and did not find a significant difference in cancer response between cases and controls. While the literature suggests that patients who experience irAEs have a more robust tumor effect from ICIs compared to patients without irAEs, we did not see this in our cohort, possibly because of a biologic difference in patients with autoimmune disease as suggested by Abdel-Wahab et al., or because of our small sample size [12, 36]. In our cohort, overall survival was similar between cases and controls, which differs from the findings of Placais et al., who found improved overall survival in the autoimmune disease group [14]. This difference may be related to Placais et al.'s focus on patients with melanoma, a cancer histology that is very responsive to ICIs, whereas our cohort included all cancer histologies.

Our study was limited by its retrospective nature, single-center design, and small sample size. The retrospective nature inherently limits causal inference. While our center is a large, urban, academic medical center, the single-center nature limits broad generalizability. We attempted to control for confounding variables with 2:1 matching of controls to cases by sex, age, cancer type, and ICI class. Additionally, our sample size was small, although we were limited by the small number of patients with pre-existing autoimmunity receiving ICI therapy due to safety uncertainties in the literature. We used a large database (N = 3,130) to identify patients and found 28 cases who had been treated with ICIs. Matching cases to controls increased the power of the study given our small case number.

5 Conclusion

These results augment the sparse literature on this topic and suggest that ICIs may be considered as a reasonable cancer treatment option for patients with pre-existing systemic autoimmunity. This is a particularly vulnerable patient population that has historically been excluded from ICI trials due to clinical uncertainty, and, therefore, physicians are understandably hesitant to administer ICIs to these patients. Current guidelines from the National Comprehensive Cancer Network are limited for this population; they recommend that oncologists consider anti-PD1/PD-L1 monotherapy rather than combination therapy and optimize immunosuppression with a goal of <10 mg of prednisone daily prior to ICI initiation [37]. The results of this study have the potential to expand available safety and efficacy data for this critical treatment option for many malignancies in this population. Nevertheless, this knowledge must ultimately be paired with an oncologist's patient-centered discussion incorporating potential immunotherapy risks.

Continued studies to identify the optimal balance of anti-tumor efficacy and toxicity with cancer immunotherapies are needed. We await the results of prospective studies to answer some of these questions, including an ongoing phase Ib trial of nivolumab for patients with

autoimmune disease and advanced malignancy sponsored by the National Cancer Institute [38].

Lastly, paired with these clinical studies, translational studies of irAE mechanisms will facilitate the development of potential therapeutic strategies to facilitate safer use of ICI treatments in a broader group of cancer patients.

Abbreviations

ICI	immune checkpoint inhibitor
irAE	immune related adverse event
PD1	programmed death protein 1
PD-L1	programmed death ligand 1
CTLA-4	cytotoxic T lymphocyte antigen 4
CTCAE	Common Terminology Criteria for Adverse Event
ICD	International Classification of Diseases
ECOG	Eastern Cooperative Oncology Group
RECIST	Response Evaluation Criteria in Solid Tumors
PD	progression of disease
SD	stable disease
PR	partial response
CR	complete response
IQR	interquartile range
SD	standard deviation

