OXFORD

JNCI J Natl Cancer Inst (2022) 114(8): djac046

https://doi.org/10.1093/jnci/djac046
First published online February 21, 2022
Brief Communications

Pre-Existing Autoimmune Disease and Mortality in Patients Treated with Anti-PD-1 and Anti-PD-L1 Therapy

Kimberly Tang, BA [1], Bruce C. Tiu, BS,[1,2] Guihong Wan, PhD,[1,3] Shijia Zhang, BA,[1,3] Nga Nguyen, BA,[1] Bonnie Leung, BSc,[1] Alexander Gusev, PhD,[4] Kerry L. Reynolds, MD,[5] Shawn G. Kwatra, MD,[6,‡] Yevgeniy R. Semenov, MD, MA [1,2,*,‡]

[1]Department of Dermatology, Massachusetts General Hospital, Boston, MA, USA; [2]Department of Dermatology, Harvard Medical School, Boston, MA, USA; [3]Department of Biomedical Informatics, Harvard Medical School, Boston, MA, USA; [4]Department of Medicine, Dana Farber Cancer Institute, Boston, MA, USA; [5]Department of Medicine, Division of Oncology, Massachusetts General Hospital, Boston, MA, USA; and [6]Department of Dermatology, Johns Hopkins University, Baltimore, MD, USA

[‡]Co-senior authors.

[*]**Correspondence to:** Yevgeniy R. Semenov, MD, MA, Department of Dermatology, Massachusetts General Hospital, Harvard Medical School, 40 Blossom Street, Bartlett Hall 6R, Room 626, Boston, MA 02114, USA (e-mail: ysemenov@mgh.harvard.edu).

Abstract

Although indications for immune checkpoint inhibitors (ICIs) have dramatically increased in the past decade, ICIs have been associated with autoinflammatory immune-related adverse events, which can resemble autoimmune diseases (ADs). Little is known about the impact of baseline AD on mortality in cancer patients treated with ICIs. Here, we identified 17 497 patients with preexisting autoimmune diagnoses prior to treatment with antiprogrammed cell death receptor-1 or antiprogrammed cell death ligand-1 therapy and 17 497 matched controls through the TriNetX Diamond network of more than 200 million patients across the United States and Europe. Using a Cox proportional hazards model, we found that patients with history of AD were not at higher risk of mortality than non-AD patients (hazard ratio [HR] = 1.03, 95% confidence interval [CI] = 1 to 1.07; $P = .05$). Additionally, history of Hashimoto disease (HR = 0.75, 95% CI = 0.62 to 0.90; $P = .002$) and vitiligo (HR = 0.52, 95% CI = 0.34 to 0.81; $P = .003$) were statistically significantly associated with decreased mortality. This suggests that underlying AD need not be a contraindication to inclusion in clinical trials and administration of ICI for treatment of cancer.

Immune checkpoint inhibitors (ICIs) have revolutionized cancer therapy and are approved for treatment of more than 19 cancer types (1). However, they have been associated with life-threatening immune-related adverse events (irAEs) that resemble autoimmune diseases (ADs) (2). Several reports have linked the occurrence of these toxicities to improved overall survival (3-5). Despite similarities between irAEs and ADs, ICI clinical trials have largely excluded patients with history of AD because of concerns of exacerbating their underlying AD, increasing risk of treatment-induced irAEs, and achieving a poorer ICI response (6). Thus, this study aims to investigate the impact of baseline history of AD on survival among cancer patients receiving ICI using observational data from a large multi-institutional cohort.

