



Original Research

Effect of corticosteroids on the outcome of patients with advanced non–small cell lung cancer treated with immune-checkpoint inhibitors



Marcus Skribek^{a,b,1}, Konstantinos Rounis^{a,b,c,1}, Soren Afshar^a,
Oscar Grundberg^{a,b}, Signe Friesland^{a,b}, Georgios Tsakonas^{a,b},
Simon Ekman^{a,b}, Luigi De Petris^{a,b,*}

^a Thoracic Oncology Center, Theme Cancer, Karolinska University Hospital, Stockholm, Sweden

^b Department of Oncology-Pathology, Karolinska Institutet, Stockholm, Sweden

^c Department of Medical Oncology, University General Hospital, Heraklion, Crete, Greece

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KEYWORDS

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Abstract *Introduction:* We analysed patients with advanced non–small cell lung cancer (NSCLC) who were treated with immune-checkpoint inhibitors (ICIs) to address the effect of the timeline and reason for corticosteroid administration on survival outcomes.

Methods: We retrospectively collected clinical data of non-oncogenic driven, advanced NSCLC patients treated with ICIs at Karolinska University Hospital, including the timeline and reason for steroid administration. Steroid administration was defined as > 10 mg prednisolone equivalent for ≥10 days. We subcategorized patients based on the aetiology of steroid administration into three subgroups: a) steroids for supportive reasons but not for cancer palliation; b) steroids for the palliation of cancer-related symptoms; c) steroids for the management of immune-related adverse events (irAEs). Furthermore, to analyse the timeline, patients were categorised into two groups; those who received corticosteroids within 2 weeks before until 2 days after ICI initiation and those who received steroids later during their treatment course.

Results: Analysed data from 196 patients showed 46.3% of patients received corticosteroids. Steroid administration due to irAEs did not affect overall survival (OS) ($p = 0.38$) compared with the steroid naïve group. Only steroid administration for the palliation of cancer-related symptoms was an independent predictor for shorter OS (HR = 2.7; 95% CI, 1.5–4.9). The timeline of steroid administration did not affect OS ($p = 0.456$) in our cohort.

* Corresponding author: Thoracic Oncology Unit D1:06 Karolinska University Hospital, 17176, Stockholm, Sweden.

E-mail address: luigi.depetris@ki.se (L. De Petris).

¹ Equal contribution.

Conclusions: Steroids due to irAEs do not appear to hamper ICI efficacy. However, the administration of high-dose steroids to palliate malignancy-associated symptoms might reflect the dismal prognosis of this patient group.

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1. Introduction

Monoclonal antibodies that act as immune-checkpoint inhibitors (ICIs) of the PD-1/PD-L1 pathway have demonstrated favourable antitumour activity against locally advanced and metastatic non-small cell lung cancer (NSCLC) [1–6]. This led to the regulatory approval of their use in the first or subsequent-line of treatment as single agents or in combination with chemotherapy. Their use in clinical practice has paved a new era in the field of NSCLC management, offering durable remissions in a significant proportion of patients. It has also introduced a new toxicity spectrum, immune-related adverse events (irAEs), which constitute autoimmune phenomena caused by the administration of ICIs [7].

PD-L1 expression in the cancer or immune cells of the tumour microenvironment has so far been the only approved biomarker for clinical decision-making to predict outcome in NSCLC patients treated with ICIs. Furthermore, beyond the molecular characteristics of an individual's malignancy, the administration of co-medications such as corticosteroids has been reported to correlate with inferior clinical outcomes in ICI-treated cancer patients [8–10].

Exogenous corticosteroid administration has been the cornerstone of treatment for autoimmune disorders for more than half a century. Steroids exert their immunosuppressive properties in a multifactorial way, suppressing both innate and adaptive immunity. They act as agonists of the glucocorticoid receptor (GR), and its subsequent activation leads to the transcriptional modification of a plethora of genes involved in the priming of innate immune responses [11]. Because of these well recognised immune suppressive properties, steroid administration >10 mg prednisolone equivalent were part of the exclusion criteria in the clinical trials that led to the approval of ICIs [1–6].

