Impact of the corticosteroid indication and administration route on overall survival and the tumor response after immune checkpoint inhibitor initiation

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Ther Adv Med Oncol

2021, Vol. 13: 1–18

DOI: 10.1177/1758835921996656

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Abstract

Background: Based on their indications, systemic corticosteroids appear to negatively affect clinical outcomes in immune checkpoint inhibitor (ICI)-treated patients. There are few data on the influence of topical and inhaled corticosteroids on the ICIs' effectiveness.

Methods: In a single-center study, we retrospectively investigated the impact of systemic corticosteroids according to their indication [an immune-related adverse event (irAE) or another indication] on overall survival (OS) and the tumor response in all consecutive patients after initiation of ipilimumab, nivolumab or pembrolizumab over a 9-year period. The impacts of topical and inhaled corticosteroids were also examined.

Results: Three hundred and seventy-two patients were included. The mean ± standard deviation age was 64.0 ± 12.1 years. The most frequently prescribed ICI was nivolumab (in 58.3% of the patients) and the most frequent indications were lung cancer (44.6%) and melanoma (29.6%). Systemic corticosteroid use for an irAE did not have a negative impact on OS [adjusted hazard ratio (HR) [95% confidence interval (CI)] 1.04 (0.56–1.95), $p = 0.902$] or the best overall tumor response [adjusted odds ratio (OR) (95% CI) 1.69 (0.52–6.56), $p = 0.413$], while systemic corticosteroid use for another indication was associated with shorter OS [adjusted HR (95% CI) 1.34 (1.05–2.03), $p = 0.046$] and a poor best overall tumor response [adjusted OR (95% CI) 2.04 (1.07–5.80), $p = 0.039$] with a cumulative dose cut-off of 3215 mg prednisolone equivalent (specificity 71.4%; sensitivity 65.3%) and a time cut-off of 132 days (specificity 71.4%; sensitivity 89.8%). The use of topical corticosteroids was associated with a longer OS; this was probably due to dermatological irAEs. Inhaled corticosteroid use did not influence OS.

Conclusion: Systemic corticosteroid use for an irAE does not impact OS or the tumor response, whereas use for other indications (themselves often associated with a worse prognosis) does. Topical and inhaled steroids do not have a negative impact on OS.

Keywords: immune checkpoint inhibitor, inhaled corticosteroid, overall survival, systemic corticosteroid, topical corticosteroid

Received: 2 January 2021; revised manuscript accepted: 27 January 2021.

Introduction

Immunotherapy (modulation of the immune response to tumor cells) has given new hope to cancer patients. After proving its effectiveness in an indication of metastatic melanoma, this approach has given good results in the treatment of other types of cancer (e.g. lung and renal cancers).[1–3] However, up to 60–80% of treated patients fail to responds to immunotherapy.[4] Several escape mechanisms have been identified.

These include the concomitant or recent use of drugs that interact with the immune system. For example, the immunosuppression produced by corticosteroids might reduce the efficacy of immune checkpoint inhibitors (ICIs) by inducing lymphopenia and impairing the T-cell response to tumor antigens.[5] Based on these immunosuppressive mechanisms, patients receiving systemic corticosteroids at baseline have been excluded from randomized controlled studies of the efficacy of ICIs in several indications.[6–8] However, several clinical studies have highlighted a negative association between systemic corticosteroid use and overall survival (OS) and tumor response.[9–12] Most of these studies focused on early corticosteroid use before ICI initiation. Ricciuti *et al.*[11] suggested that worse clinical outcomes were related to the corticosteroids' indication (namely those associated with a poor prognosis, such as cachexia and brain metastasis) rather than to the corticosteroids themselves. Although some data on clinical outcomes in ICI-treated patients receiving corticosteroids for an immune-related adverse event (irAE) have been collected, no cumulative dose or duration thresholds have been determined.[13–15] Furthermore, topical and inhaled corticosteroids are known to have systemic effects[16,17] but no data on OS are available for topical corticosteroid use in ICI-treated patients. A study of ICI-related pneumonitis in patients receiving inhaled corticosteroids did not find an influence on OS.[18]

We hypothesized that: (a) the use of systemic corticosteroids in an indication of an irAE is not associated with worse OS and a worse tumor response (unlike systemic corticosteroid use for another indication); and (b) the use of topical and inhaled corticosteroids in ICI-treated patients is associated with poorer OS and a worse tumor response.

The objectives of the present study of ICI-treated patients were thus to: (a) evaluate the impact of systemic corticosteroids (as a function of the indication: an irAE or another indication), topical corticosteroids and inhaled corticosteroids on OS and tumor response; and (b) determine the cumulative dose and duration thresholds for systemic corticosteroids associated with a worse tumor response.

Methods

Study design

We performed a retrospective, observational study of all consecutive adult patients (aged 18 years and over) treated with an anti-cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) agent (ipilimumab) and/or an anti-programmed death-1 (PD-1) agent (nivolumab or pembrolizumab) in the departments of oncology, dermatology, pulmonology, hematology and gastroenterology from December 2010 to December 2019 at Amiens University Medical Center (Amiens, France). Patients enrolled in clinical trials or receiving concurrent chemotherapy/targeted therapy were not included. Data on the patients' baseline characteristics were extracted from the hospital's electronic medical records.

Evaluation of the tumor response and OS

On the basis of data gathered from multidisciplinary team meeting reports and imaging reports, the best overall tumor response was defined as a complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD) according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria (version 1.1).[19] A good response was defined as CR or PR status. OS was calculated from the date of ICI initiation to the time of death from any cause or the date of the last follow-up examination.

Collection of data on drug use

The use of oral and topical corticosteroids in the 60 days following the initiation of ICI treatment was documented, together with the indication and dosage for oral corticosteroids. The use of inhaled corticosteroids on ICI initiation or in the 60 days thereafter was also documented.

The use of drugs inducing dysbiosis (which potentially decreases the effectiveness of ICIs) was also documented: antibiotics (ATBs), proton pump inhibitors (PPIs), drugs for gastrointestinal functional disorders (particularly phloroglucinol), anti-vitamin K (AVK) anticoagulants, antiarrhythmics, non-steroidal anti-inflammatory drugs (NSAIDs), cholecalciferol, metformin, opioids, statins, and levothyroxine.[20] With regard to ATBs and in particular: (a) the importance of the time needed for recovery of the gut microbiota after ATB discontinuation;[21] and (b) the difficulty setting an optimal time cut-off for determining whether or not ATB use influences the effectiveness of ICIs,[22,23] we included patients in the ATB group when the treatment was initiated during the 60 days preceding ICI initiation or the 60 days following ICI initiation. With regard to other

drug classes and given the lack of data about the time needed for the gut microbiota to recover after discontinuation, patients were assigned to the corresponding drug class group when the treatment was received on ICI initiation or in the 60 days thereafter.

Ethical approval and informed consent

In line with the French legislation on retrospective analyses of routine clinical practice, patients were not required to give their informed consent. On admission to hospital, however, patients could refuse the use of their medical data for research purposes. The present study protocol was approved by an institutional committee with competency for studies not requiring approval by an independent ethics committee (Clinical Research Directorate, Amiens University Medical Center, Amiens, France) and was registered with the French National Data Protection Commission (Commission Nationale de l'Informatique et des Libertés, Paris, France; reference: PI2018_843_0062, dated 11 November 2018).

