Penn Medicine

ACC India 2023 Cardiovascular Symposium

# Updates in Cardio-Oncology With a Focus on Cancer Immunotherapies

**Nosheen Reza, MD, FACC, FHFSA**
Assistant Professor of Medicine
Penn Center for Inherited Cardiovascular Disease
Section for Advanced Heart Failure, Transplantation, and Mechanical Support

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# 70-year-old man with metastatic renal cell carcinoma

Diffuse bony metastases status post right hip radiation

Cabozantinib (TKI-VEGF inhibitor) x 2 years, stopped due to progression

Ipilimumab + nivolumab (CTLA-4 and PD-1 immune checkpoint inhibitors) started

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Hypertension on amlodipine 10 mg and atenolol 75 mg
Recurrent DVTs and pulmonary embolism on rivaroxaban
Hyperlipidemia on atorvastatin 10 mg

# 15 days after ipilimumab + nivolumab initiation…

Fatigue, dyspnea, subjective fever, night sweats, myalgias x 1 week

T 38.6C HR 106 BP 123/78 RR 20 SpO2 98% RA
Comfortable-appearing
Normal S1/S2, no JVD, no murmurs/rubs/gallops
Clear lungs
No peripheral edema, warm

| | Values | Normal Values and Units |
|---|---|---|
| **Troponin I** | 1.48 → 1.73 → 1.63 → 1.69 | 0.000-0.030 ng/mL |
| **Lactic Acid** | 2.8 | 0.5 - 2.2 mmol/L |
| **Creatine Kinase (CKMB)** | 7,298 | 49 - 397 U/L |
| **NT-proBNP** | 1,819 → 1,854 | 0-125 pg/mL |
| **Creatinine** | 0.80 | 0.6 - 1.0 mg/dL |

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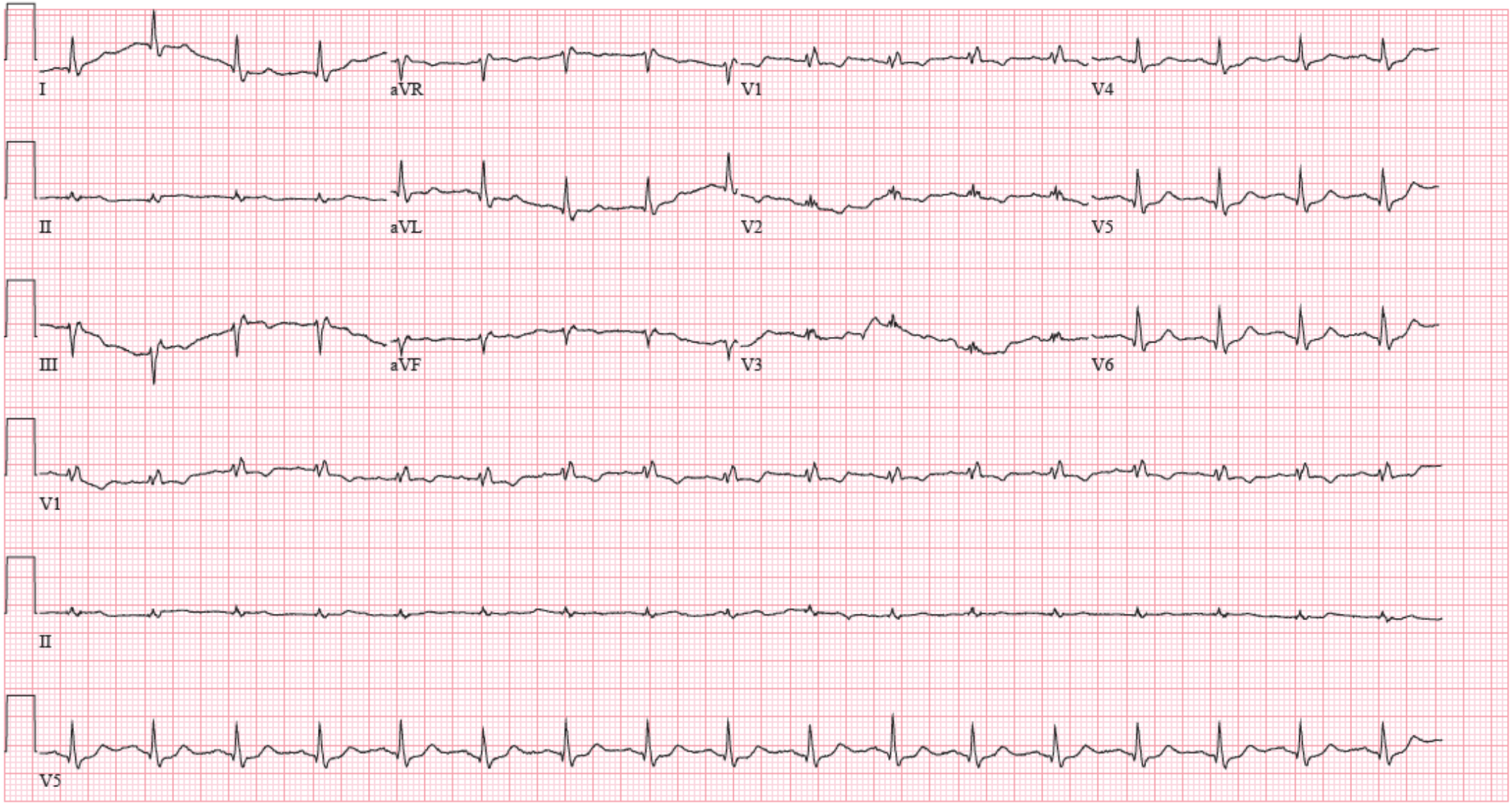

