



Cardio-oncologie

Toxicité des immunotherapies: de la
myocardite à la cardiopathie ischémique

Prof. Franck Thuny

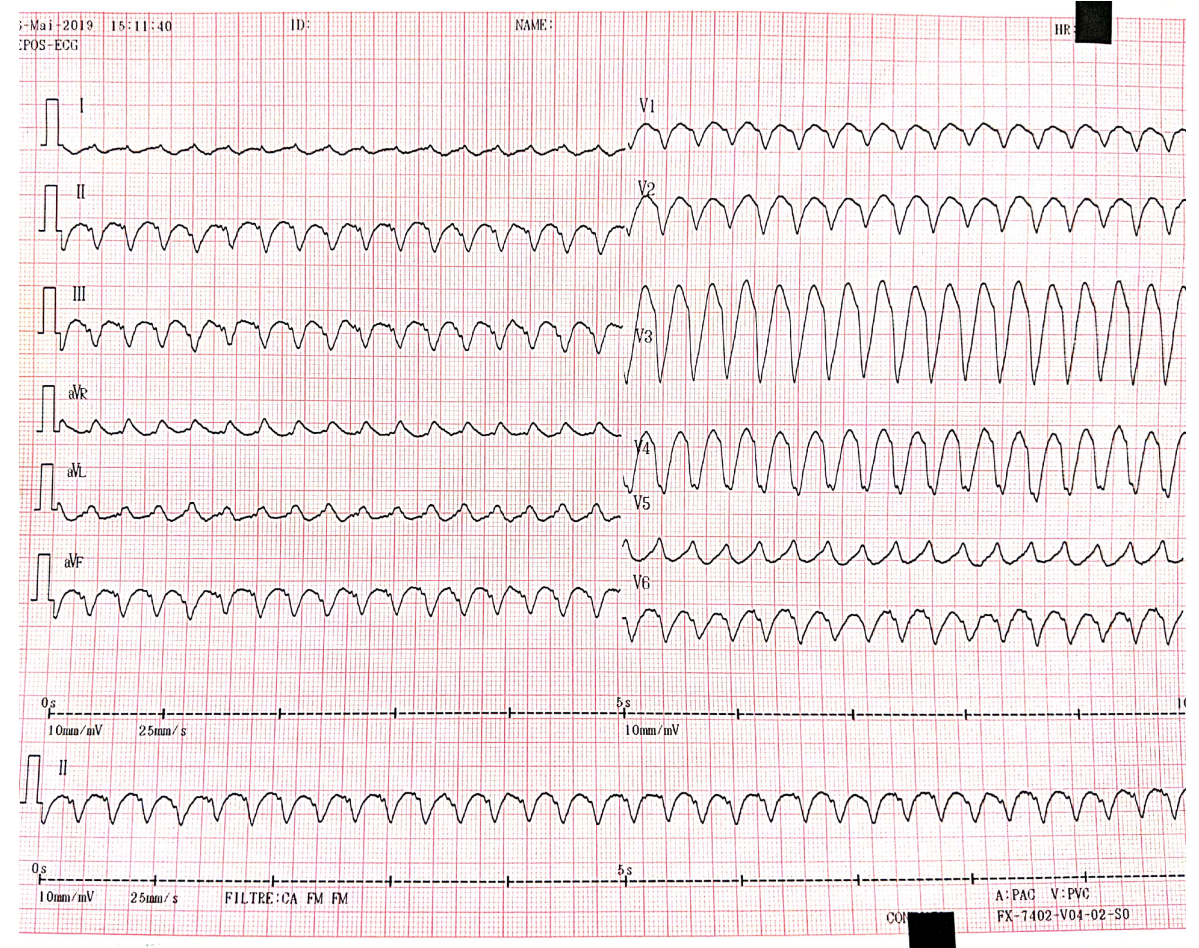
Hôpital NORD, Hôpitaux Universitaires de Marseille
Aix-Marseille University, France

Disclosure Statement of Financial Interest

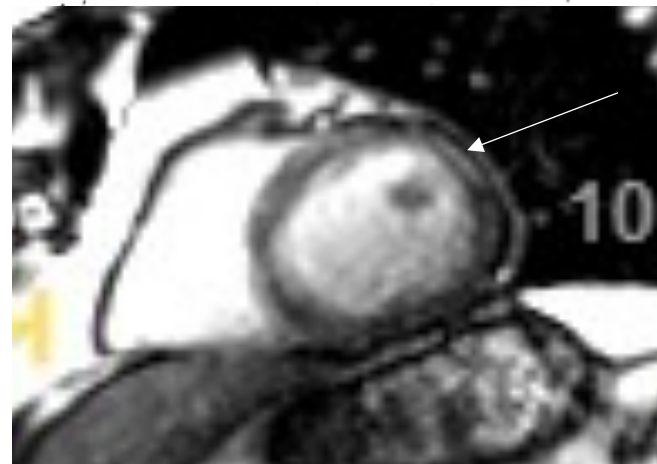
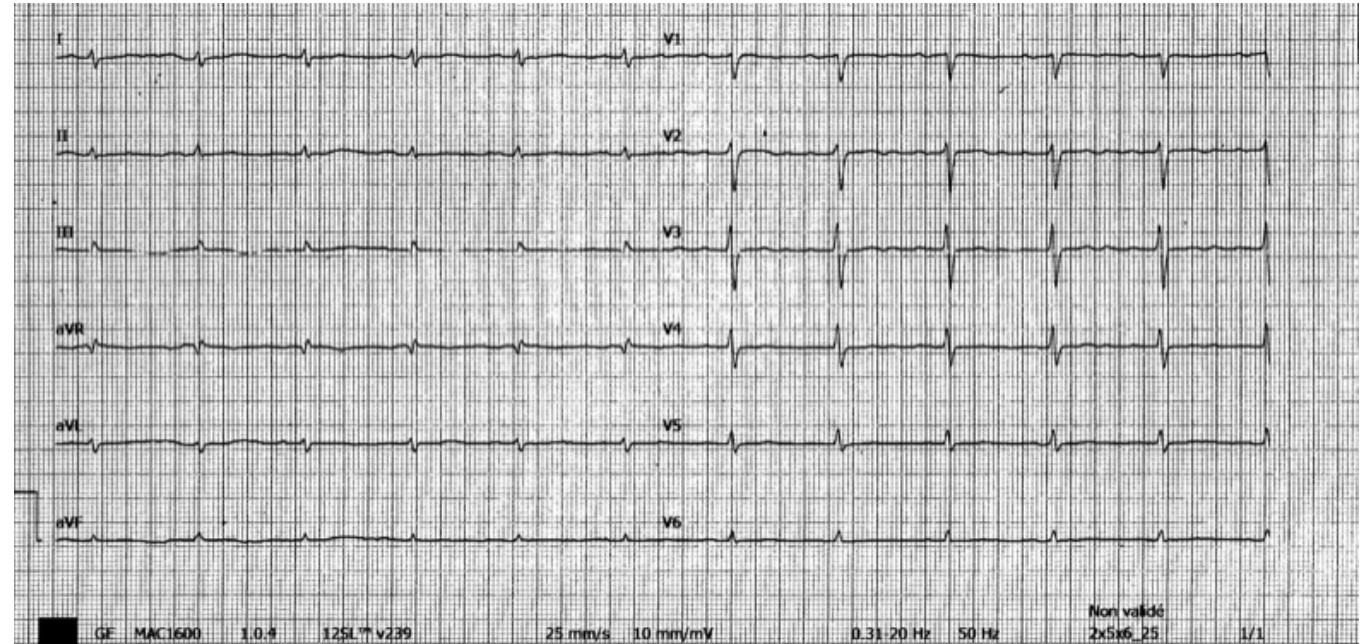
Last 2 years

- Grant/Research Support: No
- Consulting Fees/Honoraria: No
- Major Stock Shareholder/Equity: No
- Royalty Income: No
- Ownership/Founder: No
- Intellectual Property Rights: No
- Other Financial Benefit: Boehringer Ingelheim, Astra-Zeneca (congress support)

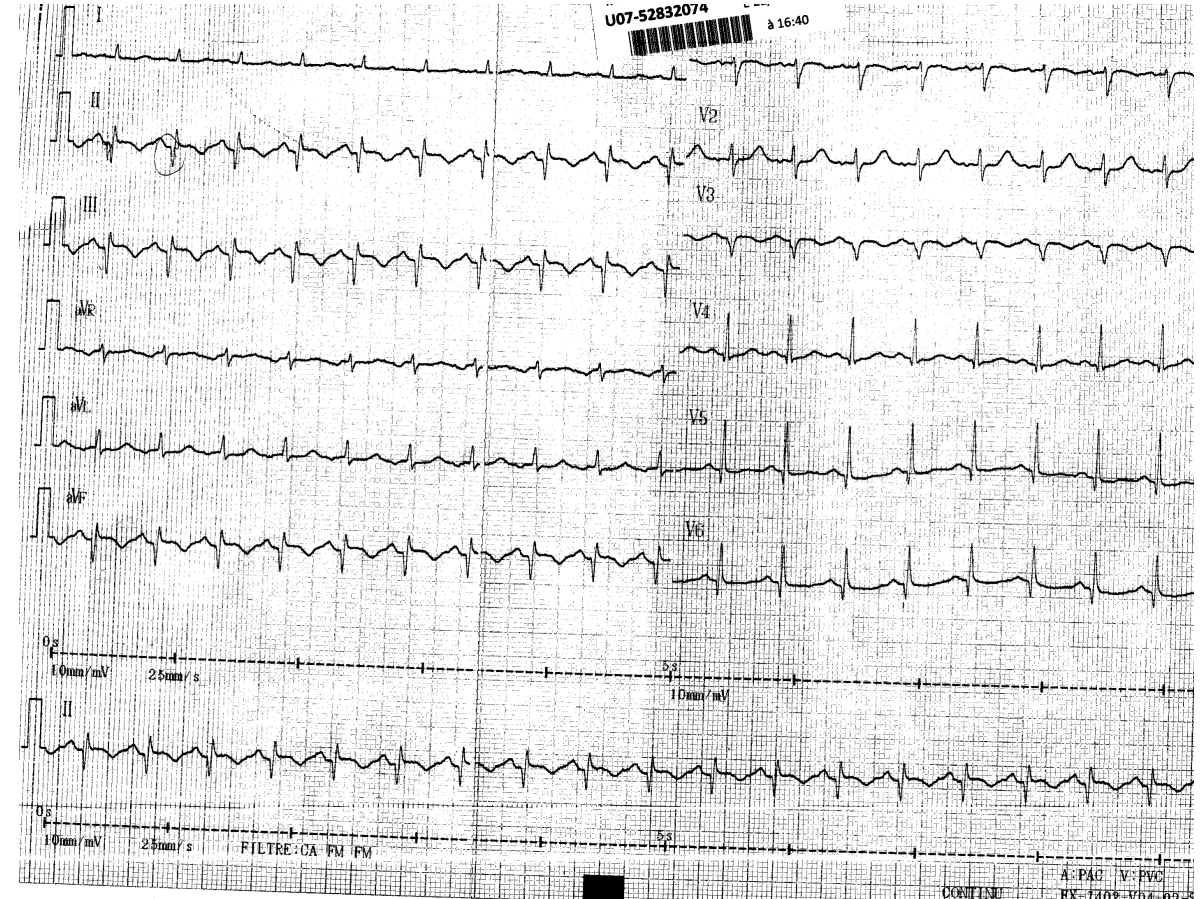
- Homme 71 ans
- HTA, SAOS
- Mélanome stade IV
- Anti-PDL-1 (atezolizumab) + Anti-Mek (cobimetinib)
- Puis Anti-CTLA-4 (ipilimumab) 2 injections
- Malaise - Dyspnée



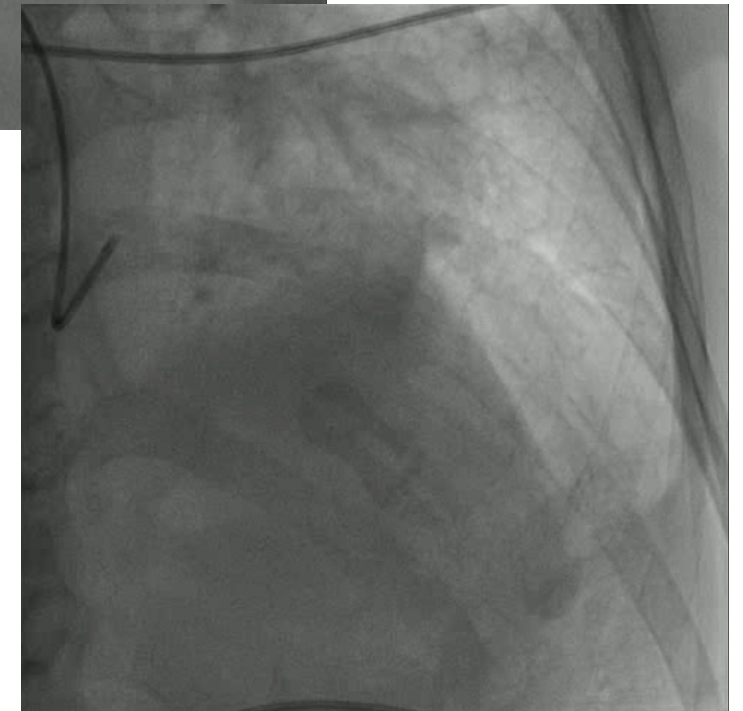
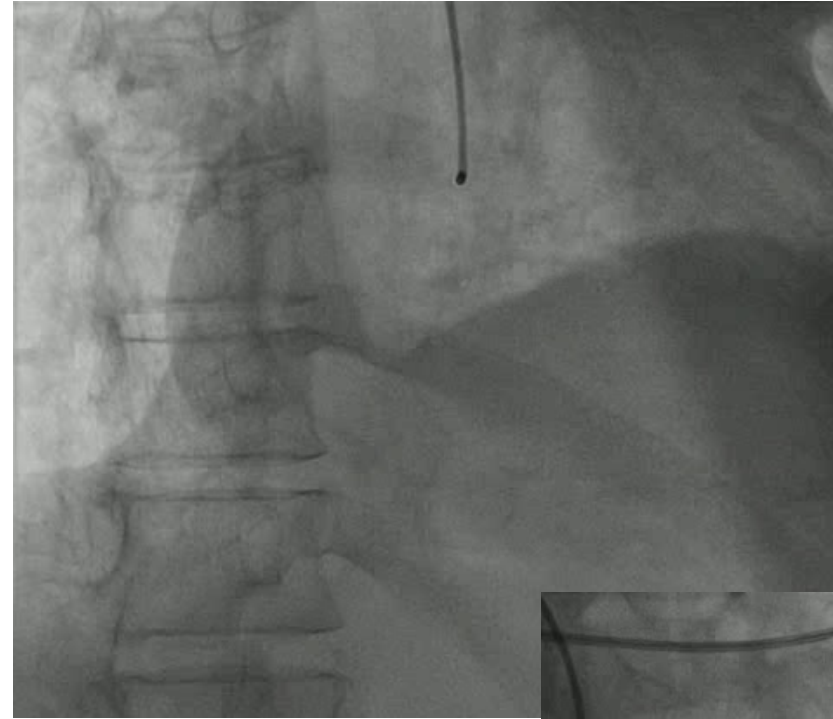
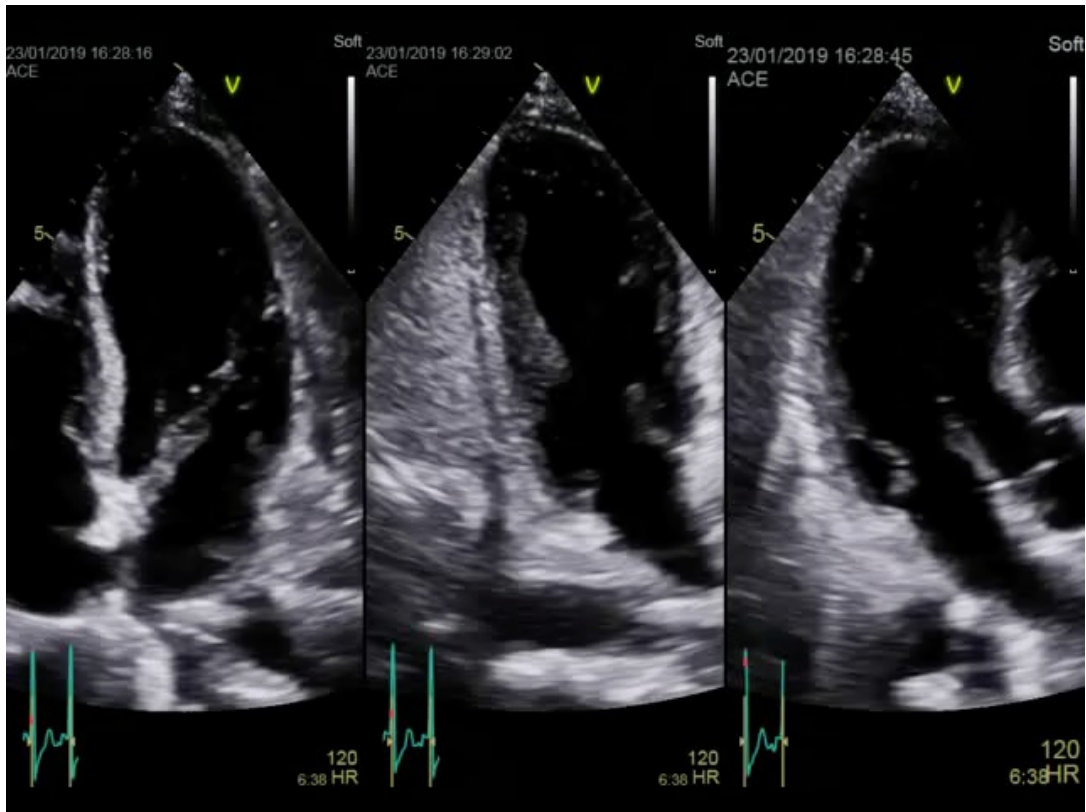
- 2 CEE
 - cTnT=45 ng/L
 - Coronarographie normale
 - ETT: FeVG-55%
 - IRM: myocardite
 - Corticothérapie
 - Arrêt définitif de l'immunothérapie
- > Progression du mélanome



