Effets Secondaires Hépatiques des Inhibiteurs de Check-Point en Cancérologie

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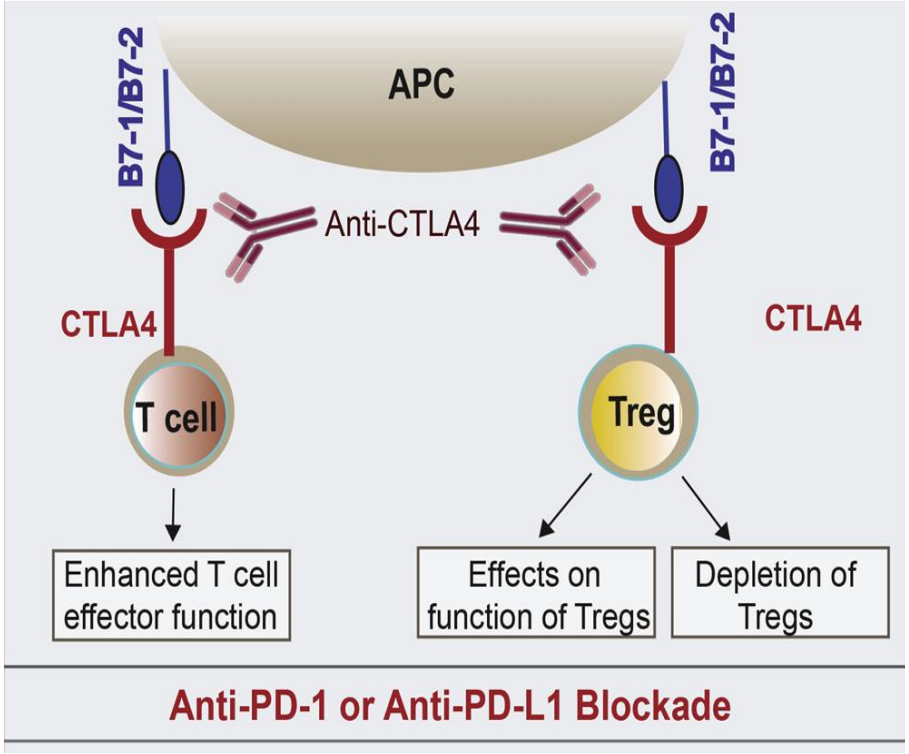
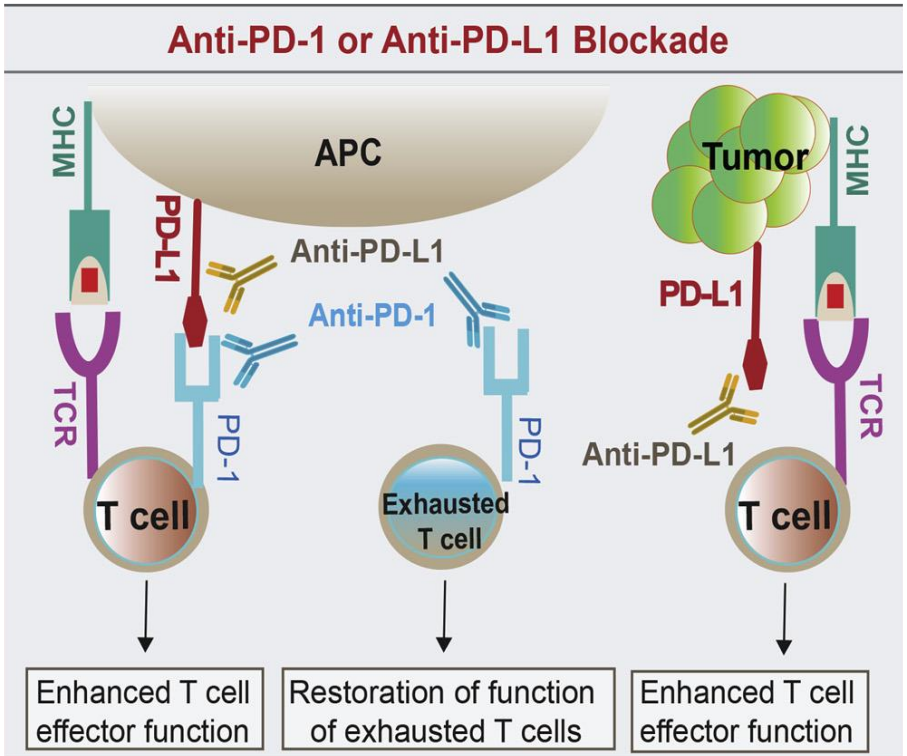
Potential Mechanism of Action of Anti-PD1 and Anti-CTLA4

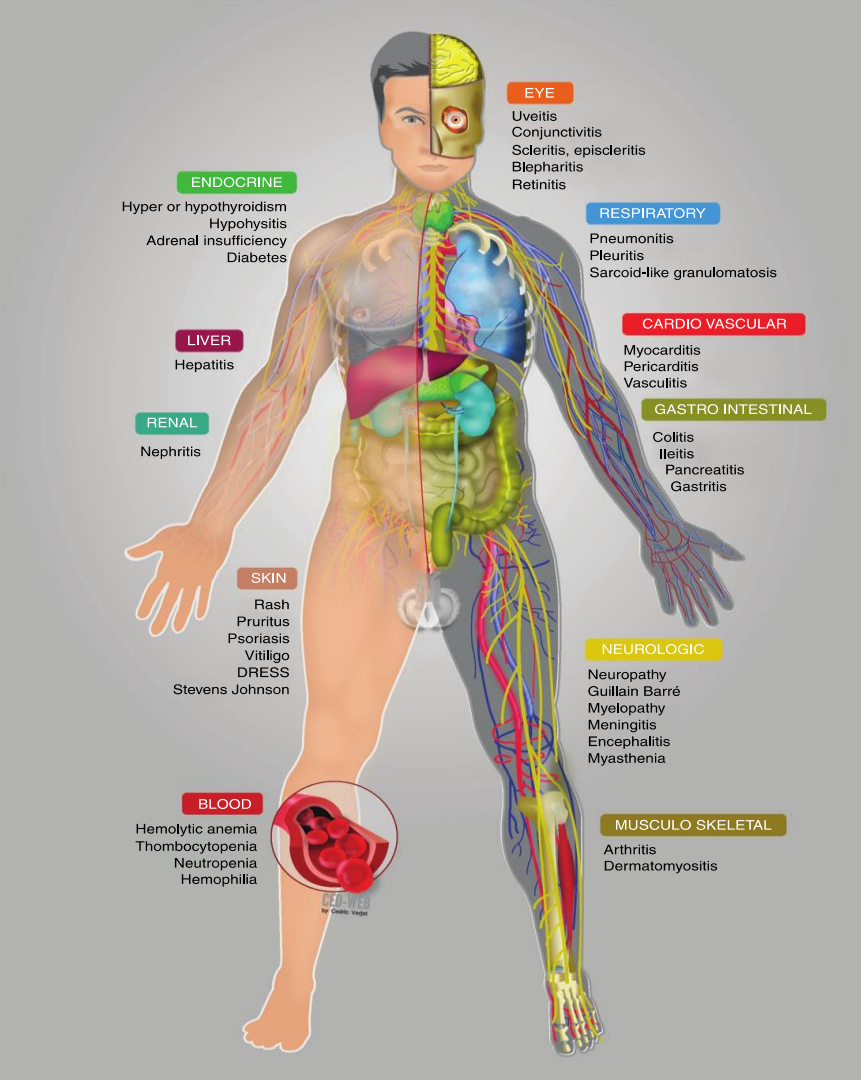


Genetic ablation of CTLA4 result in massive lympho proliferation and early death in mice



