ImmunoScience Academy

Partnering for Education & Optimizing Treatment in ImmunoScience

Liver enzyme elevations and hepatotoxicity in patients treated with checkpoint inhibitor immunotherapy

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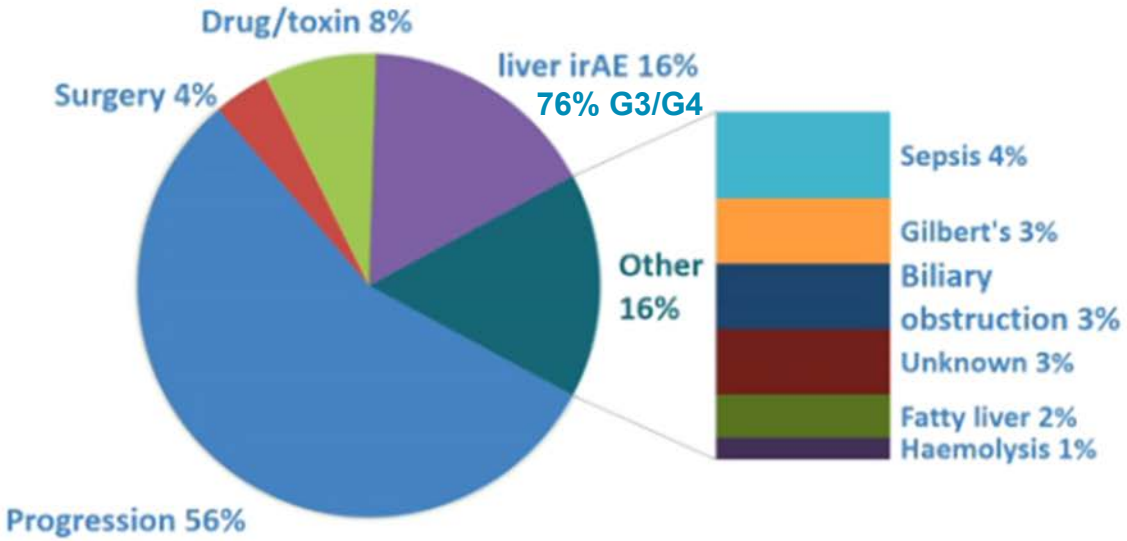
disclose no financial relationships with a commercial interest in relation to this presentation

Liver enzyme elevations in patients exposed to CPI

There's more to this than meets the eye

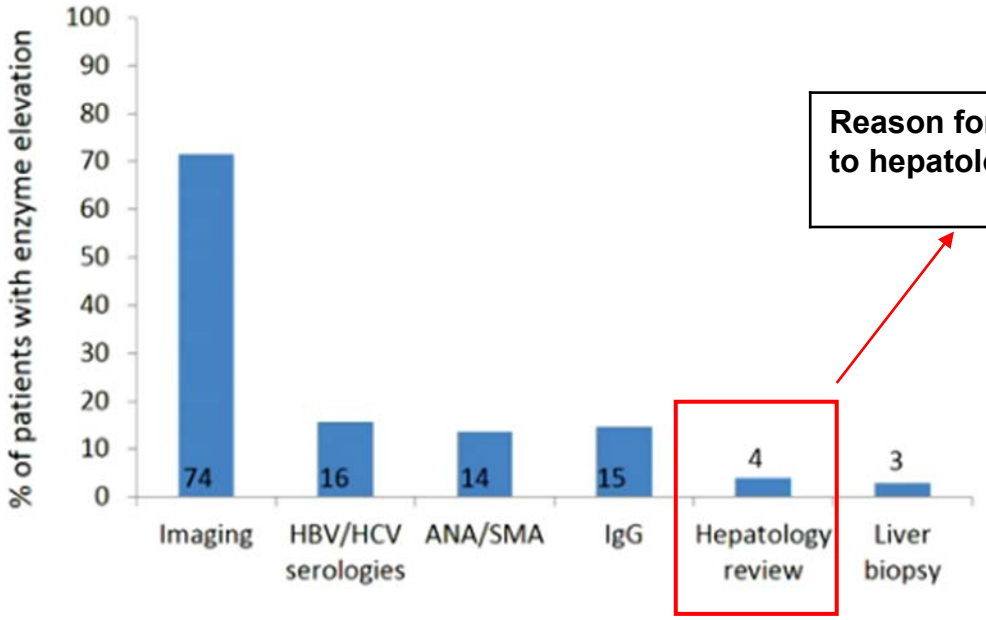
Causes of liver enzyme elevation in patients treated with CPI

- 472 patients: CTLA-4, PD-1, PD-L1 (2010 – 2018)
- ↑ AST, ALT, bilirubin : n = 102 (20.7%)



M. Cunningham et al. J Hepatol 2019;70(1):E89-E89

Assessment of liver enzyme elevation



Reason for referral to hepatology	**ALT / AST > 1000 (n=2)** **Persistent G2 ALT/AST (n=1)** **Rebound after steroid taper (n=1)**

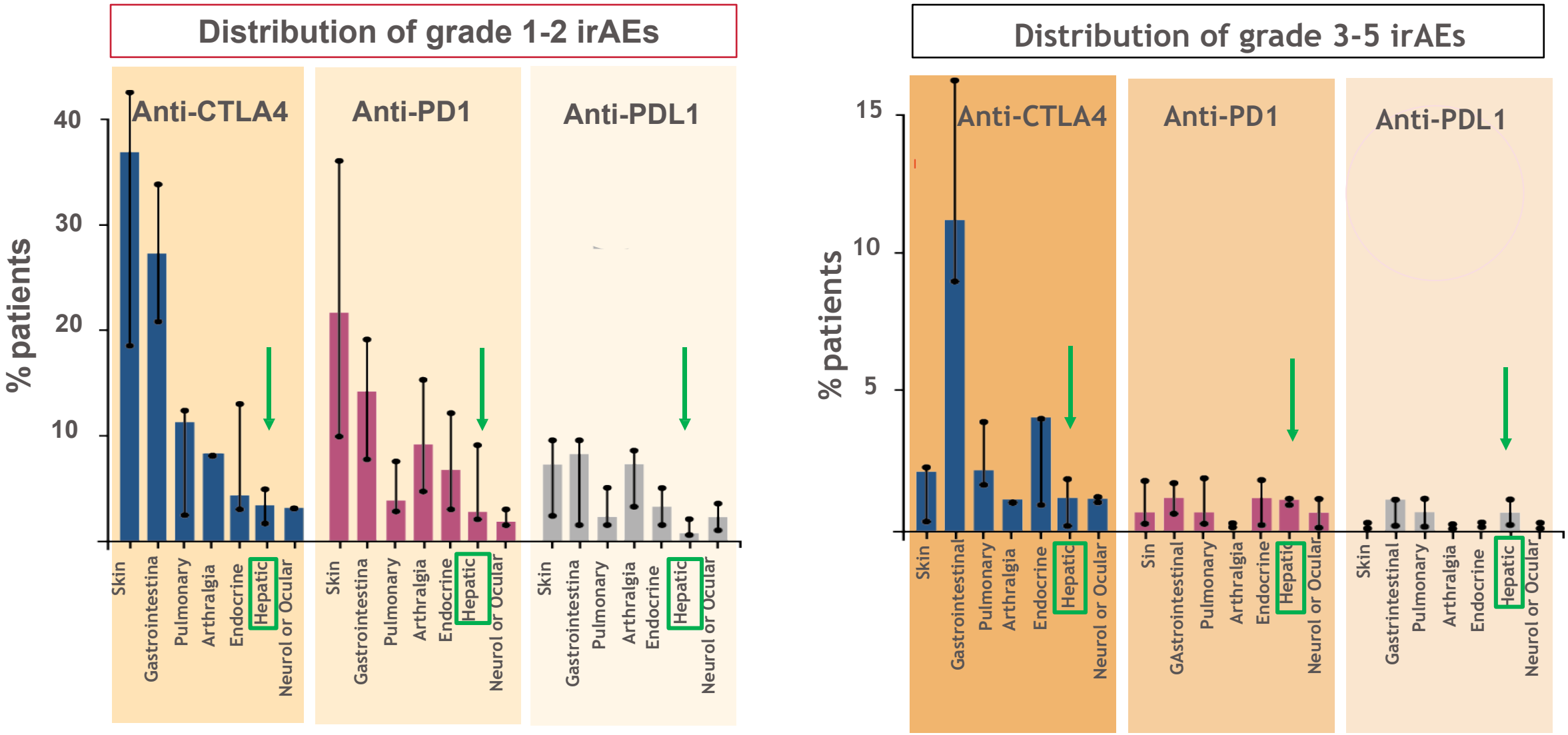
M. Cunningham et al. J Hepatol 2019;70(1):E89-E89

Immune-related hepatitis / hepatic irAEs

- Current clinical guidelines are based largely on trial protocols and case reports

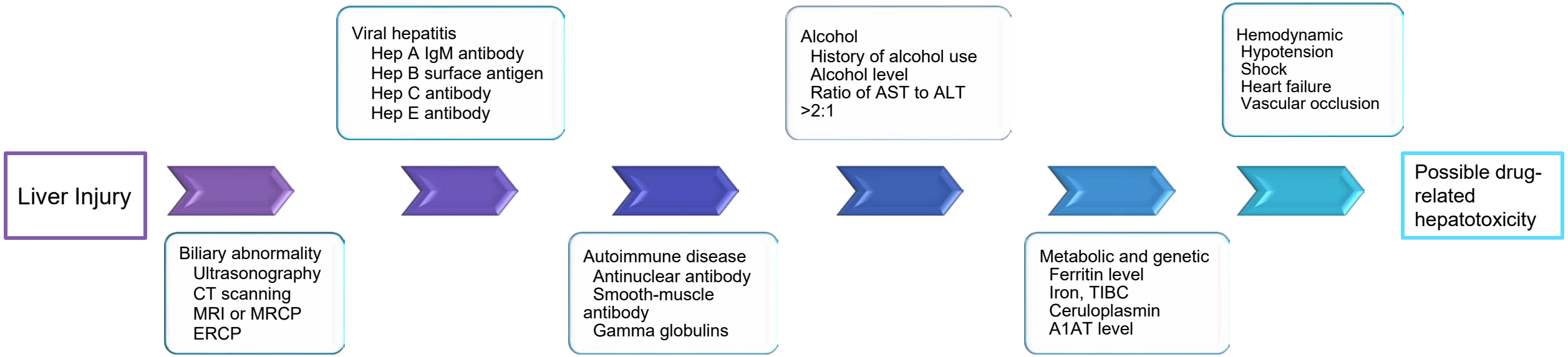
- Little data to guide investigation and management !

