

CONGRESSO

ROMA, 25 - 27 Giugno 2026

IL CUORE INFIAMMATO

MIOCARDITI DA IMMUNE CHECKPOINT INHIBITORS: COME RICONOSCERLE E TRATTARLE

Enrico Ammirati, *MD, PhD*

De Gasperis Cardio Center

ASST GRANDE OSPEDALE METROPOLITANO

NIGURDA, Milano, ITALY

enrico.ammirati@ospedaleniguarda.it

@AmmiratiEnrico

26 giugno 2025



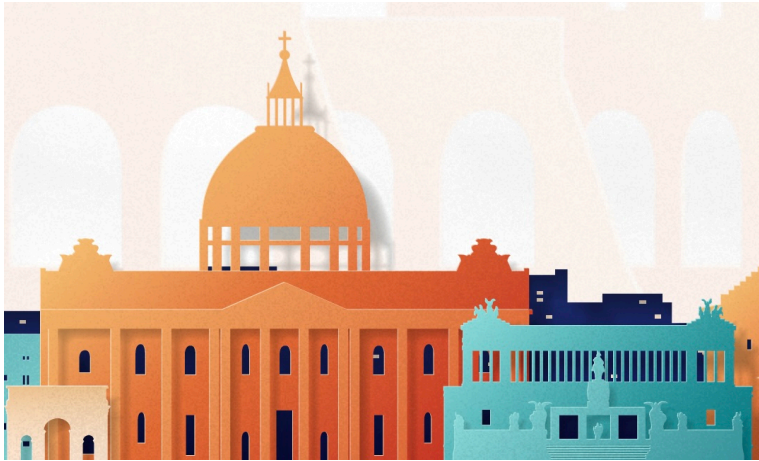
Sistema Socio Sanitario



Ospedale Niguarda



Regione
Lombardia



- **LEXEO, ICON**
Consultant
- **Summeet, HOTGEN**
Past Consultant
- **AMERICAN HEART ASSOCIATION**
Associate Editor –
CIRCULATION HF



- NextGenerationEU (PNRR-MAD-2022-12376225; PI of the **CMP-MYTHiC trial and registry** [Cardiomyopathy with Myocarditis Therapy with Colchicine])
- NextGenerationEU (PNRR-MCNT2-2023-12377618; Collaborator of the **CARIBIAM study**)
- **Belgian FWO – Project Fundamental Research G034622N (MYTHS-MR trial)**

KEY ARTICLES



ESC

European Society
of Cardiology

European Heart Journal (2025) 00, 1–13
<https://doi.org/10.1093/eurheartj/ehaf315>

CLINICAL RESEARCH

Cardio-oncology

RESEARCH ARTICLE

Abatacept/Ruxolitinib and Screening for Concomitant Respiratory Muscle Failure to Mitigate Fatality of Immune-Checkpoint Inhibitor Myocarditis



Joe-Elie Salem¹, Marie Bretagne¹, Baptiste Abbar^{1,2}, Sarah Leonard-Louis³,

Cancer Discovery 2023



ESC

European Society
of Cardiology

European Heart Journal (2025) 00, 1–17
<https://doi.org/10.1093/eurheartj/ehaf682>

FASTTRACK – CLINICAL RESEARCH

Cardio-oncology

Incidence and risk factors of immune checkpoint inhibitor myocardial and muscle toxicity: a French nationwide study

Joe-Elie Salem^{1,*}, Aya Ajrouche^{2,3}, Antoine Rozes³, Sandrine Pinto², Yann De Rycke^{2,3}, and Florence Tubach^{2,3,*}

EJH 2025

Immune checkpoint inhibitor-associated myocarditis: a novel risk score

John R. Power^{1,†}, Charles Dolladille^{2,†}, Benay Ozbay³,

EJH 2025

nature reviews cardiology

<https://doi.org/10.1038/s41569-026-01276-w>

Review article

Check for updates

Global epidemiology of myocarditis: disparities in age, sex and geography

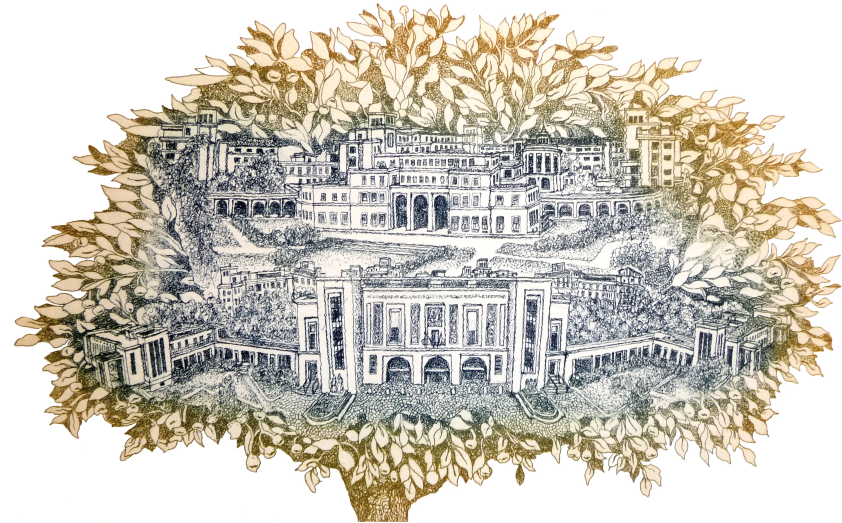
Karin Klingel^{1,✉}, Carsten Tschöpe^{2,3,4,5}, Dong Keon Yon^{6,7}, George A. Mensah⁸, Brittany N. Weber⁹, Amy R. Kontorovich¹⁰, Sooji Lee¹¹, Leslie T. Cooper¹² & Enrico Ammirati^{13,14}

Nat Rev Cardiol 2026



AGENDA – ICI-ASSOCIATED MYOCARDITIS

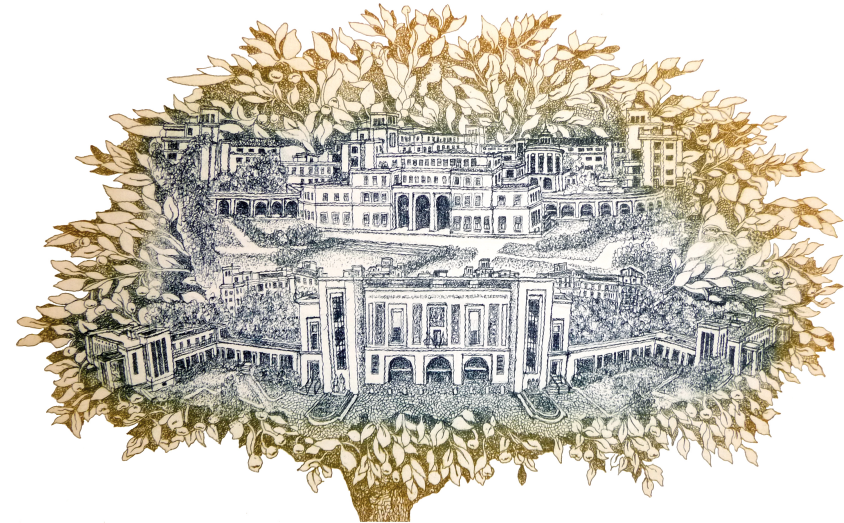
- PREVALENCE
- MECHANISMS
- DIAGNOSIS
- RISK SCORE
- THERAPY
- FINAL CONSIDERATIONS/THM





