CURSO DE AVANCES EN GASTROENTEROLOGÍA
"BUENAS PRÁCTICAS EN GASTROENTEROLOGÍA"

Hepatitis inmunomediada

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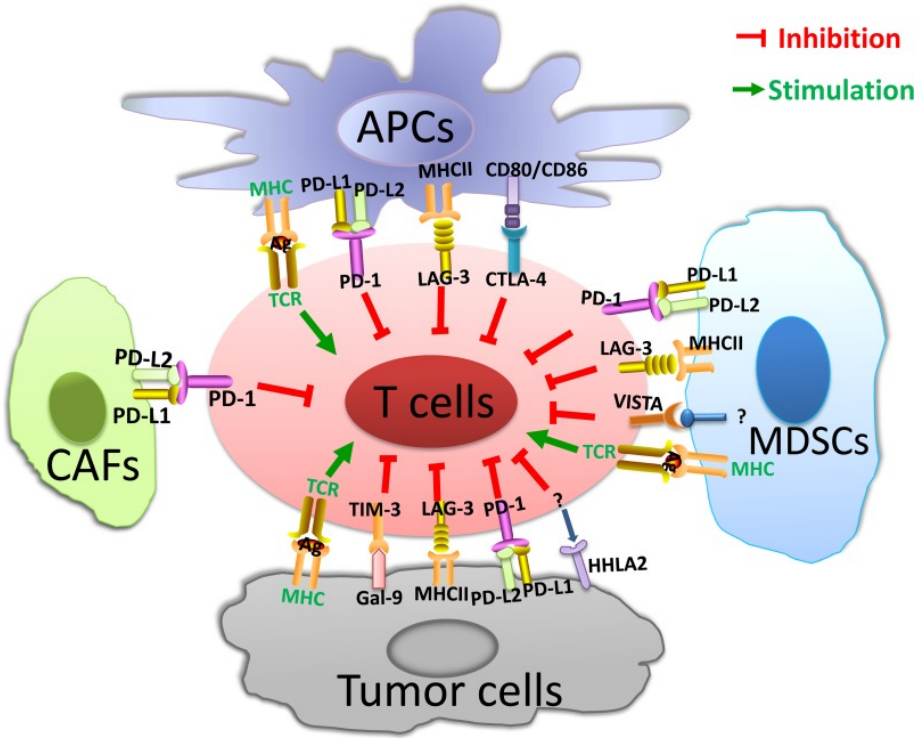
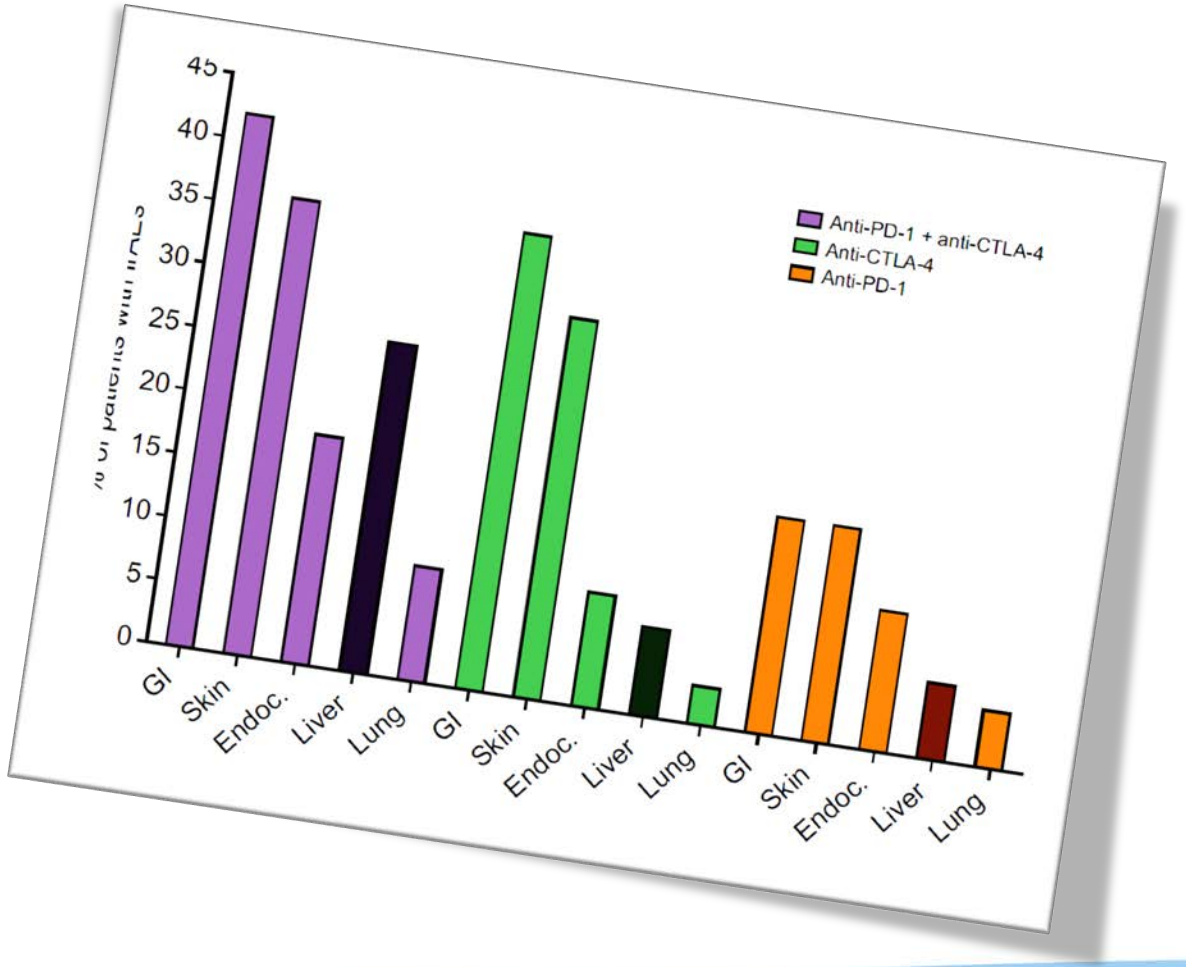
La hepatitis inmunomediada es uno de los tantos eventos adversos inmuno-relacionados que pueden presentarse en los pacientes tratados con IPCI (inhibidores de los puntos de control inmunológico).