Genetic ablation of Pdcd1 (encoding PD1) leads to autoimmune phenotypes in mice

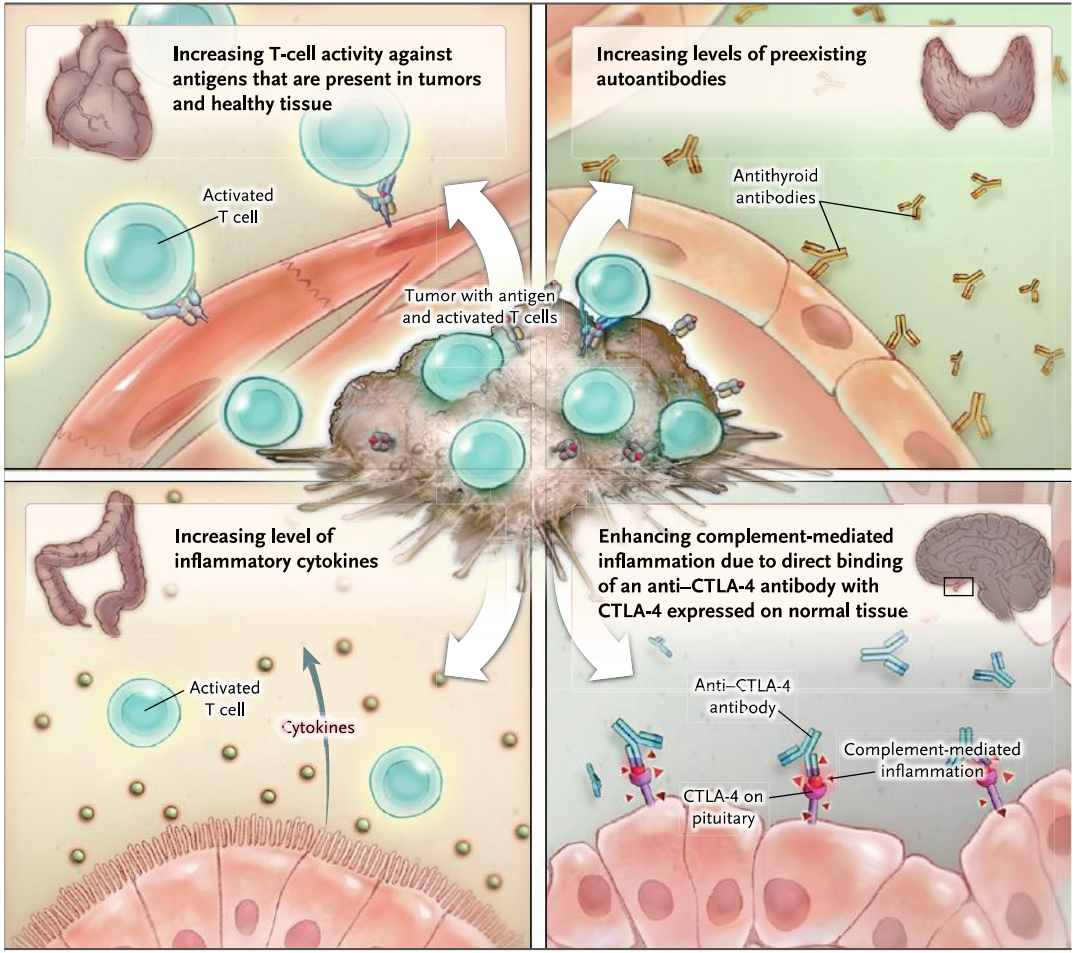
Khan, Sem in Cancer Biology in press



Spectrum of Toxicity of Immune Checkpoint Inhibitors

Champiat, Ann of Oncol 2016

Possible Mechanisms Underlying irAEs



Postow, NEJM 2018

IrAEs according to Organ Categories

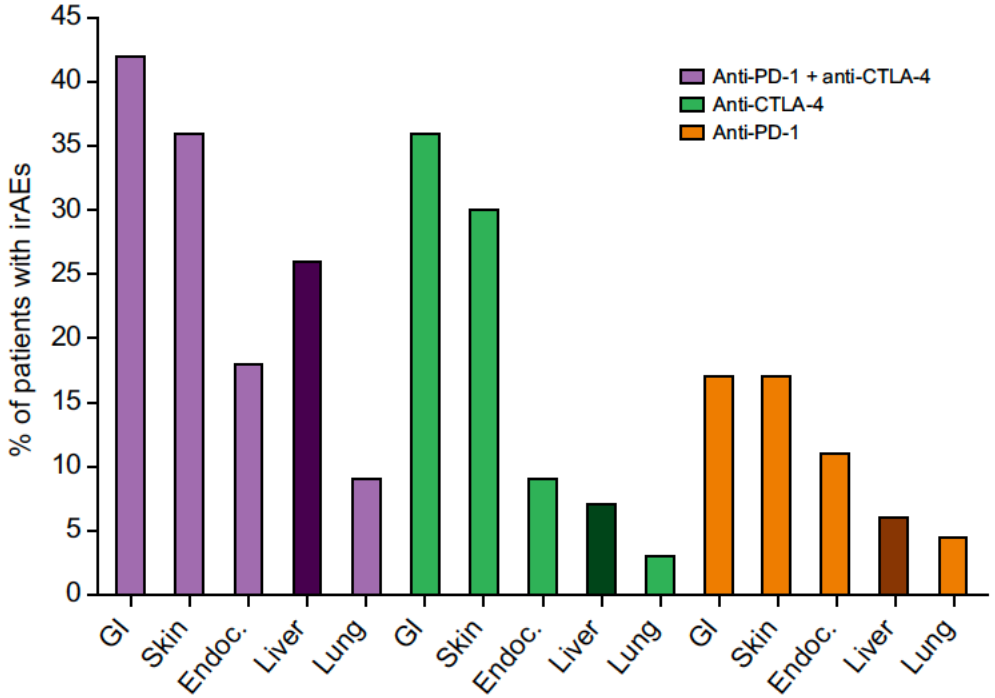


Fig. 1. Distribution of irAEs for organ categories according to treatment in the main clinical trials of ICIs. Patients were treated with anti-PD-1 + anti-CTLA-4,[4,33,36] anti-CTLA-4[4,33,104,124] and anti-PD-1.[33,34,124] The values quoted

De Martin J Hep Reports 2021

Prevalence of Hepatic IrAEs

Event	Nivolumab + Ipilimumab N=313		Nivolumab N=313		Ipilimumab N=311	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Rash	93 (30)	10 (30)	72 (23)	1 (<1)	68 (22)	5 (2)
Pruritus	112 (35)	6 (2)	67 (21)	1 (<1)	113 (36)	1 (<1)
Fatigue	119 (38)	13 (4)	114 (36)	3 (1)	89 (29)	3 (1)
Diarrhea	142 (45)	29 (9)	67 (21)	9 (3)	105 (34)	18 (6)
Vomiting	48 (15)	7 (2)	22 (7)	1 (<1)	24 (8)	1 (<1)
Increased AST	51 (16)	19 (6)	14 (4)	3 (1)	12 (4)	2 (1)
Increased ALT	60 (19)	27 (9)	13 (4)	4 (1)	12 (4)	5 (2)
Colitis	40 (13)	26 (8)	7 (2)	3 (1)	35 (11)	24 (8)

Wolchok, NEJM 2017

Variability and Unpredictability of Hepatic IrAEs

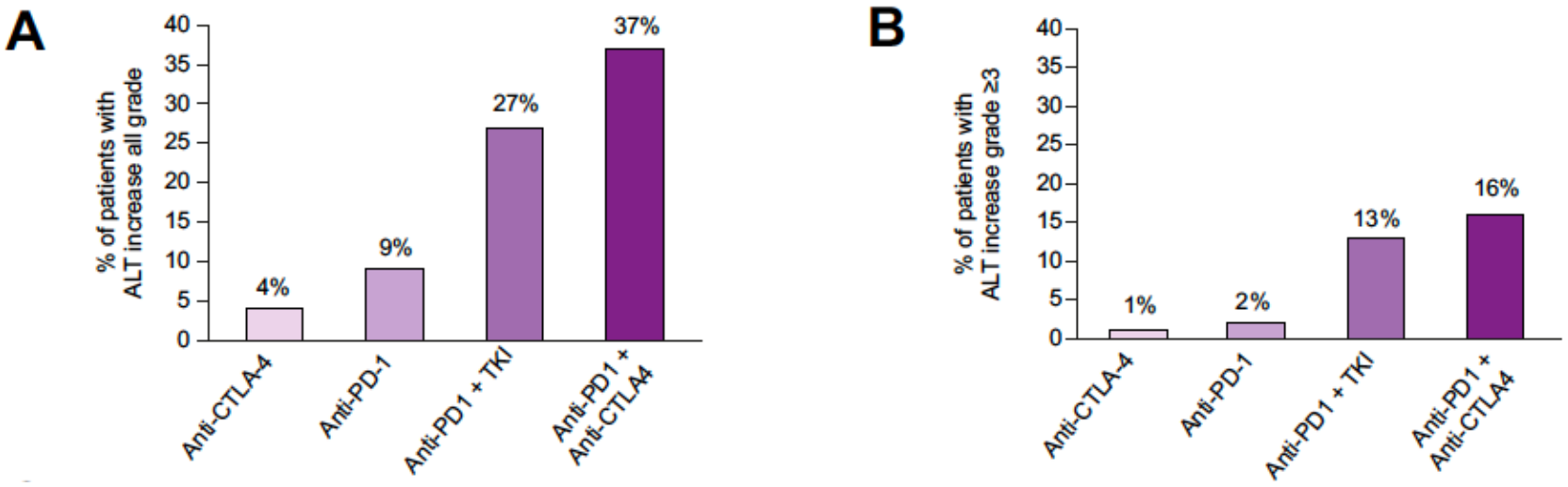
Characteristics of a population who developed grade ≥3 hepatitis

	N=16
Age, years	63 [33-84]
Sex, F	9 (56)
Interval time immunotherapy and hepatitis, weeks	**5 [1-49]**
AST, UI/L	399 [117-2289]
ALT, UI/L	416 [266-3137]
Total Bilirubin, µmol/L	18 [6-324]
GGT, UI/L	317 [39-1252]
ANA ≥ 1:80	8 (50)
IgG, g/L	9 [6-18]

Hepatitis onset even after immune checkpoint discontinuation

De Martin, J Hepatol 2018

Hepatic IrAEs in Non HCC Patients



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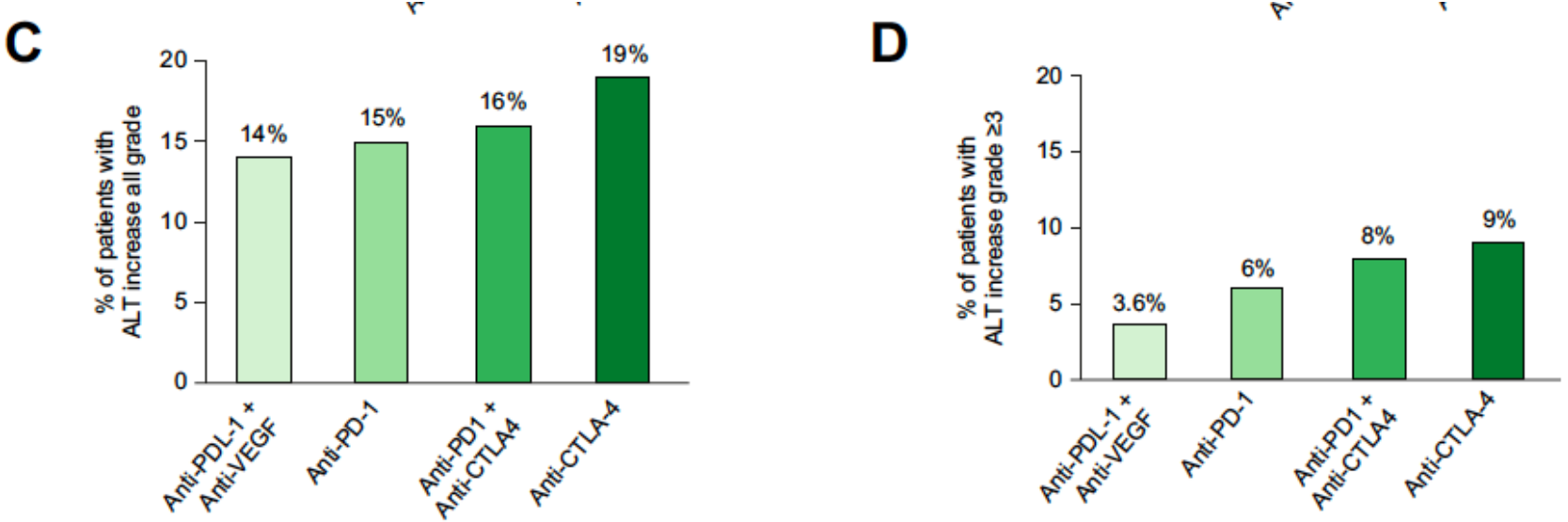
IrAEs in HCC Patients