AGENDA – ICI-ASSOCIATED MYOCARDITIS

- **PREVALENCE**
- MECHANISMS
- DIAGNOSIS
- RISK SCORE
- THERAPY
- FINAL CONSIDERATIONS/THM



Global epidemiology of myocarditis: disparities in age, sex and geography

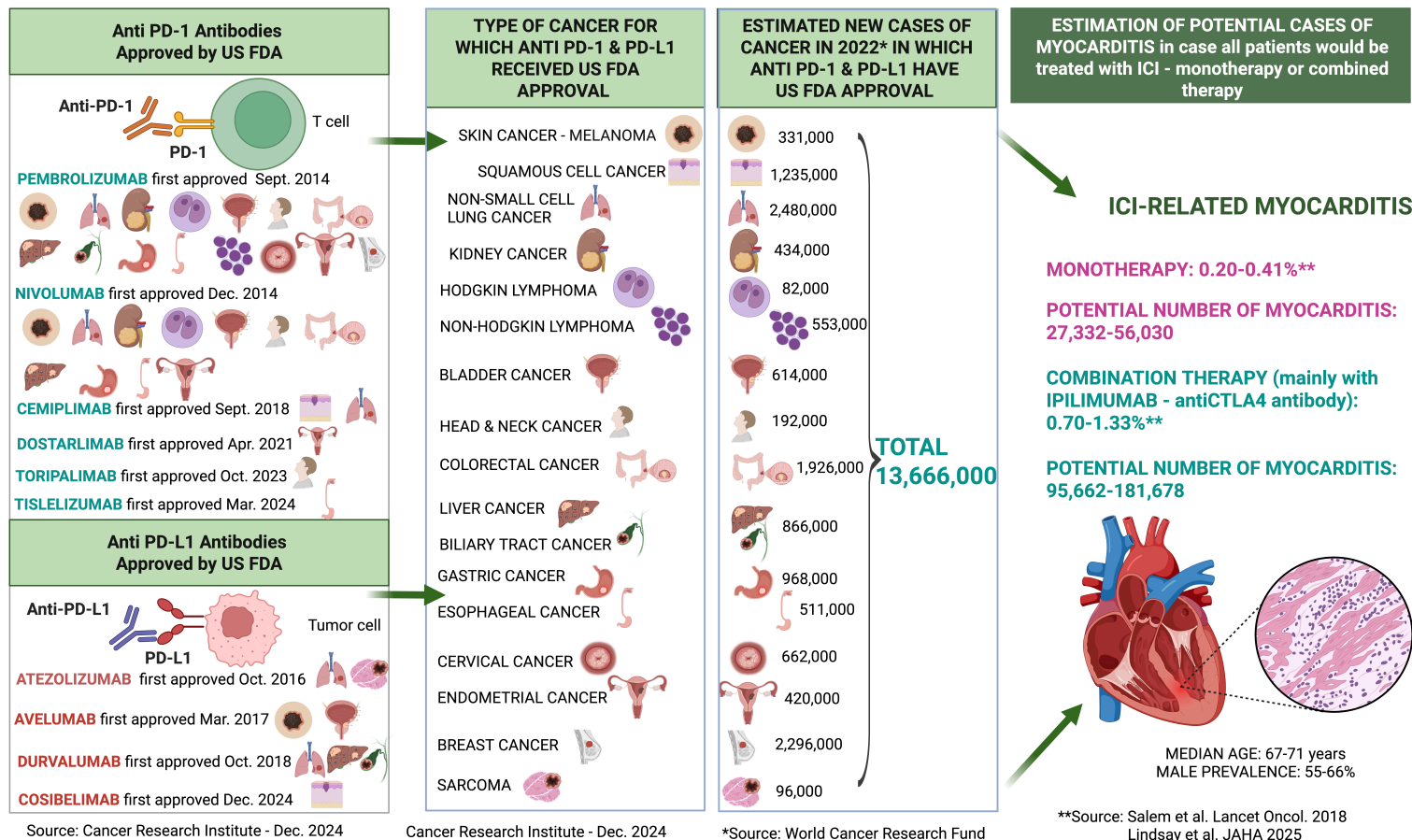
Karin Klingel¹✉, Carsten Tschöpe^{2,3,4,5}, Dong Keon Yon^{6,7}, George A. Mensah⁸, Brittany N. Weber⁹, Amy R. Kontorovich¹⁰, Sooji Lee¹¹, Leslie T. Cooper¹² & Enrico Ammirati^{13,14}

3 – 18 out of 100 MYOCARDITIS
will be ICI-mediated myocarditis

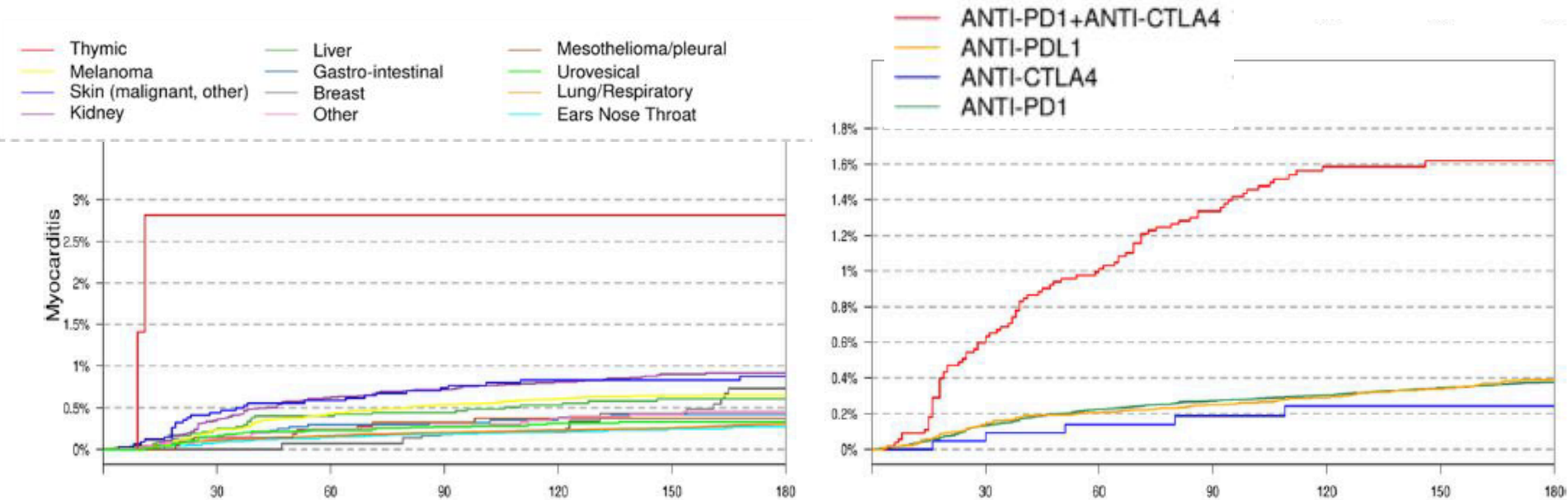
**Figures based on GBD data*

THE DIMENSION OF THE ISSUE

Estimation of potential cases of MYOCARDITIS Associated With Immune Checkpoint Inhibitors