Prevalence of hepatic irAEs for all tumor types



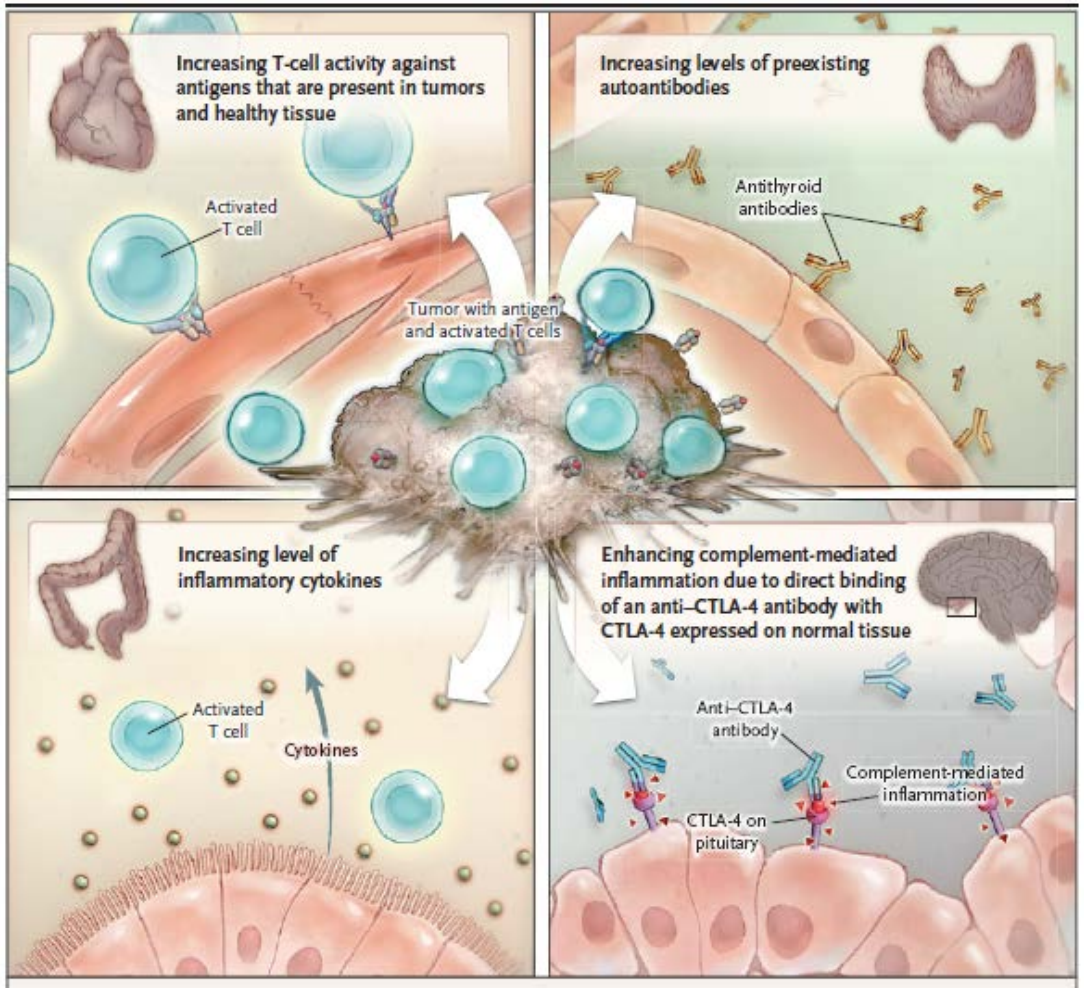
Adapted from Michot et al. Eur Journal of cancer 2016:54:139-146

Diagnostic approach



Adapted from Navarro et al. NEJM 2006;354:731-9

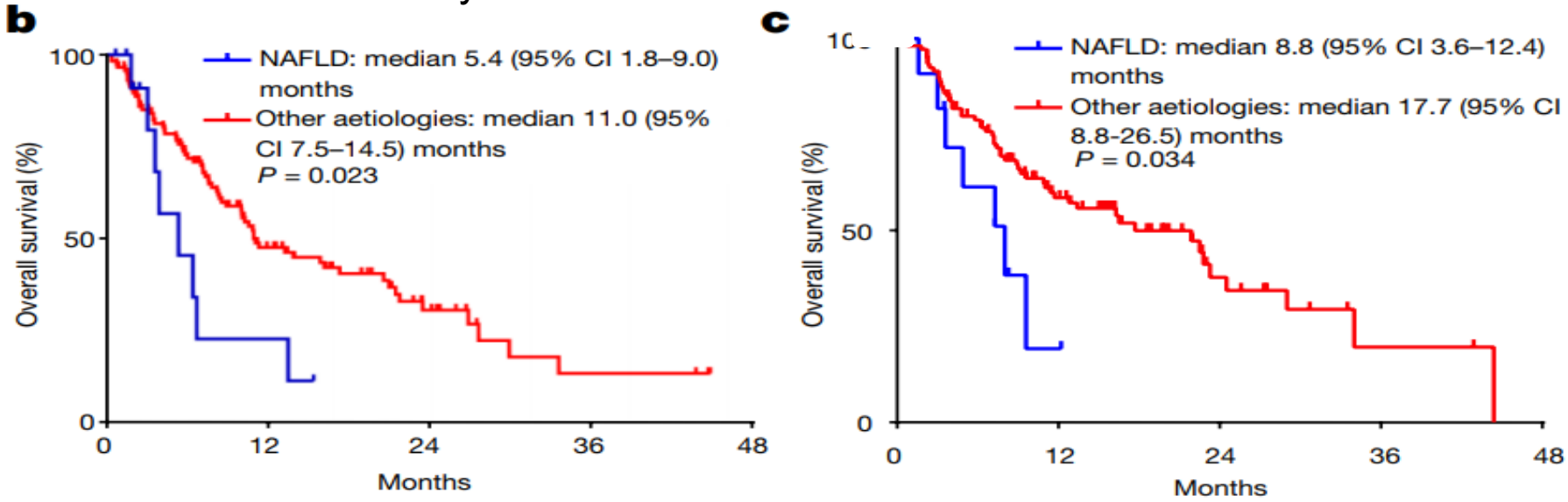
Possible mechanisms underlying irAEs



Postow NEJM 2018;378(2):158

NASH limits anti-tumour surveillance in immunotherapy-treated HCC

- Data suggest that NASH etiology limits response to immunotherapy
  - NASH disrupts the immune microenvironment, negatively impacting the response to immunotherapy + increasing the liver fibrosis
  - Driven by certain activated CD8+PD1+ T cells
  - The authors also hypothesized that patients with a metabolic syndrome and concomitant cancer at other organ sites might be at risk for liver damage in response to immunotherapy, which warrants further study



Pfister et al. Nature 2021;592(7854)450-456

Mister M.J., 65 years

In May 2017 was referred to hepatology for

grade IV hepatitis on Ipilimumab + Nivolumab

AST IU/L	**3142**	**Bili mg/dl**	**5.2**
ALT IU/L	**1975**	PT %	100
GGT IU/L	**686**	INR	0,95
ALP IU/L	**684**	Plts x10^9/L	159

Common Toxicity Criteria for Adverse Events (CTCAE)

Cancer Therapy Evaluation of the National Cancer Institute (NCI) of the National Institutes of Health

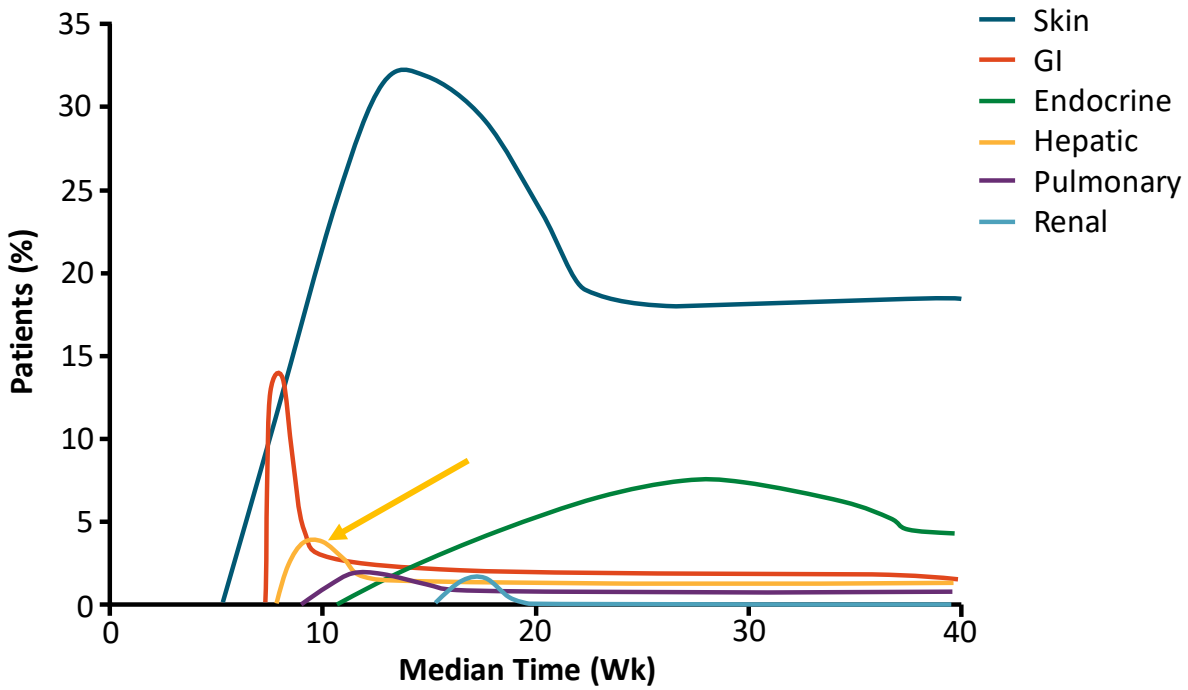
NCI CTCAE v4.03 grading of hepatic AEs[1]				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Increased ALT	• > ULN to 3 × ULN	• > 3 to 5 × ULN	• > 5 to 20 × ULN	• > 20 × ULN
Increased AST	• > ULN to 3 × ULN	• > 3 to 5 × ULN	• > 5 to 20 × ULN	• > 20 × ULN
Increased blood bilirubin	• > ULN to 1.5 × ULN	• > 1.5 to 3 × ULN	• > 3 to 10 × ULN	• > 10 × ULN

NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; ULN, upper limit of normal. 1. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) v4.03. Updated June 14, 2010. Accessed January 7, 2021. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.

- **Past medical history**
  - Coronary artery disease with stenting 2013

  - Febr 2013: diagnosis **melanoma** right leg: resection
  - March 2017: recurrence with hepatic and pulmonary metastases
  - April 2017: ipilimumab + nivolumab
  - May 2017: jaundice and hospitalization

Variability and unpredictability of hepatic irAEs



Beginning and end of a curve indicates median time to onset and median time to resolution, respectively. Peak indicates incidence of AE.

