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Characterization Of Cutaneous Immune-Related Adverse Events Due To Immune Checkpoint Inhibitors

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Characterization of cutaneous immune-related adverse events due to immune checkpoint inhibitors

A retrospective analysis performed at the Smilow Cancer Center Oncodermatology Clinic

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Abstract

Immune checkpoint inhibitors (ICI) have been associated with a multitude of immune-related adverse events (irAE), which affect multiple organ systems in the setting of increased immune activation. Cutaneous immune-related adverse events (cirAE) are among the most common irAE, occurring in up to 50% of patients treated with an ICI. The most common cirAE are maculopapular eruption, pruritus (with or without primary cutaneous eruption), lichenoid dermatitis, eczematous dermatitis, psoriasiform eruption, and vitiligo. cirAE are of concern to oncologists and dermatologists alike, as cirAE can necessitate interruption or discontinuation of life-prolonging therapy. There is a paucity of data regarding cirAE in specific patient populations, including patients with skin of color (SOC) and patients with a prior dermatologic diagnosis.

Our primary aim was to characterize the spectrum of ICI-induced cirAE diagnosed and treated by the Yale Oncodermatology Clinic. Our second aim was to characterize cirAE among patients with SOC who were diagnosed and treated by the Yale Oncodermatology Clinic. Our third aim was to characterize cirAE among patients with a history of psoriasis or eczema who were diagnosed and treated by the Yale Oncodermatology Clinic.

This retrospective case series included all patients treated with an ICI who were referred to the Yale Oncodermatology Clinic for cirAE. Patients seen for any concern other than cirAE were not included within this cohort. Data collection was performed manually due to lack of appropriate International Classification of Diseases 10th Revision (ICD-10)

codes for cirAE. All data was entered into a secure REDCap database. Descriptive analyses and chi-square tests were performed using SPSS Statistics.

Aim 1: 287 patients were treated by the Yale Oncodermatology Clinic for cirAE. Within this cohort, mean age was 66 (SD 11), 53% of patients were male, and the most common oncologic diagnoses were non-small cell lung cancer (33%), melanoma (22%), and renal cell carcinoma (8.7%). 338 cirAE were reported, of which the most frequently observed were lichenoid dermatitis (18%) and eczematous dermatitis (15%).

Aim 2: Of patients treated by the Yale Oncodermatology Clinic, 31 were included in the SOC cohort based on demographic data. The most common cirAE observed in this cohort were lichenoid dermatitis (22%) and eczematous dermatitis (22%).

Aim 3: Of patients treated by the Yale Oncodermatology Clinic, 11 had a history of eczema and 18 had a history of psoriasis. Those with a history of eczema were significantly more likely to develop eczematous dermatitis than controls (43%, versus 12%) and those with a history of psoriasis were significantly more likely to develop psoriasiform dermatitis than controls (56%, versus 6.1%).

As ICI become a cornerstone of oncologic therapy, it is critical that the presentation and treatment of cirAE in various patient populations are integrated into dermatologic training.

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Introduction

Immunotherapy is a class of cancer therapeutics that targets malignant neoplasms through activation of the innate and/or adaptive immune system.[1] Subtypes of immunotherapy include immune checkpoint inhibitors (ICI), adoptive cell transfer, oncolytic virus therapies, cancer vaccines, and cytokine therapies.[1] ICI, monoclonal antibodies (mAb) that induce the adaptive immune system to mount an antitumor response, have had a particularly profound impact on the field of oncology.[1]

A "two-signal" model has been used to describe T cell activation, which requires multiple stimulatory signals resulting from the interaction of a T cell with an antigen presenting cell (APC).[2] The initial signal results from interaction between the T cell receptor (TCR) and major histocompatibility complex (MHC) of an APC.[2] The second signal results from the interaction of the costimulatory CD28 receptor on the T cell surface with a CD80 (B7) or CD86 molecule on the APC.[2] However, cytotoxic T-lymphocyte antigen 4 (CTLA-4) receptors on the T cell surface are also capable of binding CD80 and CD86, leading to inhibition of T and B cell activation.[2] Programmed cell death protein 1 (PD-1) is a separate receptor present on T cells, as well as other immune cells of both the innate and adaptive immune system.[2] PD-1 binds programmed cell death ligand 1 (PD-L1) on parenchymal cells, which in turn inhibits the necessary stimulation signals between T cells and APC.[2] These molecules, termed "immune checkpoint proteins", function to prevent immune overactivation and autoimmunity.[3,4] However, in the setting of malignancy, persistent activation of CD8+ T cells leads to upregulation of inhibitory receptors including but not limited to CTLA-4 and PD-1, with a resulting loss of effector

functions.[3] The effect of the interaction of PD-1 and its ligand are of particular interest, as tumor cells often express PD-L1.[3] This shift in CD8+ T cell phenotype, described as "exhaustion", leads to loss of the antitumor response and allows for tumors to evade T cell immunosurveillance.[1,3]

ICI are comprised of mAb that target CTLA-4, PD-1, or PD-L1. These mAb antagonize immune checkpoint proteins, thereby activating the antitumor response of the adaptive immune system.[1] The potential benefit of immune checkpoint protein inhibition was first demonstrated in 1996 by an in vivo study demonstrating that administration of antibodies to CTLA-4 led to tumor rejection, including rejection of previously established tumors.[5] Between 2004 and 2008, a randomized, double-blind, phase 3 trial (n=676) compared the CTLA-4 inhibitor ipilimumab with and without a glycoprotein 100 peptide vaccine to the glycoprotein 100 peptide vaccine alone for treatment of unresectable stage III or IV melanoma. All patients enrolled had experienced disease progression while undergoing prior treatment for metastases.[6] Median overall survival was 10.1 months among patients receiving ipilimumab and 10.0 months among patients receiving ipilimumab plus the glycoprotein 100 vaccine, compared to 6.4 months among patients receiving the vaccine alone.[6] Of note, grade 3 and 4 immune-related adverse events (irAE) were reported in 10 to 15% of patients treated with ipilimumab versus 3% of patients treated with the vaccine alone.[6] This study was followed by a randomized, open-label, phase 1 trial of 2mg/kg (n=89) or 10mg/kg (n=84) pembrolizumab, an ICI targeting PD-1, for patients with advanced melanoma who had experienced progression of disease after two or more doses of ipilimumab.[7] Overall response rate, defined by the Response Evaluation Criteria In

Solid Tumors (RECIST) (version 1.1), was 26% in both cohorts.[7] Pruritus (19-26%) and rash (18%) were among the most common drug-related adverse events reported.[7]

