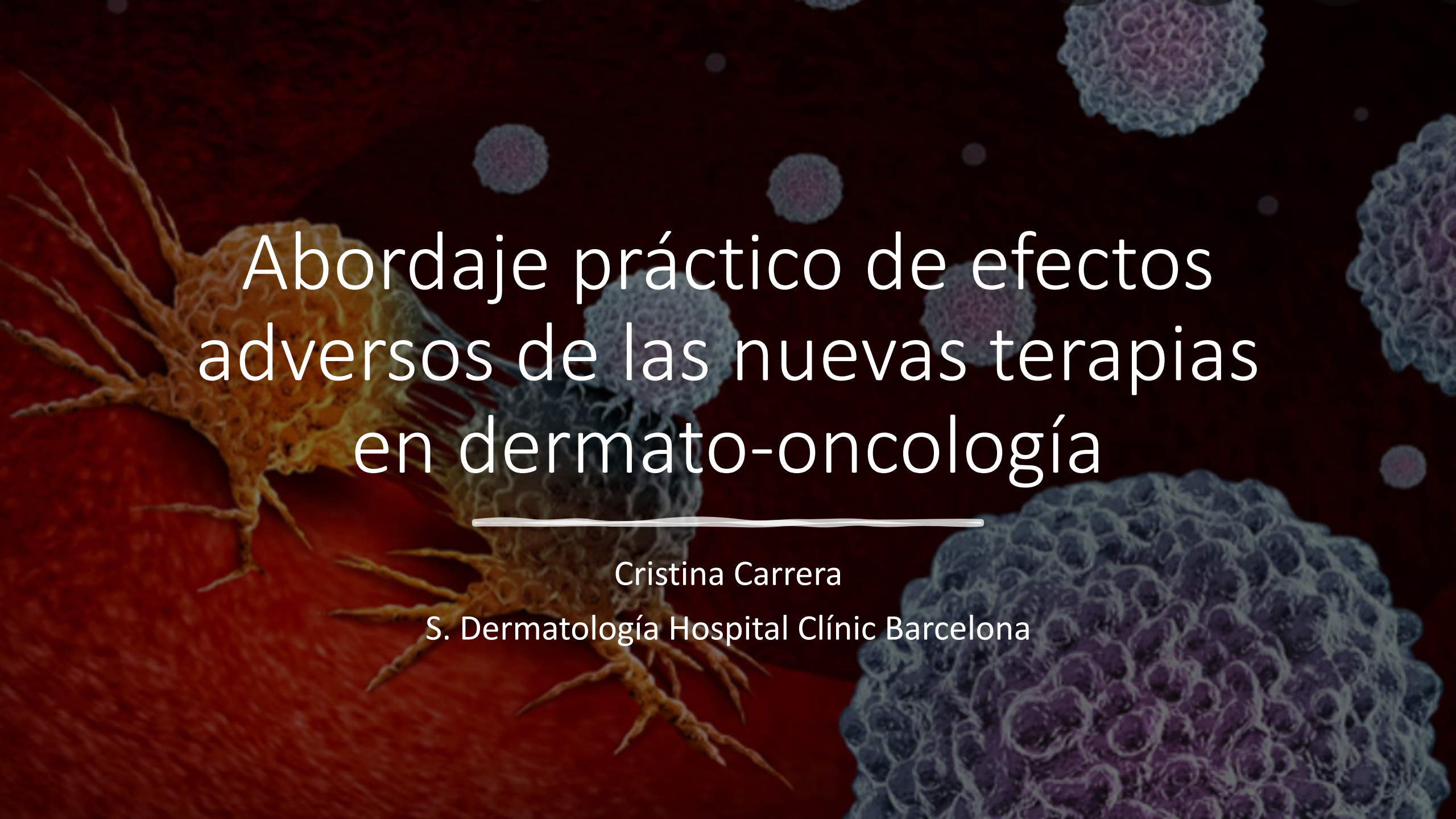


Abordaje práctico de efectos adversos de las nuevas terapias en dermato-oncología

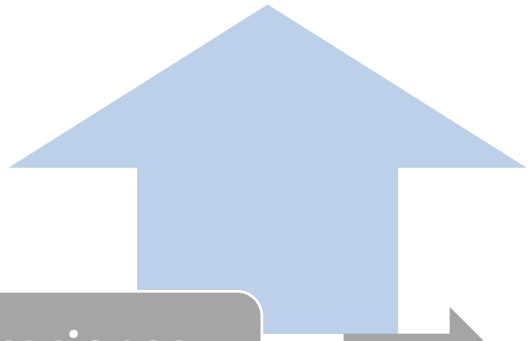
Cristina Carrera

S. Dermatología Hospital Clínic Barcelona

DECISIÓN TERAPÉUTICA: "PRIMUM NON NOCERE"

PROS/CONS

Valoración individual



RAM esperables

- **Qué y cuándo?**

Contraindicaciones

- **Absolutas / relativas ?**

Estudio BASAL / MONITORIZACIÓN

- **Qué solicitar?**

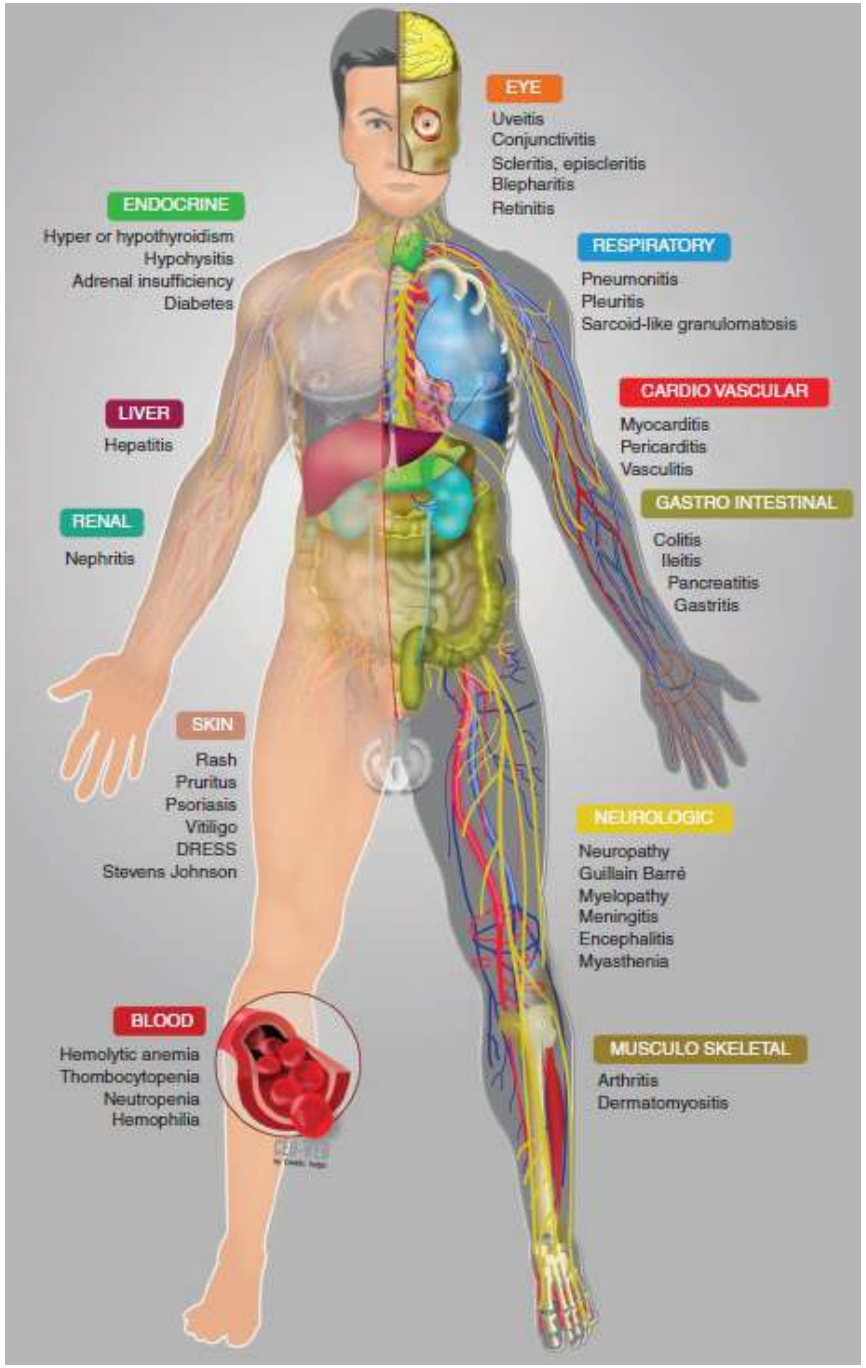
Categorizar gravedad según CTCAE v5 2017:

Grades
Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:
Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.
Grade 4 Life-threatening consequences; urgent intervention indicated.
Grade 5 Death related to AE.

Inmunoterapia en cáncer:

Desbloquear la inmunotolerancia

Cualquier "*–itis*"!!!

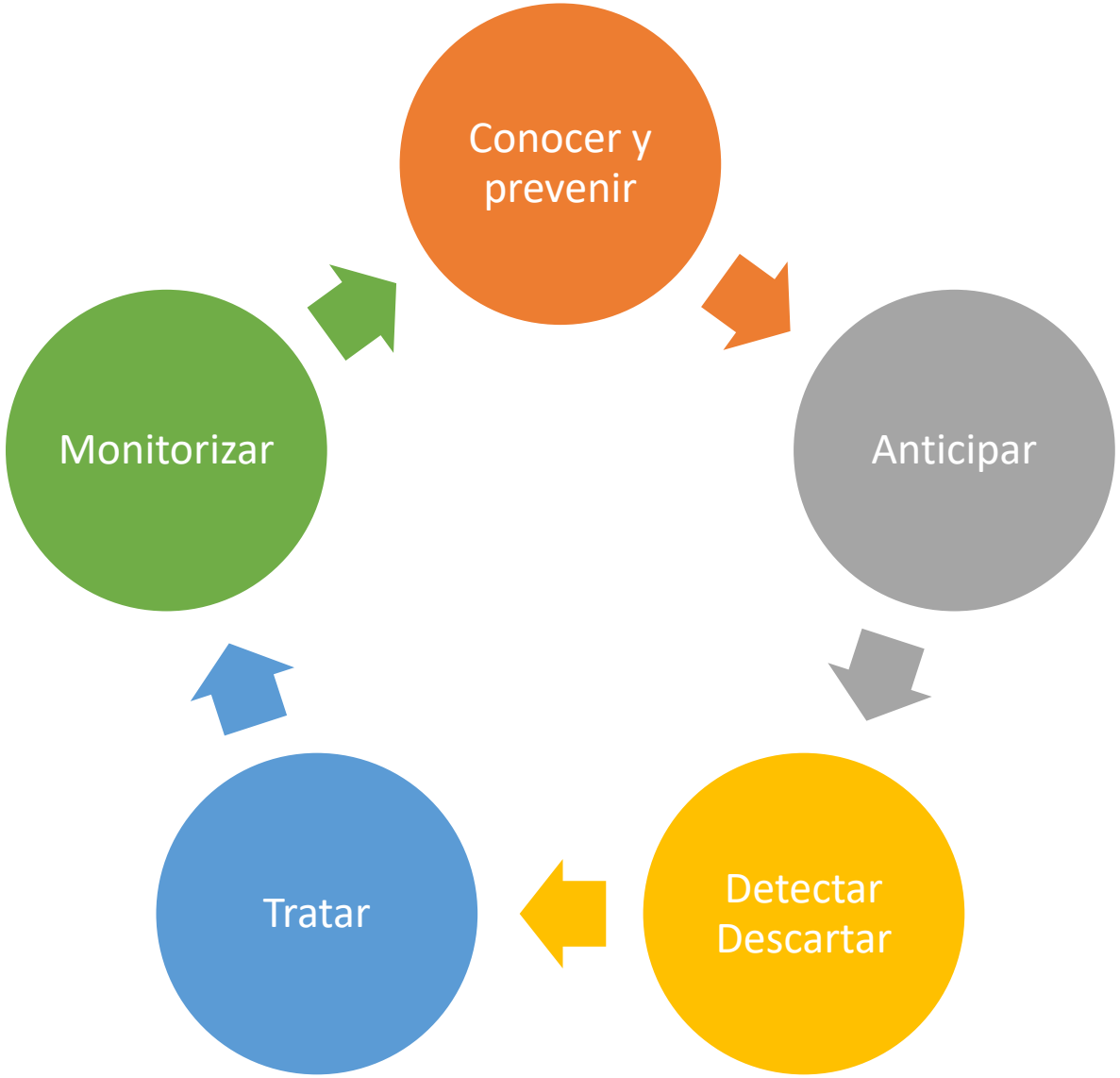


Champiat et al. Ann Oncol 2016;27:559-574

- ✓ Seguros y EAs leves (80%)

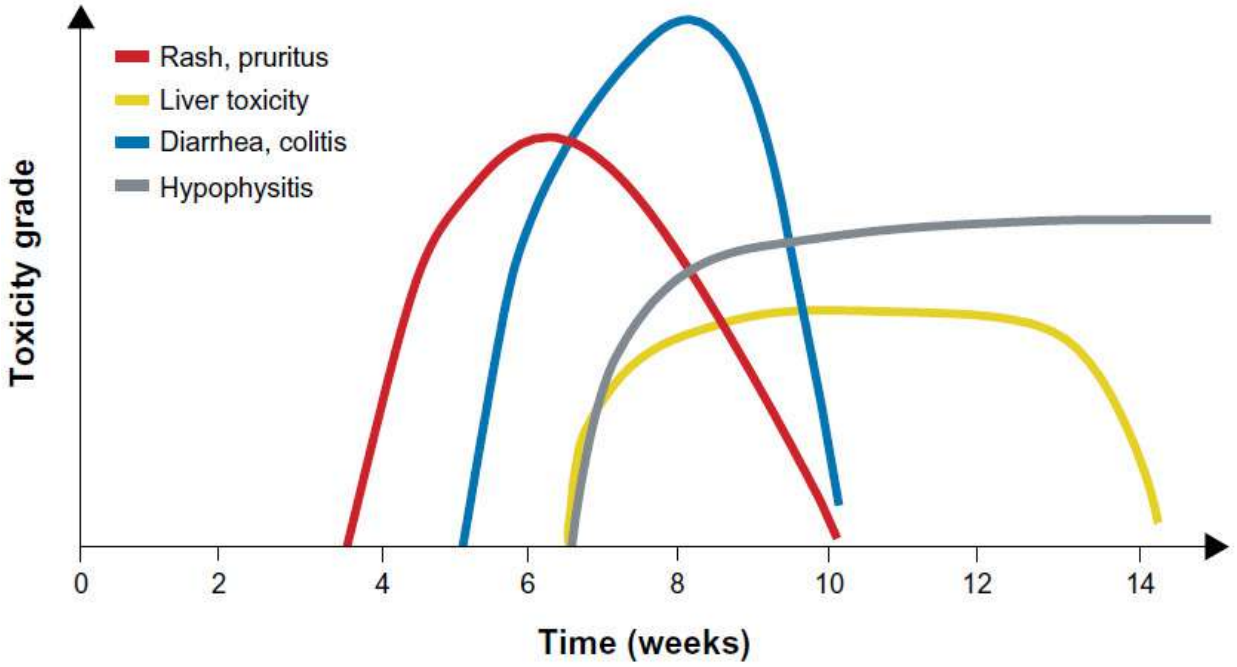
- ✓ **Importancia de sospecha y abordaje precoz MULTIDISCIPLINAR**

- ✓ Tratamiento inmunomoduladores NO modifica pronóstico oncológico

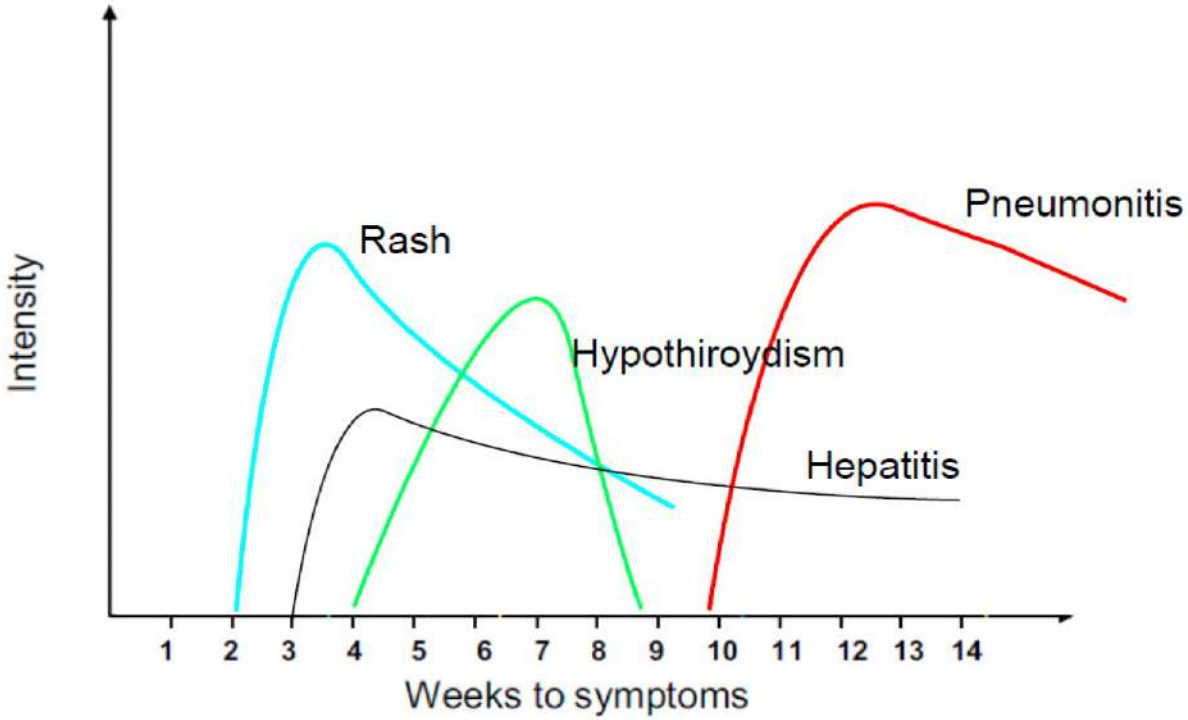


Champiat et al. Ann Oncol 2016;27:559-574

Anti CTLA4

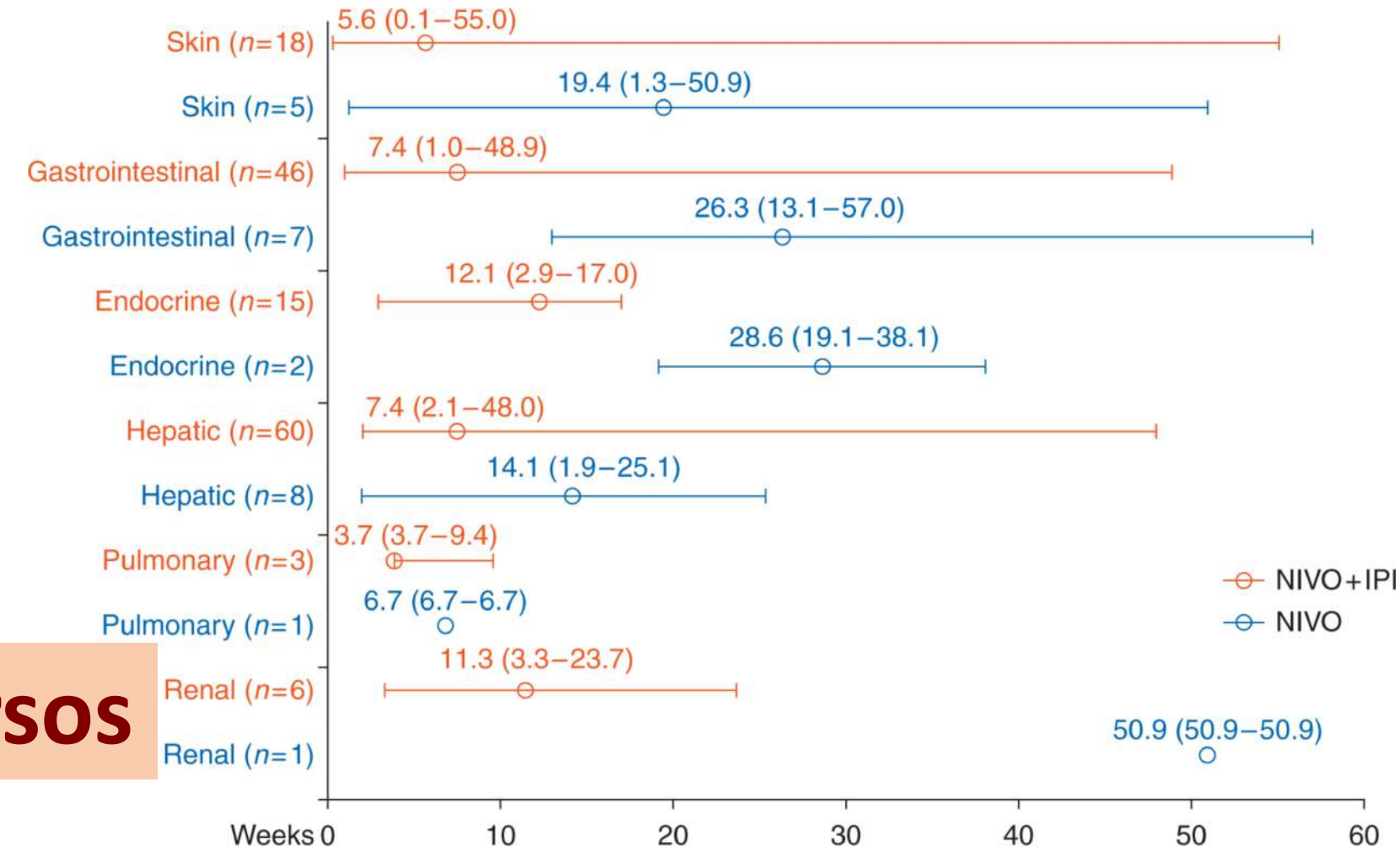


Anti PD1 / PD1L



Robert et al. NEJM 2011

Combinación antiCTLA4 + antiPD1



x 2-3 ++ ef adversos

+precozmente

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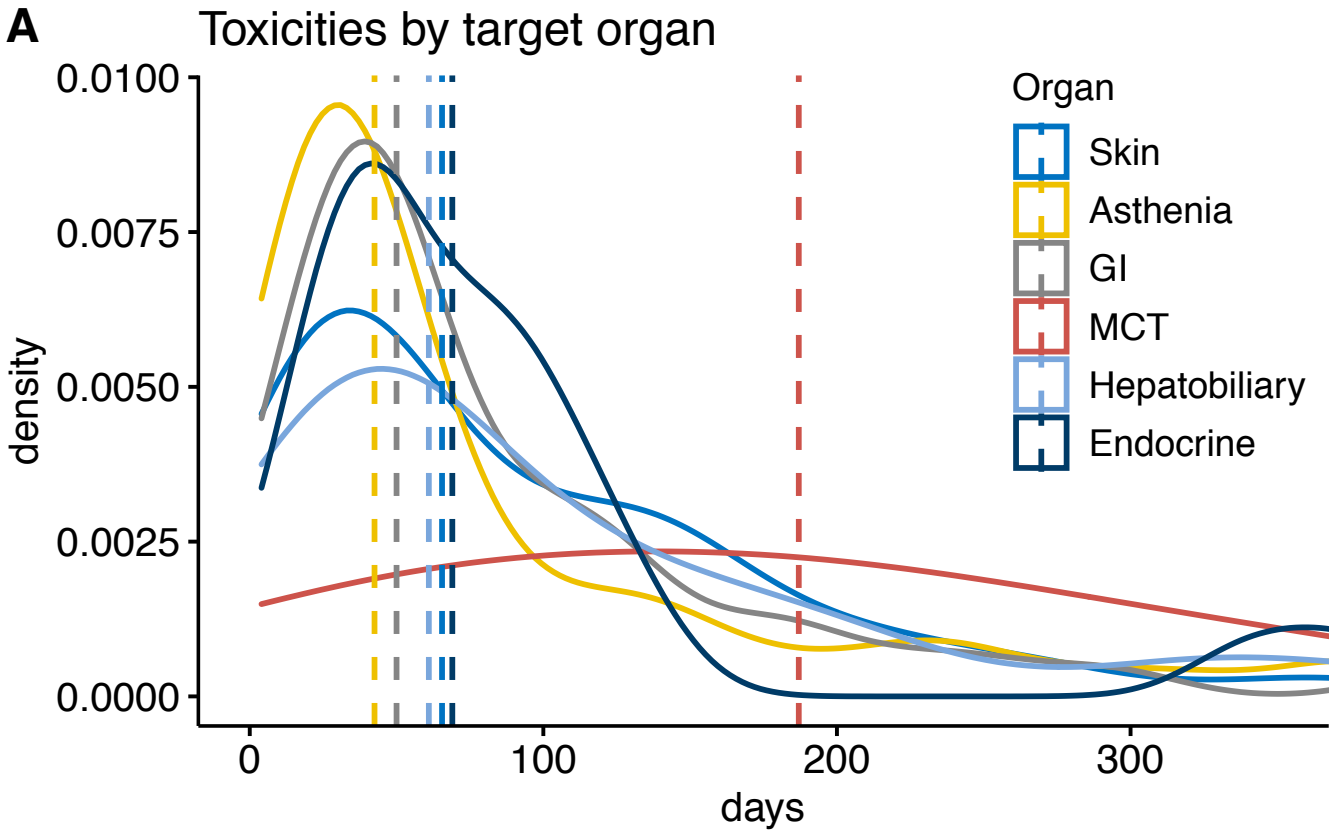
EFECTOS ADVERSOS INMUNOMEDIADOS:



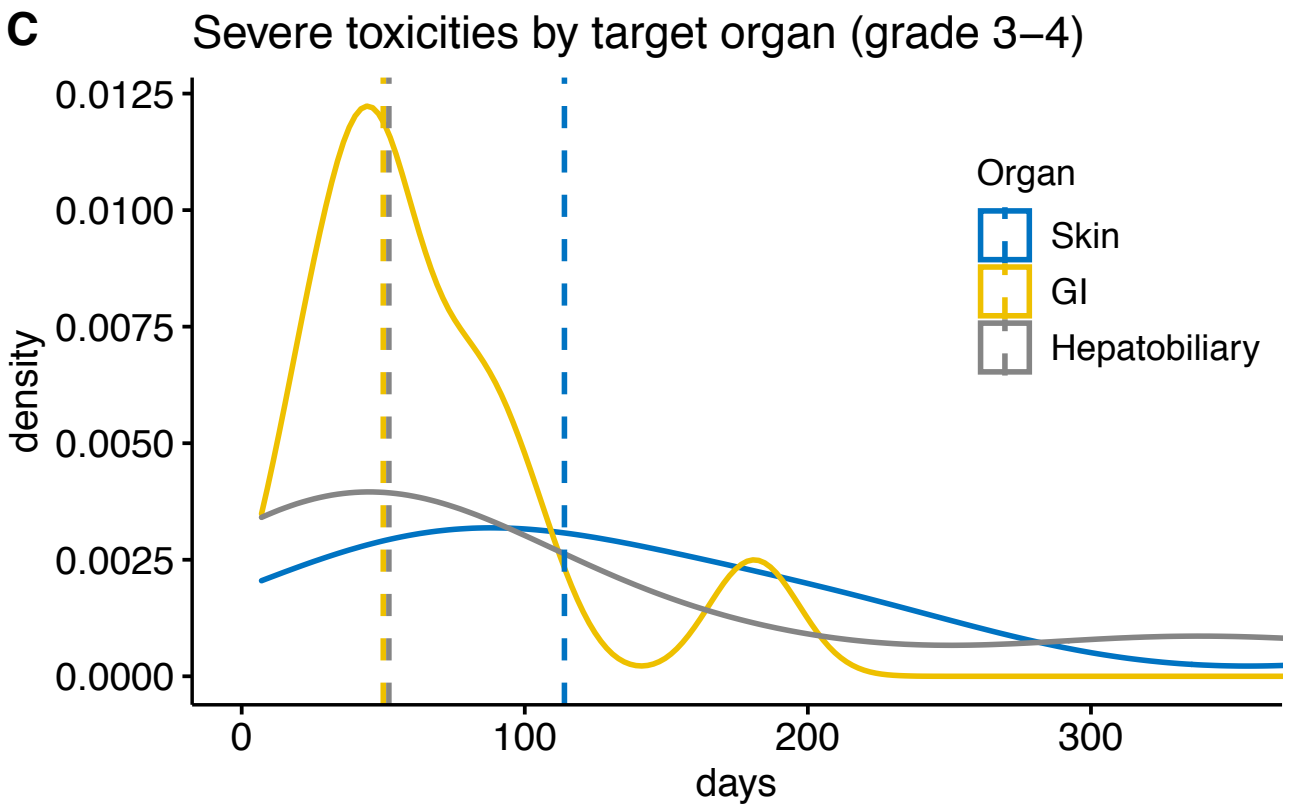
Pacientes MELANOMA HCB

>70%

Toxicidades Globales:
MEDIANA 3 - 4 MESES!!