Characteristics of patients with grade ≥ 3

Age, years (range)	63 (33–84)
Sex, female	9 (56)
Patients with past history of immunotherapy	5 (31)
Interval time between immunotherapy and acute hepatitis, weeks (range)	5 (1–49)
Number of injections (range)	2 (1–36)
Patients with previous extrahepatic IRAEs	6 (38)
Fever at the time of hepatitis	6 (38)
AST, IU/L (range)	437 (147–2,289)
ALT, IU/L (range)	460 (266–3,137)
Total bilirubin, µmol/L (range)	18 (6–324)
Alk P, IU/L (range)	309 (53–768)
GGT, IU/L (range)	317 (39–1,252)
Patients with ANA ≥1:80	8 (50)
Patients with ASMA 1:80	3 (19)
IgG, g/L (range)	9 (6–18)

Weber JCO 2017;35:785

De Martin et al. J Hepatol. 2018;68:1181-1190

- **Lifestyle**
  - Alcohol: occasionally

- **Concomitant medication**
  - Acetylsalicylic acid 80mg / day
  - Atorvastatin 40mg / day
  - Paracetamol 3g / day
  - Atenolol 100mg / day

- ***Immunotherapy, statin and paracetamol were stopped***

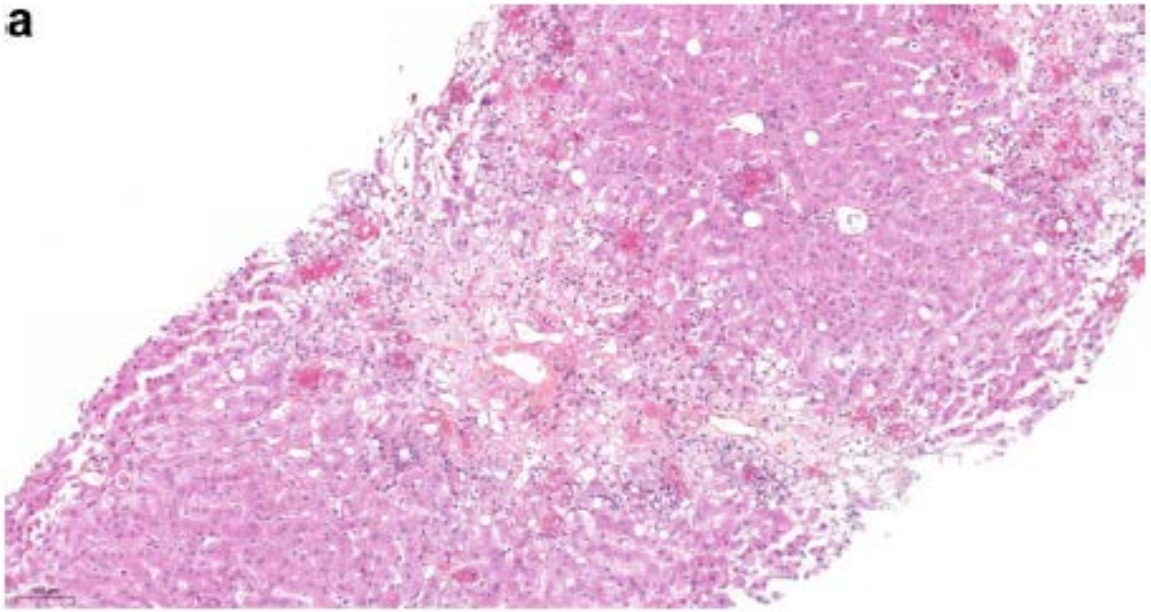
Diagnostic approach

- **Auto-immune serology**
  - ANA 1/160 (speckled), AMA, ASAM, anti-LKM1, IgG, IgA, IgM: negative
- **Infection**
  - Urine culture, blood culture, chest x ray: negative
- **Viral**
  - HAV Ab - , HbsAg -, HBs Ab+, HBc Ab -, HCV Ab -, HIV –
  - PCR CMV, EBV, HEV
- **CT liver/doppler ultrasound**: known meta's without biliary tract dilation

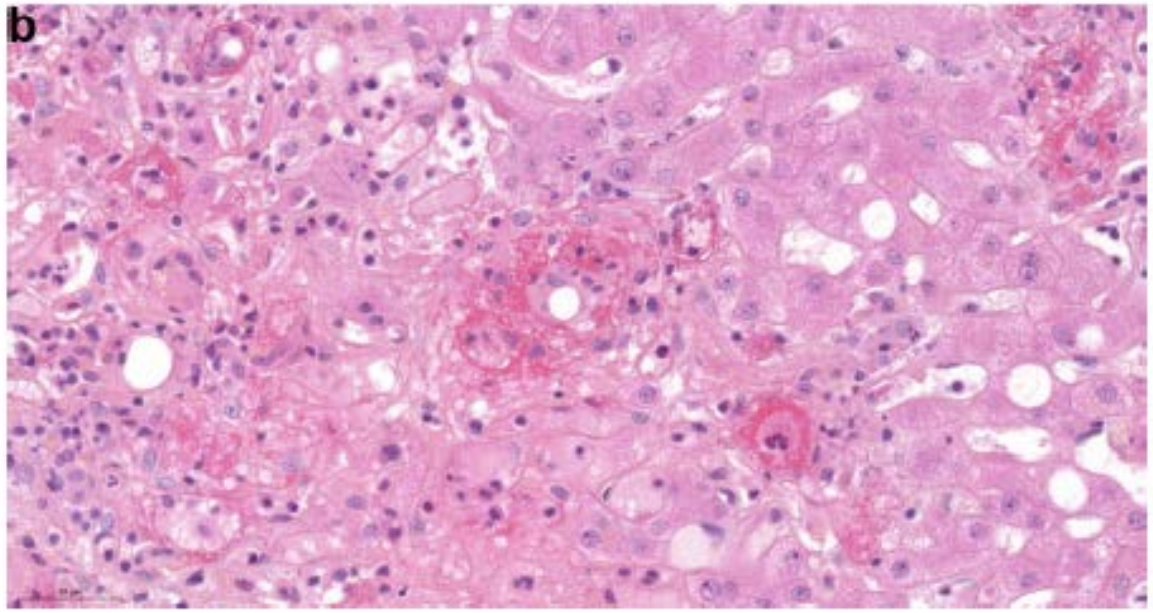
Would you perform a liver biopsy?

- Yes !

Histology: anti-CTLA4: fibring ring granuloma



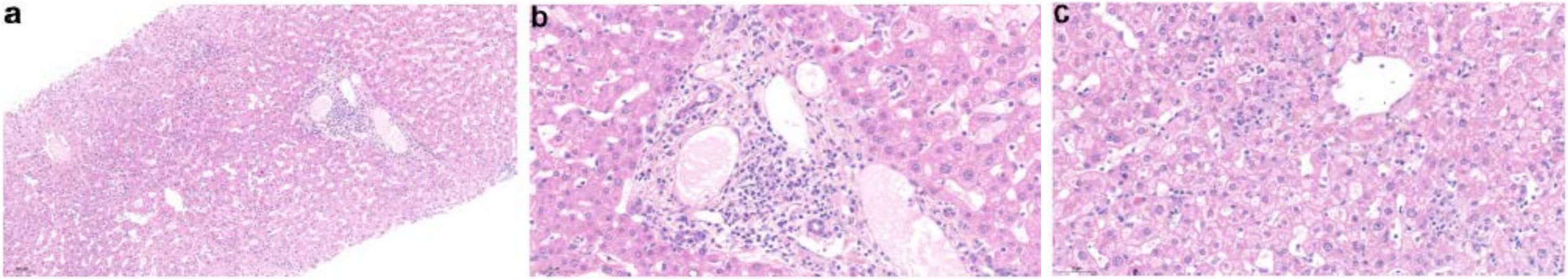
Acute hepatitis with confluent centrilobular necrosis and numerous fibrin ring granulomas (HE x100)



Granulomas: epitheloid cells without giant cell, centered by a lipid vacuole surrounded by a fibrin ring (HE X350)

Papouin et al. Ann Pathol 2018;38(6):338-351

Histology: anti-PD1: lobular hepatitis

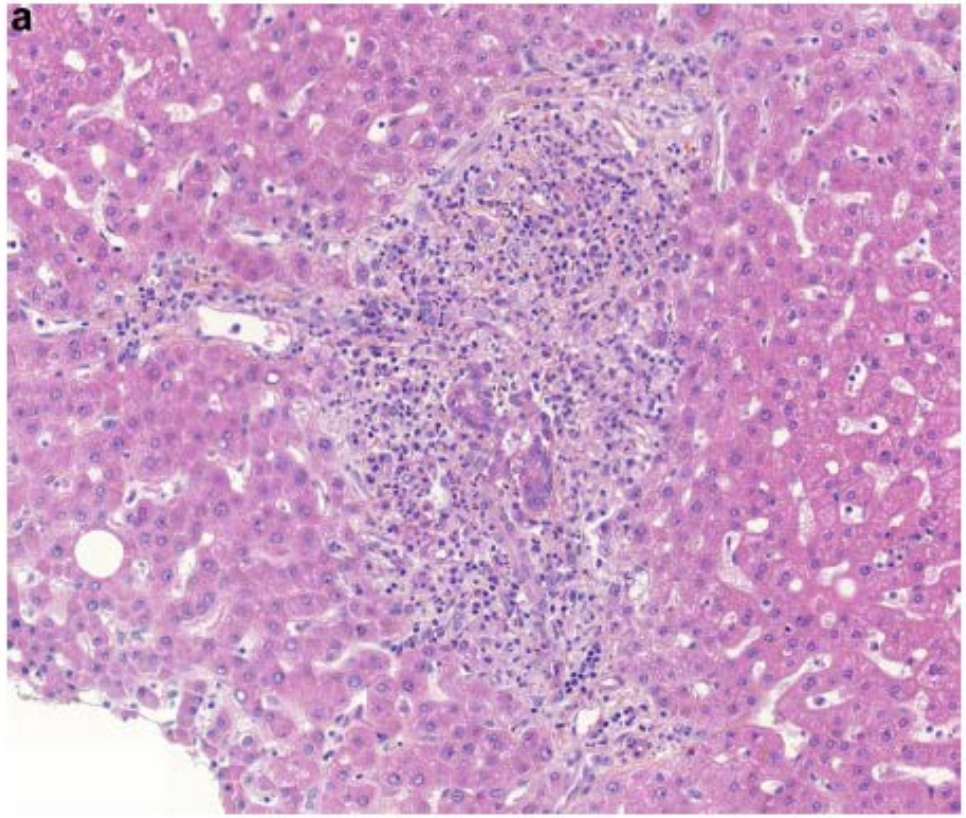


Acute hepatitis with peri-portal inflammatory infiltration and moderate necrotico-inflammatory activity (HE x100)

