RIIP

RENCONTRES EN IMMUNOLOGIE & IMMUNOTHERAPIE PRATIQUES

29 et 30 SEPTEMBRE 2022

UIC-P - Espaces Congrès
16, rue Jean Rey - 75015 Paris

IMAGE FREEPIK

Sous l'égide de :

AI2R Filière · aviesan alliance nationale pour les sciences de la vie et de la santé · CeRéMAIA · GRI · European Reference Network for rare or low prevalence complex diseases · Fédération Immunologie · Imidiate · RITA Rare Immunodeficiency AutoInflammatory AutoImmune · Société Française de Dermatologie et de Pathologie Sexuellement Transmissible · Société Française d'Immunologie · SFR société française de rhumatologie · SOFREMIP Rhumatologie & maladies inflammatoires pédiatriques · SNFEM

RIIP

RENCONTRES EN IMMUNOLOGIE & IMMUNOTHERAPIE PRATIQUES

Myocardites liées aux inhibiteurs de checkpoint : état des lieux

BRETAGNE Marie (Chef de clinique assistante)

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Centre d'Investigation Clinique Paris-Est,

Service de Pharmacologie médicale, UF Onco cardiologie, Hôpital Pitié-Salpêtrière

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Sous l'égide de :

Mme M. 66yo

Cancer history:

- Metastatic lung cancer diagnosed 10 month ago
- Progression after 1st line chemo (6 cycles carboplatin-pemetrexed)
- 2nd line, by nivolumab (240 mg q2 weeks – 3 doses)

Auto-immunity history:

- Arthritis lupus on hydroxychloroquine for ≥15y
- Thymoma treated by surgery and radiotherapy 20 years ago

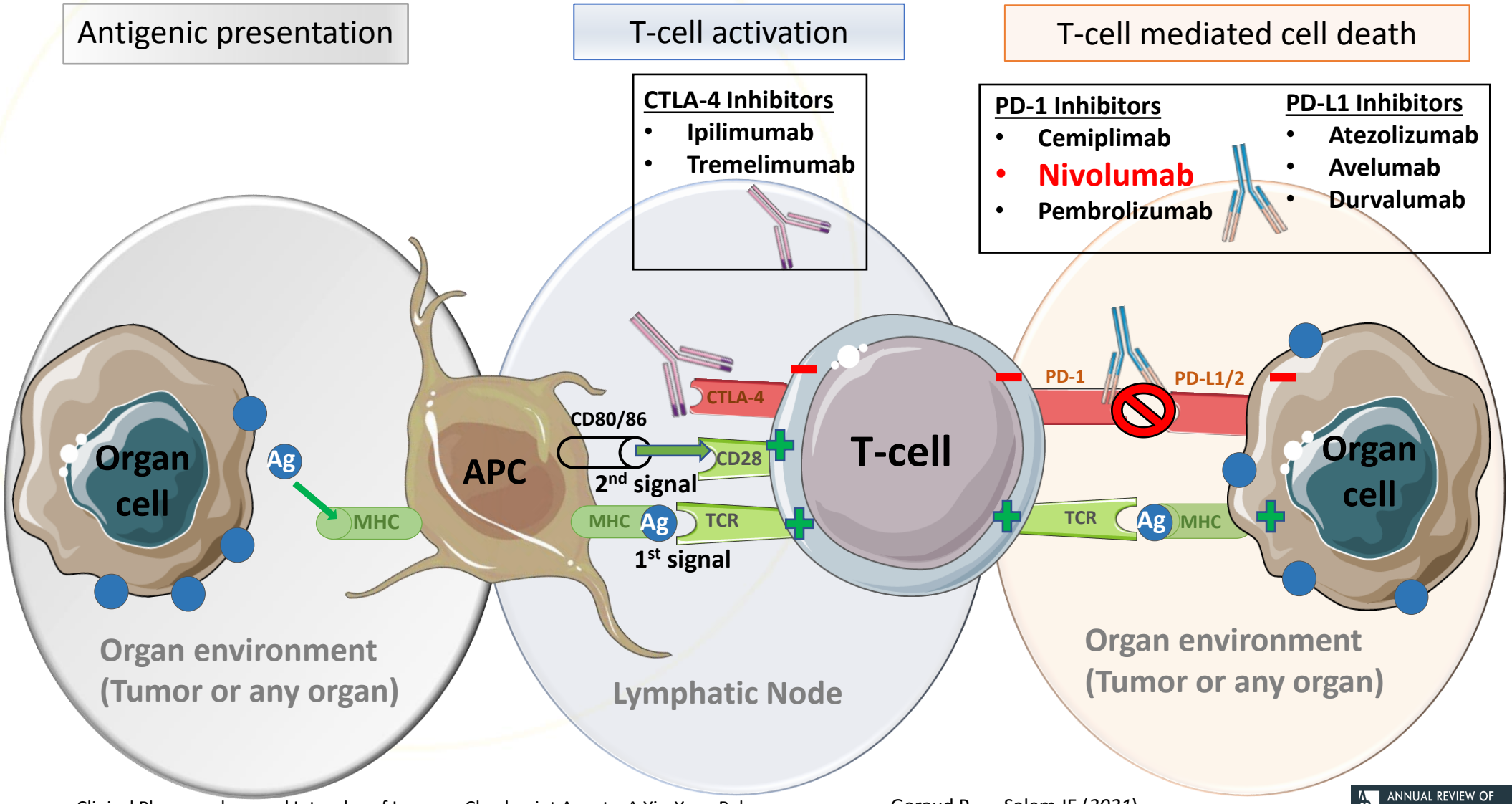
Cardiovascular risk factors:

- None (except age)

Treatment:

- Hydroxychloroquine
- Betablocker (for uncharacterized tachycardia for years)

Immune-checkpoint inhibitors (ICI) – Monoclonal antibodies



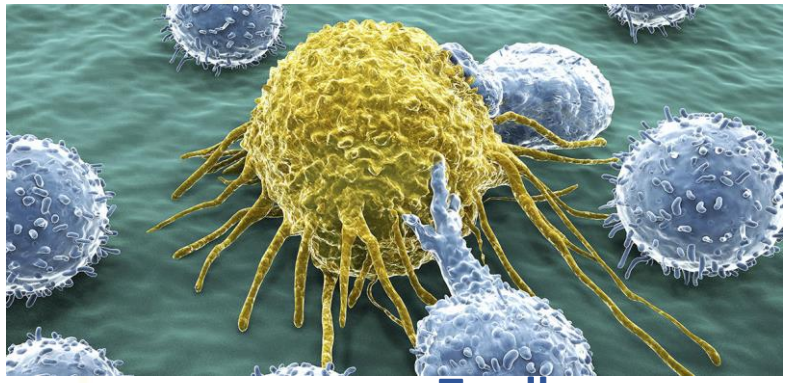
Clinical Pharmacology and Interplay of Immune Checkpoint Agents: A Yin-Yang Balance

Geraud P, …. Salem JE (*2021*)

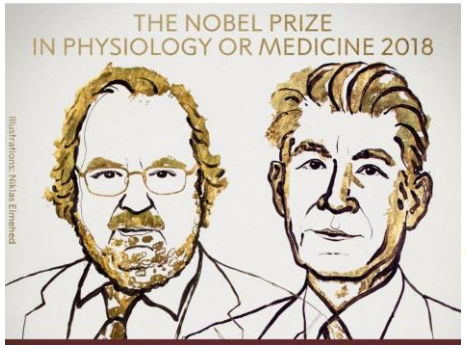
ANNUAL REVIEW OF PHARMACOLOGY AND TOXICOLOGY

An exploding class of drugs…

Cancer-cell



T-cells



ANNUAL REVIEW OF PHARMACOLOGY AND TOXICOLOGY

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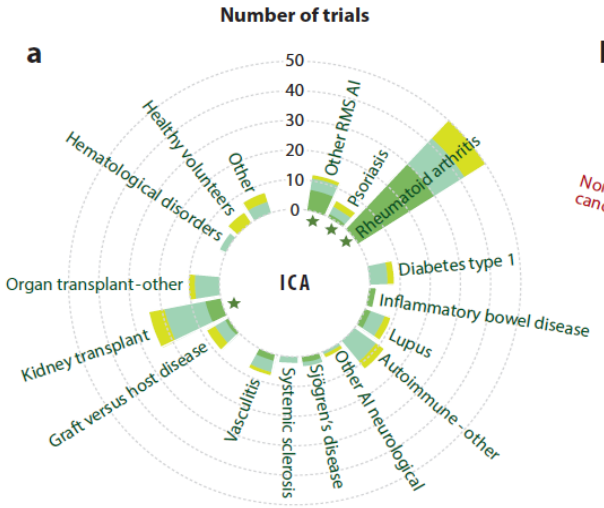
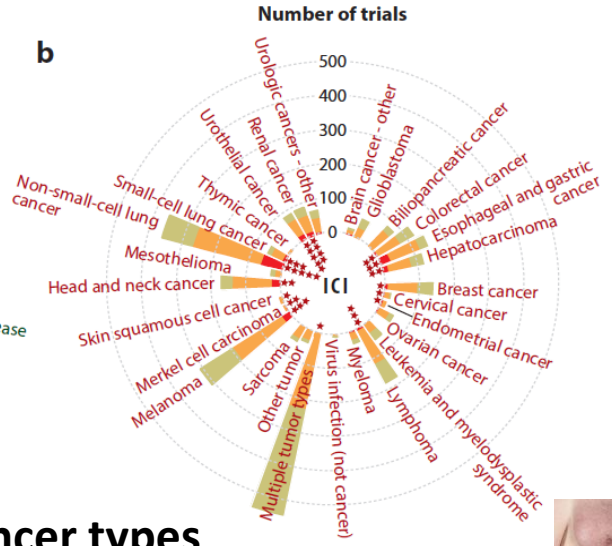
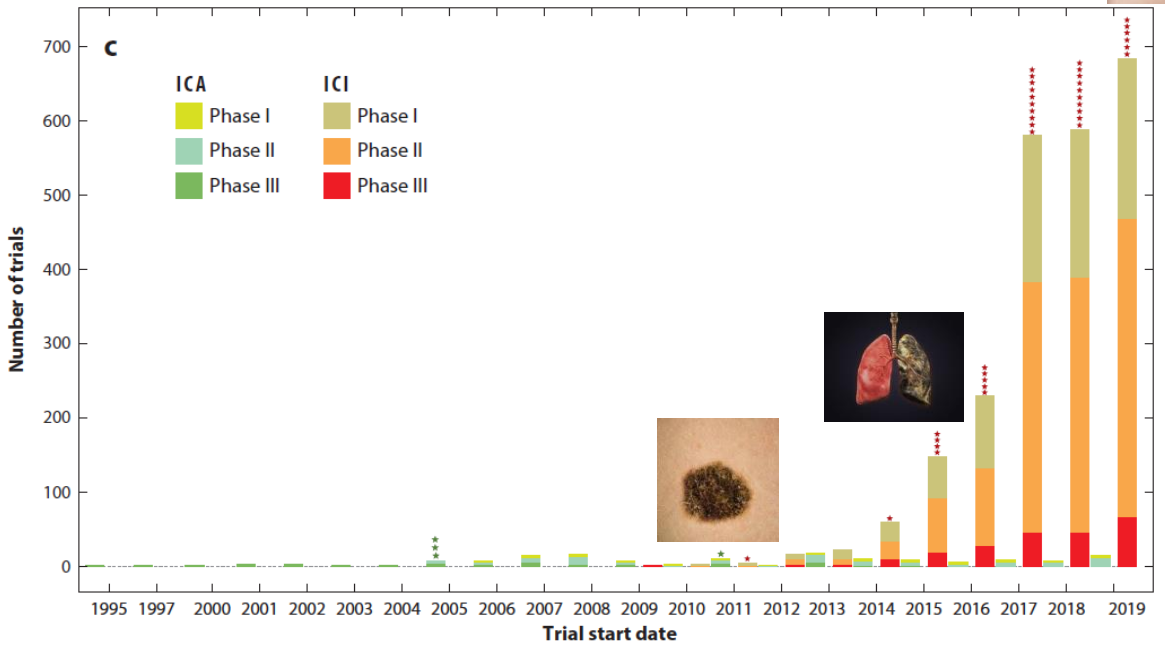




FDA approved >17 cancer types



What are the **main CV toxicities** we should think about in the follow-up of patients on **ICI**?