The Federal Drug Administration (FDA) approved the first ICI, ipilimumab, for advanced stage melanoma in 2011.[1] This was followed by approval of the first PD-1 inhibitor, pembrolizumab, in 2014 and the first PD-L1 inhibitor, atezolizumab, in 2016.[8,9] Within the following decade, the use of ICI expanded dramatically, with the approval of multiple agents targeting CTLA-4, PD-1, and PD-L1, as well as the approval of combination treatment regimens. ICI are currently approved for approximately 50 oncologic diagnoses including both solid organ tumors and hematologic malignancies.[10] Research into potential uses of ICI is ongoing; as of February 2022, there were 4,897 active clinical trials investigating ICI targeting PD-1 or PD-L1, a 278% increase since 2017.[11]

Although the introduction of ICI has been a significant advancement within the field of oncology, these drugs have a notable adverse event profile in the setting of increased immune system activation due to blockade of immune checkpoints and resulting disruption in immune homeostasis[12] irAE due to ICI most commonly involve the integumentary, gastrointestinal, and endocrine systems; however, irAE span the breadth of organ systems.[12] Severe irAE, defined by the Common Terminology Criteria for Adverse Events (CTCAE) as grade 3 or 4, occur in up to 25% of patients on an ICI targeting CTLA-4 and 20% of patients on an ICI targeting PD-1.[13] Per American Society

of Clinical Oncology Guidelines, treatment for grade 2 or greater irAE typically includes immunosuppression and/or discontinuation of the ICI.[12,14]

Cutaneous immune-related adverse events (cirAE) occur in up to 50% of patients on an ICI and often appear soon after initiation of therapy.[15-17] ICI targeting CTLA-4 (ipilimumab, tremelimumab) have been associated with the highest incidence of cirAE at 44-59%, followed by ICI targeting PD-1 (nivolumab, pembrolizumab, cemiplimab, dostarlimab) at 34-42% and ICI targeting PD-L1 (durvalumab, avelumab, and atezolizumab) at approximately 20%.[15] The incidence of cirAE increases when ICI combination therapy is used (59-72%).[15] The most common cirAE include maculopapular eruption (18-68%), pruritus (14-47%), lichenoid dermatitis (4.3-25%,) eczematous dermatitis (7.6-12%), psoriasiform eruption (3.7-17%), and vitiligo (11% with anti-CTLA4, 25% with anti-PD1).[13,16-21] Bullous dermatoses, neutrophilic dermatoses, granulomatous dermatoses, urticarial eruptions, acneiform eruptions, and Grover's disease have also been described, as have hair and nail changes including but not limited to alopecia, mucositis, stomatitis, and xerostomia.[13,16,17] Severe cutaneous adverse reactions (SCAR) that have been associated with ICI include Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP).[16] cirAE are of interest to oncologists and dermatologists alike, as they have been associated with positive response to ICI and longer recurrence-free survival.[22,23] However, cirAE may necessitate interruption or permanent discontinuation of ICI therapy in up to 5% of patients, thereby precluding life-prolonging therapy.[19,24]

Maculopapular Eruption

Maculopapular eruption is the most commonly reported cirAE. It occurs within a shorter latency period than the majority of cirAE, typically presenting three to six weeks after initiation of an ICI.[13,21] Patients develop pink or erythematous macules, papules, patches, and/or plaques of the trunk and extremities with associated pruritus.[13] Erythrodermic, photo-distributed, and urticarial phenotypes have also been described, as has koebnerization of lesions.[13,17] Histopathology demonstrates spongiotic dermatitis with a perivascular infiltrate of CD4+ T cells in the upper dermis and variable presence of eosinophils.[13,20,21] Other features that may be observed include edema within the papillary dermis and dyskeratotic keratinocytes.[13] Treatment of CTCAE grade 1 or 2 maculopapular eruption typically begins with high-potency topical corticosteroids twice daily with or without anti-histamines for symptom relief.[13,20] Systemic corticosteroids may be initiated for grade 2 eruption as needed.[13] High grade maculopapular eruption is rare.[20] CTCAE grade 3 maculopapular eruption typically requires systemic treatment with prednisone or biologics (infliximab, tocilizumab) while holding ICI therapy, while CTCAE grade 4 eruption requires discontinuation of ICI and immediate initiation of systemic medications such as methylprednisolone.[13]

Pruritus

Pruritus is the second most commonly diagnosed cirAE. Pruritus may present with or without a primary cutaneous eruption and often occurs in the setting of xerosis.[13,21] Similar to maculopapular eruption, pruritus develops approximately three to six weeks

after initiation of ICI therapy.[13] Along with generalized xerosis, secondary skin lesions associated with pruritus such as excoriations, lichenification, lichen simplex chronicus (LSC), and prurigo nodularis (PN) may be observed.[25] Histopathology of LSC and PN typically demonstrates irregular acanthosis, orthokeratosis, focal parakeratosis, and hypergranulosis.[26] Treatment of pruritus may include anti-histamines, doxepin (tricyclic antidepressant with anti-histamine properties), gabapentin and pregabalin, aprepitant, naltrexone, narrowband ultraviolet B (UVB) phototherapy, omalizumab, and/or dupilumab depending on severity.[13,17,20] Xerosis should be managed with gentle skin care including regular application of emollients and avoidance of scented and potentially irritating products. Topical corticosteroids and/or other topical therapies should be incorporated into treatment when primary cutaneous lesions are present.

Lichenoid Dermatitis

Lichenoid dermatitis typically presents six to twelve weeks after initiation of ICI with pink, erythematous, or violaceous scaly papules and plaques on the trunk and extremities.[13,17,21,27] Less common morphologies include hypertrophic plaques, papulopustules, and vesicles and less common distributions include palmoplantar and inverse lichenoid dermatitis.[17,20] Lichenoid lesions may exhibit koebnerization.[17] Patients often report severe pruritus.[13,17] The oral, perianal, and/or genital mucosa may be involved and should be thoroughly examined for ulceration, leukoplakia, and Wickham striae.[17,21] Nail dystrophy with lichenoid features has also been reported.[17,28] Histopathology demonstrates a dense lymphocytic infiltrate predominantly composed of T cells along the dermoepidermal junction with vacuolar degeneration and apoptotic or

dyskeratotic basal keratinocytes.[13,20,21,29] Hyperkeratosis, parakeratosis, hypergranulosis, acanthosis, spongiosis, and presence of eosinophils have also been associated with lichenoid dermatitis.[20,29] An immunohistochemical analysis reported that lichenoid dermatitis due to ICI is associated with denser histiocytic infiltrates when compared to lichen planus and lichen planus-like keratoses.[30] Treatment of CTCAE grade 1 or 2 lichenoid dermatitis typically begins with high-potency topical corticosteroids, with systemic therapeutics such as corticosteroids, acitretin, and narrowband UVB phototherapy integrated into treatment regimens as necessary.[13,20] Intralesional corticosteroids may be beneficial in the case of hypertrophic plaques.[17] CTCAE grade 3 or 4 lichenoid dermatitis requires systemic treatment with prednisone or biologics (infliximab, tocilizumab) while holding ICI therapy.[13]