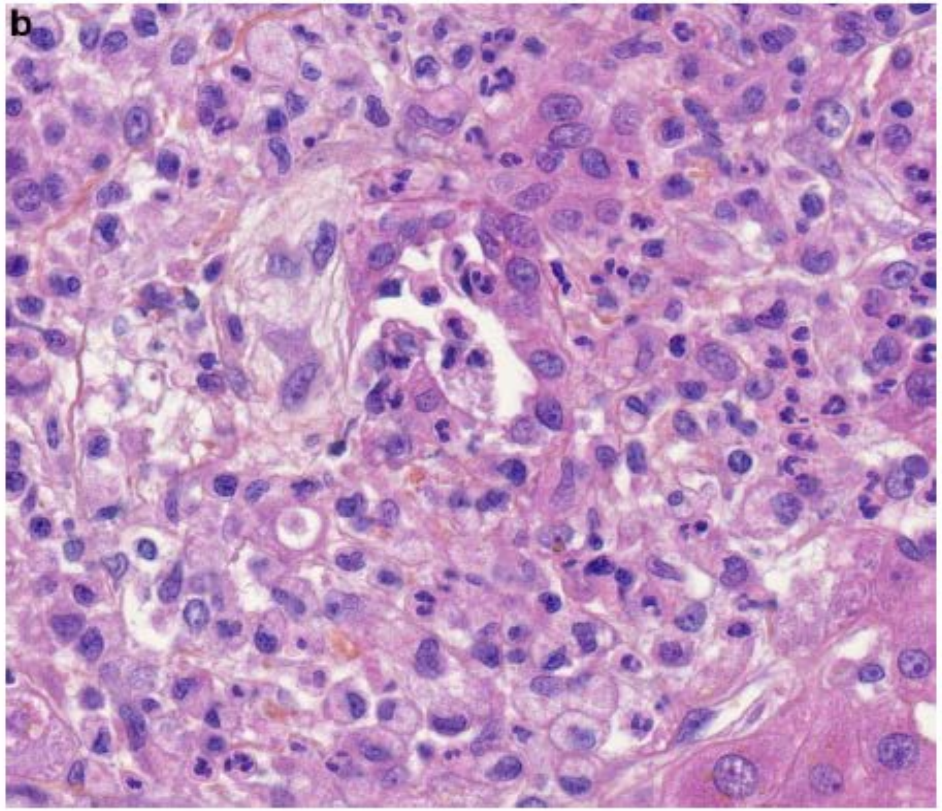
Lobular inflammatory infiltration made by histiocytes and lymphocytes often within the sinusoids. Mild piece meal necrosis (b) – Patchy lobular necrosis (c) (HE x300)

Papouin et al. Ann Pathol 2018;38(6):338-351

Histology: cholangitis, even destructive cholangitis



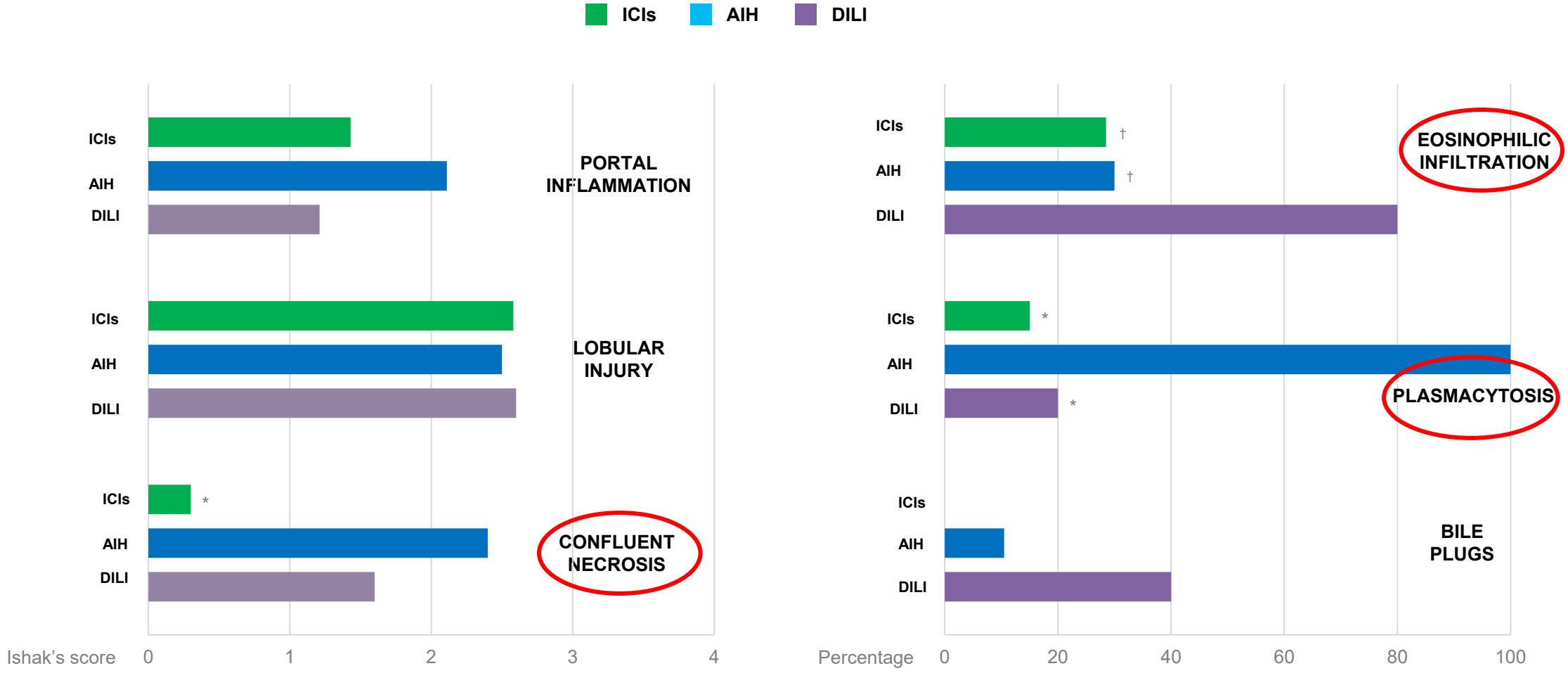
Mixed portal inflammtion with severe portal activity and cholangiolar proliferation (HE x100)



Acute destructive cholangitis (HE x400)

Papouin et al. Ann Pathol 2018;38(6):338-351

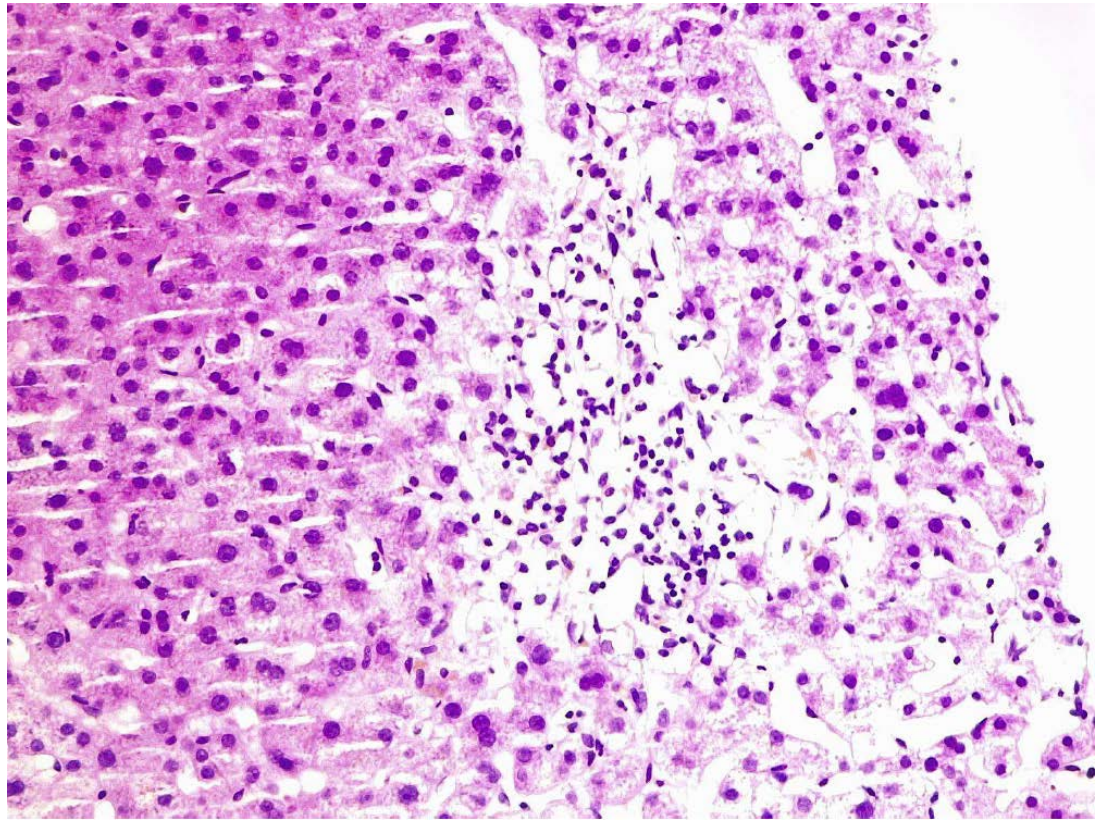
Histology: ‘it is not an classical “auto-immune” hepatitis’

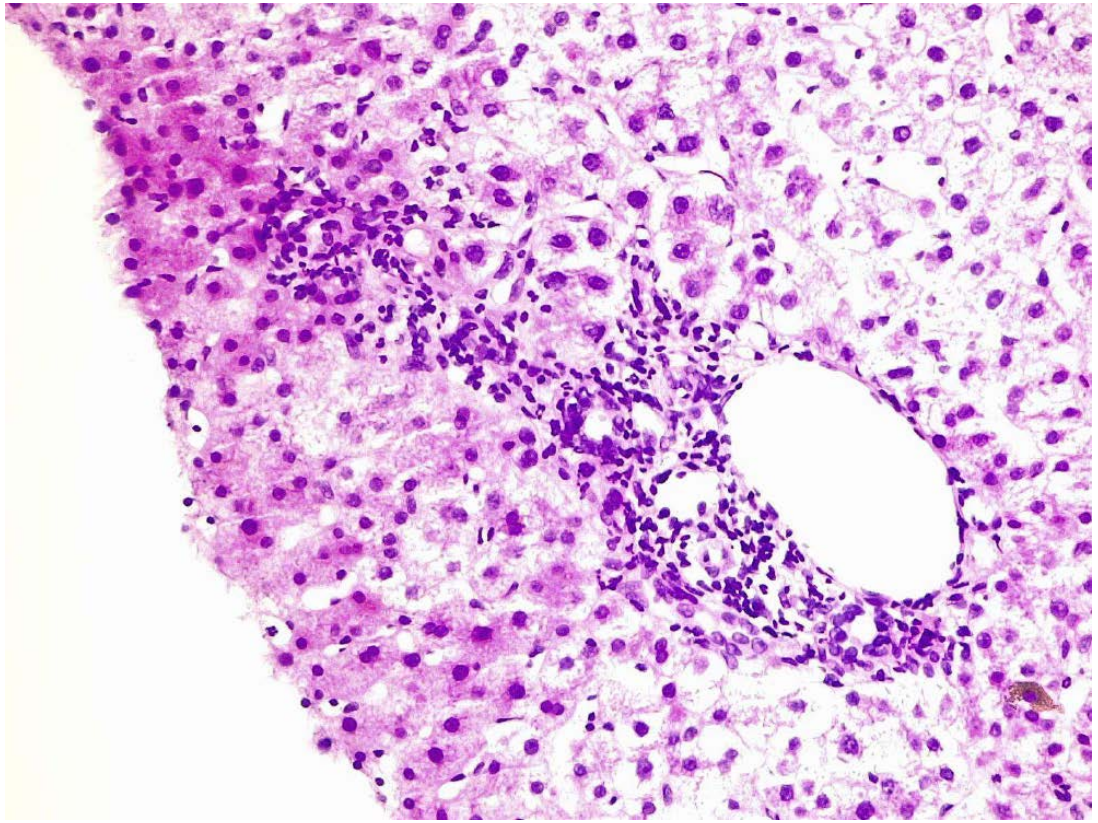


*P<0.05 vs. AIH; †P< 0.05 vs. DILI. AIH, autoimmune hepatitis; ICIs, checkpoint inhibitors; DILI, drug-induced liver injury.

