

Cardio-oncologia

Miocarditi da immunocheckpoint inibitori

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15 YEARS OF PROGRESS: EXPANDING IMMUNOTHERAPY ACCESS

Immune Checkpoint Inhibitors (ICIs)



NUMBER OF
FDA-APPROVED ICIs

2011

1

2025

15



NUMBER OF CANCERS
WITH ICI APPROVAL

1

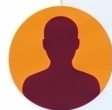
20+



MODES OF ACTION OF
FDA-APPROVED ICIs

1

4



ELIGIBLE US
CANCER PATIENTS

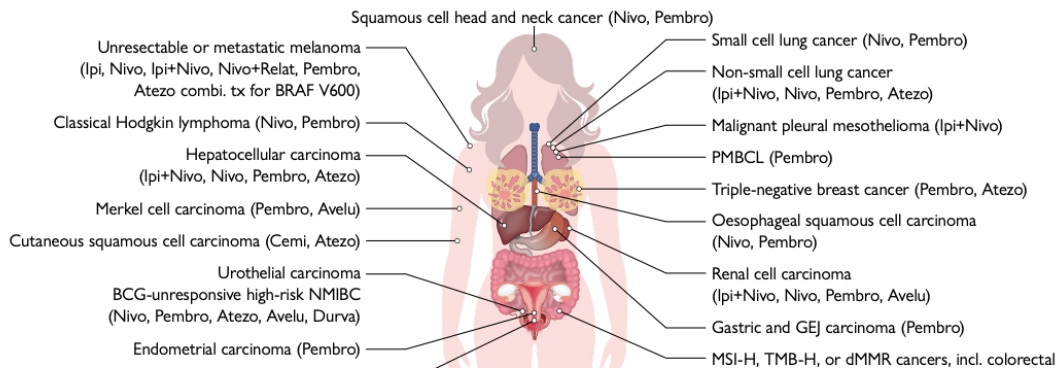
1.5%*

56.5%

AACR Cancer Progress Report 2025



Immune Checkpoint Inhibitors



Complications



- Troponin elevation of uncertain significance
- Myocarditis (smoldering, non-severe, severe/fulminant)
- Pericarditis with and without pericardial effusion
- Cardiomyopathy
- Takotsubo syndrome



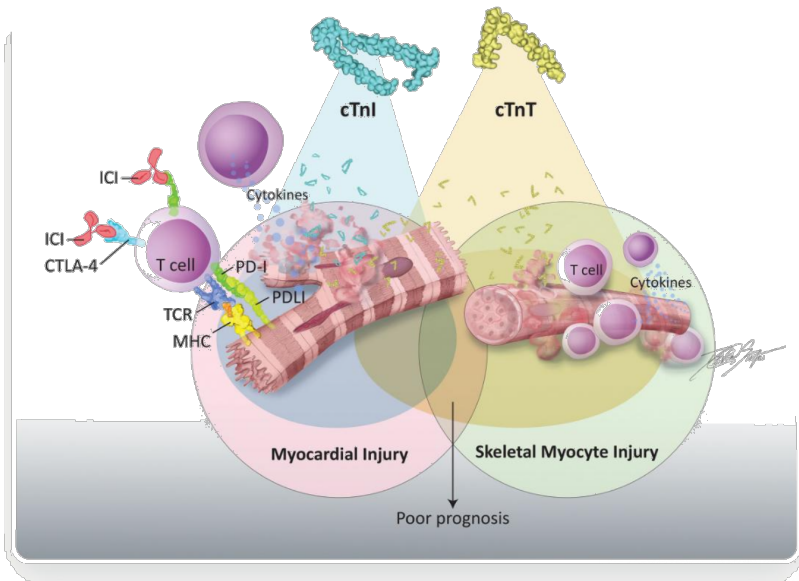
- Atrial fibrillation
- Heart block including bundle branch and AV block
- Ventricular ectopic
- Non-sustained and sustained ventricular tachycardia
- Ventricular fibrillation