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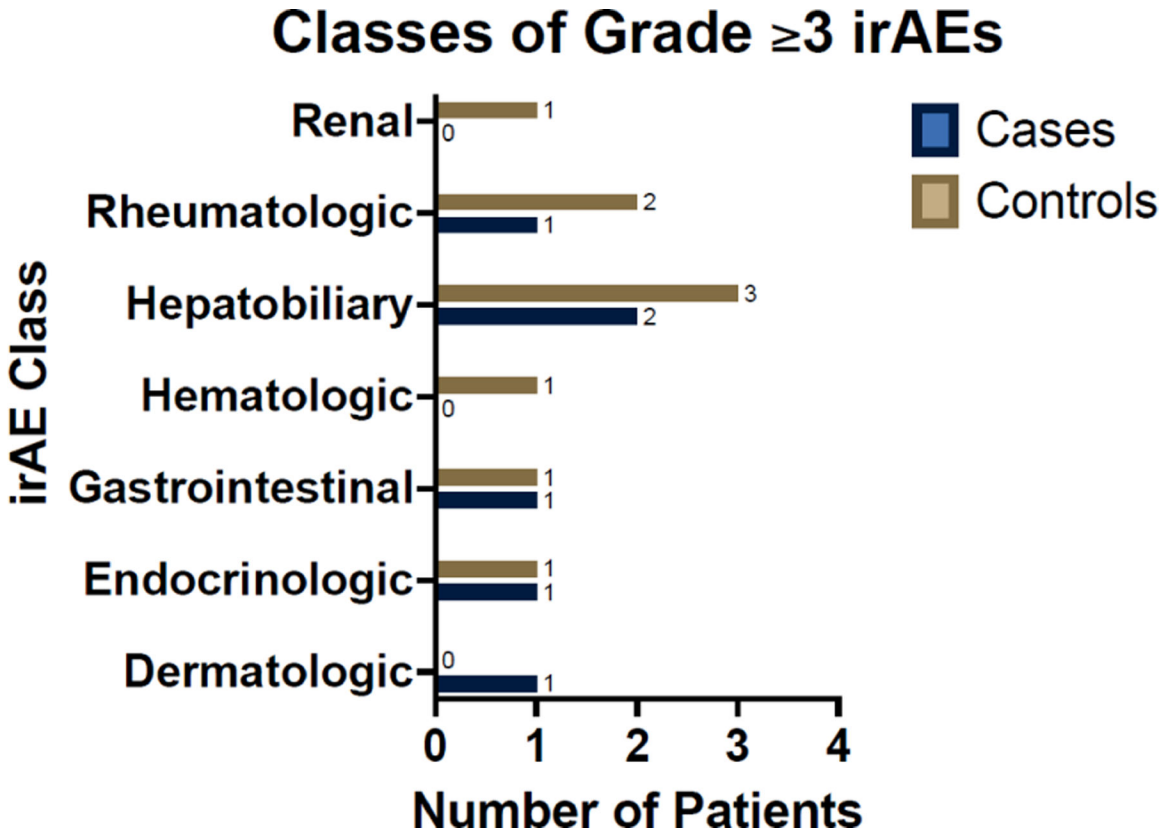

Figure 1.

Among patients with severe irAEs, the most common classes of irAEs were hepatobiliary (n = 5) and rheumatologic (n = 3).

