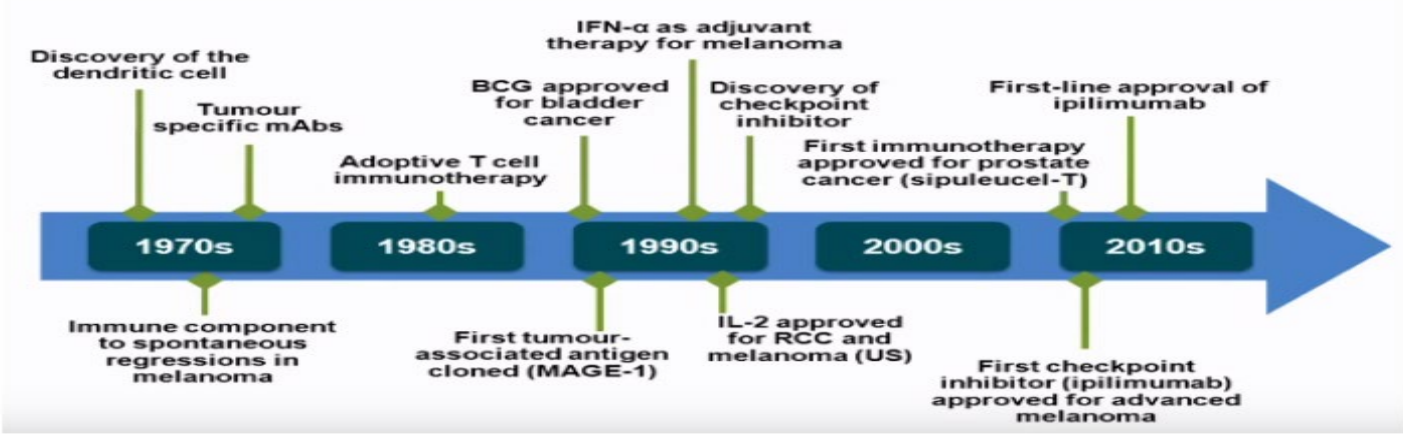
Manifestaciones digestivas autoinmunes de los fármacos inhibidores de checkpoint

Mar Riveiro-Barciela

Vall d'Hebron Barcelona Campus Hospitalari

ciberehd

Impacto de la inmunoterapia



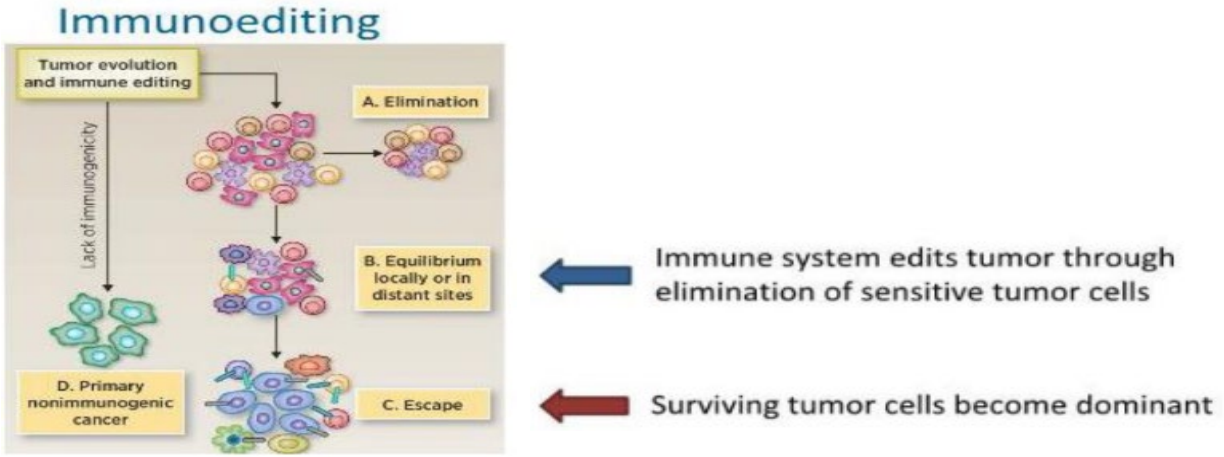
El desarrollo de la inmunoterapia ha revolucionado el pronóstico de los pacientes oncológicos

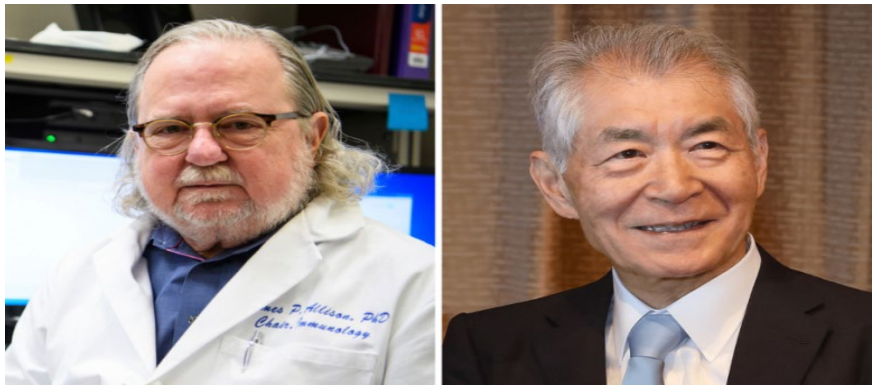
Actualmente se considera que los inhibidores de *checkpoint* podrían tener un efecto beneficioso en más de 17 tumores diferentes

Postow MA et al. NEJM 2018;378:158-68;
Johnson DB, et al.Lancet Oncol. 2020 ;21(8):e398-e404

Cancer immunoediting

Relación dual entre el sistema inmune y el crecimiento tumoral



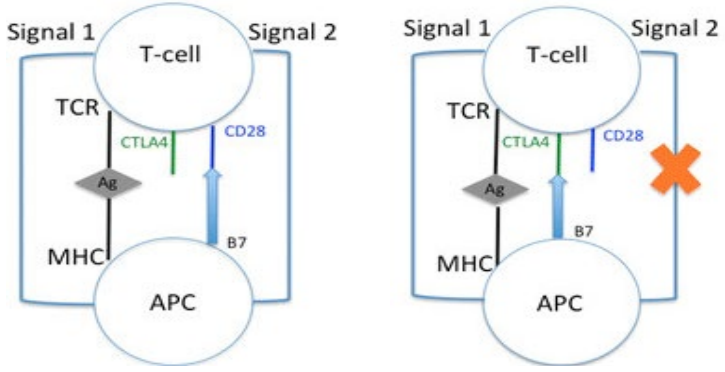


Dr JP Allison

Dr T Honjo

"Puntos de control inmune"

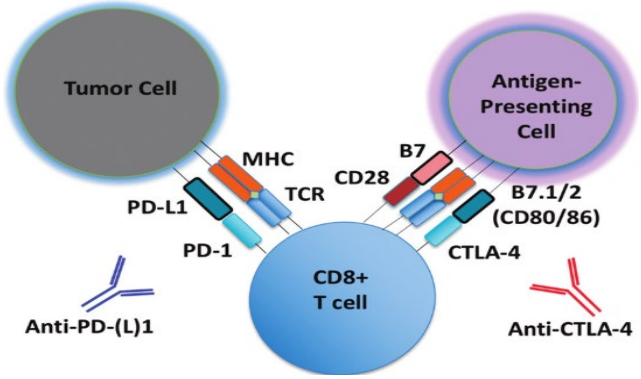
Activación de respuesta inmune celular.