Villa, Podlipnik et al Cancers 2022

EFECTOS ADVERSOS INMUNOMEDIADOS:



Pacientes MELANOMA HCB

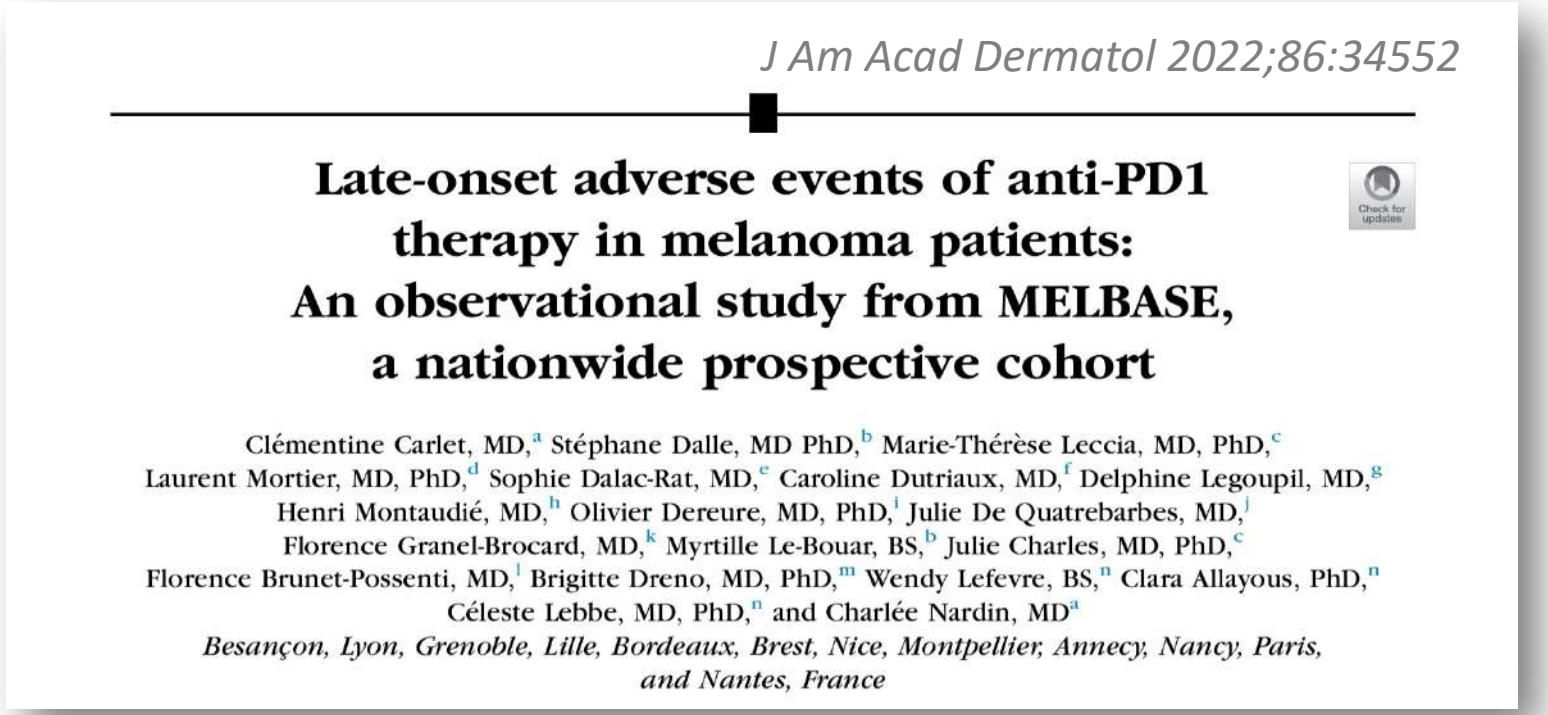
<30%

Toxicidades grados III / IV

APARECEN EN CUALQUIER MOMENTO!
INCLUSO UNA VEZ SUSPENDIDO FÁRMACO!

J Am Acad Dermatol 2021; doi: 10.1016/j.jaad.2021.03.094
Villa, Podlipnik et al Cancers 2022

EFECTOS ADVERSOS INMUNOMEDIADOS:



J Am Acad Dermatol 2022;86:34552

Late-onset adverse events of anti-PD1 therapy in melanoma patients: An observational study from MELBASE, a nationwide prospective cohort

Clémentine Carlet, MD,[a] Stéphane Dalle, MD PhD,[b] Marie-Thérèse Leccia, MD, PhD,[c] Laurent Mortier, MD, PhD,[d] Sophie Dalac-Rat, MD,[e] Caroline Dutriaux, MD,[f] Delphine Legoupil, MD,[g] Henri Montaudié, MD,[h] Olivier Dereure, MD, PhD,[i] Julie De Quatrebarbes, MD,[j] Florence Granel-Brocard, MD,[k] Myrtille Le-Bouar, BS,[b] Julie Charles, MD, PhD,[c] Florence Brunet-Possenti, MD,[l] Brigitte Dreno, MD, PhD,[m] Wendy Lefevre, BS,[n] Clara Allayous, PhD,[n] Céleste Lebbe, MD, PhD,[n] and Charlée Nardin, MD[a]

Besançon, Lyon, Grenoble, Lille, Bordeaux, Brest, Nice, Montpellier, Annecy, Nancy, Paris, and Nantes, France

119 pacientes MM ≥ 2a antiPD1

42m (25-57m)

83% EAs 13m

30% EAs grado III/IV

43% EAs TARDÍOS > riesgo:

- EAs previos
- > duración de tto

APARECEN EN CUALQUIER MOMENTO!
INCLUSO UNA VEZ SUSPENDIDO FÁRMACO!

EFECTOS ADVERSOS INMUNOMEDIADOS:

Patients reporting event	NIVO+IPI (n = 313)		NIVO (n = 313)		IPI (n = 311)	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Treatment-related AE, %	96	59	87	23	86	28
Treatment-related AE leading to discontinuation, %	42	31	13	8	15	14
Treatment-related death, n (%)	2 (1)		1 (< 1)		1 (< 1)	

Miocarditis
Hepatitis fulminante

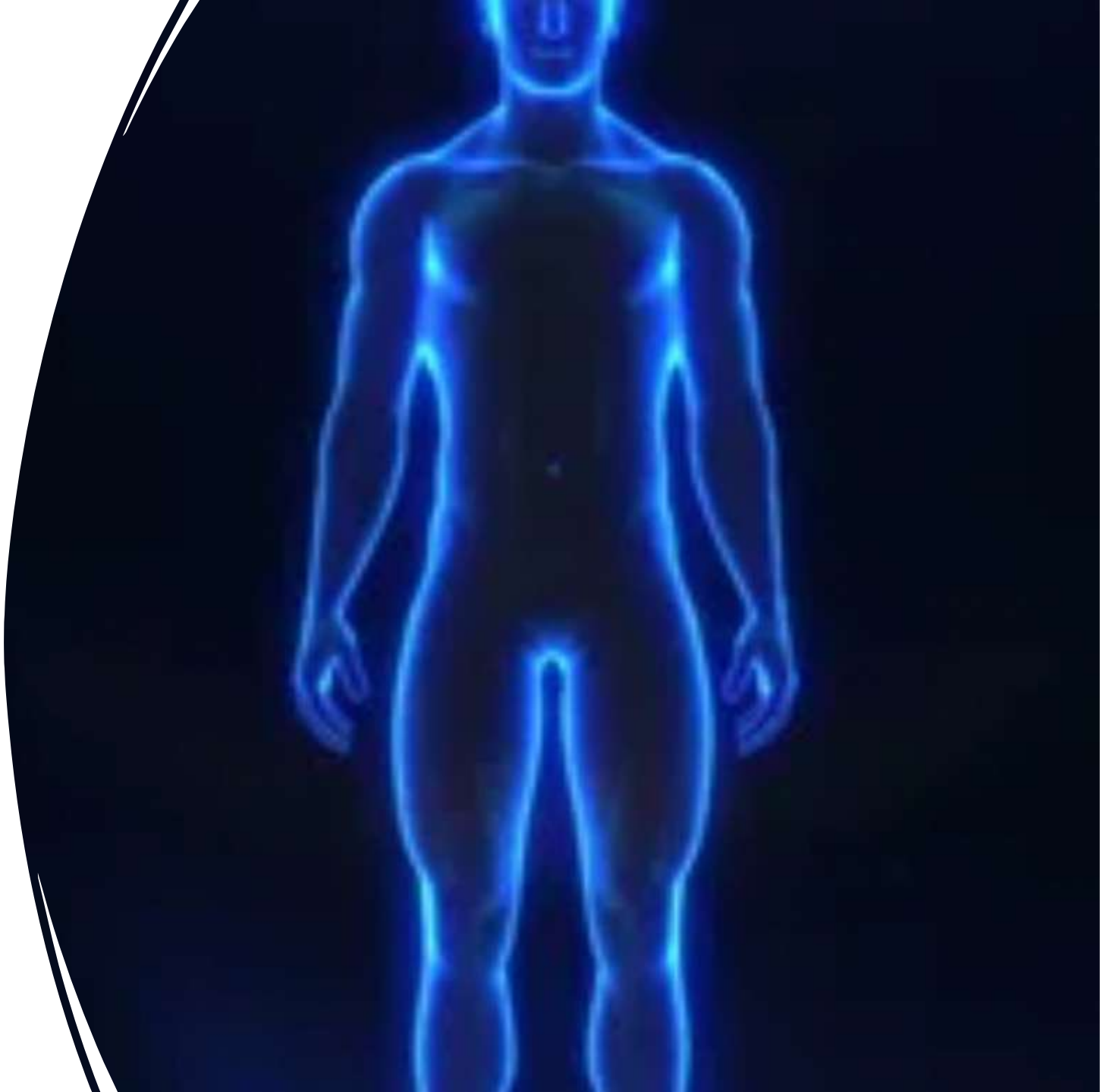
Neutropenia

Colitis

1% MORTALIDAD DIRECTA POR RAMim

Larkin et al. Five-year survival with combined nivolumab and ipilimumab in advanced melanoma. N Engl J Med. 2019;381(16):1535-1546.

“dermatitis”



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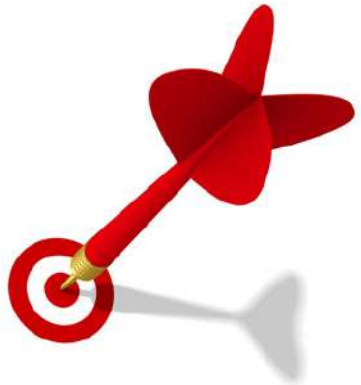
Inmunoterapia en cáncer:



Diana: sistema inmune circulante, intratumoral y el **cutáneo**!!!

>40%

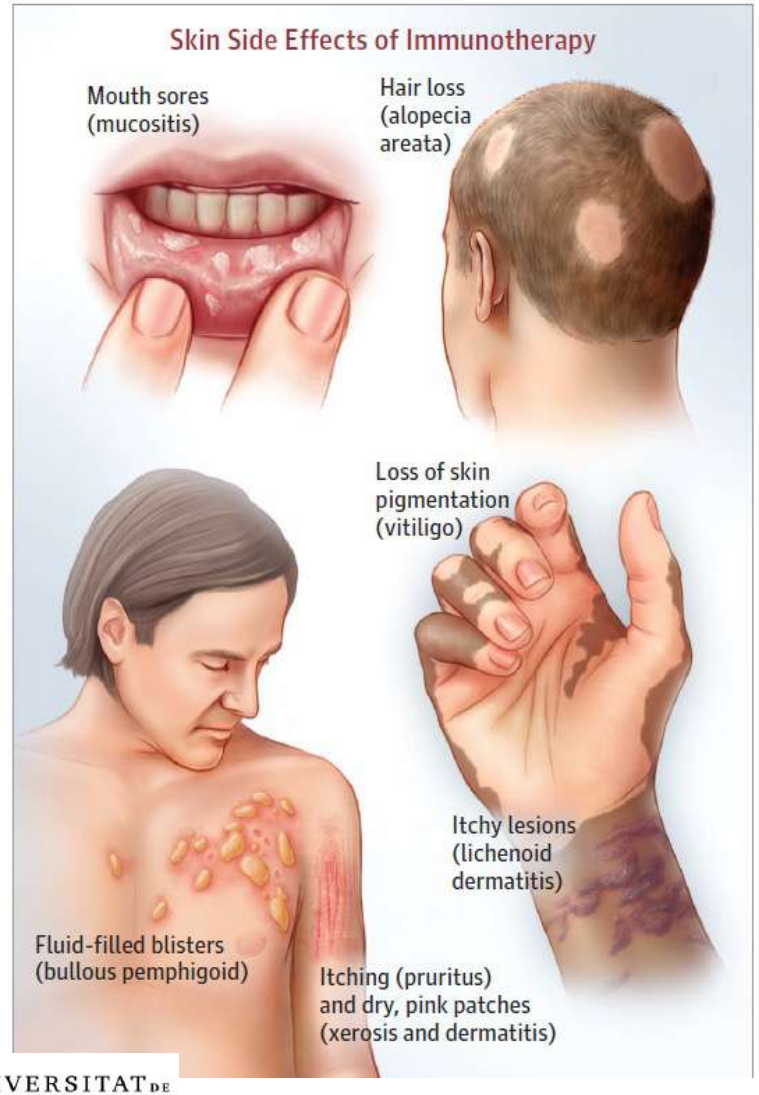
ORIGINAL ARTICLE *J Am Acad Dermatol 2021*

Epidemiology and risk factors for the development of cutaneous toxicities in patients treated with immune-checkpoint inhibitors: A United States population-level analysis

Shannon Wongvibulsin, PhD,[a,b] Vartan Pahalyants, BA,[a,c,d] Mark Kalinich, PhD,[a,c] William Murphy, AB,[a,c,d] Kun-Hsing Yu, MD, PhD,[e,f] Feicheng Wang, BA,[e,g] Steven T. Chen, MD, MPH,[a] Kerry Reynolds, MD,[h] Shawn G. Kwatra, MD,[b,i] and Yevgeniy R. Semenov, MD, MA[a]
Boston and Cambridge, Massachusetts; and Baltimore, Maryland

- Melanoma > Ca Renal > Ca Pulmón
- Combinaciones
- Dermatosis de base

ESPECTRO DERMATOSIS INMUNOMEDIADAS…



atology June 2018 Volume 154, Number 6

PRURITO, exantemas maculopapulares	**Liquen plano-like, psoriasis, eczemas**	**Vitíligo (melanoma)**
Penfigoide ampolloso	Enfermedad de Grover	Sarcoidosis
SJS/TEN, AGEP, DRESS	DM, LE, PNP-like	Rosácea – Acné Alopecia areata…

Geisler AN et al. J Am Acad Dermatol 2020;83:1255-68
J Am Acad Dermatol 2021; doi: 10.1016/j.jaad.2021.03.094

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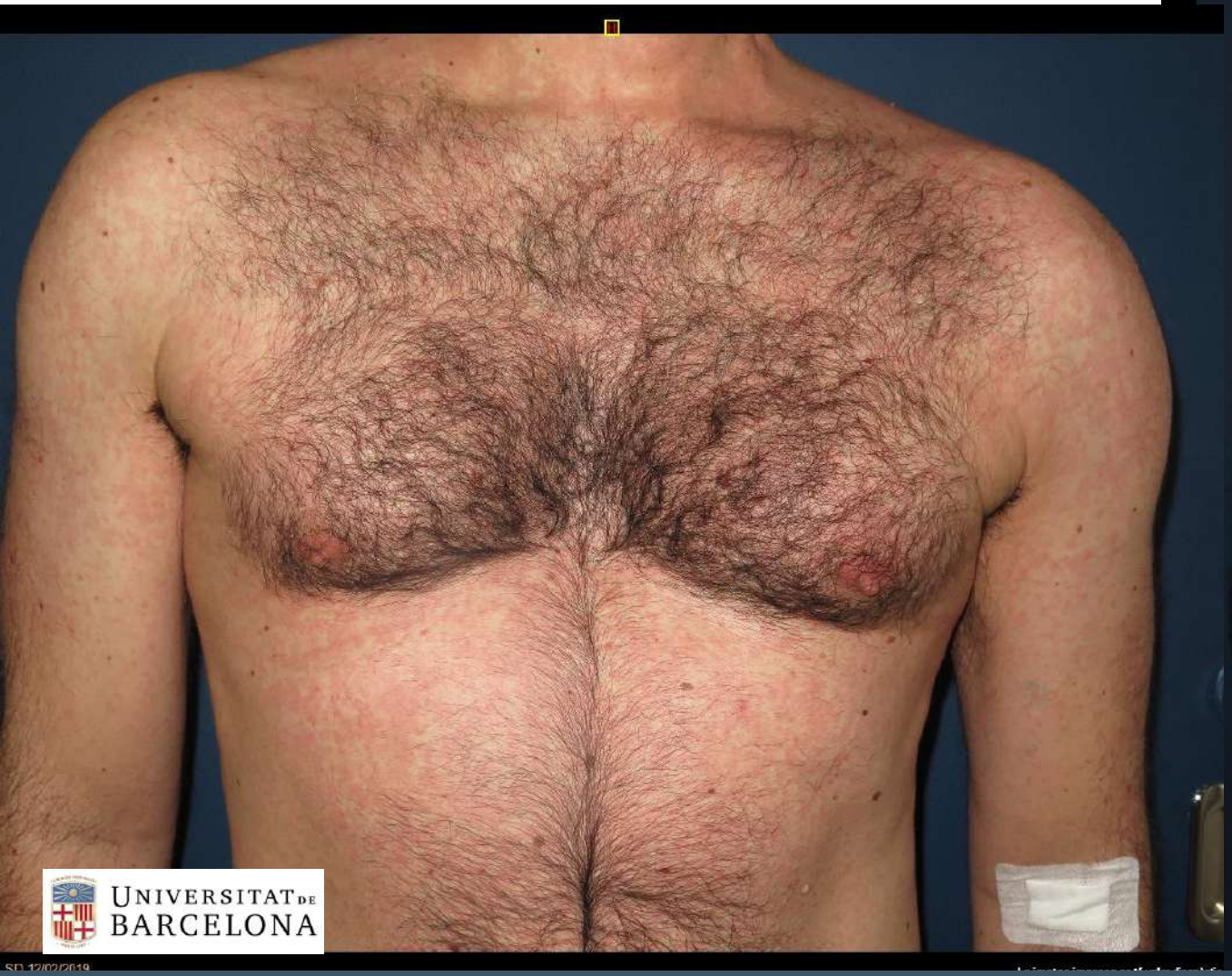
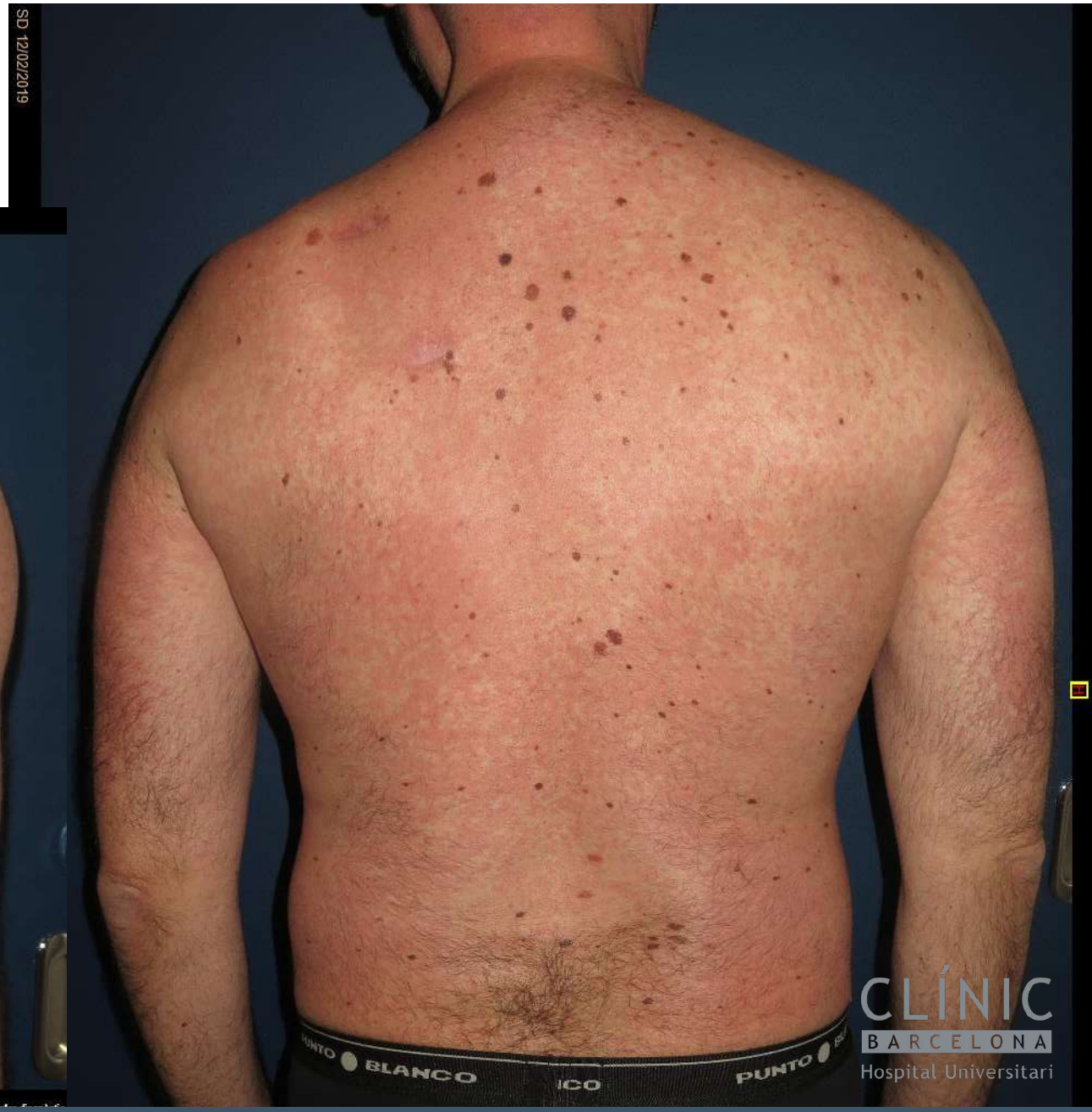
1 Exantema inespecífico

