JAMA Dermatology | Brief Report

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

Kimberly Tang, BA; Jayhyun Seo, BA; Bruce C. Tiu, BS; Thomas K. Le, BS; Vartan Pahalyants, MD; Neel S. Raval, BS; Pearl O. Ugwu-Dike, BS; Leyre Zubiri, MD, PhD; Vivek Naranbhai, PhD; Mary Carrington, PhD; Alexander Gusev, PhD; Kerry L. Reynolds, MD; Nicole R. LeBoeuf, MD, MPH; Maryam M. Asgari, MD, MPH; Shawn G. Kwatra, MD; Yevgeniy R. Semenov, MD, MA

IMPORTANCE Despite the efficacy of immune checkpoint inhibitors (ICIs), cutaneous immune-related adverse events (cirAEs) occur in 20% to 40% of all treated patients. To our knowledge, little is known about the predictive value of these cutaneous eruptions and their subtypes regarding cancer survival.

OBJECTIVE To determine the association of developing cirAEs following treatment with anti–programmed cell death 1 (PD-1) or anti–programmed cell death ligand 1 (PD-L1) therapy with patient survival.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study used data from the TriNetX Diamond Network, a database of health records and claims data from more than 200 million US and European patients, to conduct a population-level cohort analysis. The study included 7008 eligible patients who developed cirAEs after treatment with anti–PD-1 or anti–PD-L1 therapy for malignant neoplasms of digestive organs, bronchus or lung, melanoma of skin, and urinary tract who were identified through the TriNetX Diamond Network along with 7008 matched controls.

EXPOSURES Development of cirAEs within 6 months following anti–PD-1 or anti–PD-L1 therapy.

MAIN OUTCOMES AND MEASURES A 6-month analysis using a Cox proportional hazards model was performed to determine the association of cirAEs with overall survival after adjusting for demographic characteristics, cancer type, and cancer stage.

RESULTS A total of 7008 patients (3036 women [43.3%]; mean [SD] age, 68.2 [11.2] years) were matched to 7008 (3044 women [43.4%]; mean [SD] age, 68.3 [11.1] years) controls. Pruritus (hazard ratio [HR], 0.695; 95% CI, 0.602-0.803; $P < .001$), drug eruption (HR, 0.755; 95% CI, 0.635-0.897; $P = .001$), xerosis (HR, 0.626; 95% CI, 0.469-0.834; $P = .001$), nonspecific rashes (HR, 0.704; 95% CI, 0.634-0.781; $P < .001$), and appearance of any cirAE (HR, 0.778; 95% CI, 0.726-0.834; $P < .001$) were significantly protective of mortality using a Benjamini-Hochberg correction with a significance level of .05. Additionally, psoriasis (HR, 0.703; 95% CI, 0.497-0.994; $P = .045$) and lichen planus/lichenoid dermatitis (HR, 0.511; 95% CI, 0.279-0.939; $P = .03$) were significant. Eczematous dermatitis (HR, 0.612; 95% CI, 0.314-1.195), vitiligo (HR, 0.534; 95% CI, 0.254-1.123), bullous pemphigoid (HR, 0.524; 95% CI, 0.140-1.956), and Grover disease (HR, 0.468; 95% CI, 0.115-1.898) were all associated with strong protective clinical effects.

CONCLUSIONS AND RELEVANCE The results of this cohort study suggest that the development of cirAEs is strongly associated with response to ICI therapy and patient survival.

JAMA Dermatol. 2022;158(2):189-193. doi:10.1001/jamadermatol.2021.5476
Published online January 12, 2022.

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Yevgeniy R. Semenov, MD, MA, Department of Dermatology, Massachusetts General Hospital, Harvard Medical School, 40 Blossom St, Bartlett Hall 6R, Room 626, Boston, MA 02114 (ysemenov@mgh.harvard.edu).

Immune checkpoint inhibitors (ICIs) have revolutionized cancer therapy during the last decade. As of 2019, up to 230 000 patients were eligible for treatment with ICI therapy annually in the US alone.[1] Despite the efficacy of ICIs, immune-related adverse events (irAEs) occur in more than a third of all treated patients and are associated with lasting morbidity, mortality, and impaired quality of life.[2-4] Cutaneous irAEs (cirAEs) are the most frequently reported toxic effects, occurring in 20% to 40% of all treated patients. Although multiple recent reports have investigated the prognostic significance of irAEs regarding cancer outcomes, to our knowledge, little is known about the specific association of cirAEs and their subtypes with cancer survival.[5,6] In this cohort study, we present what is to our knowledge the first population-level study examining the association of cirAE development following ICI therapy with mortality for patients with cancer.