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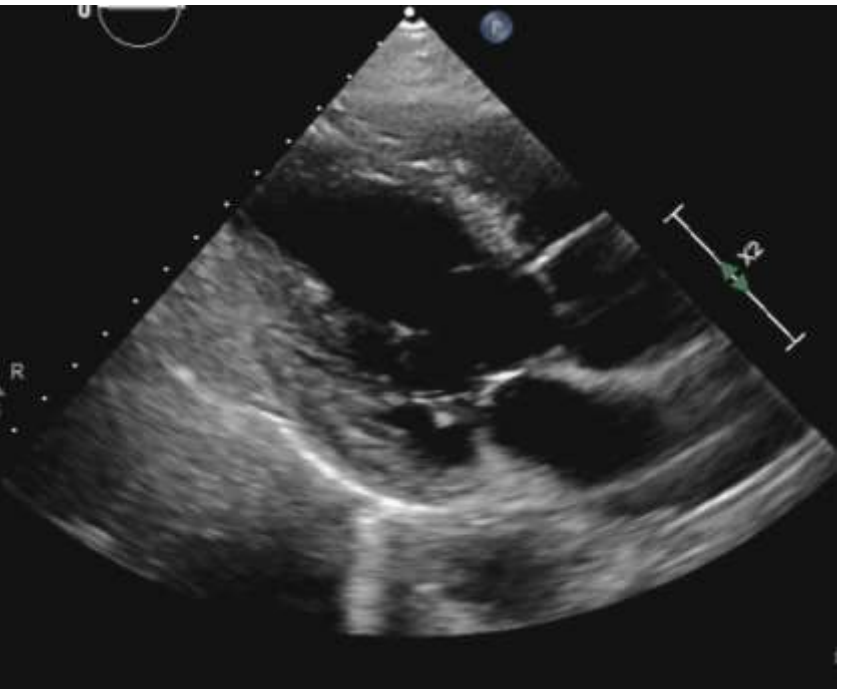
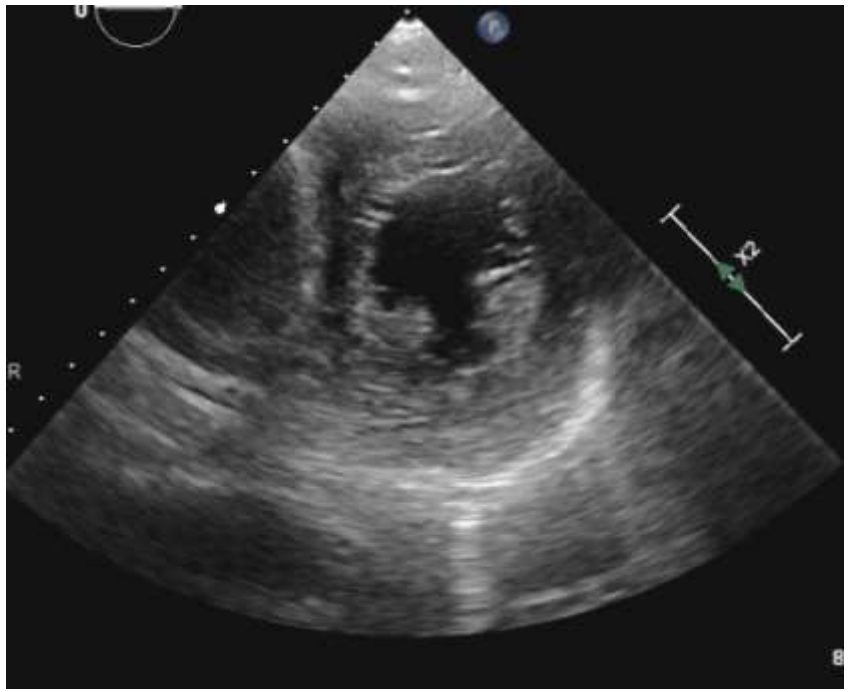
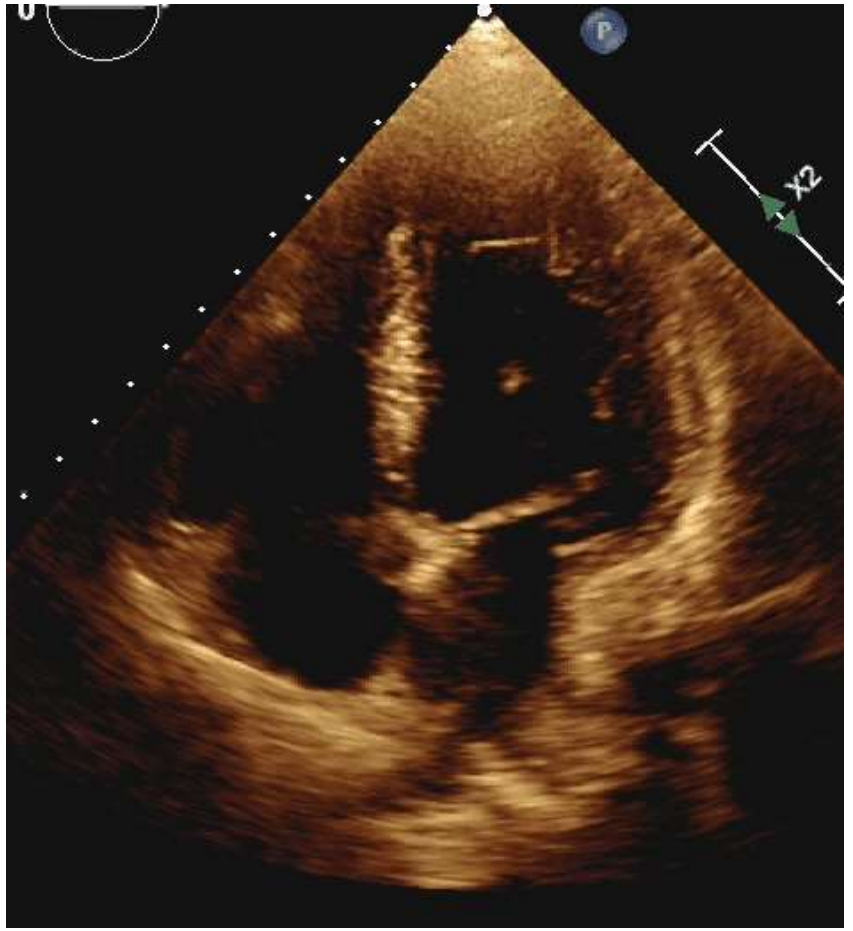


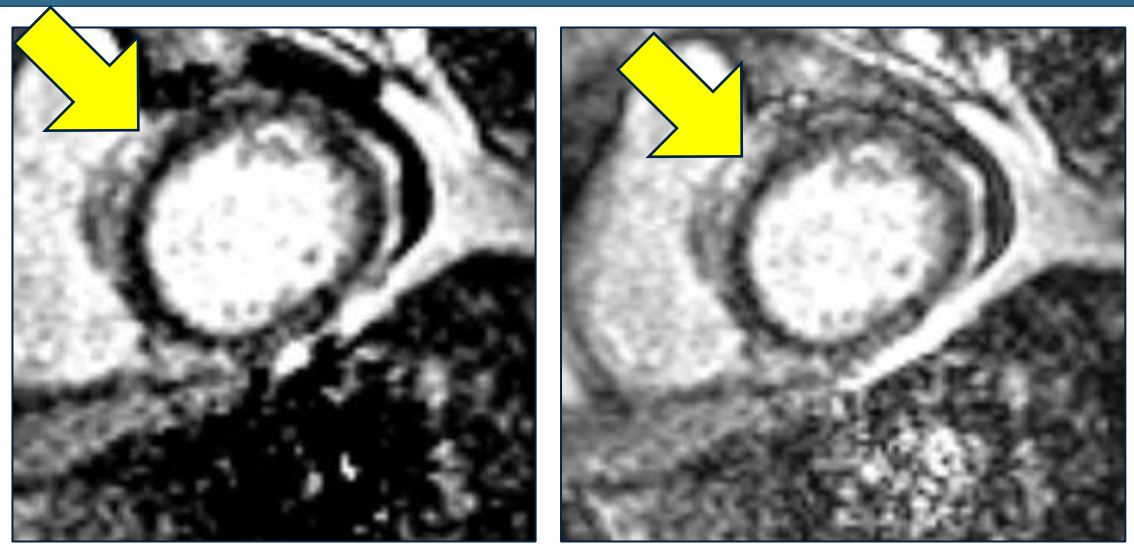


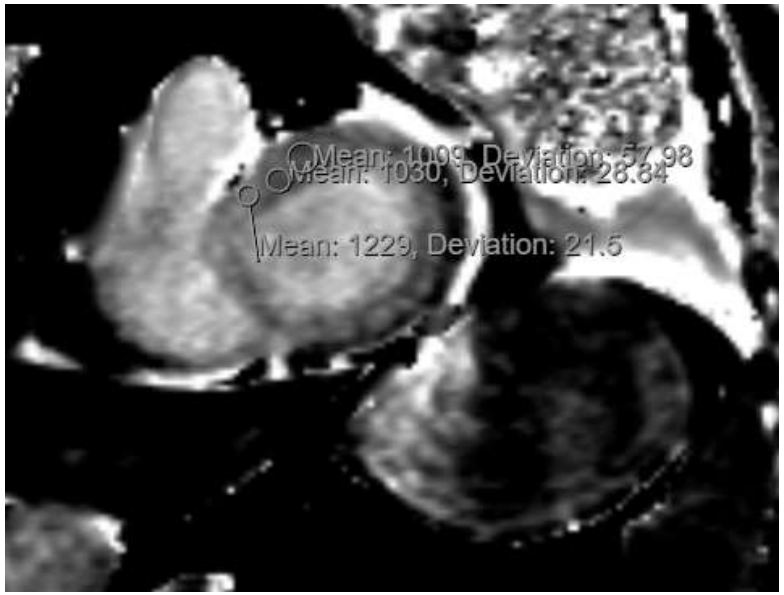


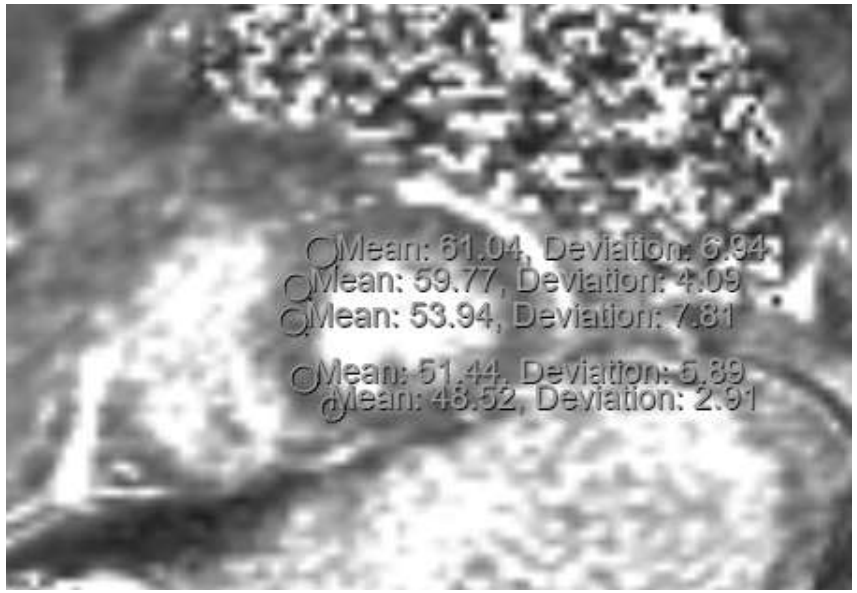
Normal LVEF
Normal diastolic function
Decreased global longitudinal strain