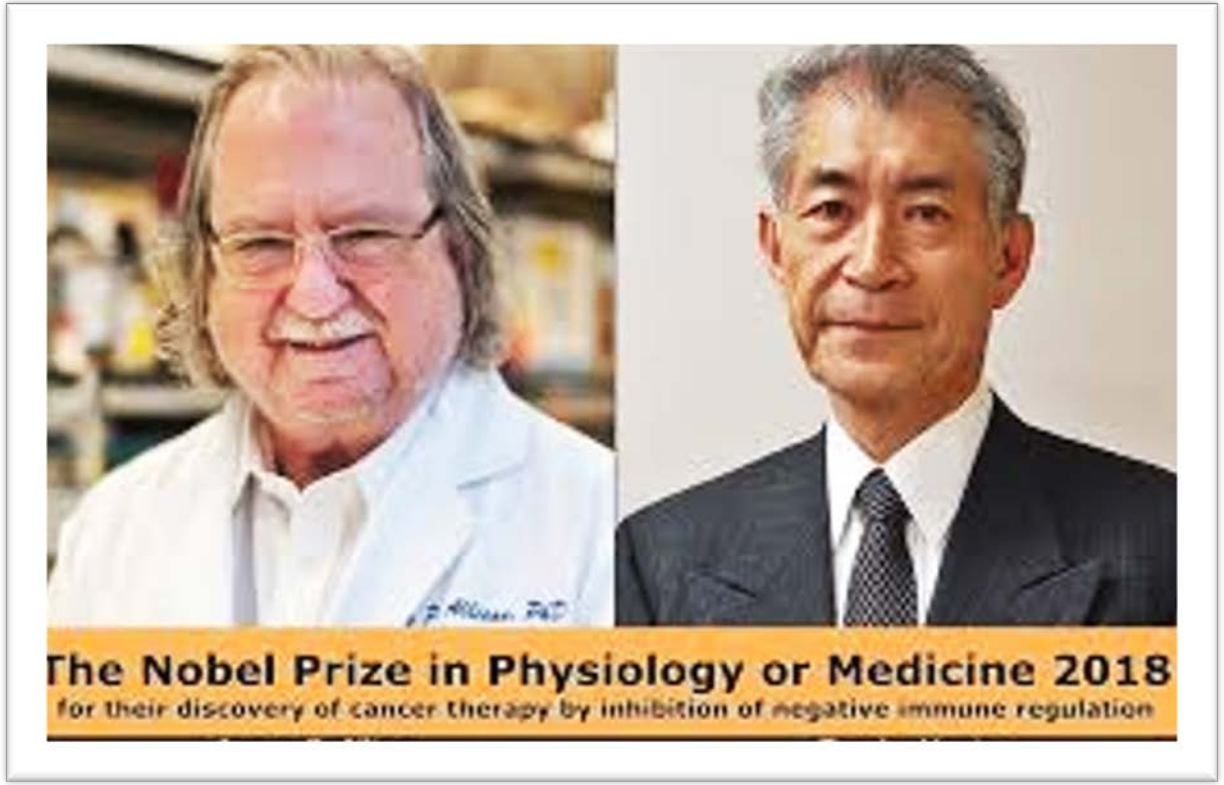




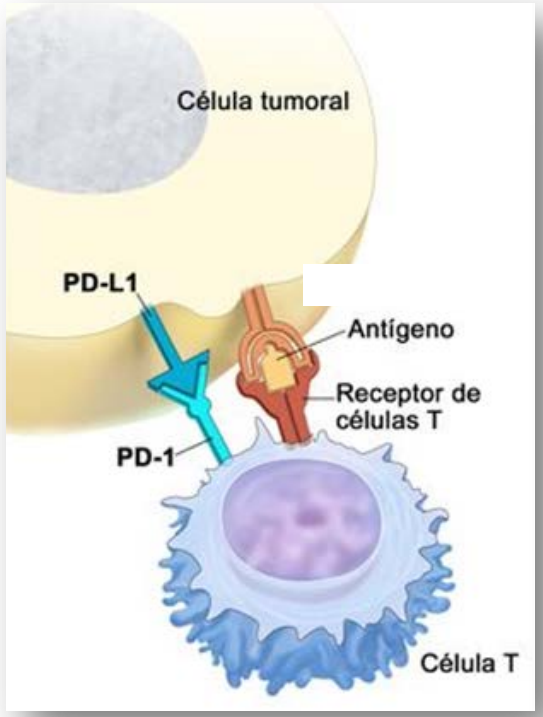
De Martin E et al. J Hep Rep 2020

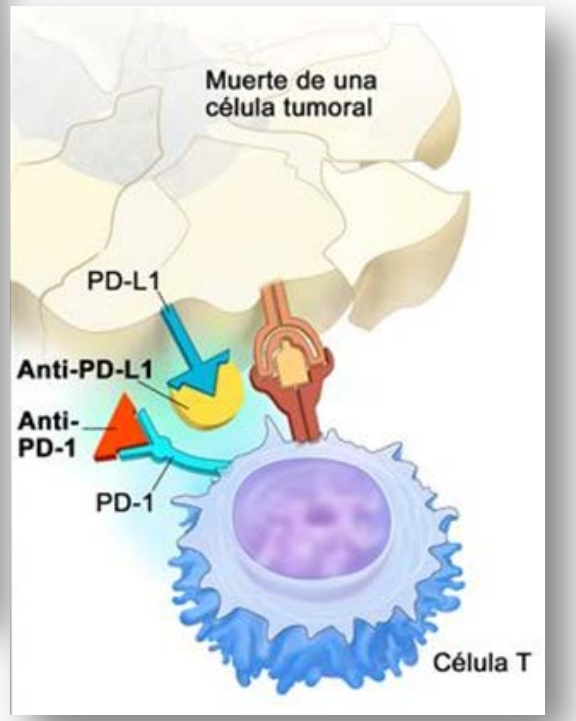
Los IPCI tienen riesgo de toxicidad en varios órganos