Adapted from Zen et al. Mod Pathol. 2018;31(6):965-973.

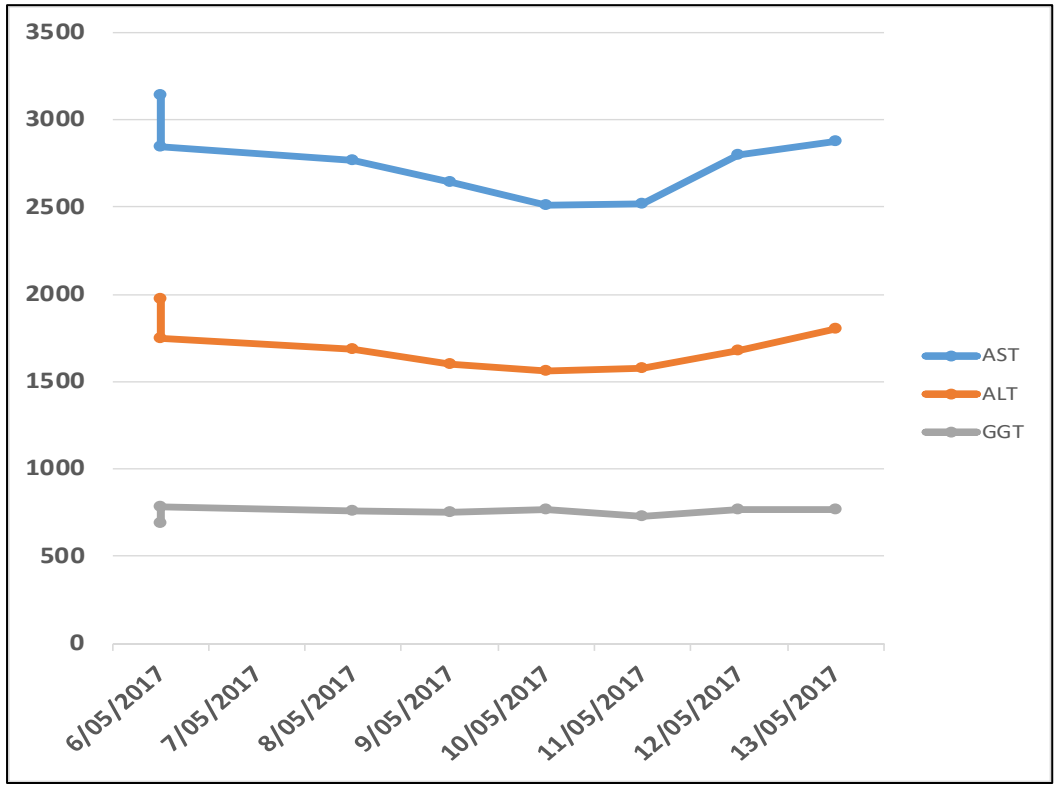
Histology of M.J.

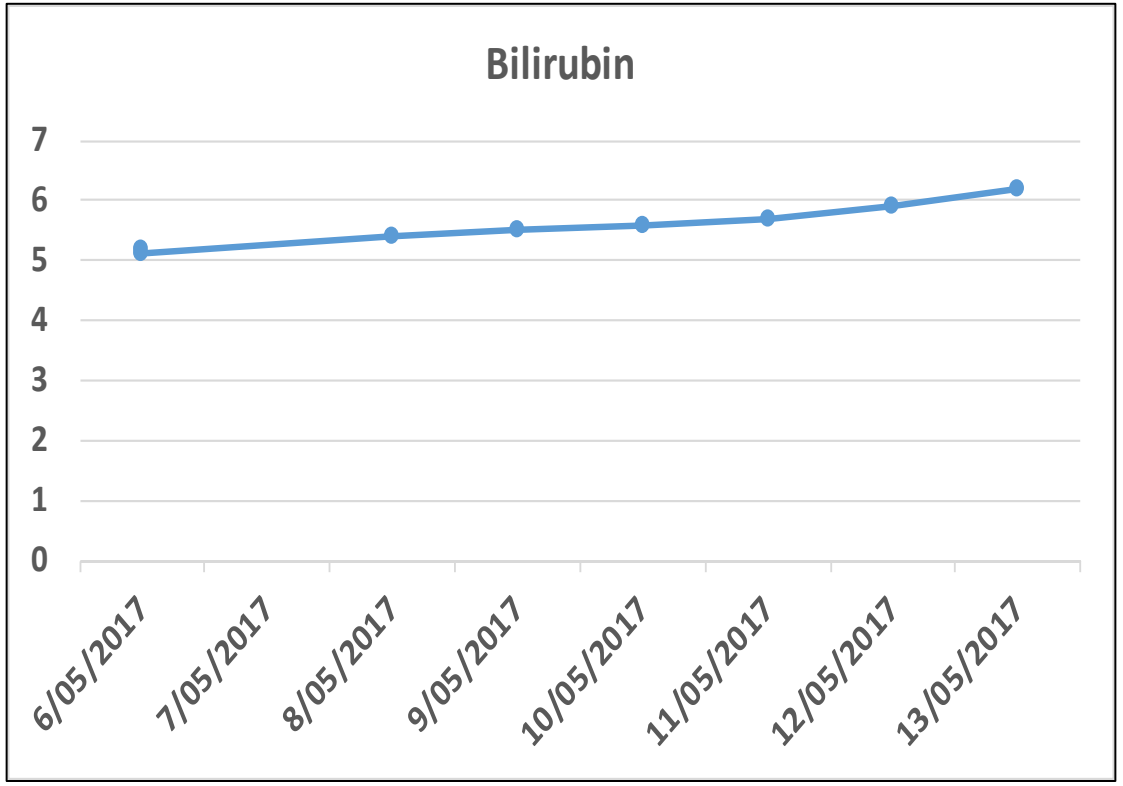




Images kindly provided by Dr. Coppens M et al.

Evolution liver tests of M.J.





Would you introduce a corticosteroid therapy?

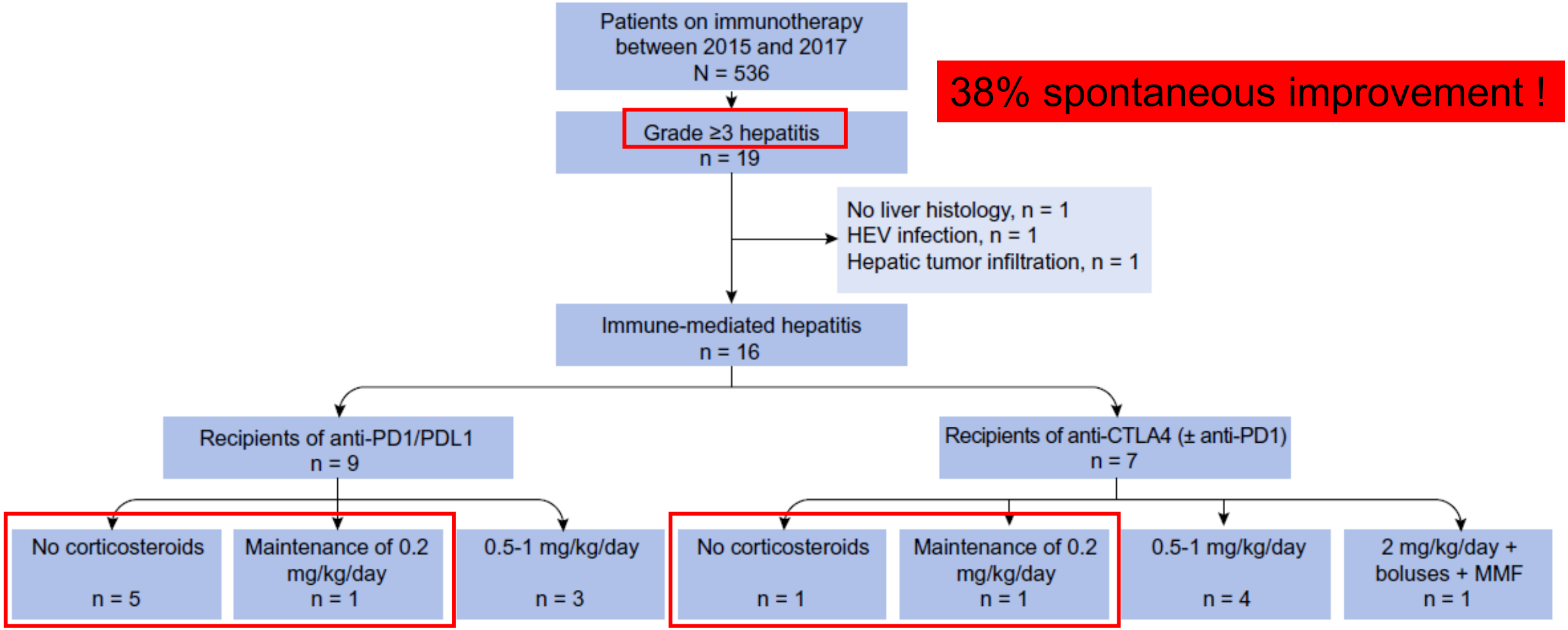
- Yes !