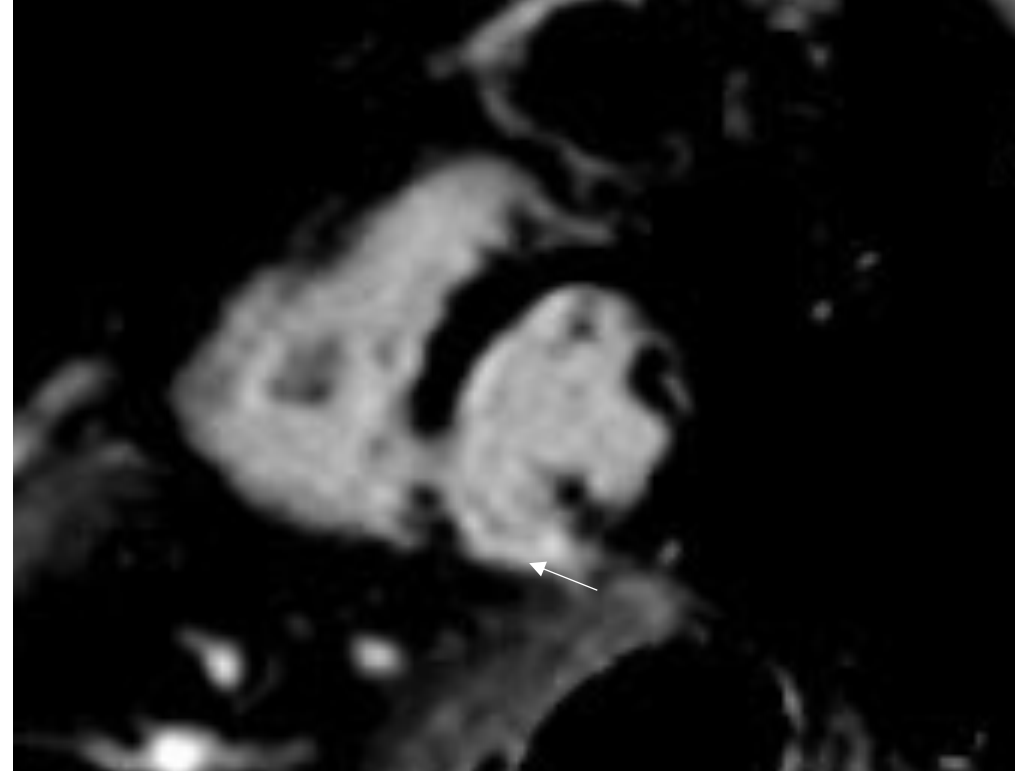
- Femme 53 ans
- C. épidermoïde bronchique
- Fdr = 0
- L1: carboplatine + docetaxel
- L2: Anti-PD-1 (nivolumab)
- L3: Anti-PDL-1 (atezolizumab) + Anti-Mek (cobimetinib)
- J5 après 1^{ère} injection : douleur thoracique



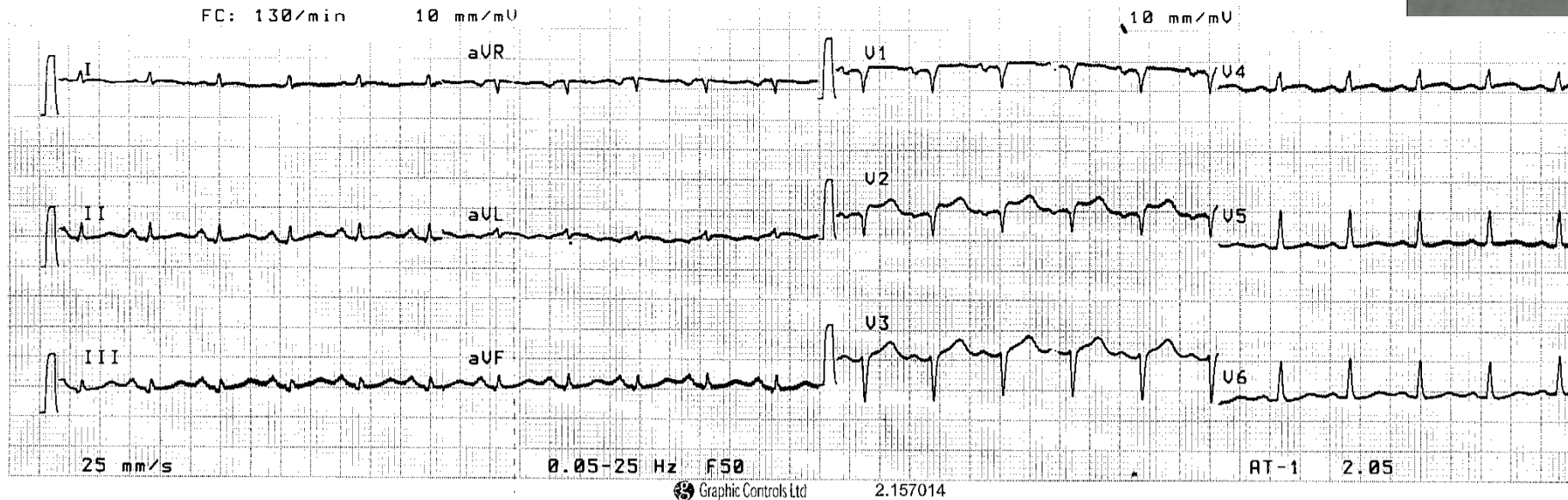
- cTnT=35 ng/L



- MINOCA
- Double anti-agrégation plaquettaire
- Autorisation 2^e injection Anti-PDL-1



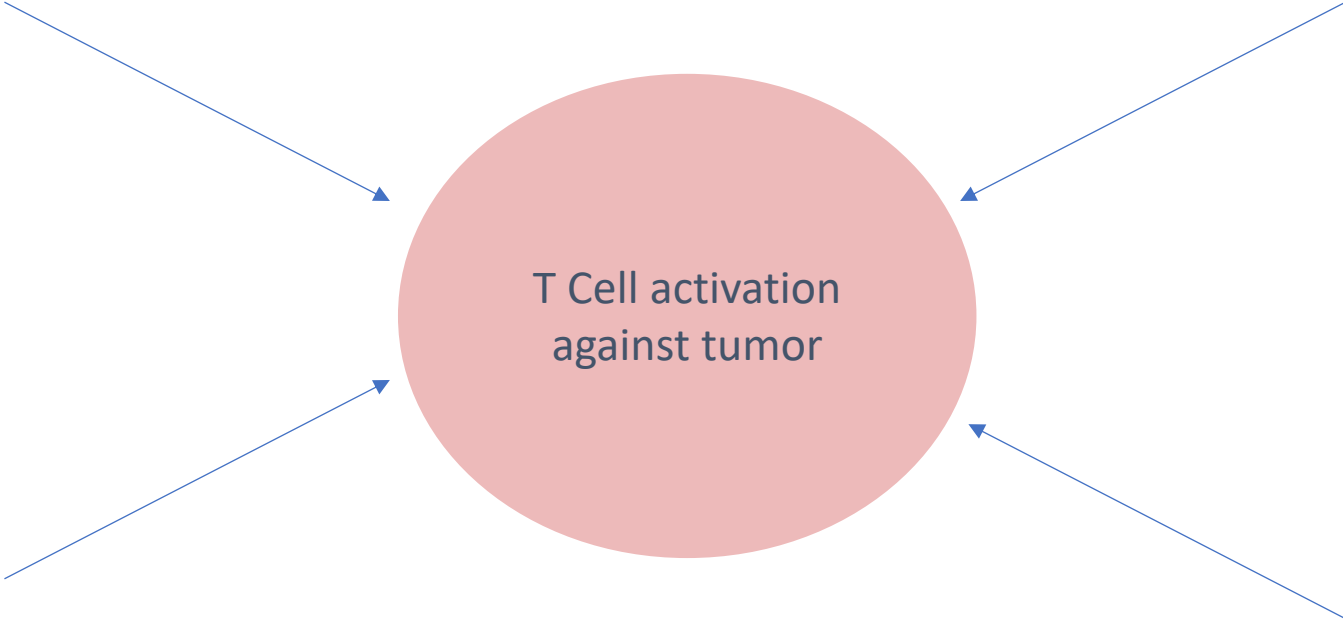
- J17 après 2^e injection
- Douleur thoracique choc cardiogénique
- STEMI



Cancer immunotherapies

Immune Checkpoint Inhibitors (ICIs)

Bispecific T Cell Engager (TCE)



T Cell activation
against tumor

Tumor-infiltrating
Lymphocytes (TIL)

Chimeric Antigen Receptor T
Cell (CAR-T) Therapy

Immune Checkpoint Inhibitors

Improved outcome in many cancers

Anti-PD1

- Nivolumab
- Pembrolizumab
- Cemiplimab

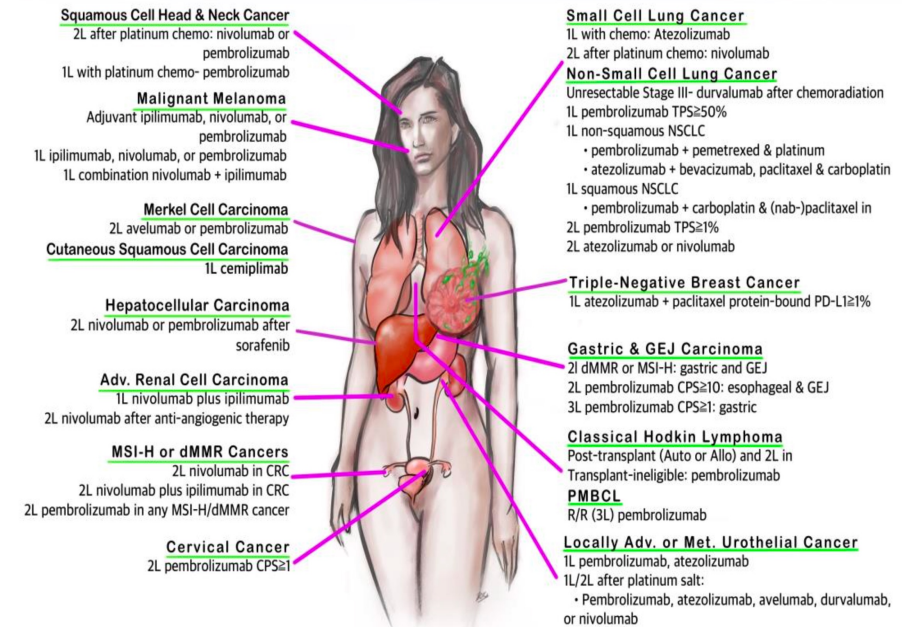
Anti-PDL1

- Avelumab
- Atezolizumab
- Durvalumab

Anti-CTLA4

- Ipilimumab
- Tremelimumab

U.S. FDA APPROVED IMMUNE-CHECKPOINT INHIBITORS

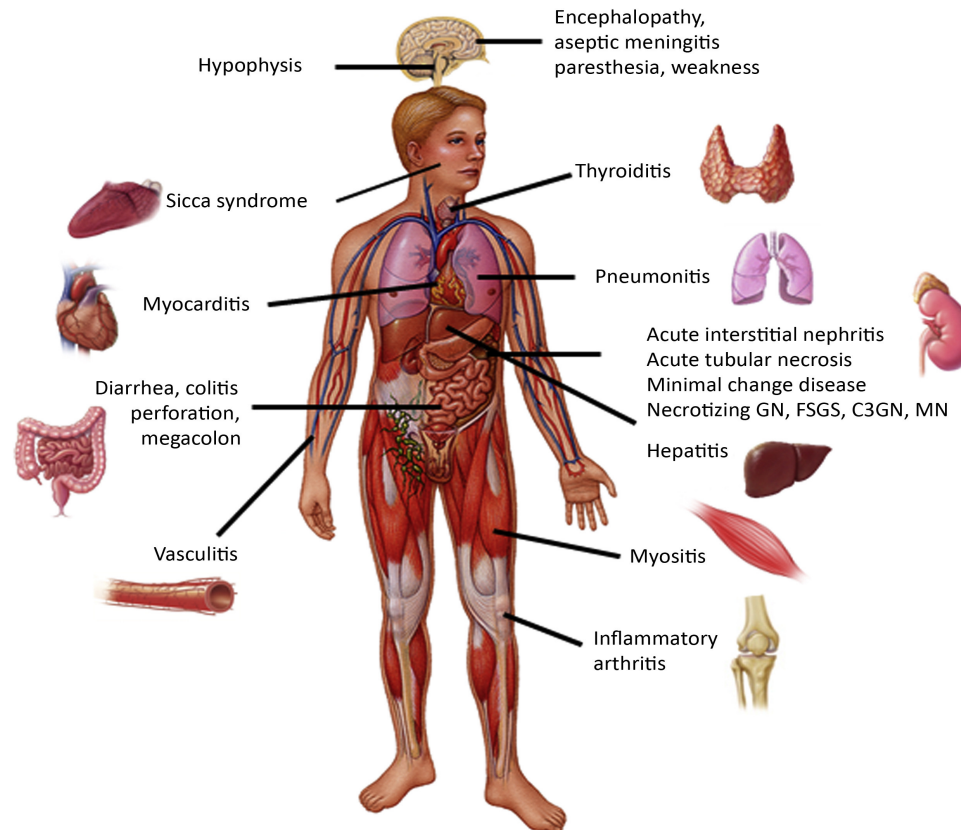


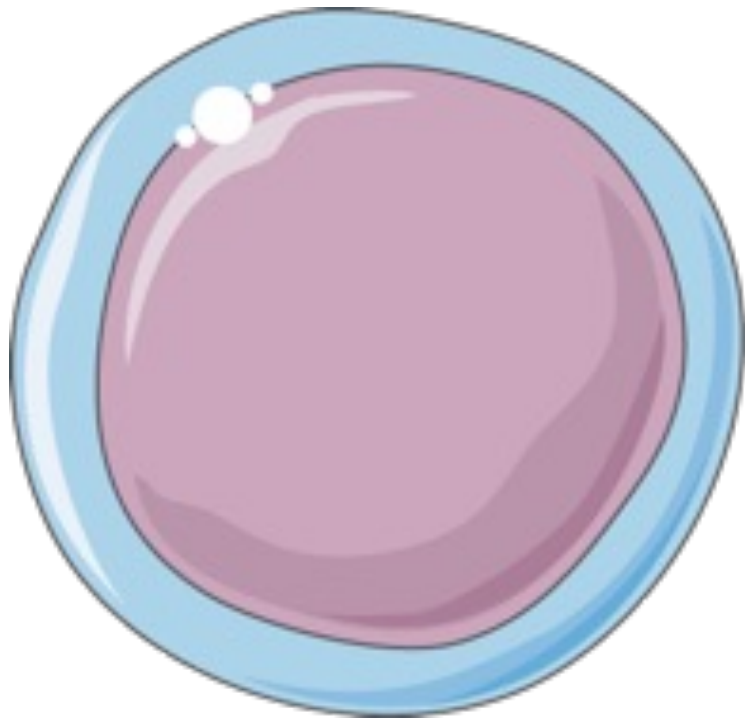
FDA-approved immune checkpoint inhibitors (copyright owned by Raju Vaddepally, et al.).