Melanoma : Nivolumab 2 meses





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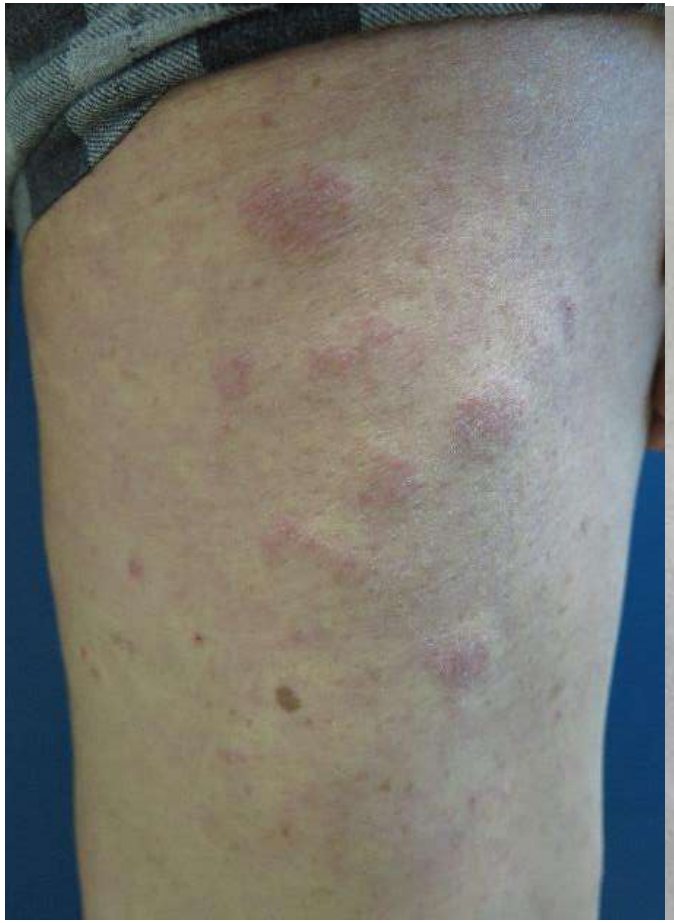
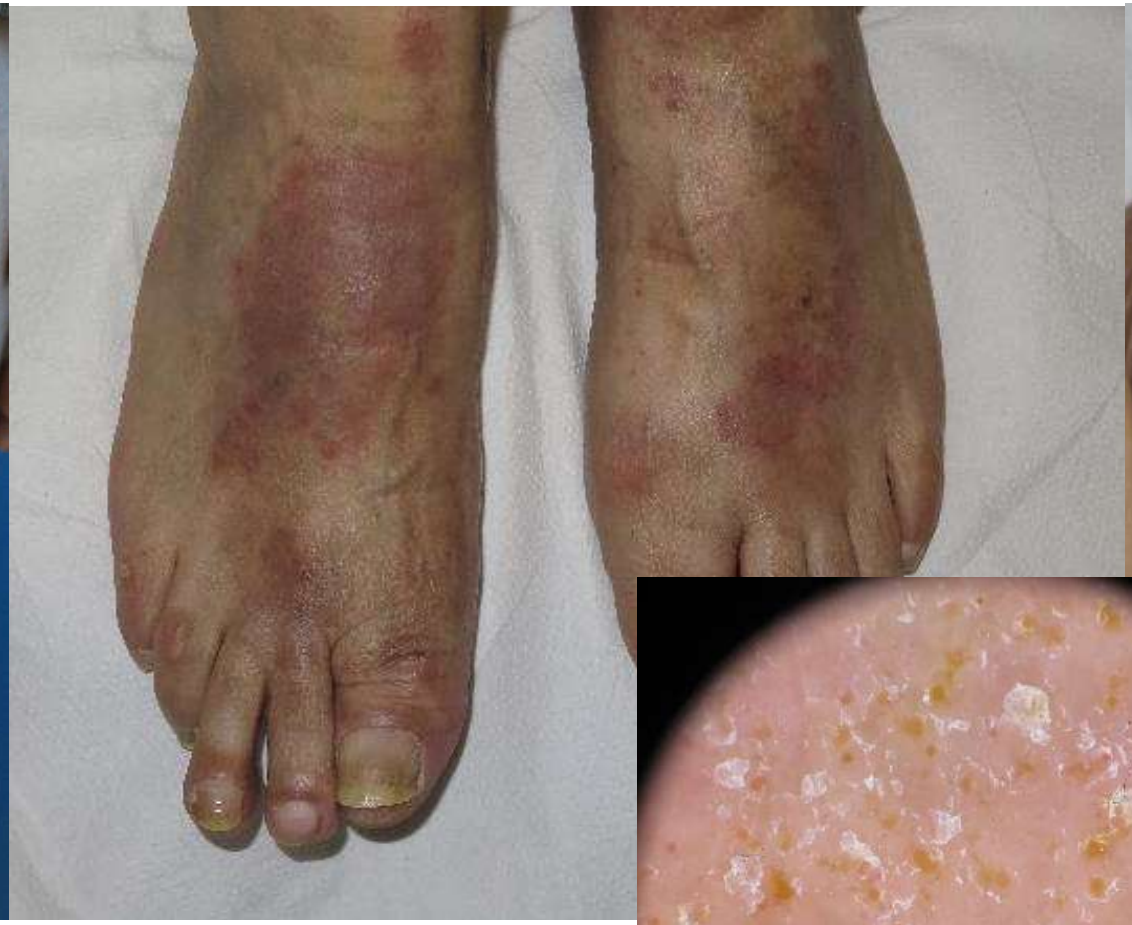
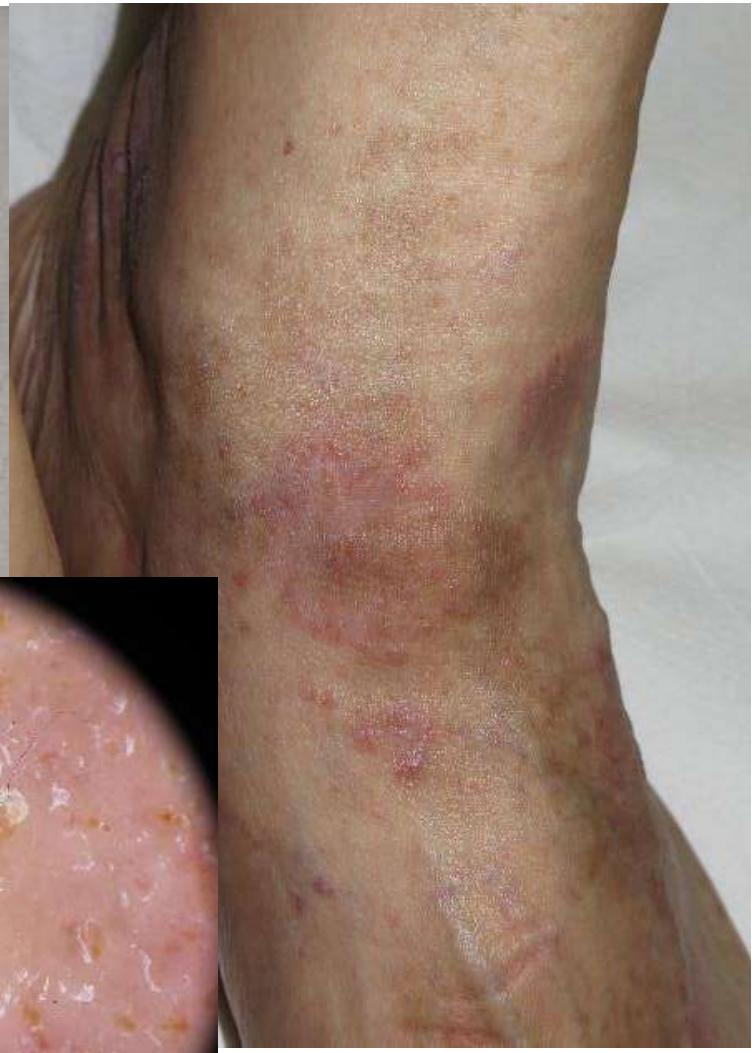
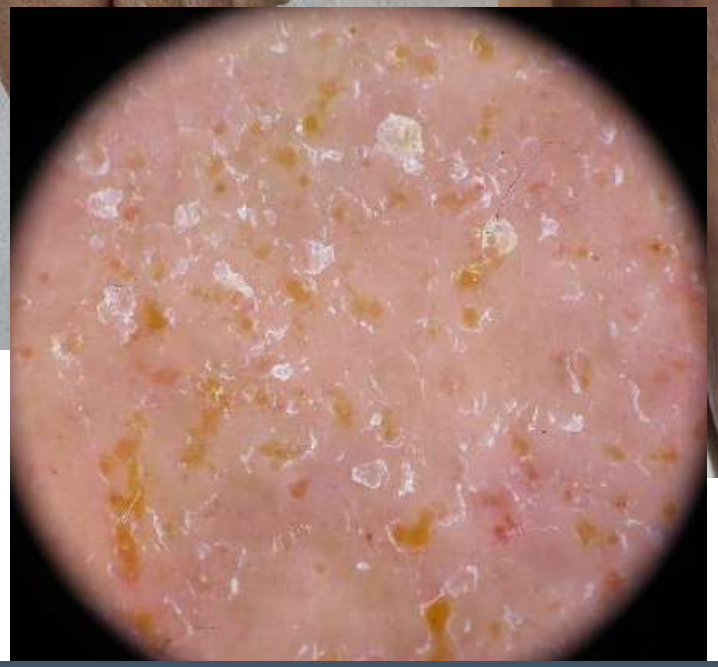
Exantema Morbiliforme/Dermatitis Espongióticas

Hepatocarcinoma + NIVOLUMAB



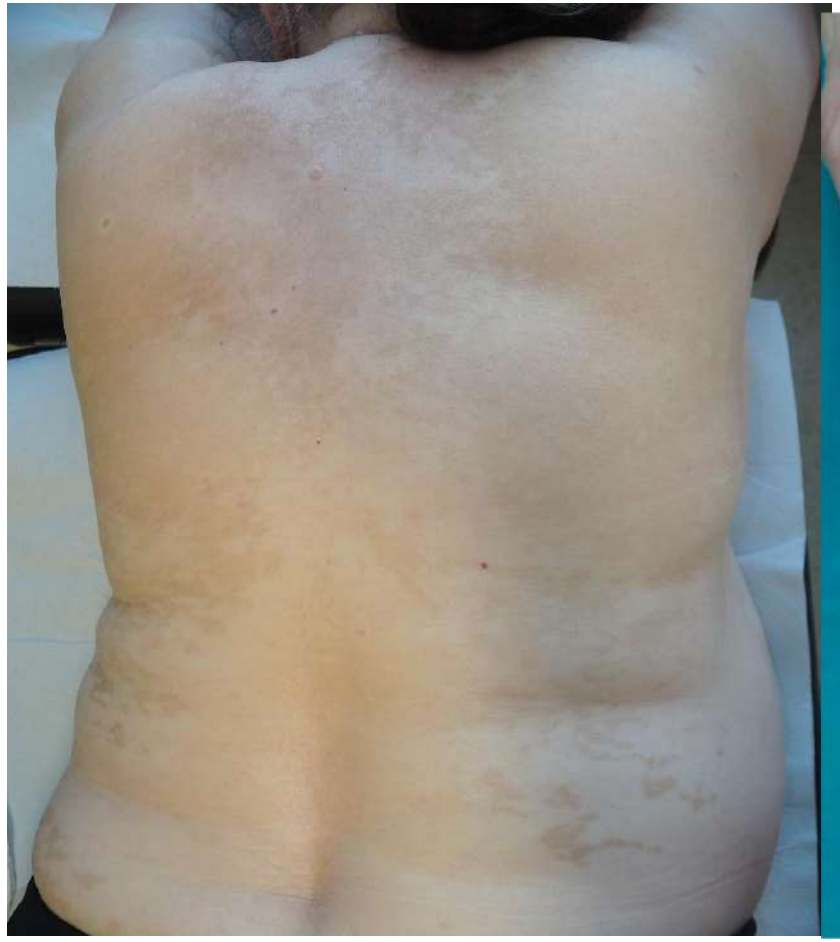


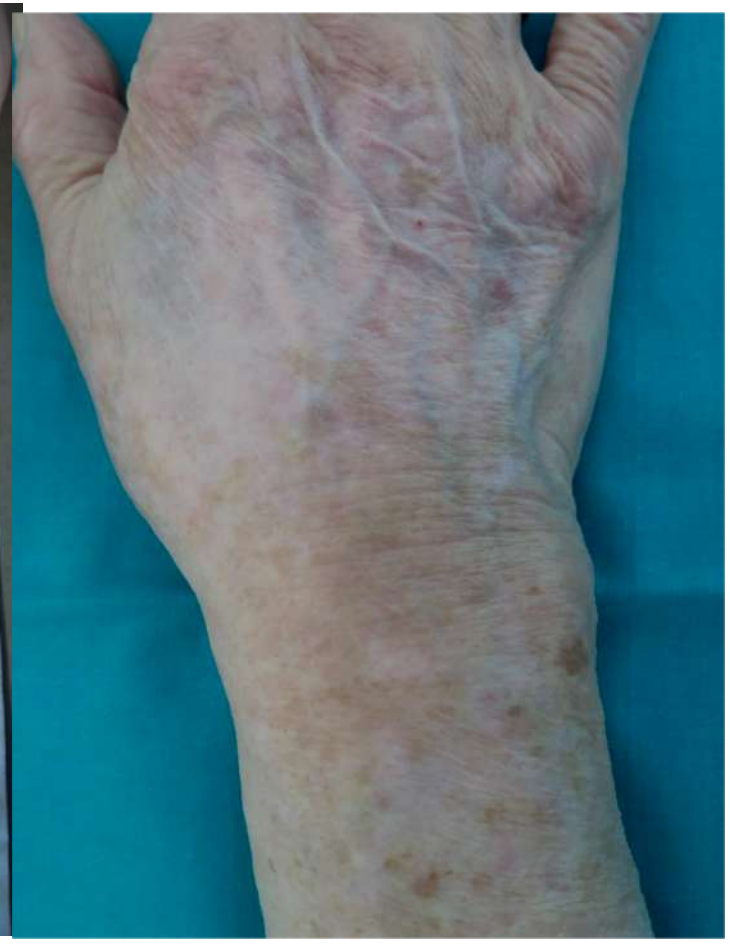




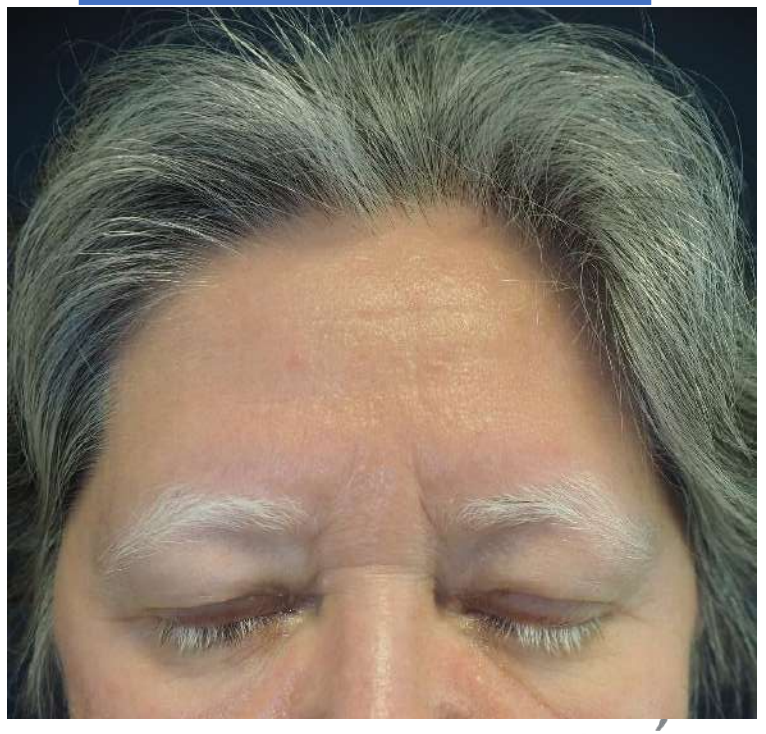
PRURITO ++++ LESIONES ECCEMATOSAS

ESPECTRO DERMATOSIS INMUNOMEDIADAS…





Vitíligo (melanoma)

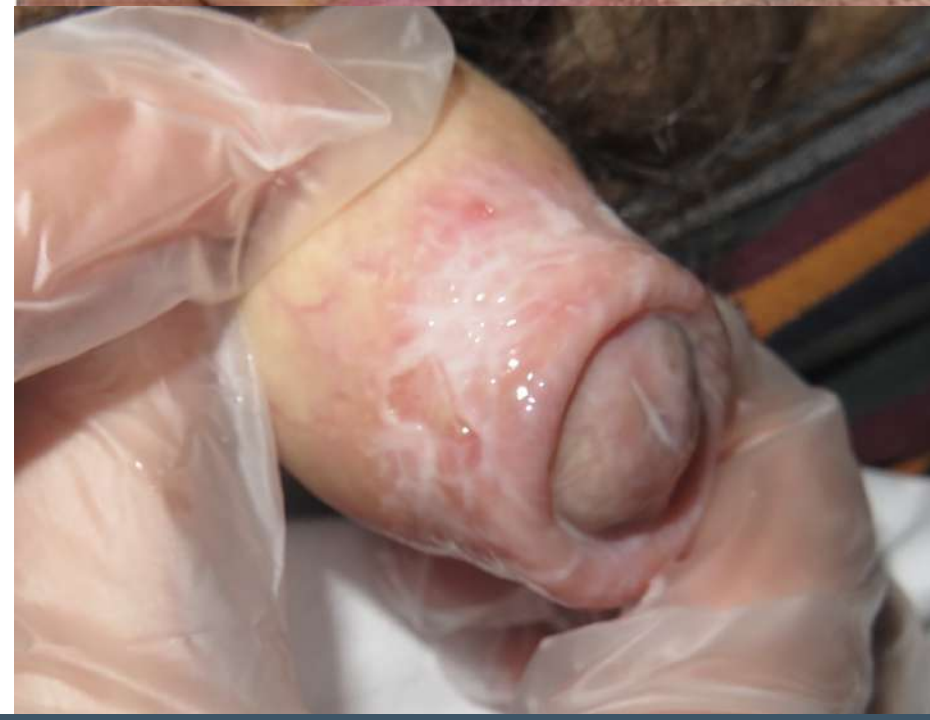


8-20% pacientes MELANOMA!!!

Geisler AN et al. J Am Acad Dermatol 2020;83:1255-68
J Am Acad Dermatol 2021; doi: 10.1016/j.jaad.2021.03.094

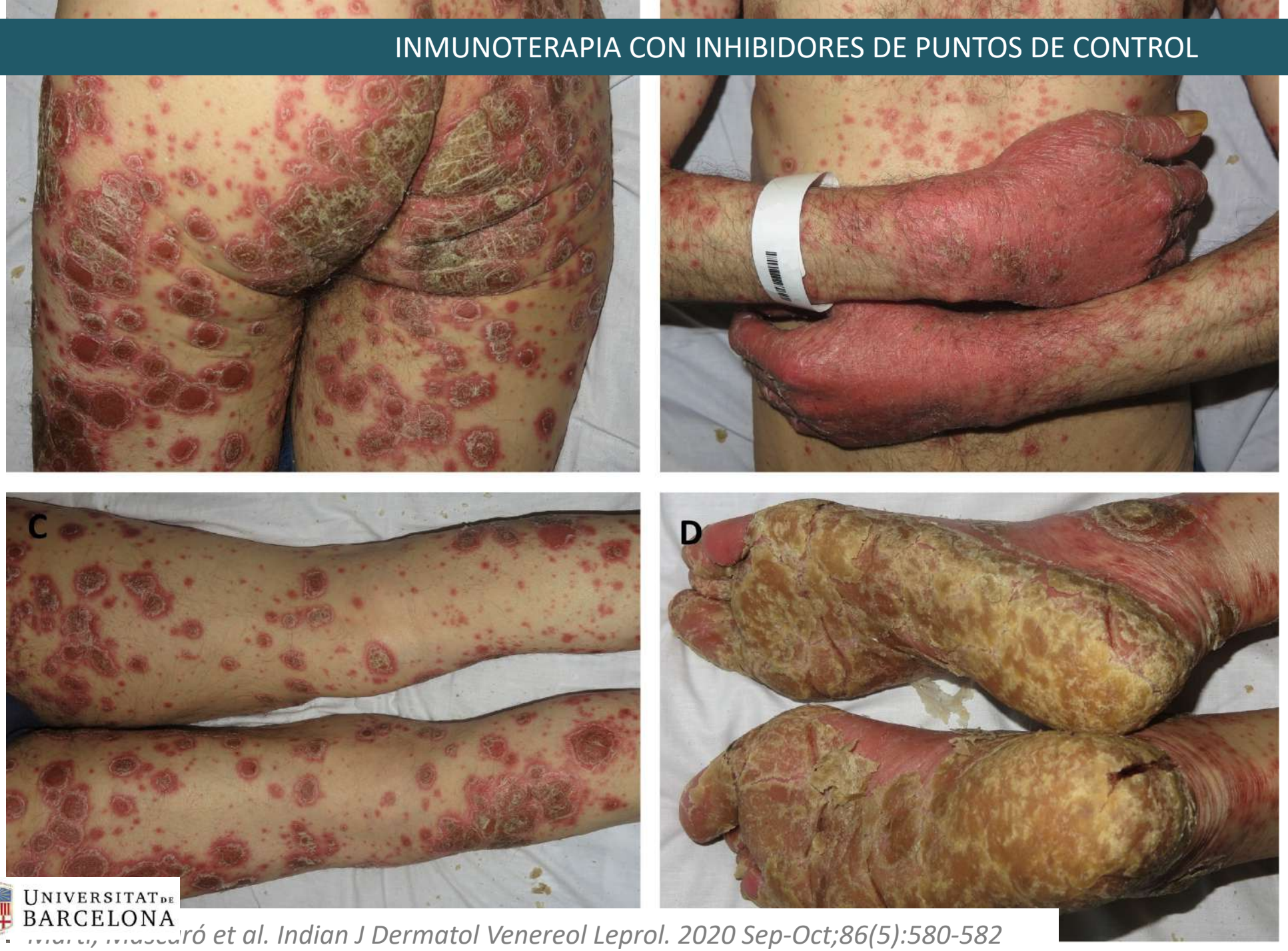
Mucositis liquenoides

- LP – like oral (≈LP clásico!!)
- Infiltrado en banda (Th1)
- + asociado a Hepatocarcinoma?



Nikolaou et al. ENCADO group. JEADV submitted
Sibaud et al. JEADV 2017

67y SCC LUNG
+2m pembrolizumab



Martí, Mascaró et al. Indian J Dermatol Venereol Leprol. 2020 Sep-Oct;86(5):580-582

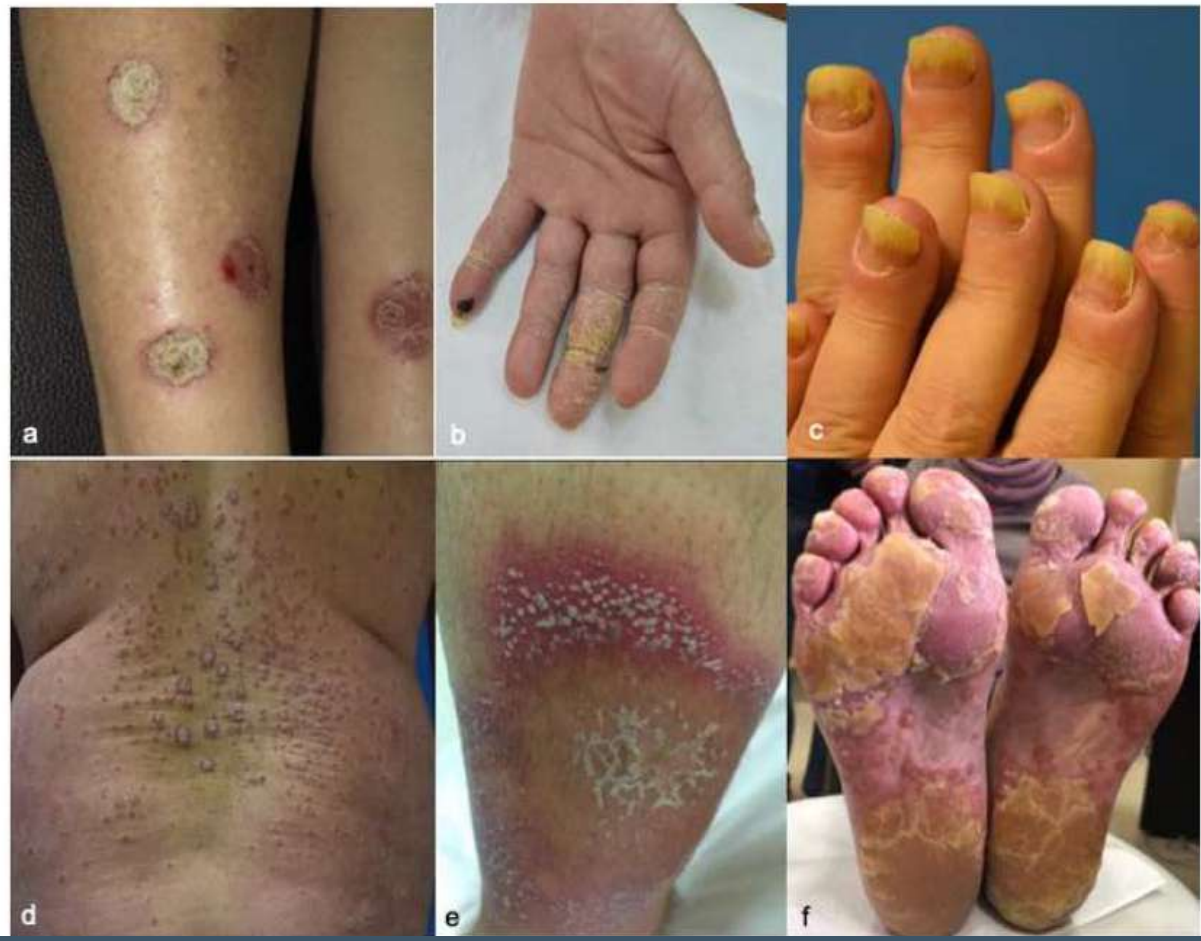
Psoriasis inducida por antiPD1

JAAD 2020

Immune checkpoint-mediated psoriasis: A multicenter European study of 115 patients from the European Network for Cutaneous Adverse Event to Oncologic Drugs (ENCADO) group

Vasiliki Nikolaou, MD,[a] Vincent Sibaud, MD,[b] Davide Fattore, MD,[c] Pietro Sollena, MD,[d,e] Ariadna Ortiz-Brugués, MD,[f] Damien Giacchero, MD,[g] Maria Concetta Romano, MD,[h] Julia Rigan Konstantinos Lallas, MD,[j] Ketty Peris, MD,[d,e] Dimitra Voudouri, MD,[a] Aimilios Lallas, MD,[j] Gabriella Fabbrocini, MD,[c] Elisabeth Lazaridou, MD,[k] Cristina Carrera, MD,[f] Maria Carmela Annunzi Ernesto Rossi, MD,[l] Angela Patri, MD,[c] Dimitrios Rigopoulos, MD,[a] Alexander J. Stratigos, MD,[j] Zoe Apalla, MD[k]

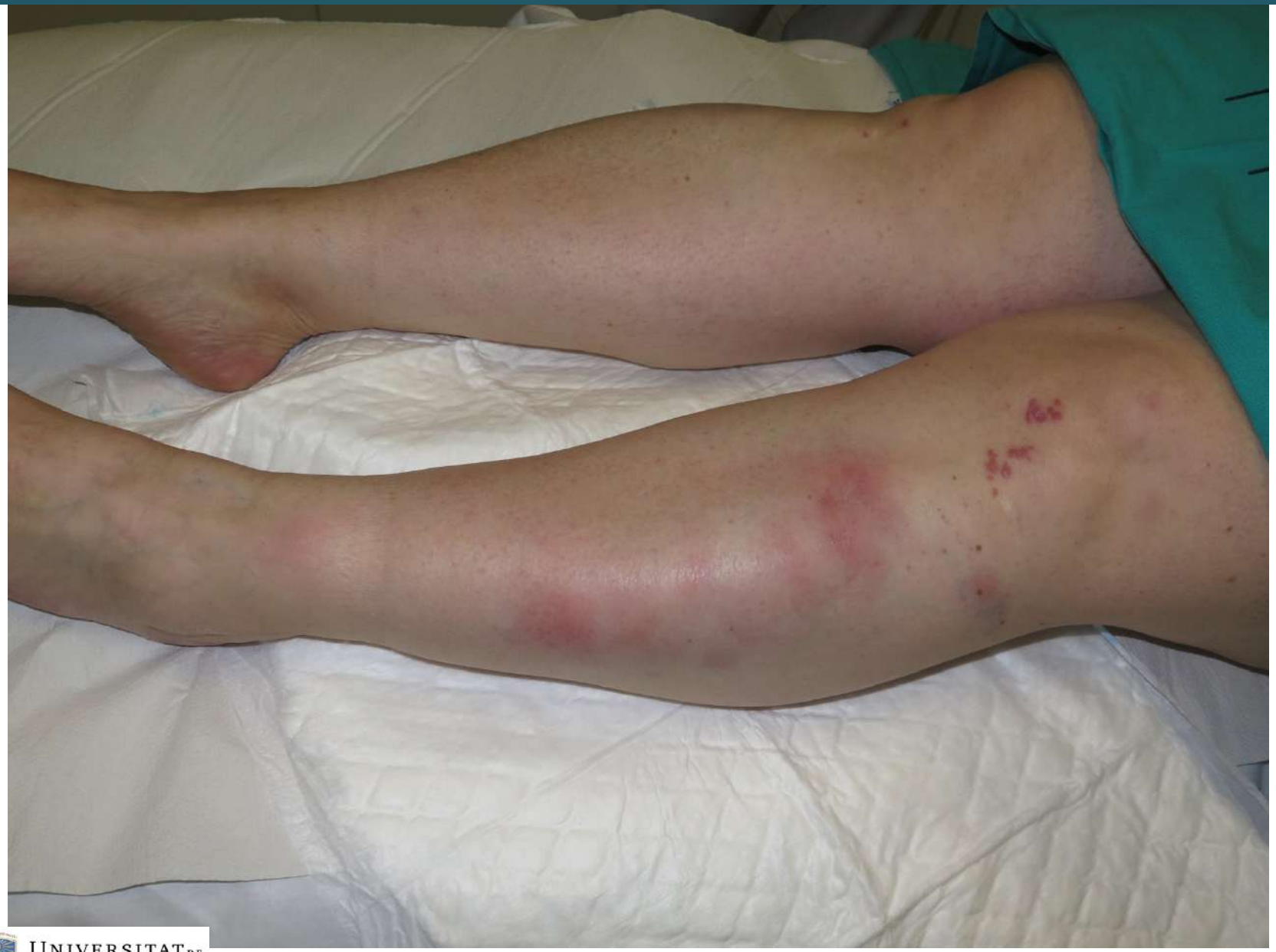
<frec asociado a MM!!!



