ONCOIMMUNOLOGY
2025, VOL. 14, NO. 1, 2494433
https://doi.org/10.1080/2162402X.2025.2494433

Taylor & Francis
Taylor & Francis Group

ORIGINAL RESEARCH

OPEN ACCESS Check for updates

# Impact of steroid dose and timing on efficacy of combination PD-1/CTLA-4 blockade

Nina B. Curkovic[a,b], Rebecca Irlmeier[c], Xue Bai[d], Can Cui[d], Fei Ye[a,c], Hannah R. Burnette[e], Aleigha R. Lawless[d], Juliane Andrade Czapla[d], Ryan Sullivan[d], and Douglas B. Johnson[e]

[a]School of Medicine, Vanderbilt University, Nashville, TN, USA; [b]Department of Internal Medicine, UT Southwestern Medical Center, Dallas, TX, USA; [c]Vanderbilt Ingram Cancer Center, Department of Biostatistics, Vanderbilt University Medical Center, Nashville, TN, USA; [d]Department of Medicine, Massachusetts General Hospital Cancer Center, Boston, MA, USA; [e]Vanderbilt Ingram Cancer Center, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA

**ABSTRACT**

With the increasing use of immune checkpoint inhibitors (ICIs) in combination regimens and in earlier stages of advanced melanoma, the effective management of immune-related adverse events (irAEs) is key to balancing immunotherapy efficacy and toxicity. Conflicting evidence exists on possible detrimental effects of immunosuppression with corticosteroids for irAEs on ICI effectiveness. We conducted a multicenter, retrospective cohort study of immunotherapy-naïve advanced melanoma patients undergoing treatment with ipilimumab and nivolumab and a small cohort treated with nivolumab/relatlimab. We utilized univariate tests to assess response, PFS, and OS based on presence of irAE, receipt of steroids for irAEs, peak dose, and time-to-steroid, as well as multivariable analysis for response, OS, and PFS in patients receiving steroids for irAEs. Among 226 total ipilimumab/nivolumab patients, those without irAEs had poorer PFS and OS compared to irAE groups regardless of steroid administration. In subgroup analysis of patients receiving steroids for an irAE, increased time-to-steroid was significantly associated with improved response (aOR, 1.026 $p = 0.0005$), PFS (aHR, 0.986 $p = 0.001$), and OS (aHR, 0.983 $p = 0.0008$). Higher peak steroid dose was significantly associated with poorer PFS (aHR, 1.002 $p = 0.005$), and OS (aHR, 1.002 $p = 0.003$). Use of additional immunosuppressants was associated with poorer OS (aHR, 1.941 $p = 0.018$). Cumulative dose was not significantly associated with outcomes. Among 42 additional patients treated with nivolumab/relatlimab, irAEs were significantly associated with improved PFS/OS, which appeared to be slightly mitigated by steroid administration; dosing relationships were limited by small numbers.

**ARTICLE HISTORY**
Received 5 November 2024
Revised 17 March 2025
Accepted 10 April 2025

**KEYWORDS**
Immune checkpoint inhibitor; immune-related adverse event - irAE; immunosuppression; immunotherapy

## Introduction

Immune checkpoint inhibitors (ICIs) have transformed the landscape of melanoma treatment within the last decade. Current ICIs used in the treatment of melanoma target the programmed death-1/ligand-1 (PD-1/PD-L1), cytotoxic T lymphocyte antigen-4 (CTLA-4), and lymphocyte activation gene-3 (LAG-3) checkpoint molecules. Under normal circumstances, activity of these checkpoints and binding by their ligands lead to dampened T-cell proliferation, effector function, and enhancement of regulatory T cell (Treg) immunosuppressive activity to regulate T cell activation and prevent auto-immune inflammation. By prohibiting their activity, ICIs disinhibit the immune system to promote tumor cytotoxicity. With broad, nonspecific activation of the immune system to generate an anti-tumor response, subsequent T cell activation and loss of self-tolerance frequently lead to off-target autoimmune-like inflammation, known as immune-related adverse events (irAEs.)[1] This inflammation can occur in virtually any organ system, leading to irAEs like hypophysitis, colitis, hepatitis, pneumonitis or very commonly, cutaneous manifestations. Nearly all patients receiving dual checkpoint blockade with anti-PD-1 and anti-CTLA-4 agents will experience some form of irAE, with severe irAEs seen in up to 50% of these patients. Though irAEs are less common in monotherapy regimens, rates of mild and severe irAEs in anti-PD-1-treated patients approach 70% and 20%, respectively.[2,3] With the increasing use of ICIs, often in combination regimens and in earlier stages of advanced melanoma, the effective management of irAEs is paramount in balancing immunotherapy administration and efficacy with its toxicities.[4]

Depending on their severity, irAEs may lead to lapses in treatment, permanent discontinuation of therapy, and significant morbidity for patients.[5,6] While indications for the treatment of irAEs with corticosteroids often vary by organ system, irAE severity, and society guidelines, the Common Terminology Criteria for Adverse Events (CTCAE) is utilized to grade the severity of irAEs from grades one (mild) through five, with grades three and above considered severe.[7] The mainstay of treatment for most moderate-to-severe irAEs in current practice guidelines is systemic corticosteroids, with additional immunosuppressants used for steroid-refractory irAEs.[8,9] Corticosteroids have historically been an effective method of mitigating irAEs due to their immunosuppressive effect directly opposing ICI-induced broad immune activation.

**CONTACT** Nina B. Curkovic nina.b.curkovic@vanderbilt.edu School of Medicine, Vanderbilt University, Nashville, TN, USA
Supplemental data for this article can be accessed online at https://doi.org/10.1080/2162402X.2025.2494433

Since ICIs must unleash immune checkpoint "brakes" to be effective, the potential for corticosteroids and other immunosuppressants to stymie the anti-tumor immune response remains an incompletely elucidated topic of concern.