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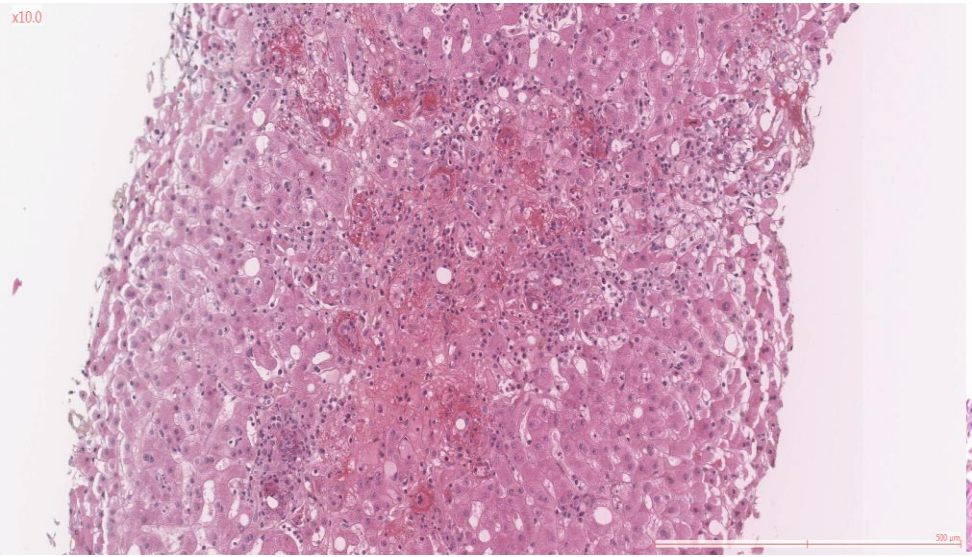
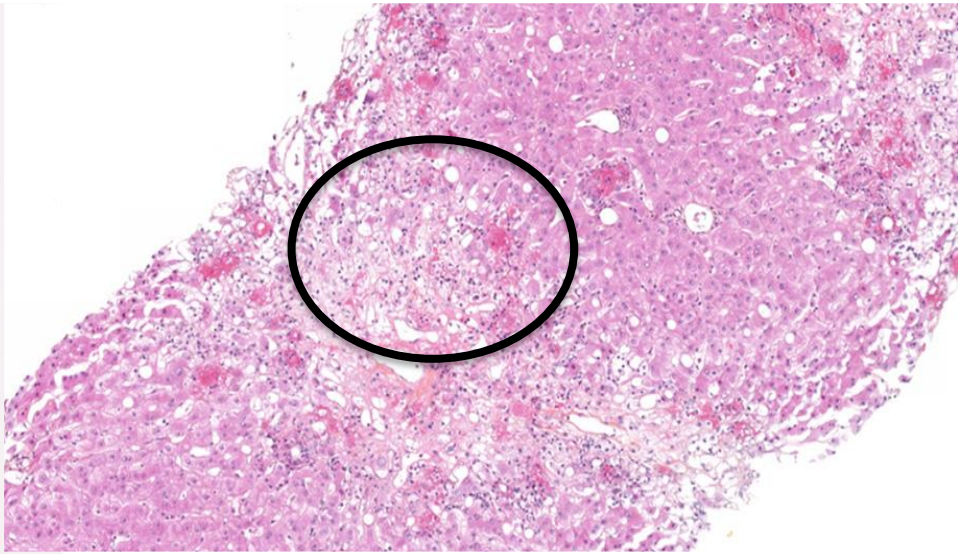
Anti-CTLA4 (Ipilimumab): Fibring Ring Granuloma



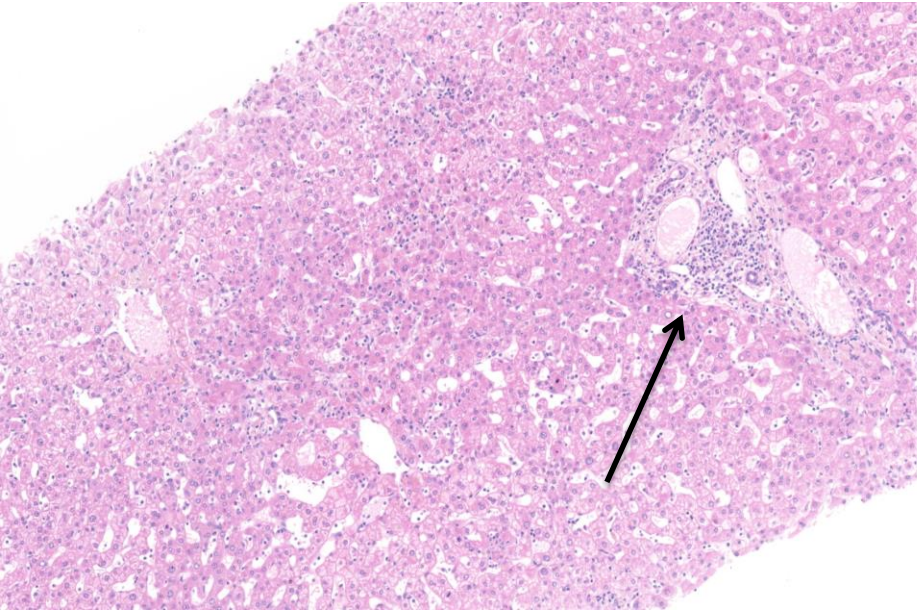
Acute hepatitis with confluent centrilobular necrosis and numerous fibrin ring granulomas (HES x 100)



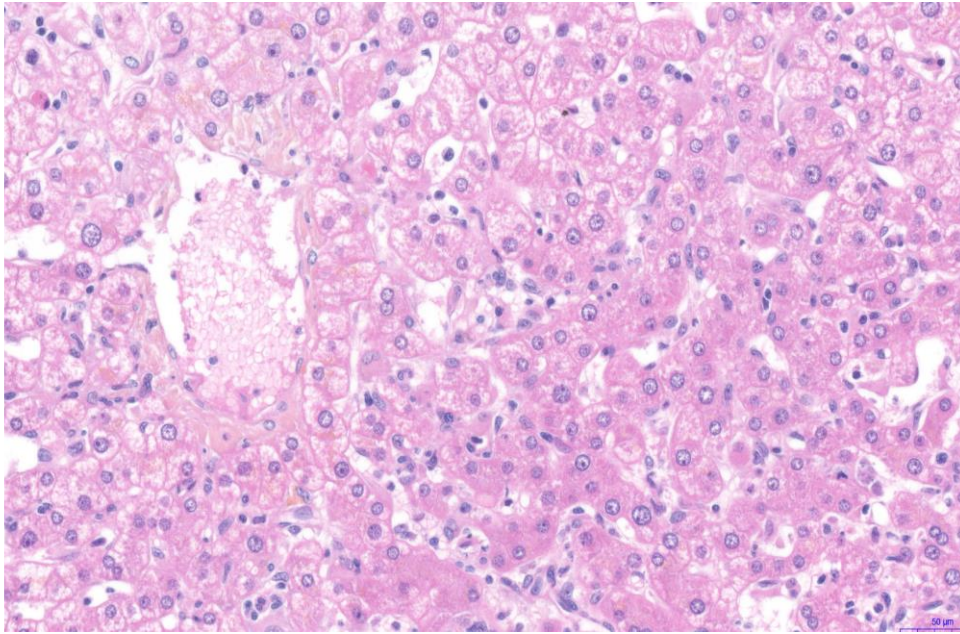
Granulomas: epithelioid cells without giant cell, centered by a lipid vacuole surrounded by a fibrin ring (HES x 350)

Papouin, Ann Pathol 2018

Anti-PD1 (Nivolumab): Lobular Hepatitis



Acute hepatitis with peri-portal inflammatory infiltration and moderate necrotico-inflammatory activity (HES x 100)



Lobular inflammatory infiltration made by histiocytes and lymphocytes (HES x 300)

Papouin, Ann Pathol 2018

Cholangitis due to ImmuneCheckpoint inhibitors

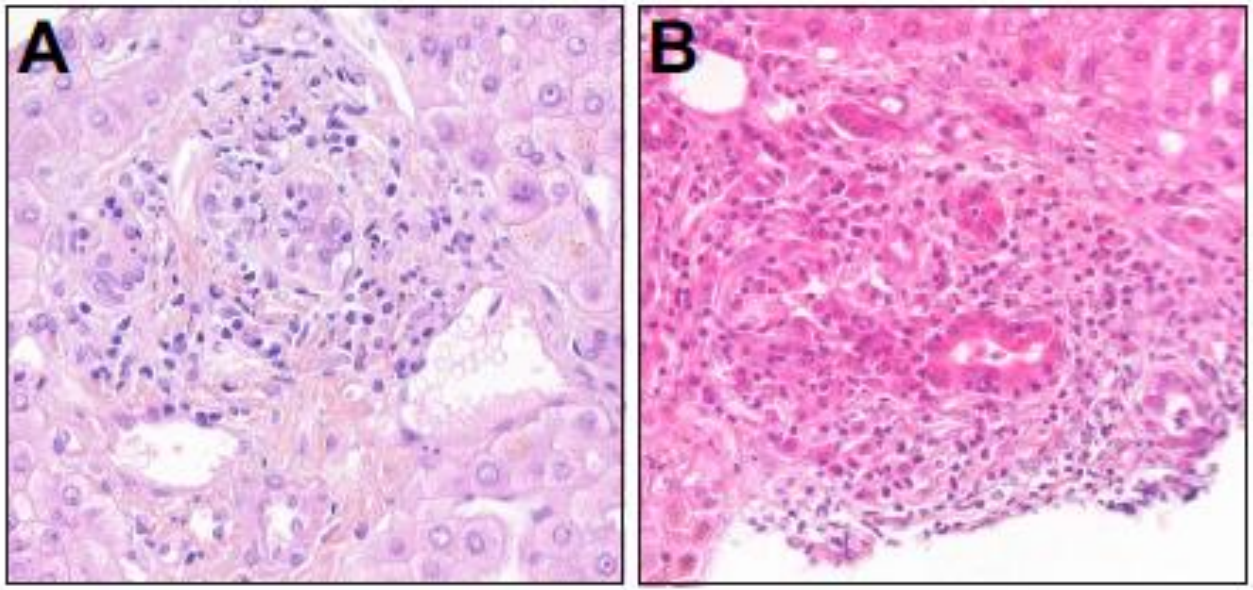
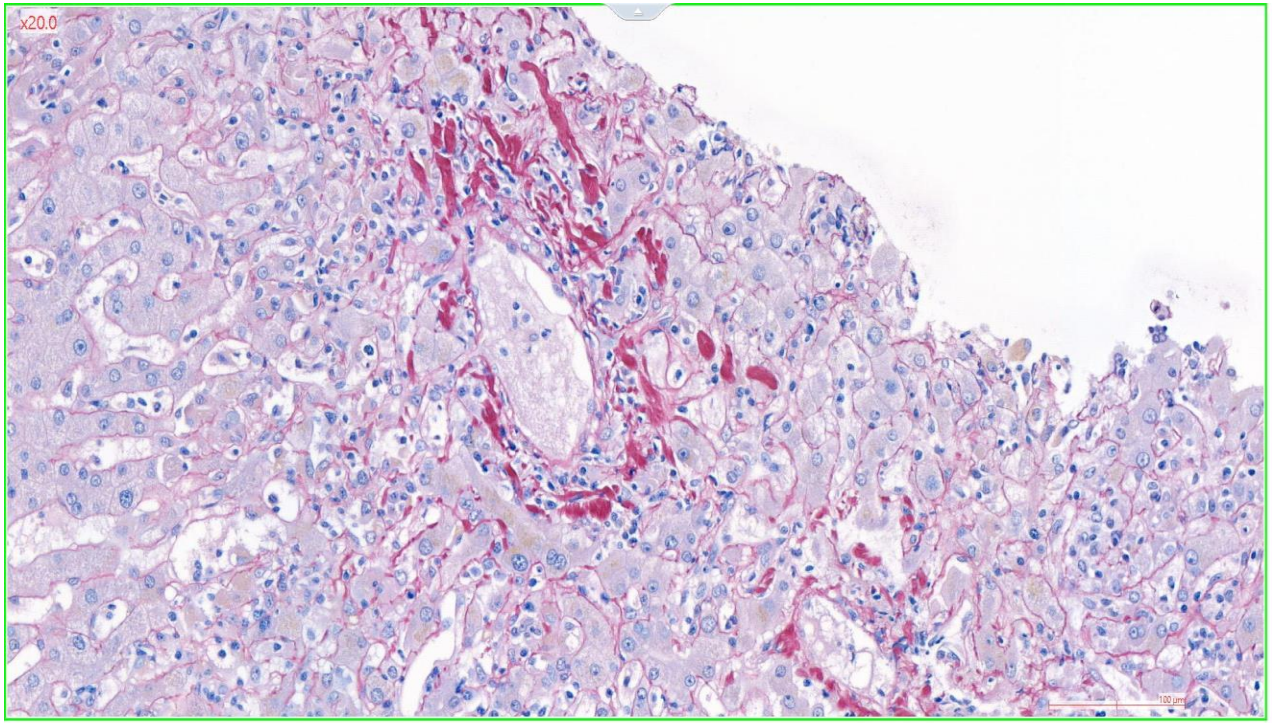


