Toxicités hépatiques de l’immunothérapie anticancéreuse

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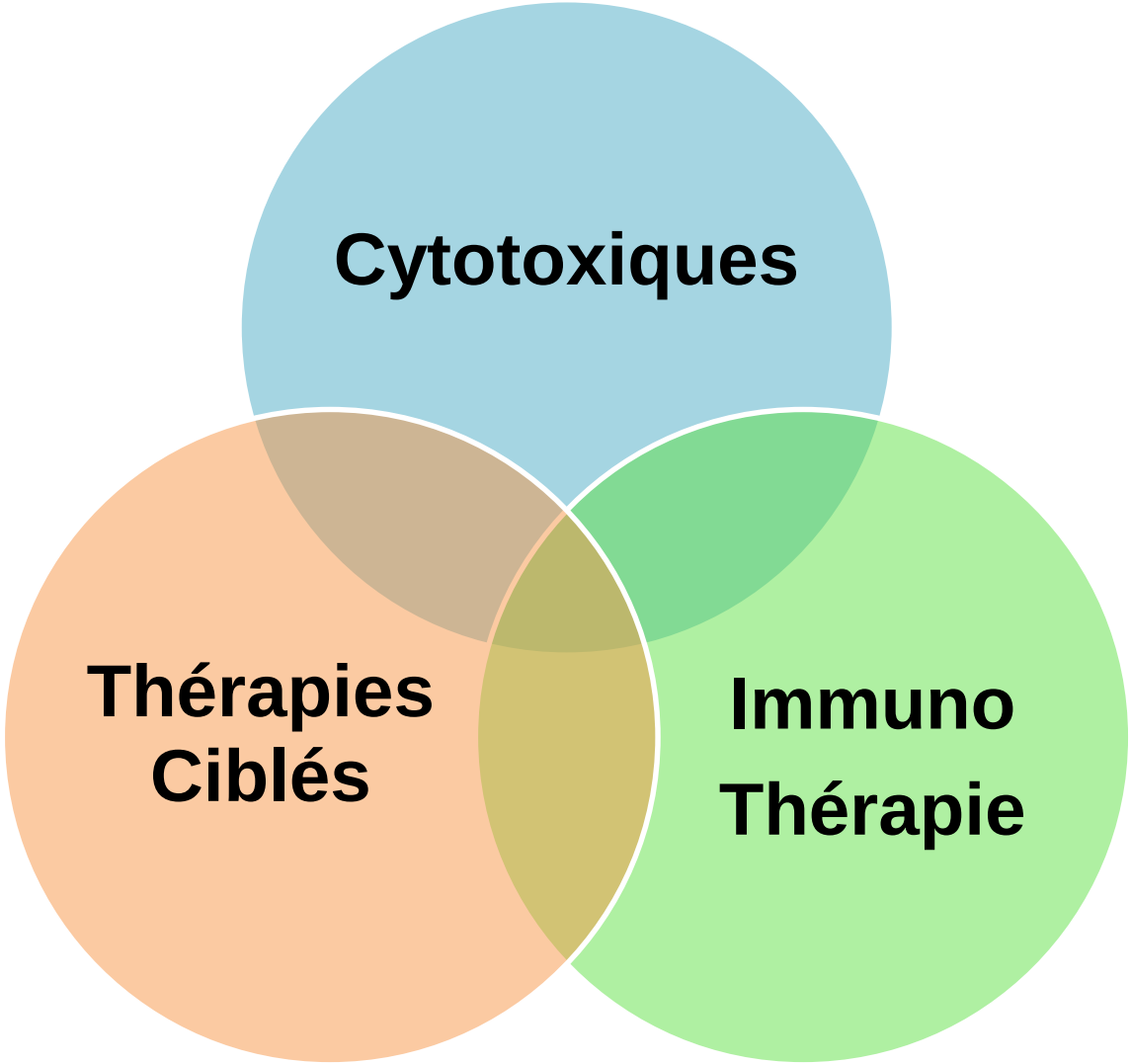
Anomalies du bilan hépatique en Oncologie

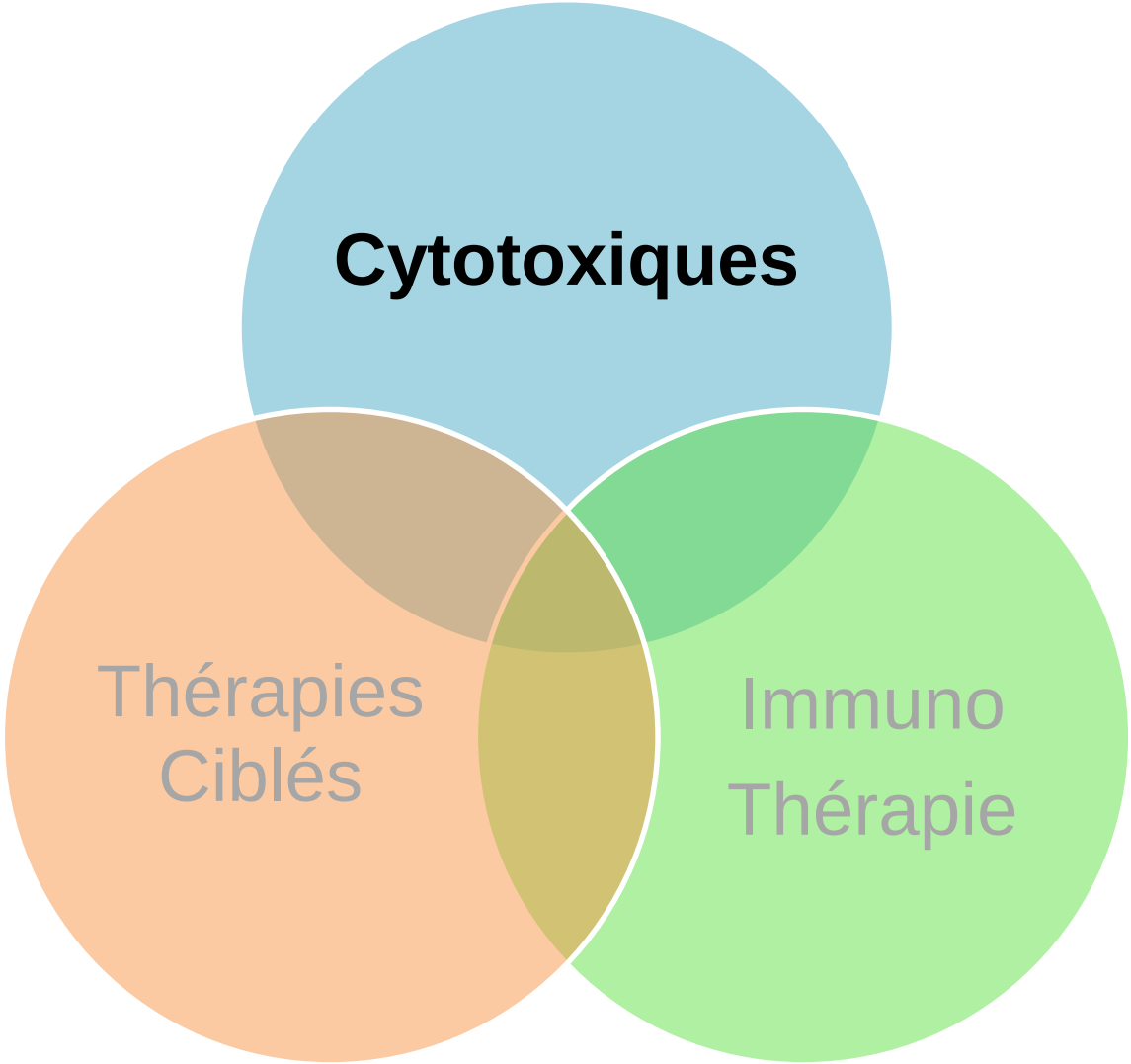
- **FREQUENTES :**
  - > 3-8 % d'anomalies du BH dans la population saine (Variations selon sexe, âge, BMI)
  - > 30 à 80 % des patients atteints de cancer auront des anomalies du BH
- **90% des anomalies sont d'origine hépatique**
  - > Vérifier CPK en cas ALT élevées isolées
  - > Vérifier hémolyse en cas d'élévation bilirubine
- **>90% sont cliniquement asymptomatiques**
- **< 2% mettent en jeu le pronostic vital**

Principales causes d'anomalies du bilan hépatique en Oncologie
Traitement anticancéreux
Médicaments de support (anti-émétiques…)
Interactions Médicamenteuses
Radiothérapie
Envahissement Hépatique Tumoral
Syndrome de Budd-Chiari
Syndrome paranéoplasique (Sd Stauffer)
Réaction type GVH
Nutrition parentérale
Hépatite Virales
Sepsis
CK élevées / Hémolyse

Traitements en Oncologie



Traitements en Oncologie



Complications Hépatiques des Chimiothérapies

Hépatotoxicité	
Méthotrexate	+++
Asparaginase	++
Carmustine	++
Mercaptopurin	++
Capecitabine	+
Chlorambucil	+
Cyclophosphamide	+
Cytarabine	+
Dacarbazine	+
Doxorubicin	+
Etoposide	+
Gemcitabine	+
Mitomycin C	+
Streptozotocin	+

Hépatotoxicité	
Busulfan	(+)
Cisplatin	(+)
5-FU	(+)
Irinotecan	(+)
Imatinib	(+)
Oxaliplatin	(+) ??
Vincristine	(+)
Bevacizumab	0
Cetuximab	0
Epirubicin	0
Hydroxyurea	0
Rituximab	0

+++ Très fréquent. ++ Fréquent. + Rare. (+) Très rare. 0 Aucune

Ramadori et al. Annals of Hepatology 2010

Principale mécanisme des complications Hépatiques des Chimiothérapies: Syndrome d'Obstruction des Sinusoïdes

- **Mécanisme**
  - > Obstruction des **petites veines** intra-hépatiques
- **Causes**
  - > Chimiothérapie **haute dose** (conditionnement pré-greffe) +++
  - > Dacarbazine, ABVD (doxorubicine, bléomycine, vinblastine, dacar), Actinomycine, 6-thioguanine, Azathioprine
  - > Folfox
- **Présentation clinique**
  - > Asymptomatique (anomalie du BH) → Forme ictérique

Complications Hépatiques des Chimiothérapies prise en charge du cancer colorectal