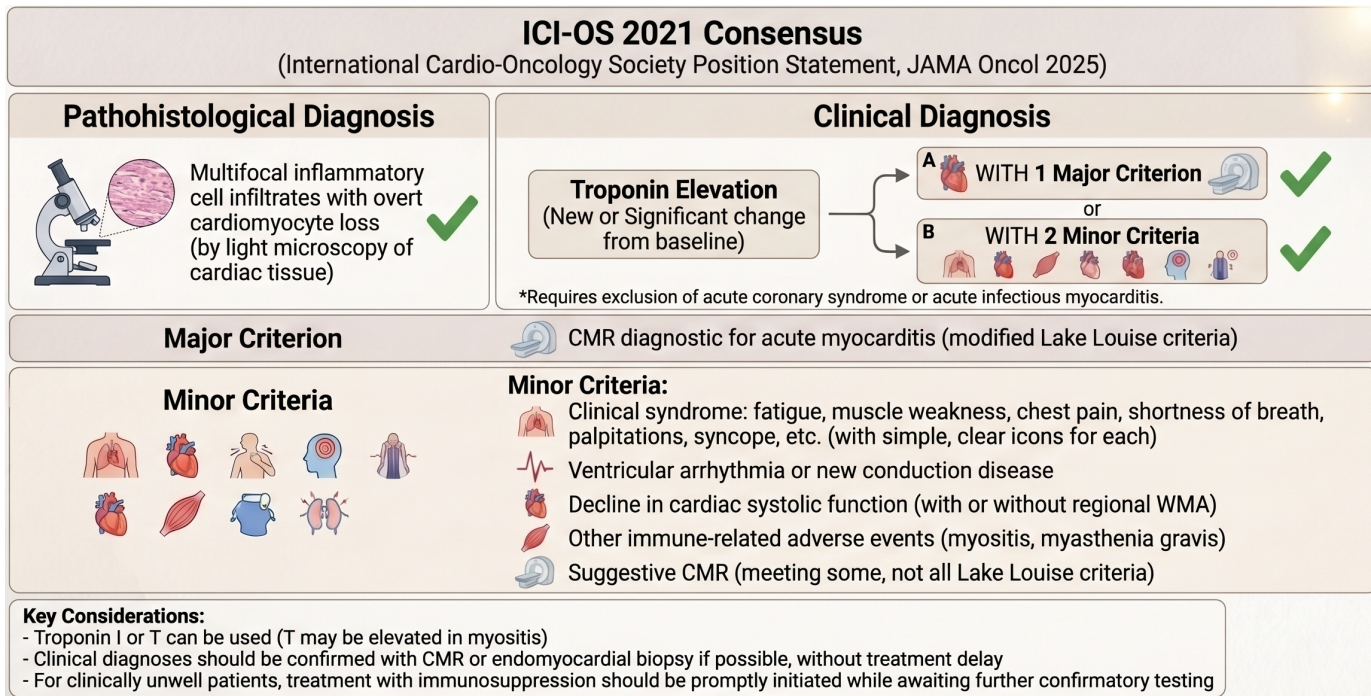
- Vasculitis
- Accelerated atherosclerosis
- Myocardial infarction
- Venous thromboembolism

The Myocarditis Challenge

- ! **High Risk Toxicity:** ICI-associated myocarditis is rare but carries significant risk of rapid progression, clinical morbidity, and mortality.
- ✓ **ESC Recommendations:** European Society of Cardiology guidelines recommend baseline measurement (Class I) followed by serial monitoring during cycles 2, 3, 4, and then every 3 cycles (Class IIa).
- ✓ **NCCN Strategy:** Supports serial testing in high-risk patients (Category 2A) to capture early inflammatory subclinical signals.
- ✓ **Implementation Gap:** Real-world protocols vary significantly across cancer institutions due to logistics and clinical triage uncertainties.