INCIDENCE OF MYOCARDIAL & MUSCULAR TOXICITY- French nationwide data



DATA from 172,363 patients treated with ICI

***ICI myotoxicities at 6 months 0.7-0.9%**

***ICI myocarditis 0.3% - co-occurring with myositis in 13-23%**

***7.1% in patients with Thymic cancer – HR 12.9**

***Melanoma HR 2.4**



AGENDA – ICI-ASSOCIATED MYOCARDITIS



- PREVALENCE



- **MECHANISMS**



- DIAGNOSIS



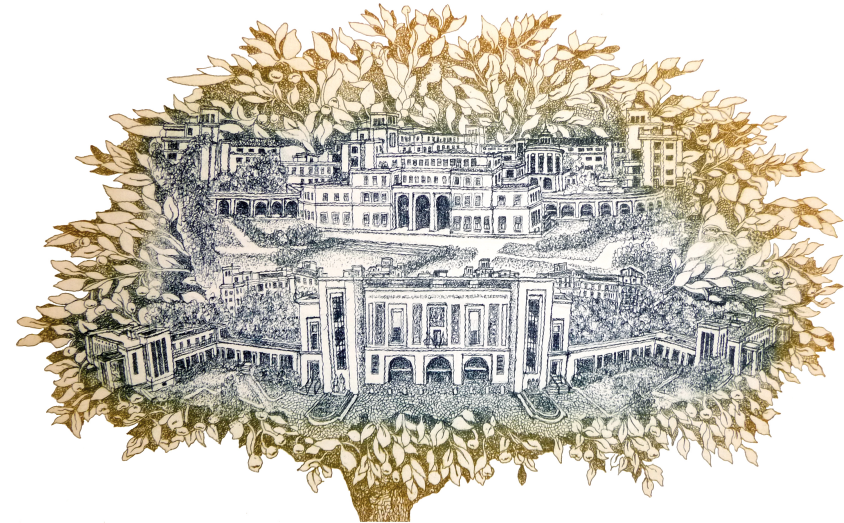
- RISK SCORE



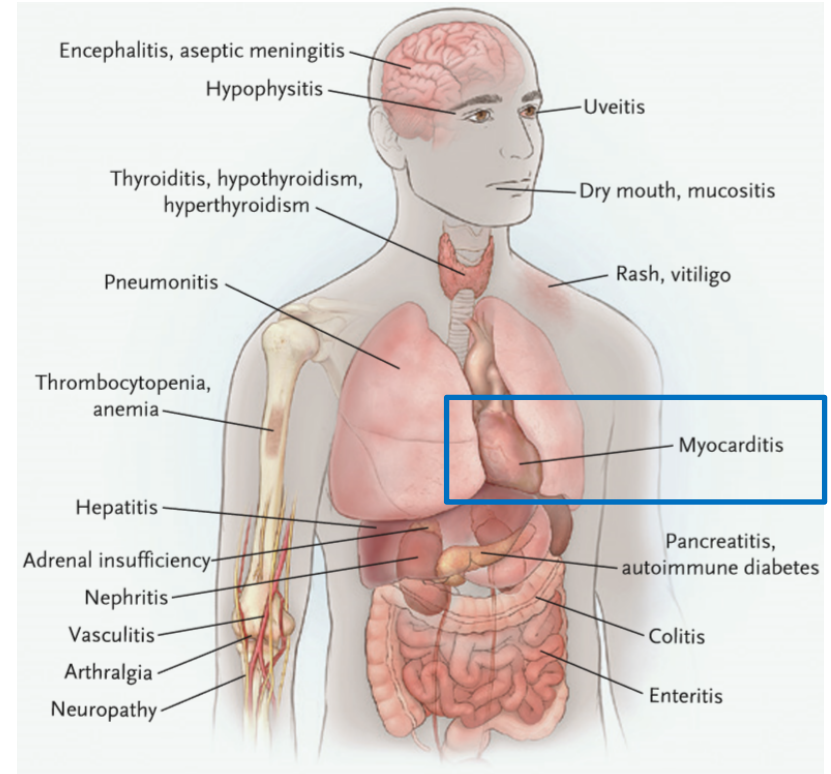
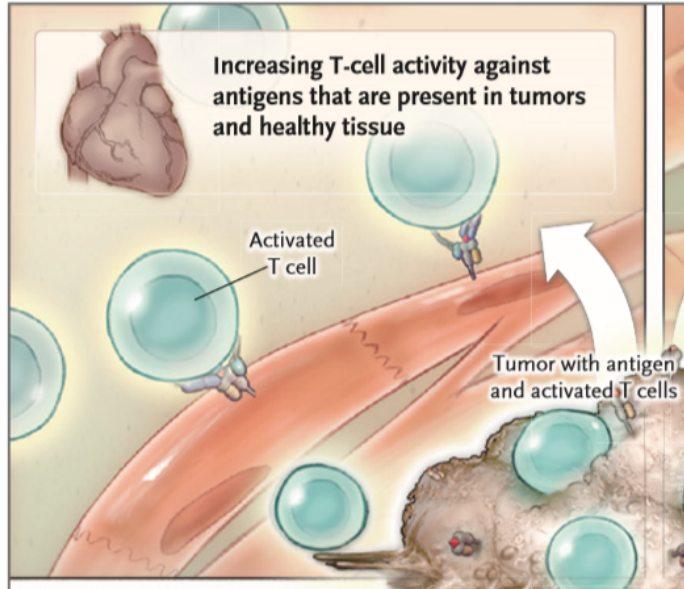
- THERAPY



- FINAL CONSIDERATIONS/THM



PROPOSED MECHANISMS OF ICI-INDUCED MYOCARDIAL INJURY IN ACUTE MYOCARDITIS

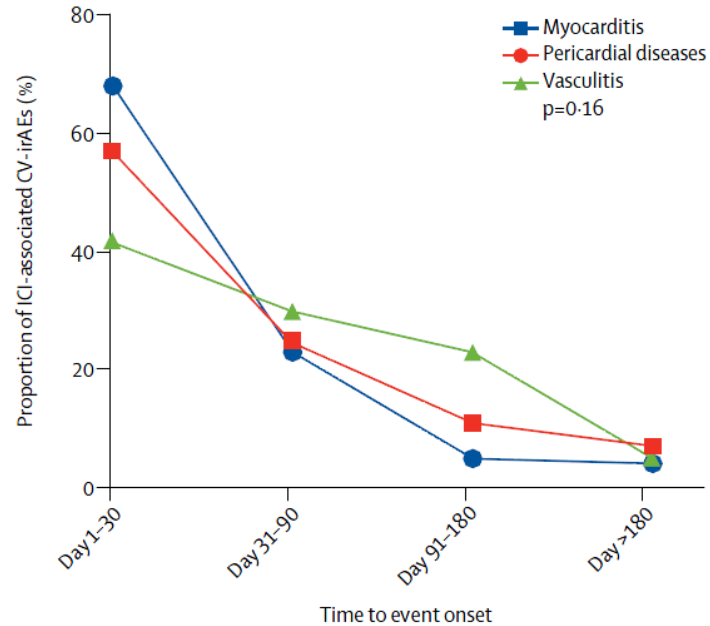
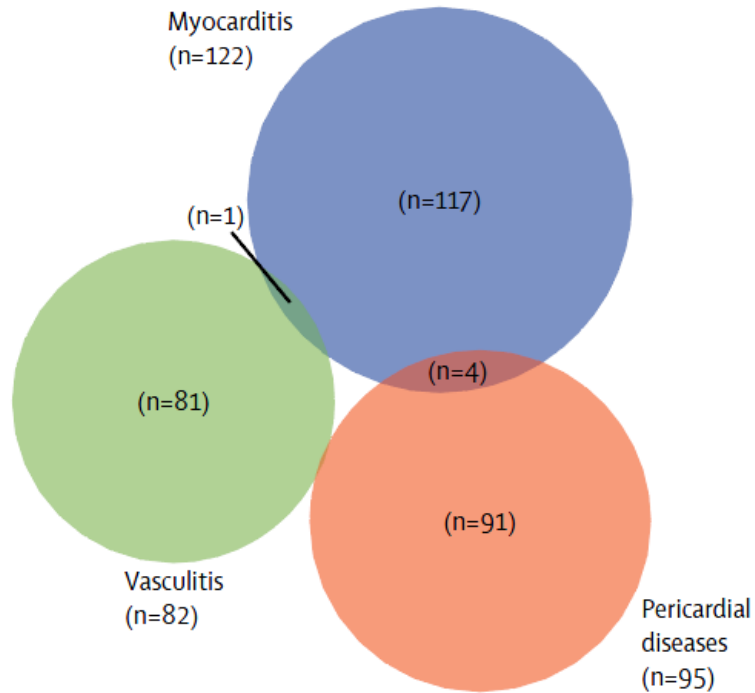


NEJM
2018

Postow MA
et al.

MYOCARDITIS is the most FATAL cardiovascular ADVERSE EVENT associated with Immune checkpoint inhibitors (ICI)

EXPECTED TIMING OF ICI-MYOCARDITIS OCCURRENCE





AGENDA – ICI-ASSOCIATED MYOCARDITIS



- PREVALENCE
- MECHANISMS



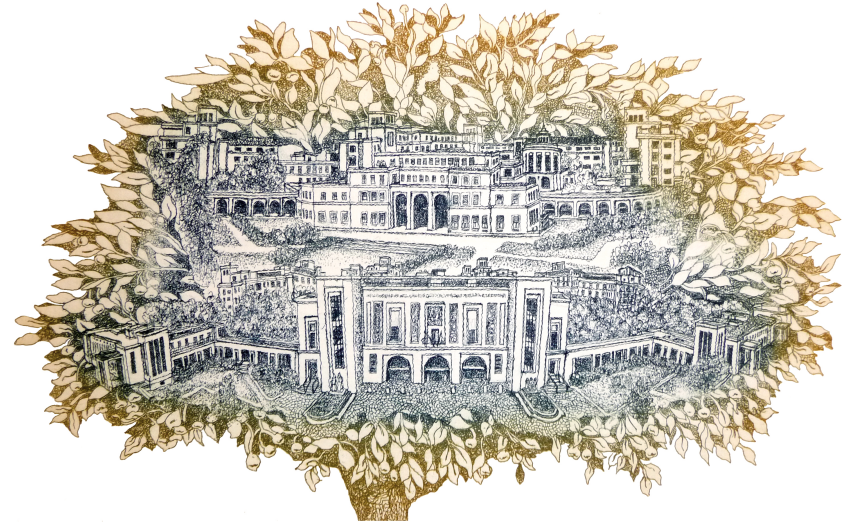
- **DIAGNOSIS**

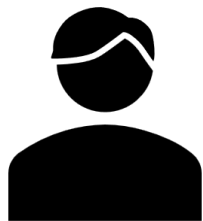


- RISK SCORE
- THERAPY



- FINAL CONSIDERATIONS/THM





SUSPECTED ICI-MYOCARDITIS

62 y-o man – JULY 2nd, 2024

9 year before inferior STEMI – PCI RC/Cx – normal EF (2015)

Locally advanced melanoma (9/2023) first finger of the left hand (pT4bN1M0)

