European Journal of Cancer 207 (2024) 114172

Contents lists available at ScienceDirect

European Journal of Cancer

journal homepage: www.ejcancer.com

Corticosteroids and other immunosuppressants for immune-related adverse events and checkpoint inhibitor effectiveness in melanoma☆

Rik J. Verheijden [a,b], Femke H. Burgers [c], Josephine C. Janssen [d], Anouk E. Putker [e], Sophie P.G. R. Veenstra [f], Geke A.P. Hospers [g], Maureen J.B. Aarts [h], Karel W. Hehenkamp [i], Veerle L. E. Doornebosch [j], Marthe Verhaert [k], Franchette W.P.J. van den Berkmortel [l], Katerina Chatzidionysiou [m], Arturo Llobell [n], Milton Barros [o], Alexandre T.J. Maria [p], Akari Takeji [q], José-Salvador García Morillo [r], Merav Lidar [s], Mick J.M. van Eijs [a,t], Christian U. Blank [u], Sandrine Aspeslagh [k], Djura Piersma [j], Ellen Kapiteijn [i], Mariette Labots [f], Marye J. Boers-Sonderen [e], Astrid A.M. van der Veldt [v], John B.A.G. Haanen [c,i,w], Anne M. May [b], Karijn P.M. Suijkerbuijk [a,*]

[a] Department of Medical Oncology, University Medical Center Utrecht, Utrecht University, Heidelberglaan 100, 3584CX Utrecht, the Netherlands
[b] Department of Epidemiology, Julius Center for Health Sciences and Primary Care, University Medical Centre Utrecht, Utrecht University, Heidelberglaan 100, 3584CX Utrecht, the Netherlands
[c] Divisions of Medical Oncology & Molecular Oncology & Immunology, Netherlands Cancer Institute, Plesmanlaan 121, 1066CX Amsterdam, the Netherlands
[d] Department of Medical Oncology and Surgical Oncology, Erasmus Medical Centre, 's Gravendijkwal 230, 3015CE Rotterdam, the Netherlands
[e] Department of Medical Oncology, Radboud University Medical Centre, Geert Grooteplein Zuid 10, 6525GA Nijmegen, the Netherlands
[f] Department of Medical Oncology, Amsterdam UMC location VUmc, Cancer Center Amsterdam, De Boelelaan 1117, 1081HV Amsterdam, the Netherlands
[g] Department of Medical Oncology, University Medical Centre Groningen, University of Groningen, Hanzeplein 1, 9713GZ Groningen, the Netherlands
[h] Department of Medical Oncology, GROW-School for Oncology and Reproduction, Maastricht University Medical Centre+, P. Debyelaan 25, 6229HX Maastricht, the Netherlands
[i] Department of Medical Oncology, Leiden University Medical Centre, Albinusdreef 2, 2333ZA Leiden, the Netherlands
[j] Department of Internal Medicine, Medisch Spectrum Twente, Koningsplein 1, 7512KZ Enschede, the Netherlands
[k] Department of Medical Oncology, Laboratory of Medical and Molecular Oncology (LMMO), Vrije Universiteit Brussel (VUB), Universitair Ziekenhuis Brussel (UZ Brussel), Laarbeeklaan 101, 1090 Jette, Belgium
[l] Department of Medical Oncology, Zuyderland Medical Centre, Dr. H. van der Hoffplein 1, 6162BG Sittard-Geleen, the Netherlands
[m] Rheumatology Unit, Department of Medicine, Karolinska Institute, 171 77 Stockholm, Sweden
[n] R3 Rheumatology, Parc Taulí University Hospital, Sabadell, Barcelona 1-08208, Spain
[o] Department of Clinical Oncology, AC Camargo Cancer Center, R. Professor Antônio Prudente, 211 Liberdade, Sao Paulo, Brazil
[p] Department of Internal Medicine, CHRU de Montpellier, 371 avenue du Doyen Gaston Giraud, 34090 Montpellier, France
[q] Division of Rheumatology, Kanazawa University Hospital, Kanazawa University, 13-1 Takara-machi, Kanazawa, Ishikawa 920–8640, Japan
[r] Unidad de Enfermedades Autoinmunes Sistemicas y Raras del Adulto, UGC Medicina Interna, Hospital Universitario Virgen del Rocío, Avda de Manuel Siurot s/n., 41013 Sevilla, Spain
[s] Rheumatology Unit, Sheba Medical Center, Derech Sheba 2, Tel HaShomer, Israel
[t] Center for Translational Immunology, University Medical Center Utrecht, Utrecht University, Lundlaan 6, 3584EA Utrecht, the Netherlands
[u] Department of Medical Oncology & Immunology, Netherlands Cancer Institute, Plesmanlaan 121, 1066CX Amsterdam, the Netherlands
[v] Department of Medical Oncology and Radiology & Nuclear Medicine, Erasmus Medical Centre, 's Gravendijkwal 230, 3015CE Rotterdam, the Netherlands
[w] Melanoma clinic, Centre Hospitalier Universitaire Vaudois, Rue du Bugnon 23, 1011 Lausanne, Switzerland

ARTICLE INFO

Keywords:
Immunosuppression
Corticosteroids
Checkpoint inhibitor

ABSTRACT

Background: Recent studies indicate an association between immunosuppression for immune-related adverse events (irAEs) and impaired survival in patients who received immune checkpoint inhibitors. Whether this is related to corticosteroids or second-line immunosuppressants is unknown. In the largest cohort thus far, we assessed the association of immunosuppressant type and dose with survival in melanoma patients with irAEs.

☆ Presentations: Parts of this study have been presented at the ESMO annual conference 2023, Madrid October 22nd, 2023. https://doi.org/10.1016/j.annonc.2023.09.2291

* Corresponding author.
E-mail address: K.Suijkerbuijk@umcutrecht.nl (K.P.M. Suijkerbuijk).

https://doi.org/10.1016/j.ejca.2024.114172
Received 14 May 2024; Accepted 30 May 2024
Available online 15 June 2024

Melanoma
Immune-related adverse events
Toxicity

Methods: Patients with advanced melanoma who received immunosuppressants for irAEs induced by first-line anti-PD-1 ± anti-CTLA-4 were included from 18 hospitals worldwide. Associations of cumulative and peak dose corticosteroids and use of second-line immunosuppression with survival from start of immunosuppression were assessed using multivariable Cox proportional hazard regression.
Results: Among 606 patients, 404 had anti-PD-1 + anti-CTLA-4-related irAEs and 202 had anti-PD-1-related irAEs. 425 patients (70 %) received corticosteroids only; 181 patients (30 %) additionally received second-line immunosuppressants. Median PFS and OS from starting immunosuppression were 4.5 (95 %CI 3.4–8.1) and 31 (95 %CI 15-not reached) months in patients who received second-line immunosuppressants, and 11 (95 % CI 9.4–14) and 55 (95 %CI 41–not reached) months in patients who did not. High corticosteroid peak dose was associated with worse PFS and OS (HR_{adj} 1.14; 95 %CI 1.01–1.29; HR_{adj} 1.29; 95 %CI 1.12–1.49 for 80vs40mg), while cumulative dose was not. Second-line immunosuppression was associated with worse PFS (HR_{adj} 1.32; 95 %CI 1.02–1.72) and OS (HR_{adj} 1.34; 95 %CI 0.99–1.82) compared with corticosteroids alone.
Conclusions: High corticosteroid peak dose and second-line immunosuppressants to treat irAEs are both associated with impaired survival. While immunosuppression is indispensable for treatment of severe irAEs, clinicians should weigh possible detrimental effects on survival against potential disadvantages of undertreatment.

