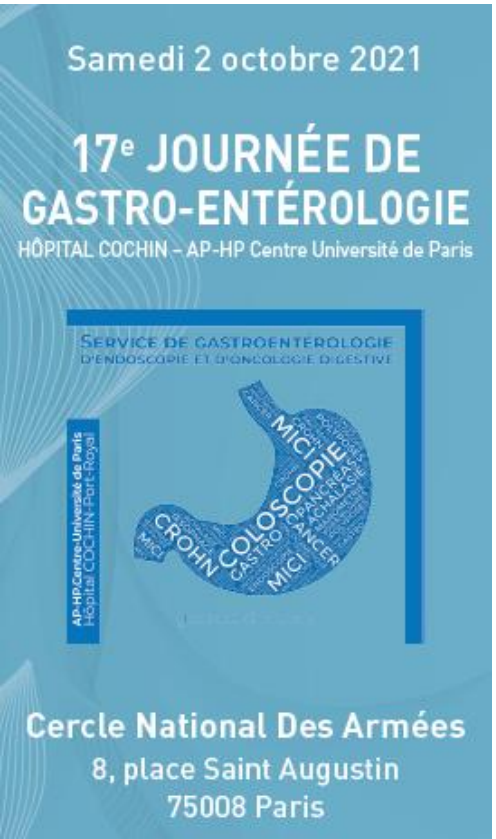


Immunothérapie
Les toxicités digestives et hépatiques ?

Romain Coriat

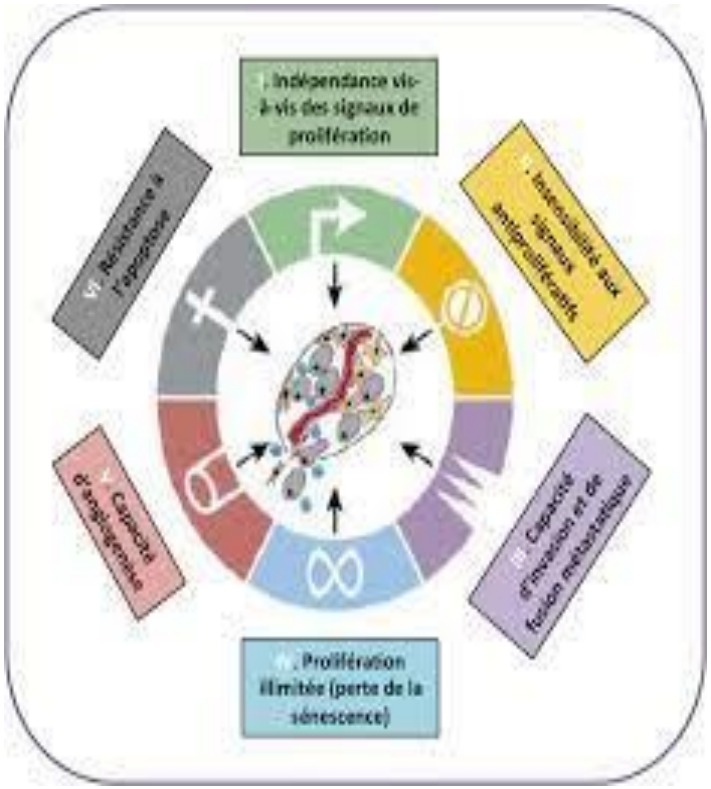
Service de gastroentérologie et d'oncologie digestive

