CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD

CRCL CENTRE DE RECHERCHE EN CANCÉROLOGIE DE LYON

UMR INSERM 1052/CNRS 5286
CISTAR *« **C**ancer **I**mmune **S**urveillance and **T**herapeutic t**AR**geting »*

Gestion des toxicités aux immunothérapies

Centre Léon Bérard – Dpt d'Oncologie Médicale

Dr Matthieu SARABI

TOX'IMM
Gestion des Toxicités des Immunothérapies

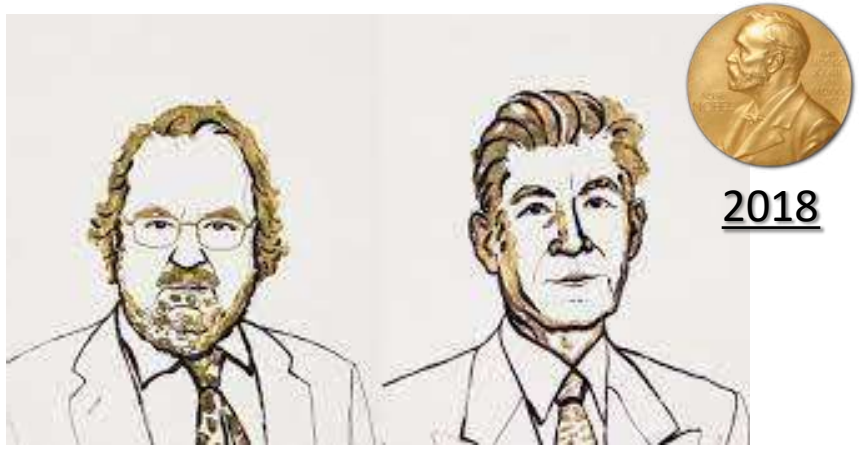
Réunion de Concertation Pluridisciplinaire

Vendredi 18/06/2021

Pas de lien d’intérêt.

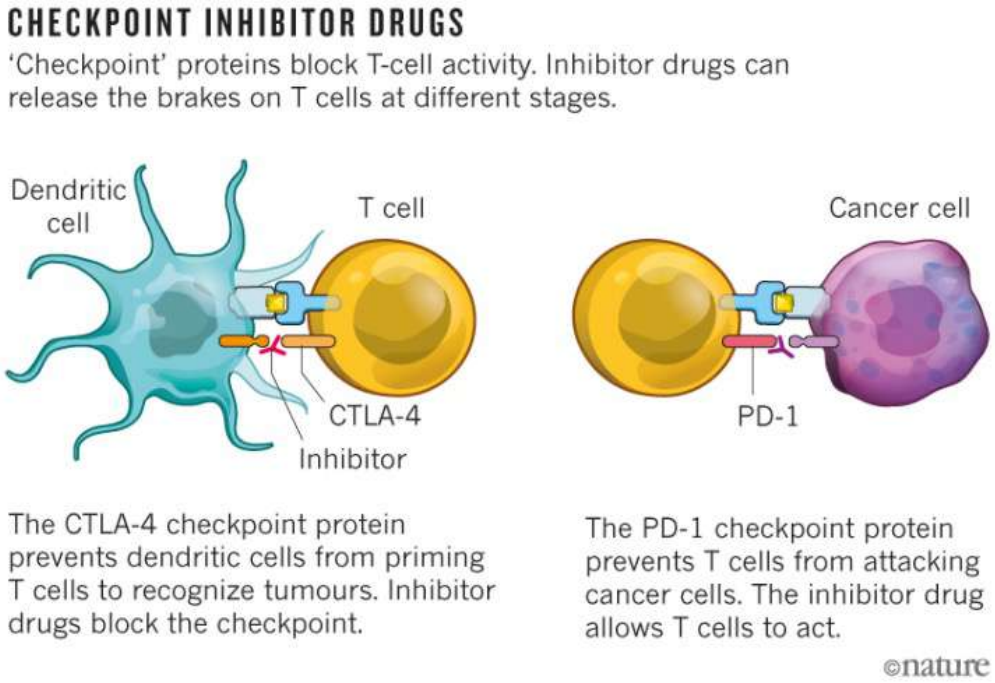
10 ans d'immunothérapies...

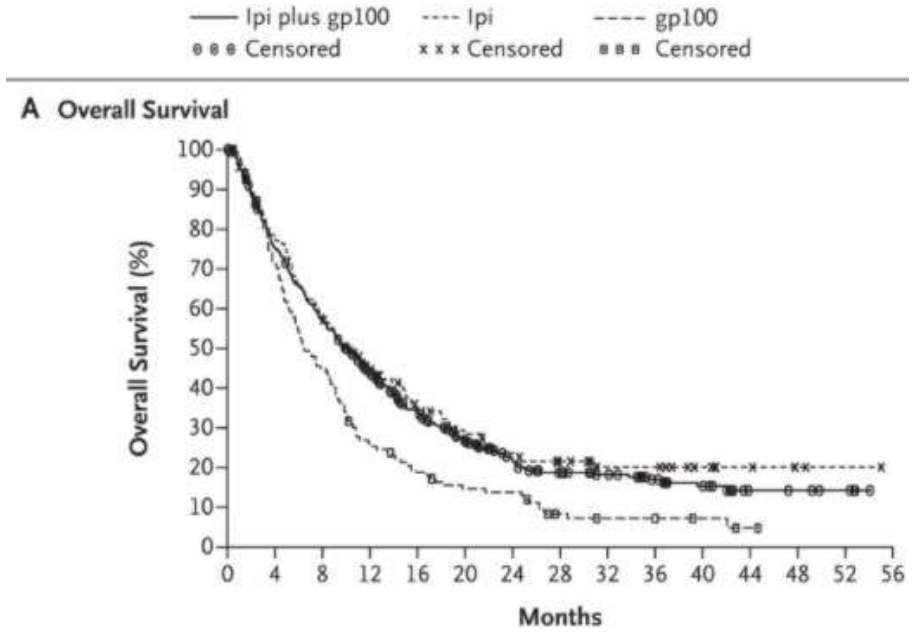
Caroline Robert *Nat Com* 2020



2018

- Moduler l'activité des lymphocytes T
  - **CTLA-4** : IPILIMUMAB
  - **PD(L)1** : PEMBROLIZUMAB/NIVOLUMAB ; ATEZOLIZUMAB/DURVALUMAB

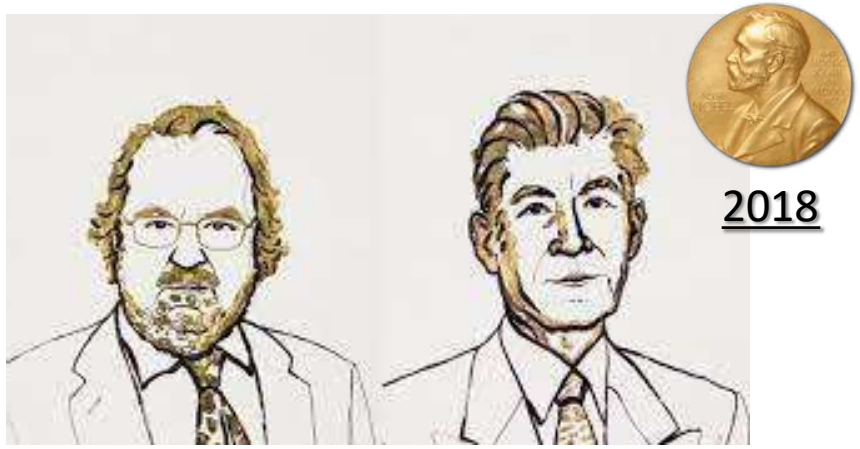




Hodi et al. *NEJM* 2010

10 ans d'immunothérapies...

Caroline Robert *Nat Com* 2020



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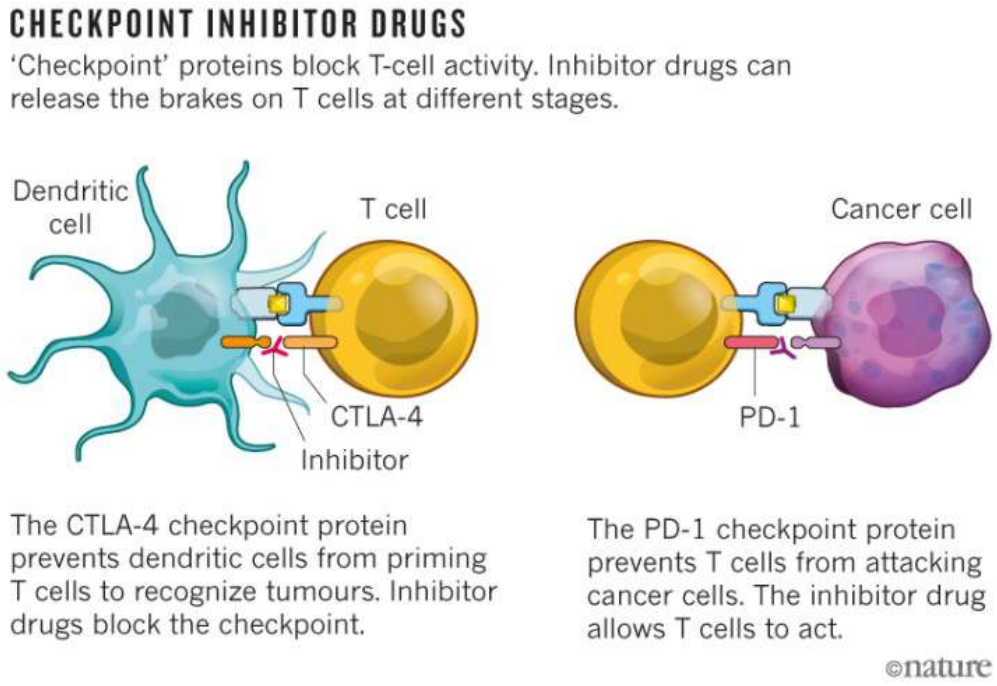
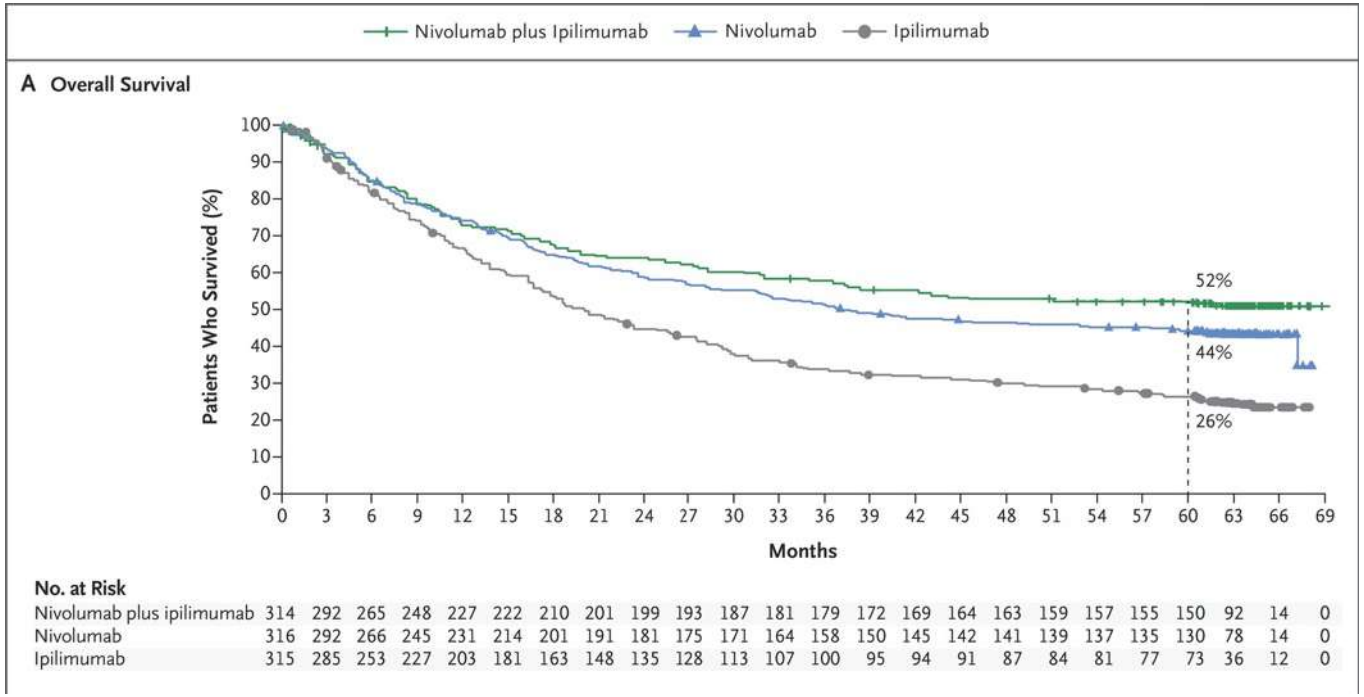
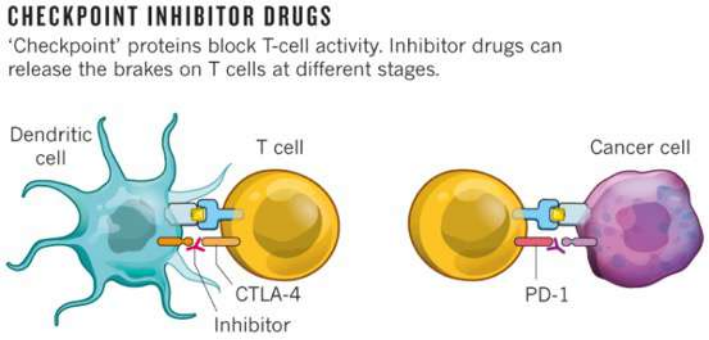




