HHS Public Access

Author manuscript

J Am Acad Dermatol. Author manuscript; available in PMC 2023 June 12.

Published in final edited form as:

J Am Acad Dermatol. 2023 June ; 88(6): 1308–1316. doi:10.1016/j.jaad.2023.02.014.

Influence of melanoma type on incidence and downstream implications of cutaneous immune-related adverse events in the setting of immune checkpoint inhibitor therapy

Nga Nguyen, MD, MPH[1,*], **Guihong Wan, PhD**[1,2,*], **Pearl Ugwu-Dike, BA**[1], **Nora A. Alexander, BS**[1], **Neel Raval, BA**[1], **Shijia Zhang, BA**[1,2], **Ruple Jairath, BS**[1], **Jordan Phillipps, BS**[1], **Bonnie Leung, BS**[1,9], **Katie Roster, MS**[1], **Jayhyun Seo, BA**[1], **Chenyue Lu, MBI**[1,2], **Kimberly Tang, BA**[1], **Min Seok Choi, MS**[1], **Mia S. DeSimone, MD, MPH**[3], **Nicholas Theodosakis, MD, PhD**[1], **Munachimso Amadife, BS**[1], **Nevada Cox, MS**[1], **Thomas K. Le, BS**[4], **Feng Liu, PhD**[5], **Wenxin Chen, MS**[1,2], **Xue Bai, MD**[6], **Genevieve Boland, MD, PhD**[7], **David Liu, MD**[6], **Marc S. Hurlbert, PhD**[8], **Nicole LeBoeuf, MD, MPH**[9], **Kerry L. Reynolds, MD**[10], **Kun-Hsing Yu, MD, PhD**[2], **Hensin Tsao, MD, PhD**[1], **Maryam Asgari, MD, MPH**[1,11], **Alexander Gusev, PhD**[6], **Shawn G. Kwatra, MD**[4,12,**], **Yevgeniy R. Semenov, MD, MA**[1,**]

[1]Department of Dermatology, Massachusetts General Hospital, Boston, MA

[2]Department of Biomedical Informatics, Harvard Medical School, Boston, MA

[3]Department of Pathology, Brigham and Women's Hospital, Boston, MA

[4]Department of Dermatology, Johns Hopkins University School of Medicine, Baltimore, MD

[5]School of Systems and Enterprises, Stevens Institute of Technology, Hoboken, NJ

[6]Department of Medicine, Dana-Farber Cancer Institute, Boston, MA

[7]Department of Surgery, Massachusetts General Hospital, Boston, MA

[8]Melanoma Research Alliance, Washington, DC

[9]Department of Dermatology, Brigham and Women's Hospital, Boston, MA

[10]Department of Medicine, Massachusetts General Hospital Cancer Center, Boston, MA

Corresponding author: 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, Phone: 617-724-6973, ysemenov@mgh.harvard.edu, Twitter handle: @EugeneSemenovMD.

*Designates co-first authors

**Designates co-senior authors

Conflicts of Interest: None declared.

Financial Disclosures:

YRS is an advisory board member/consultant and has received honoraria from Incyte Corporation, Castle Biosciences, Galderma, and Sanofi outside of the submitted work. SGK is an advisory board member/consultant for AbbVie, Celldex Therapeutics, Galderma, Incyte Corporation, Johnson & Johnson, Novartis Pharmaceuticals Corporation, Pfizer, Regeneron Pharmaceuticals, Sanofi, and Kiniksa Pharmaceuticals and has served as an investigator for Galderma, Kiniksa Pharmaceuticals, Pfizer Inc., and Sanofi. NRL is a consultant and has received honoraria from Bayer, Seattle Genetics, Sanofi, Silverback and Synox Therapeutics outside the submitted work.

IRB approval status: Reviewed and exempted by Mass General Brigham IRB.

Reprint requests: Yevgeniy R. Semenov, MD, MA

Patient consent on file: N/A

[11]Department of Population Medicine, Harvard Medical School, Boston, MA

[12]Department of Oncology, Johns Hopkins University School of Medicine, Baltimore, MD

Abstract

Background: Emerging evidence suggests that cutaneous immune-related adverse events (cirAEs) are associated with a survival benefit in the setting of advanced melanoma treated with immune checkpoint inhibitor (ICI) therapy. Previous studies have not examined the role of melanoma subtypes on cirAE development and downstream therapeutic outcomes.

Objective: Examine the impact of melanoma subtypes on cirAE onset and survival among ICI recipients.

Methods: Retrospective multi-institutional cohort study. Multivariate time-series regressions were utilized to assess relationships between melanoma subtype, cirAE development, and survival.

Results: Among 747 ICI recipients, 236 (31.6%) patients developed a cirAE. Patients with acral melanoma were less likely to develop a cirAE (HR=0.41, p=0.016) compared to patients with non-acral cutaneous melanoma. Across all melanoma subtypes, cirAEs were associated with reduced mortality (HR=0.76, p=0.042). Patients with acral (HR=2.04, p=0.005), mucosal (HR=2.30 p<0.001), and uveal (HR=4.09, p<0.001) primaries exhibited the worst survival.

Limitations: Retrospective cohort study.

Conclusion: This is the first study to demonstrate differences in cirAE development among melanoma subtypes. The presence of cirAEs was associated with better survival. Further, the lower incidence of cirAEs may be a marker of immunotherapy response, which is reflected in the association between acral melanoma and mortality.