Nonetheless, NSCLC patients often require steroid administration >10 mg of prednisolone equivalent for a wide spectrum of underlying etiologies, ranging from cerebral oedema due to brain metastases to chronic pulmonary obstructive disease (COPD) exacerbations. Steroid administration in ICI-treated patients raises concerns about hampering ICI efficacy for the aforementioned reasons. Retrospective data on metastatic NSCLC patients treated with ICIs have demonstrated worse outcomes in terms of reduced response rates,

progression-free survival (PFS) and overall survival (OS) with steroid administration > 10 mg of prednisolone equivalent [8]. Moreover, a similar retrospective study demonstrated adverse outcomes from steroid administration only in the subgroup of patients that received them for the palliation of cancer-related symptoms [9].

In addition, high-dose steroid administration (≥ 1 mg/kg/day) is the main treatment option for the management of severe grade III–IV irAEs that develop in 10–15% of patients receiving ICIs [7]. Data on the clinical outcome of patients who received steroids because of the development of irAEs are derived mostly from melanoma studies. These have reported that their administration does not influence ICI efficacy [12,13], but there is scarcity of information addressing this question in the NSCLC setting.

To further investigate the potential impact of steroid administration on the outcome of advanced NSCLC patients receiving ICIs, we conducted a retrospective data analysis of the patients treated with ICIs at Karolinska University Hospital for advanced NSCLC from 2016 to 2019.

2. Methods

2.1. Study design

We retrospectively collected clinical data of 196 patients with non-oncogenic-driven, metastatic NSCLC who received treatment with ICIs as either monotherapy or in combination with chemotherapy according to common clinical practice at Karolinska University Hospital, Stockholm, Sweden, from 2016 to 2019. Patients with driver *EGFR* mutations and *ALK* translocations and patients enrolled in prospective clinical trials were excluded from the analysis. Our study was reviewed and approved by the national ethical institutional review board (DNR 2020–02636).

2.2. Patients

Data on patient characteristics (age, gender, smoking status, performance status), disease characteristics (histology) and sites of metastases (lung, brain, liver and bone) were retrospectively collected. Disease burden was classified as high or low (≤ 2 or > 2 organs with metastases) at the beginning of ICI administration. The

rationale for this cut-off is based on the publication by Ferrara *et al.* [14], which reported that metastatic dissemination in more than two organs was associated with the development of hyperprogressive disease.

Data on the context and duration of steroid administration were also retrospectively collected. The patients were categorised as having received steroids if they had received them at a dose of >10 mg prednisolone equivalent for a duration ≥ 10 days 2 weeks before, during and 2 weeks after the last ICI administration. If a patient had received steroids at a dose equivalent of <10 mg prednisolone or for <10 days, the patient was classified as steroid naïve.

If a patient received multiple courses of steroid administration for <10 days, then the total sum was calculated and was categorised accordingly. We further subclassified the patients who received steroids into three different subgroups: a) steroids for supportive reasons but not for the palliation of cancer-related symptoms (e.g. COPD exacerbations); b) steroids for the palliation of cancer-related symptoms (e.g. symptomatic brain metastases); c) steroids for the management of irAEs. To analyse the effect of the timeline of corticosteroid administration on patient outcome, we further subcategorized patients who received steroids at ICI initiation (defined as having received steroids within 2 weeks before or 2 days after ICI initiation) or later during the course of treatment. If a patient concomitantly received steroids for any reason other than irAEs and later also developed an irAE, they were categorised in the irAE subgroup.

Clinical data on irAEs were also retrospectively collected and the patients were categorised according to the European Society of Medical Oncology clinical guidelines [15] and the Common Terminology Criteria for Adverse Events v4.

2.3. Outcome assessment

PFS was defined as the duration of time between treatment initiation with ICIs and the development of disease progression or death. Disease progression was defined according to RECIST 1.1 criteria [16]. OS was defined as the duration of time between treatment initiation with ICIs and death. Patients who had not progressed or were alive at the time of data analysis were censored at the time of their last follow-up.