ESC-ICOS Diagnostic Criteria for ICI Myocarditis



ICI-M DIAGNOSTIC CRITERIA AND SCREENING

THE CLINICAL REALITY & SURVEILLANCE



THE DIAGNOSTIC STRATEGY FOR ICI-M IS **CRITICALLY MORE COMPLEX** than for myocarditis of other etiologies.

PRIMARY SCREENING INDICATORS

1.  **Troponin Baseline**
(Serial Monitoring)
2.  **Serial ECGs**
(Before each cycle)
3.  **Symptom Screen**
(Dyspnea, Fatigue)



THE IMAGING PARADOX & CRITICAL DIAGNOSIS



WARNING:
CMRI AND
ECHOCARDIO-
GRAPHY MAY BE
**MISLEADINGLY
NORMAL**

especially early in
the clinical course.



DEFINITIVE GOLD STANDARD



**ENDOMYOCARDIAL
BIOPSY**
(Definitive Diagnosis when
imaging is non-conclusive)



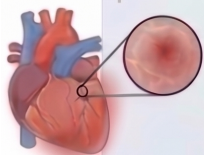
Median Days to Onset:
34 DAYS
Vigilance is Mandatory



PITFALLS OF CMR

CRITICAL ANALYSIS OF CMR LIMITATIONS FOR ICI-MYOCARDITIS

DIAGNOSTIC ANALYSIS



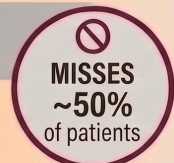
SMALL DEGREE OF INJURY CHALLENGE: CMR

May remain in cases with small degrees of injury.



Specificity Balance

HIGH SPECIFICITY
(T1+ & T2+)



SENSITIVITY BALANCE (Any Abnormal Marker)

CATCH
100%



HIGH SENSITIVITY
(suggestive criteria – Any 1 Abnormal T1 or T2)

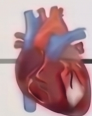


Significantly reduced Specificity



3 TIMING & TREATMENT EFFECT:

Day 1



Day 30+

Edema (T2)
Resolves early (especially after steroids).

• LGE may be a delayed finding

DIAGNOSTIC STRATEGY

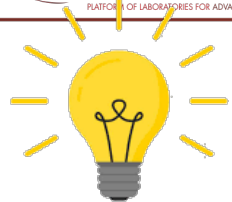


INTEGRATING CMR FINDINGS WITH OTHER CLINICAL DATA IS CRUCIAL.