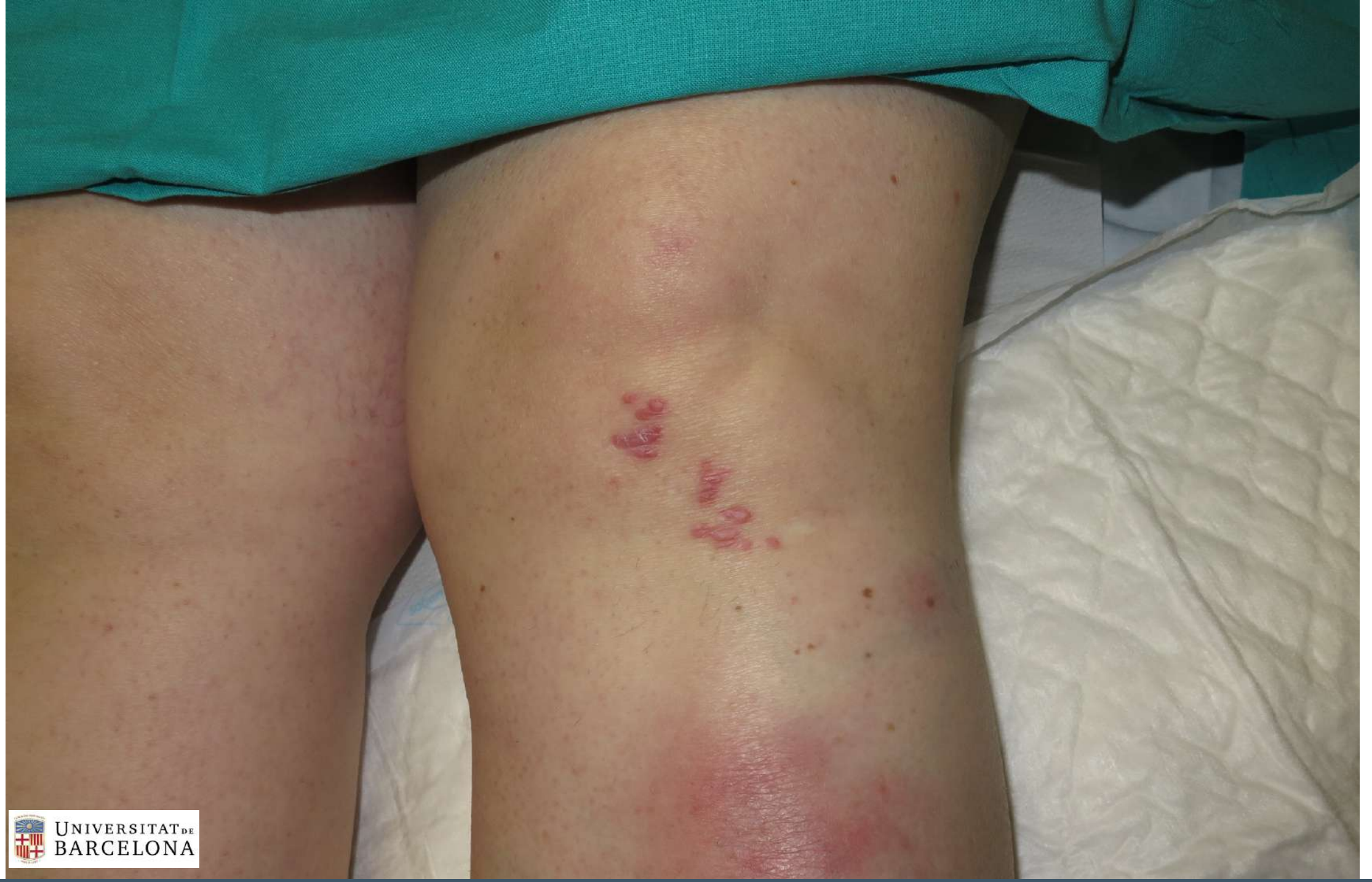
- Retrospectivo: 115 casos
- 76% varones
- Exacerbada o “de novo” (18%)
- Cualquier forma de Psoriasis
- No suele implicar suspensión

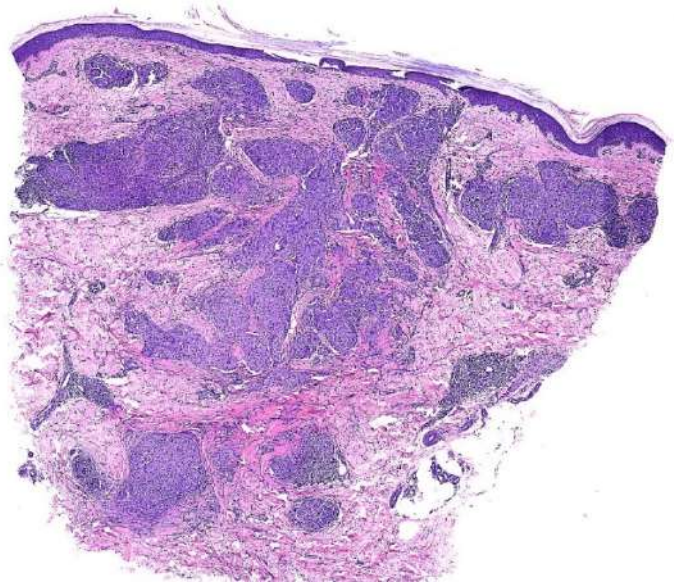
(60% leves vs 10% severas)

INMUNOTERAPIA CON INHIBIDORES DE PUNTOS DE CONTROL



51 años
Melanoma BRAF+
Pembrolizumab en RC 24meses
Suspensión de antiPD1

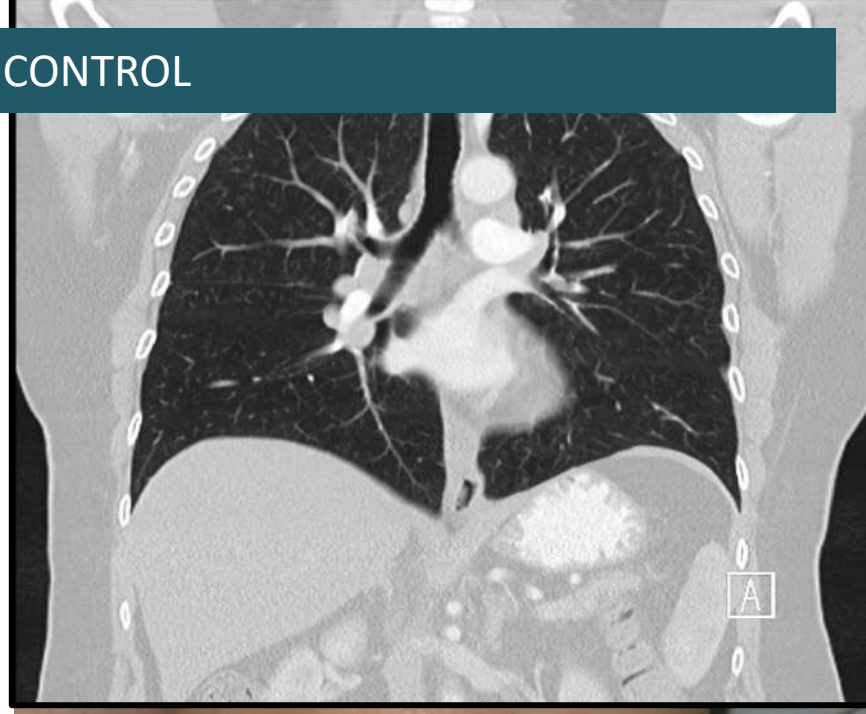


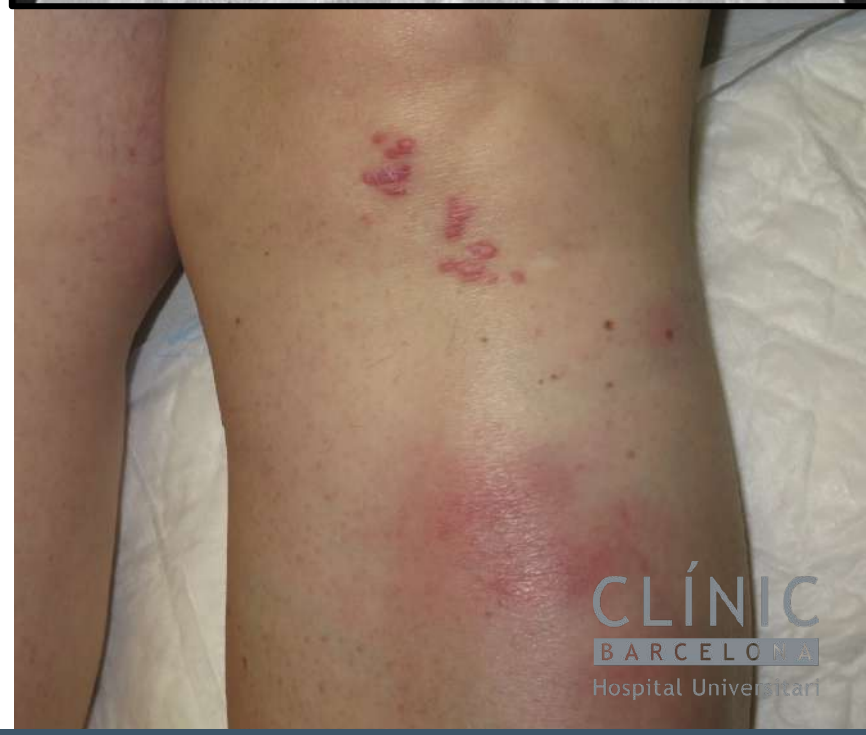


Granulomas sarcoideos

Reacciones sarcoideas:

- **Sobre todo Anti-PD-1**
- Media: 3-5 meses tras inicio
  - **10% tras la interrupción de la IT (8 a 24 meses)**
- **Hiliar > pulmonar > cutánea (30-50%)**
  - pápulas, placas y nódulos ocasionalmente sobre tatuajes o cicatrices



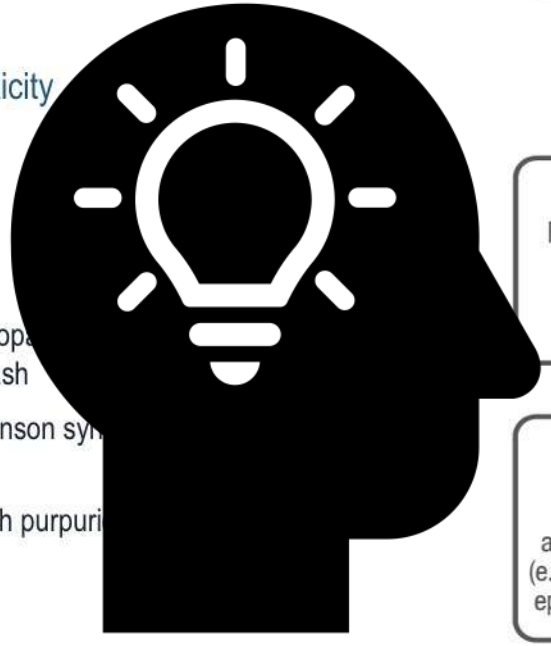


Eur J Cancer. 2021 Nov;158:208-216. doi: 10.1016/j.ejca.2021.05.041. E
J Am Acad Dermatol. 2018 Aug 6.

CLINICAL PRACTICE GUIDELINES

Immune-related skin toxicity

ICPi-related toxicity:
Management of skin rash/toxicity



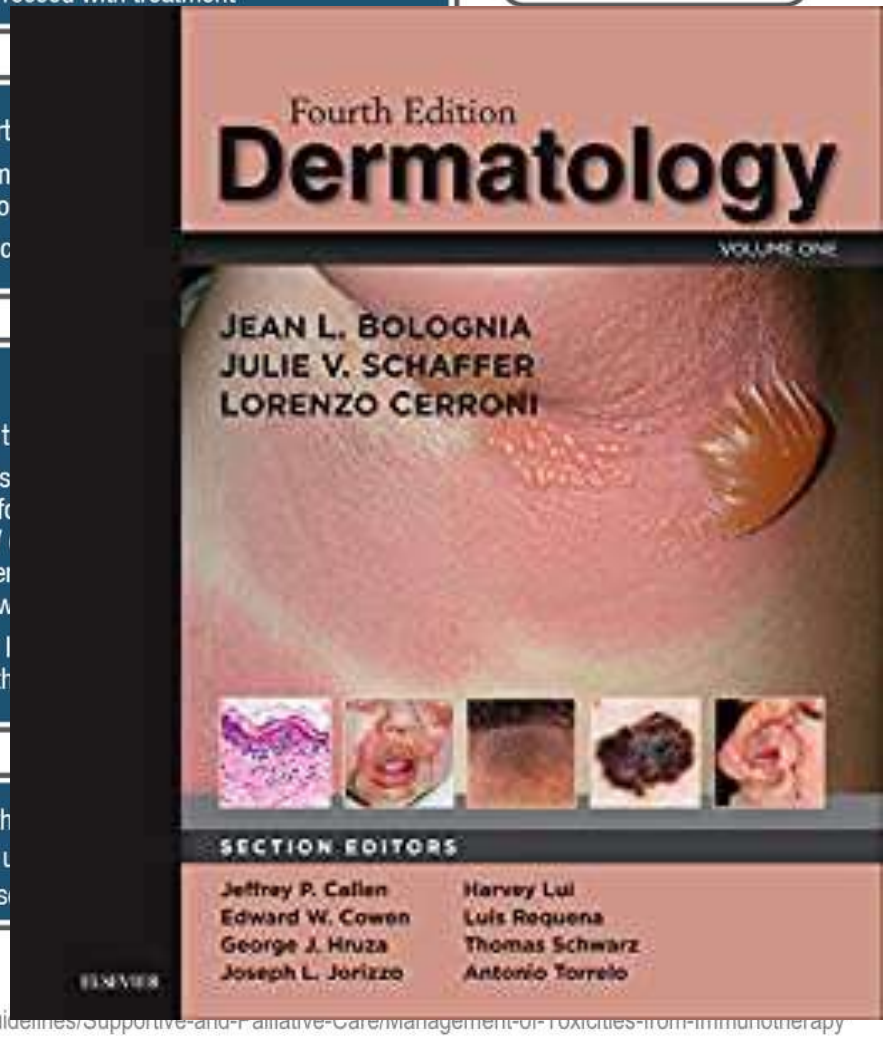
Recognised skin AEs include:

Most common: Erythema, maculopa… pustulopapular rash

Rare: TEN, Steven-Johnson sy… and DRESS

Vasculitis may also be present with purpuri…

Symptom grade	Management escalation pathway	Investigations
Grade 1: Skin rash, with or without symptoms, < 10% BSA	Avoid skin irritants, avoid sun exposure, topical emollients recommended Topical steroids (mild strength) cream od +/- oral or topical antihistamines for itch Proceed with treatment	Physical examination Exclude other causes, e.g. viral illness, infection, other drug rash
Grade 2: Rash covers 10–30% of BSA	Support… Topical steroids (m… cream bid +/- o… Proc…	
Grade 3: Rash covers > 30% BSA or grade 2 with substantial symptoms	Topical t… Initiate steroids… prednisolone od f… or if severe IV … and conver… w… Recommence … with…	
Grade 4: Skin sloughing > 30% BSA with associated symptoms (e.g. erythema, purpura, epidermal detachment)	IV (meth… Seek u… Dis…	



ESMO

J Clin Oncol 37:2746-2758. © 2019 |

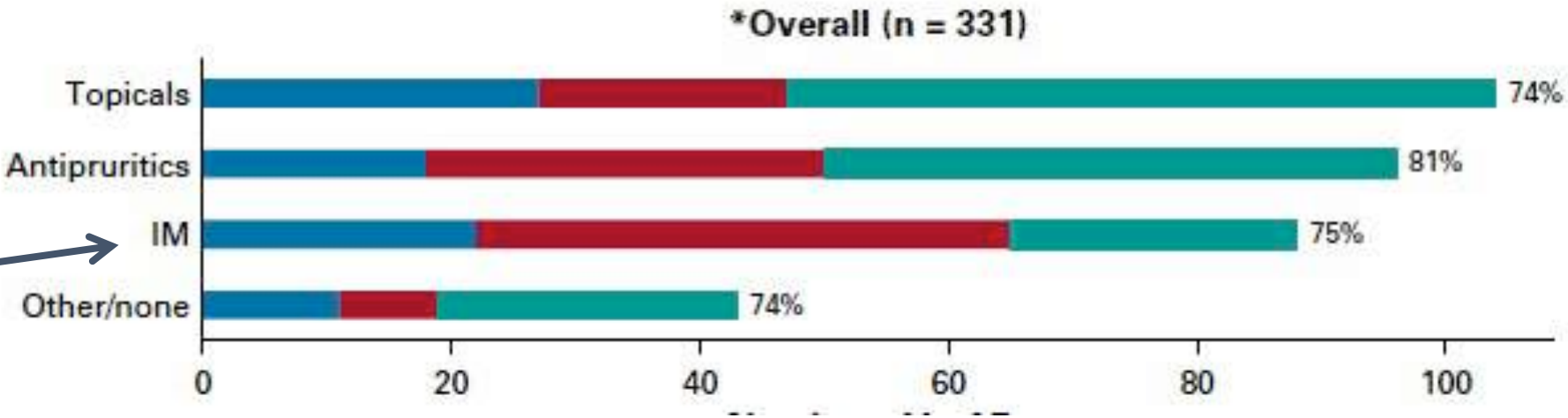
original report

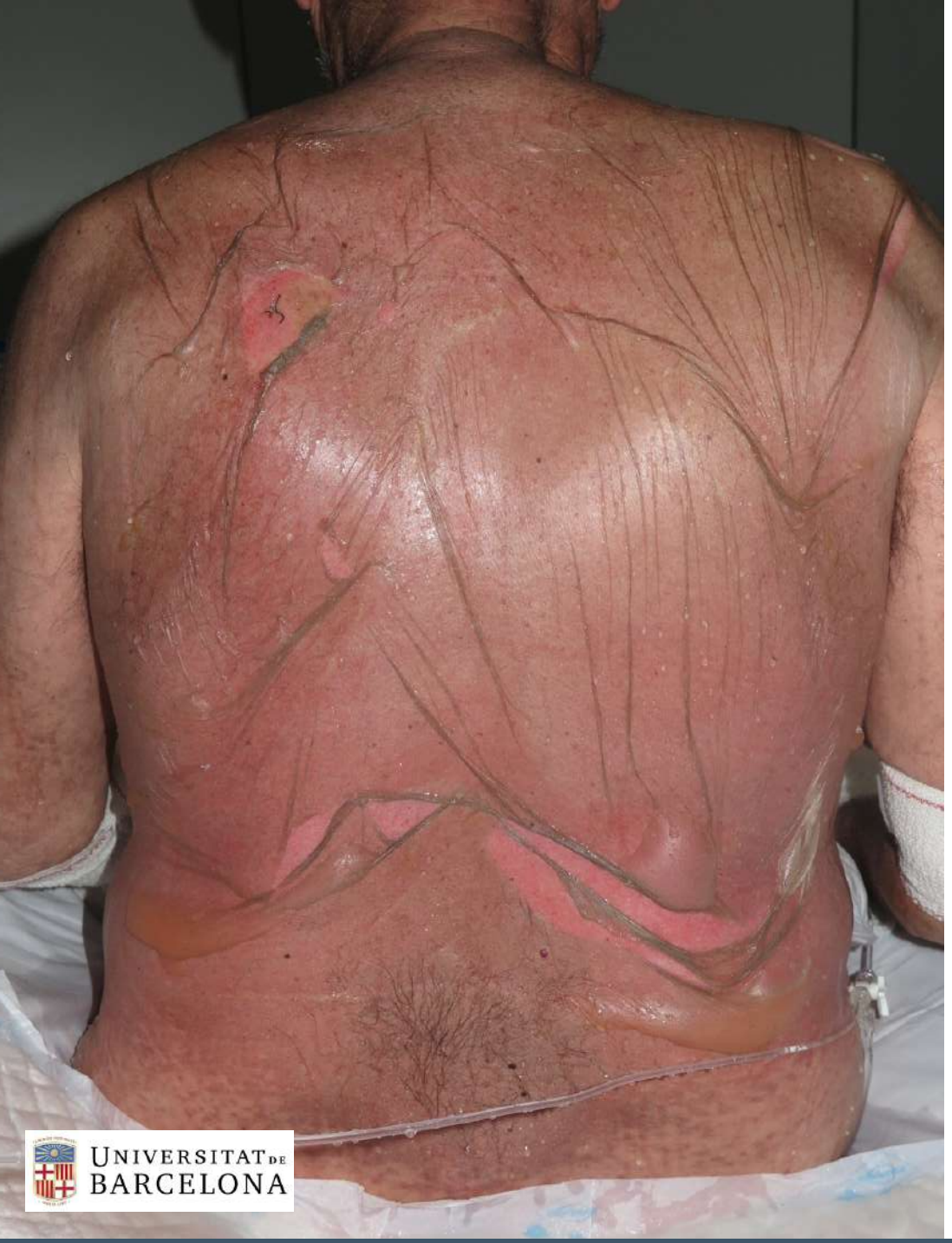
Treatment Outcomes of Immune-Related Cutaneous Adverse Events

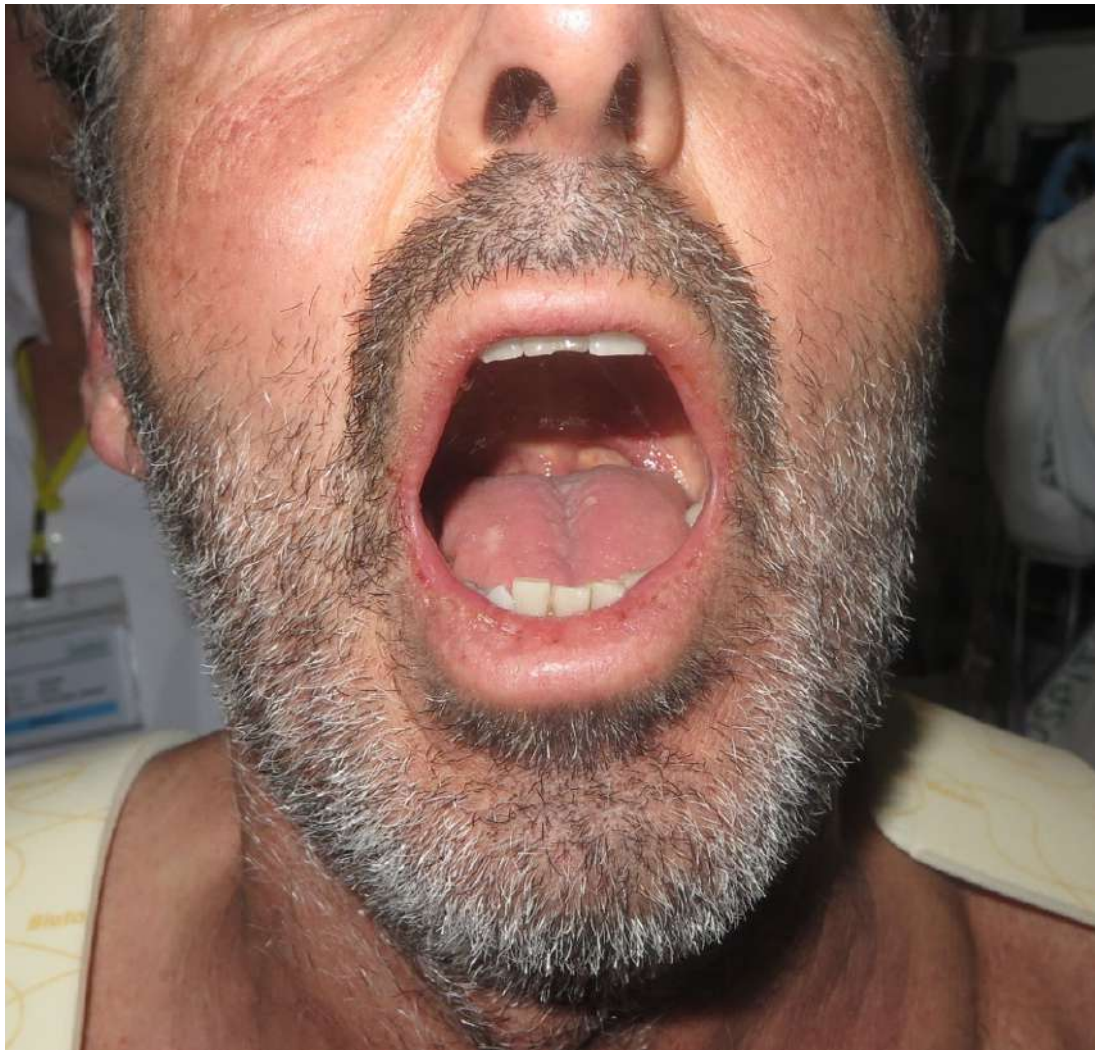
Gregory S. Phillips, BS[1]; Jennifer Wu, MD[1,2,3]; Matthew D. Hellmann, MD[1,4]; Michael A. Postow, MD[1,4]; Naiyer A. Rizvi, MD[5]; Azael Freites-Martinez, MD[1]; Donald Chan, EdM[1]; Stephen Dusza, DrPH[1]; Robert J. Motzer, MD[1,4]; Jonathan E. Rosenberg, MD[1,4]; Margaret K. Callahan, MD, PhD[1,4]; Paul B. Chapman, MD[1,4]; Larisa Geskin, MD[5]; Adriana T. Lopez, BA[5]; Vanessa A. Reed, MS[5]; Gabriella Fabbrocini, MD[6]; Maria Carmela Annunziata, MD[6]; Oluwaseun Kukoyi, BS[1]; Aliyah Pabani, MD[5]; Chih-Hsun Yang, MD[1,2,3]; Wen-Hung Chung, MD, PhD[1,2,3]; Alina Markova, MD[1,4]; and Mario E. Lacouture, MD[1,4]