2.4. Statistical analysis

Descriptive statistics were performed to analyse categorical and continuous variables. Statistical significance was set at $p < 0.05$ (two-sided test). The Kaplan–Meier method was used to assess the effect of the studied variables on PFS and OS. The curves were compared with the log-rank test. We conducted a univariate analysis using the Cox Regression method to examine

the effect of the following covariates on PFS and OS: age, smoking status, performance status, histologic subtype (squamous versus non-squamous), line of treatment of ICI administration, PD-L1 status, disease burden and reason for steroid administration. Thereafter, we conducted a multivariate analysis for PFS and OS where we included the variables that had reached statistical significance in the univariate analysis. Statistical analyses were performed using SPSS 25.00.

3. Results

3.1. Patient characteristics

Patient characteristics are summarised in Table 1. Median follow-up duration was 10.1 months. Median age of the studied population was 70.5 years. 97.4% of the patients in our cohort had received anti-PD-1/anti-PD-L1 agents as monotherapy and the rest in combination with chemotherapy. ICIs were administered as first line therapy to 21.4%, whereas the rest received them as second- or subsequent-line of therapy.

A total of 46.9% of patients had received steroids >10 mg prednisolone equivalent for ≥ 10 days. Of these, 13.8% had received steroids for supportive reasons but not for the palliation of cancer-related symptoms or for the management of irAEs. Steroids for the palliation of symptoms due to the underlying malignancy were administered to 17.3% and 15.8% had received them due to irAEs. The type and grade of irAEs are depicted in Suppl. Fig. 1.

The median duration of time under treatment with ICIs until the development of autoimmune phenomena that led to the administration of high dose steroids was 140 days (Suppl. Fig. 2). The median duration of steroid administration including tapering up to 10 mg prednisolone equivalent was 36 days (range: 11–229 days). One of the 31 patients required anti-TNF- α antibodies for irAE management. Three patients' symptoms were unresolved by high-dose steroids, where two patients died because of disease progression while on steroids tapering and one had an unresolved grade II skin rash.

3.2. Survival outcomes

Patient survival outcomes are summarised in Table 2. The four different patient subgroups that were created based on the reason of steroid administration showed different outcomes in terms of PFS at a statistically significant level (Fig. 1). Similarly, steroid administration also significantly affected OS in this patient cohort (Fig. 2). Individuals who received steroids for the palliation of cancer-related symptoms exhibited the worst outcome of all subgroups both in terms of PFS (median = 1.9 months; 95% CI, 1.3–2.6) and OS (median = 4.3 months; 95% CI, 3.4–5.2). Furthermore, the

Table 1
Patient characteristics.

Patient characteristics		Total (n = 196) n %	
Age (years)	Median	70.5	
	Range	35–84	
Gender (n%)	Male	86	43.8%
	Female	110	56.2%
ECOG performance status (n%)	0–1	167	85.2%
	2	29	14.8%
Smoking status (n%)	Never smoker	13	6.6%
	Former smoker	127	64.8%
	Active smoker	58	28.6%
Histology (n%)	Squamous	60	30.6%
	Non-squamous	136	69.4%
Line of treatment of ICI administration (n%)	1st line	42	21.4%
	2nd line	106	54.1%
	3rd or subsequent line	48	25.1%
PD-L1 expression (n%)	<1%	16	8.2%
	1% ≤ PD-L1 < 50%	60	30.6%
	PD-L1 ≥ 50%	83	42.3%
	No data	37	18.9%
Anti-PD-1/PD-L1 administration (n%)	Monotherapy	191	97.4%
	Combination with chemotherapy	5	2.6%
	Combination with anti-CTLA-4 antibody	0	0%
Number of cycles of ICIs administration (cycles)	Median	5	
	Range	1–49	
Brain metastases (n%)	Yes	35	17.2%
	No	161	82.1%
Bone metastases (n%)	Yes	61	31.1%
	No	134	68.4%
	No data	1	0.5%
Liver metastases (n%)	Yes	40	20.4%
	No	156	79.6%
Disease burden (n%)	Number of organs with metastatic disease > 2	29	14.8%
	Number of organs with metastatic disease ≤ 2	167	85.2%
Kras mutational status (n%)	Kras mutant	48	24.5%
	Kras wild type	95	48.5%
	No data	53	27%
Steroid administration > 10 mg for ≥ 10 days (n%)	Yes	92	46.9%
	No	104	53.1%
Duration of steroids administrations (n%)	Steroid naïve patients or steroid administration < 10 mg	89	45.4%
	Steroid administration > 10 mg for less than 10 days	15	7.7%
	Steroid administration > 10 mg for ≥ 10 days	92	46.9%
Reason for steroid administration (n%)	Steroid naïve patients	104	53.1%
	Steroid administration for supportive reasons (not for palliation of cancer-associated symptoms)	27	13.8%
	Steroid administration for palliation of cancer-associated symptoms	34	17.3%
	Steroid administration due to irAEs	31	15.8%
	Steroid administration for supportive reasons (not for palliation of cancer-associated symptoms) at the initiation of ICIs	15	7.7%
Timeline of steroids administration*	Steroid administration for supportive reasons (not for palliation of cancer-associated symptoms) during the disease course	12	6.1%
	Steroid administration for palliation of cancer-associated symptoms at the initiation of ICIs	17	8.7%
	Steroid administration for palliation of cancer-associated symptoms at the initiation of ICIs during the disease course	17	8.7%
	irAEs grade III or IV (n%)	21	10.7%
	Yes	21	10.7%
Type of grade III or IV irAEs (n%)	No	175	87.3%
	Pneumonitis	6	3.1%
	Colitis	7	3.6%
	Hepatitis	4	2%