1. Introduction

Immune checkpoint inhibitors (ICI) have tremendously improved prospects of patients with melanoma. However, not all patients benefit from ICIs, which can cause immune-related adverse events (irAEs) that can be severe, long-lasting, and sometimes lethal[1]. The frequency, onset, and type of irAEs differ between ICI regimens[2,3]. Severe (grade ≥3) irAEs occur in 40–60 % of patients treated with anti-cytotoxic-T-lymphocyte-associated protein 4 (anti-CTLA-4) plus anti-programmed cell death 1 (anti-PD-1) therapy and in approximately 15 % of anti-PD-1 monotherapy treated patients[4–6]. Guidelines recommend interruption of ICI therapy for most grade 2 irAEs and initiation of systemic corticosteroids for some grade 2 irAEs such as colitis and pneumonitis. For most grade ≥ 3 irAEs, permanent discontinuation of ICI and high dose corticosteroids are recommended[7–10]. When symptoms do not improve within three to five days, escalation of immunosuppression by increasing corticosteroid dose or introducing a second-line immunosuppressant is often advised for severe irAEs. The choice of this second-line immunosuppressant is usually based on experience with the conventional autoimmune disease in the same organ system, although personalized approaches have been advocated[11,12]. While tapering of immunosuppression within weeks to months is often recommended, some irAEs may relapse or become chronic, requiring long-term immunosuppression[3].

Accumulating evidence suggests that development of irAEs is associated with increased response rates to ICI and prolonged survival, even when accounting for immortal-time bias[13]. Although immunosuppressants are crucial to prevent chronicity and mortality, recent studies have demonstrated that highly dosed corticosteroids and second-line immunosuppressants, such as tumor necrosis factor (TNF) inhibitors, may counteract the initially favorable prognosis of patients with irAEs [14–18]. However, no studies have simultaneously assessed the impact of both corticosteroids and other immunosuppressants on survival while correcting for each other. Thus, it is unclear whether corticosteroids, second-line immunosuppressants, or both affect ICI-effectiveness. While randomized controlled trials would ultimately provide these insights, no trials powered to analyze effects of immunosuppression on tumor-related outcomes are expected on short notice. Meanwhile, observational studies could provide guidance if the following requirements are met[14]. First, analysis is restricted to patients with irAEs. Secondly, survival is assessed from immunosuppressant initiation (in patients without progressive disease). Finally, the study population is homogeneous in terms of tumor type and stage, line of treatment and ICI type, with subgroups large enough to stratify or adjust for heterogeneity. In this retrospective international multicenter cohort study, we analyzed the associations of corticosteroid dose and second-line immunosuppressants with survival in patients who received immunosuppression for irAEs upon ICI-treatment for advanced melanoma.

2. Methods

2.1. Study design

This retrospective international multicenter cohort study included patients from 18 hospitals in 8 countries (Supplementary Table 1) between 2015 and 2022. From eleven Dutch hospitals (n = 2434 patients), all patients receiving immunosuppressive treatment for grade ≥ 3 irAEs were identified using the prospective Dutch Melanoma Treatment registry and included. Among the UMC Utrecht and UZ Brussel, patients were (additionally) identified using pharmacy registration; leading to inclusion of all-grade irAEs in advanced melanoma patients treated with immunosuppression in those centers. Additionally, fifteen patients were included from hospitals participating in the ImmunoCancer International Registry (ICIR). This study was approved by the local ethical committees, was not considered subject to the Dutch Medical Research with Human Subjects Act by the medical review ethics committee, and informed consent was waived (MREC NedMec 22/977; Dnr 2020–03429).

2.2. Patients

Patients with advanced (irresectable/metastatic) melanoma who were treated with first-line anti-PD-1 (pembrolizumab or nivolumab) with or without anti-CTLA-4 (ipilimumab) and who received at least one systemic immunosuppressant to treat irAEs were included. Glucocorticoid suppletion for hypocortisolism was not considered immunosuppression.

2.3. Procedures

Baseline characteristics at start of ICI including age, sex, Eastern Cooperative Oncology Group (ECOG) performance status[19], lactate dehydrogenase and stage according to the American Joint Committee on Cancer, 8th edition[20] were collected from patients' files. Characteristics of the first irAE for which systemic immunosuppression was administered were retrospectively reported. irAEs were graded according to the Common Terminology Criteria for Adverse Events version 5 [21] and grouped per organ site. Peak dose of corticosteroids (maximum dose on one day) and cumulative corticosteroid dose (the sum of all daily doses) were calculated in mg prednisolone equivalent[22]. If immunosuppression was escalated because of a new irAE during the tapering phase of the initial irAE, the treatment of this new irAE was included as well, because the indication for immunosuppression was often indistinguishable. Immunosuppression was also included if restarted within 42 days to include flares after (too rapid) tapering.

2.4. Outcomes

Start of immunosuppression was considered the start date in survival analyses. This precludes confounding by time to onset of irAE or starting immunosuppression[23]. Overall survival (OS) was defined as time from starting immunosuppression until death. Progression-free survival (PFS) was defined as time from starting immunosuppression until clinician-assessed progressive disease (PD) or death due to any cause, and was only analyzed in patients who did not have progressive disease prior to starting immunosuppression. Patients who remained alive (and progression free) were censored on the date of their last follow-up visit. Melanoma-specific survival (MSS) was assessed by censoring patients who died from non-melanoma related causes at the date of death.

2.5. Statistical analysis

Median follow-up time was estimated using reverse-Kaplan Meier method. To assess the association of corticosteroids and other immunosuppressants with survival, the adjusted hazard ratio (HR_{adj}) was estimated using multivariable Cox proportional hazard regression. Age at start of ICI, sex, presence of an autoimmune disease, performance status, stage, type of ICI, and type of irAE (colitis, hepatitis, or other) were considered potential confounders and were added as covariates. Since only 4 patients (0.7 %) had missing covariate data, complete case

Table 1
Baseline characteristics of patients with melanoma treated with immunosuppressants for immune-related adverse events.