Few studies have examined associations between therapeutic outcomes and more detailed corticosteroid use characteristics for the treatment of irAEs, such as dose, duration, and their use with other steroid-sparing immunosuppressants. Furthermore, existing studies have drawn conflicting conclusions on the potential role of corticosteroids to impede therapeutic outcomes. Indication for which steroids are used (e.g. cancer-related vs immune-related) may delineate a branch point between proposed associations with decreased or improved OS and PFS, with earlier studies lacking adjustment by indication of steroid exposure. Further studies have demonstrated that steroid use for cancer-related indications, such as for central nervous system metastases (which is independently often associated with a worse prognosis), has been associated with poorer outcomes. However, the development of irAEs has also independently been correlated with improved outcomes, which may further impact this observed difference.[10–15]

As corticosteroids continue to serve as a pillar in the management of irAEs, greater investigation into the nuances of their use and subsequent impact on outcomes is warranted. Herein, we present findings associating presence, dosing, and timing of corticosteroid use with response, PFS, and OS in a cohort of immunotherapy-naïve advance melanoma patients treated with ipilimumab and nivolumab.

## Methods

### Patients and study design

This retrospective multicenter cohort study included patients from two U.S. cancer centers. Included patients were immunotherapy-naïve patients with metastatic melanoma who initiated treatment with ipilimumab and nivolumab between December 2014 and September 2023. Patients were excluded if they had received any prior immunotherapy, including single-agent checkpoint inhibition with ipilimumab or PD-1/PD-L1 blocking agents, or interleukin-2 (IL-2). An additional cohort of patients who received nivolumab/relatlimab at any line was also included and analyzed separately.

### Data collection and outcome assessment

Baseline patient and tumor characteristics were collected at the start of ICI treatment, including age, sex, primary tumor type (cutaneous, acral, mucosal, uveal, or unknown), known tumor mutations, M stage (AJCC 8th Ed.), Eastern Cooperative Oncology Group (ECOG) performance status, lactate dehydrogenase (LDH), and presence or absence of an existing autoimmune condition. Prior treatment information was collected, including lines of treatment, as well as start and end dates of treatment, total doses, and reason for treatment discontinuation. Continuation of treatment with PD-1 monotherapy and date of cessation were noted.

Best response was assessed using Response Evaluation Criteria in Solid Tumors (RECIST). Progression Free Survival (PFS, months) was defined as the time from starting treatment until progressive disease (PD) or death. Overall survival (OS, months) was defined as the time from starting treatment until death.

The irAE type, grade, date of onset, and irAE treatment details were collected for irAEs occurring within 3 months of any dose of ipilimumab and nivolumab or nivolumab/relatlimab. Steroid history for treatment of each irAE was collected including date of steroid initiation, cessation, peak dose, cumulative dose, route of administration, and use of any additional immunosuppressants. Peak and cumulative doses were converted to per os (PO) prednisone equivalents for final analysis. Topical steroids, intra-articular steroid injections, and steroids with localized absorption, such as budesonide, were not included in cumulative dose calculations for systemic steroid exposure. In patients who experienced irAEs that required adrenal replacement doses of corticosteroids, the date of cessation for irAE treatment was noted as the last day prior to decreasing to replacement level dosing (typically 5–10 mg prednisone as determined by clinician adjustment) and continuation on adrenal replacement was noted. Steroids and subsequent dose calculations were attributed to an irAE based upon clinician notes in the EHR. Multiple courses of steroids used for multiple irAEs in a single patient were separated in dose calculations per physician attribution of steroid course to individual irAEs as documented. Additionally, baseline steroid use for other indications (most commonly, cancer-related symptoms) was noted if present before or during ICI treatment. Patients were excluded if insufficient information regarding irAE grade, treatment duration, or cumulative and peak dose of corticosteroids were unable to be recorded accurately.

### Statistical methods

Baseline characteristics of independent steroid variables of interest, irAE presence and outcomes, and covariates were analyzed using descriptive statistics. Univariate tests to assess response, PFS, and OS by several groupings (presence of irAE, receipt of steroids for irAEs, peak dose quartiles, and time-to-steroid quartiles) were conducted utilizing Chi-squared test (categorical data) and Kaplan–Meier curves with log-rank test (time-to-event data). Patients were censored on the date of their last follow-up visit or death. Multivariable analysis utilizing logistic regression for response and Cox proportional hazard regression for OS and PFS in patients receiving steroids for irAEs was conducted. Steroid-specific variables of interest, including peak and total steroid dose, time-to-first steroid, and use of additional immunosuppressants were adjusted for in the model. Additional covariates included institution, age, sex, primary tumor, M stage, prior therapies, ECOG performance status, LDH elevation, baseline steroid use, and use of steroid replacement for adrenal insufficiency. Missing covariate data were imputed using multiple imputation. Due to sample size limitations, backward selection was used with a conservative cutoff to avoid

overfitting in each multivariable model. All statistical analyses were performed in R version 4.3.2.

## Results

### Patient characteristics

In total, 226 patients treated with ipilimumab and nivolumab for advanced melanoma were included; patients were treated at Vanderbilt Ingram Cancer Center (158; 69.9%) and Massachusetts General Hospital Cancer Center (68; 30.1%). A total of 183 (81.0%) patients experienced any grade irAE. Mean age of the predominantly male (63.7%) cohort was 59.3 y. Most patients had cutaneous or melanoma of unknown origin (191; 84.5%) and higher stage metastatic disease (75.2% M1c/M1d vs. 24.8% M1a/M1b) with only 10.2% of patients having received a prior line of therapy. ECOG performance status was ≤1 in most (90.3%) patients, with elevated LDH in 50.9%. Baseline use of steroids for a preexisting condition, including for cancer-related symptoms, was present in 12.4% of patients. Ultimately, following the onset of irAE, 19.0% of patients continued to replace corticosteroids for adrenal insufficiency (Table 1).

### Outcomes in patients with and without irAEs

Given the previously established association of irAE development and improved outcomes, we first compared outcomes in patients developing irAEs to those that did not. Of patients developing an irAE of any grade ($n = 183$), 53.6% responded to treatment compared with 18.6% of patients who did not develop an irAE ($p < 0.0001$). PFS and OS were longer in the irAE group, with a median PFS of 18.4 months and a median OS of 51.8 months compared with 1.2 months and 4.9 months in the non-irAE group, respectively ($p < 0.0001$) (Figure 1).