Table 1 (continued)

Patient characteristics		Total (n = 196) n %	
Duration of treatment with ICIs in patients that developed irAEs (days)	Nephritis	1	0.5%
	Immune-related skin toxicity	3	1.5%
	Median	140	
	Range	1–427	
Disease progression (n%)	Yes	134	68.4%
	No	62	31.6%
Death (n%)	Yes	97	49.5%
	No	99	50.5%
	Range	0.1–33.2	

Abbreviations: ICIs, immune-checkpoint inhibitors; PD-L1, programmed death-ligand 1; irAEs, immune-related adverse events.

* High disease burden is defined as > 2 organs affected by metastatic disease.

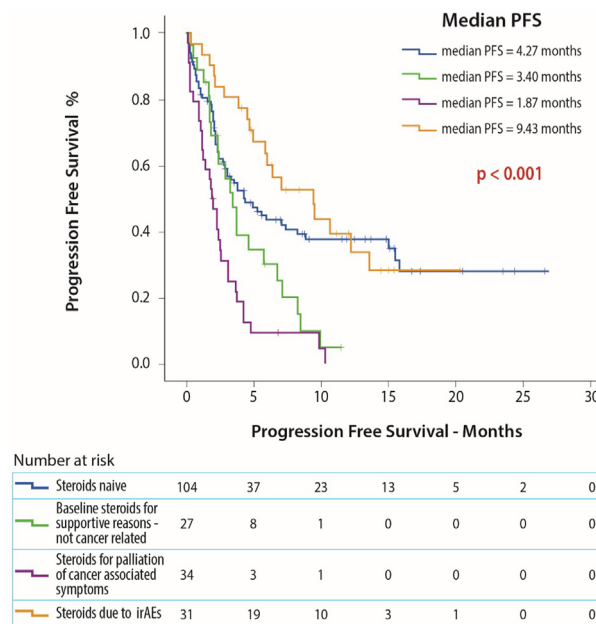
* Patients were categorised as having received steroids at ICI initiation if they had received steroids >10 mg prednisolone equivalent for ≥10 days within two weeks prior to until two days after initiation of ICIs. The remaining patients were categorised as having received steroids during the disease course.

Table 2

Patient outcomes.