Inhibición de los checkpoint inmunes

↓

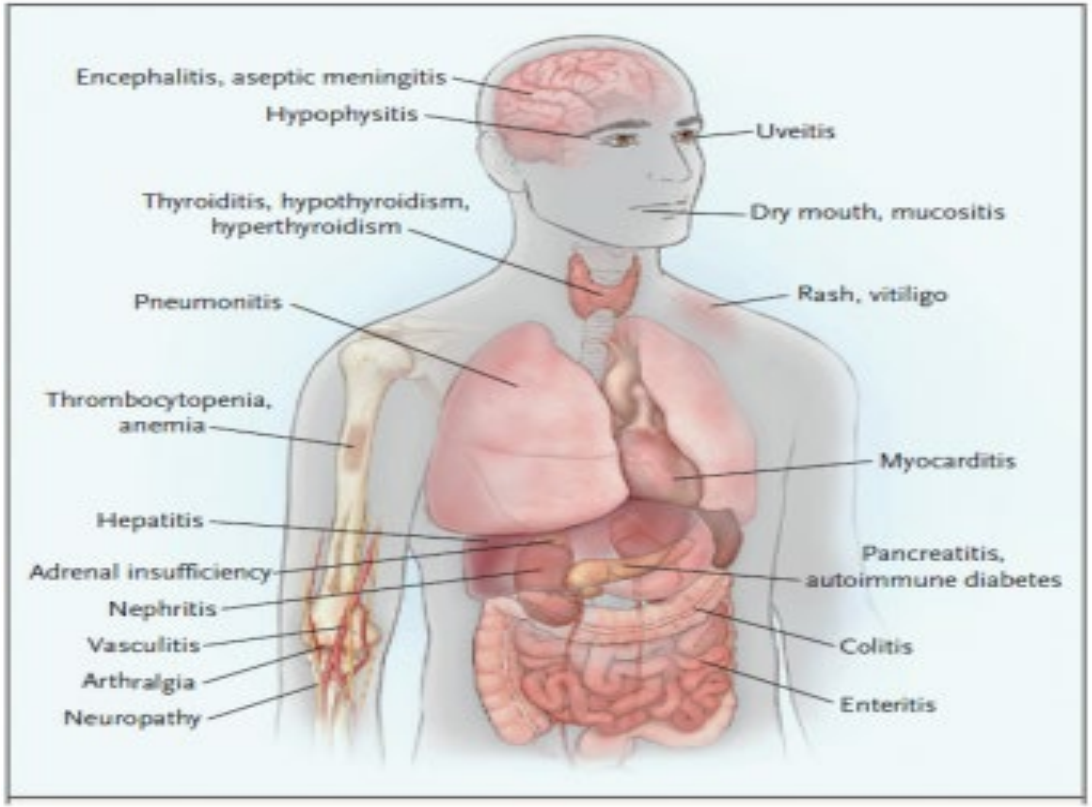
Activación del sistema inmune



Trapani JA, Darcy PK. *Aust Fam Physician* 2017
Dushyanthen et al *BMC Medicine* 2015
Pusztai et al *Clin Cancer Res* 2016

Eventos adversos inmunomediados

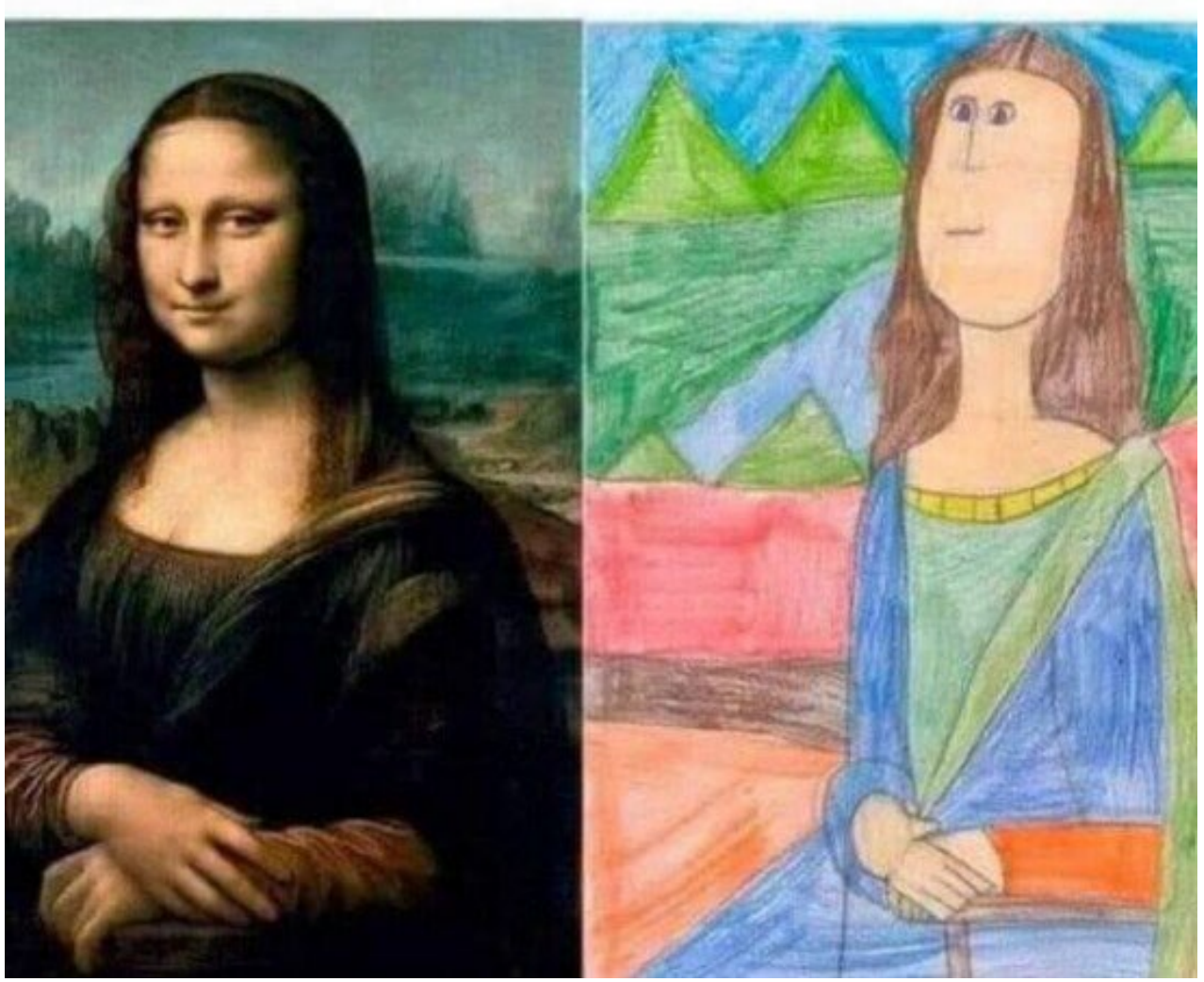
Incidencia global eventos adversos: **54% - 76%**
(datos de un meta análisis con 36 ensayos fase II/III)



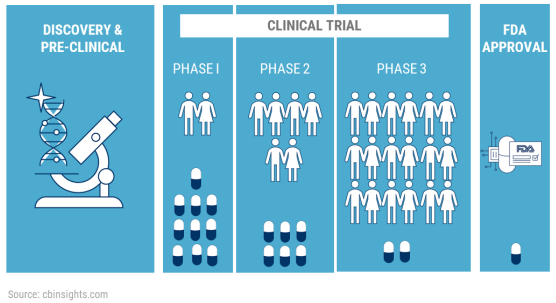
Michael A. Postow et al. NEJM 2018;378:158-68

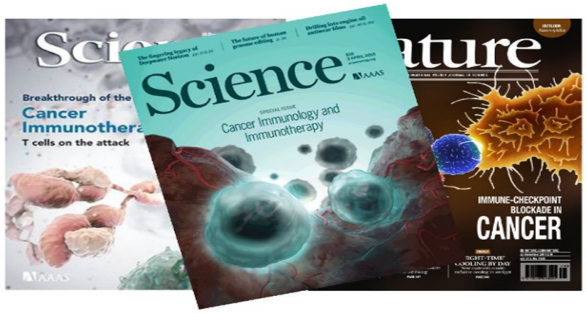
Eventos adversos inmunomediados

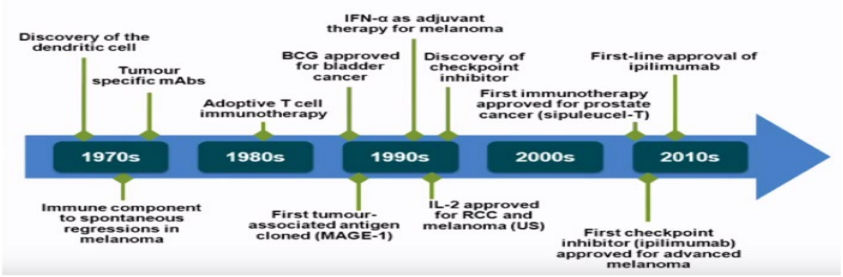
Ensayos clínicos	Práctica clinica real



Desarrollo de las guías clinicas de inmunoterapia







EAs immuno-mediados (irAes)

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE
European Society for Medical Oncology
Guidelines

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY

- Definición
- Gravedad
- Tratamiento

Toxicidades de la inmunoterapia:
De los ensayos clínicos a la práctica clínica diaria

Principales diferencias sobre los EAs inmuno-mediados (irAEs):

