16 ème Congrès National AILA
9, 10 Octobre 2025 - Hôtel El Aurassi - Alger

Complications cardiovasculaires de l'immunothérapie

S. OUABDESSELAM - S. BENKHEDDA

Introduction

- Les immunothérapies (inhibiteurs des points de contrôle immunitaires) ont révolutionné le traitement du cancer.

- Progrès thérapeutiques significatifs, mais effets secondaires notables, y compris **cardiovasculaires.**

- Effets secondaires d'ordre auto-immuns.

- Rareté relative des effets secondaires mais **gravité** potentielle.

- Impact sur la **poursuite** du traitement.

Les traitements du cancer

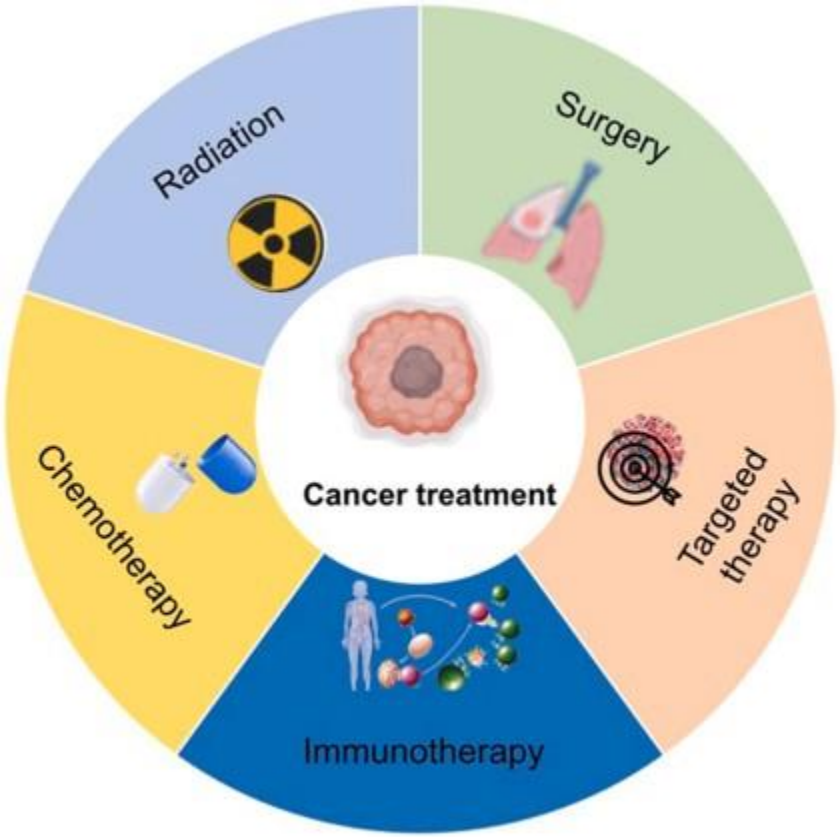
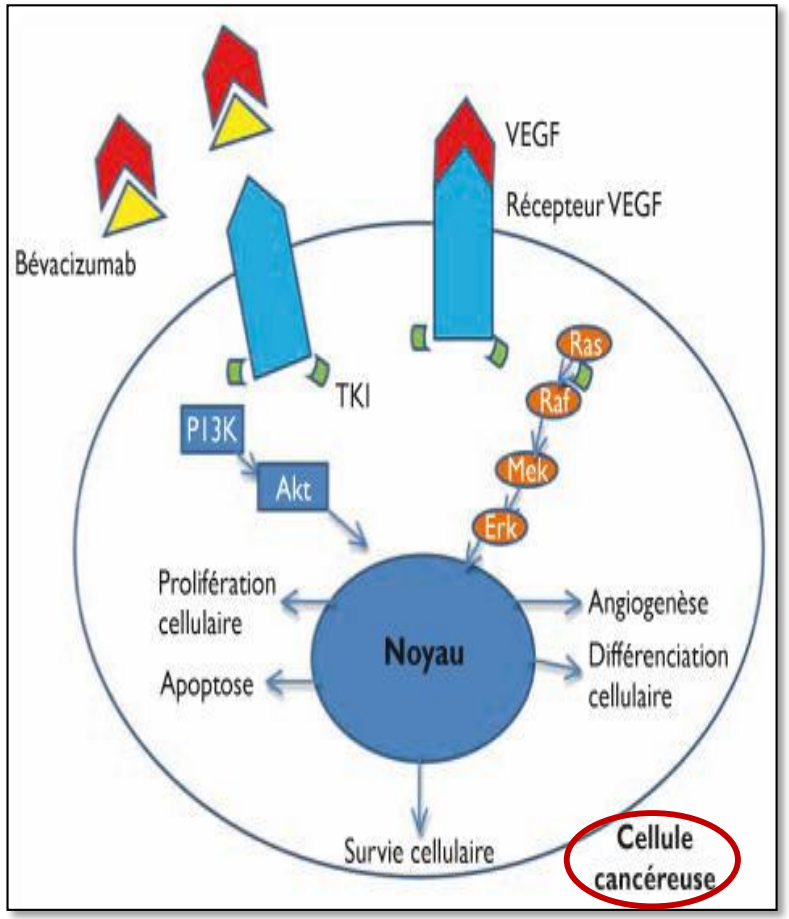


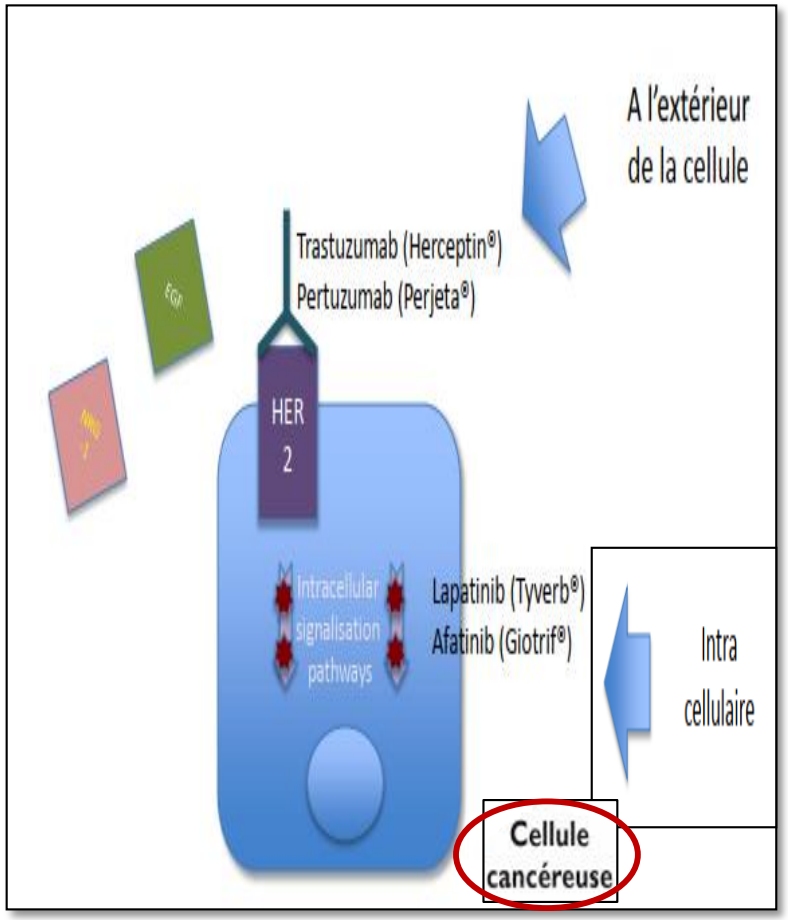
Table I Incidence of left ventricular dysfunction associated with chemotherapy drugs[10–21]

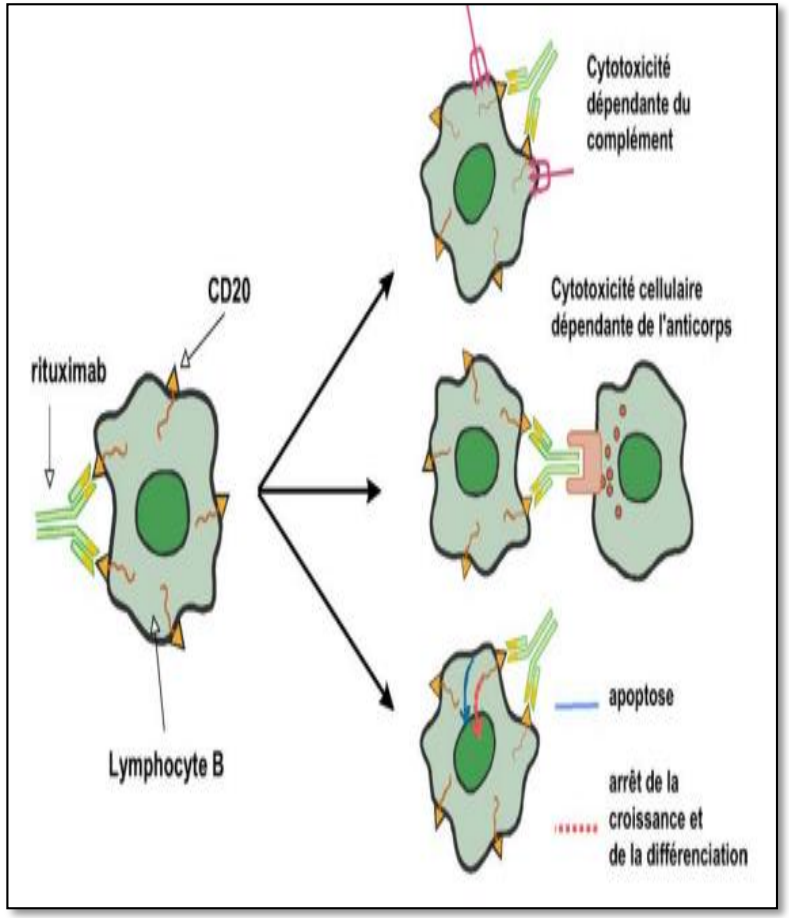
Chemotherapy agents	Incidence (%)
Monoclonal antibodies	
Trastuzumab	1.7–20.1[28a]
Bevacizumab	1.6–4[14b]
Pertuzumab	0.7–1.2
Small molecule tyrosine kinase inhibitors	
Sunitinib	2.7–19
Pazopanib	7–11
Sorafenib	4–8
Dasatinib	2–4
Imatinib mesylate	0.2–2.7
Lapatinib	0.2–1.5
Nilotinib	1

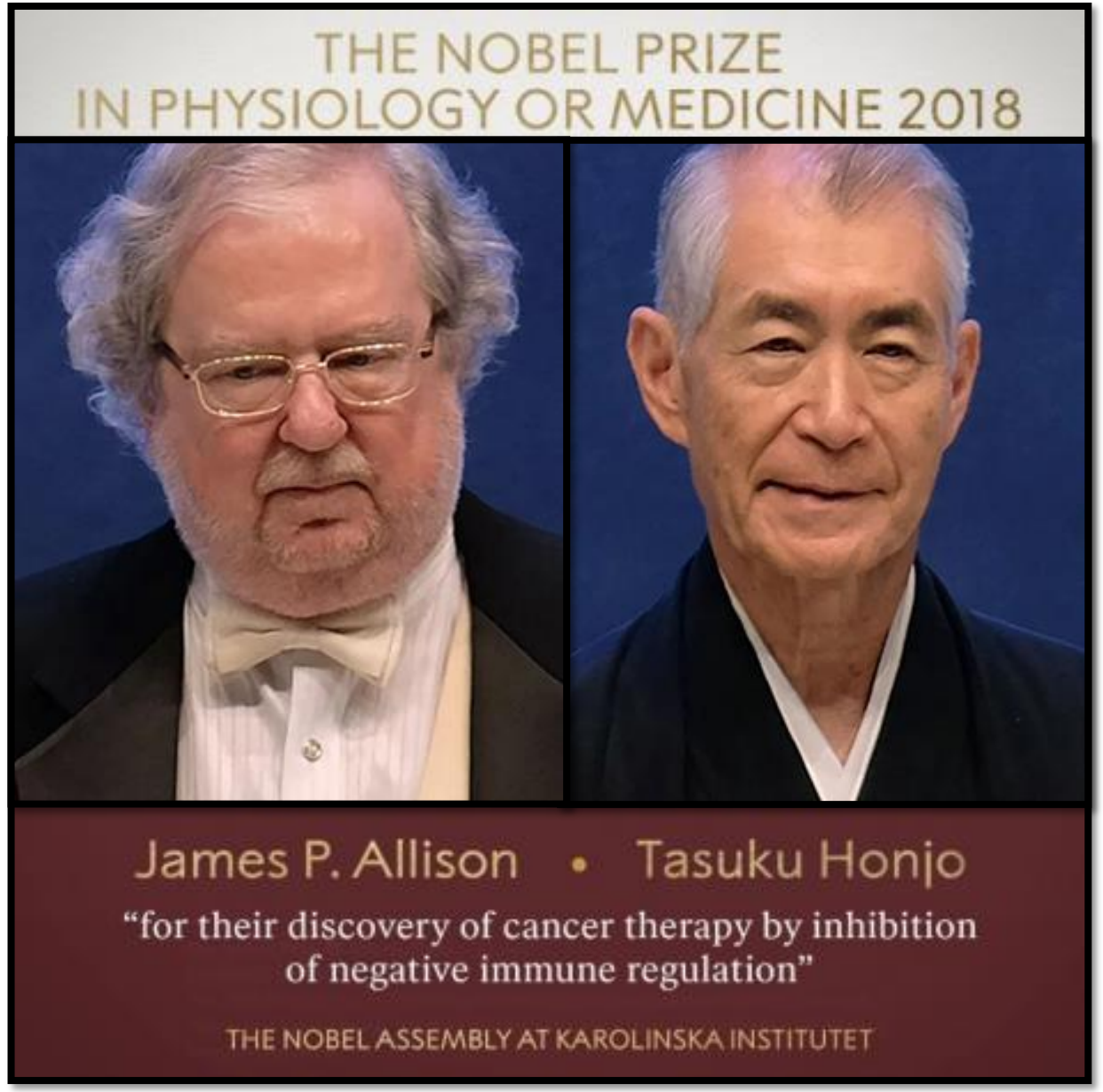
2016 ESC Position Paper on cancer treatments and cardivascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines:European heart journal