Capsule Summary:

- Differences in cirAE incidence (acral: 15.7%, mucosal: 41.2%, non-acral cutaneous: 32.2%, overall: 31.6%) were observed in melanoma subtypes, and cirAEs were associated with reduced overall mortality (HR=0.76, p=0.042).
- An understanding of ICI treatment response and cirAEs across melanoma subtypes can guide therapeutic management in patients with melanoma.

Keywords

Rare Melanoma; Cutaneous Immune-Related Adverse Events; Skin Toxicity; Immunotherapy; Immune Checkpoint Inhibitor

Introduction

Immune checkpoint inhibitor (ICI) therapy has significantly increased survival among patients with advanced melanoma[1]. Specifically, anti–cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) monoclonal antibodies (e.g., ipilimumab) and anti-programmed death 1/programmed death ligand 1 (PD-1/PD-L1) antibodies (e.g., pembrolizumab) were initially FDA approved in the setting of advanced or unresectable disease and most recently as

adjuvant therapy for patients with earlier stage disease following complete resection[2]. However, ICIs have been associated with a wide range of immune-related adverse events (irAEs), of which cutaneous irAEs (cirAEs) are the most common[3] with highly variable clinical presentations, including pruritus, vitiligo, lichen planus-like eruptions, bullous pemphigoid, psoriasiform eruptions, and many others[4]. Despite the frequency and morbidity associated with cirAEs, emerging evidence suggests that the occurrence of these events is associated with improved survival among ICI recipients, particularly those with melanoma[5, 6]. However, benefits of ICI therapy have not been consistent across all melanoma subtypes, with worse response in patients with acral, mucosal, and uveal disease[7, 8]. Furthermore, published data has yet to delineate differences in cirAE development or their effects on survival among melanoma subtypes. The goal of this study is to examine the independent impact of melanoma subtypes on cirAE onset and their downstream implications on survival. Our secondary aim is to examine the survival benefits of ICIs among patients with advanced melanoma.

Methods

Cohort Determination

Patients with metastatic melanoma receiving ICI therapy at the Massachusetts General Brigham healthcare system between December 2011 and October 2020 were included in this study. Melanomas were stratified into acral melanoma, mucosal melanoma (MM), uveal melanoma (UV), non-acral cutaneous melanoma (NACM), and melanoma of unknown primary (UPM). AM was defined as a primary melanoma on the palm, sole, or subungual regions. MM was defined as a primary melanoma affecting the mucosa of the respiratory tract, nasal cavity, paranasal sinuses, oral cavity, gastrointestinal tract, anal canal, genitourinary tract, vulva, and vagina. UV was defined as melanoma of the uvea or uveal tract, which includes the iris, ciliary body, and choroid. UPM was defined as melanoma metastasized to lymph nodes, subcutaneous sites, and visceral organs without any evidence of a primary lesion. NACM were considered as the control group. Melanomas were identified using ICD-10 codes and keyword searches of clinical notes for the above anatomic locations, followed by independent manual curation of medical records to validate the presence and subtype of melanoma.

Data Extraction

The Research Patient Data Registry (RPDR)[9] and the Enterprise Data Warehouse (EDW) are institutional clinical databases. We extracted the following variables from RPDR: patient age, sex, race/ethnicity, ICD codes, and date of death, or last follow-up. Detailed documentation of all ICI administrations (date and type received) was extracted from the EDW. ICD codes from all visits before ICI initiation were extracted to calculate the Charlson Comorbidity Index (CCI). Given that all patients had metastatic cancer, CCI was rescaled to exclude cancer diagnoses. ICI treatments were separated into four classes: anti-PD-1 (pembrolizumab, nivolumab, cemiplimab) monotherapy, anti-PD-L1 (atezolizumab, avelumab, durvalumab) monotherapy, anti-CTLA-4 (ipilimumab) monotherapy, and combination therapy (co-administration of CTLA4 and either PD-1 or PD-L1).

Chart Review

Manual chart review was conducted by two independent reviewers to ascertain the presence and timing of cirAEs following ICI therapy initiation. Suspected events were categorized and graded using Common Terminology Criteria for Adverse Events (CTCAE) version 5.0[10]. For each cutaneous eruption, a likelihood score of cirAE was assigned on a scale of 1 (highly unlikely) to 4 (highly likely). The likelihood was determined by review of rash timing, morphology, absence of competing risk factors, histologic confirmation when available, and response to therapy. Scores of 3 and 4 were categorized as having a confirmed cirAE. In cases where concordance was not achieved by the two reviewers, a third reviewer (study PI) arbitrated the cases. CirAE morphology was also recorded based on documentation in clinical notes, review of clinical photographs, and histologic examination when available.

Statistical Analysis

To compare groups, we used Pearson's chi-squared test for categorical variables and Kruskal-Wallis test for continuous variables. Kaplan-Meier (KM) curves were utilized to examine differences in survival between melanoma subtypes. For patients who do not have known mortality information, their last encounters with the system were considered their censoring dates. A multivariable Weibull accelerated failure time regression model was utilized to assess the relationship between primary melanoma subtype and cirAE development, adjusting for age at ICI initiation, sex, race/ethnicity, CCI, ICI type, year of ICI initiation, melanoma stage at ICI initiation, and whether ICI was adjuvant therapy. To account for immortal time bias[11], a time-varying, cause-specific Cox proportional hazards model was used to investigate the development of cirAEs impacted cancer-specific survival, after adjusting for primary melanoma subtype, age at ICI therapy initiation, sex, race/ethnicity, CCI score, ICI type, and year of ICI therapy initiation. All cases with non-cancer-related causes of death or competing risks to mortality were censored.