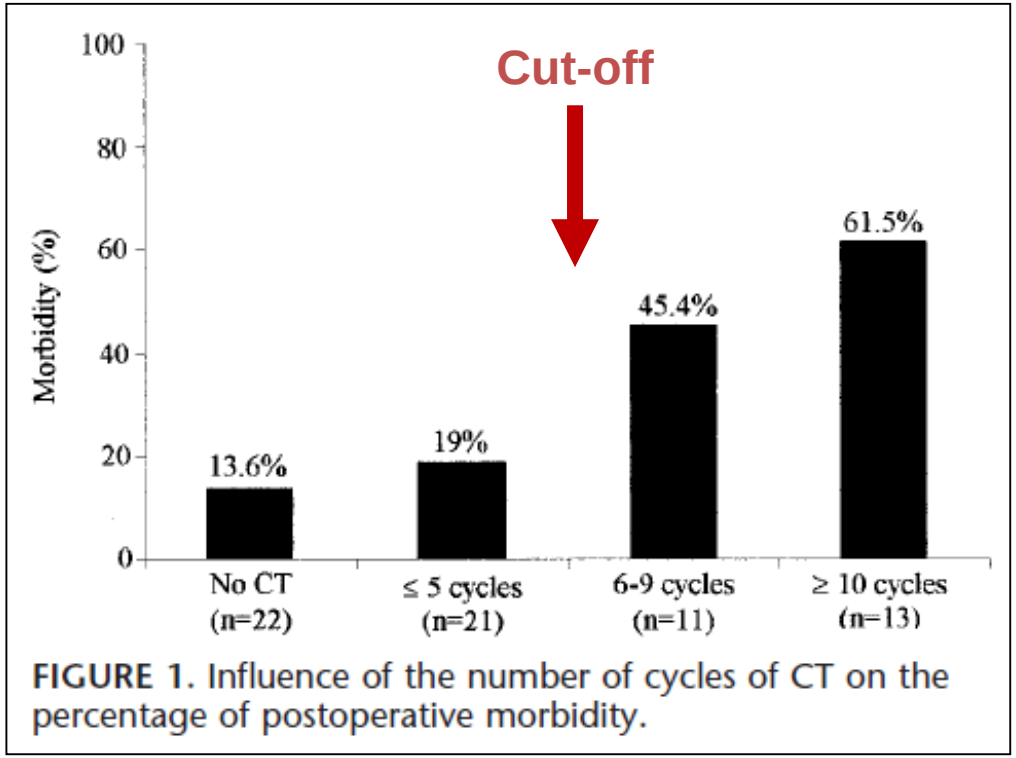


FIGURE 1. Influence of the number of cycles of CT on the percentage of postoperative morbidity.

TABLE 5. Predictive Factors for Postoperative Morbidity: Logistic Regression Model

Variable	Odds Ratio	95% CI	*P*
Associated GI procedure			
No	1	2.3–86.0	0.004
Yes	14.0		
Blood transfusion			
No	1	1.6–24.5	0.008
Yes	6.3		
Preoperative chemotherapy			
No	1	1.03–29.8	0.046
Yes	5.5		

Karoui et al. Ann Surg 2006

Drug-Induced Liver Injury (DILI)
Définition

- **DILI**
  - > Atteinte hépatique **liée à une molécule**
  - > Elévation des **tests hépatiques**
  - > Absence d'autre cause

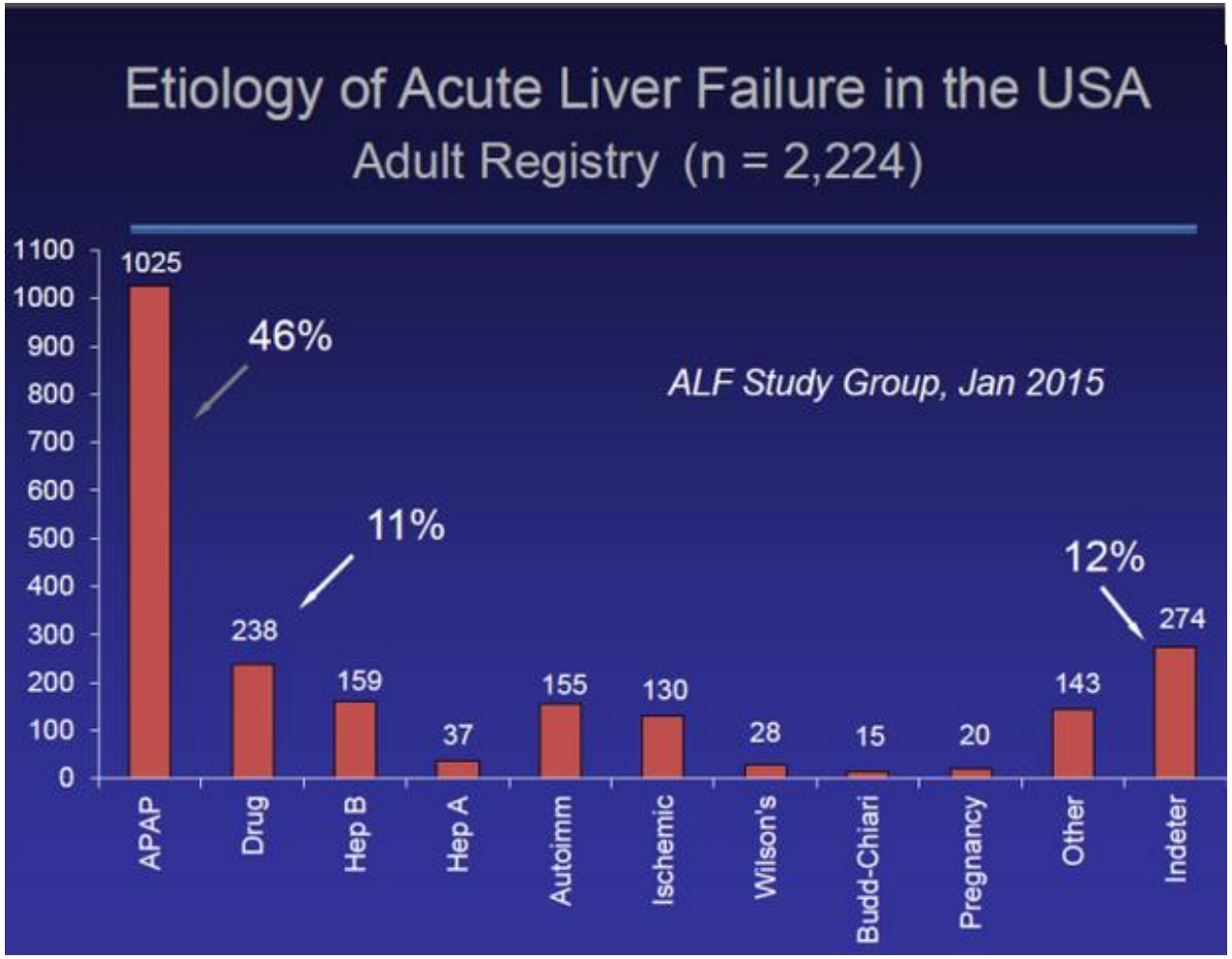
- **DILI sévère**
  - > DILI avec **insuffisance hépatocellulaire**
  - > Atteinte clinique → **décès**

- **Diagnostic difficile**
  - > Aucun résultat spécifique de DILI → Pas de diagnostic de certitude
  - > Incidence faible des cas sévères

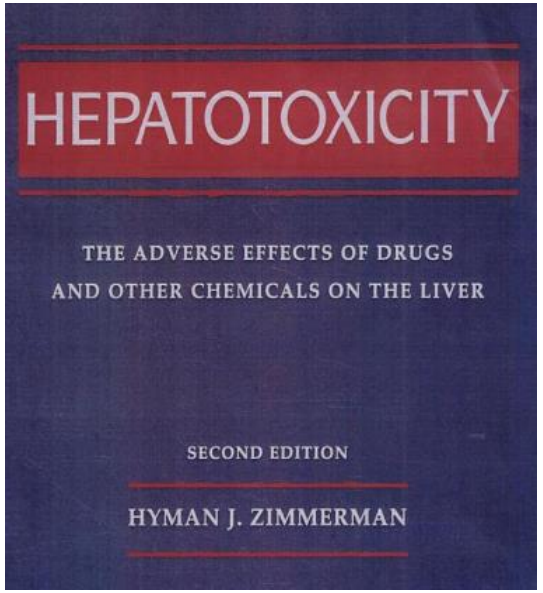
Drug-Induced Liver Injury (DILI)
Quelques notions

- Cause la plus fréquente de retrait de médicaments dans les 50 dernières années

- Cause la **plus fréquente d'insuffisance hépatocellulaire aigüe** aux USA
- **Le surdosage en paracétamol ACETAMINOPHEN (APAP) est la principale cause d'insuffisance hépatique aiguë induite par les médicaments**. Le stress oxydatif mitochondrial est considéré comme l'événement cellulaire prédominant dans les lésions hépatiques induites par l'APAP.



Drug-Induced Liver Injury (DILI)
« Hy's Law »



- **Constats**
  - > Le foie a des capacités excédentaires pour l'excrétion de la bilirubine
  - > Les atteintes hépatocellulaires sévères provoquent une **élévation de la bilirubine > 2N**

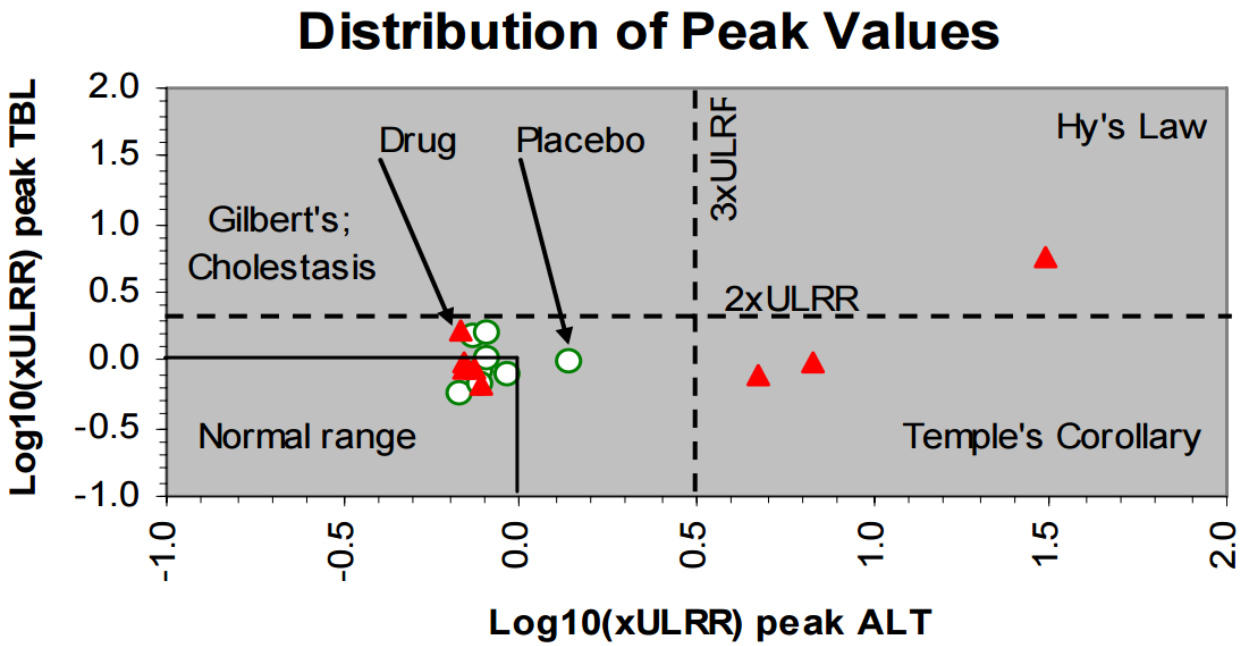
- **« Hy's Law » prédit le risque d'hépatoxicité sévère**