Thérapies ciblées








THE NOBEL PRIZE
IN PHYSIOLOGY OR MEDICINE 2018
James P. Allison • Tasuku Honjo
"for their discovery of cancer therapy by inhibition of negative immune regulation"
THE NOBEL ASSEMBLY AT KAROLINSKA INSTITUTET

Immunothérapies: les molécules

Anti–PD-1 Monoclonal Antibodies

- Nivolumab
- Pembrolizumab
- Cemiplimab-rwlc
- Dostarlimab-gxly

Anti–PD-L1 Monoclonal Antibodies

- Atezolizumab
- Avelumab
- Durvalumab

Anti–CTLA-4 Monoclonal Antibody

- Ipilimumab
- Tremelimumab

Anti–LAG-3 Monoclonal Antibody

- Relatlimab

Immunothérapies: les indications

PD-1/PD-L1 Inhibitor + VEGF Inhibitor or + TKI

- Hepatocellular carcinoma
- Endometrial carcinoma
- Renal cell carcinoma

PD-L1 Inhibitor + BRAF Inhibitor + MEK Inhibitor

- Melanoma

PD-L1 Inhibitor + Chemotherapy + VEGF Inhibitor

- Non–small cell lung cancer

LAG-3 Inhibitor + PD-1 Inhibitor

- Melanoma

PD-1/PD-L1 Inhibitor + CTLA-4 Inhibitor

- Melanoma
- MSI-H/dMMR colorectal cancer
- Renal cell carcinoma
- Hepatocellular carcinoma
- Non–small cell lung cancer (± limited chemotherapy)
- Pleural mesothelioma

PD-1/PD-L1 Inhibitor + Chemotherapy

- Non–small cell lung cancer
- Small cell lung cancer
- Squamous cell carcinoma of the head and neck
- Gastric, gastroesophageal junction, and esophageal cancers
- Triple-negative breast cancer
- Cervical cancer

Mécanisme d'action

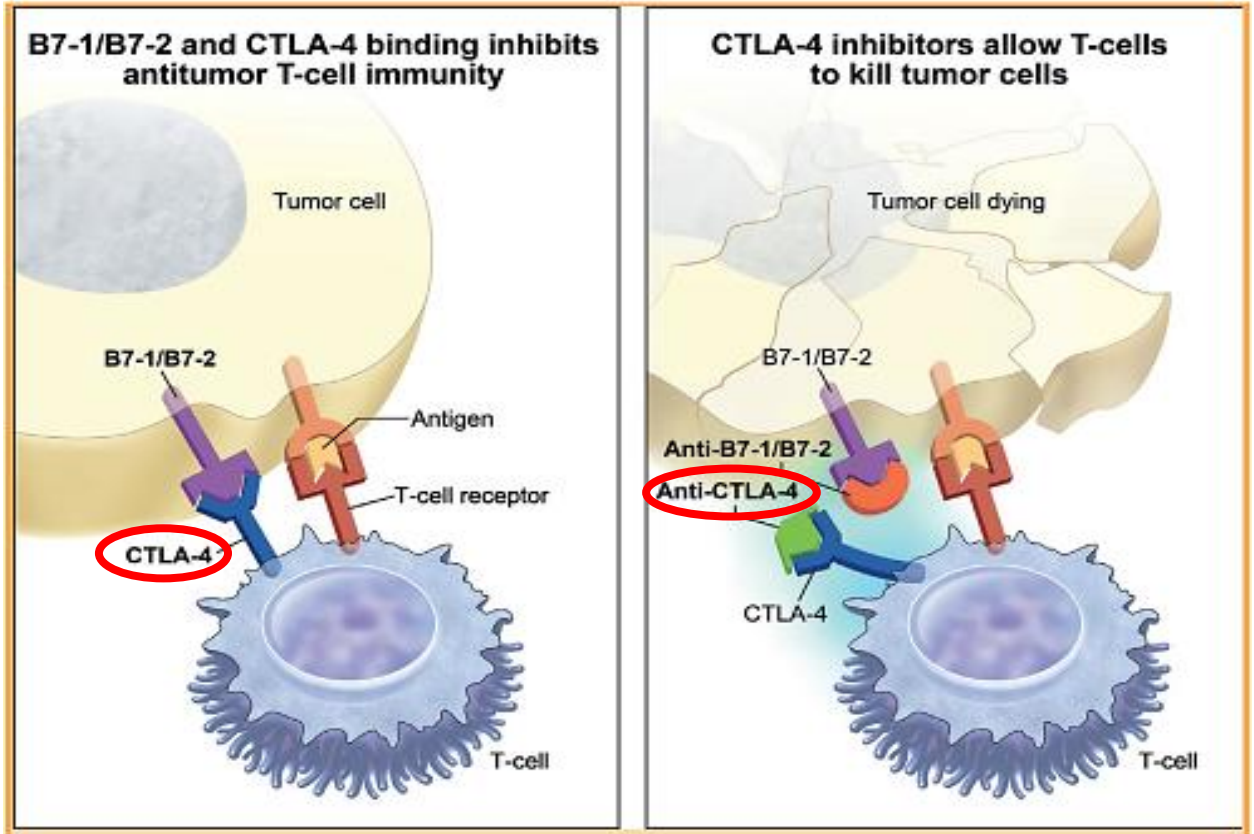


FIGURE 1. The action of cytotoxic T-lymphocyte–associated protein (CTLA) inhibitors. Ipilimumab is an anti–CTLA-4 antibody that causes blockade of CTLA-4, resulting in prolonged T-cell activation, proliferation, and antitumor response.

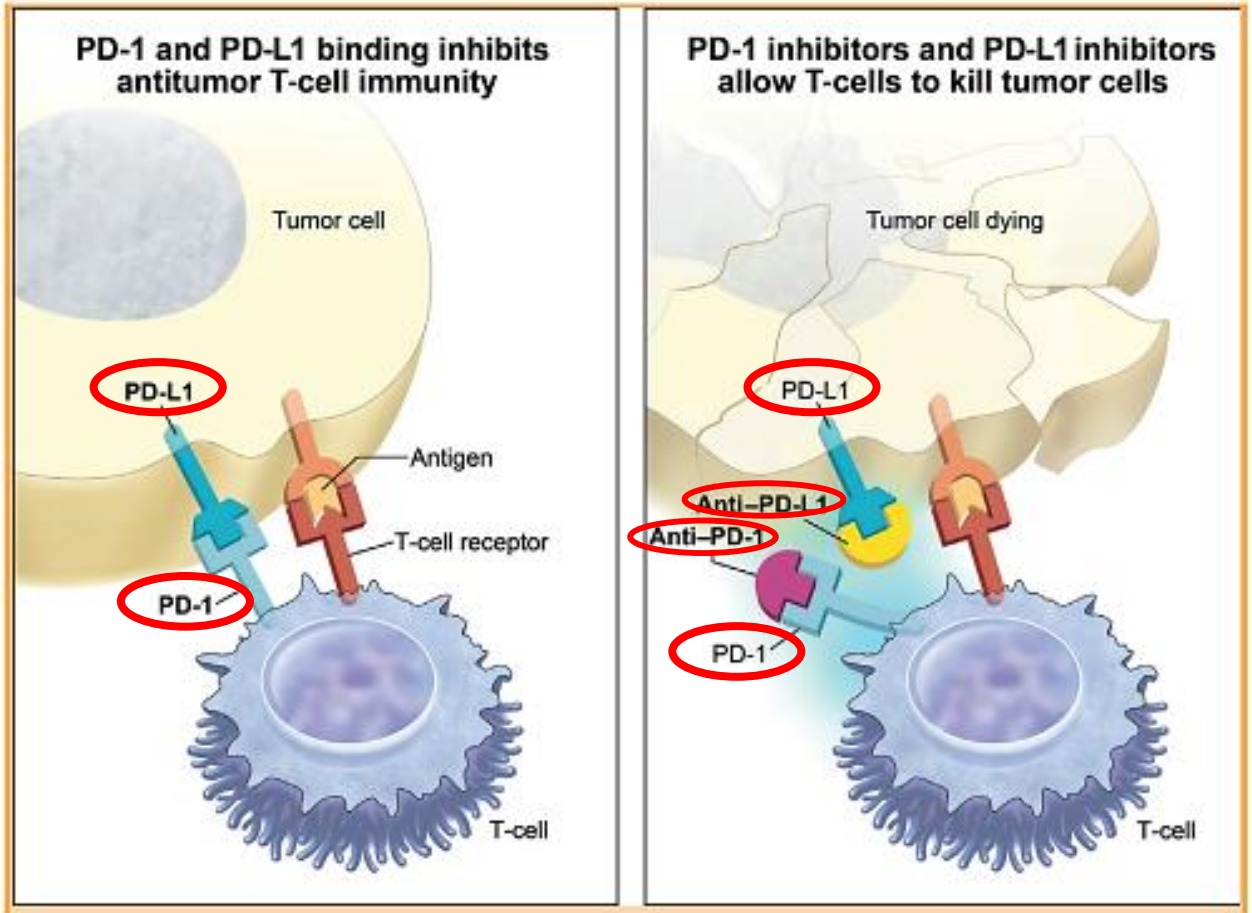
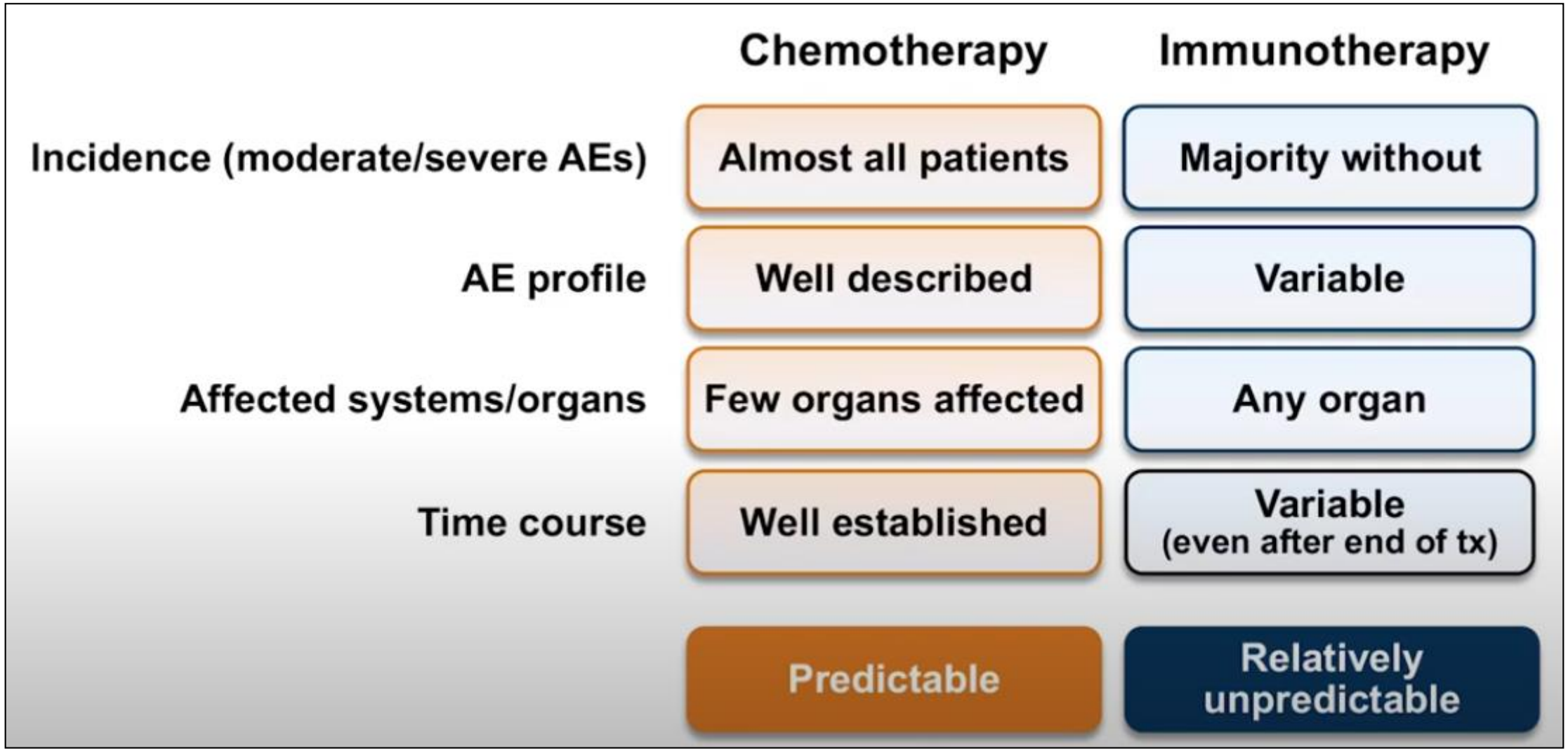


