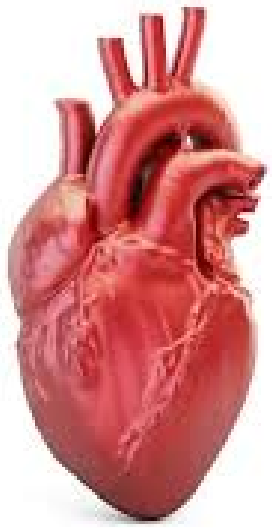
Immune Checkpoint Inhibitor Myocarditis

A Thorn in the side of a life saving treatment



David Lewandowski MD

2024 Annual Advances in Hematology & Oncology Fall Symposium

Disclosures

- None

Learning Objectives

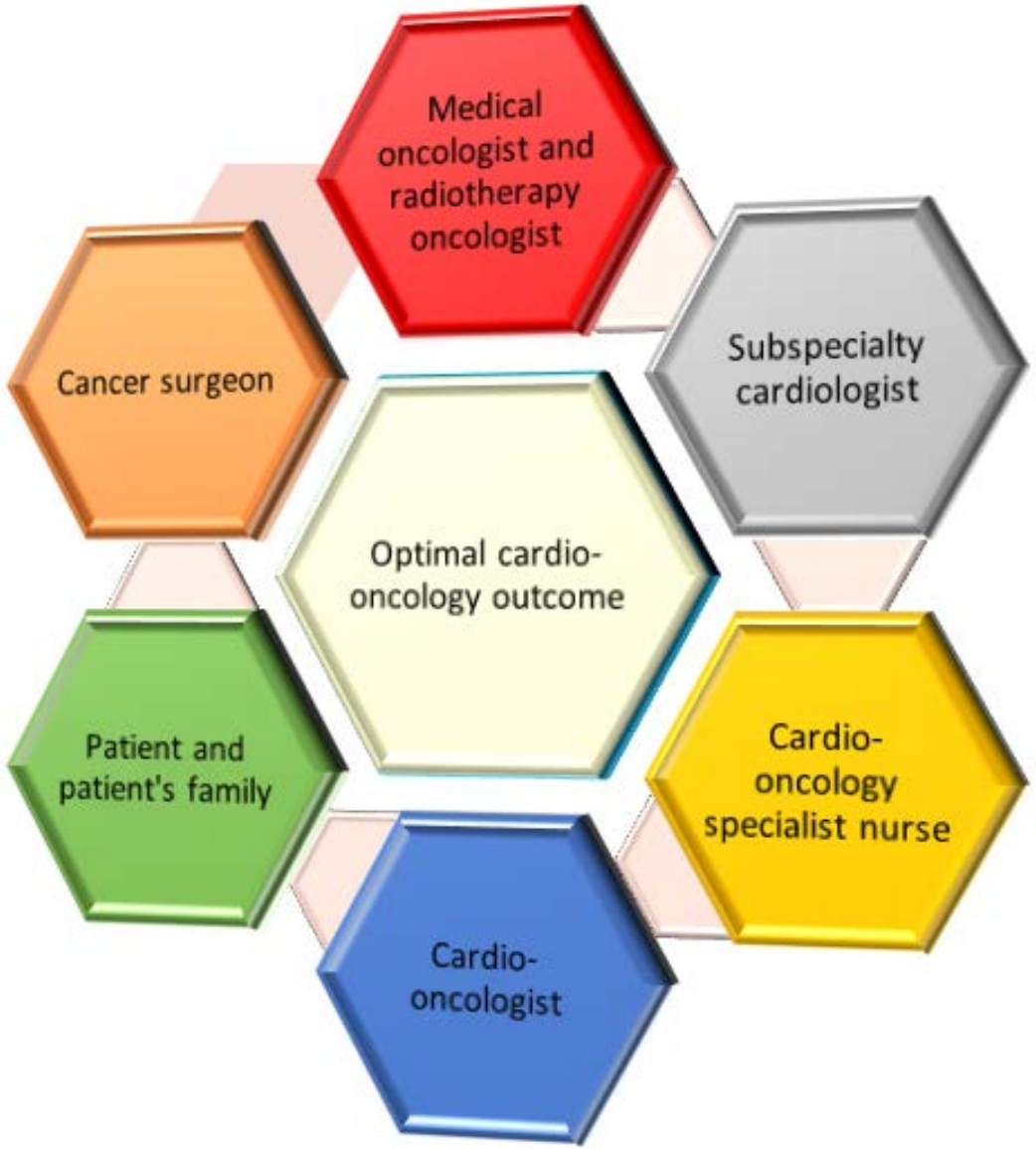
1. Recognize the signs and diagnostic pathways in the identification of immune checkpoint inhibitor (ICI) myocarditis.

2. Understand the basics of treatment of ICI myocarditis and the current philosophies on steroid refractory myocarditis.

3. Identify the main unanswered questions that exist regarding this condition, and the research gaps to be filled to answer them.

Goals of Cardio-Oncology

- Risk stratify patients undergoing cancer therapy to anticipate and prevent complications.
- Manage existing CV disease in the context of cancer therapy
- Mitigate the adverse effect of cancer therapy on the CV system while also minimizing interruptions to cancer therapy
- Manage long term complications and establish long term surveillance for cancer survivorship
- Provide collaborative management and support to other providers in primary care and cancer center.



How to Build a Cardio-Oncology Service

Oct 24, 2017 | Arjun K Ghosh, MBBS, MSc, PhD, FACC

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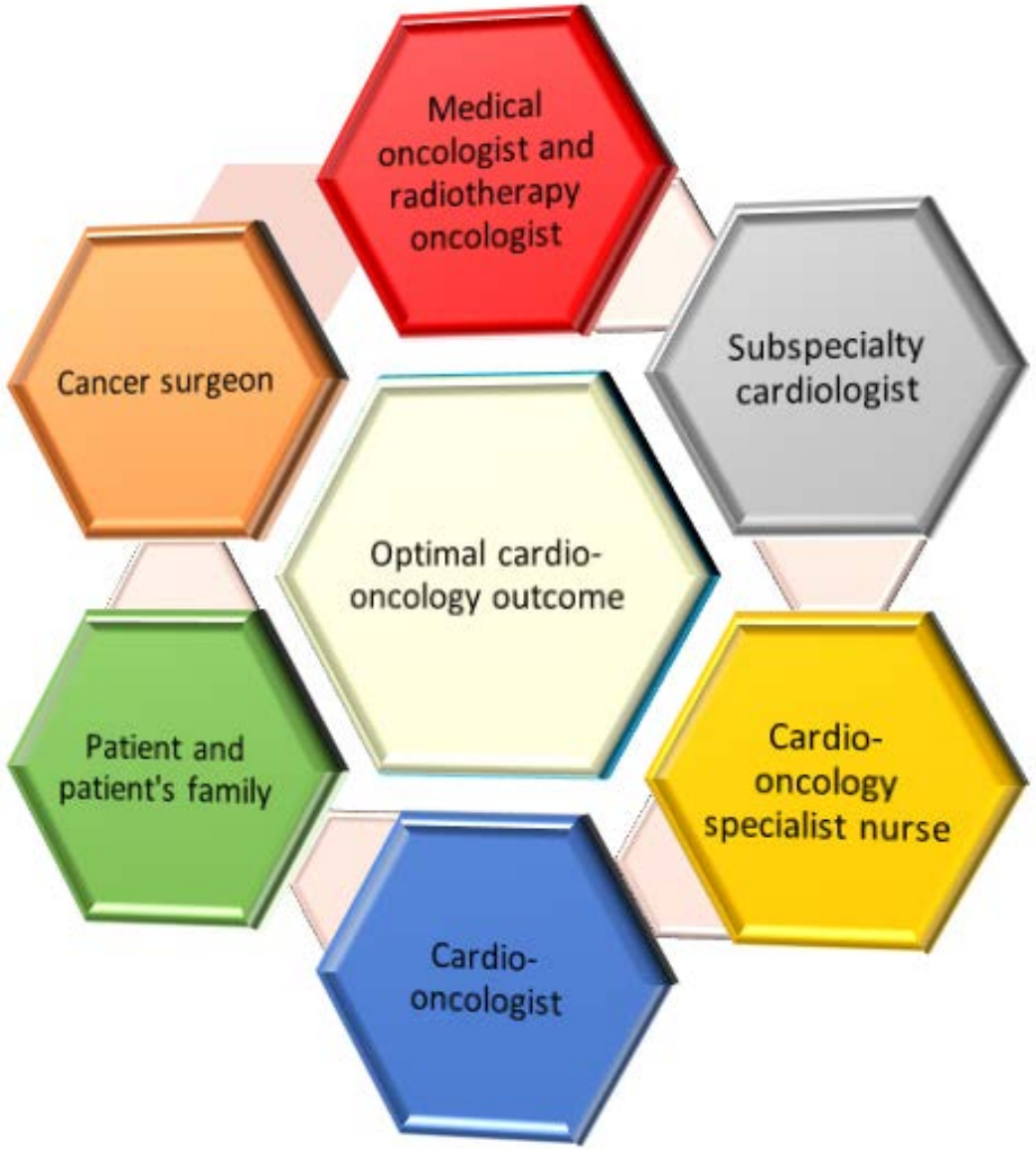

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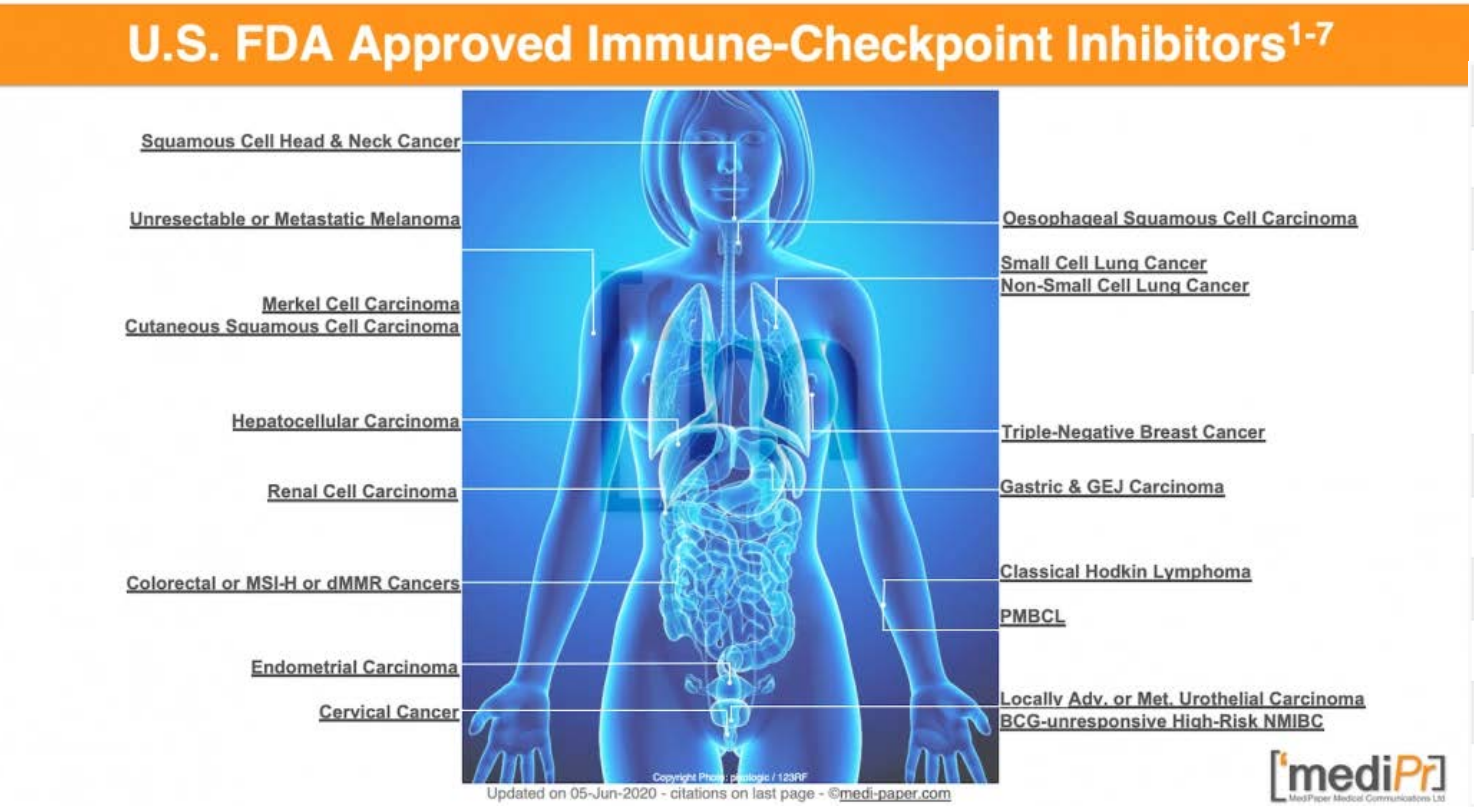
Immunotherapy Landscape 2024