	Corticosteroids only (n = 425)	Second-line immunosuppression (n = 181)	Overall (n = 606)
Sex			
Male	263 (62 %)	99 (55 %)	362 (60 %)
Female	162 (38 %)	82 (45 %)	244 (40 %)
Age (years)			
Mean (SD)	62 (13)	61 (14)	62 (13)
Autoimmune disease			
Present	18 (4 %)	10 (6 %)	28 (5 %)
ECOG performance status			
0	213 (50 %)	71 (39 %)	284 (47 %)
1	177 (42 %)	86 (48 %)	263 (43 %)
≥ 2	35 (8 %)	23 (13 %)	58 (10 %)
Missing	0 (0 %)	1 (0.6 %)	1 (0.2 %)
Stage			
III	27 (6 %)	12 (7 %)	39 (6 %)
M1a	37 (9 %)	6 (3 %)	43 (7 %)
M1b	46 (11 %)	24 (13 %)	70 (12 %)
M1c	163 (38 %)	67 (37 %)	230 (38 %)
M1d	152 (36 %)	72 (40 %)	224 (37 %)
Lactate dehydrogenase			
< 1xULN	270 (64 %)	108 (60 %)	378 (63 %)
1-2xULN	123 (29 %)	57 (32 %)	180 (30 %)
> 2xULN	30 (7 %)	15 (8 %)	45 (7 %)
Missing	2 (0.5 %)	1 (0.6 %)	3 (0.5 %)
Therapy			
Anti-PD-1	148 (35 %)	54 (30 %)	202 (33 %)
Anti-PD-1 + anti-CTLA-4	277 (65 %)	127 (70 %)	404 (67 %)
Grade of irAE			
2	94 (22 %)	20 (11 %)	114 (19 %)
3	309 (73 %)	121 (67 %)	430 (71 %)
4	19 (4 %)	37 (20 %)	56 (9 %)
5	3 (1 %)	3 (2 %)	6 (1 %)
Type of irAE*			
Gastro-intestinal	94 (22 %)	93 (51 %)	187 (31 %)
Hepatobiliary	115 (27 %)	41 (23 %)	156 (26 %)
Rheumatic	41 (10 %)	13 (7 %)	54 (9 %)
Endocrine	15 (4 %)	3 (2 %)	18 (3 %)
Pulmonary	47 (11 %)	5 (3 %)	52 (9 %)
Cutaneous	31 (7 %)	1 (1 %)	32 (5 %)
Renal	28 (7 %)	1 (1 %)	29 (5 %)
Neuromuscular	21 (5 %)	10 (6 %)	31 (5 %)
Cardiac	6 (1 %)	6 (3 %)	12 (2 %)
Other	27 (6 %)	8 (4 %)	35 (6 %)
Corticosteroid peak dose (mg)			
Median [Q1–Q3]	80 [60–107]	110 [80–160]	80 [60–140]
Corticosteroid cumulative dose (mg)			
Median [Q1–Q3]	2320 [1503–3743]	3900 [2483–5684]	2780 [1643–4363]
Missing	2 (0.5 %)	1 (0.6 %)	3 (0.5 %)
Second-line immunosuppressant			
TNF inhibition	0 (0 %)	102 (56 %)	102 (17 %)
Mycophenolate mofetyl	0 (0 %)	59 (33 %)	59 (10 %)
Tacrolimus	0 (0 %)	22 (12 %)	22 (4 %)
IVIg	0 (0 %)	20 (11 %)	20 (3 %)
Vedolizumab	0 (0 %)	9 (5 %)	9 (1 %)
Methotrexate	0 (0 %)	5 (3 %)	5 (1 %)
Other	0 (0 %)	11 (6 %)	11 (2 %)

*Type of irAE represents the irAE for which first immunosuppression was initiated.
Abbreviations: anti-PD-1: anti-programmed cell death 1; anti-CTLA-4: anti-cytotoxic-T-lymphocyte-associated protein 4; SD: standard deviation; Q1-Q3: first quartile to third quartile; ECOG: Eastern Cooperative Oncology Group; ULN: upper limit of normal; irAE: immune-related adverse event.

analysis was conducted. A minority of patients received (methyl)prednisolone pulse dosing (>1000 mg). This could lead to an underestimation of the association between corticosteroids and survival due to the high leverage of these extreme values and violation of the linearity assumption. We therefore allowed for non-linearity by modeling corticosteroid peak dose using restricted cubic splines with 3 prespecified knots at 80, 160 and 240 mg. The predicted HR_{adj} with 95 % confidence interval (CI) for each possible dose relative to 40 mg was visualized. Estimates for 80 and 160 versus 40 mg were reported, as they roughly reflect 1.0 and 2.0 versus 0.5 mg per kilogram (kg) body weight (Supplementary Figure 1). A sensitivity analysis was conducted in which highest daily dose below 1000 mg was considered as corticosteroid peak dose. Peak and cumulative dose of corticosteroids were modeled separately given their inherent correlation. The impact of ICI resumption was assessed by adding it to the multivariable model as covariate. Analyses were also stratified per ICI type. Assessment of the impact of timing of immunosuppression and possible confounding by ICI duration is described in the Extended Methods. All analyses were conducted using R version 4.3.2, with a two-sided alpha of 0.05.

2.6. Role of the funding source

There was no funding source for this study.

3. Results

In total, 606 patients with advanced melanoma who received immunosuppression for irAEs were included. Patients had a mean age of 62 years (standard deviation 13 years) and the majority (60 %) was male (Table 1, Supplementary Table 2). 404 patients (70 %) had received combined anti-PD-1 + anti-CTLA-4 treatment and 202 had received anti-PD-1 monotherapy (Supplementary Figure 2). Median follow-up since ICI initiation was 37 months (95 %CI 33–39). Most patients (71 %) started immunosuppression for grade 3 irAEs. Immunosuppression was most often started for gastro-intestinal irAEs (31 %) followed by hepatobiliary (26 %), rheumatic (9 %), and pulmonary (9 %) irAEs. irAEs occurred earlier in patients who received anti-PD-1 + anti-CTLA-4 (median after 42 days; Q1-Q3 23–63) than with anti-PD-1 monotherapy (median after 112 days; Q1-Q3 45–217; Supplementary Figure 3a). Eighteen patients (7 %) died because of irAEs; 8 due to myocarditis and/or myositis, 7 due to colitis and one each due to myasthenia gravis, capillary leak syndrome or nephritis.