- **> 10% patients respectant les Hy's Law → DILI sévère**
  → si 10 patients Hy's Law +, au moins 1 cas d'insuffisance hépatocellulaire

Drug-Induced Liver Injury (DILI)
« Hy's Law »

- **Hy's Law positif si les 3 critères suivants sont respectés**
  1. Atteinte hépatocellulaire **avec ALT > 3 x ULN**
  2. Atteinte sévère, avec élévation de la **bilirubine totale > 2 x ULN**
  3. **Pas de cholestase initiale** (ALTx/ALPx < 2N) - Pas d'autre cause explicative

- **Deux critères ou plus ont toujours conduit à la survenue de DILI sévère quand la molécule est administrée à une population plus large**

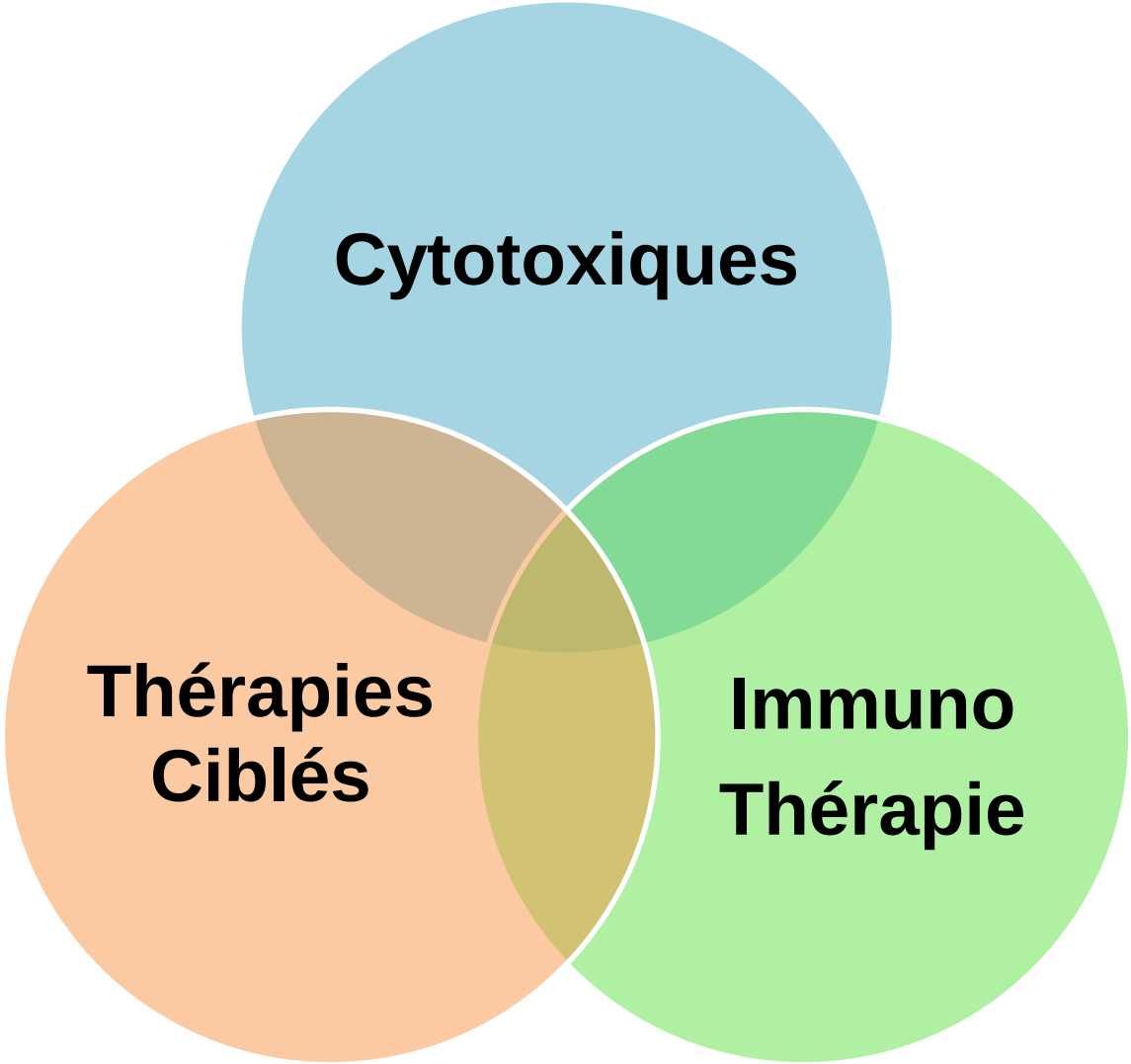


Drug-Induced Liver Injury (DILI)
Développement des nouveaux anti-cancéreux

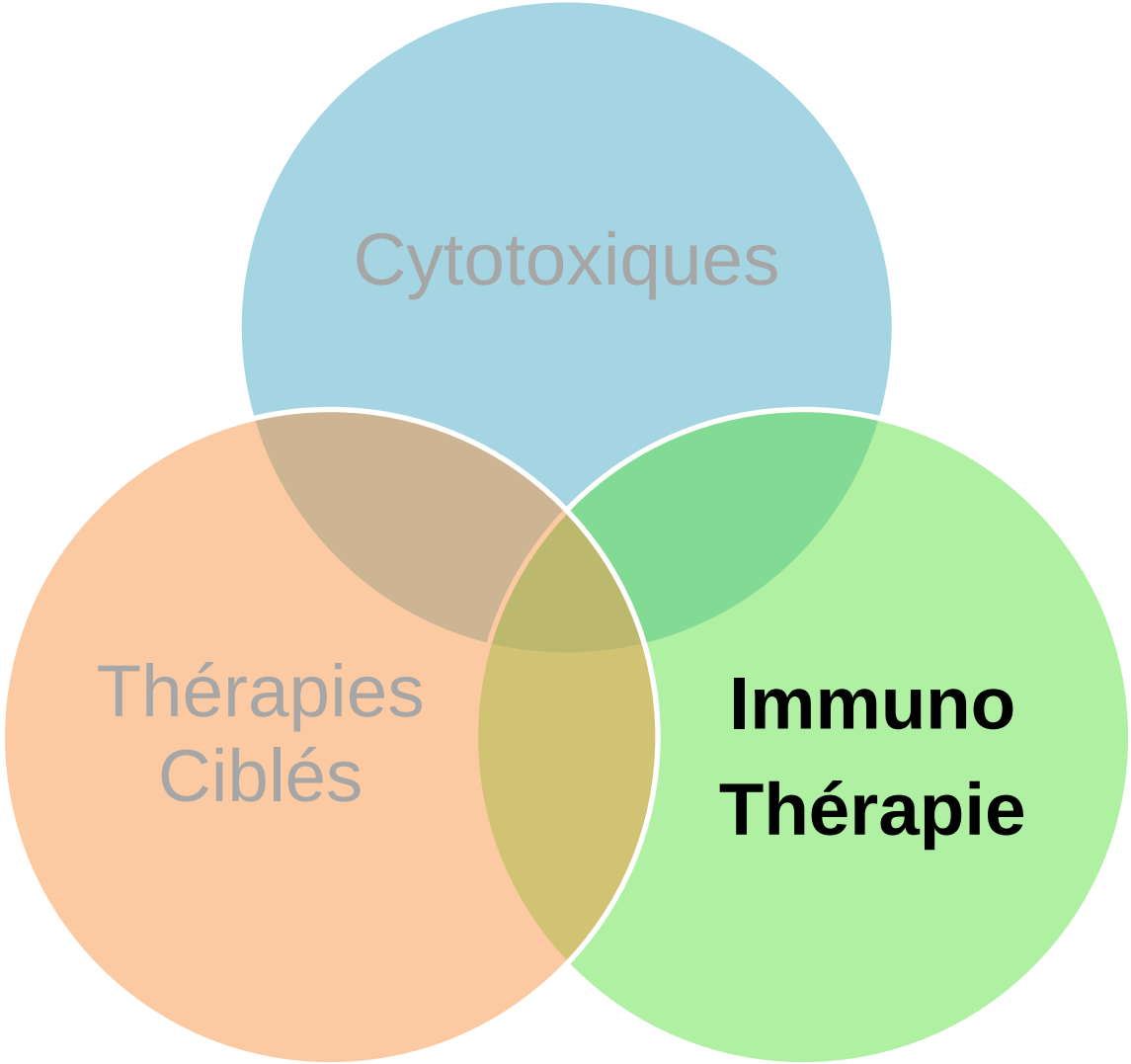
- **Recommandations pour arrêt du traitement**
  - ALT/AST > 8N ou ALT/AST > 5N pdt > 2 sem
  - ALT/AST > 3N et Bili tot > 2N ou INR > 1.5
  - ALT/AST > 3N avec symptômes (ex: fatigue, N&V, douleur hépatique, fièvre, rash) ou éosinophilie

- **Reprise du traitement : devrait généralement être évité lorsque ALT/AST > 5N sauf s'il n'existe pas d'alternative thérapeutique et après information du patient**