### Outcomes among patients without irAEs and with or without steroids for irAEs

We then assessed whether patients who received steroids had improved outcomes. Patients who received steroids for an irAE had improved response, OS, and PFS compared with those not receiving steroids (Supplemental Figure S1). To dissect the disparate impact of irAEs vs. steroids (since irAEs are known to associate with improved outcomes), we assessed patients with irAEs treated with steroids, vs. those with irAEs not treated with steroids, vs. those lacking irAEs. Notably, steroid presence or absence did not appear to impact PFS or OS, although both groups performed superiorly compared with those lacking irAEs ($p < 0.0001$) (Figure 1).

### Peak steroid dose and time-to-steroid initiation

To better understand whether specific aspects of steroid administration may impact outcomes in patients receiving steroids for irAE, as suggested by some studies, we conducted additional univariate analyses by quartiles for peak steroid dose and time-to-steroids.

Peak dose quartiles were 5–60 mg ($n = 49$), 60–80 mg ($n = 20$), 80–150 mg ($n = 36$), and 150–1250 mg ($n = 31$) in prednisone

**Table 1.** Basic demographic and treatment characteristics of the entire study cohort.

| Presence of AE: | No ($n = 43$) | Yes ($n = 183$) | Overall ($n = 226$) |
|---|---|---|---|
| **Institution** | | | |
| MGH | 6 (14.0%) | 62 (33.9%) | 68 (30.1%) |
| VUMC | 37 (86.0%) | 121 (66.1%) | 158 (69.9%) |
| **Age** | | | |
| Mean (SD) | 61.0 (13.7) | 58.8 (13.3) | 59.3 (13.3) |
| Median [Q1, Q3] | 64.0 [49.0, 69.5] | 61.0 [51.0, 68.0] | 61.5 [50.2, 69.0] |
| **Sex** | | | |
| Female | 15 (34.9%) | 67 (36.6%) | 82 (36.3%) |
| Male | 28 (65.1%) | 116 (63.4%) | 144 (63.7%) |
| **Primary Tumor** | | | |
| Cutaneous/unknown | 34 (79.1%) | 157 (85.8%) | 191 (84.5%) |
| Acral/mucosal/uveal | 9 (20.9%) | 26 (14.2%) | 35 (15.5%) |
| **M stage** | | | |
| M1a/M1b | 10 (23.3%) | 46 (25.1%) | 56 (24.8%) |
| M1c/M1d | 33 (76.7%) | 137 (74.9%) | 170 (75.2%) |
| **Therapy prior to combined aPD1/aCTLA4** | | | |
| No | 35 (81.4%) | 168 (91.8%) | 203 (89.8%) |
| Yes | 8 (18.6%) | 15 (8.2%) | 23 (10.2%) |
| **ECOG** | | | |
| 0 | 6 (14.0%) | 68 (37.2%) | 74 (32.7%) |
| 1–3 | 36 (83.7%) | 112 (61.2%) | 148 (65.5%) |
| Missing | 1 (2.3%) | 3 (1.6%) | 4 (1.8%) |
| **LDH elevated** | | | |
| No | 8 (18.6%) | 91 (49.7%) | 99 (43.8%) |
| Yes | 32 (74.4%) | 83 (45.4%) | 115 (50.9%) |
| Missing | 3 (7.0%) | 9 (4.9%) | 12 (5.3%) |
| **Baseline steroid use for preexisting condition** | | | |
| No | 34 (79.1%) | 164 (89.6%) | 198 (87.6%) |
| Yes | 9 (20.9%) | 19 (10.4%) | 28 (12.4%) |
| **If adrenal insufficiency, use of steroid therapy for AE** | | | |
| No | 43 (100%) | 140 (76.5%) | 183 (81.0%) |
| Yes | 0 (0%) | 43 (23.5%) | 43 (19.0%) |