Cardiovascular toxicities associated with immune checkpoint inhibitors: an observational, retrospective, pharmacovigilance study

THE LANCET Oncology
Volume 19, Issue 12, December 2018, Pages 1579-1589

Joe-Elie Salem, Ali Manouchehri, Melissa Moey, Bénédicte Lebrun-Vignes, Lisa Bastarache, Justin M Balko, Marc P Bonaca, Dan M Roden, Douglas B Johnson, Javid J Moslehi

1 **Myocarditis** FDA

2 **Pericarditis** New Signal

3 **Temporal arteritis** FDA

4 **Supra-ventricular arrhythmias** New Signal

~20 million reports

Uppsala Monitoring Centre

WHO Collaborating Centre for International Drug Monitoring

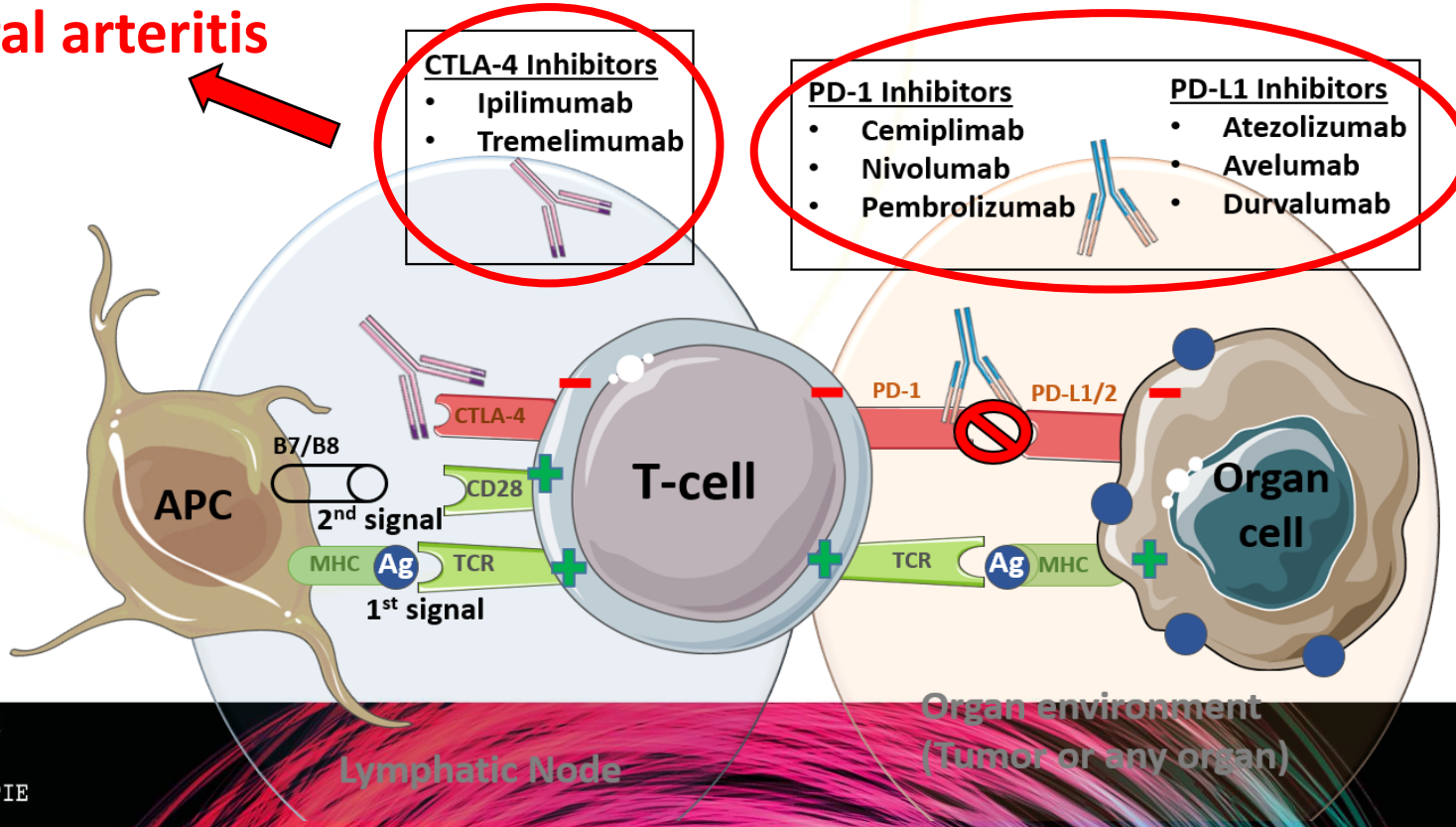
	n	IC/IC025
Myocarditis	**122 (0.39%)**	**3.47/3.2**
Pericardial diseases	**95 (0.3%)**	**1.93/1.63**
Cardiac supra-ventricular arrhythmias	**222 (0.71%)**	**0.75/0.56**
Vasculitis	**82 (0.26%)**	**0.36/0.03**
- **Temporal arteritis**	**18 (0.06%)**	**3.33/2.59**
- **Polymyalgia rheumatica**	**16 (0.05%)**	**2.12/1.33**
Heart Failure	225 (0.72%)	-0.28/-0.47
Cerebral hemorrhage	250 (0.8%)	-0.46/-0.65
Endocardial disorders	8 (0.03%)	0.38/-0.79
Hemorrhage (clinical events)	1,023 (3.27%)	-0.71/-0.80
Cerebral arterial ischemia	195 (0.62%)	-0.67/-0.88
Cardiac conductive disorders	37 (0.12%)	-0.42/-0.93
Myocardial infarction	167 (0.53%)	-0.91/-1.14
Biological hemostatic disorders favoring hemorrhage	135 (0.43%)	-0.95/-1.21
Arterial systemic ischemia	203 (0.65%)	-1.02/-1.23
Cardiac death or shock	136 (0.43%)	-1.03/-1.28
Hypertension and related end-organ damages	198 (0.63%)	-1.2/-1.42
Vascular neoplasm	4 (0.01%)	-0.33/-2.06
Torsade de pointes / Long QT	22 (0.07%)	-1.44/-2.11
Cardiac ventricular arrhythmias	22 (0.07%)	-1.52/-2.19
Pulmonary hypertension and related cardiac involvement	17 (0.05%)	-1.76/-2.53
Cardiac valve disorders	2 (0.01%)	-4.3/-6.89
Dyslipidemia	20 (0.06%)	-2.6/-3.3

ICI subgroup analysis

Total number of ICSRs	ROR and 95% CI [,] PD1 vs. CTLA4	ROR and 95% CI [,] COMB vs. MONO
Myocarditis	5.62 [2.46-12.88]	4.31 [2.86-6.38]
Pericardial diseases	2.28 [1.27-4.12]	1.1 [0.53-2.24]
Temporal arteritis	0.28 [0.11-0.74]	0.71 [0.07-3.94]