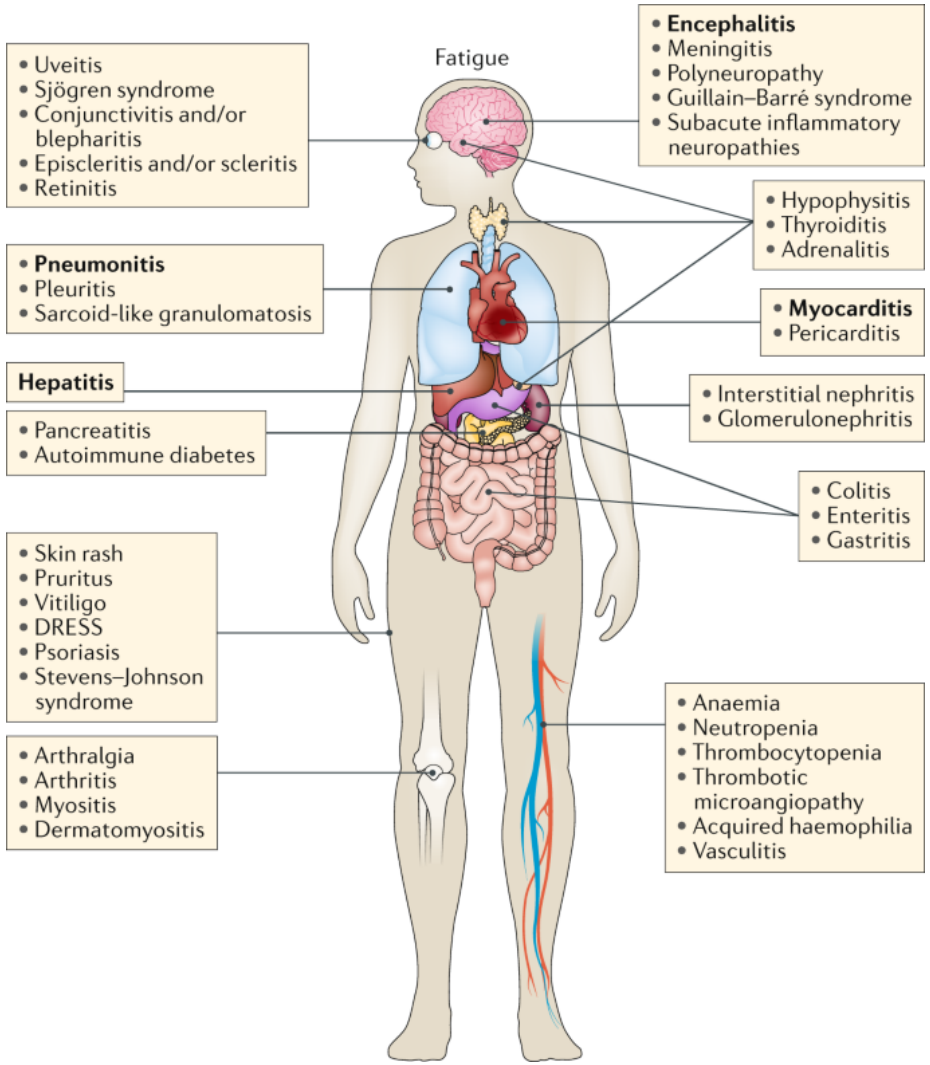


Checkpoint Inhibitor	Date of First FDA Approval	# of Total Indications	# of Mon-overlapping Indications	# of Indications Overlapping with >3 Other Drugs
Ipilimumab (Yervoy)	Mar 2011	8	0	4
Pembrolizumab (Keytruda)	Sep 2014	35	11	4
Nivolumab (Opdivo)	Dec 2014	18	2	4
Atezolizumab (Tecentriq)	May 2016	7	1	2
Avelumab (Bavencio)	Mar 2017	4	0	1
Durvalumab (Imfinzi)	May 2017	5	0	1
Cemiplimab (Libtayo)	Sep 2018	4	1	1
Tremelimumab (Imjudo)	Oct 2022	2	0	1
Retifanlimab (Zynyz)	Mar 2023	2	0	0
Dostarlimab (Jemperli)	Jul 2023	4	0	1
Toripalimab (Loqtorzi)	Oct 2023	2	0	0

US FDA approved immune-checkpoint inhibitors updated 08-Dec-2020
https://medi-paper.com/?p=28043

Jeddeo Paul et al. JCO. 2024

The spectrum of immune related adverse events (IRAE)



- ICI myocarditis occurs in 0.3-1.4% of patients treated with ICI.
- 1/2 to 2/3 of patients with myocarditis have another IRAE (myositis 25%, pneumonitis 11-29%, colitis 7-10%, myasthenia gravis 11%).
- Concomitant myasthenia and myocarditis portends a worse prognosis

Filipe Martins et al. Nature Reviews Clinical Oncology. 2019

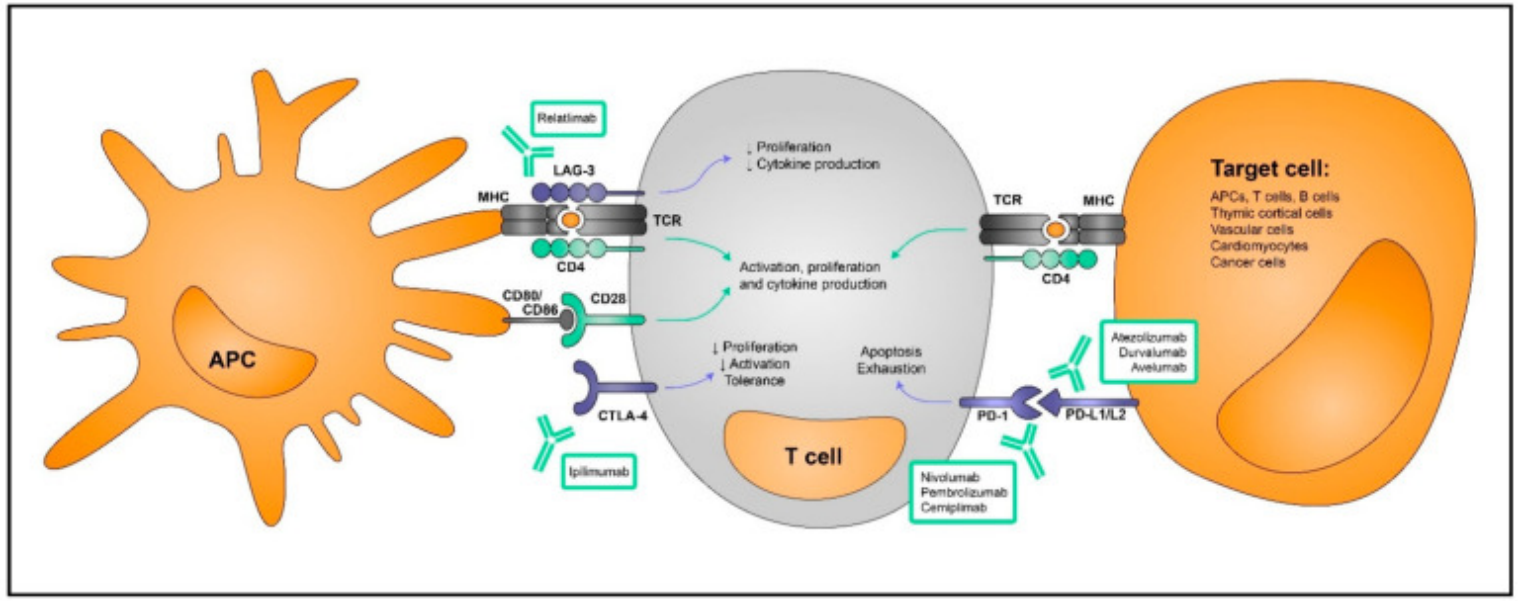
Isik Turker et al. Expert Opin Drug Saf. 2023

Who develops myocarditis?

- Patients affected tend to be older and more likely male.
- The one definite risk factor is the use of dual immune checkpoint inhibitors (4.74 fold higher risk).
- There is no evidence that pre-existing cardiovascular disease increases risk for myocarditis
- Recommendations regarding screening are divided, with some organizations recommending none, and the ESC 2022 cardio-oncology guildelines recommending baseline troponin and ECG testing, and serial monitoring in “high risk” patients.

Alexander R Lyon et al. European Heart Journal. 2022.