# 15 days after ipilimumab + nivolumab initiation…

Epicardial to mid-myocardial late gadolinium enhancement in the basal anteroseptum






Elevated T1 and T2 values in the basal-to-mid anteroseptal segments

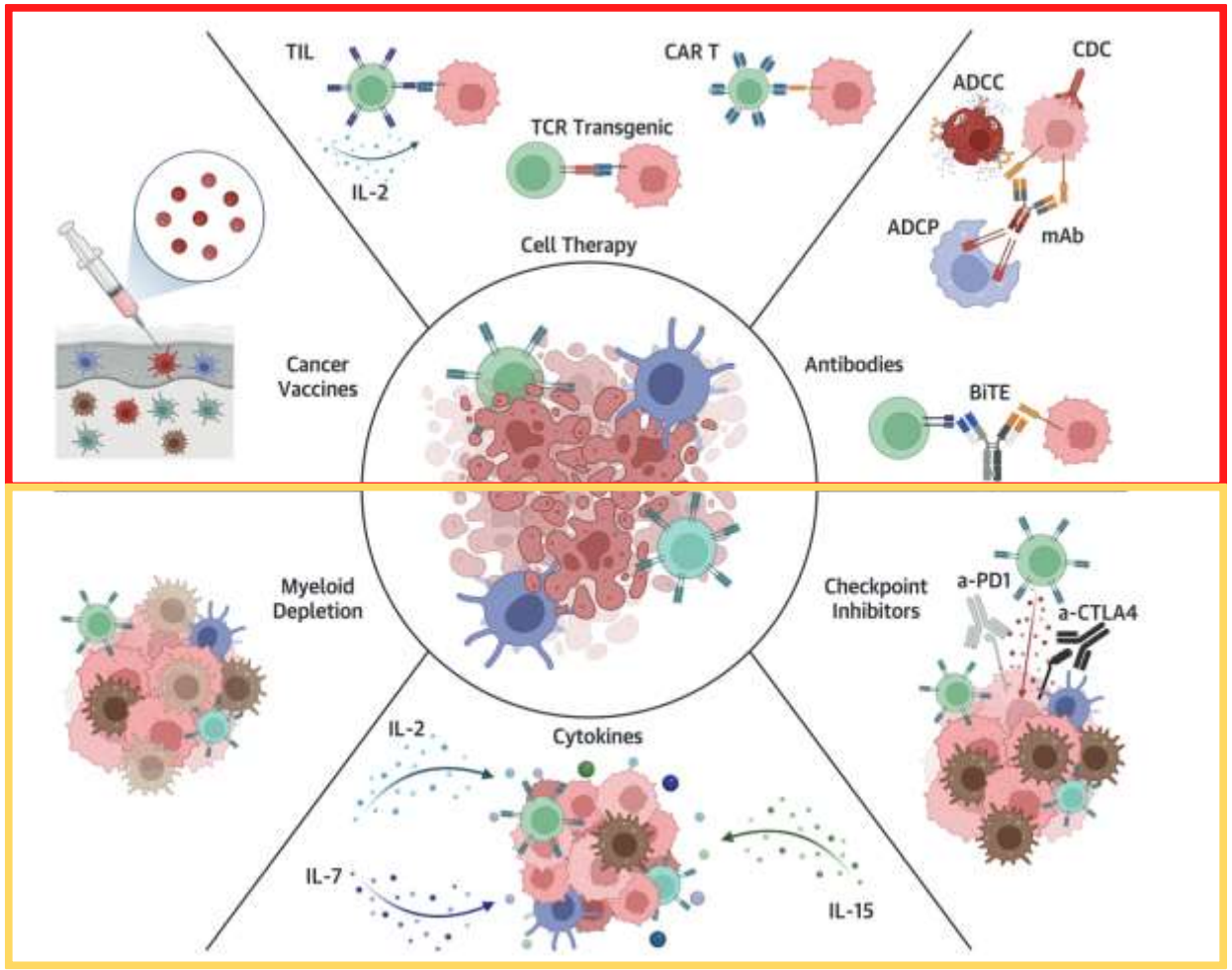
# Learning Objectives

**What are the phenomena of cardiac injury associated with immune checkpoint inhibitors?**

**How do we diagnose and treat immune checkpoint inhibitor-myocarditis?**

**What are the cardiovascular effects of T-cell immunotherapies?**

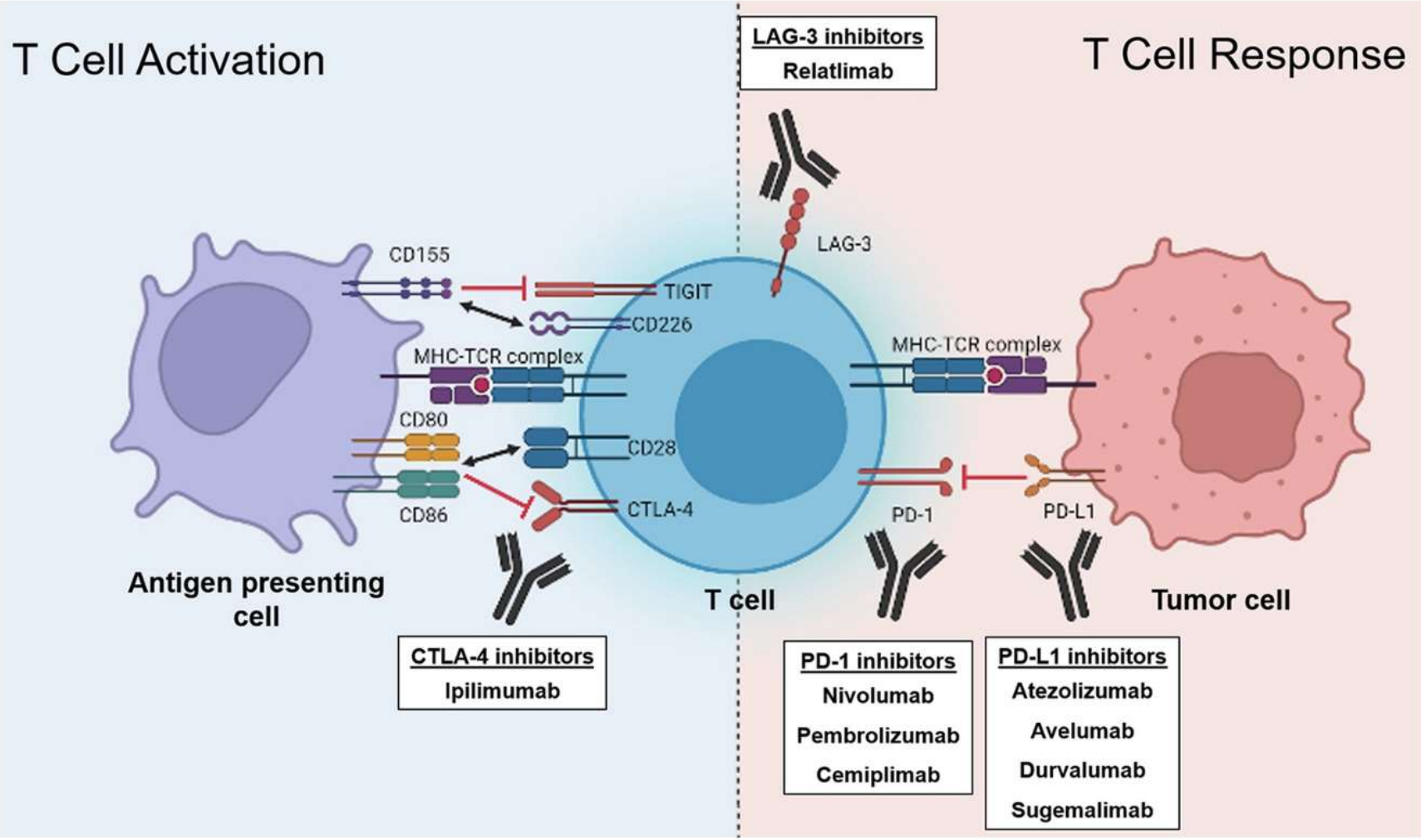
# Cancer immunotherapy works by reactivation of a stalled pre-existing immune response or by eliciting a de novo immune response