- Definición y gravedad
- Manejo de los irAEs graves

  Diagnóstico

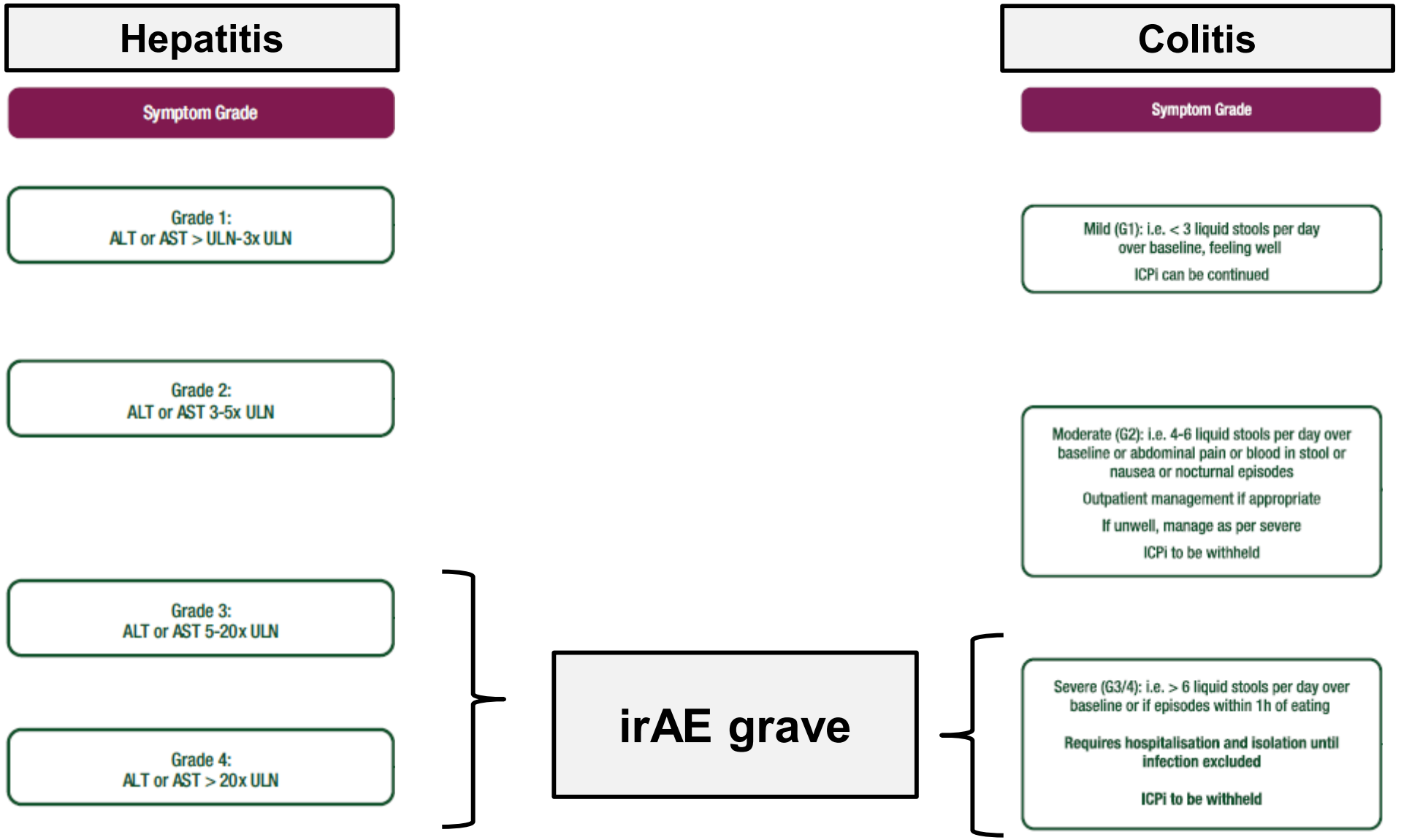
  Tratamiento
- Posibilidad de retratamiento tras un irAE grave

Eventos adversos inmuno-mediados (irAEs) digestivos

- Tanto la **hepatitis** como la **diarrea** están entre los irAEs más frecuentes
- Incidencia 5-10% (1-2% grado 3) en monoterapia
- Monoterapia: más frecuente si anti-CTLA-4
- Incidencia 25-30% combinación Ipilimumab + Nivolumab
- Desarrollo en semanas hasta meses después de la finalización del tratamiento

Haanen, et al. Ann Oncol 2017 1;28(suppl4):iv119-iv142

Definición de los irAEs digestivos según las guías Oncología



Haanen, et al. Ann Oncol 2017 1;28(suppl4):iv119-iv142

Gravedad de los irAEs digestivos: hepatitis

Hepatitis

Symptom Grade

Grade 1:
ALT or AST > ULN-3x ULN

Grade 2:
ALT or AST 3-5x ULN

Grade 3:
ALT or AST 5-20x ULN

Grade 4:
ALT or AST > 20x ULN

Valoración de la gravedad de las hepatitis agudas
✓ Bilirrubina
✓Coagulación

EASL (hep. Agudas)

Hepatitis aguda grave

Coagulopatía (INR > 1.5)

Hepatitis fulminante

- Ausencia lesión hepática crónica
- Coagulopatía (INR > 1.5)
- Encefalopatía hepática

DILI severity index

Category	Severity	Description
1	Mild	Elevated alanine aminotransferase/ alkaline phosphatase (ALT/ALP) concentration reaching criteria for DILI* but bilirubin concentration <2× upper limit of normal (ULN)
2	Moderate	Elevated ALT/ALP concentration reaching criteria for DILI* and bilirubin concentration ≥2× ULN, or symptomatic hepatitis
3	Severe	Elevated ALT/ALP concentration reaching criteria for DILI*, bilirubin concentration ≥2× ULN, and one of the following: • International normalized ratio ≥1.5 • Ascites[73] and/or encephalopathy, disease duration <26 weeks, and absence of underlying cirrhosis[31] • Other organ failure considered to be due to DILI
4	Fatal or transplantation	Death or transplantation due to DILI

Aithal GP, et al. Clin Pharmacol Ther . 2011;89(6):806-15
EASL Clinical Practical Guidelines on the management of acute (fulminant) liver failure. J Hepatol 2017 66(5):1047-1081

Gravedad de los irAEs digestivos: colitis

Colitis

Symptom Grade

Mild (G1): i.e. < 3 liquid stools per day over baseline, feeling well

ICPi can be continued

Moderate (G2): i.e. 4-6 liquid stools per day over baseline or abdominal pain or blood in stool or nausea or nocturnal episodes

Outpatient management if appropriate

If unwell, manage as per severe

ICPi to be withheld

Severe (G3/4): i.e. > 6 liquid stools per day over baseline or if episodes within 1h of eating

Requires hospitalisation and isolation until infection excluded

ICPi to be withheld

Importancia:

✓Diarrea: principal causa de suspension de los anti-CTLA-4

✓ Mortalidad estimada: 1%

La gravedad se debe valorar según los hallazgos endoscópicos:

➢**La endoscopia con biopsia es necesiaria:**

- ✓ Confirmación diagnóstica
- ✓ Descartar infección por CMV o afectación metastásica

➢ **Baja correlación entre el grado de las diarreas y los hallagos endoscópicos o histológicos**

➢ **Úlceras o pancolitis ⟶ 80% necesidad de Infliximab**

Utilidad de la endoscopia precoz (y derivación al especialista) en caso de diarrea ante la posibilidad de requerir terapia biológica

Haanen, et al. Ann Oncol 2017 1;28(suppl4):iv119-iv142; Geukes Foppen MH, et al. ESMO Open.2018;3:e000278.23

Importancia del diagnóstico diferencial

Elevación de transaminasas durante la inmunoterapia

≠

Hepatitis inmunomediada

DILI related to immunotherapy?

Ischemia?

Virus

Gallstones?

Bacterias

Infections?

Acute hepatitis during immunotherapy

Biliary obstruction?

Malignancy

Vermin

DILI related to other drugs?

HILI

Progression of the disease?

