Toxicités cardiaques des Immunothérapies

GERCOR

19 Septembre 2019

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REPIRATORY
Pneumonitis
Pleuritis
Sarcoid-like granulomatosis

EYE
Uveitis
Conjunctivitis
Scleritis, episcleritis
Blepharitis
Retinitis

ENDOCRINE
Hyper or hypothyroidism
Hypophysitis
Adrenal insufficiency
Diabetes

CARDIO VASCULAR
Myocarditis
Pericarditis
Vasculitis

- New
- Diverse
-
- Uncommon

GASTRO INTESTINAL
Colitis
Ileitis
Pancreatitis
Gastritis

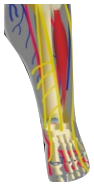
RENAL
Nephritis

LIVER
Hepatitis

NEUROLOGIC
Neuropathy
Guillain Barré
Myelopathy
Meningitis
Encephalitis
Myasthenia

SKIN
Rash
Pruritus
Psoriasis
Vitiligo
DRESS
Stevens Johnson

BLOOD
Hemolytic anemia
Thrombocytopenia
Neutropenia
Hemophilia

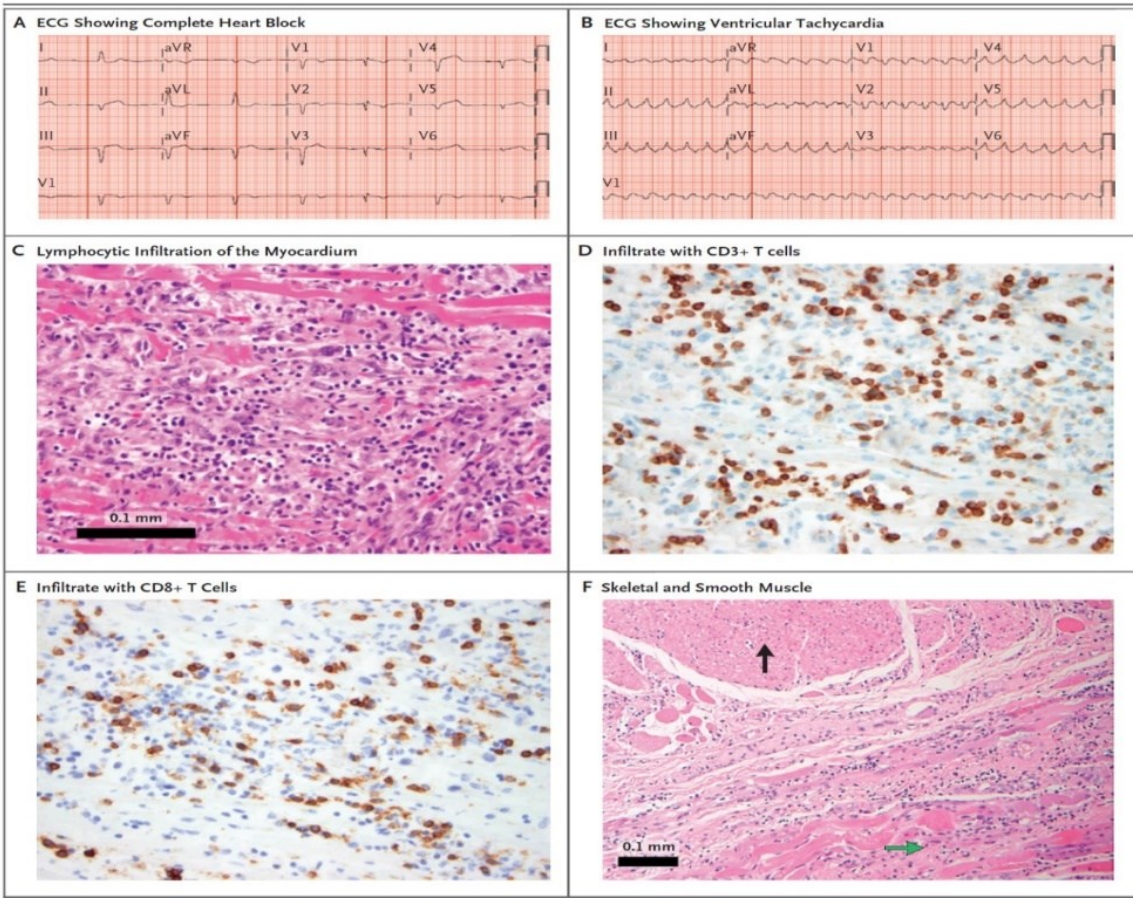


MUSCULO SKELETAL
Arthritis
Dermatomyositis

Champiat S Ann Oncol. 2016 ;27:559-74

What are the complications associated with ICI

Fulminant Myocarditis with Combination Immune Checkpoint Blockade



Johnson DB New Engl J Med 2016 ; 375 : 1749-1755

Fulminant Myocarditis with Combination Immune Checkpoint Blockade
Incidence of myocarditis in patients receiving nivolumab or Ipilimumab plus Nivolumab

Characteristics	Nivolumab (n=17620)	Nivolumab plus Ipilimumab (n=2974)
	No (%)	
Myocarditis		
Any	10 (0,06)	8 (0,27)
Fatal events	1 (< 0,01)	5 (0,17)
Myositis		
Any	27 (0,15)	7 (0,24)
Fatal events	2 (0,01)	1 (0,03)

LOW INCIDENCE

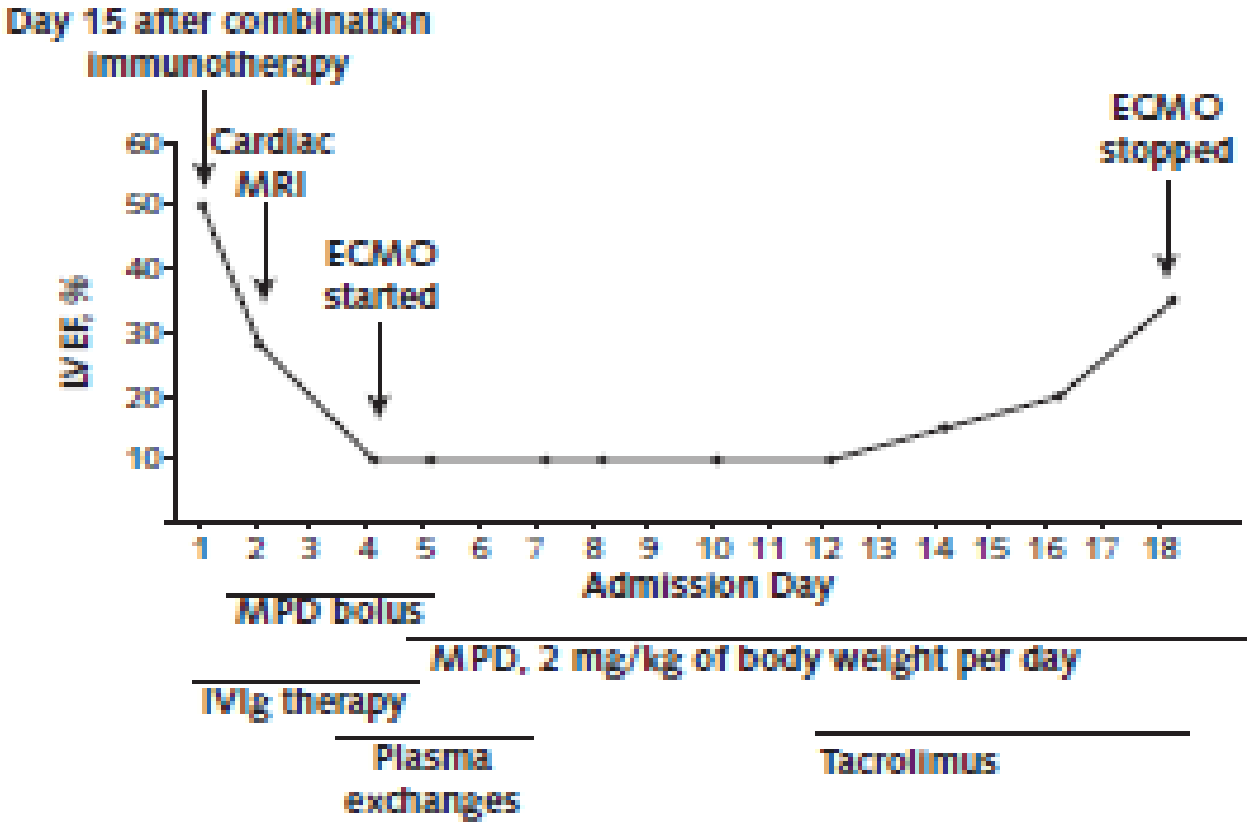
Johnson DB New Engl J Med 2016 ; 375 : 1749-1755