*Aim to stimulate a direct antitumor response*

*Aim to reactivate host immunity*

# Immune checkpoint inhibitors (ICIs) are monoclonal antibodies that activate T cells and initiate an adaptive immune response to facilitate the immune system's recognition of cancer cells




Zhang, L. et al. J Am Coll Cardiol CardioOnc. 2021;3(1):35–47.
Tan S, et al. J Am Coll Cardiol CardioOnc. 2022;4(5):579–597

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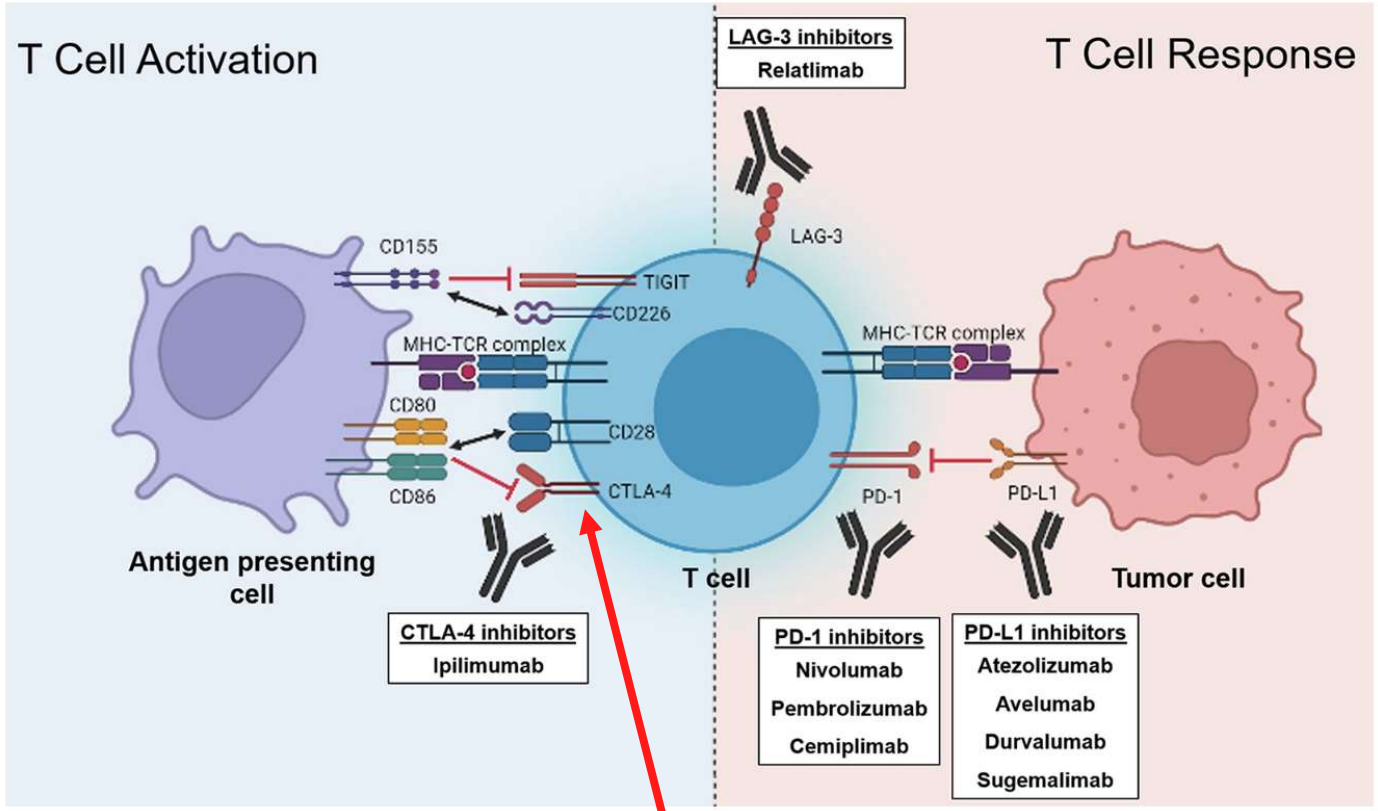


**Inhibitory receptor on T cells** ↓ T cell activity

⊘ unnecessary T cell activation

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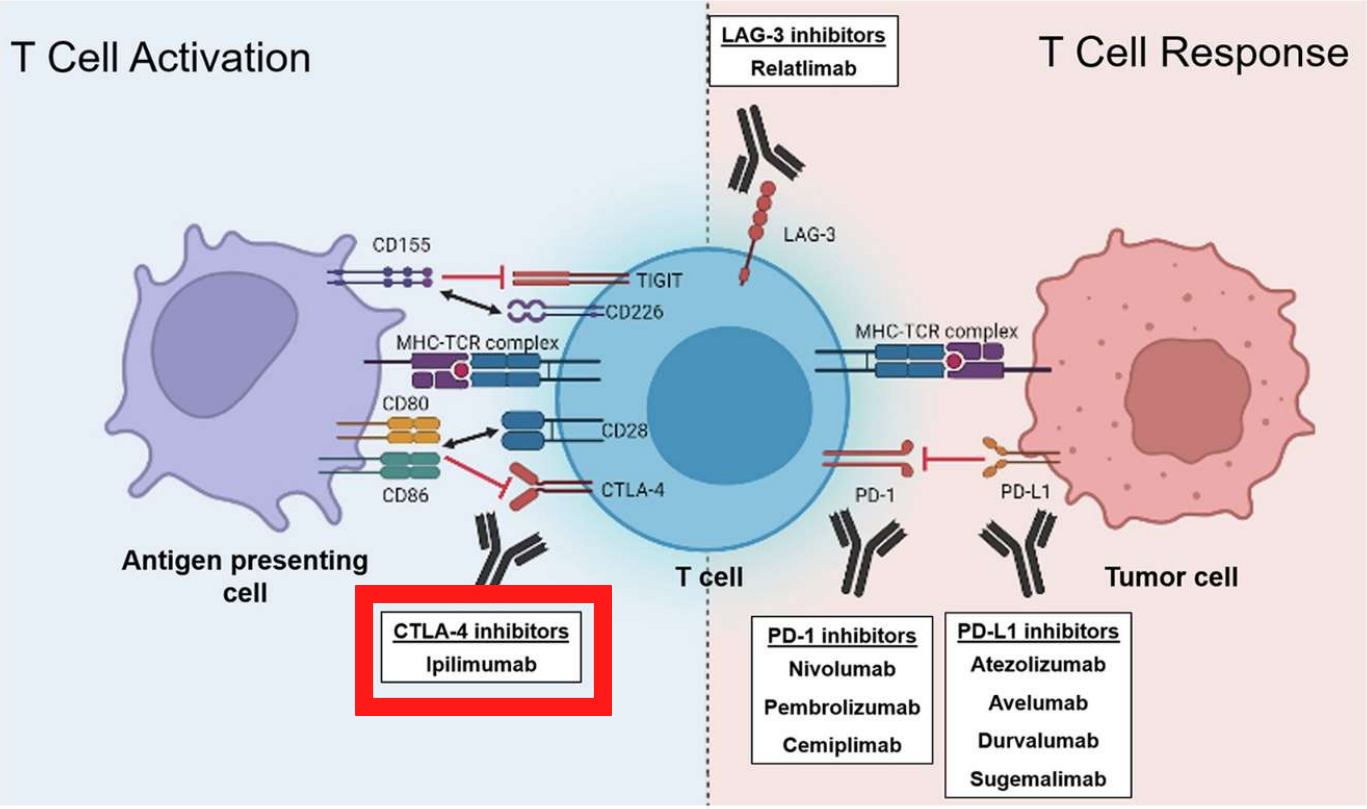