Larkin et al. *NEJM* 2019

10 ans d'immunothérapies…



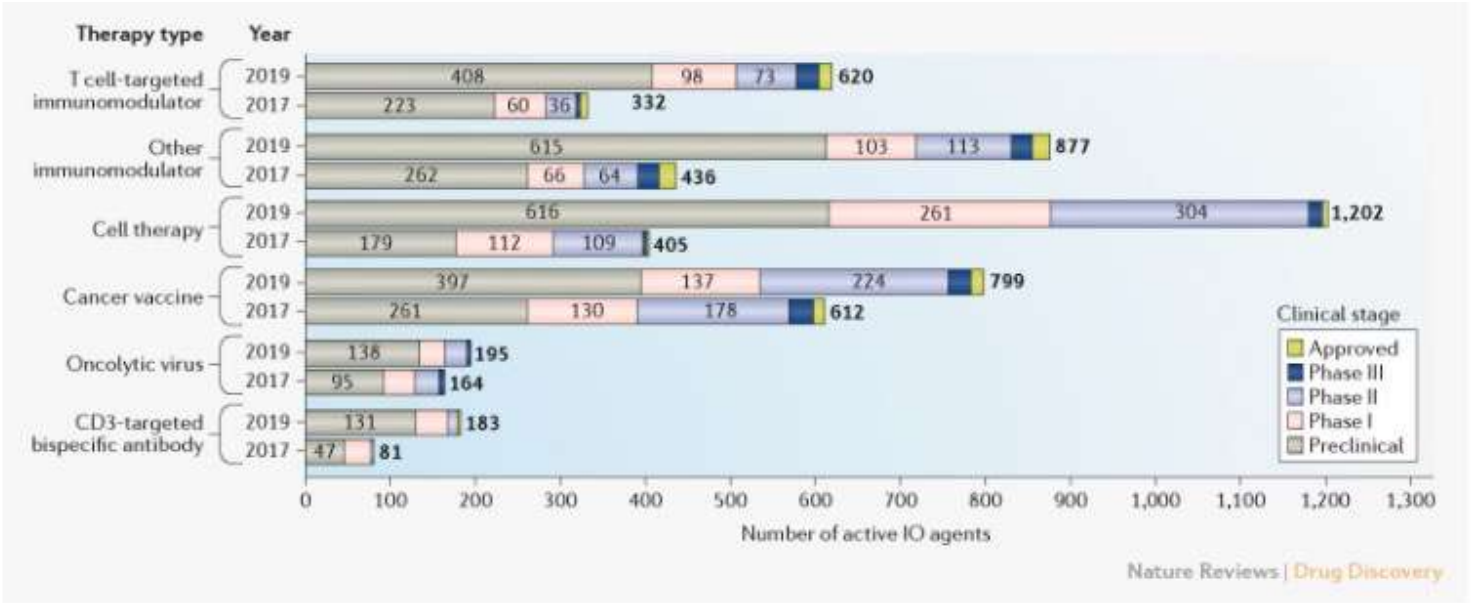


Fig. 1 | **Overview of all 3,876 active IO agents in the current global drug development pipeline.** In the past 2 years, 1,846 new agents have been added to the immuno-oncology (IO) pipeline, an increase of 91%.

Xin et al. *Nat. Rev. Drug Discov.* 2019

plan

- *Comment, quand* et *où ?*
- *Quels recommandations* et *cadre* de prise en charge?
- *Quelles particularités* pour les hépato-gastro-entérologues?
- La *réintroduction* en 2021…
- L'utilisation lors de *maladie(s) auto-immune(s)* pré-existante(s)

Mécanismes?

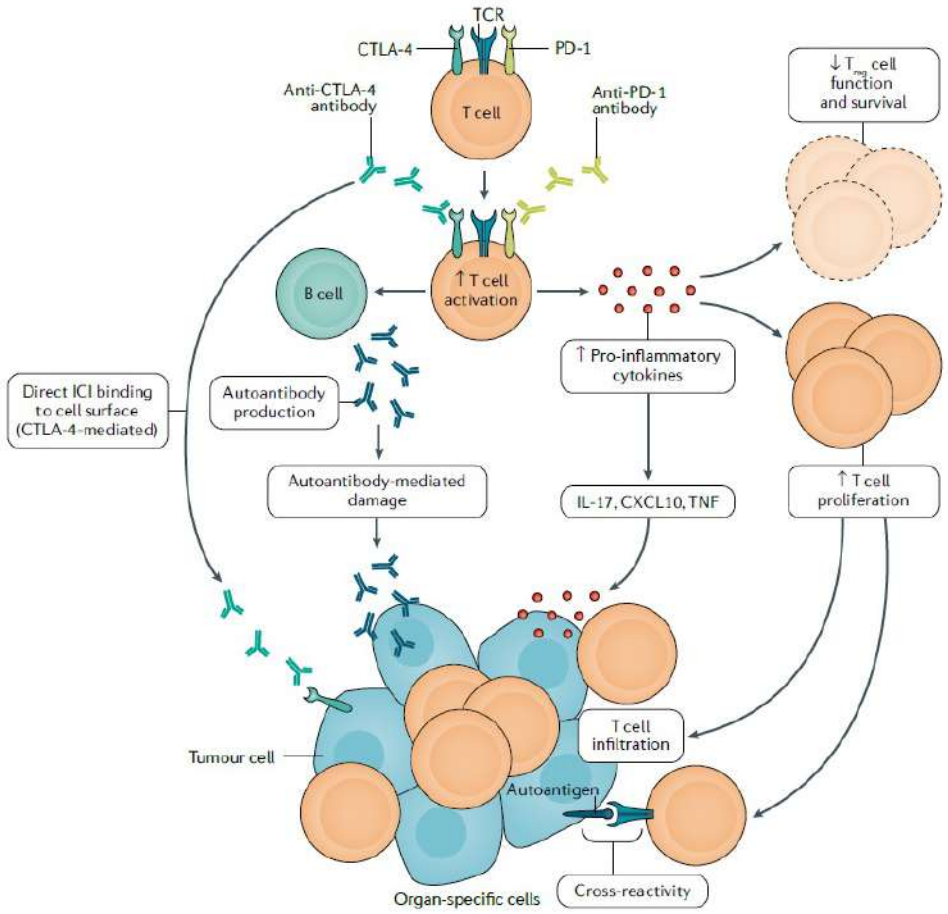


Fig. 2 | **Mechanism of immune-related adverse events.** The mechanisms of immune-related adverse events owing to immune checkpoint inhibitors (ICIs) depend on the type of ICI therapy used (anti-PD-1 or anti-PD-L1 inhibitors versus anti-CTLA-4 inhibitors). CTLA-4 inhibitors can induce several cellular alterations, such as T cell activation and proliferation, impaired $CD4^+CD25^+$ regulatory T cell (T_{reg} cell) survival and increased counts of type 17 T helper cells, in addition to the induction of cross-reactivity between anti-tumour T cells and antigens on healthy cells and autoantibody production. PD-1 and PD-L1 inhibitors lead to a reduction in T_{reg} cell survival and T_{reg} cell inhibitory function and an increase in cytokine production. TCR, T cell receptor; TNF tumour necrosis factor.

Ramos-Casals et al. Nat Rev Disease Primer 2020

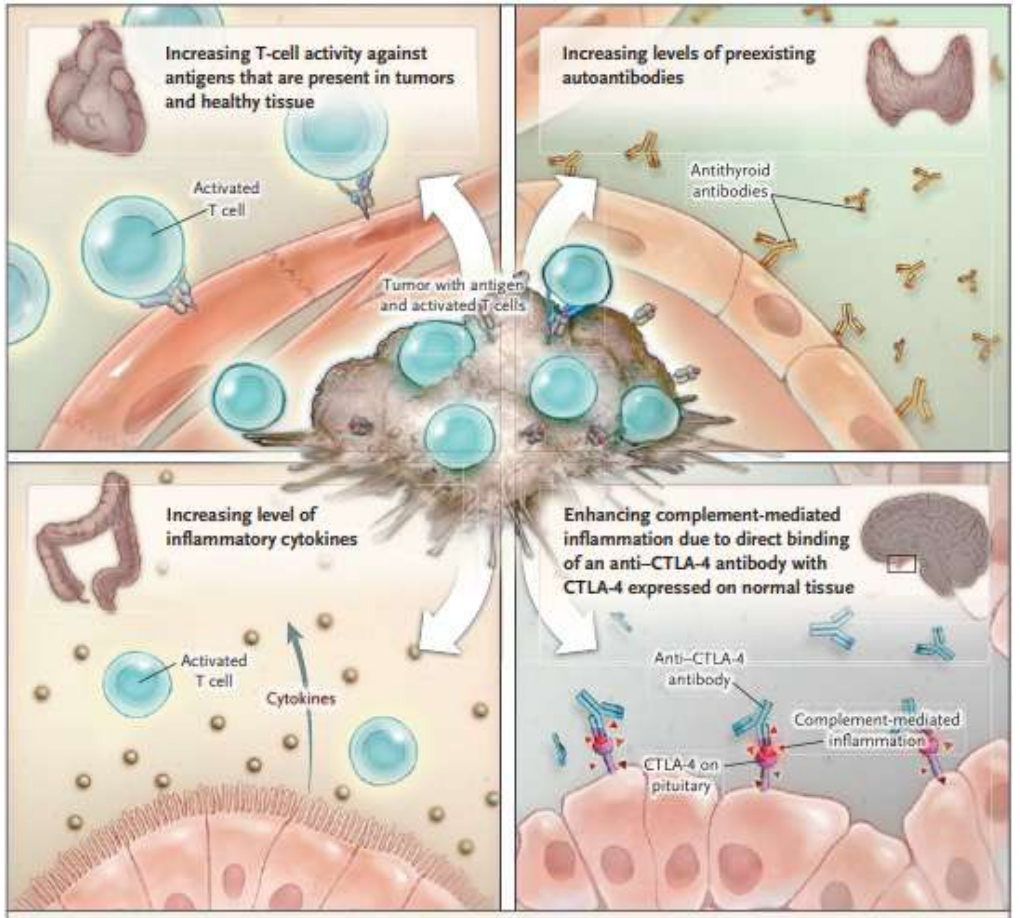
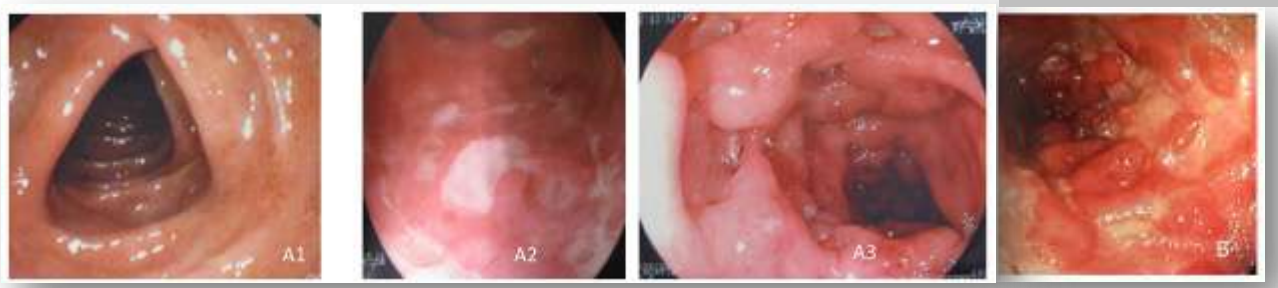


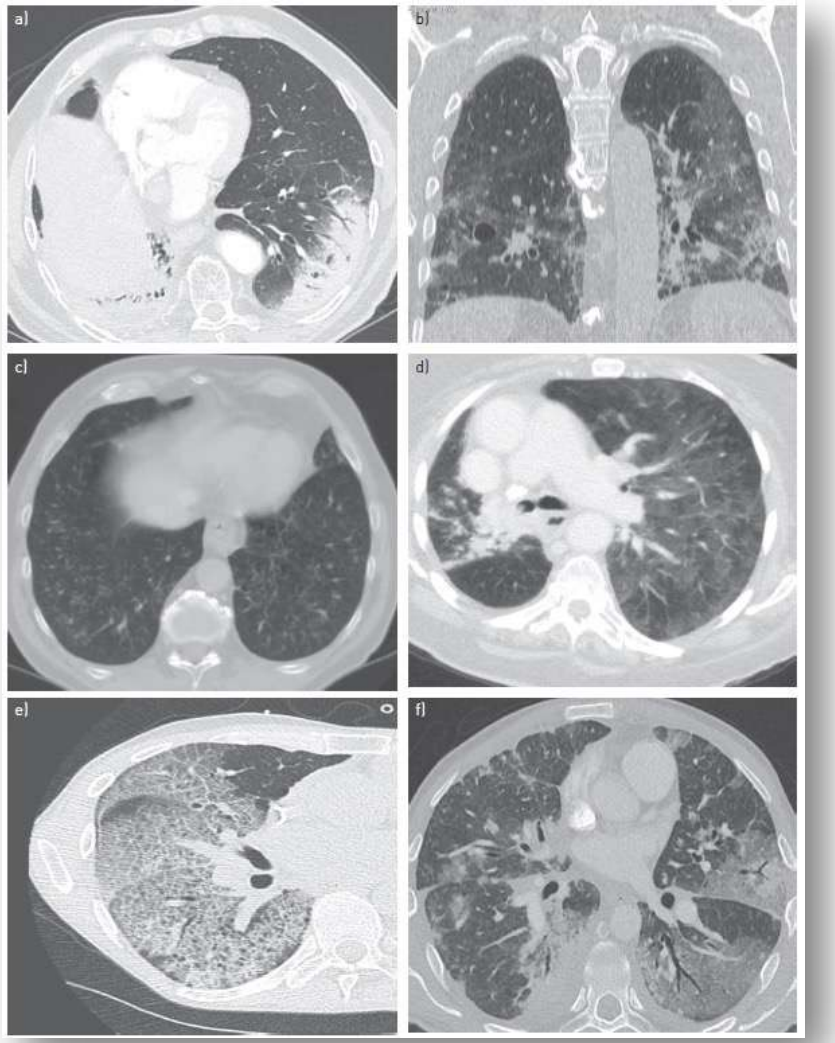
Figure 2. Possible Mechanisms Underlying Immune-Related Adverse Events.
The mechanisms that result in immune-related adverse events are still being elucidated. Some potential mechanisms include increasing T-cell activity against antigens that are present in tumors and healthy tissue, increasing levels of preexisting autoantibodies, an increase in the level of inflammatory cytokines, and enhanced complement-mediated inflammation due to direct binding of an antibody against cytotoxic T-lymphocyte antigen 4 (CTLA-4) with CTLA-4 expressed on normal tissue, such as the pituitary gland.