Summary of case reports and series of cardiovascular toxicities associated with cancer immune therapies

Author	Pts	Age/sex	Tumor type	treatment	Onset	Clinical presentation
Voskens 2013	1	61 / F	Melanoma	Ipi	16	NA
Roth 2016	1	60 / M	Melanoma	Ipi	18	Palpitations
Yun 2015	1	59 /M	Melanoma	Ipi	21	Chest pain Dyspnea
Geisler 2015	1	83/F	Melanoma	Ipi	12	Chest pain Dyspnea
Tadokoro 2016	1	69/F	Melanoma	Nivo	8	Malaise Palpitation
Laubli 2015	1	73/F	Melanoma	Pembro	15	Dyspnea
Zimmer 2016	5	49-87	Melanoma	Nivo,Pembro	2-17	fatigue
Johson 2016	2	65/F,63/F	Melanoma	Ipi+Nivo Ipi nivo	2 6	Dyspnea,Anasarca, Peripheral edema
Heinzerling 2016	1	72/M	Melanoma	ACT MAIGE A3TCR	< 1	CP arrest
Linette 2016	2	63/M,57/M	Melanoma	ACT MAGE A3TCR	< 1	HypoTa, HypoX, AMS

16 pts, Melanoma, Early onset < 21 days, paucicity of symptoms

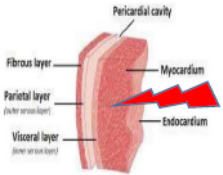
Survival After Fulminant Myocarditis induced by Immune-checkpoints inhibitors

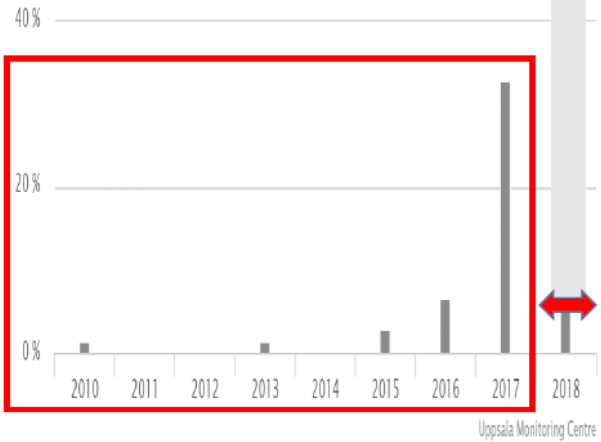


Arangalage D Ann Intern Med. 2017;167 :683-684.

Myocarditis

122 myocarditis
(thru 01/2017)





n:290

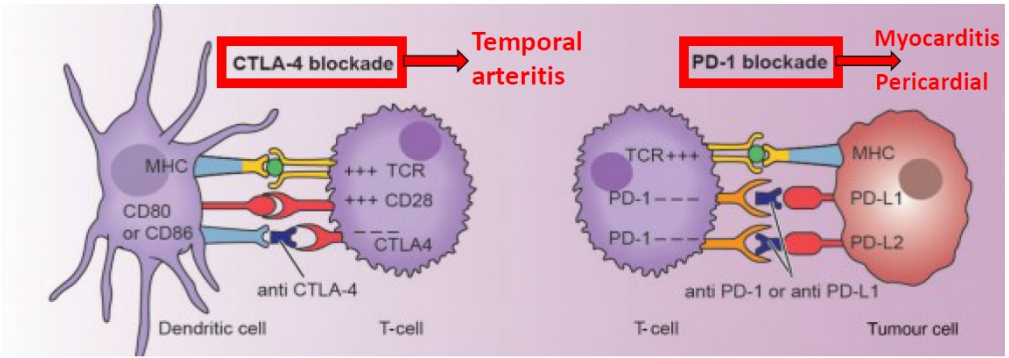
	N,%
Gender, Male	78 (66.7)
Age at onset, mean ± SD, years	66.4 ± 12.7
Monotherapy with Anti PD-1/PD-L1	84 (68.9)
Monotherapy with Anti CTLA-4	6 (4.9)
Combination therapy	32 (26.2)
Number of ICI admin before onset, median [IQR], [min-max]	1 (1-2.75) [1-8]
Time to irAE onset, days: Median, [IQR]	30 [18-60]
Death	61 (50.0)
Malignant melanoma	42 (40.7)
Lung cancer	33 (32.1)
Renal cell carcinoma	11 (10.7)
Concurrent irAE	
None (lone)	36 (29.5)
Gastro-intestinal disorders (any)	19 (15.6)
- **Hepatitis / hepatic failure**	13 (10.7)
- **Colitis / diarrhea / gastroenteritis / enteritis**	9 (7.4)
Endocrino-metabolic disorders (any)	6 (4.9)
Pulmonary disorders (Pneumonitis)	16 (13.1)
Cardiovascular disorders (any)	49 (40.2)
- **Arrhythmia**	23 (18.9)
- **Cardiac failure or shock / pulmonary edema**	19 (15.6)
Musculoskeletal disorders (Myositis/Rhabdomyolysis)	34 (27.9)
Neurologic disorders (Myasthenia gravis)	13 (10.7)

Salem JE. et al. Lancet Oncol. 2018 Dec:19(12):1579-1589.

EARLY ONSET

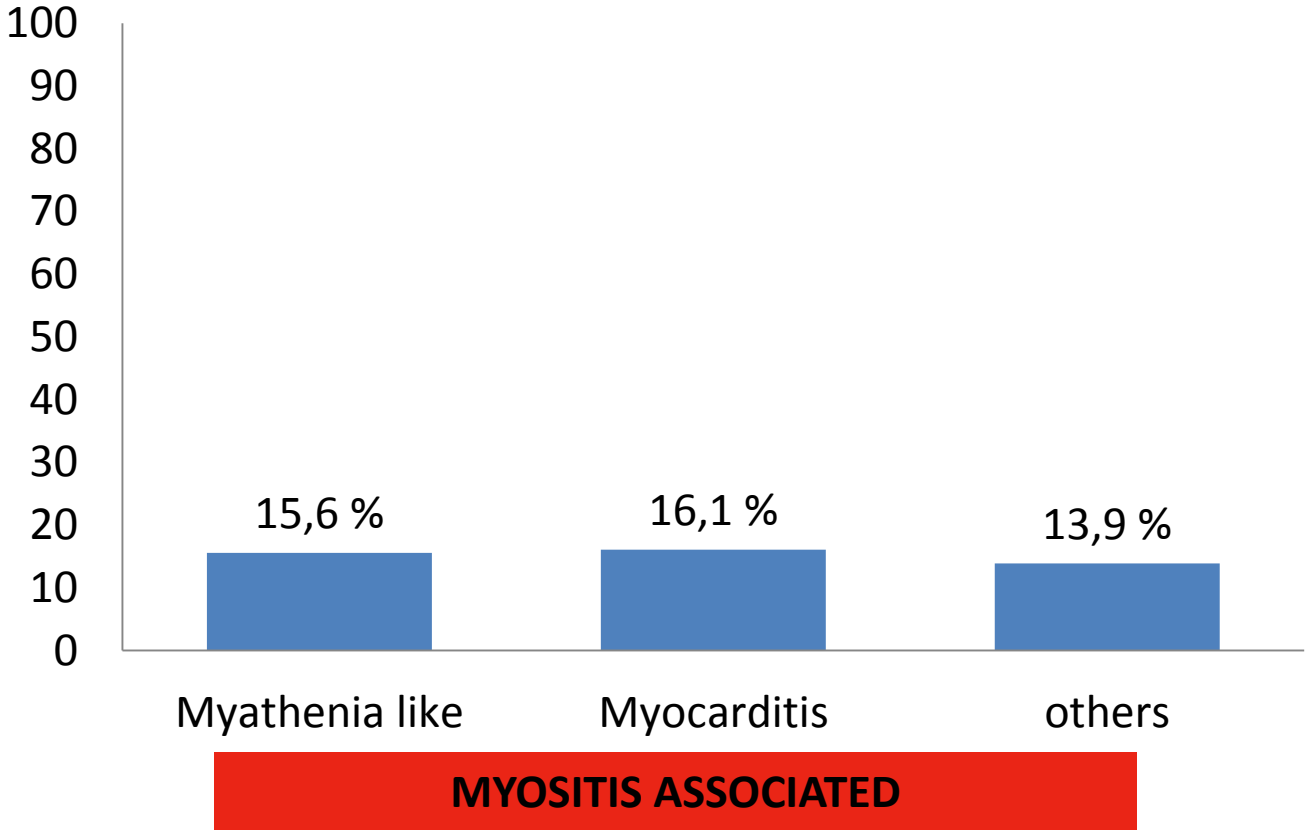
Salem JE Lancet Oncol. 2018 ;19:1579-1589

