Jan 2024 ONC-BE-2300252

Drug interference during immunotherapy

Parallel Workshop session's part 2A

Corticosteroids

H.U.B
HÔPITAL UNIVERSITAIRE DE BRUXELLES
ACADEMISCH ZIEKENHUIS BRUSSEL

INSTITUT JULES BORDET INSTITUUT
Hôpital Erasme
ULB
Hôpital Universitaire des Enfants Reine Fabiola
Universitair Kinderziekenhuis Koningin Fabiola

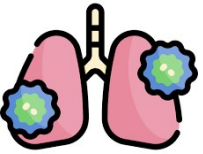
Dr. Maxime ILZKOVITZ
Jules Bordet Institute– H.U.B.
ISA meeting 10.01.2024

Plan

1. Clinical case
2. Steroids in oncology
3. Impact of steroids with immunotherapy
4. Conclusions

CASE REPORT: B.C. 70 Y.O. WOMAN

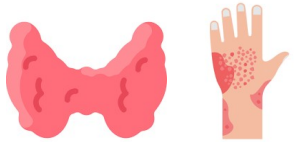
06/2016
NSCLC with brain M+



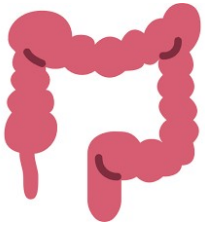
02/2018
Local relapse

irAEs

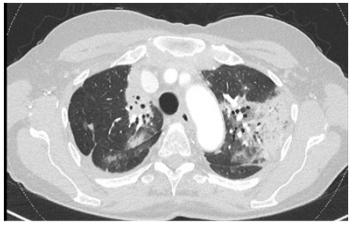
6 months



12 months



irAE 18 months



02/18 – 02/19

02/19 – 04/19

09/19 – 11/19

Carboplatin
Permetrexed

50 gray

Nivolumab
3 mg/kg

Prednisone
0.5 mg/kg

Prednisone
1 mg/kg

7.5 years survival!

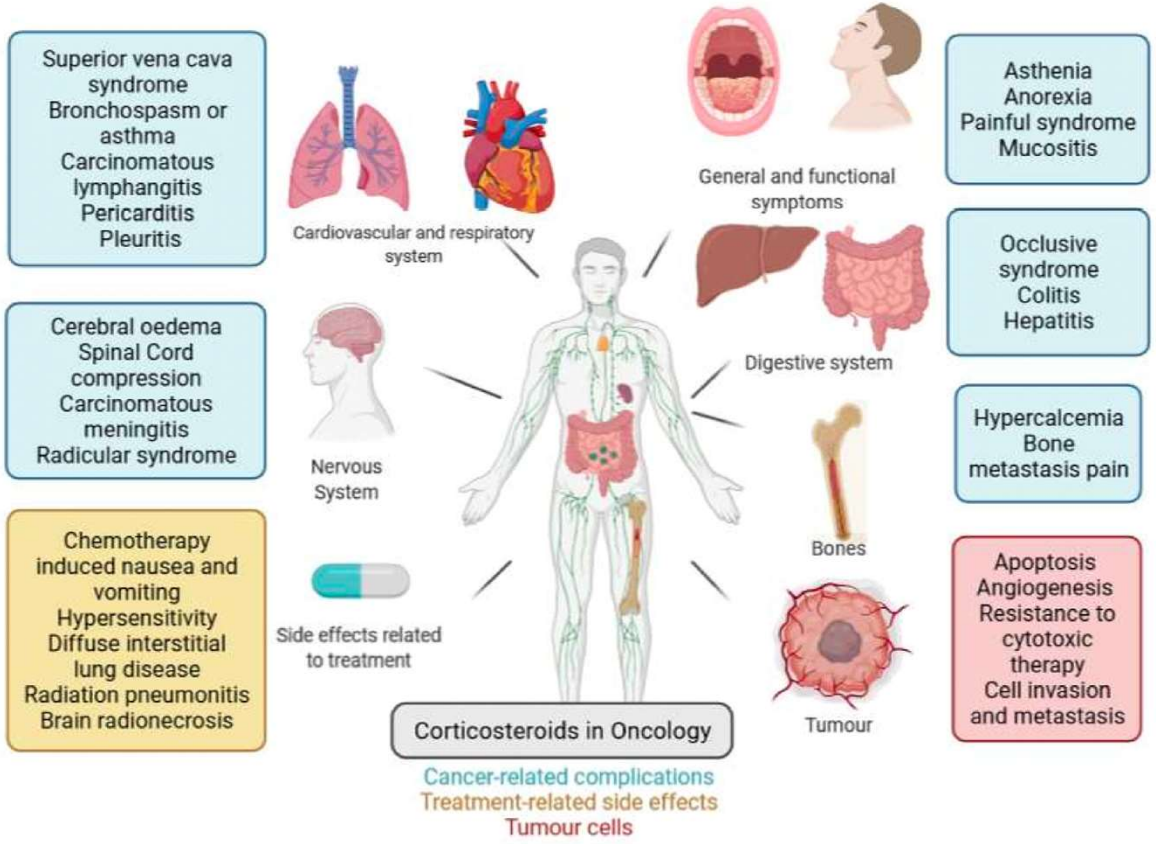
CR

CR → 01/24

CR, complete response; irAE, immune-related adverse event; M+, metastasis; NSCLC, non small cell lung cancer.