Pathophysiology



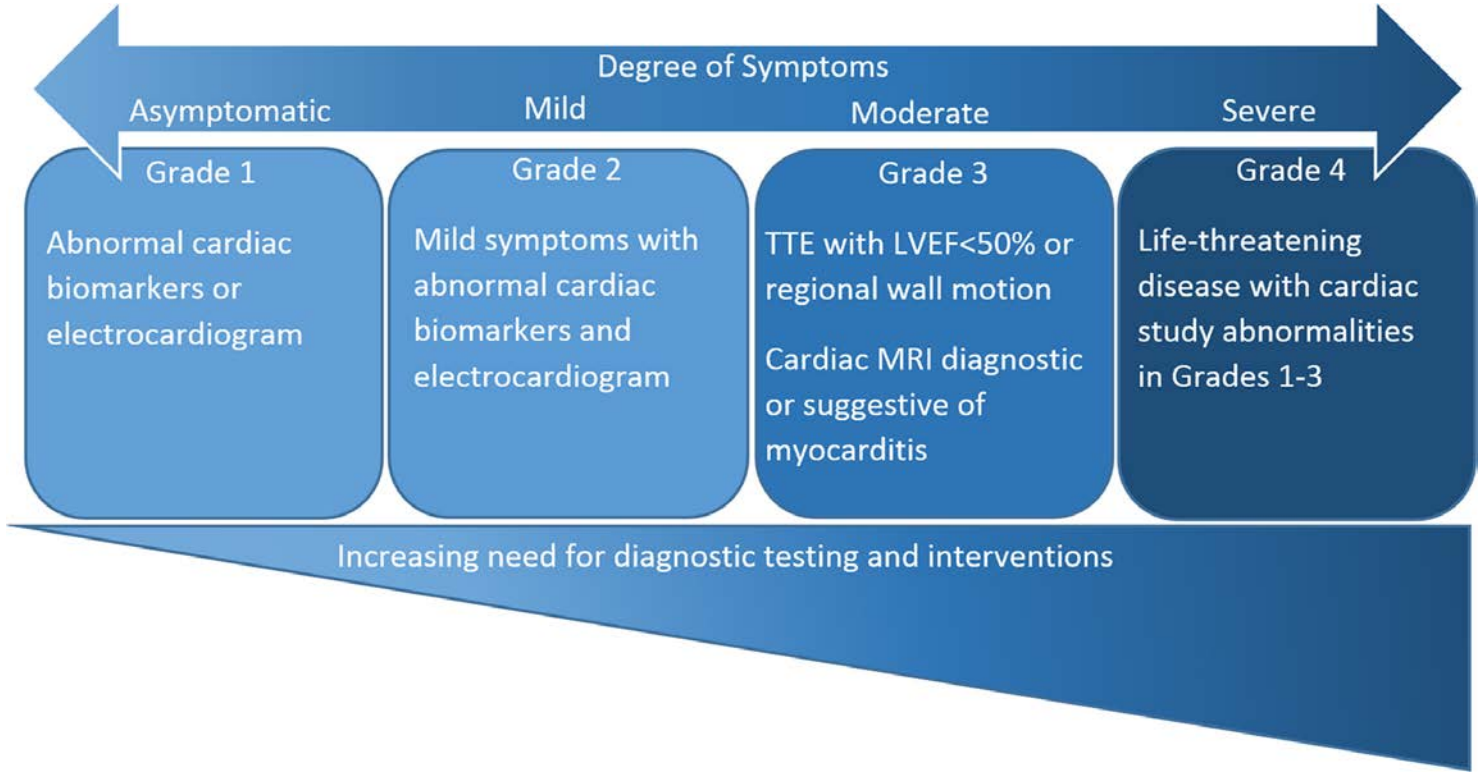
- ICI myocarditis mechanism not fully elucidated. Suspected contributing factors include:
  - Breakdown of peripheral tolerance
  - Cross reactivity of tumor antigens and cardiomyocyte antigens (alpha myosin heavy chain)
  - Elevated IL-17a levels

Rosa Jiménez-Alejandre et al. Cancers. 2022.

Daniela Čiháková et al. Circulation. 2023

ICI Myocarditis Presentation

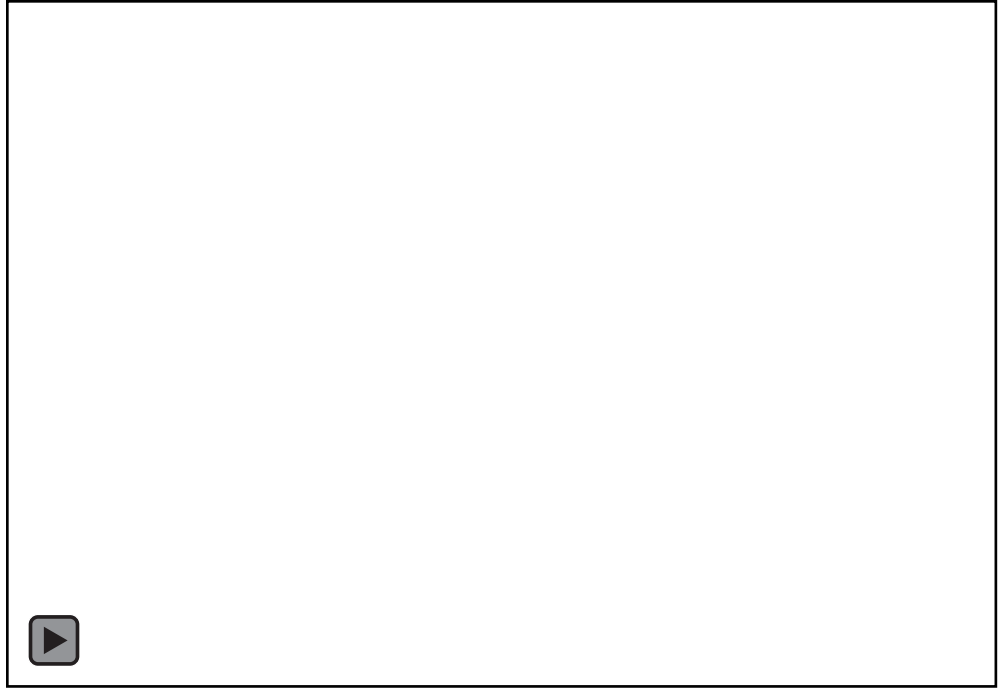
- Presentations range from fulminant myocarditis involving cardiogenic shock and ventricular arrhythmias to asymptomatic inflammation discovered on testing.
- Documented mortality is very high at 40%. However this may be outdated.
- 50-60% of patients may have normal ejection fraction on CV imaging.

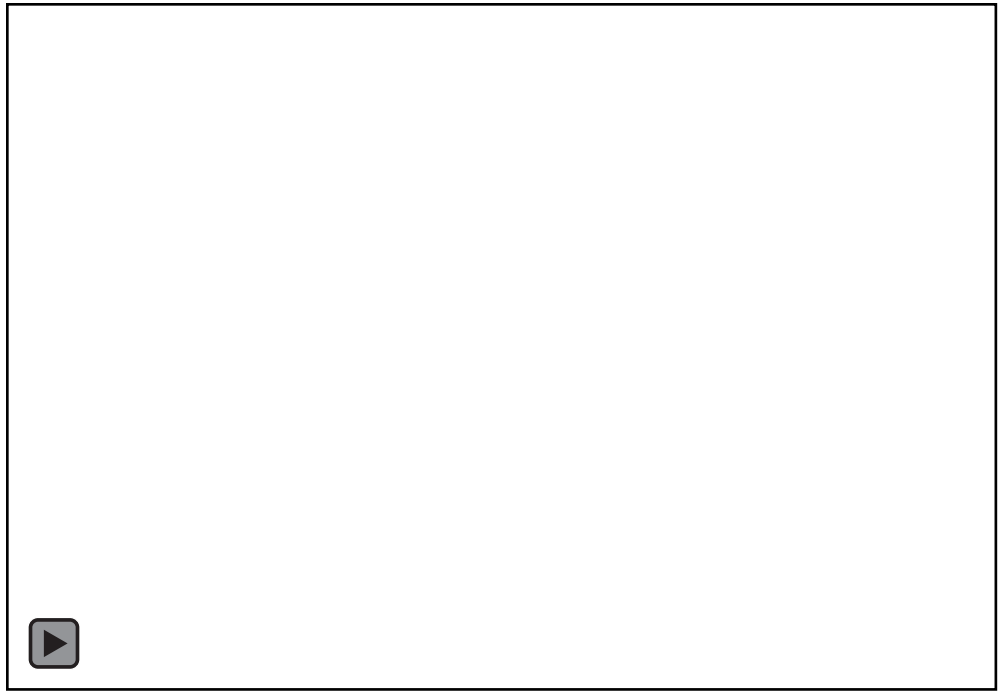


Nicolas Palaskas et al. JAHA. 2020

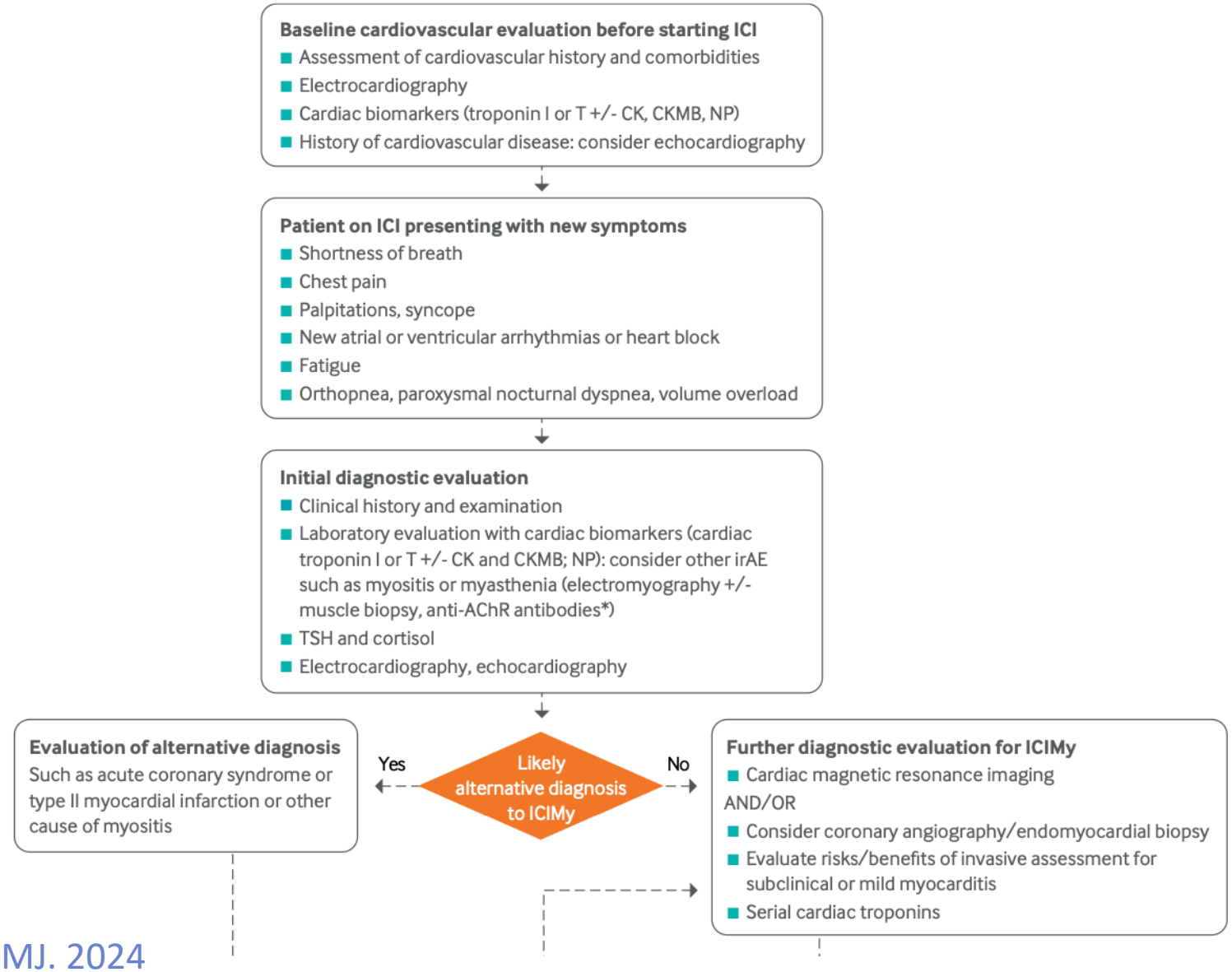
Other cardiac IRAE

- ICI associated isolated pericarditis and coronary events have been described in several case reports.
- This form of pericarditis has an increased risk of developing constrictive pericarditis and requires intensive monitoring.
- Data is conflicting on ICI impact on atherosclerosis and CV events, with some suggesting harm and others suggesting benefit.
- The largest meta analysis (32,518 patients), noted increased risk of myocardial infarction with odds ratio 1.51 (1.01-1.26)