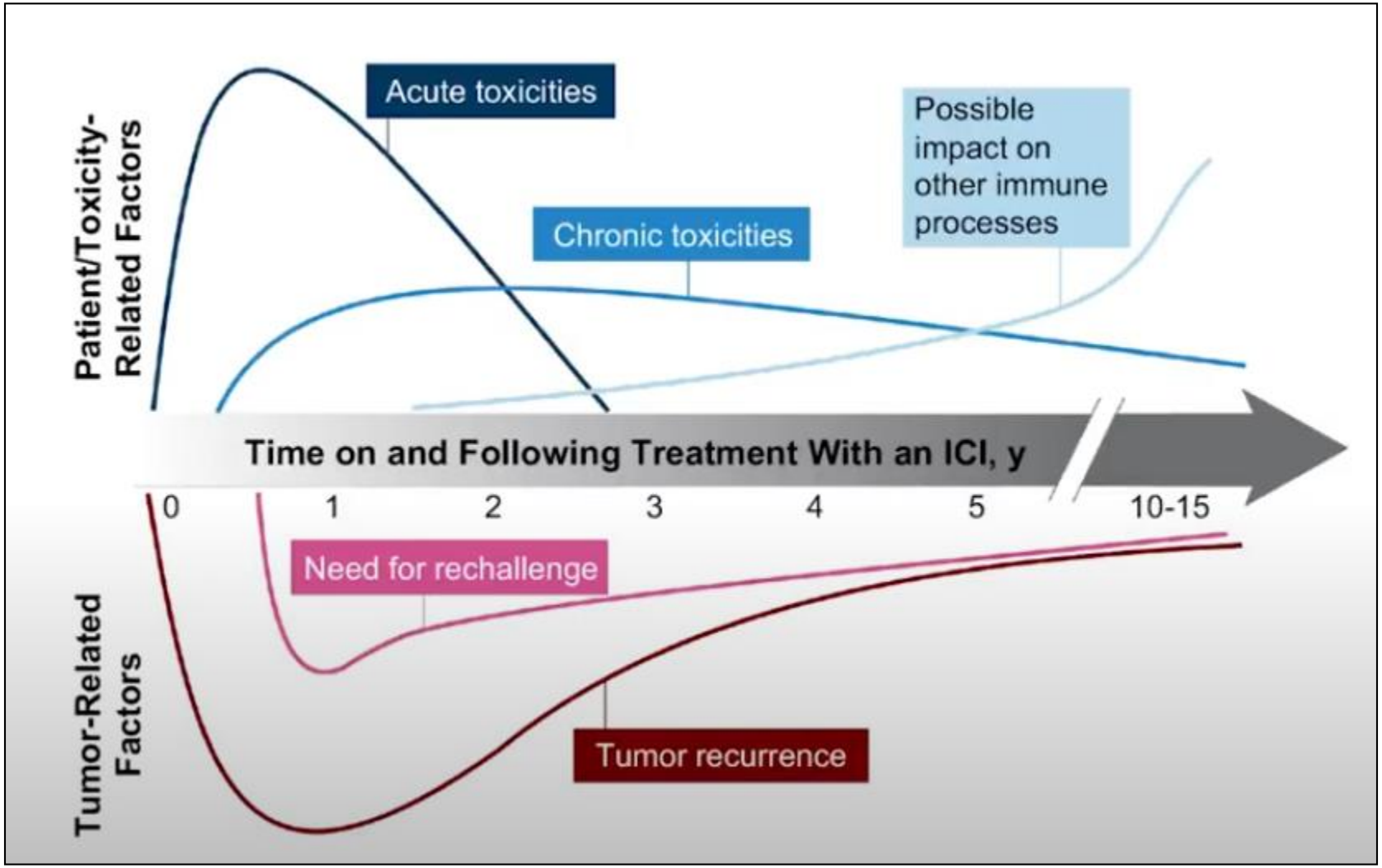
FIGURE 2. The action of anti–programmed cell death 1 (PD-1) and anti–programmed death ligand-1 (PD-L1) blockers.

Kumar AB, 2018, Mayo Clinic Proceedings

Effets secondaires auto-immuns

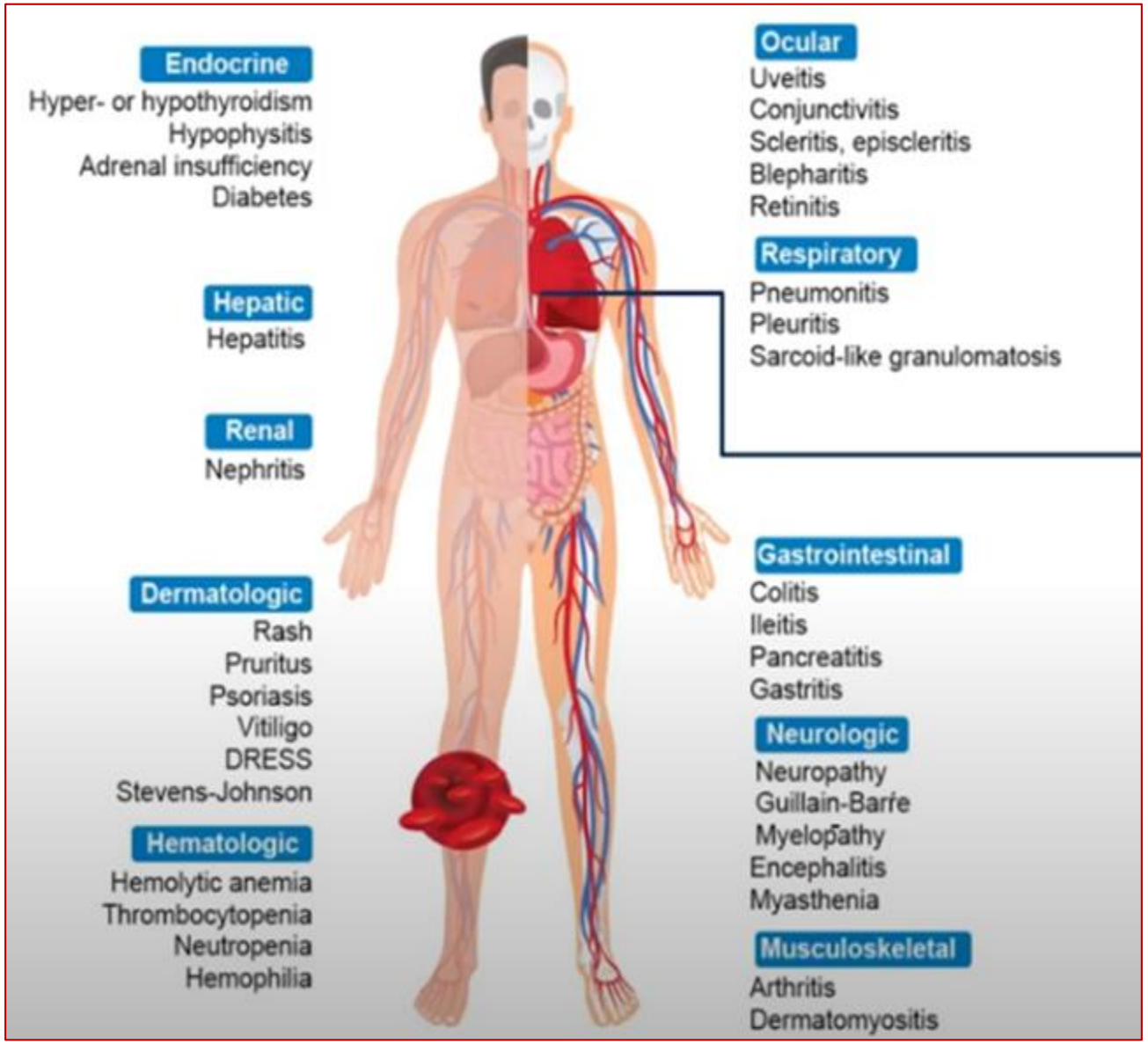


Timing des effets secondaires



Johnson DB et al. *Nat Rev Clin Oncol*. 2022;19:254-267.

Effets secondaires auto-immuns



Évaluation du risque de cardiotoxicité

Pré thérapeutique

Durant le traitement

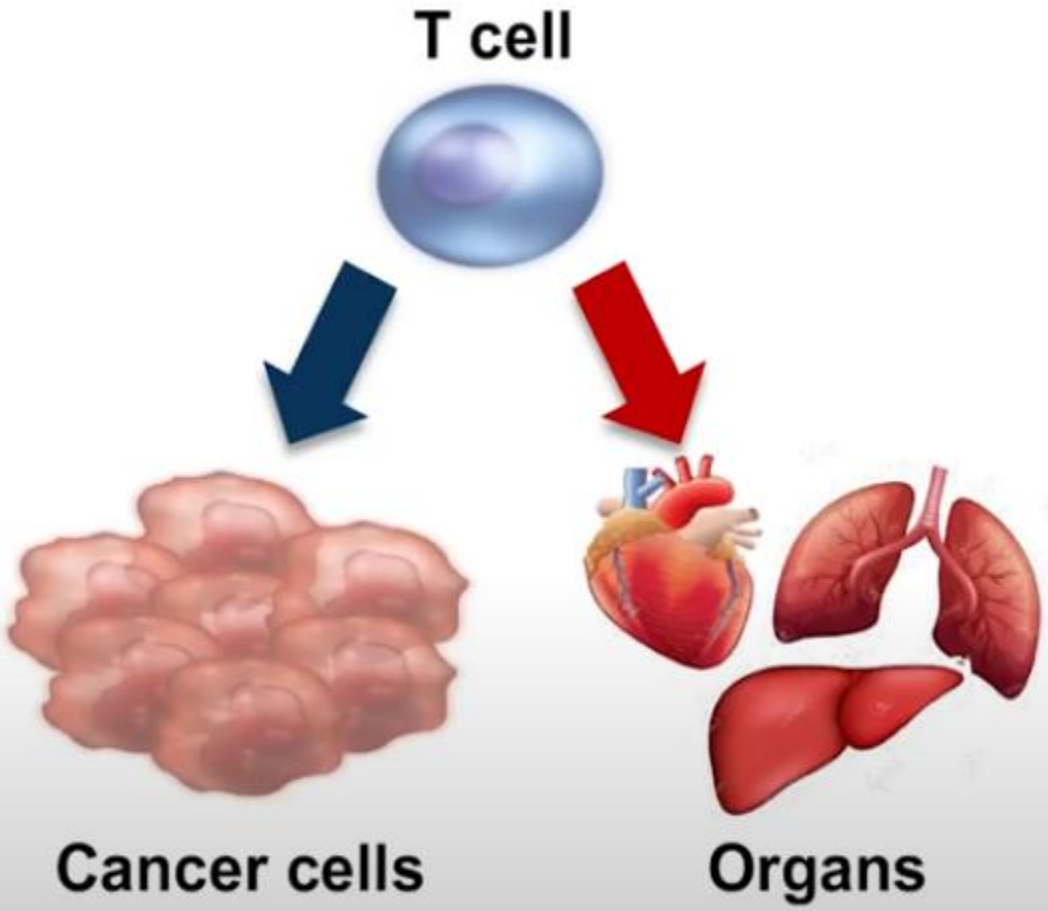
Recommendation Table 15 — Recommendations for baseline risk assessment and monitoring during immunotherapy