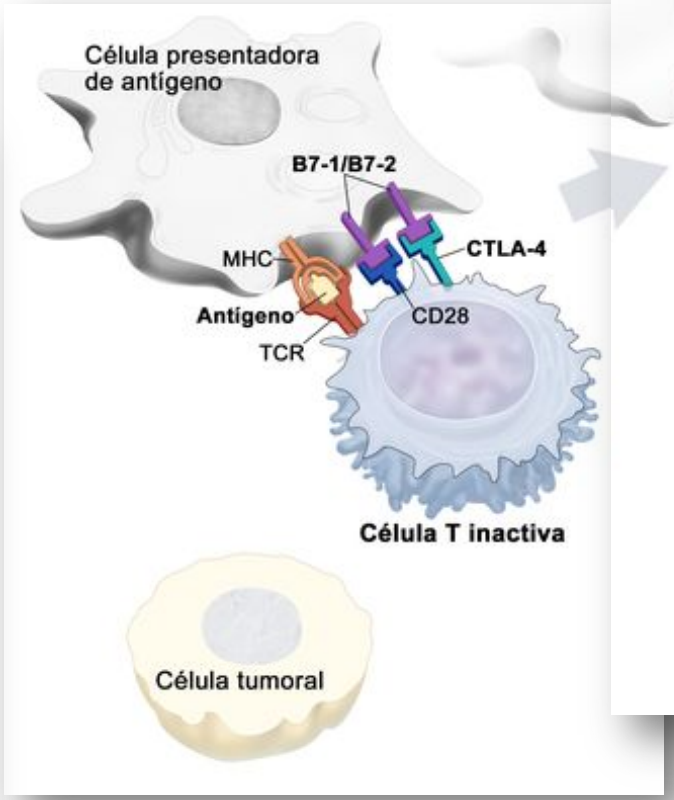
… tratamiento de tumores metastásicos con respuestas durables