Recommendations of ESMO

ALT/AST ULN	Steroids	
Grade 1 ALT/AST ≤ 3	No	Continue
Grade 2 3<ALT/AST ≤ 5	1mg/kg/day Start steroid tapering over 2 weeks when G1	Hold Continue once resolved to ≤ G1 or prednisolone ≤ 10mg
Grade 3 5 < ALT/AST ≤ 20	1mg/kg/day Start steroid tapering over 4 weeks when G2	Hold; rechallenge only at consultant discretion
Grade 4 ALT/AST > 20	2mg/kg/day If no improvement in 2-3 days, add additional/alternative immune supression	Discontinue

Haanen et al. Ann of Oncology 2017;28(4):i119-i142

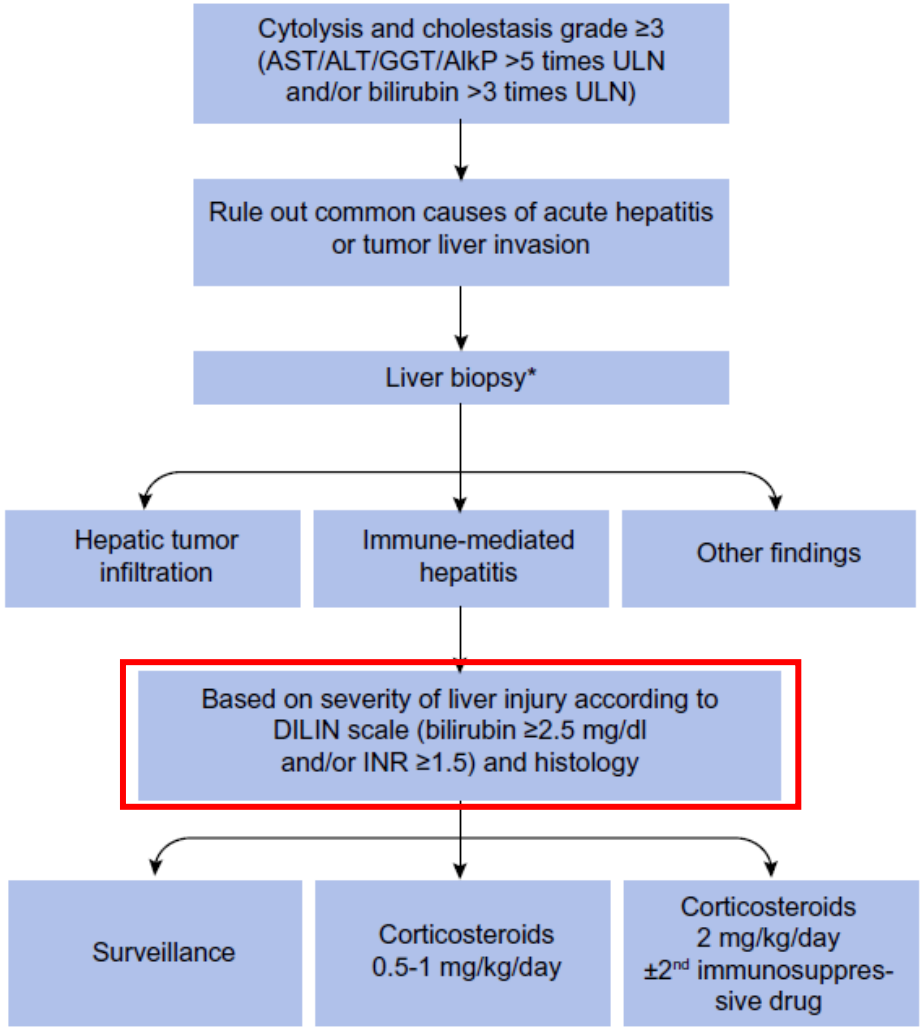
Hepatitis irAEs: *are corticosteroids always needed*?



38% spontaneous improvement !

De Martin et al. J Hepatol. 2018;68:1181-1190

Hepatitis irAEs: *are corticosteroids always needed*?

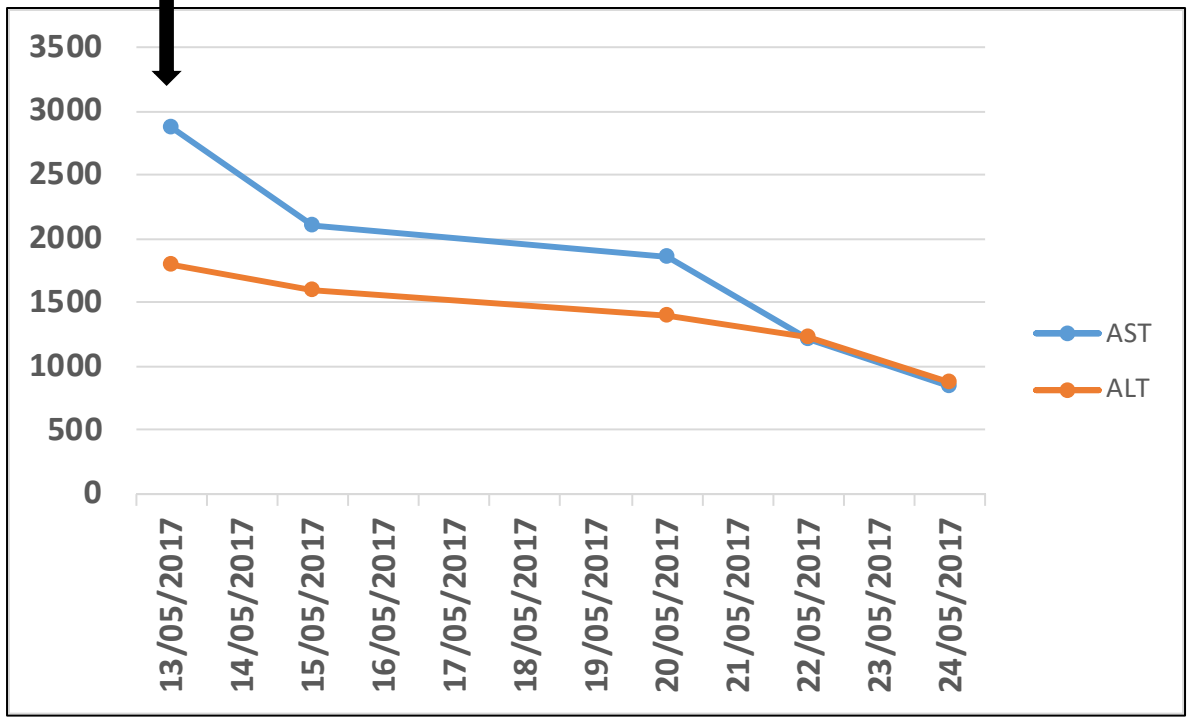


De Martin et al. J Hepatol. 2018;68:1181-1190

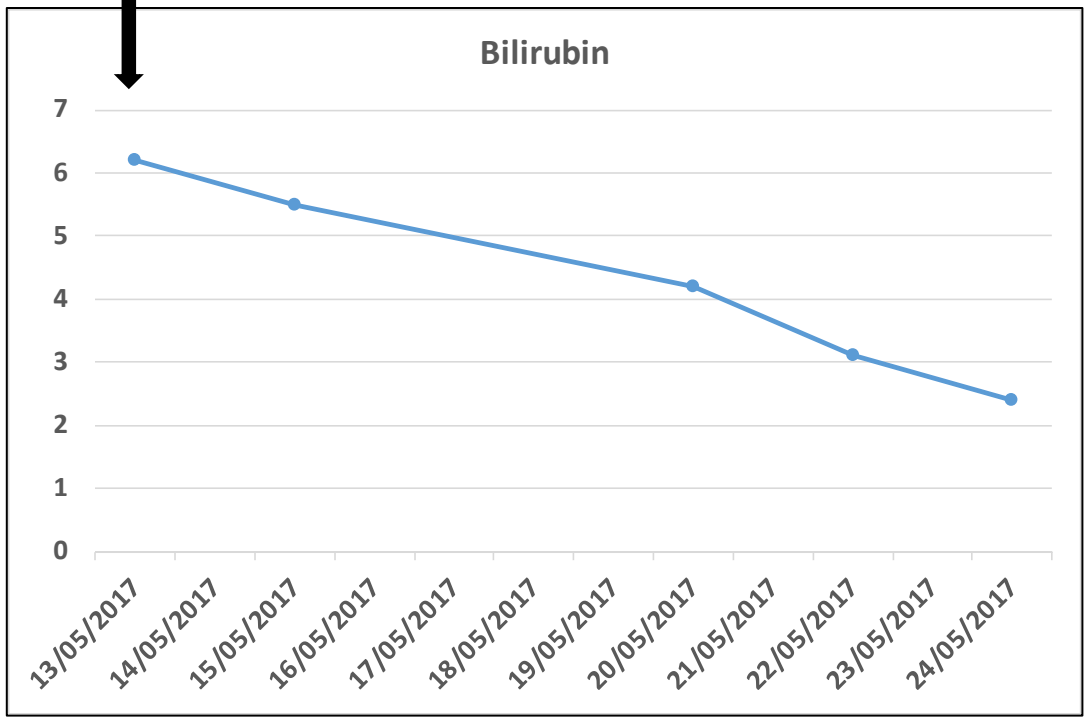
* Liver biopsy is not required in case of acute viral hepatitis

Evolution liver tests of M.J.

Corticosteroid introduction



Corticosteroid introduction



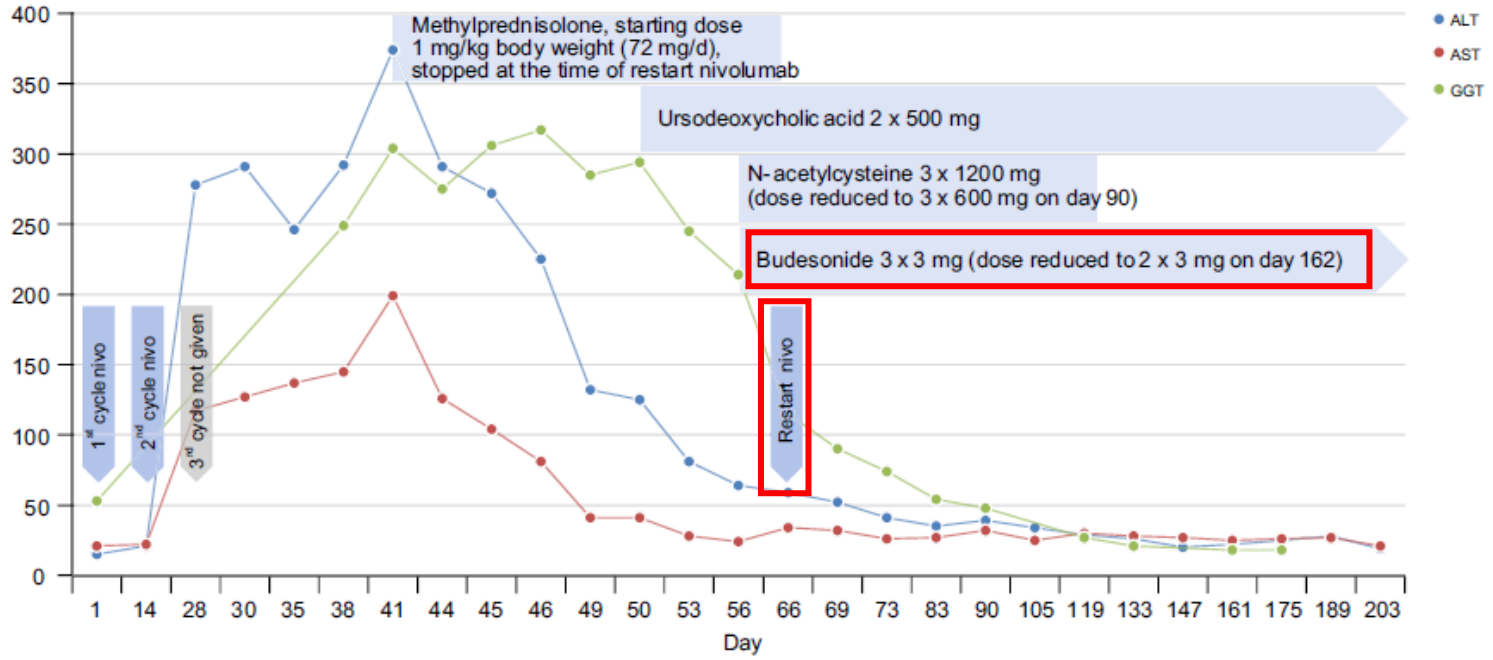
Patient M.J: few months later…

- **July 2017**: patient presented with tumor progression > 80% of hepatic lesions and non significant of pulmonary lesions