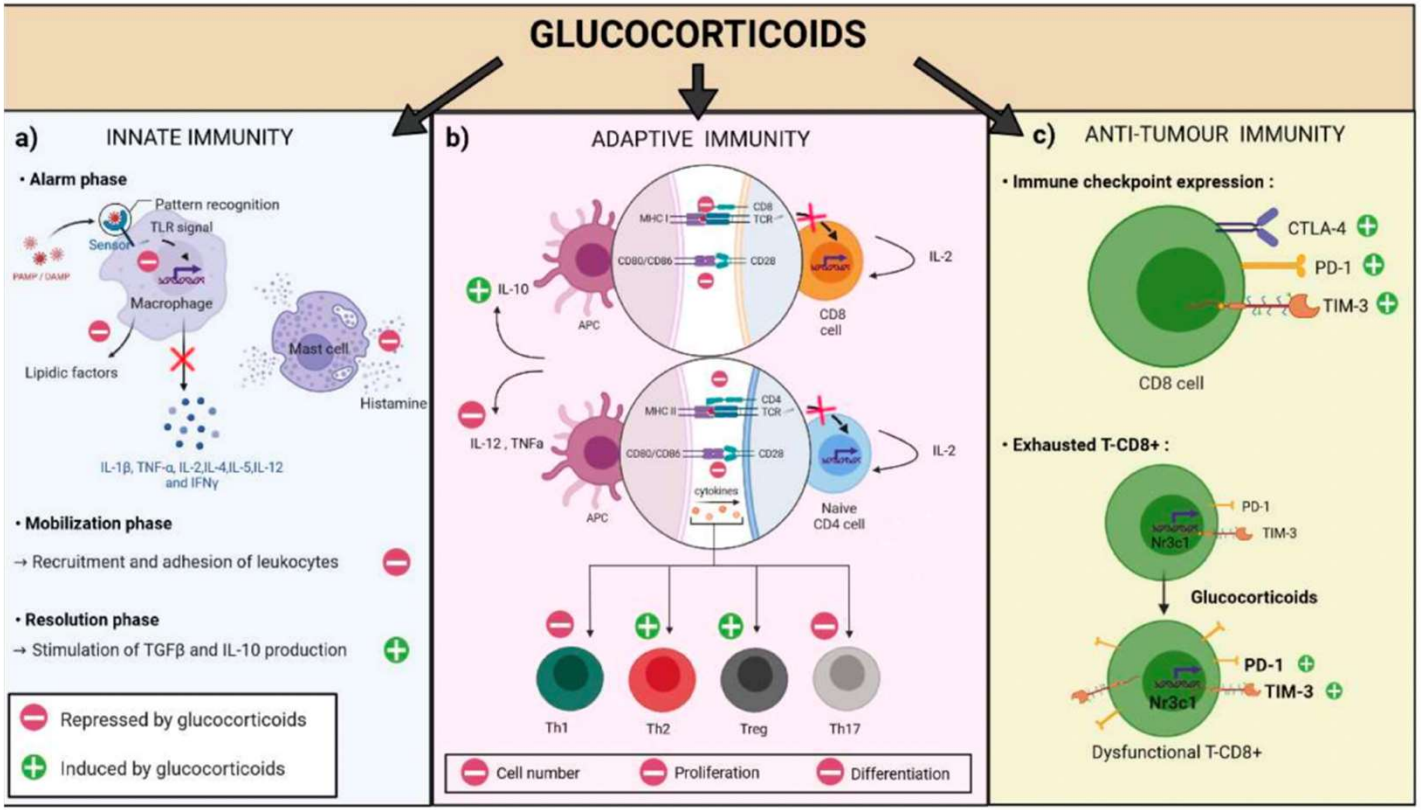
STEROIDS IN ONCOLOGY

A cornerstone in management of oncological patients



Kalfeist et al., Cells 2022

Roles of steroids on immunity



Poor response to Immunotherapy ?

Kalfeist et al., Cells 2022

IMPACT OF STEROIDS IN IMMUNOTHERAPY

- **Dose of steroids**
- **Timing of steroids**
- **Indications for steroids**

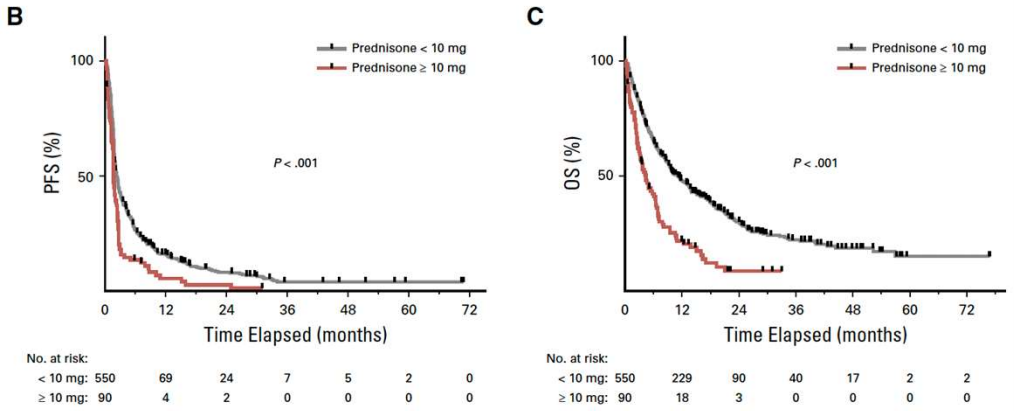
DOSE OF STEROIDS

Impact of Baseline Steroids on Efficacy of Programmed Cell Death-1 and Programmed Death-Ligand 1 Blockade in Patients With Non–Small-Cell Lung Cancer

Kathryn C. Arbour, Laura Mezquita, Niamh Long, Hira Rizvi, Edouard Auclin, Andy Ni, Gala Martínez-Bernal, Roberto Ferrara, W. Victoria Lai, Lizza E.L. Hendriks, Joshua K. Sabari, Caroline Caramella, Andrew J. Plodkowski, Darragh Halpenny, Jamie E. Chaft, David Planchard, Gregory J. Riely, Benjamin Besse, and Matthew D. Hellmann

JOURNAL OF CLINICAL ONCOLOGY

- Gustave Roussy & Memorial Sloan Kettering Cancer Center
- NSCLC – PD1i ; N= 640



NSCLC, non small cell lung cancer; OS, overall survival; PFS, progression free survival

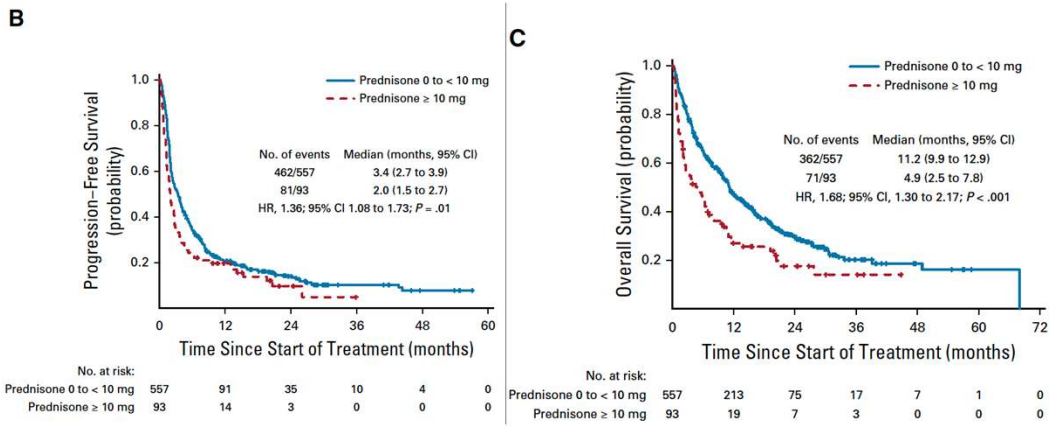
Arbour, JCO, 2018

Immune Checkpoint Inhibitor Outcomes for Patients With Non–Small-Cell Lung Cancer Receiving Baseline Corticosteroids for Palliative Versus Nonpalliative Indications

Biagio Ricciuti, MD[1]; Suzanne E. Dahlberg, PhD[1]; Anika Adeni[1]; Lynette M. Sholl, MD[2]; Mizuki Nishino, MD, MPH[2]; and Mark M. Awad, MD, PhD[1]