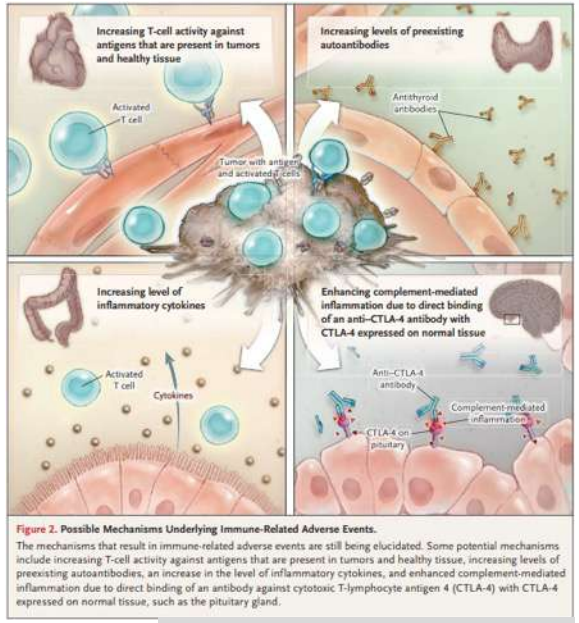
Postow et al. *NEJM* 2018

Mécanismes?

Soularue et al. Gut 2018







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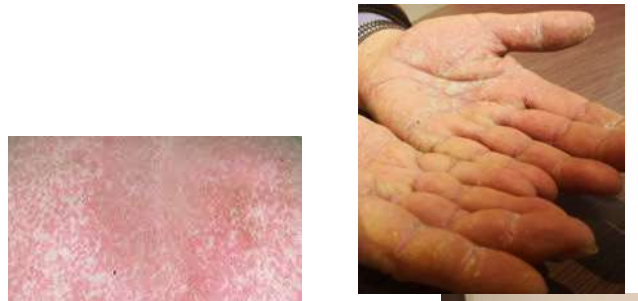
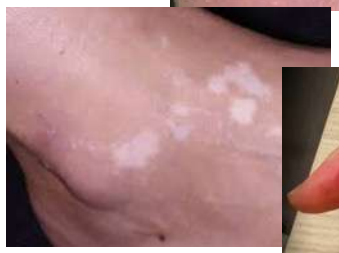
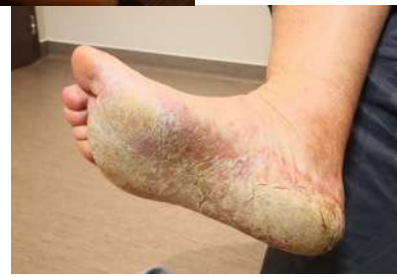
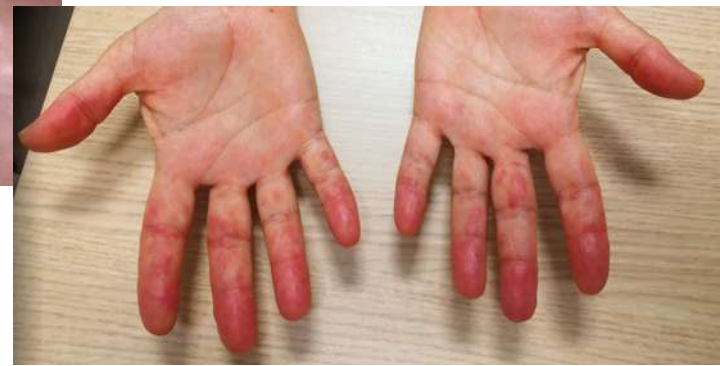
Postow et al. *NEJM* 2018

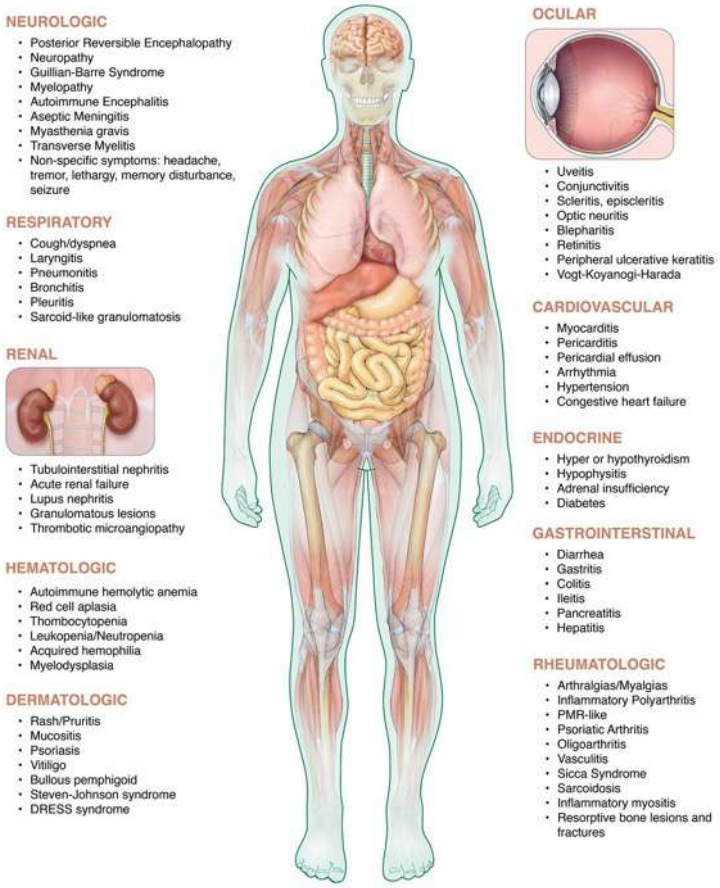








Où?



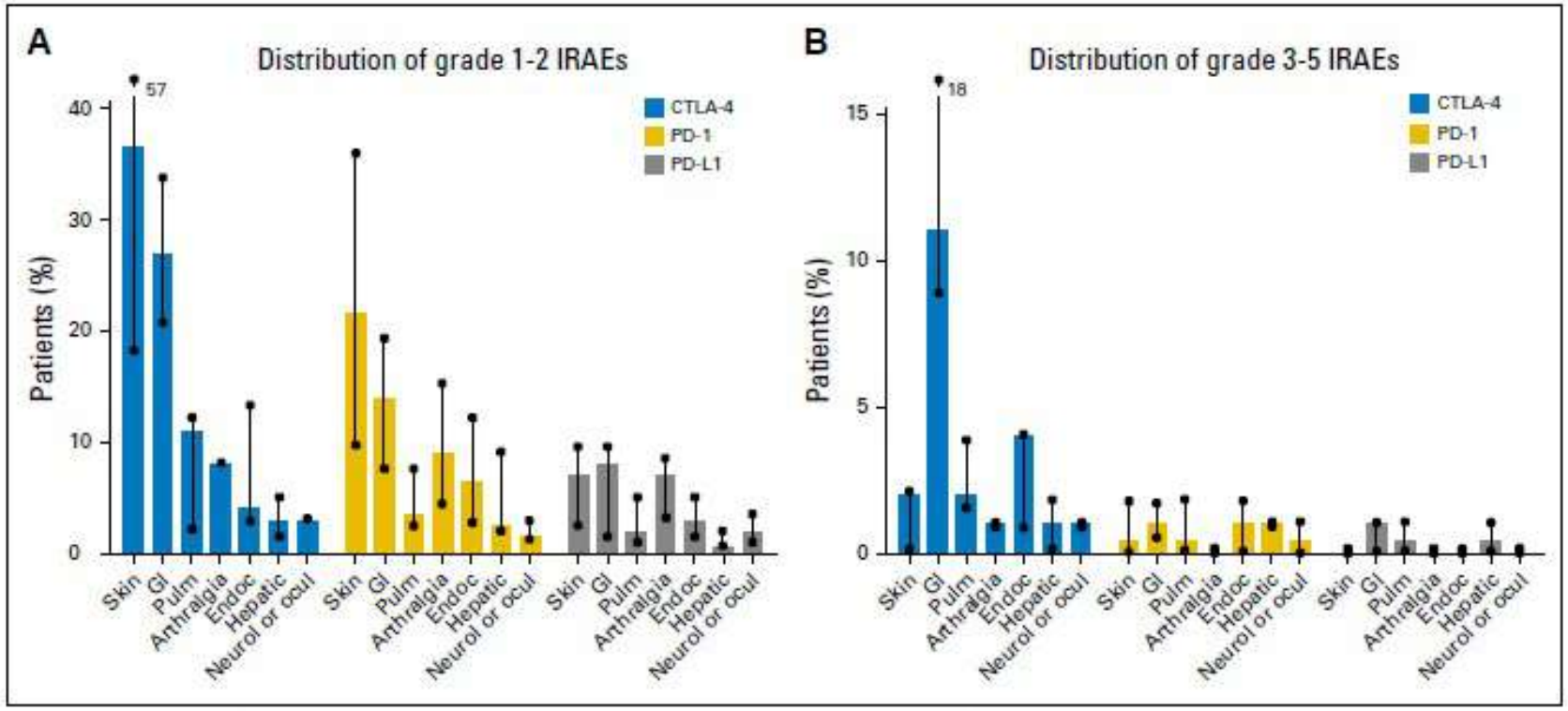


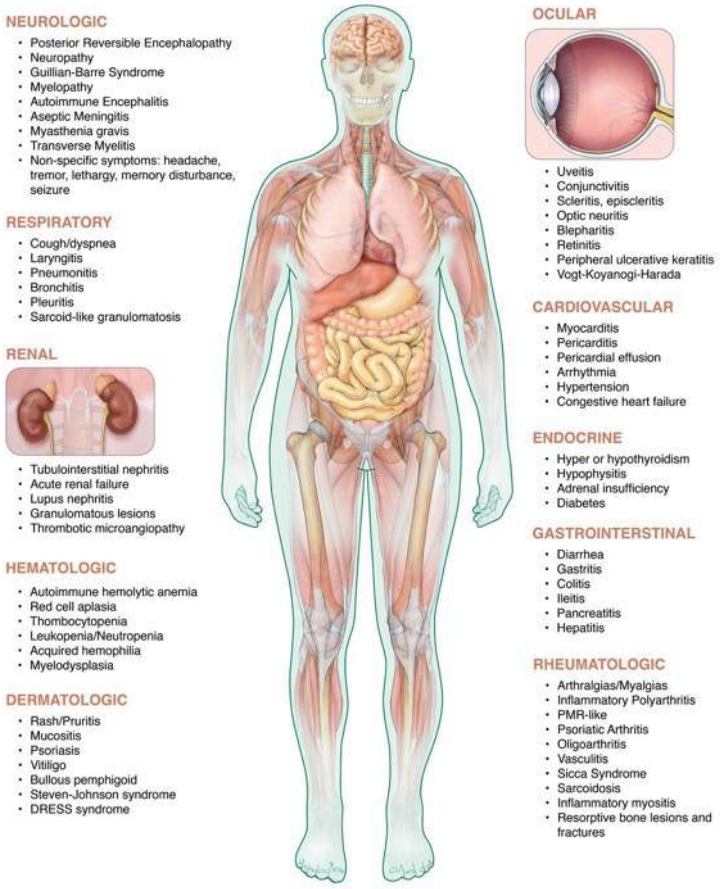
Fig A1. Distribution of (A) grade 1 to 2 and (B) grade 3 to 5 immune-related adverse events (irAEs) for all tumor types in the main clinical trials with anti– cytotoxic T-cell lymphocyte-4 (anti–CTLA-4), anti–programmed death 1 (PD-1), or anti–PD ligand 1 (PD-L1) antibodies as single therapies. The values quoted are the median (range) irAE rates for the set of clinical trials as a whole. Adapted from European Journal of Cancer, Vol 54, J.M. Michot et al, Immune-Related Adverse Events With Immune Checkpoint Blockade: A Comprehensive Review, 139-149, Copyright 2016, with permission from Elsevier. Endoc, endocrinology; Neurol, neurology; ocul, ocular; Pulm, pulmonary.

Jamal et al. 2020

Brahmer et al. *J Clin Oncol.* 2018

Où ?

- **Spécificité de profil de toxicité** avec…
  - ➢ **l'immunothérapie** administrée