Immune Checkpoint Inhibitors Toxicity

Immune-related adverse events (irAEs)

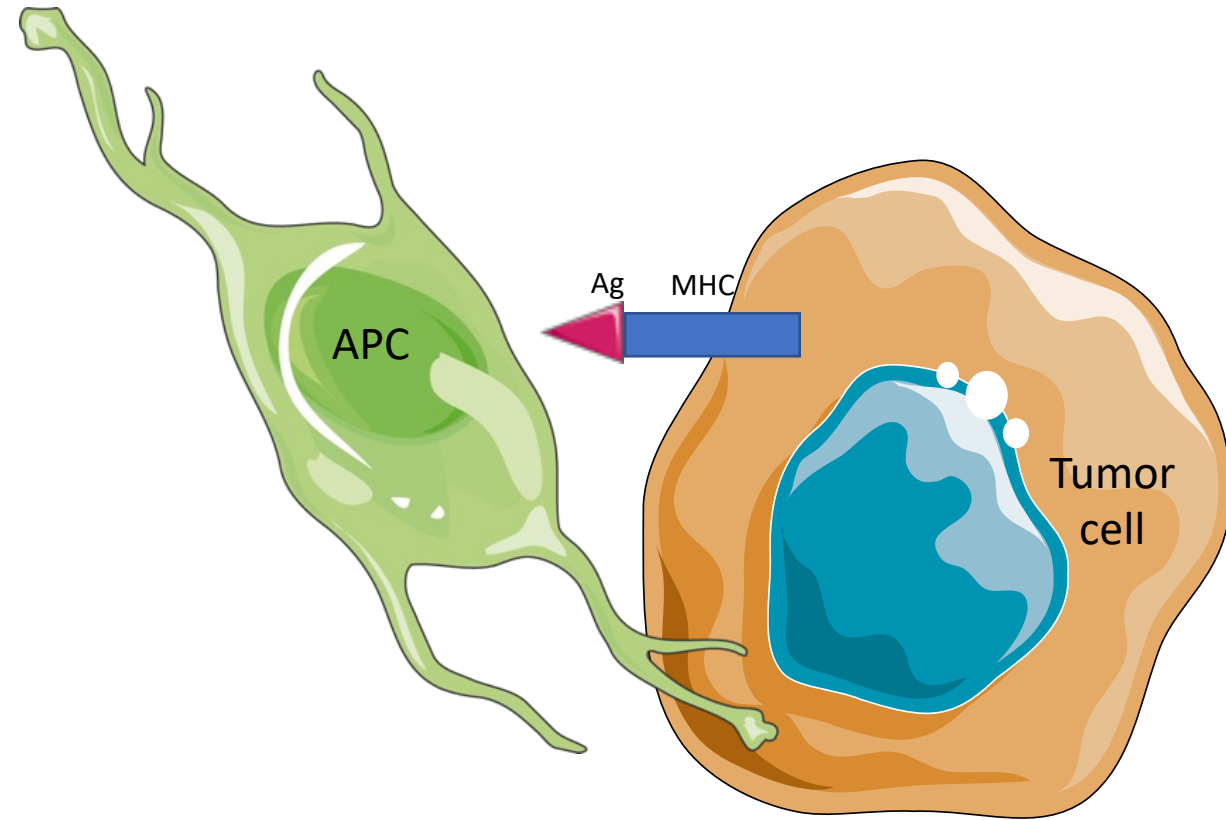
≈70%



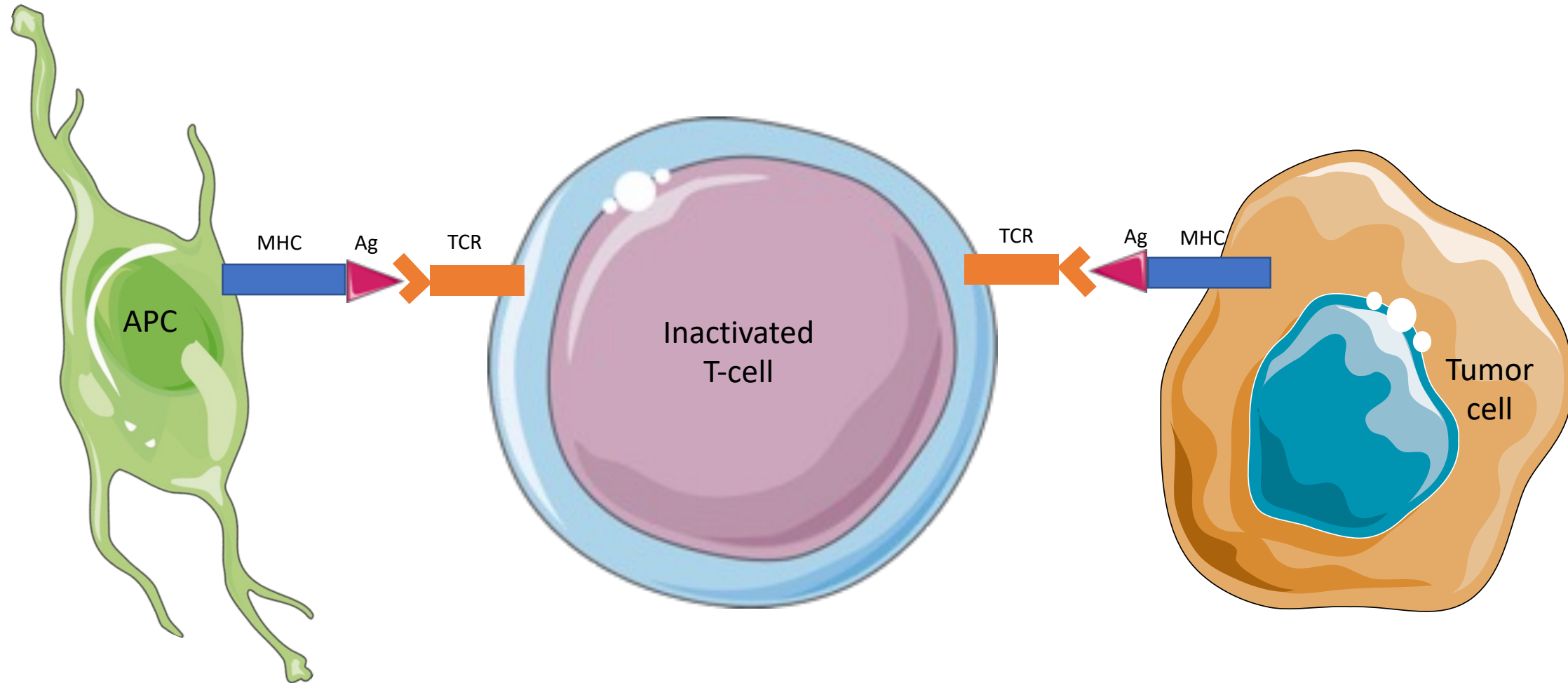


T-cell immune response
against cancer

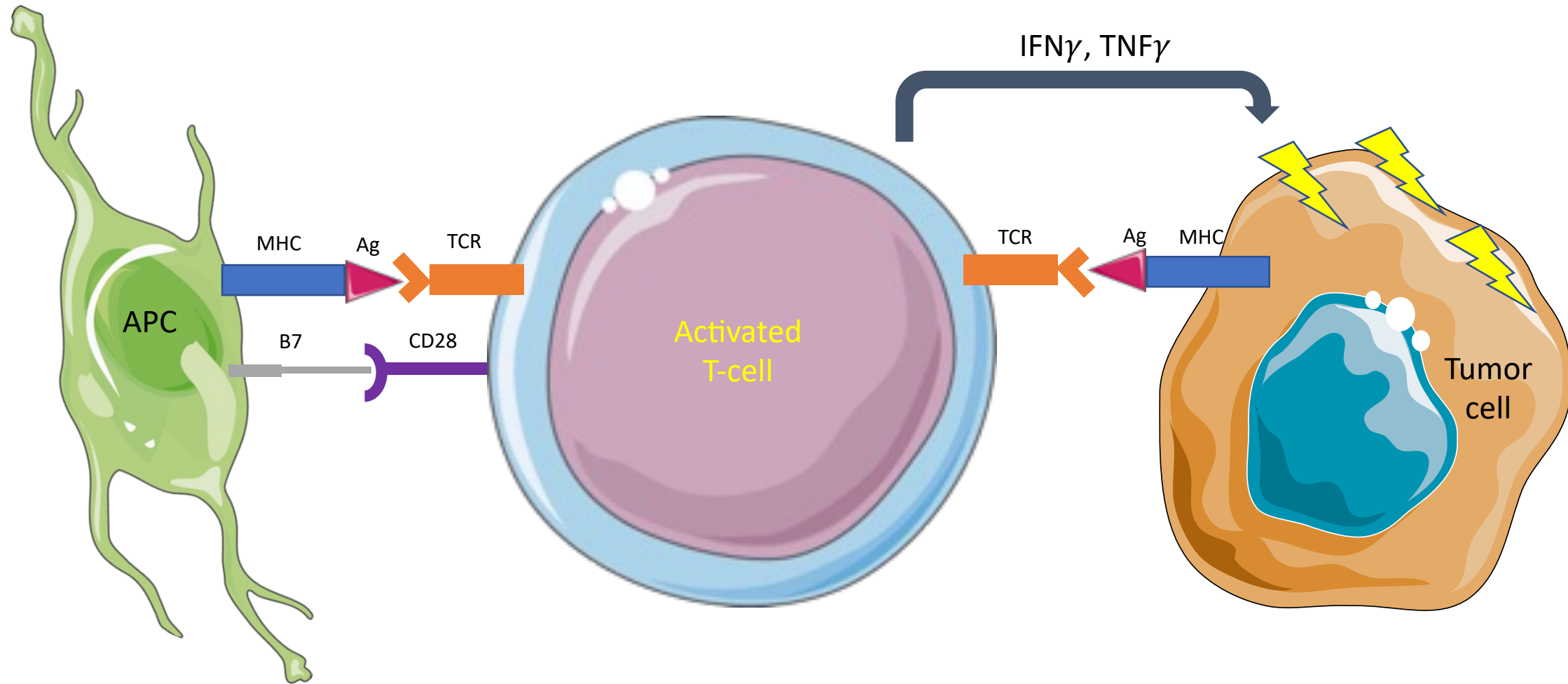
T-cell immune response



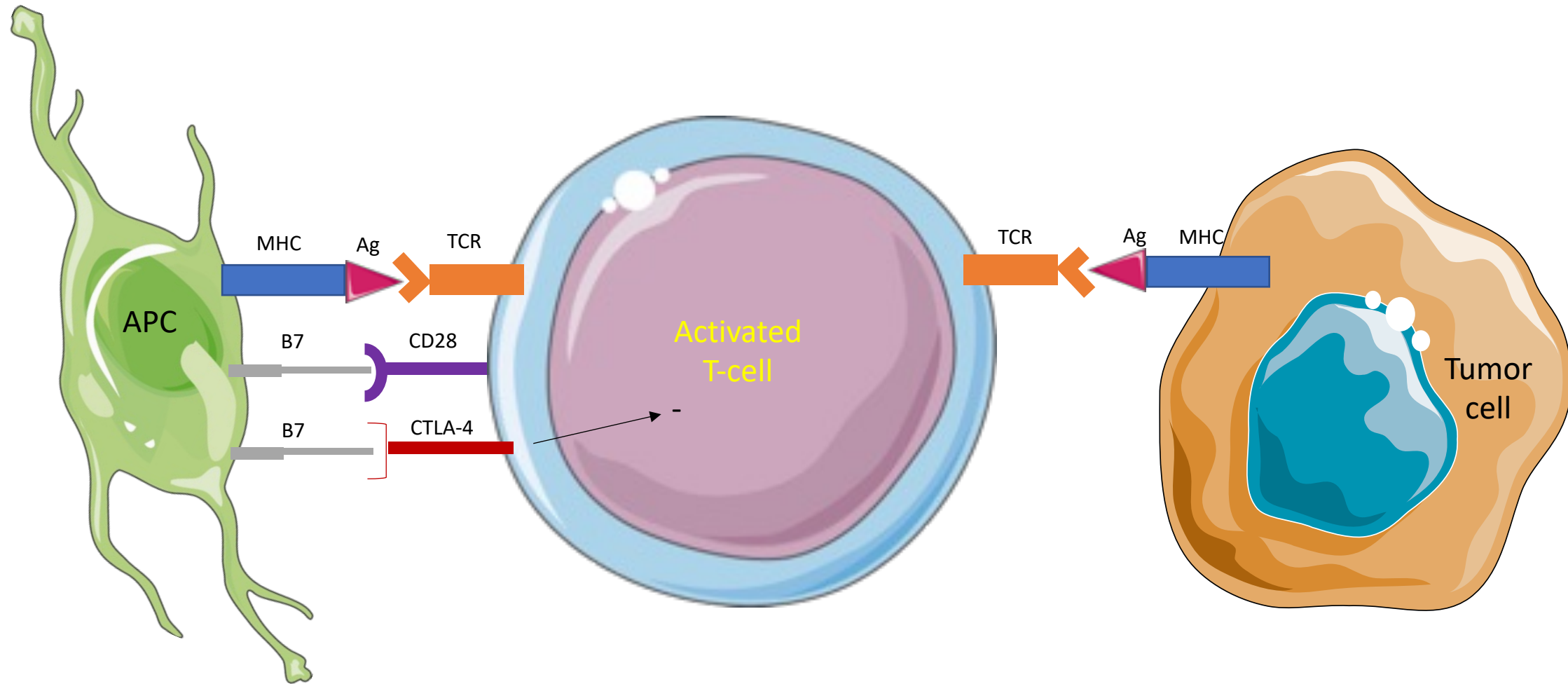
T-cell immune response



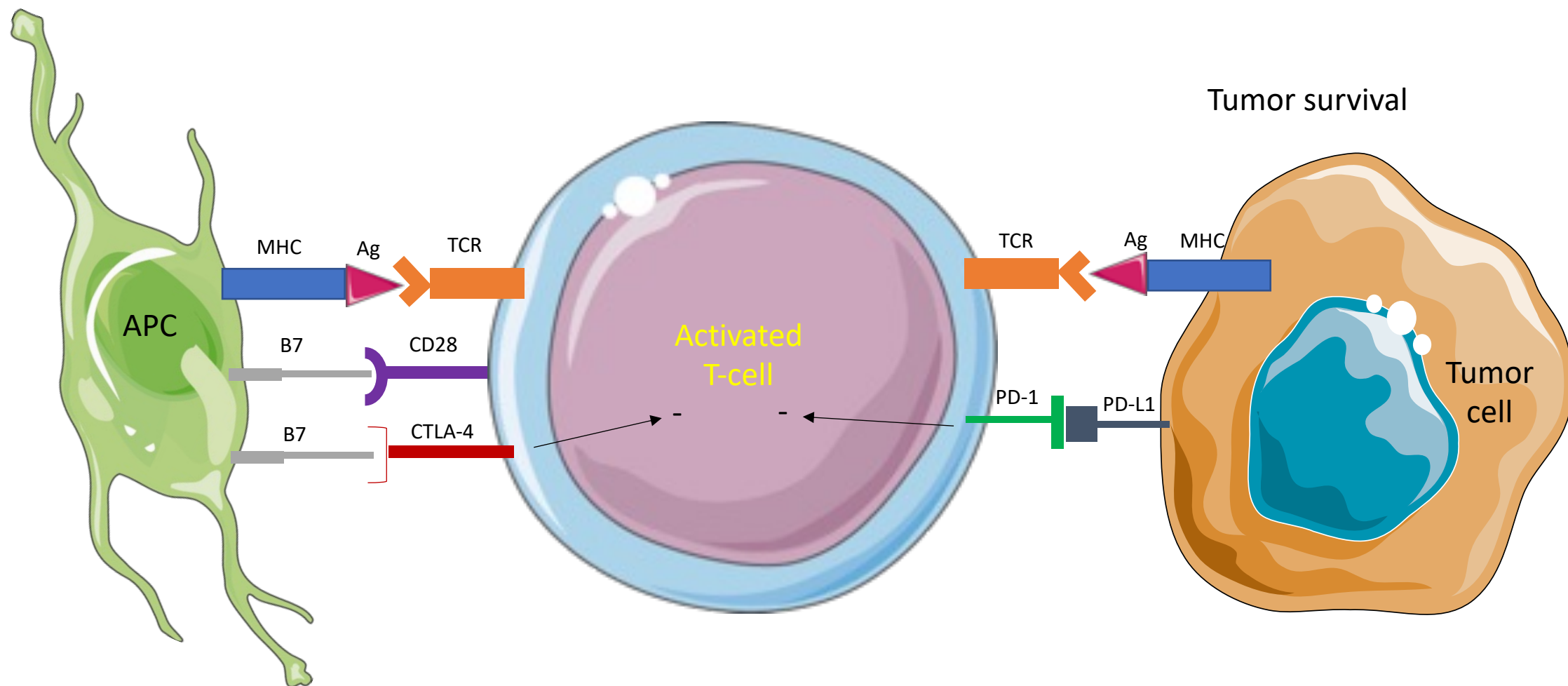
T-cell immune response



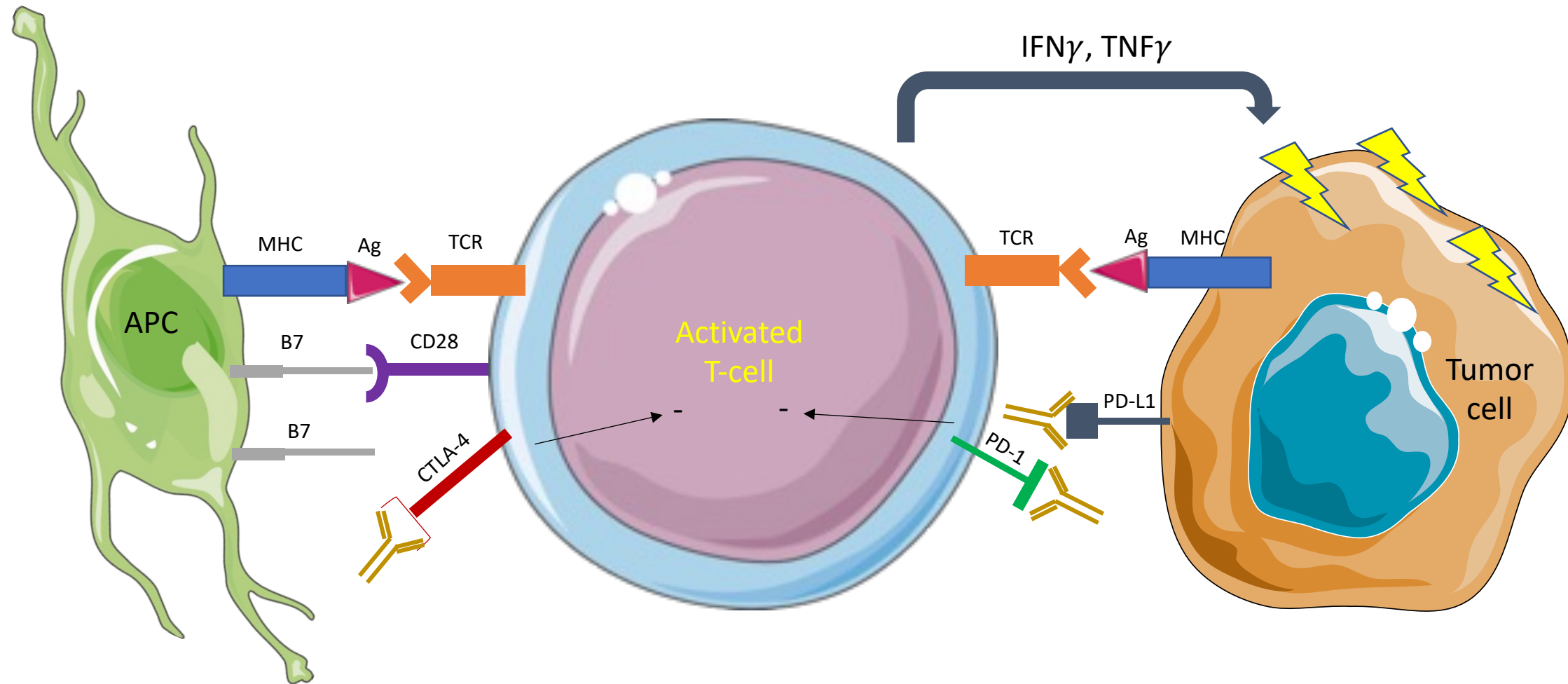
T-cell immune response



T-cell immune response



Immune Checkpoint Inhibitors



The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Fulminant Myocarditis with Combination Immune Checkpoint Blockade

Douglas B. Johnson, M.D., Justin M. Balko, Pharm.D., Ph.D., Margaret L. Compton, M.D., Spyridon Chalkias, M.D., Joshua Gorham, B.A., Yaomin Xu, Ph.D., Mellissa Hicks, Ph.D., Igor Puzanov, M.D., Matthew R. Alexander, M.D., Ph.D., Tyler L. Bloomer, M.D., Jason R. Becker, M.D., David A. Slosky, M.D., Elizabeth J. Phillips, M.D., Mark A. Pilkinton, M.D., Ph.D., Laura Craig-Owens, M.D., Nina Kola, M.D., Gregory Plautz, M.D., Daniel S. Reshef, M.D., M.P.H., Ph.D., Jonathan S. Deutsch, M.D., Raquel P. Deering, Ph.D., Benjamin A. Olenchock, M.D., Ph.D., Andrew H. Lichtman, M.D., Dan M. Roden, M.D., Christine E. Seidman, M.D., Igor J. Koralnik, M.D., Jonathan G. Seidman, Ph.D., Robert D. Hoffman, M.D., Ph.D., Janis M. Taube, M.D., Luis A. Diaz, Jr., M.D., Robert A. Anders, M.D., Jeffrey A. Sosman, M.D., and Javid J. Moslehi, M.D.



Acute Coronary Syndrome With Immune Checkpoint Inhibitors: A Proof-of-Concept Case and Pharmacovigilance Analysis of a Life-Threatening Adverse Event

Jennifer Cautela, MD,^{a,b,c} Franck Rouby, MD,^d Joe-Elie Salem, MD, PhD,^e Joachim Alexandre, MD, PhD,^{f,g,h} Ugo Scemama, MD,ⁱ Charles Dolladille, MD,^{f,g,h} Ariel Cohen, MD, PhD,^j Franck Paganelli, MD, PhD,^{a,c} Stéphane Ederhy, MD,^j and Franck Thuny, MD, PhD^{a,b,c}



Takotsubo-Like Syndrome in Cancer Patients Treated With Immune Checkpoint Inhibitors

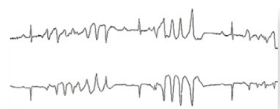
Stephane Ederhy, MD,^{a,b} Jennifer Cautela, MD,^{c,d,e} Yann Ancedy, MD,^{a,b} Marion Escudier, MD,^{c,d,e} Franck Thuny, MD, PhD,^{c,d,e} Ariel Cohen, MD, PhD^{a,b}



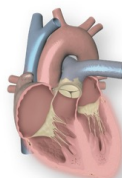
ICI-Related Cardiovascular Events

Pharmacovigilance data