3.1. Treatment of immune-related adverse events

425 (70 %) patients received corticosteroids only, 180 patients (30 %) received other immunosuppressants and one patient received non-corticosteroid immunosuppression only. Median time from irAE onset to immunosuppression initiation was 2 days, with 75 % of patients starting within one week (Supplementary Figure 3b). Median corticosteroid peak dose was 80 mg prednisolone equivalent (Q1-Q3 60–140 mg; Supplementary Figure 4a,b). Twenty patients (3 %) received (methyl)prednisolone pulse dosing, eight of whom additionally received intravenous immunoglobulins (IVIg). Cumulative corticosteroid dose was not reliably reported in 3 patients (0.5 %). Median cumulative corticosteroids dose was 2780 mg (Q1-Q3 1642–4362 mg; Supplementary Figure 4c). Median time from starting first immunosuppressant to starting second-line immunosuppression was 11 days, with more than 75 % of patients starting within one month (Supplementary Figure 3c). Most administered second-line immune modulators were TNF inhibitors (n = 102; 17 %; mostly infliximab), mycophenolate mofetil (n = 59; 10 %), tacrolimus (n = 22; 4 %) and IVIg (n = 20; 3 %). TNF inhibition was most often administered for gastro-intestinal irAEs, mycophenolate mofetil for hepatobiliary and cardiac irAEs, and IVIg for neuromuscular and cardiac irAEs (Supplementary Figure 5).

3.2. Immunosuppression and survival

Median OS from ICI initiation was 50 months (95 %CI 38–not reached). In patients who did and did not receive second-line immunosuppressants, median PFS since immunosuppression was 4.5 (95 %CI 3.4–8.1) and 11 (95 %CI 9.4–14) months, respectively. Similarly, median OS since immunosuppression was 31 (95 %CI 15–not reached) and 55 (95 %CI 41–not reached) months for these patients. In multivariable analyses, PFS and OS were worse in patients who received second-line immunosuppressants compared with those who did not (HR_{adj} 1.32; 95 %CI 1.02–1.72, and HR_{adj} 1.34; 95 %CI 0.99–1.82, respectively), which was independent of corticosteroid peak dose (Figure 1). Similarly, higher corticosteroid peak dose was non-linearly associated with worse PFS (HR_{adj} 1.14; 95 %CI 1.01–1.29 for 80 vs 40 mg and HR_{adj} 1.42; 95 % CI 1.03–1.95 for 160 vs 40 mg) and OS (HR_{adj} 1.29; 95 %CI 1.12–1.49 for 80 vs 40 mg and HR_{adj} 1.97; 95 %CI 1.36–2.85 for 160 vs 40 mg), independent of second-line immunosuppression (Table 2). The hazard of death (and progression) increases linearly with increasing corticosteroid peak dose within the normal range (0 to ± 250 mg prednisolone equivalent) but does not increase further for pulse dose (1250 mg; Supplementary Figure 6), although uncertainty beyond ± 250 mg is large given the low number of patients. This was confirmed in a sensitivity analysis in which the highest dose below 1000 mg prednisolone equivalent was considered the peak dose (Supplementary Table 3). Similar associations of corticosteroids peak dose with PFS and OS were observed when restricting to patients who did not receive second-line immunosuppressants or to patients who did (Supplementary Figure 7). When stratifying for type of ICI, associations with survival followed the same trend, albeit no longer statistically significant for patients who received anti-PD-1 + anti-CTLA-4 and stronger for patients who received anti-PD-1 monotherapy (Table 2; Supplementary Figures 8,9). Furthermore, associations of immunosuppression with MSS were comparable to those with PFS and OS (Figure 1; Supplementary Table 4).

3.3. Cumulative corticosteroid dose and survival

Higher cumulative corticosteroid dose was associated with prolonged PFS and OS (HR_{adj} 0.94; 95 %CI 0.90–0.98, and HR_{adj} 0.93; 95 % CI 0.88–0.98 for a 1000 mg increase, respectively), but this finding is prone to immortal-time bias. The cumulative corticosteroid dose is correlated with the duration of corticosteroids, and patients must at least have been alive during the course of corticosteroids. Thus, we performed a 6-month conditional landmark analysis in which patients were only included if they were alive (and progression free) at least 6 months after starting immunosuppression and received corticosteroids for less than 6 months. In this analysis the association of cumulative corticosteroid dose with PFS and OS was attenuated (HR_{adj} 0.96; 95 %CI 0.83–1.10 and HR_{adj} 1.02; 95 %CI 0.91–1.14, respectively), but sample size was limited (n = 220 and 344, respectively).

3.4. Timing of immunosuppressant initiation

It has been hypothesized that immunosuppression may have a stronger impact on ICI-effectiveness when administered early during ICI treatment. Since anti-PD-1 + anti-CTLA-4-related irAEs tend to occur earlier than anti-PD-1 monotherapy-related irAEs, we stratified analyses per ICI regimen. In patients treated with anti-PD-1 + anti-CTLA-4, the association of both corticosteroid peak dose and second-line immunosuppression with worse survival were stronger when immunosuppression was started early, with a general attenuation of the detrimental effects of immunosuppression over time (Supplementary Figure 10). For example, the association between second-line immunosuppression and worse OS was stronger in the 176 patients who received immunosuppressants for irAEs within 6 weeks (HR_{adj} 2.47; 95 %CI 1.49–4.09) than in the 351 patients who received immunosuppressants for irAEs within 12 weeks (HR_{adj} 1.27; 95 %CI 0.83–1.93). Among patients treated with