Key Points

Question What is the association of cutaneous immune-related adverse events (cirAEs) with mortality in treatment with immune checkpoint inhibitor (ICI) therapy for patients with cancer?

Findings In this retrospective cohort study of 7008 patients with cancer who developed cirAEs after treatment with anti–programmed cell death 1 or anti–programmed cell death ligand 1 therapy and 7008 matched controls, a 6-month analysis suggested that the development of pruritus, drug eruption, xerosis, nonspecific rashes, and any cirAE as a group was significantly protective of mortality.

Meaning The study results suggest that cirAE development after ICI treatment initiation is strongly associated with response to ICI therapy and patient survival.

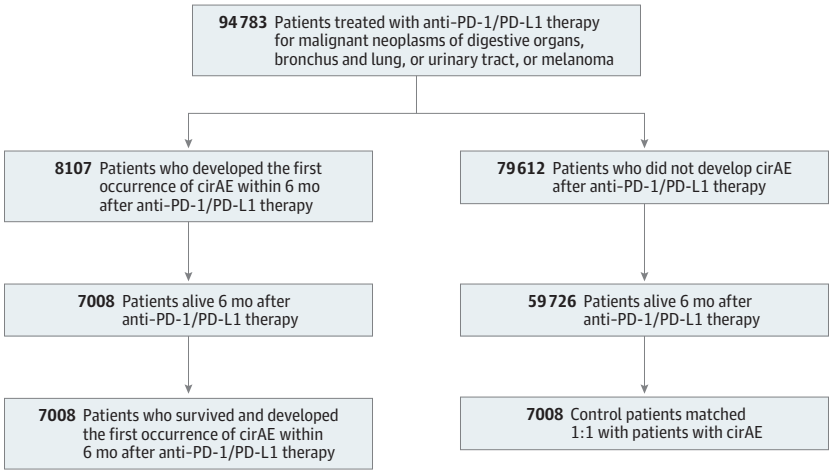
Methods

For this retrospective cohort analysis, we identified eligible patients from the TriNetX Diamond network, which is a global health research network that provides access to electronic medical records for more than 200 million US and European patients. Study participants were identified by a Prescription for Electronic Drug Information Exchange (RxNorm) record of treatment with anti-programmed cell death 1 (PD-1; cemiplimab, nivolumab, or pembrolizumab) or anti-programmed cell death ligand 1 (PD-L1; atezolizumab, avelumab, or durvalumab) therapy. Patients treated with an anti-cytotoxic T-lymphocyte-associated antigen 4 inhibitor (ipilimumab) were excluded to minimize confounding from combination immunotherapy. For the primary analyses, we included participants with the 4 most common indications for ICI therapy, which were record of any of the following *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)* malignant neoplasm diagnoses: (1) C34, bronchus and lung; (2) C15-26, digestive organs; (3) C43, melanoma; and (4) C64-68, urinary tract. Sensitivity analyses were subsequently performed across all ICI recipients independent of underlying cancer type. Identification of the cutaneous diagnoses of interest for this study were derived from published literature and expert opinion.[7,8] *Cutaneous immune-related adverse events* were defined as a new diagnosis of any of the included cutaneous eruptions within 6 months of the first instance of ICI administration, which is consistent with prior reports on peak incidence of cirAEs.[7] Patients who developed cirAEs were then age-, sex-, race-, and cancer-matched to non-cirAE controls using 1:1 propensity score matching. A greedy nearest neighbor matching algorithm with a caliper of 0.1 pooled SDs was used. We additionally matched the 2 groups based on the presence of distant metastases using the secondary cancer *ICD-10* code to control for cancer stage. The flow diagram for this study is presented in the **Figure**. The index event for patients and controls was defined as the first day of ICI treatment. Because cirAE development is a time-dependent event, it competes with the risk of mortality. This introduced potential guarantee-time bias to the study (ie, a patient has to be alive long enough to be able to develop a cirAE). An effective way to control for this type of bias is to use a landmark study design by excluding any participants who developed the outcome of interest (mortality) before a specific landmark time. In this case, a 6-month landmark analysis using a Cox proportional hazards model was performed to determine the prognostic association of cirAEs with overall survival. Patient mortality was determined by a record of death starting at 6 months following ICI administration until the end of study follow-up. For all performed analyses, we excluded patients with mortality before the 6-month landmark point. Hazard ratios (HRs) and SDs were calculated to investigate the association of cirAEs with mortality. TriNetX complies with the US Health Insurance Portability and Accountability Act (HIPAA), is certified to the ISO 27001:2013 standard, and maintains an Information Security Management System to ensure the protection of the health care data it has access to and meet the requirements of the HIPAA Security Rule. Data sets generated by the TriNetX Platform are deidentified as per the deidentification standard defined in Section §164.514(a) of the HIPAA Privacy Rule. As such, this study was exempt from institutional review board approval. A 2-sided *P* value less than .05 was considered statistically significant for exploratory analyses. A Benjamini-Hochberg (BH) correction was used to adjust for multiple comparisons when analyzing individual cirAE morphologies, with the BH *P* value of significance set at .001. All statistical analyses were performed in real-time using the TriNetX analytics platform.