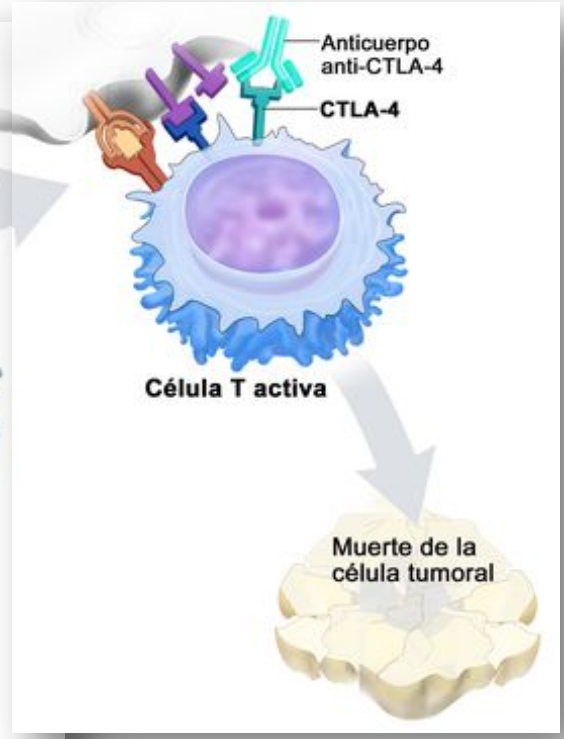


Anti programmed cell death ligand 1
atezolizumab, durvalumab



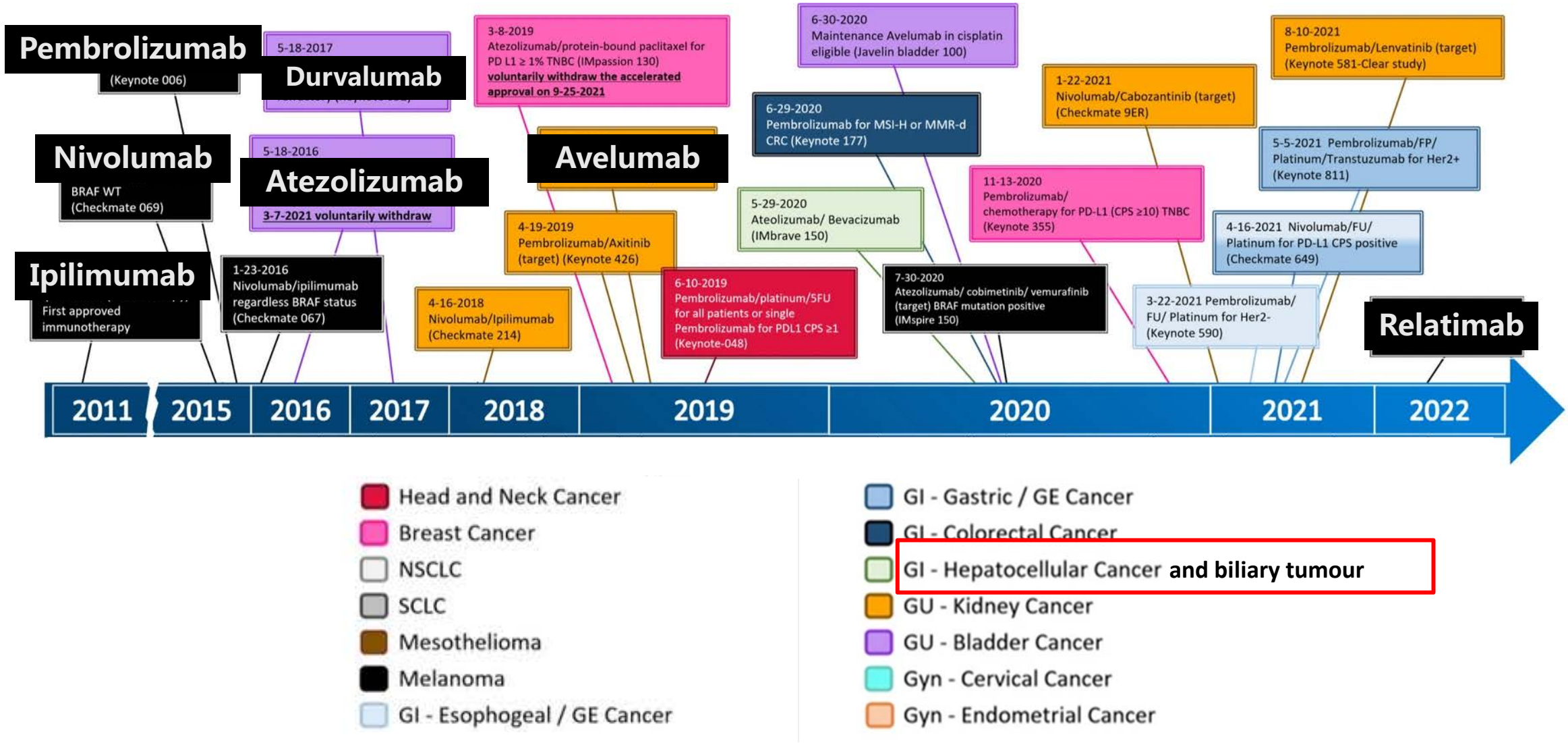






Anti-programmed cell death 1
nivolumab, pembrolizumab

Anti cytotoxic T lymphocyte antigen-4
Ipilimumab



- Head and Neck Cancer
- Breast Cancer
- NSCLC
- SCLC
- Mesothelioma
- Melanoma
- GI - Esophageal / GE Cancer
- GI - Gastric / GE Cancer
- GI - Colorectal Cancer
- GI - Hepatocellular Cancer **and biliary tumour**
- GU - Kidney Cancer
- GU - Bladder Cancer
- Gyn - Cervical Cancer
- Gyn - Endometrial Cancer

Research Article
Cancer

JOURNAL OF HEPATOLOGY

Characterization of liver injury induced by cancer immunotherapy using immune checkpoint inhibitors

Eleonora De Martin[1], Jean-Marie Michot[2], Barbara Papouin[3], Stéphane Champiat[2], Christine Mateus[4], Olivier Lambotte[5], Bruno Roche[1], Teresa Maria Antonini[1], Audrey Coilly[1], Salim Laghouati[6], Caroline Robert[4], Aurélien Marabelle[2], Catherine Guettier[3], Didier Samuel[1,*]

Todos los pacientes tratados con IPCI (536) que desarrollaron hepatitis grado 3* o más (19) fueron referidos a un Centro Hepatológico

(Agosto 2015 a Abril 2017)

Estricto protocolo de descarte (1 pte HVE+) y biopsia hepática (1 con infiltración tumoral y 1 con extensas mtx hepáticas)

16 pacientes con DILI por IPCI (3,5%)

9 casos con PD1/PDL1 (9/413: 2%)

7 casos con CTLA 4 (7/123: 6%)

- ✓14/16 altamente probables, diferentes patrones
- ✓ Latencia: 5 semanas (1 – 49)
- ✓ Fiebre (6), rash (5) y IRAEs extrahepaticos (6)
- ✓ Los AA fueron negativos o títulos bajos

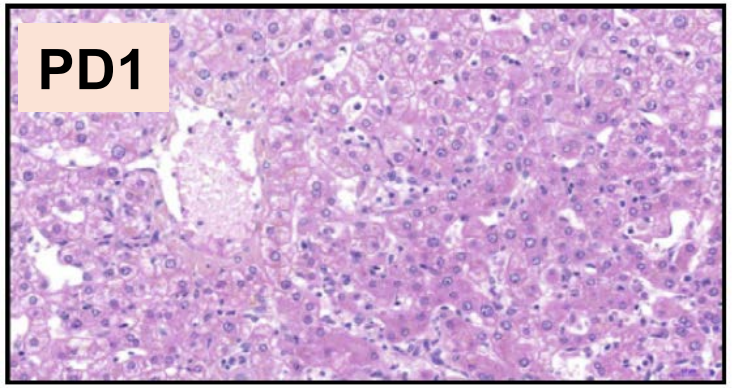
(* Citólisis o colestasis con más de 5x LSN, bilirrubina más de 3)

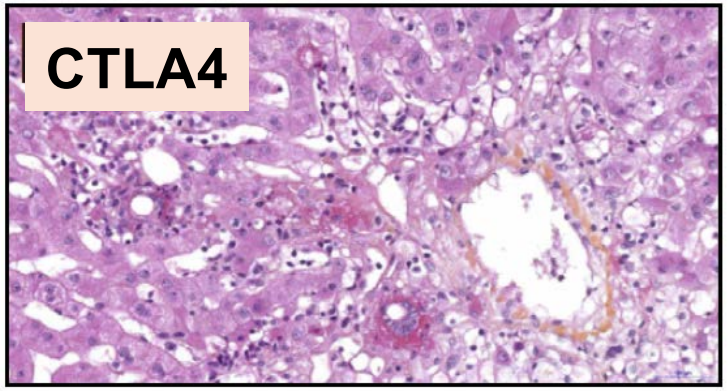
de Martin E et al. 2018;