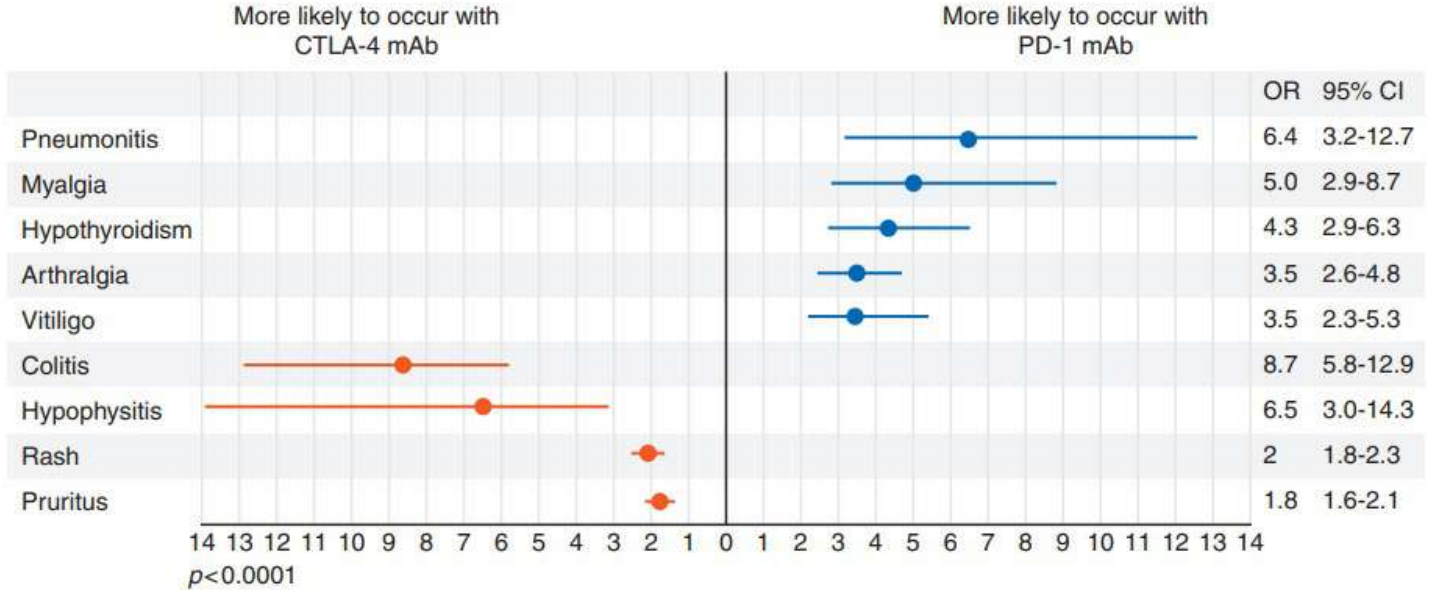
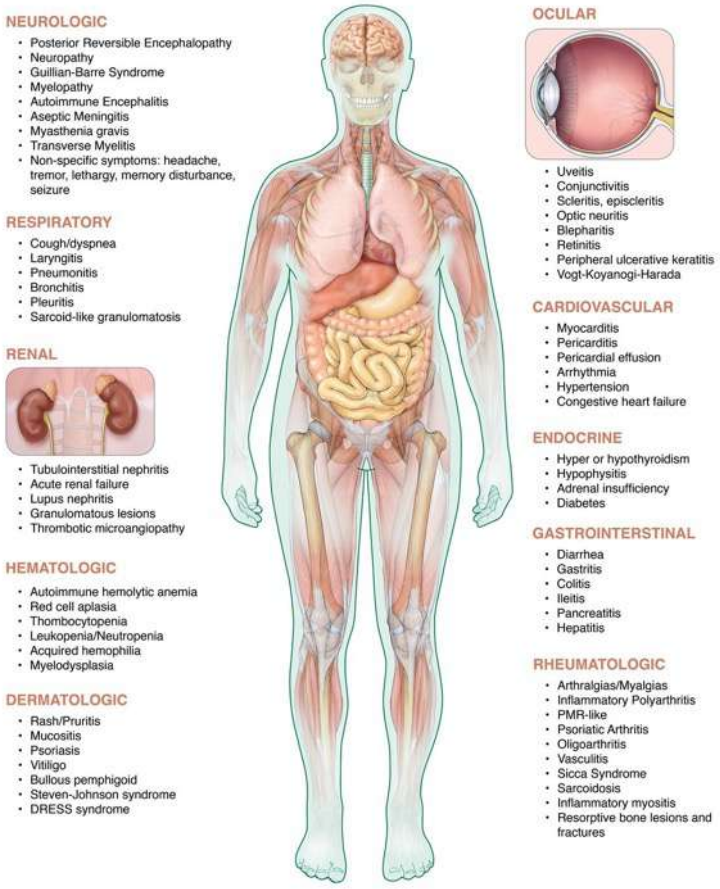


Figure 2. The odds ratio (OR) of different immune-related adverse events (all grades) comparing PD-1/PD-L1 versus CTLA-4 immune checkpoint inhibitors.

Jamal et al. 2020

Khoja et al. *Ann Oncol* 2017

Où?



Jamal et al. 2020

- **Spécificité de profil de toxicité** avec…
  - **l'immunothérapie** administrée
  - **le primitif traité** (Registre ICIR-BIOGEAS, *)

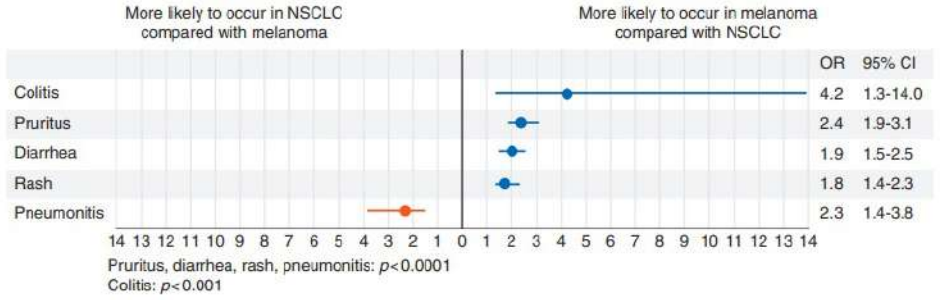


Figure 3. The odds ratio (OR) of different immune-related adverse events (all grades) comparing melanoma and non-small cell lung cancer (NSCLC) anti-PD-1 immune checkpoint inhibitor studies.

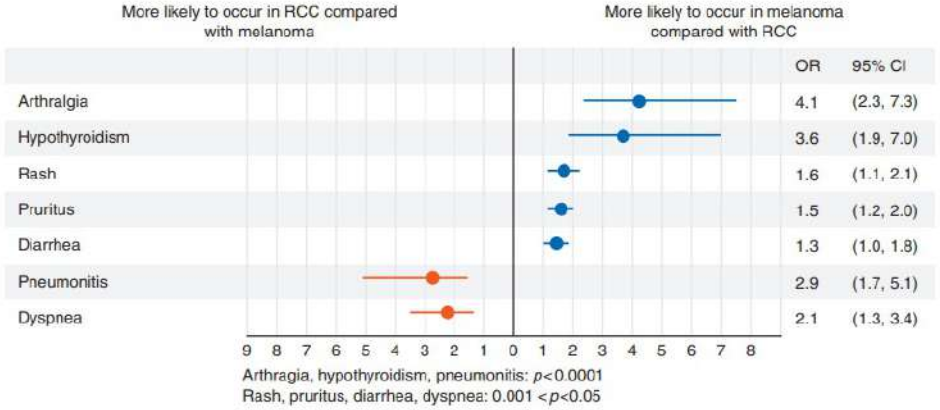


Figure 4. The odds ratio (OR) of different immune-related adverse events (all grades) comparing melanoma and renal cell carcinoma (RCC) anti-PD-1 immune checkpoint inhibitor studies.

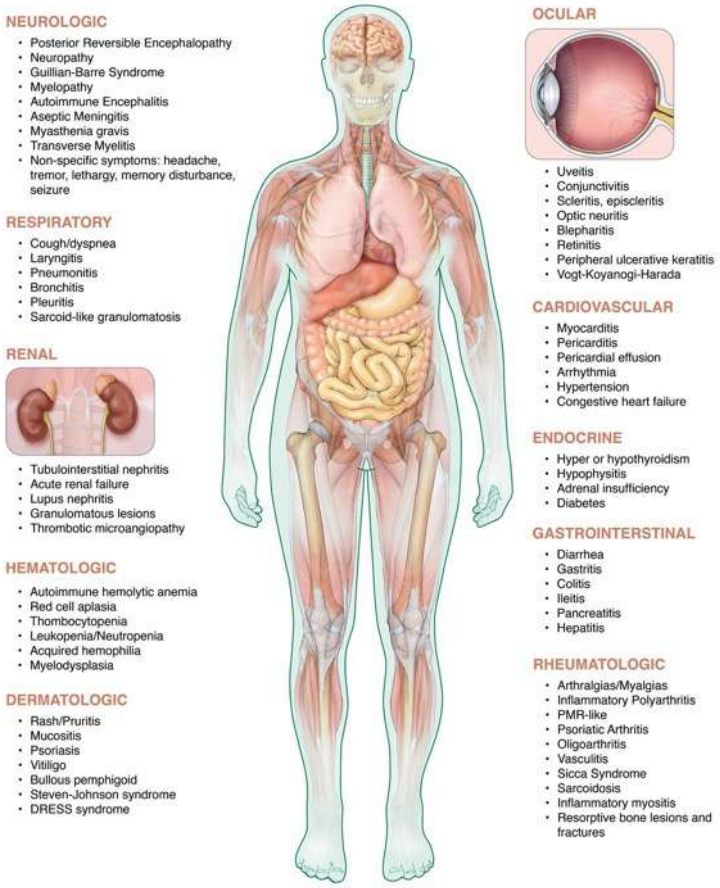
El Osta et al. CROH 2017

* Johnson et al. NEJM 2016

Khoja et al. *Ann Oncol* 2017

Où?

- **Spécificité de profil de toxicité** (Site primitif, Immunothérapie)
- **ATCD** auto-immunité
- **FdR génétique** potentiel impliqué (polymorphismes CTLA4/PDCD1)



Ac anti-	CTLA4	PD1	PDL1	CTLA4/PD1	CTLA4/PDL1
Tox. (grade 1-5)	31-53.8 %	10-26.5 %	17.1 %	90 %	61.1-90 %
Tox. (grade 3-5)	21.5 %	7.1 %	6.3 %	40-54.8 %	40 %

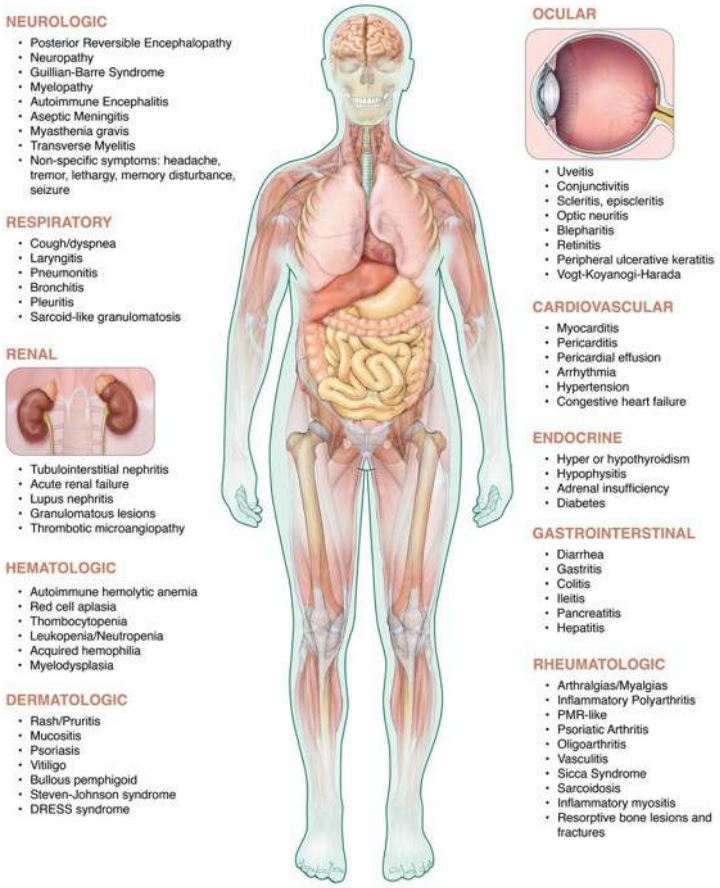
El Osta et al. CROH 2017

* Johnson et al. NEJM 2016

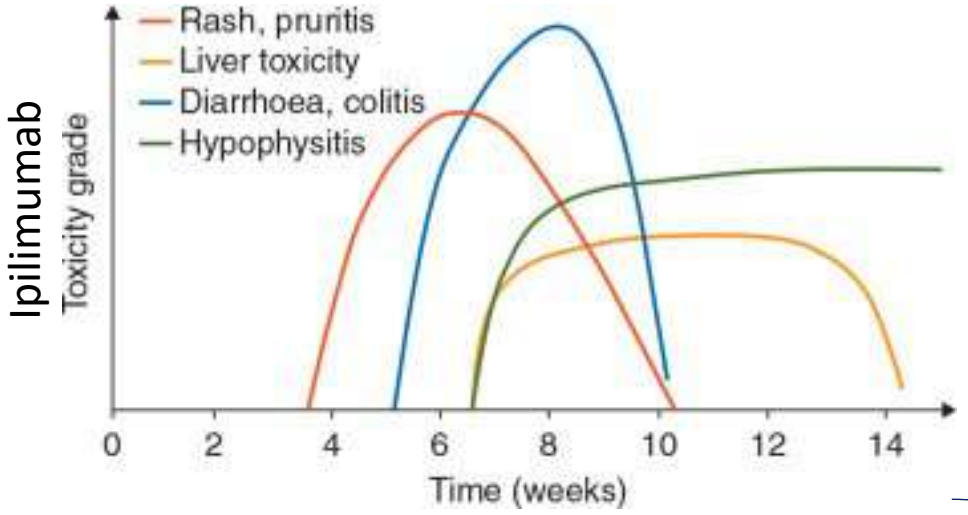
Jamal et al. 2020

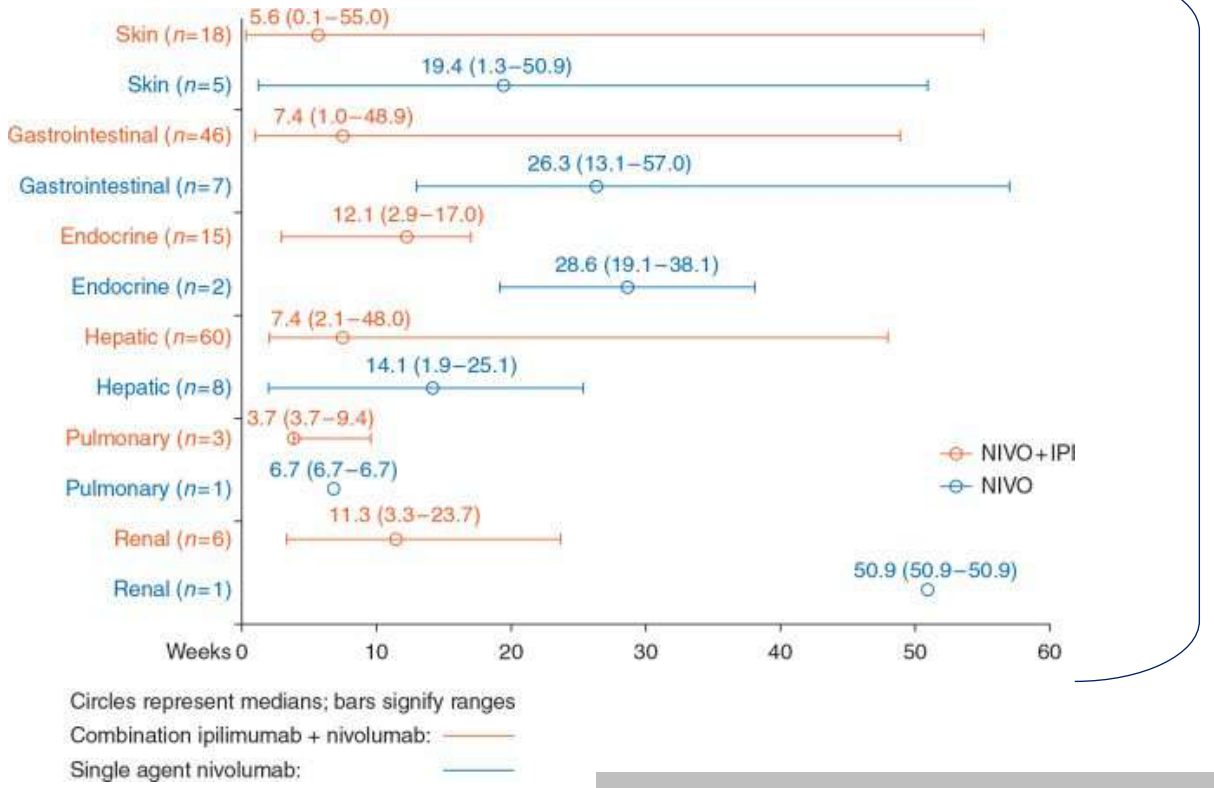
Ramos-Casals et al. Nat Rev Disease Primer 2020

Quand?