Results

We identified 7008 patients who developed cirAEs after treatment with anti-PD-1 or anti-PD-L1 therapy for any of the 4 identified malignant neoplasms and 7008 matched controls. The median survival (IQR) for the cohort group was 1278 days (558-not reached) and 1024 days (455-not reached) for the control group. Baseline characteristics of the study and matched control populations are shown in **Table 1**. After a 6-month landmark analysis, pruritus (HR, 0.695; 95% CI, 0.602-0.803; $P < .001$), drug eruption (HR, 0.755; 95% CI,

Figure. Study Flow Diagram



cirAE indicates cutaneous immune-related adverse events; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1.

Table 1. Propensity Score-Matched Baseline Characteristics for Patients Treated With Anti–PD-1 or Anti–PD-L1 Therapy

Characteristic	ICI, mean (%)		*P* value
	Without cirAE (n = 7008)	With cirAE (n = 7008)	
Age at index, mean (SD), y	68.2 (11.2)	68.3 (11.1)	.79
Sex, No. (%)			
Male	3972 (56.7)	3961 (56.5)	.85
Female	3036 (43.3)	3044 (43.4)	.89
Unknown	0	10 (0.14)	.002
Race and ethnicity, No. (%)[a]			
Asian non-Hispanic	17 (0.2)	10 (0.1)	.18
Black non-Hispanic	129 (1.8)	116 (1.7)	.40
Hispanic or Latino	111 (1.6)	77 (1.1)	.01
White non-Hispanic	1549 (22.1)	1571 (22.4)	.62
Cancer type, No. (%)			
Digestive organs	956 (13.6)	937 (13.4)	.64
Bronchus and lung	3993 (56.9)	3996 (57.0)	.96
Melanoma of skin	1300 (18.6)	1288 (18.4)	.79
Urinary tract	1306 (18.6)	1244 (17.8)	.17
Ill-defined, other secondary and unspecified sites[b]	5399 (77.0)	5396 (77.0)	.95

Abbreviations: cirAE, cutaneous immune-related adverse event; ICI, immune checkpoint inhibitor; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1.

[a] Unknown race and ethnicity comprised 74.2% of the study population.

[b] Based on *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)* code for secondary cancer to identify patients with distant metastases of their underlying cancer.