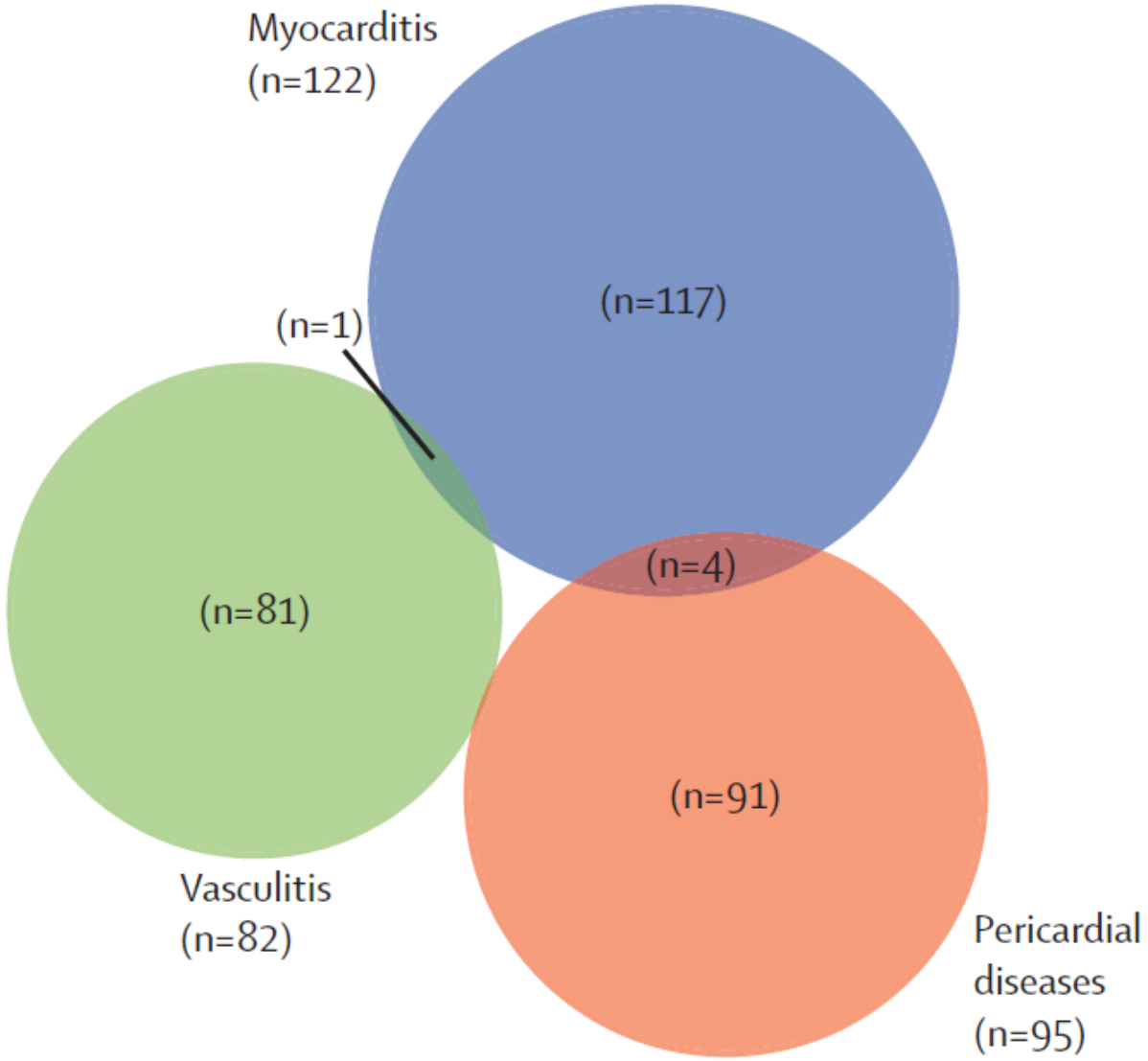
Temporal arteritis

Myocarditis
Pericarditis

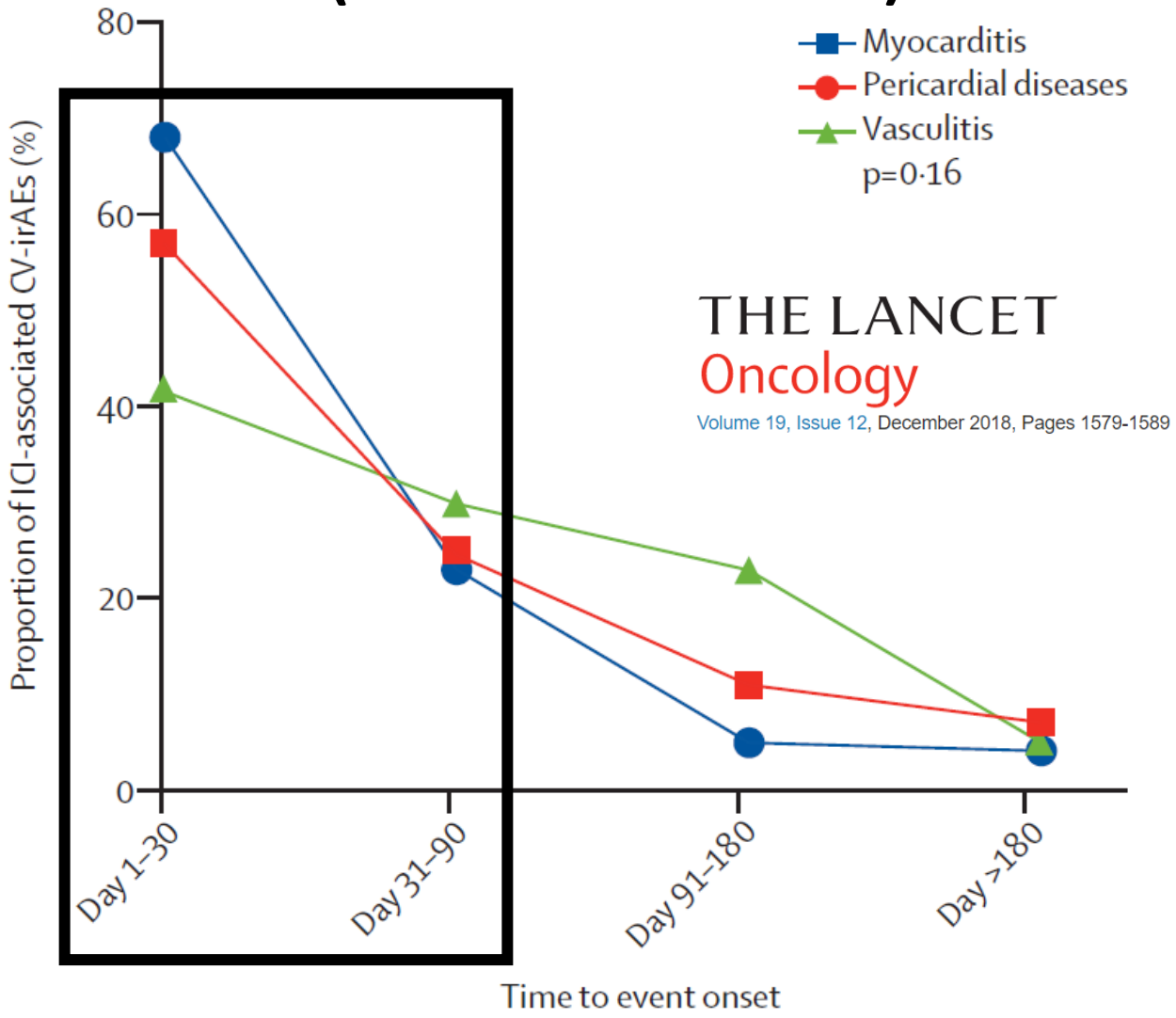


THE LANCET Oncology
Volume 19, Issue 12, December 2018, Pages 1579-1589

Very mild overlap



Short Time to onset (within 1-3 months)



Myocarditis incidence (from 0.06 to 1.14% …)

Clinical trials

Table 1. Incidence of Myocarditis and Myositis in Patients Receiving Nivolumab or Ipilimumab plus Nivolumab.

Characteristic	Nivolumab (N=17,620)	Nivolumab plus Ipilimumab (N=2974)
	no. (%)	
Myocarditis		
Any*	10 (0.06)	8 (0.27)
Fatal events	1 (<0.01)	5 (0.17)

Johnson Douglas B, …., Moslehi JJ

The NEW ENGLAND JOURNAL of MEDICINE

N ENGL J MED 375;18 NEJM.ORG NOVEMBER 3, 2016

Real-life cohorts

of the 964 patients at Massachusetts General Hospital who received an ICI between November 2013 and July 2017, 1.14% (11 patients) developed myocarditis and 0.52% developed a MACE.

Mahmood Syed S, …., Neilan TG

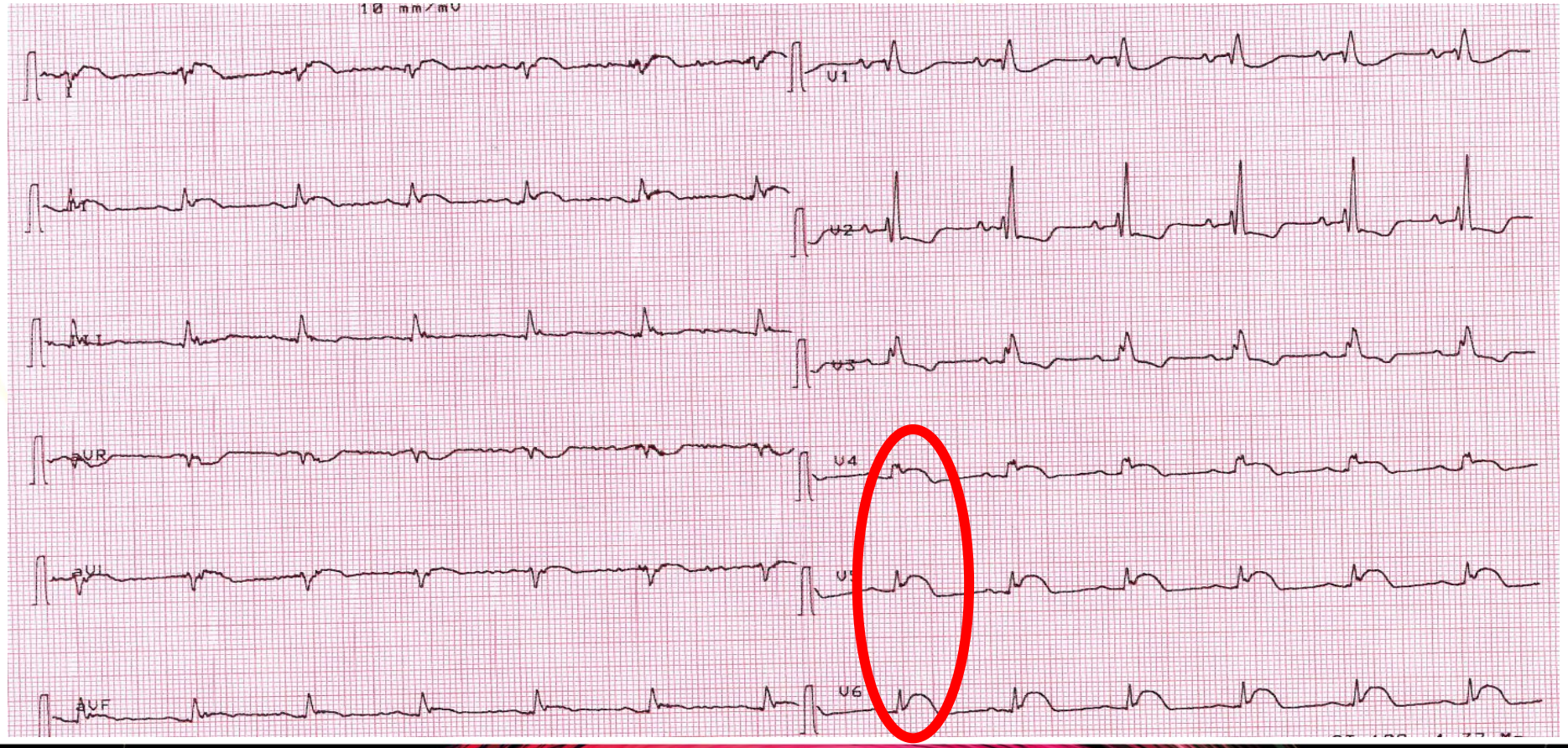
JACC JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

JACC VOL. 71, NO. 16, 2018

APRIL 24, 2018:1755-64

Mme M. 66yo

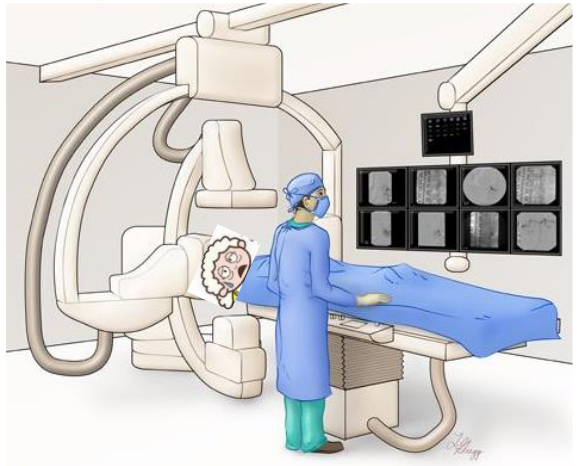
- Diplopia, and subacute, painful paresis affecting proximal muscles
- Ten days after the 3rd nivolumab dose (240 mg q2 weeks)
- 3 days later, acute chest pain

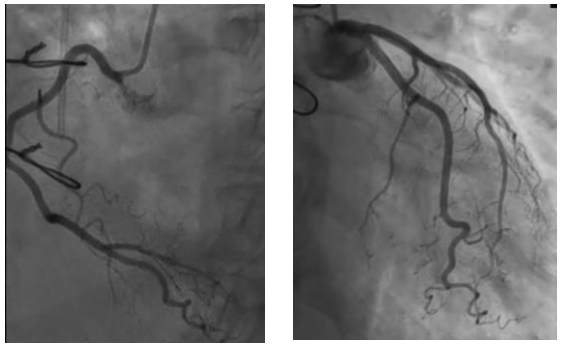


Acute ST+ ACS presentation

Mme M. 66yo

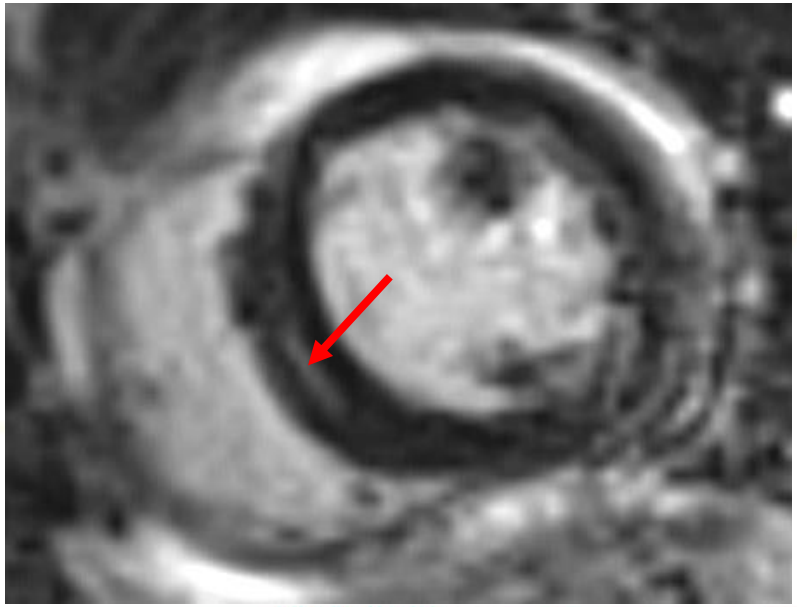
- **Normal coronary angiogram**
- Troponin-T (1616ng/L, *N<14ng/L*)
- NT-proBNP (4172ng/L)