Fig. 4. Liver biopsies of patients treated with anti-PD-L1 and with combination of anti-PD-1 and anti-CTLA-4. (A) Destructing cholangitis (HES ×400); (B) Granulomatous cholangitis HES ×300. CTLA-4, cytotoxic T lymphocyte-

De Martin J Hep Reports 2021

Lesions of central venous endothélialitis with Fibrous deposits

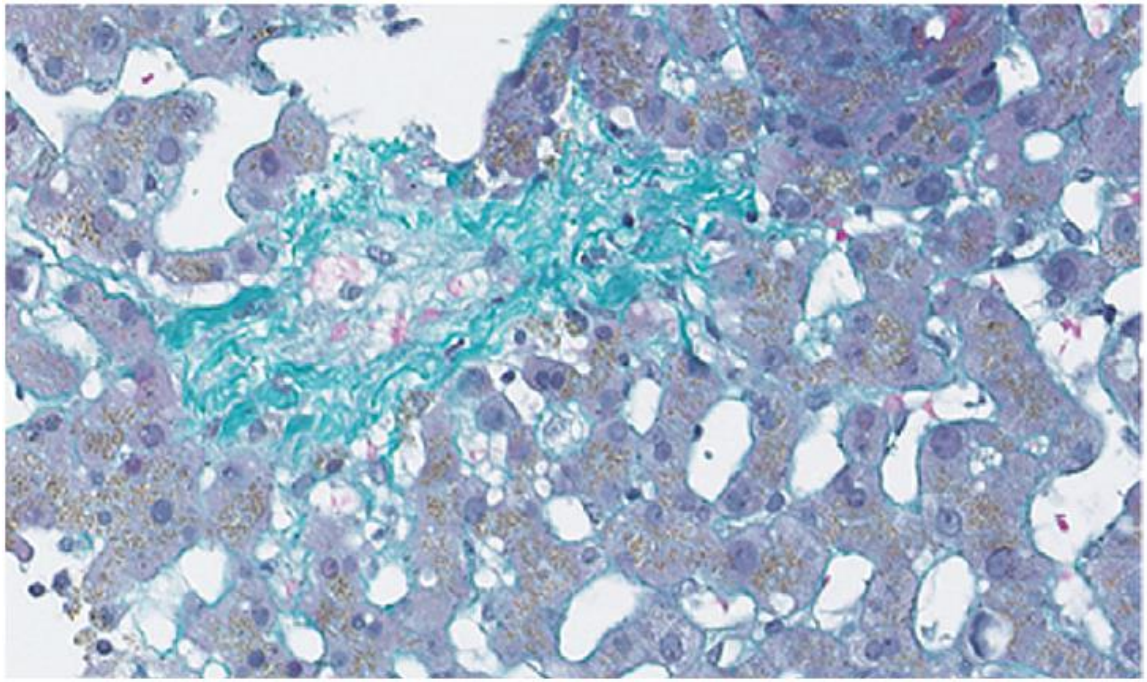


Central Venular **with intimal fibrous deposits** and endothelialitis (lymphocytes).

PicroSirius, x200

Courtesy Dr A. Laurent-Bellue

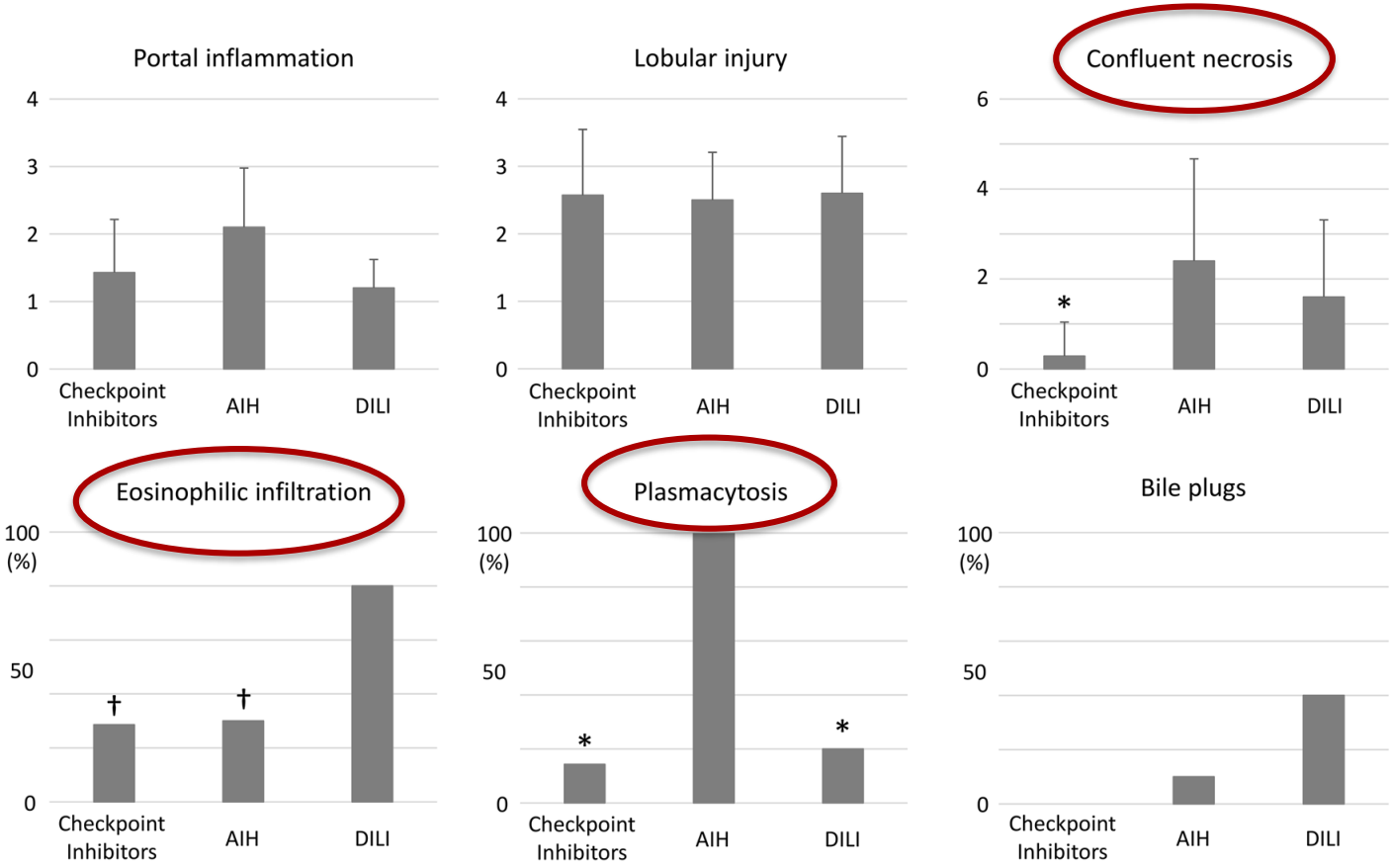
Lesions of central venous endothélialitis with Fibrous deposits (SOS)



Patient with Metastatic melanoma treated with Nivolumab (14 months)

Charvet Ann Oncol 2020

It is not an « autoimmune-like » hepatitis !!!



Zen, Mod Pathol 2018

ICI-Liver Toxicity and Autoimmune Hepatitis?

	ICI-induced liver toxicity	Autoimmune hepatitis
Presentation	Heterogeneous	Heterogeneous
Gender prevalence	None	Female
Clinical symptoms	Non-specific Possibly asymptomatic	Non-specific
Biology		
AST/ALT elevation	Present	Present
GGT/ALP elevation	Present	Present at lower level than the cytolysis (look for PBC, PSC overlap)
Bilirubin elevation	Rare	Possible
Immunology		
Anti-nuclear antibodies	Possibly positive (about 50% of patients), speckled	Positive, high titre, homogeneous pattern
Anti-smooth muscles antibodies	Possibly positive (non-anti-F actin)	Positive, high titre, anti-F actin
Anti-LKM 1 antibodies	Negative	Positive (AIH type II)
IgG	Usually normal	Elevated
Histology		
Plasmocytes	Absent or rare	Frequent
Lobular inflammation	Present	Present
Portal tract inflammation	Present	Present
Confluent necrosis	Rare	Present
Granuloma	Often present in patients on anti-CTLA-4	Absent
Cholangitis	Present – cholangitis form	Rarely present (look for PBC, PSC overlap)
Chronic hepatitis/cirrhosis	Absent	Frequently present
CD4+/CD20+	Rare	Present
CD8+	Present	Rare
Therapy		
Corticosteroids	Not always needed	Needed
Long-term therapy	No	Yes
Corticosteroid discontinuation	Yes Risk of recurrence: rare	Possible in selected patients Risk of recurrence: high

De Martin
J Hep
Reports
2021

Common Toxicity Criteria for Adverse Events : CTCAE

Cancer Therapy Evalutation Program of the National Cancer Institute (NCI) of the National Institutes of Health

		Mild	Moderate	Severe	Life-threatening
FEATURE	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
ALT	Normal	>1.0-2.5	>2.5-5.0	>5.0-20	>20
AST	Normal	>1.0-2.5	>2.5-5.0	>5.0-20	>20
Alkaline Phosphatase	Normal	>1.0-2.5	>2.5-5.0	>5.0-20	>20
GGT	Normal	>1.0-2.5	>2.5-5.0	>5.0-20	>20
Bilirubin	Normal	>1.0-1.5	>1.5-3.0	>3.0-10	>10