0.635-0.897; *P* = .001), xerosis (HR, 0.626; 95% CI, 0.469-0.834; *P* = .001), nonspecific rashes (HR, 0.704; 95% CI, 0.634-0.781; *P* < .001), and appearance of any cirAE (HR, 0.778; 95% CI, 0.726-0.834; *P* < .001) were associated with significant protection against mortality using the BH correction for multiple comparisons with a false discovery rate set at 0.05 (BH adjusted *P* value of significance = .001) (**Table 2**). Psoriasis (HR, 0.703; 95% CI, 0.497-0.994; *P* = .045) and lichen planus/lichenoid dermatitis (HR, 0.511; 95% CI, 0.279-0.939; *P* = .03) were also significant, but did not meet the BH correction for multiple comparisons. Although not reaching statistical significance, eczematous dermatitis (HR, 0.612; 95% CI, 0.314-1.195), vitiligo (HR, 0.534; 95% CI, 0.254-1.123), bullous pemphigoid (HR, 0.524; 95% CI, 0.140-1.956), and Grover disease (HR, 0.468; 95% CI, 0.115-1.898) were all associated with a protective trend against mortality. However, hyperhidrosis (HR, 1.381; 95% CI, 0.961-1.985; *P* = .08) and mucositis (HR, 1.161; 95% CI, 0.920-1.466; *P* = .21) did not show positive clinical protection. To explore the association of landmark time with mortality, a sensitivity analysis was performed for cirAE onset within 3 months (HR, 0.759; 95% CI, 0.703-0.818; *P* < .001), 9 months (HR, 0.84; 95% CI, 0.781-0.903; *P* < .001), and 1 year of ICI initiation (HR, 0.829; 95% CI, 0.765-0.898; *P* < .001). A separate sensitivity analysis expanding the cohort to include all cancer types treated with ICI yielded similar results as the primary analysis, with additional statistical significance reached for ICI-induced psoriasis (eTable in the Supplement).

Table 2. Association Between Cutaneous Eruptions and Survival Among Patients Treated With Anti–PD-1 or Anti–PD-L1 Therapy

Cutaneous diagnosis[a]	No.	Hazard ratio	*P* value[b]
Hyperhidrosis	281	1.381	.08
Mucositis	563	1.161	.21
Dermatomyositis	105	0.93	.79
Maculopapular eruption	230	0.845	.36
Erythroderma	247	0.769	.17
Drug eruption and nonspecific drug reaction	1075	0.755	.001
Hyperkeratosis	39	0.707	.49
Rash and other nonspecific eruption	3163	0.704	<.001
Psoriasis	299	0.703	.05
Pruritus	1694	0.695	<.001
Xerostomia	163	0.671	.13
Xerosis	441	0.626	.001
Eczema and atopic dermatitis	72	0.612	.15
Vitiligo	100	0.534	.09
Bullous pemphigoid	32	0.524	.33
Lichen planus	97	0.511	.03
Grover disease	18	0.468	.28
Any cutaneous diagnosis	7008	0.778	<.001

Abbreviations: PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1.

[a] Cutaneous diagnoses were identified based on published literature and expert opinion; each row represents a separate Cox proportional hazards model adjusted for demographic characteristics, cancer type, and cancer stage.

[b] Benjamini-Hochberg *P* value of significance = .001.

Discussion

To our knowledge, this is the first population-level study and largest analysis to date of the association of cirAEs with clinical outcomes among patients with advanced cancer. The results suggest that cirAE development after ICI initiation is strongly associated with response to ICI therapy and patient survival. With the exception of mucositis and hyperhidrosis, there was a clinically protective effect of cirAEs across all individual morphologies investigated in this study.

Limitations

The lack of achieved statistical significance among some dermatoses is likely because of the insufficient sample size of rarer diagnoses and few observed deaths in these subgroups during the study follow-up. The use of *ICD-10* codes to identify cirAEs in this study may present a limitation as we cannot determine with certainty that these cutaneous eruptions are cirAEs and not normal occurrences. Additionally, inherent heterogeneity in population-level databases, such as TriNetX, may result in inconsistencies in data recording across various included institutions in the US and Europe. However, similar approaches using claims data have yielded overall consistent estimates of cirAE incidence and prevalence compared with manually curated institutional registries.[7,9]

Conclusions

This cohort study suggests that cirAE development is a favorable clinical indicator and warrants further investigation into its underlying immunopathogenesis, which may provide further insights into immunotherapy response. Additional studies are needed to assess the association of cirAE management with survival outcomes and whether ICI therapy interruption or discontinuation in the setting of these toxic effects is clinically warranted or associated with overall survival.

ARTICLE INFORMATION

Accepted for Publication: November 16, 2021.