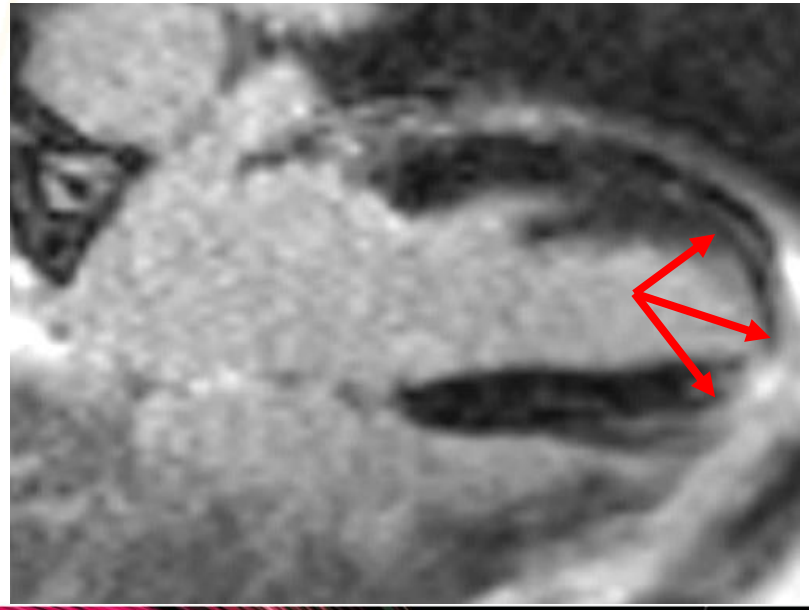




- Echocardiography: LVEF 55-60%, concentric remodeling, limited apical hypokinesia

⇨ **Cardiac MRI** **(positive septo-apical late gadolinium enhancement)**





WHITE PAPER

Myocarditis in the Setting of Cancer Therapeutics

Proposed Case Definitions for Emerging Clinical Syndromes in Cardio-Oncology

Bonaca M, …., Moslehi JJ

Mme M.

Circulation

Circulation. 2019;140:80–91.

Myocarditis – A Proposed Definition
Hierarchical definition accounting for different levels of evidence

Pathology	Imaging	ECG	Syndrome	Biomarkers

For all/other diagnosis/explanations (e.g. ACS) must be excluded

Definite Myocarditis:
- Pathology
  OR
- Diagnostic CMR + syndrome + (biomarker or ECG)
  OR
- ECHO WMA + syndrome + biomarker + ECG + negative angiography

Probable Myocarditis:
- Diagnostic CMR (no syndrome, ECG, biomarker)
  OR
- Suggestive CMR with either syndrome, ECG, or biomarker
  OR
- ECHO WMA and syndrome (with either biomarker or ECG)
  OR
- Syndrome with PET scan evidence and no alternative diagnosis

Possible Myocarditis:
- Suggestive CMR with no syndrome, ECG or biomarker
  OR
- ECHO WMA with syndrome or ECG only
  OR
- Elevated biomarker with syndrome or ECG and no alternative diagnosis

WHITE PAPER

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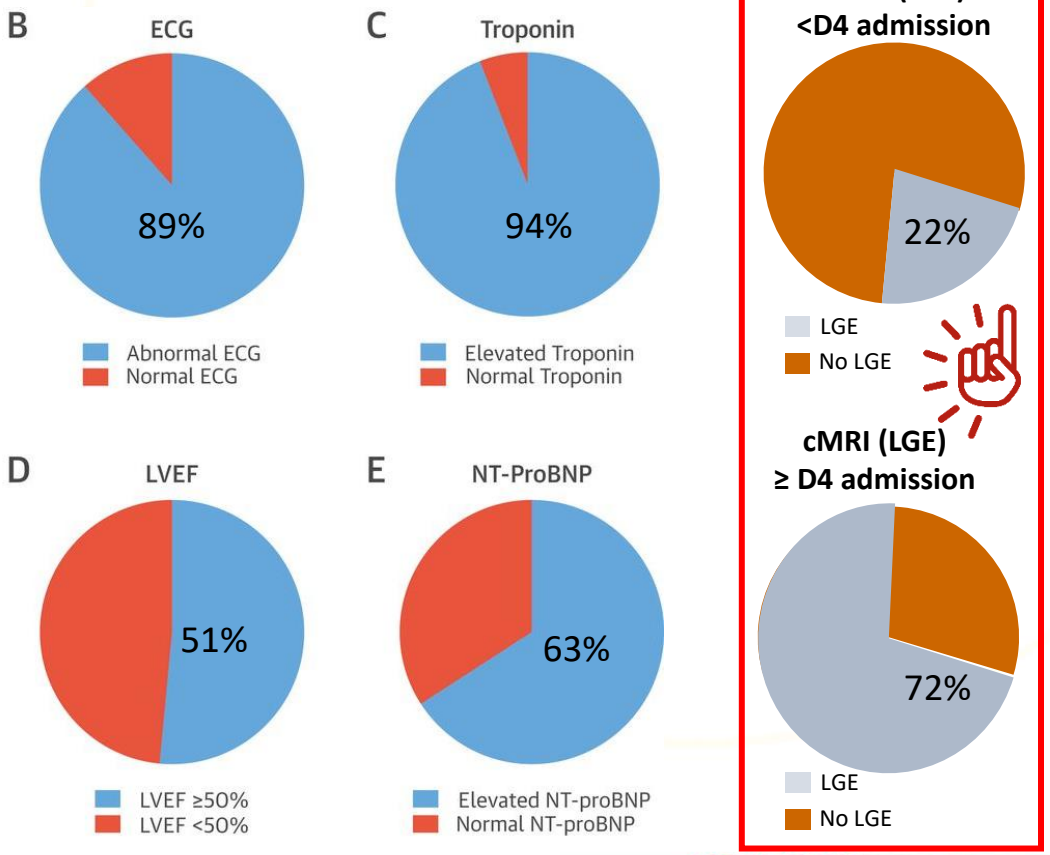
Bonaca M, et al.



Mahmood Syed S, et al.

JACC VOL. 71, NO. 16, 2018

APRIL 24, 2018:1755-64

Zhang [redacted]

European Heart Journal (2020) **41**, 1733–1743

doi:10.1093/eurheartj/ehaa051

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  OR
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Peripheral muscular involvement – a coincidence ?

- **Myositis and myasthenia gravis like syndrome** (diaphragmatitis)

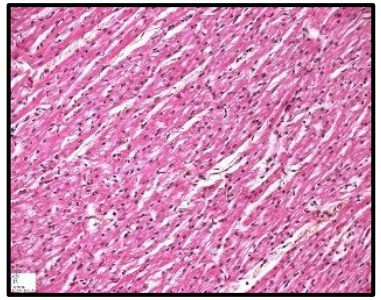
- **Negative antibodies work-up**: anti-acetylcholine receptor and muscle-specific tyrosine kinase

- **Electromyography** : myogenic syndrome without neuromuscular dysfunction

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)

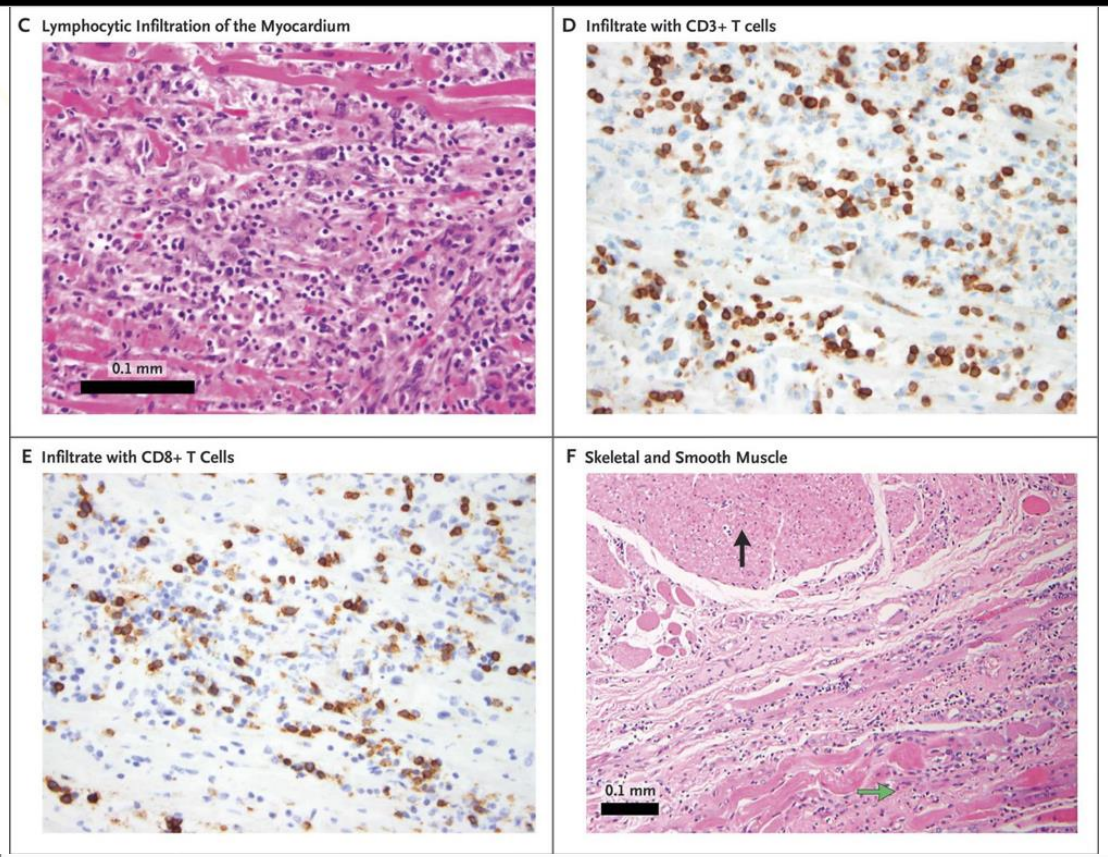
Salem JE, et al. Lancet Oncol

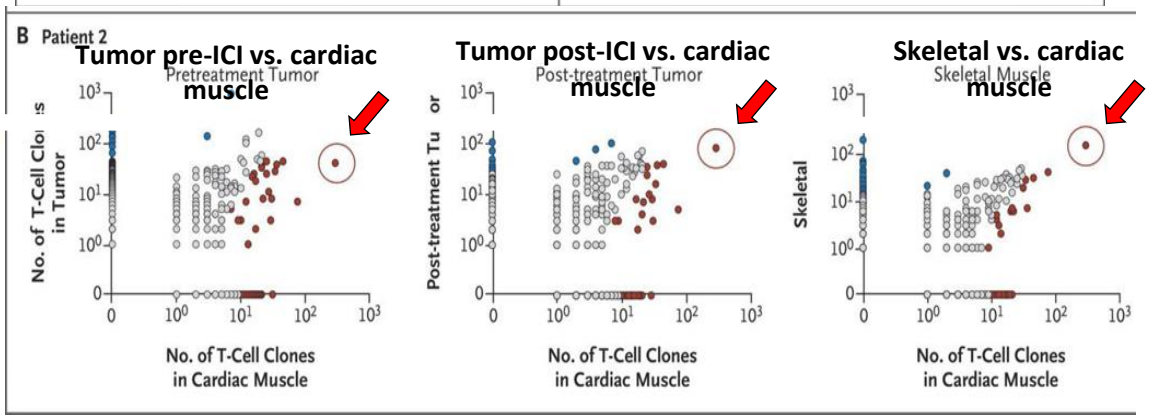
Pathophysiology



Normal cardiac biopsy

- ➡ Infiltration of myocardium and muscles with T-cells and macrophages
- ➡ Myocardium and muscle cell death
- ➡ Antigens present in myocardium, muscle recognized by same anti-reactive auto-reactive T-cell clones (Alpha-myosin)