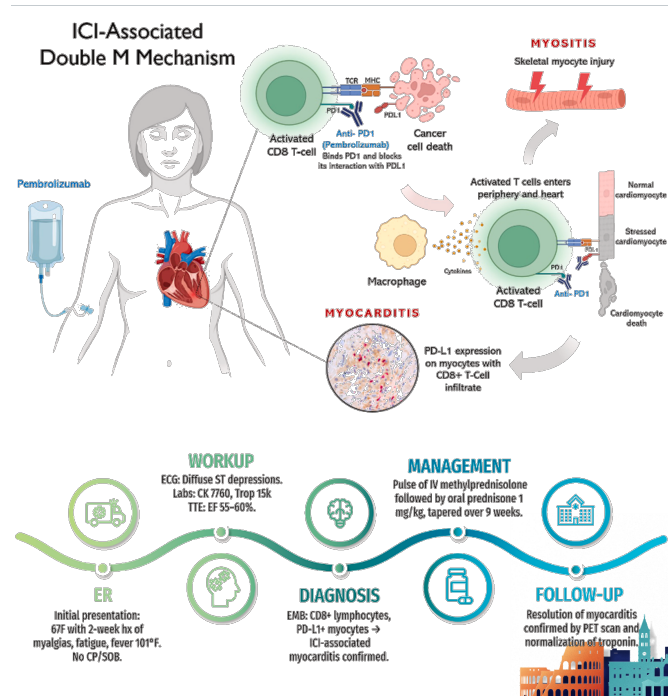
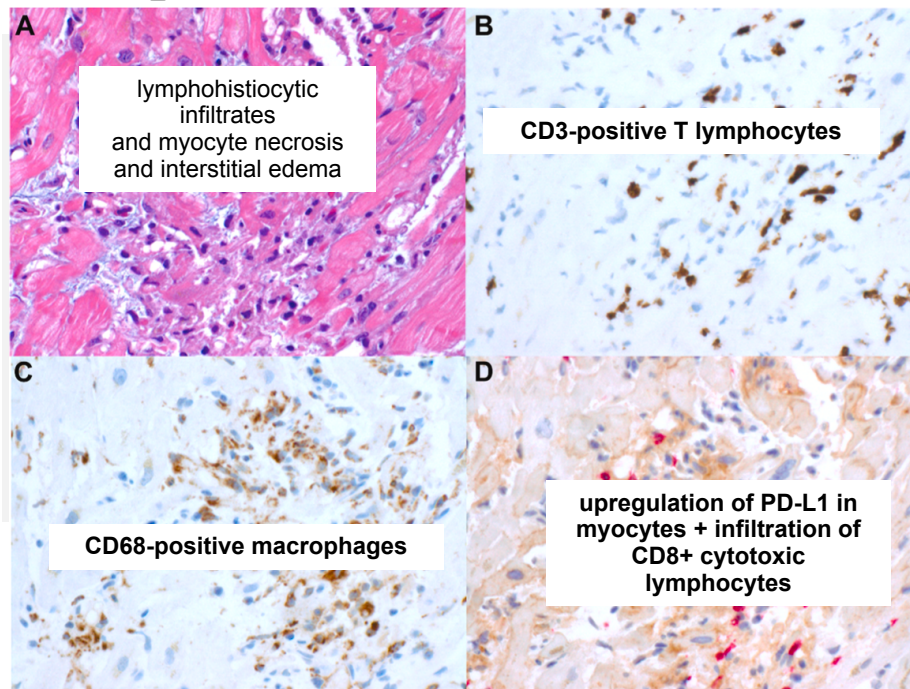


Ongoing development of more comprehensive diagnostic tools.





Smoldering Myocarditis Unmasked by Pembrolizumab-Induced Myositis



TROPONIN SURVEILLANCE DURING ICI THERAPY



Emerging Challenge: ICI-associated myocarditis carries high morbidity and mortality risks.



Guideline Gaps: ESC and NCCN recommend monitoring, but real-world implementation is highly variable.



The Need for Data: Limited evidence on how troponin influences downstream testing and oncology outcomes.



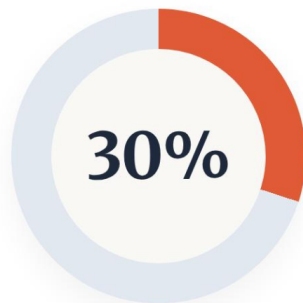
Early Detection: Moving from "emergency management" to "proactive screening."



Baseline hs-TnT Detection Rates

Tomsitz et al Eur J Cardiol 2025

Prospective Study 1



- ✓ Optimized baseline surveillance strategy using **high-sensitivity Cardiac Troponin T (hs-TnT)**.
- ✓ Concluded that **30% of oncology patients** present with detectable baseline troponin levels due to non-cardiac confounders.

van den Berg JACC Adv 2024

Prospective Study 2



- ✓ Analyzed baseline hs-TnT before first checkpoint inhibitor cycle.
- ✓ Discovered **35% detection rate** without active myocarditis, emphasizing the need for **delta-based serial testing**.



Troponin Kinetics in Immune Checkpoint Inhibitor (ICI) Therapy

1. Serial Monitoring & Baseline Confounders

• The Clinical Challenge of Static Values

Oncology patients frequently present with chronically elevated baseline high-sensitivity troponin (hs-cTn) due to age, renal impairment, or prior cardiotoxic therapies.

• Defining the Delta (Delta hs-cTn)

Rather than relying on an absolute cutoff, clinical attention focuses on the dynamic variation across consecutive cycles (Baseline vs. Pre-dose 2, 3, and 4).

