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Systemic Glucocorticoid Immunosuppression and Survival Among Immune Checkpoint Inhibitor Recipients

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Abstract

IMPORTANCE Systemic glucocorticoid immunosuppression (gsISP) is commonly used among patients receiving immune checkpoint inhibitor (ICI) therapy, but the associations of gsISP timing, dose, and duration with overall survival (OS) remain incompletely characterized.

OBJECTIVE To examine the associations of gsISP timing, dose, and duration with OS among ICI recipients.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study included ICI recipients treated at Massachusetts General Hospital, Brigham and Women's Hospital, and Dana-Farber Cancer Institute (MGBD) from May 31, 2015, through October 11, 2021, and matched ICI recipients from the TriNetX database from April 30, 2010, through October 11, 2021, for independent validation. The TriNetX cohort was matched 2:1 to the MGBD cohort using propensity scores based on patient baseline characteristics and year of ICI initiation.

EXPOSURE gsISP, evaluated according to timing relative to ICI initiation, prednisone-equivalent dose, and duration of exposure.

MAIN OUTCOMES AND MEASURES The main outcome was OS. Multivariable accelerated failure time models were used to estimate time ratios (TRs) and 95% CIs, with TR values less than 1 indicating shorter survival.

RESULTS This study included 39 258 patients, with 13 086 in the MGBD cohort and 26 172 in the TriNetX cohort. In the MGBD and TriNetX cohorts, 53.6% and 55.4% of patients were men, and 63.6% and 64.2% were younger than 70 years (mean [SD] age, 64.7 [13.0] years and 64.9 [12.6] years), respectively. In the MGBD cohort, patients who received gsISP within 1 year of ICI initiation had worse OS compared with patients not treated with gsISP, with the most pronounced association observed among patients receiving gsISP within 1 month of ICI initiation (TR, 0.49 [95% CI, 0.45-0.54]). Higher doses and longer durations were also associated with shorter OS; dosages greater than 60 mg/d were associated with 37% (95% CI, 25%-52%) shorter OS, and durations longer than 7 days were associated with 33% (95% CI, 12%-49%) shorter OS. These findings were independently validated in the TriNetX cohort.

CONCLUSIONS AND RELEVANCE In this cohort study of ICI recipients, 3 factors were associated with worse OS: gsISP near ICI initiation, higher gsISP dose, and longer gsISP duration, regardless of indication. These findings may provide clinically relevant information to guide gsISP management among ICI recipients.

Key Points

Question Among immune checkpoint inhibitor (ICI) recipients, how are the timing, dose, and duration of systemic glucocorticoid immunosuppression associated with overall survival?

Findings In this cohort study of 39 258 ICI recipients from a multicenter academic cohort and an independent population-level validation cohort, systemic glucocorticoid exposure closer to ICI initiation, at higher doses, and for longer durations was associated with worse overall survival.

Meaning These findings suggest that when systemic glucocorticoids are necessary for patients receiving ICIs, clinicians should carefully consider timing, dose, and duration.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

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Introduction

Immune checkpoint inhibitors (ICIs) improve overall survival (OS) across multiple cancers, but responses vary substantially.[1,2] One factor of interest is systemic immunosuppression (sISP), which may be associated with poorer outcomes by counteracting immune pathways activated by ICIs.

Despite this, sISP, particularly systemic glucocorticoid immunosuppression (gsISP), is routinely used among ICI recipients experiencing inflammatory symptoms. Specifically, gsISP may serve as the primary treatment for preexisting autoimmune diseases, palliative cancer symptom management, hypersensitivity prophylaxis, or immune-related adverse events (irAEs). Although irAEs have been associated with improved OS in some settings, they can be highly symptomatic and potentially fatal, and their management has largely relied on gsISP.[3-6] As such, understanding the association between gsISP and ICI outcomes, while accounting for the complex prognostic role of irAE development, has been challenging due to small sample sizes,[7-9] limited follow-up,[10,11] or studies focused on single cancer types.[12-14]

In a 2024 meta-analysis of 6 clinical trials, Verheijden et al[7] found that higher corticosteroid doses for managing irAEs were associated with poorer survival among patients receiving anti–programmed cell death-1 (PD-1) and anti–cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) therapy (hazard ratio [HR], 1.66 for 2 mg/kg and 1.21 for 1 mg/kg, compared with 0.5 mg/kg prednisolone equivalent). Despite robust clinical trial data, these findings may not be representative of clinical practice. Moreover, the generalizability of the meta-analysis by Verheijden et al[7] was limited by its evaluation of a subset of ICI recipients who received a specific combination immunotherapy, with a relatively small sample size of nearly 2000 patients. Additionally, the study did not investigate the impact of timing or duration of corticosteroid therapy on survival.

Overall, the impact of gsISP timing, dose, and duration on ICI response across multiple cancers and indications remains unclear.[15] In this study, we leveraged a large multi-institutional cohort of ICI recipients to examine the associations of these factors with OS, and we validated the findings using an independent population-level database.

Methods

Study Design, Setting, and Population

In this retrospective cohort study, we identified patients with cancer treated with PD-1, programmed death ligand-1 (PD-L1), or CTLA-4 inhibitors as monotherapy or combination therapy (eTable 1 in Supplement 1). We collected 2 cohorts (eFigure 1 in Supplement 1): one from Massachusetts General Hospital, Brigham and Women's Hospital, and Dana-Farber Cancer Institute between May 31, 2015, and June 29, 2022 (MGBD cohort); and another from a US population-based TriNetX network between April 30, 2010, and October 11, 2021 (TriNetX cohort) to which MGBD does not contribute data. The Mass General Brigham Institutional Review Board approved this study and granted a waiver of informed consent because the study met criteria for secondary research. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

For the MGBD cohort, we excluded patients with incomplete diagnosis or medication data and those initiating ICI therapy after October 11, 2021, to align with the end date of the TriNetX cohort. The TriNetX cohort was identified by a 2:1 propensity score matching to the MGBD cohort (eMethods in Supplement 1) by baseline characteristics (sex, race and ethnicity, age at initiation of ICI therapy, Charlson Comorbidity Index [CCI] score, cancer type, cancer stage, ICI type, and pre-ICI treatment) and year of ICI initiation (eTable 2 in Supplement 1 provides definitions).[16] Self-reported race (Asian, Black or African American, White, or other race [including American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, unknown race, or unavailable race]) and ethnicity (Hispanic, non-Hispanic, or unavailable) were obtained from electronic health records. Race and ethnicity data were included in this analysis as a variable owing to multiple reports suggesting differential rates of

ICI toxicities by race. The goal of this matching was not for causal effect estimation but to define a comparable external validation cohort.