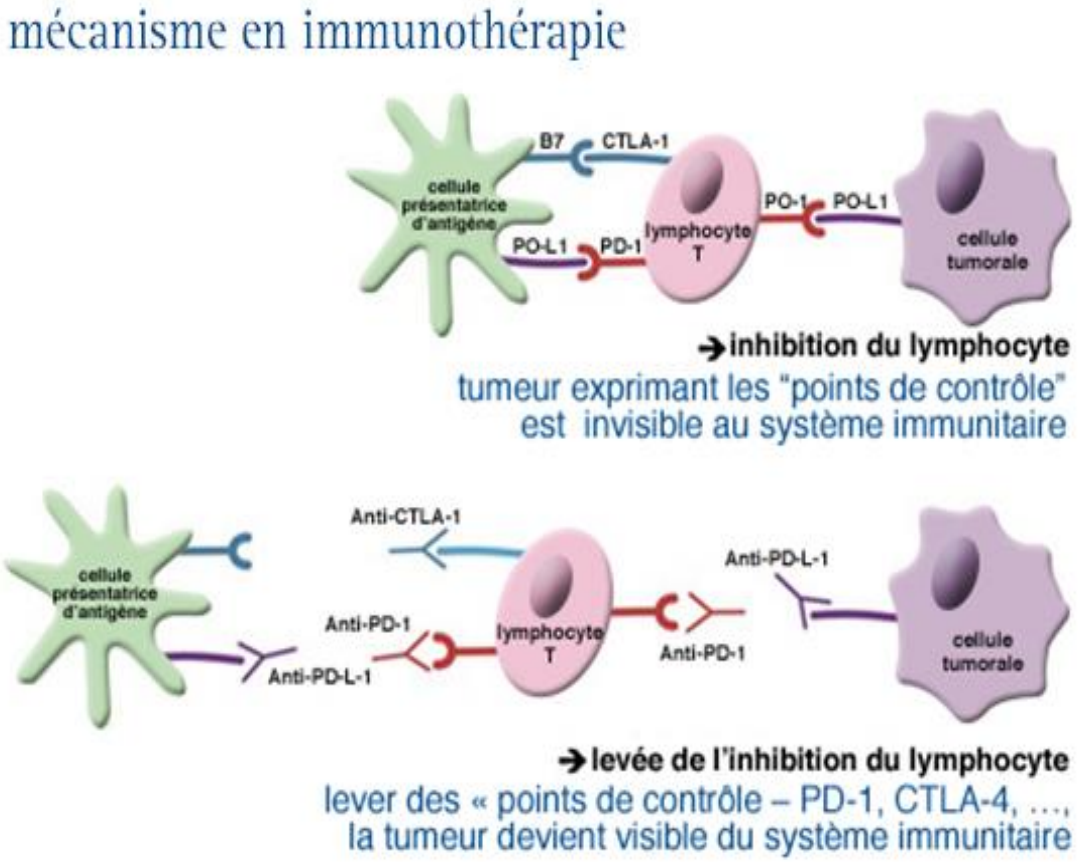
CHU Cochin

romain.coriat@aphp.fr

L'immunothérapie

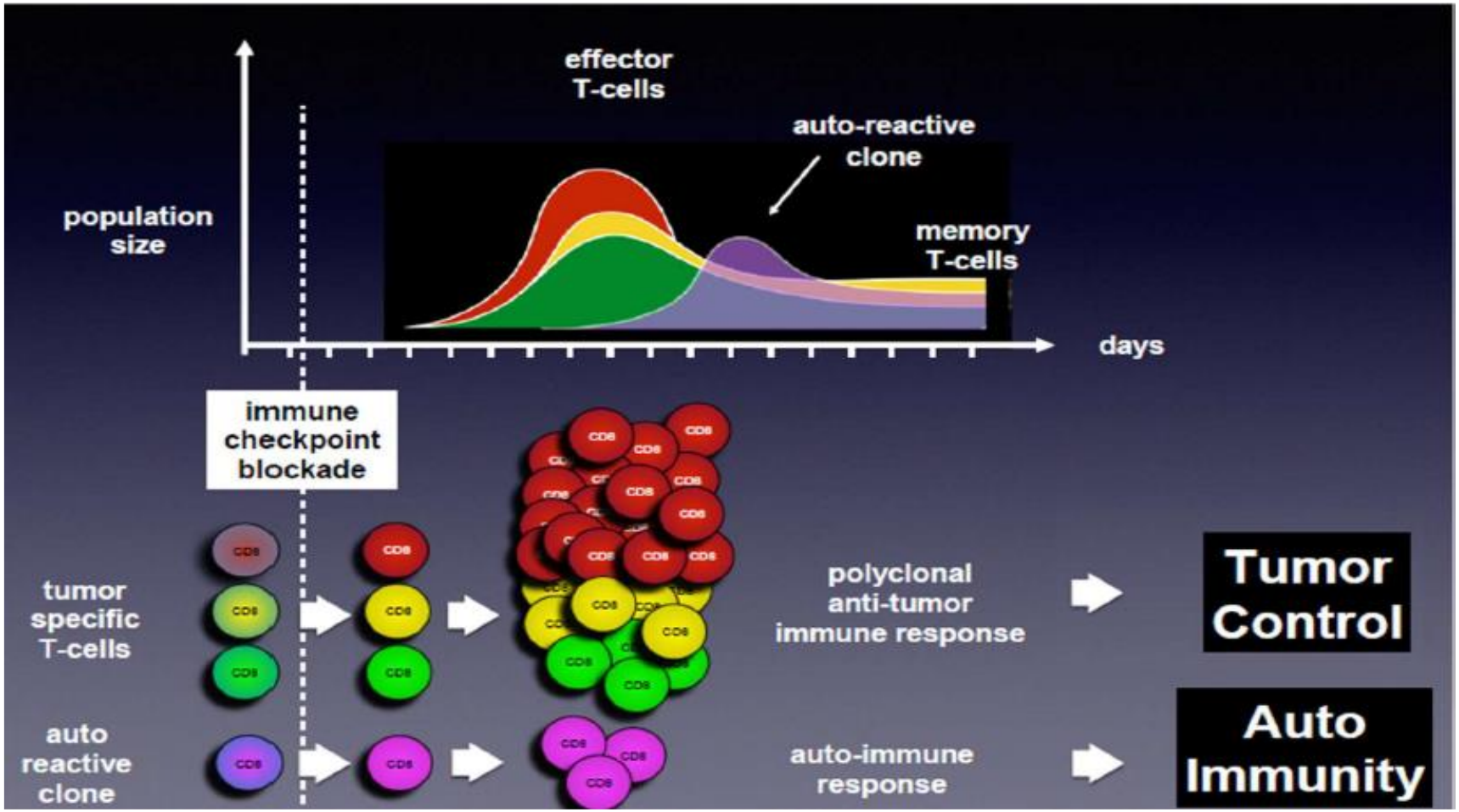
- **Le changement de paradigme de l'oncologie**



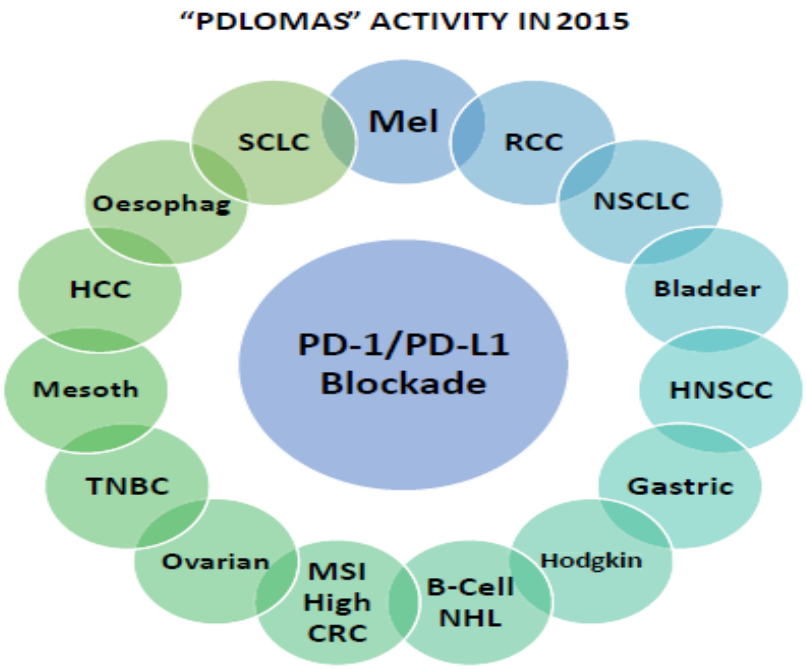


L'immunothérapie

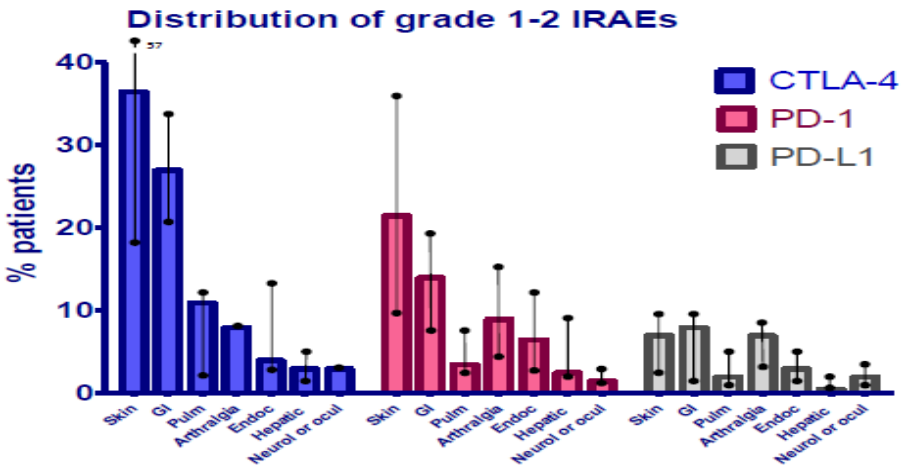
- **Les Anticorps anti PD1/PD L1 sont non spécifiques de la C tumorale**