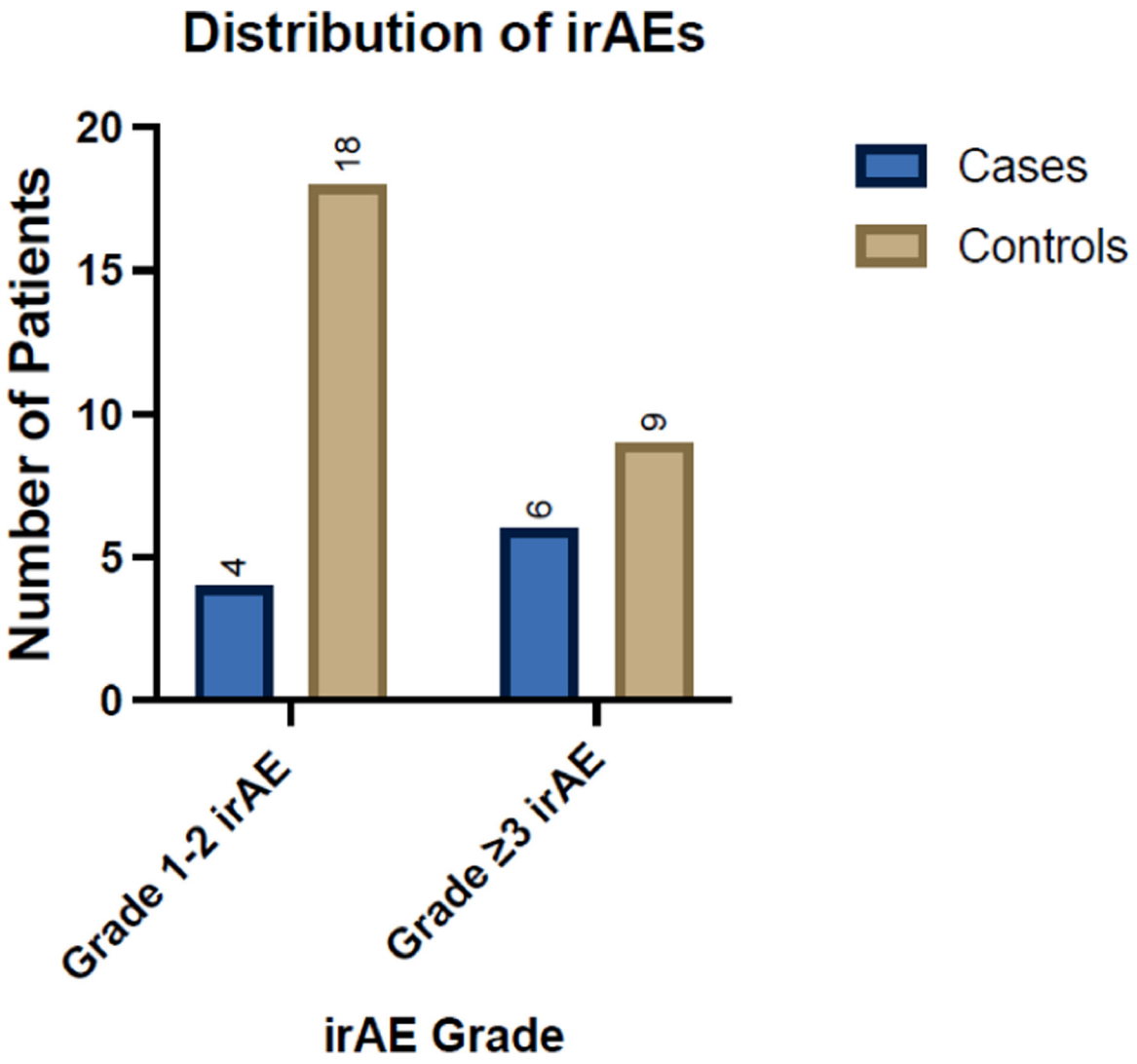

Figure 2.

4/28 (14.2%) of cases developed a low-grade (1–2) irAE compared to 18/56 (32.1%) of controls. 6/28 (21.4%) of cases developed a high-grade (≥ 3) irAE compared to 9/56 (16.1%) of controls. Cases and controls demonstrated a similar odds of developing a low-grade irAE compared to a high-grade irAE (OR 0.33, 95% CI 0.091 to 1.38, $p = 0.258$, NS).