For this retrospective cohort analysis, we identified eligible patients from the TriNetX Diamond network, a global health research network that provides access to electronic medical records from more than 200 million patients across the United States and Europe. For the primary analysis, included patients were identified by a Prescription for Electronic Drug Information Exchange record of treatment with antiprogrammed cell death receptor-1 (anti-PD-1: cemiplimab, nivolumab, or pembrolizumab) or antiprogrammed cell death ligand-1 (anti-PD-L1: atezolizumab, avelumab, or durvalumab). Secondary analyses stratified patients into monotherapy with anti-PD-1 or anti-PD-L1, or combination therapy with anti-PD-1 and anti-cytotoxic T-lymphocyte antigen-4 (CTLA-4: ipilimumab), which were performed after rematching each subgroup. We included participants with cancer diagnoses based on *International Classification of Diseases* 10th edition malignant neoplasm diagnoses, capturing the 4 most common indications for ICI (C34: bronchus and lung, C15-26: digestive organs, C43: melanoma, and C64-68: urinary tract). Preexisting AD was defined as diagnosis of any included ADs at any point prior to the first instance of ICI administration (Supplementary Table 1, available online). Patients who had baseline history of AD were then age- sex-, race-, and cancer-matched to non-AD, ICI-treated control

Received: November 29, 2021; **Revised:** January 3, 2022; **Accepted:** February 16, 2022

patients using 1:1 propensity score matching. Sex and self-reported race were identified from electronic medical records through the TriNetX database. A greedy nearest neighbor matching algorithm with a caliper of 0.1 pooled standard deviations was used. We additionally matched based on the presence of distant metastases using the secondary malignant neoplasm *International Classification of Diseases*-10 code to control for cancer stage. The index event was the first day of ICI initiation. A Cox proportional hazards model was performed to determine the prognostic impact of baseline ADs on overall survival. Patient mortality was determined by record of death following ICI administration, and those who remained alive were censored at the end of follow-up. A log-rank test was used to calculate *P* values, and a 2-sided *P* value less than 0.05 was considered statistically significant for exploratory analyses. Hazard ratios (HRs) were calculated, and a Benjamini-Hochberg (BH) correction was used to adjust for multiple comparisons. All components of the statistical analyses were performed in real-time using the TriNetX analytics platform. TriNetX is compliant with the Health Insurance Portability and Accountability Act, certified to ISO 27001:2013 standard, and maintains an information security management system to ensure protection of data. Therefore, this study was exempt from institutional review board approval.

For the primary analysis, we identified 17 497 patients who had preexisting ADs prior to treatment with anti-PD-1 or anti-PD-L1 for any of the 4 malignant neoplasm categories and 17 497 matched non-AD patients. Median duration of follow-up for the study and control populations was 1.76 years and 1.84 years, respectively. Baseline characteristics of both groups are shown in Table 1. Overall, patients with history of AD were not at statistically significantly higher risk of mortality than non-AD patients (HR = 1.03, 95% CI = 1.00 to 1.07; *P* = .05). In individual analyses, history of Hashimoto disease (HR = 0.75, 95% CI = 0.62 to 0.90; *P* = .002) and vitiligo (HR = 0.52, 95% CI = 0.34 to 0.81; *P* = .003) was statistically significantly protective of mortality after BH correction (Table 2). History of celiac disease, lichen planus, and alopecia areata was associated with a protective effect but did not meet the BH threshold for statistical significance. Conversely, patients with type 1 diabetes had statistically significant but modest increase in mortality compared with patients without AD history (HR = 1.11, 95% CI = 1.03 to 1.19; *P* = .002). Overall duration of ICI therapy was similar between AD patients and non-AD patients (7.2 vs 7.5 cycles of ICI), suggesting that history of AD did not lead to a clinically significant increase in ICI discontinuation. When stratifying by immunotherapy type and including combination immunotherapy (Supplementary Table 2, available online), history of AD was not associated with a statistically significantly increased risk of mortality in the setting of PD-L1 blockade (HR = 1.08, 95% CI = 0.98 to 1.18; *P* = .13) and combination PD-1 and CTLA-4 inhibition (HR = 1.04, 95% CI = 0.92 to 1.18; *P* = .54). There was, however, a mildly increased risk of mortality in the setting of anti-PD-1 monotherapy (HR = 1.14, 95% CI = 1.10 to 1.18; *P* < .001), which was largely driven by history of rheumatoid arthritis, inflammatory bowel disease, type 1 diabetes, and mucositis.