Recommendations of European Society of Medical Oncology

ALT/AST ULN	Steroids	Immunotherapy
Grade 1 ALT/AST≤3	No	Continue
Grade 2 3<ALT/AST≤5	0.5-1mg/Kg/day Start steroid taper over 4–6 weeks when G1	Hold Continue once resolved to ≤grade 1 and off steroids
Grade 3 5<ALT/AST≤20	1-2mg/Kg/day Start steroid taper over 4–6 weeks when G2	Hold; rechallenge only at consultant discretion
Grade 4 ALT/AST>20	2 mg/Kg/day If no improvement in 2-3 days, add additional/alternative immune suppressant	Discontinue immunotherapy

Haanen, Ann of Oncology 2018

RUCAM: Roussel-UCLAF Causality Assessment Method

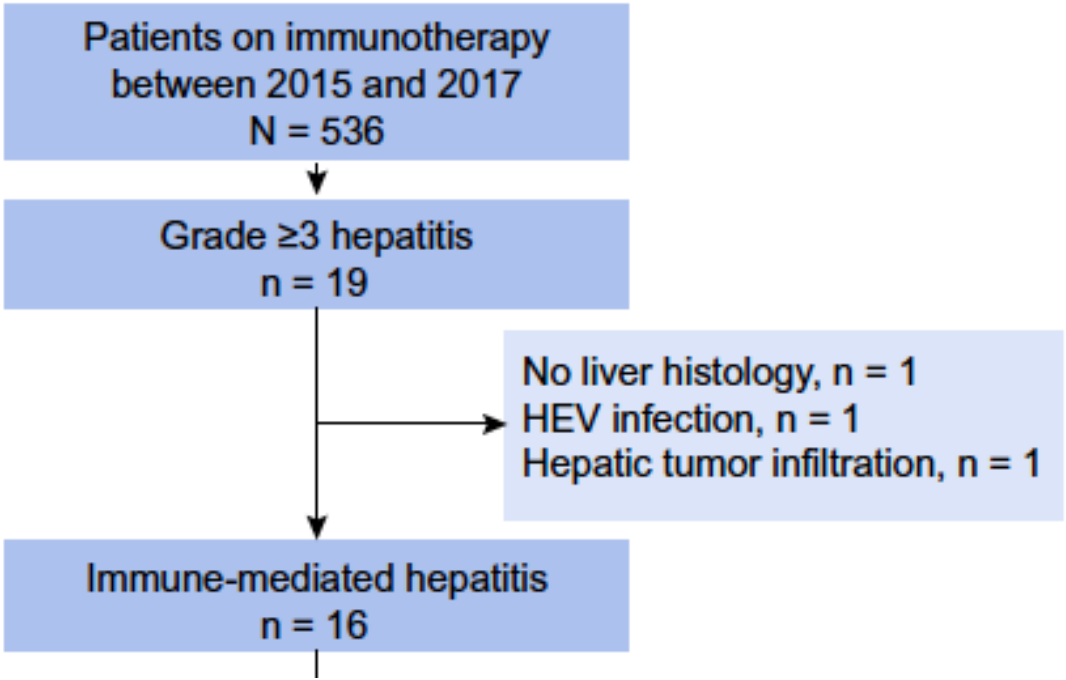
RUCAM Causality Assessment

Drug: _____ Initial ALT: _____ Initial Alk P: _____ R ratio = [ALT/ULN] ÷ [Alk P/ULN] = _____ ÷ _____ = _____

The R ratio determines whether the injury is hepatocellular (R > 5.0), cholestatic (R < 2.0), or mixed (R = 2.0 – 5.0)

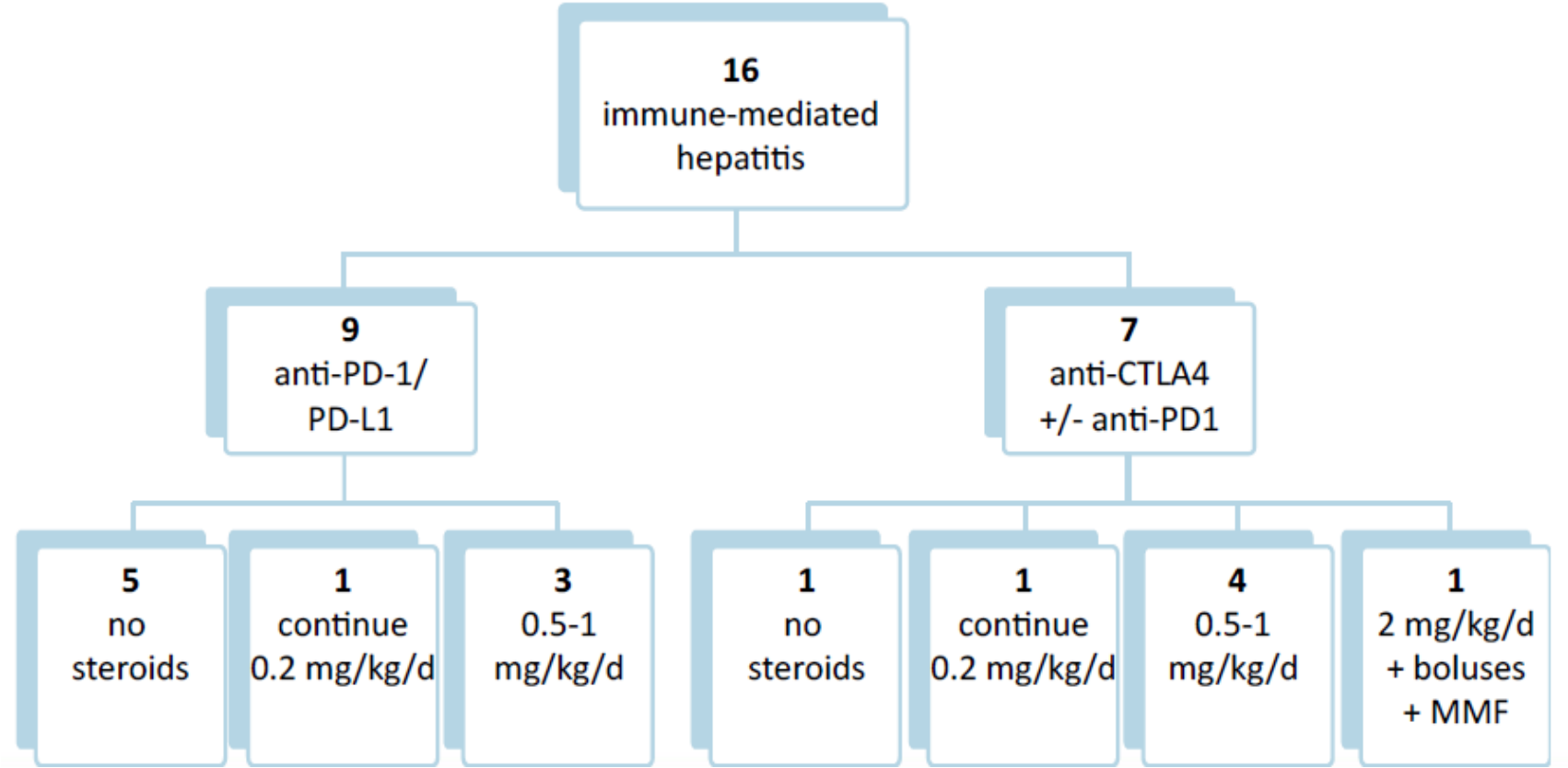
	Hepatocellular Type		Cholestatic or Mixed Type		Assessment
1. Time to onset					
	Initial Treatment	**Subsequent Treatment**	**Initial Treatment**	**Subsequent Treatment**	**Score** (check one only)
○ From the beginning of the drug:					
• Suggestive	5 – 90 days	1 – 15 days	5 – 90 days	1 – 90 days	☐ +2
• Compatible	< 5 or > 90 days	> 15 days	< 5 or > 90 days	> 90 days	☐ +1
○ From cessation of the drug:					
• Compatible	≤ 15 days	≤ 15 days	≤ 30 days	≤ 30 days	☐ +1
Note: If reaction begins before starting the medication or >15 days after stopping (hepatocellular), or >30 days after stopping (cholestatic), the injury shou be considered unrelated and the RUCAM cannot be calculated.					
2. Course	**Change in ALT between peak value and ULN**		**Change in Alk P (or total bilirubin) between peak value and ULN**		**Score** (check one only)
After stopping the drug:					
• Highly suggestive	Decrease ≥ 50% within 8 days		Not applicable		☐ +3
• Suggestive	Decrease ≥ 50% within 30 days		Decrease ≥ 50% within 180 days		☐ +2
• Compatible	Not applicable		Decrease < 50% within 180 days		☐ +1
• Inconclusive	No information or decrease ≥ 50% after 30 days		Persistence or increase or no information		☐ 0
• Against the role of the drug	Decrease < 50% after 30 days **OR** Recurrent increase		Not applicable		☐ -2
○ **If the drug is continued:**					
• Inconclusive	All situations		All situations		☐ 0
3. Risk Factors:	**Ethanol**		**Ethanol or Pregnancy (either)**		**Score** (check one for each)
○ Alcohol or Pregnancy	Presence		Presence		☐ +1
	Absence		Absence		☐ 0
○ Age	Age of the patient ≥ 55 years		Age of the patient ≥ 55 years		☐ +1
	Age of the patient < 55 years		Age of the patient < 55 years		☐ 0

Immune-Mediated Hepatitis



De Martin, J Hepatol 2018

Spontaneous Improvement of Immune-mediated Hepatitis



Spontaneous improvement: 38%

De Martin, J Hepatol 2018

Immune-mediated hepatitis

Pt	Age	Sex	Immuno therapy	Time to AE onset (weeks)	Grade of hepatitis	Steroids
1	65	M	Ipilimumab	9.3	3	No
2	38	F	Pembrolizumab	14.1	3	No
3	78	M	Ipilimumab	10.4	3	No
4	66	M	Ipilimumab	6.1	3	No
5	43	F	Ipilimumab	8.9	4	**Yes**
6	36	M	Nivolumab	9.4	4	**Yes**
7	46	M	Nivolumab	19.7	3	No
8	80	M	Ipi + Nivo	2.9	2	**Yes**
9	45	M	Ipilimumab	13.9	3	**Yes**
10	74	M	Ipilimumab	14.7	3	**Yes**