Isoniazide

Hepatitis en pacientes tratados con anti-PD1

491 pacientes tratados con **pembrolizumab** → **70 (14.3%) daño hepático*** → **20 (28.6%) hepatitis inmunomediada**

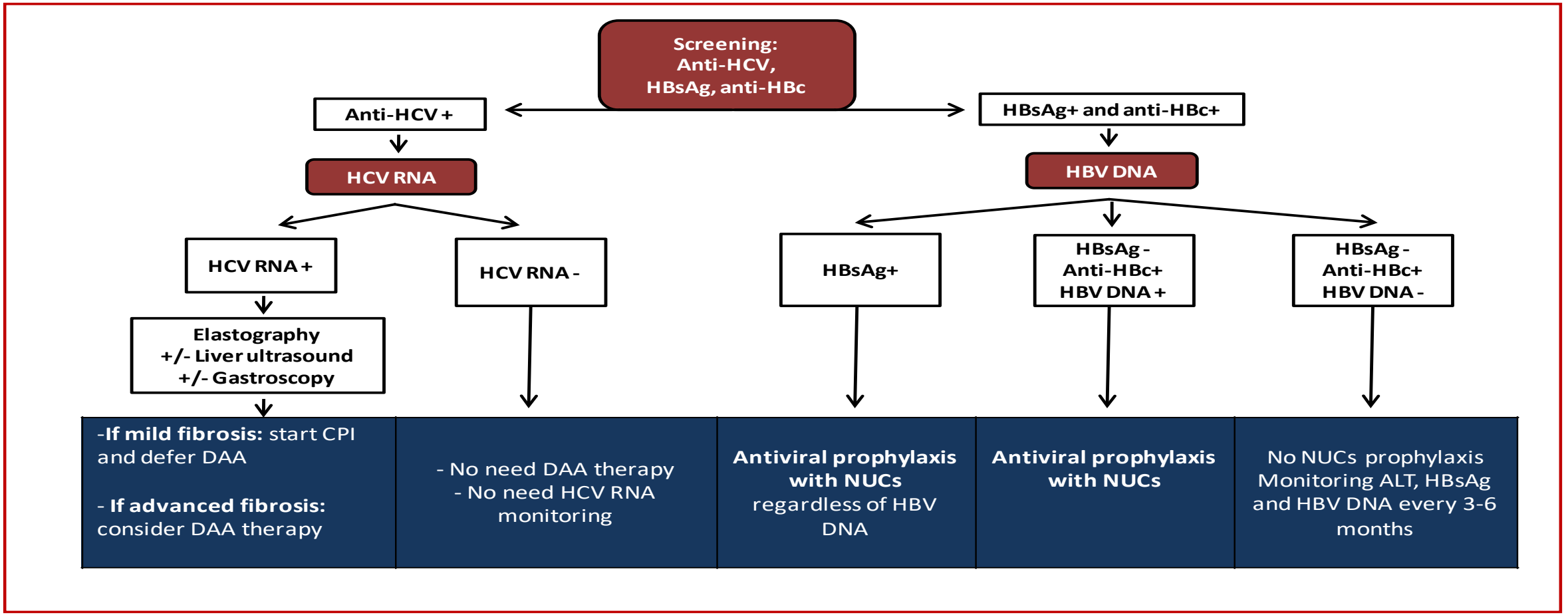
AP&T Alimentary Pharmacology & Therapeutics WILEY

Liver injury is most commonly due to hepatic metastases rather than drug hepatotoxicity during pembrolizumab immunotherapy

***Criterios daño hepatico (DILIM):**
ALT ≥ 5x LN; Fosfatasa alc. x2 LN; Bilirrubina ≥ 2.5 mg/dL

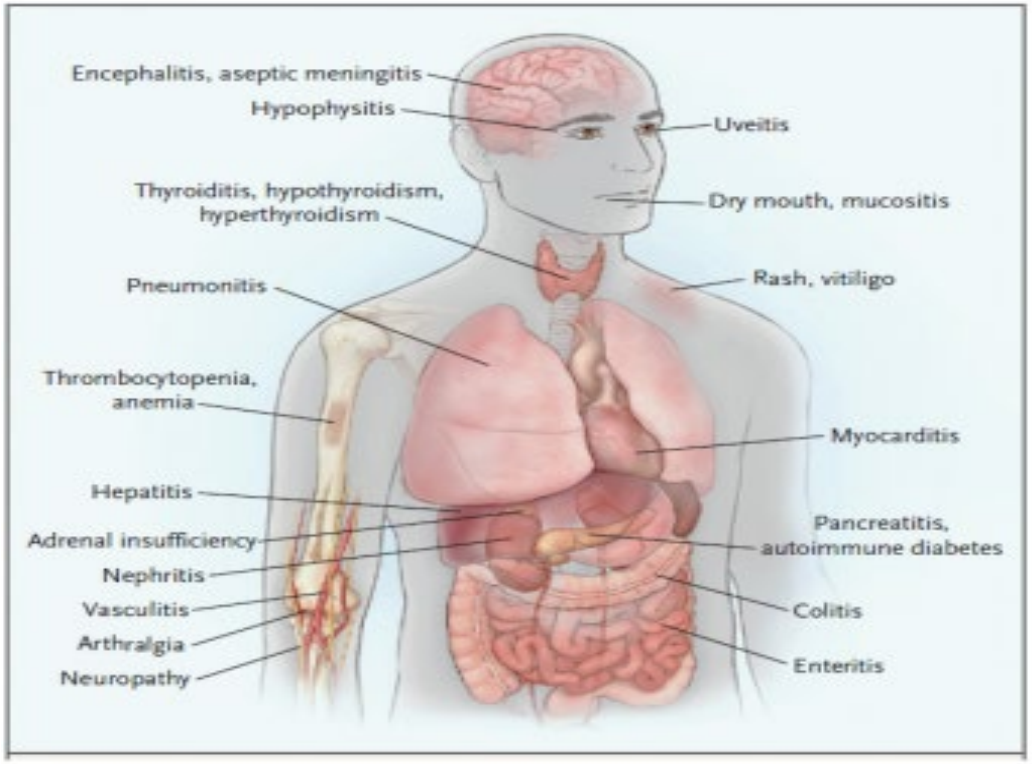
Tsung I, et al. Aliment Pharmacol Ther 2019 ;50(7):800-808

Manejo de las hepatitis virales en pacientes candidatos a inmunoterapia



González-Cao M, et al. J Immunother Cancer. 2021;9(3):e001664

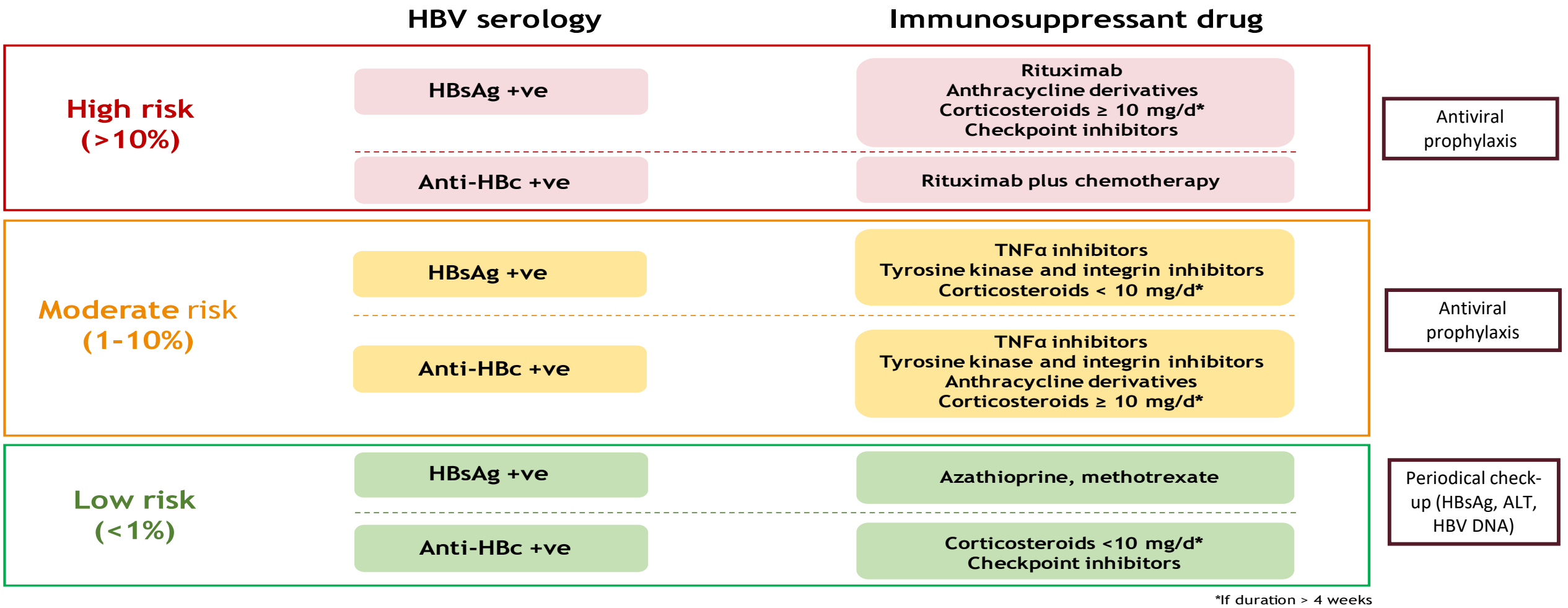
Immune-related adverse events



Backbone of treatment of the majority of irAEs

Michael A. Postow et al. NEJM 2018;378:158-68

Management of HBV infection in immunocompromised patients



*If duration > 4 weeks

Modified from Loomba R, Liang TJ. Gastroenterology. 2017

Biopsia en hepatitis inmunomediada

- **Guías ESMO/ASCO** → valorar si ausencia de respuesta a corticoides
- Hallazgos histológicos alterados por la administración de corticoides
- **Potenciales utilidades:**