Published Online: January 12, 2022. doi:10.1001/jamadermatol.2021.5476

Author Affiliations: Massachusetts General Hospital, Department of Dermatology, Boston (Tang, Seo, Tiu, Pahalyants, Raval, Ugwu-Dike, Asgari, Semenov); Harvard Medical School, Department of Dermatology, Boston, Massachusetts (Tiu, Pahalyants, Raval, Asgari, Semenov); Johns Hopkins University, Department of Dermatology, Baltimore, Maryland (Le, Kwatra); Washington University School of Medicine, St Louis, Missouri (Raval); Massachusetts General Hospital, Department of Medicine, Division of Oncology, Boston (Zubiri, Naranbhai, Reynolds); Basic Science Program, Frederick National Laboratory for Cancer Research, National Cancer Institute, Frederick, Maryland (Carrington); Ragon Institute of Massachusetts General Hospital, Massachusetts Institute of Technology, and Harvard University, Cambridge (Carrington); Laboratory of Integrative Cancer Immunology, Center for Cancer Research, National Cancer Institute, Bethesda, Maryland (Carrington); Dana Farber Cancer Institute, Department of Medicine, Boston, Massachusetts (Gusev); Dana Farber Cancer Institute, Department of Dermatology, Boston, Massachusetts (LeBoeuf); Department of Population Medicine, Harvard Medical School, Boston, Massachusetts (Asgari).

Author Contributions: Mss Tang and Seo had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Mss Tang and Seo are co–first authors, and Drs Kwatra and Semenov are co–senior authors.
Concept and design: Tang, Seo, Le, Pahalyants, Ugwu-Dike, Reynolds, Kwatra, Semenov.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Tang, Seo, Kwatra, Semenov.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Tang, Seo, Tiu, Gusev, Semenov.
Administrative, technical, or material support: Seo, Tiu, Le, Pahalyants, Raval, Zubiri, Naranbhai, LeBoeuf, Semenov.
Supervision: Tiu, Raval, Zubiri, Asgari, Kwatra, Semenov.

Conflict of Interest Disclosures: Dr Zubiri reported personal fees from Merck outside the submitted work. Dr LeBoeuf reported personal fees from Bayer, Synox, Seattle Genetics, Sanofi, and Silverback Therapeutics outside the submitted work. Dr Asgari reported grants from Pfizer outside the submitted work. Dr Semenov reported personal fees from Castle Biosciences and Incyte Corporation outside of the submitted work. No other disclosures were reported.

REFERENCES

1. Haslam A, Prasad V. Estimation of the percentage of US patients with cancer who are eligible for and respond to checkpoint inhibitor immunotherapy drugs. *JAMA Netw Open*. 2019;2(5):e192535. doi:10.1001/jamanetworkopen.2019.2535

2. Puzanov I, Diab A, Abdallah K, et al; Society for Immunotherapy of Cancer Toxicity Management Working Group. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. *J Immunother Cancer*. 2017;5(1):95. doi:10.1186/s40425-017-0300-z

3. Brahmer JR, Lacchetti C, Schneider BJ, et al; National Comprehensive Cancer Network. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol*. 2018;36(17):1714-1768. doi:10.1200/JCO.2017.77.6385

4. Phillips GS, Wu J, Hellmann MD, et al. Treatment outcomes of immune-related cutaneous adverse events. *J Clin Oncol*. 2019;37(30):2746-2758. doi:10.1200/JCO.18.02141

5. Petrelli F, Grizzi G, Ghidini M, et al. Immune-related adverse events and survival in solid tumors treated with immune checkpoint inhibitors: a systematic review and meta-analysis. *J Immunother*. 2020;43(1):1-7. doi:10.1097/CJI.0000000000000300

6. Street S, Chute D, Strohbehn I, et al. The positive effect of immune checkpoint inhibitor-induced thyroiditis on overall survival accounting for immortal time bias: a retrospective cohort study of 6596 patients. *Ann Oncol*. 2021;32(8):1050-1051. doi:10.1016/j.annonc.2021.05.357

7. Wongvibulsin S, Pahalyants V, Kalinich M, et al. Epidemiology and risk factors for the development of cutaneous toxicities in patients treated with immune-checkpoint inhibitors: a United States population-level analysis. *J Am Acad Dermatol*. Published online April 2, 2021. doi:10.1016/j.jaad.2021.03.094

8. Kalinich M, Murphy W, Wongvibulsin S, et al. Prediction of severe immune-related adverse events requiring hospital admission in patients on immune checkpoint inhibitors: study of a population level insurance claims database from the USA. *J Immunother Cancer*. 2021;9(3):e001935. doi:10.1136/jitc-2020-001935

9. Thompson LL, Krasnow NA, Chang MS, et al. Patterns of cutaneous and noncutaneous immune-related adverse events among patients with advanced cancer. *JAMA Dermatol*. 2021;157(5):577-582. doi:10.1001/jamadermatol.2021.0326