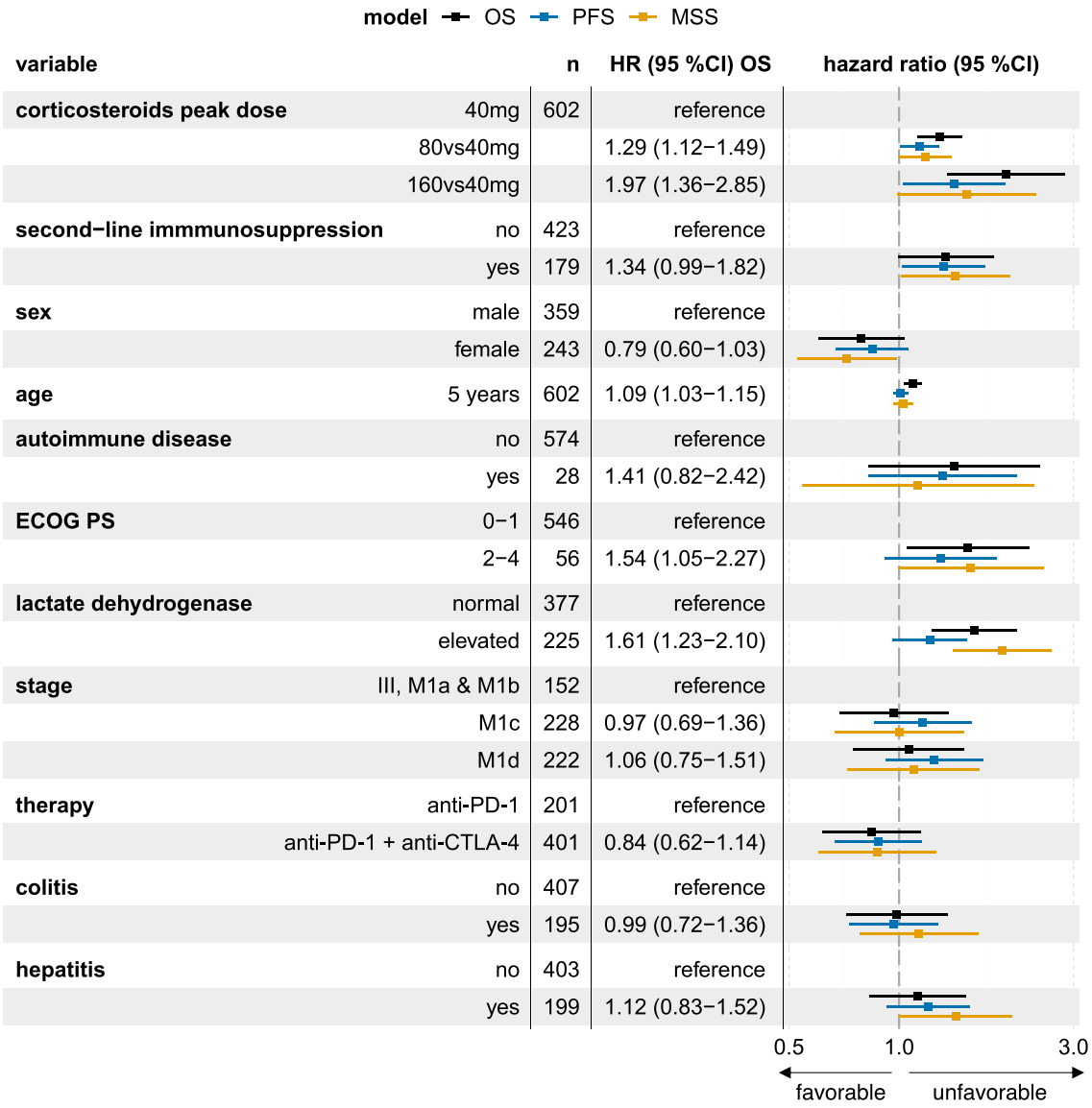

Fig. 1. Association between immunosuppressants for immune-related adverse events and survival in patients with melanoma. Multivariable cox regression model of the association of corticosteroids and second-line immunosuppression with overall survival (OS; black; text), progression-free survival (PFS; blue), and melanoma-specific survival (MSS; yellow). For corticosteroid peak dose, hazard ratios (HR) and 95 % confidence interval (CI) represent estimated adjusted HR based on restricted cubic splines models adjusted for second-line immunosuppression, sex, age, presence of autoimmune disease, performance status, lactate dehydrogenase, tumor stage, checkpoint inhibitor regimen, and type of immune related adverse event. Number of patients (n), HR and 95 %CI relate to OS analysis. All analyses consider immunosuppression initiation as starting time.

anti-PD-1 monotherapy, timing of immunosuppression had no clear impact on the association between immunosuppression and survival (Supplementary Figure 11). Importantly, these results also indicate that duration of ICI does not confound the association between immunosuppression and survival (as explained in the Extended methods).

3.5. Resumption of ICI

ICIs were resumed in 61 patients (10 %): 55 (13 %) patients who only received corticosteroids and 6 (3 %) patients who received second-line immunosuppressants. When additionally correcting for ICI resumption, associations of immunosuppression with PFS, OS and MSS remained present (Supplementary Table 5).

3.6. Specific immunosuppressants and survival

Analyzing whether the use of specific second-line immunosuppressants was associated with worse survival, power only allowed for an exploratory analysis of TNF inhibition (n = 102) and mycophenolate mofetil (n = 59), due to the low frequency of second-line immunosuppression. There was no association between TNF inhibition and PFS or OS, when correcting for corticosteroid peak dose, ICI regimen and other baseline characteristics (HR_{adj} 1.11; 95 %CI 0.77–1.59 and HR_{adj} 1.04; 95 %CI 0.69–1.58, respectively). Similarly, there was no statistically significant association between mycophenolate mofetil and PFS or OS (HR_{adj} 1.30; 95 %CI 0.89–1.89 and 1.35; 95 %CI 0.88–2.09, respectively).

4. Discussion

In this international multicenter cohort study, we observed that both corticosteroid peak dose and second-line immunosuppression are independently associated with impaired survival in patients with irAEs upon ICI for advanced melanoma, while cumulative corticosteroid dose was

Table 2
Association between immunosuppression for immune-related adverse events and survival in patients with melanoma in multivariable analysis.

	HR_{adj} (95 %CI) for progression or death	HR_{adj} (95 %CI) for death
All patients	n = 532	n = 602
80 vs 40 mg prednisolone eq	1.14 (1.01-1.29)	1.29 (1.12-1.49)
160 vs 40 mg prednisolone eq	1.42 (1.03-1.95)	1.97 (1.36-2.85)
Second-line immunosuppression	1.32 (1.02-1.72)	1.34 (0.99-1.82)
Anti-PD-1 + anti-CTLA-4	n = 367	n = 401
80 vs 40 mg prednisolone eq	1.14 (0.98-1.33)	1.14 (0.94-1.38)
160 vs 40 mg prednisolone eq	1.42 (0.94-2.15)	1.41 (0.86-2.31)
Second-line immunosuppression	1.20 (0.87-1.66)	1.15 (0.78-1.70)
Anti-PD-1 monotherapy	n = 165	n = 201
80 vs 40 mg prednisolone eq	1.18 (0.96-1.45)	1.56 (1.23-1.98)
160 vs 40 mg prednisolone eq	1.54 (0.89-2.68)	3.23 (1.72-6.08)
Second-line immunosuppression	1.73 (1.05-2.85)	1.79 (1.08-2.98)

For corticosteroid peak dose, estimated adjusted hazard ratios (HR_{adj}) based on restricted cubic splines models are presented, with adjustment for sex, age, presence of autoimmune disease, performance status, lactate dehydrogenase, tumor stage, irAE type, and if applicable checkpoint inhibitor regimen. *Abbreviations: anti-PD-1: anti-programmed cell death 1; anti-CTLA-4: anti-cytotoxic-T-lymphocyte-associated protein 4; eq: equivalent; HR_{adj}: adjusted hazard ratio; CI: confidence interval.*

not.

Our observation that higher corticosteroid peak dose to treat irAEs is associated with impaired survival is in line with previous studies[14]. In two independent cohorts of 90 and 419 patients with anti-PD-1 monotherapy-induced irAEs, Bai and colleagues demonstrated that early use of $\geq$ 60 mg prednisolone equivalent on one day was associated with worse PFS and OS[15]. Similarly, Dahl and colleagues observed that $\geq$ 75 mg prednisolone equivalent on one day was associated with worse OS in patients with colitis who also received the TNF inhibitor infliximab, suggesting that the negative association of corticosteroids peak dose with survival is independent of second-line immunosuppression [24]. Bar-Hai and colleagues did not observe a correlation between corticosteroid dose and PFS among 157 melanoma patients, although they observed that patients who received corticosteroids within the first 4 weeks upon ICI initiation had worse PFS compared with patients in whom corticosteroids were started later[25]. However, they did not account for non-linearity, included corticosteroids for other indications than irAEs, and immortal-time bias and number of ICI cycles may have affected this analysis despite the use of a landmark analysis.