JOURNAL OF CLINICAL ONCOLOGY

- NSCLC - PD1i ; N=650



Ricciuti et al., JCO 2019

TIMING OF STEROIDS

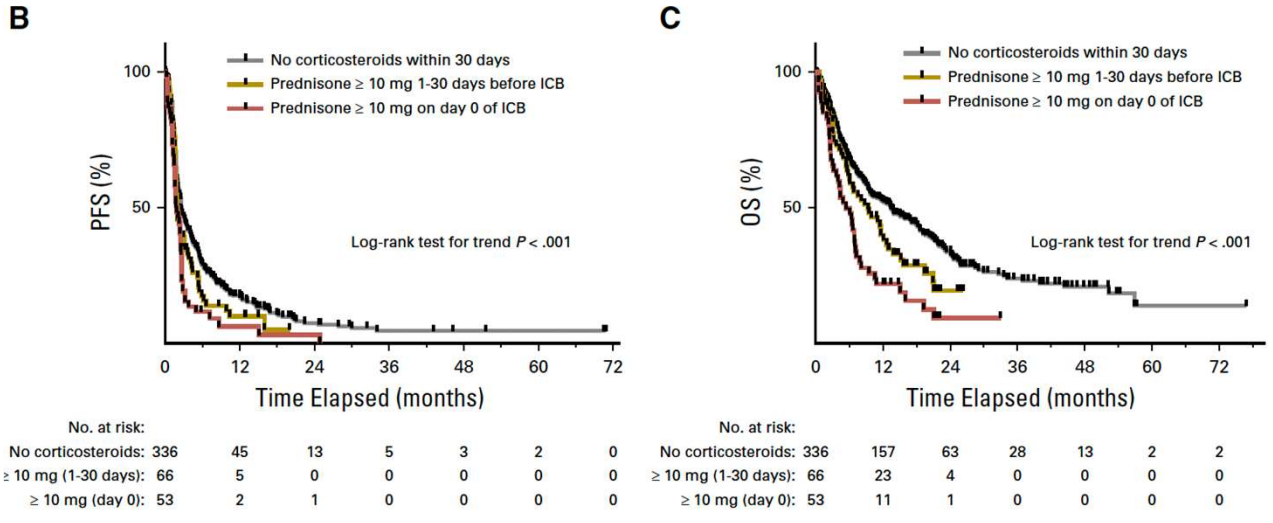
Impact of Baseline Steroids on Efficacy of Programmed Cell Death-1 and Programmed Death-Ligand 1 Blockade in Patients With Non–Small-Cell Lung Cancer

JOURNAL OF CLINICAL ONCOLOGY

Kathryn C. Arbour, Laura Mezquita, Niamh Long, Hira Rizvi, Edouard Auclin, Andy Ni, Gala Martínez-Bernal, Roberto Ferrara, W. Victoria Lai, Lizza E.L. Hendriks, Joshua K. Sabari, Caroline Caramella, Andrew J. Plodkowski, Darragh Halpenny, Jamie E. Chaft, David Planchard, Gregory J. Riely, Benjamin Besse, and Matthew D. Hellmann

- Cohorts: Gustave Roussy & Memorial Sloan Kettering Cancer Center (MSKCC)
- NSCLC –PD1i ; N= 640

MSKCC cohort



Arbour, JCO, 2018

TIMING OF STEROIDS

Modulation of peripheral blood immune cells by early use of steroids and its association with clinical outcomes in patients with metastatic non-small cell lung cancer treated with immune checkpoint inhibitors

Giovanni Fucà,[1] Giulia Galli,[1] Marta Poggi,[1] Giuseppe Lo Russo,[1] Claudia Proto,[1] Martina Imbimbo,[1] Roberto Ferrara,[1] Nicoletta Zilembo,[1] Monica Ganzinelli,[1] Antonio Sica,[2,3] Valter Torri,[4] Mario Paolo Colombo,[5] Claudio Vernieri,[1,6] Andrea Balsari,[7] Filippo de Braud,[1,8] Marina Chiara Garassino,[1] Diego Signorelli[1]

ESMO Open Cancer Horizons

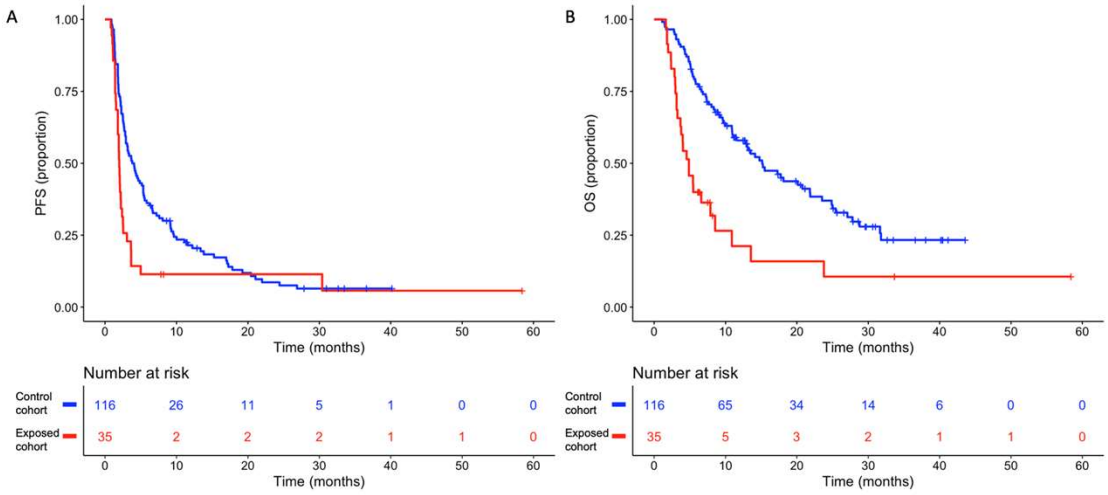
- NSCLC ; PD1i (96%) ; N= 151
- Early/baseline use of steroids is associated with worse PFS and OS
- Regardless of the indication

* Early = ≥10 mg/d prednisone-equivalent within 28 days after ICI initiation.

Multivariable analysis

PFS: HR=1.88 (1.08 to 3.28) ; p=0.03

OS : HR=2.38 (1.48 to 3.83) ; p<0.001



Fuca et al., ESMO Open, 2019

TIMING OF STEROIDS

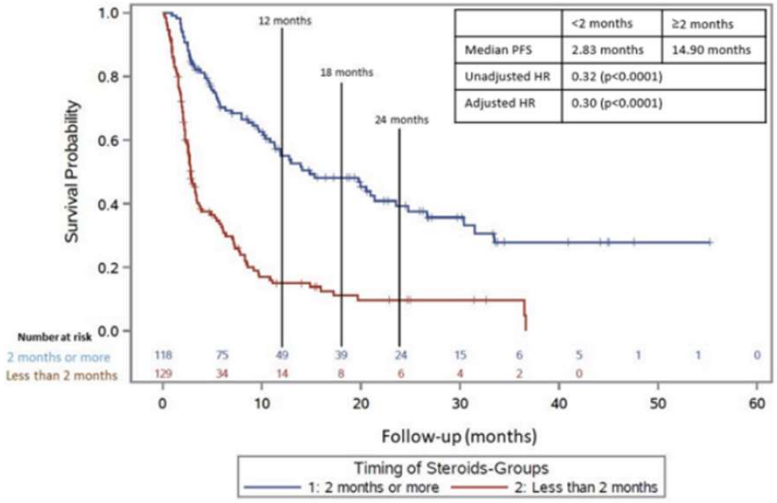
Timing of steroid initiation and response rates to immune checkpoint inhibitors in metastatic cancer