## Ipilimumab:

- 1st ICI to enter clinical use
- Only CTLA-4 inhibitor commonly used in standard practice
- Used as monotherapy or in combination with PD-1/PD-L1 inhibitors

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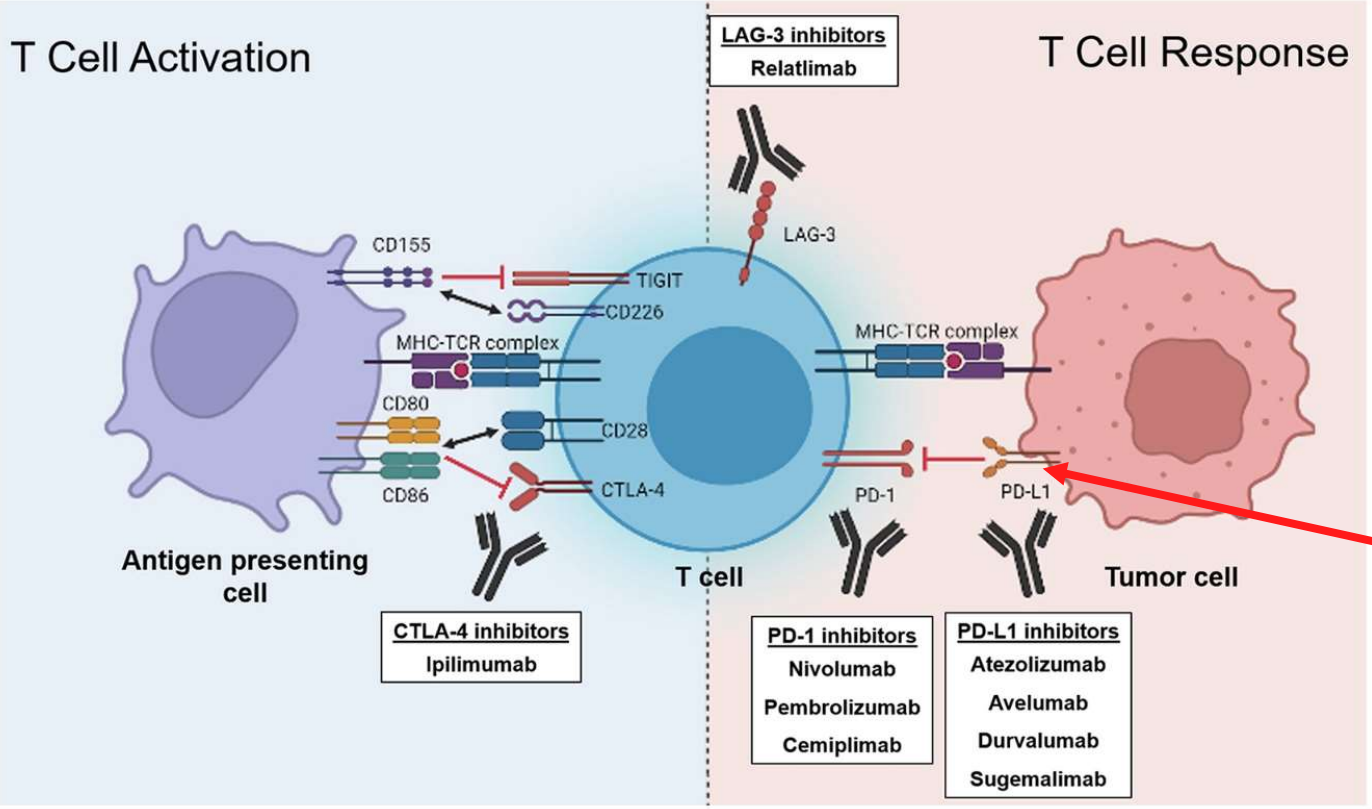


**Protein on target cells that binds to PD-1 receptors on CD8 T cells**

⊘ inflammation, immune response

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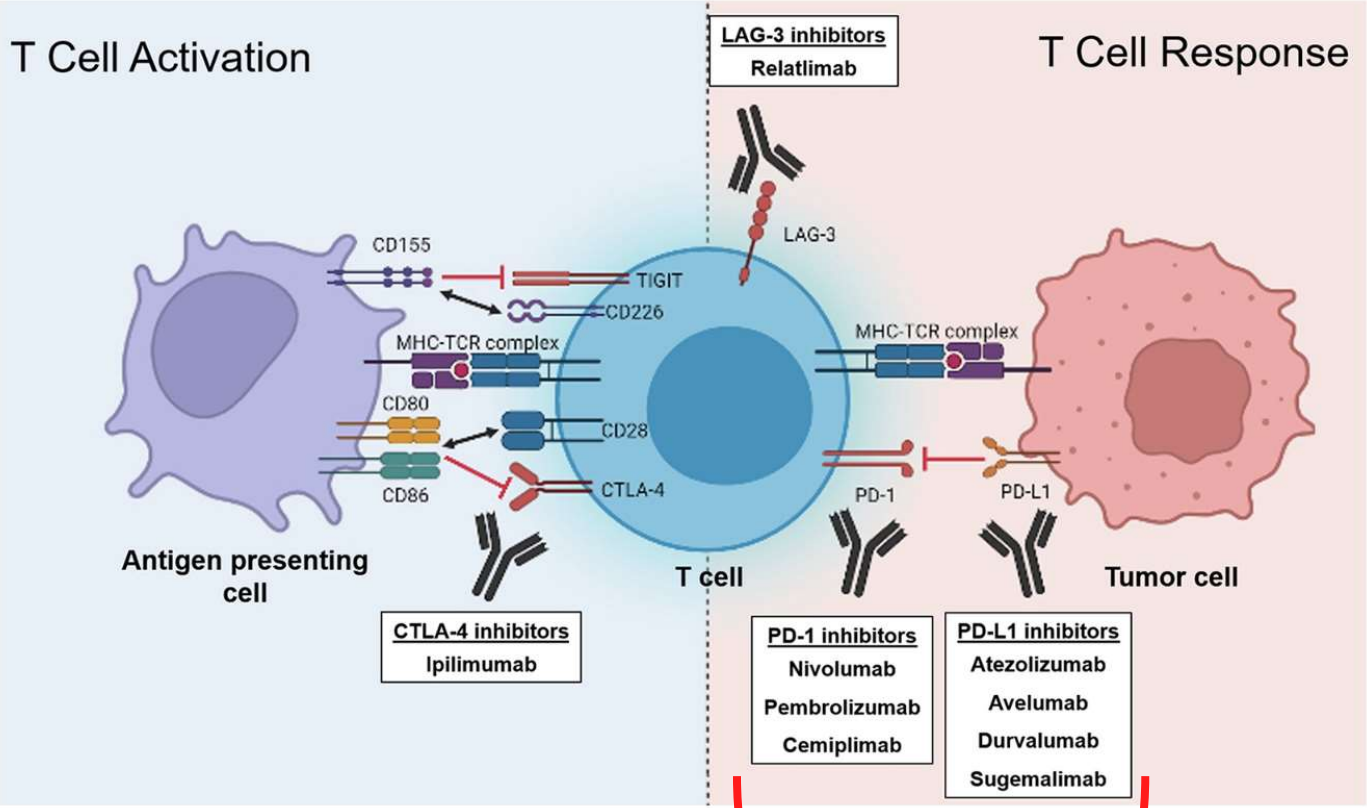


Prevent tumor escape from overexpression of PD-L1
*cytotoxic CD8 T cell-mediated tumor cell destruction*