Statistical analyses

In our descriptive analysis, categorical variables were expressed as the number (percentage), and continuous variables were expressed as the mean ± standard deviation (SD), or the median (interquartile range), depending on the data distribution.

In bivariate analyses of patients receiving corticosteroids (the CS+ group) *versus* patients not receiving corticosteroids (the CS– group), continuous variables were compared using Student's *t* test or a Wilcoxon's rank sum test (depending on the data distribution), and categorical variables were compared using a chi-square test or Fisher's exact test. The Kaplan–Meier method and a log-rank test were used to compare the OS in the various groups. The groups' tumor response rates (according to the RECIST 1.1 criteria) were also compared. These two analyses were stratified by the corticosteroid indication (an irAE or another indication). In multivariate analyses, a Cox proportional hazards model was used for OS and a multiple logistic regression model was built for the best overall tumor response. Variables with a p-value < 0.2 in the bivariate analysis and the predictors of death most frequently described in the literature (i.e. age, sex, body mass index, current or past smoking, alcohol consumption, a history of cardiovascular disease, cancer duration, and Eastern Cooperative Oncology Group (ECOG) performance status) were included in the models. In multivariate analyses, corticosteroid use was stratified by the indication.

In order to take account of the study population's heterogeneity, all the analyses were performed in subgroups: (a) patients with metastatic cancer; and (b) patients with the most common types of cancer in our population (i.e. lung cancer and melanoma). In the melanoma subgroup, known prognostic factors (i.e. brain metastasis, the serum lactate dehydrogenase (LDH) level on ICI initiation, and the melanoma's histological characteristics: ulceration, Breslow thickness, and Clark index)[24] were included in the multivariate analyses (the Cox proportional hazards model and the logistic regression). Considering the high percentage of missing data for Breslow thickness and Clark index and in order to limit the loss of statistical power, several Cox proportional hazards models and logistic regressions were applied to this subgroup.

In patients treated with systemic corticosteroids, a receiver operating characteristic (ROC) curve analysis was used to determine the cumulative dose and duration thresholds associated with a poorer response (SD or PD). These ROC curve analyses were stratified by the corticosteroid indication.

For systemic and topical corticosteroid use, OS was analyzed according to the indication for treatment.

Results

Patient characteristics

Three hundred and seventy-four patients started treatment with ipilimumab, nivolumab or pembrolizumab (alone or in combination) between 1 December 2010 and 31 December 2019. Two patients were excluded because of missing data. Hence, a total of 372 patients were included in the analysis. The mean ± SD age was 64.0 ± 12.1 years. The most frequently prescribed ICI [in 217 patients (58.3%)] was nivolumab. The most frequent cancers were lung cancers (44.6%) and melanoma (29.6%). The study population's demographic and clinicopathological characteristics are summarized in Table 1.

Table 1. Characteristics of the overall study population and the CS– and CS+ groups .

	Overall population *n* = 372	CS– group *n* = 295	CS+ group *n* = 77	*p*-Value
Age (years), mean ± SD	64.0 ± 12.1	64.8 ± 12.2	60.5 ± 11.4	0.005
Sex				
Male, *n* (%)	244 (65.6)	203 (68.8)	41 (53.2)	0.015
Female, *n* (%)	128 (34.4)	92 (31.2)	36 (46.8)	
Body mass index (kg/m²), mean ± SD	24.8 ± 5.4	24.6 ± 5.6	25.4 ± 4.9	0.245
Smoking (current or past), *n* (%)	268 (72.0)	209 (70.8)	59 (76.6)	0.388
Alcohol consumption, *n* (%)	125 (33.6)	106 (35.9)	19 (24.7)	0.084
Cardiovascular history, *n* (%)	103 (27.7)	79 (26.8)	24 (31.2)	0.533
Diabetes mellitus, *n* (%)	51 (13.7)	45 (15.3)	6 (7.8)	0.131
High blood pressure, *n* (%)	171 (46.0)	136 (46.1)	35 (45.5)	1.000
Dyslipidemia, *n* (%)	104 (28.0)	83 (28.1)	21 (27.3)	0.994
History of cancer, *n* (%)	67 (18.0)	50 (16.9)	17 (22.1)	0.381
Tumor type				
Lung, *n* (%)	166 (44.6)	122 (41.4)	44 (57.1)	0.019
Melanoma, *n* (%)	110 (29.6)	88 (29.8)	22 (28.6)	0.400
Renal and urothelial, *n* (%)	27 (7.3)	24 (8.1)	3 (3.9)	0.322
Head and neck, *n* (%)	48 (12.9)	45 (15.3)	3 (3.9)	0.007
Hodgkin lymphoma, *n* (%)	5 (1.3)	5 (1.7)	0	0.588
Digestive, *n* (%)	4 (1.1)	3 (1.0)	1 (1.3)	1.000
Cutaneous squamous cell carcinoma, *n* (%)	1 (0.3)	0	1 (1.3)	0.207
Adenocarcinoma of unknown primary, *n* (%)	5 (1.3)	3 (1.0)	2 (2.6)	0.277
Squamous cell carcinoma of unknown primary, *n* (%)	5 (1.3)	4 (1.4)	1 (1.3)	1.000
Porocarcinoma, *n* (%)	1 (0.3)	1 (0.3)	0	1.000
Metastatic cancer, *n* (%)	276 (74.2)	204 (69.2)	72 (93.5)	<0.001
Number of metastatic sites, median (IQR)	1 (0–2)	1 (0–2)	2 (1–2)	<0.001
Brain metastasis, *n* (%)	29 (7.8)	12 (4.1)	17 (22.1)	<0.001
Cancer duration (months), median (IQR)	13.7 (6.9–33.3)	13.5 (7.1–35.0)	14.9 (6.7–27.5)	0.584
ECOG performance status				
0–1, *n* (%)	295 (79.3)	236 (80.0)	59 (76.6)	0.529
2–4, *n* (%)	77 (20.7)	59 (20.0)	18 (23.4)	
Prior conventional chemotherapy, *n* (%)	219 (58.9)	170 (57.6)	49 (63.6)	0.410
Number of lines, median (IQR)	1 (1–2)	1 (1–2)	1 (1–2)	0.913

(Continued)

Table 1. (Continued)