- ✓ 44% SÓLO tto TÓPICO
- ✓ 15% RAM der grados 3 - 4

20% IM sistémicos:
- **25% resistentes!**







65y carcinoma renal + M1 SNC
1º dosis: IPI + NIVO

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SJS / NET – *like* más leves???

https://doi.org/10.1016/j.jaad.2020.03.029

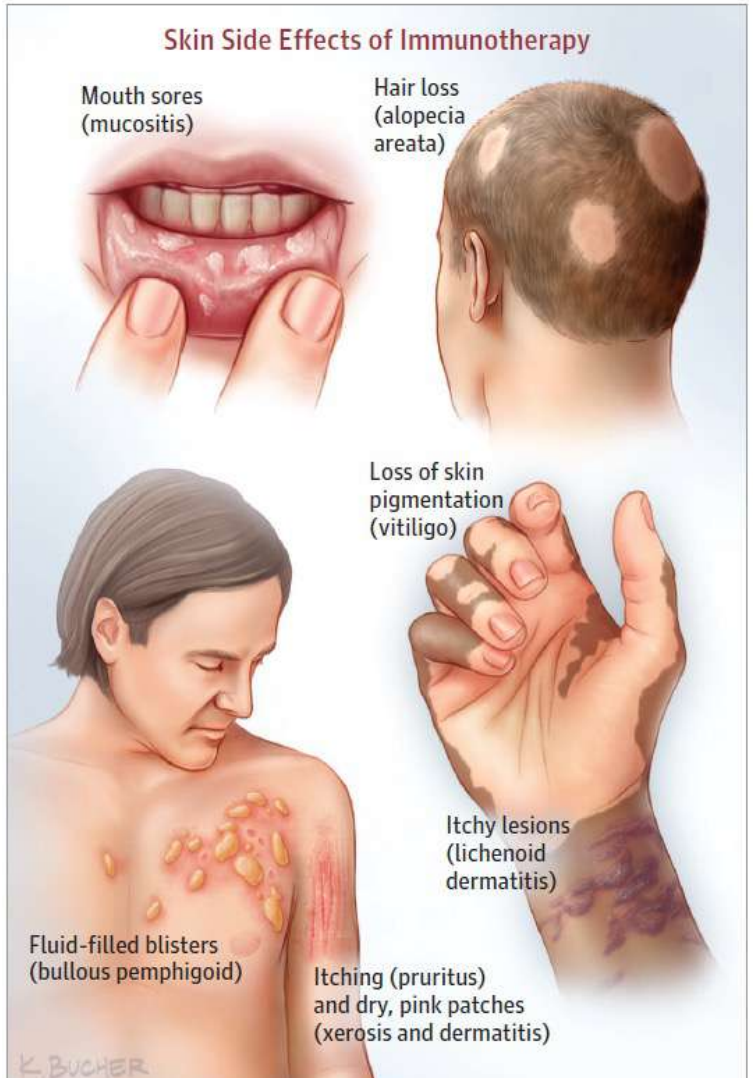
Patient No./sex/age	Neoplasm	ICI class	Concomitant medications	Time from ICI to rash onset, d	Initial rash presentation	Mucosal involvement (days after rash)	Histology	Systemic treatment approach and response	LOS, d	ICI discontinuation
1/M/64	Melanoma	CTLA-4 & PD-1	Trametinib	39	Pruritic lichenoid papules and plaques on thighs	Oral erosions; dry eyes (8)	Cytotoxic vacuolar interface dermatitis with full-thickness necrosis	IV methylprednisolone 2 mg/kg/d; cessation of rash progression and rapid symptomatic resolution	17	Yes
/F/86	SCC	PD-1	Trimethoprim-sulfamethoxazole and nitrofurantoin	63	Pruritic urticarial plaques on chest and back	Not available	Multifocal full-thickness epidermal necrosis with subepidermal cleft and PVLI	3-week prednisone taper; resolution of pruritus and blistering within 1 week	9	Previously discontinued
/F/80	NSCLC	PD-1	Prochlorperazine	25	Pruritic, painful lichenoid papules on chest	Oral and vulvar erosions; dry eyes (9)	Multifocal full-thickness epidermal necrosis with subepidermal cleft and PVLI	IV methylprednisolone 2 mg/kg/d; cessation of rash progression and rapid symptomatic resolution	11	Yes
4/M/70	RCC	PD-1	Allopurinol	210	Pruritic palmoplantar bullae	Oral erosions; odynophagia (45)	Florid interface dermatitis with subepidermal cleft and eosinophilic infiltrate	IV methylprednisolone 2 mg/kg/d; cessation of rash progression and rapid symptomatic resolution	13	Previously discontinued
5/M/59	Melanoma	CTLA-4 & PD-1	Trimethoprim-sulfamethoxazole and celecoxib	13	Diffuse, pruritic urticarial eruption	Oral pain; dysuria (5)	Full-thickness epidermal necrosis	Infliximab (1 dose) and IV methylprednisolone 2 mg/kg/d; cessation of rash progression and rapid symptomatic resolution	12	Yes
6/M/73	Melanoma	PD-1	Trimethoprim-sulfamethoxazole	253	Morbilliform eruption on trunk	Penile and perianal erosions (12)	Interface dermatitis with focal epidermal necrosis and epidermal	IV methylprednisolone 1.5 mg/kg/d; cessation of rash progression and rapid symptomatic resolution	5	Previously discontinued

BID, Twice daily; *CTLA-4*, cytotoxic T-lymphocyte antigen 4; *DLBCL*, diffuse large B-cell lymphoma; *F*, female; *ICI*, immune checkpoint inhibitor; *IV*, intravenous; *LOS*, length of stay; *M*, male; *NSCLC*, non-small cell lung cancer; *PD-1*, programmed death 1; *PVLI*, perivascular lymphocytic infiltrate; *RCC*, renal cell carcinoma; *SCC*, squamous cell carcinoma.

Progressive ICI-Related Mucous Eruptions *P I R M E* ???

https://doi.org/10.1016/j.jaad.2021.03.122

ESPECTRO DERMATOSIS INMUNOMEDIADAS…



JAMA Dermatology June 2018 Volume 154, Number 6

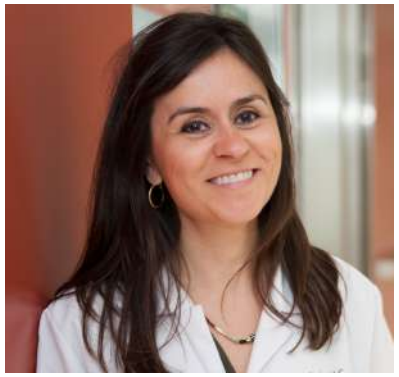
PRURITO, exantemas maculopapulares	**Liquen plano-like, psoriasis, eczemas**	**Vitíligo (melanoma)**
Penfigoide ampolloso	Enfermedad de Grover	Sarcoidosis
SJS/TEN, AGEP, DRESS	DM, LE, PNP-like	Rosácea – Acné Alopecia areata…

Geisler AN et al. J Am Acad Dermatol 2020;83:1255-68
J Am Acad Dermatol 2021; doi: 10.1016/j.jaad.2021.03.094

Onco-Dermatología & Inmuno-Dermatopatología

Dra M.Teresa Estrach

Dr. J.Manuel Mascaró



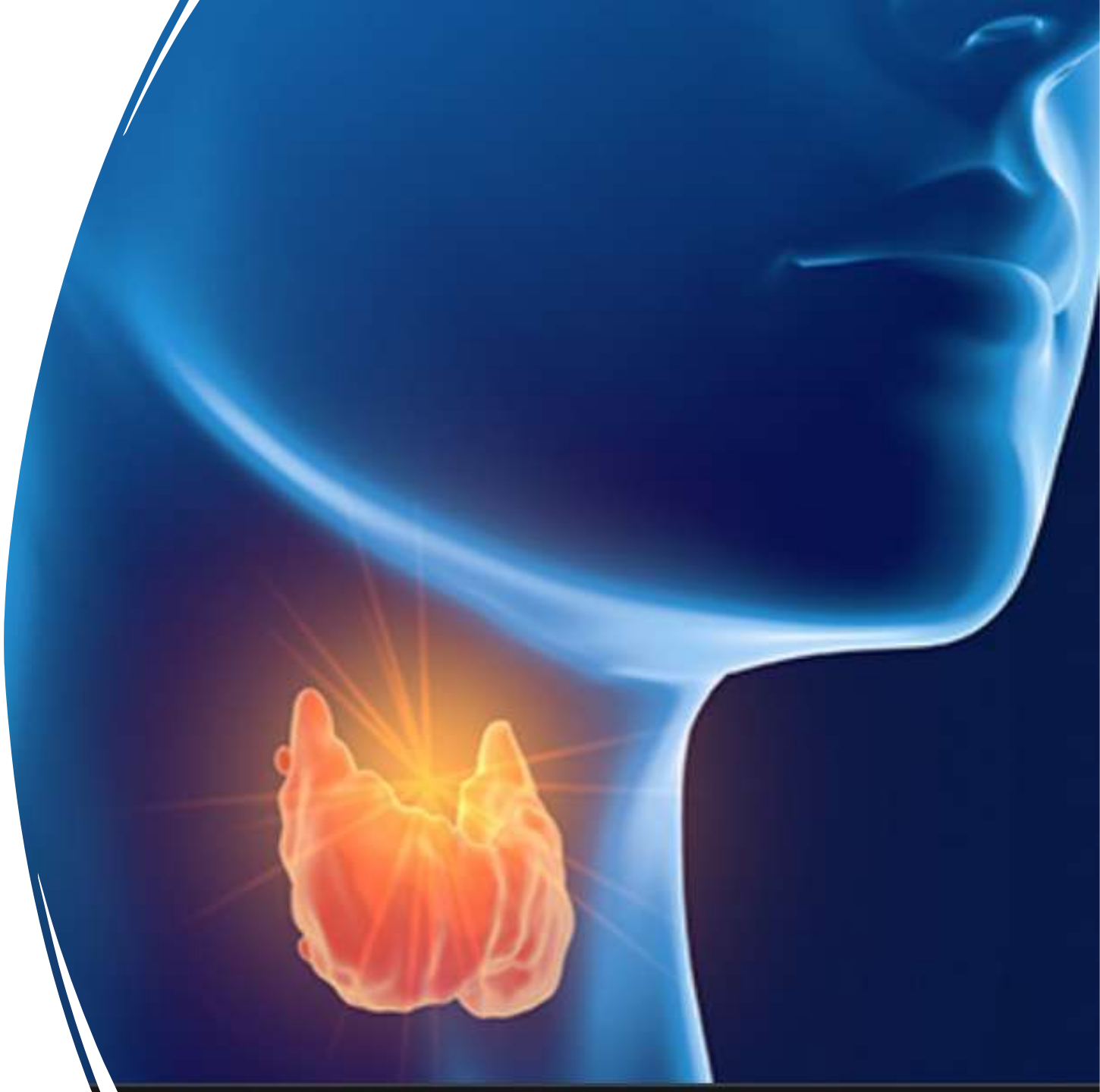
Dra Cristina Carrera

Dra Priscila Giavedoni

Grupo de trabajo INTERDISCIPLINAR:

Tiroiditis

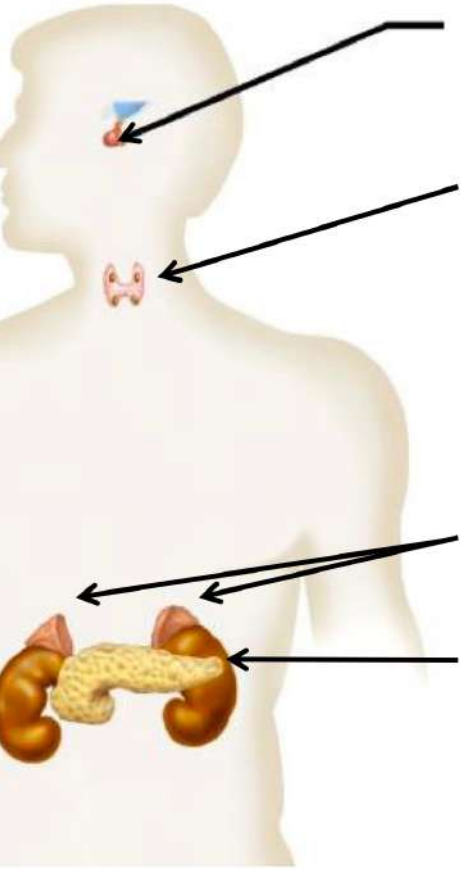
- Dra. Felicia Hanzu



CLÍNIC BARCELONA Hospital Universitari

ICMDM DIGESTIVES I METABÒLIQUES Servei d'Endocrinologia i Nutrició

Toxicidad endocrinológica



Pituitary gland
- Hypophysitis
- Corticotropin (ACTH) decrease
- Secondary adrenal insufficiency[a]

Thyroid gland
- Hyperthyroidism
- Hypothyroidism
- TSH increase or decrease
- Thyroiditis
- Free thyroxine increase or decrease
- Autoimmune thyroiditis

Adrenal glands
- Primary adrenal insufficiency[b]

Pancreas
- Diabetes mellitus

Anti-CTLA-4

Anti PD-1 y PD-L1

Anti **PD-1** y PD-L1

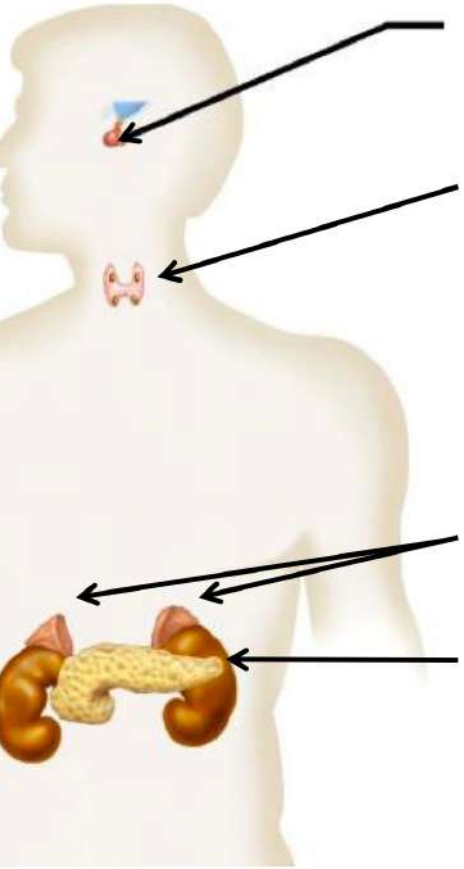
~10%

~30%

~1%

Sznol et at. Cancer Treatment Reviews 58 (2017) 70-76

Toxicidad endocrinológica



Pituitary gland
- Hypophysitis
- Corticotropin (ACTH) decrease
- Secondary adrenal insufficiency[a]

Thyroid gland
- Hyperthyroidism
- Hypothyroidism
- TSH increase or decrease
- Thyroiditis
- Free thyroxine increase or decrease
- Autoimmune thyroiditis

Adrenal glands
- Primary adren

Pancreas
- Diabetes mellit

Anti-CTLA-4

Anti PD-1 y PD-L1

Sospecha:

cefalea, cansancio, ganancia o perdida de peso, estreñimiento

alteración comportamiento, disminución líbido, mareos, frio, cambio en la voz

Sznol et at. Cancer Treatment Reviews 58 (2017) 70-76

HIPOtiroidismo

<30%

TSH ↑

T4 N/BAJA

tratamiento Hipotiroidismo:

- ***subclínico: T4 normal + TSH>10***
- ***CLÍNICO: T4 baja + síntomas***

Vigilar:

- ***Subclínico leve (T4 normal, TSH elevada <10mU/L)***

Chang et at. Endocrine Reviews 40; 17-65, 2019
Castinetti et al. Endocrine-Relatd Cancer (2019) 26; G1-G18

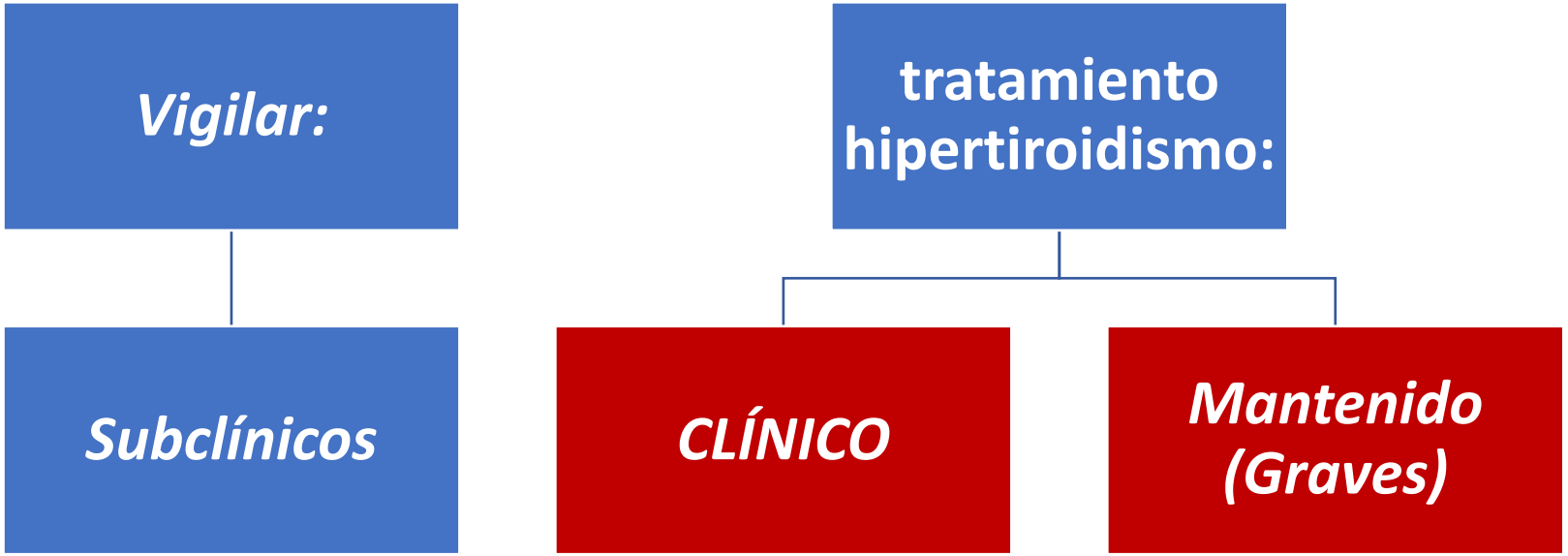
HIPERtiroidismo

<20%

- Hipertiroidismo transitorio: 3-16%
- Tirotoxicosis: 3-22%

TSH ↓

T4 normal/↑



Chang et at. Endocrine Reviews 40; 17-65, 2019
Castinetti et al. Endocrine-Relatd Cancer (2019) 26; G1-G18

Distiroidismo

- ✓**No es necesario discontinuar terapia**
- ✓hT: Tratamiento sustitutivo (levotiroxina 0.8mcg/k/d)
- ✓HT: Betabloqueante +/-antitiroideos, o corticoides orales

T4 baja + TSH normal/baja: Hipofisitis ??

hipofisitis

- Dra. Felicia Hanzu

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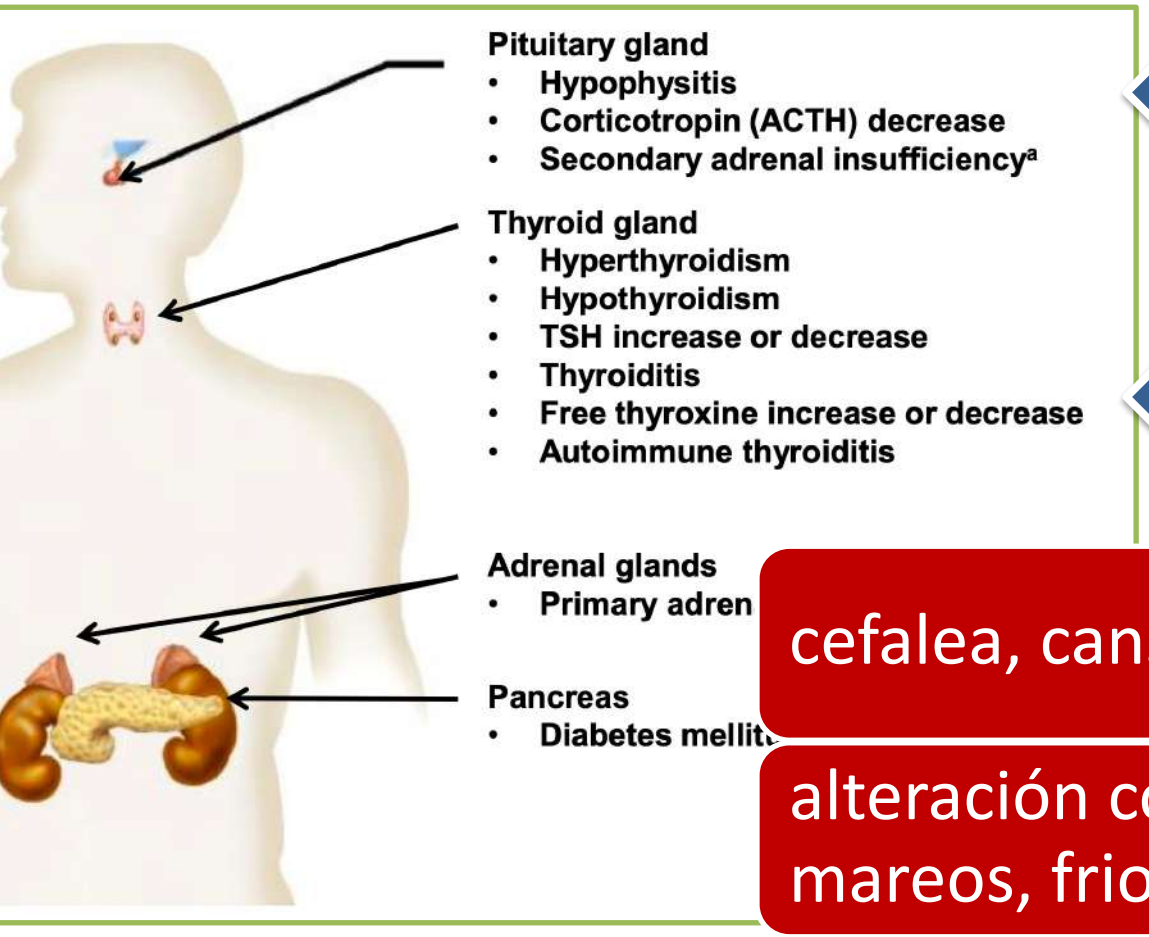
Hipofisitis



Anti-CTLA-4

Anti PD-1
y PD-L1

- ✓ antiCTLA4 >> antiPD1
- ✓ x 2-5 hombres
- ✓ antiCTLA4: 3.5% ; Mes 2-3
- ✓ antiPD1: 0.5%; Mes 3-5.