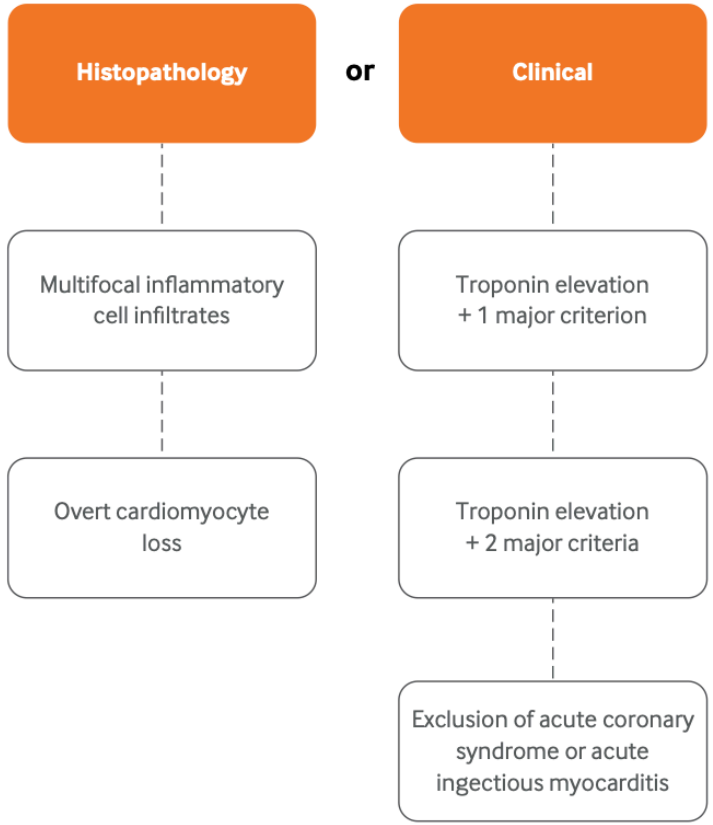




Diagnostic algorithm



Nicolas L. Palaskas et al. BMJ. 2024



Major criterion

- CMR findings of acute myocarditis based on modified Lake Louise Criteria

Minor criteria

- Clinical syndrome: shortness of breath, chest pain, fatigue, myopathy/myalgias, ptosis, diplopia, orthopnea, peripheral edema, palpitations, dizziness, syncope, shock
- Ventricular arrhythmia +/- new conduction system disease
- Decline in ejection fraction with or without regional wall motion abnormalities in non-Takotsubo pattern
- Other irAEs, particularly myositis, myopathy, myasthenia gravis
- Suggestive CMR (not meeting all modified Lake Louise Criteria)

Severity

- Severe: hemodynamic instability, mechanical ventilation, high grade heart block, significant ventricular arrhythmia
- Non-severe (clinically significant): symptomatic but hemodynamic and electric stability; reduced ejection fraction may be present
- Smoldering: subclinical, no clinical signs or symptoms
- Steroid refractory: not resolving or worsening after high dose methylprednisolone

Recovery

- Compete: resolution of symptoms, normalization of biomarkers, recovery of ejection fraction after discontinuation of immunosuppression; CMR findings suggest fibrosis but no acute edema
- Recovering: improvement in symptoms, signs, biomarkers, and imaging but not yet normalized while on immunosuppression

Common terminology criteria for adverse events: myocarditis

Grade 1: -

Grade 2: Symptoms with moderate activity or exertion

Grade 3: Severe with symptoms at rest or with minimal activity or exertion; intervention indicated; new onset of symptoms

Grade 4: Life threatening consequences; urgent intervention indicated (eg, continuous IV therapy or mechanical hemodynamic support

Grade 5: Death

National Comprehensive Cancer Network

Grade 1: Asymptomatic, abnormal cardiac biomarkers, abnormal ECG or physical findings

Grade 2: Mild symptoms or symptoms with moderate activity or exertion, abnormal screening tests (cardiac biomarkers, ECG)

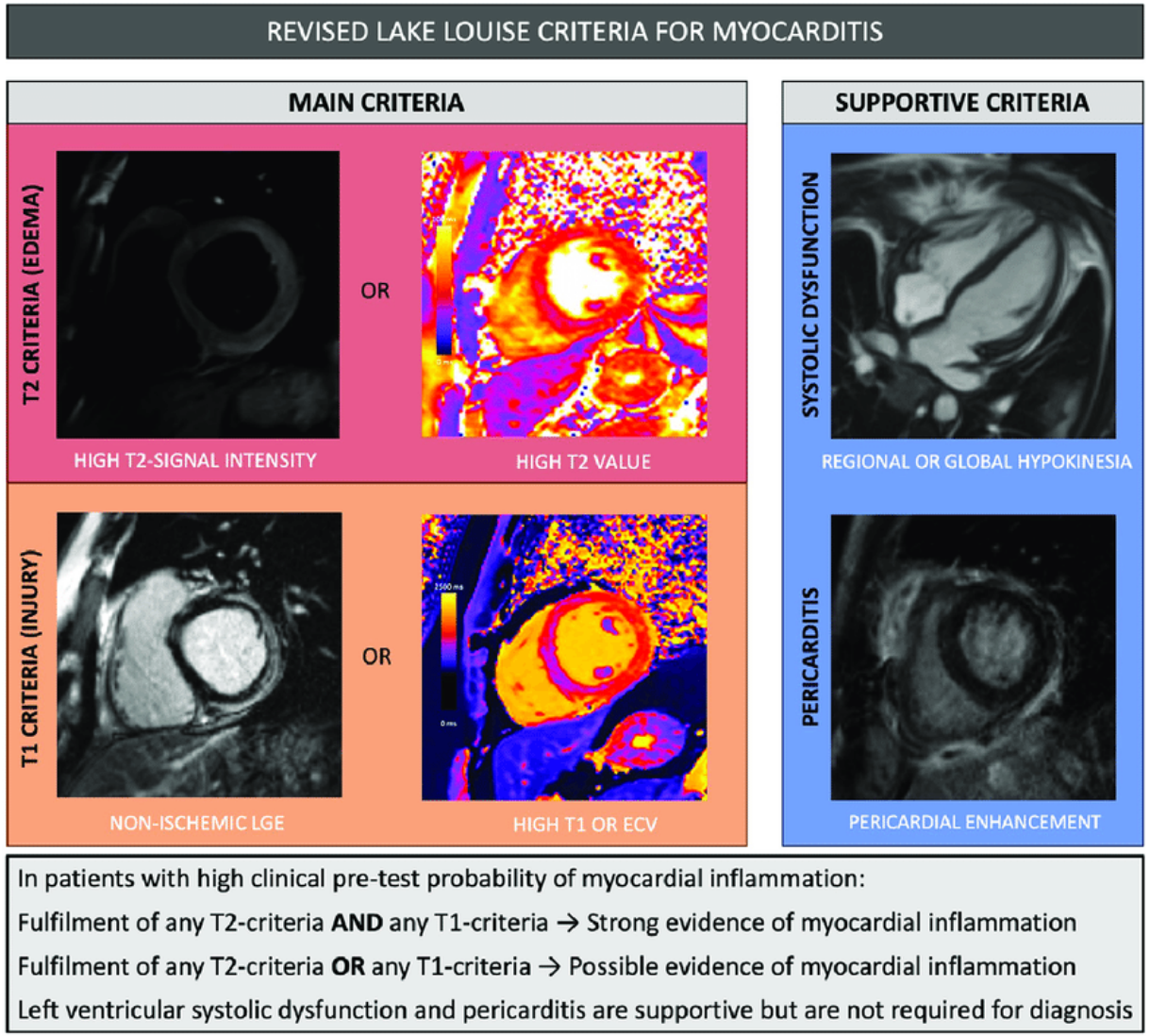
Grade 3: Symptoms at rest or with minimal activity or exertion, cardiac biomarkers, significant echocardiographic findings without hypotension

Grade 4: Moderate to severe decompensation, hemodynamic instability, cardiac biomarkers (creatine kinase and troponin >3xULN), life threatening, urgent intervention indicated (eg, continuous IV therapy or mechanical hemodynamic support)

Diagnostic tools: Troponin

- Elevations in troponin is a key criteria for diagnosing myocarditis with a very high sensitivity.
- Many centers have transitioned to high-sensitivity troponin assays (Troponin-T), which can have more cross reactivity with skeletal muscle troponin as compared to Troponin-I assays (still used widely).
- Troponin pattern will be distinct from acute coronary syndrome (ACS), with a more unpredictable or sustained pattern than crescendo-decrescendo.
- In addition to ACS, troponin elevation can occur in demand ischemia, congestive heart failure, advanced renal disease
- Also has significant utility in guiding treatment