	Overall population *n* = 372	CS− group *n* = 295	CS+ group *n* = 77	*p*-Value
Prior targeted chemotherapy, *n* (%)	66 (17.7)	51 (17.3)	15 (19.5)	0.779
Number of lines, median (IQR)	1 (1–1)	1 (1–1)	1 (1–1)	0.649
ICIs				
First-line treatment	372 (100)	295 (100)	77 (100)	1.000
Nivolumab, *n* (%)	217 (58.3)	175 (59.3)	42 (45.5)	0.531
Pembrolizumab, *n* (%)	130 (34.9)	104 (35.3)	26 (33.8)	0.913
Ipilimumab, *n* (%)	15 (4.0)	11 (3.7)	4 (5.2)	0.524
Nivolumab + ipilimumab, *n* (%)	10 (2.7)	5 (1.7)	5 (6.5)	0.036
Second-line treatment, *n* (%)	27 (7.3)	16 (5.4)	11 (14.3)	0.013
Nivolumab, *n* (%)/*n′* = *27*	11 (40.8)	5 (31.2)	6 (54.5)	0.013
Pembrolizumab, *n* (%)/*n′* = *27*	7 (25.9)	5 (31.2)	2 (18.2)	0.638
Ipilimumab, *n* (%)/*n′* = *27*	9 (33.3)	6 (37.5)	3 (27.3)	0.400
Third-line treatment, *n* (%)	2 (0.5)	1 (0.3)	1 (1.3)	0.372
Nivolumab, *n* (%)/*n′* = *2*	0	0	0	-
Pembrolizumab, *n* (%)/*n′* = *2*	1 (50.0)	0	1 (50.0)	-
Ipilimumab, *n* (%)/*n′* = *2*	1 (50.0)	1 (50.0)	0	-
Factors modifying gut microbiota				
Concomitant medications				
NSAIDs, *n* (%)	23 (6.2)	19 (6.4)	4 (5.2)	0.890
PPIs, *n* (%)	149 (40.1)	112 (38.0)	37 (48.1)	0.140
Statins, *n* (%)	83 (22.3)	69 (23.4)	14 (18.2)	0.410
Opioids, *n* (%)	173 (46.5)	131 (44.4)	42 (54.5)	0.144
Metformin, *n* (%)	17 (4.6)	16 (5.4)	1 (1.3)	0.216
AVKs, *n* (%)	16 (4.3)	14 (4.7)	2 (2.6)	0.541
Levothyroxine, *n* (%)	40 (10.8)	34 (11.5)	6 (7.8)	0.462
Cholecalciferol, *n* (%)	59 (15.9)	44 (14.9)	15 (1.5)	0.423
Phloroglucinol, *n* (%)	19 (5.1)	16 (5.4)	3 (3.9)	0.802
Antiarrhythmic drug, *n* (%)	20 (5.4)	18 (6.1)	2 (2.6)	0.352
ATB, *n* (%)	112 (30.1)	92 (31.2)	20 (26.0)	0.454
Use of food supplements	58 (15.6)	50 (16.9)	8 (10.4)	0.216

ATB, antibiotic; AVK, anti-vitamin K; CS, corticosteroid; ECOG, Eastern Cooperative Oncology Group; ICI, immune checkpoint inhibitor; IQR, interquartile range; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor.

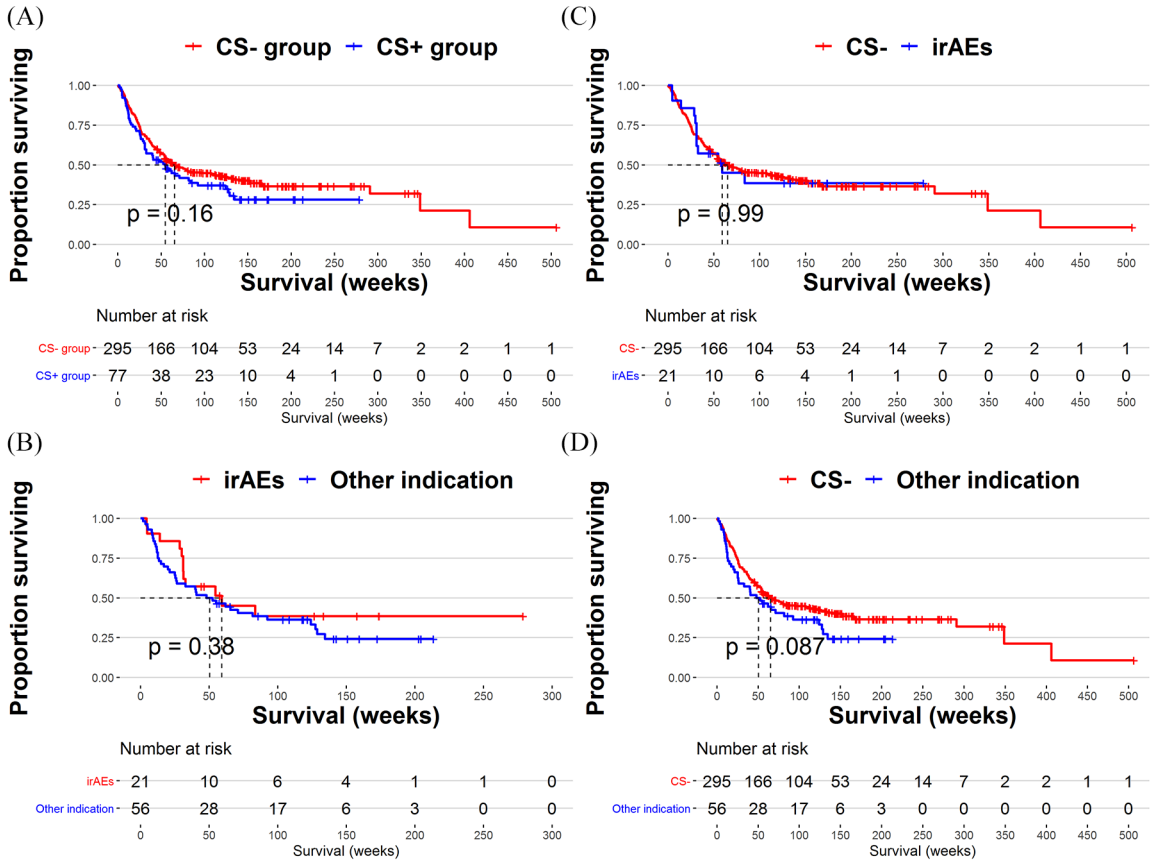

Figure 1. Overall survival in (A) patients treated with corticosteroids (the CS+ group, regardless of indication) and in patients not treated with corticosteroids (CS– group), (B) patients treated with corticosteroids for an irAE and in patients treated with corticosteroids for another indication, (C) patients treated with corticosteroids for an irAE and in patients not treated with corticosteroids and (D) patients treated with corticosteroids for an indication other than an irAE and in patients not treated with corticosteroids.
CS, corticosteroid; irAE, immune-related adverse event.

Overall survival and the tumor response

Systemic corticosteroids

Overall population. Seventy-seven (20.7%) patients received oral corticosteroids for a median (interquartile range) duration of 61 (25–114) days. The median (interquartile range) cumulative prednisolone equivalent dose was 1520 (365–4080) mg per patient. The indications for oral corticosteroids were variously irAEs in 21 patients (27.3%), brain metastasis in 21 (27.3%), arthralgia (no irAEs) in seven (9.1%), an ear, nose and throat infection in five (6.5%), an allergic reaction in one (1.3%), and a compressive mediastinal mass in two (2.6%). The indication for corticosteroids was unknown in 20 patients (25.9%); all 20 had lung cancer.

In bivariate analyses, patients in the CS+ group had a worse prognosis than those in the CS– group; this was associated with the presence of metastatic cancer (in 93.5% *versus* 69.2% of the patients, respectively; $p < 0.001$), the presence of brain metastasis (22.1% *versus* 4.1% respectively, $p < 0.001$), and the number of metastatic sites [median (interquartile range) 2 (1–2) *versus* 1 (0–2), respectively, $p < 0.001$, Table 1].