Multivariate analysis was repeated for individual cirAE morphologies to understand how the eruption morphology is associated with survival. Multivariate structural equation modeling (SEM) was utilized to investigate how immune response mediates the impact of primary melanoma subtype on survival with cirAE development serving as a proxy measure for the immune-mediated response. This is a hypothesis-generating study; therefore no strict alpha-level was used to determine statistical significance. All p-values reported are exploratory in nature. All analyses were completed in STATA v. 17 (College Station, TX)[12].

Results

A total of 747 patients were included in this study. Baseline characteristics are presented in Table 1. The median duration of follow-up was 2.8 years [IQR 1.2, 4.2]. There were 236 (31.6%) patients who developed cirAEs and 419 (56.1%) patients alive at the end of study follow-up. There were differences in cirAE incidence by melanoma subtype, with the lowest incidence (15.7%) in patients with AM and the highest incidence (41.2%) in patients with MM (p=0.017). The mean time to cirAE onset after ICI initiation was prolonged for patients with AM compared to patients with NACM (11.1 vs. 4.0 months, p=0.004). The

majority (69.9%) of patients received anti-PD-1 immunotherapy. The proportion of mucosal (37.4%) and uveal (34.4%) melanoma patients on combination immunotherapy was higher than patients with NACM (17.2%, p=0.009). There were no acral, mucosal, or UV patients on anti-PD-L1 immunotherapy. KM survival curves for melanoma subtypes are presented in Figure 1.

Further, differences were observed between melanoma type and distribution of cirAE morphologies (Table 2). Among the specific morphologies, vitiligo (50.0%) was the primary presentation for patients with AM and occurred more frequently in this subtype as compared to patients with MM (5.4%), UV (0.0%), UPM (0.0%), and NACM (7.1%, p=0.001). Additionally, lichenoid dermatitis was more likely to be observed among patients with NACM (5.2%) and UPM (6.5%) than among patients with acral, mucosal, or uveal melanomas (0%, p=0.056). Overall, the diversity of cirAE morphologies was broader for MM than AM, and included non-specific rash, maculopapular eruption, isolated pruritus without rash, vitiligo, and others. The diversity and proportions of cirAE morphologies in patients with UPM were similar to patients with NACM.

In multivariate modeling (Table 3), patients with AM were less likely to develop a cirAE (HR=0.41 p=0.016) when compared to the control group (NAC melanoma). The risk of cirAE development among patients with mucosal, uveal, and UPM was not different from controls after covariate adjustment (HR=1.15, p=0.448; HR=0.65, p=0.310; HR=1.24, p=0.291).

Additionally, the presence of cirAEs was associated with lower cancer-specific mortality (HR=0.73, p=0.043) and overall mortality (HR=0.76, p=0.042) for all melanoma patients. However, melanoma patients with acral (HR=2.04, p=0.005), mucosal (HR=2.30, p<0.001), or uveal (HR=4.09, p<0.001) primaries exhibited the worst survival despite receiving ICI therapy compared to patients with NAC melanoma. SEM demonstrated that 52.0% of the poorer survival among patients with AM is mediated by the lower rate of cirAE development by comparison to controls (Figure S1). Among all melanoma subtypes, patients who initiated ICI therapy in the latter years of the study (HR=1.27, p<0.001) or higher CCI (HR=1.12, p<0.001) had worse overall survival (Table S1).

Multivariate modeling of the influence of cirAE morphology on survival (Table S2) identified that the presence of vitiligo provided protection from mortality (HR 0.42, p=0.094). Additionally, the following inflammatory eruptions were associated with a lower risk of mortality compared to patients without a cirAE: isolated pruritus without visible manifestation of rash (HR 0.56, p=0.052), maculopapular eruption (HR 0.60, p=0.018), and non-specific rash (HR 0.46, p=0.001).

Discussion

The steadily increasing utilization of ICI therapies to treat advanced malignancies requires clinicians to understand the implications of immune-related toxicities, including cirAEs. Acral, mucosal, and uveal melanomas represent rare and challenging subtypes of melanoma that portend particularly poor prognoses. Although these subtypes can display aggressive

behavior with rapid progression, their relative rarity has been one of the main challenges in investigating determinants of immunotherapy outcomes. To our knowledge, this is the first study investigating the impact of melanoma subtype on cirAE development and the benefits of immune checkpoint inhibitors among patients with advanced melanoma.

This study demonstrates differences in cirAE development and survival among melanoma subtypes and can inform clinicians when counseling melanoma patients. We found that patients with AM were less likely to develop cirAEs than their cutaneous melanoma counterparts. Though patients with MM were more likely to develop cirAEs, this difference was largely explained by the higher utilization of combination immunotherapy. After adjusting for ICI therapy type, patients with MM were not more likely to develop cirAEs than the control population.