Traitements en Oncologie



Traitements en Oncologie



Main Checkpoints for Cancer Immunotherapy

Relâcher le frein

ANTAGONISTE

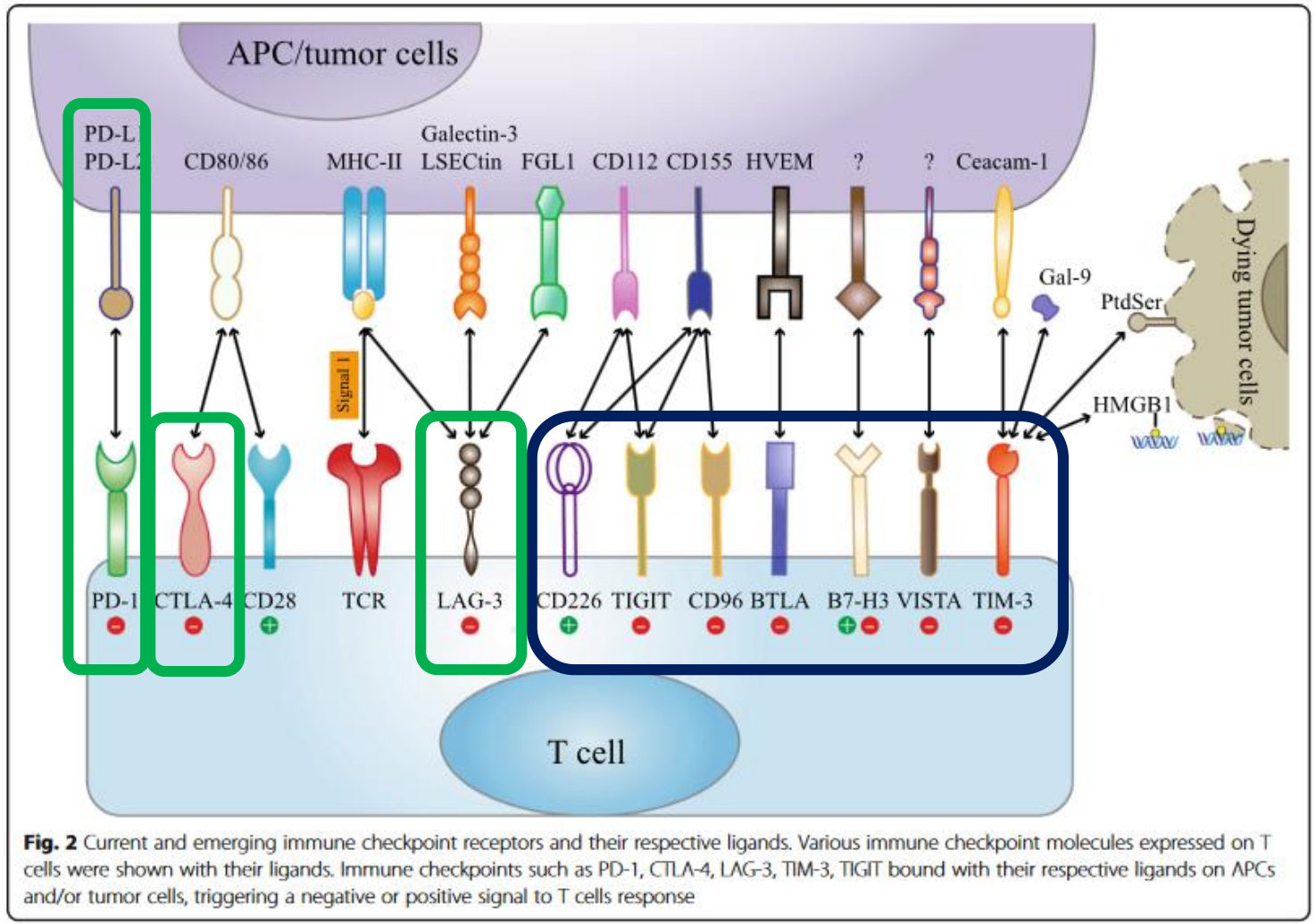


Fig. 2 Current and emerging immune checkpoint receptors and their respective ligands. Various immune checkpoint molecules expressed on T cells were shown with their ligands. Immune checkpoints such as PD-1, CTLA-4, LAG-3, TIM-3, TIGIT bound with their respective ligands on APCs and/or tumor cells, triggering a negative or positive signal to T cells response

Appuyer sur l'accélérateur

AGONISTE

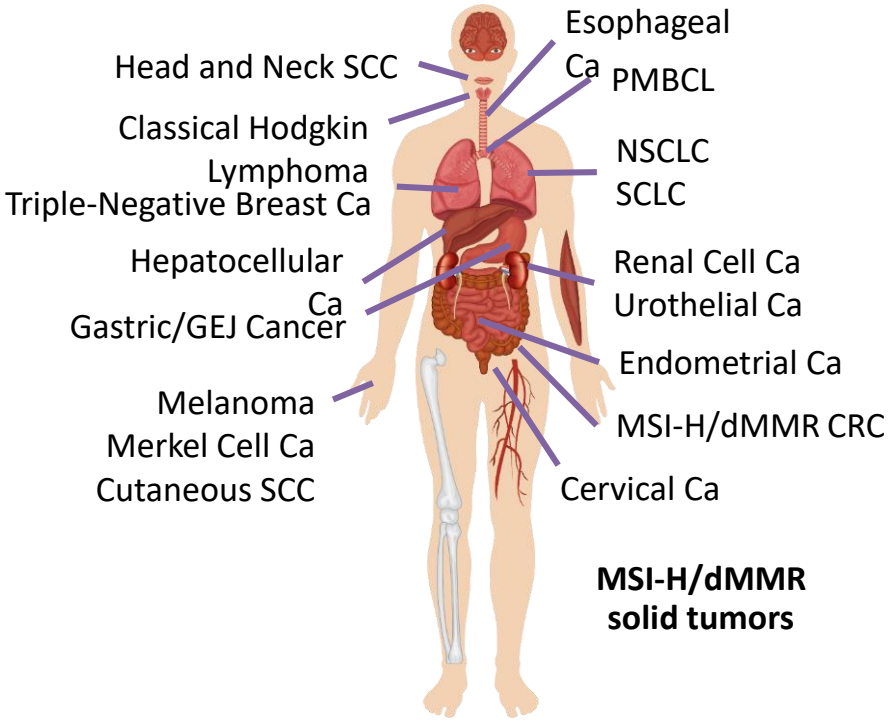
4 classes of IO drugs approved

aCTLA4
aPD1
aPDL1
aLAG3

Targets under clinical investigations

Qin et al. Molecular Cancer (2019)

Immune Checkpoint Inhibitors FDA Approved in Multiple Cancers



- **ICIs now approved as monotherapy and in combination with other ICIs or CT**
- **ICIs historically used in later-line metastatic disease, but now moving into earlier lines of therapy and earlier stages of disease**
- **Patients may receive ICI therapy for yrs, as optimal duration is unknown**
  - > Initial strategy was continuing ICI until progression/toxicity or to 2 yrs

FDA-Approved ICI by Target
Anti–CTLA-4: ipilimumab
Anti–PD-1: cemiplimab-rwlc, nivolumab, pembrolizumab
Anti–PD-L1: atezolizumab, avelumab, durvalumab
Anti-LAG3: relatlimab

Michot. Eur J Cancer. 2016;54:139. Nivolumab PI. Ipilimumab PI. Pembrolizumab PI. Atezolizumab PI. Durvalumab PI. Avelumab PI. Cemiplimab-rwlc PI.

Immune-related adverse events with immune checkpoint inhibitors

It's not about frequency… but about DIVERSITY [1-2]

Usual irAEs (>1% all grades)

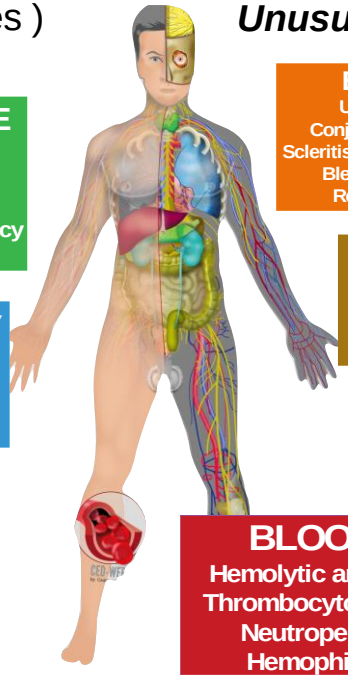
SKIN
Rash
Pruritus
Psoriasis
Vitiligo
DRESS
Stevens Johnson

ENDOCRINE
Hyper or hypothyroidism
Hypophysitis
Adrenal insufficiency
Diabetes

REPIRATORY
Pneumonitis
Pleuritis
Sarcoid-like granulomatosis

LIVER
Hepatitis

GASTRO INTESTINAL
Colitis
Ileitis
Pancreatitis
Gastritis



Unusual irAEs (<1% all grades)

EYE
Uveitis
Conjunctivitis
Scleritis, episcleritis
Blepharitis
Retinitis

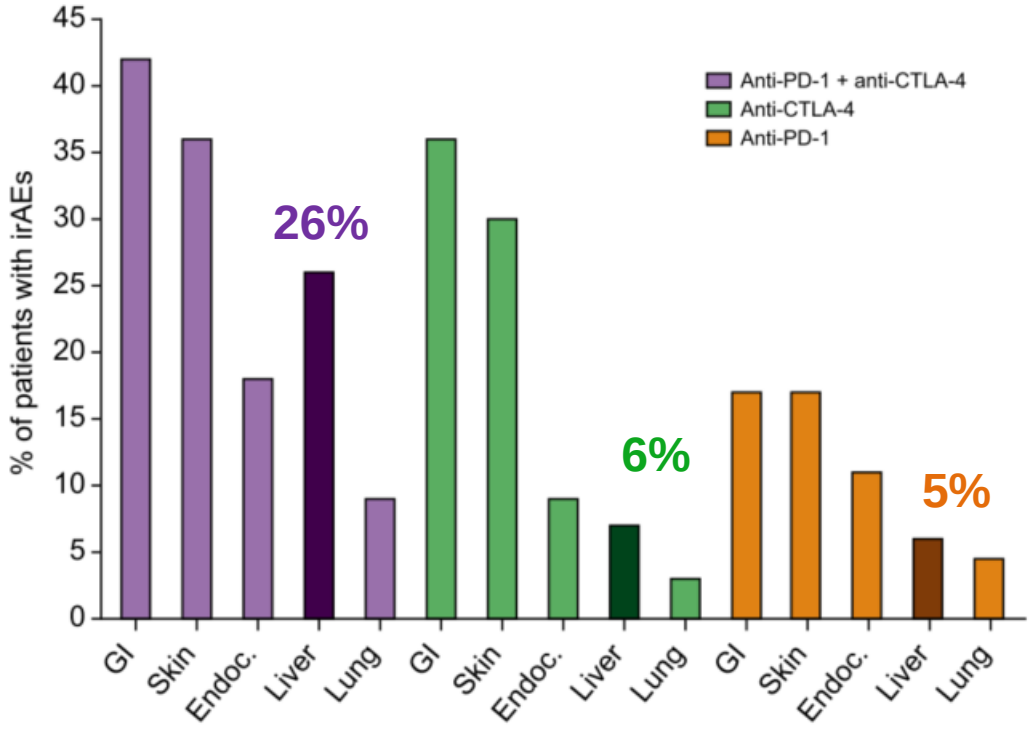
CARDIO VASCULAR
Myocarditis
Pericarditis
Vasculitis

MUSCULO SKELETAL
Arthritis
Dermatomyositis

NEUROLOGIC
Neuropathy, Guillain Barré, Myelopathy, Meningitis, Encephalitis, Myasthenia