Eczematous Dermatitis

Eczematous dermatitis occurs along a similar timeline to lichenoid dermatitis.[17] Patients typically present with pink or erythematous macules and papules coalescing into patches and plaques with overlying scale and severe pruritus.[16,17] Distinct phenotypes have been described including nummular, asteatotic, and dyshidrotic eczematous dermatitis.[17] Histopathology demonstrates spongiosis and perivascular inflammatory infiltrates with presence of eosinophils.[29] First line treatment of low grade eczematous dermatitis is typically topical corticosteroids with recommendations for gentle skin care.[17] Other topical therapies that may be utilized in an effort to pursue steroid-sparing treatment include calcineurin inhibitors and camphor-menthol for pruritus.[17] Anti-histamines, doxepin, and/or gabapentin may be added for management of pruritus.[17] Severe cases

(CTCAE grade 3 or 4) may require systemic therapy with corticosteroids, narrowband UVB phototherapy, and/or dupilumab. CTCAE grade 3 or greater eczematous dermatitis may require ICI interruption or discontinuation.[17]

Psoriasiform Eruption

Psoriasiform eruption may occur either as a flare of existing psoriasis or as de novo disease, and typically occurs within several weeks to months into treatment. Classic presentation is comprised of erythematous plaques of the trunk and extremities with thick silver and/or micaceous scale.[13,17] Psoriasiform eruptions mimicking subtypes of psoriasis other than plaque psoriasis have also been described, including guttate psoriasis, inverse psoriasis, sebopsoriasis, and palmoplantar psoriasis.[17] Development of psoriatic arthritis in the setting of ICI has also been reported.[17] Histopathology demonstrates typical findings of psoriasis including hyperkeratosis, parakeratosis, hypogranulosis, acanthosis, and elongation of rete ridges.[13,17] CTCAE grade 1 psoriasiform eruption is typically managed with high potency topical corticosteroids, with addition of narrowband UVB phototherapy, acitretin or apremilast considered for CTCAE grade 2 eruption.[13] Hypertrophic plaques may be managed with addition of keratolytics such as ammonium lactate and urea and/or intralesional corticosteroids.[17] CTCAE grade 3 eruption may require interruption or discontinuation of ICI and initiation of systemic agents such as acitretin, apremilast, immunosuppressants such as methotrexate, or biologics such as TNFα inhibitors, IL-12/23 inhibitors, and IL-23 inhibitors.[13,17]

Vitiligo

In the setting of melanoma, vitiligo was hypothesized to be due to CD8+ T cell recognition of melanocyte antigens such as MART-1 and gp100 on normal melanocytes. It is known that memory T cells that respond to melanoma are generated in the setting of autoimmune vitiligo.[31]Among patients with melanoma, incidence of vitiligo as high as 25% following treatment with the PD-1 inhibitor pembrolizumab has been reported; development of vitiligo has been associated with a favorable anti-tumor response.[32] Addition of ICI therapy was thought to increase the likelihood of T cell recognition and reactivity against these melanocyte antigens; a translational study demonstrated expansion of CD8+ T cells targeting MART-1 following treatment with a PD-1 inhibitor in those who responded to treatment.[33] However, the development of vitiligo following ICI therapy for malignancies other than melanoma has since been well-documented, leading to questions regarding the underlying pathophysiology.[13]

Vitiligo typically develops later in the course of ICI treatment compared to other cirAE, with one study reporting time to onset ranging from 52 to 453 days.[13,32] Patients typically present with progressive development of asymptomatic depigmented macules and patches in a generalized or photodistributed distribution.[13,21,34] Leukotrichia may also be observed.[21] Wood's lamp can be used to confirm depigmentation, and skin biopsy is rarely performed due to reliability of clinical diagnosis.[13,29] Treatment may include topical corticosteroids, calcineurin inhibitors, and/or narrowband UVB phototherapy; patients should be advised to use photoprotection. For patients with concerns regarding cosmesis, medical grade make-up can be recommended.[34] Unfortunately, this cirAE is typically irreversible regardless of whether immunotherapy is discontinued.

Gaps in the Literature: cirAE in Patients with Skin of Color

Prior research has demonstrated distinct patterns of cutaneous disease between racial and ethnic groups within the general population.[35] In a retrospective analysis that categorized cutaneous diseases as inflammatory, follicular, pigmentary, alopecia, neoplastic, infectious, or scarring, Black patients had significantly higher odds of inflammatory cutaneous disease, follicular cutaneous disease, alopecia, and scarring compared to white patients. In contrast, white patients had significantly higher odds of neoplastic cutaneous disease.[35] Asian patients had significantly higher odds of pigmentary cutaneous diseases compared to white patients.[35] Hispanic patients had significantly higher odds of specific pigmentary cutaneous diseases including melasma, post-inflammatory hypopigmentation, and pityriasis alba than non-Hispanic patients.[35] Along with differing prevalence of cutaneous diseases, disparities in access to dermatologic care have been reported. An analysis of the National Ambulatory Medical Care Survey demonstrated that, among patients with a primary dermatologic concern, 23.9% of Hispanic patients, 28.5% of Black patients, and 36.7% of Asian patients were treated by a dermatologist, versus 43.2% of white patients.[36] In response to historic shortcomings within the field, there has been increased commitment to education and scholarly work focused on dermatologic disease in patients with skin of color (SOC), defined as "racial groups with skin darker than Caucasians, such as Asians, Africans, Native Americans, and Pacific Islanders", within the last decade.[37]

There is a paucity of data on potential variations in cirAE incidence and morphology, as well as access to oncodermatologic care, between racial and ethnic groups. A small retrospective study reported that eczematous dermatitis and lichenoid dermatitis were the most common cirAE within a cohort of patients with SOC, comprised of 16 Black patients, 9 Hispanic patients, 4 Asian patients, and 1 Native American patient.[38] Notably, a greater proportion of patients in the SOC cohort required skin biopsies due to clinical uncertainty compared to the white cohort.[38] Dermatologist awareness of the ways in which cirAE present in various skin types is critical, as prompt diagnosis and early intervention has the potential to allow for continuation of life-prolonging oncologic therapy.