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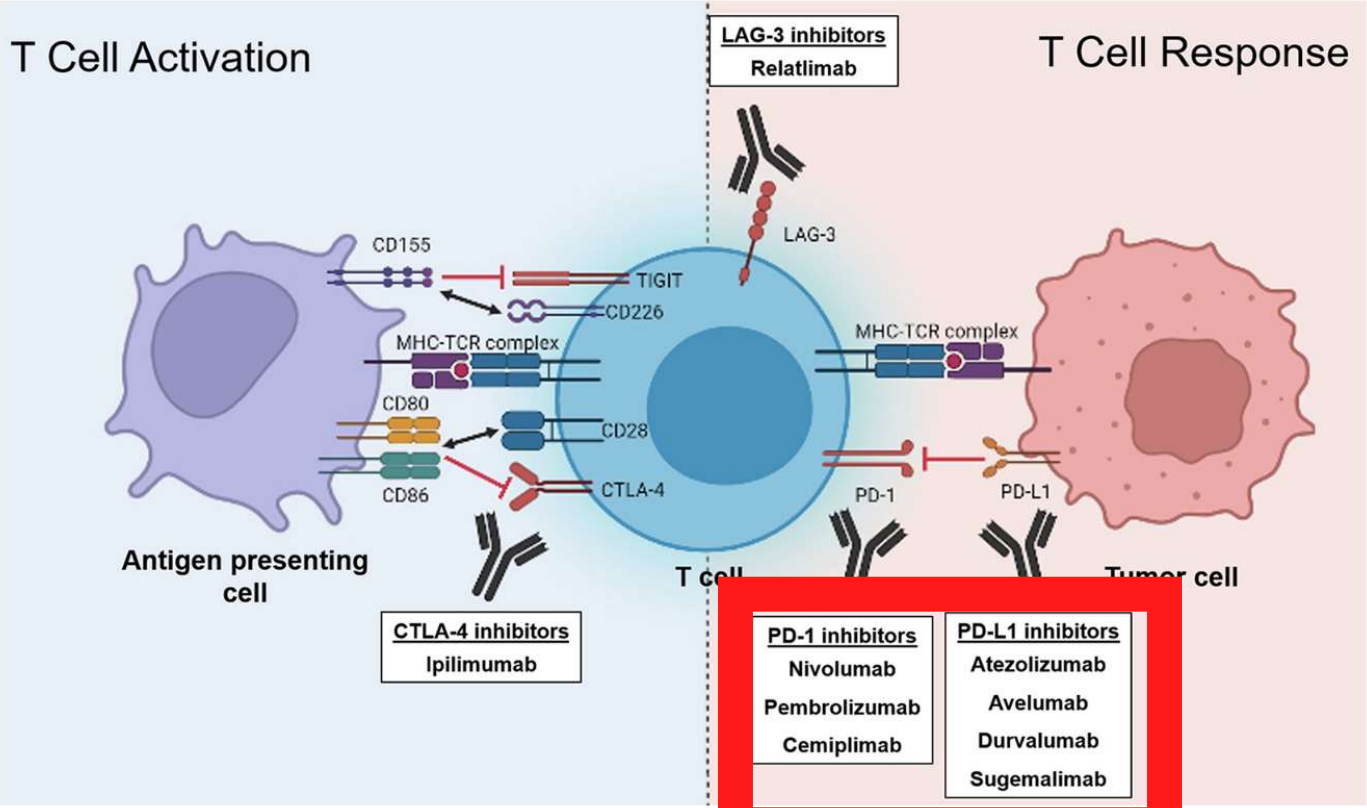


**PD-1i:**

- Nivolumab, pembrolizumab, cemiplimab

**PD-L1i:**

- atezolizumab, avelumab, durvalumab

Studied in broad range of cancers
Less toxicity than CTLA-4i

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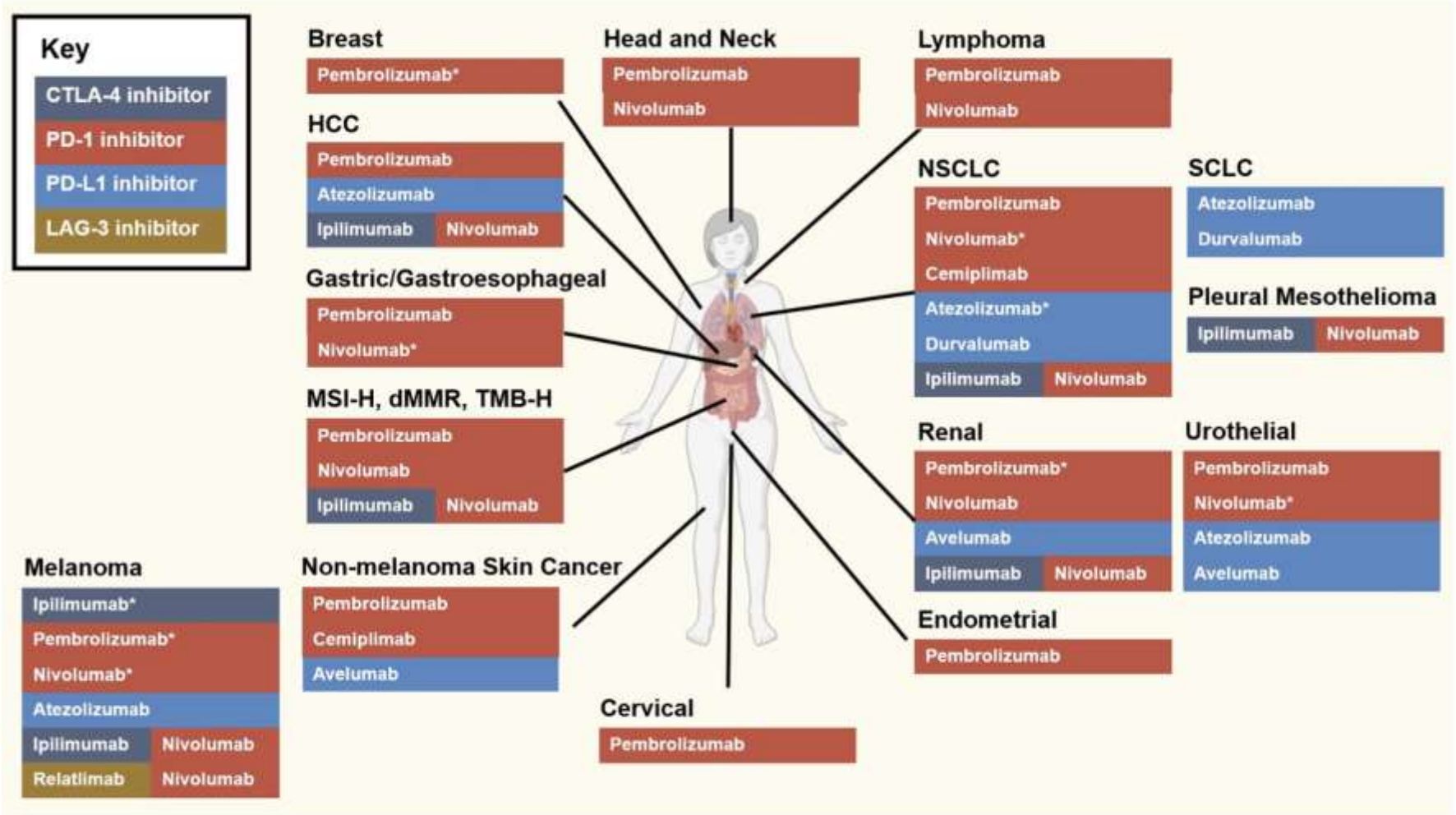
# There are ≥20 approved indications for immune checkpoint inhibitors in the U.S.