Furthermore, we found that the average time to cirAE onset was longer for patients with AM. Previously reported average times for cirAE onset were within four months of immunotherapy initiation and only 15% occurred beyond the first year[13–15]. The longer time to cirAE onset among patients with AM in our study is novel. We suspect the delayed onset of cirAEs in patients with AM may be related to tumor characteristics. Specifically, patients with AM tend to present with thicker tumors and delayed detection due to the anatomic location on plantar surfaces. Prior studies have indicated that thicker tumors correlate with a lower grade and lower density of tumor infiltrating lymphocytes (TILs),[16, 17] which may lead to decreased recognition of antigens to induce an inflammatory response in the presence of immunotherapy, resulting in reduced incidence of cirAEs and delayed cirAE onset[18–21].

Despite differences in the timing of cirAEs, the presence of cirAEs was protective of mortality across all melanoma subtypes. CirAE presence has been previously shown to be an indicator of a robust immune response in cancer therapy[8]. We suspect that a low rate of cirAE development could be a biomarker for poorer tumor response. Prior studies show distinct melanoma properties within the tumor microenvironments that can be attributed to poor response to immunotherapy[8, 22]. Kaunitz and colleagues demonstrated that PD-L1 expression in acral (31%) and mucosal (44%) melanomas is lower than chronically sun-damaged melanomas (62%)[22]. Higher PD-L1 expression levels are correlated with improved T-cell response and progression-free survival among anti-PD-1/PD-L1 recipients[23]. In addition to lower PD-L1 expression, the tumor mutational burden (TMB) is also lower in acral, mucosal, and uveal melanomas when compared to NACMs [8, 24, 25]. The lower TMB among these subtypes is attributed to the UV-independent nature of their mutational pathways and is associated with poor response rates to PD-1 therapy[8, 24]. These factors likely contribute to the poor tumor response to immunotherapy and subsequent increased risk of mortality found among our patients with metastatic melanoma patients with acral, mucosal, and uveal primaries.

This study also found that the presence of a cirAEs was inversely associated with mortality. Having observed a lower incidence of cirAEs among patients with AM by comparison to the control population, we performed a mediation analysis to identify the extent to which this lower incidence of cirAEs explained the greater mortality observed in this population. Our SEM analyses demonstrated that cirAE status accounted for 52.0% of the

relationship between AM and mortality, further demonstrating the prognostic value of cirAE development in this population.

Our study also provides insight into which cirAE morphologies provide a survival benefit to guide clinicians in their management of these toxicities. Vitiligo is the only morphologic presentation that has shown progression-free survival (PFS) and overall survival (OS) benefits in prior studies[26]. The overall decreased risk of death (HR=0.42) in our melanoma patients who developed vitiligo compared to those who did not have vitiligo is consistent with the result of a meta-analysis that analyzed 137 studies (HR=0.25)[26]. However, we also identified survival benefits with several other inflammatory cirAE morphologies, including isolated pruritus, maculopapular eruption, and non-specific rash. Vitiligo and maculopapular eruptions are T-cell mediated processes that can indicate a robust immune response to therapy. The protective effects of these morphologic presentations have not been reported in the literature or profiled based on the melanoma subtype. Notably, in our cohort, all individuals with lichenoid eruptions were alive at the end of study follow-up, therefore we were unable to assess the mortality benefit of this morphology. However, lichenoid eruption was observed exclusively among NACMs and UPMs. The similarities found between the diversity and distribution of cirAE morphologies between NACMs and UPMs supports prior findings of similarities between the genetic signatures of these melanomas and correlations with improved prognosis[27].

Lastly, we found that PD-1 therapy was associated with improved melanoma-specific survival across all melanoma subtypes. However, in contrast to prior studies where participants have untreated advanced-stage melanoma at study entry, some patients in our cohort were exposed to chemotherapy or single-agent immunotherapy regimens prior to initiating combination immunotherapy therapy. As a result, receiving PD-1 therapy in our cohort may indicate less aggressive or progressive disease with failed prior therapies leading to improved survival on PD-1 therapy.

This study was limited by its retrospective nature and by the relative rarity of acral, mucosal, and uveal melanomas. Further, most of the population in our cohort was male and Caucasian. This may limit the generalizability of our findings as immunotherapy response and survival patterns vary between sex and race. However, our cohort is still representative of the broader population affected by melanoma, including the rare subtypes.

In conclusion, our study supports increasing evidence that cirAEs are associated with improved overall survival among melanoma patients, which underscores the need for effective and supportive patient care interventions that would permit the maintenance of quality of life and dose intensity of ICI therapy while managing these toxicities. Further, we demonstrate that cirAE incidence and morphologic distribution are highly dependent on melanoma subtype. We provide a critical analysis of immunotherapy outcomes among understudied melanoma subtypes and propose a possible role of low cirAE incidence as marker for immunotherapy response leading to poorer ICI outcomes among patients with AM. Understanding the impact of cancer type on this immune response either directly or indirectly via immunotherapy toxicity development is an important and underexplored area of research. In summary, this work demonstrates a survival association of cirAEs in ICI

recipients with melanoma and adds to the existing literature by assessing the relationship between rare melanoma subtypes, cirAEs, and survival. In doing so, we provide important prognostic information to dermatologists and oncologists caring for these patients with metastatic melanoma.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding sources:

YRS is in part supported by the Department of Defense under Award Number W81XWH2110819 and by the Dermatology Foundation under the Medical Dermatology Career Development Award. KHY is in part supported by R35GM142879 from the National Institute of General Medical Sciences, NIH. SGK is supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health under Award Number K23AR077073. NRL is supported by NIH/NCI grant U54-CA225088. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