Journal for ImmunoTherapy of Cancer

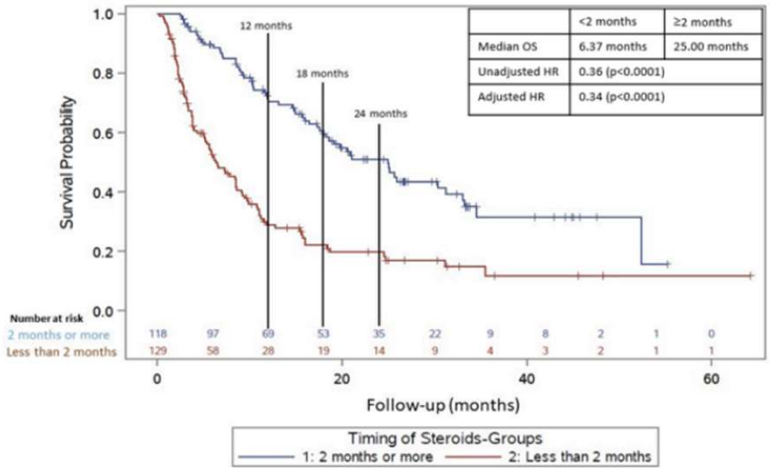
Diana V Maslov ,[1] Karine Tawagi,[2] Madhav KC,[3] Victoria Simenson,[1] Helen Yuan,[1] Cameron Parent,[1] Adi Bamnolker,[1] Richa Goel,[1] Zoe Blake,[4] Marc R Matrana,[5] Daniel H Johnson[5]

- Metastatic cancer (NSCLC=40%) ; N= 247

Progression-free survival



Overall survival



HR, Hazard ratio; NSCL, non small cell lung cancer; OS, overall survival; PFS, progression-free survival

Maslov et al., JITC, 2020

TIMING OF STEROIDS

Article

Is Timing of Steroid Exposure Prior to Immune Checkpoint Inhibitor Initiation Associated with Treatment Outcomes in Melanoma? A Population-Based Study

Nikita Nikita [1,2], Joshua Banks [3], Scott W. Keith [3], Andrew Song [4], Jennifer M. Johnson [1,2], Melissa Wilson [1,2], Swapnil Sharma [1,2] and Grace Lu-Yao [1,2,5,*]

- SEER database: Surveillance, Epidemiology, and End Results Program
- Melanoma ; **N= 3149** ; CTLA4i = 54% ; PD1i = 40% ; 6% =COMBO

- **Steroid use up to 3 months prior increased risk for mortality up to 6 months after ICI initiation**

Table 2. Steroid-exposure timing prior to ICI initiation and its time-dependent association with all-cause mortality after ICI initiation.

Timing of Steroid Exposure Prior to ICI Initiation	0 to ≤3 Months Post ICI Initiation Hazard Ratios [1] (95% CI)	3 to ≤6 Months Post ICI Initiation Hazard Ratios (95% CI)	≥6 Months Post ICI Initiation Hazard Ratios (95% CI)
No steroids in 12 months before ICI	Ref	Ref	Ref
Steroids ≤ 1 month prior to ICI	2.26 (1.65–3.08) [2]	2.00 (1.42–2.82) [2]	1.05 (0.82–1.35)
Steroids 1 to ≤3 months prior to ICI	1.51 (1.01–2.27) [2]	1.04 (0.65–1.35)	0.91 (0.68–1.22)
Steroids 3 to 12 months prior to ICI	1.02 (0.68–1.52)	1.25 (0.86–1.84)	0.98 (0.77–1.24)

[1] Hazard ratios estimated by time-dependent hazards model adjusted for sex, age, marital status, sequence of cancer diagnosis, year of diagnosis, and Charlson comorbidity index. [2] $p < 0.001$.

Nikita, Cancers 2022

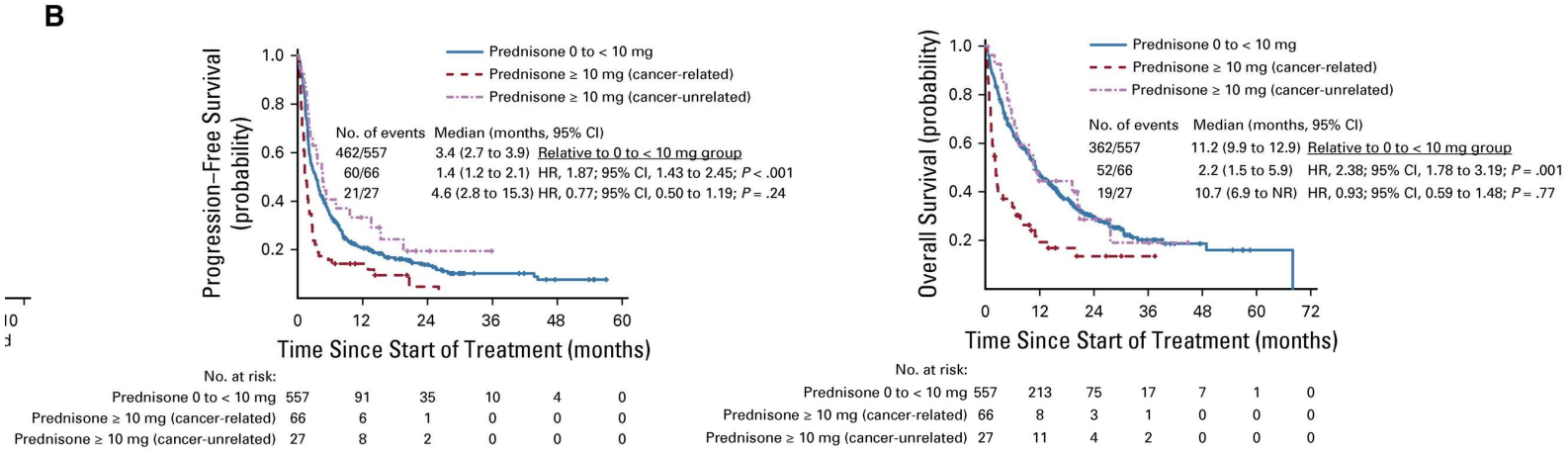
INDICATIONS FOR STEROIDS

Immune Checkpoint Inhibitor Outcomes for Patients With Non–Small-Cell Lung Cancer Receiving Baseline Corticosteroids for Palliative Versus Nonpalliative Indications

Biagio Ricciuti, MD[1]; Suzanne E. Dahlberg, PhD[1]; Anika Adeni[1]; Lynette M. Sholl, MD[2]; Mizuki Nishino, MD, MPH[2]; and Mark M. Awad, MD, PhD[1]

JOURNAL OF CLINICAL ONCOLOGY

- NSCLC & Anti-PD1 ; N=650
- PFS & OS are impact by palliative conditions rather than steroids administration at ICI initiation



Ricciuti et al., JCO 2019

HR, hazard ratio; NSCLC, non small cell lung cancer; OS, overall survival; PFS, progression-free survival