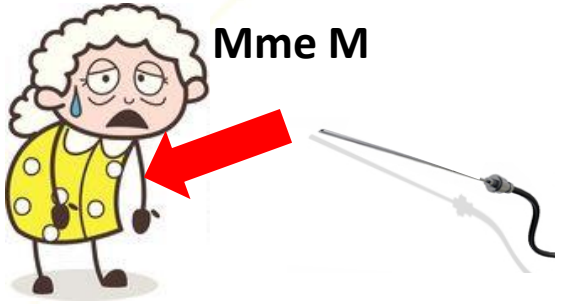




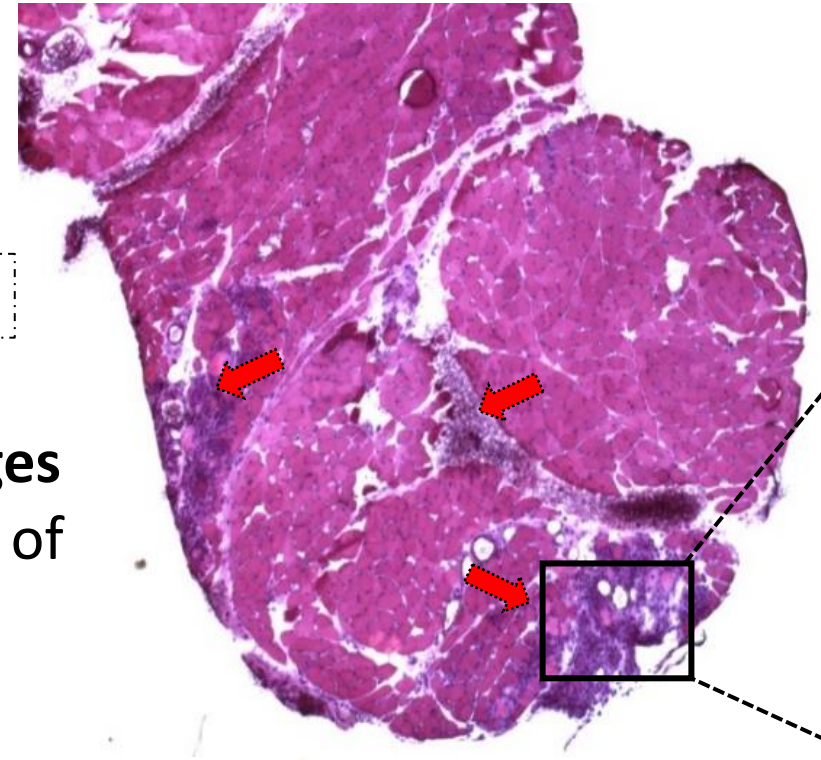
The NEW ENGLAND JOURNAL of MEDICINE

Johnson DB, …., Moslehi J. *N Engl J Med. 2016*

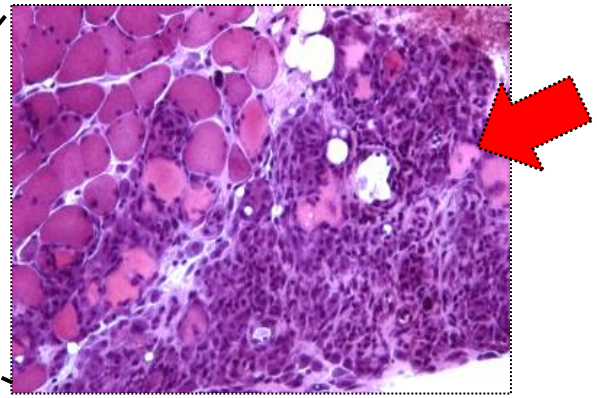
https://doi.org/10.21203/rs.3.rs-1315661/v1



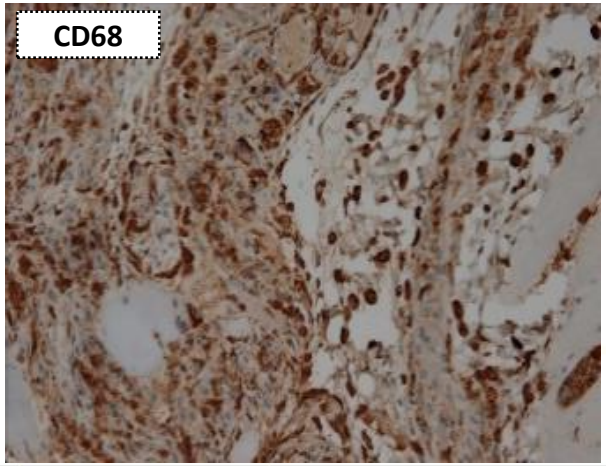
Muscle biopsy

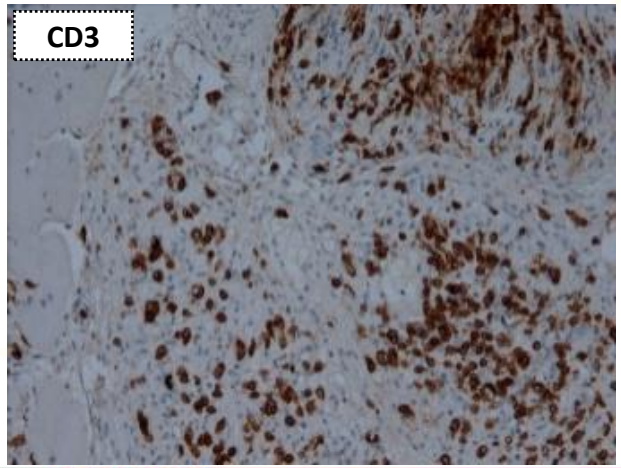


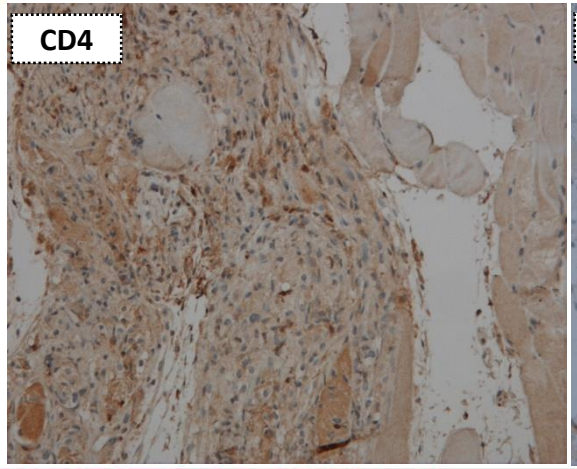
H&E staining

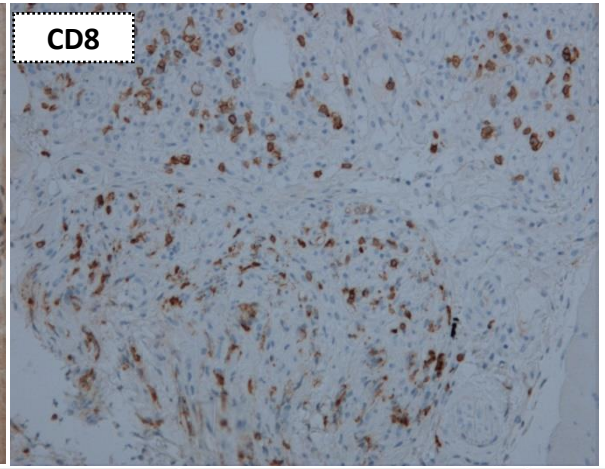


Important **T-cell** and **macrophages infiltration** with multiple lesions of focal necrosis









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 Guideline Update

Schneider BJ, et al.

2021

9.1. Myocarditis, Pericarditis, Arrhythmias, Impaired Ventricular Function With Heart Failure, and Vasculitis

Workup and evaluation
- ECG
- Troponin, and CPK to rule out concurrent myositis, especially in patients treated with combination immune therapies. Alternative reasons for elevation should be ruled out.
- If elevated, troponin should be serially monitored. With elevated troponin, be aware of the potential for triple M irAEs—myositis, myasthenia, and myocarditis—and refer to subspecialties.
- BNP
- Echocardiogram
- Chest X-ray

Additional testing to be guided by cardiology and may include:
- Stress test
- Cardiac catheterization
- Cardiac MRI

Grading	Management
G1 Abnormal cardiac biomarker testing without symptoms and with no ECG abnormalities	All grades warrant workup and intervention, given the potential for cardiac compromise. Hold ICPi for G1 elevated troponin[a] and recheck troponin 6 hours later. May consider resuming once normalized or if believed not to be related to ICPi.
G2 Abnormal cardiac biomarker testing with mild symptoms or new ECG abnormalities without conduction delay	Hold ICPi and discontinue for ≥ G2. For patients with grade ≥ 2, early (ie, within 24 hours) initiation of high-dose corticosteroids (1-2 mg/kg/d of prednisone, oral or IV depending on symptoms) should be considered as it is likely to be beneficial without adverse effects. Admit patient for cardiology consultation. Management of cardiac symptoms according to ACC/AHA guidelines and with guidance from cardiology.
G3 Abnormal cardiac biomarker testing with either moderate symptoms or new conduction delay	Immediate transfer to a coronary care unit should be considered for patients with elevated troponin or conduction abnormalities. For new conduction delay, consider a pacemaker.
G4 Moderate to severe decompensation, IV medication or intervention required, life-threatening conditions	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.[210] Consider abatacept (costimulatory molecule blockade) or alemtuzumab (CD52 blockade) as additional immunosuppression in life-threatening cases.[211,212]

1 **High dose corticosteroids**

2 If corticoresistant

Other immuno-modulators

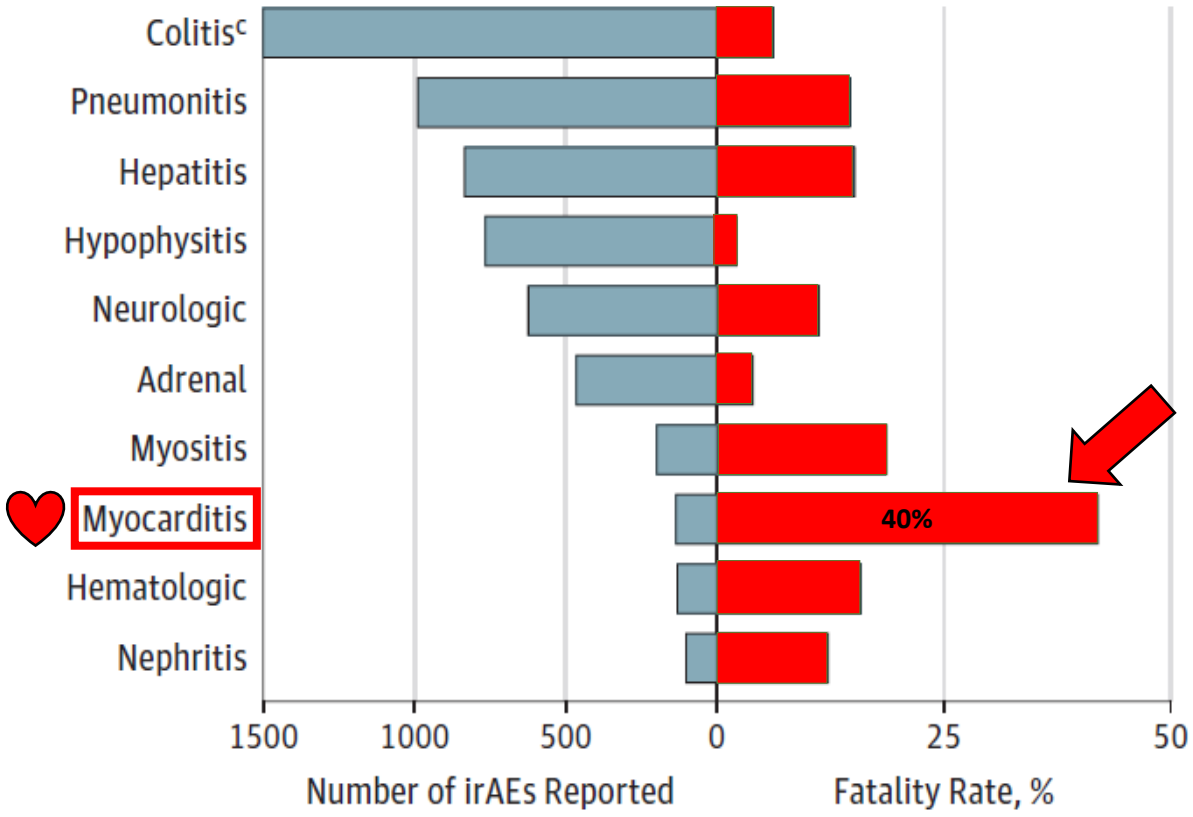
- **Mycophenolate**
- **Infliximab**
- **Antithymocyte globulin**