Diagnostic tools: Cardiac MRI

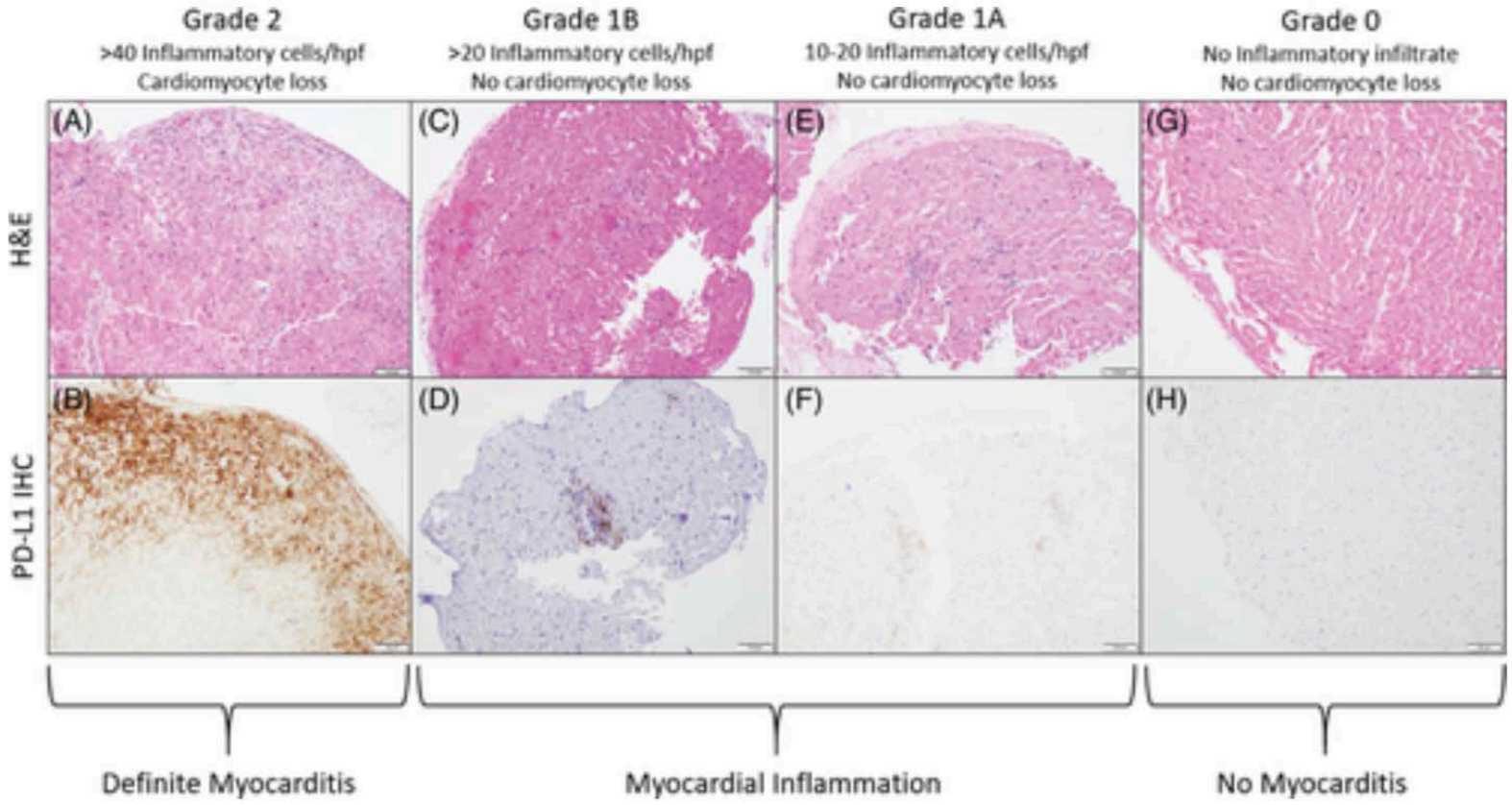


Felipe Sanchez Tijmes et al. Radiology Cardiothoracic Imaging. 2021

- Cardiac MRI is recommended for all suspected ICI myocarditis cases
- Gold standard for chamber size and function. Can also identify myocardial scarring and inflammation.
- Sensitivity may be limited early in disease course (22% in first 4 days, 72% after first 4 days). Therefore unexpected negative CMR should prompt consideration of either biopsy or repeat CMR later in course.

Diagnostic tools: endomyocardial biopsy (EMB)

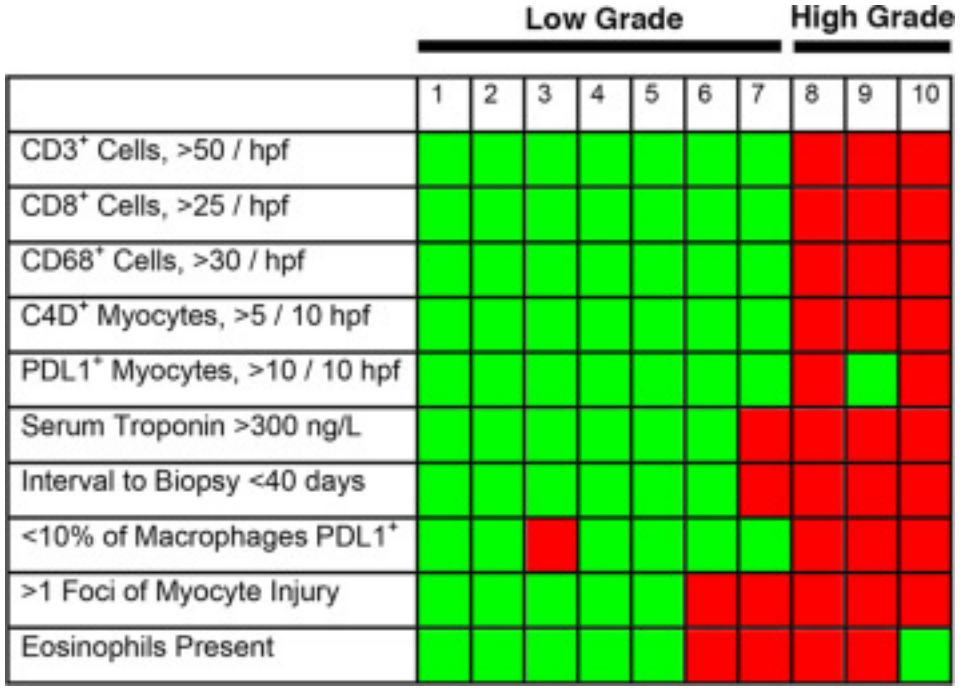
- Findings on EMB involve lymphocytic infiltrates with CD4+ and CD8+ T cells, CD68+ macrophage infiltration, fibrotic/inflammatory changes, and myocyte necrosis.
- False negatives can occur if involved area is not biopsied: inflammation in discrete foci
- ICI myocarditis has increased expression of PD-L1, higher CD68/CD3 ratio, and more lymphohistiocitic compared to transplant rejection (2R). Howeve generally these parameters thought to be insufficient to differentiate between causes of myocarditis.

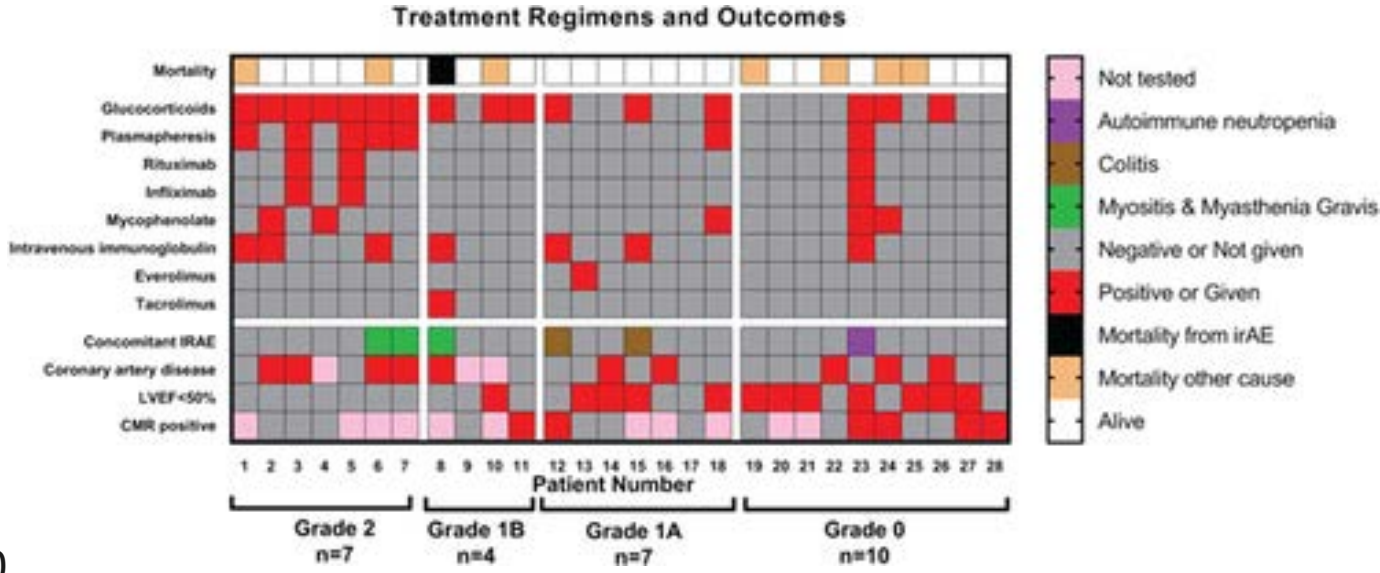


Nicolas L. Palaskas et al. European Journal Heart Failure. 2021

Can EMB influence treatment?

- Champion et al. characterized two forms of myocarditis: high grade and low grade determined by number of CD3+/HPF. Those with high grade disease (3) all died, while those with low grade disease(7) survived.
- At MD Anderson, Palaskas et al. studied 28 patients suspected of ICI myocarditis with EMB.
  - They reinforced the spectrum of myocarditis including a low grade, subclinical form.
  - High grade disease associated with shorter time of ICI initiation to symptom onset.
  - 5 patients with low grade inflammation did not receive steroids and were continued on ICI without any adverse CV events
  - All patients with suspected ICI myocarditis undergo biopsy at this institution. Is this realistic?

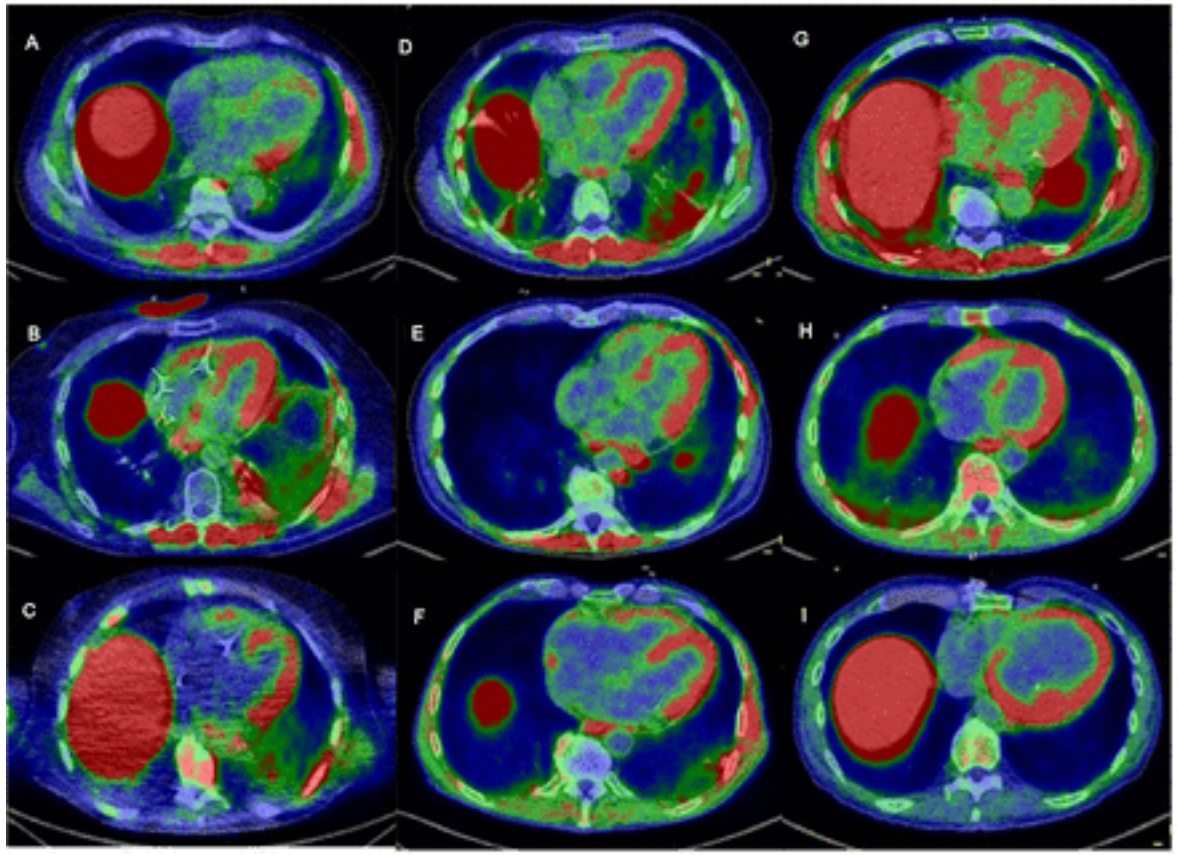




Samantha N. Champion et al. Modern Pathology. 2020.