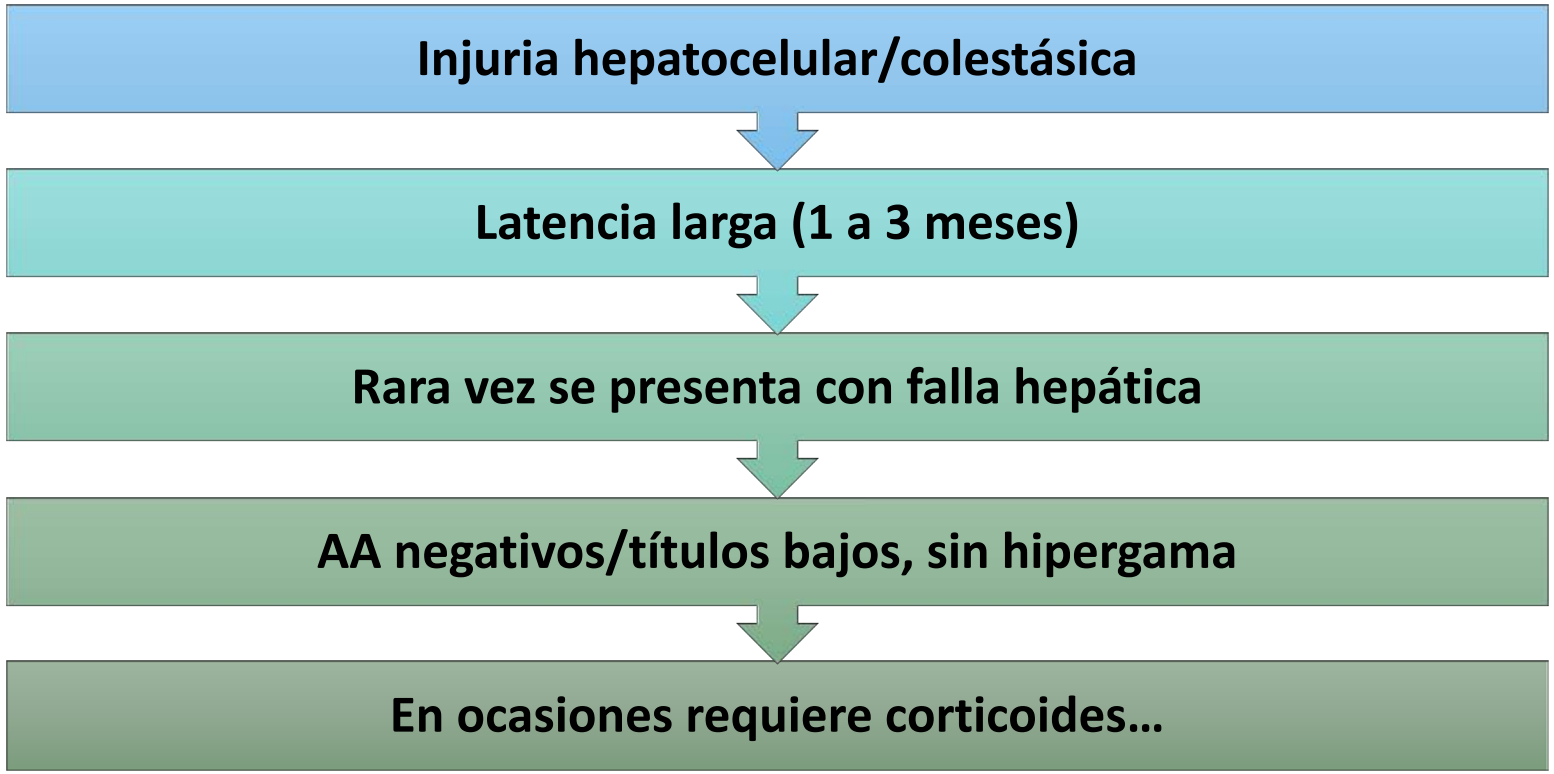
- El infiltrado inflamatorio comprendía **linfocitos** pero no células plasmáticas.

- Más de la mitad de las biopsias mostró **colangitis linfocítica y distrofia ductal.**

5 biopsias de los casos por **anti CTLA4** mostraron **hepatitis granulomatosa** (depósitos de fibrina y endotelitis de la VC) y la prevalencia de **linfocitos CD8**.







de Martin E et al. 2018; J Hepatol; Parlati L et al. J Hep Rep 2023; Hountondji L et al. J Hep Rep 2023

HEPATOTOXICIDAD IDIOSINCRATICA

HEPATOTOXICIDAD INMUNOMEDIADA

Burden of grade 3 or 4 liver injury associated with immune checkpoint inhibitors

Lucia Parlati,[1,2] Mehdi Sakka,[3] Aurelia Retbi,[4] Samir Bouam,[5] Lamia Hassani,[6] Jean-François Meritet,[7] Pierre Rufat,[4]

952 pacientes tratados con ICPI, 86 (9%) presentaron hepatitis grado 3/4* .

(anti PD1 95% , anti CTLA4 8%, anti PDL1 3%)

39 had non-ICPI DILI

28 had tumour infiltration

19 had ICPI DILI (2%)

(* Citolisis or cholestasis > 5 VVN, bilirrubina >3)