2 ★ If life-threatening

- **Abatacept**

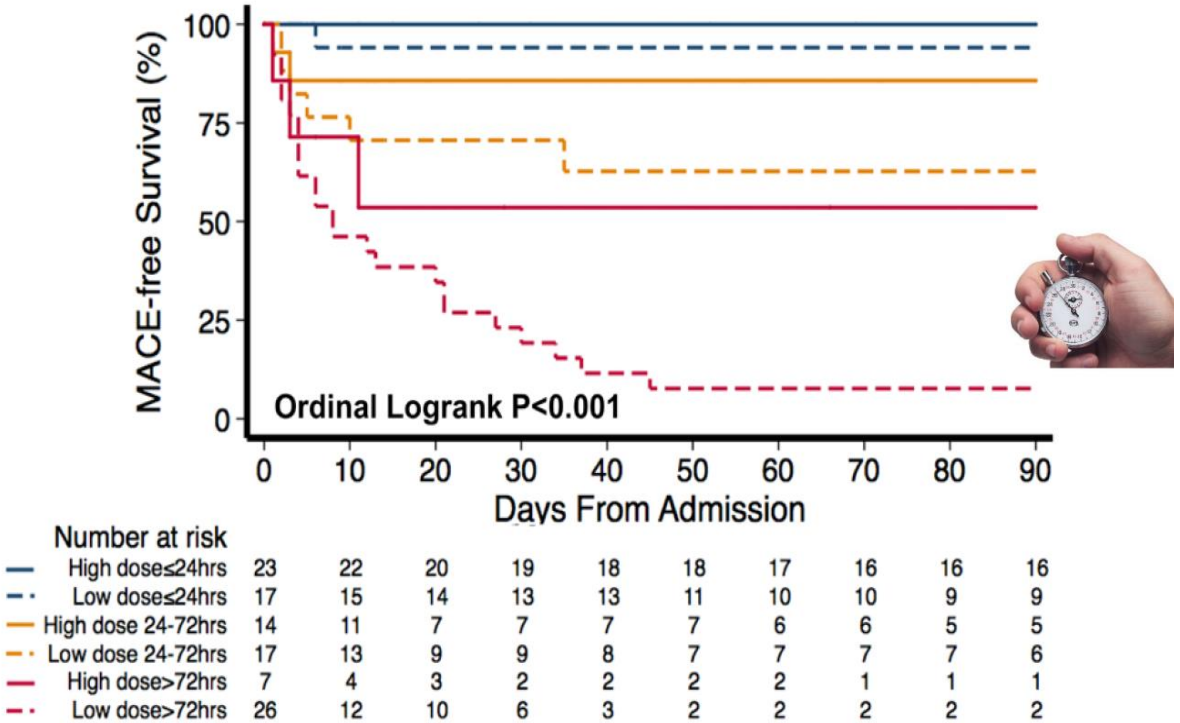
Fatal Toxic Effects of ICI-irAE in VigiBase

n:613 fatal ICI immune toxicities



Wang DY, Salem JE, et al. *JAMA Oncol*. 2018 ;4 :1721-1728. .

Major Adverse Cardiovascular Events and the Timing and Dose of Corticosteroids in Immune Checkpoint Inhibitor–Associated Myocarditis



RESEARCH LETTER Circulation

2020

Lili Zhang, MD, ScM
⋮
Tomas G. Neilan, MD, MPH

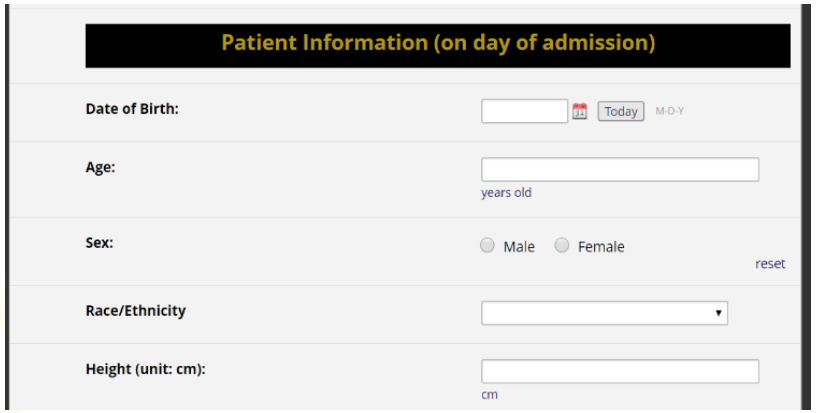
Building an international Multicenter Registry

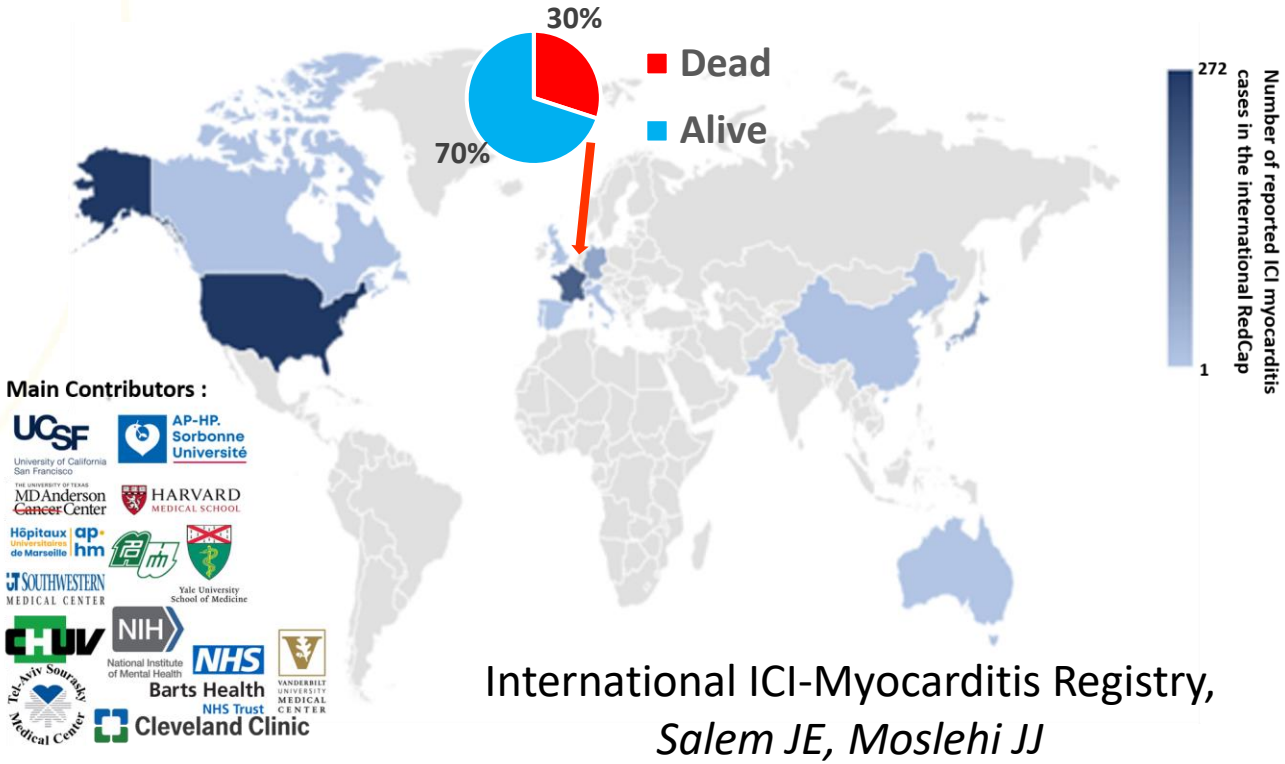
- Cases identified via literature review & clinician contacts
- Online survey:

https://is.gd/cardioonc

- >600 unique cases
- Datapoints:
  - Cardiac, autoimmune & oncologic history
  - ECG raw data
  - Clinical presentation
  - Workup & treatment
  - Mortality and prognosis evolution
  - Treatment modality