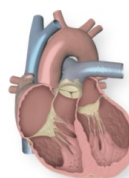
Arrhythmias



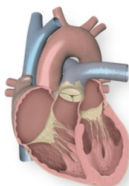
Myocarditis



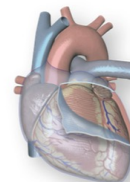
Non-inflammatory HF



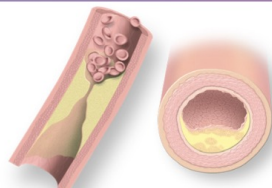
Takotsubo syndrome



Pericarditis



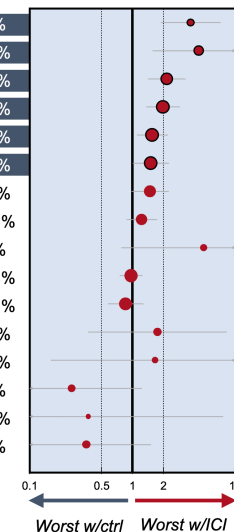
Vascular



ACS, stroke, vasculitis

Dyslipidemia

Reaction	n/N ICI	n/N ctrl	Peto OR (95%CI)	N stud/I2
Dyslipidemia	39/2,047	2/934	3.68 (1.89-7.19)	4/0%
Myocarditis	14/5,366	1/4,089	4.42 (1.56-12.50)	12/0%
Pericardial diseases	71/9,263	22/6,873	2.16 (1.42-3.29)	24/0%
Heart Failure	89/11,714	29/8,088	1.98 (1.36-2.88)	32/0%
Cerebral arterial ischemia	98/12,336	41/8,703	1.56 (1.10-2.20)	33/0%
Myocardial infarction	70/12,698	31/8,880	1.51 (1.01-2.26)	31/0%
Cardiac death or shock	67/11,943	29/8,122	1.48 (0.98-2.25)	30/0%
Hypertension	498/9,479	295/6,212	1.23 (0.87-1.73)	23/73%
Endocardial disorders	5/2,880	0/1,619	4.93 (0.78-31.29)	5/0%
Venous thromboembolic events	246/13,965	172/9,757	0.97 (0.75-1.26)	39/28%
Cardiac supra-ventricular arrhythmias	98/13,028	65/8,860	0.86 (0.57-1.28)	34/24%
Cardiac ventricular arrhythmias	6/3,368	2/2,176	1.75 (0.37-8.31)	8/13%
Torsade de pointes / QT prolongation	3/1,720	1/1,091	1.66 (0.16-17.26)	4/23%
Pulmonary hypertension and rel. card. inv.	2/2,710	5/1,696	0.26 (0.05-1.23)	6/3%
Cardiac valve disorders	1/1,769	2/1,363	0.37 (0.02-7.64)	3/41%
Cardiac conductive disorders	3/3,832	5/2,427	0.36 (0.08-1.51)	8/0%

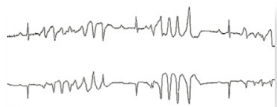


ICI-Related Cardiovascular Events

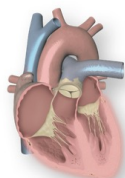
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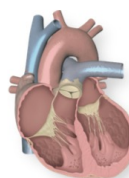
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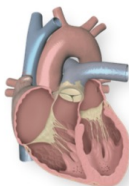
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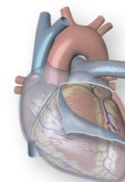
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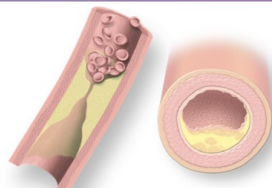
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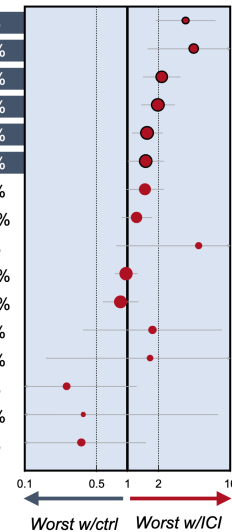
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ACS, stroke, vasculitis

Dyslipidemia

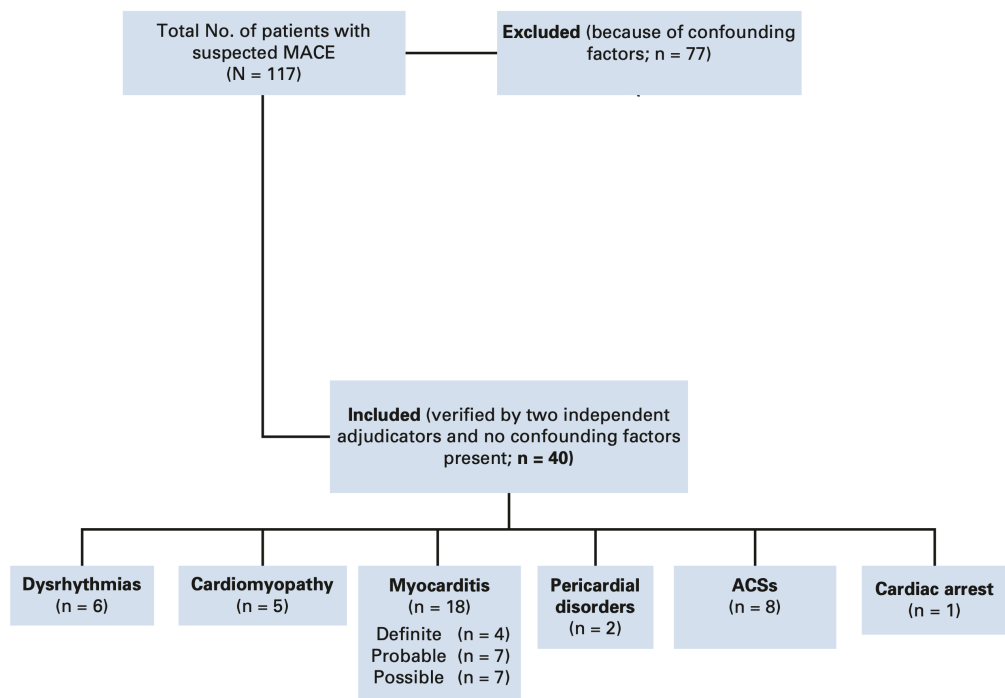
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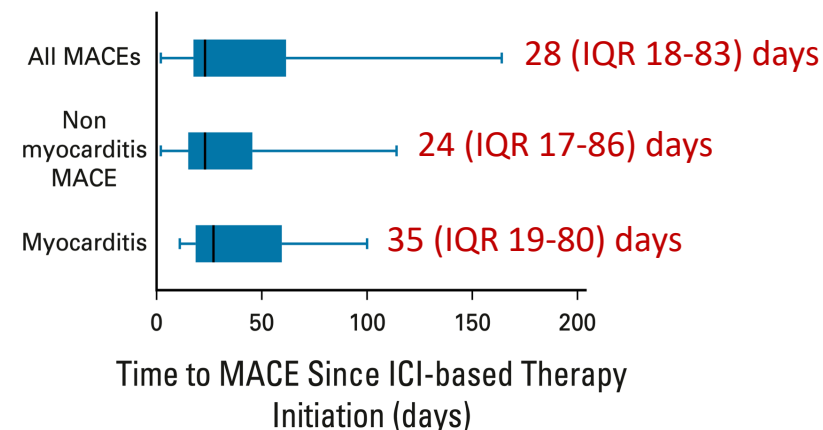
Mortality in ICI-related myocarditis = 50%