Recommendations	Class[a]	Level[b]
ECG, NP, and cTn measurements are recommended in all patients before starting ICI therapy.[333]	I	B
Baseline echocardiography is recommended in high-risk patients[c] before starting ICI therapy.[333]	I	B
Baseline echocardiography may be considered in all patients before starting ICI therapy.	IIb	C
Serial ECG and cTn measurements should be considered before ICI doses 2, 3, and 4, and if normal, reduce to every three doses until completion of therapy to detect subclinical ICI-related CV toxicity.[333]	IIa	B
CV assessment[d] is recommended every 6–12 months in high-risk patients[c] who require long-term (>12 months) ICI treatment.[321–323,335,336]	I	C
CV assessment[d] may be considered every 6–12 months in all patients who require long-term (>12 months) ICI treatment.	IIb	C

© ESC 2022

Lyon, A. R. European Heart Journal (2022) 43, 4229–4361

Facteurs de risque de toxicité



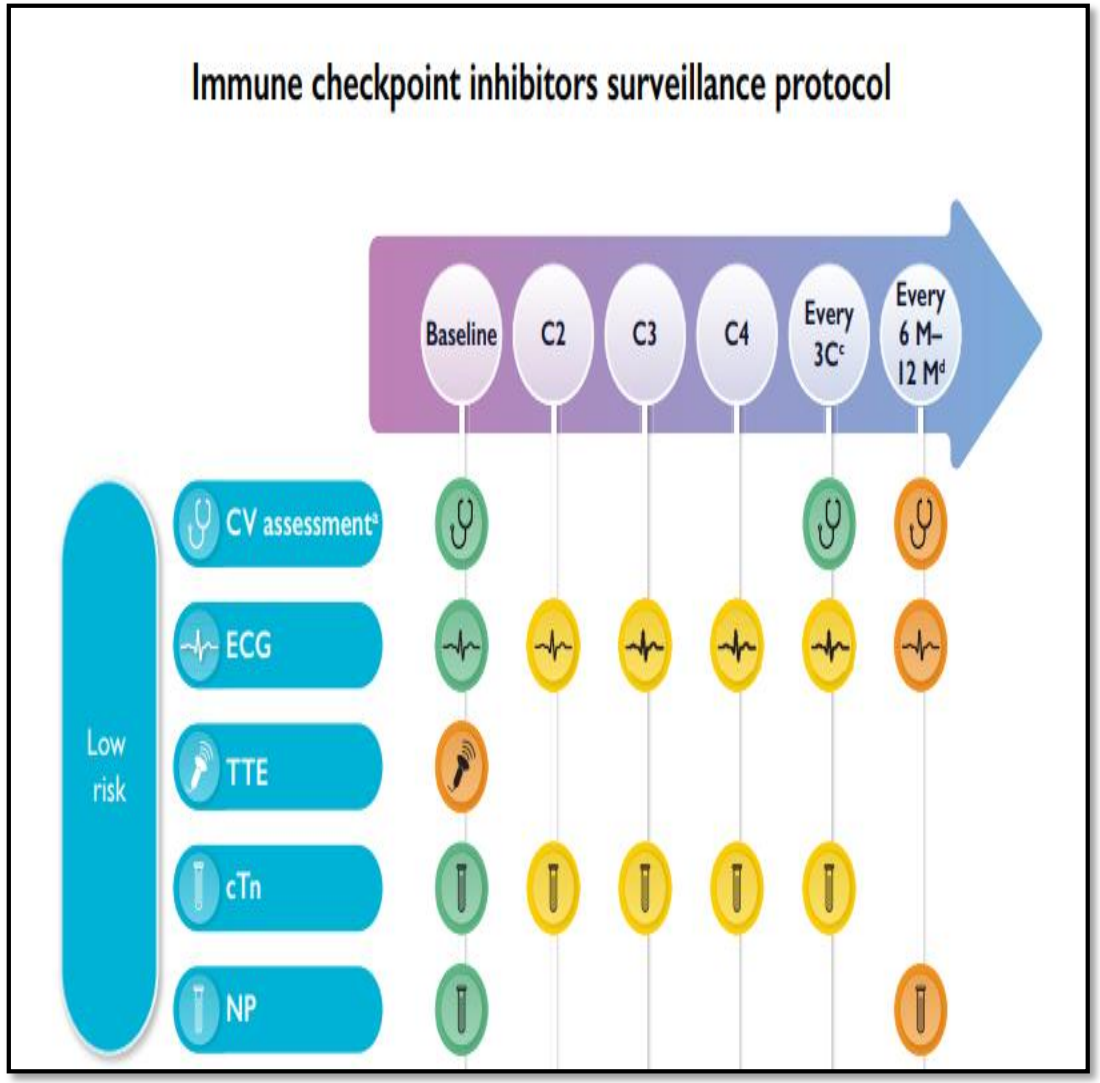
Factors for toxicity

- Autoimmune disease
- Subclinical inflammation
- Shared antigens
- Combination immune therapies

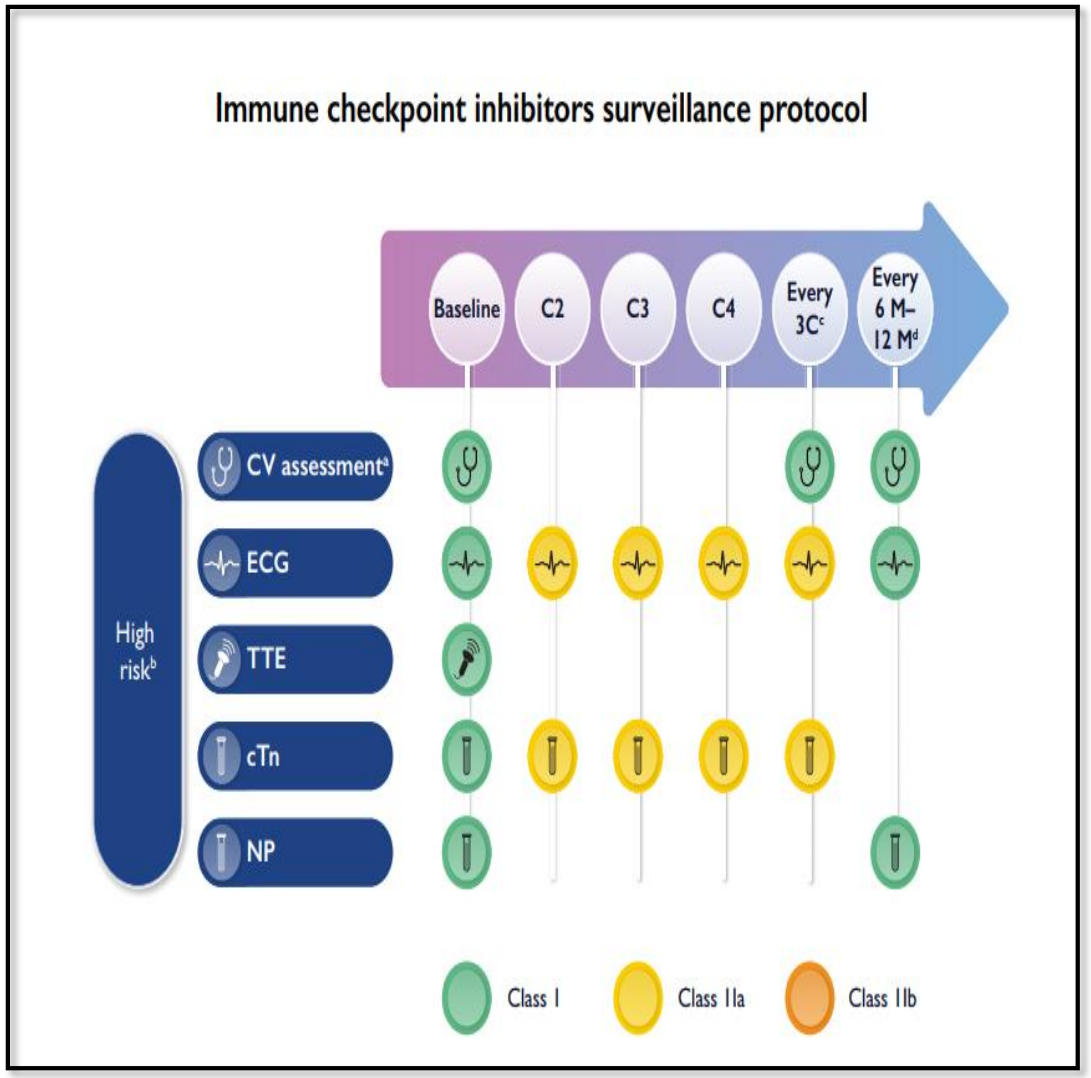
More aggressive combinations → more toxicity

- ICI-related non-CV events, prior CTRCD or CVD
- Combination ICI-cardiotoxic therapy

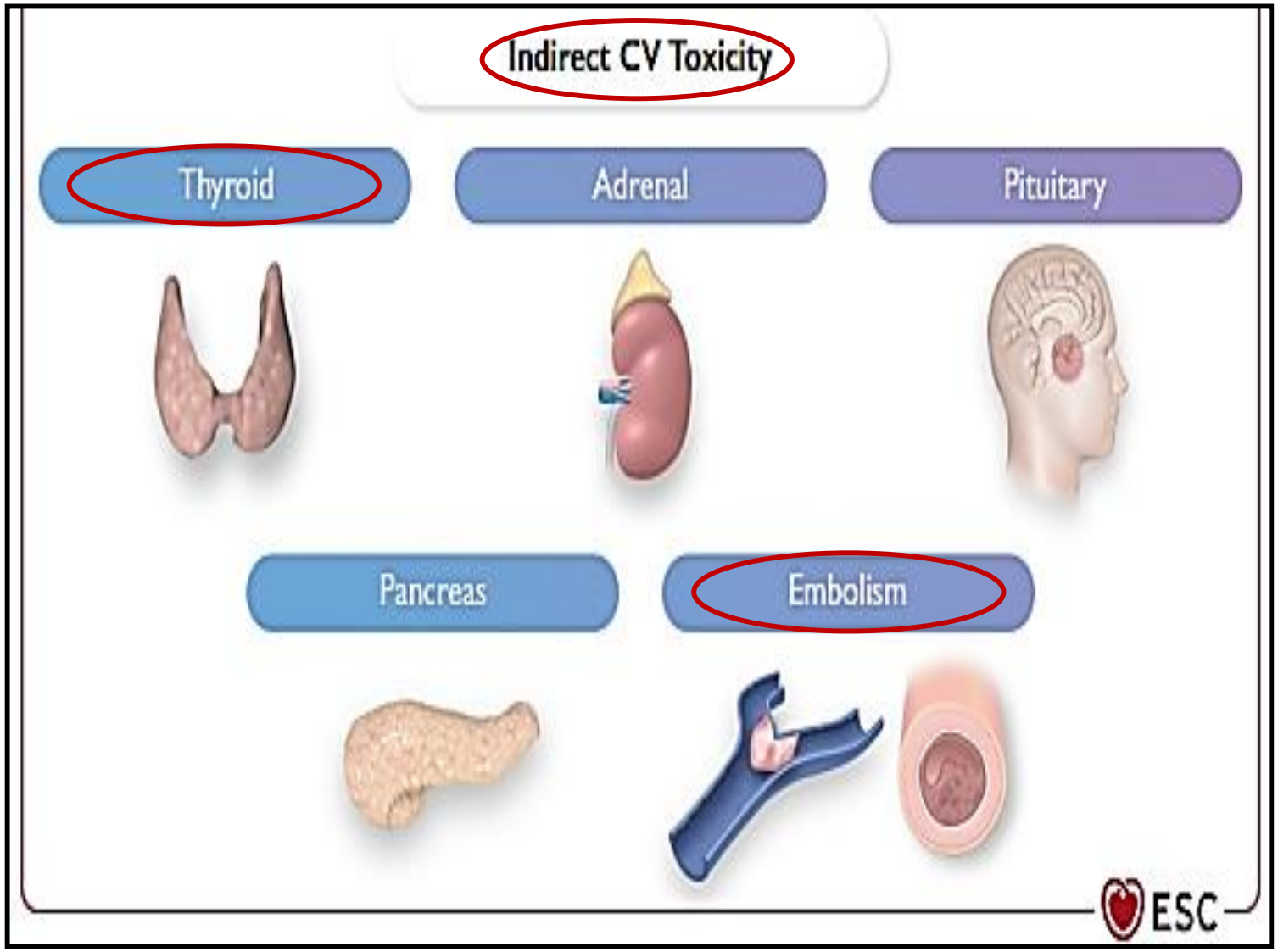
Suivi des patients à faible risque de myocardite traités par inhibiteurs des checkpoints