Data Extraction

The exposure of interest in this study was sISP. We developed a computational approach based on medication records to extract patient immunosuppression status and validated this approach by manually phenotyping a subset of patients (n = 1128) from the MGBD cohort (manual cohort) (eMethods in Supplement 1). In our manual cohort, we observed that among the sISP group, all but 1 patient received gsISP (eTable 3 in Supplement 1). Thus, for simplified and robust computational data extraction, we focused the remaining analyses on gsISP. We applied this validated approach to both the MGBD and TriNetX cohorts, followed by independent analyses using the same workflow.

Potential confounding variables were identified using causal directed acyclic graph analysis (eFigure 2 in Supplement 1) and incorporated into multivariable survival models. All variables included in this study were defined in eTable 2 in Supplement 1. Cancer stage was estimated using the secondary malignant neoplasm diagnostic code *distant* if secondary cancer was identified in distant sites; otherwise, the code *locoregional* was used (eTable 4 in Supplement 1). Pre-ICI and concurrent non-ICI treatments were determined by cytotoxic chemotherapy and targeted antineoplastic therapy a patient received before and after ICI initiation (eTable 5 in Supplement 1). The systemic immunosuppressive agents included in the manual record review are specified in eTable 6 in Supplement 1. To identify patients who developed irAEs, we used the same validated computational approach that was published previously by some of the authors of this study.[17]

Statistical Analysis

To robustly evaluate the association of gsISP timing with OS, we conducted 4 types of analyses for the MGBD, TriNetX, and manual cohorts independently: (1) Kaplan-Meier analysis, (2) multivariable landmark analyses, (3) multivariable time-window analyses, and (4) sensitivity analyses. Kaplan-Meier survival curves were used to examine differences among patients who received gsISP within time windows, including −1 to 1, −2 to 2, −3 to 3, −6 to 6, −12 to 12, and −18 to 18 months, compared with the same group of patients who did not receive gsISP within the −18- to 18-month window (control group). The −1- to 1-month group included patients who received gsISP within 1 month before or after ICI initiation, the −2- to 2-month group included patients who received gsISP within 2 months before or after ICI initiation, and so forth. As such, the −1- to 1-month group is a subset of the −2- to 2-month group.

We conducted multivariable landmark analyses with accelerated failure time (AFT) modeling.[18] At each landmark time, only patients alive were included. The gsISP group consisted of patients who received gsISP between ICI initiation and the corresponding landmark time, while the reference group included patients who did not receive gsISP during that period.

Multivariable AFT models were used to compare OS between patients who received gsISP within a specific window (eg, −1 to 1 months) and those who did not receive gsISP within this window. To account for guarantee-time bias,[19] we ensured that all patients were alive before the end date of a time window in each experiment.

Finally, we conducted multiple sensitivity analyses. To enhance robustness, we conducted multivariable time-window analyses using 1:2 propensity matching between the gsISP and control groups. We also included results from Cox proportional hazards regression models, although the proportional hazards assumption did not hold. A separate analysis focusing on gsISP initiation no earlier than 1 month before ICI start was performed to reflect the time when clinicians are actively considering ICI therapy and weighing the risks and benefits of concomitant gsISP therapy.

All multivariable models were adjusted for sex, race and ethnicity, age at ICI initiation, CCI score, cancer type, cancer stage, ICI type, ICI cycles, and non-ICI cancer treatment (eTable 2 in Supplement 1). Landmark analyses were additionally adjusted for pre-ICI gsISP use within 3 months before ICI initiation. The log-normal distribution was chosen for AFT models based on Akaike

information criterion and bayesian information criterion values. Time ratios (TRs) and 95% CIs were calculated, with a TR of less than 1 indicating shorter survival and a TR greater than 1 indicating longer survival. Sample size calculations confirmed adequate power (eMethods in Supplement 1).

Subanalyses using the manual cohort were conducted for deeper insights. Variations in glucocorticoid dose and duration within the −12- to 12-month window were analyzed using AFT modeling, comparing each gsISP-treated group with a common control group of patients who did not receive gsISP during the period. Dose was calculated as the total cumulative prednisone-equivalent dose of glucocorticoids (eTable 7 in Supplement 1) divided by the total number of gsISP days. Duration was defined by total gsISP days and categorized using thresholds (eTable 2 in Supplement 1). Additionally, we compared patients who received gsISP and those who did not among populations who developed irAEs.

Given multiple related comparisons across prespecified time windows, landmarks, and dose and duration thresholds, our findings were interpreted based on effect sizes, 95% CIs, consistency across analyses, and replication across cohorts, rather than nominal *P* values alone. Bonferroni correction was additionally applied within each family of related analyses to adjust for multiple comparisons.

Two-tailed $P < .05$ was considered significant. Analyses were conducted using R, version 4.5.1 (R Project for Statistical Computing).

Results

Patient Characteristics

This study included 39 258 patients: 13 086 in the MGBD cohort (mean [SD] age, 64.7 [13.0] years; 6072 female [46.4%] and 7014 male [53.6%]) and 26 172 in the TriNetX cohort (mean [SD] age, 64.9 [12.6] years; 11 671 female [44.6%] and 14 501 male [55.4%]) (eTable 8 in Supplement 1). In the MGBD and TriNetX cohorts, 430 patients (3.3%) and 787 patients (3.0%) were Asian, 364 (2.8%) and 746 (2.9%) were Black or African American, 11 791 (90.1%) and 23 534 (89.9%) were White, and 501 (3.8%) and 1105 (4.2%) were of other race, respectively; 366 (2.8%) and 849 (3.2%) were Hispanic and 11 896 (90.9%) and 23 663 (90.4%) were non-Hispanic (ethnicity was unavailable for 824 [6.3%] and 1660 [6.3%]), respectively.

More than half of the MGBD and TriNetX cohorts (8326 [63.6%] and 16 799 [64.2%], respectively) were younger than 70 years. The mortality rate among the MGBD and TriNetX cohorts was 56.2% (n = 7358 deaths) and 38.3% (n = 10 021 deaths), respectively. The median duration of follow-up was 317 (IQR, 113-712) days and 249 (IQR, 91-616) days, respectively. The censoring proportion in every 6-month interval within the 2-year follow-up duration in the 2 cohorts is presented in eTable 9 in Supplement 1.