Sospecha:

cefalea, cansancio, alteraciones de visión

alteración comportamiento, disminución líbido, mareos, frio, cambio en la voz, hipoNatremia

Sznol et at. Cancer Treatment Reviews 58 (2017) 70-76

Hipofisitis

Sospecha HIPOFISITIS

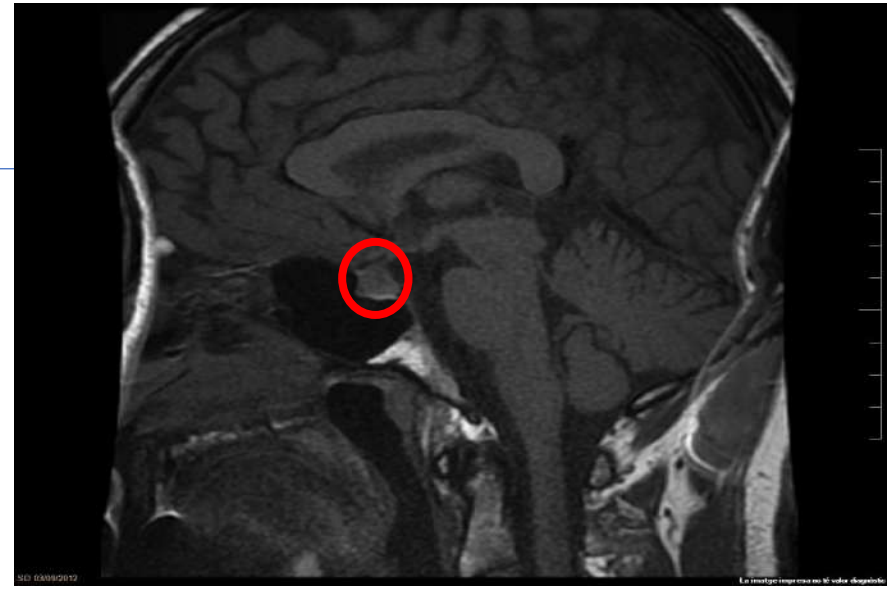
Clínica Aguda → **Endocrino URGENTE**

Estudio déficits hormonales → Cortisol ↓, T4L ↓, ADH ↓, Estradiol, Testosterona → No se sustituye en agudo

100 mg HA im -> 60 mg/d en 2-3 dosis

Tratamiento sustitutivo

- *Tiroxina (No iniciar tiroxina antes de con corticoides)*
- **RMN hipofisaria**
- **Consenso con endocrinólogo**



Colitis

- Dra. Ingrid Ordas

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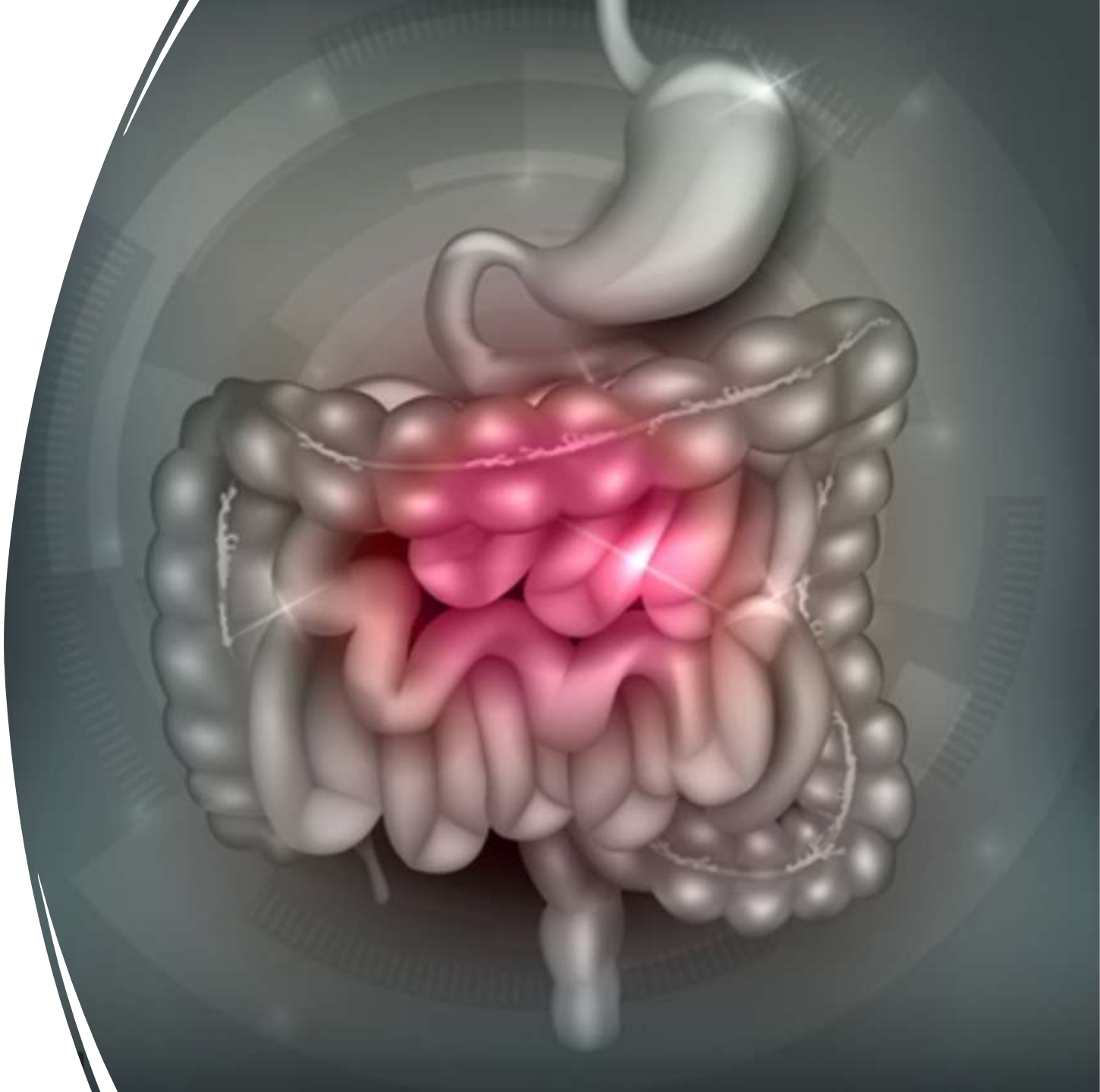
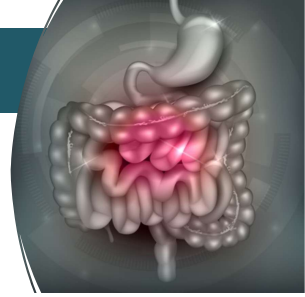
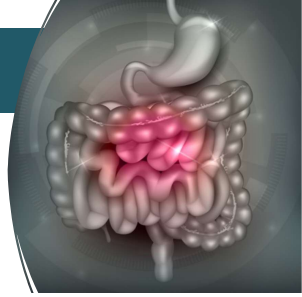




COLITIS

Factores de riesgo

- ✓ COMBO (14%) > anti-CTLA-4 (7%) > anti-PD-1 (1%)
- ✓ **EII pre-existente: sobre 30% de riesgo de brote**
- ✓ Microbiota enriquecida con *Firmicutes* y pobre de *Bacterioides* (con ipilimumab)
- ✓ **Melanoma** > riesgo que cáncer de pulmón o renal

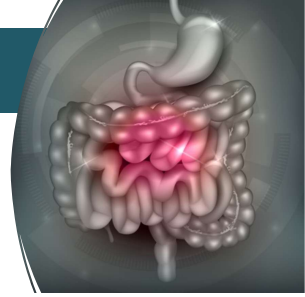


Gravedad de la Toxicidad Gastrointestinal

Efecto Adverso	Grado I	Grado II	Grado III	Grado IV
Diarrea	< 4 dps/d*	**4-6 dps/d**	≥ 7 dps/d Incontinencia Afectación estado general	**peligro vital** Colapso hemodinámico
Colitis	Asintomática	**Dolor abdominal** **Sangre o moco**	Dolor severo Deposiciones nocturnas Fiebre Íleo - Peritonismo	Perforación Hemorragia Isquemia Megacolon tóxico

*Respecto a su basal

Soularue E, Gut2018



COLITIS

Grado 1	**Mantener tratamiento + descartar infecciones** **Asociar tratamiento sintomático: loperamida / racecadotril**
Grado 2: IC gastro	**Suspender siguiente dosis** **GC** 1mg/kg prednisona (2-3m stop)
Grado 3	**ingreso + GC ev dosis altas** 1-2mg/kg prednisona **Valorar infliximab / vedolizumab**

Racecadotril (tiorfan®) tiene un efecto antisecretorio, reduciendo la secreción de agua y electrólitos al intestino, sin afectar la motilidad.
La loperamida (fortasec®) afecta la motilidad.

hepatitis

- Dra. Maria C. Londoño

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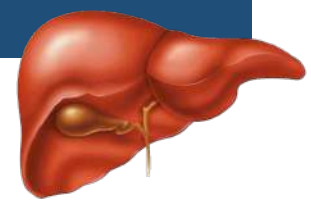
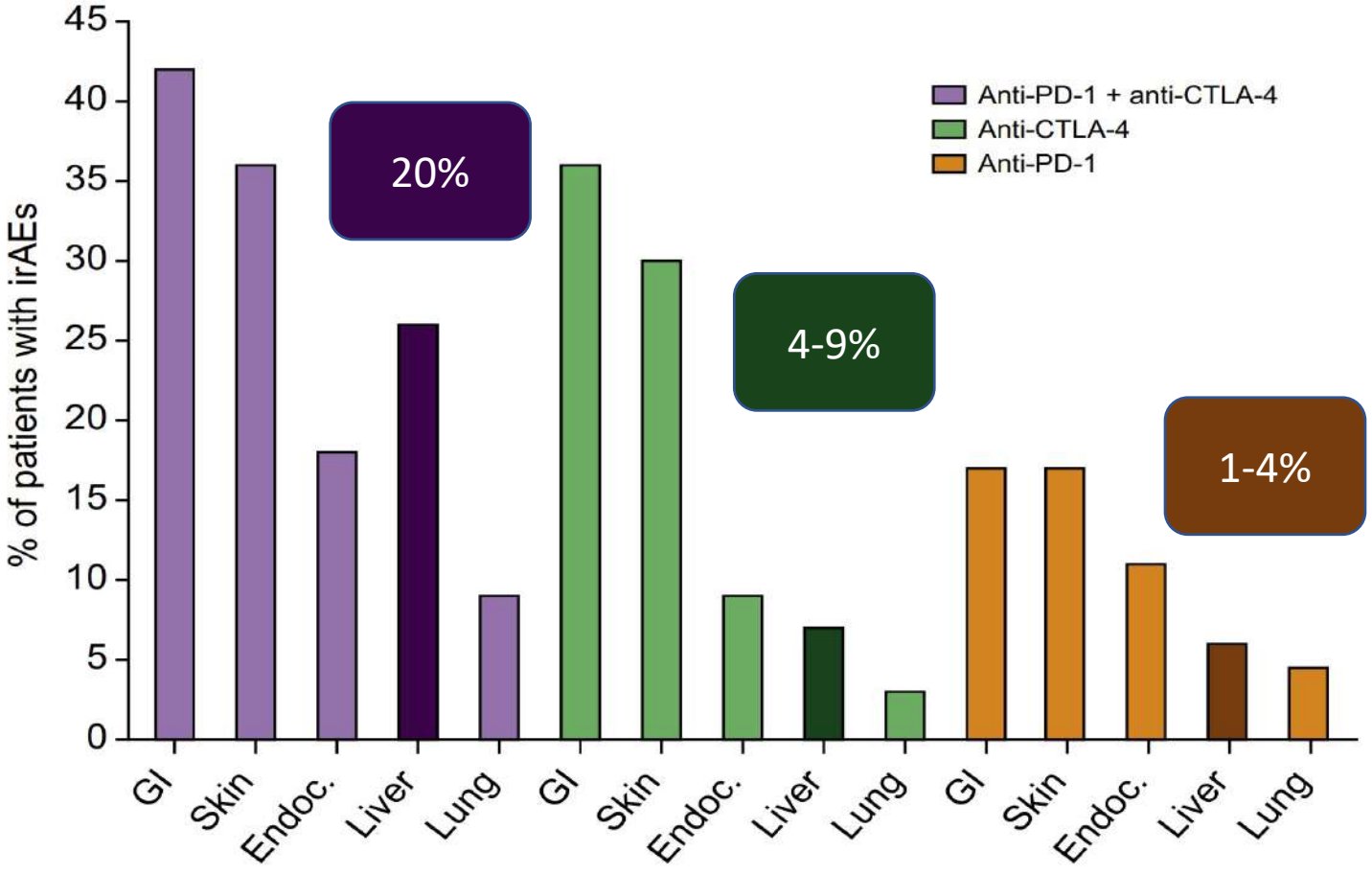


EAim HEPÁTICOS:



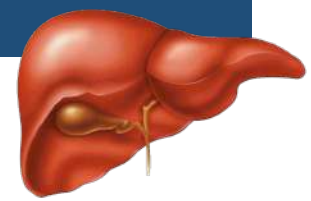
~2m (rango amplio)

25% asintomáticos

→ fiebre, dolor HCD

+ 30-40% otros EAs

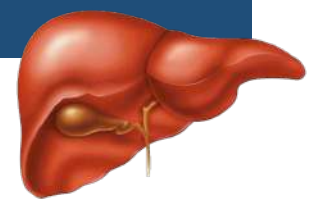
De Martin et al. JHEP Reports 2020, Postow et al. NEJM 2018, Wolchok et al. NEJM 2017, Cheng et al. J Gastroenterol Hepatol 2015, Boyer et al. BJ Cancer 2016, Mok et al. Lancet 2019



Severidad de transaminitis:

Grado 1	• AST/ALT < 3 x LSN*, Bilirrubina < 1,5 x LSN
Grado 2	• AST/ALT 3-5 x LSN, Bilirrubina 2-3 x LSN
Grado 3	• AST/ALT 5-20 x LSN, Bilirrubina > 3 LSN
Grado 4	• AST/ALT > 20 x LSN
Grado 5	• Muerte debida a toxicidad hepática

*En pacientes con pruebas hepáticas alteradas, el valor basal se considera el límite superior de la normalidad.



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Grado 1	• AST/ALT < 3 x LSN*, Bilirrubina < 1,5 x LSN
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Grado 3	• AST/ALT 5-20 x LSN, Bilirrubina > 3 LSN
Grado 4	• AST/ALT > 20 x LSN

e debida a

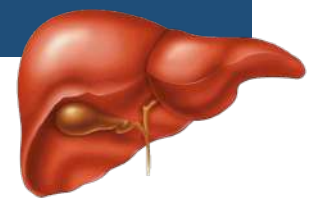
DESCARTAR OTRAS CAUSAS

- Enol – Fármacos - Dietéticos
- Hepatitis virales
- Patología vascular hepática
- Hepatitis autoinmune
- Hígado graso - Patología biliar
- M1 hepáticas

ESTUDIOS:

- Historia clínica
- Serologías virales:
  - anti-VHC, HbsAg, IgM HBc, VHE (RNA), CMV, HHV
- ANA, AML, IgG
- ECO abdominal - TAC

*En pacientes con [illegible] alteradas, el valor basal se considera el límite superior de la normalidad.



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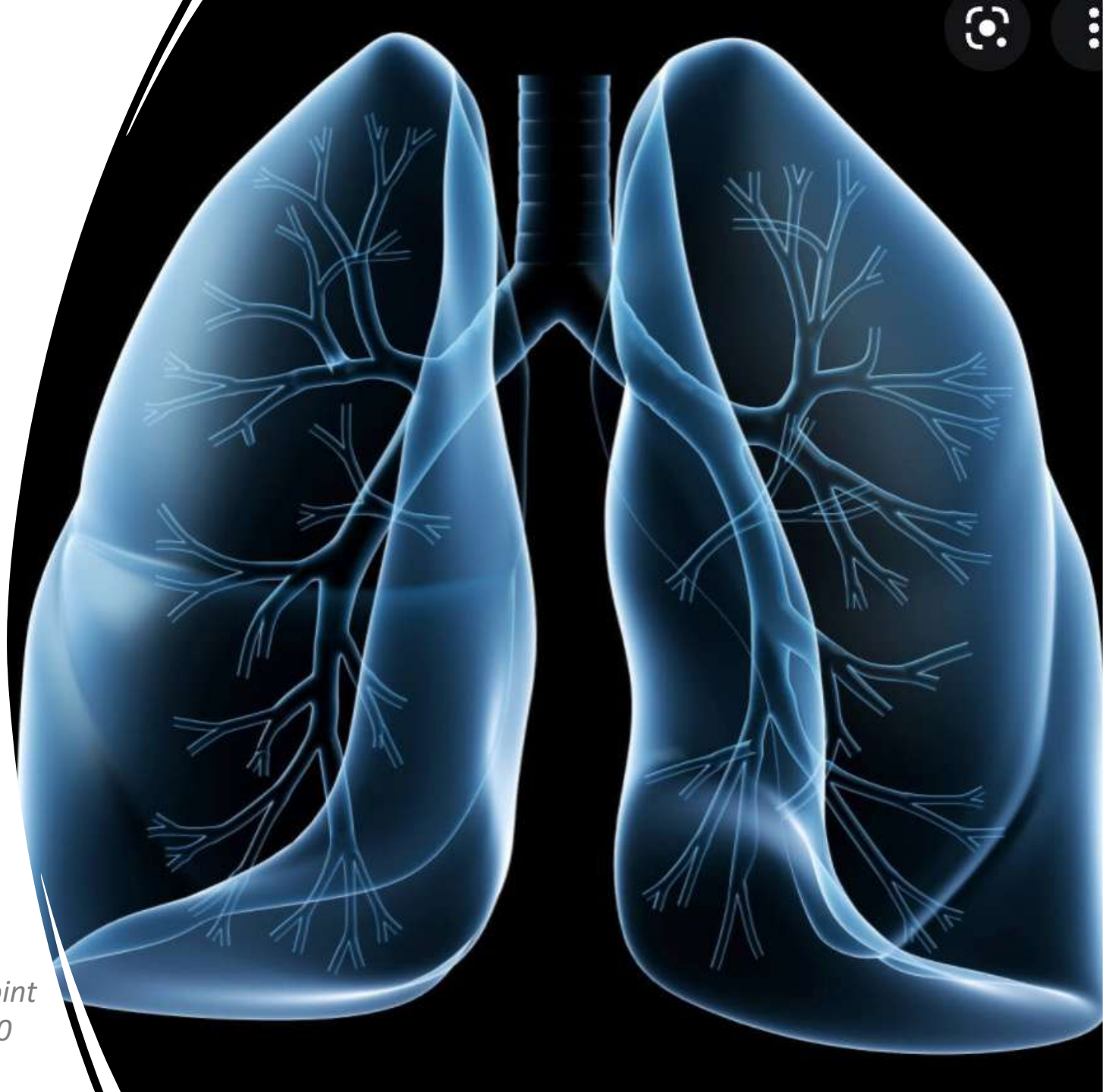
SUSPENDER TTO
IC HEPATOLOGÍA

*En pacientes con pruebas hepáticas alteradas, el valor basal se considera el límite superior de la normalidad.

Neumonitis

*EPI**

- Dr. Jacobo Sellarés



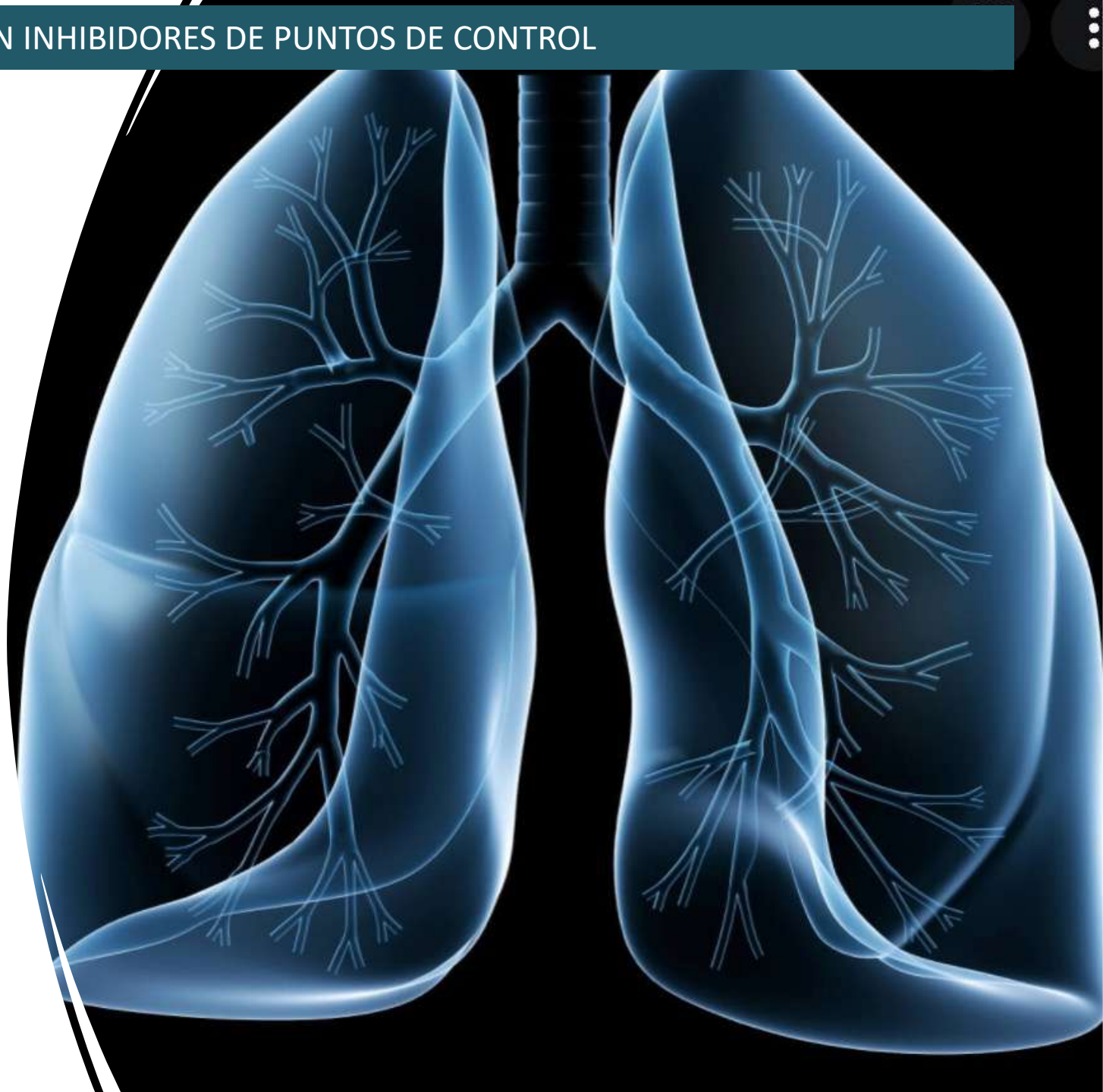
**Interstitial lung disease (ILD) secondary to immune-checkpoint inhibitors (ICI). Delaunay et al. Eur Respir J 2017; 50: 1700050*

NEUMONITIS

2.7-3.5%

Factores de riesgo:

- Ca Pulmón >> MM
- Enf. autoinmunes previas
- Infecciones oportunistas
- IPI + nivo >> antiPD1



Nishino M et al. JAMA Oncol 2016; 2(12):1607–1616
Delaunay et al. Eur Respir J 2017; 50: 1700050

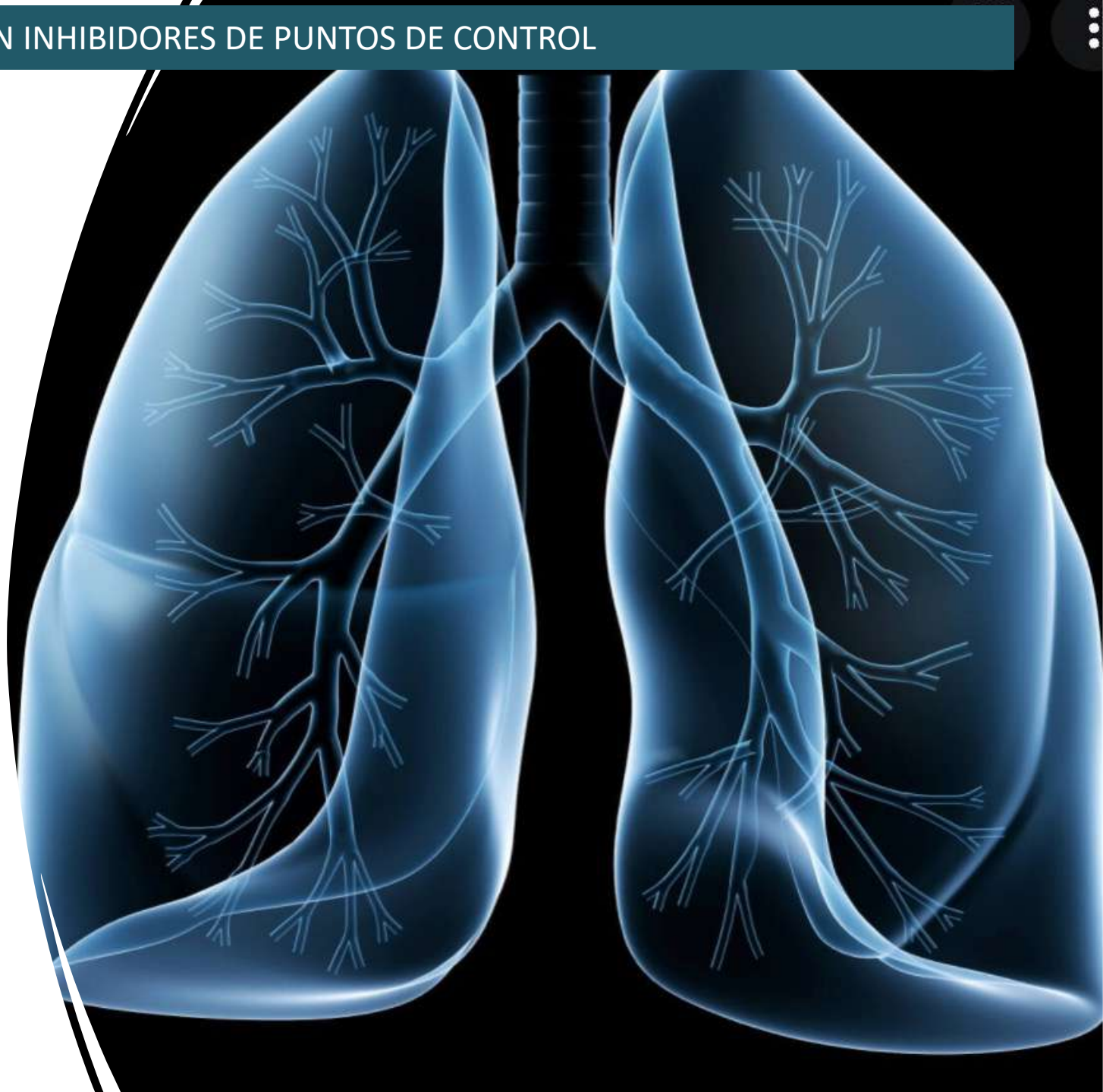
NEUMONITIS

2.7-3.5%

Factores de riesgo:

- Ca Pulmón >> MM
- Enf. autoinmunes previas
- Infecciones oportunistas
- IPI + nivo >> antiPD1