Gaps in the Literature: cirAE in Patients with Underlying Cutaneous Disease

A second gap in the literature surrounds the impact of a prior dermatologic diagnosis on the risk of developing cirAE. Despite the fact that inflammatory cutaneous eruptions including eczematous dermatitis and psoriasiform eruption are among the most common cirAE, there is little data within the literature regarding the impact of a prior diagnosis of psoriasis or eczema on the morphology of cirAE due to ICI. This is particularly relevant in light of the significant prevalence of psoriasis and eczema within the general population. A multicenter retrospective analysis demonstrated that, among patients with a prior diagnosis of psoriasis who were treated with an ICI, 57% experienced a psoriasis flare at a median of 44 days after ICI initiation.[39] 51% of patients developed a cutaneous flare, while 9% developed a flare of extracutaneous manifestations such as psoriatic arthritis and iritis.[39] 9% of flares were reported as CTCAE grade 3 or 4, and 7% of

patients required discontinuation of ICI due to psoriasis flare.[39] A greater understanding of the impact of prior dermatologic diagnoses on cirAE incidence and morphology has the potential to impact dermatologic monitoring, prophylactic therapy, and therapeutic management prior to initiation of and during treatment with ICI in this patient population.

Statement of Purpose

We performed a retrospective analysis of cirAE among patients treated with an ICI at our institution. Our first aim was to characterize the spectrum of cirAE due to ICI diagnosed and managed by the Yale Oncodermatology Clinic. Our second aim was to characterize the spectrum of cirAE in patients with SOC who were treated at the Yale Oncodermatology Clinic. Our third aim was to compare the morphology of cirAE in patients with a history of inflammatory dermatoses (eczema or psoriasis) to patients with no history of eczema or psoriasis.

Methods

Human Subjects Research

This retrospective case series was approved by expedited review by the Yale University Institutional Review Board (Protocol ID: 2000031188). This study had a waiver of consent.

Ethics Statement

This research was performed in accordance with the protocol approved by the Yale University Institutional Review Board. This research was performed in line with the principles put forth by the Declaration of Helsinki.

Special consideration was given to the data pertaining to cirAE in SOC. It is important to note that the US Census Bureau categories that are used to define race and ethnicity within this manuscript are not an ideal measure. However, we are limited by the variables included within the electronic medical record (EMR). Although we have used this data to define our SOC cohort, we have acknowledged the shortcomings of this approach within the limitations.

Setting and Identification

This retrospective case series was conducted within the Yale New Haven Hospital system. The Yale Joint Data Analytics Teams (JDAT) completed a search of the EMR for all patients treated with an ICI who were referred to the Yale Oncodermatology Clinic, which is embedded within the Smilow Cancer Center. This included the following ICI:

ipilimumab, tremelimumab, nivolumab, pembrolizumab, cemiplimab, dostarlimab, durvalumab, avelumab, and atezolizumab.

Screening for Study Inclusion

Study personnel screened all patients identified in the search completed by JDAT. Dermatologic adverse events (dAE) managed by the Yale Oncodermatology Clinic were identified through a comprehensive, manual review of oncodermatology notes within the EMR. Patients who were not seen for a cirAE were excluded; other indications for referral to oncodermatology included total body skin examination and dAE due to other oncologic agents (targeted therapy, chemotherapy, radiation therapy). All duplicates due to either consecutive or concurrent treatment with multiple ICI were removed.

Data Collection

Data collection was performed manually by study personnel and entered into a secure REDCap database. Demographic information was collected, including age at cirAE diagnosis, sex, race, ethnicity, city of residence, zip code, and insurance coverage. Data on substance use history and past dermatologic history including but not limited to psoriasis and eczema were collected. Oncologic history was collected through manual review of medical oncology notes within the EMR and included oncologic diagnosis, stage at diagnosis, surgical therapy, medical therapy (including immunotherapy), radiation therapy, and response to oncologic treatment. cirAE history was collected through manual review of oncodermatology notes and included responsible ICI, time from medication initiation to development of cirAE, dermatologic examination findings,

dermatopathology findings when relevant, and cirAE diagnosis as determined by an oncodermatologist. Diagnostic categories included psoriasiform eruption, lichenoid dermatitis, eczematous dermatitis (eczema craquele, asteatotic, nummular, etc.), maculopapular eruption, urticarial eruption, acneiform eruption (folliculitis, rosaceiform, etc.), granulomatous dermatosis (sarcoidosis, granuloma annulare, etc.), bullous dermatosis (bullous pemphigoid, etc.), connective tissue irAE (eosinophilic fasciitis, etc.), SCAR (SJS, TEN, DRESS, AGEP, etc.), Grover's disease, vitiligo, alopecia, mucositis, and pruritus. cirAE that did not fit within one of these diagnostic categories were included, with details on diagnosis recorded as free text. cirAE of multiple morphologies were recorded as such. Dermatologist-directed treatment of cirAE, as well as response to treatment, was recorded. Data on discontinuation of oncologic therapy due to cirAE was recorded, as was whether rechallenge was pursued after drug holiday. cirAE grade was determined using CTCAE, version 6.0. For patients with multiple, distinct cirAE, each cirAE with associated data was recorded separately within the REDCap database.

Statistical Methods

Descriptive analysis of the full cohort, as well as of the SOC versus white cohort, was performed using SPSS Statistics. Chi-square tests were performed using SPSS Statistics to compare patients with a history of psoriasis or eczema to patients with no history of either inflammatory dermatosis.

Contributions

Annika Belzer wrote the research grant, which was submitted to the Office of Student Research. Annika Belzer wrote the protocol, which was submitted to and approved by the Yale Institutional Review Board. Annika Belzer completed the JDAT data request and created the REDCap database. Annika Belzer completed screening for inclusion and exclusion criteria, completed all manual data collection, and entered all data into the REDCap database. Annika Belzer and Ryland Mortlock completed data analysis using SPSS Statistics software. Dr. Jonathan Leventhal, Dr. Jeffrey Cohen, and Dr. Kelly Olino supervised the work incorporated into this thesis and reviewed all manuscripts submitted as a result of this work.

Results

Aim 1

In total, 287 patients met inclusion criteria and underwent complete EMR review (Table 1). The mean age was 66 (SD 11) and 53% of the cohort was male. The majority of patients were being treated for non-small cell lung cancer (NSCLC) (33%), melanoma (22%), or renal cell carcinoma (RCC) (8.7%). A total of 34 distinct malignancies were reported within this cohort.