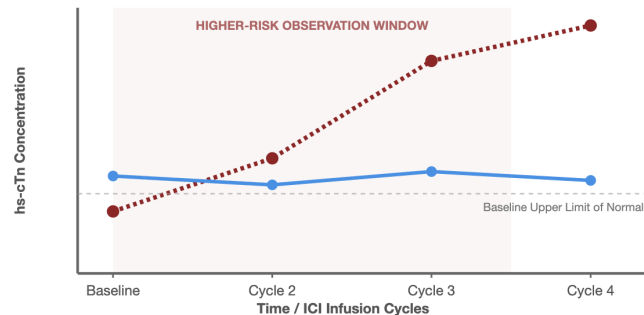
• Subclinical Detection Window

Early variations often precede clinical symptoms or overt echocardiographic changes, providing a narrow window for multidisciplinary cardio-oncological assessment.

Potential Confounders to Consider:

- Concomitant Immune-Related Myositis (causing cross-reactivity or subclinical skeletal injury)
- Asymptomatic chronic myocardial stress vs. active, immune-mediated myocarditis

2. Conceptualizing Longitudinal Trends



.... Pattern A: Significant Delta Trend

Suggested Action: Evoke investigative protocols (ECG, CMR) to rule out injury.

— Pattern B: Stable Chronicity

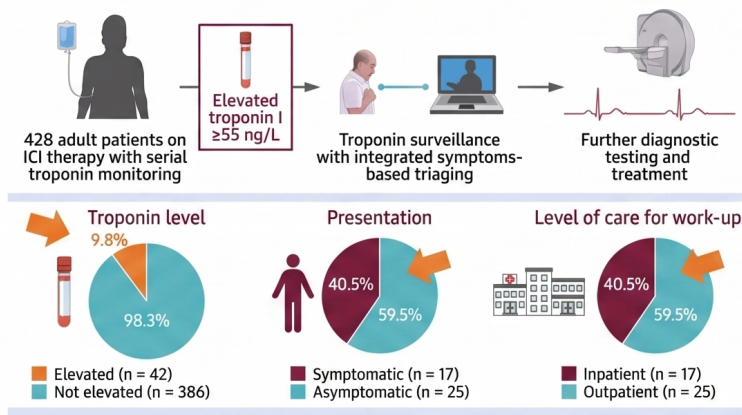
Suggested Action: Consider vigilant continuation & routine monitoring.



How to manage isolated Tn elevation in clinical practice?



cTn Screening and Clinical Outcomes in Patients Receiving ICI



	Asymptomatic	Symptomatic
MACE at 2-Year Follow-Up	N = 1	N = 7
Myocarditis	1 1.4% Myocarditis Incidence 5	1
Myocardial infarction	0	1
Congestive heart failure	0	1
Mortality at 2-Year Follow-Up	N = 9	N = 12
Cancer-related death	7	10
Cardiac-related death	0	0
Other/unknown cause of death	2	2

PRINCIPLES OF CARDIO-ONCOLOGY CARE

- 1 Cardio-Oncology Triage is Essential**
- 2 Active Symptom Catching**
- 3 Immunotherapy Preservation**
- 4 Myocarditis is rare**
- 5 Zero cardiac mortality at 2 years**



A New Broad Entity: ICI Myotoxicity

>170k

PATIENTS ANALYZED

French National Cohort Study
(SNDS)

0.3%

—

0.6%

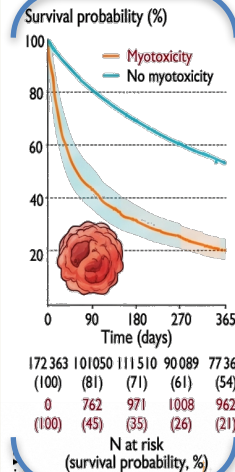
OVERALL INCIDENCE

Rare but high-severity adverse
event



Clinical Manifestations

- ✓ **High Myocarditis Co-occurrence:** Ranging between **13% and 23%** of all documented myotoxicity cases.
- ✓ **Involved Organ Systems:** Overlap of cardiac muscle (Myocarditis) and skeletal muscle (Myositis/Myasthenia Gravis).
- ✓ **Fatal Prognosis Risk:** Early recognition is paramount due to swift escalation trends.