References

1. da Silveira Nogueira Lima JP, Georgieva M, Haaland B, de Lima Lopes G. A systematic review and network meta-analysis of immunotherapy and targeted therapy for advanced melanoma. Cancer Med. Jun 2017;6(6):1143–1153. doi:10.1002/cam4.1001 [PubMed: 28463413]
2. Jamal S, Hudson M, Fifi-Mah A, Ye C. Immune-related Adverse Events Associated with Cancer Immunotherapy: A Review for the Practicing Rheumatologist. J Rheumatol. Feb 2020;47(2):166–175. doi:10.3899/jrheum.190084 [PubMed: 31308203]
3. Thompson LL, Krasnow NA, Chang MS, et al. Patterns of Cutaneous and Noncutaneous Immune-Related Adverse Events Among Patients With Advanced Cancer. JAMA Dermatol. May 1 2021;157(5):577–582. doi:10.1001/jamadermatol.2021.0326 [PubMed: 33760001]
4. 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. Apr 2 2021;doi:10.1016/j.jaad.2021.03.094
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. Feb 1 2022;158(2):189–193. doi:10.1001/jamadermatol.2021.5476 [PubMed: 35019948]
6. Zhang S. Cutaneous immune-related adverse events are protective of patient survival in advanced cancer patients - a multi-institutional cohort study (Abstract). Presented at the: American Academy of Dermatology Annual Meeting; March 26, 2022. 2022;
7. Yang J, Manson DK, Marr BP, Carvajal RD. Treatment of uveal melanoma: where are we now? Ther Adv Med Oncol. 2018;10:1758834018757175. doi:10.1177/1758834018757175 [PubMed: 29497459]
8. Mao L, Qi Z, Zhang L, Guo J, Si L. Immunotherapy in Acral and Mucosal Melanoma: Current Status and Future Directions. Front Immunol. 2021;12:680407. doi:10.3389/fimmu.2021.680407 [PubMed: 34149718]
9. Nalichowski R, Keogh D, Chueh HC, Murphy SN. Calculating the benefits of a Research Patient Data Repository. AMIA Annu Symp Proc. 2006:1044.
10. Common Terminology Criteria for Adverse Events (CTCAE) v. 5.0. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5×11.pdf
11. Levesque LE, Hanley JA, Kezouh A, Suissa S. Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes. BMJ. Mar 12 2010;340:b5087. doi:10.1136/bmj.b5087 [PubMed: 20228141]
12. Statistical Software: Release 17. StataCorp; 2021.

13. Wang LL, Patel G, Chiesa-Fuxench ZC, et al. Timing of Onset of Adverse Cutaneous Reactions Associated With Programmed Cell Death Protein 1 Inhibitor Therapy. JAMA Dermatol. Sep 1 2018;154(9):1057–1061. doi:10.1001/jamadermatol.2018.1912 [PubMed: 30027278]

14. Bottlaender L, Amini-Adle M, Maucort-Boulch D, Robinson P, Thomas L, Dalle S. Cutaneous adverse events: a predictor of tumour response under anti-PD-1 therapy for metastatic melanoma, a cohort analysis of 189 patients. J Eur Acad Dermatol Venereol. Sep 2020;34(9):2096–2105. doi:10.1111/jdv.16311 [PubMed: 32078191]

15. Apalla Z, Papageorgiou C, Lallas A, et al. Cutaneous Adverse Events of Immune Checkpoint Inhibitors: A Literature Review. Dermatol Pract Concept. Jan 2021;11(1):e2021155. doi:10.5826/dpc.1101a155 [PubMed: 33614223]

16. Castaneda CA, Castillo M, Torres-Cabala C, et al. Relationship between tumor-associated immune infiltrate and p16 staining over clinicopathological features in acral lentiginous melanoma. Clin Transl Oncol. Sep 2019;21(9):1127–1134. doi:10.1007/s12094-019-02033-x [PubMed: 30778854]

17. Castaneda CA, Torres-Cabala C, Castillo M, et al. Tumor infiltrating lymphocytes in acral lentiginous melanoma: a study of a large cohort of cases from Latin America. Clin Transl Oncol. Dec 2017;19(12):1478–1488. doi:10.1007/s12094-017-1685-3 [PubMed: 28577153]

18. Li F, Li C, Cai X, et al. The association between CD8+ tumor-infiltrating lymphocytes and the clinical outcome of cancer immunotherapy: A systematic review and meta-analysis. EClinicalMedicine. Nov 2021;41:101134. doi:10.1016/j.eclinm.2021.101134 [PubMed: 34585125]

19. Antohe M, Nedelcu RI, Nichita L, et al. Tumor infiltrating lymphocytes: The regulator of melanoma evolution. Oncol Lett. May 2019;17(5):4155–4161. doi:10.3892/ol.2019.9940 [PubMed: 30944610]

20. Nakamura Y, Zhenjie Z, Oya K, et al. Poor Lymphocyte Infiltration to Primary Tumors in Acral Lentiginous Melanoma and Mucosal Melanoma Compared to Cutaneous Melanoma. Front Oncol. 2020;10:524700. doi:10.3389/fonc.2020.524700 [PubMed: 33392063]

21. Clemente CG, Mihm MC Jr., Bufalino R, Zurrida S, Collini P, Cascinelli N. Prognostic value of tumor infiltrating lymphocytes in the vertical growth phase of primary cutaneous melanoma. Cancer. Apr 1 1996;77(7):1303–10. doi:10.1002/(SICI)1097-0142(19960401)77:7<1303::AID-CNCR12>3.0.CO;2-5 [PubMed: 8608507]