We observed that second-line immunosuppression was associated with reduced survival independent of corticosteroids dose, which is in line with our previous observations in two partially overlapping cohorts [16,17]. In a study of 222 patients with anti-PD-1 and/or anti-CTLA-4 induced irAEs, patients who received corticosteroids plus TNF inhibition had statistically significantly worse OS compared with patients who only received corticosteroids[16]. Subsequently, in a cohort of 350 patients with severe anti-PD-1 + anti-CTLA-4-related irAEs, we observed impaired PFS and OS in patients who received second-line immunosuppression, which was statistically non-significant for TNF inhibition in multivariable analyses[17,18]. Both studies did not correct for corticosteroid dose. Maximally 23 % and 57 % of patients in the current study overlapped with the previous two reports. Conversely, in three small cohorts, numerically but statistically non-significantly improved survival was observed in patients who received second-line immunosuppressants compared with corticosteroids alone[26–28].

Different second-line immunosuppressants may affect ICI-effectiveness differently. For example, Zou and colleagues observed that patients with ICI-induced colitis who received TNF inhibition had worse OS than patients who received the α4β7-integrin inhibitor vedolizumab in a cohort of 156 patients[29]. Similarly, in a cohort of 147 patients with rheumatic irAEs, Bass and colleagues observed worse PFS and OS in patients treated with TNF inhibition or the interleukin-6 receptor blocker tocilizumab compared with methotrexate[30]. Surprisingly, no association between TNF inhibition and survival was observed in our current study. As we also did not observe an association of TNF inhibition with survival when not correcting for corticosteroid dose (data not shown), confounding by corticosteroid dose does not explain the disparity of current findings with previous studies. As TNF inhibition was observed to have a beneficial effect on tumor control in mice when administered upfront together with ICI[31,32], the effects of TNF inhibition in the irAE setting on survival remain controversial[33]. Alouani and colleagues observed no survival difference between 11 patients who received mycophenolate mofetil in addition to corticosteroids compared with 49 patients with corticosteroids only for ICI-related hepatitis[34]. Similarly, we did not observe a statistically significant association between mycophenolate mofetil and survival. Taken together, given the diverging results and small sample size, no definite conclusions can yet be drawn on the impact of specific second-line immunosuppressants on ICI-effectiveness.

Since ICIs elicit their effect early, with long-term tumor control even after discontinuing treatment, it has been hypothesized that early immunosuppression may be more harmful, while late introduction of immunosuppression may hamper ICI-effectiveness only to a limited extend. We observed that the associations between immunosuppression and impaired survival are stronger when administered early in patients who received anti-PD-1 + anti-CTLA-4 therapy. Although Bai and colleagues have observed that early corticosteroids may hamper survival in anti-PD-1 monotherapy-treated patients[15], our results in patients with anti-PD-1 monotherapy-related irAEs were inconclusive, possibly due to the limited sample size. Our analyses also indicate that the association between immunosuppressants and survival is not confounded by ICI duration. Whether ICI duration itself is associated with survival cannot be determined with our data.

ICI rechallenge upon irAE resolution has been deemed safe in some cases[35,36]. Recently presented data suggest that ICI resumption was strongly associated with prolonged survival[37]. In our cohort, ICI was rarely resumed following immunosuppression for irAEs, and resumption did not confound the association between immunosuppression and survival. However, we were unable to analyze the impact of resumption itself on survival due to immortal-time bias that we were unable to account for. A randomized controlled trial to rule out bias by indication is needed to clarify whether resumption of ICI before progression truly improves survival.

This study has several limitations. Despite describing the largest cohort of patients receiving immunosuppression for irAEs thus far, no definite conclusions on specific second-line immune modulators and tapering regimens can be drawn. Given the observational design of this study, residual confounding cannot be completely ruled out. Randomized controlled trials would ultimately answer which immunosuppressive strategies are least harmful in terms of ICI-effectiveness. These require tremendous collaborative efforts, are costly and logistically challenging, and will take time to produce meaningful results. Meanwhile, using data of already treated patients to emulate such a trial could be insightful[38]. This requires highly granular data of thousands of patients to be able to compare well-defined treatment trajectories in a homogenous population.

In conclusion, we observed that treatment of irAEs with high corticosteroid peak dose and administration of a second-line immunosuppressant are associated with impaired survival, while cumulative corticosteroid dose is not. These data argue for a reconsideration of the current dogma to start with high dose corticosteroids for severe irAEs.

However, clinicians should be careful with postponing or refraining from immunosuppression initiation based on these data, especially in case of life threatening irAEs. In other cases, the need for immediate highly dosed corticosteroids or second-line immunosuppression should be weighed against the possible detrimental effects on ICI-effectiveness.

Study Protocol

Available from Prof. Dr. K.P.M. Suijkerbuijk (e-mail, K.Suijkerbuijk@umcutrecht.nl).

Statistical code

All analysis scripts are available online via https://github.com/rjverheijden/ICITIS-M.

Data set

The individual patient data underlying this article cannot be shared due to privacy regulations. Not all patients consented to make their data publicly available.

Funding

There was no funding source for this study.

CRediT authorship contribution statement

Rik J. Verheijden: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Visualization, Writing – original draft. **Femke H. Burgers:** Data curation, Project administration, Resources, Writing – review & editing. **Josephine C. Janssen:** Data curation, Project administration, Resources, Writing – review & editing. **Anouk E. Putker:** Data curation, Project administration, Resources, Writing – review & editing. **Sophie P. G.R. Veenstra:** Data curation, Project administration, Resources, Writing – review & editing. **Geke A.P. Hospers:** Data curation, Project administration, Resources, Writing – review & editing. **Maureen J.B. Aarts:** Data curation, Project administration, Resources, Writing – review & editing. **Karel W. Hehenkamp:** Data curation, Project administration, Resources, Writing – review & editing. **Veerle L.E. Doornebosch:** Data curation, Project administration, Resources, Writing – review & editing. **Marthe Verhaert:** Data curation, Project administration, Resources, Writing – review & editing. **Franchette W.P. J. van den Berkmortel:** Data curation, Project administration, Resources, Writing – review & editing. **Katerina Chatzidionysiou:** Data curation, Project administration, Resources, Writing – review & editing. **Arturo Llobell:** Data curation, Project administration, Resources, Writing – review & editing. **Milton Barros:** Data curation, Project administration, Resources, Writing – review & editing. **Alexandre T.J. Maria:** Data curation, Project administration, Resources, Writing – review & editing. **Akari Takeji:** Data curation, Project administration, Resources, Writing – review & editing. **José-Salvador García Morillo:** Data curation, Project administration, Resources, Writing – review & editing. **Merav Lidar:** Data curation, Project administration, Resources, Writing – review & editing. **Mick J.M. van Eijs:** Data curation, Project administration, Resources, Writing – review & editing. **Christian U. Blank:** Resources, Writing – review & editing. **Sandrine Aspeslagh:** Resources, Writing – review & editing. **Djura Piersma:** Resources, Writing – review & editing. **Ellen Kapiteijn:** Resources, Writing – review & editing. **Mariette Labots:** Resources, Writing – review & editing. **Marye J. Boers-Sonderen:** Resources, Writing – review & editing. **Astrid A.M. van der Veldt:** Resources, Writing – review & editing. **John B.A.G. Haanen:** Resources, Writing – review & editing. **Anne M. May:** Conceptualization, Formal analysis, Investigation, Methodology, Supervision, Validation, Visualization, Writing – review & editing. **Karijn P.M. Suijkerbuijk:** Conceptualization, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – review & editing, Formal analysis.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