Risk Factors for ICI-Myotoxicity



Hazard Ratios (sHR) for Myotoxicity Risk



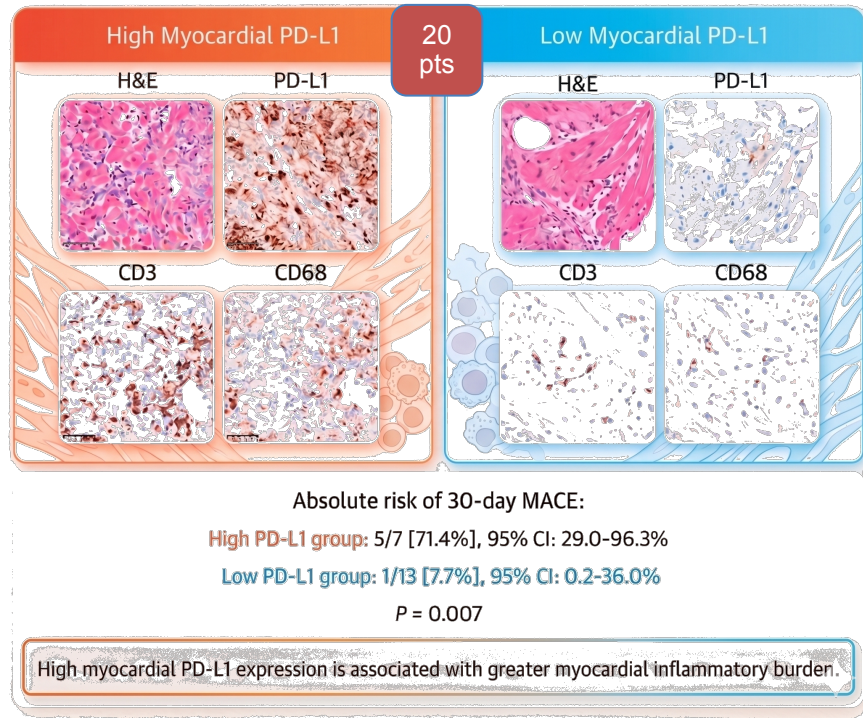
Key Takeaways

- ✓ **Thymic Pathology** remains the single strongest predictor of fatal outcomes.
- ✓ **Dual Checkpoint Blockade** (e.g., Nivolumab + Ipilimumab) significantly multiplies safety risks.
- ✓ **Pre-existing Autoimmunity** requires rigorous baseline screening protocols.





Myocardial Expression of PD-L1 as a Marker of Poor Prognosis in ICI-Associated Myocarditis



PROGNOSTIC RISK INDEX: POWER SCORE

SEVERITY RISK PREDICTOR

Severity Score by Power

A validated 5-point clinical scoring system developed to predict 30-day major adverse events (severe arrhythmia, heart failure, respiratory muscle failure, or death) in patients presenting with ICI-associated myocarditis.

-  **Active Thymoma:** Presence of thymic tumor malignancy (+1 Point)
-  **Cardio-Muscular Symptoms:** Concurrent myositis, myasthenia, or dyspnea (+1 Point)
-  **Low QRS Voltage on ECG:** Sokolow-Lyon index ≤ 0.5 mV in limb leads (+1 Point)
-  **Depressed LVEF:** Left Ventricular Ejection Fraction < 50% (+1 Point)
-  **Troponin Elevation:** Graded by fold-increase above reference limits (+1 Point)

30-Day Risk Stratification

Score 0 (Low Risk) ~3.9% Risk

Score 1-2 (Intermediate) ~15 – 30% Risk

Score 3 (High Risk) ~50% Risk

Score ≥ 4 (Extreme Risk) ~81.3% Risk

Clinical Impact: Low-risk cohorts (Score 0) demonstrated a 100% negative predictive value, allowing potential management with close monitoring without aggressive immunosuppression.