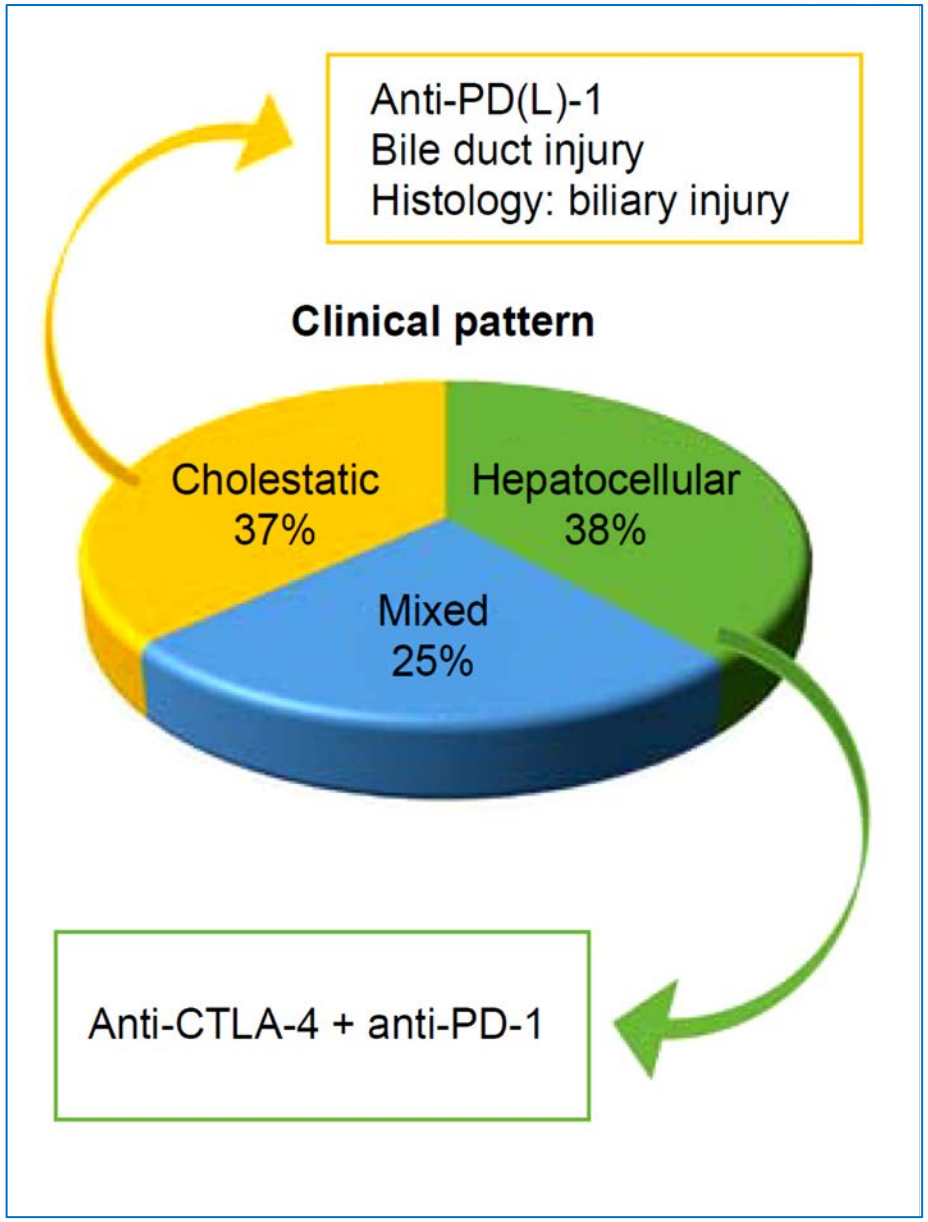
Parlati L et al. J Hep Rep 2023

n = 117 patients
CHeckpoint Inhibitor-induced Liver Injury

Age: 63 years old
Male: 53.8%

82% Grade 3 or 4

Anti-PD(L)1 60%	Anti-PD(L)1 + anti-CTLA-4 36%
Anti-CTLA-4 3%	Anti-PD(L)1 + anti-LAG-3 1%



Lina Hountondji et al. J Hep Rep 2023

Immune-related cholangitis induced by immune checkpoint inhibitors: a systematic review of clinical features and management

Borui Pi[a,*], Jin Wang[b,*], Yifan Tong[c], Qiao Yang[a], Fangfang Lv[a] and Yunsong Yu[a]

European Journal of Gastroenterology & Hepatology 2021

Revisión… 53 casos
(29 grandes ductos, 12 ductos pequeños, y 12 combinado)

Nivolumab	28
Pembrolizumab	19
Atezolizumab	2

Latencia variable (1 a 27 ciclos)
Mayor en grandes ductos (7 vs 2.5; p 0.02)

FAL p: 1328 (237 a 4635)
LD > SD (1683 vs 671; p 0,02)

Discontinuación: todos

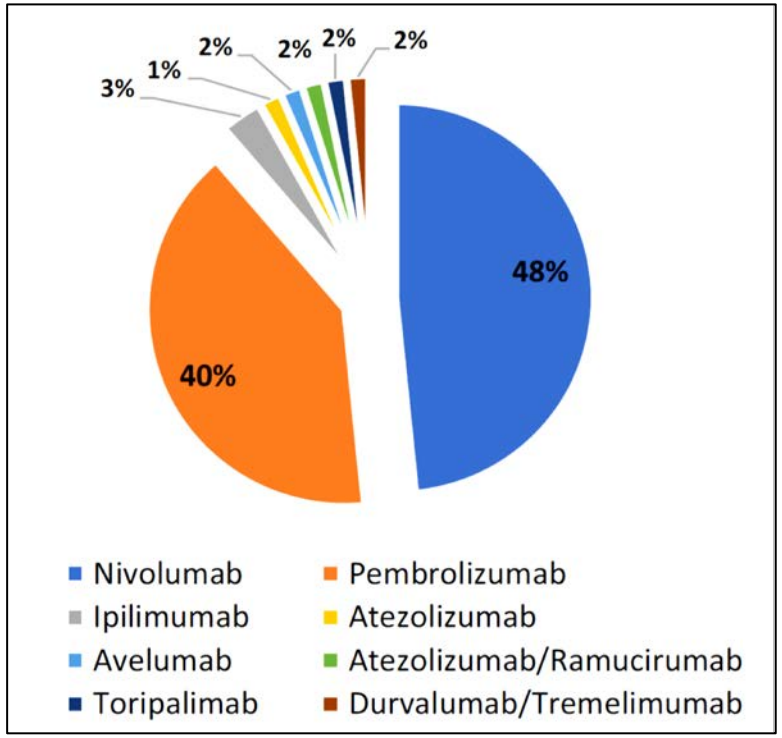
Inmunosupresión: 48/53

70% respuesta parcial, 21% peoría

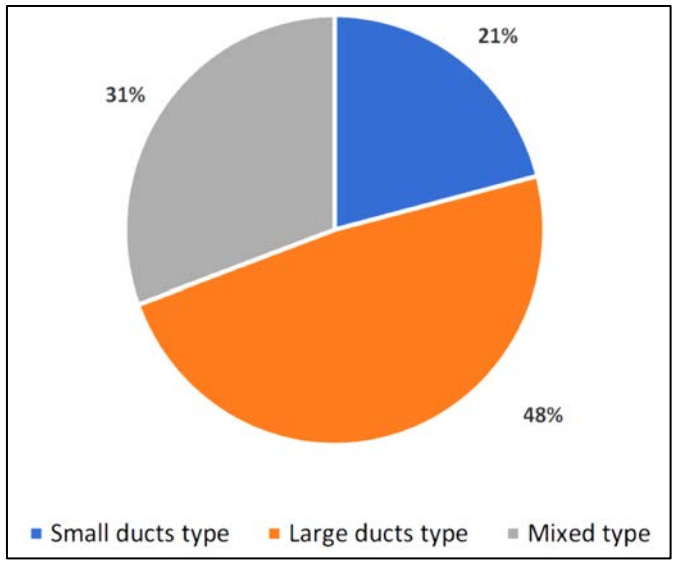
Secondary Sclerosing Cholangitis due to Drugs With a Special Emphasis on Checkpoint Inhibitors

Einar S. Bjornsson[1,2] | Daiana Arnedillo[3,4] | Fernando Bessone[3,4]