GAPH reports consultancy/advisory relationships with Amgen, Bristol-Myers Squibb, Roche, Merck Sharp and Dome, Pfizer, Novartis, Sanofi, Pierre Fabre and has received research funding from Bristol-Myers Squibb and Seerave. All paid to institution.

MJBA reports consultancy/advisory relationships with Amgen, Bristol Myers Squibb, Novartis, Merck Sharp and Dome, Merck-Pfizer, Pierre Fabre, Sanofi, Astellas and Bayer, and received research funding from Merck-Pfizer. All paid to institution.

KC reports consultancy fees from Eli Lilly AbbVie and Pfizer.

ATJM has received fees from AbbVie, Actelion, CSL Behring, Experf, Novartis, and Shire and declares speaking fees from AstraZeneca, Sanofi-Aventis and Bristol-Myers Squibb.

CUB reports consulting/advisory relationships with AstraZeneca, Bristol-Myers Squibb, GenMab, GSK, Lilly, Merck Sharp and Dome, Novartis, Pfizer, Pierre Fabre, Roche and Third Rock Ventures, and received research funding from 4SC, Bristol-Myers Squibb, NanoString and Novartis. All paid to institution. His is co-founder of and owns shares in Immagene BV and Signature Oncology, and is inventor on several related patents (including submitted): WO 2021/177822 A1, N2027907 and P091040NL2.

SA reports consulting/advisory relationships with Merck Sharp and Dome, Sanofi, Roche, Bristol-Myers Squibb, Pfizer, Ipsen and Galapagos. All paid to institution.

DP reports consultancy/advisory relationships with Pierre Fabre and Novartis. Partly paid to intstitution.

EK reports consultancy/advisory relationships with Bristol Myers Squibb, Novartis, Pierre Fabre, Immunocore and Lilly, and received research grants not related to this paper from Bristol Myers Squibb, Delcath, Novartis and Pierre-Fabre. Not related to current work and paid to institute.

ML reports consultancy/advisory relationships with Bristol-Myers Squibb and Janssen-Cilag B.V. All paid to institution.

AMMvdV reports consultancy/advisory relationships with Bristol-Myers Squibb, Merck Sharp and Dome, Sanofi, Pfizer, Novartis, Roche, Eisai, Merck, Pierre Fabre and Ipsen. All paid to institution.

JBAGH reports consultancy/advisory relationships with Achillus Tx, AstraZenica, BioNTech, Bristol-Myers Squibb, CureVac, GlaxoSmithKline, Imcyse, Iovance Bio, Instil Bio, Ipsen, Merck, Merck Sharp and Dome, Molecular Partners, Neogene TX, Novartis, Pfizer, PokeAcell, Roche, Sanofi, Scenic, T-Knife and TRV, and received research funding from Amgen, Bristol-Myers Squibb, BioNTech, Merck Sharp and Dome, Novartis and Sastra Cell Therapy. All paid to institution.

KPMS reports consulting/advisory relationships with Bristol-Myers Squibb, Merck Sharp and Dome, Abbvie, Pierre Fabre, Novartis, Sairopa. She received honoraria from Novartis and Merck Sharp and Dome, and research funding from TigaTx, Bristol Myers Squibb, Philips and Genmab. All paid to institution.

All remaining authors have declared no conflicts of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2024.114172.

References

[1] Wang DY, Salem JE, Cohen JV, Chandra S, Menzer C, Ye F, et al. Fatal toxic effects associated with immune checkpoint inhibitors. JAMA Oncol 2018;4(12):1721.