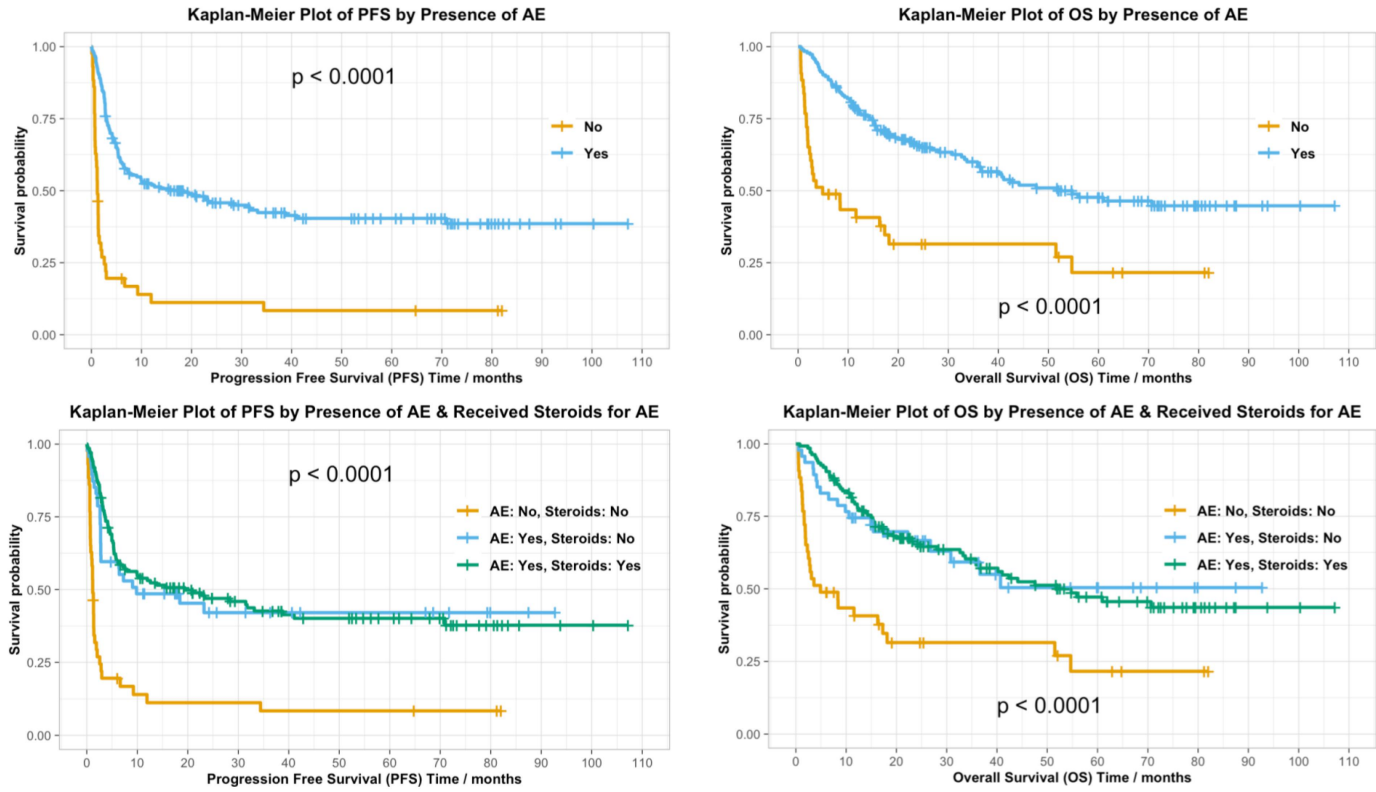


**Figure 1.** Kaplan–Meier curves for PFS and OS in patients with and without irAEs (top panel) and in patients who received steroids for an irAE, patients who developed an irAE but did not receive steroids, and patients without irAEs (bottom panel).

equivalents. Response rates by quartile (in order of increasing peak doses) were 71.4%, 60.0%, 36.1%, and 45.2%. Median PFS by quartile was not reached, 31.7, 5.0, and 5.0 months. Similarly, median OS in the 5–60 mg quartile (not reached) and 60–80 mg quartile (not reached) was longer than for those patients receiving peak doses above 80 mg (18.3 and 55.9 months). Differences in response ($p = 0.0077$), PFS ($p = 0.0011$), and OS ($p = 0.00074$) were significant (Figure 2).

Similarly, time-to-first-steroid exposure was assessed in quartiles from 0–28 d ($n = 40$), 28–49 d ($n = 30$), 49–70.2 d ($n = 32$), and 70.2–144 d ($n = 34$). Response rates appeared to decrease with shorter time-to-steroid initiation at 32.5%, 50.0%, 65.6%, 73.5% for quartiles increasing in time-to-steroid as listed previously. Median PFS by increasing quartile was 5.36, 7.84, not reached, and 70.92 months, respectively. Median OS was 23.6, 32.6 months and not reached in the quartiles beyond 49 d. Differences in response ($p = 0.002$), PFS ($p = 0.009$), and OS ($p = 0.002$) were significant (Figure 2).

### *Multivariable regression: cumulative and peak dose, time-to-steroids, and use of additional immunosuppressants*

Given that outcomes may be impacted by a multitude of factors apart from steroid use, we conducted multivariable regression analyses adjusting for several covariates including institution, age, sex, primary tumor, M stage, prior therapy, ECOG performance status, LDH elevation, baseline steroid use, use of steroid replacement for adrenal insufficiency, time to first steroid, peak steroid dose, cumulative steroid dose, and use of additional immunosuppressants.

In subgroup analysis of patients receiving steroids for an irAE, increased time-to-steroid was significantly associated with improved response (aOR, 1.026 [95% CI 1.011–1.041] $p < 0.001$), PFS (aHR, 0.986 [95% CI 0.977–0.994] $p = 0.001$), and OS (aHR, 0.983 [95% CI 0.973–0.993] $p < 0.001$). Higher peak steroid dose was significantly associated with poorer PFS (aHR, 1.002 [95% CI 1.000–1.003] $p = 0.005$), and OS (aHR, 1.002 [95% CI 1.001–1.004] $p = 0.003$). Likewise, use of additional immunosuppressants was associated with poorer OS (aHR, 1.941 [95% CI 1.123–3.357] $p = 0.018$). Cumulative dose was not significantly associated with response and was not retained in the final models for OS and PFS by backward selection. Acral/mucosal/uveal primary tumor type was associated with poorer response, while prior therapy was associated with poorer OS (aHR, 3.037 [95% CI 1.245–7.410] $p = 0.015$). Both ECOG performance status of 1–3 (aHR, 0.535 [95% CI 0.306–0.936] $p = 0.029$) and use of replacement steroid therapy for adrenal insufficiency (HR, 0.441 [95% CI 0.216–0.897] $p = 0.024$) were associated with improved OS (Figures 3, 4 through 5).

In the entire study population ($n = 226$), presence of an irAE (aOR, 3.57 [95% CI 1.271–10.021] $p = 0.016$) and use of replacement steroid therapy for adrenal insufficiency (aOR, 2.19 [95% CI 1.003–4.760] $p = 0.049$) were significantly associated with improved response, while acral/mucosal/uveal primary tumor types were significantly associated with lowered response (aOR, 0.237 [95% CI 0.092–0.612] $p = 0.003$). Similarly, the presence of an irAE, male sex, and the use of