We identified 3649 patients (27.8%) who received gsISP in the MGBD cohort (**Table 1**), 4526 (17.3%) in the TriNetX cohort (eTable 10 in Supplement 1), and 415 (36.8%) in the manual cohort (eTable 11 in Supplement 1). We evaluated the concordance of extracting gsISP data between the computational method and manual record review (eTable 12 in Supplement 1). The overall concordance rate was 0.83 (95% CI, 0.80-0.85). The positive predictive value was 0.85 (95% CI, 0.81-0.89). The negative predictive value was 0.82 (95% CI, 0.79-0.84).

Within the MGBD cohort (Table 1), the mortality rate was 66.1% (n = 2412 deaths) in the gsISP group compared with 52.4% (n = 4946 deaths) in the control group ($P < .001$). The median duration of follow-up was 226 (IQR, 79-572) days in the gsISP group compared with 350 (IQR, 139-751) days in the control group ($P < .001$). Within the manual cohort where cause-specific mortality could be ascertained, mortality was overwhelmingly due to cancer-related causes in both the gsISP group (157 of 173 [92.3%]) and the control group (308 of 350 [88.0%]) (eTable 13 in Supplement 1). Within the TriNetX cohort (eTable 10 in Supplement 1), the mortality rate was 43.5% (n = 1970 deaths) in the gsISP group compared with 37.2% (n = 8051 deaths) in the control group ($P < .001$). The median

Table 1. Characteristics of the MGBD Cohort[a]

Characteristic[b]	gsISP recipients (n = 3649)[c]	Control group (n = 9437)	*P* value
Sex			
Female	1739 (47.7)	4333 (45.9)	.08
Male	1910 (52.3)	5104 (54.1)	
Race			
Asian	123 (3.4)	307 (3.3)	.72
Black or African American	110 (3.0)	254 (2.7)	
White	3281 (89.9)	8510 (90.2)	
Other[d]	135 (3.7)	366 (3.9)	
Ethnicity			
Hispanic	100 (2.7)	266 (2.8)	<.001
Non-Hispanic	3426 (93.9)	8470 (89.8)	
Unavailable	123 (3.4)	701 (7.4)	
Age at ICI initiation, y			
≤60	1348 (36.9)	2821 (29.9)	<.001
61-70	1130 (31.0)	3027 (32.1)	
71-80	894 (24.5)	2505 (26.5)	
≥81	277 (7.6)	1084 (11.5)	
Charlson Comorbidity Index score			
0	1 (0.0)	76 (0.8)	<.001
1-2	289 (7.9)	1372 (14.5)	
3-4	257 (7.0)	670 (7.1)	
≥5	3102 (85.0)	7319 (77.6)	
Cancer type			
Thoracic	875 (24.0)	2450 (26.0)	<.001
Male genital or urinary	414 (11.3)	1346 (14.3)	
Digestive	407 (11.2)	1219 (12.9)	
Melanoma	413 (11.3)	905 (9.6)	
Other skin malignant neoplasm	182 (5.0)	515 (5.5)	
Breast	210 (5.8)	686 (7.3)	
Lymphoid or hematopoietic	305 (8.4)	408 (4.3)	
Female genital	139 (3.8)	497 (5.3)	
Brain, nervous system, or eye	246 (6.7)	306 (3.2)	
Oral, lip, or pharynx	136 (3.7)	352 (3.7)	
Other	322 (8.8)	753 (8.0)	
Cancer stage			
Distant	3082 (84.5)	7170 (76.0)	<.001
Locoregional	567 (15.5)	2267 (24.0)	
Non-ICI treatment			
Conventional chemotherapy	1636 (44.8)	3823 (40.5)	<.001
Targeted therapy	513 (14.1)	1258 (13.3)	
None	1500 (41.1)	4356 (46.2)	
ICI type			
PD-1	2678 (73.4)	7227 (76.6)	<.001
PD-L1	379 (10.4)	1457 (15.4)	
CTLA-4	77 (2.1)	65 (0.7)	
Combination[e]	515 (14.1)	688 (7.3)	
No. of ICI cycles			
1	788 (21.6)	969 (10.3)	<.001
2	779 (21.3)	1101 (11.7)	
3	607 (16.6)	1277 (13.5)	
4	701 (19.2)	2061 (21.8)	
≥5	774 (21.2)	4029 (42.7)	

(continued)

Table 1. Characteristics of the MGBD Cohort[a] (continued)

Characteristic[b]	gsISP recipients (n = 3649)[c]	Control group (n = 9437)	*P* value
Mortality status			
Alive	1237 (33.9)	4491 (47.6)	<.001
Dead	2412 (66.1)	4946 (52.4)	
Duration of follow-up, median (IQR), d	226 (79-572)	350 (139-751)	<.001

Abbreviations: CTLA-4, cytotoxic T-lymphocyte–associated protein 4; gsISP, systemic glucocorticoid immunosuppression; ICI, immune checkpoint inhibitor; MGBD, Massachusetts General Hospital, Brigham and Women's Hospital, and Dana-Farber Cancer Institute; PD-1, programmed death receptor-1; PD-L1, programmed death ligand-1.

[a] Unless indicated otherwise, values are presented as No. (%) of patients.

[b] Definitions of variables are provided in eTable 2 in Supplement 1.

[c] Patients received gsISP within 3 months before or after initiation of ICI therapy (−3 to 3 months); the remainder not treated with gsISP comprised the control group. To compare the treated group with the control group, we used the Pearson χ^2 test for categorical variables and the *t* test for continuous variables.

[d] Includes American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, or unknown race.

[e] Combination CTLA-4 and PD-1/PD-L1 therapy.

duration of follow-up was 125 (IQR, 50-336) days in the gsISP group compared with 285 (IQR, 107-663) days in the control group (*P* < .001).

Timing of Systemic Immunosuppression

Figure 1 presents the KM curves within 3 years of follow-up after ICI initiation. For the MGBD cohort (Figure 1, A), the gsISP groups consistently had poorer OS than the control group. The steepest drop-off in OS probability was observed among patients who received gsISP within 1 month before or after ICI initiation. The TriNetX cohort (Figure 1, B) achieved generally consistent results. KM curves with extended follow-up for the MGBD, TriNetX, and manual cohorts were consistent (eFigure 3 in Supplement 1).