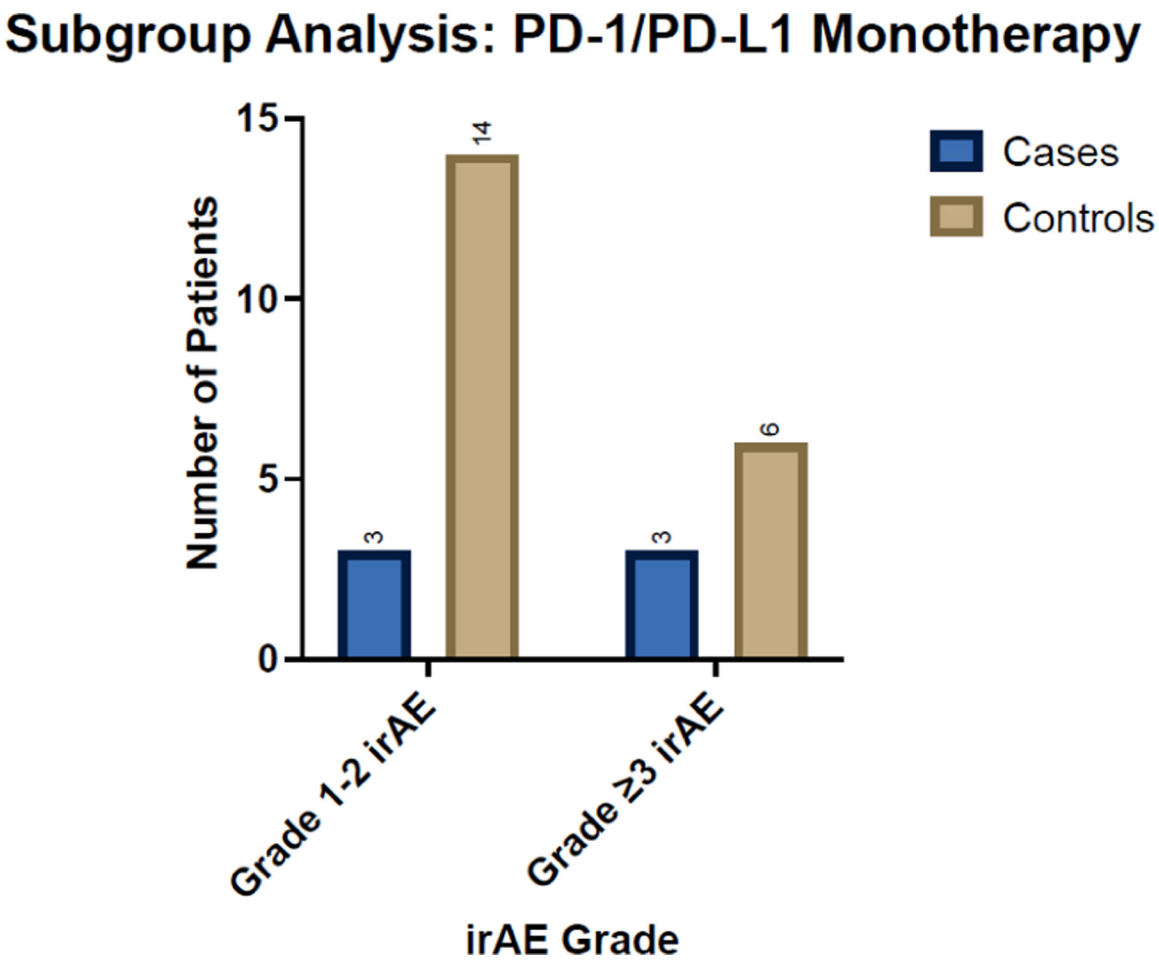

Figure 3.

In an anti-PD-1/PDL-1 monotherapy subgroup analysis, the odds of developing a low-grade (1–2) irAE were not significantly different than the odds of developing a high-grade (≥ 3) irAE among cases and controls (OR 0.43, 95% CI 0.083 to 2.33, $p = 0.627$, ns).

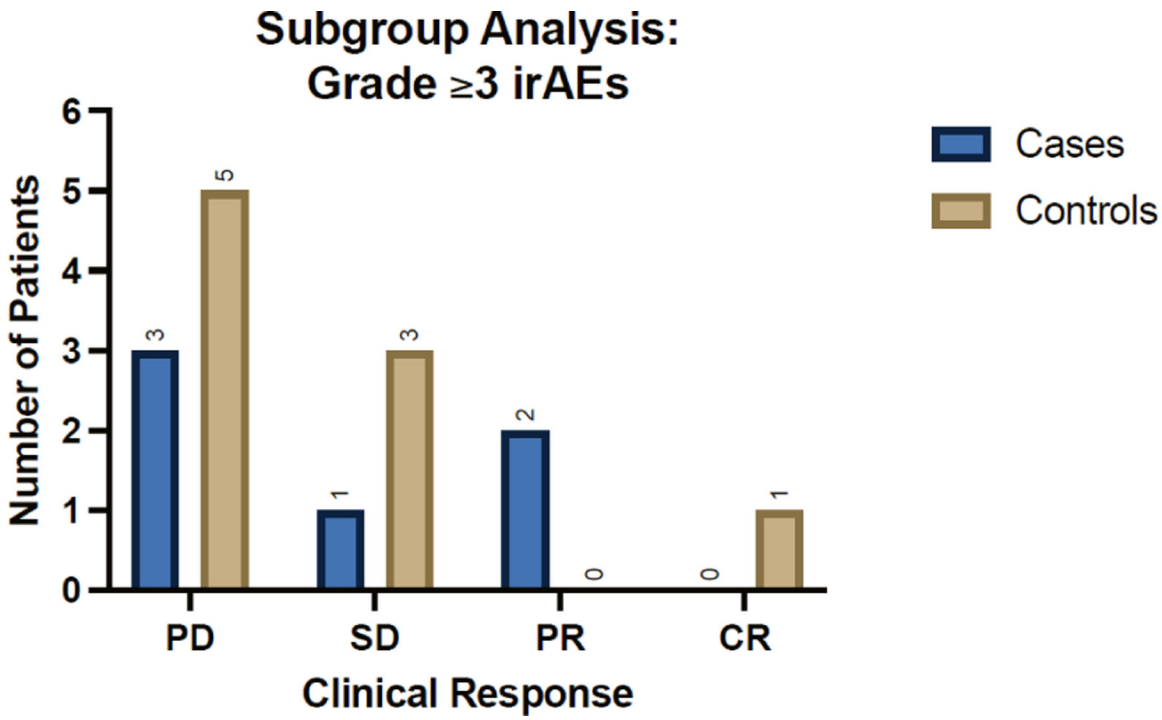

Figure 4.