Table 1	**N=287**
Age[1]	
	66 (11)
Sex[2]	
Female	135 (47%)
Male	152 (53%)
Oncologic Diagnosis[2]	
Non-Small Cell Lung Cancer	95 (33%)
Melanoma	63 (22%)
Renal Cell Carcinoma	25 (8.7%)
Head and Neck Squamous Cell Carcinoma	13 (4.5%)
Small Cell Lung Cancer	12 (4.2%)
Bladder Cancer	9 (3.1%)
Breast Cancer	7 (2.4%)
Endometrial Cancer	7 (2.4%)
Colon Cancer	6 (2.1%)
Hematologic Malignancy	6 (2.1%)
Gastric Cancer	4 (1.4%)
Hepatocellular Carcinoma	4 (1.4%)
Merkel Cell Carcinoma	3 (1.0%)
Mesothelioma	3 (1.0%)
Neuroendocrine Cancer	3 (1.0%)
Ovarian Cancer	3 (1.0%)
Pancreatic Cancer	3 (1.0%)
Prostate Cancer	3 (1.0%)
Esophageal Cancer	2 (0.7%)
Sarcoma	2 (0.7%)

Adenoid Cystic Carcinoma of the Tongue	1 (0.3%)
Ampullary Cancer	1 (0.3%)
Basal Cell Carcinoma	1 (0.3%)
Cecal Adenocarcinoma	1 (0.3%)
Cervical Cancer	1 (0.3%)
Chondrosarcoma	1 (0.3%)
Gallbladder Adenocarcinoma	1 (0.3%)
Gastroesophageal Junction Cancer	1 (0.3%)
Glioblastoma Multiforme	1 (0.3%)
Hepato-Cholangiocarcinoma	1 (0.3%)
Osteosarcoma	1 (0.3%)
Thyroid Cancer	1 (0.3%)
Vaginal Squamous Cell Carcinoma	1 (0.3%)
Vulvar Carcinoma	1 (0.3%)

[1]Mean (SD); [2]n (%). SD: Standard deviation

Table 1: Demographics and oncologic diagnoses within the comprehensive cohort

Among the 287 patients included in this cohort, 338 cirAE due to ICI were reported (Table 2). The most common cirAE within this cohort was lichenoid dermatitis (18%). cirAE that occurred in greater than ten patients included eczematous dermatitis (15%), psoriasiform eruption (9.5%), maculopapular eruption (8.3%), vitiligo (6.5%), bullous dermatosis (5.9%), pruritus without primary cutaneous lesion (5.9%), and acneiform eruption (5.0%). 36 cases of cirAE of mixed morphology were observed (11%). CTCAE grade 1 (44%) and grade 2 (34%) cirAE were most common. Twenty-eight CTCAE grade 3 cirAE were observed, as was one grade 4 cirAE. The majority of patients who received treatment for cirAE and had follow up with oncodermatology demonstrated positive clinical response; 42% had complete response and 44% had partial response to dermatologic therapy. 9% of cirAE remained stable despite treatment and progression of

disease occurred in 6% of cases. cirAE necessitated ICI interruption in 46 cases; 16 of these individuals were able to restart ICI after drug holiday.

Table 2	**N=338**
Morphology of cirAE[1]	
Lichenoid	62 (18%)
Eczematous	50 (15%)
Mixed Morphology	36 (11%)
Psoriasiform	32 (9.5%)
Maculopapular	28 (8.3%)
Vitiligo	22 (6.5%)
Bullous	20 (5.9%)
Pruritus	20 (5.9%)
Acneiform	17 (5.0%)
Urticarial	5 (1.5%)
Granulomatous	3 (0.9%)
Grover's Disease	3 (0.9%)
Connective Tissue cirAE	2 (0.6%)
SCAR	2 (0.6%)
Alopecia	1 (0.3%)
Other	35 (10%)
CTCAE Grade[1]	
Grade 1	150 (44%)
Grade 2	115 (34%)
Grade 3	28 (8.3%)
Grade 4	1 (0.3%)
Not Recorded	44 (13%)
Response to cirAE Treatment[1]	
Complete Response	99 (29%)
Partial Response	102 (30%)
Stable	20 (5.9%)
Progression	13 (3.8%)
No Follow Up	78 (23%)
Not Treated	26 (7.7%)
[1]n (%)	

Table 2: cirAE morphology and CTCAE grade, as well as response to oncodermatologist-directed therapy, within the comprehensive cohort

Aim 2

The SOC cohort was comprised of 20 individuals who identified as Black, 6 individuals who identified as Hispanic, 1 individual who identified as Black and Hispanic, 2 individuals who identified as Asian, and 2 individuals who identified as American Indian or Alaskan Native (n=31) (Table 3). The white cohort was comprised of patients who identified as white and non-Hispanic (n=256). Within the SOC cohort, the mean age was 63 (SD 13) versus 67 (SD 11) in the white cohort. 68% of the SOC cohort was male versus 51% of the white cohort.

Table 3	**Skin of Color, N = 31**	**White, N = 256**
Age[1]		
Mean Age (SD)	63 (13)	67 (11)
Sex[2]		
Female	10 (32%)	125 (49%)
Male	21 (68%)	131 (51%)
Race/Ethnicity[2]		
American Indian or Alaska Native	2 (6%)	
Asian	2 (6%)	
Black or African-American	20 (65%)	
Hispanic	6 (19%)	
Black or African-American, Hispanic	1 (3%)	
White		256 (100%)
[1]Mean (SD); [2]n (%)		

Table 3: Demographics of the SOC cohort and white cohort

The most common oncologic diagnoses within the SOC cohort included NSCLC (32%), melanoma (13%), and hepatocellular carcinoma (HCC) (9.7%) (Table 4). In comparison,

the most common oncologic diagnoses within the white cohort were NSCLC (33%), melanoma (23%), and RCC (9.4%).

Table 4	Skin of Color, N = 31	White, N = 256
Oncologic Diagnosis[1]		
NSCLC	10 (32%)	85 (33%)
Melanoma	4 (13%)	59 (23%)
HCC	3 (9.7%)	1 (0.4%)
Breast Cancer	2 (6.5%)	5 (2.0%)
Colon cancer	2 (6.5%)	4 (1.6%)
Gastric Cancer	2 (6.5%)	2 (0.8%)
Hematologic Malignancy	2 (6.5%)	4 (1.6%)
Prostate Cancer	2 (6.5%)	1 (0.4%)
Bladder Cancer	1 (3.2%)	8 (3.1%)
RCC	1 (3.2%)	24 (9.4%)
SCLC	1 (3.2%)	11 (4.3%)
HNSCC	0 (0%)	13 (5.1%)
Endometrial Cancer	0 (0%)	7 (2.7%)
Merkel Cell Carcinoma	0 (0%)	3 (1.2%)
Mesothelioma	0 (0%)	3 (1.2%)
Neuroendocrine Cancer	0 (0%)	3 (1.2%)
Ovarian Cancer	0 (0%)	3 (1.2%)
Pancreatic Cancer	0 (0%)	3 (1.2%)
Other	1 (3.2%)	17 (6.6%)