22. Kaunitz GJ, Cottrell TR, Lilo M, et al. Melanoma subtypes demonstrate distinct PD-L1 expression profiles. Lab Invest. Sep 2017;97(9):1063–1071. doi:10.1038/labinvest.2017.64 [PubMed: 28737763]

23. Cho J, Ahn S, Yoo KH, et al. Treatment outcome of PD-1 immune checkpoint inhibitor in Asian metastatic melanoma patients: correlative analysis with PD-L1 immunohistochemistry. Invest New Drugs. Dec 2016;34(6):677–684. doi:10.1007/s10637-016-0373-4 [PubMed: 27491654]

24. Yarchoan M, Hopkins A, Jaffee EM. Tumor Mutational Burden and Response Rate to PD-1 Inhibition. N Engl J Med. Dec 21 2017;377(25):2500–2501. doi:10.1056/NEJMc1713444 [PubMed: 29262275]

25. Wessely A, Steeb T, Erdmann M, et al. The Role of Immune Checkpoint Blockade in Uveal Melanoma. Int J Mol Sci. Jan 29 2020;21(3)doi:10.3390/ijms21030879

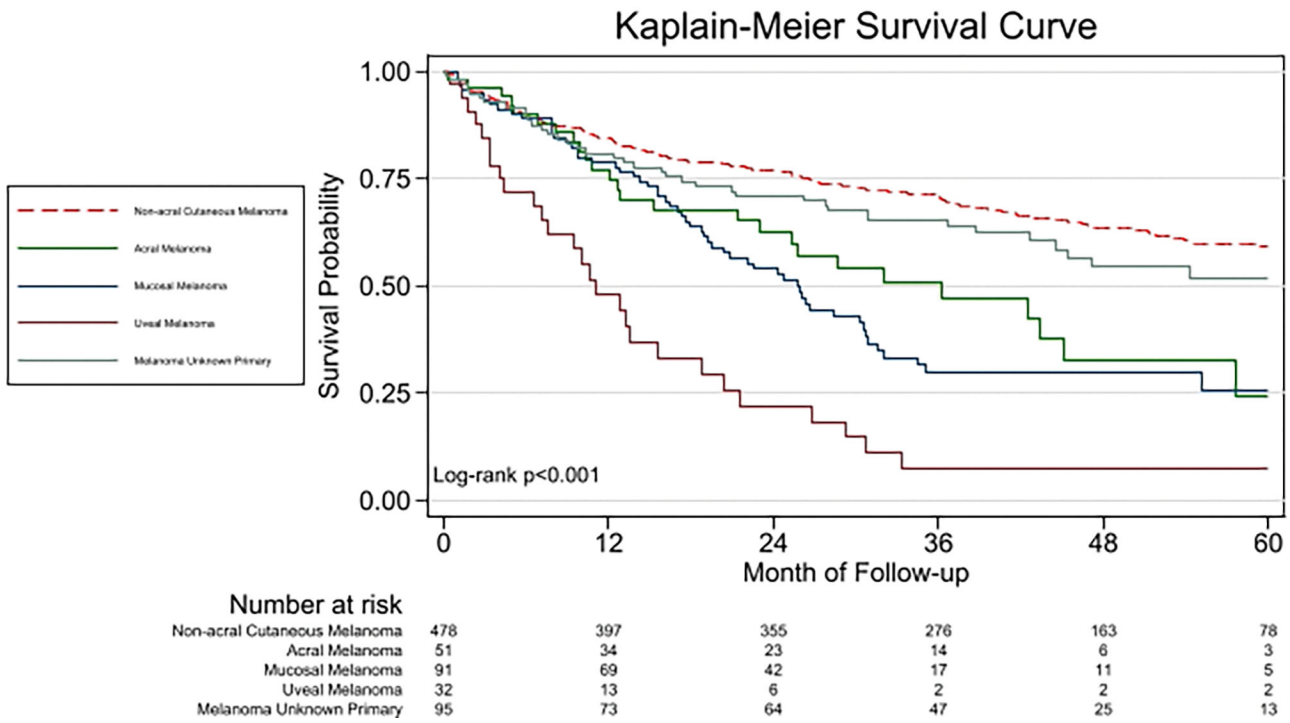
26. Teulings HE, Limpens J, Jansen SN, et al. Vitiligo-like depigmentation in patients with stage III-IV melanoma receiving immunotherapy and its association with survival: a systematic review and meta-analysis. J Clin Oncol. Mar 1 2015;33(7):773–81. doi:10.1200/JCO.2014.57.4756 [PubMed: 25605840]

27. Egberts F, Bergner I, Kruger S, et al. Metastatic melanoma of unknown primary resembles the genotype of cutaneous melanomas. Ann Oncol. Jan 2014;25(1):246–50. doi:10.1093/annonc/mdt411 [PubMed: 24276025]

28. Chen S, LeBoeuf N, Reynolds K, Semenov Y. 1263 Dermatologic immune related adverse event disease definitions: a multi-institutional Delphi consensus project presented on behalf of the oncodermatology working group. vol 10. 2022:A1309–A1309.

29. Lu C, Zhang S, Tang K, et al. 215 Cutaneous immune-related adverse events predict longer patient survival in advanced cancer patients. J Investig Dermatol. 2022;142(8):S36.