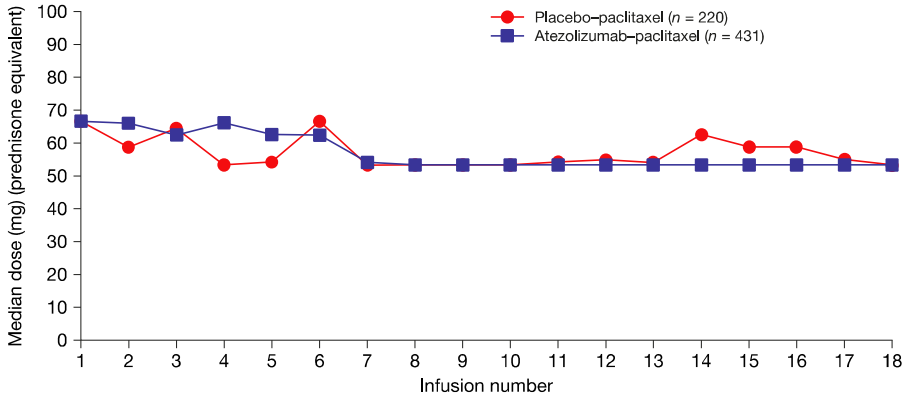
INDICATIONS FOR STEROIDS

Prophylactic steroid in immuno-chemotherapy - IMpassion 130 vs 131

Table 1 Impassion130 and Impassion131 trials

	IMpassion130 (n=902)		IMpassion131 (n=651)	
Disease setting	1st line metastatic TNBC		1st line metastatic TNBC	
Trial design	Phase III, randomised (1:1), placebo controlled		Phase III, randomised (2:1), placebo controlled	
PD-L1 testing	SP142		SP142	
Intervention	Atezolizumab or placebo combined with nab-paclitaxel		Atezolizumab or placebo combined with paclitaxel	
Primary endpoint	PFS and OS ITT and PD-L1+ (hierarchical)		PFS PD-L1+ and ITT (hierarchical)	
PFS PD-L1+ (intervention vs control)	7.5 vs 5.0 months (HR: 0.62; 95% CI 0.49 to 0.78)		6.0 vs 5.7 months (HR: 0.82; 95% CI 0.60-1-12 p=0.20)	
PFS ITT (intervention vs control)	7.2 vs 5.5 months (HR 0.80; 95% CI 0.69 to 0.92)		5.7 vs 5.6 months (HR: 0.86; 95% CI 0.70 to 1.05)	
OS PD-L1+ (intervention vs control)	25.4 vs 17.9 months (HR: 0.67; 95% CI 0.53 to 0.86)		22.1 vs 28.3 months (HR: 1.12; 95% CI 0.76 to 1.65)	
OS ITT (intervention vs control)	21.0 vs 18.7 months (HR: 0.87; 95% CI 0.75 to 1.02)		19.2 vs 22.8 months (HR 1.11; 95% CI 0.87 to 1.42)	
Study population (reported)				
Trial arms (ITT)	**Atezolizumab**	**Placebo**	**Atezolizumab**	**Placebo**
Median age	55 (20–82)	56 (26–86)	54 (22–85)	53 (25–81)
PD-L1+	41%	41%	44%	46%
Liver metastases	28%	26%	27%	28%
>3 metastatic sites	26%	24%	24%	22%
Prior taxane	51%	51%	48%	49%
Prior anthracycline	54%	54%	49%	50%
De novo metastatic TNBC	37%	37%	30%	31%
Use of concomitant steroids	Not required		8–10 mg dexamethasone or equivalent for at least the first two infusions	

CI, Confidence interval; HR, Hazard ratio; ITT, Intention-to-treat; ITT, intention to treat; OS, Overall survival; PD-L1, programme death ligand 1; PFS, Progression-free survival; TILs, tumour-infiltrating lymphocytes; TNBC, triple-negative breast cancer.



Miles, et al., Ann Oncol. 2021
Franzoi & De Azambuja, Esmo Open 2020

INDICATIONS FOR STEROIDS

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

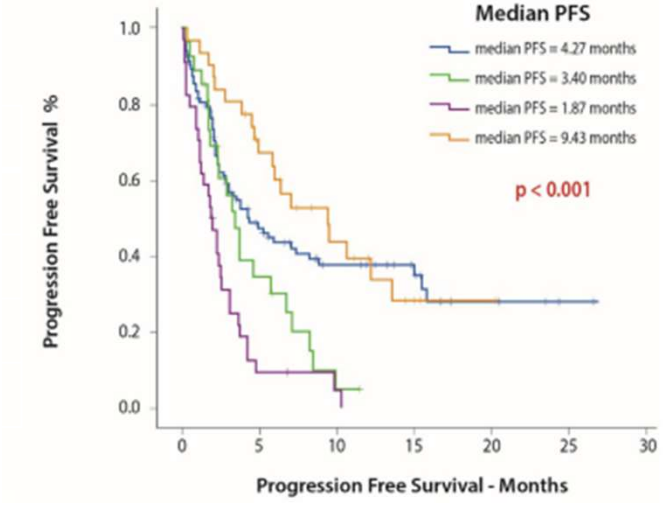
Marcus Skribek [a,b,1], Konstantinos Rounis [a,b,c,1], Soren Afshar [a], Oscar Grundberg [a,b], Signe Friesland [a,b], Georgios Tsakonas [a,b], Simon Ekman [a,b], Luigi De Petris [a,b,*]

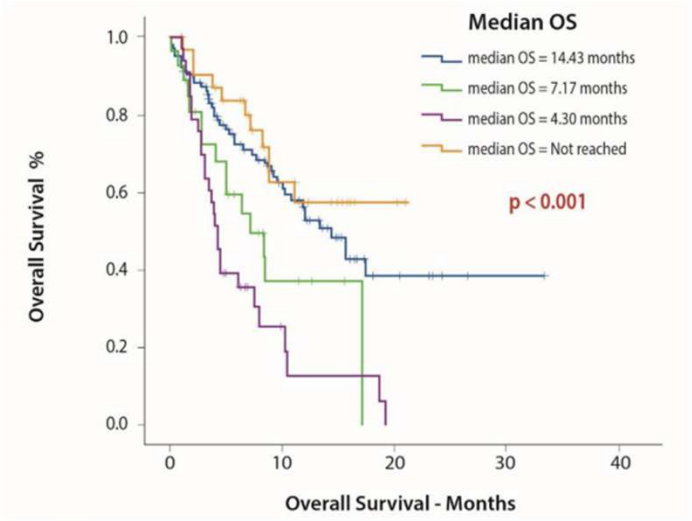
EJC EUROPEAN JOURNAL OF CANCER

- NSCLC – PD1/PDL1i (97%) – N= 196

Reasons for steroid

Naïve	53.1%
Supportive care	13.8%
Palliation	17.3%
irAEs	15.8%





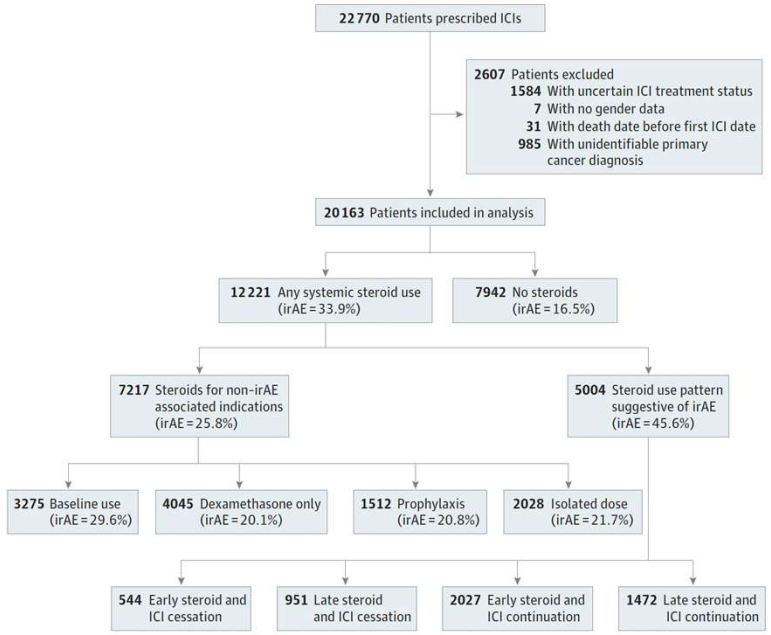
irAEs, immune-related adverses events; NSCLC, non small cell lung cancer; OS, overall survival; PFS, progression-free survival