Trials' pooled analysis

All MACEs = **0.6%**
(Myocarditis = **0.26%**)



- Single-agent anti-PD(L)1: **0.47%**
- anti-PD(L)1 + anti-CTLA-4: **0.90%**
- anti-PD(L)1 + targeted therapy: **2.1%**
- anti-PD(L)1 + chemotherapy: **0.83%**

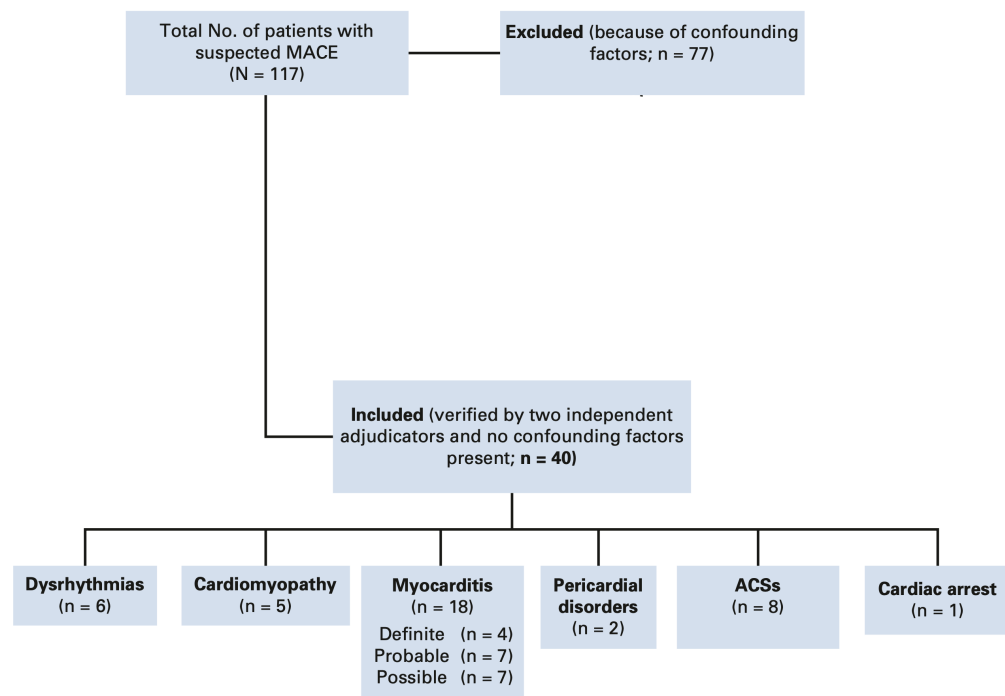


ICI-Related Cardiovascular Events

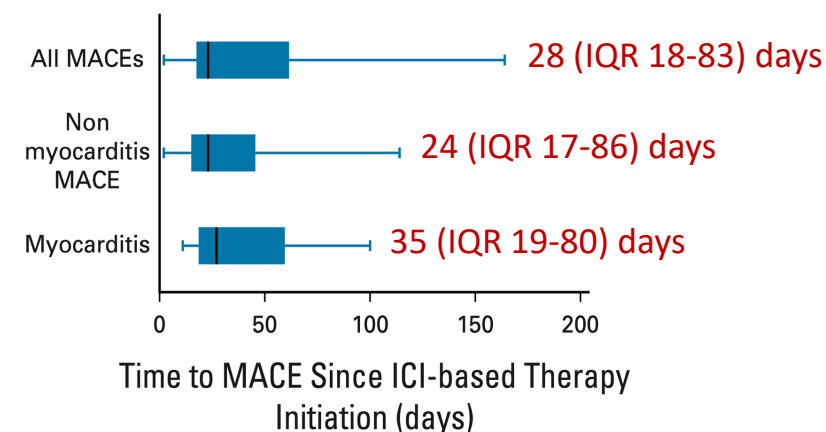
Trials' pooled analysis

All MACEs = **0.6%**
(Myocarditis = **0.26%**)

Mortality in ICI-related myocarditis = **22%**



- Single-agent anti-PD(L)1: **0.47%**
- anti-PD(L)1 + anti-CTLA-4: **0.90%**
- anti-PD(L)1 + targeted therapy: **2.1%**
- anti-PD(L)1 + chemotherapy: **0.83%**

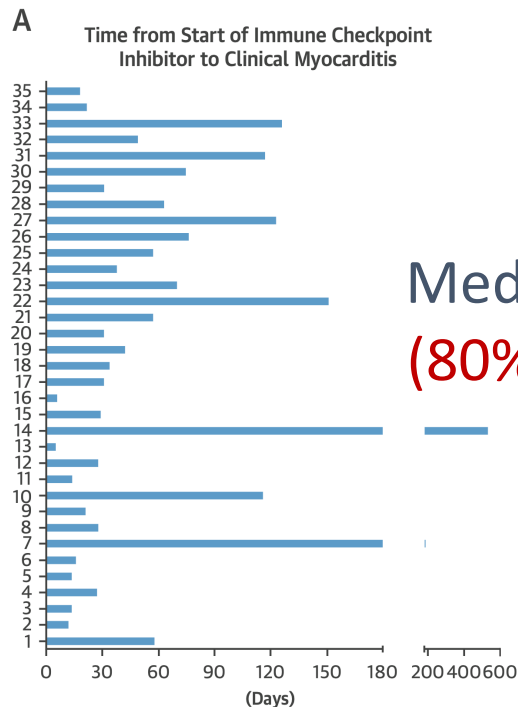




ICI-Related Cardiovascular Events

Real life data
FU = 4 years

Myocarditis = 1.14%



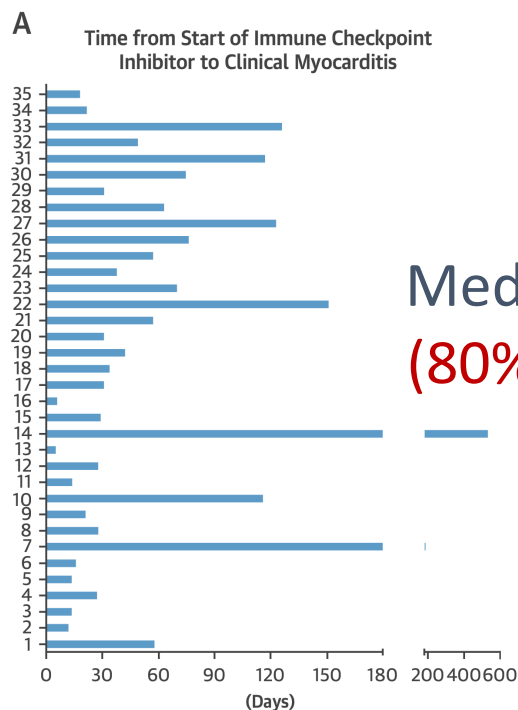
- Single-agent anti-PD1: 0.5%
- Single-agent anti-PDL1: 2.4%
- Single-agent anti-CTLA4: 3.3%
- anti-PD1 + anti-CTLA-4: 2.4%

ICI-Related Cardiovascular Events

Real life data
FU = 4 years

Myocarditis = 1.14%

CV Mortality = 17%



- Single-agent anti-PD1: 0.5%
- Single-agent anti-PDL1: 2.4%
- Single-agent anti-CTLA4: 3.3%
- anti-PD1 + anti-CTLA-4: 2.4%

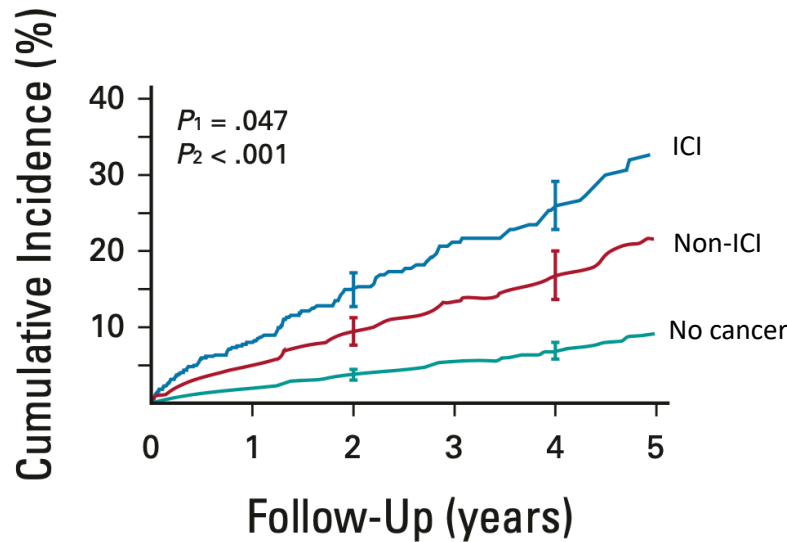


ICI-Related Cardiovascular Events

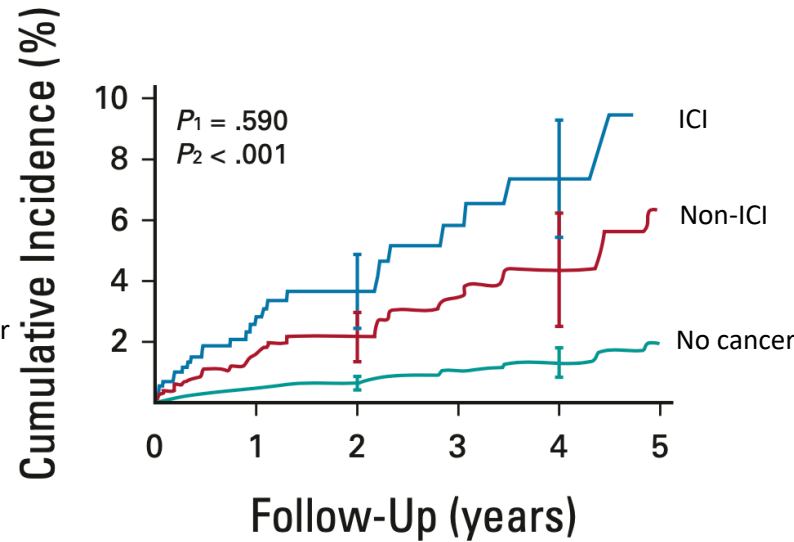
Real life data

All MACEs = 10.3%
More frequent than in non-ICI

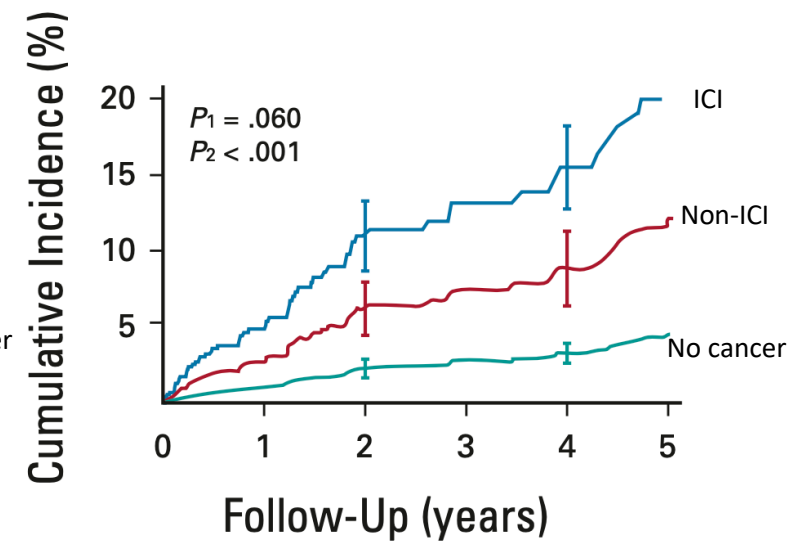
All MACEs



ACS

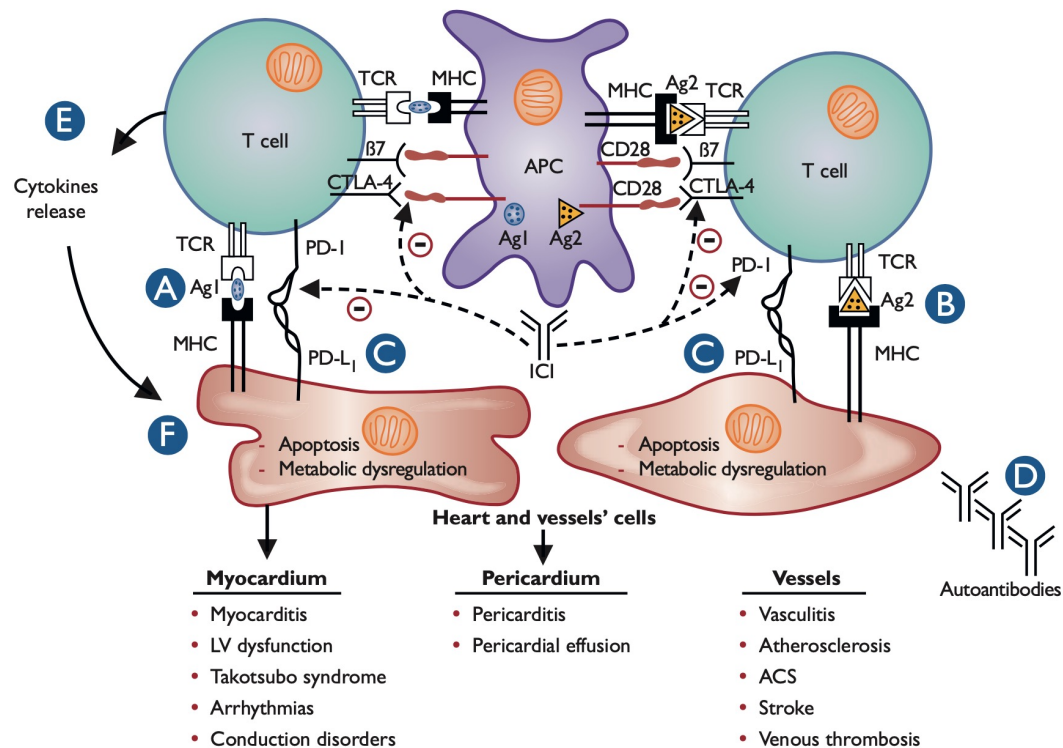


HF



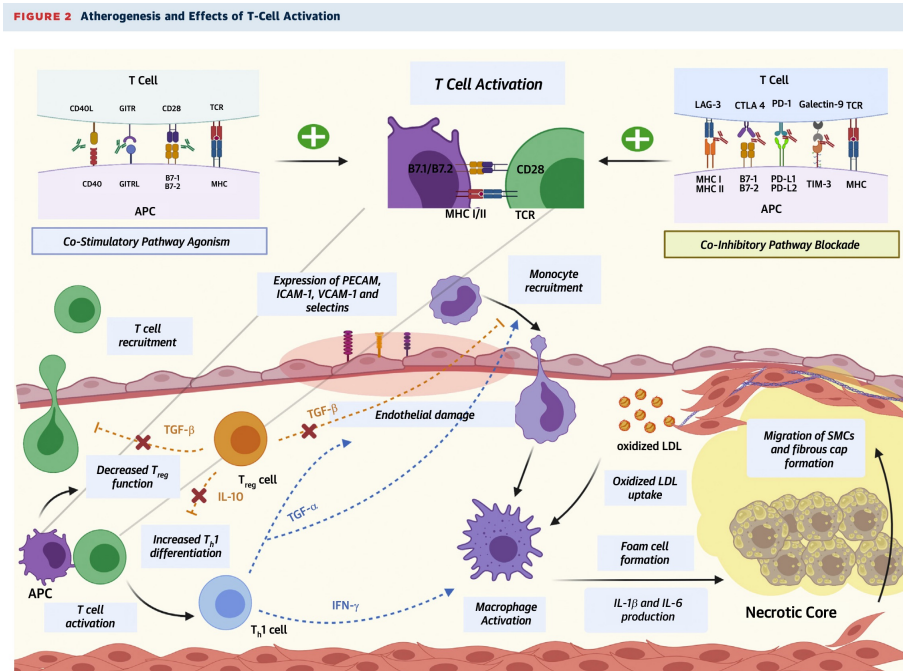
ICI-Related Cardiovascular Events

Proposed pathophysiology

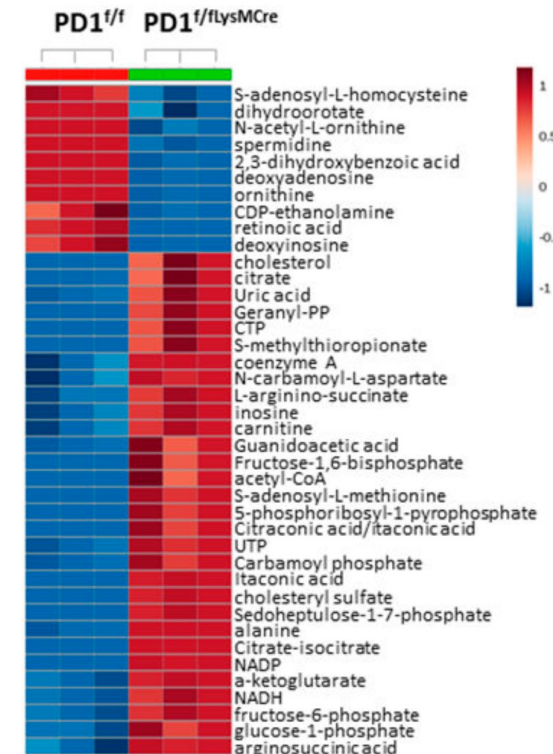


ICI-Related Cardiovascular Events

Proposed pathophysiology



Promote atherogenesis and plaque destabilization



PD-1-deficient myeloid progenitors up-regulate genes involved in lipid synthesis, mainly cholesterol, and uptake and down-regulate genes promoting cholesterol metabolism