In patients who experienced Grade ≥ 3 irAEs, the odds of developing progressive disease versus developing stable disease or a positive clinical response were not significantly different among cases and controls (OR 0.80, 95% CI 0.13–5.10, $p = 0.999$, ns). PD: Progressive Disease; SD: Stable Disease; PR: Partial Response; CR: Complete Response.

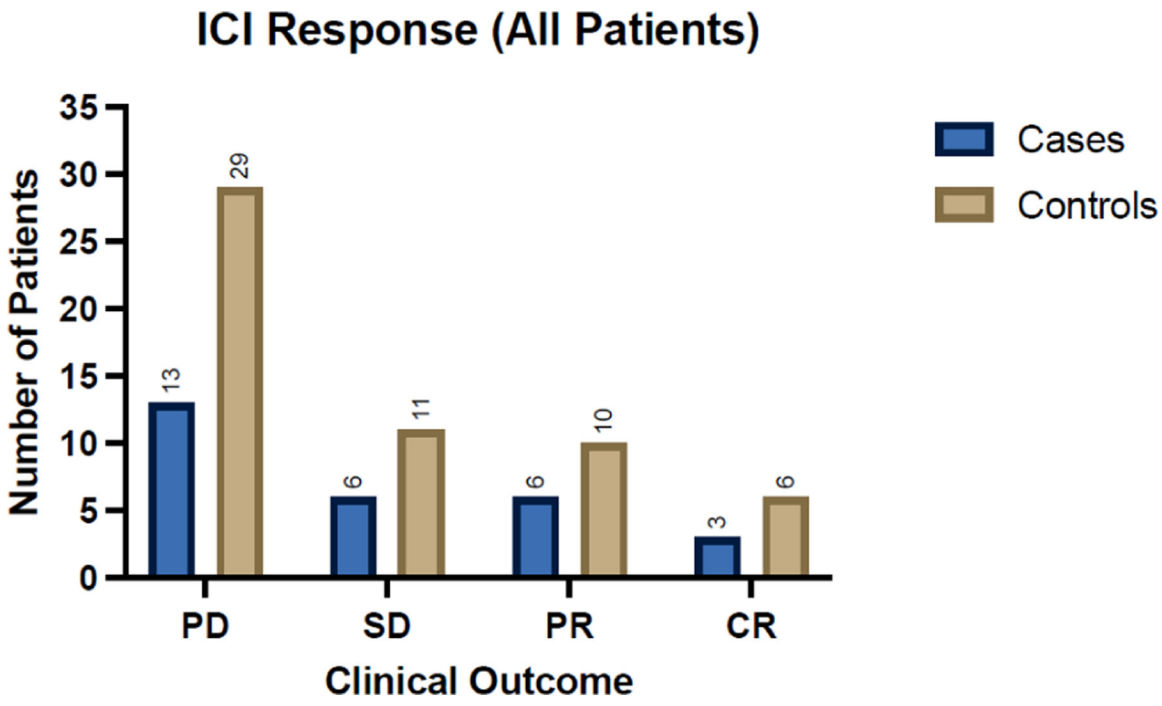

Figure 5.

There was not a significant difference between type of clinical outcome among cases and controls $X^2(3.0, 84) = [0.26]$, $p = 0.967$, ns. PD: Progressive Disease; SD: Stable Disease; PR: Partial Response; CR: Complete Response.