Liver International, 2025; 45:e16163



Principal causa de colangitis esclerosante farmacológica



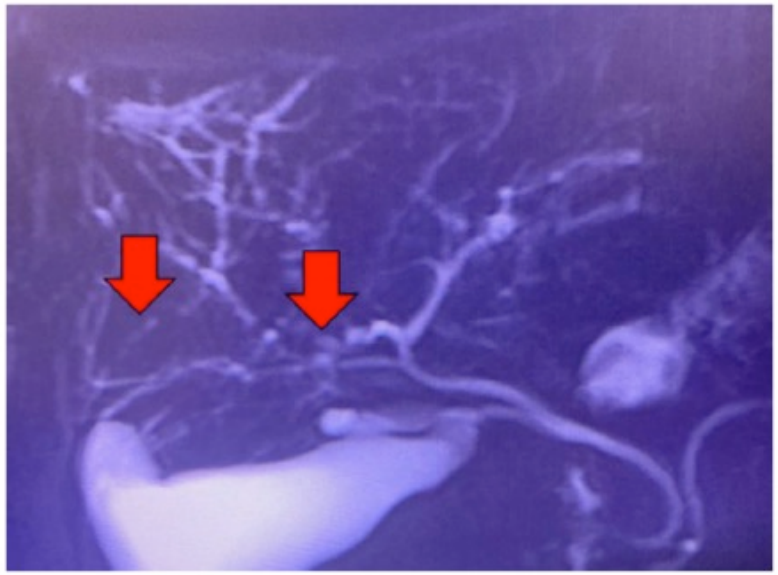


FIGURE 2 | 62-year-old male patient who developed SSC after 3 months of treatment with Pembrolizumab and epilimumab for kidney cancer. Alternating areas of stenosis with bile duct dilation on MRCP are shown in this picture (Arrows). (Courtesy of Prof. Raymundo Paraná from Federal University of Salvador de Bahia, Brazil).

Hepatitis inmunomediada x IPCI sin respuesta a corticoides (patrón colestásico/mixto)

→ Colangitis IR/ES? →

Biopsia Hepática
Colangioresonancia

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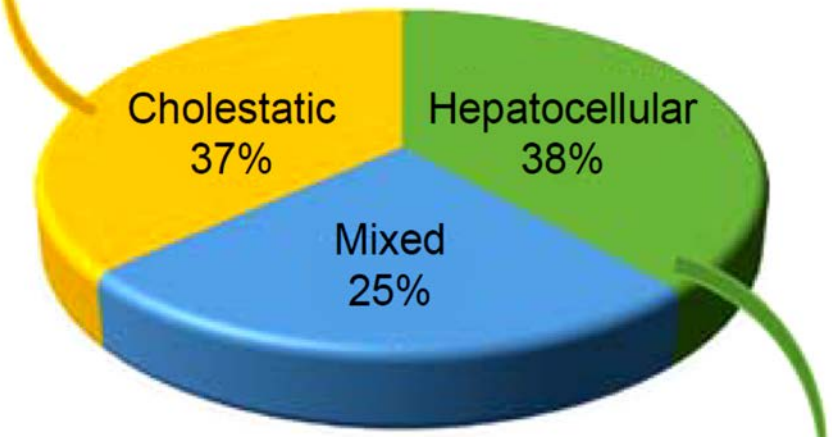
Anti-PD(L)-1
Bile duct injury
Histology: biliary injury

Clinical pattern



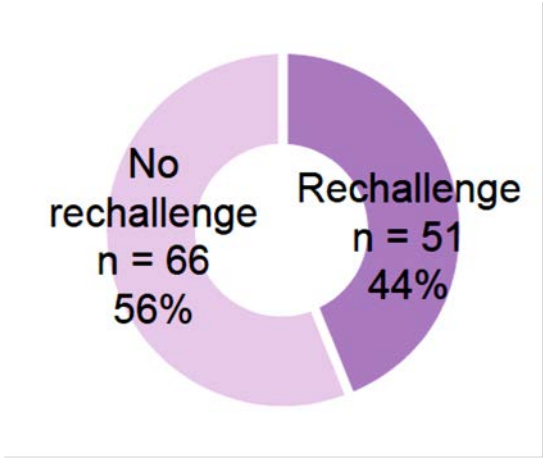
Anti-CTLA-4 + anti-PD-1

Resolución espontánea: 17 (15%)

Esteroides: 62 (53%)

Esteroides + UDCA: 31 (26%)

UDCA solo: 7 (6%)



Hepatitis recurrence
n = 12
23.5%

Antes de iniciar IPCI: bioquímica hepática, HBV y HCV status, imagen.

Durante la terapia: bioquímica hepática antes de cada infusión

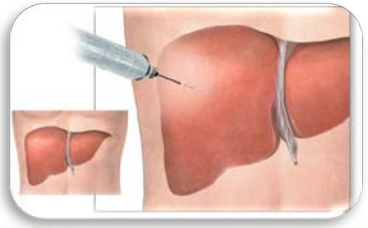
Enzimas normales o < 2-3 VVN, con brb normal: continuar la terapia y volver a chequear

Chequear antes de cada ciclo

nivel de enzimas ≥ 5 VVN

Interrumpir, descartar otras causas de lesión hepática y referir al hepatólogo.

Considerar MRI si patrón colestásico y evaluar CES



- Descartar otras causas o reforzar el diagnóstico
- Colestasis prolongada sin lesión ductal en la resonancia
- Agravación a pesar del tratamiento

Before starting therapy: liver chemistry, HBV and HCV status, imaging.