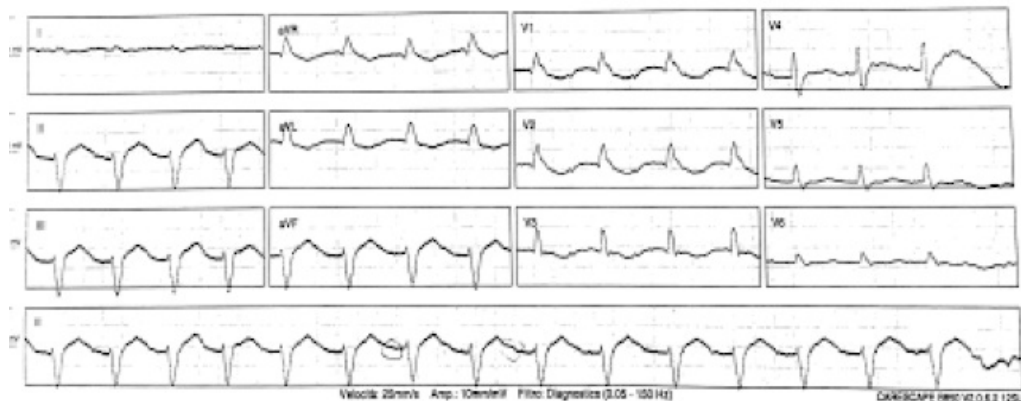
Adjuvant Treatment with **anti-PD-1 (pembrolizumab)** + **anti-TIGIT** (stopped in May 2024 due to hypophysitis)

- *Dyspnea/fatigue

- *hypotension/bradycardia

- *EKG: 3rd AVB

*TIGIT = *T cell immunoreceptor with immunoglobulin and ITIM domain*



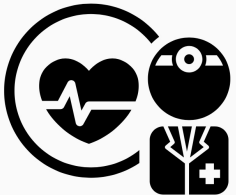
- hs-Troponin I **17,348** ng/L (nv<25)

- NTproBNP **7,474** ng/L

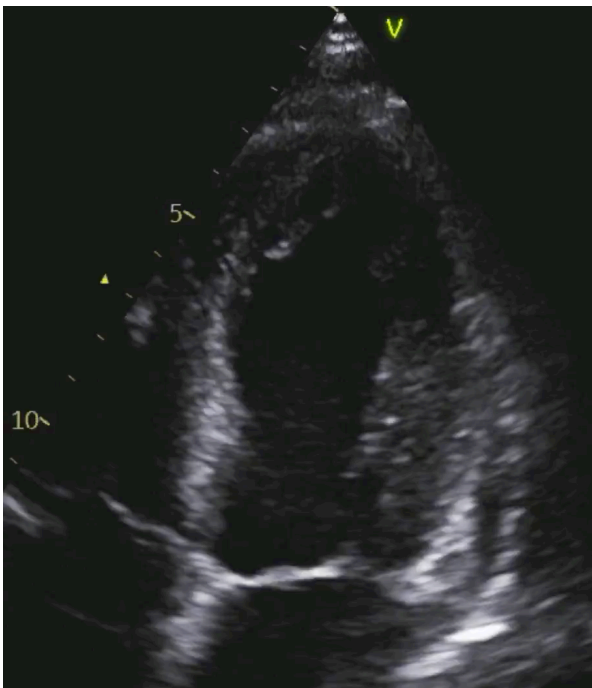
- creatinine/bilirubin not increased

TRANSFERRED TO Niguarda H

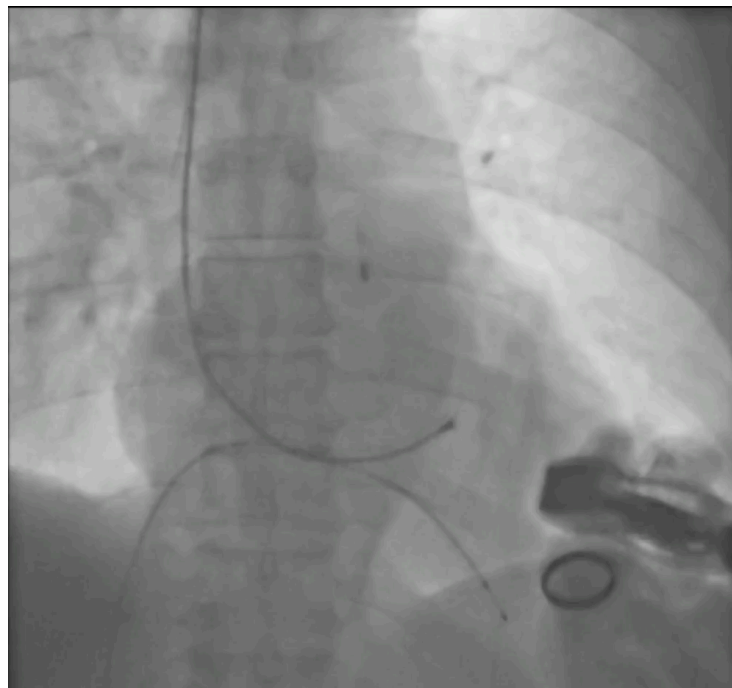




SUSPECTED ICI-MYOCARDITIS



*ECHO: LVEF 30%



*No progression of CAD

*Temporary PM

*POSITIONING IABP + inotropic support

EXPECTED CLINICAL PRESENTATION OF ICI-ASSOCIATED-MYOCARDITIS

Table 1. Target and Half-life of Immune Checkpoint Inhibitors

ICI	Target	Half-life
Ipilimumab ^a	CTLA-4	15 d
Atezolizumab ^a		27 d
Avelumab ^a	PD-L1	6.1 d
Durvalumab ^a		21 d
Nivolumab ^a		25 d
Pembrolizumab ^a		27.3 d
Cemiplimab ^a		19 d
Toripalimab	PD-1	7.7-14.2 d ^b
Sintilimab		NA
Camrelizumab		2.9-11 d ^b
Tislelizumab		17 d
Dostarlimab ^a		25 d

Abbreviations: CTLA-4, cytotoxic T-lymphocyte-associated protein 4; NA, not available; PD-1, programmed cell death protein 1; PD-L1, programmed ligand-death 1.

^a Denotes immune checkpoint inhibitor that has been approved by US Food and Drug Administration.

^b Based on doses reported thus far in clinical trials.

Table 2. Summary of Clinical and Imaging Features Based on the Current Literature^{8,10,11,15}

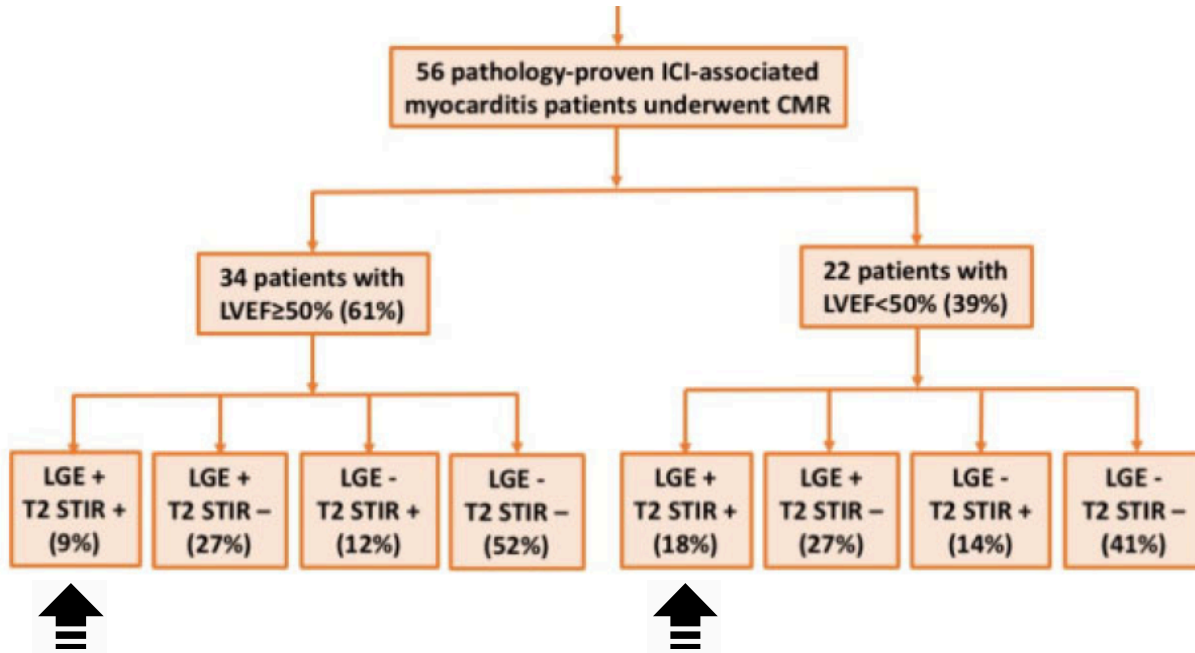
Feature	Incidence in patients with ICI-associated myocarditis, %
Chest pain	14-37
Dyspnea/fatigue	71-76
Myasthenialike syndrome	11-30
Arrhythmia	
Ventricular	≤27
Supraventricular	≤30
Conduction abnormalities	≤17
Cardiac arrest	7-9
ECG changes	46-89
Increase in troponin	46-94
Increase in NT-proBNP	65-100
cMRI LGE	23-48
Short tau inversion recovery	26
Decrease in LVEF (echocardiography)	49-51
Myositis	23-30

Abbreviations: cMRI, cardiac magnetic resonance imaging; ECG, electrocardiogram; ICI, immune checkpoint inhibitor; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide.