Diagnostic tools: PET

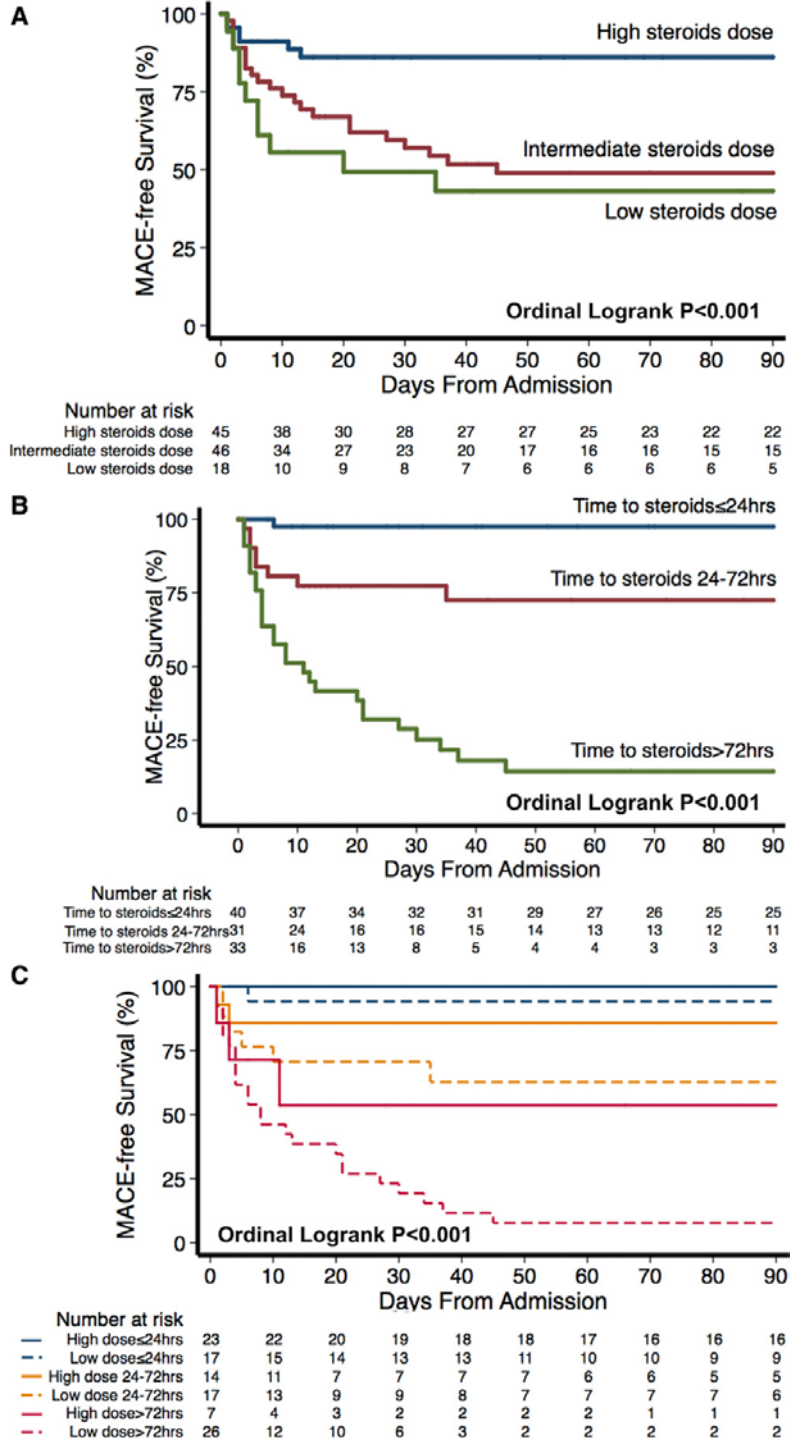
- Not commonly utilized in the diagnosis of ICI myocarditis, but a technology that is under rapid evolution.
- ^{18}F-fluorodeoxyglucose PET/CT, commonly utilized to assess for myocardial inflammation, demonstrated only 9.5% sensitivity in patients with definite myocarditis.
- In contrast, ^{68}Ga-DOTATOC demonstrated improved sensitivity in a small study.
- Further research is required before considering PET in the diagnostic algorithm for myocarditis.



Sarah Boughdad et al. Journal for Immunotherapy of Cancer. 2021

Treatment of ICI myocarditis

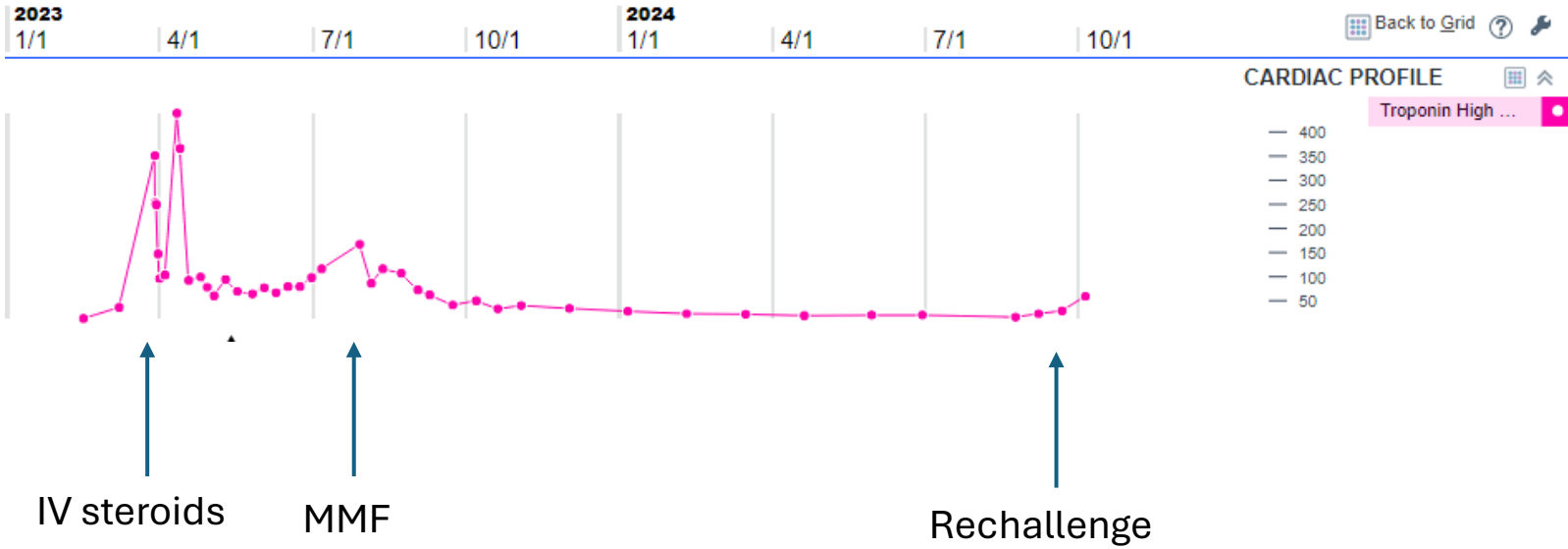
- Need to stop checkpoint inhibitor treatment at the first sign of suspicion. Then begin diagnostic evaluation.
- Once diagnosis confirmed, or suspicion adequate with no better alternative diagnoses, it is recommended that patients receive 500-1000mg of IV steroids for 3-5 days.
- Early high dose steroids has been associated with reduction in MACE



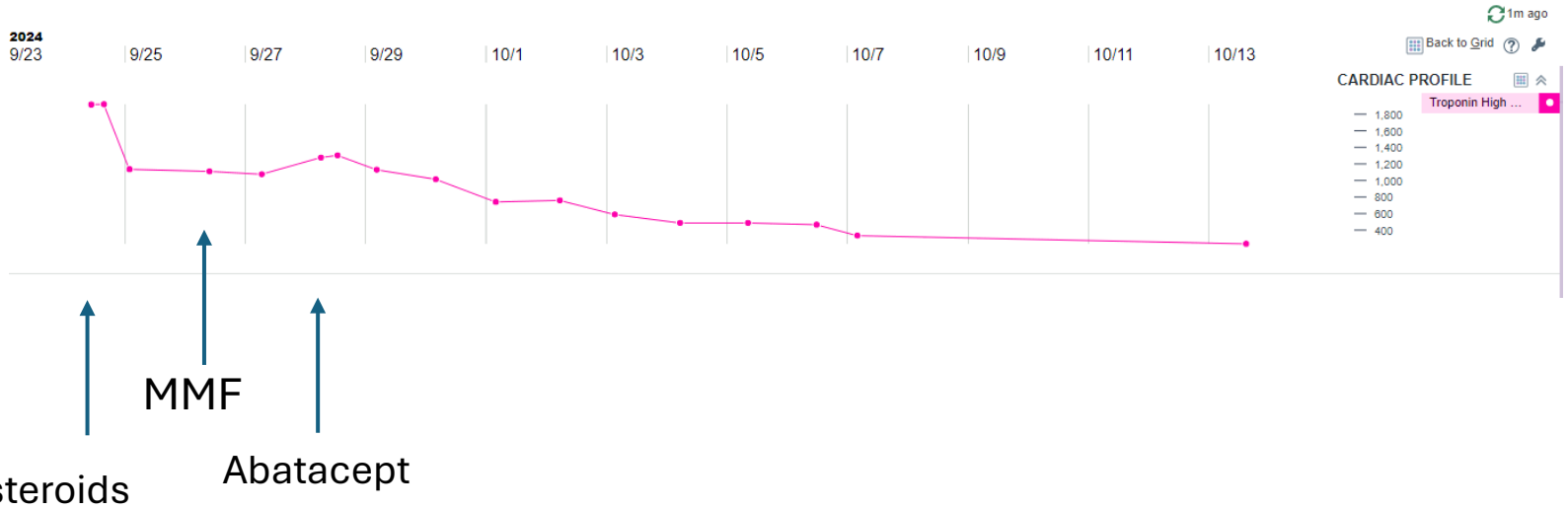
Lili Zhang et al. Circulation 2020

- After ”clinical improvement” (troponin decline by 50% and improvement in ventricular function) transition IV to PO steroids 1mg/kg/day.
- Monitoring closely clinically and with biomarker assessment, taper steroids by 10mg per week.
- Troponin is important, but clinical situation > troponin.
- Anecdotally I have found some success with more prolonged steroid tapers.