Suivi des patients à haut risque de myocardite traités par inhibiteurs des checkpoints



Lyon, A. R. European Heart Journal (2022) 43, 4229–4361

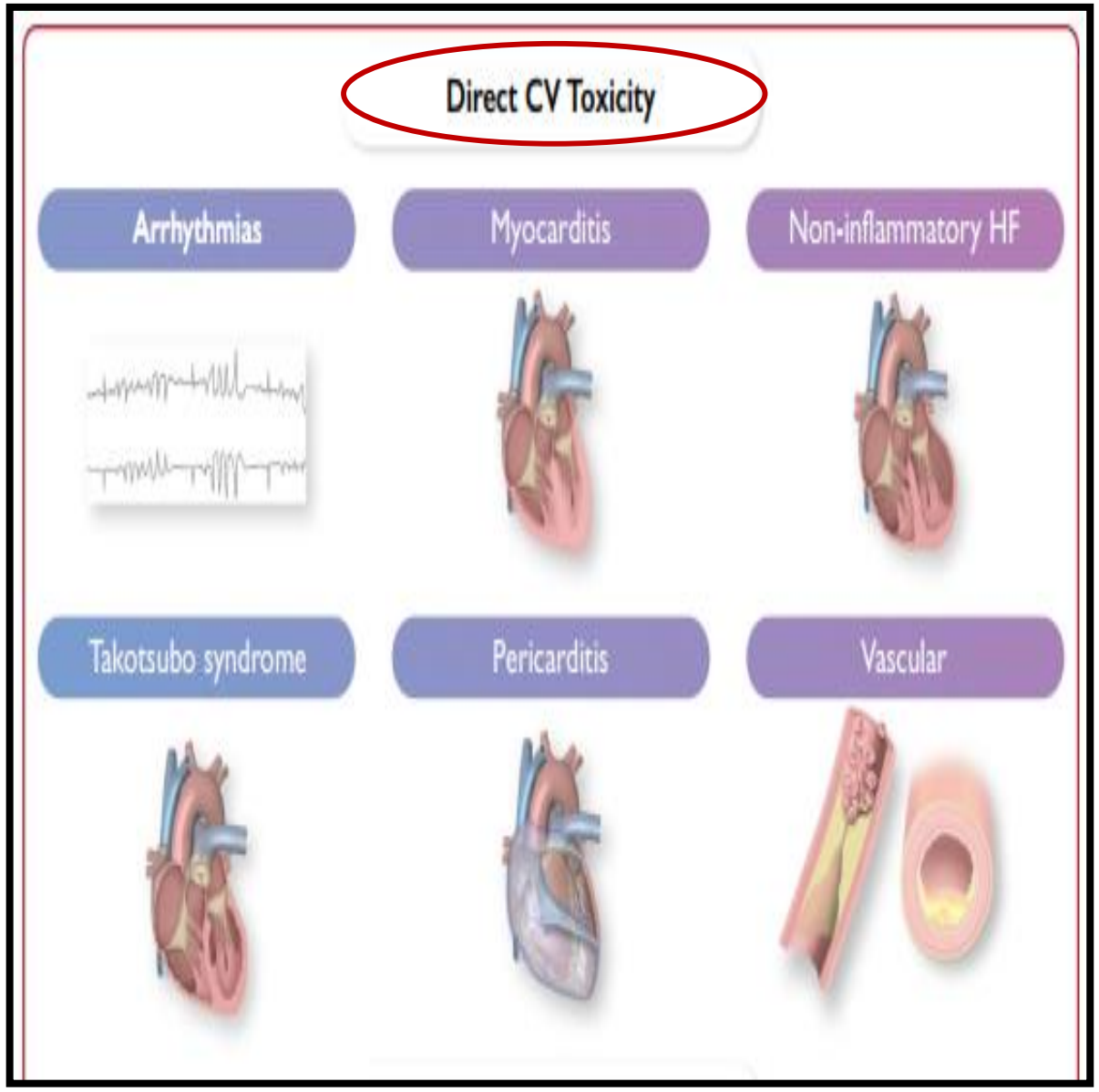


Lyon, A. R. European Heart Journal (2022) 43, 4229–4361

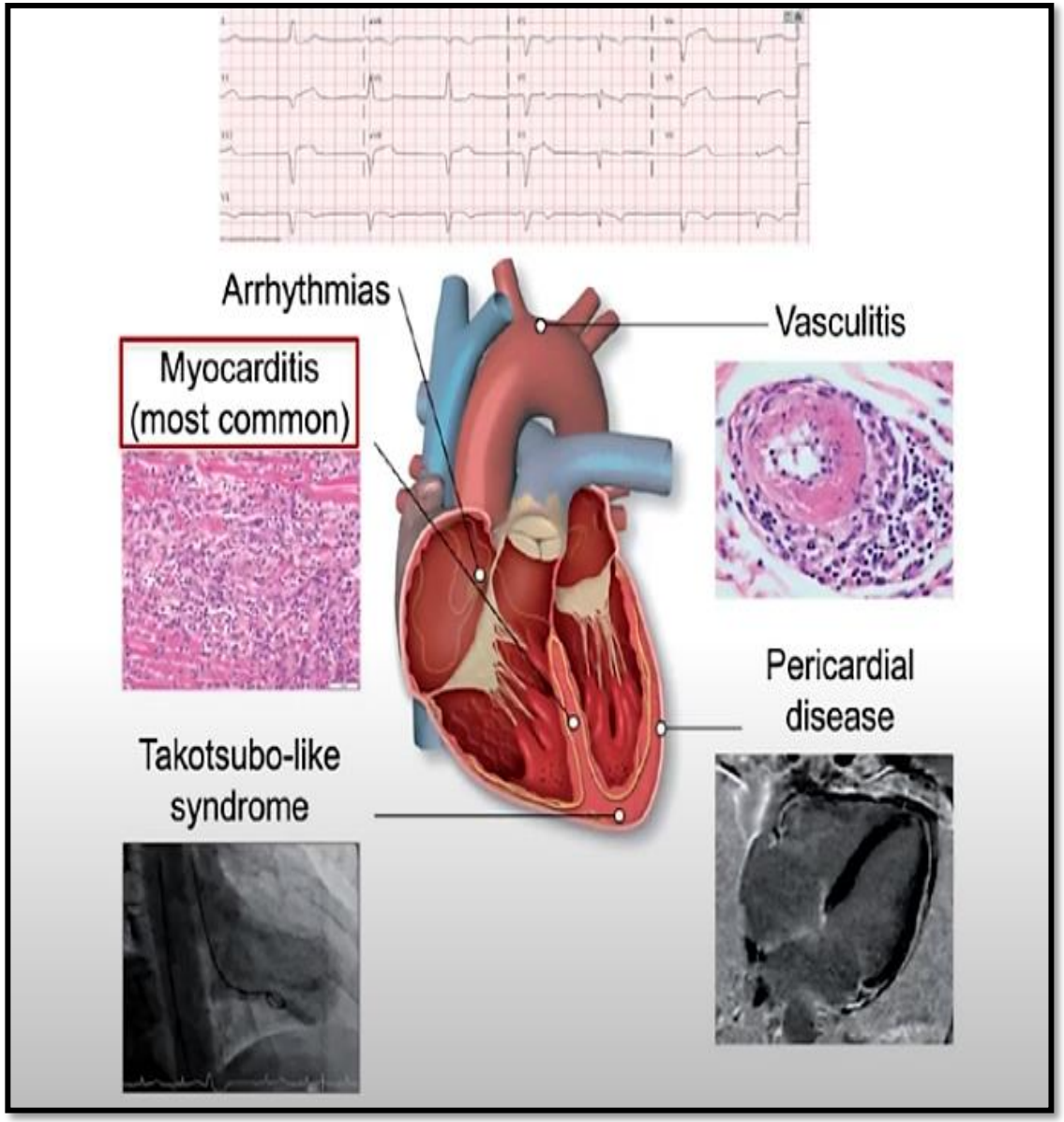
Dysthyroïdie:

Hyperthyroïdie = cardiothyréose, FA

Maladies thrombo-emboliques veineuses: TVP, EP = progression de la maladie ?



Lyon, A. R. European Heart Journal (2022) 43, 4229–4361



1. Hu J-R et al. *Cardiovasc Res.* 2019;115:854-868. 2. Johnson D et al. *N Engl J Med.* 2016;375:1749-1755. 3. Moslehi JJ et al. *Lancet.* 2018;391:933. 4. Mahmood SS et al. *J Am Coll Cardiol.* 2018;71:1755-1764. 5. Salem J-E et al. *Lancet Oncol.* 2018;19:1579-1589.

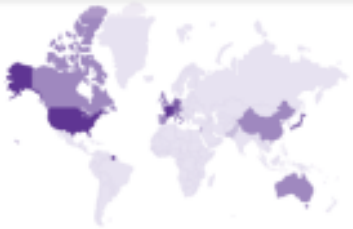
Arythmies

- Éliminer une myocardite +++
- Pas d’indication à la prescription de corticoïdes.
- **FA :** toxicité directe ? suivre les recommandations de PEC de la FA.
- Beaucoup de gaps of evidence.

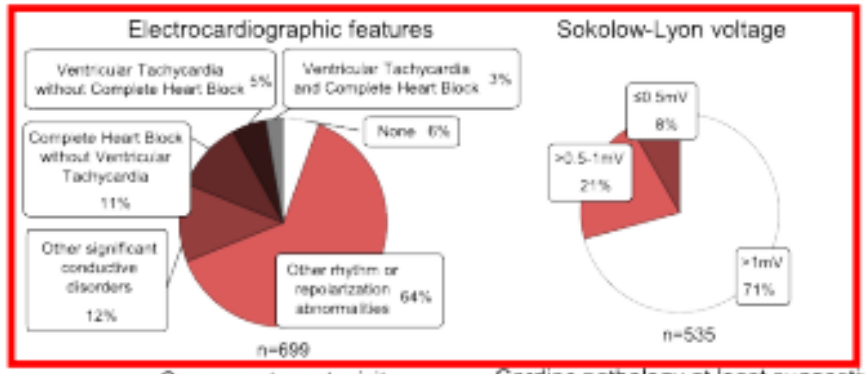
ICI myocarditis and arrhythmias rates

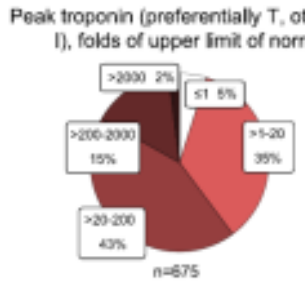
Major Cardiomyotoxic Events

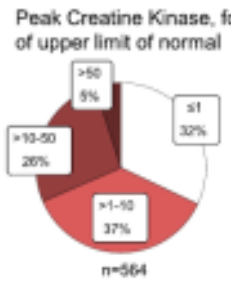
Discovery international ICI myocarditis cohort