Total number of ICSRs	Overall immunotherapy (IMU; n: 31,321)			Full database (full; starting 2008; n: 12,455,401)	ROR and 95% CI [,] PD1 vs. CTLA4	ROR and 95% CI [,] COMB vs. MONO	ROR and 95% CI [,] IMU vs. full
	MONO (n: 28,909)		COMB (n: 2,412)				
	MONO-PD1 (n: 20,643)	MONO-CTLA4 (n: 8,266)					
Number of ICSRs by CV-ADR subgroup							
Myocarditis	84 (0.41%)	6 (0.07%)	32 (1.3%)	4,454 (0.04%)	**5.62 [2.46-12.88]**	**4.31 [2.86-6.38]**	**11.21 [9.36-13.43]**
Pericardial diseases	74 (0.36%)	13 (0.16%)	8 (0.33%)	10,009 (0.08%)	**2.28 [1.27-4.12]**	1.1 [0.53-2.24]	**3.8 [3.08-4.62]**
Vasculitis	56 (0.27%)	18 (0.22%)	8 (0.33%)	20,987 (0.2%)	1.25 [0.73-2.12]	1.3 [0.62-2.67]	**1.56 [1.25-1.94]**
Number of ICSRs in vasculitis-ADR subgroup							
Temporal arteritis	7 (0.03%)	10 (0.12%)	1 (0.04%)	568 (<0.01%)	**0.28 [0.11-0.74]**	0.71 [0.07-3.94]	**12.99 [8.12-20.77]**
Polymyalgia rheumatica	14 (0.07%)	1 (0.01%)	1 (0.04%)	1254 (0.01%)	5.61 [0.74-42.66]	0.8 [0.08-4.62]	**5.13 [3.13-8.40]**



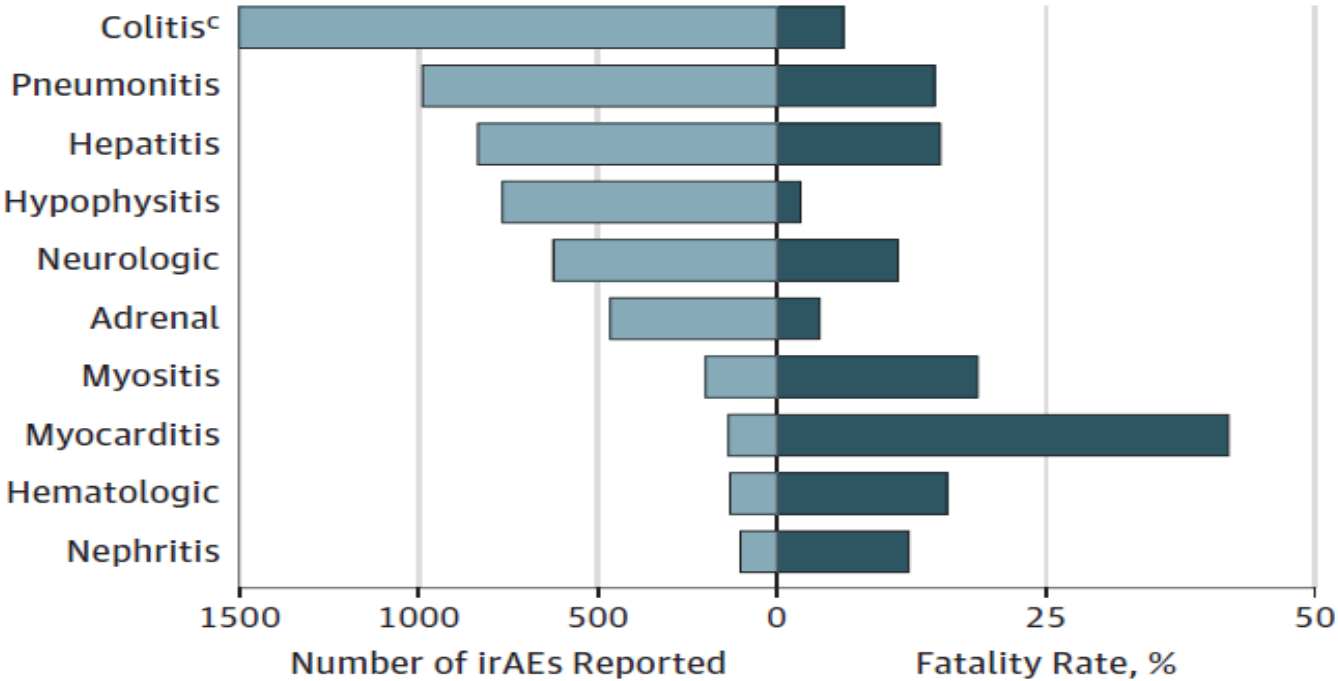
COMBOTHERAPY = RISK FACTOR

Immune checkpoint inhibitor-associated myositis
Description of pts with ICI associated Myositis
n= 180



Anquetil C Circulation. 2018 ; 138 : 743-745

Number of cases and fatality rate for each class of toxic effect



High Fatality Rate

Wang DY, JAMA Oncol. 2018 ;4 :1721-1728.