50% Spontaneous improvement
More frequent with antiPD1

Gauci, J Hepatol 2018

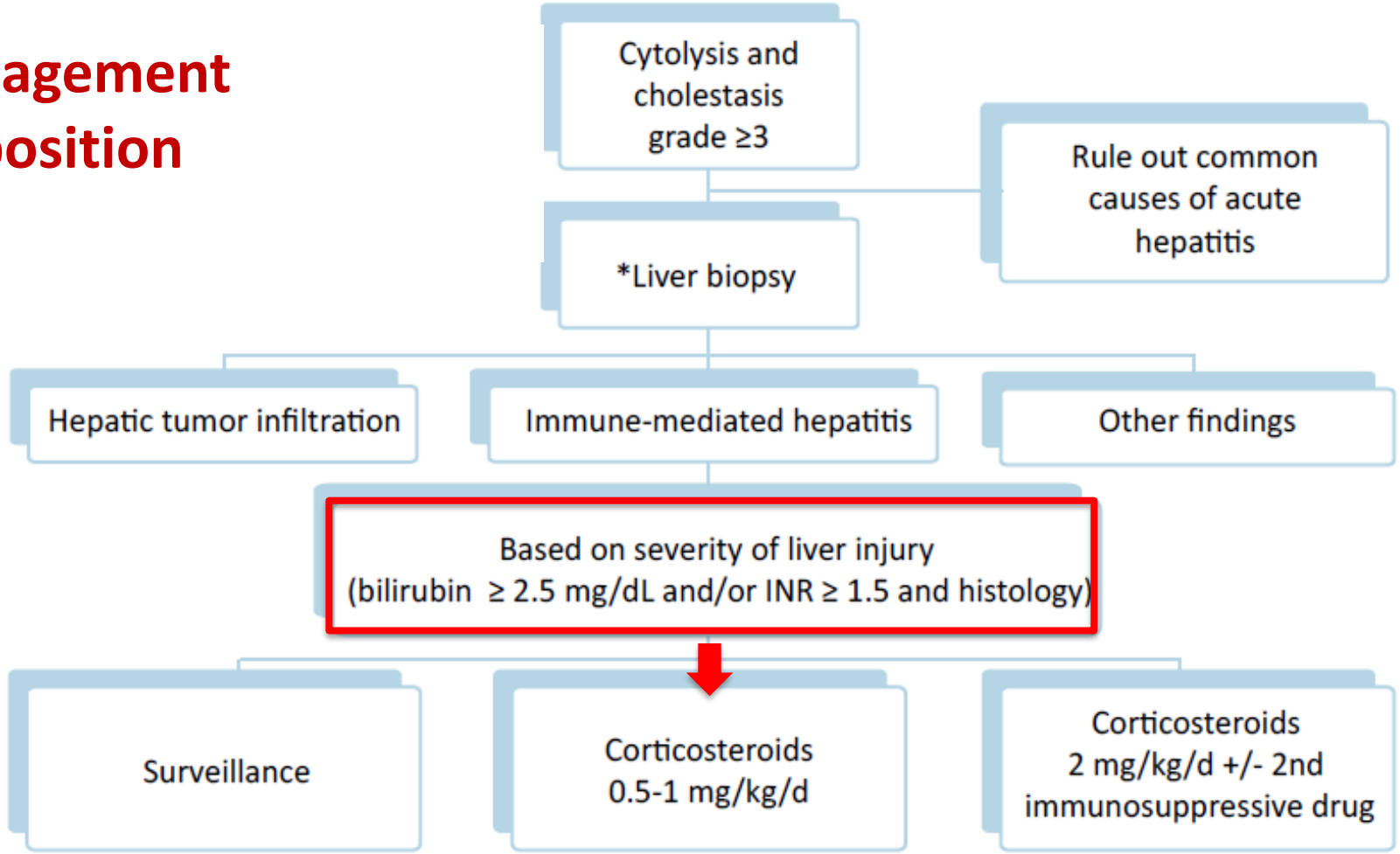
ICI induced Cholangitis

Table 2 Principal characteristics of patients with immune-related sclerosing cholangitis and hepatitis

Type of injury	No	Age	Sex	Disease	Drug	Pattern of onset	ALT/ALP (at the worst ALT)	Biopsy site
irSC	1	M	81	NSCLC	Pembro	Cholestatic	419/1987	Liver & bile duct
	2	F	83	NSCLC	Pembro	Cholestatic	237/4847	Liver
	3	M	71	NSCLC	Nivo	Cholestatic	74/1613	Bile duct
	4	M	68	NSCLC	Nivo	Cholestatic	91/3117	None
irHepatitis	1	M	68	NSCLC	Pembro	Hepatocellular	580/531	None
	2	F	31	Melanoma	Ipi + Nivo	Hepatocellular	1976/323	None
	3	F	56	Melanoma	Ipi + Nivo	Hepatocellular	1293/683	None
	4	F	78	Melanoma	Ipi + Nivo	Cholestatic	215/880	None
	5	M	54	Melanoma	Ipi + Nivo	Mixed	809/1446	None
	6	F	68	Melanoma	Ipi	Mixed	425/589	None
	7	M	55	Melanoma	Ipi	Mixed	236/512	None
	8	M	54	Renal cancer	Ipi + Nivo	Hepatocellular	614/1096	None

Takinami Invest New Drugs 2021

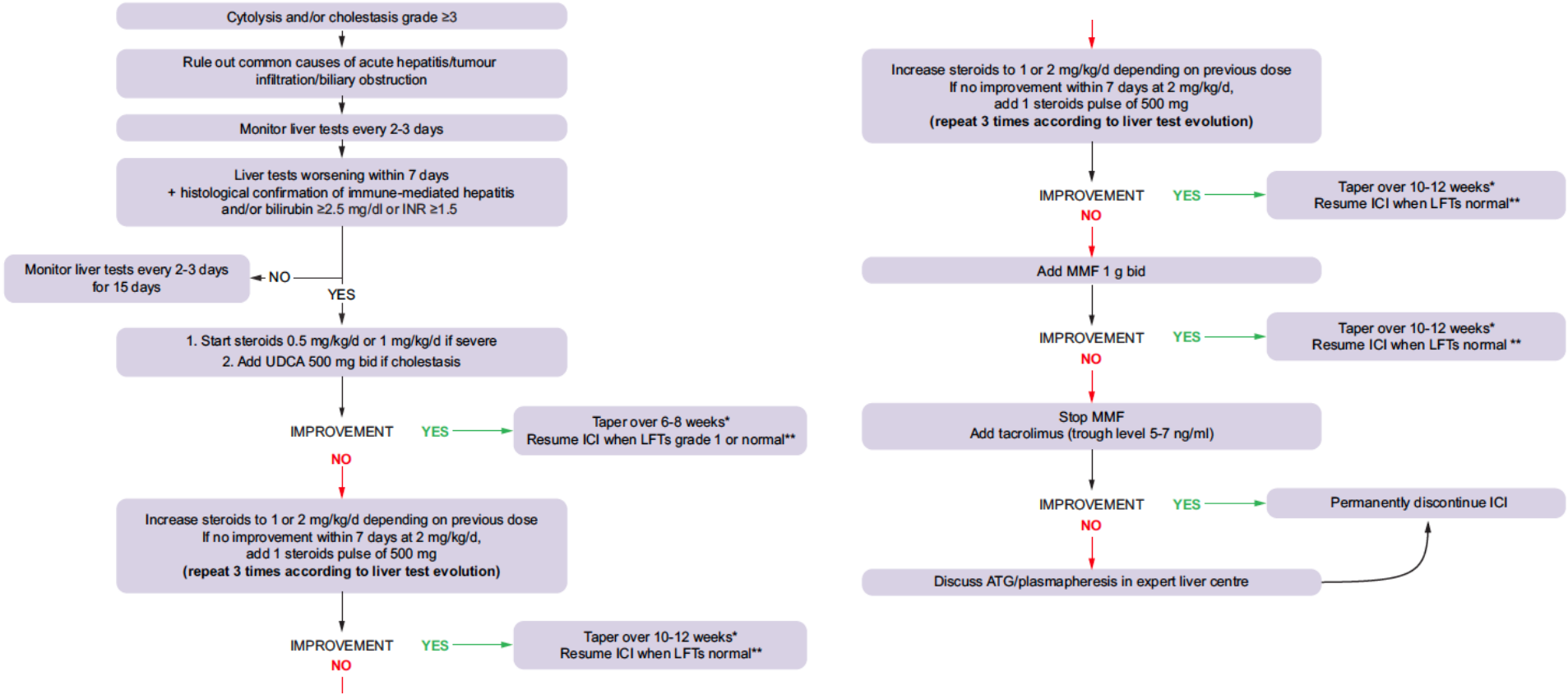
Management proposition



* the biopsy is not recomended if viral hepatitis

De Martin, J Hepatol 2018

Management of ImmuneCheckpoint inhibitors Hepatitis



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Fulminant hepatitis due to immune checkpoint inhibitors

Case Report

Acute Liver Failure from Anti-PD-1 Antibody Nivolumab in a Patient with Metastatic Lung Squamous Cell Carcinoma

Sarmen, Austin Oncol 2016

Case Report

Mortality due to immunotherapy related hepatitis

Bhave, J Hepatol 2018

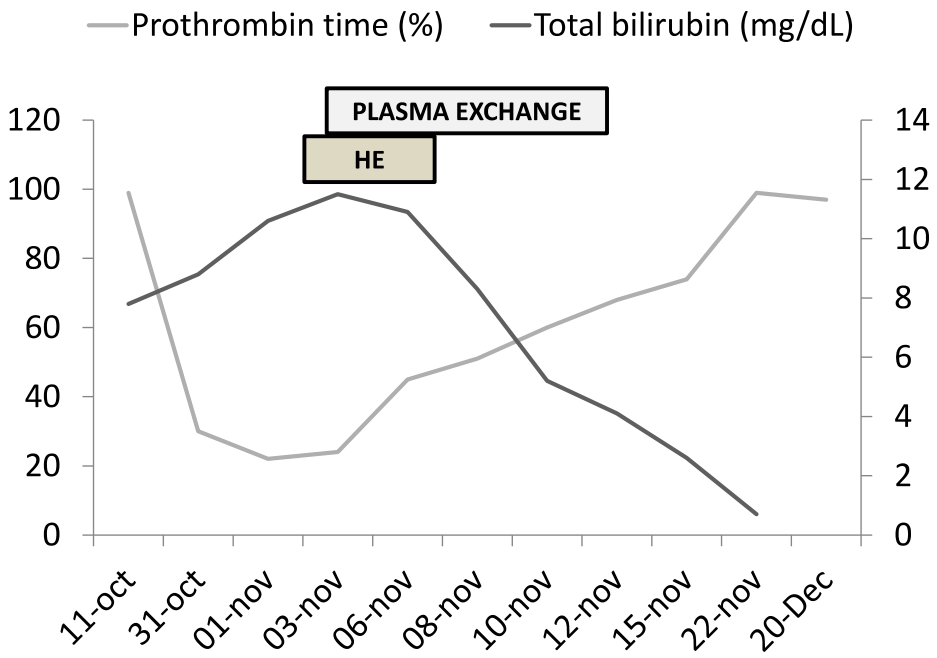
Fulminant hepatitis related death:

- on Vigilyze-Vigibase, the World Health Organization pharmacovigilance database (31.059 treated patients) : **0.4%**
- In a multicenter study (3545 treated patients) : **0.14%**

Wang, JAMA Oncology 2018

Fulminant Hepatitis Treated with Plasma Exchange

- 76-year-old patient with an ovarian cancer → grade 2 hepatitis on **Nivolumab** improved by corticosteroids.
- Introduction of **Ipilimumab** due to cancer progression → no response to 2mg/kg/day of steroids + 1.5 g/day of MMF.
- **Development of fulminant hepatitis**.
- Resolution with **plasma exchange**.