30. Zhang S, Tang K, Wan G, et al. Cutaneous immune-related adverse events are associated with longer overall survival in advanced cancer patients on immune checkpoint inhibitors: a multi-institutional cohort study. J Am Acad Dermatol. 2022; Accepted.



Number at risk

Non-acral Cutaneous Melanoma	478	397	355	276	163	78
Acral Melanoma	51	34	23	14	6	3
Mucosal Melanoma	91	69	42	17	11	5
Uveal Melanoma	32	13	6	2	2	2
Melanoma Unknown Primary	95	73	64	47	25	13

Figure 1: Kaplan-Meier Survival Curves by Primary Melanoma Subtype

Table 1:

Characteristics of Study Cohort by Primary Melanoma Subtype

Characteristic	Non-Acral Cutaneous Melanoma N=478	Acral Melanoma N=51	Mucosal Melanoma N=91	Uveal Melanoma N = 32	Melanoma Unknown Primary N = 95	p-value
Age at ICI Initiation						
Median [IQR], year	64.8 [56.2, 73.9]	67.2 [56.1, 76.7]	65.4 [59.0, 74.4]	65.9 [58.5–69.8]	63.8 [54.0– 72.3]	0.47
Sex, n (%)						<0.001
Female	160 (33.5%)	24 (47.1%)	53 (55.9%)	19 (59.4%)	38 (40.0%)	
Male	318 (66.5%)	27 (52.9%)	38 (44.1%)	13 (40.6%)	57 (60.0%)	
Race or Ethnicity, n (%)						<0.001
African American	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Asian	1 (0.5%)	1 (2.2%)	3 (2.9%)	1 (3.1%)	0 (0.0%)	
Hispanic or Latino	0 (0.0%)	3 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Unknown	10 (1.5%)	0 (0.0%)	1 (1.5%)	0 (0.0%)	0 (0.0%)	
White	467 (98.0%)	47 (91.1%)	87 (95.6%)	31 (96.9%)	95 (100.0%)	
Charleston Comorbidity Index						
Median [IQR]	4.0 [2.0, 6.0]	4.0 [2.0, 6.0]	4.0 [2.0, 5.0]	4.0 [3.0,5.0]	3.0 [2.0,5.0]	0.77
ICI Type, n (%)						0.009
Combination	82 (17.2%)	9 (17.6%)	34 (37.4%)	11 (34.4%)	20 (21.1%)	
Anti-CTLA-4	41 (8.6%)	4 (7.8%)	3 (3.3%)	3 (9.4%)	9 (9.5%)	
Anti-PD1	347 (72.6%)	38 (74.5%)	54 (59.3%)	18 (56.3%)	65 (68.4%)	
Anti-PDL1	8 (1.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)	
Year of ICI Initiation, n (%)						0.057
2011–2013	12 (2.5%)	1 (2.0%)	3 (2.9%)	2 (6.3%)	4 (4.2%)	
2014–2017	328 (67.0%)	29 (56.9%)	48 (50.0%)	16 (50.0%)	62 (65.3%)	
2018–2020	138 (29.9%)	21 (41.2%)	40 (47.1%)	14 (43.8%	29 (30.5%)	
AJCC Stage at ICI Initiation, n (%)						<0.001
II	11 (2.3%)	2 (3.9%)	1 (1.1%)	0 (0.0%)	1 (1.1%)	
III	165 (35.2%)	24 (47.1%)	30 (33.0%)	1 (3.1%)	15 (16.1%)	
IV	293 (62.5%)	25 (49.0%)	60 (65.9%)	31 (96.9%)	77 (82.8%)	
Adjuvant ICI Therapy, n (%)						<0.001
No	355 (75.2%)	30 (58.8%)	73 (80.2%)	31 (97.4%)	80 (86.0%)	
Yes	117 (24.8%)	21 (41.2%)	18 (19.8%)	1 (2.6%)	13 (14.0%)	
Duration of Follow-up						

Characteristic	Non-Acral Cutaneous Melanoma	Acral Melanoma	Mucosal Melanoma	Uveal Melanoma	Melanoma Unknown Primary	p-value
	N=478	N=51	N=91	N = 32	N = 95	
Median [IQR], year	3.3 [1.9, 4.5]	1.8 [0.8, 3.2]	1.7 [1.0, 2.6]	0.8 [0.4, 1.6]	3.0 [1.1,4.1]	<0.001
CirAE, n (%)						0.017
No	324 (67.8%)	43 (84.3%)	54 (58.8%)	26 (81.3%)	64 (67.4%)	
Yes	154 (32.2%)	8 (15.7%)	37 (41.2%)	6 (18.8%)	31 (31.6%)	
Time to CirAE Onset						
Median [IQR], year	0.2 [0.1, 0.5]	0.5 [0.2, 1.1]	0.2 [0.1, 0.5]	0.2 [0.1,0.6]	0.1 [0.0,0.2]	<0.051
Mortality, n (%)						0.001
Dead	178 (37.2%)	26 (51.0%)	57 (62.6%)	27 (84.4%)	40 (42.1%)	
Alive	300 (62.8%)	25 (49.0%)	34 (37.4%)	5 (15.6%)	55 (57.9%)	

Abbreviations: CI, confidence interval; cirAE, cutaneous immune-related adverse events; HR, hazard ratio; ICI, immune checkpoint inhibitor; IQR, interquartile range.