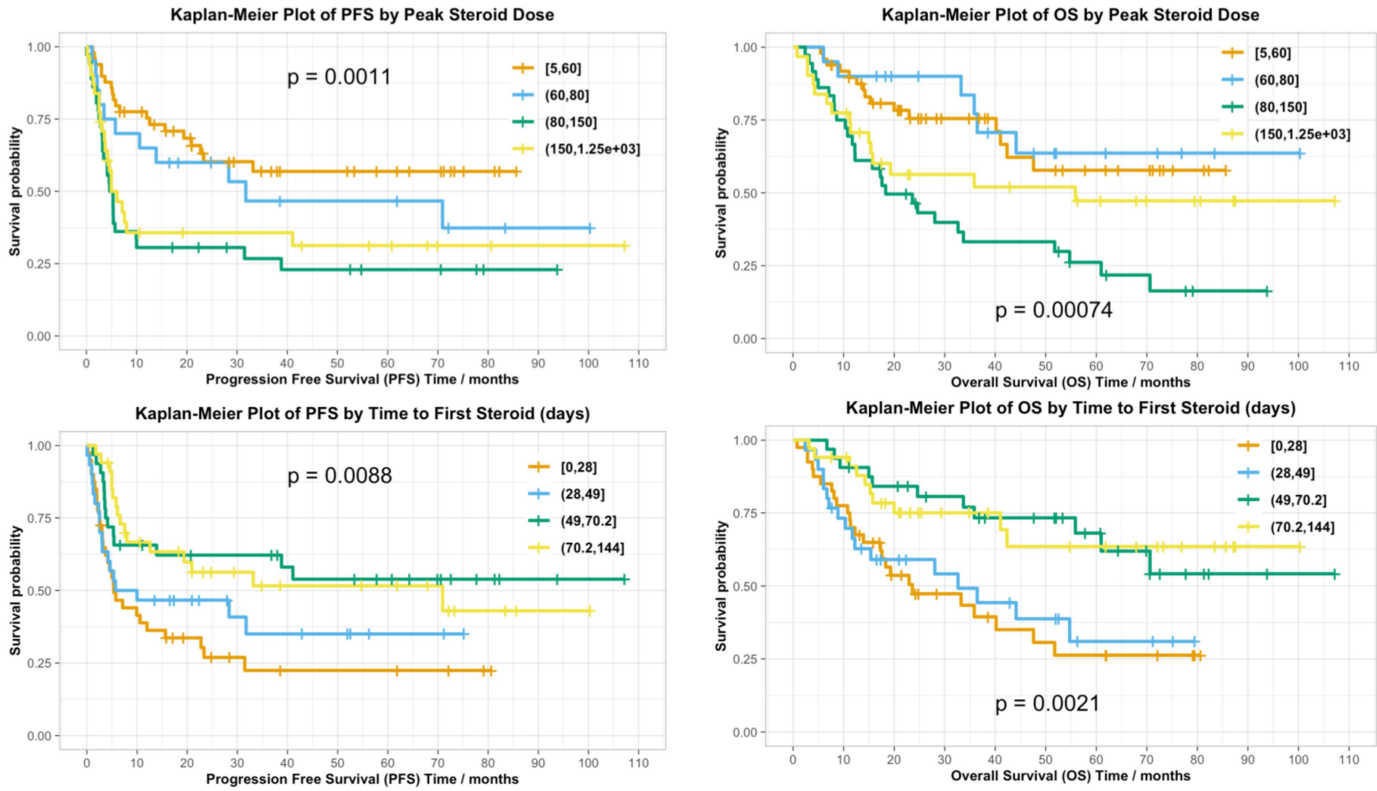


**Figure 2.** Kaplan–Meier curves for PFS and OS in patients who received steroids for an irAE divided into dose quartiles (top panel) and in patients who received steroids for an irAE divided into time-to-first-steroid exposure quartiles (bottom panel.) peak dose quartiles shown are 5–60 mg ($n = 49$), 60–80 mg ($n = 20$), 80–150 mg ($n = 36$), and 150–1250 mg ($n = 31$) in prednisone equivalents. Time-to-first-steroid exposure quartiles shown are from 0–28 d ($n = 40$), 28–49 d ($n = 30$), 49–70.2 d ($n = 32$), and 70.2–144 d ($n = 34$).

| | Response | | | | |
|---|---|---|---|---|---|
| | Estimate | Odds Ratios | CI - Lower | CI - Upper | p |
| Intercept | 0.1995 | 1.2207 | 0.4016 | 3.7110 | 0.7251 |
| Primary tumor - Acral/mucosal/uveal | -1.5610 | 0.2099 | 0.0647 | 0.6816 | **0.0094** |
| M stage - M1c/M1d | -0.6517 | 0.5212 | 0.2132 | 1.2741 | 0.153 |
| Therapy prior to combined aPD1/aCTLA4 - Yes | -1.3255 | 0.2657 | 0.0447 | 1.5789 | 0.1449 |
| Time to first steroid in days | 0.0257 | 1.0260 | 1.0112 | 1.0411 | **5e-04** |
| Total steroid dose | -0.0002 | 0.9998 | 0.9996 | 1.0000 | 0.0634 |

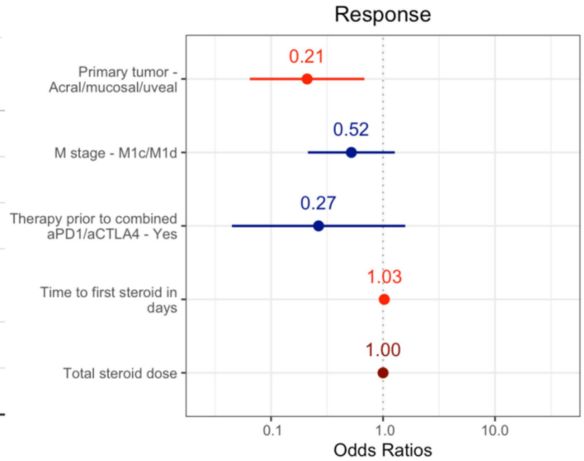


**Figure 3.** Table and forest plot demonstrating odds ratios (OR) for response and covariates listed among patients who received steroids for an irAE ($n = 136$). The logistic regression model was significant for primary tumor (acral/mucosal/uveal) and time-to-first-steroid initiation. Significant ORs are denoted in red.

replacement steroid therapy for adrenal insufficiency were significantly associated with improved PFS and OS. Baseline use of steroids was significantly associated with poorer PFS and OS, while higher M stage (M1c/M1d) was significantly associated with poorer PFS only (Supplemental Figure S2). Receipt of steroids for an irAE was not significantly associated with response, PFS, or OS.