[1]n (%)

Table 4: Oncologic diagnoses within the SOC cohort and white cohort

Within the SOC cohort, 36 cirAE were recorded; 26 patients presented with one cirAE and five patients presented with two distinct cirAE. The median time to cirAE development was 92 days (IQR 69, 301) with a range of 14 to 907 days, versus a median

of 180 days in the white cohort (IQR 63, 363). cirAE due to PD-1 inhibitors, PD-L1 inhibitors, CTLA-4 inhibitors, and combination ICI therapy were observed (Table 5). The majority of cirAE occurred in patients treated with a PD-1 inhibitor (61%; 15 pembrolizumab, 7 nivolumab). cirAE due to a PD-L1 inhibitor (22%; 4 atezolizumab, 3 durvalumab, 1 avelumab), CTLA-4 inhibitor (2.8%; 1 tremelimumab), and combination therapy (14%; 4 ipilimumab + nivolumab, 1 tremelimumab + durvalumab) were less common.

Table 5	**Skin of Color, N = 36**	**White, N = 302**
ICI Class[1]		
PD-1 Inhibitor	22 (61%)	220 (73%)
PD-L1 Inhibitor	8 (22%)	35 (12%)
CTLA-4 Inhibitor	1 (2.8%)	3 (1.0%)
Combination Therapy	5 (14%)	44 (15%)
[1]n (%)		

Table 5: ICI class responsible for cirAE within the SOC cohort and white cohort

The most common cirAE within the SOC cohort were lichenoid dermatitis (22%, versus 18% in the white cohort) and eczematous dermatitis (22%, versus 14% in the white cohort) (Table 6). 17% of the SOC cohort presented with cirAE of mixed morphology (versus 9.9%), including one case of mixed psoriasiform/eczematous dermatitis, mixed eczematous/maculopapular dermatitis, mixed urticarial/maculopapular dermatitis, mixed lichenoid/acneiform dermatitis, and mixed maculopapular/acneiform dermatitis, respectively. 11% of the SOC cohort presented with pruritus without primary dermatosis (versus 5.3%). Less common cirAE within the SOC cohort included psoriasiform eruption (5.6%, versus 9.9%), acneiform eruption including but not limited to folliculitis

(5.6, versus 5.0%), and urticarial eruption (5.6%, versus 1.0%). There was one case of maculopapular eruption, vitiligo, granulomatous dermatosis, and paronychia, respectively, in the SOC cohort. cirAE observed in the white cohort but not in the SOC cohort included Grover's disease, connective tissue cirAE, SCAR, and alopecia. 18 of 31 patients within the SOC cohort reported post-inflammatory hyperpigmentation (PIH) as a result of cirAE.

CTCAE grade was recorded for 29 of the 36 cirAE within the SOC cohort (Table 6). 47% were grade 1 (versus 44%), 28% were grade 2 (versus 35%), and 5.6% were grade 3 (versus 8.6%). No grade 4 cirAE were reported, compared to one case in the white cohort.

Table 6	Skin of Color, N = 36	White, N = 302
Morphology of cirAE[1]		
Lichenoid	8 (22%)	54 (18%)
Eczematous	8 (22%)	42 (14%)
Mixed Morphology	6 (17%)	30 (9.9%)
Pruritus	4 (11%)	16 (5.3%)
Psoriasiform	2 (5.6%)	30 (9.9%)
Acneiform	2 (5.6%)	15 (5.0%)
Urticarial	2 (5.6%)	3 (1.0%)
Maculopapular	1 (2.8%)	27 (8.9%)
Vitiligo	1 (2.8%)	21 (7.0%)
Granulomatous	1 (2.8%)	2 (0.7%)
Bullous	0 (0%)	20 (6.6%)
Grovers Disease	0 (0%)	3 (1.0%)
Connective Tissue cirAE	0 (0%)	2 (0.7%)
SCAR	0 (0%)	2 (0.7%)
Alopecia	0 (0%)	1 (0.3%)
Other	1 (2.8%)	34 (11%)
CTCAE Grade[1]		
Grade 1	17 (47%)	133 (44%)
Grade 2	10 (28%)	105 (35%)
Grade 3	2 (5.6%)	26 (8.6%)
Grade 4	0 (0%)	1 (0.3%)
Not recorded	7 (19%)	37 (12%)
[1]n (%)		

Table 6: cirAE morphology and CTCAE grade within the SOC cohort and white cohort

Within the SOC cohort, 39% of patients were treated with topical therapy, 2.8% were treated with anti-pruritic therapy, and 14% were treated with both topical and anti-pruritic therapy. 39% of the SOC cohort required systemic therapy for management of cirAE,

including narrowband UVB phototherapy, antibiotics such as doxycycline, prednisone, hydroxychloroquine, acitretin, and biologics such as dupilumab. 5.6% of patients deferred treatment.

The majority of patients within the SOC cohort who received treatment for cirAE and had follow up demonstrated a positive clinical response (79%, versus 87% in the white cohort) (Table 7). 8% of cirAE remained stable despite treatment (versus 9%) and 13% experienced progression of cirAE (versus 5%). Oncologic therapy was discontinued due to cirAE in two patients within the SOC cohort; one of these patients was able to restart therapy after drug holiday.

Table 7	**Skin of Color, N = 36**	**White, N = 302**
Response to cirAE Treatment[1]		
Complete Response	9 (25%)	90 (30%)
Partial Response	10 (28%)	92 (30%)
Stable	2 (5.6%)	18 (6.0%)
Progression	3 (8.3%)	10 (3.3%)
No Follow Up	10 (28%)	68 (23%)
Not Treated	2 (5.6%)	24 (7.9%)
[1]n (%)		

Table 7: Response to oncodermatologist-directed therapy within the SOC cohort and white cohort

Aim 3

Within our cohort, 11 individuals had a history of eczema and 18 individuals had a history of psoriasis; 270 had no history of eczema or psoriasis (Table 8). Age was similar between the baseline eczema, baseline psoriasis, and control cohorts. The baseline

eczema and baseline psoriasis cohorts were comprised of more female than male patients (eczema: 64%, psoriasis: 56%), whereas the control cohort was comprised of more male than female patients (54%). All cohorts were comprised of predominantly white patients (eczema: 82%, psoriasis: 94%, control: 87%).