EXPECTED CLINICAL PRESENTATION OF ICI-ASSOCIATED-MYOCARDITIS

Type of Myocarditis	Median age Sex prevalence	Sample Size Study design	Characteristic Findings	Risk factors	Typical clinical presentation	Outcome
Immune checkpoint inhibitor-associated acute myocarditis ^{18,19}	Median age at presentation of approximately 66 y ¹⁸ Male, 67% ¹⁸ 	Cohort of 122 patients Retrospective study	Generally presenting as lymphocytic myocarditis Median time from exposure to myocarditis, 30 d (IQR, 18-60) ¹⁸	The most important risk factor is combination treatment with CTLA-4 inhibitor (eg, ipilimumab) and PD-1 inhibitor (eg, nivolumab or pembrolizumab) vs monotherapy (OR, 4.3 [95% CI, 2.9-6.4]) ¹⁸	Dyspnea/fatigue in 71%-76% Chest pain in 14%-37% Myositis in 23%-30% Myasthenia-like syndrome (diplopia) in 11%-30% LVEF ≤50% on echocardiogram in 48% ¹⁹ 	Estimated mortality up to 50% ¹⁸

CMR FOR THE DIAGNOSIS OF ICI-MYOCARDITIS



RISK SCORE

****Definite LLC in LVEF $\geq 50\%$ in 9%**

****Definite LLC in LVEF $< 50\%$ in 18%**

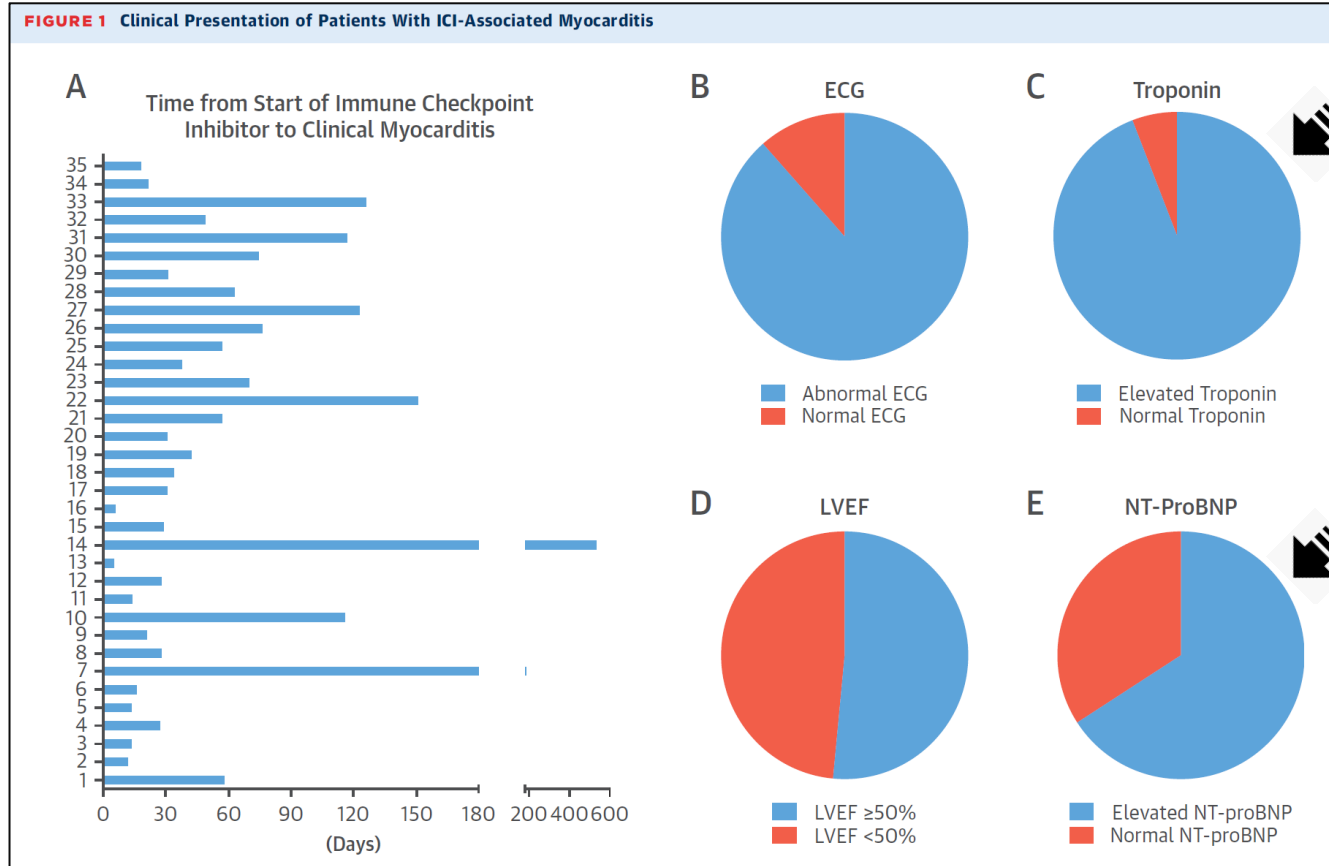
JACC 2020 -

Thavendiranathan

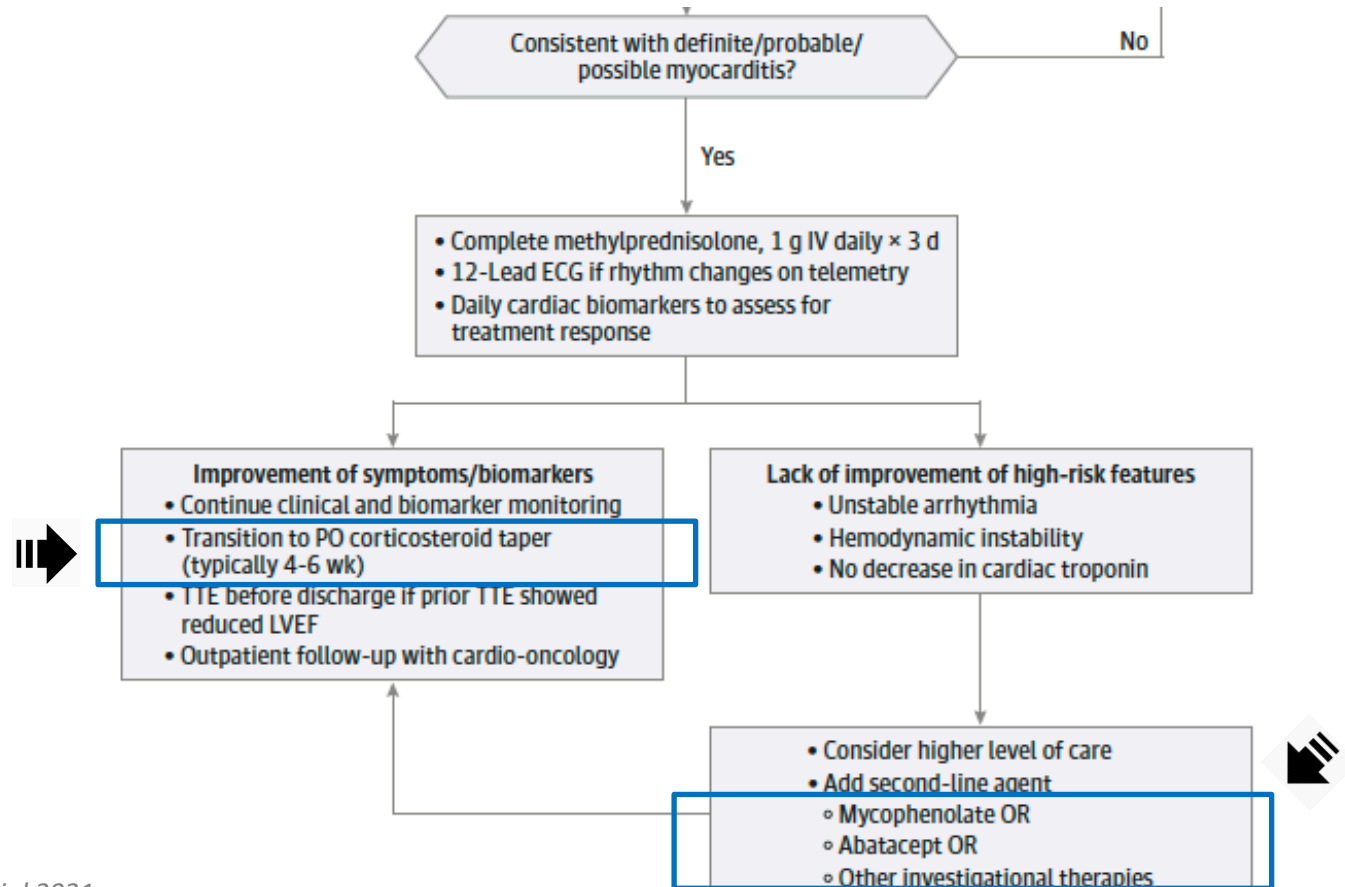
****Using T2 mapping criteria: 53% reached the edema criteria**