BLOOD
Hemolytic anemia
Thrombocytopenia
Neutropenia
Hemophilia

RENAL
Nephritis

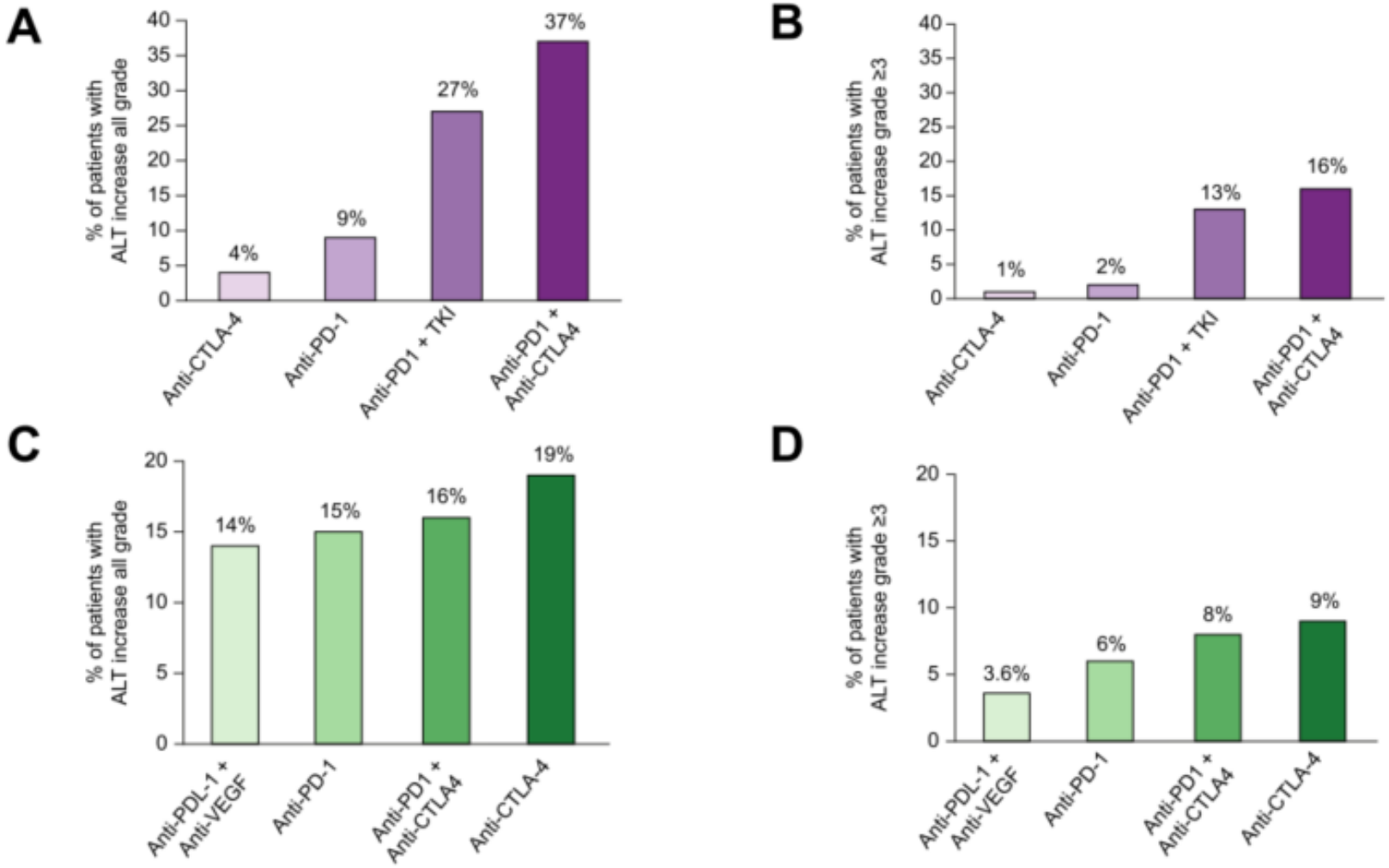


1- S Champiat, Ann. of Oncol., 2015; 2- Michot JM, Eur J Cancer, 2016; 2- DB Johnson, BMC Cancer, 2
3-DB Johnson, BMC Cancer, 2017; 2- G Manson, JITC, 2019. E De Martin, JHEP

Distribution of ALT increase with immune checkpoint inhibitors

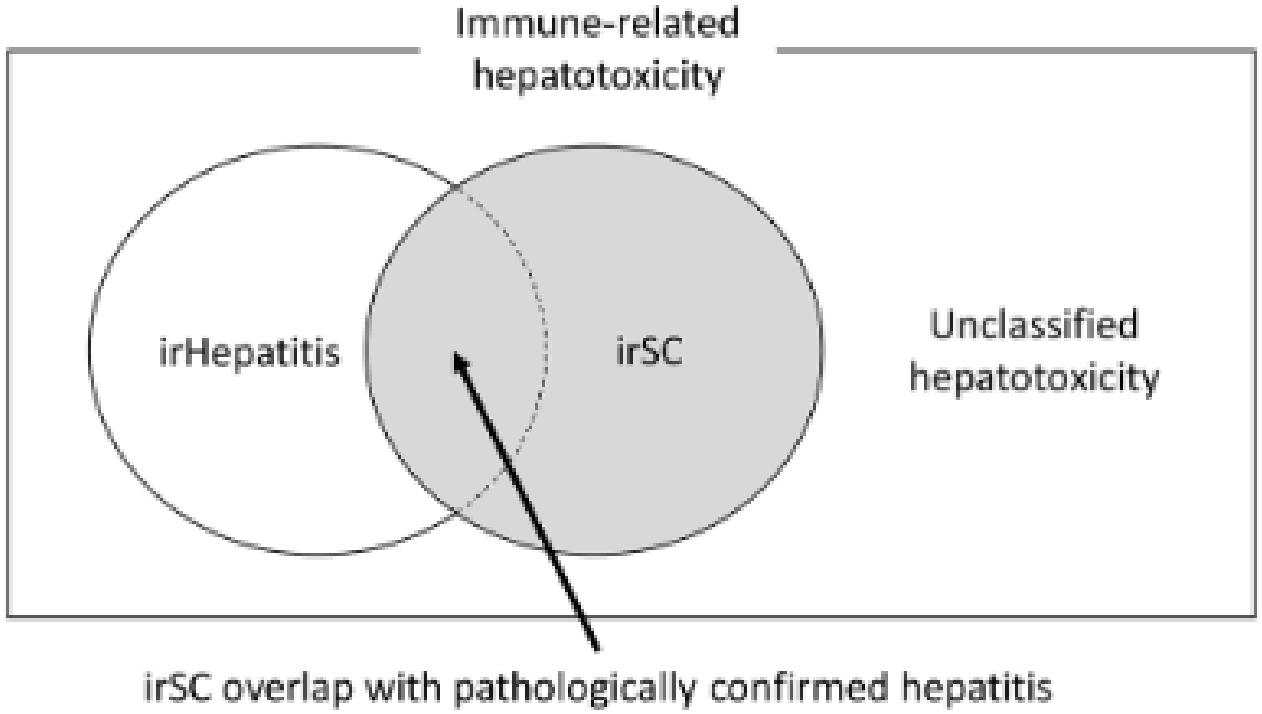
patients treated for non-HCC malignancies

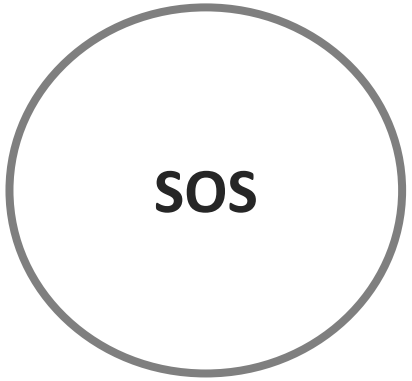
patients treated for HCC malignancies



E De Martin, JHEP 2020

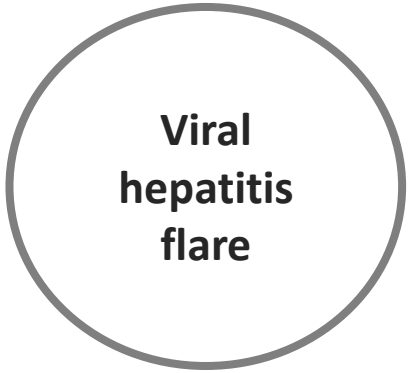
Different types of immune-related liver toxicities with immune checkpoint inhibitors





SOS: Syndrome Obstructio Sinusoïdale

Œdèmes généralisés



Previous viral hepatitis (HBV)

Takinami M, Inv New Drugs, 2021

Velev M, EJC, 2021

X Zhang, J Immunotherapy, 2019

Autoimmune hepatitis and immune-related liver toxicities, which differences?

	AI hepatitis	Immune-related hepatitis
Population	Without cancer Female predominance Younger patients	With cancer Male predominance Older patients
Auto AB	High ANA titers Elevated IgG	ANA negative
Biopsy	Prominent plasma cell infiltration	Prominent T-cell infiltration

Facteurs de risque de sévérité des immune-related hepatitis with immune checkpoint inhibitors

Immune related hepatitis characteristics	P value for severiy and resistance to corticosteroids
Previous known hepatic disease	<0,01
Severity of ALT / ALT elevation > G3	<0,01
Severity og GGT elevation	0,021
Albumin decrease	0,012
PT decrease	0,018
Bilirubin total increase	<0,001
Clinical symptoms associated with hepatitis	0,015

E Alouani, EJC, 2023

How to manage immune related liver toxicity?

TABLE 2 Recommended medical evaluation for immune checkpoint inhibitor-treated patients with liver injury

Competing etiologies	Diagnostic testing
Other drugs or hepatotoxins	Medical history Drug and supplement use Alcohol intake Lab testing Urine toxicology Serum phosphatidyl ethanol
Viral hepatitis	Lab testing Hepatitis A IgM HBsAg, anti-HBc Anti-HCV and HCV-RNA Anti-HEV IgM and HEV-RNA[a]
Autoimmune hepatitis	Lab testing ANA, anti-SMA Quantitative immunoglobulins Liver biopsy[b]
Metastatic tumor to the liver (choledocholithiasis/biliary obstruction)	Imaging Liver ultrasound with Doppler CT or MRI with contrast MRCP
Liver vascular disease (hepatic ischemia/portal vein thromboses)	Medical history Prior hypotension/arrhythmia, heart disease Imaging Liver ultrasound with Doppler Liver CT or MRI with contrast
Secondary testing	
Opportunistic infections	Medical history Fever, skin rash Lab testing CMV-DNA, anti-CMV IgM HSV-DNA, anti-HSV IgM Heterophile ab, EBV-DNA, EBV serologies Liver biopsy
Other etiologies (Liver micrometastases, hepatic steatosis)	Liver biopsy