SCENARIO 1: INCONCLUSIVE PRESENTATION

CTCAE GRADE 1

Troponin Elevation of Uncertain Significance

-  **Clinical Status:** Asymptomatic elevation of cardiac Troponin (cTn) without immediate diagnostics pointing directly to myocarditis.
-  **Initial Action:** **Continue ICI therapy** while initiating a comprehensive cardiac workup to rule out alternative causes.
-  **Monitoring:** Mandate serial troponin measurements and clinical checks until levels completely normalize.
-  **Escalation:** Proceed to immediate hospitalization and initiate steroid treatment if clinical status deteriorates or biomarkers rise sharply.



ICOS Position Statement Hermann et al adapted from JAMA Oncol 2025



SCENARIO 2: SMOLDERING MYOCARDITIS

CTCAE GRADE 2

Confirmed Myocarditis Without Clinical Signs

-  **Diagnostic Confirmation:** Meets established diagnostic criteria for ICI myocarditis (typically via CMR imaging or tissue biopsy).
-  **Presentation:** Absence of clinical symptoms or physical signs of cardiotoxicity; patient remains stable.
-  **Clinical Action:** Mandate a prompt **multidisciplinary discussion** to evaluate oncology risks versus cardiac preservation.
-  **Intervention Path:** Consider close observation under strict cardiac surveillance versus initiating early, low-to-moderate-dose steroid therapy.

Diagnostic Cornerstones

Smoldering myocarditis is often found incidentally. Standard assessment includes:

- 1. Cardiac MRI (CMR):** Look for Late Gadolinium Enhancement (LGE) and T1/T2 mapping abnormalities.
- 2. Biomarkers:** Persistent, lower-level cTn elevation above reference values.

Note: Early clinical suspicion is vital before symptomatology develops.



SCENARIO 3: CLINICAL MYOCARDITIS

CTCAE GRADE 3

Nonfulminant Myocarditis

Characterized by a nonsevere clinical presentation upon diagnostic confirmation.

-  **Admission:** Direct hospitalization with telemetry monitoring.
-  **Treatment:** Start early empirical intravenous steroid therapy and supportive cardiovascular medication.
-  **Surveillance:** Serial troponin and continuous ECG monitoring; escalate treatment immediately if clinical signs worsen.