Figure 2 (MGBD and TriNetX cohorts) and eFigure 4 in Supplement 1 (manual cohort) show the results of the landmark survival analyses. Trends across the 3 cohorts were consistent and demonstrated that patients who received gsISP had poor OS, with the most pronounced negative association observed in patients who received gsISP within 2 months before or after ICI initiation (*P* < .001). For the MGBD cohort, the TRs at the 1-, 2-, and 3-month landmark times were 0.56 (95% CI, 0.52-0.62), 0.74 (95% CI, 0.68-0.79), and 0.85 (95% CI, 0.80-0.90), respectively. For the TriNetX cohort, the TRs at these landmark times were 0.47 (95% CI, 0.43-0.52), 0.58 (95% CI, 0.53-0.63), and 0.66 (95% CI, 0.61-0.71), respectively. For the manual cohort, the TRs at these landmark times were 0.53 (95% CI, 0.37-0.78), 0.61 (95% CI, 0.45-0.82), and 0.71 (95% CI, 0.54-0.92), respectively.

Table 2 presents the results of the multivariable time-window analyses, showing poorer OS when gsISP was administered closer to ICI initiation. In both the MGBD and TriNetX cohorts, gsISP was associated with reduced OS, with TRs ranging from 0.44 (95% CI, 0.40-0.49) to 0.85 (95% CI, 0.74-0.98). In the MGBD cohort, the worst OS was observed when gsISP was given within 1 month before or after ICI initiation (TR, 0.49 [95% CI, 0.45-0.54]). In the TriNetX cohort, a similar trend was observed. The minimum sample size required for each analysis and the reasonably narrow CIs indicated that our models were adequately powered. Details of the models for the −1- to 1-month and −3 to 3-month windows for the 2 cohorts are shown in eTables 14 to 17 in Supplement 1. Consistent results were also observed in the manual cohort and sensitivity analyses (eTables 18-22 in Supplement 1). Bonferroni correction did not materially change the findings (eTable 23 in Supplement 1).

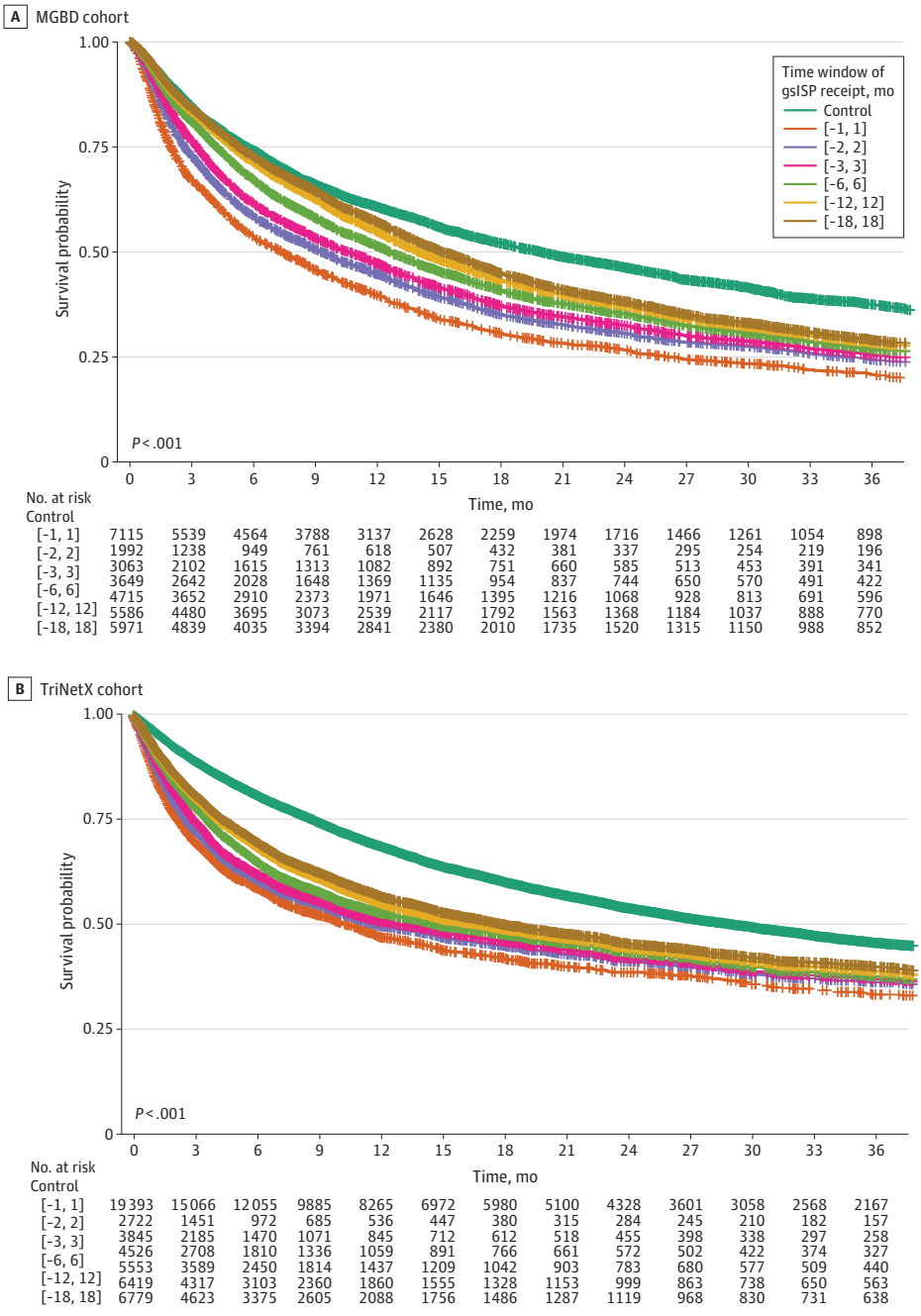
For the subanalyses of the manual cohort, eTable 24 in Supplement 1 presents the percentages of patients categorized by gsISP indication across time windows from −1 to 1 month and from −6 to 6 months, with most patients receiving gsISP for cancer-associated symptom palliation or irAE

treatment. eTable 25 in Supplement 1 provides the median gsISP duration among patients initiating the therapy within the −1- to 1-month, 2- to 4-month, and 4- to 6-month windows (median, 68 [IQR, 34-86], 127.5 [84-142], and 150 [116-250] days, respectively), with longer durations observed at later initiation times.