Jamal et al. 2020

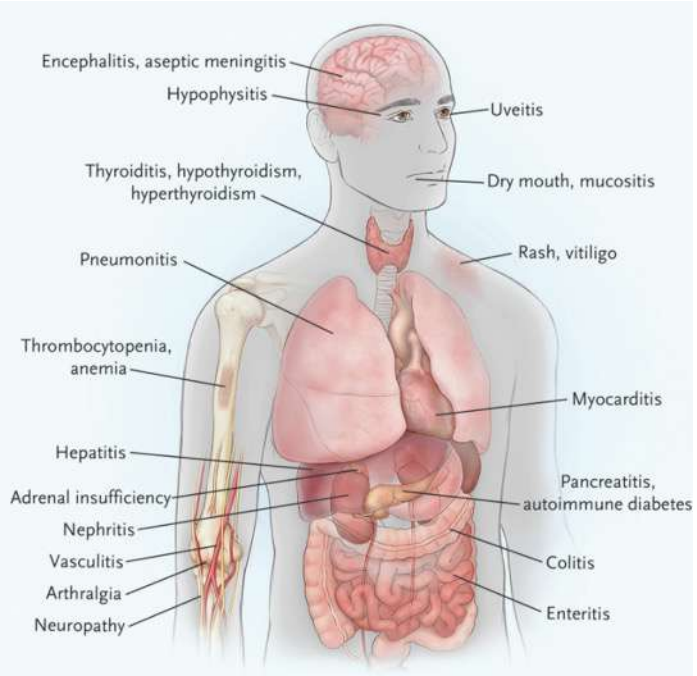




Haanen et al. *Ann Oncol* 2017 (ESMO GL)

Les Recommandations

- ESMO / ASCO
- Sociétés savantes (spé. d'organes)
- Applications mobiles
- RCPs dédiées




VOLUME 36 · NUMBER 17 · JUNE 10, 2018

JOURNAL OF CLINICAL ONCOLOGY | ASCO SPECIAL ARTICL


ESMO

CLINICAL PRACTICE GUIDELINES

Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

J. B. A. G. Haanen[1], F. Carbonnel[2], C. Robert[3], K. M. Kerr[4], S. Peters[5], J. Larkin[6] & K. Jordan[7], on behalf of the ESMO Guidelines Committee*

Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline


Manuel
Manuel Pratique d'oncologie

MANUEL PRATIQUE D'ONCOLOGIE DE GUSTAVE ROUSSY

À L'USAGE DES INTERNES

Détresses vitales, Médecine, Chirurgie, Anesthésie-Réanimation, Soins de supports, Immunothérapie, Enfant et adolescents

- DÉTRESSES VITALES
- MÉDECINE
- CHIRURGIE
- SOINS DE SUPPORT
- IMMUNOTHÉRAPIE
- THERAPIES INNOVANTES
- ENFANTS - ADOLESCENTS
- CORONAVIRUS

TOX'IMM
Gestion des Toxicités des Immunothérapies

Réunion de Concertation Pluridisciplinaire

CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD

HCL HOSPICES CIVILS DE LYON

ImmuCare : gestion des toxicités liées aux immunothérapies

TOX'IMM
Gestion des Toxicités des Immunothérapies

Réunion de Concertation Pluridisciplinaire

Dr Souad ASSAAD

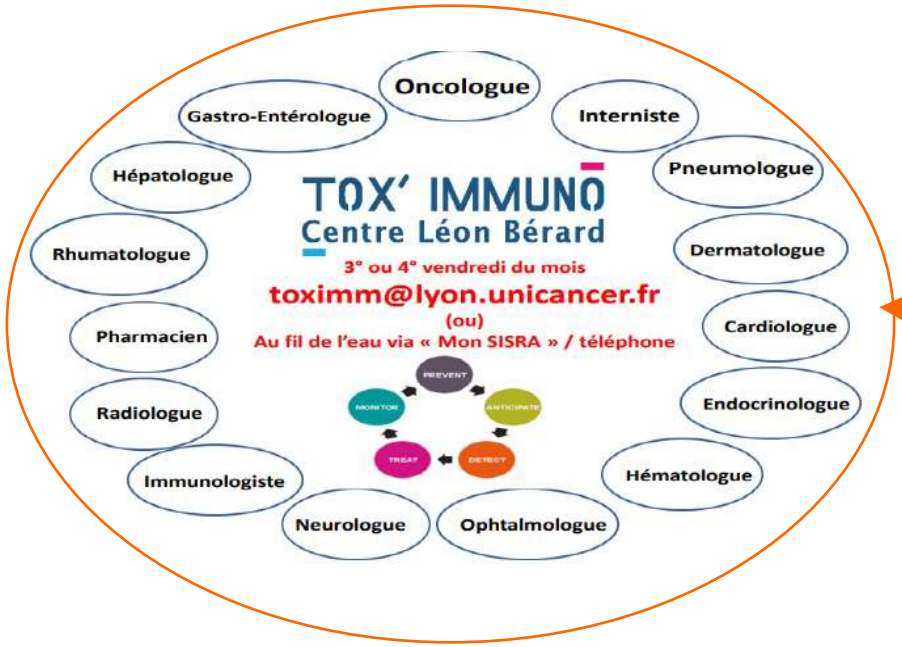
Dr Virginie Avrillon

- 1ère RCP 15/12/2017 → 264 dossiers discutés
- Prochaine RCP 25/6/2021: Venez! Ou connectez vous!

CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD

HCL HOSPICES CIVILS DE LYON

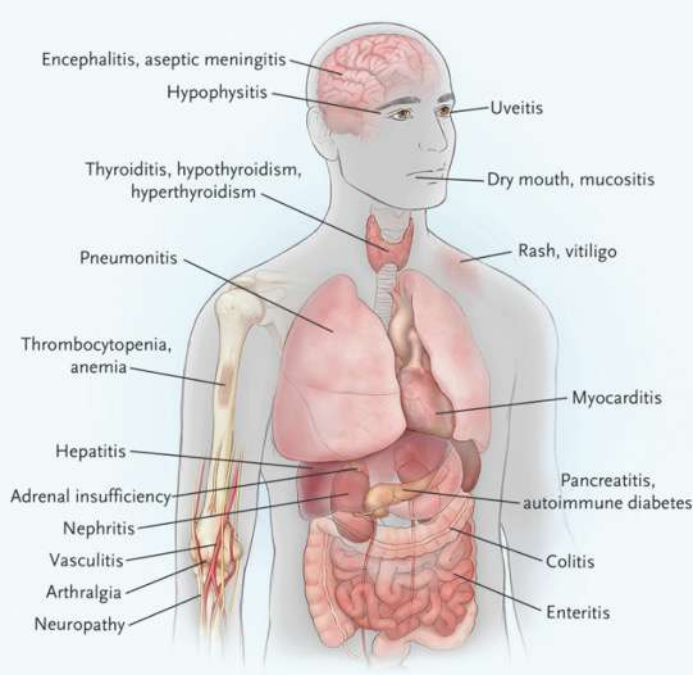
CENTRE HOSPITALIER Saint Joseph · Saint Luc
AU CŒUR DE LA VIE, AU CŒUR DE LA VILLE

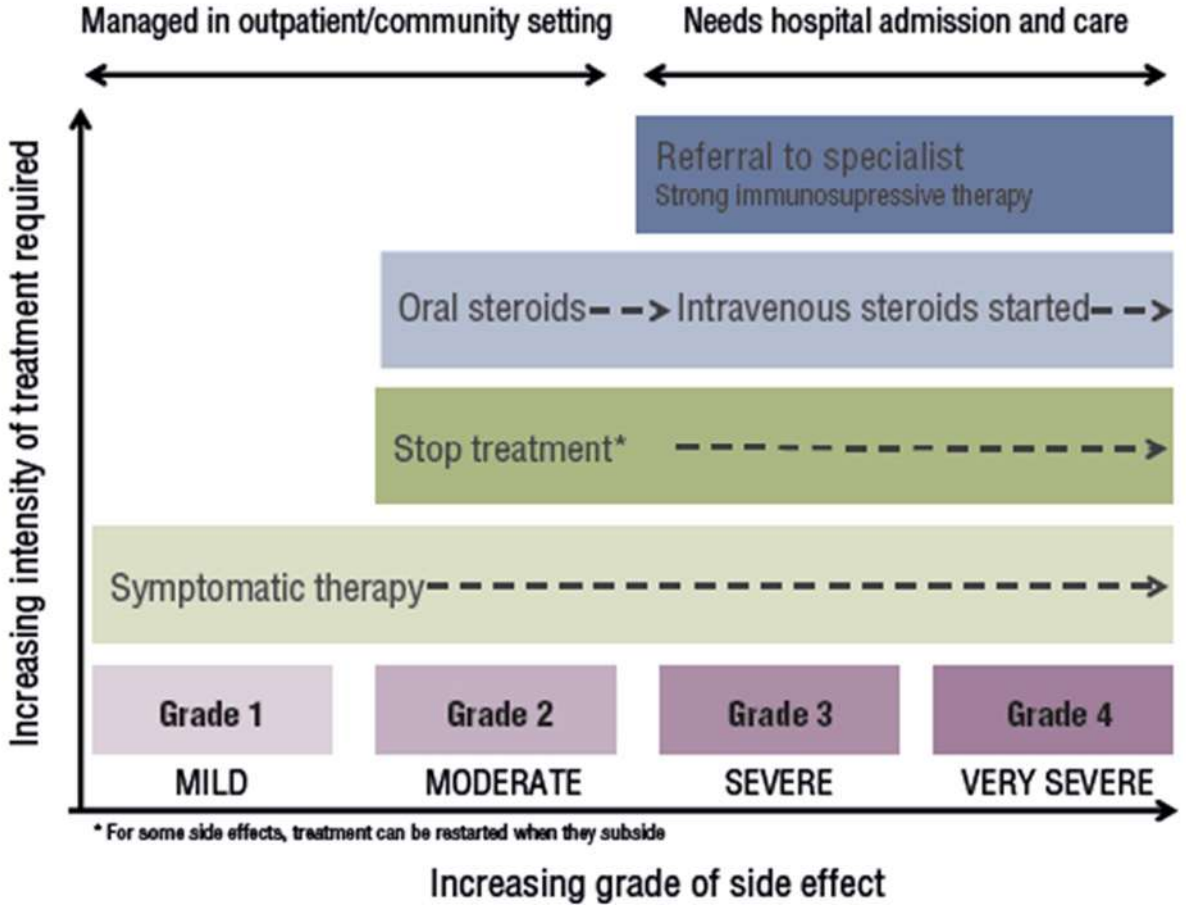


toximm@lyon.unicancer.fr → Mme Barbara MANNEVY

Les Recommandations

- Des principes généraux:

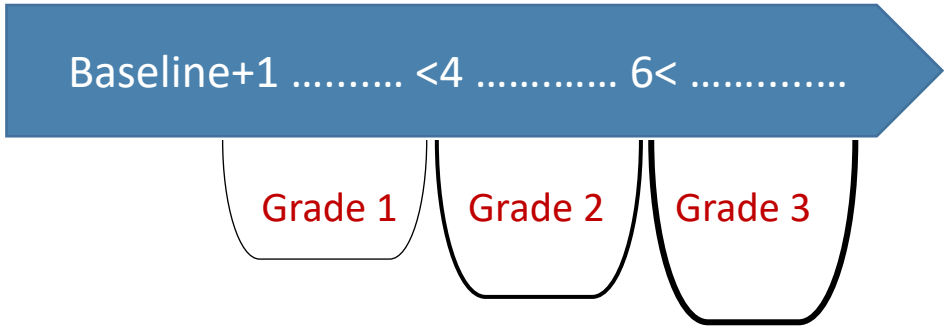




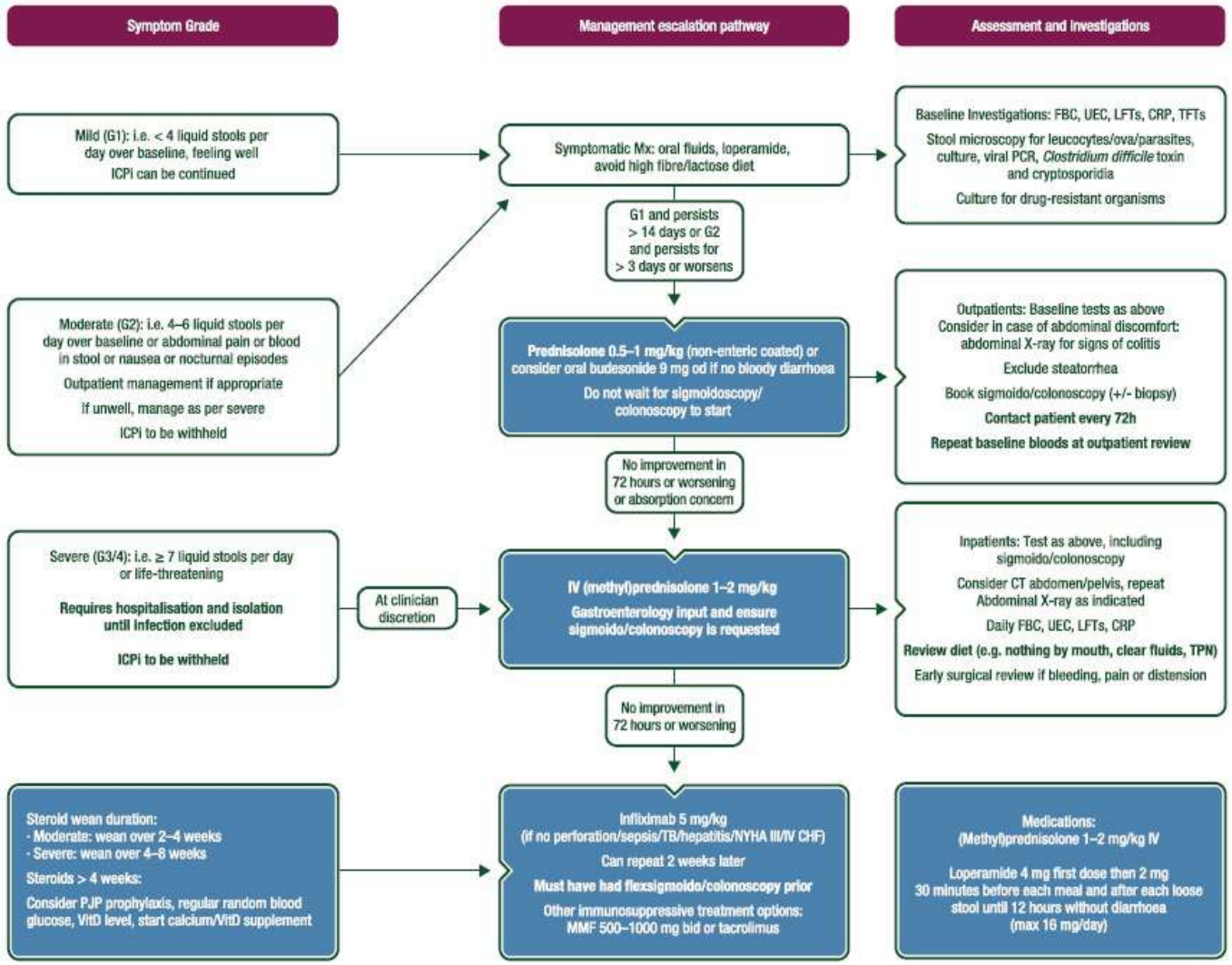
Boutros et al. *Nat Rev* 2016

Les Recommandations

Colite



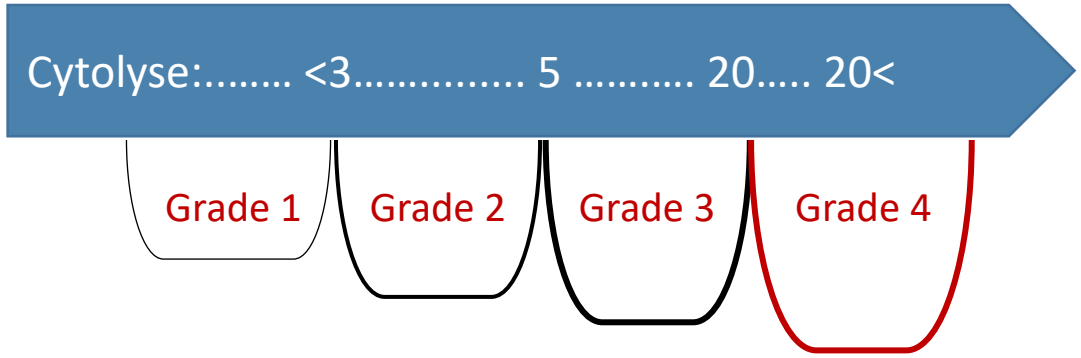
- Ecarter les diag. Différentiels
- Evaluation endoscopique++



Haanen et al. *Ann Oncol* 2017 (ESMO GL)

Les Recommandations

Hépatite



- Bilirubinémie, TP/INR
- Ecarter les diag. différentiels
- **Biopsie hépatique ?**

Symptom Grade	Management escalation pathway	Assessment and Investigations
Grade 1: ALT or AST > ULN-3x ULN	Continue treatment	If > ULN–3x ULN repeat in 1 week
Grade 2: ALT or AST 3-5x ULN	Withhold ICPi treatment If rising ALT/AST when re-checked start oral prednisolone 1 mg/kg	Re-check LFTs/INR/albumin every 3 days Review medications, e.g. statins, antibiotics and alcohol history Perform liver screen: Hepatitis A/B/C serology, Hepatitis E PCR, anti-ANA/SMA/LKM/SLA/LP/LCI, iron studies Consider imaging for metastases/clot
Grade 3: ALT or AST 5-20x ULN	Cease treatment ALT/AST < 400 and normal bilirubin/INR/albumin: oral prednisolone 1 mg/kg ALT/AST > 400 or raised bilirubin/INR/low albumin: i.v. (methyl)prednisolone 2 mg/kg	As above; daily LFTs/INR/albumin Perform US with Doppler Low threshold to admit if clinical concern
Grade 4: ALT or AST > 20x ULN	i.v. (methyl)prednisolone 2 mg/kg Permanently discontinue treatment	As above; hepatology consult Consider liver biopsy

Steroid wean:
- G2: once G1, wean over 2 weeks; re-escalate if worsening; treatment may be resumed once prednisolone ≤ 10 mg
- G3/4: once improved to G2, can change to oral prednisolone and wean over 4 weeks; for G3, rechallenge only at consultant discretion

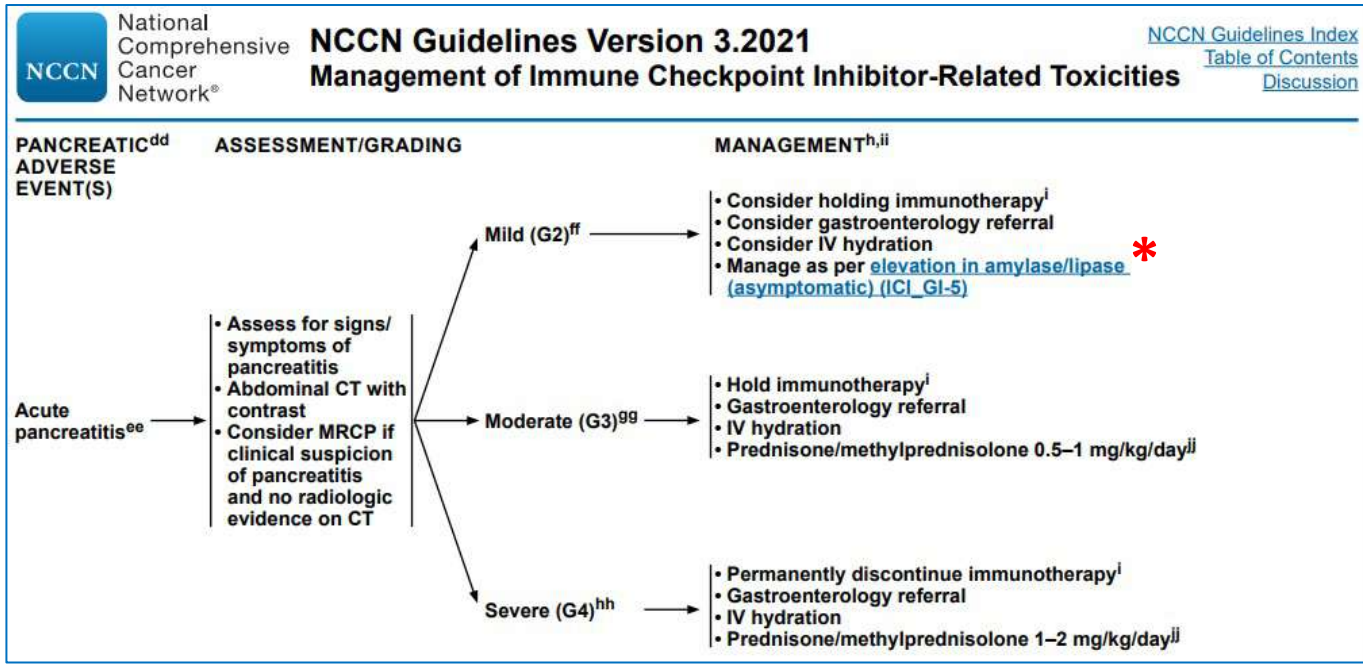
Worsening despite steroids:
- If on oral change to i.v. (methyl)prednisolone
- If on i.v. add MMF 500-1000 mg bd
- If worse on MMF, consider addition of tacrolimus
- A case report has described the use of anti-thymocyte globulin in steroid + MMF-refractory fulminant hepatitis [31]

Haanen et al. *Ann Oncol* 2017 (ESMO GL)

Les Recommandations

Pancreatite

- « *A rare irAE* »
- NCCN (*mars 2021*)



- ≠ élévation de la lipase/amylase*
  - ➢ Ecarter pancréatite: Douleur + Imagerie

Anti-	CTLA4	PD1	PDL1	PD1+CTLA4	PDL1+CTLA4
Augmentation lipase	0.30 %	0.30 %	-	4.80 %	12.1 %

- Prise en charge
  - ➢ Pancréatite aigue: Jeun, Antalgie, AEp, Hydratation/Oxygène
  - ➢ Evaluation gravité
  - ➢ NCCN : **corticothérapie** si douleur/vomissement (« G3 ») ou défaillance/menace vitale (« G4 »)
  - ➢ Corticothérapie jusqu'à retour Grade 1 puis décroissance sur 4-6 semaines

Remarque dosage ELASTASE fécale++

El Osta et al. *CROH* 2017

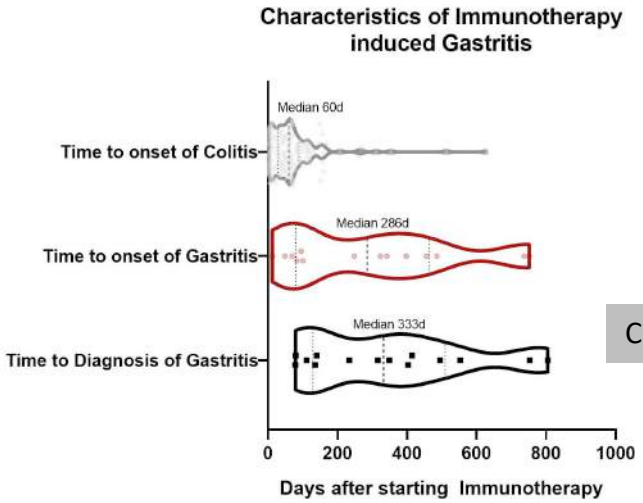
Ahmed et al. *WJG* 2018

Vege et al. *Gastroenterology* 2018

NCCN Guiddelines Version 3.2021

Rogers et al. *J Adv Pract Oncol* 2020

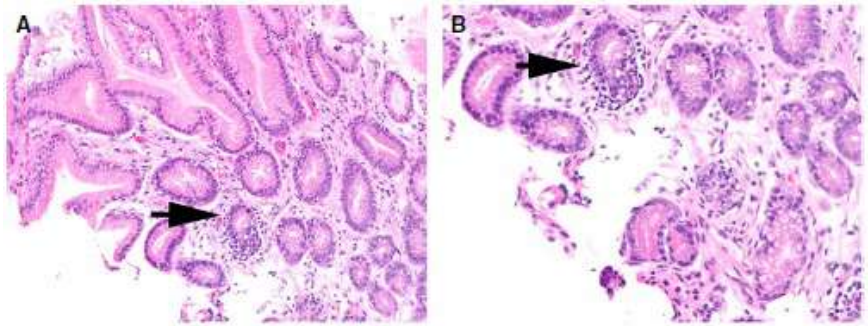
Les Recommandations

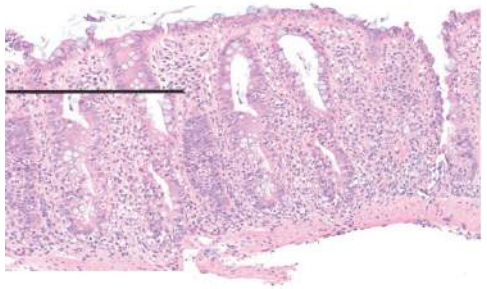


Cheung et al. Gut *2019*

Gastrite-Enterite

- Clinique ≠ → Retard à PEC (50j.)
  - « diarrhée »
  - Anorexie/dyspepsie, nausées (vomissement), perte de poids+++
  - Toxicité plus tardive++
- L'évaluation endoscopique précoce
  - → Résolution plus rapide des symptômes + exposition moindre CS
  - Avec biopsies duodénales et gastriques
- Prise en charge
  - IPP → Corticoïdes → Anti-TNFa





Zhang et al. *Histopathology* 2020

MASCC 2020 recommandations - Dougan et al. Supportive Care in Cancer 2020

En pratique

Bilan pré-immunothérapie

Biologie avant 1ere cure:
- NFP (Faire RAI si Hb=<8g/dL)
- créatininémie, ionogramme sanguin, glycémie à jeun,
- calcémie, albuminémie
- ASAT, ALAT, GGT, PAL et bilirubine totale et conjuguée
- LDH, CRP
- Troponine ultrasensible, pro BNP, CPK

- Bilan endocrinien : TSH ; T4 ; cortisol à 8 h (en l'absence de traitement par glucocorticoïdes) ;
- LH, FSH et testostérone totale (chez l'homme)
- ou LH, FSH et œstradiol (chez la femme non ménopausée sans contraception orale)
Ou FSH seulement (chez la femme ménopausée)

- Sérologies HIV HBV HCV CMV (+/-Qtiferon/IDR)
- ACAN

Bilan suivi

- NFP (Faire RAI si Hb=<8g/dL)
- créatininémie, ionogramme sanguin, glycémie à jeun
- calcémie, albuminémie,
- ASAT-ALAT-GGT-PAL-bilirubine totale et conjuguée, CRP
- Bilan endocrinien : TSH ; T4L (tous les mois), cortisol à 8h en l'absence de traitement par glucocorticoïdes de synthèse ; testostérone totale chez l'homme
- CPK, Troponine ultrasensible

Maladie Auto-Immune (MAI) préexistante

- FdR exacerbation .....
- Activité MAI pré-immunothérapie: non prédictive de poussée

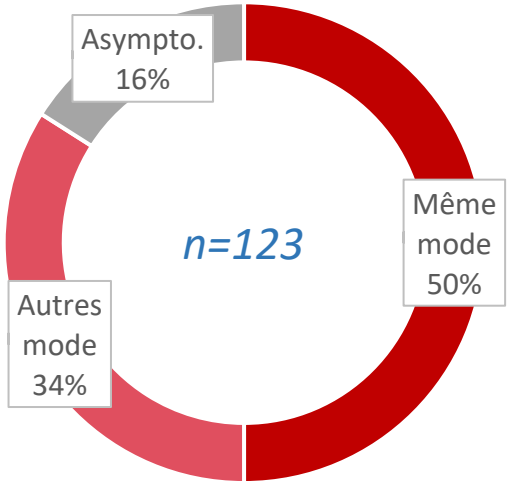


Table 2. CPI-Related Adverse Events Reported in the Literature in Patients With Cancer and Preexisting Autoimmune Disease

Preexisting Autoimmune Disease	CPI Used	Patients, *n*	Active Preexisting Autoimmune Disease/Reported Cases, *n/N*	Receiving Treatment for Autoimmune Disease/Reported Cases, *n/N*	Adverse Events, *n*		
					Any	Exacerbation of Autoimmune Disease	De Novo irAE
(...)							
Ulcerative colitis†	Ipilimumab	6	3/5	1/3	3	3	1
	Nivolumab or pembrolizumab	2	1/1	1/1	2	2	0
	All	8	4/6	2/4	5	5	1
Crohn disease	Ipilimumab	4	1/4	2/4	2	0	2
	Pembrolizumab	1	0/1	0/1‡	1	1	0
	All	5	1/5	2/5	3	1	2
(...)							
Celiac disease	Ipilimumab	1	0/1	0/1	0	0	0

Abdel-Wahab et al. *Ann Int Med* 2018

Pre existing autoimmune disease

Table 3
Outcomes for REISAMIC patients: IrAEs, survival and the ORR.