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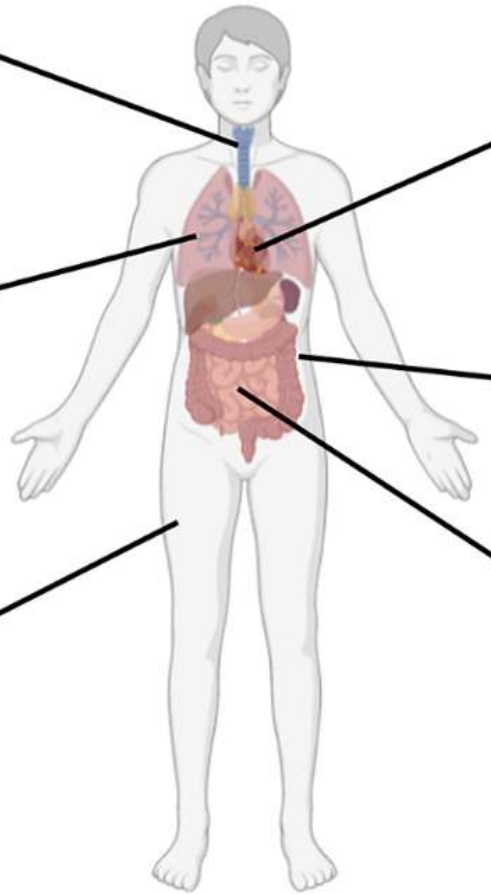
# ICIs can cause immune related adverse events (irAEs) which are autoimmune-like adverse reactions that can occur in any organ



**Endocrine**
- Thyroid disease
- Adrenal insufficiency
- Hypophysitis

**Lung**
- Pneumonitis

**Cutaneous**
- Maculopapular rash
- Pruritis
- Vitiligo-like lesions

**Cardiovascular**
- Myocarditis
- Pericarditis
- Arrhythmias
- Coronary artery disease
- Left ventricular dysfunction

**Renal**
- Nephritis

**Gastrointestinal**
- Diarrhea
- Colitis
- Hepatitis

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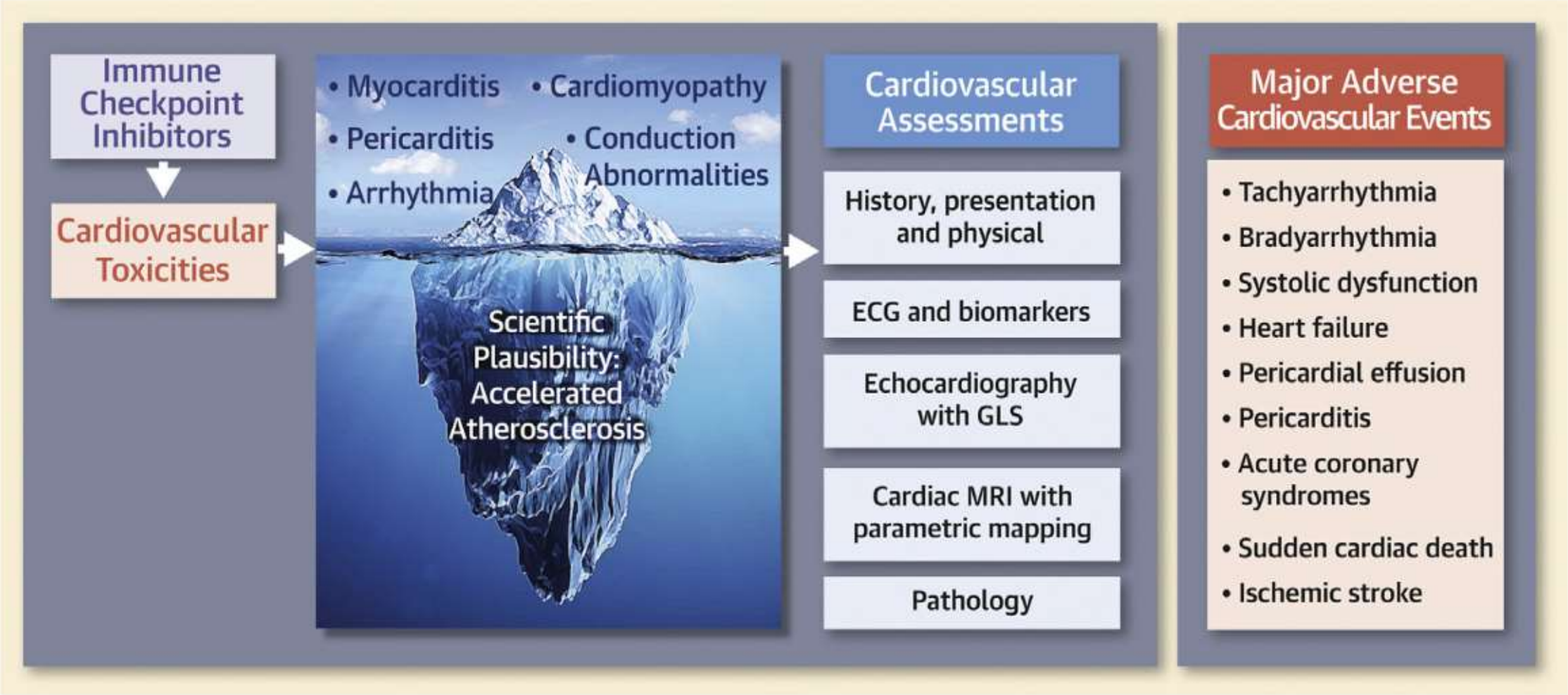
# Real-world data suggest a 6-10% increased risk of cardiovascular events while receiving ICI therapy

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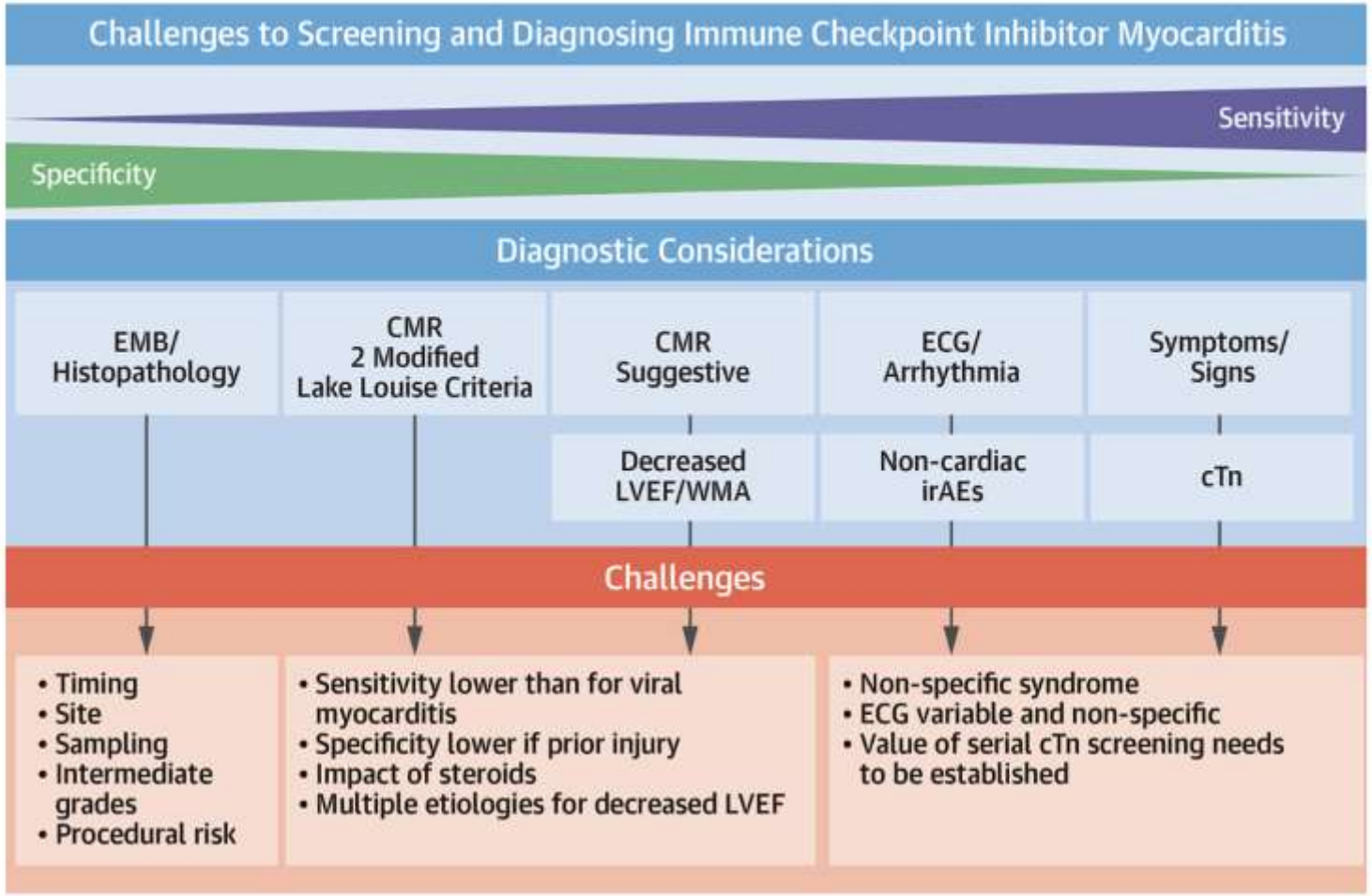
# Making the diagnosis of ICI–induced myocarditis can be challenging because of heterogeneous clinical, biological, and imaging features