Dose and Duration of Systemic Immunosuppression

Our results demonstrate a dose-dependent relationship between immunosuppression use and OS in the manual cohort (**Figure 3**, A). There was a 19% (95% CI, 11%-28%) reduction in OS with

Figure 1. Kaplan-Meier Curves by Time Windows of Systemic Glucocorticoid Immunosuppression (gsISP) With 3 Years of Follow-Up



A and B, Overall, there was a decrease in survival probability as systemic glucocorticoid immunosuppression administered closer to the initiation of immune checkpoint inhibitor (ICI) therapy for both the Massachusetts General Hospital, Brigham and Women's Hospital, and Dana-Farber Cancer Institute (MGBD) (A) and TriNetX (B) cohorts ($P < .001$). The control group included patients who did not receive systemic glucocorticoid immunosuppression within approximately 18 months of ICI initiation. The study groups were categorized by systemic glucocorticoid immunosuppression timing relative to the initiation of ICI therapy, where intervals such as [−12, 12] denote patients who received systemic glucocorticoid immunosuppression within approximately 12 months of the initiation of ICI therapy, and patients in a larger time window (eg, [−12 to 12 months]) are a superset of patients in a smaller window (eg, [−6 to 6 months]).

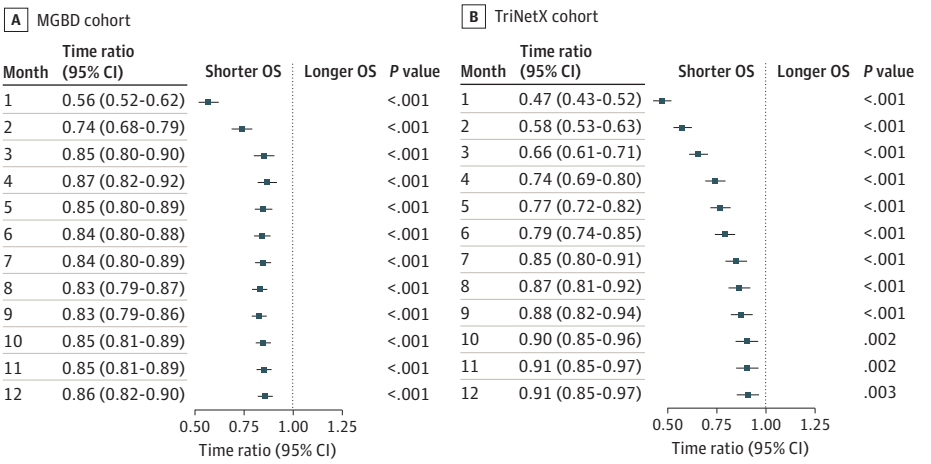
immunosuppressant use of 5 mg or more daily, gradually approaching a 37% (95% CI, 25%-52%) reduction with use of 60 mg or more daily, compared with patients who did not receive gsISP within the −12- to 12-month window. eFigures 5A and 6A in Supplement 1 present the percentage of each immunosuppression indication, stratified by the dose category.

Our data also suggested a negative association of immunosuppression duration with OS (Figure 3, B). Specifically, patients who received immunosuppressants for 2 to 5 days had an 18% (95% CI, 12%-36%) decrease in OS. Beyond 5 days, survival outcomes continued to worsen, approaching a 33% (95% CI, 12%-49%) reduction among patients receiving gsISP for 7 days or longer. Overall, indications for gsISP use across different durations (eFigures 5B and 6B in Supplement 1) were diverse and multifactorial. Patients rarely received gsISP for a single indication; instead, most were treated for a combination of reasons, including cancer symptom palliation, management of irAEs, and coexisting conditions such as preexisting autoimmune diseases.

Systemic Immunosuppression Among the irAE Population

We identified 3284 patients who developed irAEs in the MGBD cohort, among whom 1038 (31.6%) received gsISP within a −3- to 3-month window (eTable 26 in Supplement 1). In addition, we identified 5538 patients who developed irAEs in the TriNetX cohort, among whom 1299 (23.5%)

Figure 2. Forest Plots of Landmark Survival Analysis for the Association of Systemic Glucocorticoid Immunosuppression With Overall Survival (OS)



A and B, Systemic glucocorticoid immunosuppression was associated with shorter OS (time ratio [TR] <1) in the Massachusetts General Hospital, Brigham and Women's Hospital, and Dana-Farber Cancer Institute (MGBD) (A) and TriNetX (B) cohorts. TRs were measured at various landmark times (months) following the initiation of immune checkpoint inhibitor (ICI) therapy. Separate multivariable accelerated failure time models, adjusted for sex, race and ethnicity, age at ICI, Charlson Comorbidity Index score, cancer type, cancer stage, non-ICI treatment, ICI type, and ICI cycles (eTable 2 in Supplement 1), were used at different landmark times. In each analysis, the reference group corresponded to patients who did not receive systemic immunosuppression within the landmark time.

Table 2. Systemic Glucocorticoid Immunosuppression and Overall Survival Using Multivariable AFT Modeling

Time window from ICI initiation, mo	Study cohort							
	MGBD				TriNetX			
	Sample size	Required sample size	Adjusted TR (95% CI)[a]	*P* value	Sample size	Required sample size	Adjusted TR (95% CI)	*P* value
−12 to 12	5963	1100	0.71 (0.64- 0.79)	<.001	10 330	7180	0.85 (0.74- 0.98)	.03
−6 to 6	8586	1600	0.75 (0.69-0.82)	<.001	15 398	2820	0.75 (0.67-0.83)	<.001
−5 to 5	9107	1880	0.76 (0.70- 0.83)	<.001	16 613	1860	0.74 (0.66-0.81)	<.001
−4 to 4	9689	2100	0.78 (0.72- 0.85)	<.001	18 032	1800	0.70 (0.64-0.78)	<.001
−3 to 3	10 356	1800	0.75 (0.69-0.83)	<.001	19 633	800	0.62 (0.56-0.68)	<.001
−2 to 2	11 190	980	0.67 (0.62-0.74)	<.001	21 468	620	0.55 (0.50-0.60)	<.001
−1 to 1	12 155	300	0.49 (0.45-0.54)	<.001	23 562	400	0.44 (0.40-0.49)	<.001

Abbreviations: AFT, accelerated failure time; ICI, immune checkpoint inhibitor; MGBD, Massachusetts General Hospital, Brigham and Women's Hospital, and Dana-Farber Cancer Institute; TR, time ratio.