Cardiovascular toxicities associated with immune checkpoints inhibitors
An observational, retrospective, pharmacovigilance study

	ICRs reported for ICI (n=31 321)	ICRs reported in the full database (n=16 343 451)	IC (IC_{025})
Myocarditis	122 (0,39%)	5515 (0,03%)	3,47 (3,20)
Pericardial disease	95 (0,30%)	12800 (0,08%)	1,93 (1,63)
SV arrhythmias	222 (0,71%)	68 597 (0,42%)	0,75 (0,66)
Vasculitis	82 (0,26%)	33 289 (0,20%)	0,36 (0,03)
Endocardial Disorders	8(0,03%)	3149 (0,02%)	0,38 (-0,79)
Conductive Disorders	37 (0,12%)	26 008 (0,16%)	-0,42 (-0,93)

Salem JE Lancet Oncol. 2018 ;19:1579-1589

How should we diagnose ICI related myocarditis

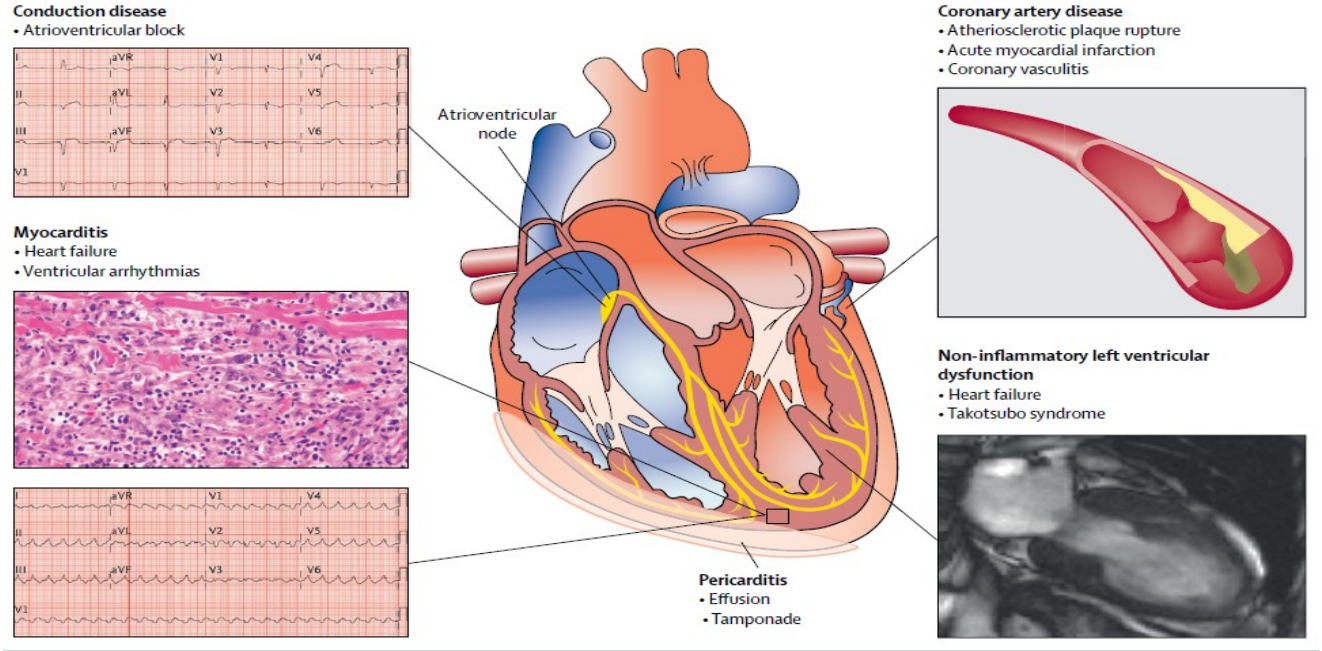
Common Terminology Criteria for Adverse Events (CTCAE)

Version 5.0

Published: November 27, 2017

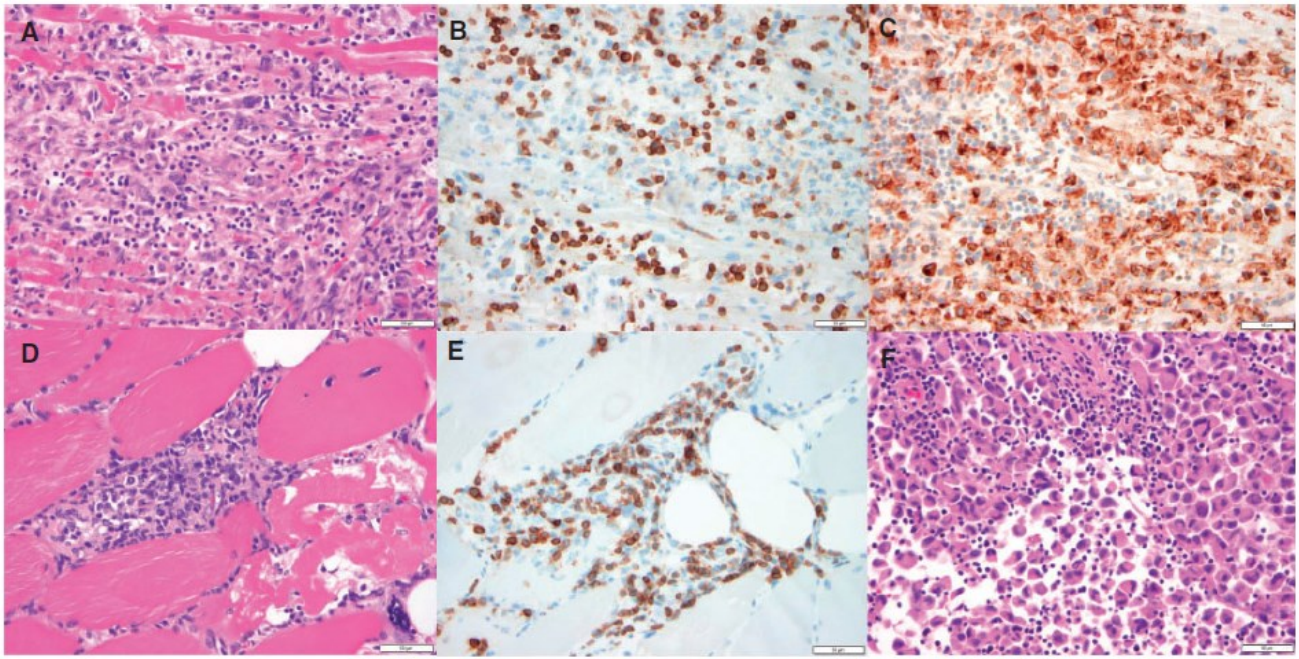
Cardiac disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Myocarditis	-	Symptoms with moderate activity or exertion	Severe with symptoms at rest or with minimal activity or exertion; intervention indicated; new onset of symptoms	Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)	Death
Definition: A disorder characterized by inflammation of the muscle tissue of the heart. **Navigational Note:** -					

How to diagnose Myocarditis



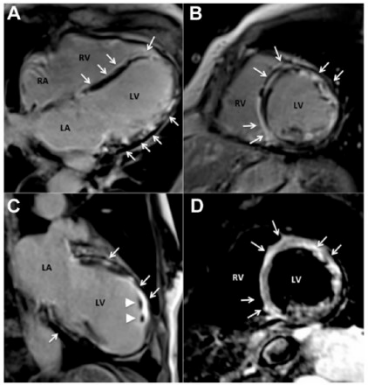
Clinical - ECG – Troponin – Echo – CMR - EBM