Table 8	**Eczema, N = 11**	**Psoriasis, N = 18**	**No Dermatologic History, N = 270**
Age[1]			
<90	63 (59, 67)	68 (62, 74)	68 (59, 74)
90 or above	1	0	4
Sex[2]			
Female	7 (64%)	10 (56%)	125 (46%)
Male	4 (36%)	8 (44%)	145 (54%)
Race[2]			
American Indian or Alaska Native	0 (0%)	0 (0%)	2 (0.7%)
Asian	1 (9.1%)	0 (0%)	1 (0.4%)
Black or African-American	1 (9.1%)	0 (0%)	20 (7.4%)
White	9 (82%)	17 (94%)	235 (87%)
Other or Patient Refused	0 (0%)	1 (5.6%)	12 (4.4%)
Ethnicity[2]			
Hispanic or Latino/a	0 (0%)	0 (0%)	7 (2.6%)
Not Hispanic or Latino/a	11 (100%)	17 (94%)	260 (96%)
Unknown	0 (0%)	1 (5.6%)	3 (1.1%)

[1]Median (IQR); [2]n (%). IQR: Interquartile range

Table 8: Demographics of the baseline eczema cohort, the baseline psoriasis cohort, and the control cohort

Among the 351 cirAE reported within this cohort, 14 were diagnosed in patients with a prior diagnosis of eczema, 23 were diagnosed in patients with a prior history of psoriasis, and 314 were diagnosed in patients with no prior reported history of eczema or psoriasis

(Table 9). Among the baseline eczema cohort, eczematous dermatitis comprised 43% of all cirAE, compared to 12% within the control cohort ($p=0.006$). All patients with eczematous dermatitis presented with a component of pruritus. Within this cohort, 29% of cirAE were CTCAE grade 1 and 64% were CTCAE grade 2. Among the baseline psoriasis cohort, psoriasiform eruption comprised 56% of all cirAE, compared to 6.1% within the control cohort ($p<0.001$). Of patients in this cohort who presented with psoriasiform cirAE, only 8% presented with pruritus. Within this cohort, 52% of cirAE were CTCAE grade 1, 35% were CTCAE grade 2, and 4.3% were CTCAE grade 3. Within the control cohort, the most common cirAE were lichenoid dermatitis (20%) and eczematous dermatitis (12%).

Table 9	Eczema, N = 14	Psoriasis, N = 23	No Dermatologic History, N = 314
Cutaneous Immune-Related Adverse Event[1]			
Psoriasiform	0 (0%)	13 (56%)	19 (6.1%)
Eczematous	6 (43%)	2 (8.7%)	39 (12%)
Lichenoid	3 (21%)	0 (0%)	63 (20%)
Maculopapular	0 (0%)	1 (4.3%)	28 (8.9%)
Vitiligo	1 (7.1%)	1 (4.3%)	23 (7.3%)
Pruritus	0 (0%)	0 (0%)	22 (7.0%)
Bullous	1 (7.1%)	1 (4.3%)	18 (5.7%)
Acneiform	0 (0%)	1 (4.3%)	16 (5.1%)
Urticarial	0 (0%)	1 (4.3%)	4 (1.3%)
Granulomatous	0 (0%)	0 (0%)	3 (1.0%)
Grover's Disease	0 (0%)	0 (0%)	3 (1.0%)
Connective Tissue cirAE	0 (0%)	0 (0%)	2 (0.6%)
Mucositis	0 (0%)	0 (0%)	2 (0.6%)
SCAR	0 (0%)	0 (0%)	2 (0.6%)
Alopecia	0 (0%)	0 (0%)	1 (0.3%)
Mixed Morphology cirAE	2 (14%)	1 (4.3%)	32 (10%)
Other	1 (7.1%)	2 (8.7%)	37 (12%)
CTCAE Grade[1]			
Grade 1	4 (29%)	12 (52%)	136 (43%)
Grade 2	9 (64%)	8 (35%)	104 (33%)
Grade 3	0 (0%)	1 (4.3%)	27 (8.6%)
Grade 4	0 (0%)	0 (0%)	1 (0.3%)
Not recorded	1 (7.1%)	2 (8.7%)	46 (15%)
[1]n (%)			

Table 9: cirAE morphology and CTCAE grade within the baseline eczema cohort, the baseline psoriasis cohort, and the control cohort

Discussion

Aim 1

The patterns of cirAE reported in our cohort are in line with prior research characterizing lichenoid dermatitis, eczematous dermatitis, psoriasiform eruption, maculopapular eruption, vitiligo, and pruritus as the most common cirAE. Within our cohort, there were also a significant number of bullous cirAE, most commonly bullous pemphigoid, and acneiform cirAE, including acneiform eruption, rosaceiform eruption, and folliculitis. SCAR reported within this cohort included CTCAE grade 3 AGEP and CTCAE grade 4 SJS/TEN.

Within our full cohort, 86% of patients who underwent dermatologist-directed management of cirAE had a positive clinical response. This high rate supports the integration of dermatologists into interdisciplinary oncology teams. Access to oncodermatology care has been shown to improve not only clinical outcomes, but also patient quality of life and satisfaction with treatment.[40,41]

Aim 2

To our knowledge, this is the largest retrospective analysis of cirAE in patients with SOC. Lichenoid and eczematous dermatitis were the most commonly observed cirAE within the SOC cohort; this is in line with a retrospective analysis that found lichenoid dermatitis and eczematous dermatitis to be the most common cirAE in the general population, along with maculopapular eruption.[15] Lichenoid and eczematous dermatitis

were observed at a greater frequency than within the white cohort, although sample size was not large enough to demonstrate significance.[38]

Presentation with a mixed morphology cirAE was observed in a greater proportion of the SOC cohort than the white cohort. Of the five patients who presented with a mixed morphology cirAE, three underwent biopsy for histologic evaluation. When clinical presentation is ambiguous, histopathology, along with studies such as direct immunofluorescence when relevant, should be pursued. Clinicopathologic correlation can then allow for proper diagnosis and management, with incorporation of therapy targeting both cirAE when dual morphology is present.

Eighteen patients within the SOC cohort presented with PIH, which is known to disproportionately impact patients with SOC.[42,43] Specifically, PIH is more common in patients with Fitzpatrick skin types III to VI.[42] In a prospective study of acne vulgaris, PIH was reported in 65% of Black patients and 48% of Hispanic patients, compared to 25% of white patients.[42,43] PIH is highly resistant to treatment, and preventative measures such as photoprotection and treatment of the primary cirAE are therefore critical.[42] Following development, management of PIH is comprised of combination topical therapy, typically including hydroquinone, retinoids, corticosteroids, vitamin C, and/or azelaic acid.[42] Chemical peels and laser therapy may be pursued in severe or refractory cases.[42]

Within our cohort, a significant majority of patients who underwent dermatologist-directed management of cirAE had a positive clinical response. The proportion of patients with complete or partial response was similar between the SOC and white cohorts. A majority of our patients were treated with topical corticosteroids, which are a mainstay of treatment for cirAE.