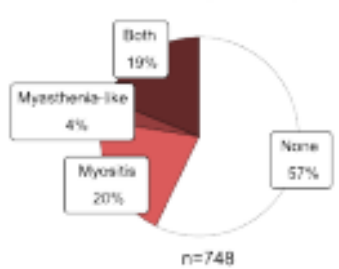


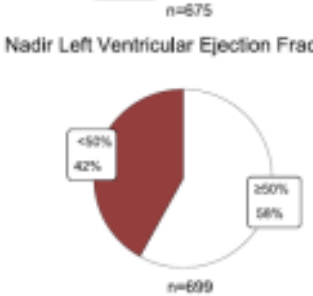
748

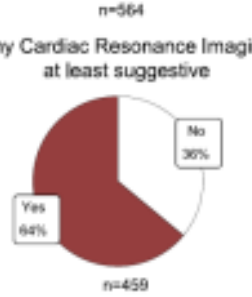


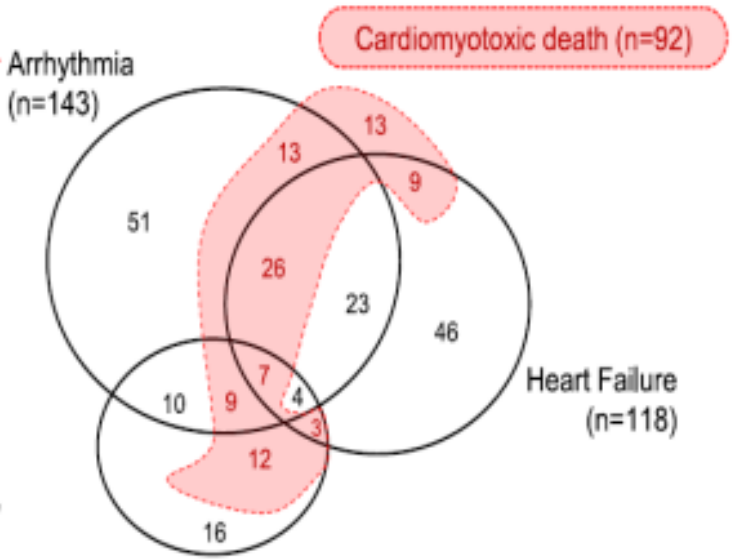


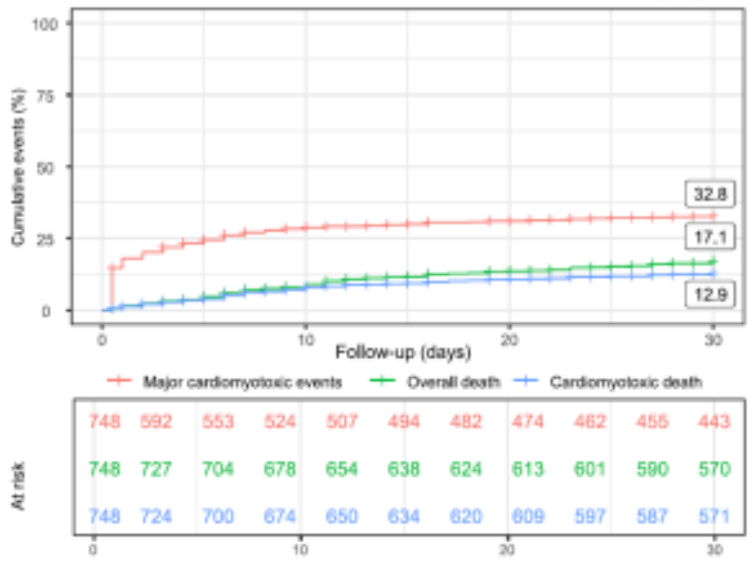












ESC European Society of Cardiology
European Heart Journal (2025) **00**, 1–13
https://doi.org/10.1093/eurheartj/ehaf315

Power J, Dolladille C, ..., Salem JE

Péricardite (1)

- **Fréquence :** 0,2 à 3,3 %
- **Molécules:** Anti PDL1, Anti PD1, pas les anti CTLA4.
- **Délai de survenue:** durant les 3 premiers mois.
- **Facteurs favorisants:** sexe masculin avec cancer du poumon ayant reçu une corticothérapie.
- Plutôt associée à un épanchement pleural.
- **Diagnostic:** écho – TDM
- **Diagnostic différentiel:** infection, hypothyroïdie, syndrome néphrotique, myocardite +++

Adler Y, et al. 2015, Eur Heart J 2015;36:2921–2964, Gong J, J Immunother Cancer 2021 , Inno A, Maurea , Immunother 2021;70:3041–3053

Péricardite (2)

Diagnosis and management of ICI-associated pericarditis		
Multimodality CV imaging (echocardiography, CMR ± CT), ECG and measurement of cardiac biomarkers are recommended to confirm the diagnosis, assess the haemodynamic consequences of pericardial disease, and rule out associated myocarditis.	I	C
Prednisolone and colchicine are recommended for patients with ICI-associated pericarditis.[326,624,625,630]	I	C
Interruption of ICI treatment in patients with confirmed ICI-associated pericarditis with moderate-to-severe pericardial effusion is recommended.	I	C
A multidisciplinary discussion is recommended before restarting ICI treatment.	I	C

© ESC 2022

Péricardite (3)

Common Terminology Criteria for Adverse Events (CTCAE)

Version 5.0

Published: November 27, 2017

Cardiac disorders			
CTCAE Term			Grade 5
Pericarditis	**Discuter l'interruption temporaire du TRT** **Traitement classique: aspirine ou AINS + colchicine ..**	**Arrêt du TRT** **Prednisolone** 1mg/Kg avec ou sans Colchicine +/- drainage péricardique	Death

Gravité: forme asymptomatique à la tamponnade et décès.

Surveillance: 1 écho /mois jusqu'à disparition de l'épanchement

Rechallenge: RCP de Cardio-Oncologie

J Immunother Cancer 2021 , Inno A, Maurea , Immunother

Complications vasculaires : SCA

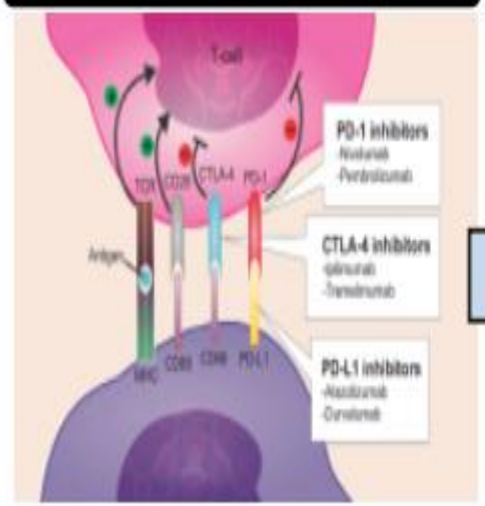
- Peu de données
- Fréquence: 0,4 à 1,1 %
- Mécanisme physiopathologique inconnu
- Pas de corticoïdes
- Éliminer une myocardite et faire une imagerie coronaire

Kondapalli L, Circulation 2020;142:2312–2315

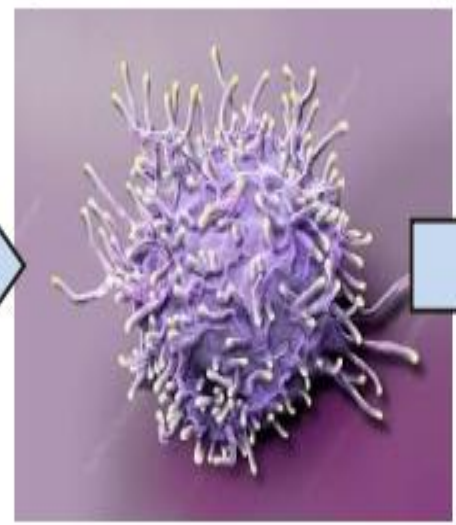
The potential impact of ICIs on CV surrogates and CV events

Hypothesis

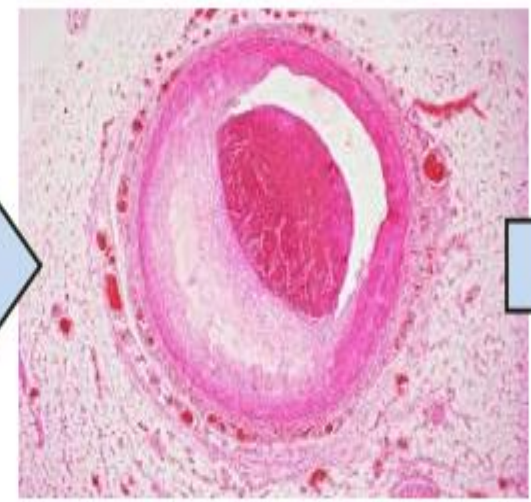
Immune Checkpoint Inhibitors



Enhanced immune response



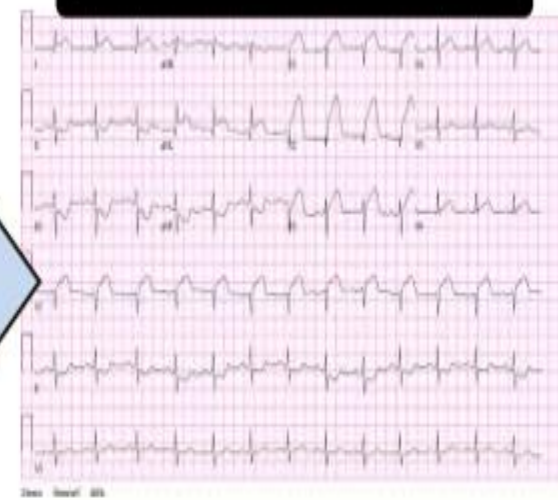
?



?

Accelerated atherosclerosis

Increased cardiovascular events



Toxicités myocardiques non-inflammatoires

- **Définition :** baisse de la FEVG à moins de 50 % avec ou sans insuffisance cardiaque aigue.
- **Syndrome de Takotsubo like**
- Toujours éliminer une myocardite ou un SCA
- Plutôt tardif après **6 mois**
- **Pas de corticoïdes**, traiter l'IC

Roth ME, Am J Ther 2016;23: e1925–

La myocardite immuno-induite

Fréquence 1 %

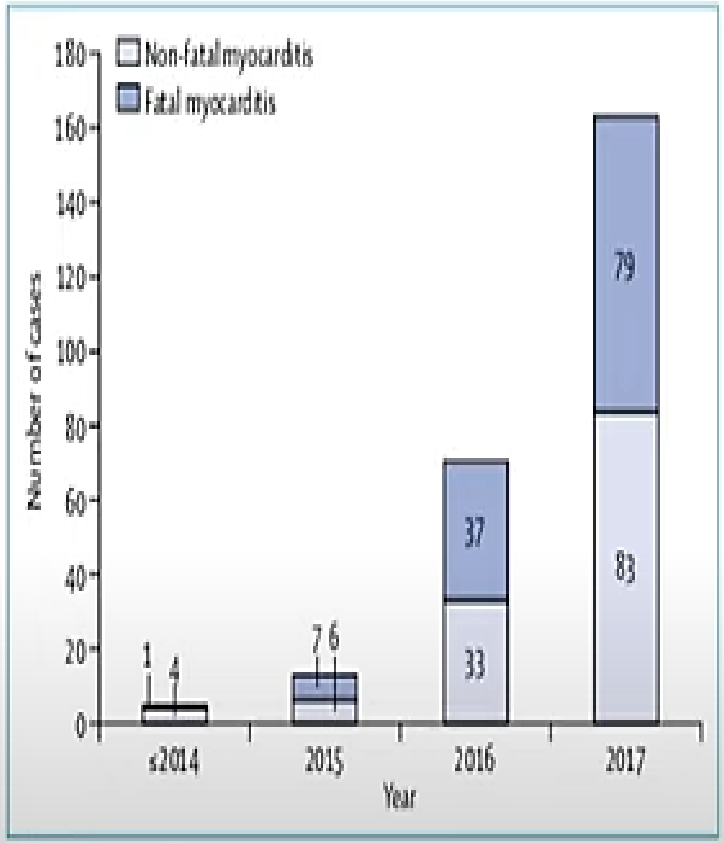
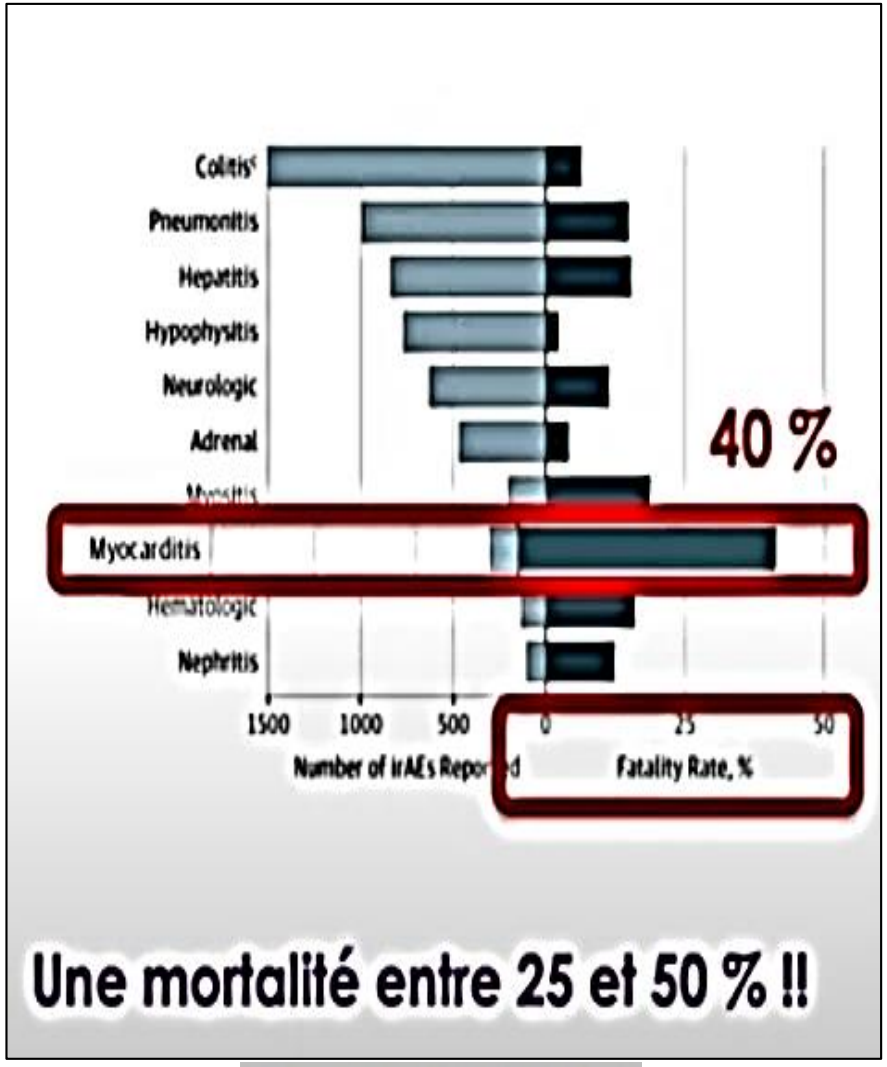