Table 2:

CirAE Morphology Characteristics by Primary Melanoma Subtype

Characteristic	Non-acral Cutaneous Melanoma	Acral Melanoma	Mucosal Melanoma	Uveal Melanoma	Melanoma Unknown Primary	p-value
	N = 154 / 478	N = 8 / 51	N = 37 / 91	N = 6 / 32	N = 31 / 95	
Morphology, n (%) *						0.066
Rash NOS	45 (29.2%)	2 (25.0%)	12 (32.4%)	2 (33.3%)	13 (41.9%)	
Drug Hypersensitivity	12 (7.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.2%)	
Eczematous Eruption	8 (5.2%)	0 (0.0%)	1 (2.7%)	0 (0.0%)	1 (3.2%)	
Lichenoid Eruption	8 (5.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (6.5%)	
Maculopapular Eruption	33 (21.4%)	1 (12.5%)	13 (35.1%)	3 (50.0%)	6 (19.4%)	
Isolated Pruritus	22 (14.3%)	0 (0.0%)	5 (13.5%)	1 (16.7%)	5 (16.1%)	
Vitiligo	11 (7.1%)	4 (50.0%)	2 (5.4%)	0 (0.0%)	0 (0.0%)	
Other **	15 (9.7%)	1 (12.5%)	4 (10.8%)	0 (0.0%)	3 (9.7%)	

* For the first cirAE only.

** Includes individual morphologies with fewer than 10 observed cases in the study population - acneiform eruption, bullous eruption, erythema-multiforme-like eruption, mucositis, panniculitis, psoriasiform eruption, and SJS/TEN-like eruption.

Abbreviations: NOS, not otherwise specified.

Table 3.

Results of Multivariable Accelerated Failure Time Regression Model of CirAE Onset by Primary Melanoma Subtype

Characteristic	HR	95% CI		p-value
Primary Melanoma				
Non-acral Cutaneous Melanoma	*ref	*ref	*ref	*ref
Acral Melanoma	0.41	0.20	0.85	0.016
Mucosal Melanoma	1.16	0.79	1.72	0.448
Uveal Melanoma	0.65	0.28	1.49	0.310
Melanoma of Unknown Primary	1.24	0.83	1.84	0.291
Age at ICI Initiation	0.99	.98	1.01	0.426
Sex				
Male	*ref	*ref	*ref	*ref
Female	1.02	0.78	1.34	0.874
Race or Ethnicity				
White	*ref	*ref	*ref	*ref
Asian	1.46	0.45	4.70	0.525
Hispanic or Latino	<0.001	0.00	–	0.992
Unknown	0.25	0.03	1.79	0.168
ICI Type				
Anti-CTLA-4	*ref	*ref	*ref	*ref
Combination	1.78	1.00	3.20	0.051
Anti-PD-1	0.84	0.49	1.43	0.522
Anti-PD-L1	0.90	0.26	3.15	0.865
Charleston Comorbidity Index	1.04	0.98	1.11	0.212
Year of ICI Initiation	1.23	1.12	1.36	<0.001
AJCC Stage at ICI Initiation				
II	*ref	*ref	*ref	*ref
III	1.09	0.44	2.71	0.847
IV	0.72	0.28	1.82	0.486
Adjuvant Therapy				
No	*ref	*ref	*ref	*ref
Yes	0.76	0.52	1.12	0.167

*Reference group.

Abbreviations: CI, confidence interval; cirAE, cutaneous immune-related adverse events; HR, hazard ratio; ICI, immune checkpoint inhibitor.

Table 4.

Results of A Multivariate Time-Varying Cox Model for Cancer-Specific Mortality by Primary Melanoma Subtypes

Characteristic	HR	95% CI		p-value
CirAE	0.73	0.53	0.99	0.043
Primary Melanoma				
Non-Acral Cutaneous Melanoma	*ref	*ref	*ref	*ref
Acral Melanoma	2.04	1.24	3.36	0.005
Mucosal Melanoma	2.30	1.58	3.35	<0.001
Uveal Melanoma	4.09	2.50	6.68	<0.001
Melanoma of Unknown Primary	1.22	0.80	1.84	0.351
Age at ICI initiation	1.01	1.00	1.02	0.149
Sex				
Male	*ref	*ref	*ref	*ref
Female	1.29	0.99	1.70	0.064
Race or Ethnicity				
White	*ref	*ref	*ref	*ref
Asian	0.57	0.14	2.36	0.439
Hispanic or Latino	2.31	0.30	17.78	0.421
Unknown	0.47	0.06	3.39	0.452
ICI Type				
Anti-CTLA-4	*ref	*ref	*ref	*ref
Combination	0.91	0.53	1.57	0.745
Anti-PD-1	0.45	0.28	0.74	0.002
Anti-PD-L1	<0.001	0	–	1.000
Charleston Comorbidity Index	1.12	1.06	1.19	<0.001
Year of ICI Initiation	1.27	1.15	1.40	<0.001
AJCC Stage at ICI Initiation				
II	*ref	*ref	*ref	*ref
III	2.35	0.32	17.13	0.399
IV	4.18	0.57	30.49	0.158
Adjuvant Therapy				
No	*ref	*ref	*ref	*ref
Yes	0.62	0.38	1.00	0.050

*Reference group.

Abbreviations: CI, confidence interval; CirAE, cutaneous immune-related adverse events; HR, hazard ratio; ICI, immune checkpoint inhibitor.