Overall survival was lower in the CS+ group than in the CS– group [median (95% confidence interval (CI) OS time 54.7 (31.3–124) *versus* 65.3 (54.1–113) weeks, respectively; crude hazard ratio (HR) (95% CI) 1.25 (0.91–1.71), $p = 0.160$, Figure 1A]. When stratified by indication, OS was: (a) similar in patients receiving oral corticosteroids for an irAE (the irAE subgroup) and in the CS– group [median (95% CI) OS time 59.3 (31.1–NA) *versus* 65.3 (54.1–113) weeks, respectively; crude HR (95% CI) 1.01 (0.56–1.80), $p = 0.990$, Figure 1C]; and (b) lower in patients receiving oral corticosteroids for another indication (the 'other indication' subgroup) than in the

CS– group [median (95% CI) OS time 50.4 (26.1–124) *versus* 65.3 (54.1–113) weeks, respectively; crude HR (95% CI) 1.35 (0.96–1.91), $p = 0.087$, Figure 1D]. The Cox proportional hazards model showed: (a) significantly shorter OS in patients in the 'other indication' subgroup than in the CS– group or the irAE subgroup [adjusted HR (95% CI) 1.34 (1.05–2.03), $p = 0.046$]; and (b) similar OS value in the irAE subgroup, the CS– group and the 'other indication' subgroup [adjusted HR (95% CI) 1.04 (0.56–1.95), $p = 0.902$, Table 2]. Finally, worse ECOG status [adjusted HR (95% CI) 2.67 (1.89–3.78), $p < 0.001$] and ATB use [adjusted HR (95% CI) 1.43 (1.04–1.97), $p = 0.040$] were also associated with worse OS (Table 2).

Moreover, the proportion of responders was lower in the CS+ group than in the CS– group (11.8% *versus* 29.6%, respectively; $p = 0.024$, Figure 2). In bivariate analyses, patients in the CS+ group had a worse prognosis than those in the CS− group; this was associated with the presence of metastatic cancer (in 91.2% *versus* 75.0% of the patients, respectively; $p = 0.008$) and the number of metastatic sites [median (interquartile range) 2 (0–5) *versus* 1 (0–5), respectively, $p = 0.006$, Supplemental Table 1]. The Cox proportional hazards model confirmed the trend seen on the Kaplan–Meier curves [adjusted HR (95% CI) 1.79 (1.23–2.59), $p = 0.002$, Table 2].

In bivariate analyses, the proportion of responders was significantly lower in the CS+ group than in the CS– group (16.9% *versus* 27.8%, respectively; $p = 0.025$). When stratified by indication, the proportion of responders did not differ significantly in the irAE subgroup and CS– group (28.6% *versus* 27.8%, respectively; $p = 0.296$) but was significantly lower in the 'other indication' subgroup than in the CS– group (12.5% *versus* 27.8%, respectively; $p = 0.008$, Figure 2). After adjusting for confounders, the logistic regression model confirmed these trends: the use of oral corticosteroids for an irAE was not significantly associated with a worse tumor response [adjusted odds ratio (OR) (95% CI) 1.69 (0.52–6.56), $p = 0.413$], while the use of oral corticosteroids for an indication other than an irAE was associated with a worse tumor response [adjusted OR (95% CI) 2.04 (1.07–5.80), $p = 0.039$]. Finally, a worse ECOG status [adjusted OR (95% CI) 2.61 (1.15–6.57), $p = 0.029$], ATB use [adjusted OR (95% CI) 6.60 (3.08–15.70), $p < 0.001$] and PPI use [adjusted OR (95% CI) 1.84 (1.03–3.34), $p = 0.043$] were associated with a worse tumor response (Table 3).

With regard to patients with PD, the ROC analysis showed: (a) a time-dependent harmful effect (area under the curve 69.8%) with a threshold value of 114 days of corticosteroid treatment (specificity 61.5%; sensitivity 82.8%; Figure 3A); and (b) a dose-dependent harmful effect (area under the curve 62.0%) with a cumulative dose threshold value of 3215 mg prednisolone equivalent (specificity 53.8%, sensitivity 67.2%, Figure 3B). These results were improved after stratification by indication. When considering oral corticosteroid use for an irAE, the ROC analysis evidenced a smaller time-dependent effect (area under the curve 63.3%) with a threshold value of 114 days of corticosteroid treatment (specificity 50.0%; sensitivity 73.3%; Figure 3C) and a smaller dose-dependent effect (area under the curve 58.9%) with a cumulative dose threshold value of 1138.75 mg prednisolone equivalent (specificity 83.3%, sensitivity 60.0%, Figure 3D). When considering oral corticosteroid use for an indication other than an irAE, the ROC analysis showed a greater time-dependent effect (area under the curve 77.6%) with a threshold value of 132 days of corticosteroid treatment (specificity 71.4%; sensitivity 89.8%; Figure 3C) and a greater dose-dependent effect (area under the curve 66.5%) with a cumulative dose threshold value of 3215 mg prednisolone equivalent (specificity 71.4%, sensitivity 65.3%, Figure 3D).

Patients with metastatic cancer. Of the 276 patients with metastatic cancer, 72 (26.1%) received oral corticosteroids, including 18 (6.6%) for an irAE and 54 (19.9%) for another indication. Relative to the metastatic CS– group, patients in the metastatic CS+ group were younger (63.8 ± 12.4 *versus* 60.5 ± 11.6 years, respectively, $p = 0.044$) and were more likely to have lung cancer (40.5% *versus* 57.8% of the patients, respectively, $p = 0.006$) or brain metastases (5.9% *versus* 23.6%, respectively, $p < 0.001$) (Supplemental Table S1).

Overall survival was shorter in patients who received oral corticosteroids than in patients who did not [median (95% CI) OS time 52.6 (31.3–128) *versus* 85.3 (60.3–168) weeks, respectively; crude HR (95% CI) 1.38 (0.98–1.94), $p = 0.067$, Supplemental Figure S1A]. When stratified by indication, OS (a) did not differ significantly in patients receiving oral corticosteroids for an irAE

Table 2. Univariate and multivariate analyses of overall survival (Cox regression model).

	n (%)	Crude model		Adjusted model	
		HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Age	372 (100)	1.00 (0.99–1.01)	0.556	1.01 (0.99–1.02)	0.275
Body mass index	372 (100)	0.95 (0.93–0.98)	<0.001	0.98 (0.95–1.02)	0.296
Sex					
Male	244 (65.6)	Reference		Reference	
Female	128 (34.4)	0.80 (0.60–1.06)	0.100	0.79 (0.58–1.09)	0.155
Smoking					
Never	104 (28.0)	Reference		Reference	
Current or past	268 (72.0)	1.65 (1.22–2.26)	0.001	0.99 (0.66–1.50)	0.965
Alcohol consumption					
No	247 (66.4)	Reference		Reference	
Yes	125 (33.6)	1.57 (1.20–2.06)	<0.001	1.19 (0.84–1.68)	0.335
History of cardiovascular disease					
Absence of cardiovascular disease	269 (72.3)	Reference		Reference	
Presence of cardiovascular disease	103 (27.7)	1.10 (0.82–1.46)	0.500	0.83 (0.61–1.13)	0.245
Type of cancer					
Lung	166 (44.6)	Reference		Reference	
Melanoma	110 (29.6)	0.45 (0.32–0.63)	<0.001	1.14 (0.60–2.15)	0.684
Renal and urothelial	27 (7.3)	0.76 (0.45–1.28)	0.306	0.92 (0.39–2.17)	0.844
Head and neck	48 (12.9)	1.05 (0.70–1.57)	0.824	0.70 (0.43–1.13)	0.141
Hodgkin lymphoma	5 (1.3)	0.45 (0.11–1.81)	0.260	0.47 (0.11–2.05)	0.314
Digestive	4 (1.1)	6.08 (2.19–16.85)	<0.001	3.75 (1.13–12.39)	0.030
Cutaneous squamous cell carcinoma	1 (0.3)	3.27 (0.45–23.58)	0.240	5.52 (0.68–45.06)	0.111
Adenocarcinoma of unknown primary	5 (1.3)	0.46 (0.11–1.86)	0.275	0.66 (0.16–2.79)	0.575
Squamous cell carcinoma of unknown primary	5 (1.3)	0.86 (0.27–2.70)	0.794	0.34 (0.10–1.15)	0.084
Porocarcinoma	1 (0.3)	2.11 (0.29–15.15)	0.459	2.74 (0.33–23.09)	0.353
Cancer duration	372 (100)	1.00 (0.99–1.00)	0.081	1.00 (0.99–1.00)	0.313
ECOG performance status					
0–1	295 (79.3)	Reference		Reference	
2–4	77 (20.7)	2.90 (2.15–3.90)	<0.001	2.67 (1.89–3.78)	<0.001
Metastatic cancer					
No	96 (25.8)	Reference		Reference	
Yes	276 (74.2)	0.74 (0.55–0.98)	0.040	0.89 (0.62–1.27)	0.510