Les principales indications de l'immunothérapie



- **Les principales indications d'immunothérapie**



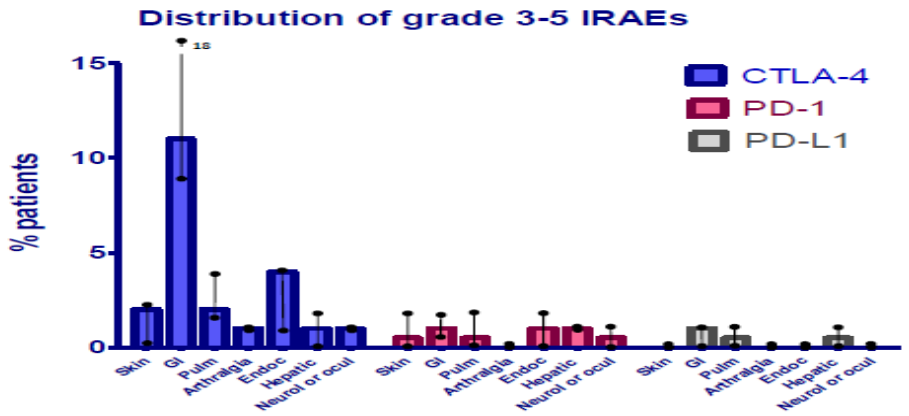
Prévention de la toxicité? (FDR)

→Pas de biomarqueur prédictif

→Antécédent de maladie auto immune

→Pathologies chroniques (CV, respiratoires, hépatiques..)

→Infections sévères récentes, virales chroniques



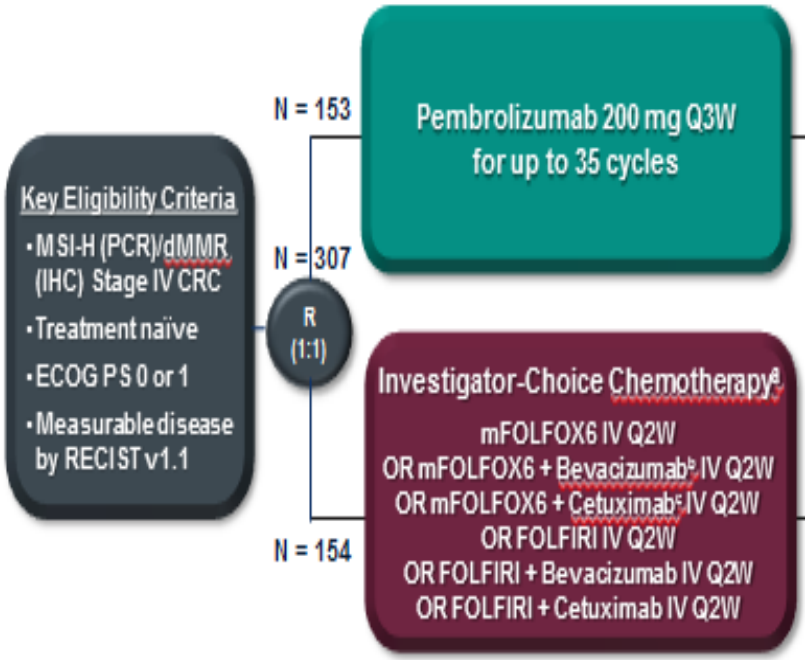
L'intérêt de l'immunothérapie

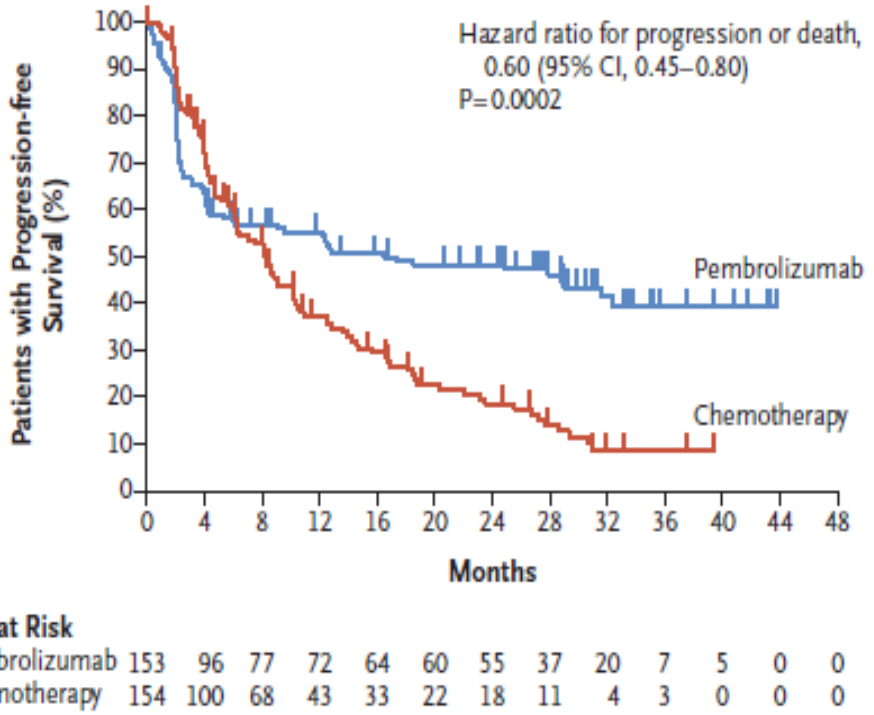
• Exemple du cancer colorectal MSI (pMMR)

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 DECEMBER 3, 2020 VOL. 383 NO. 23

Pembrolizumab in Microsatellite-Instability–High Advanced Colorectal Cancer

Keynote-177 : 1ère étude de phase III montrant un bénéfice significatif (en SSP) du pembrolizumab vs chimiothérapie dans les CCRm MSI .