Skribek et al., EJC, 2021

Original Investigation | Oncology

Survival Among Veterans Receiving Steroids for Immune-Related Adverse Events After Immune Checkpoint Inhibitor Therapy

Inga Van Buren, MD; Cecelia Madison, MS; Aimee Kohn, MD, PhD; Elizabeth Berry, MD; Rajan P. Kulkarni, MD, PhD; Reid F. Thompson, MD, PhD



- Retrospective multicentric review (2010-2021)
- Data base: Veterans Health Administration's Corporate Data Warehouse
- All cancers (54% NSCLC) – **N= 20.163**

- **3 groups:**
  - **No steroids**
  - **Steroids for irAE (ICD codes or suggestive pattern)**
  - **Steroids for non-irAE**

- **Outcome: OS at 5 years**

Van Buren, *JAMA Network Open. 2023*

ICD, International Classification of Diseases; ICI, immune-checkpoint inhibitor; irAE, immune-related adverse event; OS, overall survival.

SURVIVAL IN PATIENTS RECEIVING STEROIDS DURING ICI-THERAPY

Table. Characteristics of the Veteran Cohort

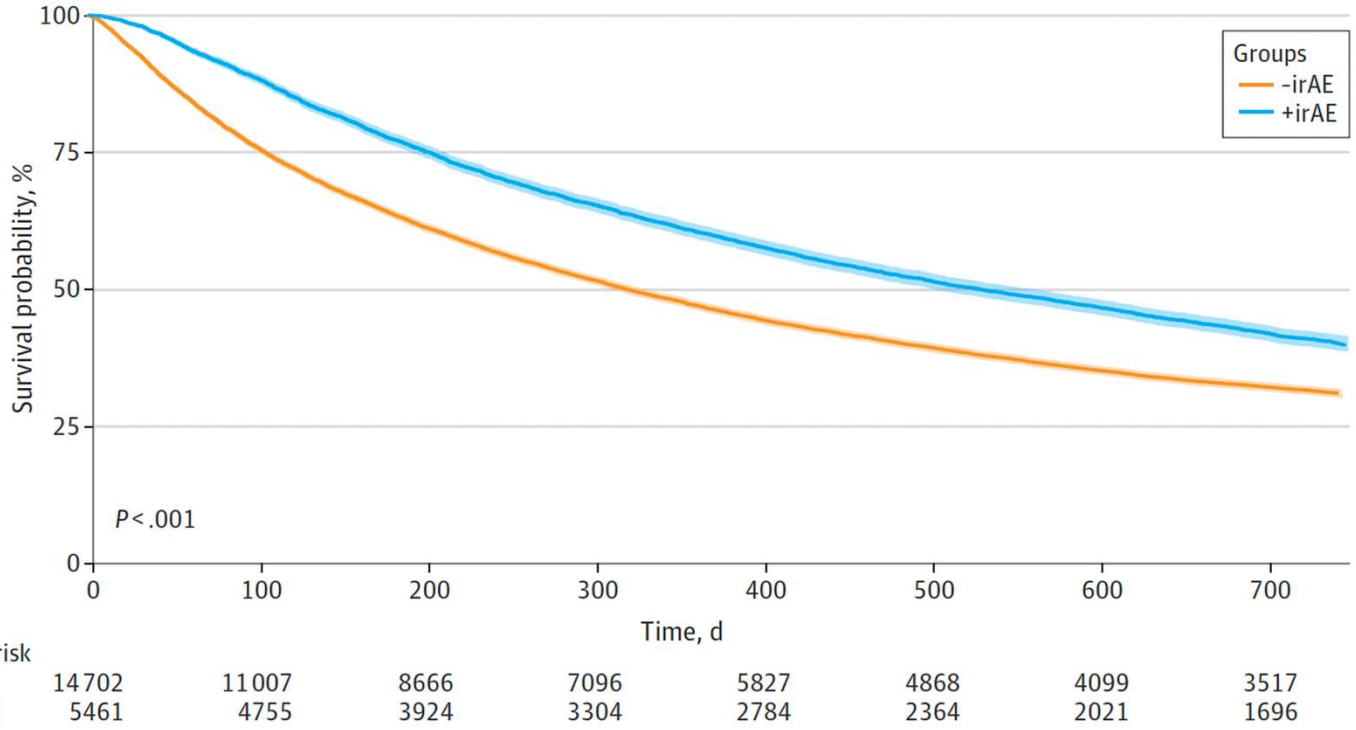
Characteristic	Patients, No. (%) (N = 20 163)		
	No steroid use (n = 7942)	Any systemic steroid use (n = 12 221)	*P* value
Age at first ICI treatment, mean (SD) [range], y	70.3 (8.5) [26-98]	69.5 (8.0) [20-98]	<.001
Sex			
Male	7747 (97.5)	11 830 (96.8)	.002
Female	195 (2.5)	391 (3.2)	NA
Body mass index, mean (SD) [range][a]	26.7 (5.8) [15-50]	26.9 (5.6) [15-50]	.04
No. of ICI treatments, mean (SD) [range]	8.5 (11.1) [1-137]	11.7 (13.5) [1-140]	<.001
Charlson Comorbidity index score, mean (SD) [range]	12.8 (4.0) [1-31]	12.8 (3.9) [2-30]	.68
Immune-related adverse event code present	1313 (16.5)	4148 (33.9)	<.001
Race			
African American or Black	1213 (15.3)	1973 (16.1)	.10
American Indian or Alaska Native	46 (0.6)	70 (0.6)	.95
Asian	24 (0.3)	36 (0.3)	.92
Declined or unknown	515 (9.4)	669 (5.5)	.003
Native Hawaiian or Pacific Islander	59 (0.8)	79 (0.6)	.42
White	1213 (15.3)	9394 (76.9)	.69
Predominant steroid[b]			
Dexamethasone	NA	6166 (50.5)	NA
Prednisone	NA	3447 (28.2)	NA
Methylprednisolone	NA	1102 (9.0)	NA
Hydrocortisone	NA	813 (6.7)	NA
Prednisolone	NA	3 (0.02)	NA
≥2 steroids	NA	690 (5.6)	NA
ICI target			
Anti-PD-1 monotherapy	6160 (77.6)	8850 (72.4)	<.001
Anti-PD-L1 monotherapy	1039 (13.1)	1685 (13.8)	.15
Anti-CTLA-4 monotherapy	211 (2.6)	240 (2.0)	.001
Anti-CTLA-4 and PD-L1 combination therapy	357 (4.5)	822 (6.7)	<.001
Mixed[c]	175 (2.2)	624 (5.1)	<.001
Smoking status			
Current or former smoker	5114 (64.4)	7703 (63)	<.001
Never smoker	1588 (20)	2077 (17)	<.001
Primary cancer		()	
Bronchus or lung	3565 (44.9)	7427 (60.8)	<.001
Urinary tract	1377 (17.3)	1576 (12.9)	<.001
Melanoma	1025 (12.9)	1324 (10.8)	<.001
Head and neck	603 (7.6)	728 (6.0)	<.001
Liver	725 (9.1)	488 (4.0)	<.001
Gastroesophageal	249 (3.1)	272 (2.2)	<.001
Colorectal	147 (1.9)	131 (1.1)	<.001
Squamous of skin	81 (1.0)	51 (0.4)	<.001
Mesothelioma	40 (0.5)	58 (0.5)	.77
Merkel	44 (0.6)	52 (0.4)	.19
Hodgkin	39 (0.5)	55 (0.5)	.67
Anal	32 (0.4)	29 (0.2)	.04
Breast	15 (0.2)	30 (0.2)	.41
Metastasis			
Any metastases	5655 (71.2)	10 230 (83.7)	<.001
Lymph node metastases	2684 (33.8)	5237 (42.9)	<.001
Centra nervous system metastases	933 (11.7)	2808 (23.0)	<.001

