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Conflicts of interest

McSweeny is a sub-investigator and Tziotzios is a principal and (national) chief investigator on the Pfizer-funded ALLEGRO clinical trial in alopecia areata. Dr Tziotzios provides consulting services to Pfizer and has received speaker fees from Leo Pharma. Drs Kloczko, Chadha, Sarkany, Fassihi, and McGrath have no conflicts of interest to declare.

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Tumor-infiltrating lymphocytes as a predictive biomarker of cutaneous immune-related adverse events after immune checkpoint blockade in patients with advanced melanoma

To the Editor: Predictive clinical biomarkers that can be used to monitor immunotherapeutic responses after immune checkpoint inhibitor (ICI) therapy are becoming increasingly necessary for effectively planning cancer treatment.[1] Tumor-infiltrating lymphocytes (TIL) have been identified as a favorable prognostic indicator in melanoma,[2-5] though little is known about TIL as a potential biomarker for cutaneous or non-cutaneous immune-related adverse event (cirAE/irAE) development. We thus sought to examine the association between TIL status on primary melanoma biopsy and cirAE or irAE development among a cohort of melanoma patients receiving ICIs.

Using billing codes, we screened patients with melanoma initiating ICI therapy at our institution between January 1, 2016 and June 29, 2021 who developed possible cirAEs and confirmed cirAE status through manual chart review. Demographics, clinical history, TIL status on primary biopsy, and cirAE/irAE history was abstracted. The same variables were collected for melanoma patients receiving ICIs between January 1, 2016 and June 29, 2021 without cirAEs. TIL status was abstracted by the study team from pathology reports and categorized into brisk, non-brisk, or absent. Multivariable logistic regression was used to examine associations between TIL presence or absence and cirAE/irAE characteristics. Additional methodological details are discussed in the Supplemental File 1, available via Mendeley at https://data.mendeley.com/datasets/bp7f6gn8ks/1.

Among patients with melanoma with cirAEs (n = 123, median age: 66, 33.3% female), 4 (3.3%) had brisk TIL, 98 (79.7%) had non-brisk TIL, and 21 (17.1%) had absent TIL. In the non-cirAE group (n = 87, median age: 63, 26.4% female), 2 (2.3%) had brisk TIL, 65 (74.7%) had non-brisk TIL, and 20 (23.0%) had absent TIL (Table I). Multivariable analysis demonstrated no significant associations between TIL status and cirAE/irAE development or cirAE severity. When examining cirAE subtypes, TIL presence at time of primary biopsy showed a trend toward decreased later incidence of vitiligo (odds ratio: 0.21, 95% CI: 0.04-1.22, P = .081), though the association did not reach statistical significance (Table II).

In this study, we found no significant associations between TIL status at time of primary biopsy and cirAE development. The presence of TIL is thought to be a positive prognostic factor in patients with melanoma, though results may depend on the population of individual lymphocyte subsets comprising tumor infiltrates.[2,5] Our negative results may thus be a consequence of having more T cells with limited prognostic impact in the setting of immune-checkpoint blockade, such as $FOXP3^+$ T-regs.[5] These regulatory lymphocyte subsets may have also contributed to less immune activation and autoreactivity after ICI therapy, potentially explaining the trend towards a lower incidence of vitiligo. Although difficult to quantify, the fact that our cohort of patients had advanced melanoma necessitating ICI therapy may reflect the low incidence of brisk TIL in the overall cohort, and by extension, decreased anti-tumor T-cell activity at baseline.

Study limitations include the small sample size, notably of patients with brisk TIL; single-center retrospective design; and inability to examine specific lymphocyte subtypes, limiting our ability to examine more granular associations related to tumor microenvironment. Nonetheless, our findings represent an important exploratory analysis examining potential associations between TIL and cirAE risk. Larger studies are needed to better elucidate the predictive role of TIL and other prognostic tumor-related biomarkers and the development of ICI-mediated immunotoxicities.

Table I. Demographics and clinical characteristics of patients with melanoma by cutaneous immune-related adverse event status ($N = 210$)

Characteristic	Patients with cirAE (N = 123)*	Patients without cirAE (N = 87)*	P value
Demographics			
Age, years—median (IQR)†	66 (56-75)	63 (56-75)	.620
Female sex—no. (%)†	41 (33.3)	23 (26.4)	.361
Melanoma history			
Cancer stage—median (IQR)‡	3 (3-4)	3 (3-4)	**.002**
TIL status at primary biopsy—no. (%)			-
Brisk	4 (3.3)	2 (2.3)	
Non-brisk	98 (79.7)	65 (74.7)	
Absent	21 (17.1)	20 (23.0)	
ICI regimen—no. (%)			.107
Anti-PD-1/PD-L1	92 (74.8)	75 (86.2)	
Anti-CTLA-4	8 (6.5)	4 (4.6)	
Anti-PD-1/PD-L1 and Anti-CTLA-4	23 (18.7)	8 (9.2)	
cirAE and irAE characteristics			
Time to first cirAE, days—median (IQR)‡	42 (16-119)	-	-
Peak cirAE CTCAE v5.0 severity—median (IQR)§	1 (1-2)	-	-
Morphology of first cirAE—no. (%)			
Maculopapular or papulopustular, NOS‖	73 (59.3)	-	-
Eczematous	6 (4.9)	-	-
Lichenoid	4 (3.3)	-	-
Isolated pruritus	21 (17.1)	-	-
Psoriasiform	4 (3.3)	-	-
Vitiligo	7 (5.7)	-	-
Other¶	8 (6.5)	-	-
Multiple cirAE—no. (%)	27 (22.0)	-	-
Any non-cutaneous irAE—no. (%)	86 (69.9)	37 (42.5)	**<.001**
Multiple non-cutaneous irAE—no. (%)	38 (30.9)	10 (11.5)	**.001**