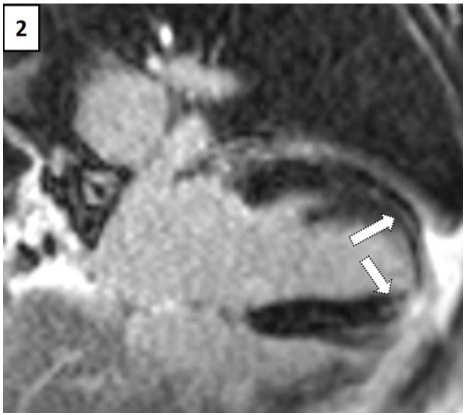
Endocardial Biopsy and ICI

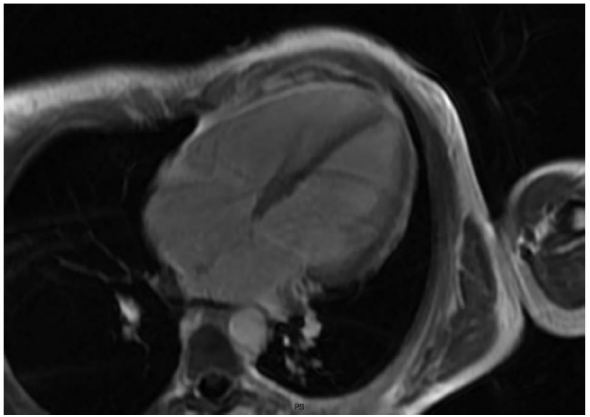


Hu Cardiovascular research 2019 ; 115 : 854 -868

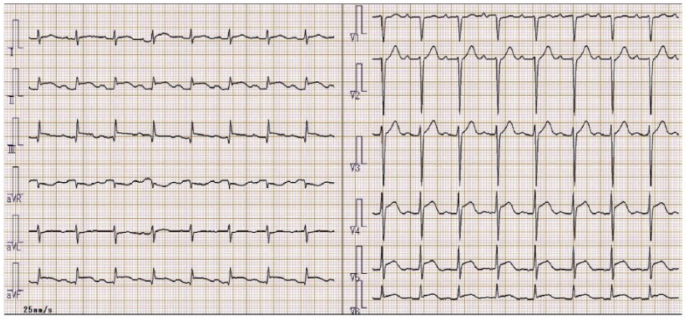
CMR and ICI myocarditis

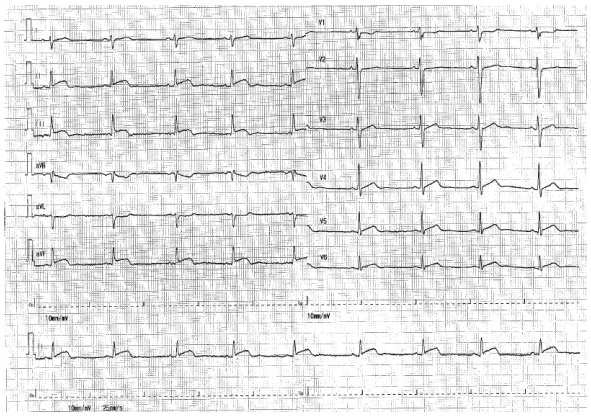


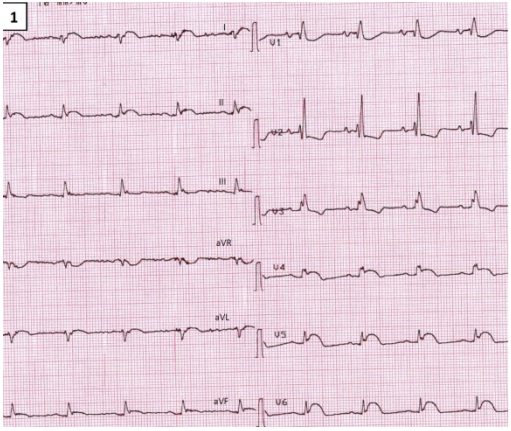




ECG and myocarditis





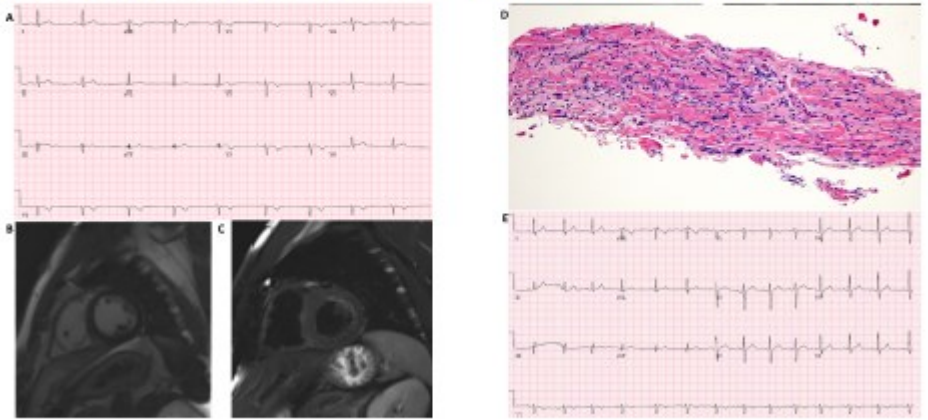


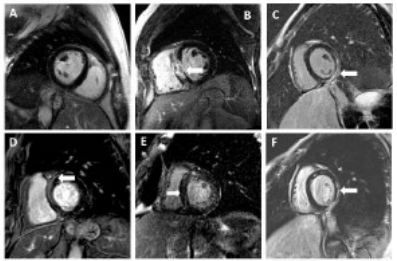
However……

Late Gadolinium Enhancement in Patients with Myocarditis from Immune Checkpoint Inhibitors

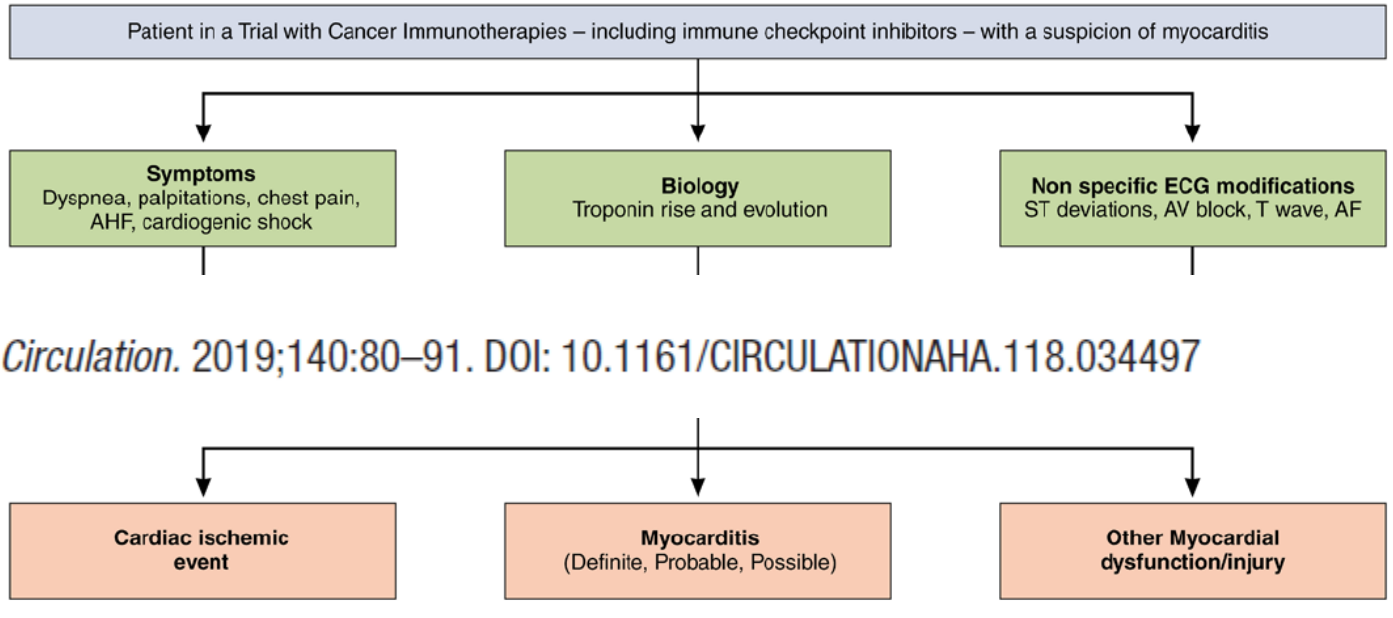
Lili Zhang MD, MS, Magid Awadalla, MD, Syed S. Mahmood MD, MPH, John D. Groarke, MB BCH, MPH; Kerry L. Reynolds, MD, Raza M. Alvi, MD, Shiying Liu, MD, Malek Z.O. Hassan, MD, Justine V. Cohen, DO, Anju Nohria, MD, Adam Rokicki, BS, Maeve Jones-O'Connor, MD, Sean P.T. Murphy, MD, Lucie M. Heinzerling, MD, MPH, Michael C. Kirchberger, MD, Merna Armanious, MD, Gagan Sahni MD, Javid J. Moslehi, MD, Ryan J. Sullivan, MD, Carol L. Chen, MD, Dipti Gupta, MD, MPH, Sachin P. Shah, MD, Sarju Ganatra, MD, Stephane Ederhy, MD, Franck Thuny, MD, PhD, Alexander R. Lyon, MD, Carlo G. Tocchetti, MD, PhD, Muhammad A. Rizvi, MD, Donald P. Lawrence, MD, Paaladinesh Thavendiranathan, MD, Michael G. Fradley, MD, Tomas G. Neilan, MD, MPH

Figure 4. A representative Case of ICI-associated Myocarditis With a Normal CMR: A 49-year old man with metastatic renal cell carcinoma was started with Nivolumab in March 2018. One month later, he presented with diaphoresis, nausea and fatigue. He had abnormal EKG (A), normal LGE images for fibrosis, normal T2 images for myocardial edema (C). But EMB showed lymphocytic myocarditis, similar to grade 3B transplant rejection (D). After being treated with high dose, his EKG had normalized (E).