(Continued)

Table 2. (Continued)

	n (%)	Crude model		Adjusted model	
		HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Brain metastasis					
No	343 (92.2)	Reference		Reference	
Yes	29 (7.8)	1.13 (0.70–1.83)	0.600	1.21 (0.94–2.44)	0.509
Prior conventional chemotherapy					
No	153 (41.1)	Reference		Reference	
Yes	219 (58.9)	1.72 (1.30–2.28)	<0.001	1.52 (0.94–2.44)	0.087
Prior targeted chemotherapy					
No	306 (82.3)	Reference		Reference	
Yes	66 (17.7)	1.17 (0.83–1.63)	0.400	1.27 (0.78–2.08)	0.330
ICIs					
Nivolumab	217 (58.3)	Reference		Reference	
Pembrolizumab	130 (34.9)	0.58 (0.43–0.77)	<0.001	0.65 (0.45–0.95)	0.028
Ipilimumab	15 (4.0)	0.36 (0.17–0.78)	0.009	0.46 (0.19–1.15)	0.097
Nivolumab + Ipilimumab	10 (2.7)	0.56 (0.21–1.50)	0.247	1.07 (0.36–3.23)	0.901
ATB use					
No	260 (69.9)	Reference		Reference	
Yes	112 (30.1)	1.75 (1.33–2.30)	<0.001	1.43 (1.04–1.97)	0.040
PPI use					
No	223 (59.9)	Reference		Reference	
Yes	149 (40.1)	0.84 (0.54–1.29)	0.150	0.81 (0.61–1.09)	0.162
Opioid use					
No	199 (53.5)	Reference		Reference	
Yes	173 (46.5)	1.82 (1.40–2.37)	<0.001	1.32 (0.56–1.95)	0.064
Oral corticosteroid use for an irAE					
No	351 (94.4)	Reference		Reference	
Yes	21 (5.6)	1.25 (0.53–1.71)	0.900	1.04 (0.56–1.95)	0.902
Oral corticosteroid use for another indication					
No	316 (84.9)	Reference		Reference	
Yes	56 (15.1)	1.35 (0.96–1.90)	0.087	1.34 (1.05–2.03)	0.046

ATB, antibiotic; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; PPI, proton pump inhibitor

and patients who did not [median (95% CI) OS time 59.3 (31.1–NA) *versus* 85.3 (60.3–168) weeks, respectively; crude HR (95% CI) 1.10 (0.58–2.11), $p=0.770$, Supplemental Figure S1C] and (b) was significantly lower in patients receiving oral corticosteroids for another

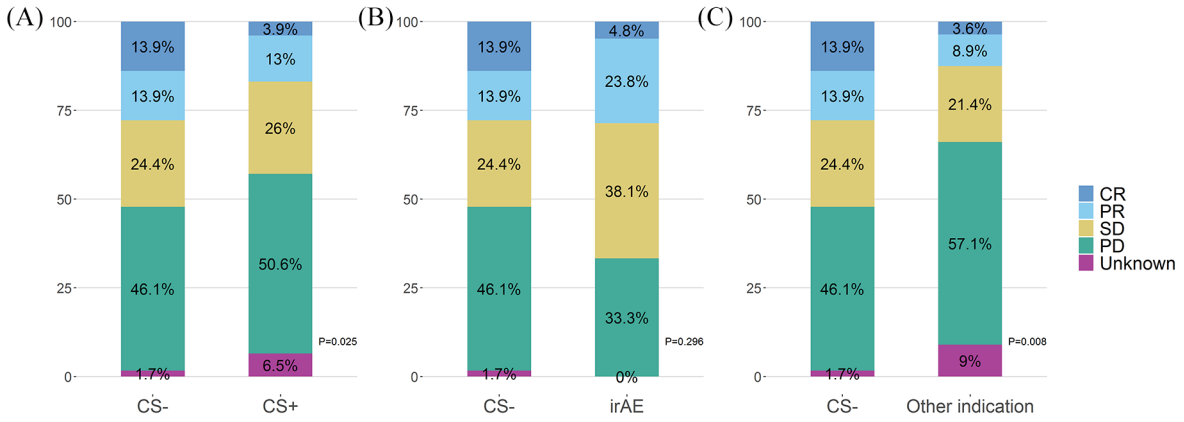

Figure 2. The best overall tumor response, according to systemic corticosteroid use: (A) the CS– group *versus* the CS+ group (regardless of the indication), (B) the CS– group *versus* the irAE subgroup and (C) the CS– group *versus* the 'other indication' subgroup. CR, complete response; CS, corticosteroid; irAE, immune-related adverse event; PD, progressive disease; PR, partial response; SD, stable disease.

indication than in patients who did not [median (95% CI) OS time 50.4 (26.1–128) *versus* 85.3 (60.3–168) weeks, respectively; crude HR (95% CI) 1.47 (1.01–2.13), $p=0.041$, Supplemental Figure S1D]. The Cox proportional hazards model showed: (a) significantly shorter OS in patients receiving oral corticosteroids for another indication than in patients who did not receive oral corticosteroids or who received oral corticosteroids for an irAE [adjusted HR (95% CI) 1.35 (1.02–1.81), $p=0.043$]; and (b) no difference in OS among patients receiving oral corticosteroids for an irAE, those who did not receive oral corticosteroids, and those who received oral corticosteroids for an indication other than an irAE [adjusted HR (95% CI) 1.04 (0.51–2.12), $p=0.916$]. Finally, a worse ECOG status [adjusted HR (95% CI) 3.47 (2.23–5.41), $p<0.001$] and ATB use [adjusted HR (95% CI) 1.39 (1.05–2.04), $p=0.039$] were associated with shorter OS (Supplemental Table S2).