Patient 1

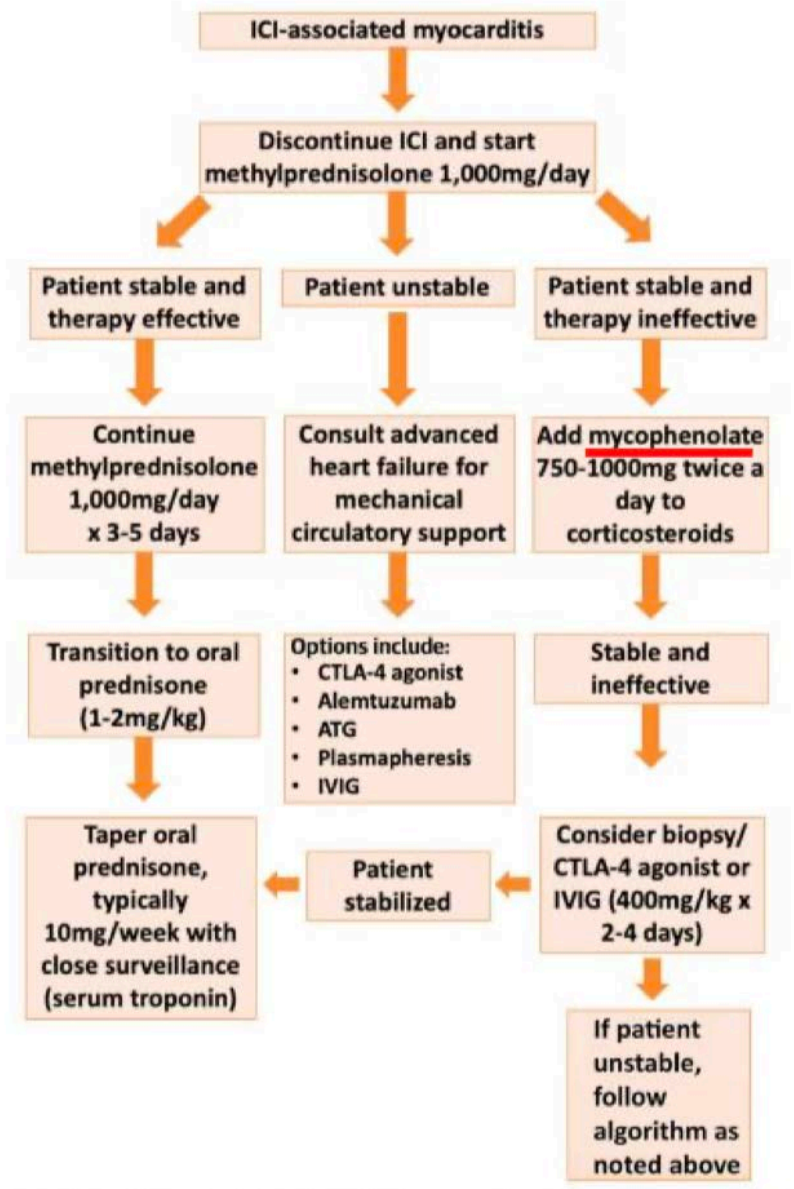


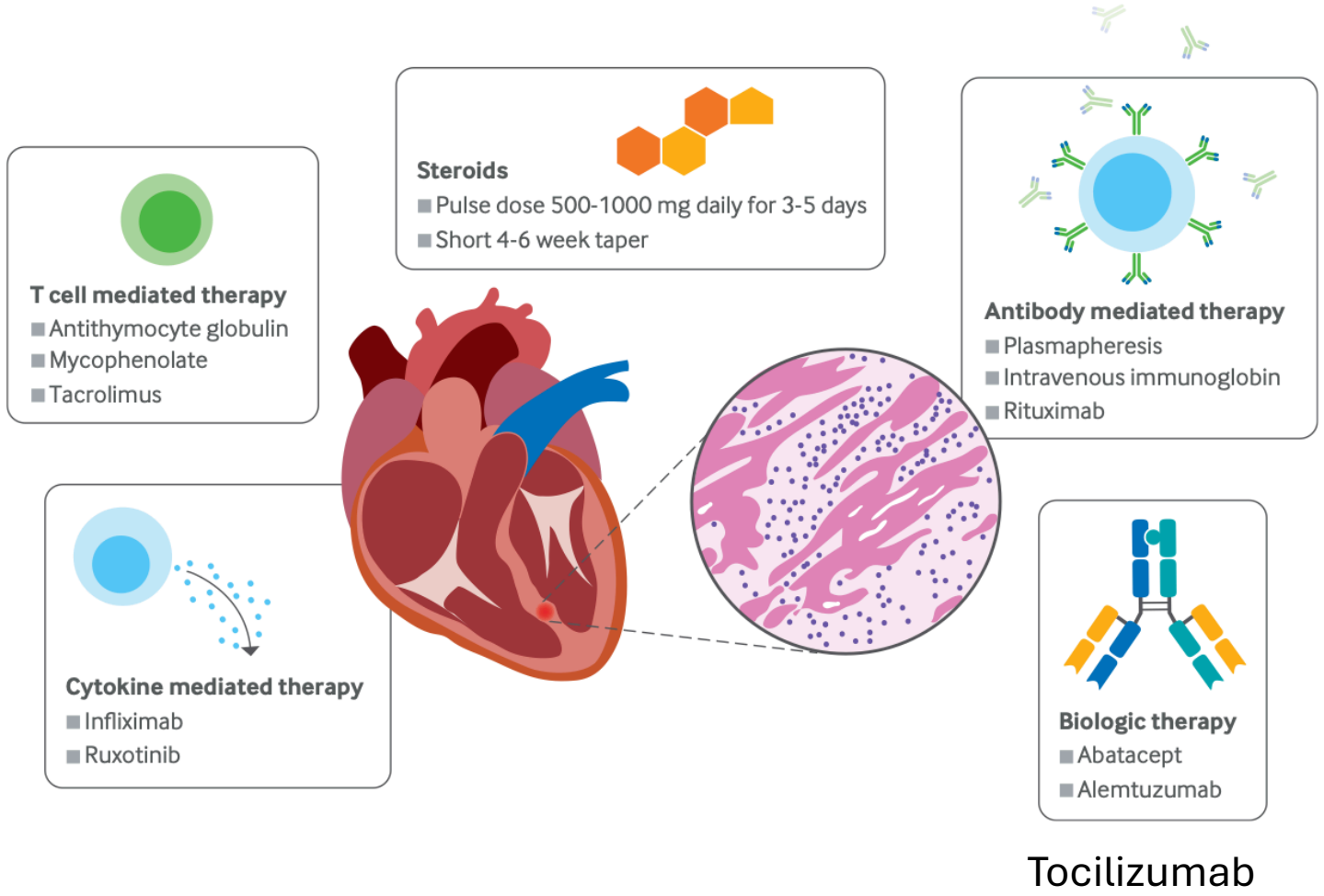
Patient 2



Time to venture into the wild west

Nonsteroidal immunosuppression





Tocilizumab

Lili Zhang et al. Current Treatment Options in Cardiovascular Medicine. 2019

Abatacept for immune checkpoint inhibitor associated myocarditis: ATRIUM

- Multicenter Randomized controlled trial comparing abatacept + steroids to placebo + steroids

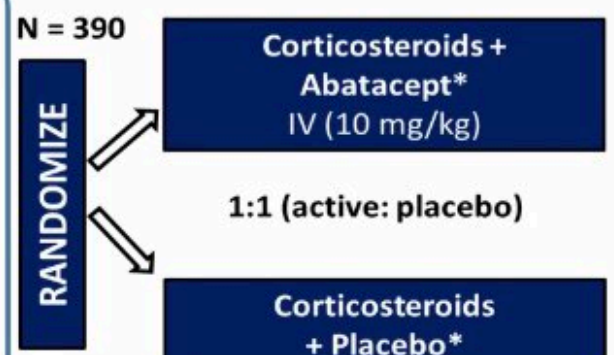
Key Inclusion Criteria

- Age ≥18 years
- Active treatment with an FDA-approved ICI
- Hospitalized
- Diagnosed with ICI Myocarditis

Key Exclusion Criteria

- Prior exposure to abatacept/belatacept
- Active Infection
- Already has a component of the primary endpoint
- Is currently enrolled in another interventional study focused on the management of ICI toxicities.
- Female who is considering becoming pregnant.
- Male who is considering fathering a child or donating sperm during the study or for approximately 30 days after the last dose of study drug.

Study Schema



repeated at 24 hours after first infusion of study drug, and at 14 (±2) days after first infusion of study drug, and an optional 4th infusion at 28 (±2) days after first infusion of the study drug.

Endpoints

Primary: Major Adverse Cardiac Events, defined as a composite of cardiovascular death, cardiogenic shock, cardiac arrest, significant ventricular tachyarrhythmia, significant bradyarrhythmia and acute decompensated heart failure.

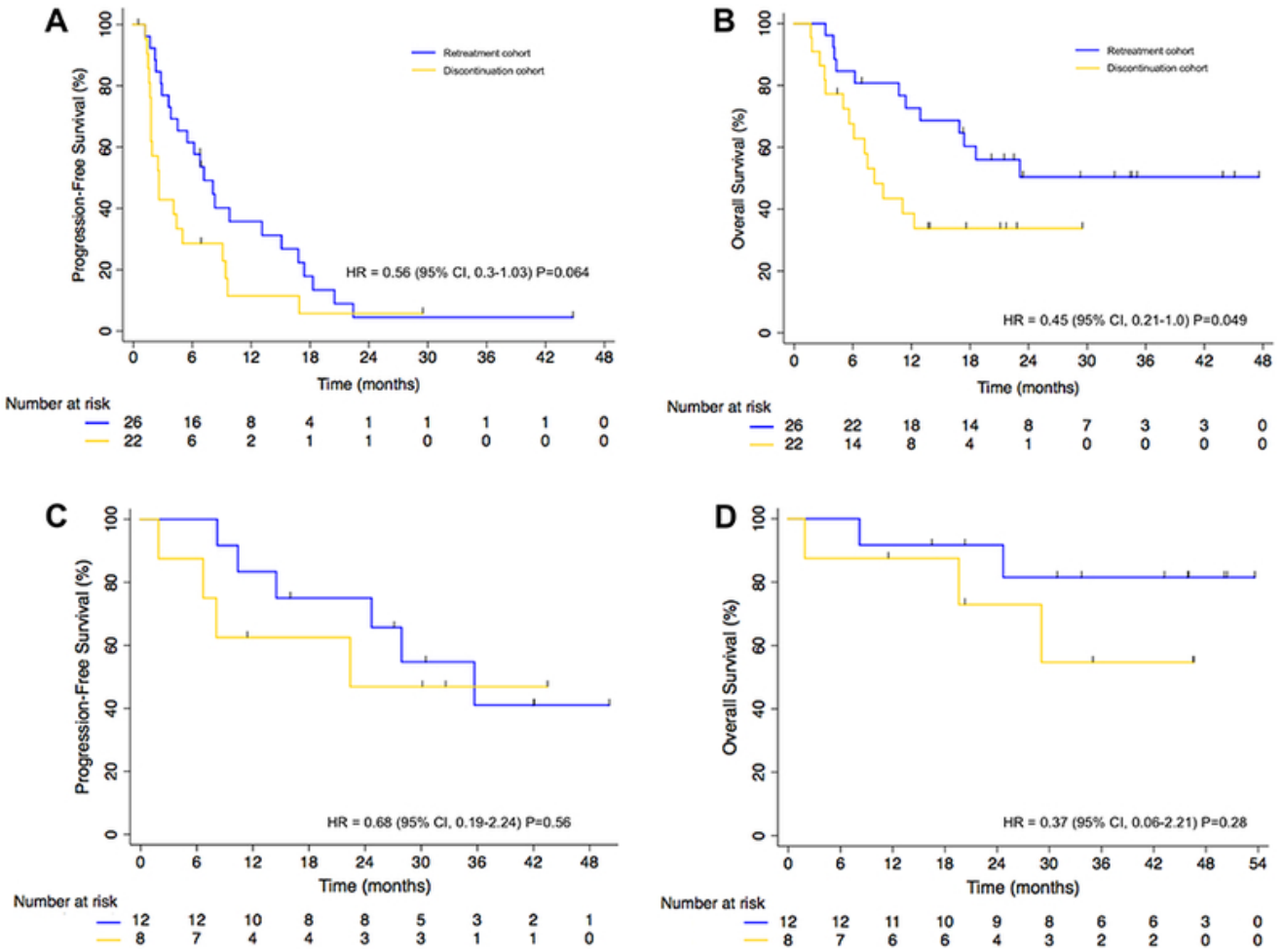
Secondary:

- Individual components of the primary endpoint.
- Change in serum troponin.
- The combination of the composite primary endpoint plus a troponin increase.
- Myocarditis Illness severity using an ordinal scale.
- Clinical status at 90 days and 6 months.
- Rates of fatal and non-fatal DVT and PE.
- Treatment-related adverse events between the two groups.

NCT05335928

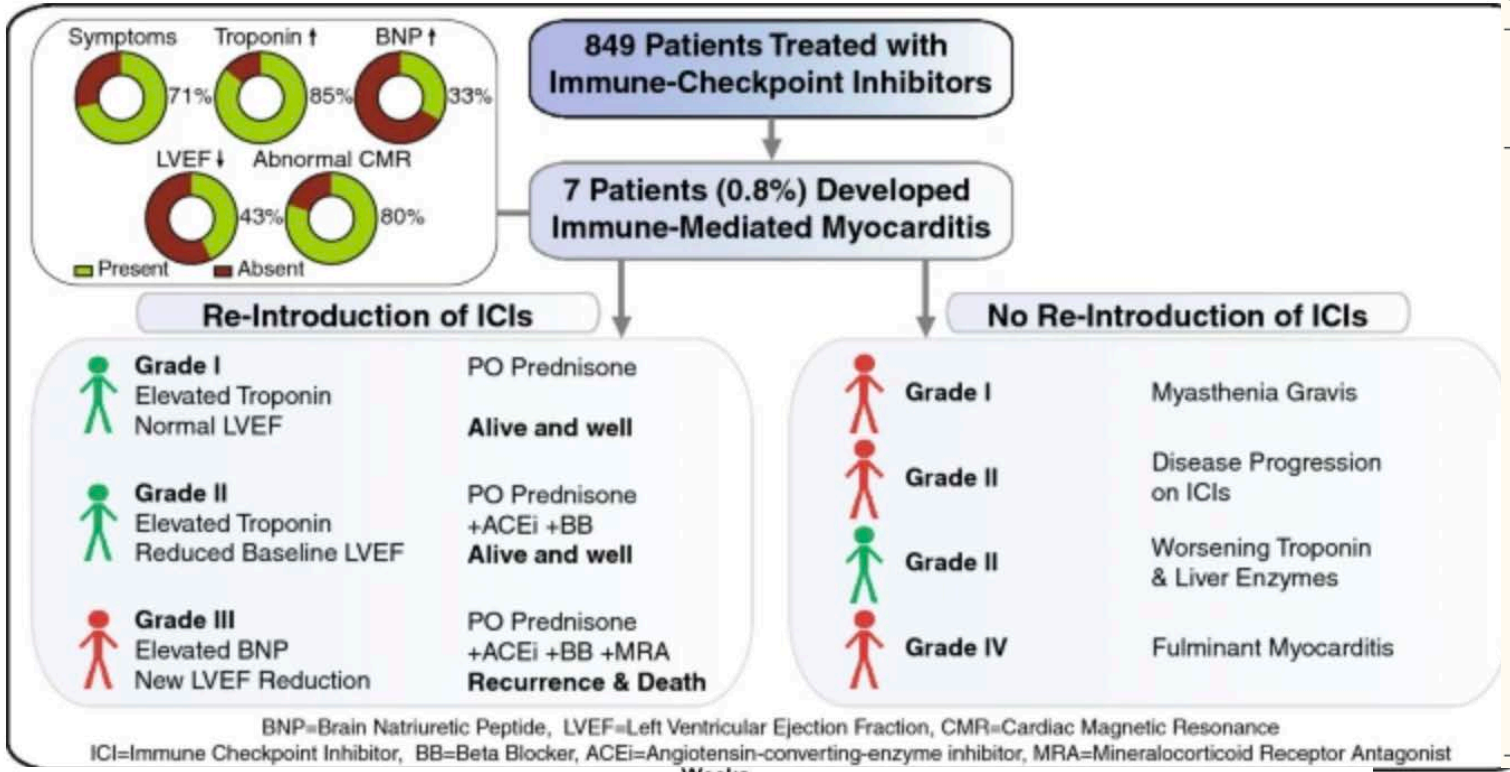
What about rechallenge?

- Very controversial
- One cohort has reported a 29% recurrence rate of the same IRAE upon rechallenge in a cohort of 24,079.
- In a small cohort of patients not in remission rechallenged after initial IRAE, patients that were rechallenged had higher overall survival at 4 years.



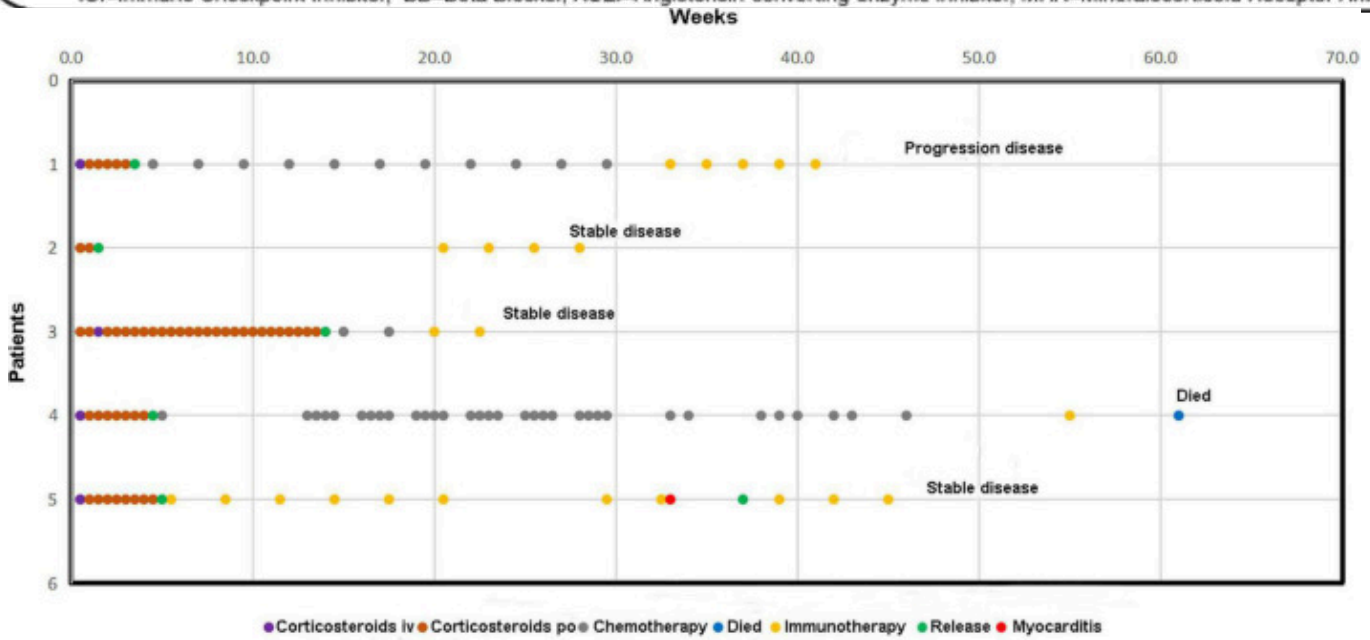
Outcomes in patients who did NOT achieve complete or partial remission.

Fernando C. Santini et al. Cancer Immunol Res. 2018



Case reports and series of rechallenge of ICI after myocarditis.

Reference	Number of Patients Rechallenged	Grade of Myocarditis			Adverse Event after Rechallenging
		Grade 1	Grade 2–3	Grade 4	
Xue Chen et al., 2022 [38]	5	0	5	0	1 patient: grade 2 myocarditis 1 patient: cancer death after 1 year
Peleg Hasson S. et al., 2021 [39]	3	1	2	0	1 patient: worsening cardiac symptoms
Dae Hyun Lee et al., 2020 [40]	1	0	0	1	None
Menachery Sherin M. et al., 2023 [41]	1	0	0	1	Cancer death after <1 year
Eslinger Cody et al., 2023 [42]	1	0	0	1	None
Rossi A. Valentina et al., 2023 [43]	1	0	1	0	Grade 1 myocarditis
Yeshan Chen et al., 2022 [44]	1	0	1	0	None
Dinu Valentin Balanescu et al., 2020 [45]	2	0	2	0	None
Shen et. al., 2021 [46]	1	0	1	0	Grade 2 myocarditis



- Data on rechallenge in ICI myocarditis is very sparse.
- Patients with Grade IV myocarditis are rarely rechallenged.
- Case reports described mixed outcomes.
- The decision should be multi-disciplinary and patient centered, taking into account cancer status and treatment options as well as CV risks.

Xue Chen et a. Front Cardiovasc med. 2022
Shira Peleg Hasson et a. Clinical Research in Cardiology. 2020
Cyrille Coustal et al. J Immunother Cancer. 2023

Summary

- Immunotherapy mediated myocarditis is a rare but disruptive and life-threatening adverse event.
- High clinical suspicion, particularly with use of dual ICI therapy with other IRAEs and proper use of troponin, cardiac MRI, and endomyocardial biopsy, can lead to rapid and accurate diagnosis.
- Treat myocarditis with high dose IV steroids, and taper cautiously, incorporating clinical data. Refractory cases can be treated with nonsteroidal immunosupressants, with more research needed to establish best practices.
- ICI myocarditis cases are not uniform, and further research on outcomes may help us understand more about controversial subjects such as ICI re-challenge.