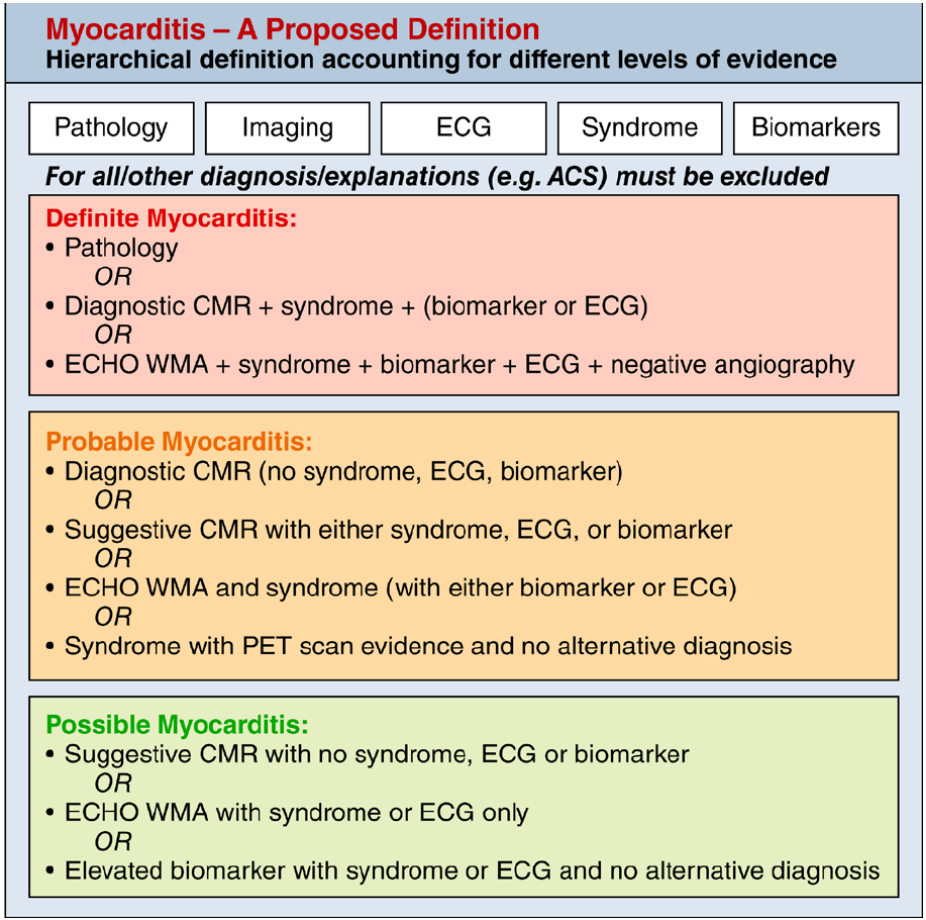


A proposed approach to diagnosis of myocarditis in the setting of ICI use

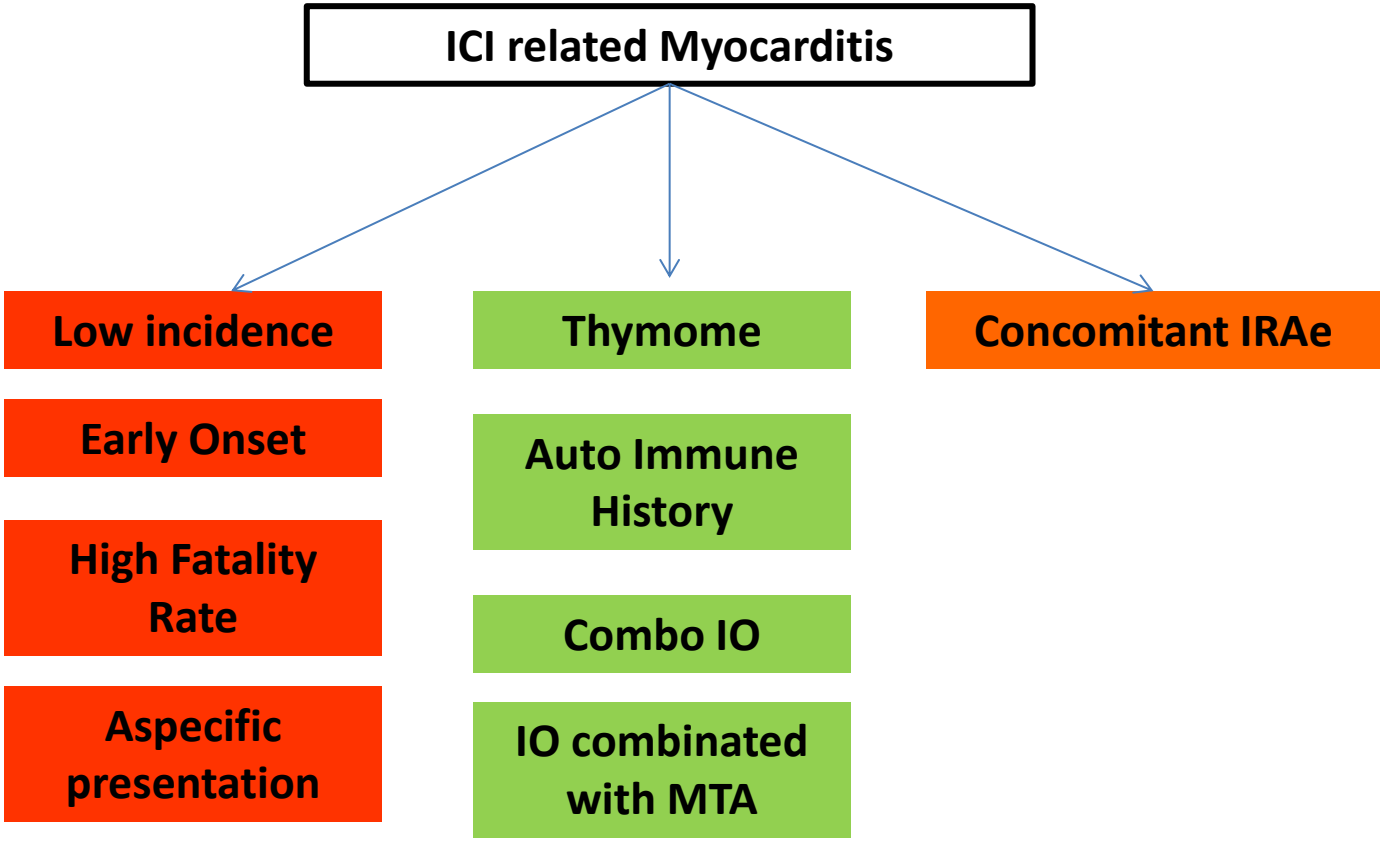


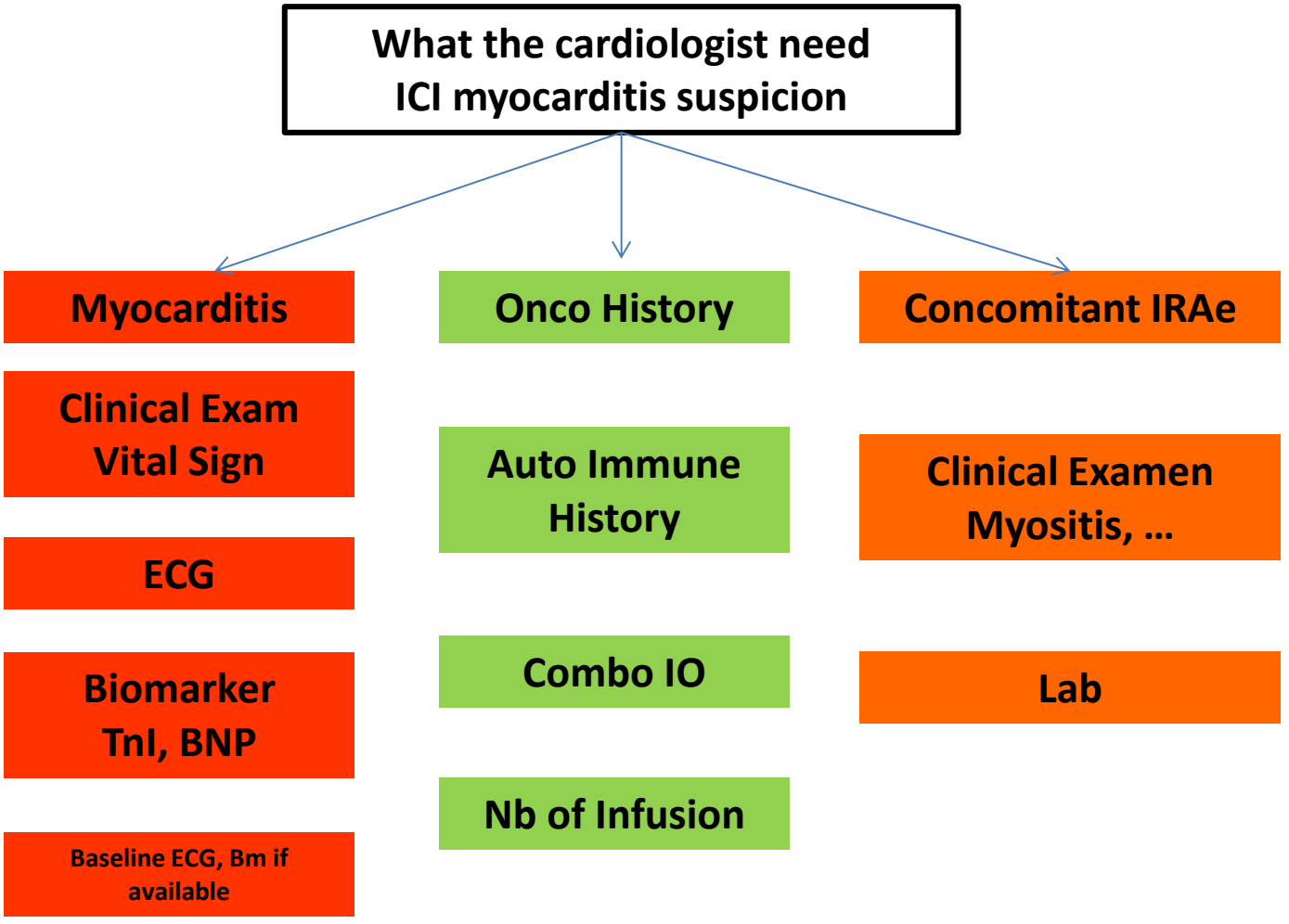
Bonaca Circulation 2019 ;140 :80-91

A proposed approach to diagnosis of myocarditis in the setting of ICI use

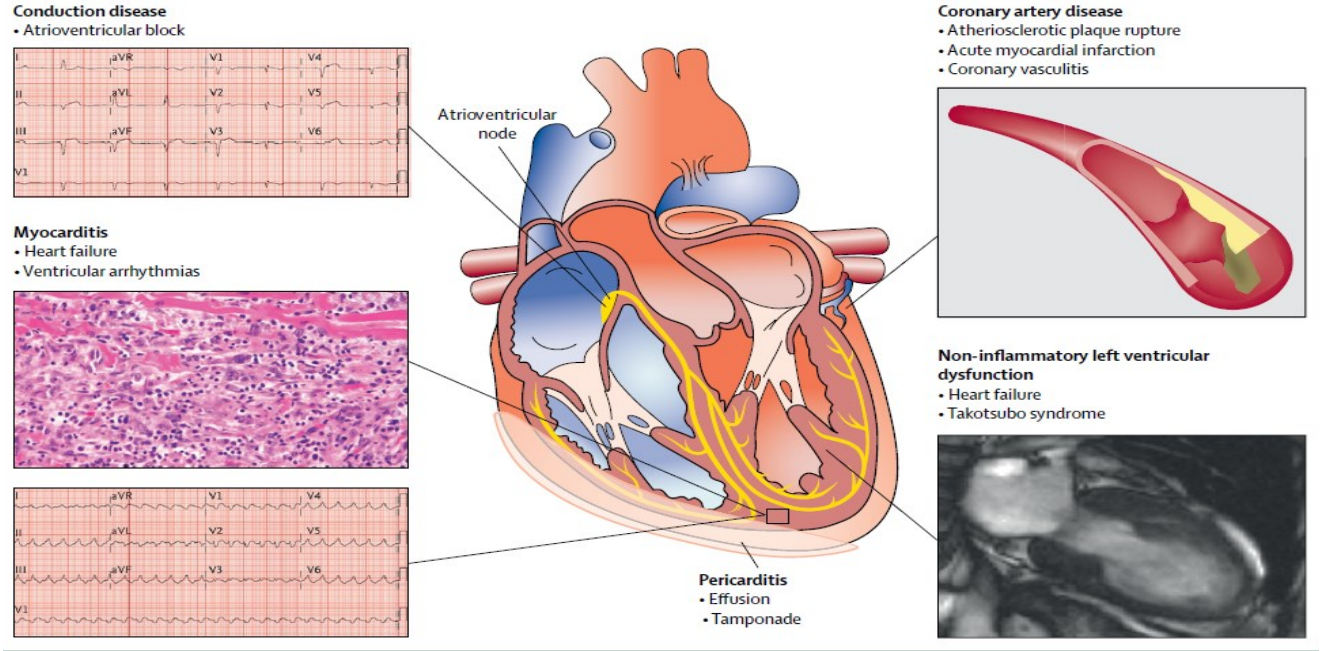


Bonaca Circulation 2019 ;140 :80-91


ICI related Myocarditis
Low incidence
Early Onset
High Fatality Rate
Aspecific presentation
Thymome
Auto Immune History
Combo IO
IO combinated with MTA
Concomitant IRAe


What the cardiologist need
ICI myocarditis suspicion
Myocarditis
Clinical Exam
Vital Sign
ECG
Biomarker
TnI, BNP
Baseline ECG, Bm if available
Onco History
Auto Immune History
Combo IO
Nb of Infusion
Concomitant IRAe
Clinical Examen
Myositis, …
Lab

How to diagnose Myocarditis



Clinical - ECG – Troponin – Echo – CMR - EBM

How to treat ICI related myocarditis ?

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 28 (Supplement 4): i119–i142, 2017
doi:10.1093/annonc/mdx225

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*

Cardiac toxicity

- When a myocarditis is suspected, admit the patient and immediately start high-dose (methyl)prednisone (1–2 mg/kg). In the case of deterioration, consider adding another immunosuppressive drug (MMF or tacrolimus) [V, B].

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JOURNAL OF CLINICAL ONCOLOGY
ASCO SPECIAL ARTICLE

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

Brahmer JR, et al.