Andre T, NEJM 2019

L'intérêt de l'immunothérapie

• Exemple du cancer colorectal MSI (pMMR)

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Table 3. Adverse Events in the As-Treated Population.*

Event	Pembrolizumab (N=153)		Chemotherapy (N=143)	
	Any	Grade ≥3	Any	Grade ≥3
	number of patients (percent)			
Any adverse event†	149 (97)	86 (56)	142 (99)	111 (78)
Diarrhea	68 (44)	9 (6)	89 (62)	16 (11)
Fatigue	58 (38)	6 (4)	72 (50)	13 (9)
Nausea	47 (31)	4 (3)	85 (59)	6 (4)
Abdominal pain	37 (24)	8 (5)	42 (29)	8 (6)
Decreased appetite	36 (24)	0	58 (41)	7 (5)
Vomiting	33 (22)	2 (1)	53 (37)	7 (5)
Aspartate aminotransferase increase	24 (16)	4 (3)	12 (8)	3 (2)
Upper abdominal pain	20 (13)	2 (1)	11 (8)	1 (1)
Nasopharyngitis	20 (13)	0	10 (7)	0
Asthenia	19 (12)	3 (2)	31 (22)	6 (4)

Toxicités

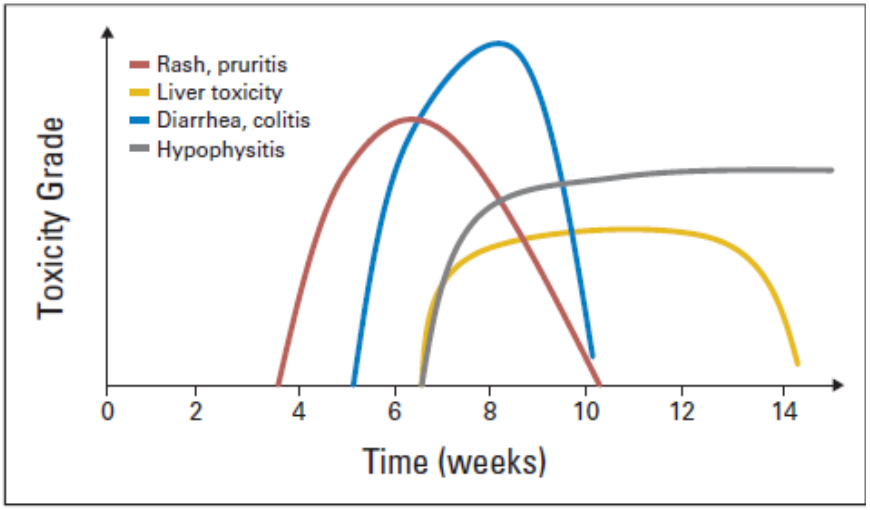
Aussi fréquentes

Moins sévères

Plus variées

Andre T, NEJM 2019

La toxicité des immunothérapies



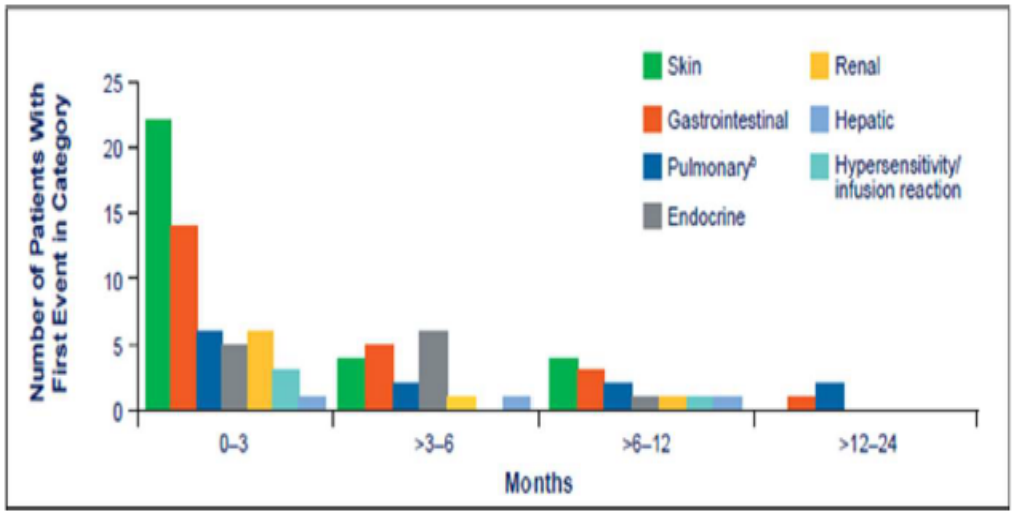
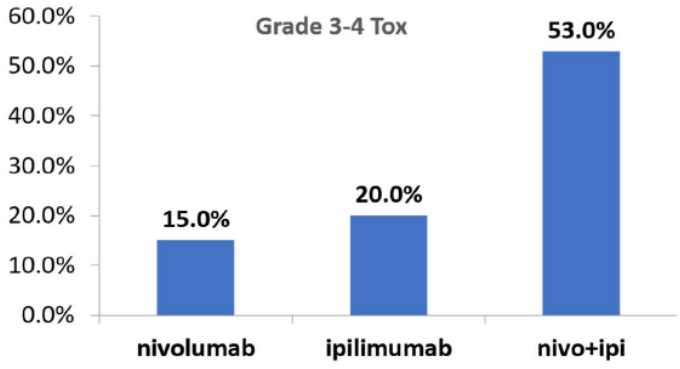


Fig 2. Kinetics of appearance of immune-related adverse event.

Digestif
10-15%



La combinaison d'immunothérapie augmente fortement la toxicité

Les principes généraux de la prise en charge

Common Terminology Criteria for Adverse Events (CTCAE)