Features	AID patients (n = 45)
IrAEs	
Patients with IrAE, n (%)	20 (44.4%)
CTCAE grade, median [IQR]	2 (1–5)
Time (months) between ICI initiation and the irAE, median [IQR]	2.1 (0.7–3.1)
IrAE not associated with pre-existing AID, n (%)	10 (22.2%)
Flare of pre-existing AID, n (%)	11 (24.4%)
Anti-PD-1 antibody discontinued due to irAE, n (%)	5 (11.1%)
Treatment of the irAE	6 (13.3%); 40 [30–80]
- Corticosteroids, n (%); median dose [IQR] (mg/d)	0
- Immunosuppressive drugs, n (%)	10 (43.5%)
Complete resolution of the irAE, n (%)	2.8 (1.3–13.2)
Time (months) between diagnosis and resolution of the irAE, median [IQR]	1 (33.3%)
Re-introduction of anti-PD-1 antibody after resolution of the irAE, n (%)	
Survival and death	
Survival at last follow-up, n (%)	26 (57.8%)
Cancer status at last follow-up	
- Complete response, n (%)	4 (9%)
- Partial response, n (%)	13 (29%)
- Stable disease, n (%)	6 (13%)
- Progressive disease, n (%)	21 (47%)
Lost to follow-up, n (%)	1 (2%)
Death, n (%)	
- Due to cancer progression, n (%)	18 (40%)
- Due to the irAE, n (%)	0
- Due to unknown causes, n (%)	1 (2.2%)

AID, autoimmune or inflammatory disease; irAE, immune-related adverse event; CTCAE, Common Terminology Criteria for Adverse Events; PD-1, programmed death 1.

Registre **REISAMIC**

- Traité par Anti-PD1 (3/4 Pembrolizumab)

➢ n = 45

- 53 désordres auto-immun/inflammatoire(s)

- Grade 2 / 3 / 4 / 5: 70% / 25% / 0% / 0%
- Arret immunothérapie: 4 patients /20

➢ MAI est FdR de Tox'Imm
… **mais** *55.6% n'ont pas eu d'exhacerbation de leur MAI* **!**

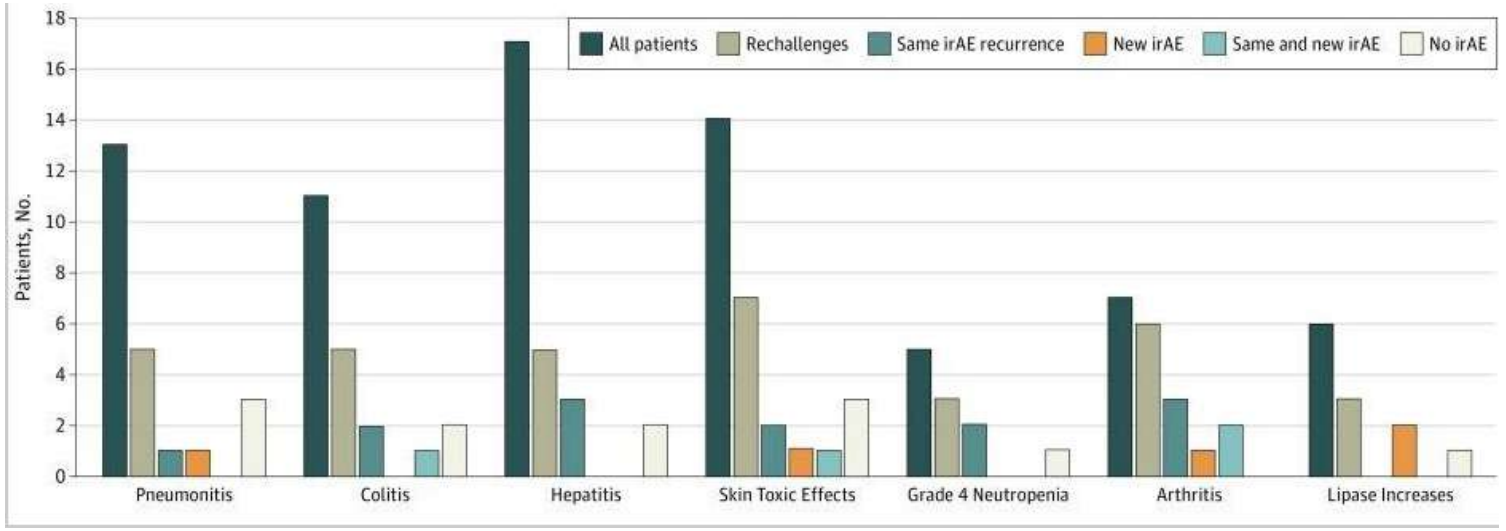
➢ **Pas de différence de survie**

Danlos et al *Eur J Cancer* 2018

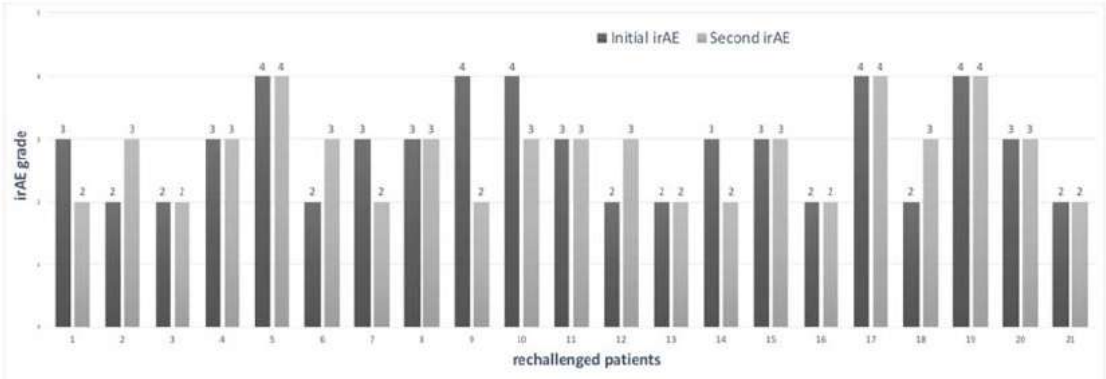
La réintroduction après toxicité sévère?

55% de 2ème Tox'Imm

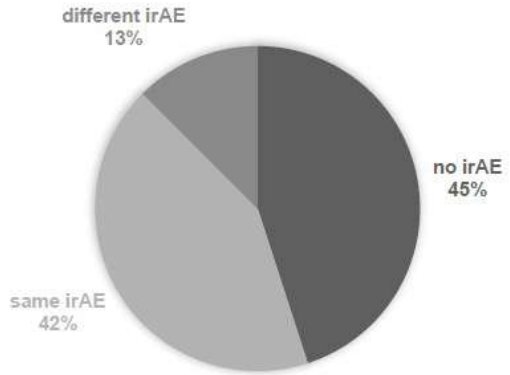
n = 96 → n (rechallenge) = 40 patients



eFigure 3. Severity Grade: Comparison of the Initial and Second irAEs



eFigure 2. Outcome After Anti-PD-1 or Anti-PD-L1 Rechallenge



Parmi 40 patients « rechallengés »

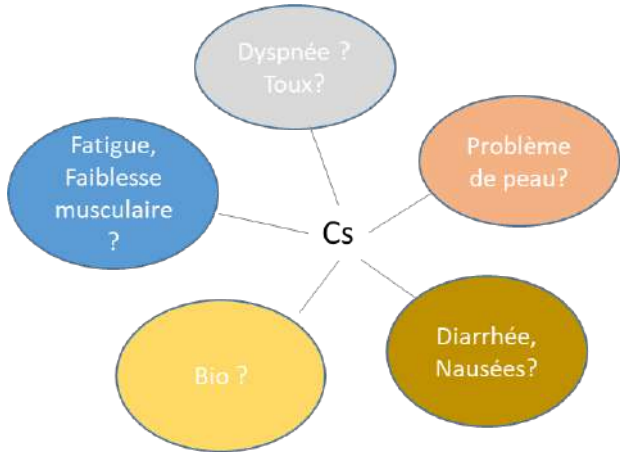
→ 17 (42.5%) même toxicités

→ 5 (12,5%) nouvelle toxicités (dont 4 patients les 2)

Simonaggio et al. JAMA Oncol 2019

Pour conclure

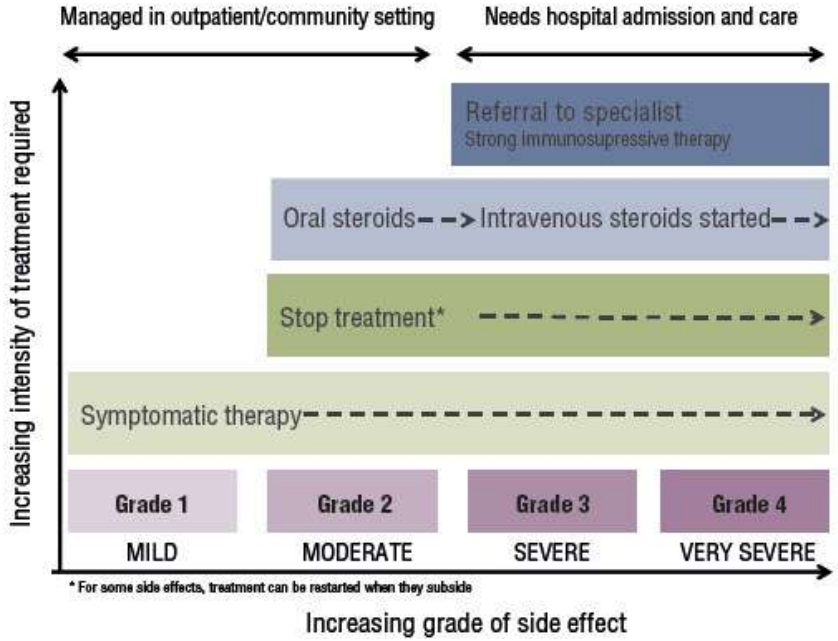
- Identifier



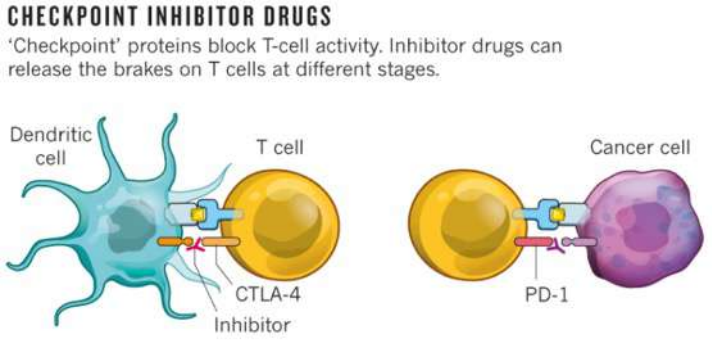
- Discuter

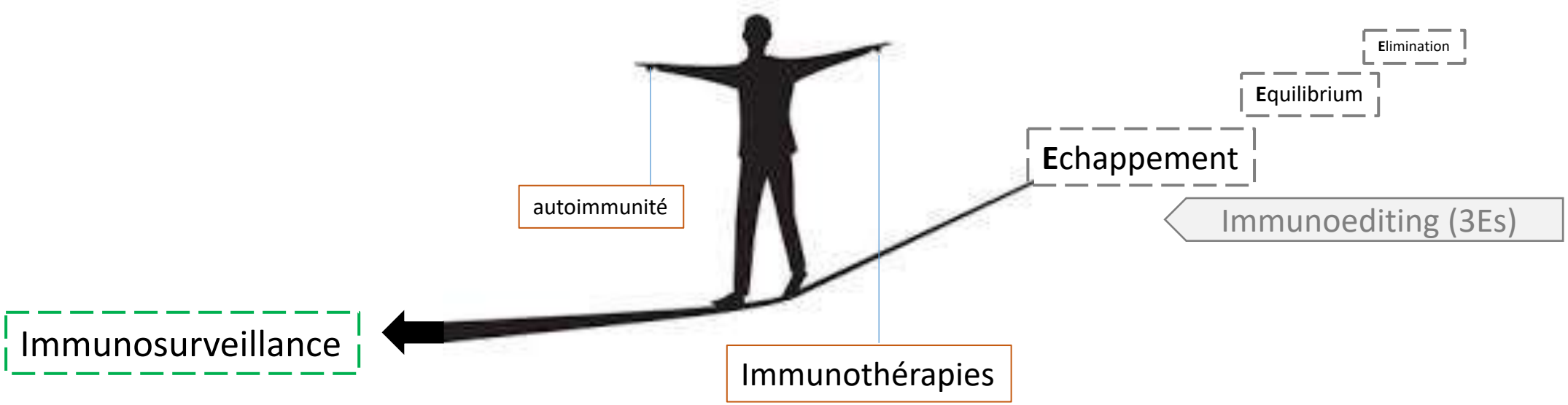
RCP toxicités immuno-induite

- Avant d'agir…



Objectif du juste milieu ?