Caracterización de la lesión hepática e identificación fármaco causal

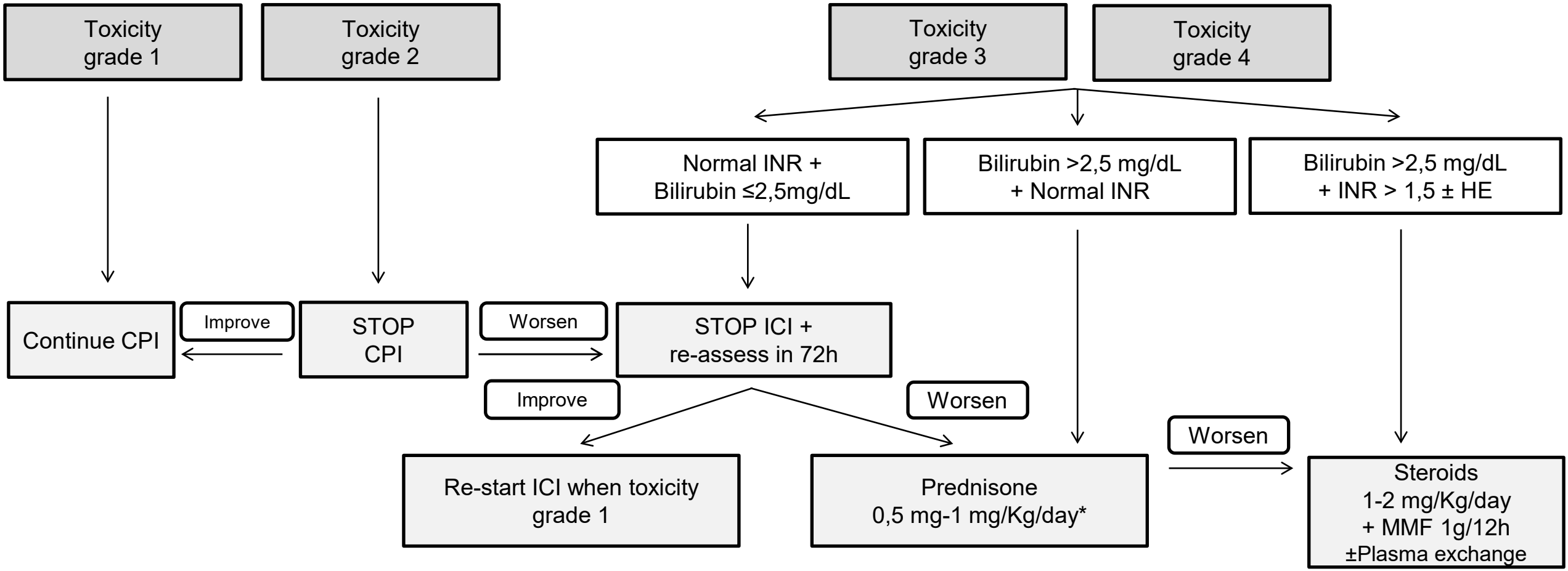
Anti-PD-1/PD-L1

Hepatitis lobular

Anti-CTLA-4

Hepatitis granulomatosa
Granulomas con anillo de fibrina
Endotelitis vena central

Tratamiento de las hepatitis inmunomediadas



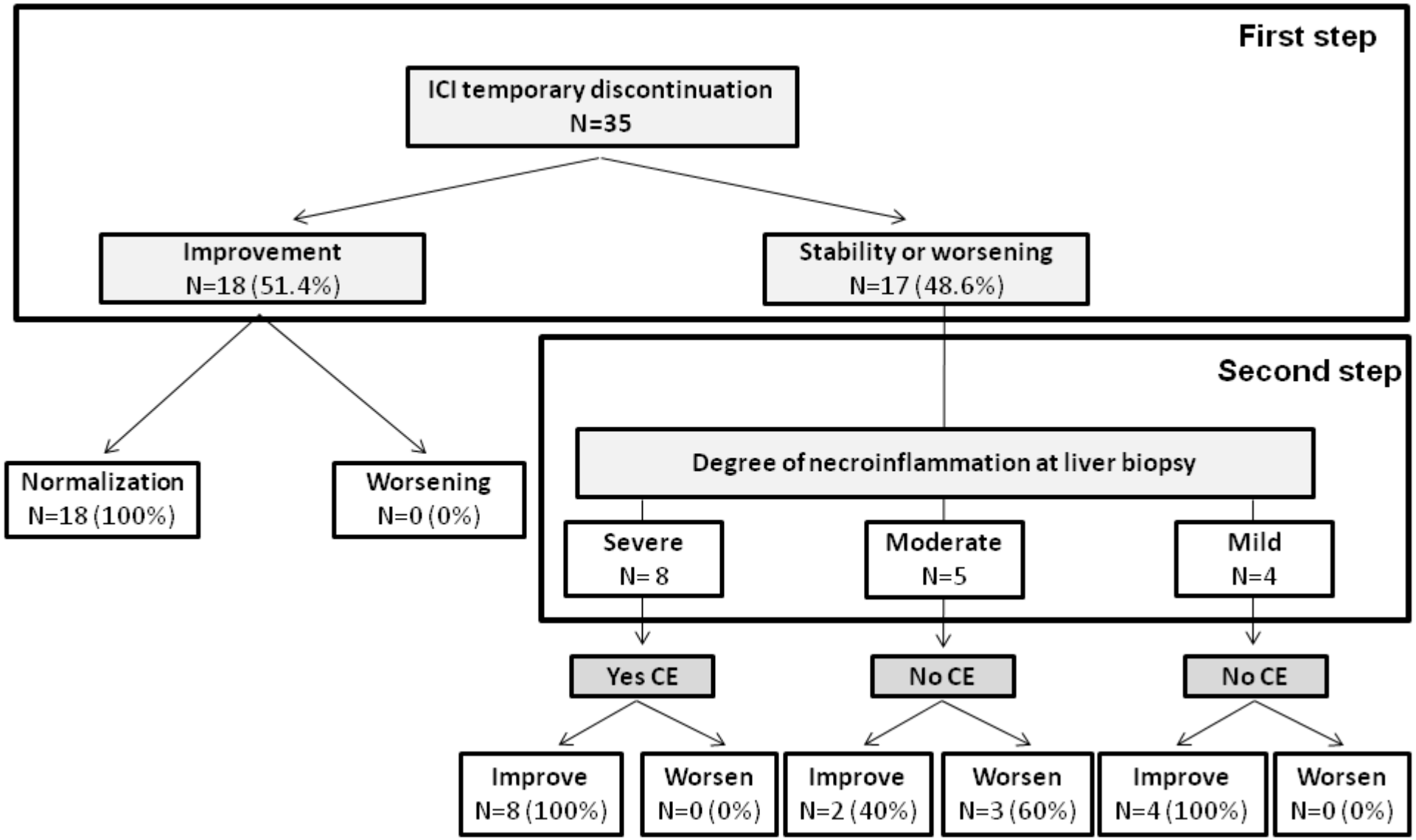
*** Assess the performance of liver biopsy, mainly in case of alternative diagnosis (other drugs, cancer infiltration...)**

If bilirubin levels > 2.5 mg/dL, the beginning of steroids should NOT be delayed more than 48h

HE: Hepatic encephalopathy

Documento de consenso de la AEEH-SEPD-AEG-GETECCU para el manejo de las toxicidades digestivas de los inhibidores de checkpoint

Biopsia en hepatitis inmunomediada



Submitted

If corticoids are needed, which dosage?