REDCap



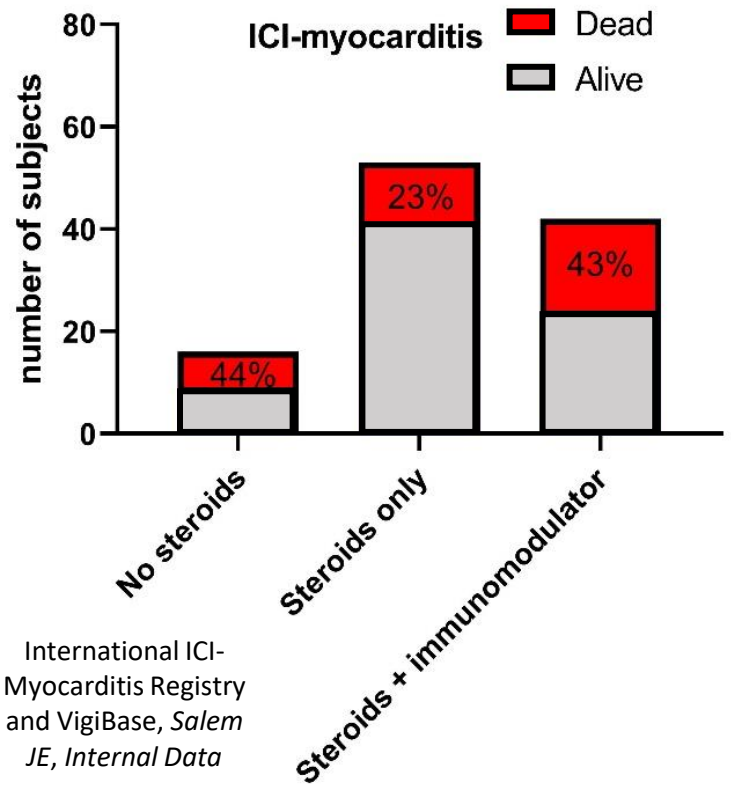


International ICI-Myocarditis Registry,
Salem JE, Moslehi JJ

ICI-myocarditis prognosis

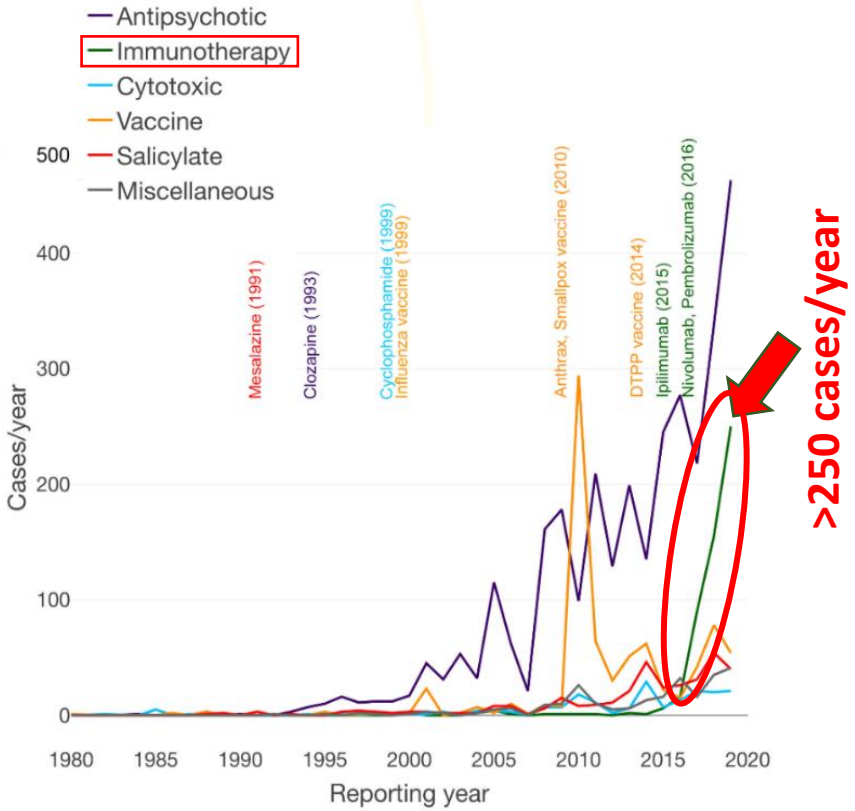
High Fatality Rate
X2 when corticoresistant (Myocarditis)
Fatality: 45%→25% over time

Fatality depending of treatments
Using an ongoing international registry
n:180

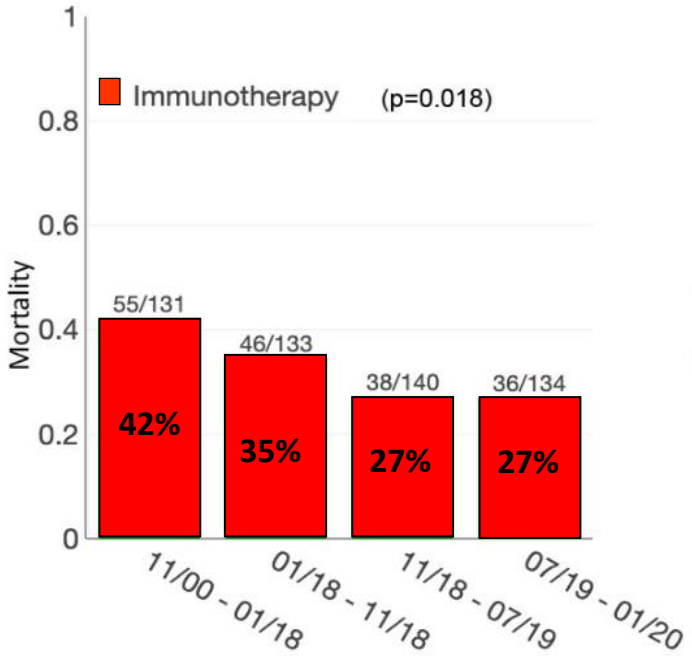


International ICI-Myocarditis Registry and VigiBase, *Salem JE, Internal Data*

Cases/year and fatality rate over years for ICI-myocarditis reporting within VigiBase (thru 2020)

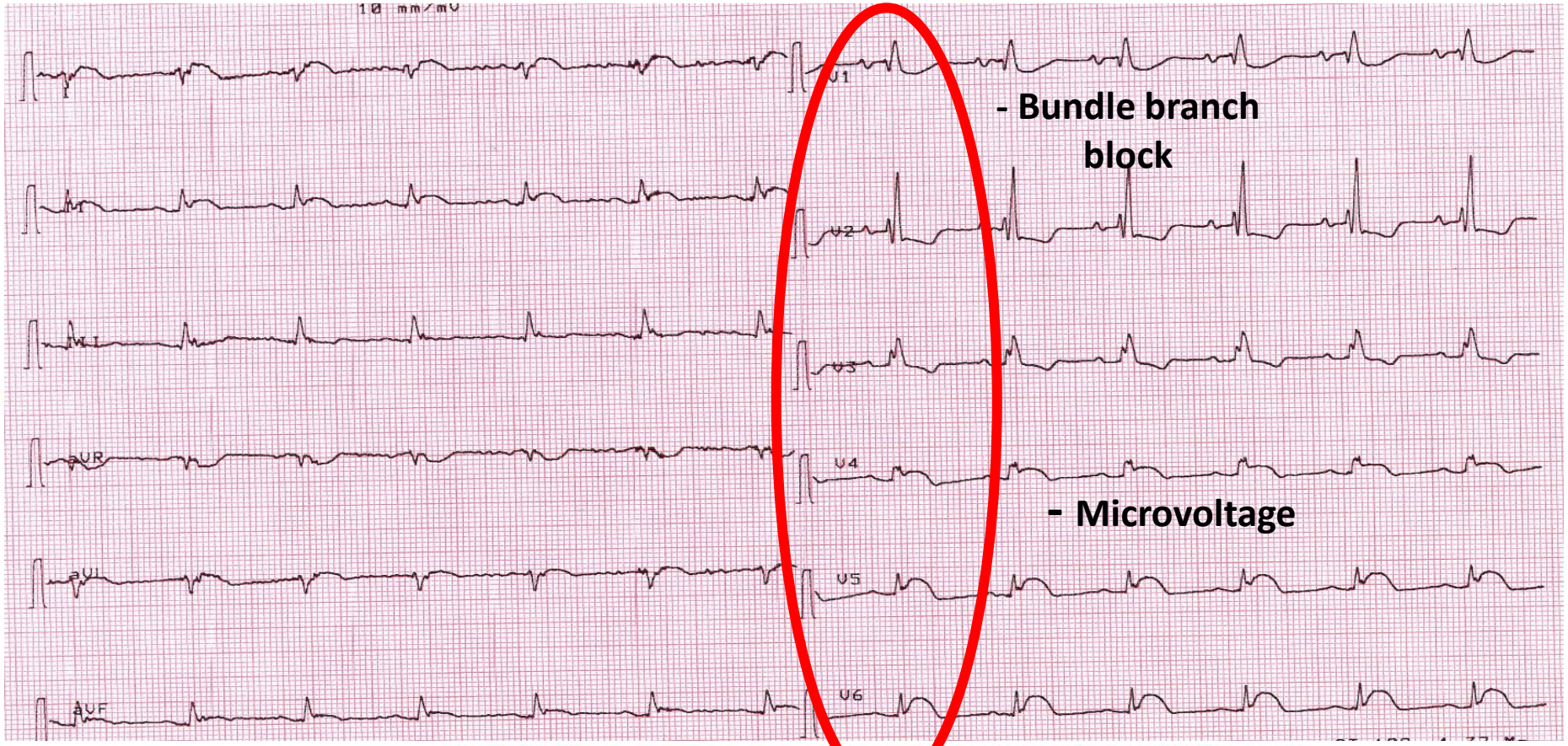


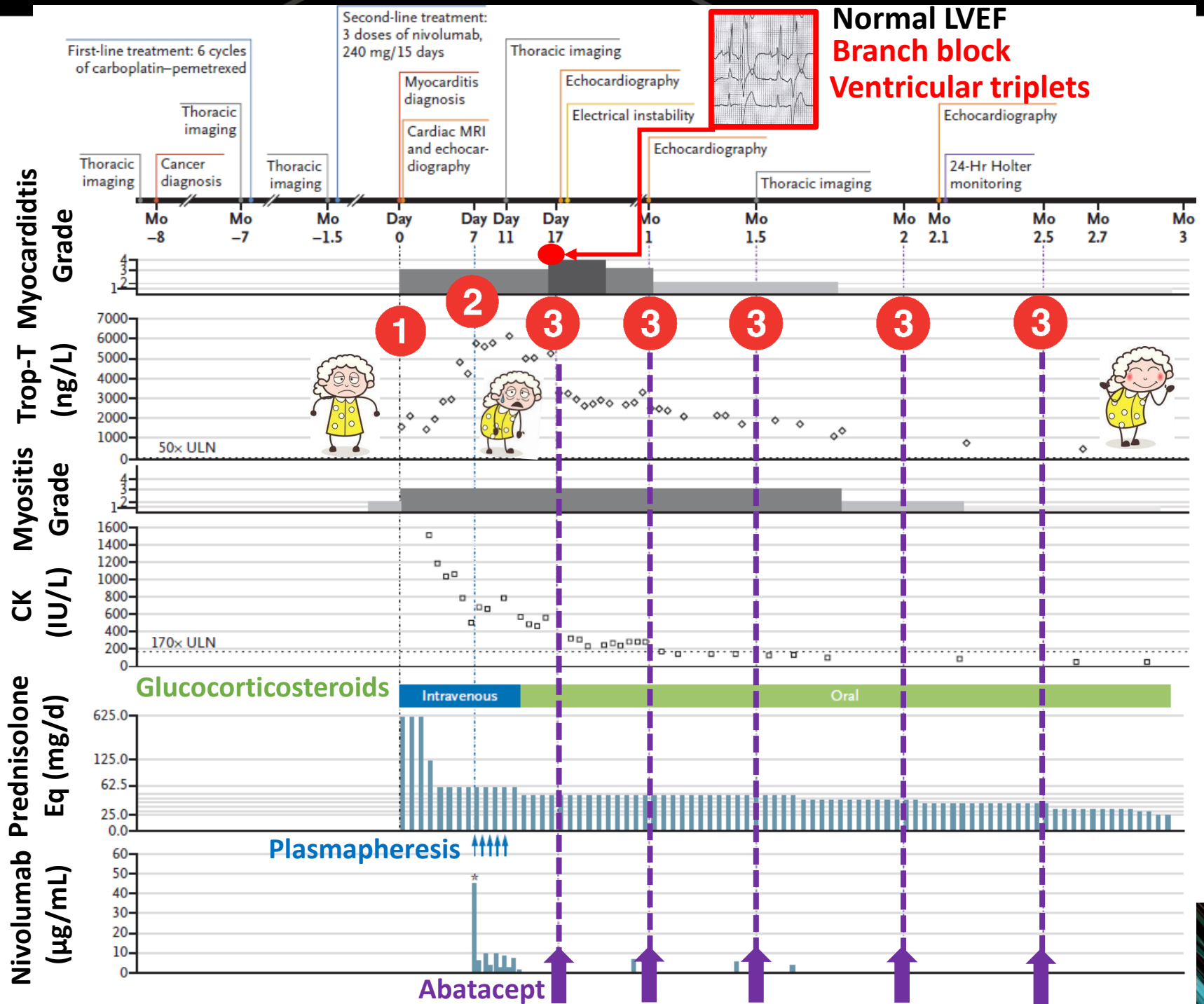
Nguyen LS, …, Salem JE
Nat Commun. 2022



Mme M. 66yo

- Diplopia, and subacute, painful paresis affecting proximal muscles
- Ten days after the 3rd nivolumab dose (240 mg q2 weeks)
- 3 days later, acute chest pain