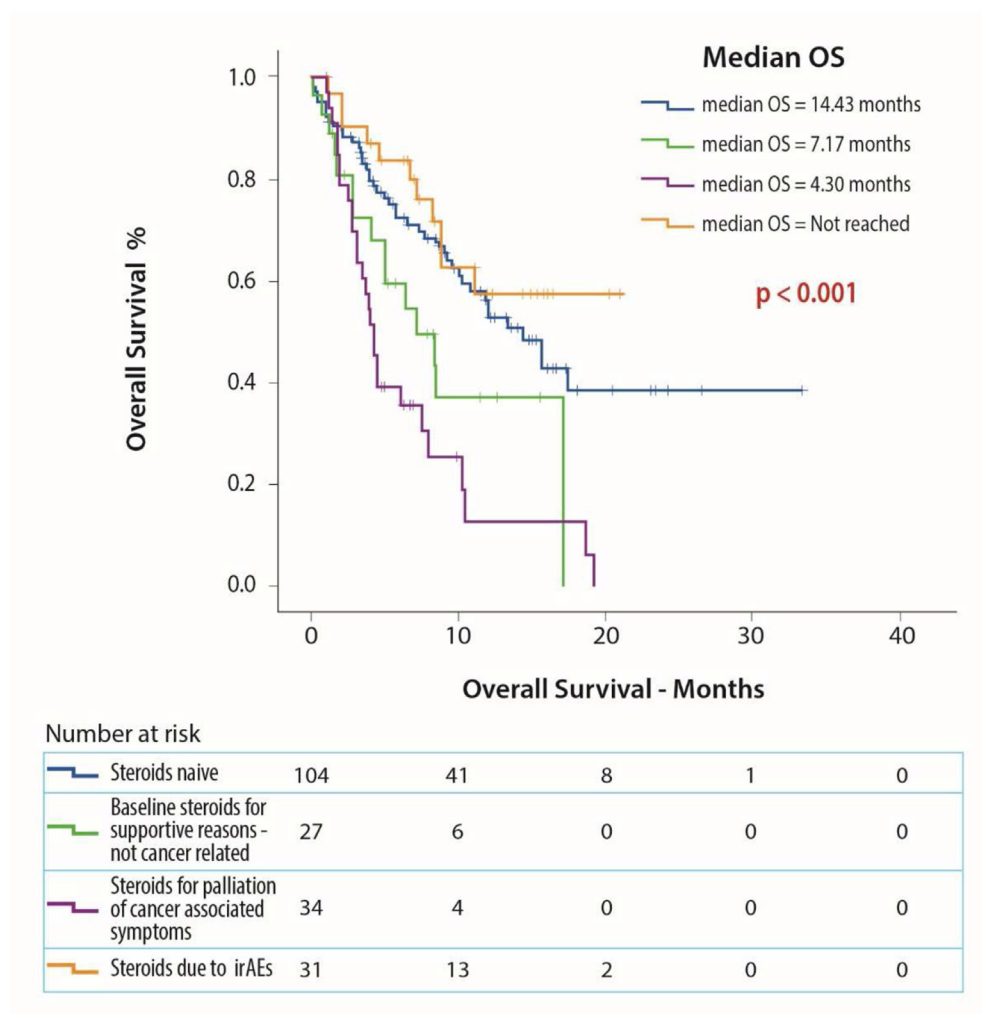
Patient outcomes		Total (n = 196)	95% confidence interval
Progression-free survival (months)	Median	3.7	2.3–4.7
	Range	0.1–33.4	
Overall survival (months)	Median	10.5	8.1–12.9
	Range	0.1–33.4	
Overall survival (months) (Since the initiation of first line systemic treatment for metastatic NSCLC)	Median	24.5	17.96–31.04
	Range	1.07–80.77	
Follow-up (months)	Median	10.1	7.7–12.7

NSCLC, non–small cell lung cancer.



Abbreviations: PFS=Progression-Free Survival, irAEs=Immune-Related Adverse Events.

Fig. 1. Kaplan–Meier curves demonstrating the PFS of the different patient subgroups that were created according to the underlying aetiology of steroid administration. PFS, progression-free survival; irAEs, immune-related adverse events.



Abbreviations: OS=Overall Survival, irAEs=Immune-Related Adverse Events.

Fig. 2. Kaplan–Meier curves demonstrating the OS of the different patient subgroups that were created according to the aetiology of steroid administration. OS, overall survival; irAEs, immune-related adverse events.

timeline of steroid administration in the subgroup of patients who received steroids for cancer palliation or other supportive reasons did not affect patient survival (Fig. 3).