### *Nivolumab/relatlimab cohort*

We identified 42 patients treated with nivolumab/relatlimab (Supplemental Table S1). Median age was 74 y, 26 patients (62%) were male, 50% had stage IV M1c/d disease, and 17 (40%) had prior therapy. As with ipilimumab and nivolumab, outcomes were improved in patients with irAEs ($n = 25$) vs. those without ($n = 17$) for response (60% vs. 11.8%, $p = 0.005$), PFS (median 31.5 vs. 9.0

| | PFS | | | | |
|---|---|---|---|---|---|
| | Estimate | Hazard Ratios | CI - Lower | CI - Upper | p |
| Sex - Male | -0.3467 | 0.7070 | 0.4454 | 1.1225 | 0.1415 |
| Primary tumor - Acral/mucosal/uveal | 0.4933 | 1.6377 | 0.9199 | 2.9158 | 0.0937 |
| M stage - M1c/M1d | 0.2879 | 1.3336 | 0.7912 | 2.2479 | 0.2798 |
| ECOG - 1-3 | -0.3829 | 0.6819 | 0.4275 | 1.0878 | 0.1081 |
| Time to first steroid in days | -0.0145 | 0.9856 | 0.9769 | 0.9943 | **0.0013** |
| Peak steroid dose | 0.0015 | 1.0015 | 1.0004 | 1.0026 | **0.0054** |
| Use of additional immunosuppressants - Yes | 0.4857 | 1.6253 | 0.9925 | 2.6614 | 0.0536 |
| If adrenal insufficiency, use of steroid therapy for AE - Yes | -0.5029 | 0.6047 | 0.3339 | 1.0954 | 0.0971 |

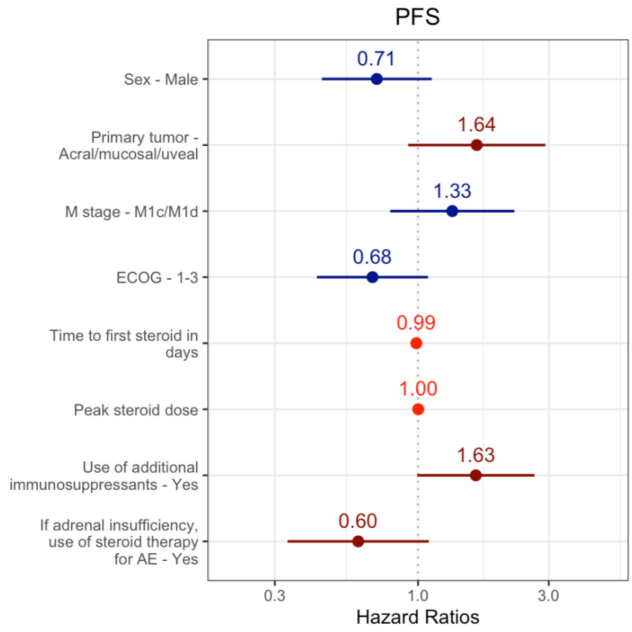


**Figure 4.** Table and forest plot demonstrating hazard ratios (HR) for PFS and covariates listed among patients who received steroids for an irAE ($n = 136$). The cox regression model was significant for time-to-first-steroid initiation and peak steroid dose. Significant HRs are denoted in red.

| | OS | | | | |
|---|---|---|---|---|---|
| | Estimate | Hazard Ratios | CI - Lower | CI - Upper | p |
| Age | 0.014 | 1.014 | 0.993 | 1.036 | 0.1868 |
| Primary tumor - Acral/mucosal/uveal | 0.593 | 1.809 | 0.956 | 3.423 | 0.0685 |
| Therapy prior to combined aPD1/aCTLA4 - Yes | 1.111 | 3.037 | 1.245 | 7.410 | **0.0146** |
| ECOG - 1-3 | -0.626 | 0.535 | 0.306 | 0.936 | **0.0285** |
| Time to first steroid in days | -0.017 | 0.983 | 0.973 | 0.993 | **8e-04** |
| Peak steroid dose | 0.002 | 1.002 | 1.001 | 1.004 | **0.0029** |
| Use of additional immunosuppressants - Yes | 0.663 | 1.941 | 1.123 | 3.357 | **0.0176** |
| If adrenal insufficiency, use of steroid therapy for AE - Yes | -0.819 | 0.441 | 0.216 | 0.897 | **0.0239** |

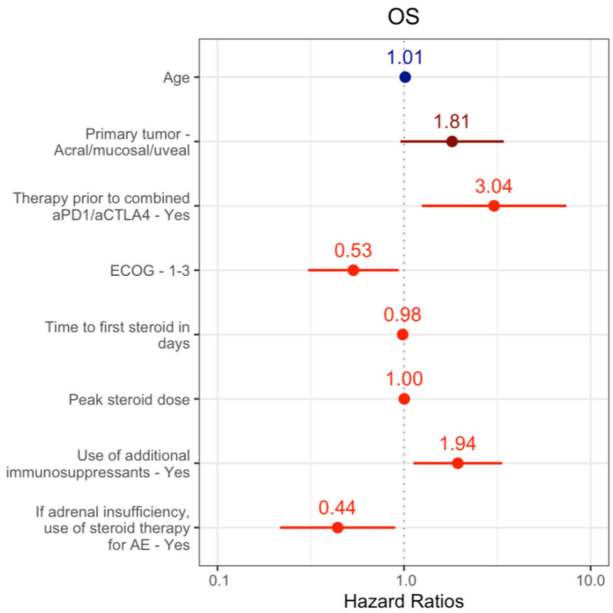


**Figure 5.** Table and forest plot demonstrating hazard ratios (HR) for OS and covariates listed among patients who received steroids for an irAE ($n = 136$). The cox regression model was significant for all covariates listed, except age and primary tumor (acral/mucosal/uveal), including prior therapy, ECOG 1–3, time-to-first-steroid initiation, peak steroid dose, use of additional immunosuppressants, and use of adrenal replacement dose steroid therapy following irAE development. Significant HRs are denoted in red.

months, $p = 0.002$), and OS (median 96.4 vs. 19.3 months, $p < 0.001$). In contrast, there were only non-statistically significant trends toward improvement among patients who received steroids for irAEs ($n = 16$) vs. those who did not ($n = 26$) for response (62.5% vs. 26.9%, $p = 0.05$), PFS (median 19.5 vs. 12.9 months, $p = 0.16$) and OS (median 96.4 vs. 67.4 months, $p = 0.18$) (Supplemental Figure S3). There was no clear difference in clinical outcome based on peak steroid dose, although only 16 patients received steroids.

## Discussion

In this multicenter retrospective cohort study, we identified several factors related to steroid use for irAEs that impacted response, PFS, and OS. Steroid use overall did not impact outcomes; however, both univariate and multivariate analyses suggested that shorter time to steroid administration, higher peak dose of steroids, and use of additional immunosuppressants did correlate with inferior clinical outcomes. In contrast, cumulative (total) dose was not significantly associated with

outcomes, at least once controlled for peak dose. In addition, baseline use of steroids (such as for cancer-related symptoms) was significantly associated with poorer PFS and OS.