[2] Martins F, Sofiya L, Sykiotis GP, Lamine F, Maillard M, Fraga M, et al. Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance. Nat Rev Clin Oncol 2019;16(9):563–80.
[3] Suijkerbuijk KPM, van Eijs MJM, van Wijk F, Eggermont AMM. Clinical and translational attributes of immune-related adverse events. Nat Cancer 2024:1–15.
[4] Wolchok JD, Chiarion-Sileni V, Gonzalez R, Grob JJ, Rutkowski P, Lao CD, et al. Long-term outcomes with nivolumab plus ipilimumab or nivolumab alone versus ipilimumab in patients with advanced melanoma. J Clin Oncol 2022;40(2):127–37.
[5] Wang Y, Zhou S, Yang F, Qi X, Wang X, Guan X, et al. Treatment-related adverse events of PD-1 and PD-L1 inhibitors in clinical trials: a systematic review and meta-analysis. JAMA Oncol 2019;5(7):1008–19.
[6] Somekawa K, Horita N, Kaneko A, Tagami Y, Fukuda N, Matsumoto H, et al. Adverse events induced by nivolumab and ipilimumab combination regimens. Ther Adv Med Oncol 2022;14:17588359211058393.
[7] Schneider BJ, Naidoo J, Santomasso BD, Lacchetti C, Adkins S, Anadkat M, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: ASCO guideline update. J Clin Oncol J Am Soc Clin Oncol 2021;39(36):4073–126.
[8] Haanen J, Obeid M, Spain L, Carbonnel F, Wang Y, Robert C, et al. Management of toxicities from immunotherapy: ESMO clinical practice guideline for diagnosis, treatment and follow-up. Ann Oncol J Eur Soc Med Oncol 2022;33(12):1217–38.
[9] Brahmer JR, Abu-Sbeih H, Ascierto PA, Brufsky J, Cappelli LC, Cortazar FB, et al. Society for immunotherapy of cancer (sitc) clinical practice guideline on immune checkpoint inhibitor-related adverse events. J Immunother Cancer 2021;9(6).
[10] Thompson JA, Schneider BJ, Brahmer J, Andrews S, Armand P, Bhatia S, et al. NCCN guidelines insights: management of immunotherapy-related toxicities, version 1.2020: featured updates to the NCCN guidelines. J Natl Compr Canc Netw 2020;18(3):230–41.
[11] Esfahani K, Elkrief A, Calabrese C, Lapointe R, Hudson M, Routy B, et al. Moving towards personalized treatments of immune-related adverse events. Nat Rev Clin Oncol 2020;17(8):504–15.
[12] Martins F, Sykiotis GP, Maillard M, Fraga M, Ribi C, Kuntzer T, et al. New therapeutic perspectives to manage refractory immune checkpoint-related toxicities. Lancet Oncol 2019;20(1):e54–64.
[13] Dall'Olio FG, Rizzo A, Mollica V, Massucci M, Maggio I, Massari F. Immortal time bias in the association between toxicity and response for immune checkpoint inhibitors: a meta-analysis. Immunotherapy 2021;13(3):257–70.
[14] Verheijden RJ, van Eijs MJM, May AM, van Wijk F, Suijkerbuijk KPM. Immunosuppression for immune-related adverse events during checkpoint inhibition: an intricate balance. Npj Precis Oncol 2023;7(1):1–11.
[15] Bai X, Hu J, Warner AB, Quach HT, Cann CG, Zhang MZ, 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 2021;27(21):5993–6000.
[16] Verheijden RJ, May AM, Blank CU, Aarts MJB, Berkmortel FW, Eertwegh AJ, et al. Association of Anti-TNF with decreased survival in steroid refractory ipilimumab and anti-PD1-treated patients in the Dutch melanoma treatment registry. Clin Cancer Res 2020;26(9):2268–74.
[17] van Not OJ, Verheijden RJ, van den Eertwegh AJM, Haanen JBG, Aarts MJB, van den Berkmortel FWJ, et al. Association of immune-related adverse event management with survival in patients with advanced melanoma. JAMA Oncol 2022;8(12):1794–801.
[18] van Not OJ, Verheijden RJ, Suijkerbuijk KPM. Steroid dose and duration, immortal time bias, and survival after high-grade immune-related adverse events—reply. JAMA Oncol 2023;9(5):724.
[19] ECOG-ACRIN Cancer Research Group. ECOG-ACRIN Cancer Research Group. [cited 2023 Jun 22]. ECOG Performance Status Scale. Available from: ⟨https://ecog-acrin.org/resources/ecog-performance-status⟩/.
[20] Gershenwald JE, Scolyer RA. Melanoma staging: american joint committee on cancer (AJCC) 8th edition and beyond. Ann Surg Oncol 2018;25(8):2105–10.
[21] National Cancer Institute, editor. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 [Internet]. U.S. Department of Health and Human Services; 2017 [cited 2023 Feb 1]. Available from: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm
[22] Schimmer BP, Funder JW. Adrenocorticotropic hormone, adrenal steroids, and the adrenal cortex. In: Brunton LL, Hilal-Dandan R, Knollmann BC, editors. Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 13e. New York, NY: McGraw-Hill Education; 2017.
[23] Reid P, Sparks JA, Bass AR. Steroid dose and duration, immortal time bias, and survival after high-grade immune-related adverse events. JAMA Oncol 2023;9(5):723–4.
[24] Dahl EK, Abed OK, Kjeldsen J, Donia M, Svane IM, Dige A, et al. Safety and efficacy of infliximab and corticosteroid therapy in checkpoint inhibitor-induced colitis. Aliment Pharm Ther 2022;56(9):1370–82.
[25] Bar-Hai N, Ben-Betzalel G, Stoff R, Grynberg S, Schachter J, Shapira-Frommer R, et al. Better late than never: the impact of steroidal treatment on the outcome of melanoma patients treated with immunotherapy. Cancers 2023;15(11):3041.
[26] Lev-Ari S, Serzan M, Wu T, Ip A, Pascual L, Sinclaire B, et al. The impact of immunosuppressive agents on immune checkpoint inhibitor efficacy in patients with advanced melanoma: A real-world, multicenter, retrospective study. Cancer 2023;129(12):1885–94.
[27] Tomsitz D, Ruf T, Zierold S, French LE, Heinzerling L. Steroid-refractory immune-related adverse events induced by checkpoint inhibitors. Cancers 2023;15(9):2538.
[28] Gente K, Diekmann L, Daniello L, Will J, Feisst M, Olsavszky V, et al. Sex and anti-inflammatory treatment affect outcome of melanoma and non-small cell lung cancer patients with rheumatic immune-related adverse events. J Immunother Cancer 2023;11(9):e007557.
[29] Zou F, Faleck D, Thomas A, Harris J, Satish D, Wang X, et al. Efficacy and safety of vedolizumab and infliximab treatment for immune-mediated diarrhea and colitis in patients with cancer: a two-center observational study. J Immunother Cancer 2021;9(11).
[30] Bass AR, Abdel-Wahab N, Reid PD, Sparks JA, Calabrese C, Jannat-Khah DP, et al. Comparative safety and effectiveness of TNF inhibitors, IL6 inhibitors and methotrexate for the treatment of immune checkpoint inhibitor-associated arthritis. Ann Rheum Dis 2023;82(7):920–6.
[31] Bertrand F, Montfort A, Marcheteau E, Imbert C, Gilhodes J, Filleron T, et al. TNFα blockade overcomes resistance to anti-PD-1 in experimental melanoma. Nat Commun 2017;8(1):2256.
[32] Perez-Ruiz E, Minute L, Otano I, Alvarez MM, Ochoa MC, Belsue V, et al. Prophylactic TNF blockade uncouples efficacy and toxicity in dual CTLA-4 and PD-1 immunotherapy. Nature 2019;569(7756):428–32.
[33] Chen AY, Wolchok JD, Bass AR. TNF in the era of immune checkpoint inhibitors: friend or foe? Nat Rev Rheuma 2021;17(4):213–23.
[34] Alouani E, Laparra A, Perret A, Sakkal M, Messayke S, Danlos FX, et al. Immunosuppressant mycophenolate mofetil for patients with steroid-refractory immune-related hepatitis induced by checkpoint inhibitors in oncology. Eur J Cancer Oxf Engl 1990 2023;193:113313.
[35] Haanen J, Ernstoff M, Wang Y, Menzies A, Puzanov I, Grivas P, et al. Rechallenge patients with immune checkpoint inhibitors following severe immune-related adverse events: review of the literature and suggested prophylactic strategy. J Immunother Cancer 2020;8(1):e000604.
[36] Plazy C, Hannani D, Gobbini E. Immune checkpoint inhibitor rechallenge and resumption: a systematic review. Curr Oncol Rep 2022;24(9):1095–106.
[37] Maloney A, Giobbie-Hurder A, Fogarasi MC, Ott PA, Hodi FS, Sussman TA, et al. Role of nivolumab maintenance therapy in advanced melanoma patients following severe immune-related adverse events from combination nivolumab and ipilimumab. J Clin Oncol 2023;41(16_suppl).
[38] Hernán MA, Robins JM. Using big data to emulate a target trial when a randomized trial is not available. Am J Epidemiol 2016;183(8):758–64.