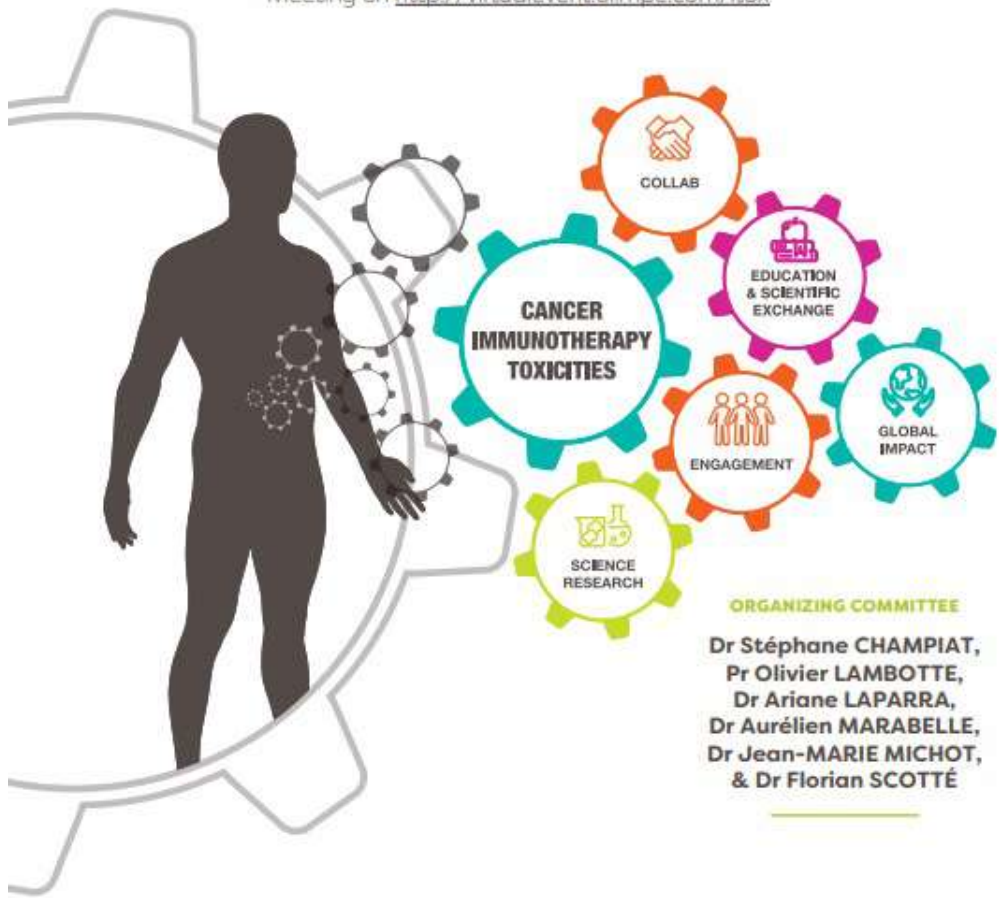
Dunn et al. *Annu Rev Immunol.* 2004

iTOX 2021

100% DIGITAL

4th Symposium on
Cancer Immunotherapy Adverse Events

EDUCATIONAL SESSIONS (in french)
WEDNESDAY, SEPTEMBER 8th 2021 from 04:00 - 07:15 pm
ORAL PRESENTATIONS (in english)
THURSDAY, SEPTEMBER 9th 2021 from 04:00 pm - 07:15 pm
Meeting on http://virtualevent.olimpe.com/itox



ORGANIZING COMMITTEE

Dr Stéphane CHAMPIAT,
Pr Olivier LAMBOTTE,
Dr Ariane LAPARRA,
Dr Aurélien MARABELLE,
Dr Jean-MARIE MICHOT,
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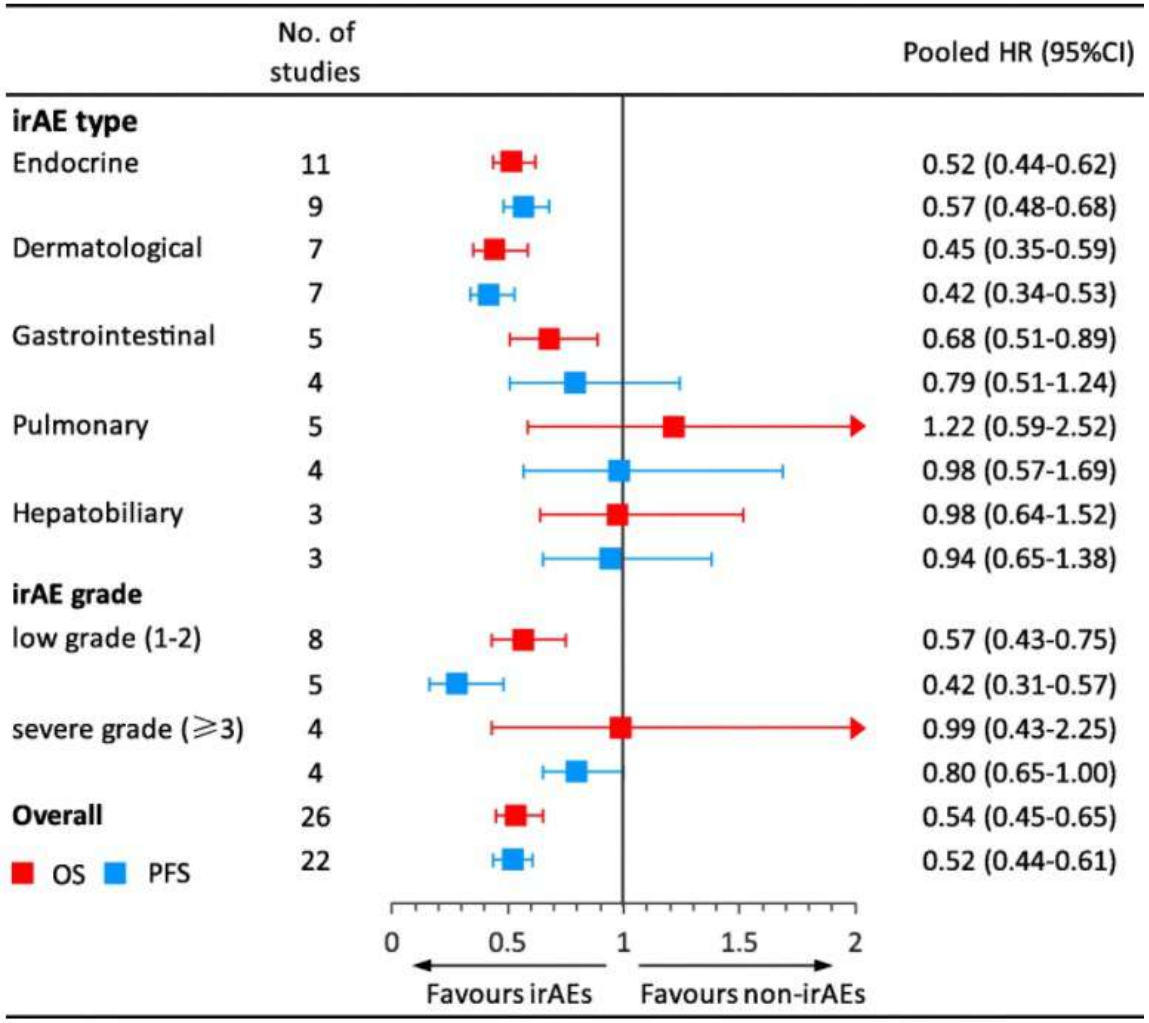
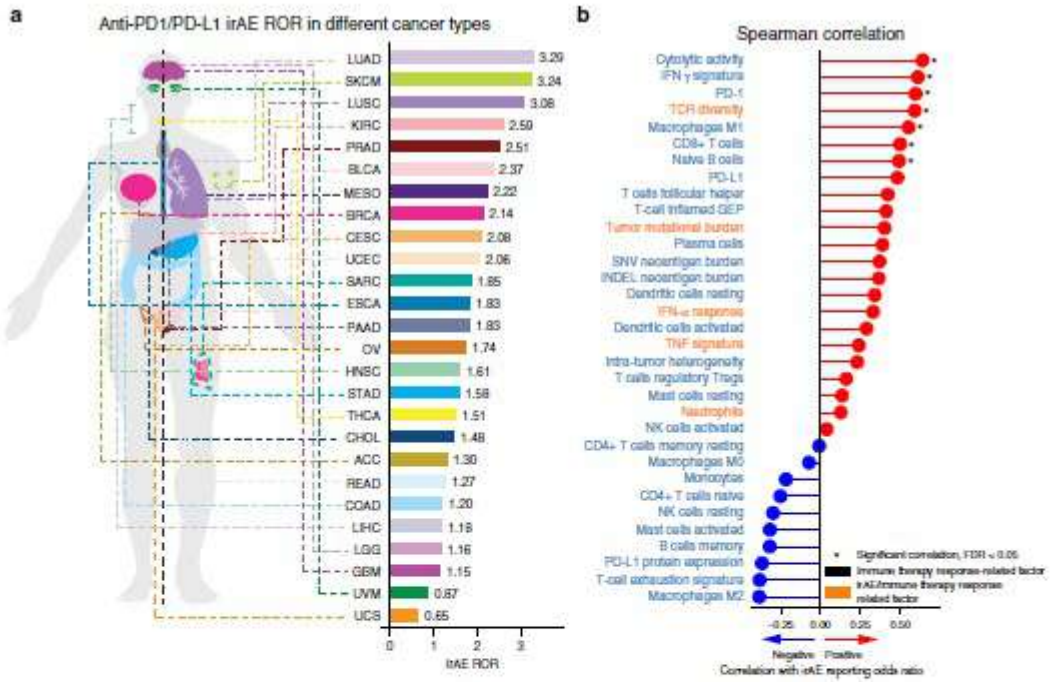
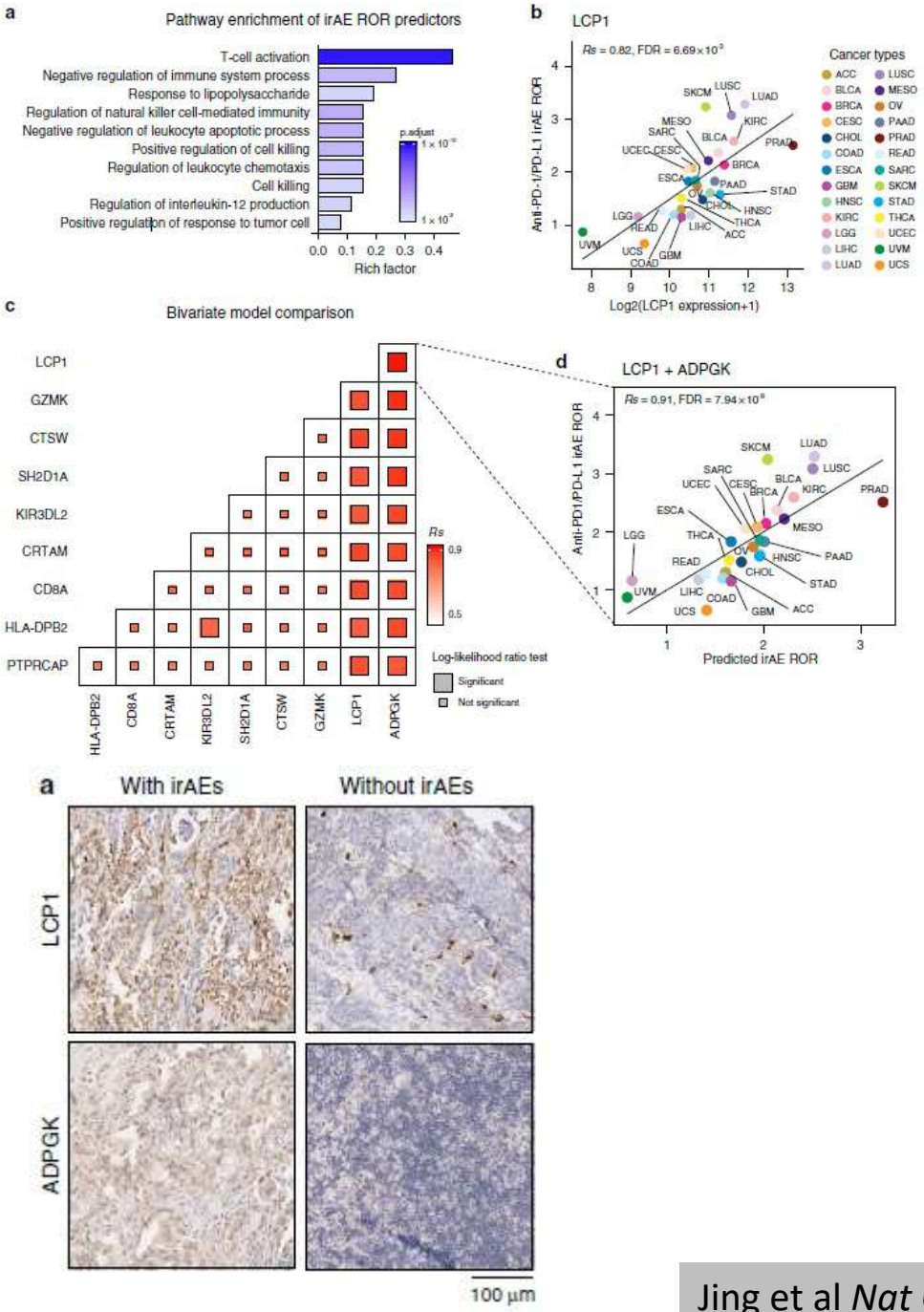
La toxicité: *un élément prédictif*?



Zhou et al *BMC Medicine* 2020

Et *prédire* la toxicité?





Jing et al *Nat Com* 2020