1

High dose corticosteroids

2

Plasmapheresis

3

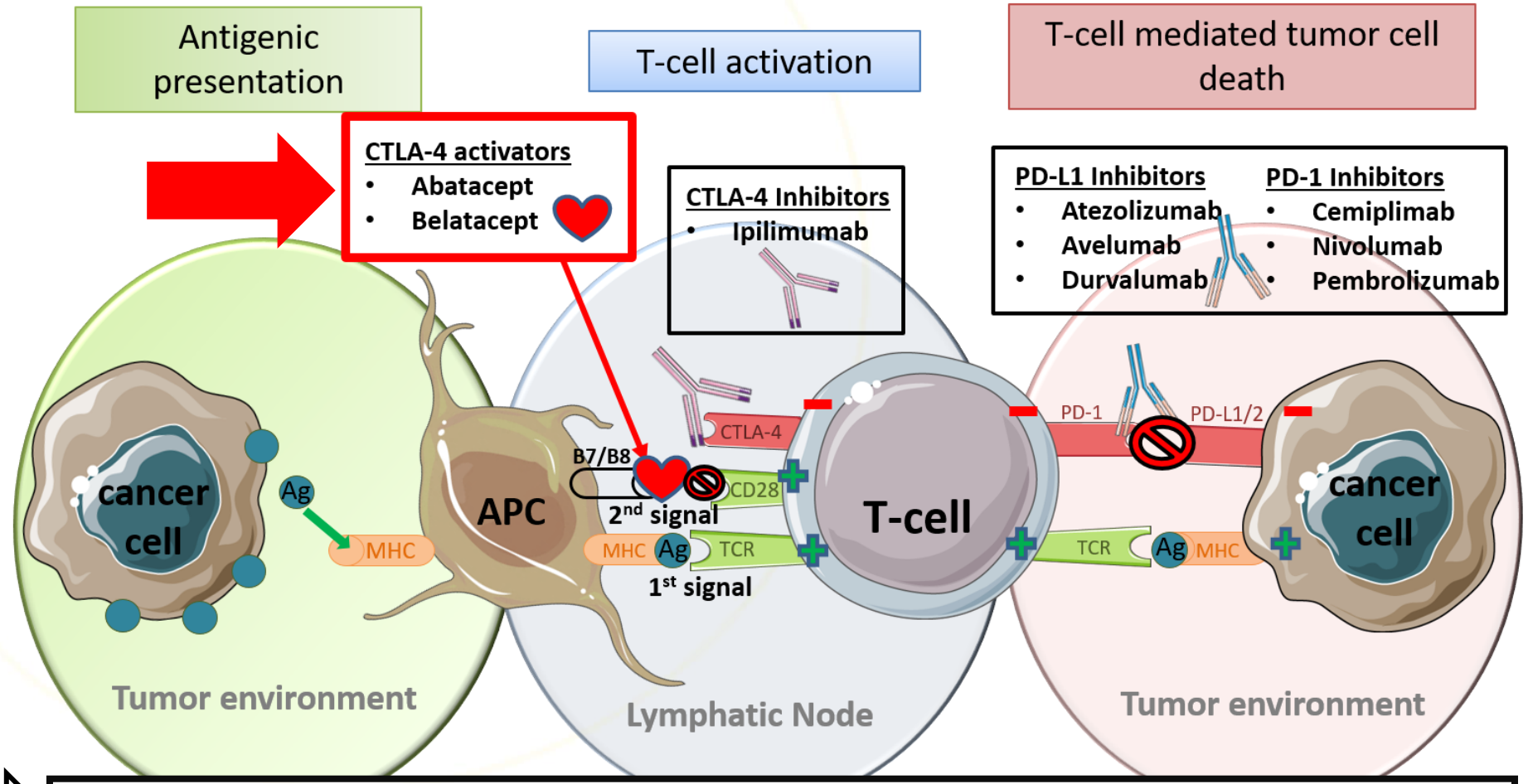
Abatacept

The NEW ENGLAND JOURNAL of MEDICINE

N ENGL J MED 380;24 NEJM.ORG JUNE 13, 2019

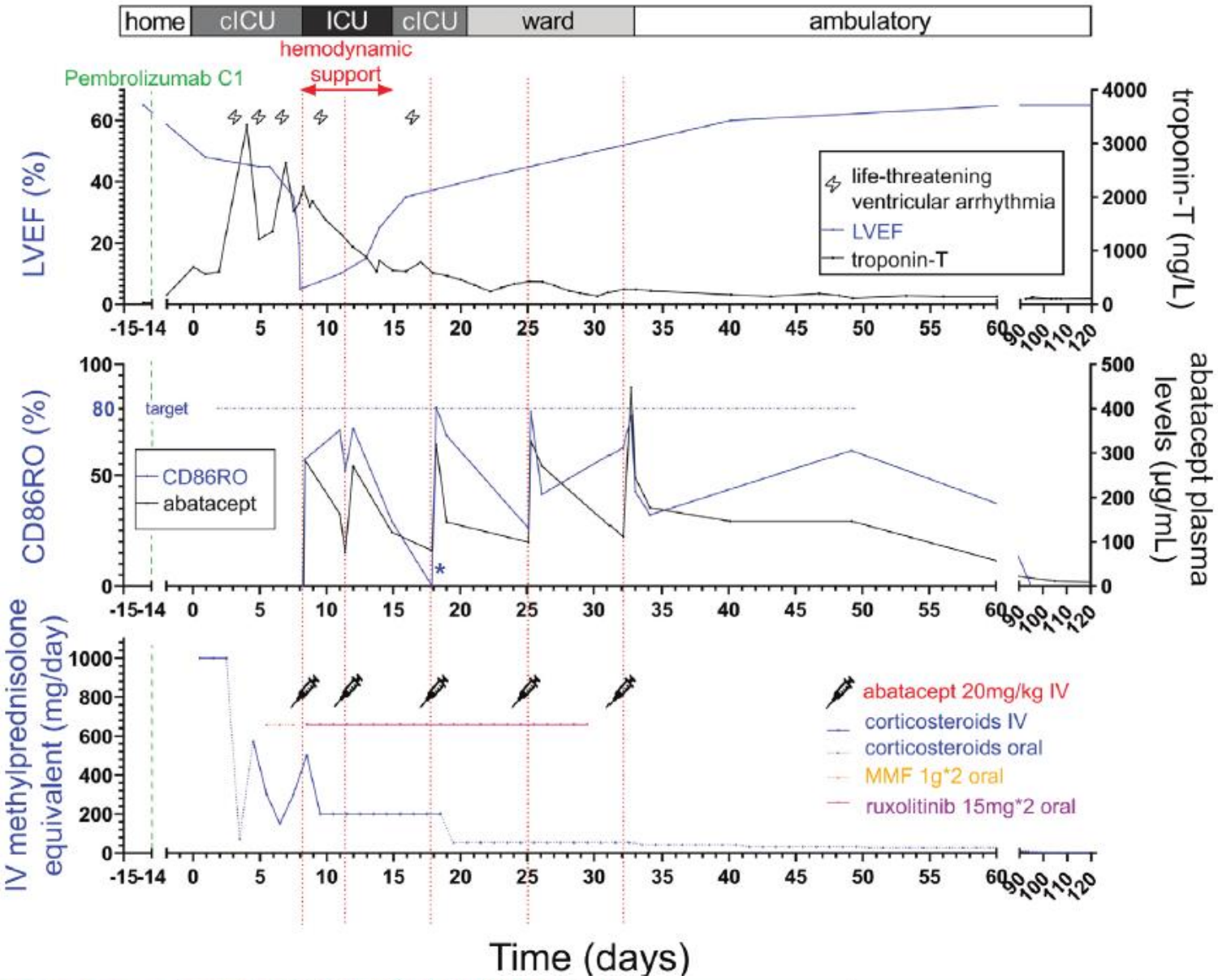
29 et 30 SEPTEMBRE 2022
UIC-P - Espaces Congrès
16, rue Jean Rey - 75015 Paris

Abatacept, a CTLA-4 agonist … A reversal agent for severe cortico-resistant immune related adverse event?



Phase II trial testing abatacept for ICI-myocarditis at APHP.Sorbonne University

Reversal of ICI fulminant myocarditis using **personalized-dose-adjusted abatacept** and ruxolitinib: **Proof of concept**



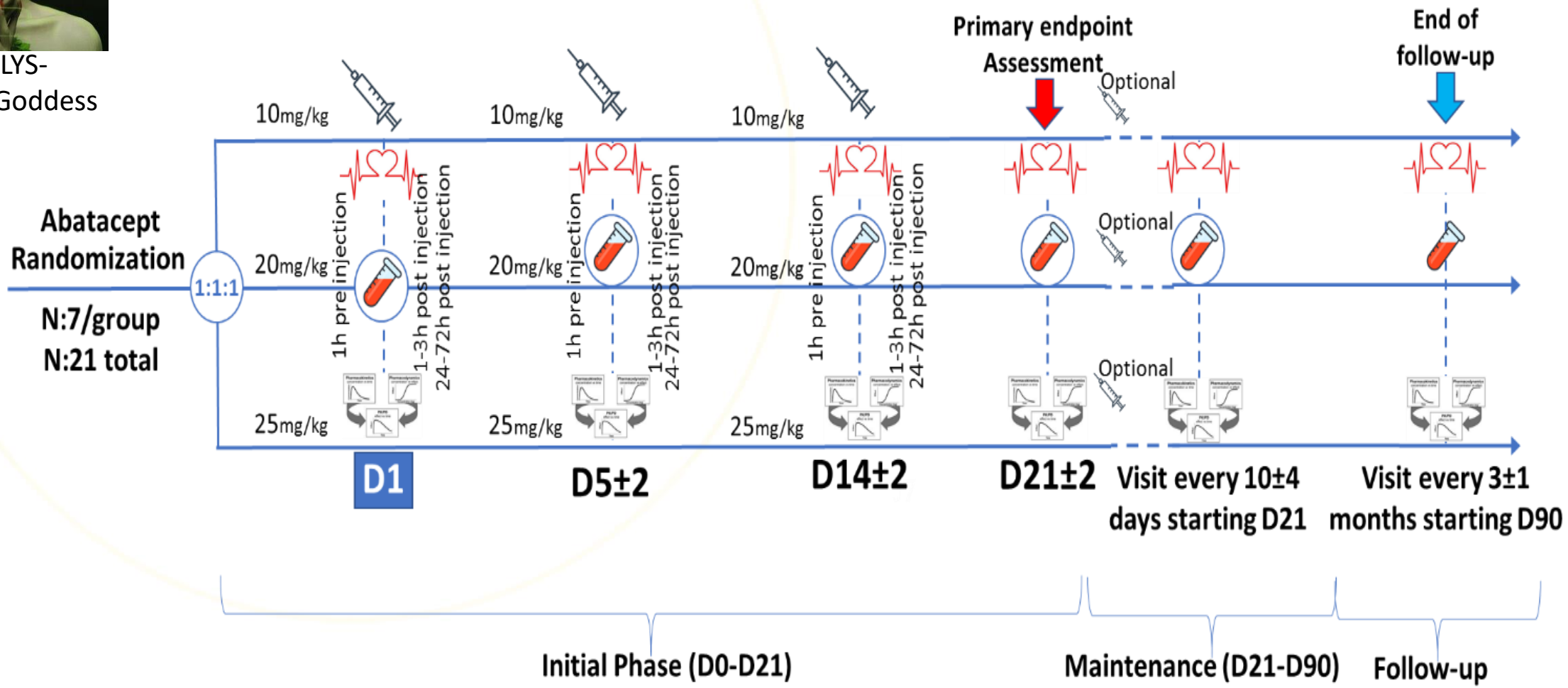
Journal for ImmunoTherapy of Cancer

Nguyen L, …, Salem JE (*2022*)

ACHLYS-
Poison Goddess

AbataCept for the Treatment of Immune-cHeckpoint Inhibitors Induced mYocarditiS (ACHLYS)

ACHLYS Trial - *NCT05195645*



ICI Myocarditis APHP.Sorbonne University Crew