CLINICAL ASSESSMENT FOR SYMPTOMATIC PATIENTS

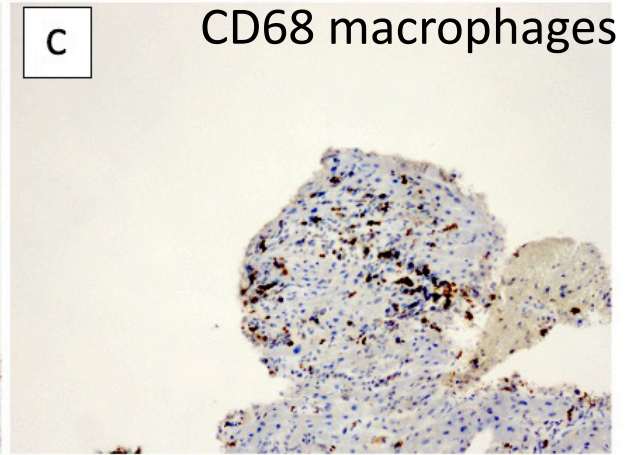
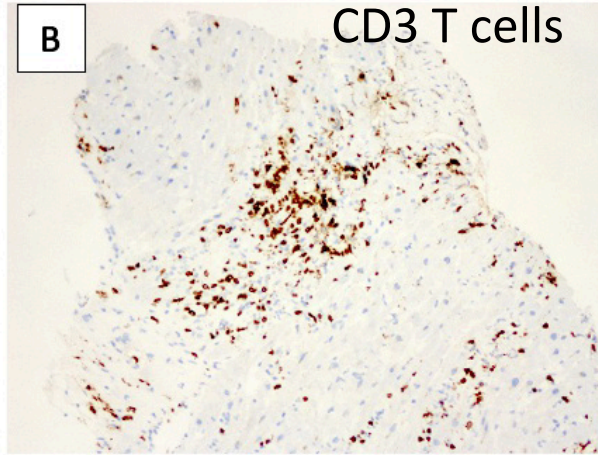
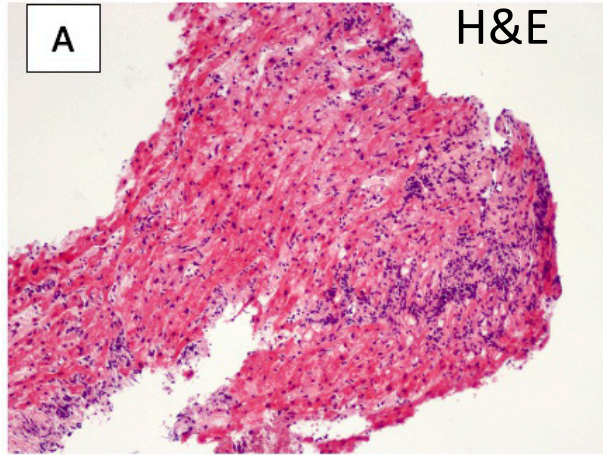
FIGURE 1 Clinical Presentation of Patients With ICI-Associated Myocarditis



CLINICAL ASSESSMENT FOR SYMPTOMATIC PATIENTS



LYMPHOCYTIC ACTIVE MYOCARDITIS - THERAPY





AGENDA – ICI-ASSOCIATED MYOCARDITIS



- PREVALENCE



- MECHANISMS



- DIAGNOSIS

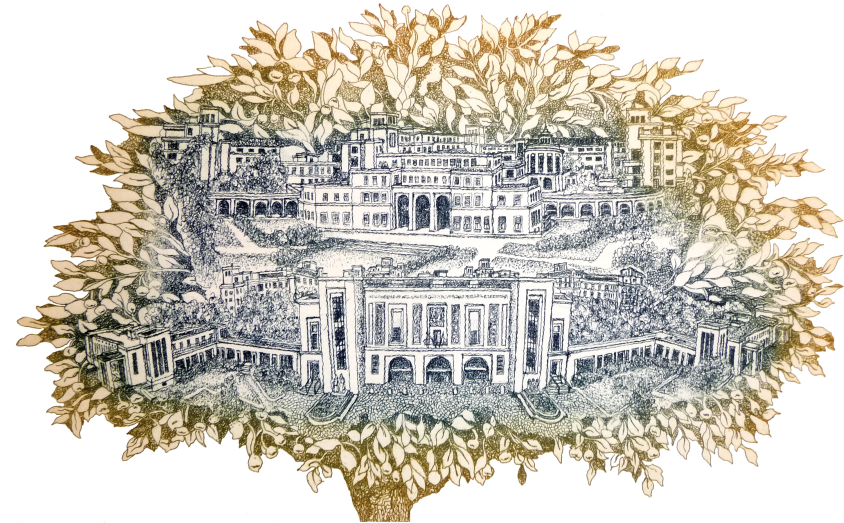
- **RISK SCORE**



- THERAPY



- FINAL CONSIDERATIONS/THM



PROGNOSIS

ICI myotoxicity occurrence was the factor impacting most mortality after ICI start:

HR 3.51 (95%CI 3.17-3.89) at 1 month

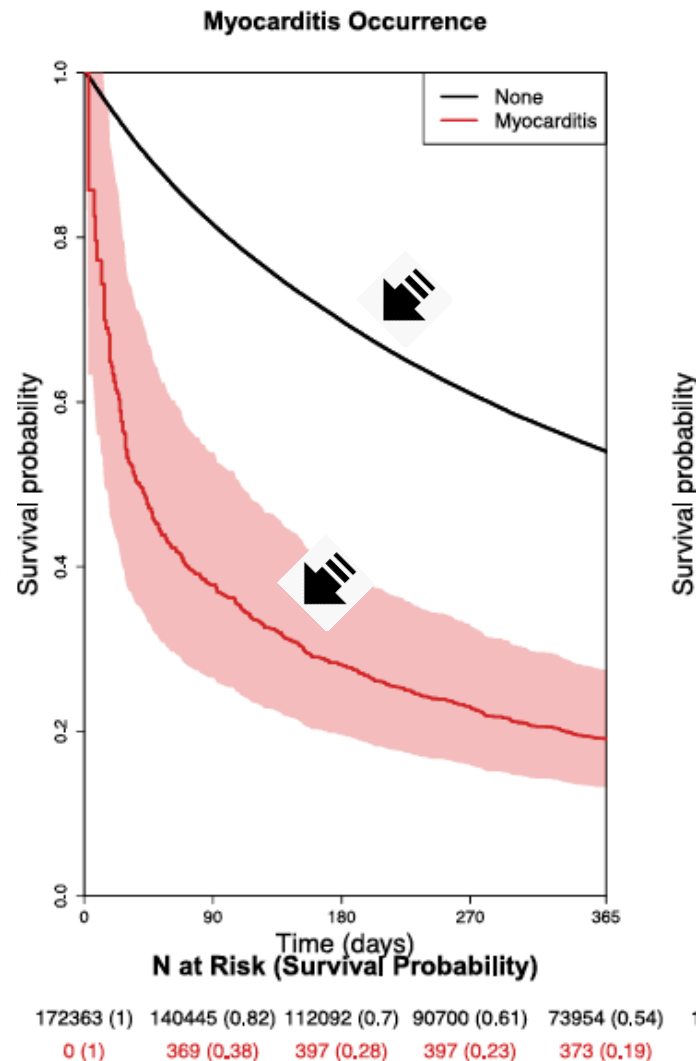
Over metastatic status HR 1.55

ICI myotoxicity patients, 1-month fatality was 20.3% and increased if:

***Severe arrhythmia (risk ratio 1.64)**

***Heart failure (RR 1.49)**

***Respiratory failure (RR 1.50)**



MYOTOXICITY SEVERITY AND TROPONIN T LEVELS

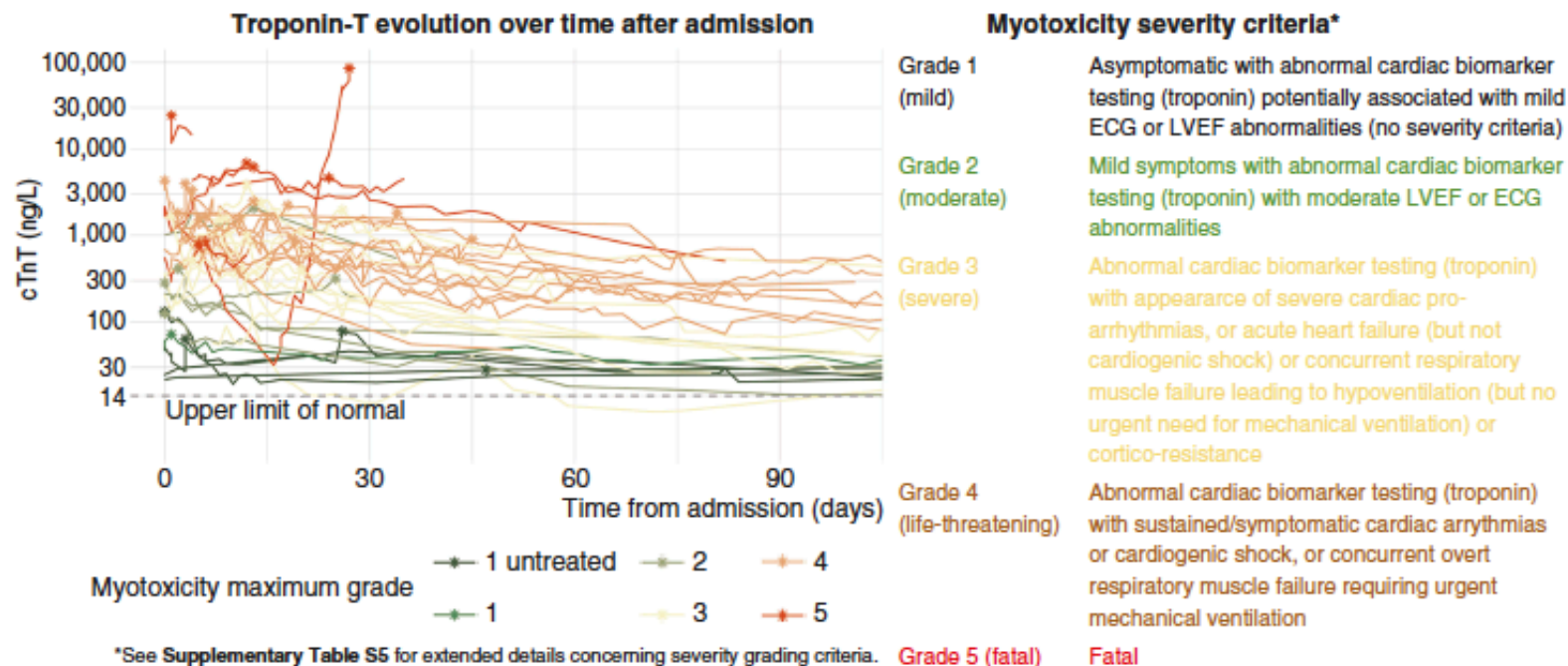


Figure 2. Troponin-T circulating levels as a function of ICI myotoxicity severity. Evolution of circulating troponin-T levels (cTnT, ng/L) as a surrogate for myotoxicity severity grade in the 40 ICI myocarditis patients included in our study. All patients had increased troponin-T levels on admission. Peak values of troponin-T levels per patient are represented by * and track the severity grading of these patients. Five patients had grade 1 asymptomatic myocarditis, 4 of whom were not treated with any immunosuppressant (but ICI withhold) and evolved favorably. LVEF, left ventricular ejection fraction.

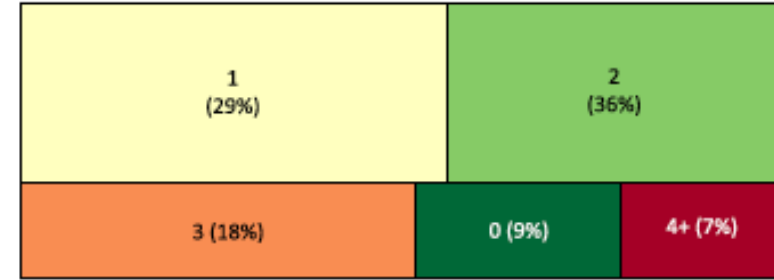
ICI-MYOCARDITIS-NOVEL RISK SCORE (1)

A

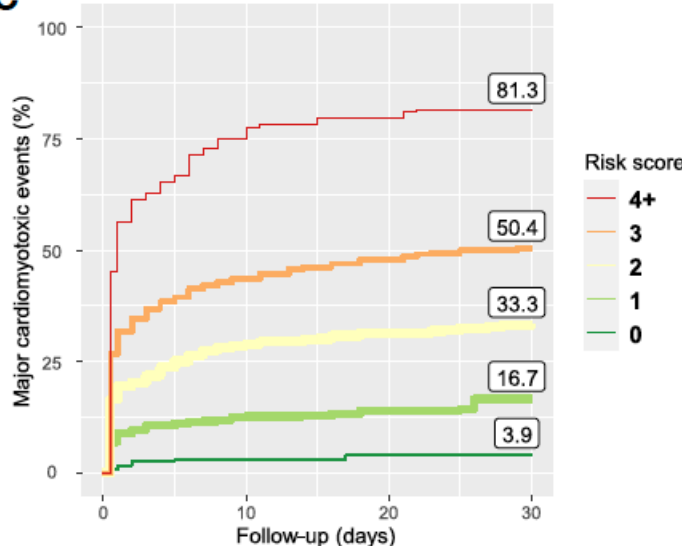
Risk score parameters	Points
Active thymoma	+2
Cardiomuscular symptoms	+1
EKG: Sokolow-Lyon voltage $\leq 0.5\text{mV}$	+1
Left ventricular ejection fraction $< 50\%$	+1
Troponin (preferentially T, otherwise I) > 20 to 200 folds the ULN	+1
Troponin (preferentially T, otherwise I) > 200 to 2000 folds the ULN	+2
Troponin (preferentially T, otherwise I) > 2000 folds the ULN	+3



N=748



C



RISK SCORE

****CARDIOMUSCULAR SYMPTOMS: +1**

LAB:

****Troponin T > 20 to 200 above URL: + 1**

****Troponin T > 200 to $2,000$ above URL: + 2**

****Troponin T $> 2,000$ above URL: + 3**

ECHO:

****LVEF $< 50\%$: +1**

ECG:

****QRS-low voltages: +1**

**Our patient
score: 3**



AGENDA – ICI-ASSOCIATED MYOCARDITIS



- PREVALENCE



- MECHANISMS



- DIAGNOSIS

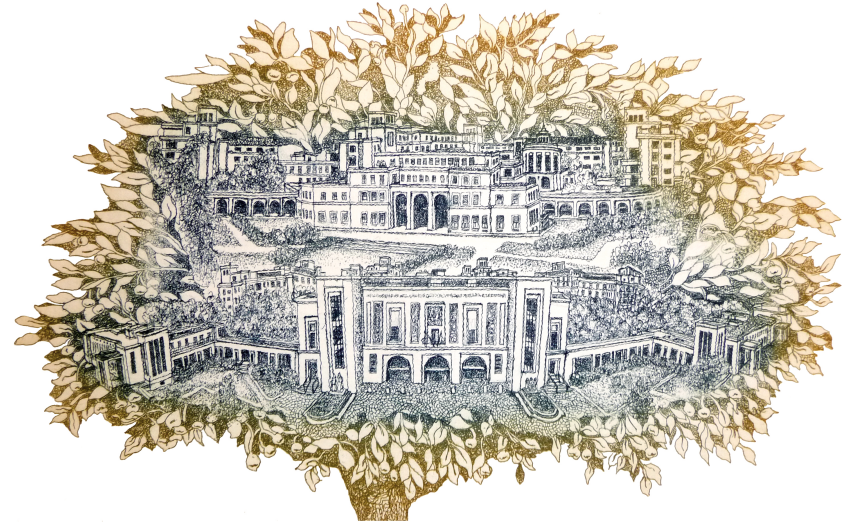
- RISK SCORE



- **THERAPY**



- FINAL CONSIDERATIONS/THM



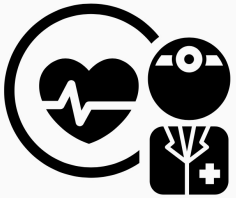
POSSIBLE MEDICATIONS FOR ICI-MYOCARDITIS