ESMO

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY

"For grade 3 or 4 transaminase or total bilirubin elevation, ICI therapy should be permanently discontinued, and corticosteroids started at 1–2 mg/kg/day (methyl)prednisolone or equivalent"

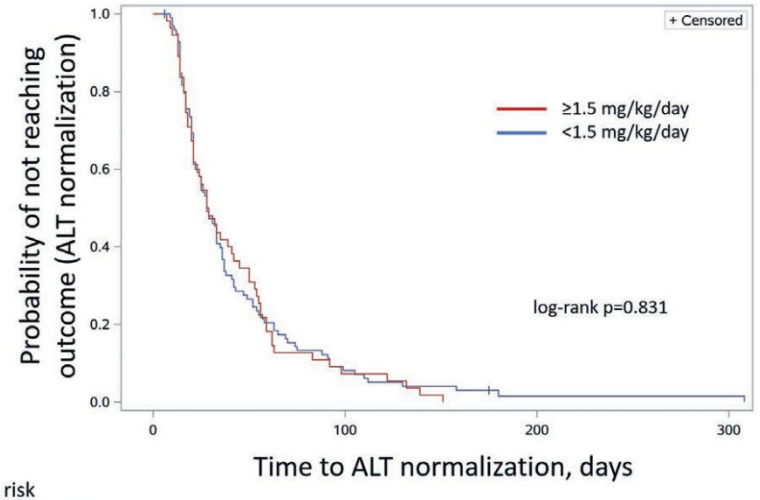
Effect of corticosteroid dosing on outcomes in high-grade immune checkpoint inhibitor hepatitis

HEPATOLOGY

AASLD

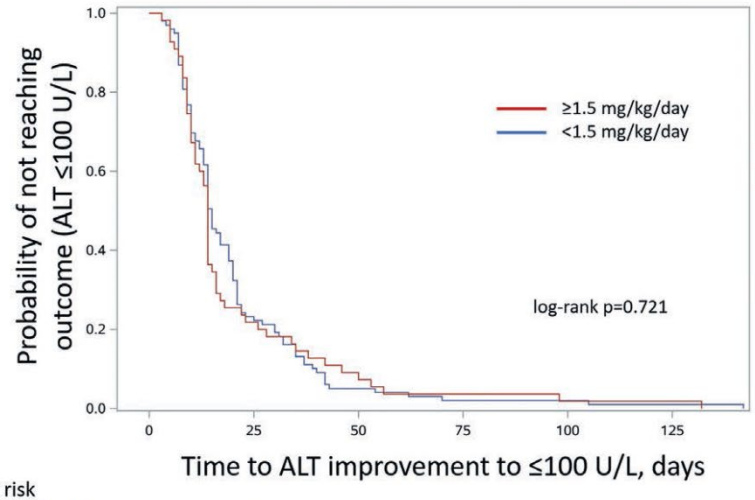
Retrospective study including subjects with ≥ grade-3 hepatitis treated with *methylprednisolone:*

- 87 received dose ≥1.5 mg/kg
- 128 received dose <1.5 mg/kg



No. at risk

<1.5 mg/kg/day	99	8	1	0
≥1.5 mg/kg/day	55	4	0	0



No. at risk

<1.5 mg/kg/day	99	22	5	2	2	1
≥1.5 mg/kg/day	55	12	4	2	1	1

Li M, et al. Hepatology. 2022;75(3):531-540

Retratamiento tras una hepatitis inmunomediada

Toxicity grade 1	Toxicity grade 2

Reiniciar tratamiento tras normalización o mejoría a grado 1

Possibility of retreatment after a severe irAE

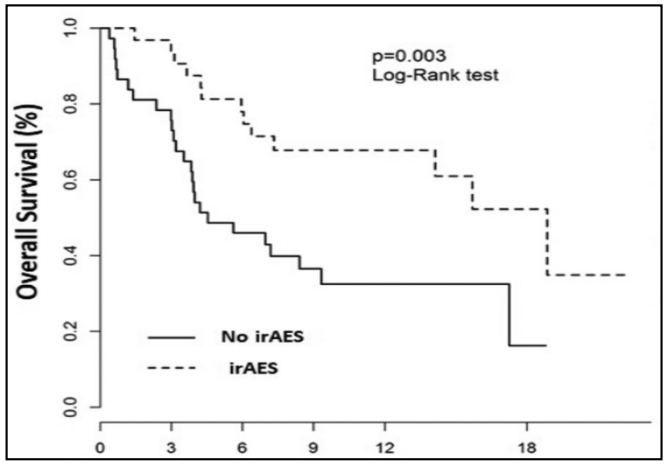
ESMO

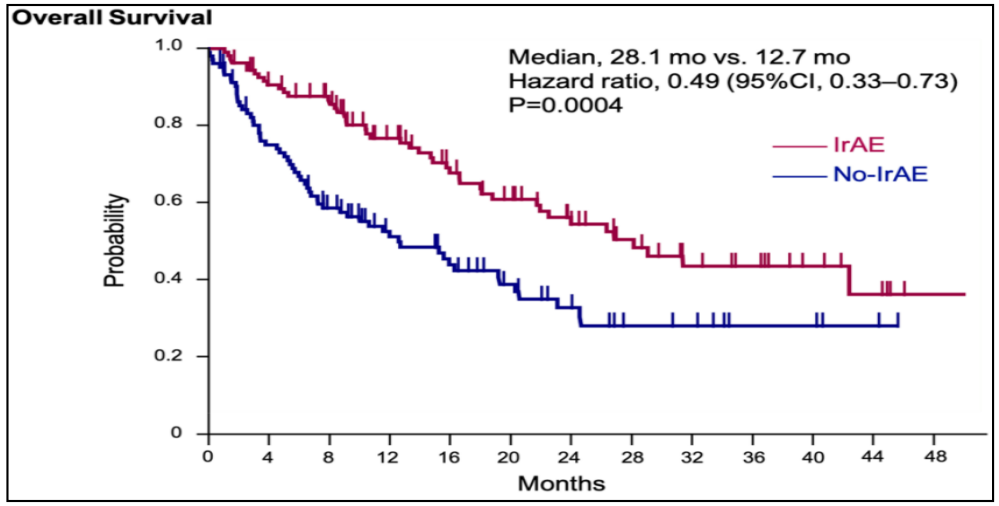
ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY

"For grade 3 or 4 transaminase or total bilirubin elevation, ICI therapy should be permanently discontinued, and corticosteroids started at 1–2 mg/kg/day (methyl)prednisolone or equivalent"

Clinical practice

The higher severity of the irAEs, the better prognosis



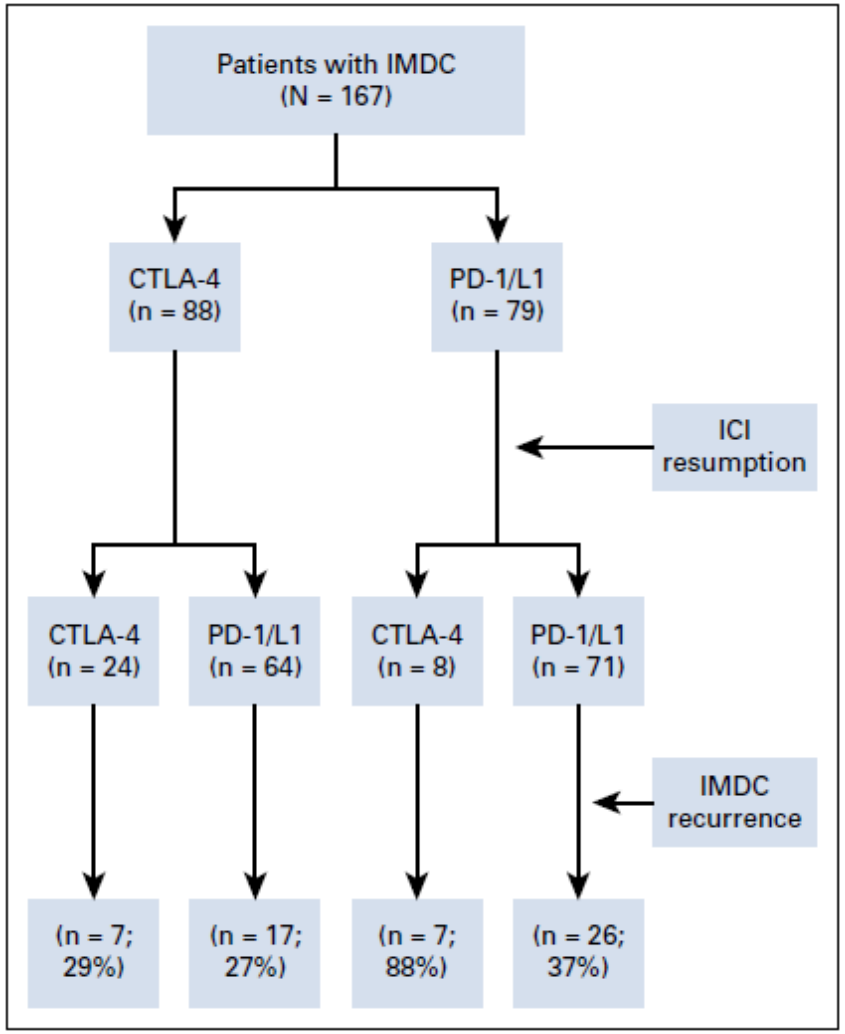


Risk of recurrence of the irAE??