Version 5.0

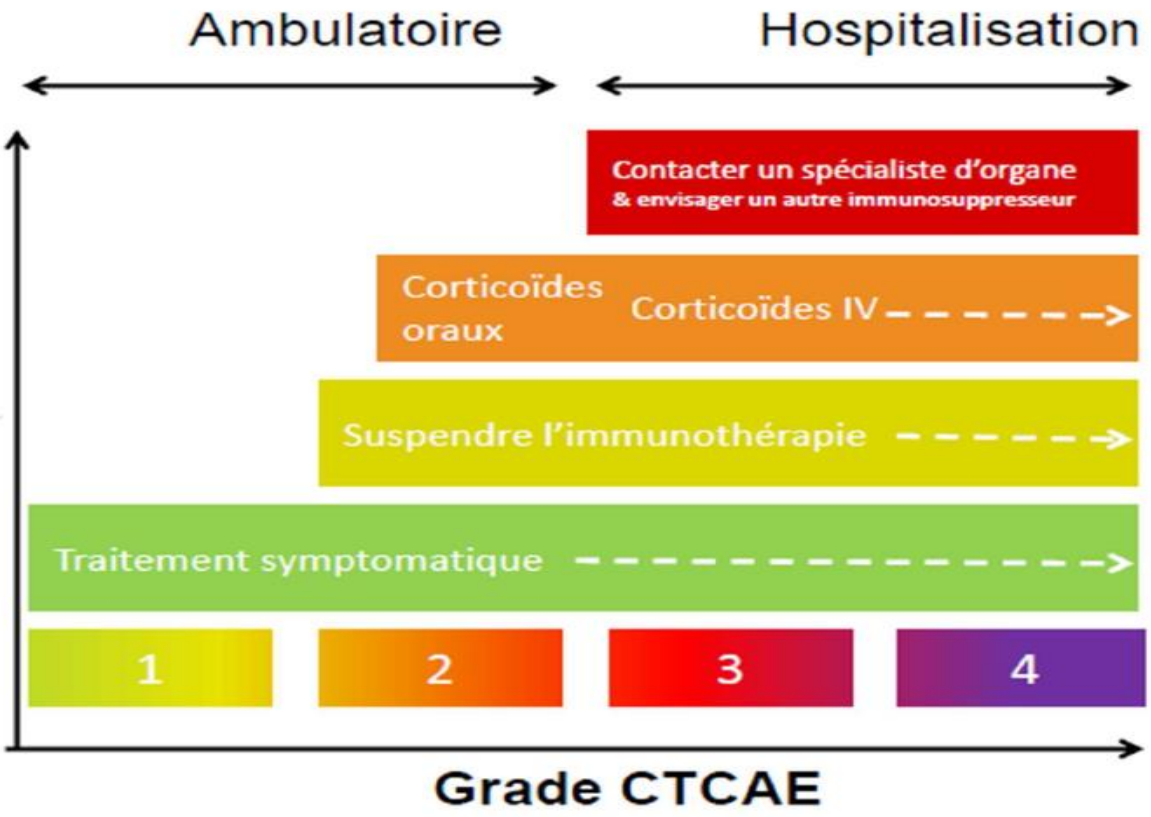
Grades

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

- Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.
- Grade 4 Life-threatening consequences; urgent intervention indicated.
- Grade 5 Death related to AE.

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Duodenal perforation	-	Invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the duodenal wall.					
Enterocolitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Abdominal pain; mucus or blood in stool	Severe or persistent abdominal pain; fever; ileus; peritoneal signs	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the small and large intestines. **Navigational Note:** If reporting a known abnormality of the colon, use Gastrointestinal disorders: Colitis. If reporting a documented infection, use Infections and infestations: Enterocolitis infectious.					
Autoimmune disorder	Asymptomatic; serologic or other evidence of autoimmune reaction, with normal organ function; intervention not indicated	Evidence of autoimmune reaction involving a non-essential organ or function (e.g., hypothyroidism)	Autoimmune reactions involving major organ (e.g., colitis, anemia, myocarditis, kidney)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by loss of function or tissue destruction of an organ or multiple organs, arising from humoral or cellular immune responses of the individual to his own tissue constituents.					

Les principes généraux de la prise en charge



Management of immune checkpoint blockade dysimmune toxicities: a collaborative position paper

S. Champiat[1,2], O. Lambotte[3,4,5,6], E. Barreau[7], R. Belkhir[8], A. Berdelou[9], F. Carbonnel[10], C. Cauquil[11], P. Chanson[12,13,14], M. Collins[10], A. Durrbach[15], S. Ederhy[16], S. Feuillet[17,18], H. François[15], J. Lazarovici[19], J. Le Pavec[17,18,20], E. De Martin[21,22], C. Mateus[23], J.-M. Michot[1], D. Samuel[21,22], J.-C. Soria[1,2], C. Robert[2,23], A. Eggermont[24] & A. Marabelle[1,24,25*]

Les principes généraux de la prise en charge

Réflexe corticoïdes

→ Y penser tôt

→ Ne pas les arrêter trop tôt

→ Attention aux diagnostics différentiels infectieux (PNP, colite)

→ Décroissance progressive ≥ 1 mois

→ Prophylaxie Bactrim

Suspendre l'immunothérapie

→ Reprendre si G ≤ 1

→ ARRET DEFINITIF

>> Menace du pronostic vital
>> G3 qui récidive
>> Impossibilité de diminuer la CTC

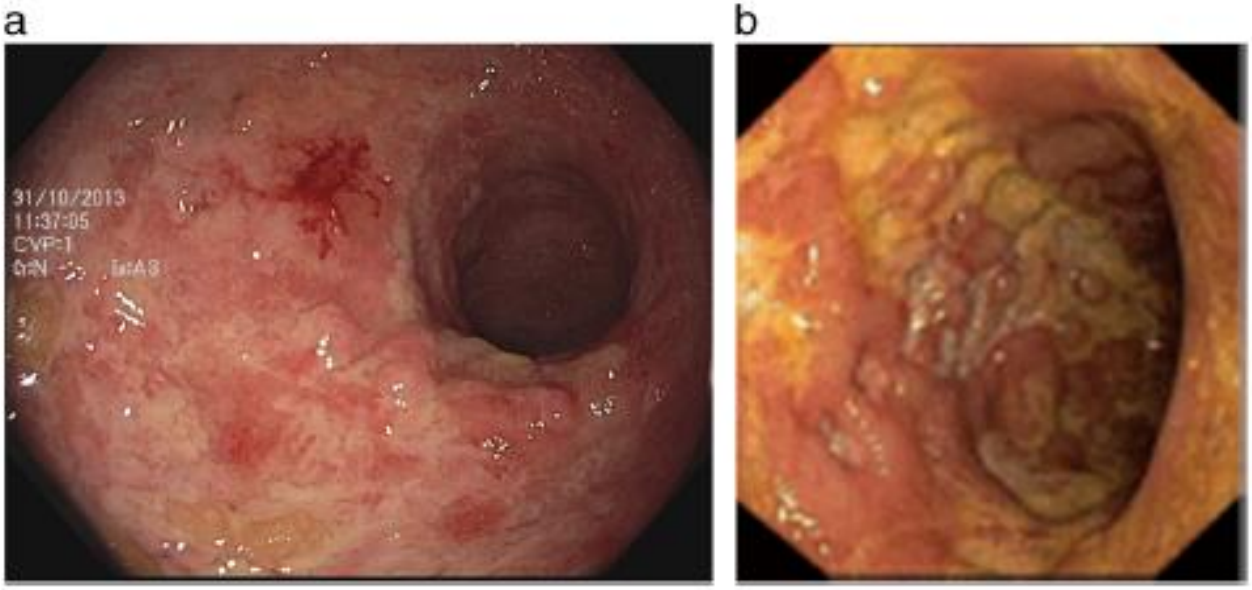
Management of immune checkpoint blockade dysimmune toxicities: a collaborative position paper