Type of myocarditis	Therapies based on cases series or recommendations based on experts' consensus ^a	Potential adverse effects of therapies (rates of adverse events)
Immune checkpoint inhibitor-associated acute myocarditis ^{1,78}	Withdrawal of immune checkpoint inhibitor therapy <u>Initial IV pulses of methylprednisolone (500-1000 mg for 3 d) used in most of cases as first line</u> Additional regimens in refractory to steroids cases based on case reports: IV abatacept (a CTLA-4 agonist), 10 mg/kg-25 mg/kg, on days 0, 5, and 12 <u>IV ATG, 1 mg/kg, usually single dose or IV alemtuzumab (anti-CD-52 antibody), 30 mg, single dose or ruxolitinib, 10-15 mg, by mouth twice a day (usually treated for 2-4 wk)</u>	Methylprednisolone: see above Abatacept: risk of respiratory infection (>10%), risk of urinary tract/herpetic infection (1%-10%), hypertension (1%-10%) ATG: see above Alemtuzumab: see above Ruxolitinib: risk of thrombocytopenia or anemia (>10%) and bruising (>10%)
CONSIDER: CYCLOSPORINE/TACROLIMUS		

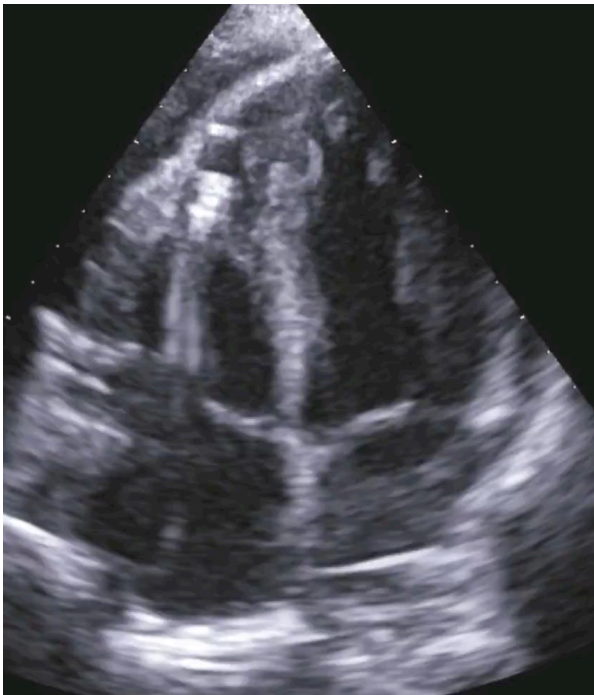
Alemtuzumab anti CD52 on mature T cells

Ruxolitinib (Janus Kinase inhibitor – JAK 1 and JAK2

Alternative regimen including TACROLIMUS



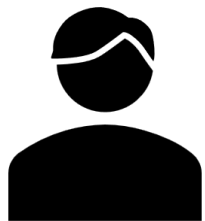
SUSPECTED ICI-MYOCARDITIS



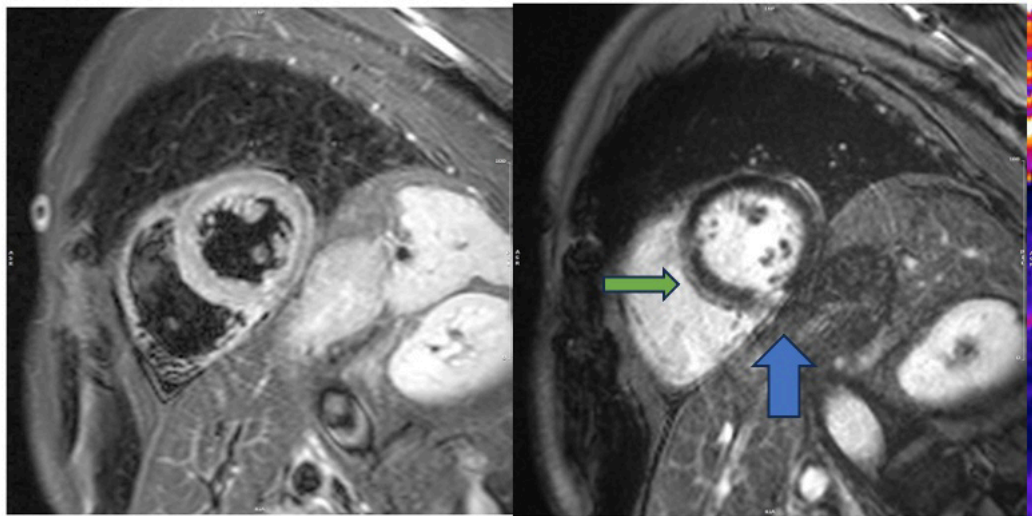
*IV methylprednisolone 1g od x 3 days + **single dose 0.5 mg/kg iv thymoglobulines** (after 24 hours weaning off inotropes + sinus Rhythm)

*Followed by 2 mg/kg/day + **maintenance therapy with tacrolimus** (0.075 mg/kg)

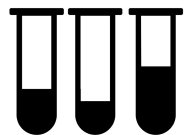
*With a tapering schedule



SUSPECTED ICI-MYOCARDITIS



***AT DISCHARGE:**



- hs-Troponin T **31** ng/L (nv<14)
- NTproBNP **813** ng/L

***CMRI (after 15 days): STIR + LGE + septal involvement**



AGENDA – ICI-ASSOCIATED MYOCARDITIS



- PREVALENCE

- MECHANISMS



- DIAGNOSIS

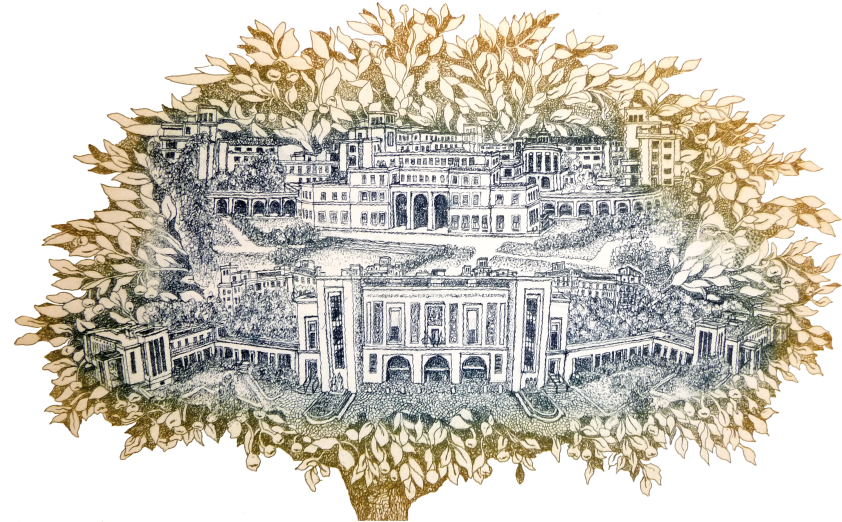
- RISK SCORE

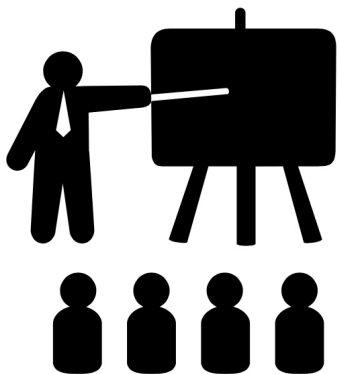


- THERAPY



- **FINAL CONSIDERATIONS/THM**





TAKE-HOME MESSAGE IN ICI ASSOCIATED MYOCARDITIS

1. Those with events have **higher admission - peak troponin T value**
2. A **higher initial steroid dose** was associated with a lower rate of events
3. Significant proportion of patients without full response to steroids
4. **DO NOT UNDERESTIMATE RESPIRATORY MUSCLE INVOLVEMENT**
5. When and how consider rechallenging with ICIs after myocarditis



enrico.ammirati@ospedaleniguarda.it

@AmmiratiEnrico



CONGRESSO
ROMA, 25 - 27 Giugno 2026

 **OSPEDALE NIGUARDA
CA' GRANDA**
"DE GASPERIS" CARDIO CENTER