Administration of steroids due to irAEs ($n = 31$) did not influence patient outcome compared to the steroid naïve individuals. Patients in this subgroup did not experience inferior PFS (9.4 months versus 4.3 months; $p = 0.308$) nor OS (not reached versus 14.3 months; $p = 0.380$) (Suppl. Fig. 3A & 3B). Patients who suffered from irAEs and ICI was discontinued ($n = 20$), the median PFS was 1.2 months (95% CI, 0–2.9) (Suppl. Fig. 4).

3.3. Univariate and multivariate analysis

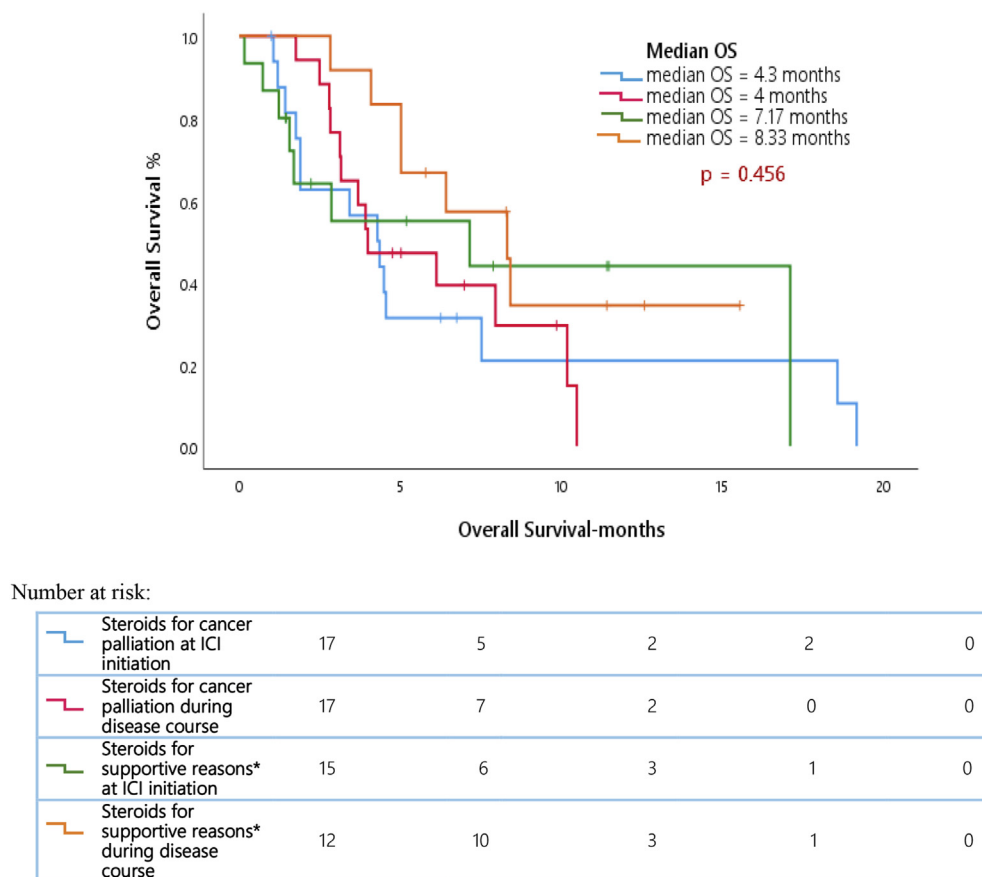
Univariate and multivariate analyses are summarised in Table 3. In the multivariate analysis for PFS, the presence of brain and bone metastases, PD-L1 levels <50%

and the administration of steroids for cancer palliation were independent predictors for shorter PFS. In addition, performance status 2, presence of liver and bone metastases and steroids for the palliation of cancer-related symptoms independently predicted for shorter survival.

4. Discussion

This retrospective cohort with ICI-treated metastatic NSCLC patients found that corticosteroid administration for the palliation of malignancy-related symptoms had a negative effect on PFS and OS. Furthermore, steroid administration due to irAEs did not appear to negatively affect patient outcomes.

We categorised patients in our cohort according to steroid administration if they had received steroids at a dosage of >10 mg prednisolone equivalent for ≥ 10 days. This cut-off was used as short courses of low-to-



Abbreviation: ICI=Immune Checkpoint Inhibitor, OS=Overall Survival.