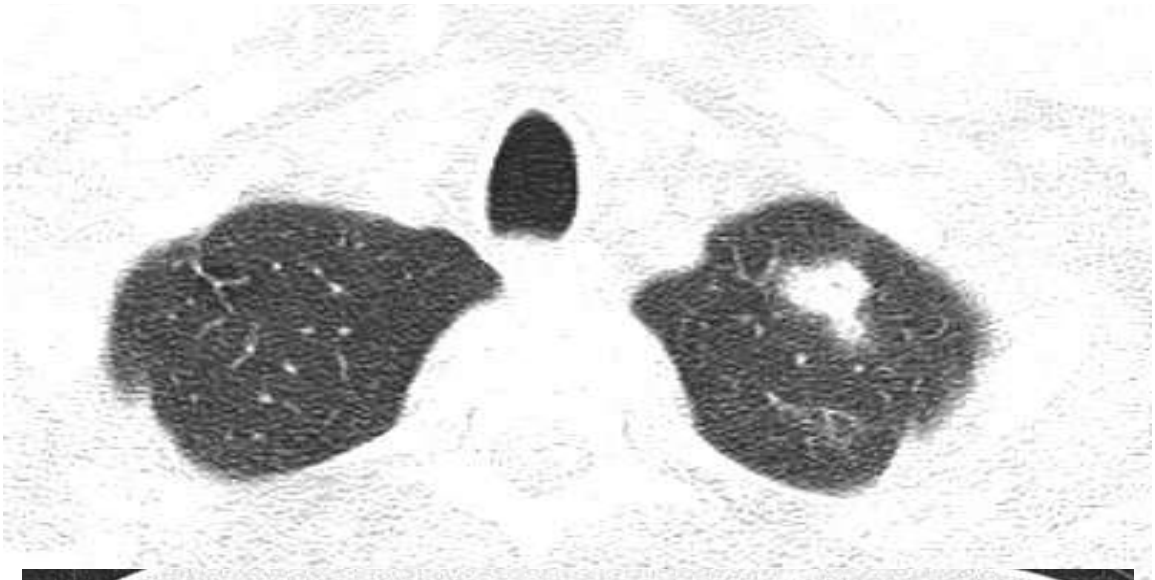
~ 20% MORTALIDAD

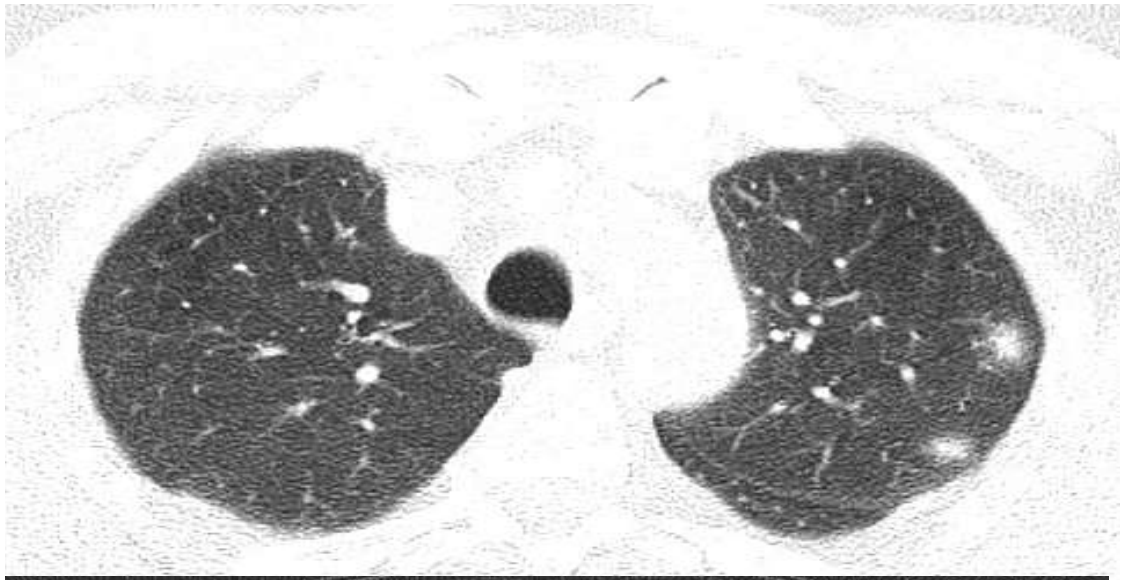


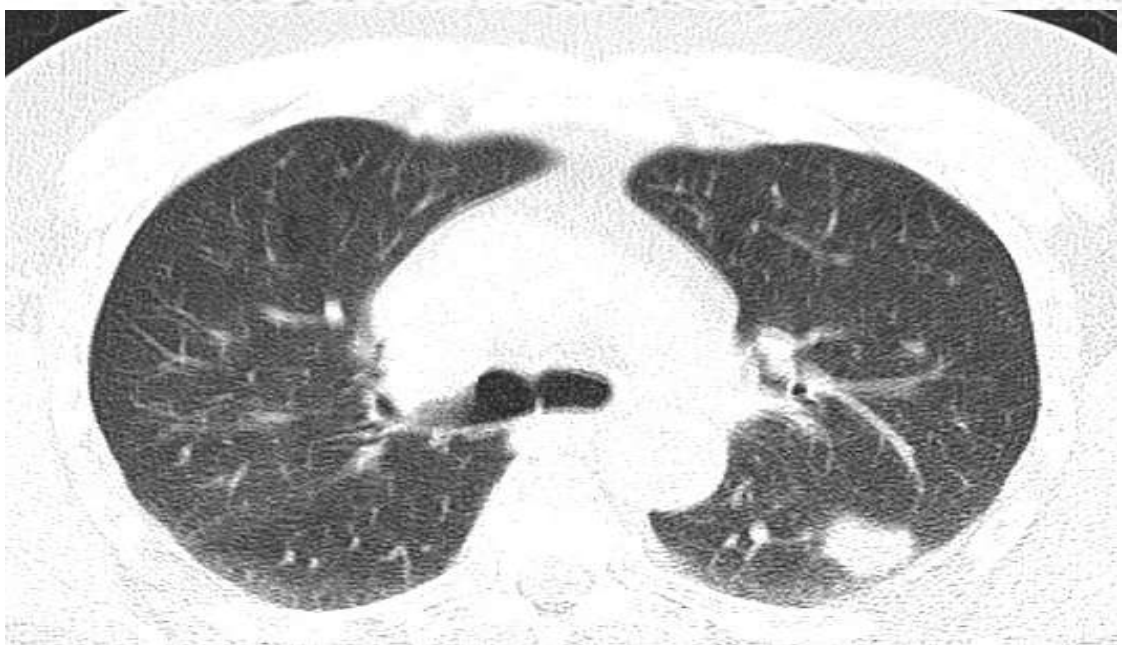
Nishino M et al. JAMA Oncol 2016; 2(12):1607–1616
Delaunay et al. Eur Respir J 2017; 50: 1700050

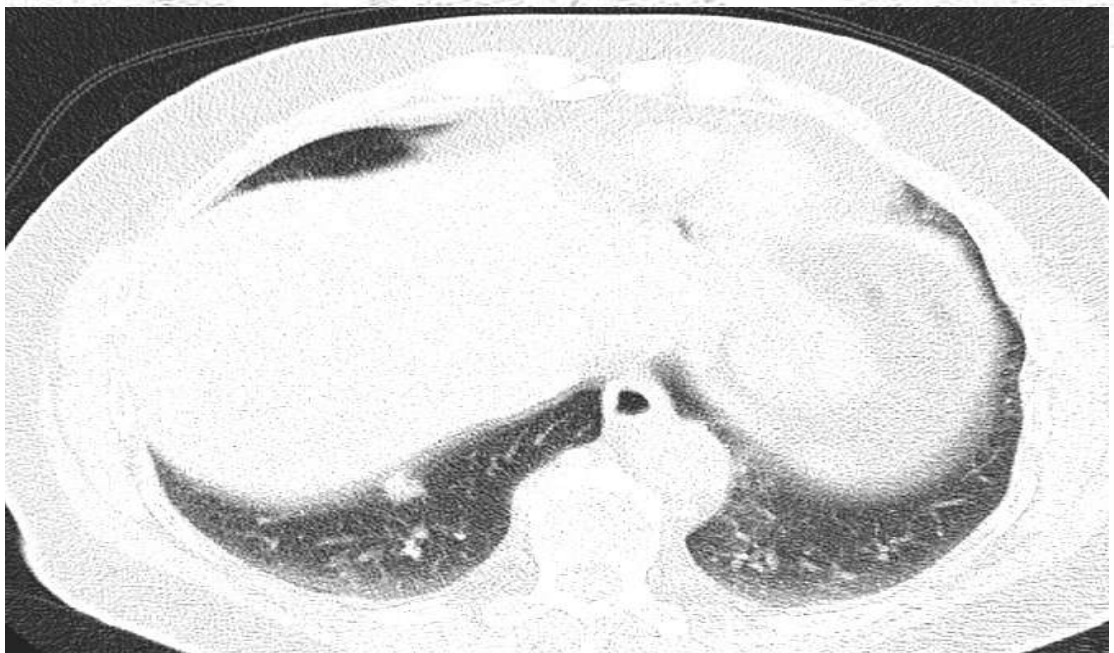
♂ 54 a. Melanoma estadio IIIB: Pembro en adyuvancia 12m, fin Julio 17 (EORTC 1375)

Asintomático: Agosto'17 nódulo inespecífico ➔ +3m Octubre'17



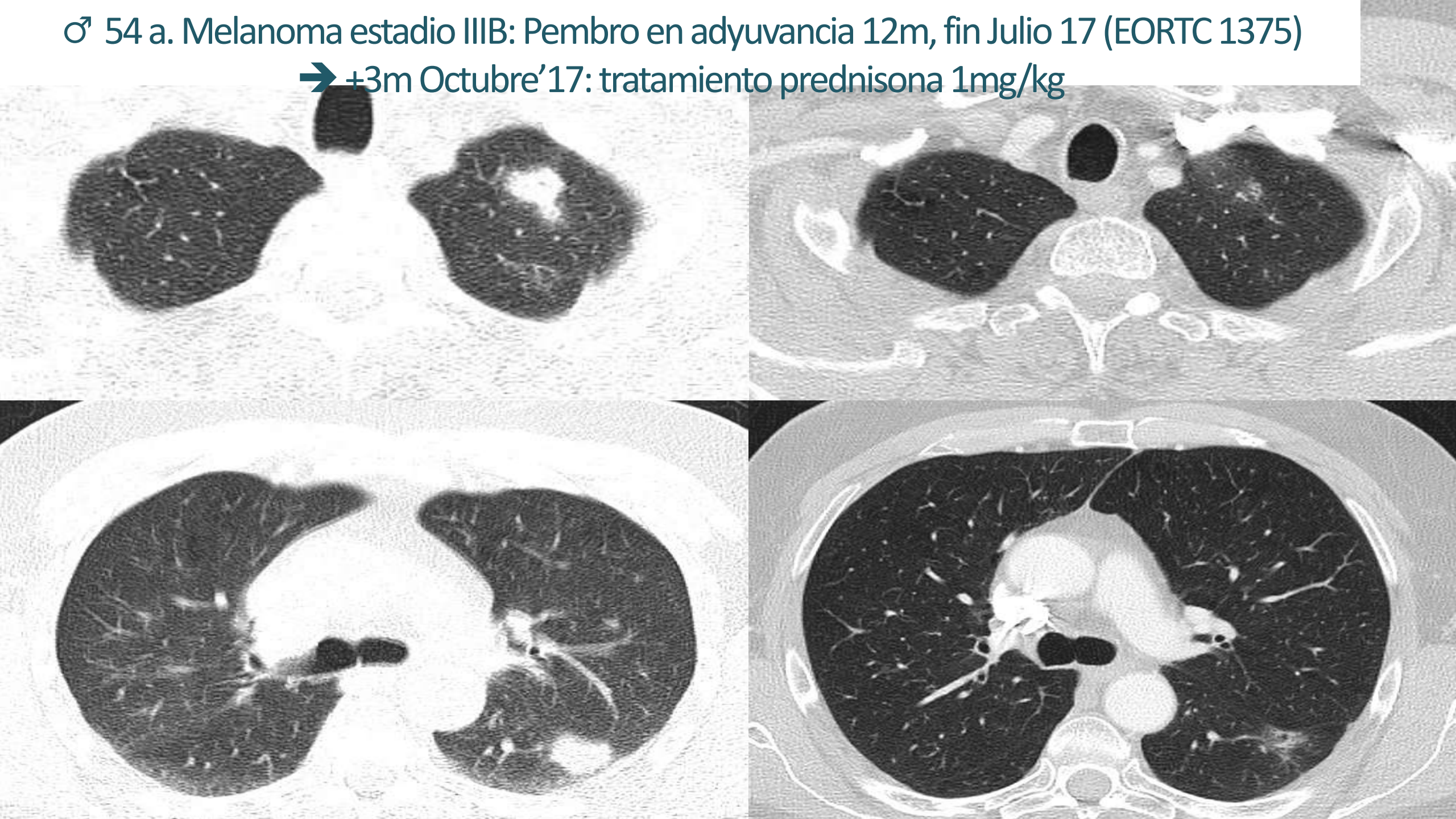


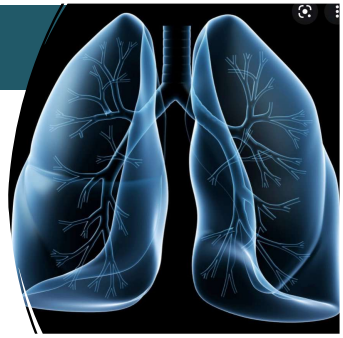




♂ 54 a. Melanoma estadio IIIB: Pembro en adyuvancia 12m, fin Julio 17 (EORTC 1375)

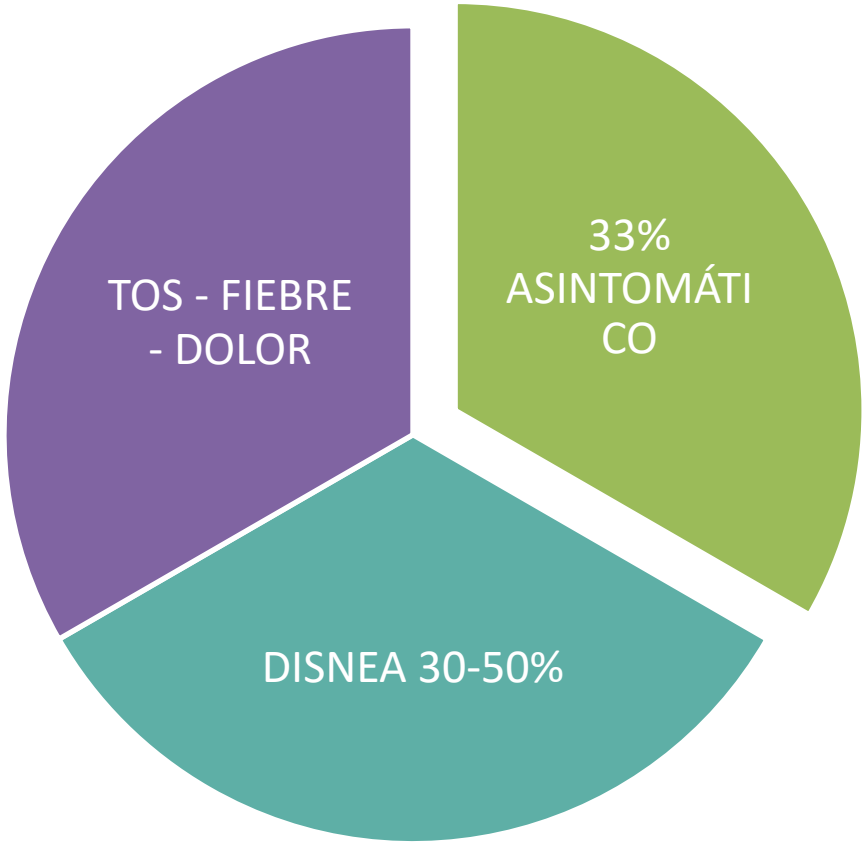
➔ +3m Octubre'17: tratamiento prednisona 1mg/kg





NEUMONITIS

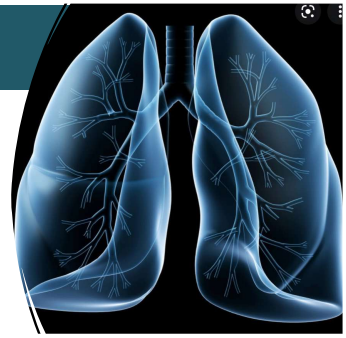
Inicio: 2 - 3 meses de tto (9 días-19.2 meses)



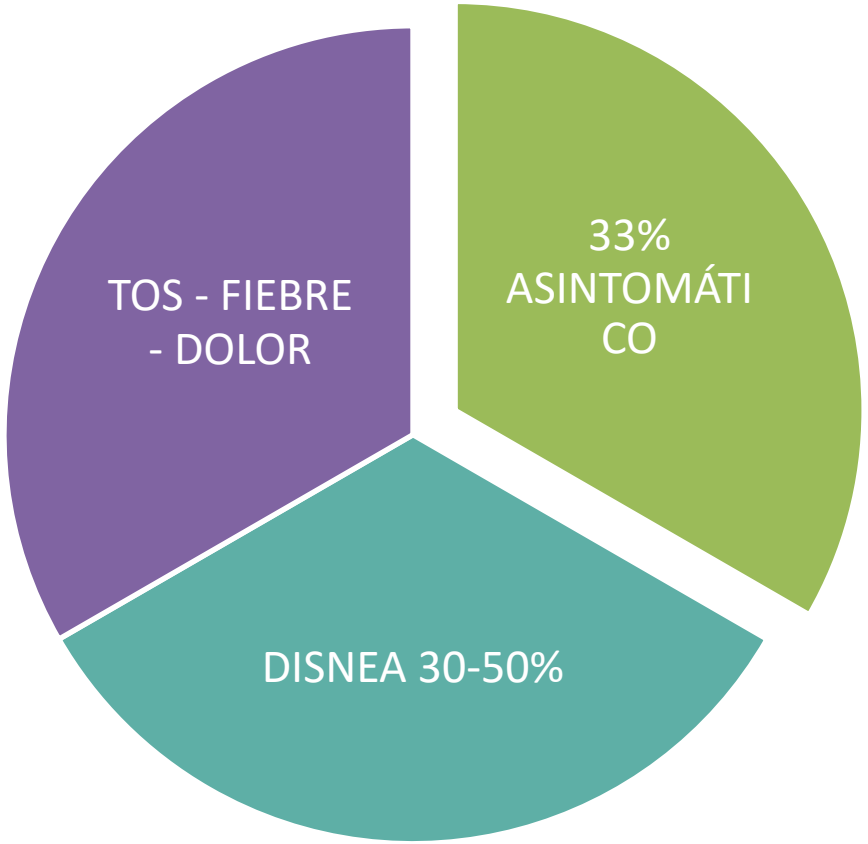
G1:	• Asintomático. Cambios radiológicos asociados (hallazgo incidental)
G2:	• **Síntomas leves o moderados.**
G3:	• Síntomas severos. Necesidad de oxigenoterapia.
G4:	• Compromiso vital respiratorio. Necesidad de IOT / UCI

Nishino M et al. JAMA Oncol 2016; 2(12):1607–1616

NEUMONITIS



Inicio: 2 - 3 meses de tto (9 días-19.2 meses)

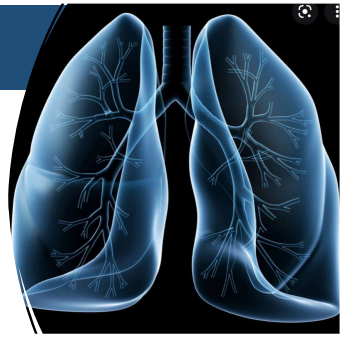


80 % patrón vidrio deslustrado

G1:	• **TAC-ALTA RESOLUCIÓN URGENTE (24-48H)**
G2:	• **IC NEUMO COMITÉ + INICIAR TTO**
G3:	• Síntomas severos. Necesidad de oxigenoterapia.
G4:	• Compromiso vital respiratorio. Necesidad de IOT / UCI

Nishino M et al. JAMA Oncol 2016; 2(12):1607–1616

NEUMONITIS

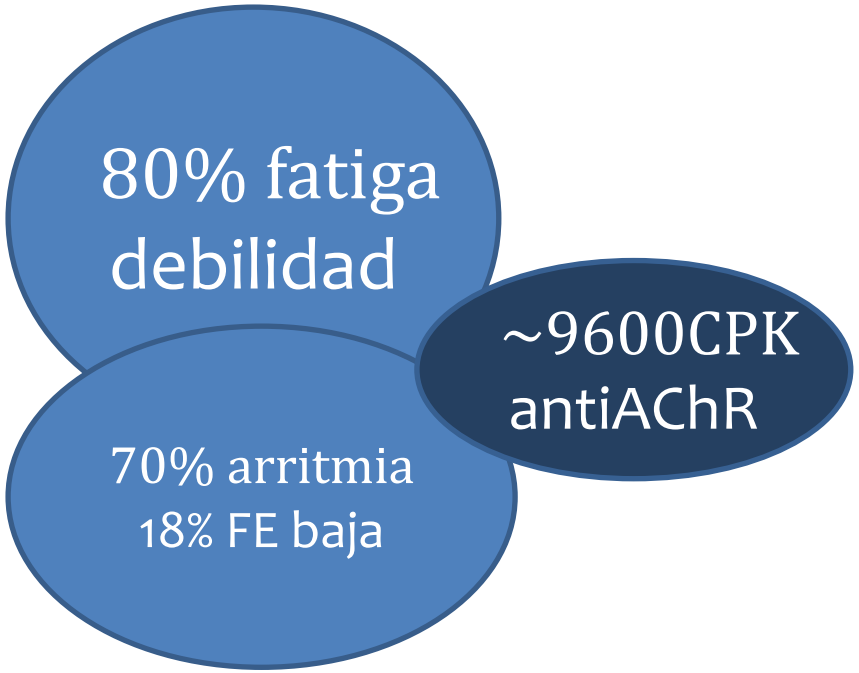


Grado 1	**RETRASAR CICLO** **Monitorizar + tratamiento sintomático**
Grado 2	**Suspender siguiente dosis** **GC** 1mg/kg prednisona
Grado 3	**Interrumpir + GC ev dosis altas** 2-4mg/kg prednisona
Grado 4	**IOT- UCI respiratoria**

Comité multidisciplinar
DESCENSO LENTO GC

Miositis / miocarditis

MIOSITIS – MIOCARDITIS – M. GRAVIS



<0.1-1%

♂ 70%, media 71a

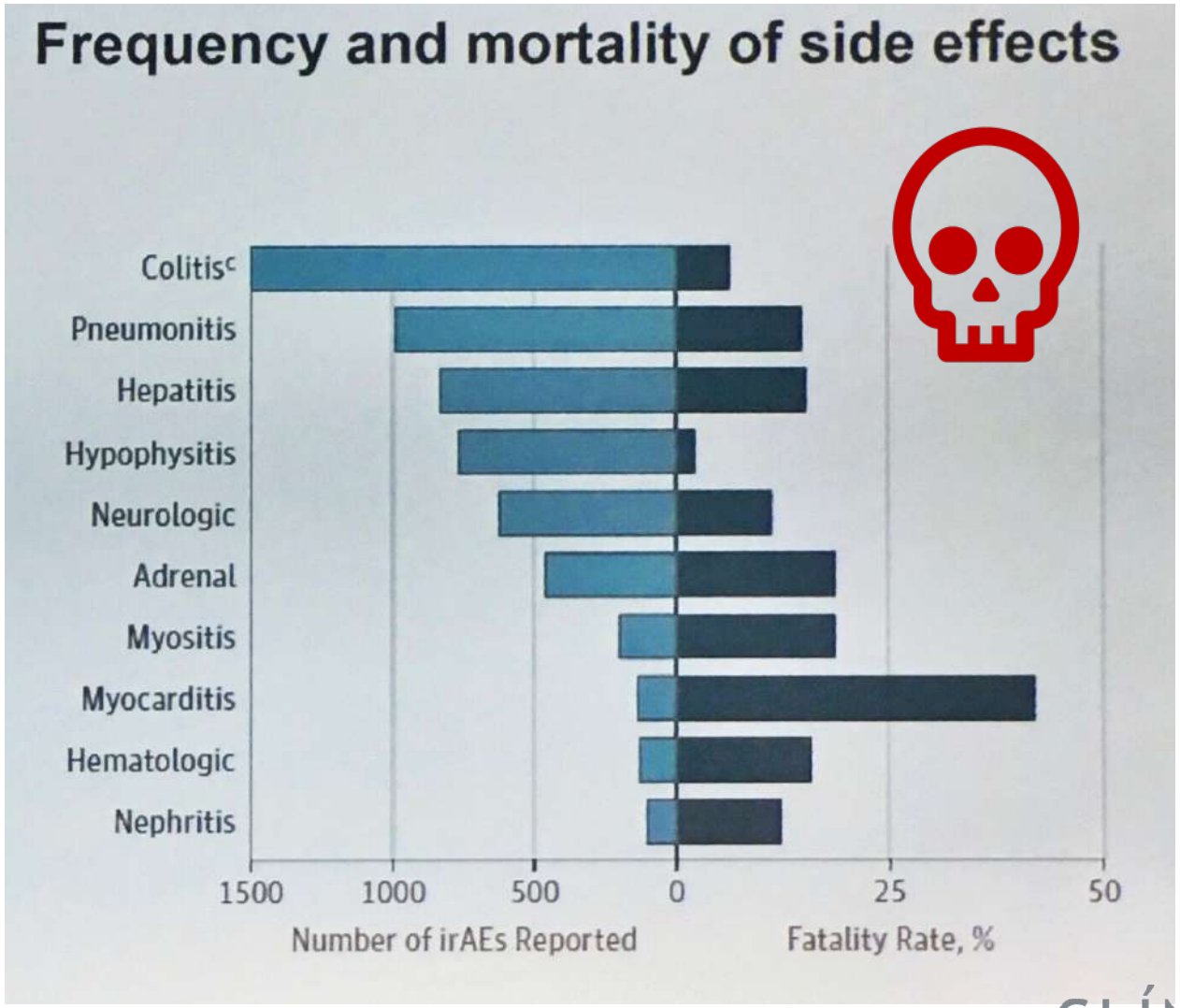
Debut mediana 1er ciclo

60% Mortalidad

Pathak et al. The Oncologist 2021;26:1052–1061

URGENCIA: ESPECIALIDADES IMPLICADAS!!

- Enterocolitis (18%)
- **MIOCARDITIS fulminantes (15%)**
- **Neuromusculares GB (13%)**
- Pancitopenias



Assoun et al. Intensive Care Med. 2019, 45, 988–997
Wang et al. JAMA Oncol 2018

CLINICAL PRACTICE GUIDELINES

An ESMO Product

Management of toxicities from immunotherapy

ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

J. Haanen, F. Carbonnel, C. Robert, K. Kerr, S. Peters, J. Larkin and K. Jordan,
on behalf of the ESMO Guidelines Committee

*For details of author affiliations, correspondence and versions, please see the full version at esmo.org/Guidelines/Supportive-and-Palliative-Care

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

INMUNOTERAPIA CON INHIBIDORES DE PUNTOS DE CONTROL

J Clin Oncol 39:4073-4126. © 2021

Check for updates

ASCO special articles

Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: ASCO Guideline Update

Bryan J. Schneider, MD[1]; Jarushka Naidoo, MD[2,3]; Bianca D. Santomasso, MD, PhD[4]; Christina Lacchetti, MHSc[5]; Sherry Adkins, MS[6]; Milan Anadkat, MD[7]; Michael B. Atkins, MD[8]; Kelly J. Brassil, PhD[6]; Jeffrey M. Caterino, MD, MPH[9]; Ian Chau, MD[10]; Marianne J. Davies, DNP[11]; Marc S. Ernstoff, MD[12]; Leslie Fecher, MD[1]; Monalisa Ghosh, MD[13]; Ishmael Jaiyesimi, DO, MS[14]; Jennifer S. Mammen, MD, PhD[15]; Aung Naing, MD[6], Loretta J. Nastoupil, MD[6]; Tanyanika Phillips, MD[16]; Laura D. Porter, MD[17]; Cristina A. Reichner, MD[18]; Carole Seigel, MBA[19], Jung-Min Song, MSN, RN, CNS[20]; Alexander Spira, MD, PhD[21]; Maria Suarez-Almazor, MD[6]; Umang Swami, MD[22]; John A. Thompson, MD[23]; Praveen Vikas, MD[24]; Yinghong Wang, MD[6]; Jeffrey S. Weber, MD, PhD[25]; Pauline Funchain, MD[20]; and Kathryn Bollin, MD[26]

INMUNOTERAPIA CON INHIBIDORES DE PUNTOS DE CONTROL

Open access Position article and guidelines

Journal for ImmunoTherapy of Cancer

Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adverse events

Julie R Brahmer,[1] Hamzah Abu-Sbeih,[2] Paolo Antonio Ascierto ,[3] Jill Brufsky,[4] Laura C Cappelli,[5] Frank B Cortazar,[6,7] David E Gerber,[8] Lamya Hamad,[9] Eric Hansen,[10] Douglas B Johnson,[11] Mario E Lacouture,[12] Gregory A Masters,[13] Jarushka Naidoo,[1,14] Michele Nanni,[10] Miguel-Angel Perales,[12] Igor Puzanov,[10] Bianca D Santomasso,[15] Satish P Shanbhag,[5,16] Rajeev Sharma,[10] Dimitra Skondra,[17] Jeffrey A Sosman,[18] Michelle Turner,[1] Marc S Ernstoff [19]

Journal for ImmunoTherapy of Cancer 2021;9:e002435. doi:10.1136/jitc-2021-002435

INMUNOTERAPIA CON INHIBIDORES DE PUNTOS DE CONTROL

Grupo de trabajo INTERDISCIPLINAR H Clínic BCN:

cancers

MDPI

Review

Multidisciplinary Clinical Approach to Cancer Patients with Immune-Related Adverse Events Induced by Checkpoint Inhibitors

Maria-Carlota Londoño [1,*], Maria Reig [2,*] and on behalf of the RETOINMUNO Multidisciplinary Group [†]

1 Liver Unit, Hospital Clinic Barcelona, IDIBAPS, University of Barcelona, CIBERehd, 08036 Barcelona, Spain
2 Liver Cancer Group (BCLC), Liver Unit, Hospital Clínic Barcelona, IDIBAPS, University of Barcelona, CIBERehd, 08036 Barcelona, Spain
* Correspondence: mlondono@clinic.cat (M.-C.L.); mreig1@clinic.cat (M.R.)
† Membership of the RETOINMUNO Multidisciplinary Group is provided in the Acknowledgments.