Swanson L, Clin Liver Disease 2024

Importance to check virus in immune related liver toxicity

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

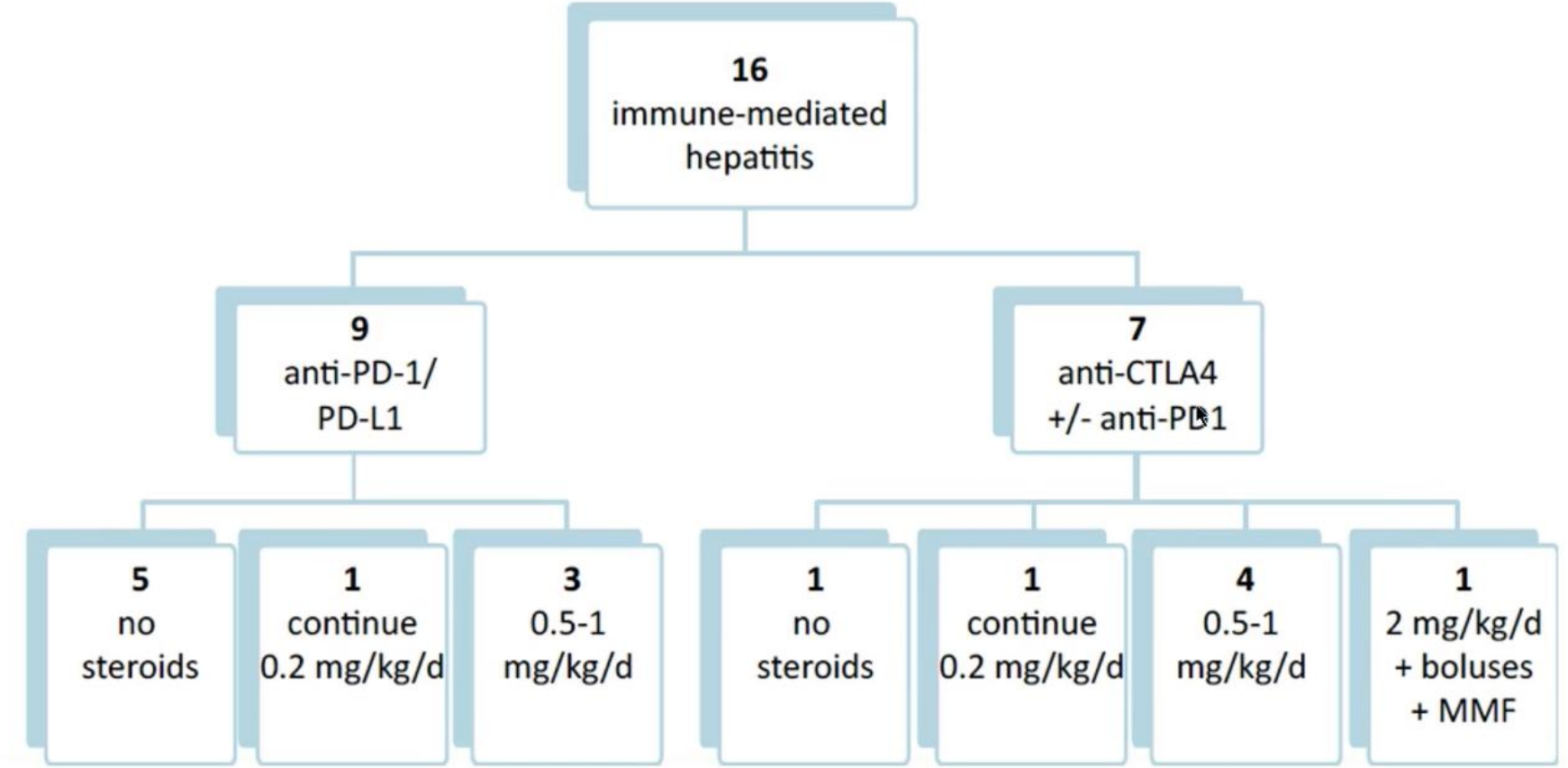
Table 2 Details of the 6 Patients with HBV reactivation

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

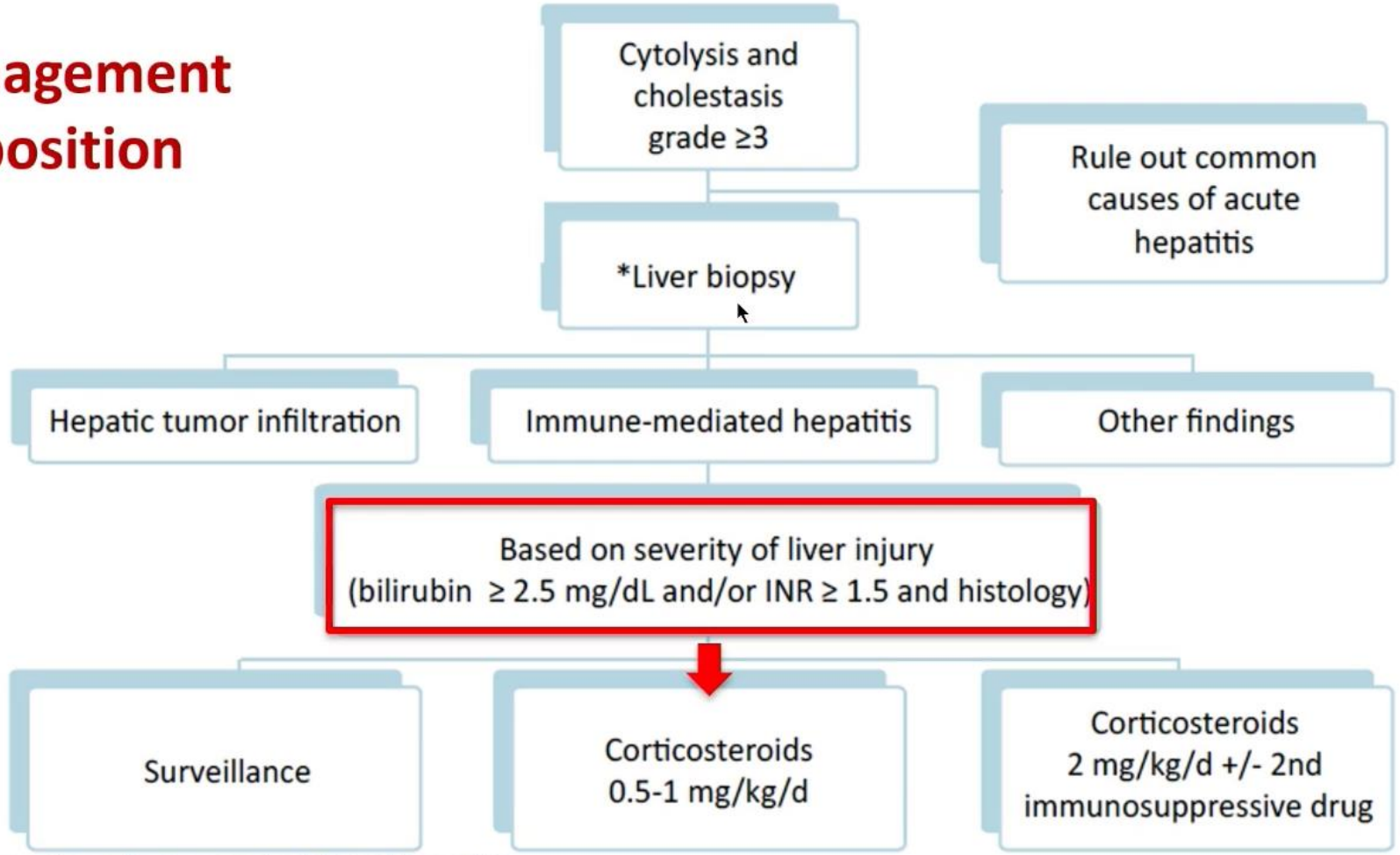
Spontaneous Improvement of Immune-mediated Hepatitis



Spontaneous improvement: 38%

De Martin, J Hepatol 2018

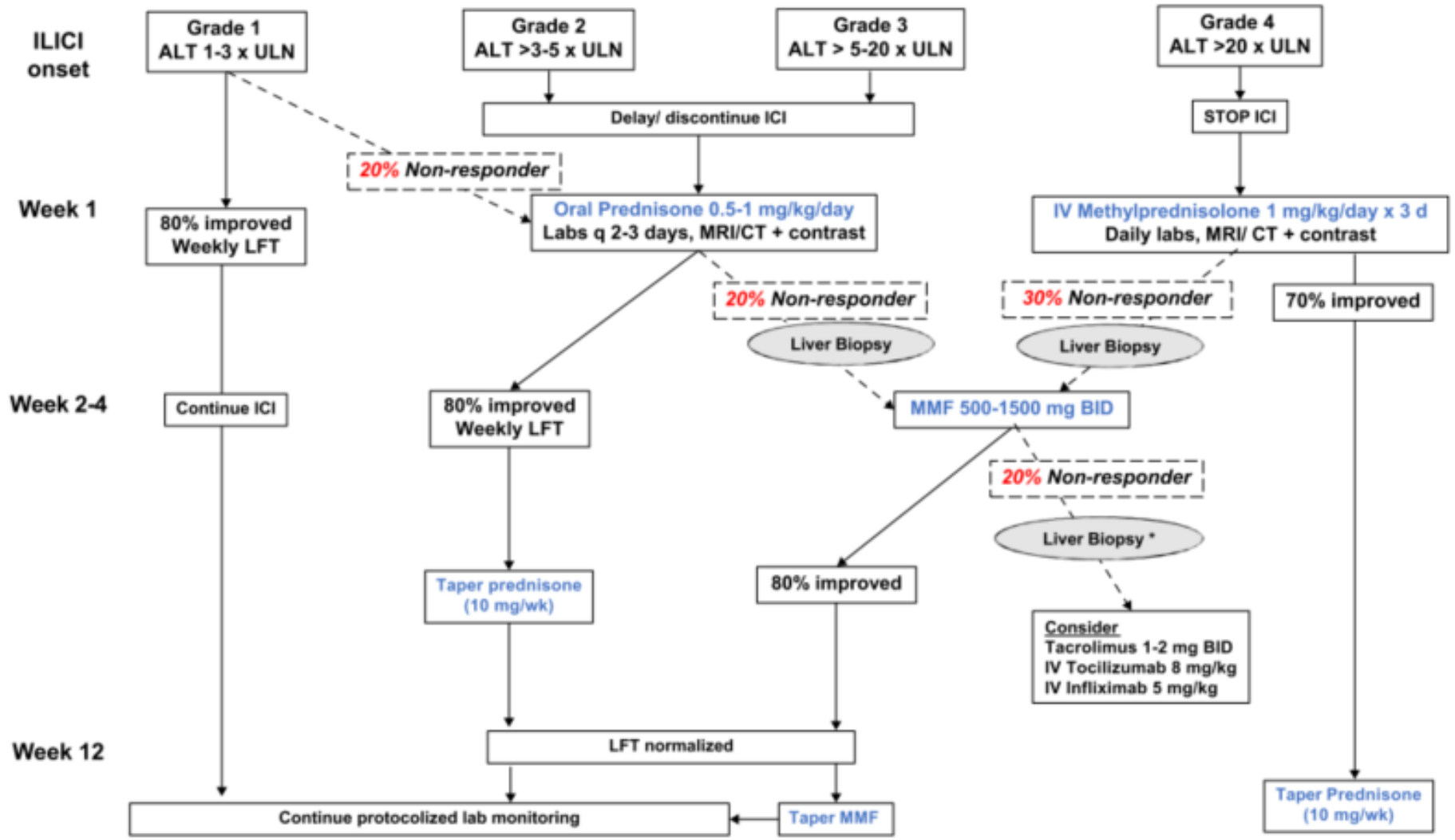
Management proposition



* the biopsy is not recomended if viral hepatitis

De Martin, J Hepatol 2018

How to manage immune related liver toxicity?