- ***Would you re-introduce an immune checkpoint inhibitor?***

Re-introduction of immunotherapy after severe hepatitis: budesonide prophylaxis

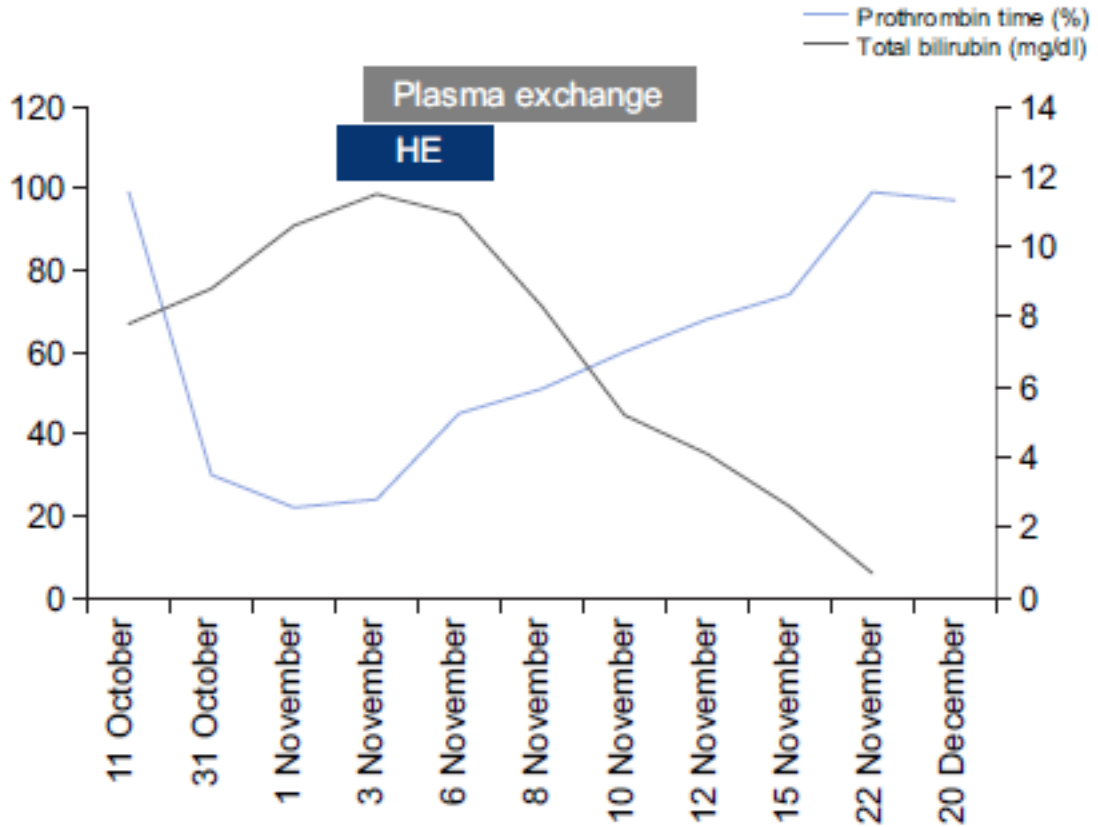
- 73 year-old patient with metastatic melanoma → grade 3 hepatitis after 2 cycle of nivolumab
- No hepatitis recurrence after immunotherapy reintroduction **on budesonide prohylaxis**



Ziemer et al. 2017 J Hepatol 66:657-665

Fulminant hepatitis after immunotherapy re-introduction

- 76 year-old patient with ovarian cancer → grade 2 hepatitis on nivolumab improved by corticosteroids
- Introduction of ipilimumab due to cancer progression → development of fulminant hepatitis

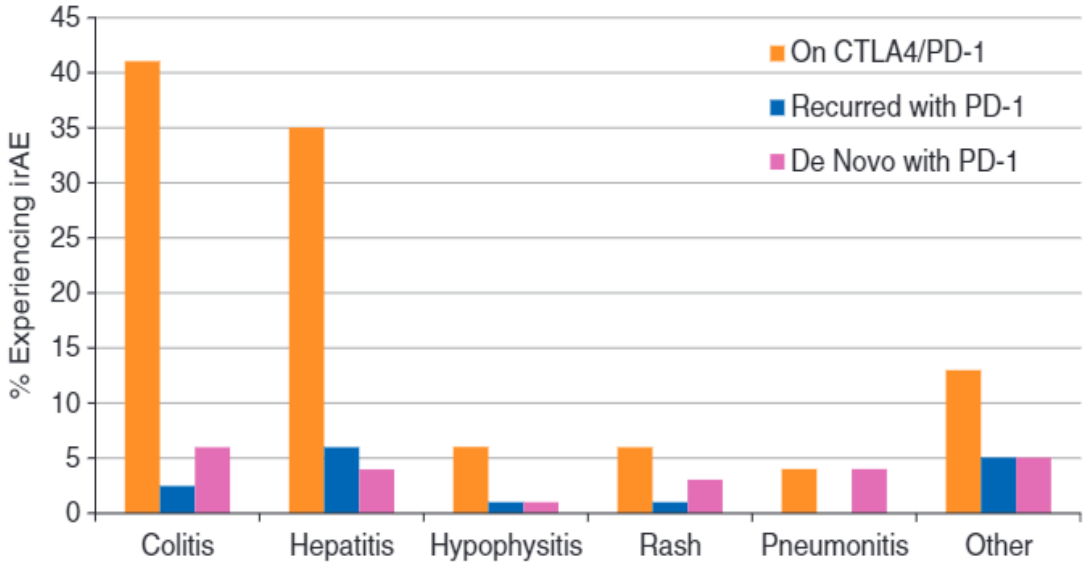


HE: hepatic encephalopathy

Riveiro-Barcela Jhepatol 2019;70:548-577

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
- 5/29 (17%) patients had hepatitis recurrence



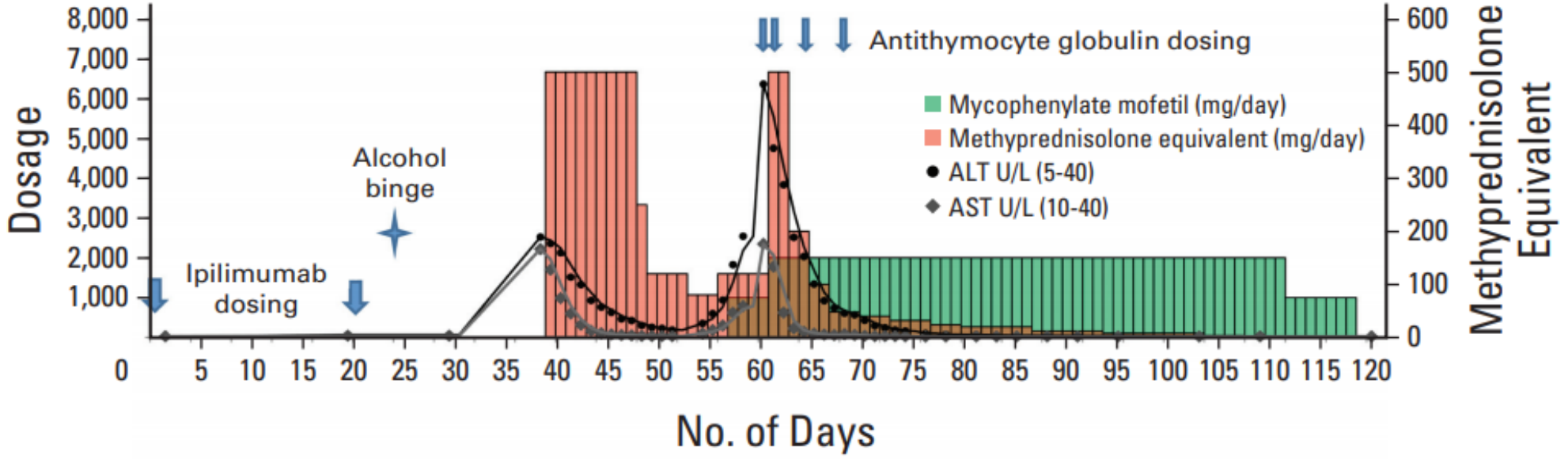
Pollack et al. Ann Oncol 2018;29:250-255

The end of the story M.J.

- A checkpoint inhibitor (pembrolizumab) was re-introduced
  - No recurrence of hepatic irAEs
  - Immune related colitis, treated with corticosteroids: good response

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 tread with add of **MMF** and **antithymocyte globulin**



Chmiel JD. Et al,. J of Clinical Oncology 2011;29(9):e237-e240

Fatal hepatic irAEs according to Vigilyze-Vigibase (WHO pharmacovigilance database)

- 0,4% fatal hepatic irAEs among 31059 patients on immunotherapy

Variable	Ipilimumab (n = 193) n(%)	Anti–PD-1/PD-L1 (n = 333) n(%)	Combination (n = 87) n(%)	P VALUE
Types of cancer[a]				<0.001
Melanoma	136 (96)	50 (18)	49 (66)	
Lung Cancer	0	152 (54)	17 (23)	
Other	5 (4)	78 (28)	8 (11)	
Type of fatal irAE				
Colitis	135 (70)	58 (17)	32 (37)	<0.001
Pneumonitis	15 (8)	115 (35)	12 (14)	<0.001
Hepatitis	31 (16)	74 (22)	19 (22)	0.23

a Percent of known (52 patients treated with ipilimumab, 53 with anti–PD-1/PD-L1, and 13 with combination did not list cancer types)

Table adapted from Wang et al. JAMA Oncol 2018;4(12):1721–1728.