Figure: Number of fatal and non-fatal cases of myocarditis reported to the US Food and Drug Administration, by year

US and Germany registries

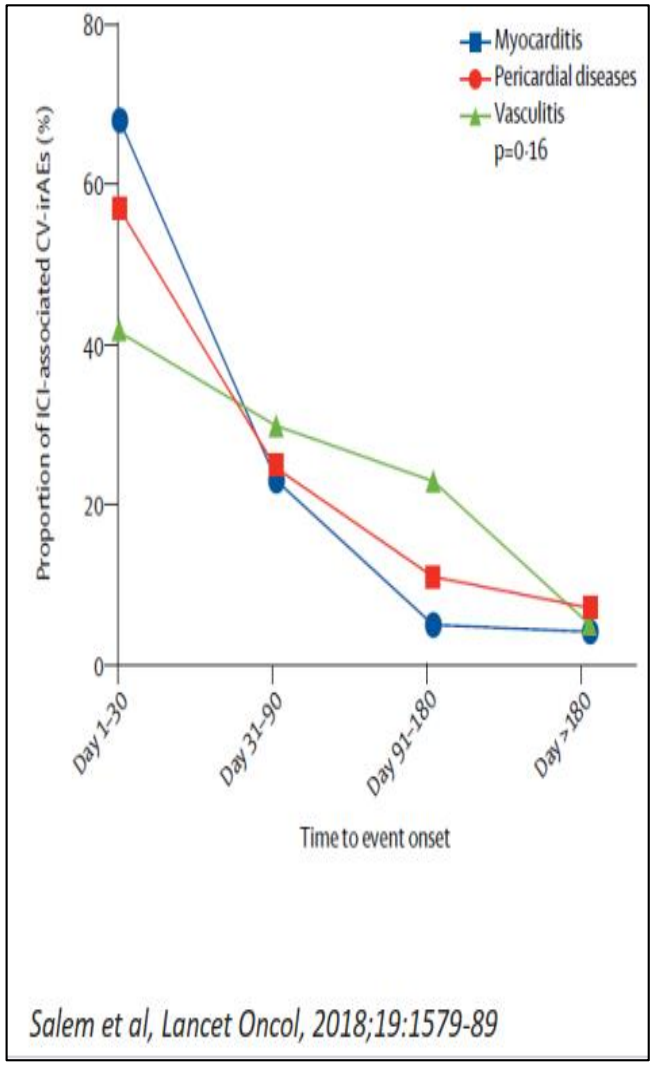
Mahmood SS, J Am Coll Cardiol 2018

Gravité



Salem et al. JAMA Oncol 2018

Délai d'apparition



Salem et al, Lancet Oncol, 2018;19:1579-89

Myocardite immuno-induite: diagnostic

Clinical diagnosis[d]	**cTn elevation** (new or significant change from baseline)[e] **with 1 major criterion or 2 minor criteria,** after exclusion of ACS and acute infectious myocarditis based on clinical suspicion[f]
	Major criterion: • CMR diagnostic for acute myocarditis (modified Lake Louise criteria)[g]
ICI myocarditis (either pathohistological diagnosis or clinical diagnosis)	
Pathohistological diagnosis (EMB)	Multifocal inflammatory cell infiltrates with overt cardiomyocyte loss by light microscopy
	Minor criterion: • Clinical presentation (new onset of, or worsening of, dyspnoea, shortness of breath, orthopnoea, lower-extremity oedema, palpitations, light-headedness/dizziness, syncope, muscle weakness, cardiogenic shock) • Ventricular arrhythmia (including cardiac arrest) and/or new conduction system disease • Decline in LV systolic function, with or without regional wall motion abnormalities in a non-Takotsubo pattern • Other immune-related adverse events, particularly myositis, myopathy, myasthenia gravis • Suggestive CMR[h]

Lyon, A. R. European Heart Journal (2022) 43, 4229–4361

How common are baseline troponin values > assay

Contents lists available at ScienceDirect

European Journal of Cancer

journal homepage: www.ejcancer.com

Optimized monitoring for immune checkpoint inhibitor induced myocarditis using high-sensitivity troponin-T

Dirk Tomsitz [a], Ulrich Grabmaier [b], Judith Spiro [c], Leo Nicolai [b,d], Lars E. French [b,e], Steffen Massberg [b], Lucie Heinzerling [a,d,e,*]

[a] Department of Dermatology and Allergy, University Hospital, LMU Munich, Munich, Germany
[b] Department of Medicine I, LMU University Hospital, LMU Munich, Munich, Germany

JACC: ADVANCES VOL. 3, NO. 12, 2024

© 2024 THE AUTHORS. PUBLISHED BY ELSEVIER ON BEHALF OF THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION. THIS IS AN OPEN ACCESS ARTICLE UNDER THE CC BY LICENSE

ORIGINAL RESEARCH

HEART FAILURE AND CARDIOMYOPATHIES

Elevations of Cardiac Troponin in Patients Receiving Immune Checkpoint Inhibitors

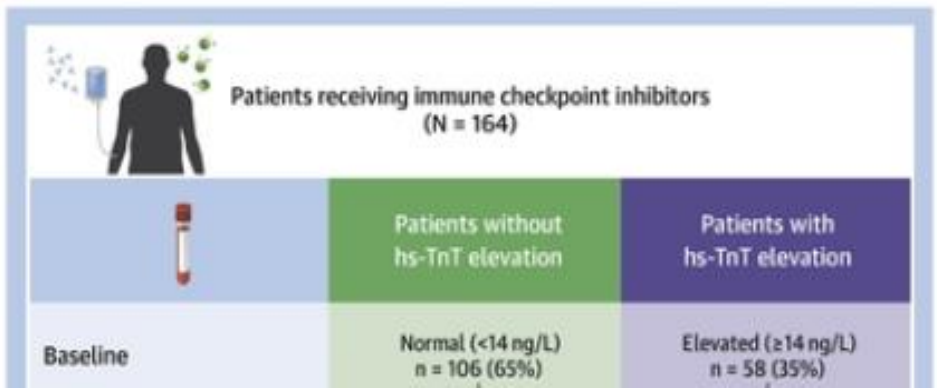
Data From a Prospective Study

Pieter F. van den Berg, MD,[a] Valentina Bracun, MD,[a] Michel Noordman, MSc,[b] Peter van der Meer, MD, PhD,[a] Cannia Shi, MD,[c] Sjoukje F. Oosting, MD, PhD,[b] Joseph Pierre Abboumalem, PhD,[a] Sanne de Wit, MSc,[a] Wouter C. Meijers, MD, PhD,[a,c] Mathilde Jalving, MD, PhD,[b] Michel van Kruchten, MD, PhD,[b]

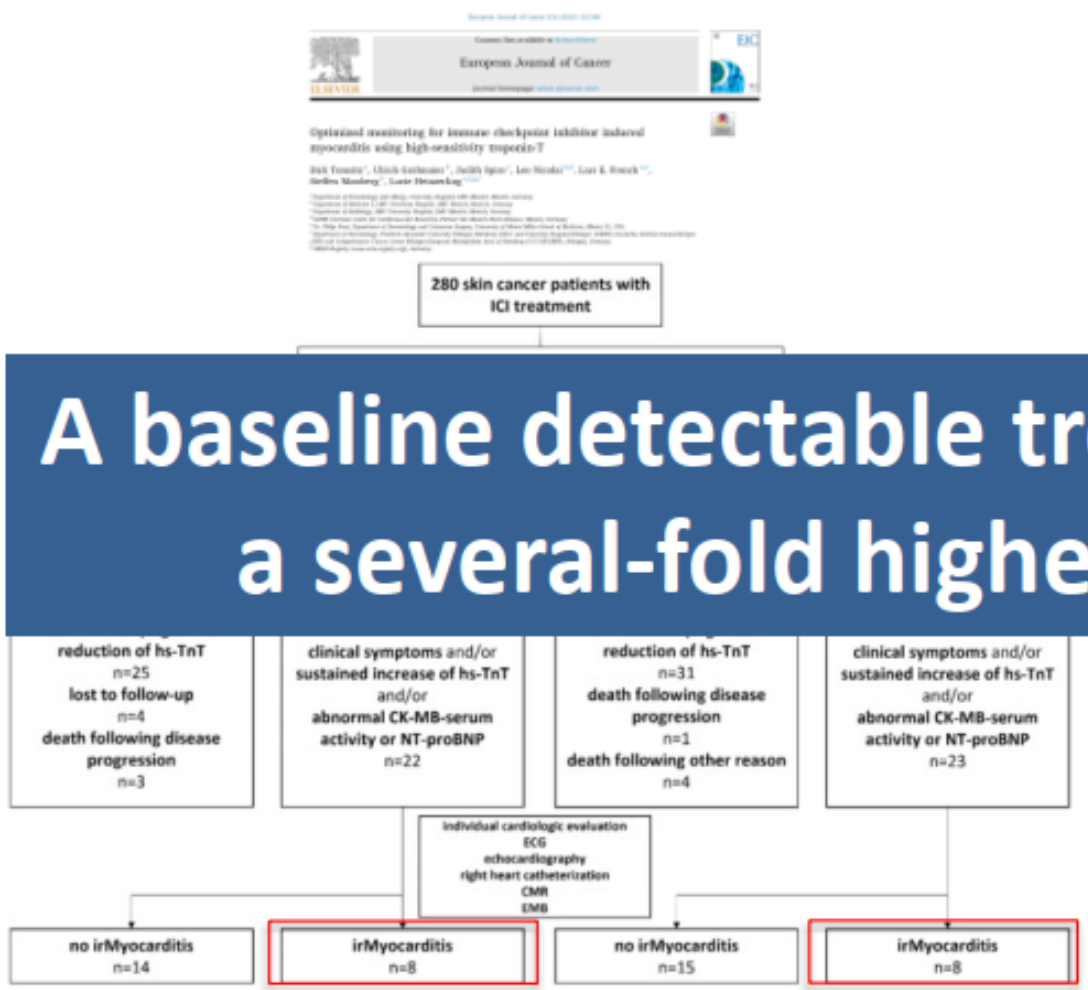
Baseline troponin detectable range of 30-35%