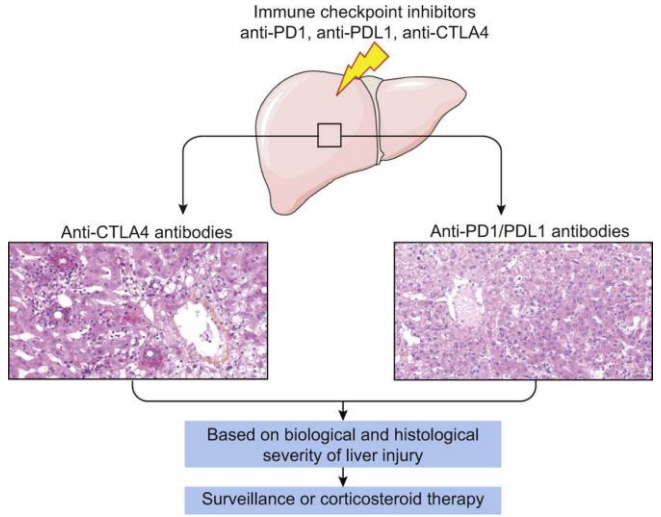
Swanson L, Clin Liver Disease 2024

Liver biopsy should be considered in management

TABLE 3 Considerations regarding liver biopsy in liver injury associated with checkpoint inhibitors

Benefits	Limitations
Diagnosis confirmation	Specificity of findings
Findings can strengthen diagnosis if uncertain or atypical presentation or labs (lobular inflammation, endotheliitis, granulomas, and apoptosis)	No pathognomonic histological findings for ILICI
Prognosis	Periprocedural risk
Eosinophils and granulomas have better outcomes	1%–2% risk of severe bleeding/ hospitalization
Severe necrosis and fibrosis have poorer outcomes	30% require analgesics
Identify pre-existing liver disease	Logistics
Metabolic-associated liver disease in 10%–20% of general US population	Scheduling Delay in corticosteroids
Alternative etiology and management	Clinical impact
Malignant infiltration of the liver will worsen with immunosuppression	< 10% have an alternative etiology
Opportunistic viral infection (HSV, CMV) will worsen with immunosuppression	> 80% of Grade 2–4 patients rapidly respond to corticosteroids
Cholestatic patients may have small duct sclerosing cholangitis only seen on biopsy	—

Abbreviations: CMV, cytomegalovirus; HSV, herpes simplex virus; ILICI, immune-mediated liver injury from checkpoint inhibitor.



Swanson L, Clin Liver Disease 2024

Michot JM

Possibility to resume an IO after a previous iTOX if the patient can benefit.

Key Points

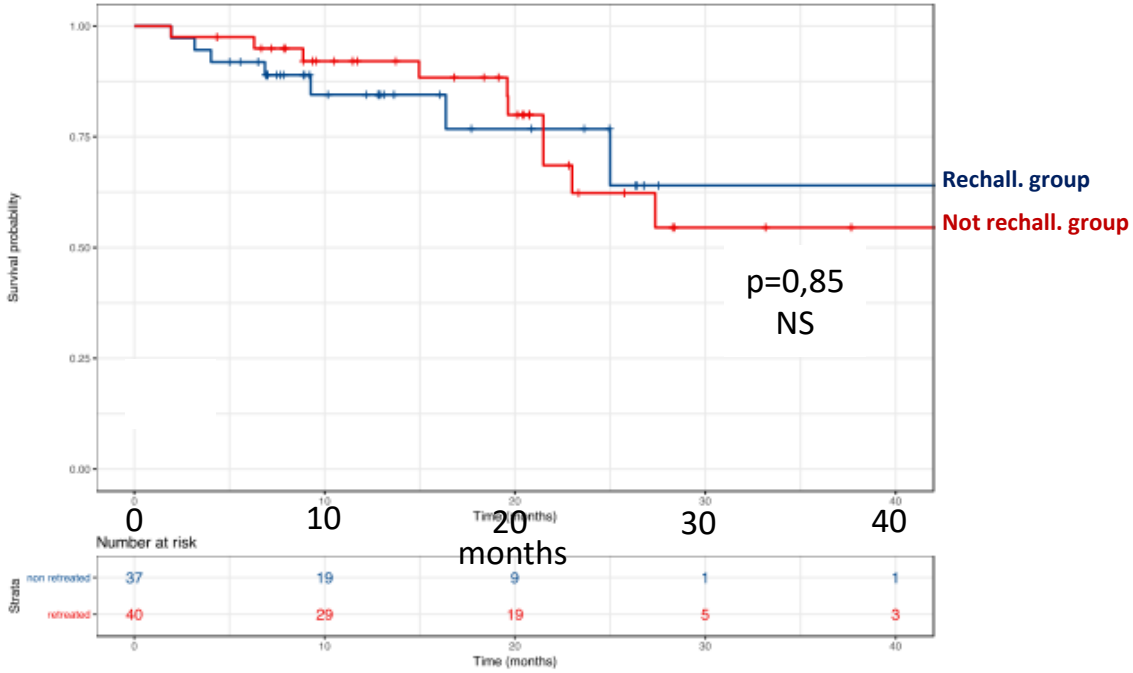
Question After a grade 2 or higher immune-related adverse event, is an anti–PD-1 or anti–PD-L1 inhibitor rechallenge safe?

Findings In this cohort study of 93 French adults who experienced a grade 2 or higher immune-related adverse event and had an anti–PD-1 or anti–PD-L1 rechallenge, 55% experienced a second adverse event. Earlier initial toxic effect was associated with more frequent recurrence, and the second event was not as severe as the first.

Meaning The risk-reward ratio for anti–PD-1 or anti–PD-L1 rechallenge appears to be acceptable, although these patients require close monitoring; rechallenge conditions warrant further investigation in a prospective clinical trial.

Overall survival of patients who were rechallenged *versus* non-rechallenged[1].

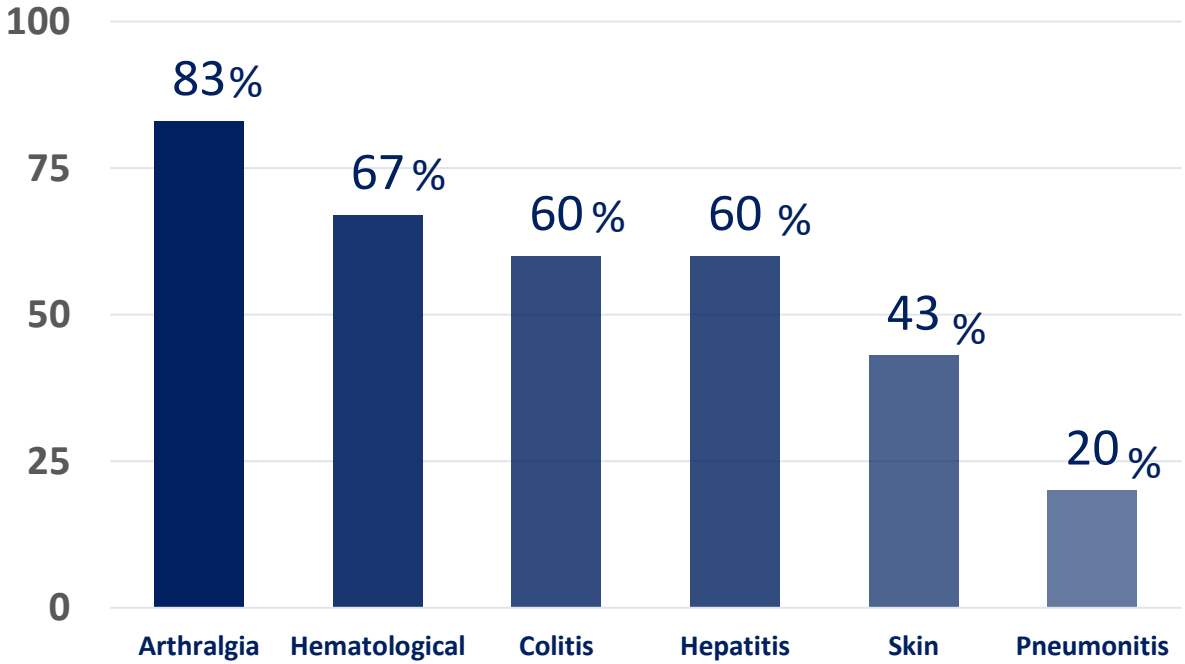
(following iTOX G2 in 46% of cases or G3-4 in 54% of cases. Patients with tumor progression at time to selection were not included in the analysis).



Michot JM

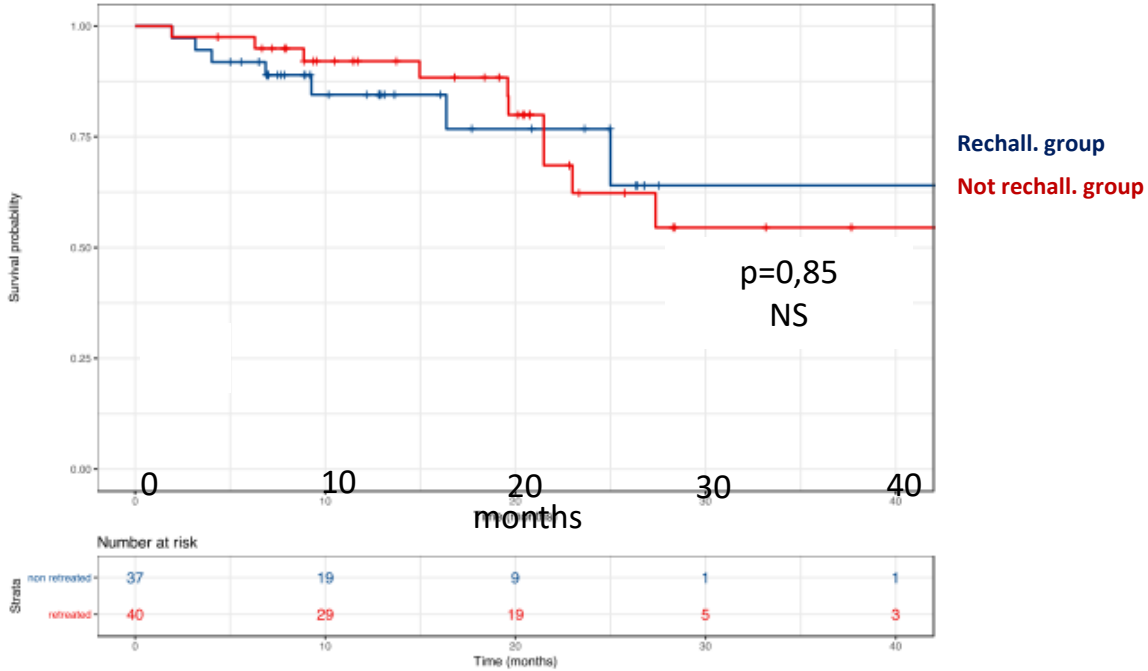
How to resume an IO after a previous iTOX if the patient can benefit.

% of risk for recurrence following a-PD-1 or PD-L1 rechallenge[1].