ICI-Related Cardiovascular Events

Proposed pathophysiology

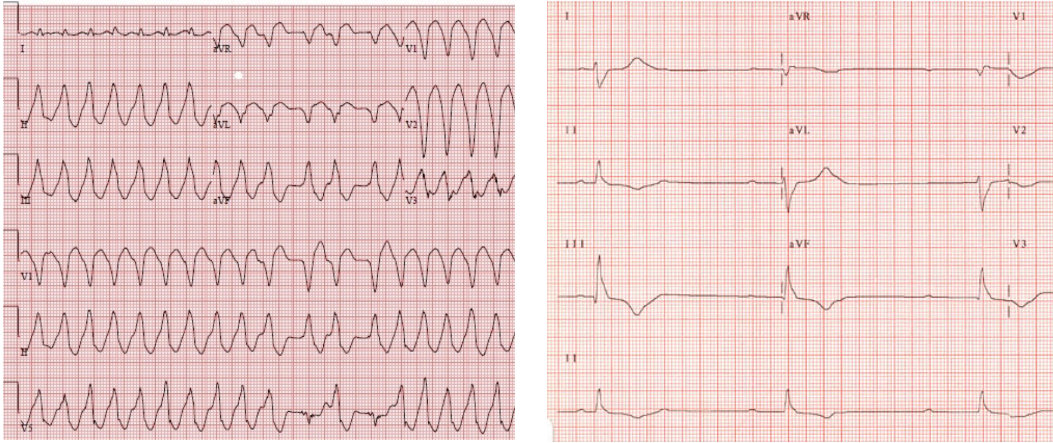


Watch out for the long-term effects

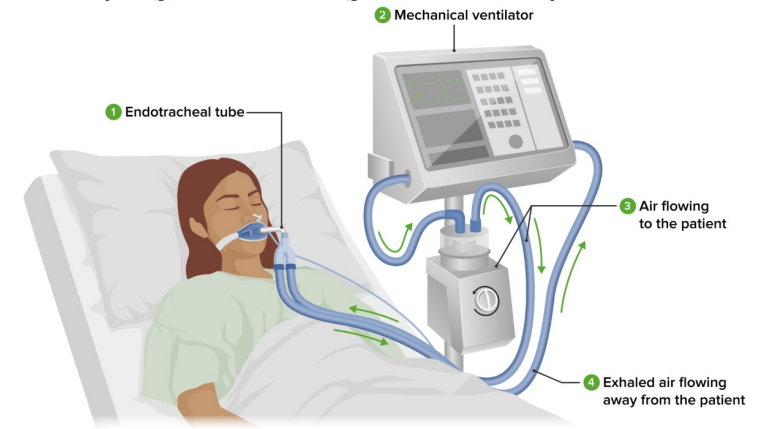
Promote atherogenesis and plaque destabilization

PD-1-deficient myeloid progenitors up-regulate genes involved in lipid synthesis, mainly cholesterol, and uptake and down-regulate genes promoting cholesterol metabolism

Ventricular arrhythmia / AV block

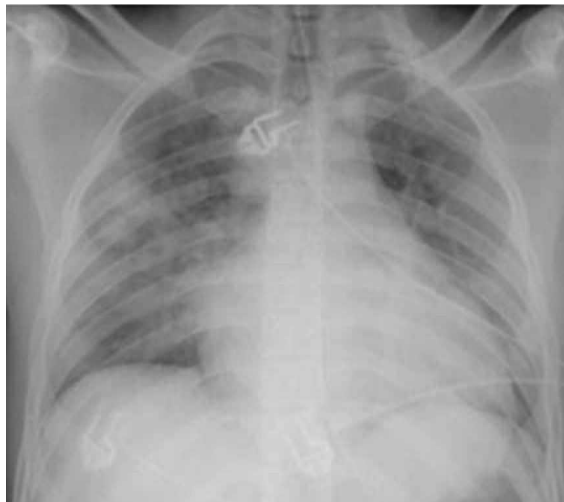


Other associated irAE (myositis/myasthenia)

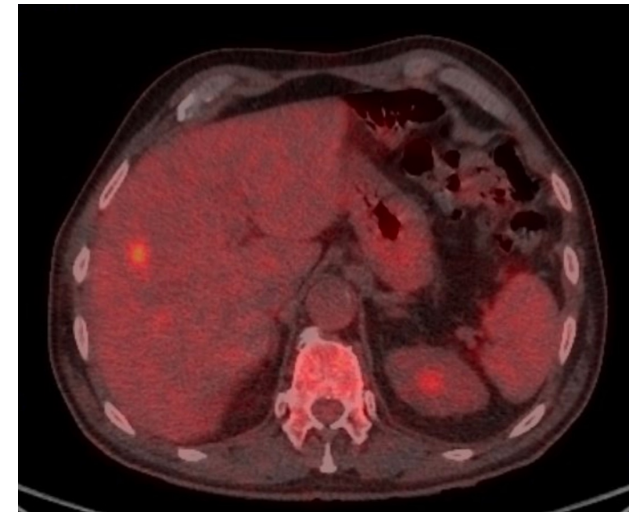


20-50% mortality rate

Heart failure

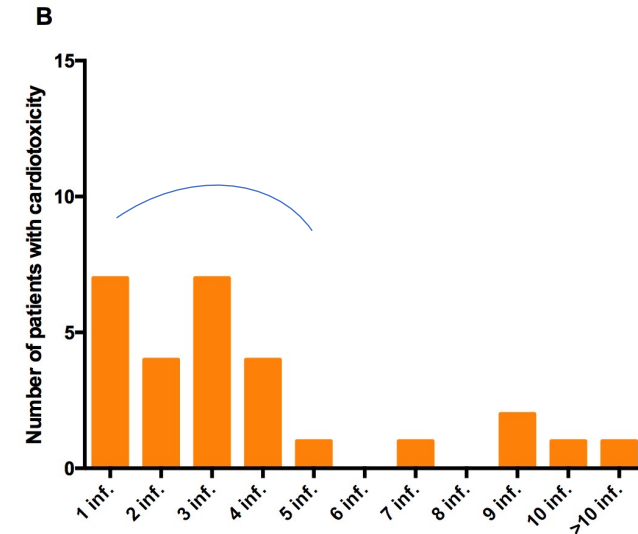
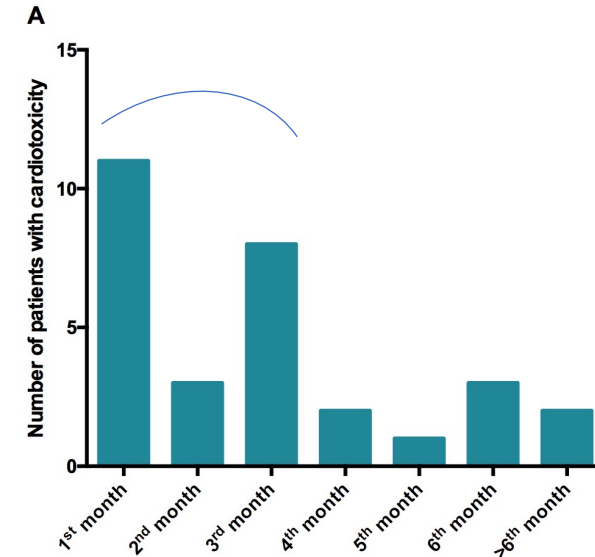


Cancer progression



ICI-Induced Myocarditis

- **1-2% of patients**
- **80% within 3 months**

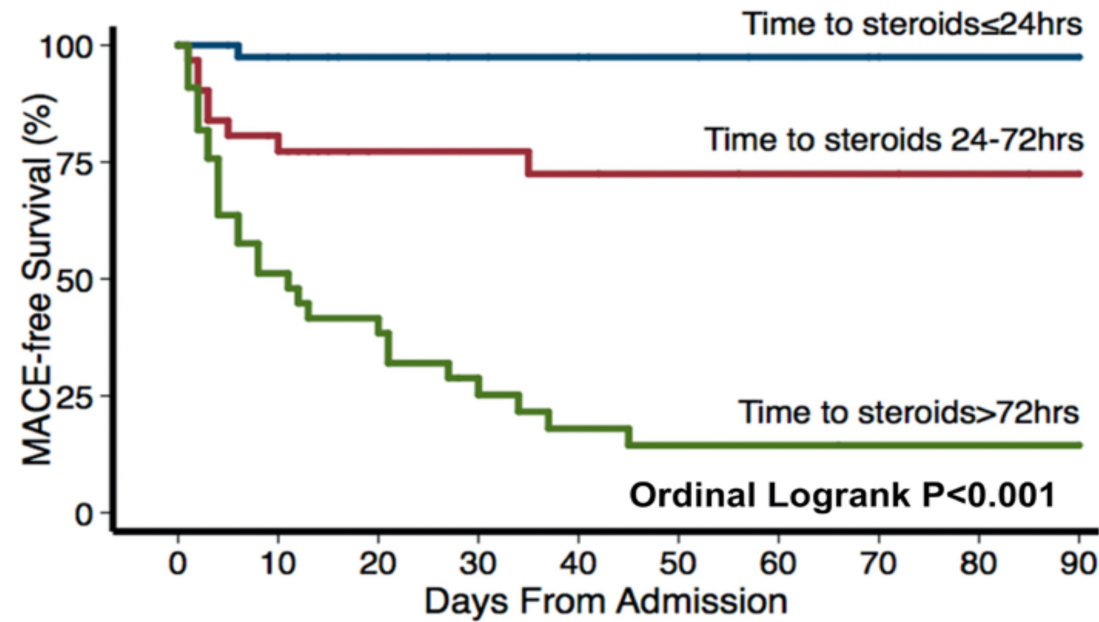


ICI-Induced Myocarditis

A Diagnostic Challenge

ICI-Induced Myocarditis – A Diagnostic Challenge

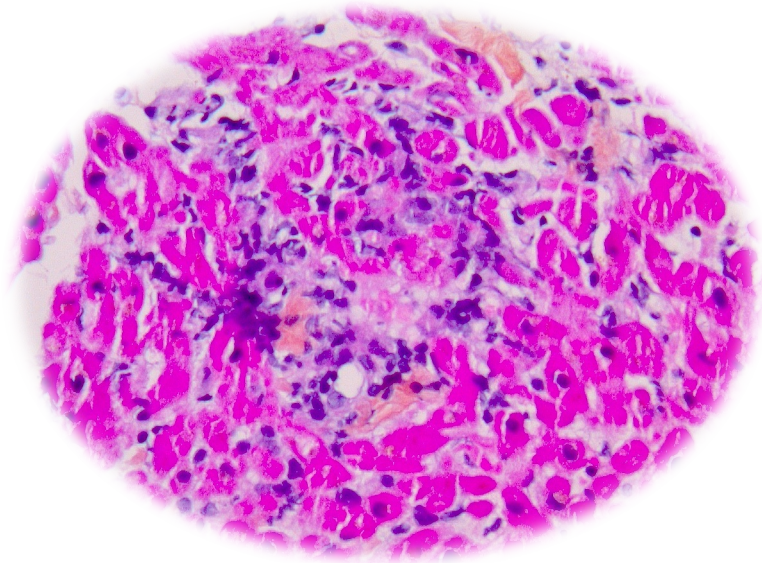
Diagnosis should be made **PROMPTLY**
and corticosteroids should be started **EARLY**



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The diagnosis of ICI-myocarditis has focused on methods traditionally used for diagnosing on non-ICI myocarditis

Endomyocardial biopsy



ESC clinical-biological-imaging criteria

Table 4 Diagnostic criteria for clinically suspected myocarditis

Clinical presentations*

Acute chest pain, pericarditic, or pseudo-ischaemic
New-onset (days up to 3 months) or worsening of: dyspnoea at rest or exercise, and/or fatigue, with or without left and/or right heart failure signs
Subacute/chronic (> 3 months) or worsening of: dyspnoea at rest or exercise, and/or fatigue, with or without left and/or right heart failure signs
Palpitation, and/or unexplained arrhythmia symptoms and/or syncope, and/or aborted sudden cardiac death
Unexplained cardiogenic shock

Diagnostic criteria

I. ECG/Holter/stress test features

Newly abnormal 12 lead ECG and/or Holter and/or stress testing, any of the following: I to III degree atrioventricular block, or bundle branch block, ST/T wave change (ST elevation or non ST elevation, T wave inversion), sinus arrest, ventricular tachycardia or fibrillation and asystole, atrial fibrillation, reduced R wave height, intraventricular conduction delay (widened QRS complex), abnormal Q waves, low voltage, frequent premature beats, supraventricular tachycardia

II. Myocardiocytolysis markers

Elevated TnT/TnI

III. Functional and structural abnormalities on cardiac imaging (echo/angio/CMR)

New, otherwise unexplained LV and/or RV structure and function abnormality (including incidental finding in apparently asymptomatic subjects): regional wall motion or global systolic or diastolic function abnormality, with or without ventricular dilatation, with or without increased wall thickness, with or without pericardial effusion, with or without endocavitary thrombi

IV. Tissue characterization by CMR

Oedema and/or LGE of classical myocarditic pattern (see text)

Clinically suspected myocarditis is if ≥ 1 clinical presentation and ≥ 1 diagnostic criteria from different categories, in the absence of: (1) angiographically detectable coronary artery disease (coronary stenosis $\geq 50\%$); (2) known pre-existing cardiovascular disease or extra-cardiac causes that could explain the syndrome (e.g. valve disease, congenital heart disease, hyperthyroidism, etc.) (see text). Suspicion is higher with higher number of fulfilled criteria.

*If the patient is asymptomatic ≥ 2 diagnostic criteria should be met.