Shimozaki K, et al. Cancer Manag Res 2020 16;12:4585-4593; Bouhlel L, et al. Bull Cancer. 2020;107(9):946-58

Retreatment with CPIs after and immune-related colitis

N= 167 with diarrhea and/or immune-related colitis (≥ grade 2) retreated with CPIs



Global recurrence colitis: 56 (23.7%)

Recurrence colitis grade 3-4: 26 (15.6%)

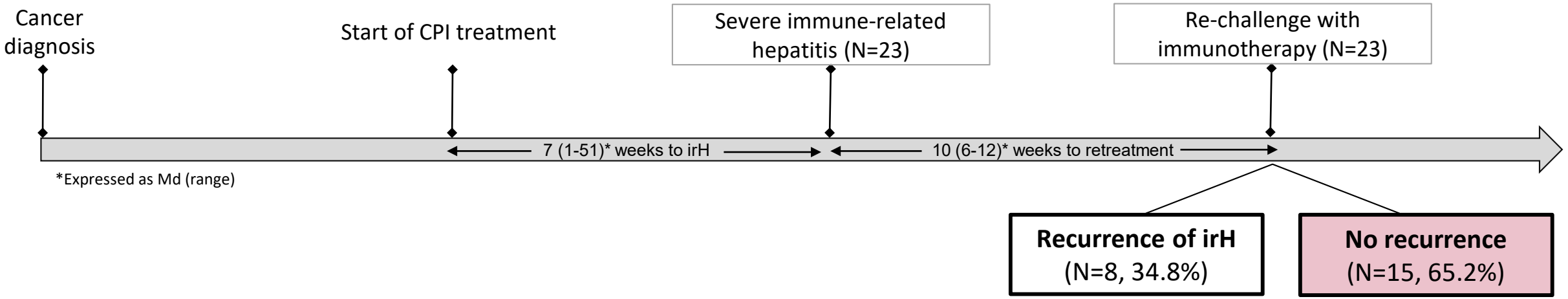
Multivariate analysis of factors associated with recurrence

Covariate	Odds Ratio	95% CI	*P*
Initial ICI type			
Anti–CTLA-4		Reference	
Anti–PD-1/L1	3.45	1.59 to 7.69	.002
ICI type resumed			
Anti–CTLA-4		Reference	
Anti–PD-1/L1	0.30	0.11 to 0.81	.019
Grade of initial diarrhea*			
1		Reference	
2	1.19	0.37 to 3.80	.775
3-4	2.19	0.66 to 7.29	.202
Required immunosuppressive therapy initially	3.22	1.08 to 9.62	.019
Duration of initial IMDC symptoms	1.01	1.00 to 1.03	.031

Abu-Sbeih H, et al. J Clin Oncol . 2019 20;37(30):2738-2745

Retratamiento tras hepatitis inmunomediada grave

Data from a prospective, multicenter, non-interventional Spanish study



	Recurrence (N=8)	Not recurrence (N=15)	*p value*
Underlying autoimmune disease, n(%)	2 (25%)	2 (13.3%)	0.435
CTCAE severe irH **3** **4**	 8 (100%) 0 (0%)	 11 (73.3%) 4 (26.7%)	0.154
Time until retreatment (weeks), Md (range)	9 (5-11)	10 (1-54)	0.342
Corticosteroids at the beginning of retreatment, n(%)	3 (37.5%)	5 (33.3%)	0.596
Normal ALT value at retreatment, n(%)	5 (62.5%)	6 (40.0%)	0.278
Antinuclear antibodies (ANAs) ≥1/80, n(%)	4 (50%)	3 (20%)	0.156
Immunological background[ɣ], n (%)	6 (75%)	4 (26.7%)	0.037

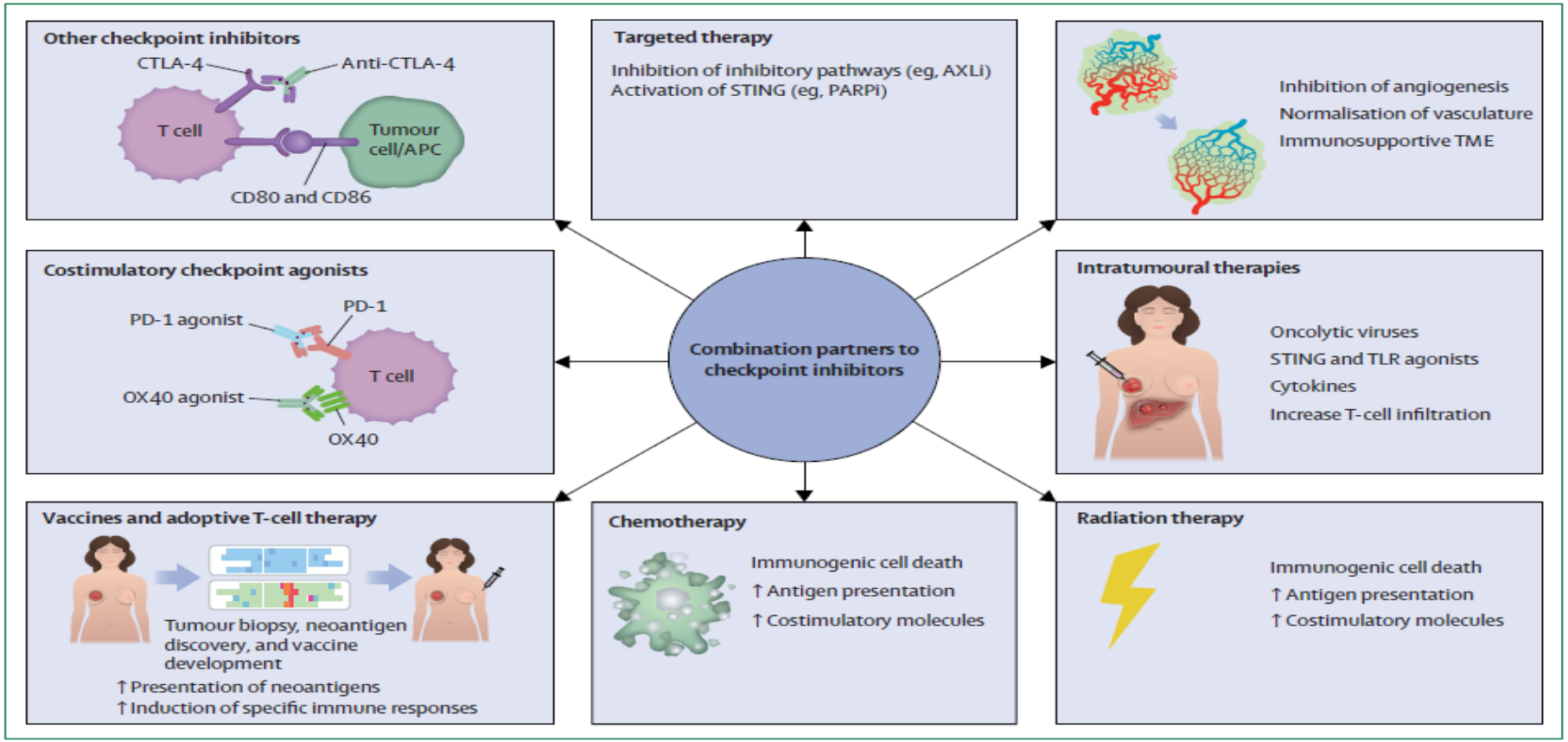
ɣ Defined as underlying autoimmune disorder and/or ANAs ≥1/80

Riveiro-Barciela M, et al. Clin Gastroenterol Hepatol. 2022 26:S1542-3565(22)00403-7