June 2018

9.0 Cardiovascular Toxicities

9.1 Myocarditis, pericarditis, arrhythmias, impaired ventricular function with heart failure and vasculitis

Definition: Signs and symptoms may include chest pain, arrhythmia, palpitations, peripheral edema, progressive or acute dyspnea, pleural effusion, fatigue

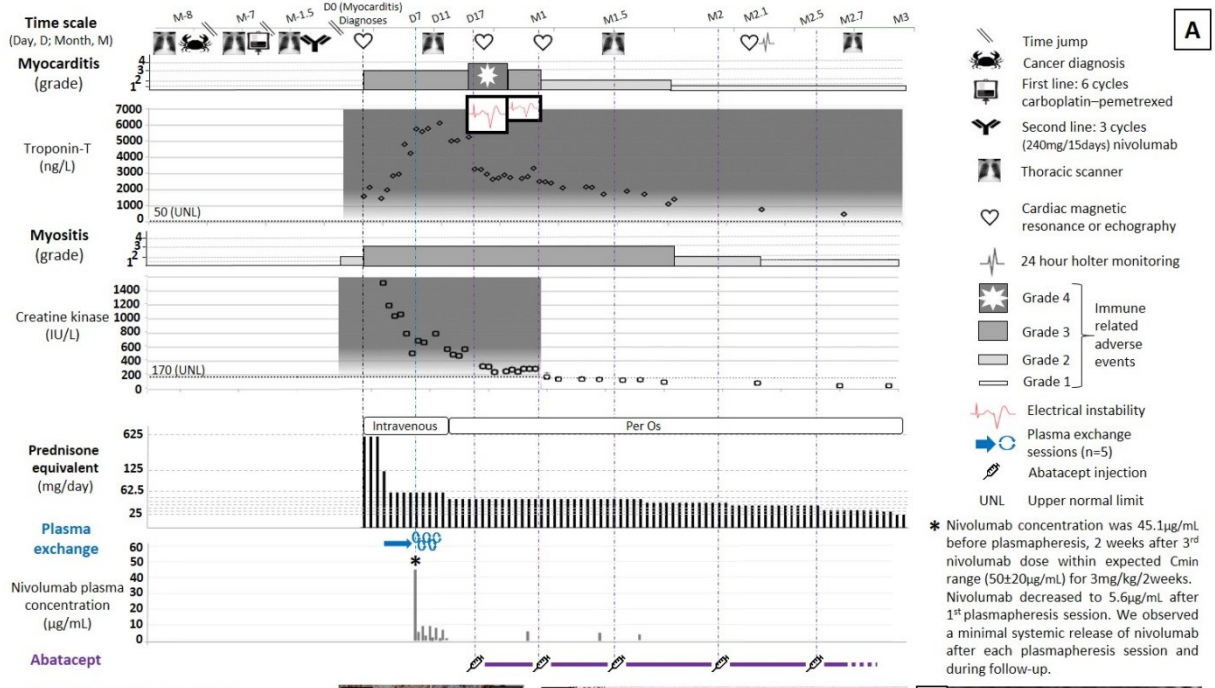
Diagnostic work-up

- At baseline
  - ECG
  - Consider troponin, especially in patient treated with combination immune therapies
- Upon signs/symptoms (consider cardiology consult)
  - ECG
  - Troponin
  - BNP
  - Echocardiogram
  - CXR
- Additional testing to be guided by cardiology and may include
  - Stress test
  - Cardiac catherization
  - Cardiac MRI

Grading	Management
G1 Abnormal cardiac biomarker testing, including abnormal ECG	All grades warrant work-up and intervention given potential for cardiac compromise
G2 Abnormal screening tests with mild symptoms	Consider the following:
G3 Moderately abnormal testing or symptoms with mild activity	Hold ICPi and permanently discontinue after G1
G4 Moderate to severe decompensation, IV medication or intervention required, life-threatening conditions	High-dose corticosteroids (1-2 mg/kg of prednisone) initiated rapidly (oral or IV depending on symptoms) Admit patient, cardiology consultation Management of cardiac symptoms according to ACC/AHA guidelines and with guidance from cardiology Immediate transfer to a coronary care unit for patients with elevated troponin or conduction abnormalities In patients without an immediate response to high-dose corticosteroids, consider early institution of cardiac transplant rejection doses of corticosteroids (methylprednisolone 1 g every day) and the addition of either mycophenolate, infliximab, or antithymocyte globulin

Qualifying statement: Treatment recommendations are based on anecdotal evidence and the life-threatening nature of cardiovascular complications. Holding checkpoint inhibitor therapy is recommended for all grades of complications. The appropriateness of rechallenging remains unknown. Note that infliximab has been associated with heart failure and is contraindicated at high doses in patients with moderate-severe heart failure.[108]

Abatacept for Severe Immune Checkpoint Inhibitor–Associated Myocarditis



Salem JE, *et al.* *N Engl J Med*. 2019 Jun 13;380(24):2377-2379.

PHRC-K 2019

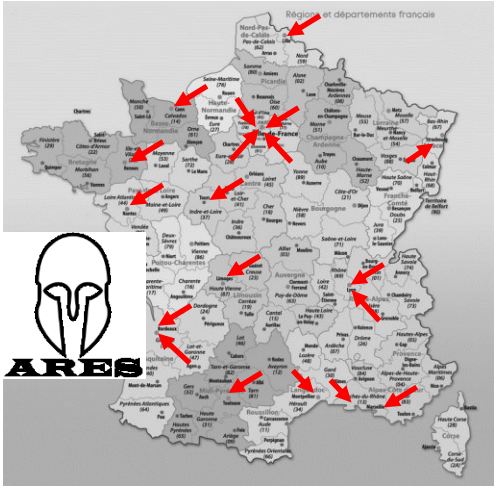
INSTITUT NATIONAL DU CANCER

18 ImmunoTox Networks

Liberté • Égalité • Fraternité
RÉPUBLIQUE FRANÇAISE

MINISTÈRE DES SOLIDARITÉS ET DE LA SANTÉ

Project title
ARES01 – Abatacept, for treatment of severe cortico-resistant immune checkpoint inhibitors Related adversE eventS



ARES

GENERAL INFORMATION

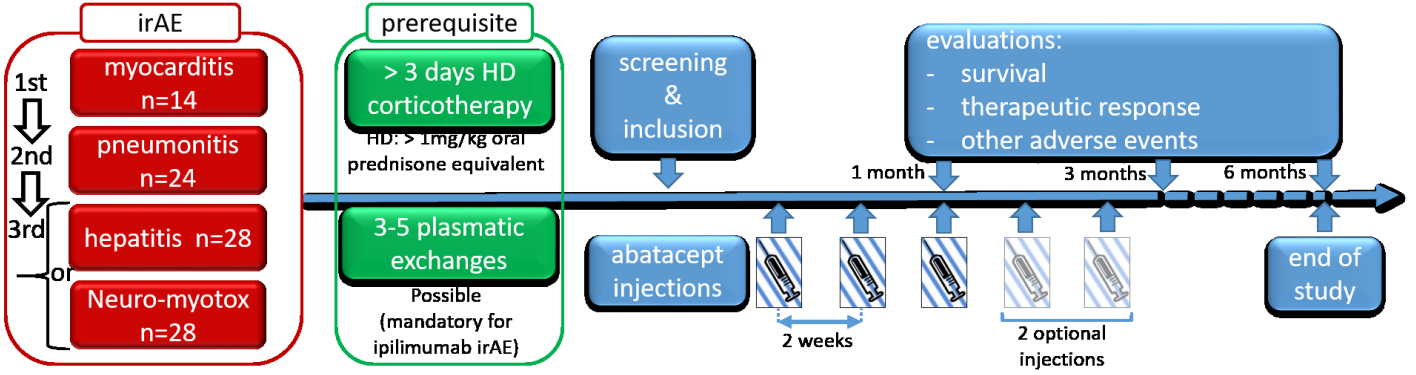
First name and name of coordinator	Joe-Elie Salem

Primary objective : 3 months overall mortality

Power calculation: decrease ≥50% vs. prior estimates

A priori mortality

Myocarditis:	*Pneumonitis*:	*Hepatitis*:	*Neuro-Myotox*:
40%	25%	20%	20%



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