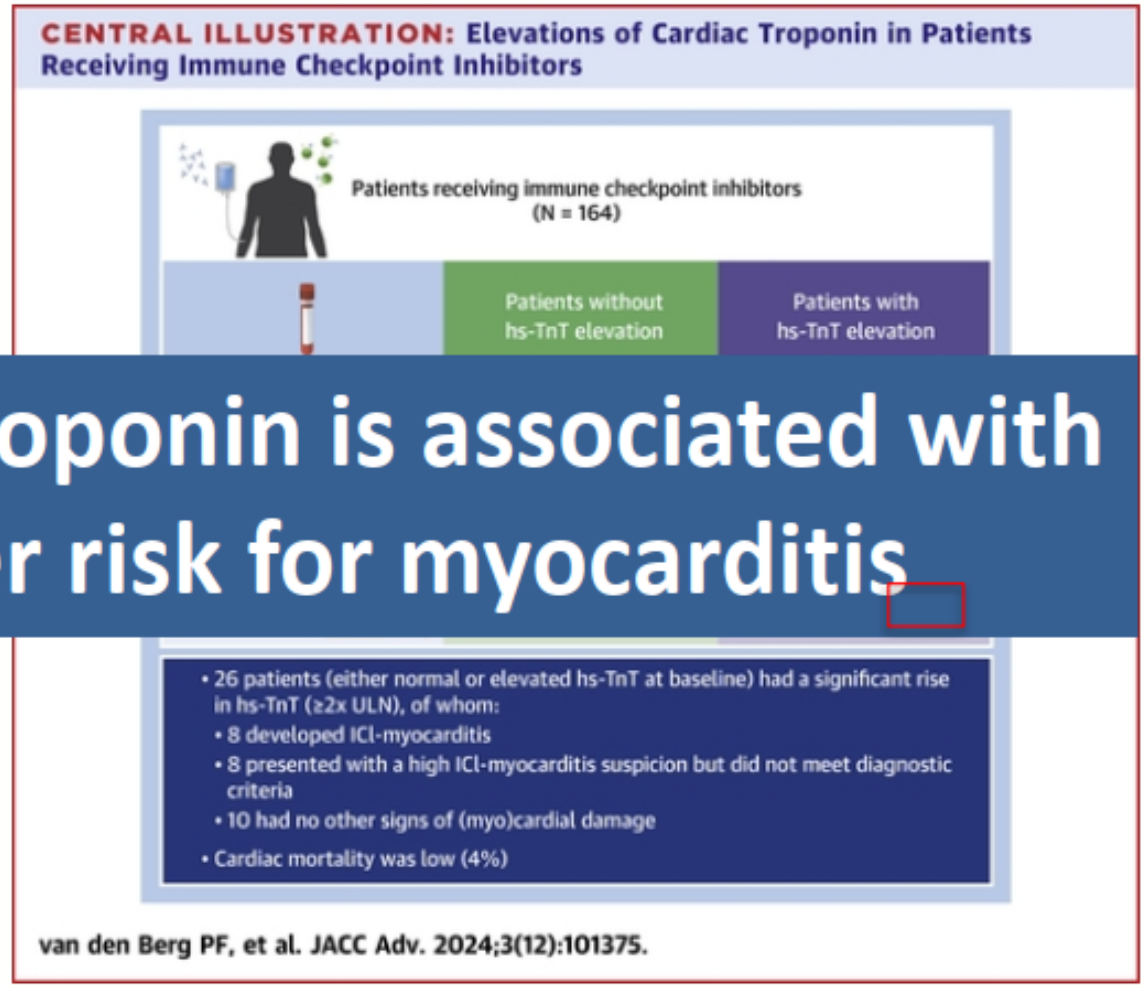
35% (58 patients) with a detectable baseline troponin (hs-TnT > 14 ng/L)

Receiving Immune Checkpoint Inhibitors



Do baseline detectable troponin values have prognostic implications?





A baseline detectable troponin is associated with a several-fold higher risk for myocarditis

Recommendations	Class[a]	Level[b]
Diagnostic triage within 24 h is recommended[c] in patients with suspected myocarditis induced by ICI to initiate treatment rapidly.[495,496,501,504]	I	C
Immediate disruption of ICI and administration of high-dosage corticosteroids are recommended in patients with ICI-associated myocarditis in order to stop the inflammatory reaction and stabilize the patient.[504]	I	C
Second-line immunosuppression treatment should be considered in patients with steroid-refractory ICI-associated myocarditis.[501,504]	IIa	C
Second-line immunosuppression treatment may be considered in patients with fulminant/severe ICI-associated myocarditis.[501,504]	IIb	C

© ESC 2025

ICI, immune checkpoint inhibitor.
[a]Class of recommendation.
[b]Level of evidence.
[c]See *Figure 5*.

2025 ESC Guidelines for the management of myocarditis and pericarditis. EHJ 2025

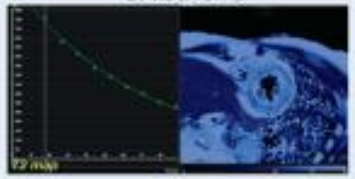
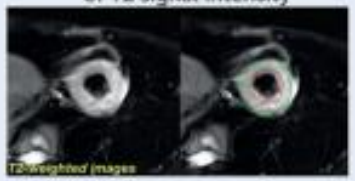
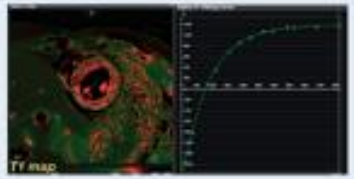
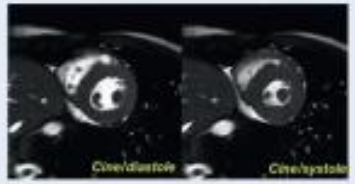
Myocardite immuno-induite: diagnostic

- **ECG:** arythmies, troubles conductifs…SCA
- IC avec **FE basse : 50 % des cas.**
- **Mais : ETT** peut être normale ce qui **n'exclu pas** la myocardite.
- Association fréquente avec une **myosite** périphérique (détresse respiratoire).
- **PET scan:** oui, mais de faible sensibilité. Peut être considéré si IRM indisponible ou contre indiquée.
- **Biopsie endo myocardique:** si doute diagnostic ou patient instable.
- Toujours éliminer une **autre cause cardiaque**: myocardite infectieuse, SCA…

Lyon, A. R. European Heart Journal (2022) 43, 4229–4361
Pradhan R, Int J Cardiol 2019

IRM cardiaque

CENTRAL ILLUSTRATION **Overview of the Updated Lake Louise Criteria**

	2018 Lake Louise Criteria	CMR Image Examples
Main Criteria	**Myocardial Edema** (T2-mapping or T2W images)	Regional or global increase of native T2  or Regional or global increase of T2 signal intensity 
	Non-ischemic Myocardial Injury (Abnormal T1, ECV, or LGE)	Regional or global increase of native T1  or Regional or global increase of ECV  or Regional LGE signal increase 
Supportive Criteria	**Pericarditis** (Effusion in cine images or abnormal LGE, T2, or T1)	Pericardial effusion 
	Systolic LV Dysfunction (Regional or global wall motion abnormality)	Regional or global hypokinesis 

Ferreira, V.M. et al. J Am Coll Cardiol. 2018;72(24):3158-76.

ECV = extracellular volume; LGE = late gadolinium enhancement; T2W = T2-weighted.

Classification de la sévérité de la myocardite

Severity of myocarditis	• **Fulminant:** Haemodynamic instability, HF requiring non-invasive or invasive ventilation, complete or high-grade heart block, and/or significant ventricular arrhythmia • **Non-fulminant:** including symptomatic but haemodynamically and electrically stable patients and incidental cases diagnosed at the same time as other immuno-related adverse events. Patients may have reduced LVEF but no features of severe disease • **Steroid refractory**: non-resolving or worsening myocarditis (clinical worsening or persistent troponin elevation after exclusion of other aetiologies) despite high-dose methylprednisolone

Lyon, A. R. European Heart Journal (2022) 43, 4229–4361

Myocardite immuno-induite: que faire

- **Arrêt** de l'immunothérapie dés suspicion de myocardite immuno-induite.
- Faire les investigations nécessaires.

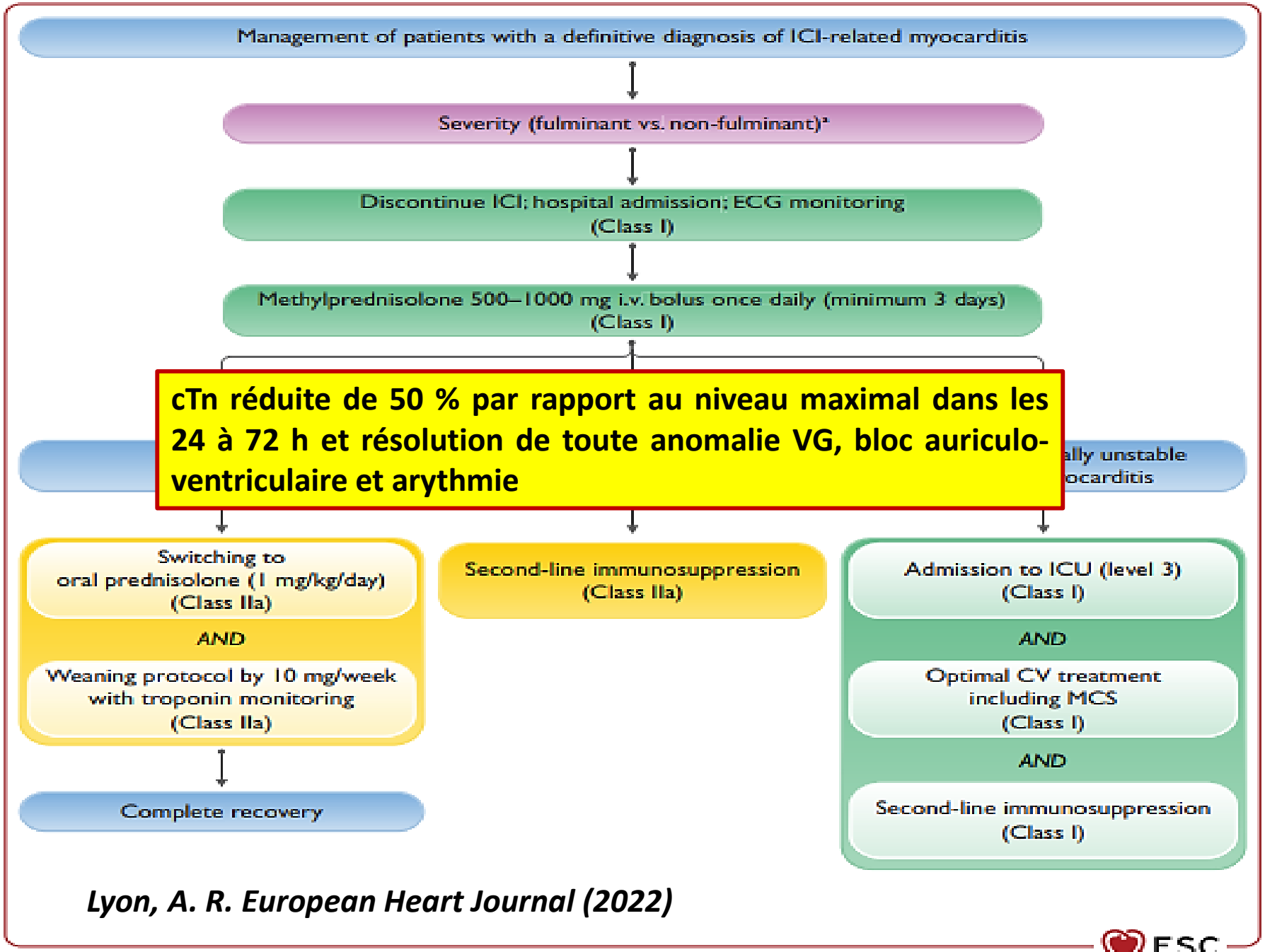
- Si myocardite suspectée mais **non confirmée**: discussion **multidisciplinaire** recommandée pour déterminer le rapport risque/bénéfice de l'arrêt définitif ou de la reprise du traitement.

- **Arrêt** du traitement **recommandé** si patient atteint de cancer avec une myocardite fulminante ou non fulminante immuno-médiée avec hospitalisation en soins intensifs.

- Traitement des complications CV selon les recommandations en vigueur.

Lyon, A. R. European Heart Journal (2022)

Schéma thérapeutique



Lyon, A. R. European Heart Journal (2022)

Traitement de la myocardite

ICI-induced myocarditis	
1st line therapy	Withdraw ICI, reassess Non-severe: methylprednisolone 500–1000 mg/day × 3 days, then taper with oral prednisone Severe: i.v. methylprednisolone 7–14 mg/kg/day × 3 days, then 1 mg/kg/day
2nd line therapy	If no response in 24–48 h: mycophenolate mofetil[b], ATG[g] abatacept[l], alemtuzumab[m]
3rd line therapy	Infliximab[j] or adalimumab[k], rituximab[i]

© ESC 2025

2025 ESC Guidelines for the management of myocarditis and pericarditis. European Heart Journal (2025) 00, 1–90

Take home messages

- Nouveaux traitements, extension des indications, révolution en oncologie.
- Vaccination anti - cancer.
- Plusieurs toxicités cardiaques.
- Myocardite immuno - induite : Prise en charge adaptée et surtout précoce.
- Arrêt du traitement.
- Corticothérapie à forte dose dés la suspicion.
- Possibilité de reprendre le traitement dans certaines situations après discussion multidisciplinaire.

MERCI POUR VOTRE ATTENTION