El futuro de la Oncología

Enhancing anti-tumour efficacy with immunotherapy combinations

THE LANCET

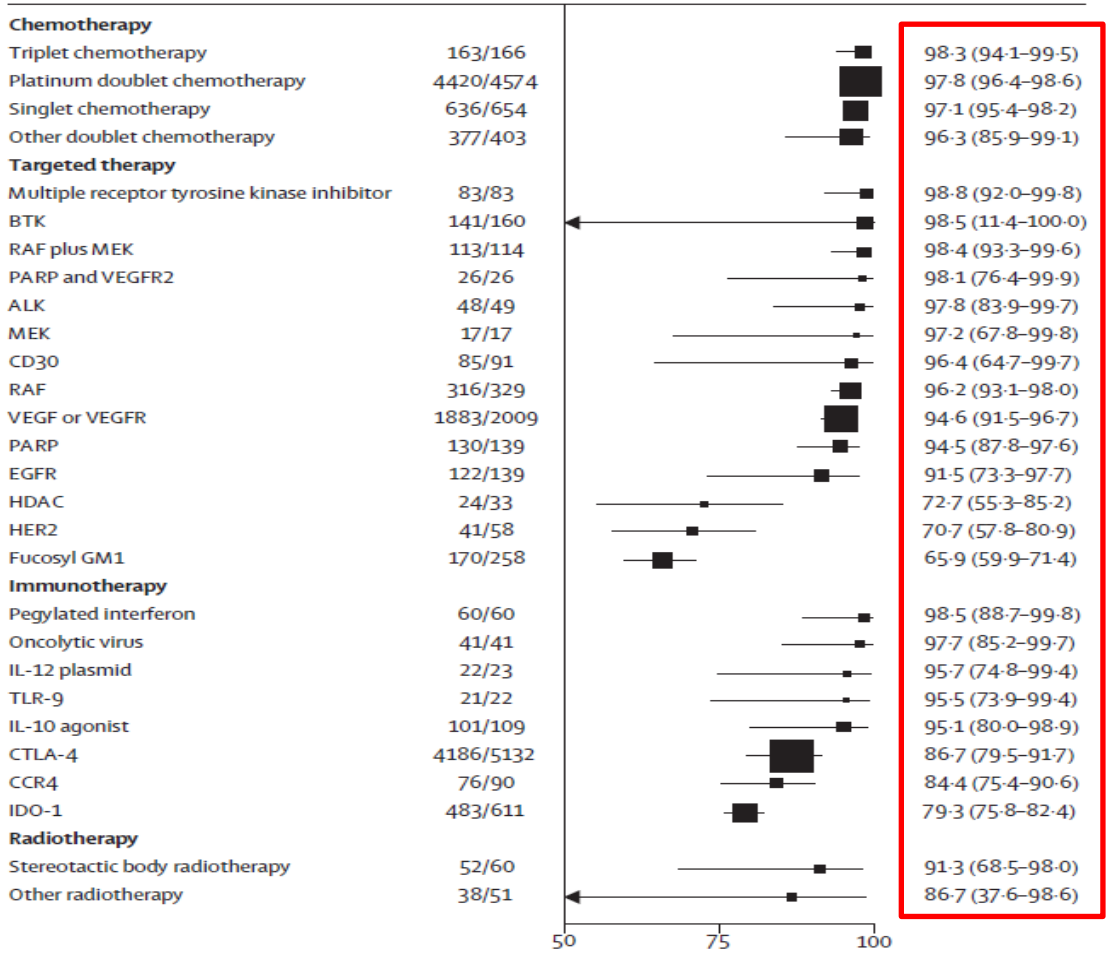


"Although combinations might enhance efficacy, they can also enhance toxicity…"

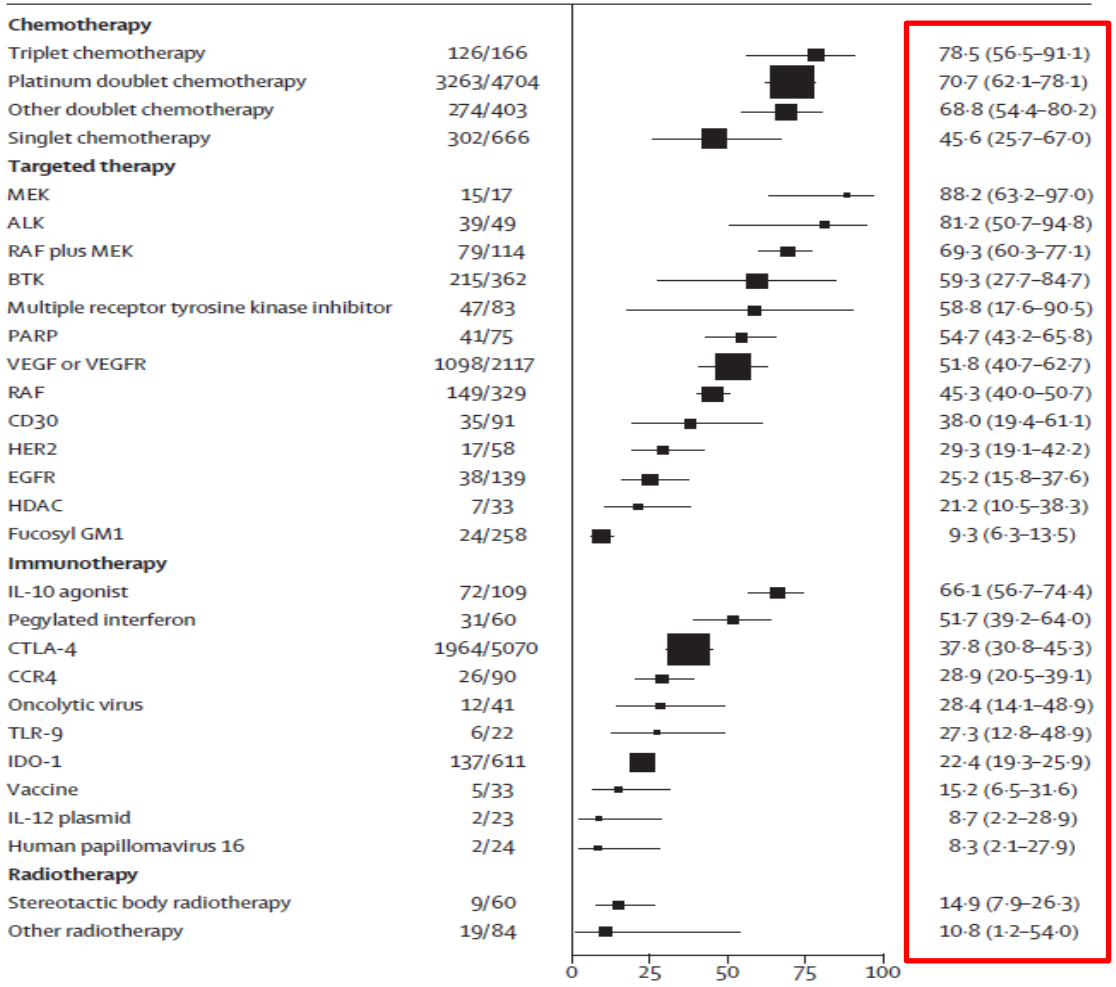
Meric-Bernstam F, et al. Lancet . 2021 13;397(10278):1010-1022

Incidencia de efectos adversos de las combinaciones con anti-PD1 o anti-PD-L1

Todos los grados



Grado 3 y grado 4



Zhou X, et al. Lancet Oncol 2021;22(9):1265-1274

Futuro del manejo de los irAEs

Real-world challenges in the management of irAEs

- **Unexpected presentations**
- **Severity criteria**
- **Fatal or concomitant irAEs**
- **Immunosuppressant therapy**
- **Rechallenge**

Multidisciplinary teams

- Hepatology
- Neurology
- Internal medicine
- **Oncology**
- Dermatology
- Rheumatology
- Cardiology

Riveiro-Barciela M, Felip E, Suarez-Almazor ME. Front Med. 2023

Mensajes para llevar a casa

44 años afecta de neoplasia de recto estadio IV (hepática, pulmonar)

Actualmente 4ª línea de tratamiento dentro de EC (pembro + lenvatinib)

Inicio junio/21--- agosto/21:

- ➢ STOP corticoides. Rápida normalización de transaminasas
- ➢ **Se autoriza continuar en el estudio**
- ➢ Verano 2022: Ciclo 14 de pembro + lenvatinib
- ➢ **AG pre-C14: AST 33, ALT 29**
- ➢ **Respuesta oncológica: Estabilidad**

- Ir
- TC
- IC Hepatología (según protocolo)
- Ampliar estudio +/- biopsia

- **Exclusión EC (hepatitis grado 4)**

ARN VHE 6x10E6 UI/mL

Eventos adversos digestivos inmuno-mediados

- Prevalencia creciente...¡y más que lo será!
- Fundamental ser sistemáticos en el **diagnóstico diferencial** (sobre todo hepatitis)
- Importancia del estudio endoscópico precoz ⟶ Infliximab?
- **Tratamiento** (si función hepática normal):
    1. Suspender inmunoterapia (temporal)
    2. Corticoides (empeoramiento o necroinflamación ≥ moderada)
- **Retratamiento** (individualizar): ¡la recidiva no es universal!