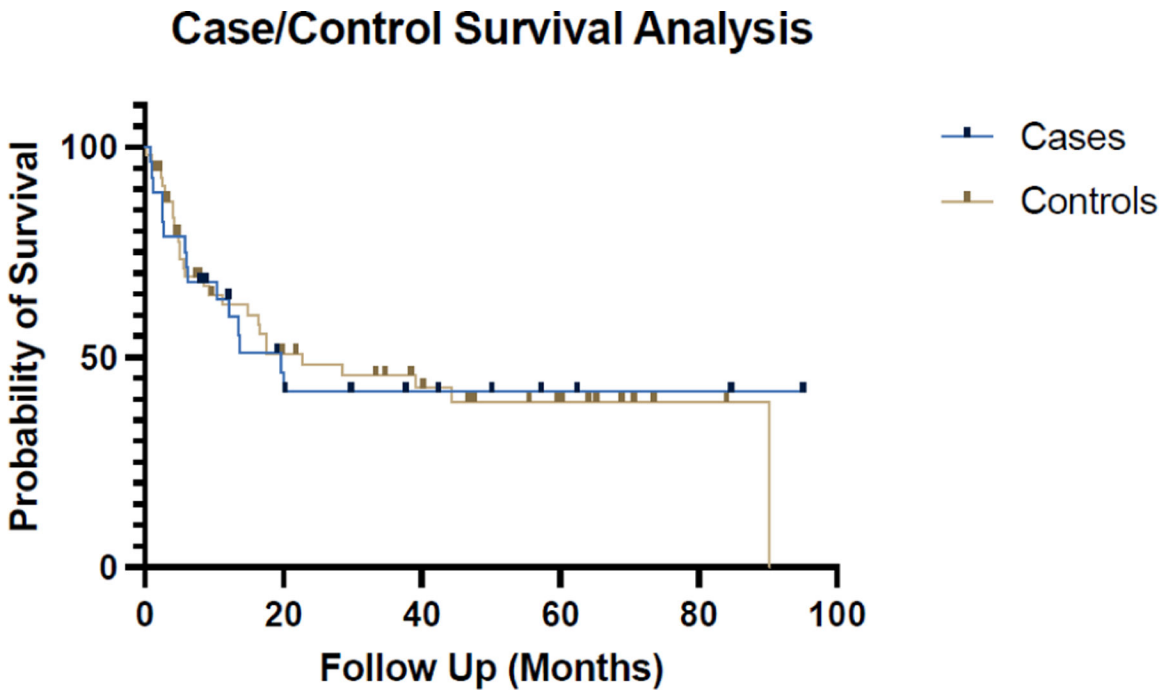

Figure 6.

Overall survival of patients with pre-existing autoimmunity (cases) and matched individuals without pre-existing autoimmune disease (controls) treated with immune checkpoint inhibitor therapy ($p = 0.998$, ns, Mantel-Cox test).

Table 1

Baseline characteristics of cases and controls

Clinical Parameter	Cases (28) n (%)	Controls (56) n (%)	*p*-Value
Age (years)			
20–29	2 (7.1%)	1 (1.8%)	
30–39	0 (0.0%)	3 (5.4%)	
40–49	0 (0.0%)	3 (5.4%)	
50–59	4 (14.3%)	7 (12.5%)	
60–69	12 (42.9%)	18 (32.1%)	
70–79	7 (25.0%)	16 (28.6%)	
80–89	2 (7.1%)	7 (12.5%)	
90–99	1 (3.6%)	1 (1.8%)	> 0.999
Sex			
Female	13 (46.4%)	26 (46.4%)	
Male	15 (53.6%)	30 (53.6%)	> 0.999
ECOG			
0	9 (32.1%)	22 (39.3%)	
1	12 (42.9%)	28 (50.0%)	
2	2 (7.1%)	2 (3.6%)	
3	2 (7.1%)	1 (1.8%)	
N/A	3 (10.7%)	3 (5.4%)	0.202
Metastatic Disease			
Y	22 (78.6%)	50 (89.3%)	
N	6 (21.4%)	6 (10.7%)	0.202
Cancer Type			
Genitourinary	8 (28.6%)	16 (28.6%)	
Gynecologic	3 (10.7%)	6 (10.7%)	
Head & Neck	1 (3.6%)	2 (3.6%)	
Hepatobiliary	3 (10.7%)	6 (10.7%)	
Lung	7 (25.0%)	14 (25.0%)	
Melanoma	4 (14.3%)	8 (14.3%)	
Ovarian	1 (3.6%)	2 (3.6%)	
Pancreatic	1 (3.6%)	2 (3.6%)	> 0.99
ICI Regimen			
CTLA-4	0 (0.0%)	0 (0.0%)	
PD-1	22 (78.6%)	33 (58.9%)	
PD-L1	1 (3.6%)	11 (19.6%)	
CTLA-4 + PD-1	5 (17.9%)	11 (19.6%)	
CTLA-4 + PD-L1	0 (0.0%)	0 (0.0%)	
PD-1 + PD-L1	0 (0.0%)	1 (1.8%)	0.10