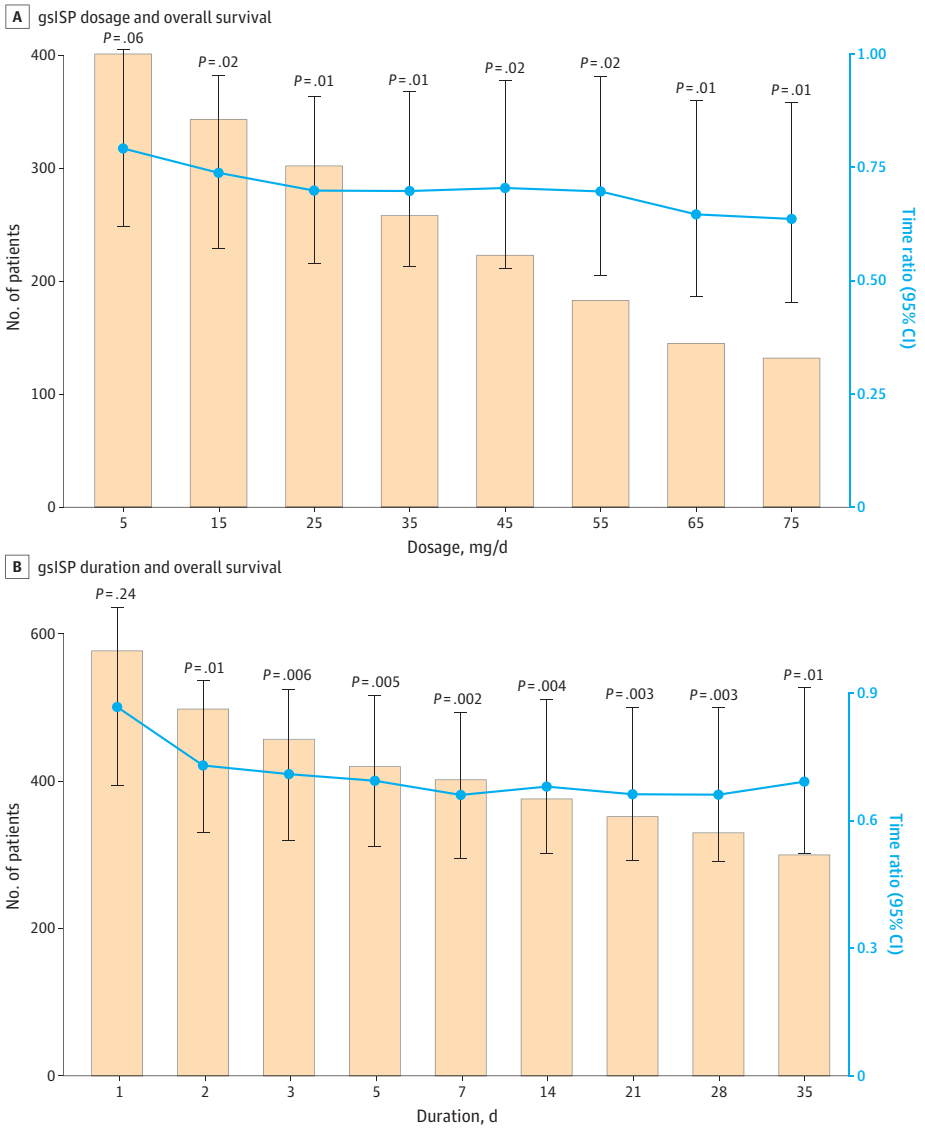
[a] Derived from multivariable log-normal AFT models and represented their exponentiated coefficients. The AFT models were adjusted by sex, age at ICI initiation, race and ethnicity, cancer type, cancer stage, Charlson Comorbidity Index score, ICI type, and ICI cycles (eTable 2 in Supplement 1). A TR of less than 1 indicates that the covariate (eg, systemic glucocorticoid immunosuppression) is associated with shorter survival; a TR greater than 1 indicates that the covariate is associated with longer survival.

received gsISP (eTable 27 in Supplement 1) within a −3- to 3-month window. We observed that patients who experienced irAEs and received gsISP within 1 year after ICI initiation had worse outcomes compared with patients with irAEs who did not receive gsISP in that time frame (eFigure 7 in Supplement 1). This association was most pronounced in patients receiving gsISP nearest to ICI initiation and began to plateau after 4 months of ICI initiation.

Discussion

To our knowledge, this is the largest study to examine the association of gsISP with OS among ICI recipients, analyzing 39 258 patients across 3 medical centers and a population-level database. In our study population, gsISP use ranged from 17.3% to 36.8%, consistent with existing literature.[3,4,20] Across the 3 cohorts, gsISP use was consistently associated with shorter OS, with TRs ranging from 0.44 to 0.85 in the primary analyses, indicating clinically meaningful associations rather than statistical artifacts of large sample size.

Figure 3. Bar Graphs of Dose and Duration of Glucocorticoid Immunosuppression (gsISP) and Overall Survival Using the Manual Cohort



A and B, The x-axes represent glucocorticoid immunosuppression dose categories in prednisone equivalents (in milligrams per day) (A) and glucocorticoid immunosuppression duration categories (in days) (B). Each bar indicates the number of patients in each dose category (A) or duration group (B), and the horizontal lines represent the time ratio. In panel A, the results indicate a trend of decreasing overall survival as dose increases, with smaller time ratio values observed in higher dose groups. In panel B, the results indicate a decline in overall survival as immunosuppression duration increases, with smaller time ratio values observed in longer duration groups.

In the MGBD cohort, gsISP exposure was associated with shorter median OS, and this finding was validated in the TriNetX cohort. These results are consistent with prior literature, including reviews showing worse survival among ICI recipients exposed to systemic corticosteroids.[7-14,21,22]

Furthermore, this study evaluated the association of gsISP timing with OS across a broad interval spanning 12 months before to 12 months after ICI initiation. In both univariate and multivariable analyses, gsISP use during this period was associated with worse OS in the MGBD and TriNetX cohorts, with the most pronounced association observed within 1 month of ICI initiation (TR, 0.49 [95% CI, 0.45-0.54]; $P < .001$). These findings are broadly consistent with prior studies focused on baseline or early post-ICI corticosteroid exposure.[8,10,14,21,23,24] However, those prior studies focused on narrower time windows of up to 3 months after ICI, and they did not explicitly examine more distant pre-ICI exposure. In our cohorts, the association attenuated after approximately 4 months but gsISP use remained associated with decreased OS through at least 12 months after ICI initiation. The only prior study to explicitly examine pre-ICI gsISP used a Surveillance, Epidemiology, and End Results–based melanoma cohort of 1671 patients.[23] That study found worse survival with gsISP exposure 1 to 3 months before ICI and particularly within 1 month before ICI initiation. Our results validate and expand on that study by confirming similar survival disadvantages within a larger pan-cancer population.