This is the first population-level study and largest analysis to date of the impact of underlying ADs on clinical outcomes among ICI-treated cancer patients. Overall, our results demonstrate that history of AD does not negatively impact mortality in cancer patients treated with ICI and, in some cases, is associated with a more favorable prognosis. We hypothesize that the differential effect on mortality between individual ADs observed here may relate to whether systemic corticosteroids are used in typical treatment of those diseases, as steroids are known to blunt the immune response elicited by ICIs (7,8). Hashimoto disease, vitiligo, lichen planus, celiac disease, and alopecia areata were seen here to be protective against mortality and are also

Table 1. Propensity score-matched baseline characteristics for patients treated with anti-PD-1 or anti-PD-L1 therapy

Baseline characteristic	ICI with baseline autoimmunity	ICI without baseline autoimmunity	P[a]
Total No. of patients	17 497	17 497	
No. alive	10 668	10 827	
No. deceased	6829	6670	
Mean age at index (SD), y	68.6 (10.9)	68.9 (10.6)	.001
Sex, No. (%)			
Male	8923 (51.0)	8875 (50.7)	.61
Female	8564 (48.9)	8617 (49.2)	.57
Unknown	10 (0.1)	10 (0.1)	.99
Race and ethnicity, mean No. (%)[b]			
Asian non-Hispanic	52 (0.3)	50 (0.3)	.84
Black non-Hispanic	542 (2.4)	475 (2.1)	.03
Hispanic or Latino	428 (2.4)	370 (2.1)	.04
White non-Hispanic	4854 (27.7)	4826 (27.6)	.74
Cancer type, mean No. (%)			
Digestive organs	3378 (19.3)	3402 (19.4)	.75
Bronchus and lung	11 079 (63.3)	11 118 (63.5)	.67
Melanoma of skin	3948 (22.6)	3903 (22.3)	.56
Urinary tract	3307 (18.9)	3235 (18.5)	.32
Ill-defined, other secondary, and unspecified sites[c]	13 524 (77.3)	13 617 (77.8)	.23

[a]P values were included to demonstrate that the matching algorithm has worked. Baseline characteristics were compared using χ^2 tests for categorical variables and independent-sample *t* tests for continuous variables, 2 sided. Anti-PD-1 = antiprogrammed cell death receptor-1; Anti-PD-L1 = antiprogrammed cell death ligand-1.
[b]Demographic data was not available for all patients in TriNetX. Propensity score matching was used to match patients with known demographics. Patients with unknown demographics (67.2%) were matched based on unknown status.
[c]Based on *International Classification of Diseases* code for secondary malignancy to identify patients with distant metastases of their underlying cancer.

Table 2. Association between baseline autoimmunity and survival among patients treated with anti-PD-1 or anti-PD-L1 therapy

Autoimmune diagnosis	No.	Hazard ratio (95% CI)[a]	P[b]
Myasthenia gravis	108	1.31 (0.85 to 2.02)	.21
Morphea	205	1.29 (0.93 to 1.79)	.13
Vasculitis	494	1.18 (0.97 to 1.44)	.09
Scleroderma	128	1.12 (0.77 to 1.63)	.55
Type 1 diabetes	3960	1.11 (1.03 to 1.19)	.002
Psoriasis	1827	1.07 (0.96 to 1.19)	.24
Mucositis	3181	1.04 (0.97 to 1.12)	.30
Inflammatory bowel disease	10 415	1.03 (0.99 to 1.08)	.17
Ankylosing spondylitis	164	1.02 (0.72 to 1.46)	.90
Rheumatoid arthritis	3176	1.01 (0.93 to 1.09)	.80
Autoimmune hepatitis	109	1.00 (0.64 to 1.57)	.99
Graves disease	416	0.96 (0.76 to 1.20)	.68
Multiple sclerosis	281	0.93 (0.70 to 1.23)	.60
Dermatomyositis	79	0.93 (0.55 to 1.55)	.77
Atopic dermatitis	1057	0.89 (0.77 to 1.03)	.12
Systemic lupus erythematosus	541	0.89 (0.74 to 1.06)	.19
Addison disease	920	0.88 (0.76 to 1.01)	.08
Bullous pemphigoid	59	0.86 (0.46 to 1.60)	.64
Hashimoto disease	655	0.75 (0.62 to 0.90)	.002
Celiac disease	241	0.74 (0.57 to 0.97)	.03
Lichen planus	292	0.70 (0.53 to 0.93)	.01
Alopecia areata	94	0.61 (0.39 to 0.97)	.04
Vitiligo	161	0.52 (0.34 to 0.81)	.003
Any cutaneous diagnosis	17 497	1.03 (1.00 to 1.07)	.05

[a]Hazard ratio of the impact of preexisting autoimmune disease on overall survival when compared with patients without preexisting autoimmune disease. Anti-PD-1 = antiprogrammed cell death receptor-1; Anti-PD-L1 = antiprogrammed cell death ligand-1; CI = confidence interval.