Note: ECOG: Eastern Cooperative Oncology Group; ICI: Immune checkpoint inhibitor; CTLA-4: Cytotoxic T lymphocyte antigen; PD-1: Programmed death protein; PD-L1: Programmed death ligand

Table 2

Summary of Grade 3 & 4 irAEs and their outcomes reported in case subjects with pre-existing autoimmune disease

Case	Sex	Age at Cancer Diagnosis	Pre-Existing Autoimmune Disease	Status of Autoimmune Condition	Cancer	Metastatic Disease prior to ICI Therapy	ICI Line of Therapy	Mono vs. Dual ICI Therapy	ICI(s)	Treatment Response	irAE Type	irAE Grade
1	F	54	Multiple Sclerosis	Controlled off medications	Endometrial	Yes	Third	Mono	Pembrolizumab (46 cycles)	Stable	Hyperglycemia	3
2	M	64	Multiple Sclerosis	Controlled on glatiramer acetate	Renal	Yes	Third	Dual	Ipilimumab (2 cycles), Nivolumab (6 cycles)	Progressive	Bullous Dermatitis	3
3	M	61	Rheumatoid Arthritis	Controlled on methotrexate	Melanoma	Yes	First	Dual	Ipilimumab (4 cycles), Nivolumab (22 cycles)	Progressive	Diarrhea	5
4	F	54	Rheumatoid Arthritis	Controlled off medications	Melanoma	Yes	First	Dual	Ipilimumab (4 cycles), Nivolumab (4 cycles)	Partial	Transaminitis	4
5	M	69	Polyarthritis	Controlled off medications	Urothelial	Yes	Second	Mono	Nivolumab (31 cycles)	Progressive	Transaminitis	3
6	F	21	Juvenile Rheumatoid Arthritis	Controlled off medications	Ovarian	No	Second	Mono	Nivolumab (9 cycles)	Partial	Arthritis	3

Note: irAEs: immune related adverse events; ICI: immune checkpoint inhibitor

Table 3

Summary of Grade 3 & 4 irAEs and their outcomes reported in control subjects

Control	Sex	Age at Cancer Diagnosis	Cancer	Metastatic Disease prior to ICI Therapy	ICI Line of Therapy	Mono vs. Dual ICI Therapy	ICI(s)	Treatment Response	irAE Type	irAE Grade	irAE Treatment	Rechalle
1	F	67	Lung	Yes	Second	Mono	Pembrolizumab (1 cycle)	Stable	Hyponatremia	3	Supportive Measures	No
2	F	62	Urothelial	Yes	Second	Mono	Durvalumab (3 cycles)	Progressive	Nephritis	3	Supportive Measures	Yes
3	F	61	Urothelial	Yes	First	Dual	Ipilimumab (3 cycles), Nivolumab (3 cycles)	Complete	Arhritis	3	Steroids, Methotrexate	Yes
4	F	60	Cervical	Yes	Third	Mono	Pembrolizumab (9 cycles)	Stable	Arhritis	3	Steroids	Yes
5	F	26	Cervical	Yes	Third	Mono	Nivolumab (1 cycle)	Progressive	Hepatitis	5	Steroids	No
6	F	32	Cervical	Yes	Second	Mono	Pembrolizumab (7 cycles)	Progressive	Anemia	4	Steroids, Transfusions	No
7	F	72	Hepatobiliary	Yes	>Third	Mono	Nivolumab (4 cycles)	Progressive	Hepatitis	3	Steroids	Yes
8	M	75	Lung	Yes	Second	Dual	Nivolumab (2 cycles), Ipilimumab (2 cycles), Atezolizumab (6 cycles), Durvalumab (1 cycle)	Progressive	Hepatitis	3	Steroids	Yes
9	M	70	Melanoma	Yes	First	Dual	Ipilimumab (2 cycles), Nivolumab (2 cycles)	Stable	Colitis	3	Steroids	No

Note: irAEs: immune related adverse events; ICI: immune checkpoint inhibitor