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...but ICI-myocarditis is a NOVEL ENTITY

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HETEROGENEOUS clinical presentation

ASYMPTOMATIC with

- ECG abnormalities
- Troponin ↑
- Other irAEs

- Dyspnea
- Palpitations
- Chest pain
- Syncope
- Weakness

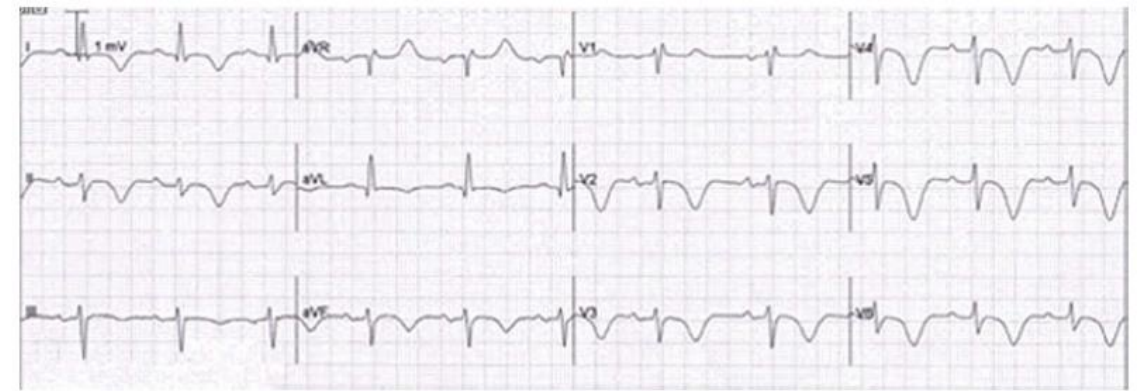
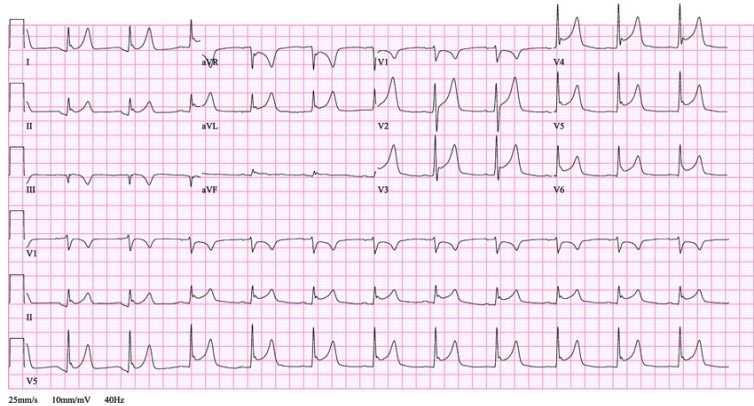
- Pulmonary edema
- Cardiogenic shock
- SV/V Arrhythmias
- Conduction abnormalities
- Takotsubo-like syndrome

- Sudden death
- HF-related death

**Myositis or pseudo-myasthenia syndrome
are associated > 30% of cases**

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No specific ECG abnormalities



Normal: 30%

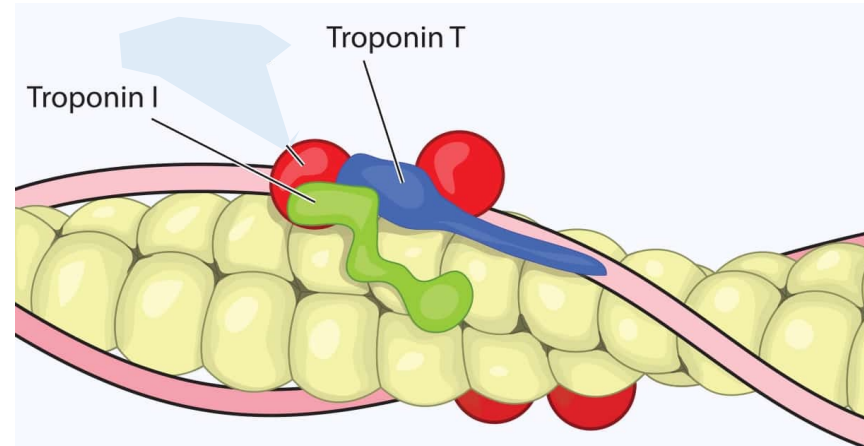
AF: 30%

Ventricular arrhythmia: 27%

AV block: 17%

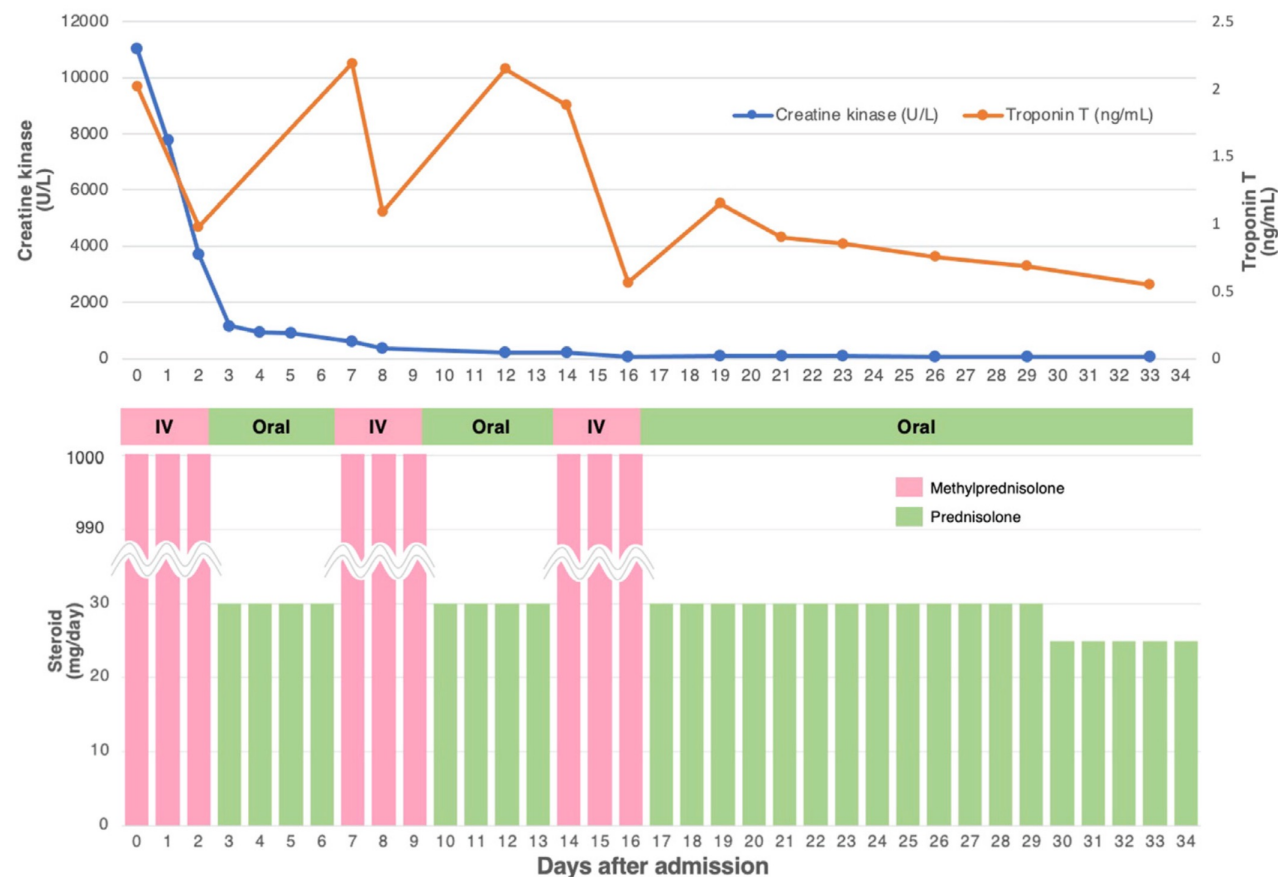
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An UNUSUAL troponin profile



- **cTnT +** (including by later generation assays) **in patients with inflammatory myopathies (including myositis) in the absence of cardiac involvement and without an increase in TnI.**
- **Regenerating skeletal muscle tissue** undergoes a phenotype switch, in which previously repressed cTnT (**along with CK-MB**) is re-expressed in adult, regenerating skeletal muscle tissue, as has been demonstrated in skeletal muscle biopsies from patients with polymyositis

An UNUSUAL troponin profile



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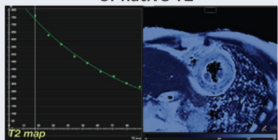
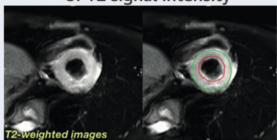
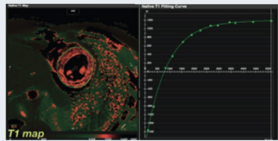
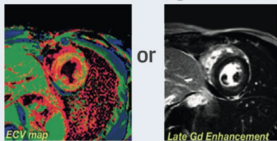
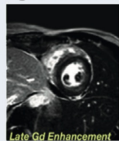
An UNUSUAL MRI profile

ICI myocarditis vs. Non-ICI myocarditis

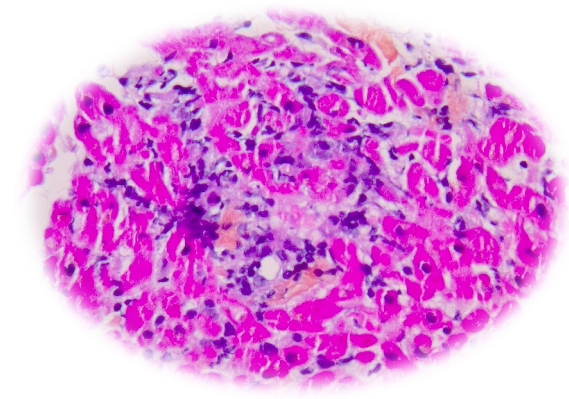
2018-LL criteria (2/2) sensitivity: **52%** vs. 88%

LGE: 56% vs. 80-98% (72% when MRI was performed after Day 4)

More frequent septal and midwall LGE in ICI-M

2018 Lake Louise Criteria		CMR Image Examples	
Main Criteria	Myocardial Edema (T2-mapping or T2W images)	Regional or global increase of native T2 	Regional or global increase of T2 signal intensity 
	Non-ischemic Myocardial Injury (Abnormal T1, ECV, or LGE)	Regional or global increase of native T1 	Regional or global increase of ECV  or Regional LGE signal increase 

More indications for EMB



Ferreira VM, et al. J Am Coll Cardiol 2018;72:3158-76

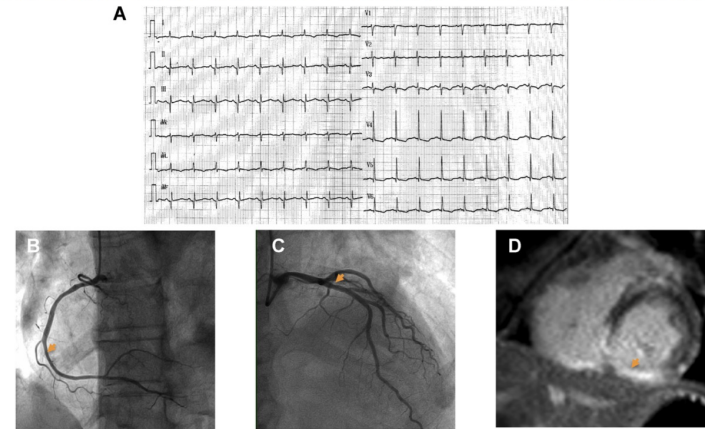
Zhang L, et al. Eur Heart J 2020;41:1733-1743

Thavendiranathan PP, et al. J Am Coll Cardiol 2021;77:1503-16

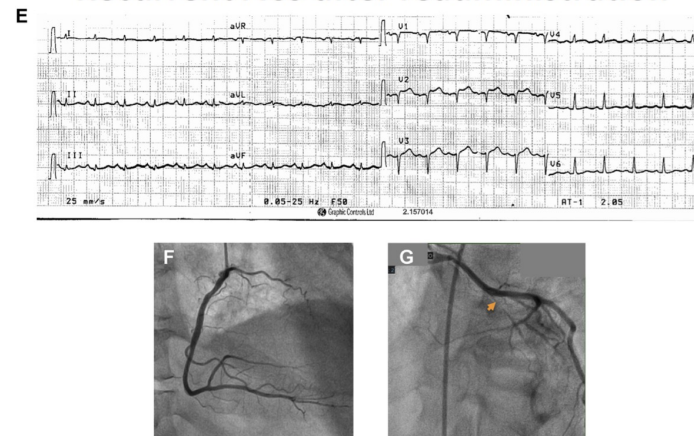
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DIFFERENTIAL diagnosis: **ACS**

ACS after first administration of PD-L1 inhibitor



Recurrent ACS after readministration

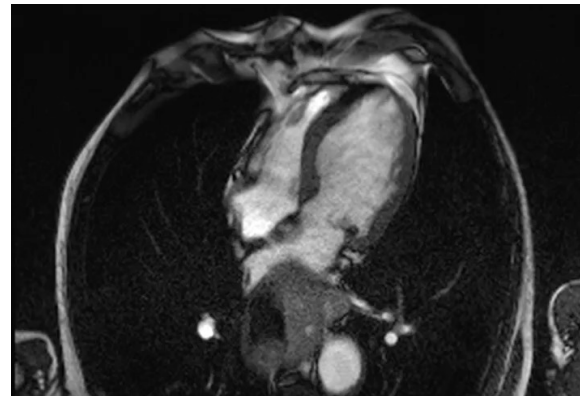


OTHER differential diagnoses

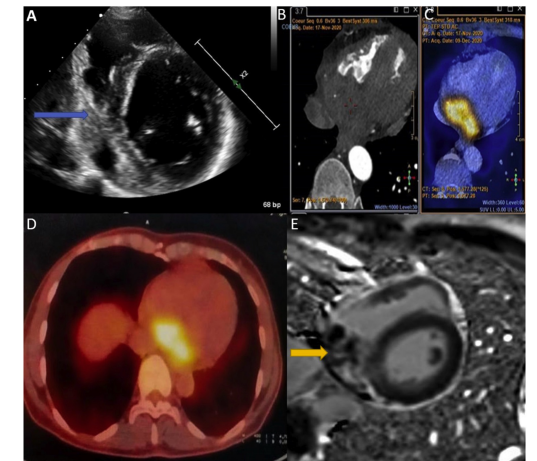
Pericardial disease



**LV dysfunction without
acute myocarditis
(Takotsubo/smoldering myocarditis)**



Cardiac metastases



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DIAGNOSTIC CRITERIA IC-OS-2021 Consensus and ESC 2022

✓ **ENDOMYOCARDIAL BIOPSY** (lymphocytic infiltrates and cardiomyocytes loss)

OR

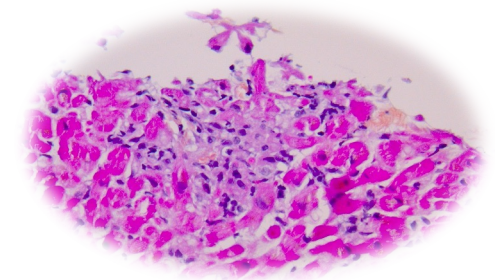
✓ **CLINICAL DIAGNOSIS**

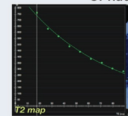
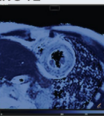
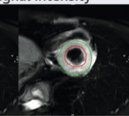
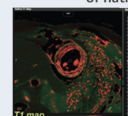
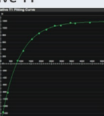
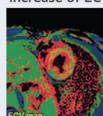
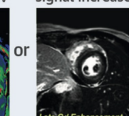
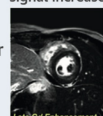
↑Tn and diagnostic CMR (2/2 Lake Louise criteria)

OR

↑Tn and 2 minor criteria

- Clinical syndrome
- Ventricular arrhythmia or conduction disorder
- Decline in LV function or WMA (non takotsubo)
- Suggestive CMR (1/2 Lake Louise criteria)
- Other immune-related AEs