HE: hepatic encephalopathy

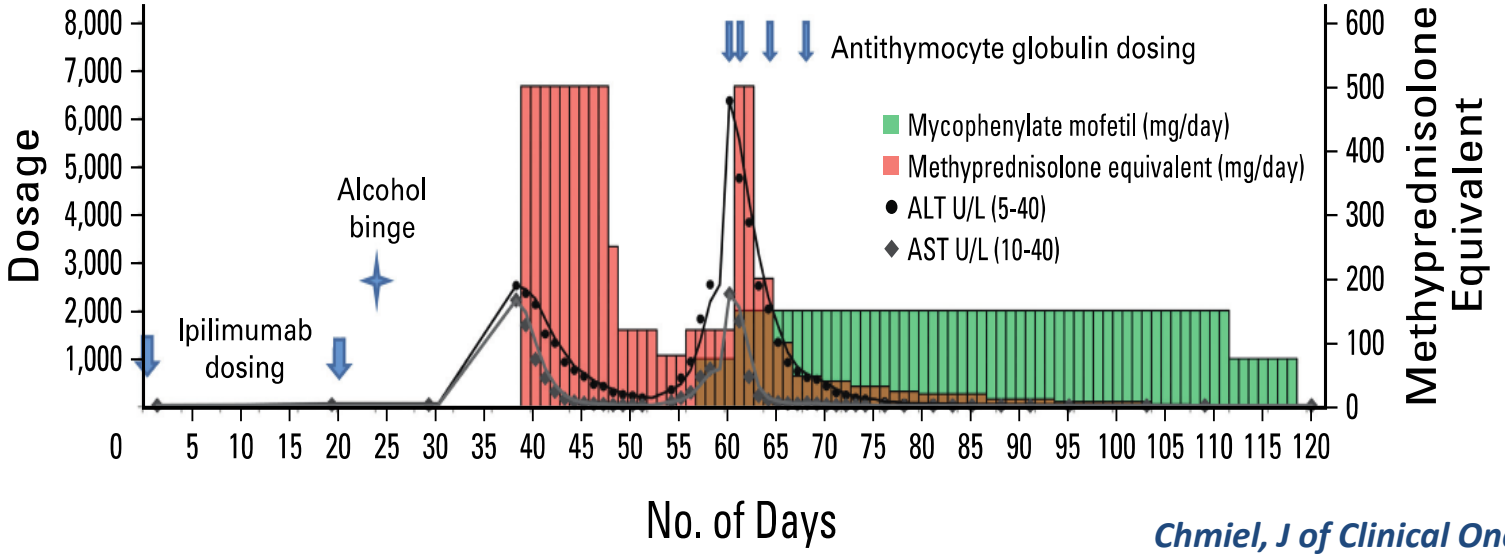
Riveiro-Barcela, J Hepatol 2018

Corticosteroid-Resistant Liver Toxicity

- 60 year-old patient with metastatic melanoma treated with ipilimumab, developed a grade 3 hepatitis

- After a first improvement with corticosteroids, he relapsed

  He was successfully treated with the add of **MMF** and **Antithymocyte globulin**



Chmiel, J of Clinical Oncol 2011

Liver Toxicity Treated with Triple Immunosuppression

- 50 year-old patient with metastatic melanoma treated with ipilimumab, developed a grade 3 hepatitis
- She was started on 2mg/kg/day of **methylprednisolone** without improvement
- **MMF** and **Antithymocyte globulin** were added with hepatitis resolution

Table 2 Liver function tests and absolute lymphocyte count during treatment

Test	Normal range	D0 Baseline	D1 MEP 1st dose	D2 MEP 2nd and ATGAM 1st dose	D3 MEP 3rd and ATG 2nd dose	D4 MEP 4th	D15	D30
ALT	<34 U/L	19	640	4700	1460	1520	40	20
AST	<31 U/L	16	936	7280	265	205	35	18
GGT	<38 U/L	29	186	244	174	181	30	25
ALP	42–98 U/L	91	366	604	326	304	89	76
Bilirubin (total)	<20 μmol/L	11	15	30	12	12	11	9
Absolute lymphocyte count	$1–4\times10^9$	1.47	1.08	0.86	0.07	0.08	1.1	2.2

ALP, alkaline phosphatase; (ATGAM) Horse anti thymocytic globulin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT,γ-glutamyl transferase; MEP, methylprednisolone.

Ahmed, BMJ Case Rep 2015

HCV Reactivation during Immune Checkpoint Inhibitors ?

Study	Type of study	N of patient	Immunotherapy	Viral load before therapy	Evolution
Minter (2013)	Case report	1	Anti-CTLA-4	Positive	Reduction of viral load with a slight increase after therapy discontinuation
Sangro (2013)	Multicenter open-lable phase 1b trial	21	Anti-CTLA-4	Positive	Reduction of viral load
Ravi (2014)	Case series	4	Anti-CTLA-4	Positive	Reduction of viral load for 2 patients. stabilization in 1 patient and possible drug-induced hepatitis in 1 patient which improved with corticosteroids
Davar (2015)	Case report	2	Anti-PD1 (1 patient) Anti-CTLA-4 (1 patient)	Positive	Both patients with HCV monoinfection and HCV/HIV coinfection = stability of viral load and liver tests.
El-Khoueiry (2017)	Multicenter open-label phase 1-2 trial	50	Anti-PD1	Positive	Transient reduction of viral load
Duffy (2017)	Single center prospective study	16	Anti-CTLA4	Positive in 14 patients	Reduction of viral load in most of the patients
Zhu (2018)	Multicenter non-randomized open-label phase 2 trial	26	Anti-PD1	Positive	No flares

- Viral load reduction

HBV Flares during Immune Checkpoint Inhibitors ?

Study	Type of study	N of patient	Immunotherapy	Viral load before therapy	Evolution
HBV					
Ravi (2014)	Case series	5	Anti-CTLA-4	Negative in 2 patients and positive but on antiviral therapy in 3 patients	No reactivation or increase of viral load or liver tests
Lake (2017)	Case report	1	Anti-PD-1	negative	Reactivation on immunotherapy Resolution on tenofovir
Koksal (2017)	Case report	1	Anti-CTLA-4 followed by Anti-PD-1	HBsAg+ HBV-DNA not known	Reactivation on immunotherapy Resolution on tenofovir
El-Khoueiry (2017)	Multicenter open-label phase 1-2 trial	15 (dose escalation) 51 (dose expansion)	Anti-PD1	< 100 IU/mL	Patients were on antiviral therapy. No reactivation and no AcHbs seroconversion
Duffy (2017)	Single center prospective study	5	Anti-CTLA-4	4 patients = negative 1 patient = positive	4 patients were on antiviral therapy and had no reactivation; 1 patient without therapy showed reduction in viral load
Zhu (2018)	Multicenter non-randomized open-label phase 2 trial	22	Anti-PD1	< 100 IU/mL	Patients were on antiviral therapy. No reactivation

- Most of the patients on antiviral therapy
- 2 case reports of reactivation

Possibility of HBV Reactivation in HBsAg +ve patients on Immunotherapy

Table 3 Efficacy of antiviral prophylaxis in HBsAg-positive patients

Events	No. (%) of patients			Difference between groups, % (95% CI)	OR (95% CI)	*P* value[a]
	Total ($n = 114$)	Patients without antiviral prophylaxis ($n = 29$)	Patients with antiviral prophylaxis ($n = 85$)			
Hepatitis						
All grades	35 (30.7)	8 (27.6)	27 (31.8)	4.2 (−16.01–20.83)	0.82 (0.32–2.08)	0.674
Grade 3/4	10 (8.8)	4 (13.8)	6 (7.1)	6.7 (−4.50–23.89)	2.10 (0.55–8.07)	0.467
HBV reactivation	6 (5.3)	5 (17.2)	1 (1.2)	16.0 (5.05–33.33)	17.50 (1.95–157.07)	0.004
HBV-related hepatitis	5 (4.4)	4 (13.8)	1 (1.2)	12.6 (2.80–29.40)	13.44 (1.44–152.79)	0.019
Immunotherapy disruption[b]	11 (9.6)	4 (13.8)	7 (8.2)	5.6 (−5.78–22.88)	1.78 (0.48–6.60)	0.609

Table 2 Details of the 6 Patients with HBV reactivation

Patients Characteristics				Baseline			At reactivation						
Patient	Age (years)	Gender	Cancer type	Anti-tumor therapy	HBV DNA (IU/mL)	Antiviral prophylaxis	Weeks from start of immunotherapy	HBV DNA (IU/mL)	Peak ALT (U/L)	Anti-PD-1/PD-L1 therapy disruption	Antiviral treatment	Time for achieving HBV-DNA undetectable (weeks)	Time for ALT recovery (weeks)
1	48	M	NPC	Camrelizumab	Undetectable	Nil	3	7.81×10^3	191.4	Delayed	Entecavir	1	2
2	47	M	NPC	Camrelizumab	Undetectable	Nil	16	6.98×10^4	203.0	Delayed	Entecavir	4	4
3	39	M	Melanoma	Pembrolizumab	Undetectable	Nil	28	2.10×10^3	27.6	No	Nil	5	NA
4	36	M	HCC	Nivolumab	Undetectable	Entecavir	12	1.80×10^3	298	Discontinued	Entecavir plus tenofovir	1	3
5	45	M	HNSCC	Toripalimab	Undetectable	Nil	35	4.04×10^6	281.2	Delay	Entecavir	3	6
6[a]	41	F	Soft Tissue Sarcoma	Nivolumab	Undetectable	Nil	20	6.00×10^7	465.1	NA	Entecavir	8	4

[a]HBV reactivation in this patient occurred 6 weeks after immunotherapy was discontinued; other HBV reactivation occurred during anti-PD-1/PD-L1 thearpy
Abbreviations: *M* male, *F* female, *HBV* hepatitis B virus, *NPC* nasopharyngeal carcinoma, *HCC* hepatocellular carcinoma, *HNSCC* head and neck squamous cell cancer, *ALT* alanine aminotransferase, *NA* not applicable