Aim 3

Patients with a preexisting inflammatory dermatosis were significantly more likely to develop cirAE mirroring the morphology of their baseline diagnosis when compared to controls. Due to this predilection, patients with baseline eczema or psoriasis demonstrated less variability in the morphology of cirAE than controls. The data reported pertaining to psoriasis is in line with a multicenter, retrospective cohort study performed at eight academic centers.[39] To our knowledge, this is the first study demonstrating this trend among patients with a prior diagnosis of eczema. It is important that patients with a preexisting inflammatory dermatosis are counseled on the risk of developing cirAE mirroring their prior diagnosis.

In light of the data presented, patients with a history of eczema or psoriasis should have management of their underlying dermatosis optimized prior to initiating ICI therapy and should be followed closely by a dermatologist during treatment with an ICI. Within the baseline eczema cohort, treatment regimens for eczematous dermatitis included emollients, camphor-menthol lotion, topical corticosteroids (with or without occlusion), anti-pruritic therapy (anti-histamines, doxepin, gabapentin), narrowband UVB

phototherapy, cephalexin, prednisone, and dupilumab. Dilute bleach baths were recommended for patients within this cohort who had secondary bacterial infection. Within the baseline psoriasis cohort, treatment regimens for psoriasiform eruption included topical corticosteroids (with and without occlusion), topical Vitamin D analogs (calcipotriene), ketoconazole shampoo (in the setting of sebopsoriasis morphology), anti-pruritic therapy (anti-histamines, gabapentin), narrowband UVB phototherapy, acitretin, apremilast, and biologic agents (e.g., anti-TNF alpha or anti-IL23 monoclonal antibodies).

The impact of biologic agents on antitumor response has not been fully elucidated. In a recently published retrospective study of patients with ICI-induced bullous pemphigoid (n=35), eleven patients were treated with biologics (rituximab, omalizumab, or dupilumab) and systemic corticosteroids.[44] Eight of the eleven patients demonstrated complete clinical response with no further flares following ICI treatment.[44] Compared to patients who were not treated with biologics or systemic corticosteroids, this cohort had significantly longer overall survival.[44] Further long-term studies are needed to evaluate the impact of systemic immunomodulators such as biologic agents on the antitumor response in patients being treated with an ICI.

Challenges and Limitations

This research, and the subanalyses in particular, are limited by sample size; future directions may include multicenter studies to allow for increased power. Another limitation is lack of data on patients who were not referred to oncodermatology. However, the Yale Oncodermatology Clinic is highly integrated with the Departments of Oncology and Dermatology, such that more severe and recalcitrant presentations were likely captured within our cohort whereas milder presentations may have been managed by oncology teams without referral. Educating referring oncologists to better recognize the spectrum of cirAE, particularly in patients with SOC, through materials such as educational pamphlets may further improve multidisciplinary care. Future studies investigating factors that increase or decrease the likelihood of referral to oncodermatology for cirAE are warranted.

The greatest challenge we faced in the development and completion of this research was deciding how to define the SOC cohort for our second aim. We recognize that the US Census Bureau race and ethnicity categories are social and cultural constructs rather than distinctions rooted in biology.[45] Unfortunately, the EMR does not reflect skin pigmentation consistently or reliably, preventing categorization of patients into mild, moderate, and deep pigmentation. We considered using the Fitzpatrick skin type scale to define our patient cohorts. However, the Fitzpatrick scale was created to describe phototype and sun sensitivity, not race or ethnicity, in individuals with "white skin".[46,47] The initial scale was comprised of skin types I through IV, whereas skin types V and VI were included retroactively.[46,47] We therefore chose not to use Fitzpatrick skin type to

avoid conflation with race and ethnicity. We instead used the US Census Bureau race and ethnicity categories to define our SOC cohort, which we recognize is a significant limitation of this research.

Pertaining to our third aim, a preexisting history of eczema or psoriasis may have led to physician bias. We acknowledge that knowing a patient's dermatologic history may have influenced the provider's clinical suspicions, therefore leading to confirmation bias.

Conclusion

As use of ICI continues to expand, the role of the dermatologist within multidisciplinary teams caring for patients with a diagnosis of cancer must expand as well. Along with the potential to force drug holiday or discontinuation, cirAE can have significant impact on patient quality of life due to physical and/or cosmetic concerns and effects on activities of daily living. Dermatologists must therefore be aware of the epidemiology and presentation of cirAE to allow for prompt diagnostic work up and treatment initiation.

Dissemination

The data pertaining to cirAE in SOC was published in the *Journal of the American Academy of Dermatology (JAAD).* This manuscript is entitled "The spectrum of cutaneous immune-related adverse events in patients with skin of color". The data pertaining to cirAE in patients with a history of eczema or psoriasis was accepted to *JAAD*. This manuscript is entitled "The effect of baseline eczema or psoriasis on the morphology of cutaneous immune-related adverse events (cirAE) due to immune checkpoint inhibitor (ICI) therapy".

Two case series within the field of oncodermatology resulted from this thesis work. The first, entitled "Psoriasiform and lichenoid eruptions as a potential harbinger of bullous dermatoses in the setting of immune checkpoint inhibitors: A case series", was accepted by the *International Journal of Dermatology.* The second, entitled "The spectrum of dermatologic adverse events (dAE) associated with amivantamab, a novel bispecific inhibitor of EGFR and MET", was accepted by *JAMA Dermatology.*

Multiple case reports resulting from this thesis work were published during this research year. "Skin Eruption Involving Bilateral Breasts Following Radiation Therapy for Invasive Ductal Carcinoma of the Left Breast" was published in the *International Journal of Women's Dermatology*. "Mucosal hemangioma in the setting of treatment with ado-trastuzumab emtansine (T-DM1)" was published in the *British Journal of Dermatology.* Case reports within the field of oncodermatology were also presented at international dermatology conferences. "Treatment of Underlying Monoclonal Gammopathy of Clinical Significance (MGCS) with Lenalidomide for IVIG-Resistant Scleromyxedema" was presented at the

American Academy of Dermatology Annual Meeting in 2022. “Atypical bullous pemphigoid due to radiation therapy” was presented at the Society for Investigative Dermatology Annual Meeting in 2022. “Fluoroscopy-Induced Chronic Radiation Fibrosis: A Rare Dermatologic Adverse Event” was included in the Atlantic Dermatology Society Annual Meeting conference booklet in 2022.

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