The proportion of responders was significantly lower in the metastatic CS+ group than in the metastatic CS– group (18.1% *versus* 28.9%, respectively; $p=0.030$). When stratified by indication, the proportion of responders did not differ significantly in the metastatic irAE subgroup and the metastatic CS– group (33.4% *versus* 28.9%, respectively; $p=0.339$), and the proportion of responders was significantly lower in the metastatic 'other indication' subgroup than in the metastatic CS– group (13.0% *versus* 28.9%, respectively; $p=0.012$, Supplemental Figure S2). After adjusting for confounders, the logistic regression model confirmed these trends: the use of oral corticosteroids for an irAE was not significantly associated with a worse tumor response [adjusted OR (95% CI) 1.64 (0.43–7.62), $p=0.491$], while the use of oral corticosteroids for an indication other than an irAE was associated with a worse tumor response [adjusted OR (95% CI) 1.68 (1.07–5.10), $p=0.042$]. Finally, worse ECOG status [adjusted OR (95% CI) 4.91 (1.51–22.63), $p=0.017$], ATB use [adjusted OR (95% CI) 10.83 (3.58–44.69), $p<0.001$], and PPI use [adjusted OR (95% CI) 2.32 (1.13–4.92)] were associated with a worse tumor response (Supplemental Table S3).

Patients with melanoma. Of the 110 patients with melanoma, 22 (20.0%) received oral corticosteroids, including seven (6.4%) for an irAE and 15 (13.6%) for another indication. Compared with the melanoma CS– group, the patients in the melanoma CS+ group were younger (66.9 ± 14.8 *versus* 56.4 ± 14.9, respectively, $p=0.003$) and the proportion of patients receiving the nivolumab + ipilimumab combination (4.5% *versus* 22.7% respectively, $p=0.015$) was lower. The Breslow thickness was missing for 28 (25.5%) patients, the Clark index was missing for 43 (39.1%), and the LDH level was missing for two (1.8%) (Supplemental Table S4).

Overall survival was shorter in patients who received oral corticosteroids than in patients who did not [median (95% CI) OS time 81.7 (32.9–NA) *versus* 291.0 (152.9–NA) weeks, respectively; crude HR (95% CI) 2.52 (1.37–4.63), $p=0.002$, Supplemental Figure S3A]. When stratified by indication, OS (a) did

Table 3. Univariate and multivariate analysis (logistic regression) of the tumor response (comparison of non-responders with responders, according to the RECIST 1.1 criteria).

	n (%)*	Crude model		Adjusted model	
		OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
Age	362 (100)	1.00 (0.99–1.02)	0.640	1.02 (0.99–1.04)	0.183
Body mass index	362 (100)	0.94 (0.90–0.98)	0.003	0.98 (0.93–1.04)	0.514
Sex					
Male	237 (65.5)	Reference		Reference	
Female	125 (34.5)	0.73 (0.45–1.18)	0.193	0.73 (0.39–1.37)	0.332
Smoking					
Never	101 (27.9)	Reference		Reference	
Current or past	261 (72.1)	1.78 (1.07–2.93)	0.025	0.79 (0.37–1.68)	0.547
Alcohol consumption					
No	239 (66.0)	Reference		Reference	
Yes	123 (34.0)	1.51 (0.91–2.57)	0.115	0.94 (0.46–1.92)	0.867
History of cardiovascular disease					
Absence of cardiovascular disease	263 (72.7)	Reference		Reference	
Presence of cardiovascular disease	99 (27.3)	1.45 (0.85–2.57)	0.183	0.94 (0.49–1.82)	0.854
Type of cancer					
Lung	158 (43.6)	2.27 (1.39–3.80)	0.001	0.88 (0.22–2.97)	0.849
Melanoma	108 (29.3)	0.28 (0.17–0.46)	<0.001	0.82 (0.17–3.36)	0.790
Renal and urothelial	27 (7.5)	1.61 (0.64–4.94)	0.347	2.57 (0.38–16.91)	0.326
Head and neck	48 (13.3)	1.22 (0.62–2.63)	0.574	0.73 (0.15–3.18)	0.681
Cancer duration	362 (100)	0.99 (0.99–1.00)	0.045	0.99 (0.99–1.00)	0.061
ECOG performance status					
0–1	288 (79.6)	Reference		Reference	
2–4	74 (20.4)	3.57 (1.73–8.35)	0.001	2.61 (1.15–6.57)	0.029
Metastatic cancer					
No	95 (26.2)	Reference		Reference	
Yes	267 (73.8)	0.87 (0.50–1.47)	0.600	1.27 (0.61–2.66)	0.520
Brain metastasis					
No	335 (92.5)	Reference		Reference	
Yes	27 (7.5)	1.26 (0.52–3.54)	0.622	1.61 (0.48–5.97)	0.452

(Continued)

Table 3. (Continued)

	n (%)*	Crude model		Adjusted model	
		OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
Prior conventional chemotherapy					
No	151 (41.7)	Reference		Reference	
Yes	211 (58.3)	2.60 (1.62–4.22)	<0.001	1.66 (0.71–3.89)	0.238
Prior targeted chemotherapy					
No	296 (81.8)	Reference		Reference	
Yes	66 (18.2)	1.03 (0.57–1.94)	0.921	0.91 (0.38–2.24)	0.832
ICI					
Nivolumab	209 (57.7)	Reference		Reference	
Pembrolizumab	128 (35.4)	0.48 (0.29–0.80)	0.004	0.73 (0.34–1.55)	0.405
Ipilimumab	15 (4.1)	0.49 (0.16–1.64)	0.212	1.11 (0.27–4.95)	0.883
Nivolumab + Ipilimumab	10 (2.8)	0.16 (0.04–0.60)	0.007	0.20 (0.03–1.16)	0.078
ATB use					
No	253 (69.9)	Reference		Reference	
Yes	109 (30.1)	5.72 (2.90–12.67)	<0.001	6.60 (3.08–15.70)	<0.001
PPI use					
No	217 (59.9)	Reference		Reference	
Yes	145 (40.1)	0.89 (0.44–1.95)	0.768	1.84 (1.03–3.34)	0.043
Opioid use					
No	195 (53.9)	Reference		Reference	
Yes	167 (46.1)	2.60 (1.59–4.34)	<0.001	1.72 (0.93–3.18)	0.082
Oral corticosteroid use for an irAE					
No	341 (94.2)	Reference		Reference	
Yes	21 (5.8)	0.88 (0.35–2.54)	0.803	1.69 (0.52–6.56)	0.413
Oral corticosteroid use for another indication					
No	311 (85.9)	Reference		Reference	
Yes	51 (14.1)	2.48 (1.14–6.21)	0.033	2.04 (1.07–5.80)	0.039

*Ten patients were excluded from this analysis because of missing data for the tumor response.
ATB, antibiotic; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; PPI, proton pump inhibitor; RECIST, response evaluation criteria in solid tumors

not differ significantly in patients receiving oral corticosteroids for an irAE *versus* patients who did not [median (95% CI) OS time NA (28.7–NA) *versus* 291.0 (152.9–NA) weeks, respectively; crude HR (95% CI) 2.06 (0.63–6.79), $p = 0.220$, Supplemental Figure S3C] and (b) was significantly lower in patients receiving oral corticosteroids for another indication than in patients who