Special cases

Anti-PD1-related ‘SSC’ (‘*Secondary’ Sclerosing Cholangitis*)

- A 71-year-old caucasian man developed a **new onset cholestasis of unknown origin**.
- His past medical history includes **non-small cell lung cancer** with cerebral metastasis treated by surgery 24 months before cisplatin-pemetrexed based chemotherapy during 10 months and **anti-PD1** immunotherapy (5 cycles)

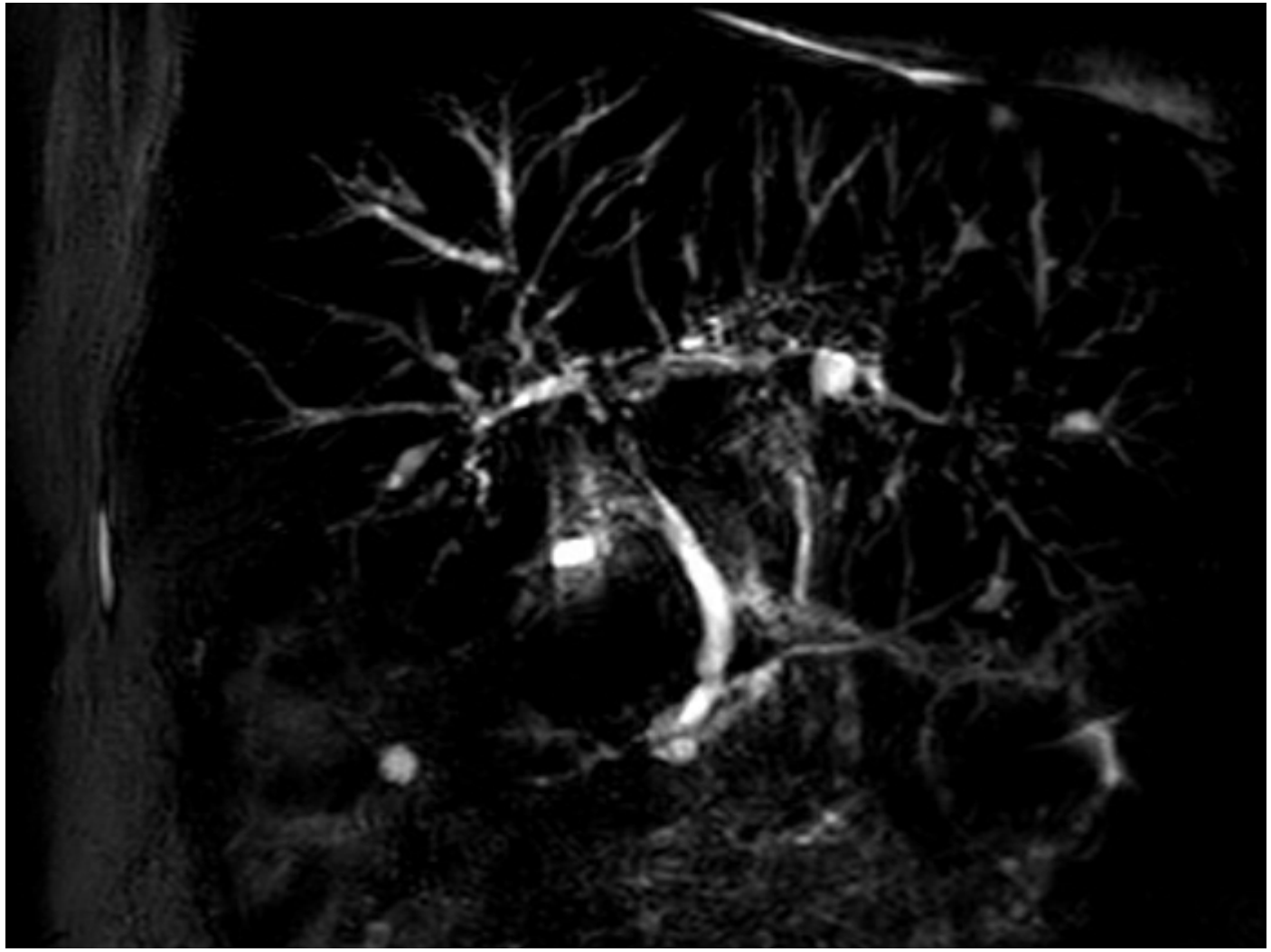
Total Bilirubin	++	7.71	mg/dl	0.20-1.00
Direct Bilirubin	++	7.93	mg/dl	<0.20
AST	+	135	U/L	15-37
ALT	++	835	U/L	30-65
GGT	++	984	U/L	< 60
Alk Phosphatase	++	558	U/L	50-136

Abdominal **computed tomography** with contrast was normal

Differential diagnosis includes cardiac outflow problems, drug induced liver injury, sarcoidosis, primary biliary cholangitis, tumor infiltration, autoimmune cholangitis (Ig G4, sclerosing cholangitis), eosinophilic cholangitis or parasitosis,…

Histological findings revealed the presence of a T lymphoid infiltrate (predominantly $CD8^+$) in portal-central vein spaces with signs of biliary damages and cholangitis

Prof. Van Steenkiste et all. (Submitted for publication in Liver International)



MRCP showed abnormal intrahepatic small bile ducts with irregular walls and stenosis.

Prof. Van Steenkiste et all. (Submitted for publication in Liver International)

- Case of **anti-PD1-related secondary sclerosing cholangitis**. Time to resolution of liver enzymes is very long and response to steroid administration is disappointing

Prof. Van Steenkiste et all. (Submitted for publication in Liver International)

Hepatic irAEs in patients treated for HCC

Nivolumab - CheckMate 040[1]

Patients, n (%)	All Patients (N = 48)	
	Any Grade	Grade 3/4
Laboratory TRAEs (≥ 10% of patients)		
AST increase	10 (21)	5 (10)
ALT increase	7 (15)	3 (6)

Tremelimumab + ablation[2]

Toxicity	All Patients (N = 32) n	
	Grade ≥ 2	Grades 3/4
Hyperbilirubinemia	7	9% 3
AST increase	11	22% 7
ALT increase	6	9% 3

Pembrolizumab – Keynote 240[3]

Adverse Event	Pembrolizumab (n= 279) n (%)		Placebo (n=134) n(%)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
AST increased	63 (22.6)	37 (13.3)	22 (16.4)	10 (7.5)
Blood Bilirubin increased	52 (18.6)	21 (7.5)	17 (12.7)	7 (5.2)

Atezolizumab/bevacizumab – Imbrave 150[4]

Event	Atezolizumab-Bevacizumab (n= 329) n (%)		Sorafenib (n=156) n(%)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
AST increase	64 (19.5)	23 (7.0)	26 (16.7)	8 (5.1)
Blood Bilirubin increase	43 (13.1)	8 (2.4)	22 (14.1)	10 (6.4)
ALT increase	46 (14.0)	12 (3.6)	14 (9.0)	2 81.3)

Tables adapted from 1.El-Khoueiry AB et al. Lancet. 2017;389(10088):2492-2502 2.Duffy et al. J Hepatol. 2017;66(3):545-551 3. Zhu AX et al. Lancet Oncol. 2018 Jul;19(7):940-9 4. Finn RS et al. N Engl J Med 2020; 382:1894-1905

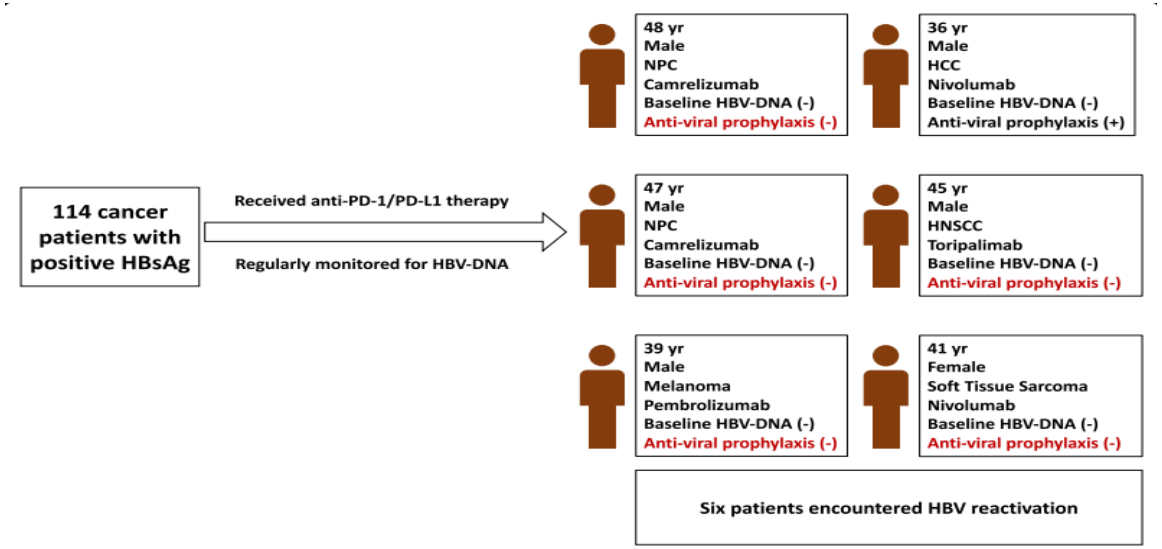
*Any off-label data shown are used to support the educational message of the presentation and not intended to endorse use of any therapy in any way

HBV reactivation in HBsAg^{+} patients in CPI

Events	No. (%) of patients Total (n = 114)	Patients without antiviral prophylaxis (n = 29)	Patients with antiviral prophylaxis (n = 85)	Difference between groups, % (95% CI)	OR (95% CI)	P value [a]
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

a Determined using the $\chi 2$ test b Included ten cases of immunotherapy delay and one case of discontinuation

Characteristics of the six patients suffering from HBV reactivation.



HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; PD-1, programmed cell death 1; PD-L1, programmed cell death-ligand 1; NPC, nasopharyngeal carcinoma; HCC, hepatocellular carcinoma; HNSCC, head and neck squamous cancer

Zhang X et al. J Immunother Cancer. 2019 Nov 21;7(1):322.

Key takeaways

- Hepatic irAEs are characterized by a variability (clinical, biological and histological)
- Liver biopsy helps to confirm the diagnosis and evaluates the severity of liver injury
- Corticosteroid therapy should be critically evaluated, even for grade 3-4 toxicity, according to the biological and histological severity of hepatitis
- Re-introduction is possible with risk since predictive factors for hepatitis recurrence or other irAEs are lacking
- The rate of irAEs seems low in patients with pre-existing cirrhosis, however the use of CPI in NASH induced liver cirrhosis warrants further evaluation