Most patients treated with ipilimumab and nivolumab (81.0%) experienced any grade irAE, reflective of the toxicity profile of dual checkpoint blockade with ipilimumab and nivolumab. Patients lacking irAEs had dismal outcomes, with ORR < 20%. Although similar trends have been reported with anti-PD-1 monotherapy, this striking finding suggests that patients who lack even minor irAEs with combination checkpoint blockade may lack the ability to mount any kind of robust immune response.[3,16,17]

The severity and steroid-responsiveness of an irAE frequently dictates management of irAEs regarding dose, time-to-initiation, and use of additional steroid sparing agents, which have demonstrated variable association with outcomes. A recent multicenter study also found that high corticosteroid peak dose was associated with worse PFS and OS (aHR 1.14; 95% CI 1.01–1.29; aHR 1.29; 95% CI 1.12–1.49 for 80 vs 40 mg), while cumulative dose was not.[18] Methylprednisolone pulse dosing (500–1000 mg) was also associated with poorer OS and PFS in one study.[19] Our study findings are consistent with these prior studies, adding to a growing body of literature regarding the effect of peak steroid doses on therapeutic outcomes.

Several studies also report timing of steroid initiation may play a role, with initiation within 4 weeks or under 2 months, impacting PFS and OS, respectively.[12,13] We similarly saw an association between greater time-to-steroid initiation and improved response, PFS, and OS.

The use of additional steroid-sparing immunosuppressants in cases of steroid-refractory irAEs is also relatively common. In some studies, as in our present study, they have been associated with worse PFS and OS, with others demonstrating improved OS and PFS compared with patients being treated with steroids alone.[18,20–22]

To our knowledge, we also performed the first assessment of steroid dose and nivolumab/relatlimab outcomes. We observed broadly similar trends, with poor outcomes for patients lacking all irAEs, and no obvious impact of steroid administration. However, the sample size (particularly the number of patients receiving steroids) did not allow for more nuanced considerations, and larger cohorts will be needed to provide more granularity for PD-1/LAG-3 blockade.

The relation between irAEs, steroids, and clinical outcomes has been nuanced and ill-defined, but our study and other recent data have provided some clarity. First, irAEs, particularly associated with combination PD-1/CTLA-4 blockade clearly associate with superior outcomes. Second, low doses of steroids and those given later in a patient's course (e.g. >50 d in our study) do not appear to severely hamper ongoing immune responses, although higher doses, earlier administration, and additional agents could potentially blunt the anti-tumor response. Finally, peak steroid dose, but not total dose, correlates with worse outcomes, although the two are inextricably entwined. Despite these findings, steroids remain a cornerstone of management, though efforts to test lower doses (and perhaps delay administration) are needed. Ultimately, the immediate risk of severe, life-threatening adverse events must be balanced with the risk of potential detriment to ICI effectiveness when determining a treatment approach.

## Disclosure statement

RJS serves on advisory boards or consults for Bristol Myers Squibb, Merck, Marengo, Pfizer, Novartis, Replimune, and receives research funding from Merck. DBJ serves on advisory boards or consults for AstraZeneca, Bristol Myers Squibb, Merck, Novartis, Pfizer, and Teiko, and receives research funding from Incyte.

## Funding

DBJ is funded by R01CA227481 and R01HL155990 National Institutes of Health [R01CA227481 and R01HL155990].

## ORCID

Nina B. Curkovic http://orcid.org/0000-0003-2200-4988

## Abbreviations

| | |
|---|---|
| AJCC | American Joint Committee on Cancer |
| CI | Confidence interval |
| CTLA-4 | Cytotoxic T-lymphocyte-associated protein 4 |
| ECOG | Eastern Cooperative Oncology Group |
| aHR | adjusted Hazard ratio |
| ICIs | Immune checkpoint inhibitors |
| IL-2 | interleukin- 2 |
| irAE | immune-related adverse event |
| LAG-3 | lymphocyte activation gene-3 |
| LDH | Lactate Dehydrogenase |
| Mg | milligram |
| aOR | adjusted Odds ratio |
| OS | Overall survival |
| PD-1 | Programmed cell death protein 1 |
| PD-L1 | Programmed death-ligand 1 |
| PFS | Progression-free survival |
| PO | per os |
| RECIST | Response Evaluation Criteria in Solid Tumors |

## Authors' contributions

Conception: NBC, DBJ. Data collection: NBC, HRB, ARL, JAC, XB, CC. Data analysis: RI, FY. Writing of manuscript: NBC, DBJ. Manuscript editing: all authors.

## Availability of data and material

Data are available on reasonable request. All data relevant to the study are included in the article or uploaded as online supplementary information. The corresponding author may be contacted with any requests.

## Consent for publication

Not required. A waiver of consent was granted by the IRB.

## Ethics approval

This retrospective study was performed under IRB approval at each participating institution (Vanderbilt University Medical Center IRB #150625).