S. Champiat[1,2], O. Lambotte[3,4,5,6], E. Barreau[7], R. Belkhir[8], A. Berdelou[9], F. Carbonnel[10], C. Cauquil[11], P. Chanson[12,13,14], M. Collins[10], A. Durrbach[15], S. Ederhy[16], S. Feuillet[17,18], H. François[15], J. Lazarovici[19], J. Le Pavec[17,18,20], E. De Martin[21,22], C. Mateus[23], J.-M. Michot[1], D. Samuel[21,22], J.-C. Soria[1,2], C. Robert[2,23], A. Eggermont[24] & A. Marabelle[1,24,25*]

Les toxicités digestives de l'immunothérapie

• Rectite / Colite

Tableau de poussée d'une maladie inflammatoire
Intensité : souvent minime (rectite) / Parfois majeure (anti TNF Corticoides)



Toxicité de l'immunothérapie sous Ipilimumab

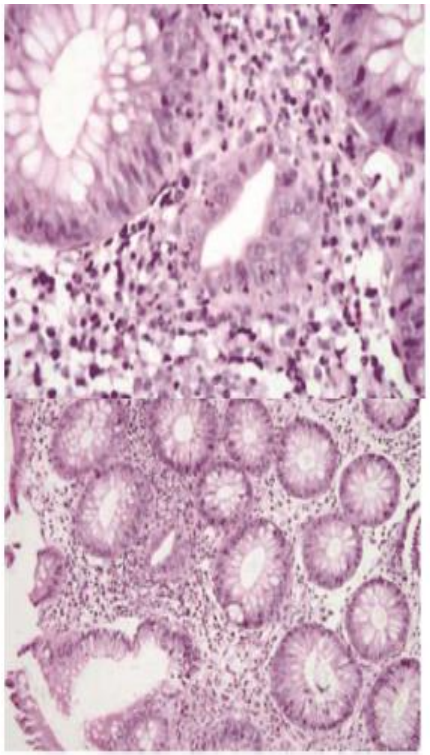


Fig. 2 Histopathology of a biopsy of immune checkpoint inhibitor-induced colitis showing crypt destruction and neutrophilic infiltrates in the crypt epithelium. Reproduced with permission from Maker et al. [37]

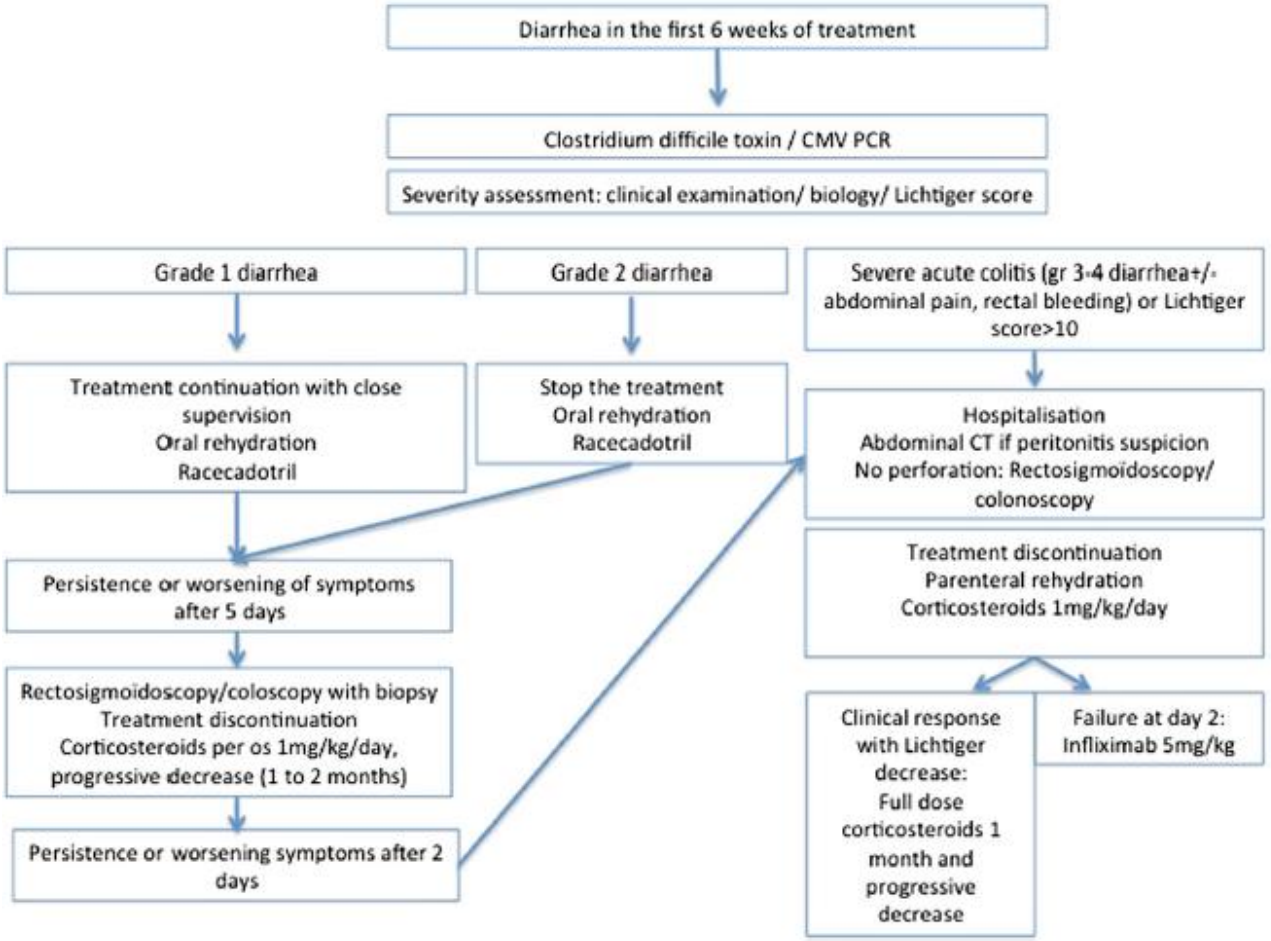
Indication d'examen endoscopique + Biopsies pour évaluer la gravité et faire la balance béénfice risque

Les toxicités digestives de l'immunothérapie

Score de lichtiger

Number of stools per day (more than usual)	0–2	0
	3–4	1
	5–6	2
	7–9	3
	10 and more	4
Stool during the night	No	0
	Yes	1
Rectal bleeding (percentage)	Absent	0
	<50%	1
	> or =50%	2
	100%	3
Fecal incontinence	No	0
	Yes	1
Abdominal pain	None	0
	Light	1
	Mild	2
	Intense	3
General condition	Perfect	0
	Very good	1
	Good	2
	Mild	3
	Bad	4
	Very bad	5
Provoked abdominal pain	None	0
	Light	1
	Mild and diffuse	2
	Important	3
Anti-diarrheal necessity	No	0
	Yes	1
TOTAL:		