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check for updates

INMUNOTERAPIA CON INHIBIDORES DE PUNTOS DE CONTROL

GESTACIÓN (latencia 3-5 m)

ENF. AUTOINMUNES ACTIVAS SEVERAS (precisen >10mg prednisona 21d)

CONTRAINDICACIONES

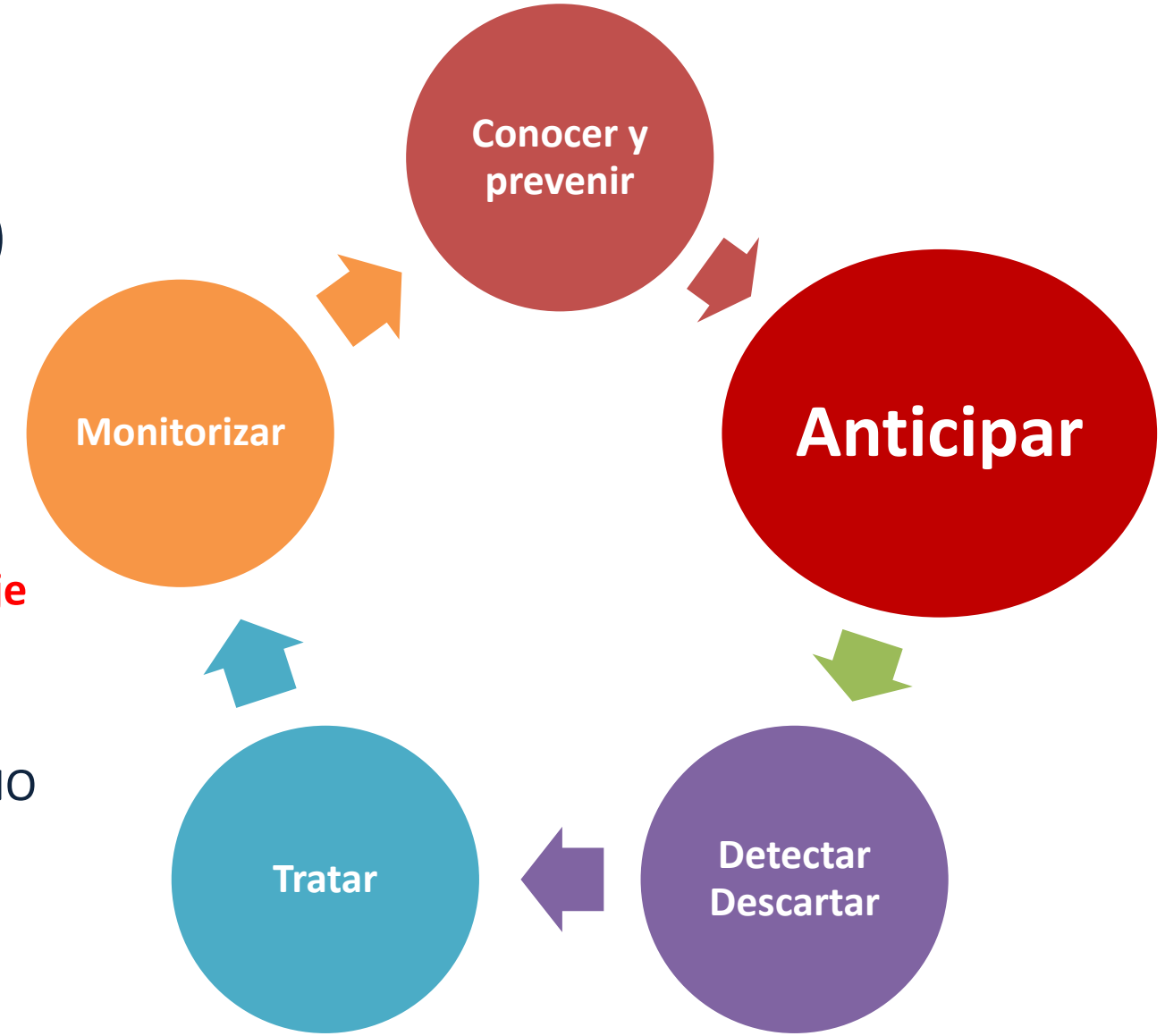
TRASPLANTADOS (renal 50% rechazo)

Insuf renal / hepática /cardiovasc moderadas NO contraindican*

Weber JS et al. The Oncologist 2016

Postow MA et al. NEJM 2018

- ✓ Seguros y EAs leves (80%)
- ✓ **Importancia de sospecha y abordaje precoz MULTIDISCIPLINAR**
- ✓ Tratamiento inmunomoduladores NO modifica pronóstico oncológico

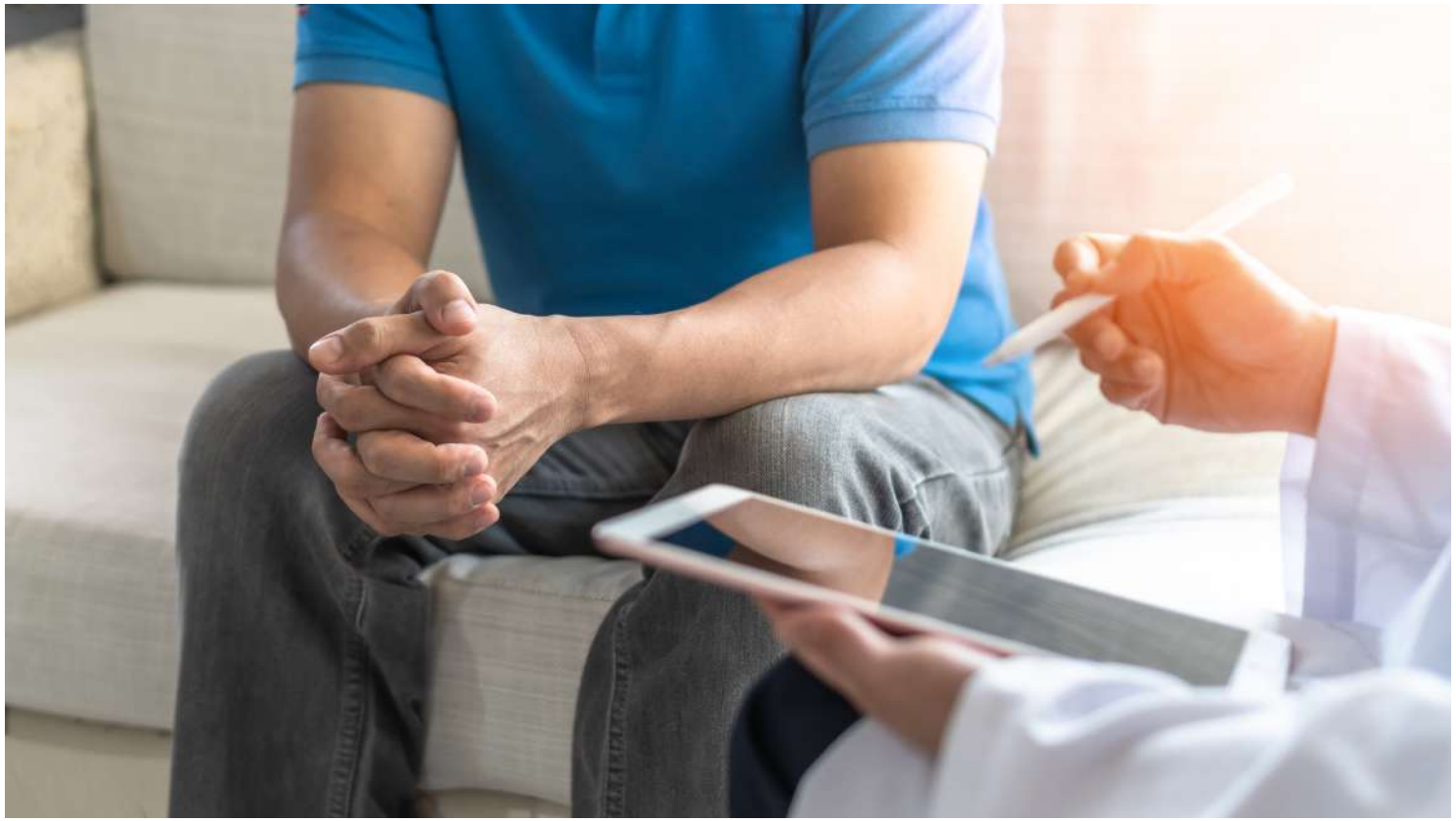


Champiat et al. Ann Oncol 2016;27:559-574

INMUNOTERAPIA CON INHIBIDORES DE PUNTOS DE CONTROL

PACIENTE & MÉDICO/ENFERMERÍA: Alertar de posibles signos / síntomas

CIRCUITOS CONTACTO!



Monitorización:

Basal

- **ECG – AP INTERÉS!!!!**
- **Test embarazo***
- **Hemograma, HbA1**
- **Coagulación**
- **VSG, PCR**
- **Bioquímica GLUCOSA, hepato-renal, LDH y electrolitos**
- **Lipasa, amilasa, CPK**
- **Orina reciente (prot/creat)**
- **TSH, T4L,** cortisol basal, testosterona/estradiol* + FSH/LH
- **Serologías VIH, VHB, VHC**
- Autoinmunidad*
- ProPNT – ECG*
- Quantiferon / PPD*

Antes de cada tratamiento

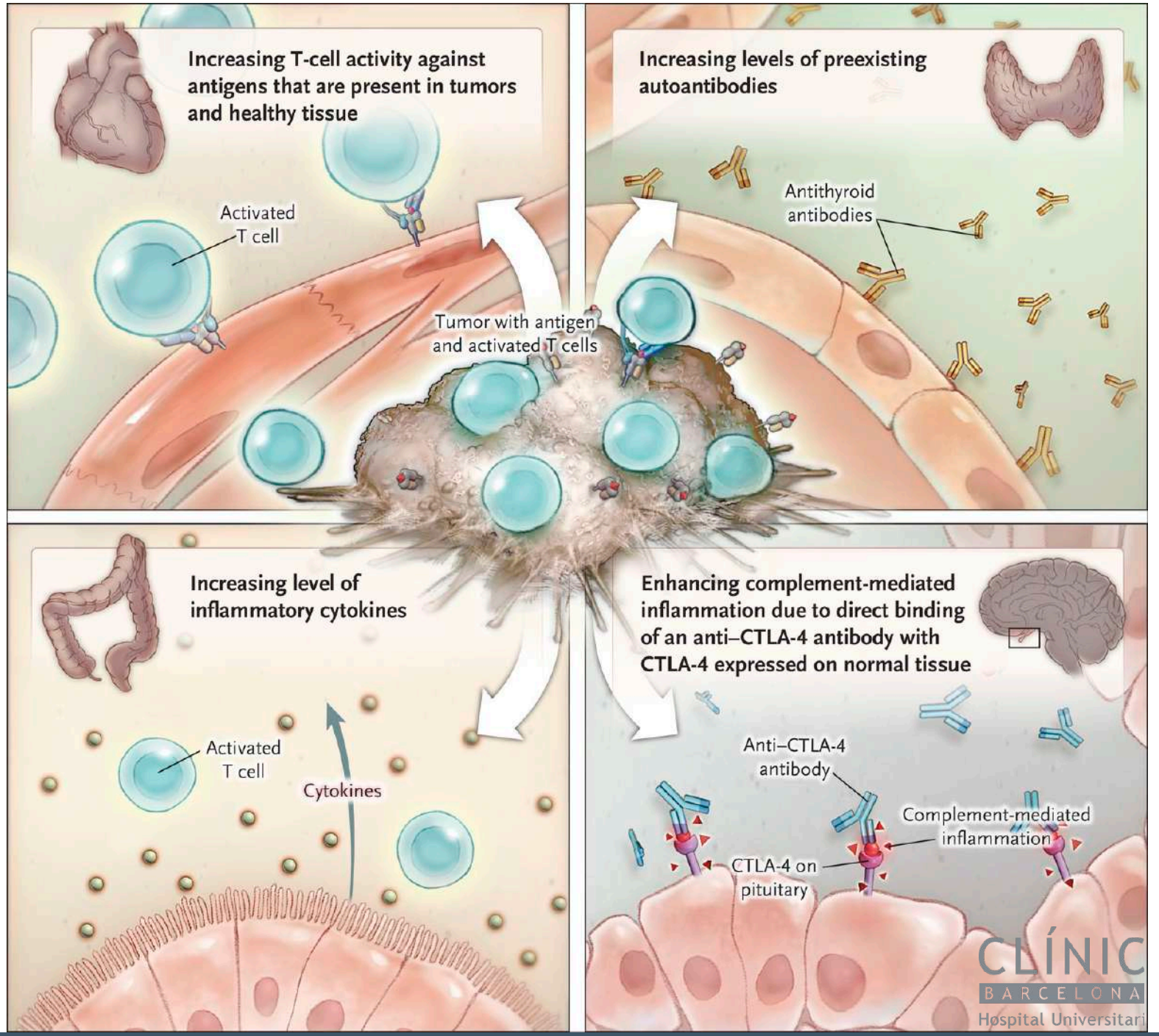
- Hemograma
- Coagulación
- VSG, PCR
- Bioquímica hepato-renal, LDH y electrolitos
- Lipasa, amilasa, CPK
- Orina reciente (prot/creat)
- **TSH, T4L**

- **+ según síntomas/signos: hormonal, autoinmunidad, serologías, metab óseo,…**
- **DESCARTAR INFECCIONES, RECAÍDA, PROCESOS DE BASE…**

Lo que vendrá….

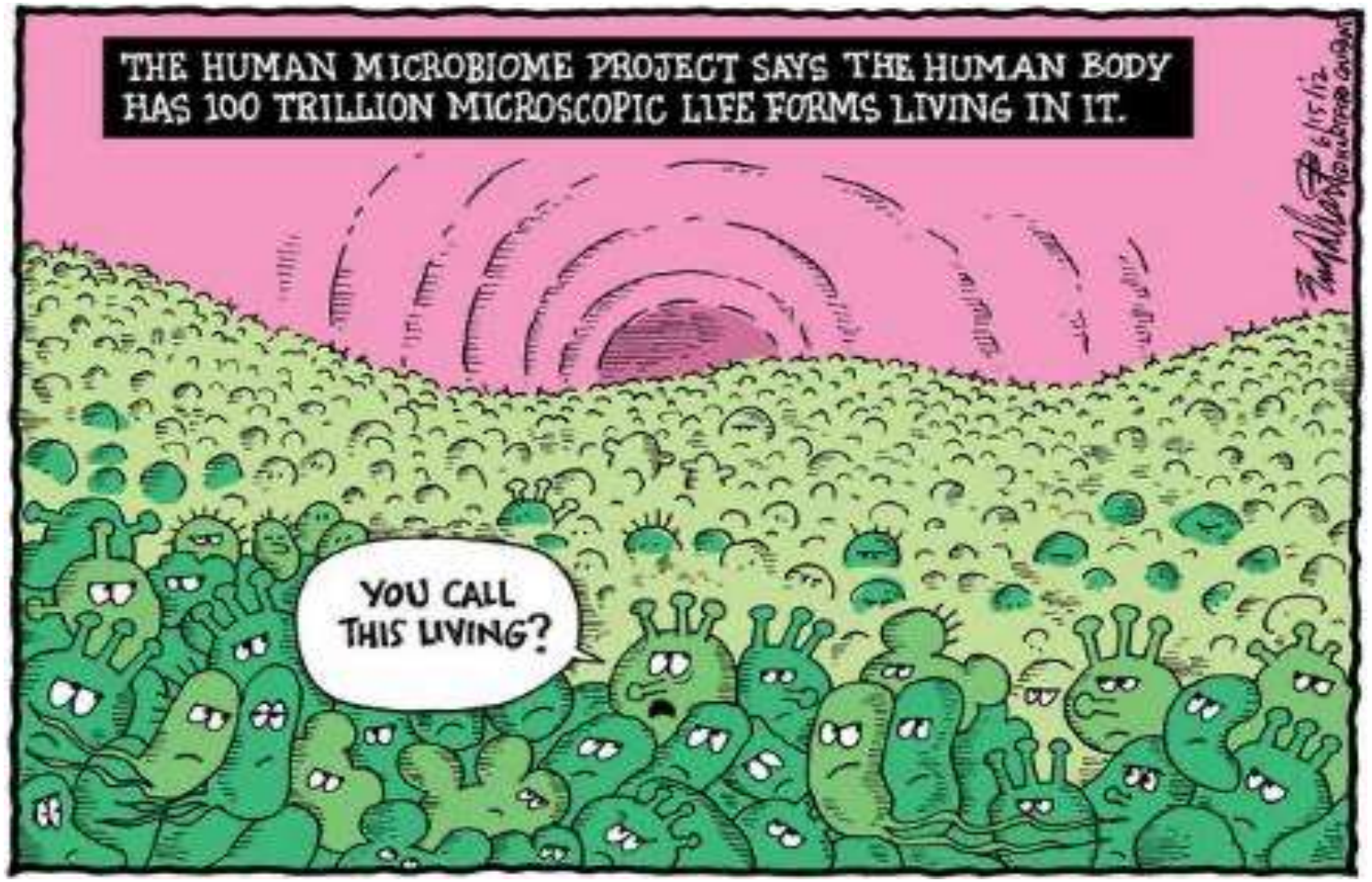
DIFERENTE RESPUESTA Y TOXICIDAD DEPENDE DE…

TUMOR - ÓRGANO DIANA
PACIENTE…
FARMACO-GENÉTICA…?



Postow, N Engl J Med 2018

Biomarcadores riesgo Microbiota Antibióticos ?



Wolchok JD. Cancer Immun 2010
Chaput N. Ann of Oncol 2017

Efecto adverso = marcador pronóstico?

Efecto adverso = marcador pronóstico?

Cancer Treatment Reviews 92 (2021) 102134

Contents lists available at ScienceDirect

Cancer Treatment Reviews

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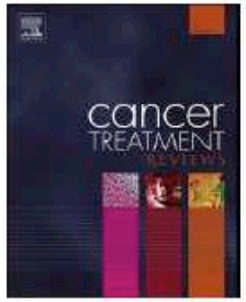


Systematic or Meta-analysis Studies

Association between immune-related side effects and efficacy and benefit of immune checkpoint inhibitors – A systematic review and meta-analysis

Syed Hussaini [a], Rania Chehade [b], Ronald Gabriel Boldt [c], Jacques Raphael [a], Phillip Blanchette [a], Saman Maleki Vareki [c,d,e,*], Ricardo Fernandes [a,e,*]

Efecto adverso = marcador pronóstico?

S. Hussaini et al. Cancer Treatment Reviews 92 (2021) 102134

Study or Subgroup	log[Hazard Ratio]	SE	irAE+ Total	irAE- Total	Weight	Hazard Ratio IV, Fixed, 95% CI
Abu-Sbeih et al 2019	-0.5798	0.1591	173	173	43.5%	0.56 [0.41, 0.76]
Chan et al 2019	-0.7765	0.3537	33	49	8.8%	0.46 [0.23, 0.92]
Dick et al 2016	-0.7985	0.3651	75	11	8.3%	0.45 [0.22, 0.92]
Eggermont et al 2020	-0.4943	0.2282	381	633	21.1%	0.61 [0.39, 0.95]
Indini et al 2019	-0.755	0.3021	102	71	12.1%	0.47 [0.26, 0.85]
Nakamura et al 2017	-1.3863	0.4189	9	26	6.3%	0.25 [0.11, 0.57]
Total (95% CI)			773	963	100.0%	0.51 [0.42, 0.63]

Heterogeneity: Chi² = 4.13, df = 5 (P = 0.53); I² = 0%
Test for overall effect: Z = 6.38 (P < 0.00001)

Hazard Ratio IV, Fixed, 95% CI

0.05 0.2 1 5 20
Favours irAE+ Favours irAE-

Progression Free SURVIVAL

Study or Subgroup	log[Hazard Ratio]	SE	irAE+ Total	irAE- Total	Weight	Hazard Ratio IV, Fixed, 95% CI
Abu-Sbeih et al 2019	-0.6349	0.1973	173	173	58.7%	0.53 [0.36, 0.78]
Dick et al 2016	-0.7985	0.3207	75	11	22.2%	0.45 [0.24, 0.84]
Indini et al 2019	-0.9676	0.3812	102	71	15.7%	0.38 [0.18, 0.80]
Nakamura et al 2017	-1.8971	0.8212	9	26	3.4%	0.15 [0.03, 0.75]
Total (95% CI)			359	281	100.0%	0.46 [0.35, 0.62]

Heterogeneity: Chi² = 2.63, df = 3 (P = 0.45); I² = 0%
Test for overall effect: Z = 5.07 (P < 0.00001)

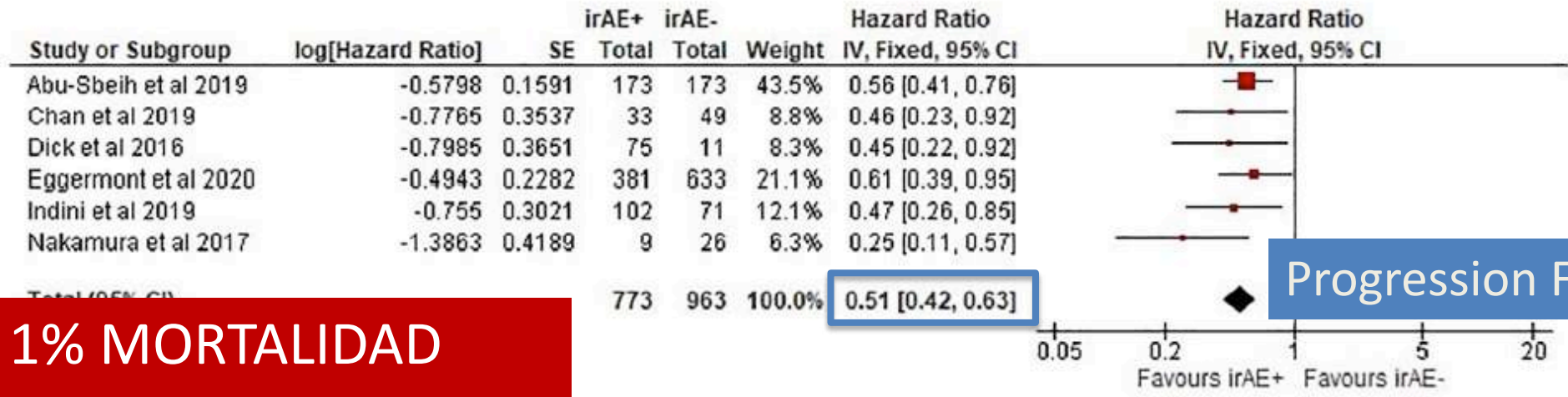
Hazard Ratio IV, Fixed, 95% CI

0.02 0.1 1 10 50
Favours irAE+ Favours irAE-

Overall SURVIVAL

Efecto adverso = marcador pronóstico?

S. Hussaini et al. Cancer Treatment Reviews 92 (2021) 102134



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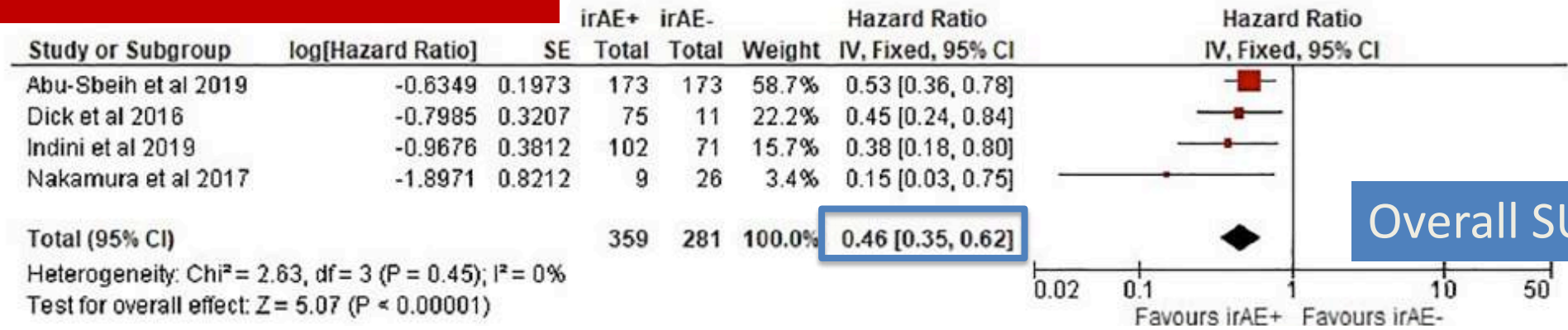
			773	963	100.0%	0.51 [0.42, 0.63]

Progression Free SURVIVAL

1% MORTALIDAD DIRECTA POR RAMim



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Heterogeneity: Chi² = 2.63, df = 3 (P = 0.45); I² = 0%
Test for overall effect: Z = 5.07 (P < 0.00001)

Overall SURVIVAL

Nuevo perfil efectos adversos

Indicaciones + SPV

+ duración terapias

Dermatológicos: más frecuentes!!

Amplio espectro de “ *-ITIS*”

Globalmente bien tolerados

Cualquier momento, mayoria 3-4m, incluso finalizada

Riesgo POTENCIALES – MULTIDISCIPLINAR!

UNIVERSITAT DE BARCELONA

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ccarrera@clinic.cat