Fig. 3. The log-rank test depicting the effect of the timeline of steroids administration during ICI therapy on overall survival amongst the patients who received steroids for the palliation of cancer-associated symptoms and those who received steroids for supportive reasons but not for cancer palliation. ICI, immune-checkpoint inhibitor; OS, overall survival.

moderate doses of prednisone (up to 1 mg/kg), and chronic use of prednisone < 10 mg have not shown to increase the risk of infections, thereby not causing significant immunosuppression [17]. When patients were categorised into three different subgroups based on the underlying aetiology of steroid administration, only steroid administration for the palliation of malignancy-related symptoms was an independent predictor for reduced PFS and OS. Steroid administration for reasons other than the palliation of cancer-related symptoms or irAEs was not an independent predictor for adverse outcome in this cohort.

These results are in accordance with previous reports by Ricciuti *et al.* [9] and De Giglio *et al.* [10]; both reported that steroid administration for cancer-related reasons independently predicted for reduced survival in cancer patients treated with ICIs. The majority of NSCLC patients who receive steroids for reasons unrelated to cancer generally received steroids in short courses (<10 days) with intermediate dosages (0.25–0.50 mg/kg), which do not significantly affect the immune system [17]. Cumulative use of short courses of intermediate dosages of steroids within a specific

timeframe have much less immunosuppressive effects than continuous administration. Palliation of cancer-related symptoms with steroids is a common practice in NSCLC patients for a variety of reasons (brain oedema due to brain metastases, anorexia or dyspnoea). The necessity for continuous steroid administration of >10 mg prednisolone equivalent in these patients may reflect an aggressive underlying malignancy that is resistant to treatment, and their poor outcome may not be attributed only to steroid administration *per se*. It remains unclear if intermediate dosage of steroids for other reasons in these patients actually affects treatment outcome, but short courses appear to be safe. The aforementioned findings further complicate the treatment decision-making process considering the poor treatment effect for patients who require corticosteroids because of cancer symptoms prior to ICI initiation. Therefore, there is a clear need to reconsider the value of ICI therapy in this patient category, even with regards to the apparent PFS of 1.9 months and OS of 4.3 months.

The subgroup of patients who received steroids at ICI initiation versus later during the disease course were also analysed; effect on patient survival could not be

Table 3

Univariate and multivariate analysis using the Cox regression method.

Cox regression	PFS		OS	
	HR (95% Confidence Intervals)	p-value	HR (95% Confidence Intervals)	p-value
Univariate analysis				
Age \geq 70 years old	0.690 (0.491–0.970)	0.033	0.585 (0.389–0.879)	0.010
Active or former smoker	0.671 (0.351–1.271)	0.228	0.926 (0.634–1.353)	0.692
Performance status 2	1.587 (1.011–2.493)	0.045	2.307 (1.392–3.824)	0.001
Squamous histology	1.046 (0.732–1.449)	0.806	0.944 (0.621–1.435)	0.787
Brain metastases	2.322 (1.525–3.536)	<0.001	2.504 (1.552–4.039)	<0.001
Liver metastases	1.488 (0.998–2.217)	0.051	1.947 (1.260–3.009)	0.003
Bone metastases	1.896 (1.339–2.687)	<0.001	1.807 (1.207–2.705)	0.004
High disease burden	1.797 (1.152–2.803)	0.010	2.187 (1.346–3.553)	0.002
PD-L1 < 50%	2.096 (1.416–3.105)	<0.001	1.647 (1.034–2.624)	0.035
ICIs as second- or subsequent-line of treatment	1.434 (1.119–1.837)	0.004	1.373 (1.021–1.846)	0.036
Steroids for supportive reasons (not for palliation of cancer-associated symptoms)	1.728 (1.055–2.831)	0.030	1.820 (1.008–3.288)	0.047
Steroids for irAEs	0.572 (0.342–0.957)	0.033	0.553 (0.286–1.070)	0.078
Steroids for palliation of cancer-associated symptoms	2.709 (1.779–4.124)	<0.001	2.724 (1.694–4.382)	<0.001
Multivariate analysis				
	HR (95% confidence intervals)	p-value	HR (95% confidence intervals)	p-value
Age \geq 70 years old	1.035 (0.678–1.578)	0.874	0.965 (0.564–1.617)	0.863
Performance status 2	1.490 (0.852–2.606)	0.161	3.266 (1.684–6.337)	<0.001
Brain metastases	1.817 (1.127–2.931)	0.014	1.363 (0.763–2.434)	0.295
Liver metastases			2.207 (1.265–3.849)	0.005
Bone metastases	1.611 (1.052–2.466)	0.028	1.679 (1.017–2.773)	0.043
High disease burden	0.923 (0.535–1.763)	0.971	1.362 (0.629–2.947)	0.433
PD-L1 < 50%	1.848 (1.223–2.793)	0.003	1.081 (0.588–1.984)	0.801
ICIs as second- or subsequent-line of treatment	1.143 (0.805–1.622)	0.465	1.359 (0.961–1.921)	0.083
Steroids for supportive reasons (not for palliation of cancer-associated symptoms)	1.237 (0.679–2.254)	0.487	1.028 (0.500–2.341)	0.840
Steroids for irAEs	0.853 (0.491–1.483)	0.547		
Steroids for palliation of cancer-associated symptoms	2.064 (1.291–3.299)	0.002	2.688 (1.487–4.856)	0.001