[b]Benjamini-Hochberg *P* value of statistical significance at ≤.006. Log-rank test was used to calculate *P* values, 2-sided.

diseases not commonly treated with systemic corticosteroids. On the contrary, rheumatoid arthritis, inflammatory bowel disease, and mucositis are diseases that tend to be more severe, often requiring systemic immunosuppression, which may be responsible for the increased association with mortality in subgroup analyses. Limitations of TriNetX prevented reliable analysis on the use and impact of corticosteroids on mortality in the setting of AD prior to and during ICI therapy, which should be the subject of future studies.

Our study suggests that baseline AD does not statistically significantly worsen clinical outcomes in cancer patients treated with ICI. Despite the potential for flares of baseline disease, preexisting ADs were not strongly associated with mortality. This preliminary data demonstrates that underlying ADs need not be contraindication to inclusion in clinical trials and administration of ICI. Further studies are necessary to examine interactions of ICI molecular targets with influence of AD on immunotherapy outcomes and determine the impact of systemic immunosuppressive agents on mortality in the setting of AD.

Funding

Not Applicable.

Notes

Role of the funder: Not applicable.

Disclosures: The authors have no disclosures to report.

Author contributions: Conceptualization: KT, YRS. Methodology: KT, BCT, YRS. Formal Analysis: KT, BCT, YRS. Investigation: KT, BCT, YRS. Resources: SGK, YRS. Data Curation: KT, YRS. Writing-Original Draft: KT, YRS. Writing-Review & Editing: All authors. Visualization: KT, YRS. Supervision: SGK, YRS. Funding Acquisition: SGK, YRS.

Data Availability

The authors confirm that the data supporting the findings of this study are available within the article and/or its supplementary materials (available online).

References

1. Twomey JD, Zhang B. Cancer immunotherapy update: FDA-approved checkpoint inhibitors and companion diagnostics. *AAPS J*. 2021;23(2):39.
2. Rakshit S, Molina JR. Immunotherapy in patients with autoimmune disease. *J Thorac Dis*. 2020;12(11):7032–7038.
3. Zhou X, Yao Z, Yang H, Liang N, Zhang X, Zhang F. Are immune-related adverse events associated with the efficacy of immune checkpoint inhibitors in patients with cancer? A systematic review and meta-analysis. *BMC Med*. 2020;18(1):87.
4. Park R, Lopes L, Saeed A. Anti-PD-1/L1-associated immune-related adverse events as harbinger of favorable clinical outcome: systematic review and meta-analysis. *Clin Transl Oncol*. 2021;23(1):100–109.
5. Tang K, Seo J, Tiu BC, et al. Association of cutaneous immune-related adverse events with increased survival in patients treated with anti-programmed cell death 1 and anti-programmed cell death ligand 1 therapy. *JAMA Dermatol*. 2022;158(2):189.
6. Baik CS, Rubin EH, Forde PM, et al. Immuno-oncology clinical trial design: limitations, challenges, and opportunities. *Clin Cancer Res*. 2017;23(17):4992–5002.
7. Riudavets M, Mosquera J, Garcia-Campelo R, et al. Immune-related adverse events and corticosteroid use for cancer-related symptoms are associated with efficacy in patients with non-small cell lung cancer receiving anti-PD-(L)1 blockade agents. *Front Oncol*. 2020;10:1677.
8. Bai X, Hu J, Betof Warner A, et al. Early use of high-dose-glucocorticoid for the management of irAE is associated with poorer survival in patients with advanced melanoma treated with anti-PD-1 monotherapy. *Clin Cancer Res*. 2021;27(21):5993–6000.