Definition: **acute severe colitis defined by a score ≥ 10**



Prise en charge par un gastroentérologue ++++

Prieux et al, Immune check point inhibitor induced colitis : diagnosis and managment, Target Oncol 2017

Les toxicités hépatiques de l'immunothérapie

• Surveillance systématique +++

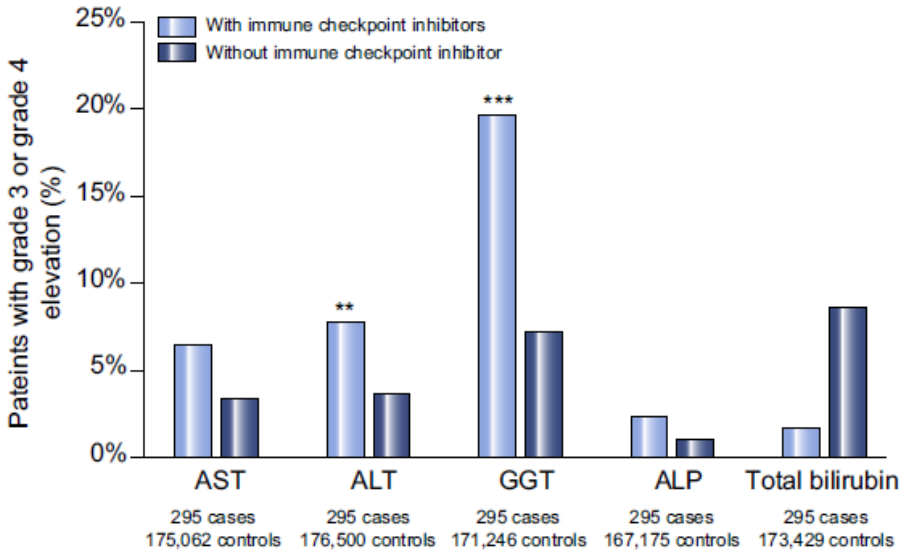
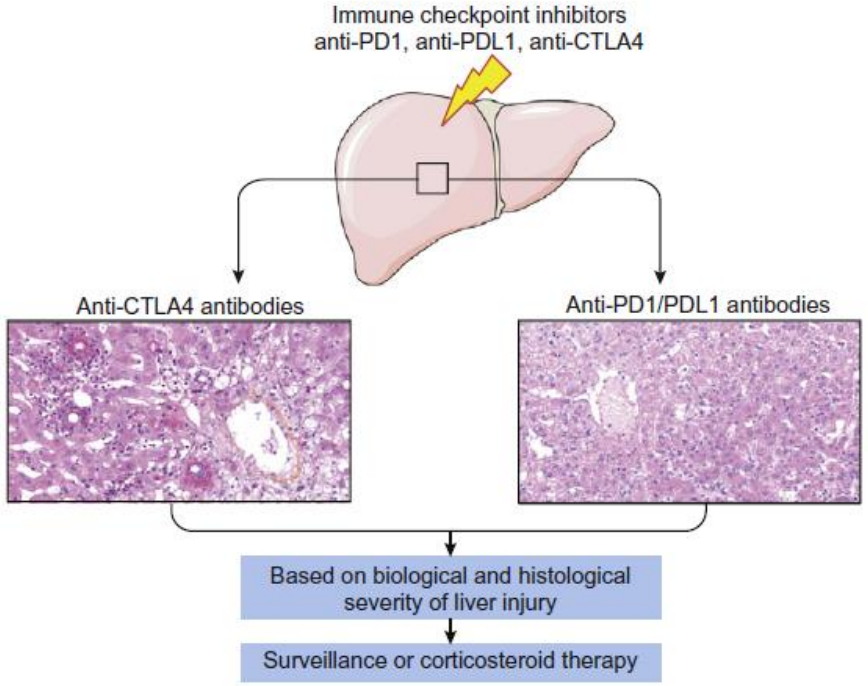


Fig. 1. Frequencies of grade 3 and 4 AST/ALT/GGT/ALP and total bilirubin elevations among immune checkpoint inhibitor (n = 303) and control (n = 299,491) patients over an eight-year observational period in a teaching hospital. Differences between groups were computed with logistic regressions adjusted for age, sex, and prescription unit. $^{**}p < 0.05$, $^{***}p < 0.001$. ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase.