Van Buren, *JAMA Network Open. 2023*

CTLA-4, Cytotoxic T-lymphocyte associated protein 4; ICI, immune-checkpoint inhibitor; PD-1, programmed death-1; PD-L1, programmed death ligand-1.

SURVIVAL IN PATIENTS RECEIVING STEROIDS DURING ICI-THERAPY

Overall survival according to irAE



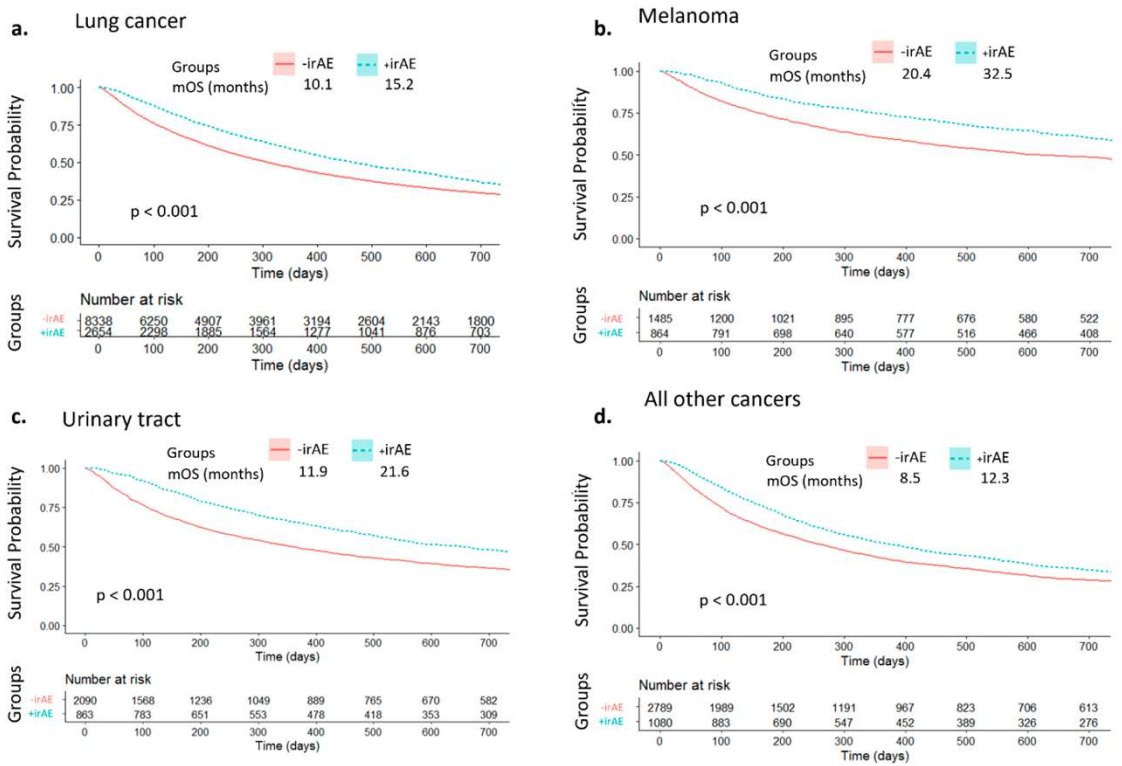
- All type cancers
- Metastatic or not

Van Buren, *JAMA Network Open. 2023*

ICI, immune-checkpoint inhibitor; irAE, immune-related adverse event.

STEROIDS FOR IRAES

eFigure 2. irAE diagnosis and survival across cancer types



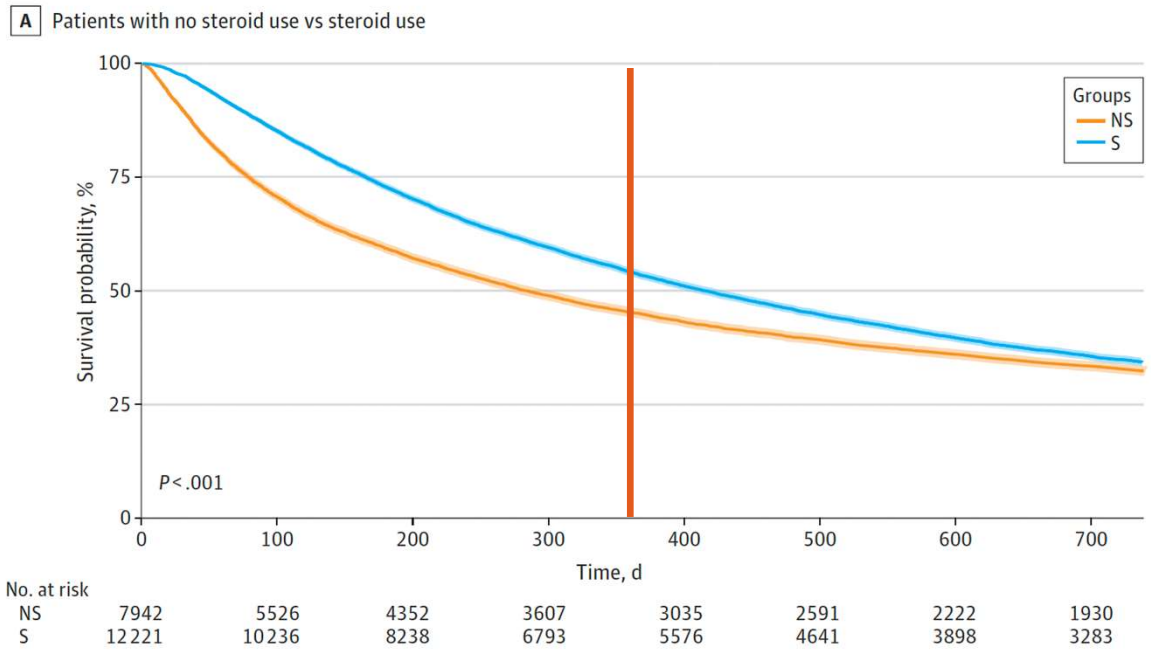
Kaplan-Meier (KM) curves showing overall survival in patients across cancer types without irAE related ICD codes (red) and irAE related ICD codes (blue). Survival probability shown on y-axis over time (in days) on x-axis. Table below graphs demonstrate remaining number of patients at risk over 8 time points. Median overall survival in months for each group shown under figure key. **a.** Lung cancer **b.** Melanoma **c.** Urinary tract cancer **d.** All other remaining cancers.