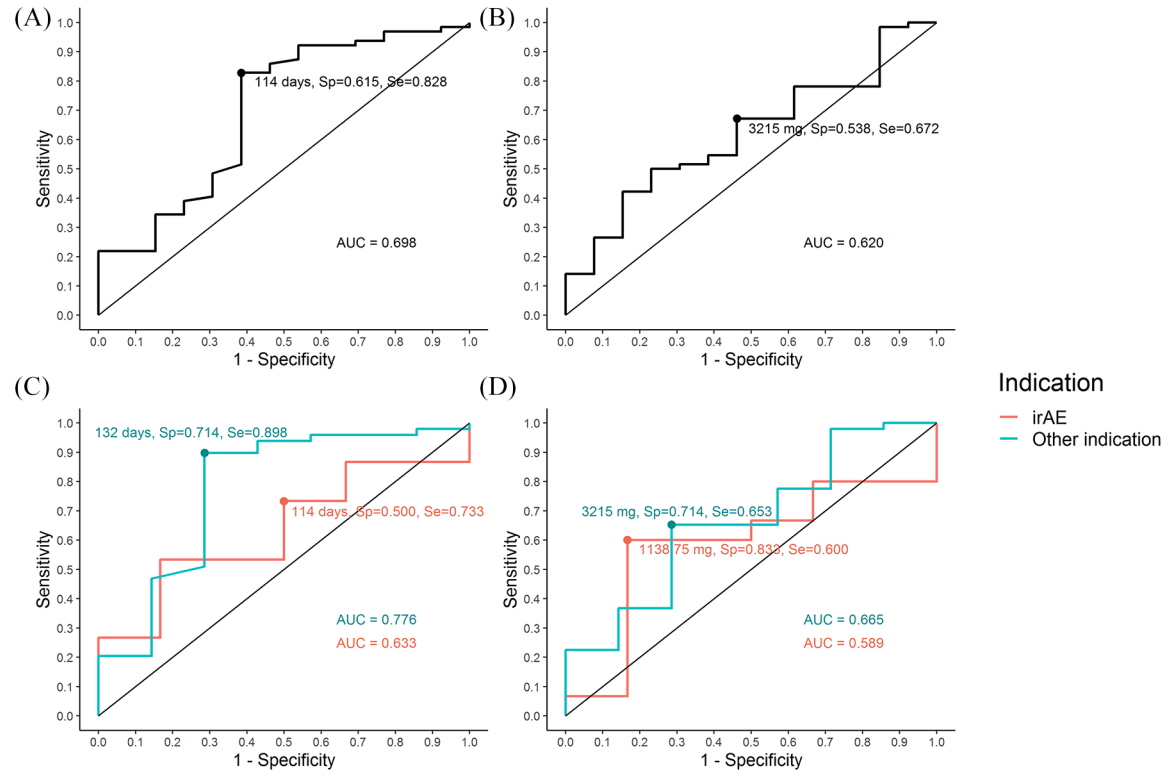

Figure 3. Relationships (ROC curve analysis) between stable disease or progressive disease and (A) the duration of systemic corticosteroid use (regardless of the indication), (B) the cumulative dose of systemic corticosteroids (regardless of the indication), (C) the duration of systemic corticoid use for an irAE and for another indication and (D) the cumulative dose of systemic corticoids for an irAE and for another indication.
AUC, area under the curve; irAE, immune-related adverse event; ROC, receiver operating characteristic; Se, sensitivity; Sp, specificity.

did not [median (95% CI) OS time 81.7 (25.4–NA) *versus* 291.0 (152.9–NA) weeks, respectively; crude HR (95% CI) 2.69 (1.39–5.20), $p=0.002$, Supplemental Figure S3D]. The Cox proportional hazards models showed: (a) significantly shorter OS in patients receiving oral corticosteroids for an indication other than an irAE than in patients who did not receive oral corticosteroids or those who received oral corticosteroids for an irAE [adjusted HR (95% CI) 5.76 (2.10–15.79), $p<0.001$]; and (b) no difference in OS in patients receiving oral corticosteroids for an irAE *versus* patients who did not receive oral corticosteroids or who received oral corticosteroids for an indication other than an irAE [adjusted HR (95% CI) 3.60 (0.66–19.81), $p=0.141$, Supplemental Table S5A]. The use of corticosteroids for an indication other than an irAE was still associated with shorter OS after adjusting for Breslow thickness [adjusted OR (95% CI) 16.28 (3.74–70.95), $p<0.001$, Supplemental Table S5B] and for Clark index [adjusted OR (95% CI) 38.98 (5.28–287.74), $p<0.001$, Supplemental Table S5C].

The proportion of responders was significantly lower in the melanoma CS+ group than in the melanoma CS– group (22.7% *versus* 48.9% respectively; $p=0.040$). When stratified by indication, the proportion of responders did not differ significantly in the melanoma irAE subgroup *versus* the melanoma CS– group (42.9% *versus* 48.9% respectively; $p=0.101$), and the proportion of responders was significantly lower in the melanoma 'other indication' subgroup than in the melanoma CS– group (13.4% *versus* 48.9% respectively; $p=0.005$, Supplemental Figure S4). After adjusting for confounders, the logistic regression model confirmed these trends: the use of oral corticosteroids for an irAE was not significantly associated with a worse tumor response [adjusted OR (95% CI) 1.82 (0.15–28.69), $p=0.643$], while the use of oral corticosteroids for an indication other than an irAE was associated with a worse tumor response [adjusted OR (95% CI) 4.83 (1.05–62.71), $p=0.039$, Supplemental Table S6A]. The use of corticosteroids for an indication other than an irAE was still associated

with a poorer tumor response after adjusting for Breslow thickness [adjusted OR (95% CI) 12.65 (2.09–400.23), $p = 0.036$, Supplemental Table S6B].

Patients with lung cancer. Of the 166 patients with lung cancer, 44 (26.5%) received oral corticosteroids, including 11 (6.6%) for an irAE and 33 (19.9%) for another indication (including 20 for an unknown indication). Overall survival did not differ significantly in patients who received oral corticosteroids than in patients who did not [median (95% CI) OS time 50.4 (31.1–92.4) *versus* 47.9 (37.6–64.1) weeks, respectively; crude HR (95% CI) 1.00 (0.66–1.52), $p = 0.990$, Supplemental Figure S5A]. Even after stratification by indication, OS did not differ significantly between the groups (Supplemental Figure S5B, S5C and S5D). The proportion of responders did not differ significantly in the lung cancer CS+ group *versus* the lung cancer CS– group (15.9% *versus* 17.2%, respectively; $p = 0.947$) – even after stratification by indication (Supplemental Figure S6).

Topical corticosteroids. Twenty-three (6.2%) patients received topical corticosteroids for a median (interquartile range) duration of 34 (26.9–49.1) weeks. The indications for topical steroids were dermatological irAEs in 17 patients (73.9%), psoriasis in four patients (17.4%), prurigo in one patient (4.3%) and maculopapular exanthema in one patient (4.3%). Overall survival was longer in patients who received topical corticosteroids than in those who did not [median (95% CI) OS time NA (124.1–NA) *versus* 55 (48.1–75.3) weeks, respectively; crude HR 0.42 (0.22–0.83), $p = 0.010$ in a log-rank test; Supplemental Figure S7A]. After stratification by indication, the OS in patients receiving topical corticosteroids for a dermatological irAE was higher than in those who were not [median (95% CI) OS time 141.4 (71.9–NA) *versus* 55.7 (48.3–77.7) weeks, respectively; crude HR (95% CI) 0.54 (0.26–0.98), $p = 0.029$ in a log-rank test; Supplemental Figure S7B].