CTCAE GRADE 4-5

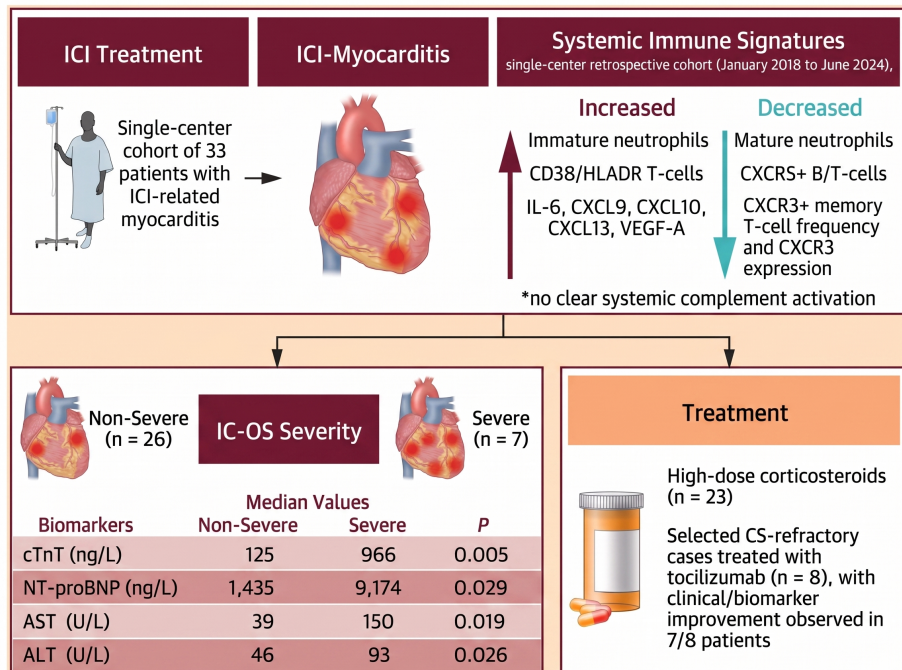
Fulminant Myocarditis

Severe clinical presentation characterized by hemodynamic instability or complex arrhythmias.

-  **Action:** Immediate emergency hospitalization and direct transfer to the Intensive Care Unit (ICU).
-  **Support:** Prompt consideration of mechanical circulatory support (MCS) and high-dose IV steroid boluses.
-  **Therapeutic Shift:** Rapidly escalate to second-line immunosuppressive drugs if unresponsive to standard steroids.



Decoding ICI-Myocarditis: From Systemic Immune Signatures to Severity Biomarkers





The FAST-TRACK ICI Protocol

Ambulatory Triage (83%)

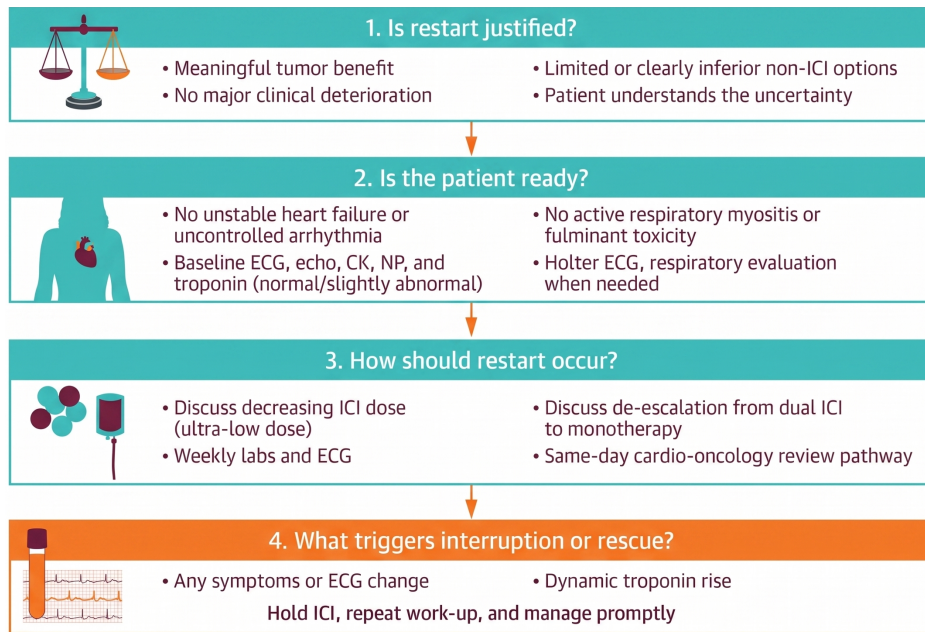
- Suitable for asymptomatic patients with subtle biomarker changes.
- Allows brief postponement of oncology treatments pending cardiac workup.
- Mandates clinical, ECG, and echocardiographic evaluation within 48h.
- Provides safe, structured surveillance avoiding hospital admission in 83% of cases.

Immediate Hospitalization

- **Clinical Instability:** Dyspnea at rest, chest pain, syncope, or palpitations.
- **ECG Abnormality:** New-onset AV blocks, bundle branch blocks, or arrhythmias.
- **High-Risk Therapies:** Combined dual immunotherapy regimens.
- **Rapid Biomarkers:** Rapidly escalating troponin values on repeated tests.



A Practical Framework for Safe ICI Rechallenge



Key principle: Rechallenge should be carefully considered, individualized, and safest in a specialist cardio-oncology program