We further evaluated associations of gsISP with OS among patients with irAEs. This is an important subgroup because some irAEs, particularly cutaneous and endocrine, have been associated with improved survival, and prior studies of gsISP use have shown mixed results.[3,11,17,24,25] In our study, gsISP-treated patients with irAEs had worse OS than patients with irAEs who did not receive gsISP throughout the 12 months after ICI initiation (eFigure 7 in Supplement 1), with the most pronounced association within the first 4 months. This pattern suggests that gsISP exposure may attenuate the favorable survival associations observed among patients who developed irAEs. In the manual cohort, most deaths were cancer related, and irAE-related death was uncommon (eTable 13 in Supplement 1). Thus, the negative association of gsISP with OS is less likely to be mediated by irAE-related or other noncancer mortality and reflects a direct association mediated by reduced ICI efficacy. While these findings remain speculative, they support careful consideration of the risks and benefits of gsISP use, particularly near ICI initiation.

One possible biologic explanation for the most pronounced associations observed near ICI initiation relates to known immunologic effects of glucocorticoids, including suppression of T-cell activation and proliferation and modulation of checkpoint-related pathways.[26,27] These mechanisms are biologically consistent with our findings but are not established by the present study. Pre-ICI gsISP exposure may also extend into the early post-ICI period, when checkpoint blockade is still being established.[28-30] This could help explain the attenuation of the observed association at later time points, although this remains speculative.

We also identified dose- and duration-dependent associations of gsISP with survival in the manual cohort. Unlike prior studies that selected variable cutoff points to compare the effects of high-dose to low-dose gsISP, or combined glucocorticoid-naive patients with low-dose users,[12,13,24] our analyses characterized survival trends across a broader range of gsISP doses. In the manual cohort, any gsISP dosage of at least 1 mg/d prednisone equivalent was associated with shorter survival, with dosages of at least 60 mg/d associated with 37% (95% CI, 25%-52%) shorter survival time. Similarly, Ricciuiti et al[13] found poorer survival among patients with non–small cell lung cancer receiving at least 10 mg prednisone within 24 hours of ICI initiation compared with those receiving less than 10 mg. In our study, the association was most pronounced between 15 and 55 mg/d and then appeared to plateau at dosages greater than 65 mg/d. These findings suggest that clinicians should minimize the daily dose of gsISP when feasible.

Verheijden et al[7] also reported in a pooled analysis of 6 clinical trials that a peak median corticosteroid dosage of 75 mg/d prednisone equivalent was associated with increased mortality, whereas cumulative dose was not associated with survival. Our findings are consistent with this pattern and extend prior work by providing more granular dose-specific associations. Higher gsISP doses were also more common among patients treated for cancer-related indications (eFigure 5 in

Supplement 1), a subgroup previously associated with particularly poor survival.[11-13] Although this raises the possibility that administered dose contributes to these associations, confounding by underlying cancer burden remains possible. In addition, longer gsISP duration was associated with worse survival, with attenuation of the association after approximately 7 days of exposure (eFigure 6 in Supplement 1). Taken together, these findings support minimizing gsISP exposure, dose, and duration when clinically feasible.

Limitations

This study has several limitations. First, its retrospective design and reliance on computational data extraction leave residual confounding unavoidable and limit ascertainment of medication adherence, particularly in the TriNetX cohort where manual record review was not possible. However, we validated our computational approaches through rigorous manual phenotyping at MGBD, demonstrating high concordance between manual and computational methods. Second, cancer-specific mortality data and glucocorticoid dose and duration were not uniformly available across cohorts. However, we conducted detailed analyses in the manual cohort where these data were available. Third, follow-up, particularly in the TriNetX cohort, was relatively short and may have underestimated longer-term associations. Fourth, exclusions before and during propensity score matching may have reduced representativeness of the US population, particularly when driven by missing covariate data. Fifth, because glucocorticoids predominated in the study population and were commonly given as first-line immunosuppressive therapy, we could not reliably isolate the independent associations of nonglucocorticoid immunosuppression or steroid-sparing therapies (eg, anti–tumor necrosis factor-α and interleukin-6 inhibitors), especially in the TriNetX cohort. However, the association between gsISP and mortality was larger in the MGBD cohort than in the TriNetX cohort, where nonglucocorticoid immunosuppression was more common, highlighting an area for future studies to clarify the possible positive associations of nonsteroidal or more targeted systemic immunosuppressive therapies with ICI outcomes.

Furthermore, several potentially important confounders were not uniformly available across cohorts, including irAE severity, PD-L1 expression, tumor mutational burden, nutritional or socioeconomic factors, and key indicators of baseline disease severity such as performance status, symptom burden, and pace of disease progression. These variables may independently influence both gsISP exposure and survival and therefore may bias the observed associations. In addition, although we accounted for guarantee-time bias, confounding by indication remains possible, particularly for early gsISP administration, because patients requiring gsISP early—whether for cancer-related symptoms or more severe treatment-related toxicity—may have had adverse clinical features not fully captured by measured covariates. Early irAE development itself, however, is not generally considered a marker of more aggressive underlying disease.[31] Accordingly, residual confounding and confounding by indication remain possible, particularly for patients who received gsISP near ICI initiation.

Conclusions

This cohort study used 2 large computational cohorts and a manual cohort to examine the associations of gsISP timing, dose, and duration with OS across a pan-cancer population of ICI recipients. Three factors were associated with worse OS: gsISP near ICI initiation, higher gsISP dose, and longer gsISP duration, regardless of indication. These findings suggest that when gsISP is necessary, clinicians should carefully weigh timing relative to ICI initiation and consider minimizing dose and duration when feasible.

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REFERENCES

1. Paul J, Mitchell AP, Kesselheim AS, et al. Overlapping and non-overlapping indications for checkpoint inhibitors in the US. *J Clin Oncol*. 2024;42:11057. doi:10.1200/JCO.2024.42.16_suppl.11057

2. Tan S, Day D, Nicholls SJ, Segelov E. Immune checkpoint inhibitor therapy in oncology: current uses and future directions. *JACC CardioOncol*. 2022;4(5):579-597. doi:10.1016/j.jaccao.2022.09.004

3. 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*. 2023;88(5):1024-1032. doi:10.1016/j.jaad.2022.12.048

4. Cook S, Samuel V, Meyers DE, et al. Immune-related adverse events and survival among patients with metastatic NSCLC treated with immune checkpoint inhibitors. *JAMA Netw Open*. 2024;7(1):e2352302. doi:10.1001/jamanetworkopen.2023.52302