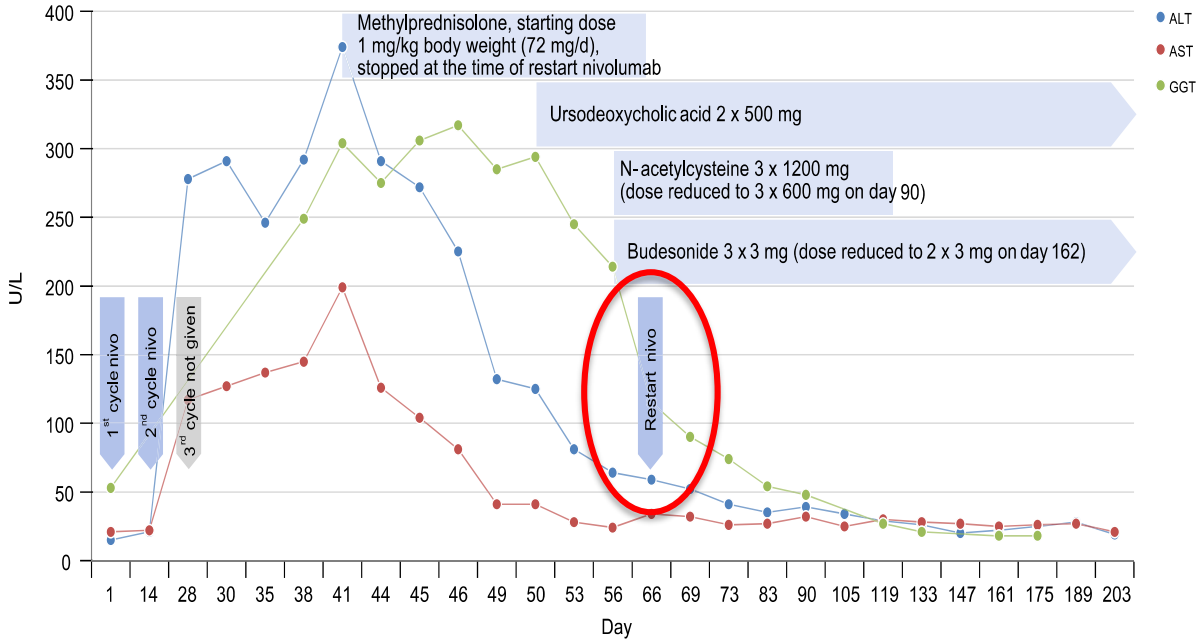
X Zhang J Immunotherapy Cancer 2019

Reintroduction of a checkpoint inhibitor ?

Re-introduction of Immunotherapy after Severe Hepatitis: Budesonide Prophylaxis

- 73-year-old patient with metastatic melanoma → grade 3 hepatitis after 2 cycle of **Nivolumab**.
- No hepatitis recurrence after immunotherapy reintroduction **on budesonide prophylaxis**.

Evolution of AST, ALT and GGT

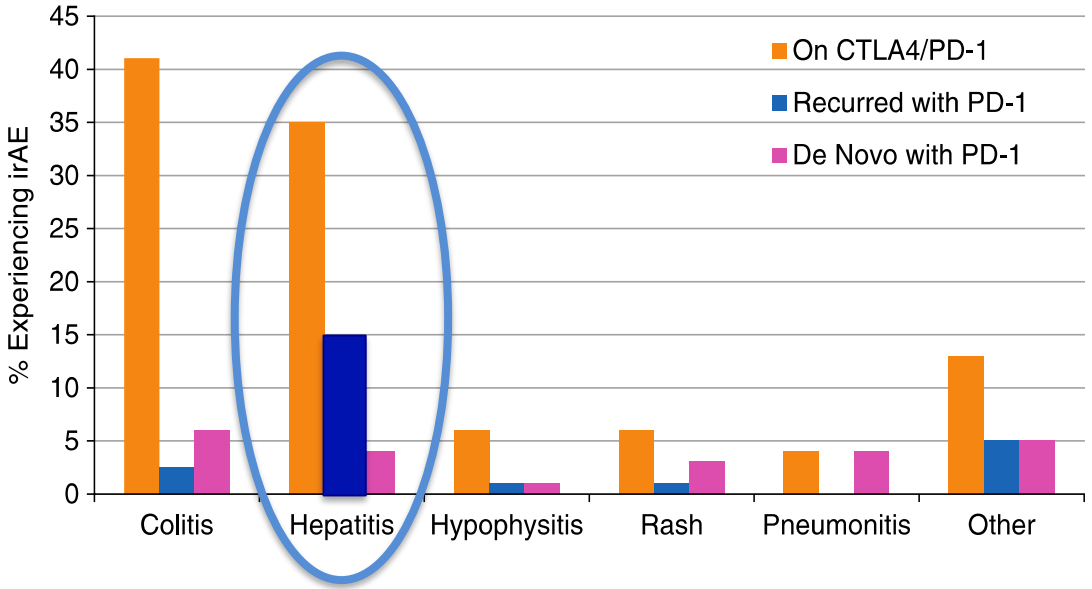


Ziemer, J Hepatol 2016

Safety of Resuming Anti-PD1 after IrAEs with Combination Therapy Anti-PD1 + Anti-CTLA4

- 80 patients treated with combination therapy.
- All discontinued immunotherapy due to irAEs, 29 (36%) for hepatitis, 19 (24%) grade 3 or 4.
- All patients resumed **anti-PD1** therapy and 50% experienced a toxicity.
- **5 (17%) patients had hepatitis recurrence.**

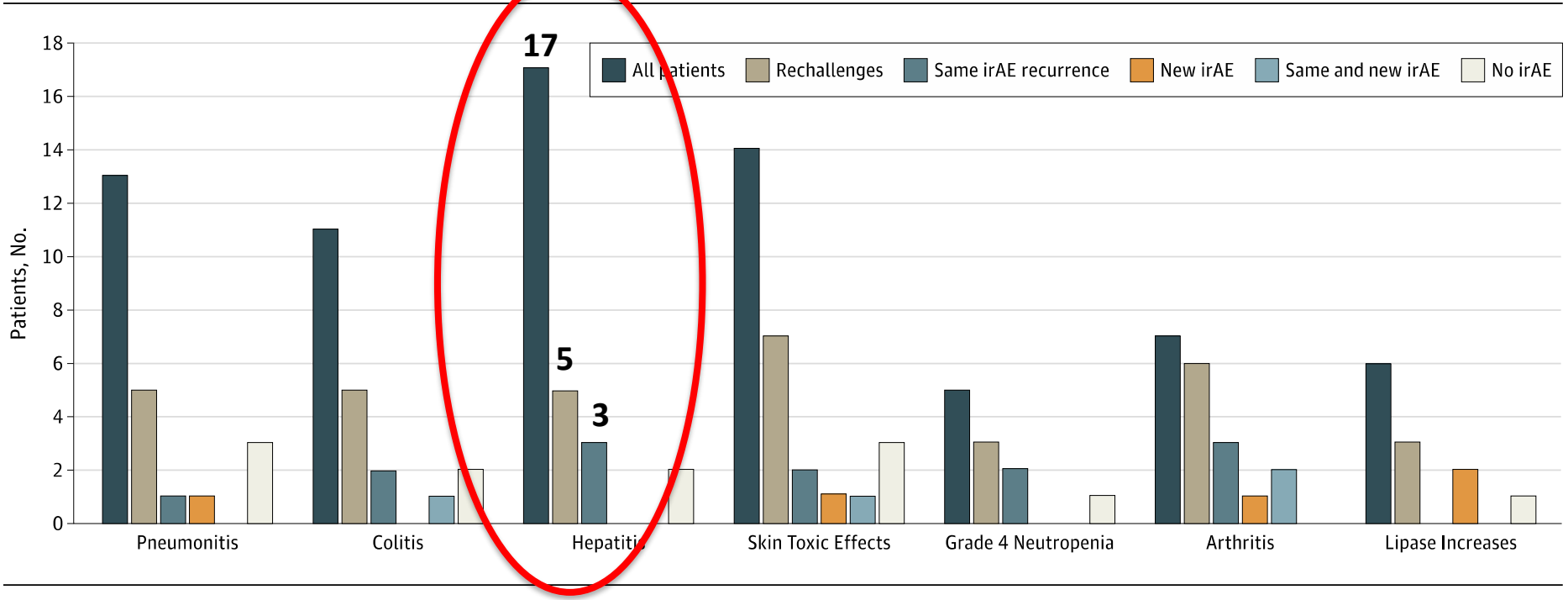
Percentage of patients with toxicities with combination therapy and after resuming anti-PD1



Pollack, Ann Oncol 2018

Safety of Resuming Anti-PD1 or Anti-PD-L1 after IrAEs

Figure. Patient Outcomes After Anti–PD-1 or Anti–PD-L1 Rechallenge as a Function of Immune-Related Adverse Event (irAE) Type



3/5 (60%) patients developed an hepatitis after the rechallenge → irAEs is not systematic

Simonaggio, JAMA Oncol 2019

Rechallenge after ICI-Liver Toxicity

Table 3. Re-challenge with ICIs after resolved immune-mediated hepatitis.

Study	Patients retreated with ICI after liver toxicity	ICI first therapy	Grade of first liver toxicity ≥3	ICI re-challenge	Time between toxicity and reintroduction Days (median, range)	Liver toxicity recurrence	Other irAEs
Ziemer 2016	2	Anti-PD-1	2	Anti-PD-1	103 and 38	0	0
Spankuch 2017	1	Anti-CTLA-4 + anti-PD-1	1	Anti-PD-1	n.a.	0	0
Spain 2017	2	Anti-CTLA-4 + anti-PD-1	2	Anti-CTLA-4 + anti-PD-1	n.a.	1 (grade 4)	1
Pollack 2018	29	Anti-CTLA-4 + anti-PD-1	19	Anti-PD-1	58 (14-395)	5	n.a.
De Martin 2018	3	Anti-CTLA-4 + anti-PD-1	3	Anti-PD-1	n.a.	1	0
Gauci 2018	5	Anti-CTLA4 or Anti-PD-1	NA	Anti-CTLA-4 or Anti-PD-1	n.a.	0	0
Riveiro-Barciela 2019	1	Anti-PD-1	0	Anti-CTLA-4	n.a.	1 (grade 4)	0
Simonaggio 2019	5			Anti-PD-1 or Anti-PDL-1		3	0
Cheung 2019	4	Anti-CTLA-4 + anti-PD-1	2	Anti-PD-1	n.a.	0	0
Riveiro-Barciela 2020	6	Anti-PD-1 or Anti-PD-L1 or Anti-CTLA-4 (2)	0	Anti-PD-1	n.a.	0	0
Total	**58**		**29 (50%)**			**11 (19%)**	

De Martin
J Hep Reports 2021

Conclusion

- Hepatic irAEs are characterized by an extreme variability.
- In patients with immune-mediated hepatitis liver biopsy helps to confirm the diagnosis and to evaluate the severity of liver injury.
- Corticosteroid therapy should not be given systematically, even for grade 3-4 toxicity, but according to the biological and histological severity of hepatitis.
- In patients who experience immune-mediated hepatitis, immunotherapy reintroduction is possible with risk since predictive factors for hepatitis recurrence or immune toxicity of another organ are lacking.
- Specific aspects such as viral coinfection and baseline liver function should be taken into account

Multidisciplinary approach

Oncologist, Immunologist, Pharmacologist, Organ specialists..

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