Hepatite auto immune like

Cholangite auto immune like

Overlap syndrome auto immun

De Martin et al, J Hepatol, 2018
Parlati et al. . *J Hepatol* 2018

Les toxicités hépatiques de l'immunothérapie

- **Surveillance systématique +++**

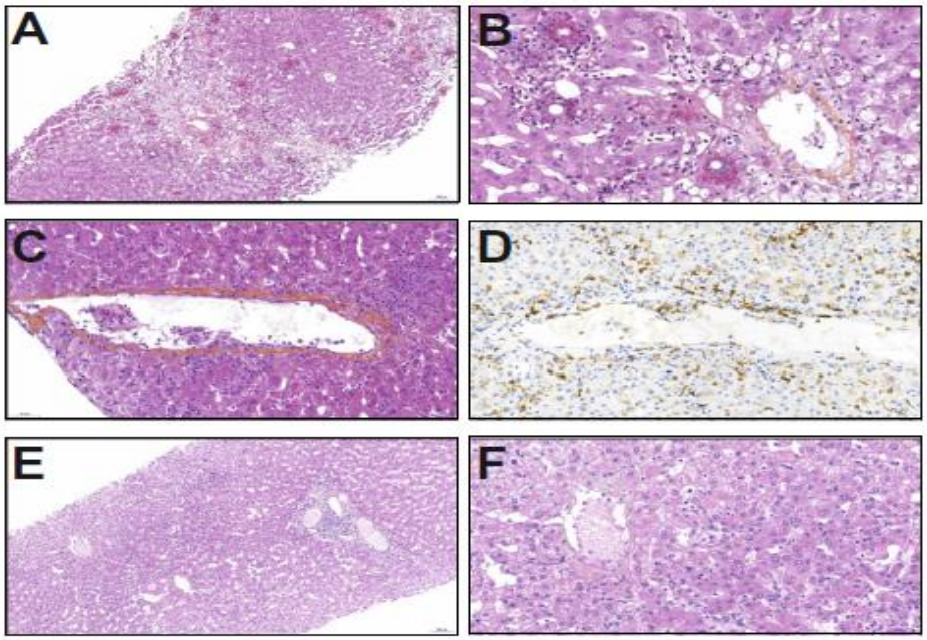


Fig. 2. Histological patterns in patients treated with anti-cytotoxic T lymphocyte antigen 4 (CTLA-4) *vs.* anti-programmed cell death 1 (PD1) monoclonal antibodies (mAbs). (A and B) First liver biopsy of Patient 5 (who received anti-CTLA4 mAbs). (A) Centrilobular confluent necrosis with fibrin ring granulomas [haematoxylin-eosin-saffron (HES) ×100]. (B) Fibrin ring granuloma and sinusoidal inflammatory infiltrates comprising activated lymphocytes and histiocytes, without plasma cell (HES ×300). (C and D) Liver biopsy of Patient 2 (who received anti-CTLA4 mAbs). (C) Endotheliitis of a centrilobular vein with perivenular and subendothelial infiltration by lymphocytes and histiocytes and focal disruption of the endothelium (HES ×40). (D) Perivenular and subendothelial lymphocytes are CD8+ cytotoxic T lymphocytes (immunohistochemistry CD8 ×40). (E and F) Liver biopsy of Patient 8 (who received anti-PD1 mAbs). (E) Active hepatitis with mild periportal and moderate lobular activity (HES ×100). (F) Lobular lymphocytes and histiocytes without plasma cells (HES ×300). (This figure appears in colour on the web.)

Type and Severity of irAE	Management
Hepatitis G1 AST or ALT>ULN to 3 x ULN and/or Total bilirubin >ULN to 1.5 x ULN	• Continue ICPT mAb therapy • Continue liver function test monitoring If worsens: • Treat as G2 or G3/4
Hepatitis G2 AST or ALT>3 to ≤5 x ULN and/or Total bilirubin >1.5 to ≤3 x ULN	• Delay ICPT mAb therapy • Increase frequency of monitoring to every 3 days
Hepatitis G3/4 AST or ALT>5 x ULN or Total bilirubon>3 x ULN	• Admit to hospital for IV corticosteroids (methylprednisolone 1-2 mg/kg daily dose) • Supportive care including IV fluids, supplemental oxygen and antibiotics • Withhold hepatotoxic drugs • Consider further diagnostic imaging or procedures

Belli et al. . *Liver toxicity and immune check point inhibitor : a practical approach, Crit Rev in oncol 2018*

Les toxicités hépatiques de l'immunothérapie

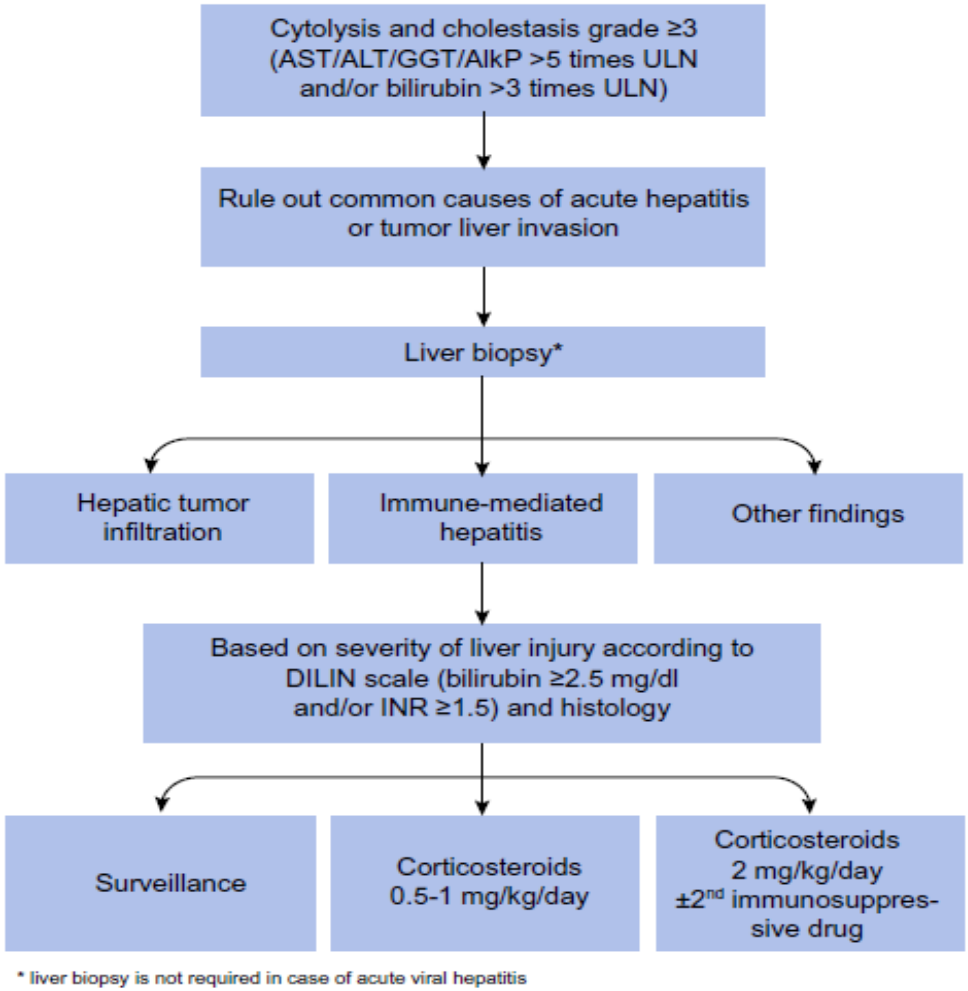


Fig. 3. Algorithm for the assessment and management of patients with acute hepatitis during immunotherapy for metastatic cancer. ALT, alanine aminotransferase; Alk P, alkaline phosphatase; ASMA, anti-smooth muscles antibodies; AST, aspartate aminotransferase; DILIN, Drug-Induced Liver Injury Network; GGT, gamma-glutamyltransferase.

Prise en charge par un hépatologue ++++

De martin et al, J Hepatol 2018

Les toxicités digestives et hépatiques de l'immunothérapie

L'immunothérapie est une nouvelle arme thérapeutique en oncologie qui a permis un allongement notable de la survie globale des patients traités.

L'efficacité se fait au prix d'une toxicité différente de la chimiothérapie

La toxicité colique peut aller de la rectite minime à la colite aigue grave.

La toxicité hépatique peut aller de la cholestase minime à l'hépatite fulminante.

Dans tous les cas la toxicité digestive de grade > 2 justifie une prise en en charge par un hépato gastroentérologue.