Van Buren, *JAMA Network Open. 2023*

ICI, immune-checkpoint inhibitor; irAE, immune-related adverse event.

SURVIVAL IN PATIENTS RECEIVING STEROIDS DURING ICI-THERAPY

Overall survival in patients receiving steroids



No-steroids
Steroids

→ **Especially the 1st year**

ICI, immune-checkpoint inhibitor.

Van Buren, *JAMA Network Open. 2023*

INDICATIONS FOR STEROIDS

Original Investigation | Oncology

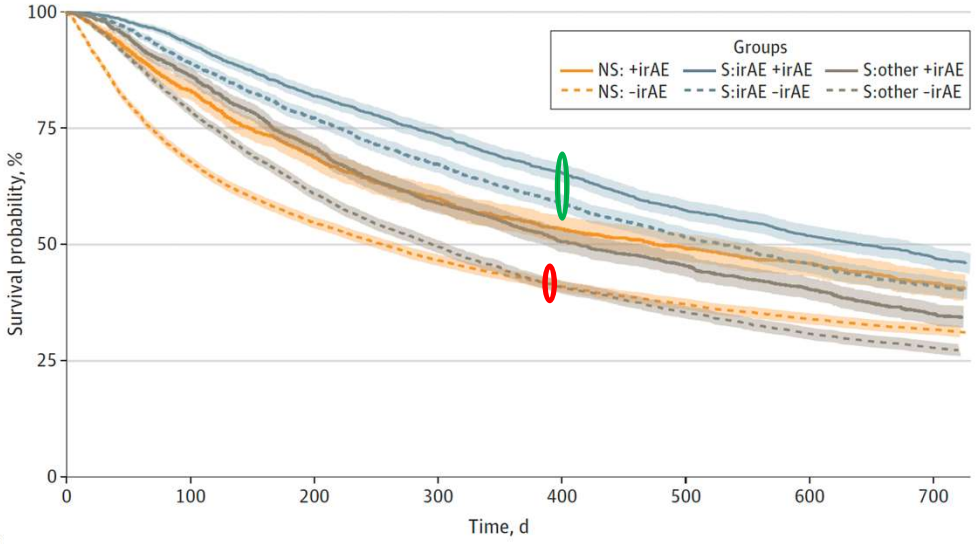
Survival Among Veterans Receiving Steroids for Immune-Related Adverse Events After Immune Checkpoint Inhibitor Therapy

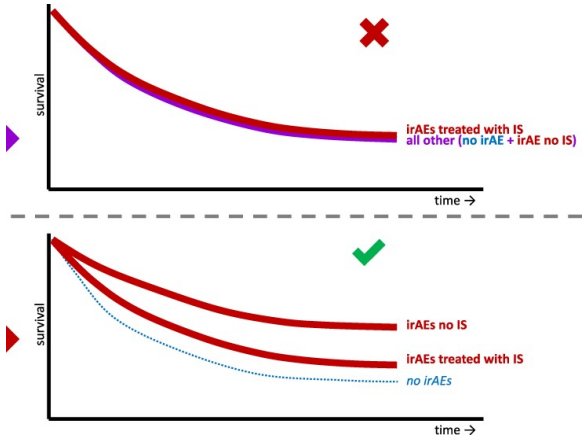
JAMA Network Open

Inga Van Buren, MD; Cecelia Madison, MS; Aimee Kohn, MD, PhD; Elizabeth Berry, MD; Rajan P. Kulkarni, MD, PhD; Reid F. Thompson, MD, PhD

- Retrospective multicentric review (2010-2021)
- Data base: Veterans Health Administration's Corporate Data Warehouse
- All cancers (54% NSCLC) - PD1/PDL1i – **N= 20.163**

B No steroid use vs steroid use for irAE and non-irAE





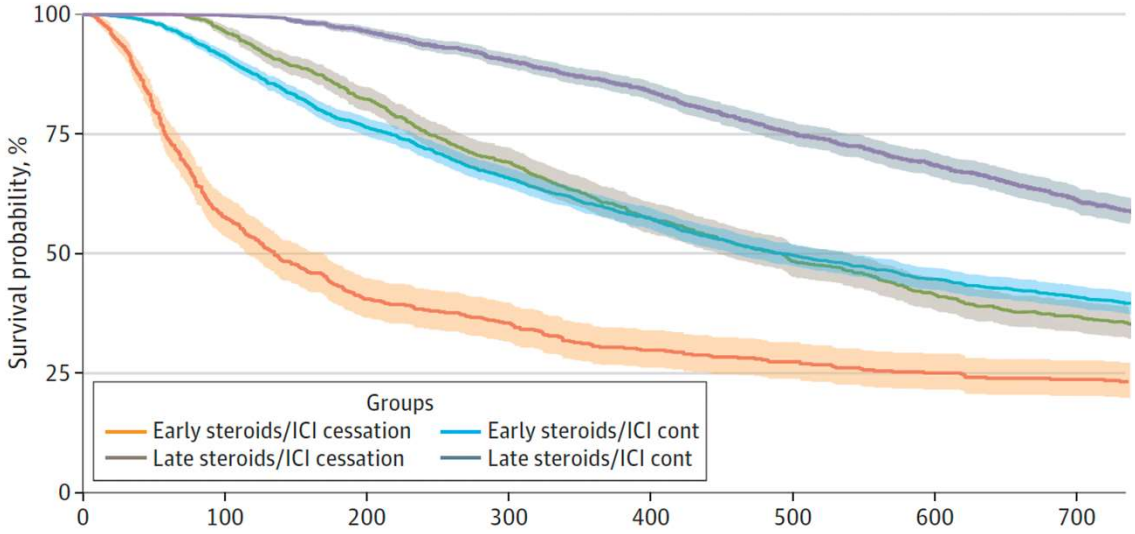
ICI, immune-checkpoint inhibitor; irAE, immune-related adverse event, NSCLC, non small cell lung cancer.

Verheijden, R.J., *npj Precis. Onc.* 2023
Van Buren, *JAMA Network Open. 2023*

EARLY STEROIDS IN IMMUNOTHERAPY

Early vs Late steroid initiation & ICI management

Early: < 2 months **Late: > 2 months**



Groups	Median (IQR) OS in months
Late steroid – ICI continuation	29.2 (16.5 to 53.5)
Early steroid – ICI continuation	16.0 (7.1 to not reached)
Late steroid – ICI cessation	16.0 (8.0 to 42.2)
Early steroid – ICI cessation	4.4 (1.9 to 19.5)

ICI, immune checkpoint inhibitor; OS, overall survival.

Van Buren, *JAMA Network Open. 2023*

CONCLUSIONS

How to manage steroids in the era of immunotherapy?

- Caution when interpretating results → Immortal-time bias
- Steroids: Interference with immunotherapy or Prognostic factor ?
- Need for prospective trials

Thank you for your attention

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