5. Hussaini S, Chehade R, Boldt RG, et al. Association between immune-related side effects and efficacy and benefit of immune checkpoint inhibitors: a systematic review and meta-analysis. *Cancer Treat Rev*. 2021;92:102134. doi:10.1016/j.ctrv.2020.102134

6. Martins F, Sofiya L, Sykiotis GP, et al. Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance. *Nat Rev Clin Oncol*. 2019;16(9):563-580. doi:10.1038/s41571-019-0218-0

7. Verheijden RJ, de Groot JS, Fabriek BO, Hew MN, May AM, Suijkerbuijk KPM. Corticosteroids for immune-related adverse events and checkpoint inhibitor efficacy: analysis of six clinical trials. *J Clin Oncol*. 2024;42(31):3713-3724. doi:10.1200/JCO.24.00191

8. Maslov DV, Tawagi K, Kc M, et al. Timing of steroid initiation and response rates to immune checkpoint inhibitors in metastatic cancer. *J Immunother Cancer*. 2021;9(7):9. doi:10.1136/jitc-2020-002261

9. Gaucher L, Adda L, Séjourné 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*. Published online February 27, 2021. doi:10.1177/1758835921996656

10. Tison A, Quéré G, Misery L, et al; Groupe de Cancérologie Cutanée, Groupe Français de Pneumo-Cancérologie, and Club Rhumatismes et Inflammations. Safety and efficacy of immune checkpoint inhibitors in patients with cancer and preexisting autoimmune disease: a nationwide, multicenter cohort study. *Arthritis Rheumatol*. 2019;71(12):2100-2111. doi:10.1002/art.41068

11. Skribek M, Rounis K, Afshar S, et al. Effect of corticosteroids on the outcome of patients with advanced non-small cell lung cancer treated with immune-checkpoint inhibitors. *Eur J Cancer*. 2021;145:245-254. doi:10.1016/j.ejca.2020.12.012

12. Riudavets M, Mosquera J, Garcia-Campelo R, et al. Immune-related adverse events and corticosteroid use for cancer-related symptoms are associated with efficacy in patients with non-small cell lung cancer receiving anti-PD-(L)1 blockade agents. *Front Oncol*. 2020;10:1677. doi:10.3389/fonc.2020.01677

13. Ricciuti B, Dahlberg SE, Adeni A, Sholl LM, Nishino M, Awad MM. Immune checkpoint inhibitor outcomes for patients with non-small-cell lung cancer receiving baseline corticosteroids for palliative versus nonpalliative indications. *J Clin Oncol*. 2019;37(22):1927-1934. doi:10.1200/JCO.19.00189

14. Bar-Hai N, Ben-Betzalel G, Stoff R, et al. Better late than never: the impact of steroidal treatment on the outcome of melanoma patients treated with immunotherapy. *Cancers (Basel)*. 2023;15(11):15. doi:10.3390/cancers15113041

15. 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

16. Austin PC. A critical appraisal of propensity-score matching in the medical literature between 1996 and 2003. *Stat Med*. 2008;27(12):2037-2049. doi:10.1002/sim.3150

17. Wan G, Chen W, Khattab S, et al. Multi-organ immune-related adverse events from immune checkpoint inhibitors and their downstream implications: a retrospective multicohort study. *Lancet Oncol*. 2024;25(8):1053-1069. doi:10.1016/S1470-2045(24)00278-X

18. Morgan CJ. Landmark analysis: a primer. *J Nucl Cardiol*. 2019;26(2):391-393. doi:10.1007/s12350-019-01624-z

19. Lévesque LE, Hanley JA, Kezouh A, Suissa S. Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes. *BMJ*. 2010;340:b5087. doi:10.1136/bmj.b5087

20. Jayathilaka B, Mian F, Franchini F, et al. Cancer and treatment specific incidence rates of immune-related adverse events induced by immune checkpoint inhibitors: a systematic review. *Br J Cancer*. 2025;132(1):51-57.

21. Zhang H, Li X, Huang X, Li J, Ma H, Zeng R. Impact of corticosteroid use on outcomes of non-small-cell lung cancer patients treated with immune checkpoint inhibitors: a systematic review and meta-analysis. *J Clin Pharm Ther*. 2021;46(4):927-935. doi:10.1111/jcpt.13469

22. Jessurun CAC, Hulsbergen AFC, de Wit AE, et al. The combined use of steroids and immune checkpoint inhibitors in brain metastasis patients: a systematic review and meta-analysis. *Neuro Oncol*. 2021;23(8):1261-1272. doi:10.1093/neuonc/noab046

23. Nikita N, Banks J, Keith SW, et al. Is timing of steroid exposure prior to immune checkpoint inhibitor initiation associated with treatment outcomes in melanoma? A population-based study. *Cancers (Basel)*. 2022;14(5):14. doi:10.3390/cancers14051296

24. 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

25. 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*. 2022;158(2):189-193. doi:10.1001/jamadermatol.2021.5476

26. Liberman AC, Budziñski ML, Sokn C, Gobbini RP, Steininger A, Arzt E. Regulatory and mechanistic actions of glucocorticoids on T and inflammatory cells. *Front Endocrinol (Lausanne)*. 2018;9:235. doi:10.3389/fendo.2018.00235

27. Schuyler MR, Gerblich A, Urda G. Prednisone and T-cell subpopulations. *Arch Intern Med*. 1984;144(5):973-975. doi:10.1001/archinte.1984.00350170119021

28. Xing K, Gu B, Zhang P, Wu X. Dexamethasone enhances programmed cell death 1 (PD-1) expression during T cell activation: an insight into the optimum application of glucocorticoids in anti-cancer therapy. *BMC Immunol*. 2015;16:39. doi:10.1186/s12865-015-0103-2

29. Agrawal S, Feng Y, Roy A, Kollia G, Lestini B. Nivolumab dose selection: challenges, opportunities, and lessons learned for cancer immunotherapy. *J Immunother Cancer*. 2016;4:72. doi:10.1186/s40425-016-0177-2

30. Patnaik A, Kang SP, Rasco D, et al. Phase I study of pembrolizumab (MK-3475; anti-PD-1 monoclonal antibody) in patients with advanced solid tumors. *Clin Cancer Res*. 2015;21(19):4286-4293. doi:10.1158/1078-0432.CCR-14-2607

31. Fang Q, Qian Y, Xie Z, Zhao H, Zheng Y, Li D. Predictors of severity and onset timing of immune-related adverse events in cancer patients receiving immune checkpoint inhibitors: a retrospective analysis. *Front Immunol*. 2025;16:1508512. doi:10.3389/fimmu.2025.1508512

SUPPLEMENT 1.