Inhaled corticosteroids. Twenty-two (5.9%) patients received long-term treatment with inhaled corticosteroids (the inhaled CS+ group); the indication was chronic obstructive pulmonary disease in 21 patients and asthma for one patient. Sixteen of the 22 patients had lung cancer, three patients had head and neck cancer, two patients had melanoma, and one patient had urothelial cancer. Overall survival was similar in the inhaled CS+ group and inhaled CS– groups [median (95% CI) OS time 53.7 (28.1–NA) *versus* 63.6 (53.9–85.3) weeks, respectively; crude HR (95% CI) 1.16 (0.69–1.98), $p = 0.560$ in a log-rank test; Supplemental Figure S8].

Discussion

Our results showed that corticosteroid use for an indication other than an irAE had a negative impact on OS [median (95% CI) OS time 50.4 (26.1–124) *versus* 65.3 (54.1–113) weeks in the 'other indication' subgroup and CS– group, respectively; adjusted HR (95% CI) 1.34 (1.05–2.03), $p = 0.046$] and on the proportion of patients with a good tumor response [12.5% *versus* 27.8%, respectively; $p = 0.008$, adjusted OR (95% CI) 2.04 (1.07–5.80), $p = 0.039$]. However, patients receiving corticosteroids for an irAE and those not treated with corticosteroids did not differ significantly with regard to OS – suggesting that irAEs have a positive effect on OS. Indeed, patients who experience irAEs survive for longer than patients who do not.[25–27] Our findings are in line with studies showing that: (a) the early use of corticosteroids in an indication other than an irAE is harmful on ICI initiation; [9,10,12] and (b) the use of corticosteroids to treat irAEs during immunotherapy does not affect OS.[13–15] Therefore, the fact that corticosteroids do not impact OS in the setting of irAE suggests survival is affected by the indication for corticosteroids, rather than corticosteroid use *per se*.

Our analyses of subgroups of patients with metastatic cancer or melanoma were consistent with these findings. In contrast to the literature data, however, the use of oral corticosteroids did not appear to affect OS or tumor response in patients with lung cancer.[9–11] There are several possible explanations for the discrepancy. Firstly, the clinical outcomes in the studies by Arbour *et al.*[9] and Ricciuti *et al.*[11] concerned the early use of oral corticosteroids (i.e. before ICI initiation), whereas we focused on corticosteroid use after ICI initiation. Secondly, Ricciuti *et al.*[11] categorized the reasons for corticosteroid use as either cancer-related (for palliative indications) or cancer-unrelated (for non-palliative indications); hence, poorer outcomes might have been related to prognostic factors rather than corticosteroid use *per se*. In the present study, the indication for corticosteroid use was an irAE or another indication (including both those related to cancer, such as brain metastasis, and those not). Moreover, data

on the indication were missing for 20 of our 44 lung cancer patients receiving corticosteroids. Thirdly, the PD-L1 tumor proportion score and the tumor mutational burden – known predictive biomarkers for the effectiveness of ICIs in non-small-cell lung carcinoma (NSCLC)[28] – were not available in the present study.

In the present study, and considering the use of corticosteroids for an indication other than an irAE, ROC analyses showed that: (a) a threshold value at 132 days of corticosteroid treatment (specificity 71.4%; sensitivity 89.8%); and (b) a cumulative threshold dose of 3215 mg prednisolone equivalent (specificity 71.4%; sensitivity 65.3%) are associated with progression of disease. Therefore, caution should be taken when these thresholds are reached.

To the best of our knowledge, the present study is the first to have reported on the influence of topical steroids on OS in patients treated with ICIs. However, it is well established that topical corticosteroids can pass into the circulation.[16] Our results showed that treatment with topical corticosteroids is associated with longer OS [crude HR (95% CI) 0.42 (0.22–0.83), $p = 0.010$ in a log-rank test]. The most frequent indication for topical steroid use was a dermatological irAE; this might explain why OS was longer in these patients because dermatological irAEs are associated with better OS.[25,26] Finally, our results showed that OS was similar in patients treated with inhaled corticosteroids and in those not treated with these drugs, as already described by Li *et al.*[18] Thus, the use of this corticosteroid administration route does not appear to influence the effectiveness of ICIs.

Finally, our present results showed that ATB use is associated with shorter OS [adjusted HR (95% CI) 1.43 (1.04–1.97), $p = 0.040$] and a worse tumor response [adjusted OR (95% CI) 6.60 (3.08–15.70), $p < 0.001$] in the overall patient population, in patients with metastatic cancer [adjusted HR (95% CI) 1.39 (1.05–2.04), $p = 0.039$ for OS; adjusted OR (95% CI) 10.83 (3.58–44.69), $p < 0.001$ for tumor response], and in patients with melanoma [adjusted HR (95% CI) 2.58 (1.04–6.38), $p = 0.040$ for OS; adjusted OR (95% CI) 4.48 (1.05–23.09), $p = 0.049$ for tumor response]. These results are in line with previous studies.[23,29–32] ATBs appear to have an indirect negative impact on the ICIs' effectiveness by modifying the composition of gut microbiota.[29,33] However, these results could also be explained by the indication bias – that is, the infection for which the ATB is used – and not the ATB itself.

The present study had some limitations, including the biases associated with its retrospective single-center design. In the absence of a comparator arm, it is also difficult to affirm that the use of oral corticosteroids for an indication other than an irAE (rather than the indications themselves, i.e. prognostic factors reported by Ricciuti *et al.*)[11] is associated with a worse outcome. However, a prospective, randomized, controlled trial with a comparator arm would be difficult to set up. Furthermore, our study's retrospective design prevented us from collecting certain data (e.g. the PD-L1 tumor proportion score, the tumor mutational burden in the NSCLC population, and some of the indications for corticosteroids) and thus our ability to draw a robust conclusion for patients with NSCLC. Finally, our analyses of topical and inhaled corticosteroid use lacked statistical power.

Conclusion

Our present results show that after ICI initiation, systemic corticosteroid use for an irAE does not appear to affect the patients' clinical outcomes, whereas systemic corticosteroid use for another indication does. This negative impact appears to be greater after 134 days of treatment or beyond a cumulative prednisolone equivalent dose of 3215 mg. Topical and inhaled corticosteroids did not appear to influence the effectiveness of ICIs. These results must be confirmed in larger studies.

Author contributions

Louis Gaucher contributed to the conception/design of the work, acquisition and interpretation of data for the work, and drafting the manuscript. He approved the version to be published, and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Leslie Adda contributed to the acquisition and interpretation of data for the work. She approved the version to be published, and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Alice Séjourné contributed to the acquisition and interpretation of data for the work, and drafting the manuscript. She approved the version to be published, and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Camille Joachim revised the work critically for important intellectual content, approved the version to be published, and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Guillaume Chaby revised the work critically for important intellectual content, approved the version to be published, and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Claire Poulet revised the work critically for important intellectual content, approved the version to be published, and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Sophie Liabeuf revised the work critically for important intellectual content, approved the version to be published, and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Valérie Gras-Champel revised the work critically for important intellectual content, approved the version to be published, and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Kamel Masmoudi revised the work critically for important intellectual content, approved the version to be published, and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Aurélie Moreira revised the work critically for important intellectual content, approved the version to be published, and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Youssef Bennis contributed to the conception/design of the work and interpretation of data for the work, and drafting the manuscript. He approved the version to be published, and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Benjamin Batteux contributed to the conception/design of the work, acquisition, analysis, and interpretation of data for the work, and drafting the manuscript. He approved the version to be published, and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Supplemental material

Supplemental material for this article is available online.

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