Values in boldface indicate statistical significance ($P < .05$).

cirAE, Cutaneous immune-related adverse event; *CTCAE*, common terminology criteria for adverse events; *CTLA-4*, cytotoxic T-lymphocyte associated protein 4; *DRESS*, drug reaction with eosinophilia and systemic symptoms; *ICI*, immune checkpoint inhibitor; *irAE*, immune-related adverse event; *NOS*, not otherwise specified; *PD-1*, programmed death-1; *PDL-1*, programmed-death ligand 1; *TIL*, tumor-infiltrating lymphocyte.

*Data are presented as number (percentage) of patients unless otherwise indicated.

†Age, sex, and cancer stage were determined for the date of first ICI therapy dose.

‡Denotes time interval between start of first ICI therapy and date of development of first cirAE.

§Peak cirAE CTCAE v5.0 grade represents the highest grade reported by any evaluating physician based on published guidelines by the US National Cancer Institute.

‖Includes maculopapular and papulopustular skin eruptions, as well as non-specific rash without further morphologic data available or specified (rash NOS).

¶Other morphologies of first cirAE include: erythema multiforme (1), bullous eruption (2), DRESS (1), drug hypersensitivity (1), macular erythema (1), morbilliform (1), urticarial (1).

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Table II. Multivariate outcomes of cutaneous immune-related adverse event characteristics and immune-related adverse event development based on tumor-infiltrating lymphocytes status at time of primary melanoma diagnosis

Characteristic [present (brisk or non-brisk) vs absent TIL]	OR* (95% CI)	*P* value
cirAE development (all subtypes)	1.57 (0.74-3.33)	.240
cirAE development (subtype: vitiligo)	0.21 (0.04-1.22)	.081
cirAE severity		
Grade 1-2	1.23 (0.58-2.62)	.584
Grade 3-4	-	-
Non-cutaneous irAE development (all organ systems)	0.66 (0.32-1.36)	.259

All models included age at the start of ICI regimen, sex, and additional clinical features significant to $P < .10$ as covariates, with details as follows for each model.
- cirAE development (all subtypes and subtype: vitiligo): age, sex, cancer stage, any irAE development.
- cirAE severity: age, sex, cancer stage, any irAE development.
- Non-cutaneous irAE development (all non-skin organ systems): age, sex, cancer stage, cirAE development.
cirAE, Cutaneous immune-related adverse event; *irAE*, immune-related adverse event; *OR*, odds ratio; *TIL*, tumor-infiltrating lymphocytes.
*Binomial logistic regression was used for all models.

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Key words: cutaneous immune-related adverse event; dermatologic toxicity; immune checkpoint inhibitor; immunotherapy; melanoma; prognostic biomarkers; tumor-infiltrating lymphocytes.

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Conflicts of interest

Dr Chen has received consulting fees from Pfizer, Novartis, and Scholar Rock. Dr Stephens; Authors Asdourian, Jacoby, and Shah; and Drs Thompson, Otto, Semenov, Reynolds, Sullivan, and Foreman have no conflicts of interest to declare.

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Changes in skin cancer screening rates in the United States from 2005 to 2015

To the Editor: Despite the rising incidence of melanoma in the United States,[1] the current US Preventive Services Task Force guidelines state there is insufficient evidence to recommend population-based skin cancer screening by total body skin examination (TBSE). This results in screening being driven by patient request or physician suggestion and potentially a discordance between who is screened and who may benefit most from screening. Increased diagnostic scrutiny, including skin cancer screening, has been implicated as a potential cause of the increase in melanoma incidence.[1] Measuring screening rates using claims data is challenging as skin cancer screening is not a billable service.

To better estimate trends in population-based skin cancer screening (vs surveillance in high-risk patients) we evaluated the rates of self-reported TBSEs within the previous 5 years among participants 18 years or older without a personal history of skin cancer (melanoma or non-melanoma skin cancer) or a first-degree relative with a history of melanoma in 2005 (28,233 participants), 2010 (24,113 participants), and 2015 (29,902 participants) (Table I) utilizing the National Health Interview Survey data. Subpopulation logistic regression models were performed utilizing STATA/MP 17.0 to explore changes in TBSE rates in 2005 versus 2015.

The weighted prevalence of participants reporting having a TBSE within the last 5 years increased from 4.8% in 2005 to 6.1% in 2015 (adjusted odds ratio, 1.09; 95% CI, 1.04-1.14; $P < .001$). Non-Hispanic Whites were the only race/ethnicity with