## References


1. Johnson DB, Chandra S, Sosman JA. Immune checkpoint inhibitor toxicity in 2018. JAMA. 2018;320(16):1702–1703. doi: 10.1001/jama.2018.13995.
2. Johnson DB, Jakubovic BD, Sibaud V, Sise ME. Balancing cancer immunotherapy efficacy and toxicity. J Allergy Clin Immunol Pract. 2020;8(9):2898–2906. doi: 10.1016/j.jaip.2020.06.028.
3. Goodman RS, Johnson DB, Balko JM. Corticosteroids and cancer immunotherapy. Clin Cancer Res. 2023;29(14):2580–2587. doi: 10.1158/1078-0432.CCR-22-3181.
4. Blank CU, Lucas MW, Scolyer RA, van de Wiel BA, Menzies AM, Lopez-Yurda M, Hoeijmakers LL, Saw RPM, Lijnsvelt JM, Maher NG, et al. Neoadjuvant nivolumab and ipilimumab in resectable stage III melanoma. N Engl J Med. Published online 2024 June 2;391(18):1696–1708. doi: 10.1056/NEJMoa2402604.
5. Wang DY, Salem JE, Cohen JV, Chandra S, Menzer C, Ye F, Zhao S, Das S, Beckermann KE, Ha L, et al. Fatal toxic effects associated with immune checkpoint inhibitors: a systematic review and meta-analysis. JAMA Oncol. 2018;4(12):1721–1728. doi: 10.1001/jamaoncol.2018.3923.
6. Wang LX, Quach HT, Moodabigil NV, Davis EJ, Sosman JA, Dusetzina SB, Johnson DB. Health care utilization and steroid-refractory toxicities from immune checkpoint inhibitors. Cancer. 2020;126(2):322–328. doi: 10.1002/cncr.32542.
7. Common Terminology Criteria for Adverse Events (CTCAE). Published online 2017.
8. Curkovic NB, Johnson DB. Updates in toxicities associated with immune checkpoint inhibitors. Expert Rev Clin Immunol. 2023;19(9):1117–1129. doi: 10.1080/1744666X.2023.2221434.
9. Brahmer JR, Abu-Sbeih H, Ascierto PA, Brufsky J, Cappelli LC, Cortazar FB, Gerber DE, Hamad L, Hansen E, Johnson DB, et al. Society for immunotherapy of cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adverse events. J Immunother Cancer. 2021;9(6):e002435. doi: 10.1136/jitc-2021-002435.
10. Bruera S, Suarez-Almazor ME. The effects of glucocorticoids and immunosuppressants on cancer outcomes in checkpoint inhibitor therapy. Front Oncol. 2022;12:928390. doi: 10.3389/fonc.2022.928390.
11. Gaucher L, Adda L, Séjourné A, Joachim C, Chaby G, Poulet C, Liabeuf S, Gras-Champel V, Masmoudi K, Moreira A, et al. Impact of the corticosteroid indication and administration route on overall survival and the tumor response after immune checkpoint inhibitor initiation. Ther Adv Med Oncol. 2021;13:1758835921996656. doi: 10.1177/1758835921996656.
12. Bar-Hai N, Ben-Betzalel G, Stoff R, Grynberg S, Schachter J, Shapira-Frommer R, Asher N. Better late than never: the impact of steroidal treatment on the outcome of melanoma patients treated with immunotherapy. Cancers. 2023;15(11):3041. doi: 10.3390/cancers15113041.
13. Van Buren I, Madison C, Kohn A, Berry E, Kulkarni RP, Thompson RF. Survival among veterans receiving steroids for immune-related adverse events after immune checkpoint inhibitor therapy. JAMA Netw Open. 2023;6(10):e2340695. doi: 10.1001/jamanetworkopen.2023.40695.
14. Dimitriou F, Staeger R, Ak M, Maissen M, Kudura K, Barysch MJ, Levesque MP, Cheng PF, Dummer R, Mangana J. Frequency, treatment and outcome of immune-related toxicities in patients with immune-checkpoint inhibitors for advanced melanoma: results from an institutional database analysis. Cancers. 2021;13(12):2931. doi: 10.3390/cancers13122931.
15. Bai X, Hu J, Betof Warner A, Quach HT, Cann CG, Zhang MZ, Si L, Tang B, Cui C, Yang X, et al. Early use of high-dose glucocorticoid for the management of irAE is associated with poorer survival in patients with advanced melanoma treated with anti–PD-1 monotherapy. Clin Cancer Res Off J Am Assoc Cancer Res. 2021;27(21):5993–6000. doi: 10.1158/1078-0432.CCR-21-1283.
16. Rogado J, Sánchez-Torres JM, Romero-Laorden N, Ballesteros AI, Pacheco-Barcia V, Ramos-Leví A, Arranz R, Lorenzo A, Gullón P, Donnay O, et al. Immune-related adverse events predict the therapeutic efficacy of anti–PD-1 antibodies in cancer patients. Eur J Cancer Oxf Engl 1990. 2019;109:21–27. doi: 10.1016/j.ejca.2018.10.014.
17. Quach HT, Dewan AK, Davis EJ, Ancell KK, Fan R, Ye F, Johnson DB. Association of anti–programmed cell death 1 cutaneous toxic effects with outcomes in patients with advanced melanoma. JAMA Oncol. 2019;5(6):906–908. doi: 10.1001/jamaoncol.2019.0046.
18. Verheijden RJ, Burgers FH, Janssen JC, Putker AE, Veenstra SPGR, Hospers GAP, Aarts MJB, Hehenkamp KW, Doornebosch VLE, Verhaert M, et al. Corticosteroids and other immunosuppressants for immune-related adverse events and checkpoint inhibitor effectiveness in melanoma. Eur J Cancer. 2024;207:114172. doi: 10.1016/j.ejca.2024.114172.
19. Matsukane R, Suetsugu K, Hata K, Matsuda K, Nakao S, Minami H, Watanabe H, Hirota T, Egashira N, Ieiri I. Systematic surveillance of immune-related adverse events in clinical practice and impact of subsequent steroid medication on survival outcomes. Int J Clin Oncol. 2023;28(7):860–871. doi: 10.1007/s10147-023-02349-3.
20. van Not OJ, Verheijden RJ, van den Eertwegh AJM, Haanen JBAG, Aarts MJB, van den Berkmortel FWPJ, Blank CU, Boers-Sonderen MJ, de Groot JWB, Hospers GAP, et al. Association of immune-related adverse event management with survival in patients with advanced melanoma. JAMA Oncol. 2022;8(12):1794–1801. doi: 10.1001/jamaoncol.2022.5041.
21. Cariou PL, Pobel C, Michot JM, Danlos F-X, Besse B, Carbonnel F, Mariette X, Marabelle A, Messayke S, Robert C, et al. Impact of immunosuppressive agents on the management of immune-related adverse events of immune checkpoint blockers. Eur J Cancer. 2024;204:114065. doi: 10.1016/j.ejca.2024.114065.
22. Syed S, Hines J, Baccile R, Rouhani S, Reid P. Studying outcomes after steroid-sparing immunosuppressive agent vs. Steroid-only treatment for immune-related adverse events in non-small-cell lung cancer (NSCLC) and melanoma: a retrospective case-control study. Cancers. 2024;16(10):1892. doi: 10.3390/cancers16101892.