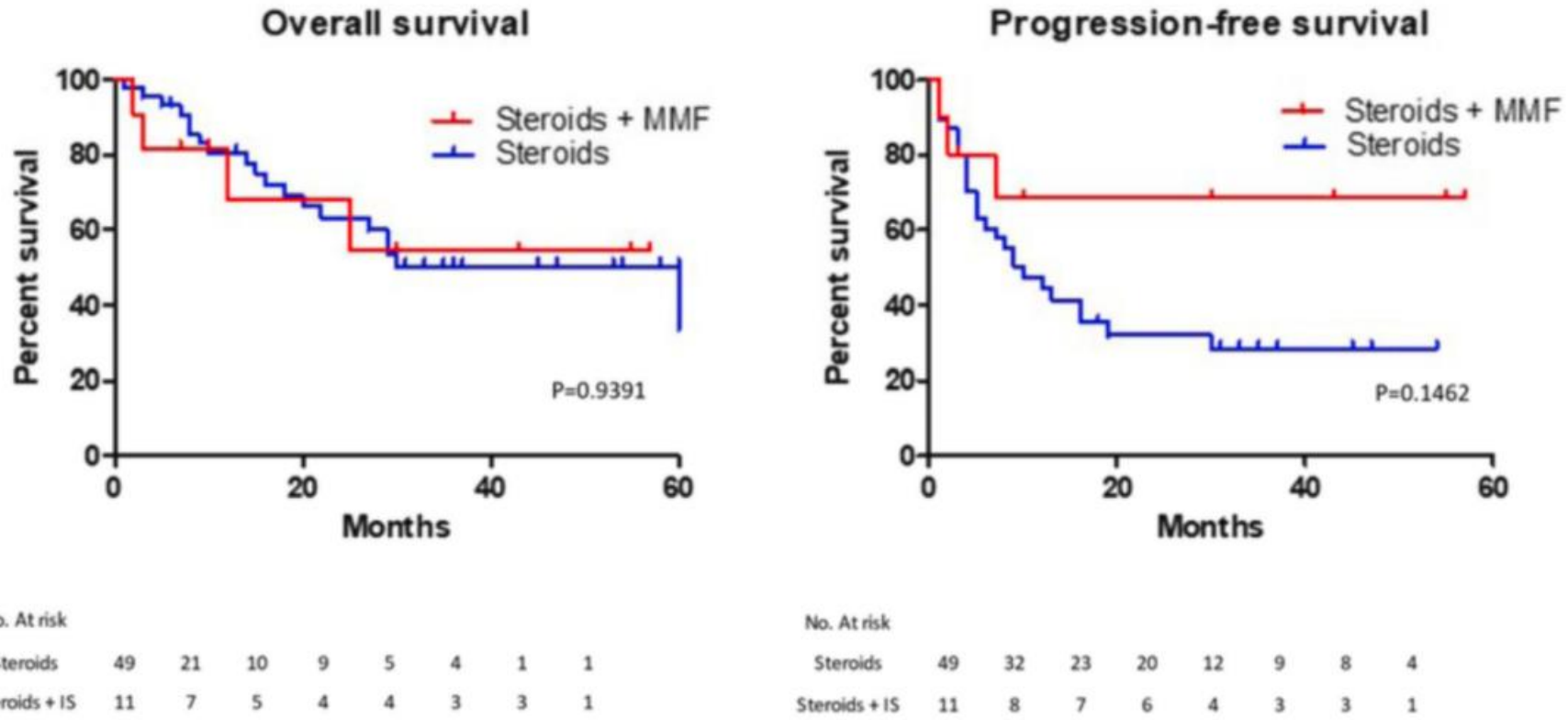
Overall survival of patients who were rechallenged *versus* non-rechallenged[1].

(following iTOX G2 in 46% of cases or G3-4 in 54% of cases. Patients with tumor progression at time to selection were not included in the analysis).



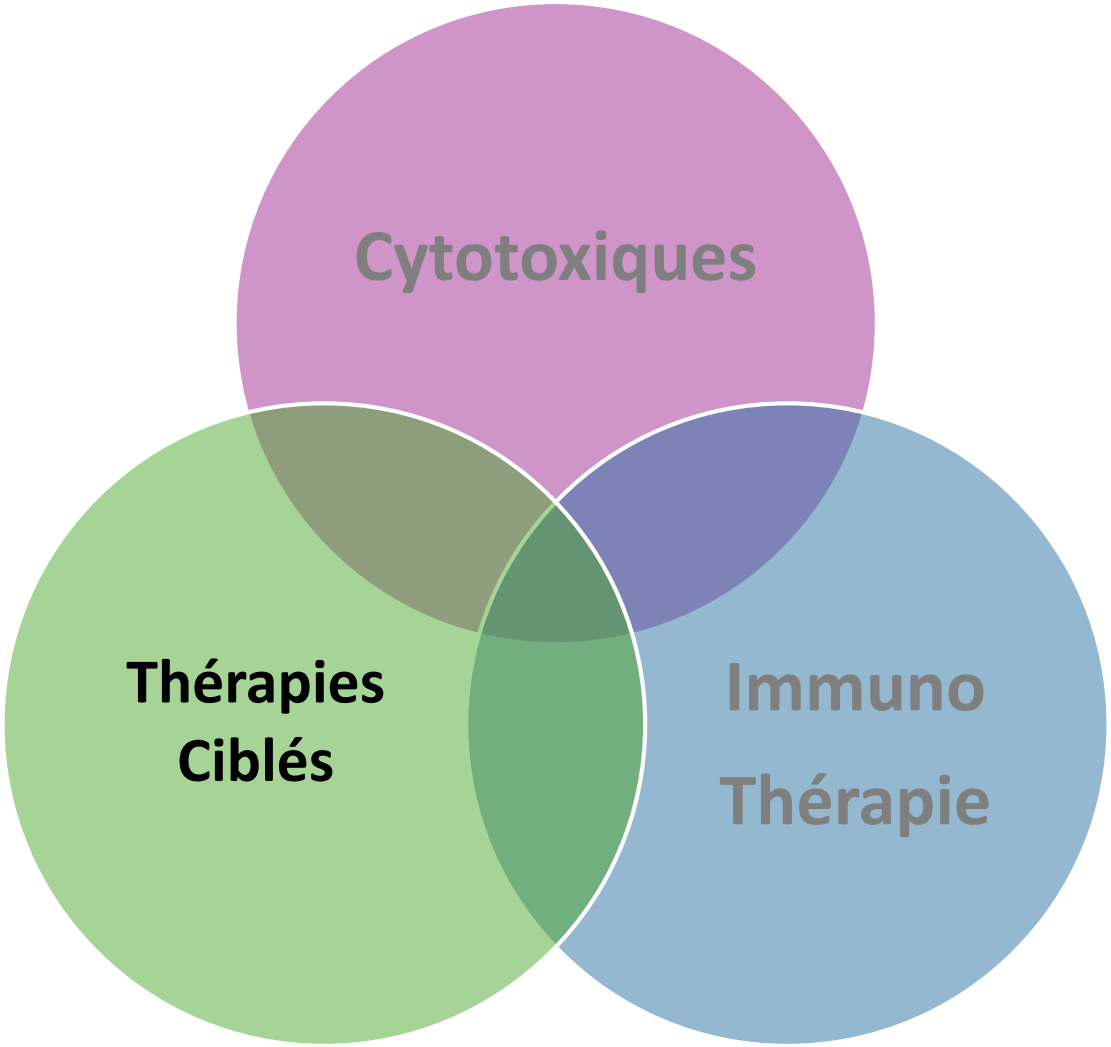
MMF as second line therapy for patients with immune-related hepatitis resistant to corticosteroids

E. Alouani et al. / European Journal of Cancer 193 (2023) 113313

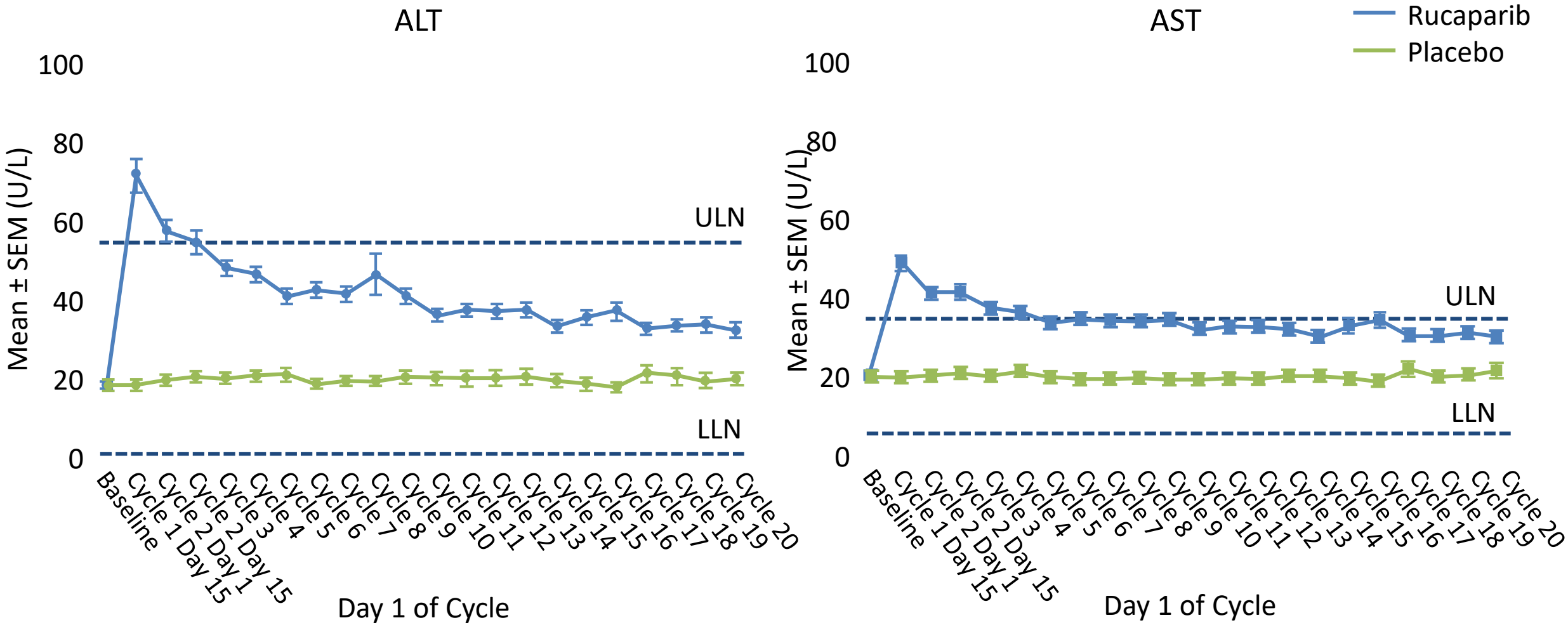


E Alouani, EJC, 2023

Traitements en Oncologie



ALT/AST Increases With Rucaparib Occur in Cycle 1 and Then Resolve



Managing PARP Inhibitor–Associated Toxicity

Grade	Intervention
Grade 1	Continue treatment; may **initiate symptomatic** management
Grade 2	Continue treatment **Dose interruption** **Dose reduction** if toxicity remains uncontrolled
Grade 3/4	Withhold **until resolution/improvement of** AE **Dose reduction** should be considered when treatment is resumed If lasts more than 28 days despite dose reduction/interruption, **treatment should be discontinued**

En conclusion

- Élévations tests hépatiques = **cause fréquente** en oncologie
- Les signes de sévérité reste proche de **loi de Hy's Law** avec
  - > **bilirubine élevée 2N**
  - > **Signes généraux**
- En l'absence de sévérité, une approche **première *observationnelle*** est possible
- La **biopsie PBH doit être discutée** pour clarifier les diagnostics et leurs sévérités
- Le traitement des hépatites immunomédiées est basé
  - > sur la **corticothérapie**
  - > **MMF** en cas de corticorésistance ou corticodépendance
- En cas de combinaison avec thérapie ciblée, **c'est la thérapie ciblée** qui doit être primitivement suspendue
- Le **rechallenge de l'immunothérapie** doit rester une possibilité selon le bénéfice antitumoral attendu

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New treatment goals

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