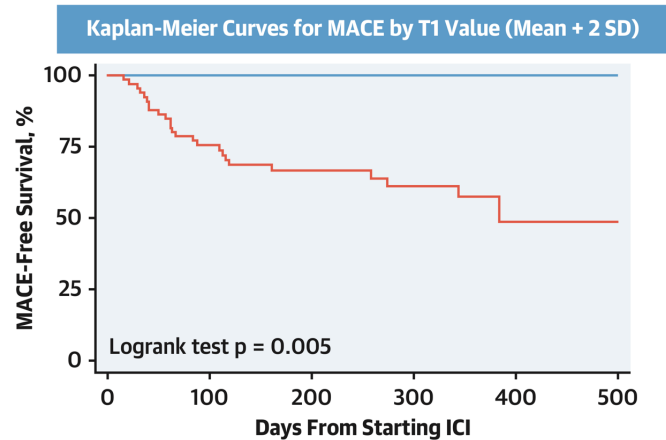
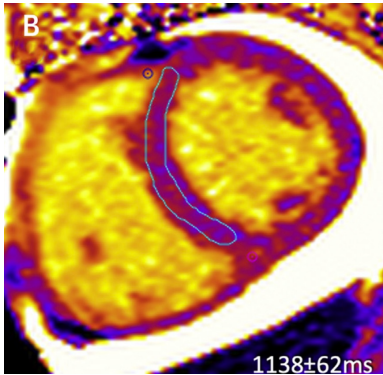


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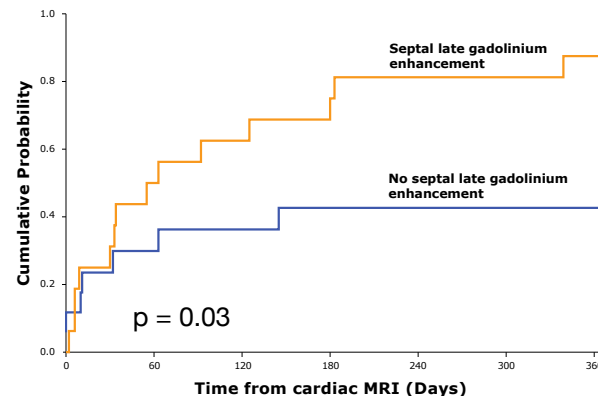
➡ **But not yet validated**

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Predictors of poor outcome



Tavendiranathan P, et al. J Am Coll Cardiol 2021;77:1503-16



Caddour F, Cautela J, Thuny F. Radiology 2022;303:512-521

Clinical factors
- Pre-existing cardiovascular disease - ICI-combination - Early first symptoms/signs after ICI initiation - Cardiac arrest - Heart failure and cardiogenic shock - Oxygen dependence - Low diastolic blood pressure - Simultaneous non-cardiovascular-irAE, especially myositis and myasthenia gravis
Electrocardiogram
- Severe conduction disorders and ventricular arrhythmias - QRS $\geq 100\text{ms}$ - Decreased in QRS voltage
Echocardiography
- Low GLS in echocardiography - GLS $< 13\%$ if LVEF $< 50\%$ - GLS $< 16\%$ if LVEF $\geq 50\%$
Cardiac magnetic resonance imaging
- Myocardial native T1 value on CMR - T1 $>$ mean value ± 2 standard deviations of the site norm - Septal LGE on CMR
Serum biomarkers
- Troponin - High troponin T values at admission/peak/discharge - Discharge troponin T value $\geq 1.5\text{ng/mL}$ - Admission troponin I value $\geq 3.73\text{ng/mL}$ - Absolute lymphocyte count decrease $\geq 35\%$ to admission - Neutrophile/lymphocyte ratio increase $\geq 100\%$ to admission
Endomyocardial biopsy
- Degree of lymphocytes infiltration on EMB > 50 CD3+ cells/high-power field
Management
- Delay in initiation of high-doses corticosteroids - Requirement of intensified immunosuppressive therapy

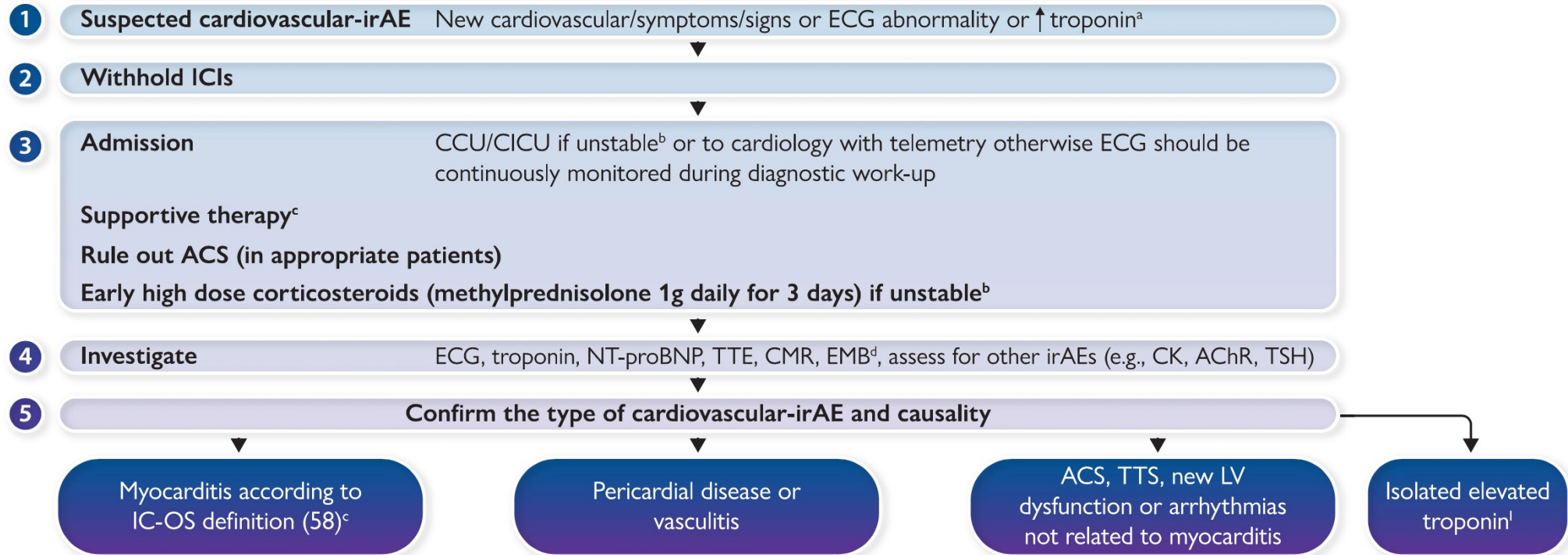
Thuny F, Naidoo J, Neilan TG. Eur Heart J 2022



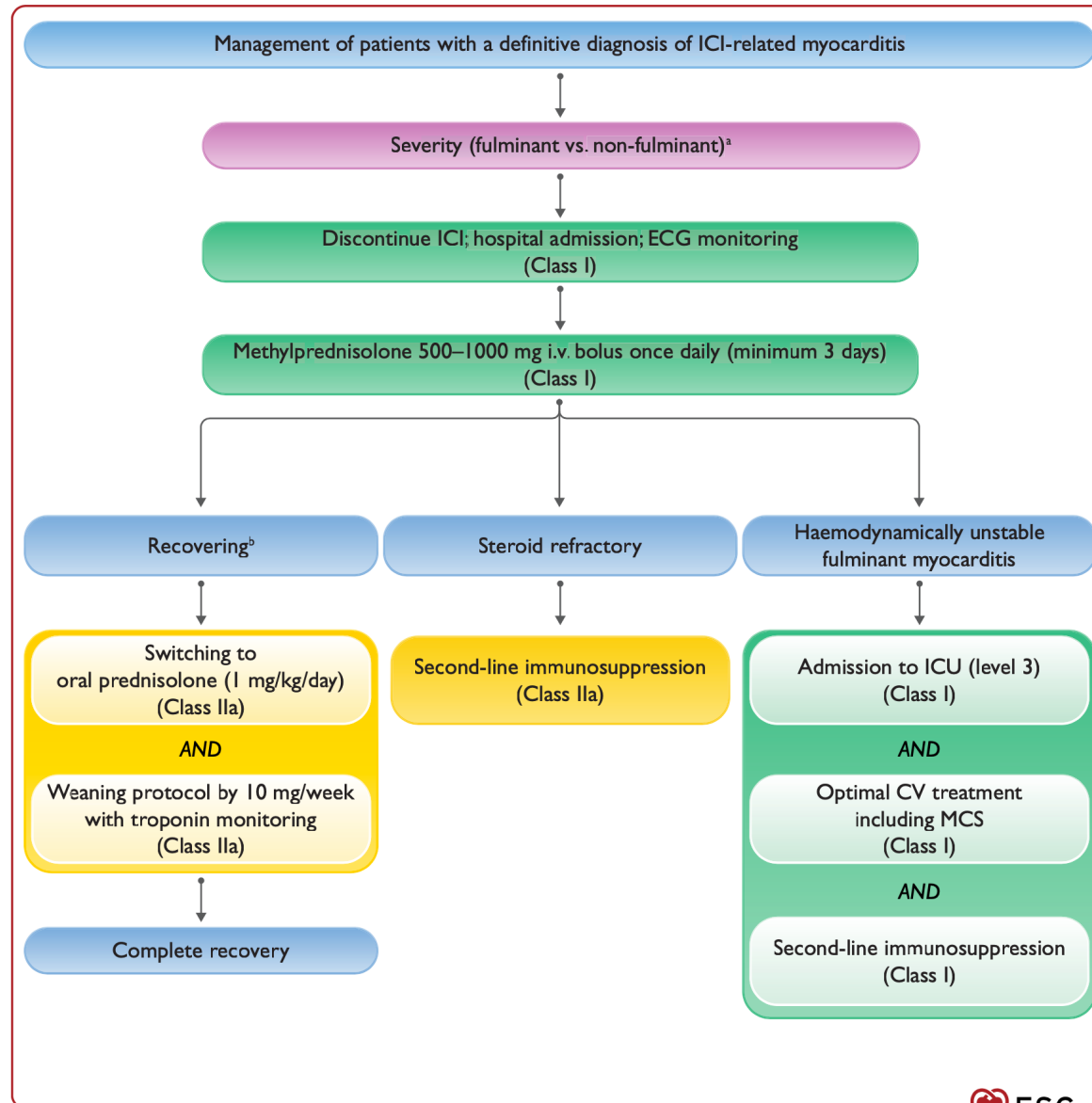
ICI-Induced Myocarditis

A Therapeutic Challenge

ICI-Induced Myocarditis – A Therapeutic Challenge



ICI-Induced Myocarditis – A Therapeutic Challenge



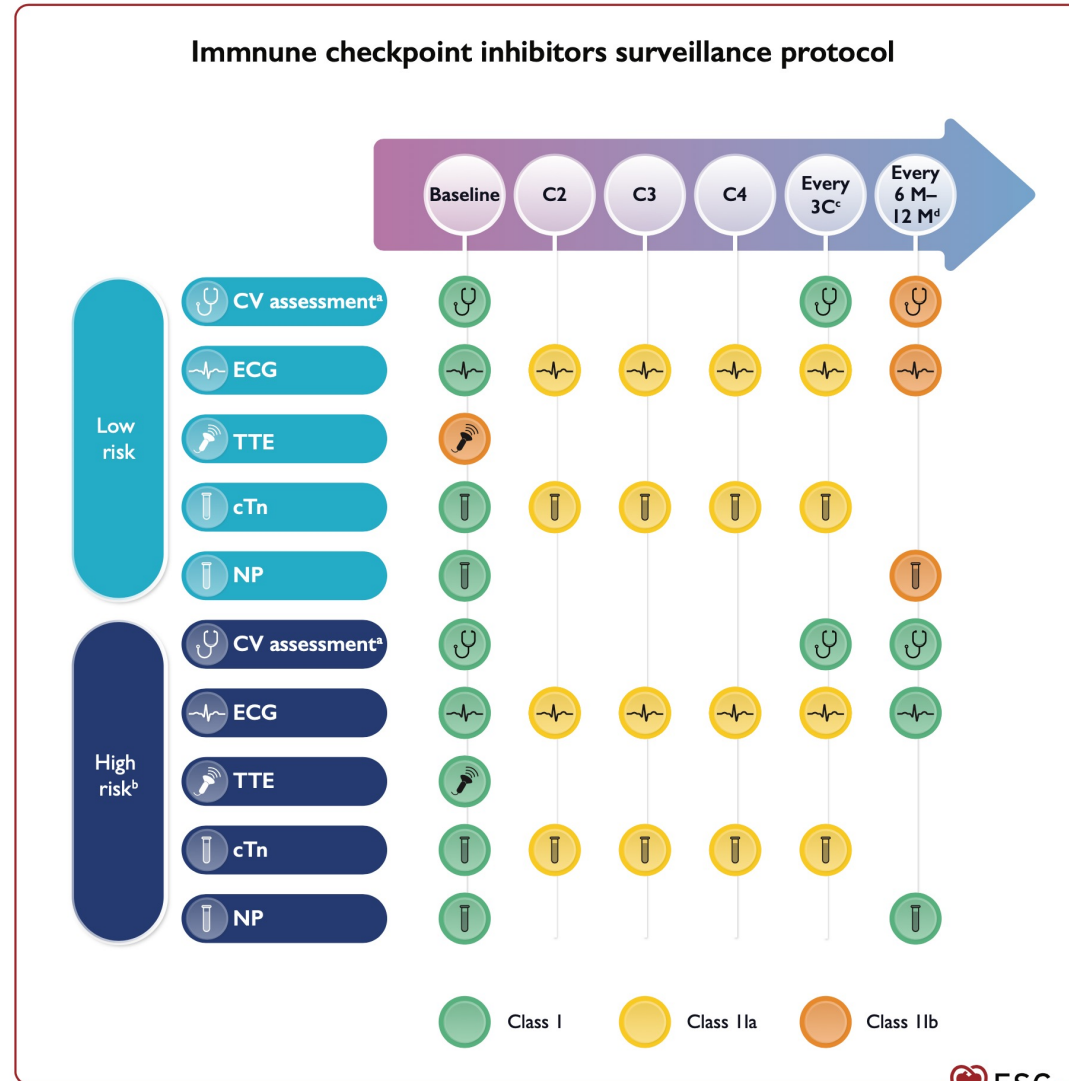


ICI-Induced Myocarditis

A Screening Strategy?

ICI-Induced Myocarditis – Screening Strategy?

2022 ESC Guidelines on cardio-oncology
developed in collaboration with the European
Hematology Association (EHA), the European
Society for Therapeutic Radiology and Oncology
(ESTRO) and the International Cardio-Oncology
Society (IC-OS)



^a Including physical examination, BP, lipid profile, and HbA1c

^b Dual ICI, combination ICI-cardiotoxic therapy, ICI-related non-CV events, prior CTRCD or CVD

^c Every three cycles until completion of therapy to detect subclinical ICI-related CV toxicity

^d In patients who require long-term (>12 months) ICI treatment.

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ICI-Induced Myocarditis – Screening Strategy?

Prospective Cardiovascular Surveillance of Immune Checkpoint Inhibitor–Based Combination Therapy in Patients With Advanced Renal Cell Cancer: Data From the Phase III JAVELIN Renal 101 Trial

Brian I. Rini, MD¹; Javid J. Moslehi, MD^{2,3}; Marc Bonaca, MD, MPH⁴; Manuela Schmidinger, MD⁵; Laurence Albiges, MD, PhD⁶; Toni K. Choueiri, MD⁷; Robert J. Motzer, MD⁸; Michael B. Atkins, MD⁹; John Haanen, MD, PhD¹⁰; Mariangela Mariani, PhD¹¹; Jing Wang, PhD¹²; Subramanian Hariharan, MD¹³; and James Larkin, MD, PhD¹⁴

“Although patients in the ICI arm who had high baseline cTnT values were at higher risk of MACE versus patients with low values, **routine cardiac investigations in asymptomatic patients were not useful for early detection of myocarditis** »

- **ICI-Myocarditis: a severe complication with special features**
- **Early management with corticosteroids/immunos-**
- **Other CV and metabolic adverse effects might have long term impact**

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