ICIs, immune-checkpoint inhibitors; irAEs, immune-related adverse events; HR, hazards ratio; PD-L1, programmed death-ligand 1; PFS, progression-free survival; OS, overall survival.

established. Unfortunately, a multivariate analysis could not be performed because of the low statistical power. These results show indirectly that the underlying reason for steroid administration is more important than the timeline of steroid administration, because the necessity for steroid administration is a confounding factor for poor prognosis reflecting a more aggressive underlying disease biology.

Patients who received high-dose steroids because of irAEs did not experience inferior outcomes in comparison to the steroid naïve population. Retrospective studies in melanoma patients who received ICIs have demonstrated that steroid administration due to irAEs did not affect treatment outcome [12,13]. In addition, the emergence of irAEs has been associated with favourable outcomes in patients receiving ICIs for a spectrum of malignancies, such as NSCLC, melanoma and urothelial cancer, either in the metastatic or in the adjuvant setting [18–20]. Nevertheless, studies with longer follow-up are necessary to further confirm that steroid administration due to irAEs in long-term responders has no effect on the duration of response.

Finally, performance status 2 and the presence of liver and bone metastases independently predicted for

shorter OS in our patient cohort. Our results concerning the adverse effect on liver and bone metastases are in accordance with previous retrospective analyses [21,22], and their presence should constitute an additional stratification factor in future clinical trials.

To our knowledge this is the first study in advanced NSCLC treated with ICIs that investigated the impact of steroid administration for the management of irAEs on patient outcome. Moreover, its findings on the adverse effect of steroid administration for the palliation of cancer-associated symptoms further reinforce the few previous clinical reports that demonstrated similar results.

The two major limitations of our study are the retrospective nature of the data analysed and the heterogeneity of the studied population as we included patients who received ICIs in the first, second or subsequent-line of treatment. Although our results are statistically significant, larger prospective studies should be carried out and evaluated to further validate the results of our trial. Furthermore, due to the few number of patients who received ICI combined with chemotherapy, a subgroup analysis for this patient group could not be performed.

5. Conclusion

Corticosteroid administration for the palliation of malignancy-related symptoms had an adverse effect on patient outcome. This emphasises the need for a more careful patient selection for ICI therapy. In addition, steroid administration due to irAEs does not appear to negatively affect patient outcome.

Ethical approval

This study was approved by the Ethics Review Board for each institute. Informed consent was not required for participation due to the investigation being a retrospective study. All authors had full access to all the data in the study. The procedures followed were in accordance with the precepts of Good Clinical Practice and the Declaration of Helsinki.

Authors' contribution

All authors contributed to the publication according to the ICMJE guidelines for the authorship. All authors read and approved the manuscript and agree to be accountable for all aspects of the research in ensuring that the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Availability of data and materials

The data sets used during the present study are available from the corresponding authors upon reasonable request.

Conflict of interest statement

The authors declare no conflict of interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejca.2020.12.012>.

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