During therapy: liver chemistry before each infusion

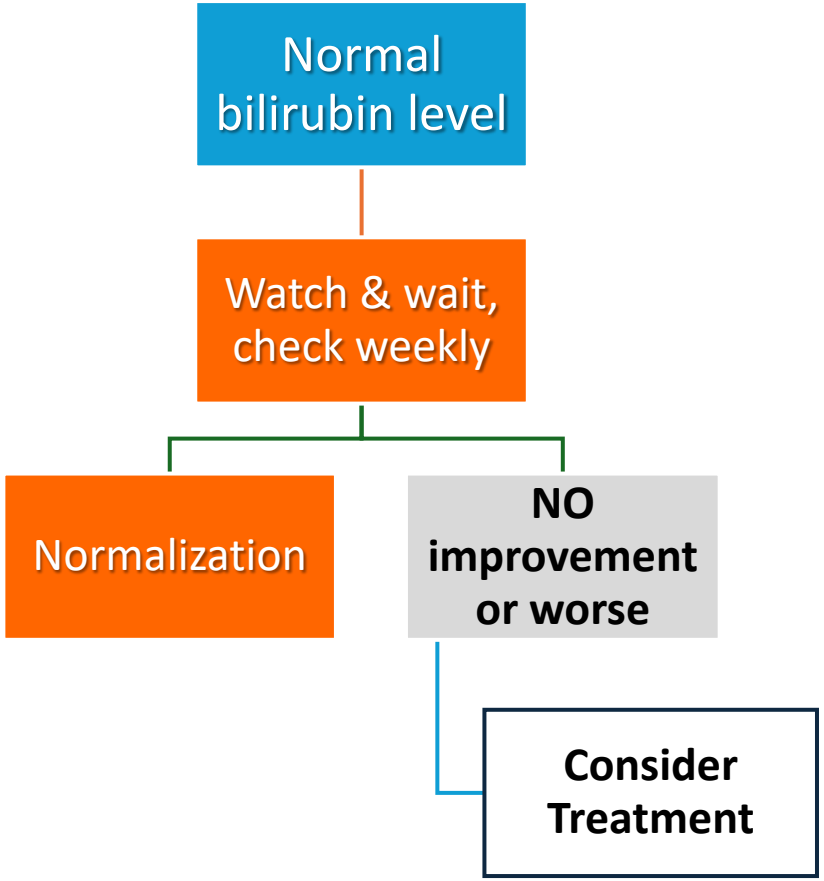
Normal enzymes or < 2-3 ULN: continue but check again

Continue but check again every cycle.

≥ 5 ULN enzymes levels

Stop therapy, rule out other causes of liver injury, and refer to an hepatologist.

≥ 5 ULN enzymes levels



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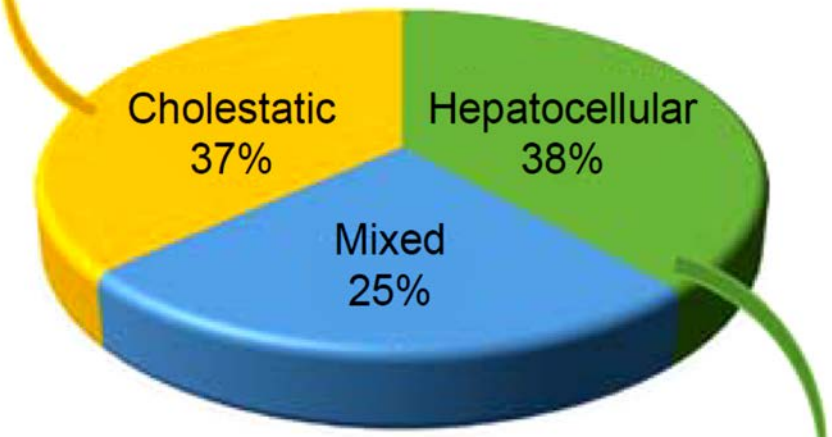

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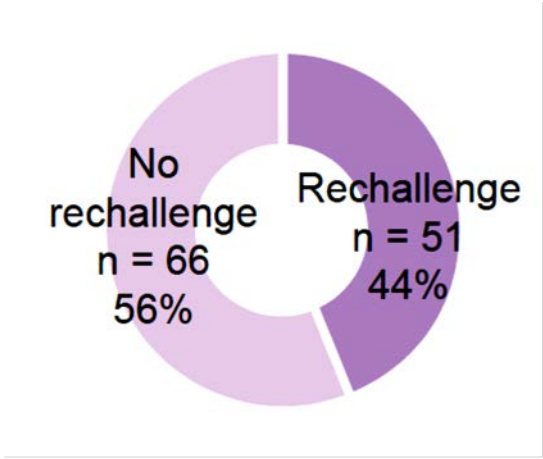

Hepatitis recurrence
n = 12
23.5%

REVIEW

OPEN

Hepatology Communications. 2024;8:e0525.

Steroid-refractory immune checkpoint inhibitor (ICI) hepatitis and ICI rechallenge: A systematic review and meta-analysis

Soo Young Hwang[1,2] | Pinghsin Hsieh[1] | Wei Zhang[2]

Revisión sistemática & meta análisis
(44 estudios de Asia, Europa, NA y Australia)

↓

1856 ICILI (56% grade 3-4)

↓

1184 recibieron esteroides

Duración de tratamiento variable (3 a 365 días).

Gran variación en las dosis : 0,5 mg/k prednisona… 2 mg/k metilprednisolona

82 casos refractarios: micofenolato 83%

40% rechallenge → 22% recurrencia

Retreatment with Checkpoint inhibitors after a severe immune-related hepatitis: Results from a prospective multicenter study

Mar Riveiro-Barciela, Ana Barreira-Díaz, Ana Callejo-Pérez, Eva Muñoz-Couselo, Nely Díaz-Mejía, Álvaro Díaz-González, María-Carlota Londoño, Maria-Teresa Salcedo, María Buti

Prospectivo, 23 pacientes.

Type of CPI, n(%)	
Anti-PD1 or anti-PD1/PD-L1	18 (78.3%)
Anti-CTLA-4 ± anti-PD1	4 (17.3%)
CD40 agonist antibodies	1 (4.3%)

Bilirubin (mg/dL), Md (IQR)	0.86 (0.6-1.1)

RUCAM score, n(%)	
Possible	1 (4.3%)
Probable	8 (34.8%)
Highly probable	14 (60.9%)
CTCAE grade of the hepatitis, n(%)	
3	19 (82.6%)
4	4 (17.4%)
DILI severity score, n(%)	
Mild	19 (82.6%)
Moderate	4 (17.4%)

10 pacientes con EIR

8 hepatitis (2 colitis): 35%

2 hipofisitis

Leve: 4
Moderado 3
Severo: 1

- ✓ Los IPCI tienen como contrapartida a su eficacia antitumoral, severos eventos inmunomediados (consecuencia de la pérdida de la auto-tolerancia).

- ✓ El patrón de presentación es variable, rara vez con falla hepática.

- ✓ El tratamiento debe ser la suspensión del agente sospechoso con o sin un curso de esteroides.

- ✓ La evaluación histológica y la decisión del retratamiento deben ser analizados caso a caso.