Thuny, F. et al. J Am Coll Cardiol CardioOnc. 2022 Dec, 4 (5) 624–628

# Making the diagnosis of ICI–induced myocarditis can be challenging because of heterogeneous clinical, biological, and imaging features

**International Cardio-Oncology Definition for Immune Checkpoint Inhibitor Myocarditis**

Diagnosis

Either pathohistological diagnosis: Multifocal inflammatory cell infiltrates with overt cardiomyocyte loss by light microscopy of cardiac tissue samples

Or clinical diagnosis[a,b]

A troponin elevation[c] (new, or significant change from baseline) with 1 major criterion or a troponin elevation (new, or significant change from baseline) with 2 minor criteria after exclusion of acute coronary syndrome or acute infectious myocarditis based on clinical suspicion

Major criterion

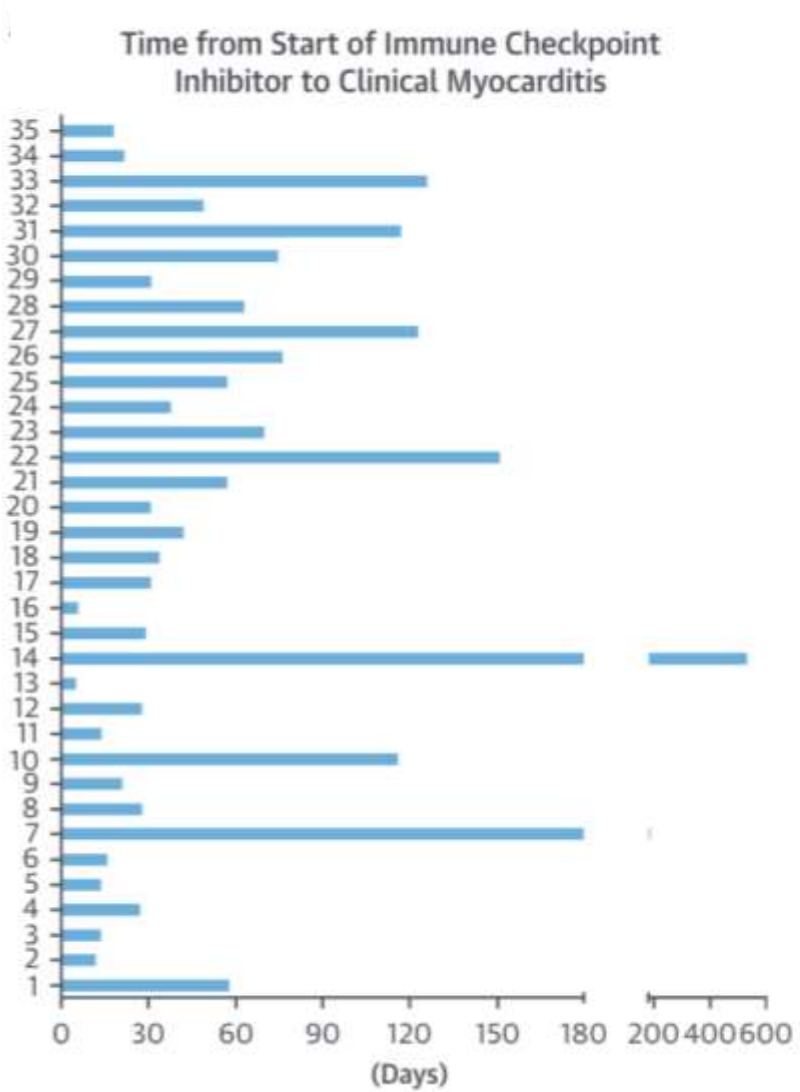
- CMR diagnostic for acute myocarditis (modified Lake Louise criteria)

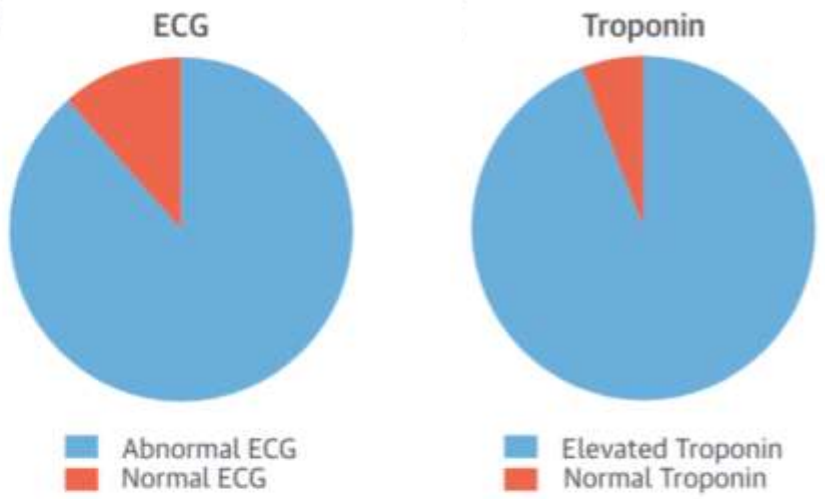
Minor criteria

- Clinical syndrome (including any one of the following: fatigue, muscle weakness, myalgias, chest pain, diplopia, ptosis, shortness of breath, orthopnea
- Lower extremity edema, palpitations, light-headedness/dizziness, syncope, cardiogenic shock)
- Ventricular arrhythmia and/or new conduction system disease
- Decline in cardiac (systolic) function, with or without regional WMA in a non-Takotsubo pattern
- Other immune-related adverse events, particularly myositis, myopathy, myasthenia gravis
- Suggestive CMR (meeting some, but not all, of the modified Lake Louise criteria)

[a]Clinical diagnoses should be confirmed with cardiac magnetic resonance imaging (CMR) or endomyocardial biopsy if possible and without causing delays of treatment. [b]In a patient that is clinically unwell, treatment with immunosuppression should be promptly initiated while awaiting further confirmatory testing. [c]Both troponin I and troponin T can be used; however, troponin T may be falsely elevated in those with concomitant myositis.

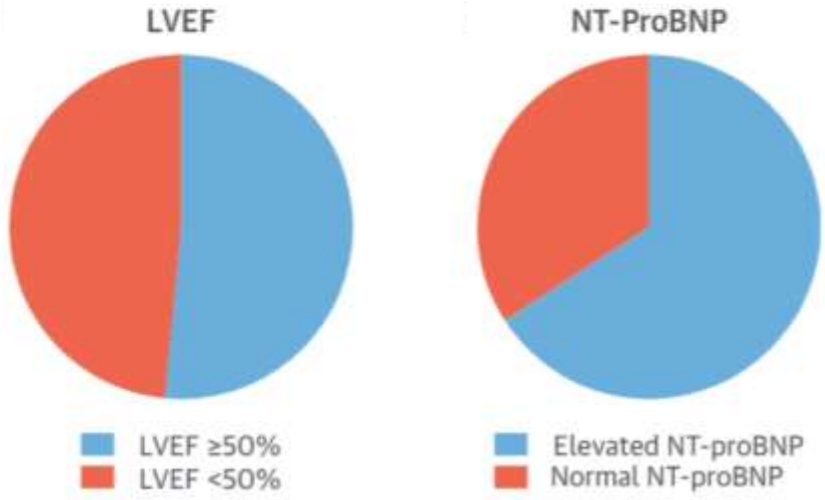
# Data suggest that ICI-associated myocarditis typically presents early after starting treatment, with majority of cases reported in first 6-12 weeks







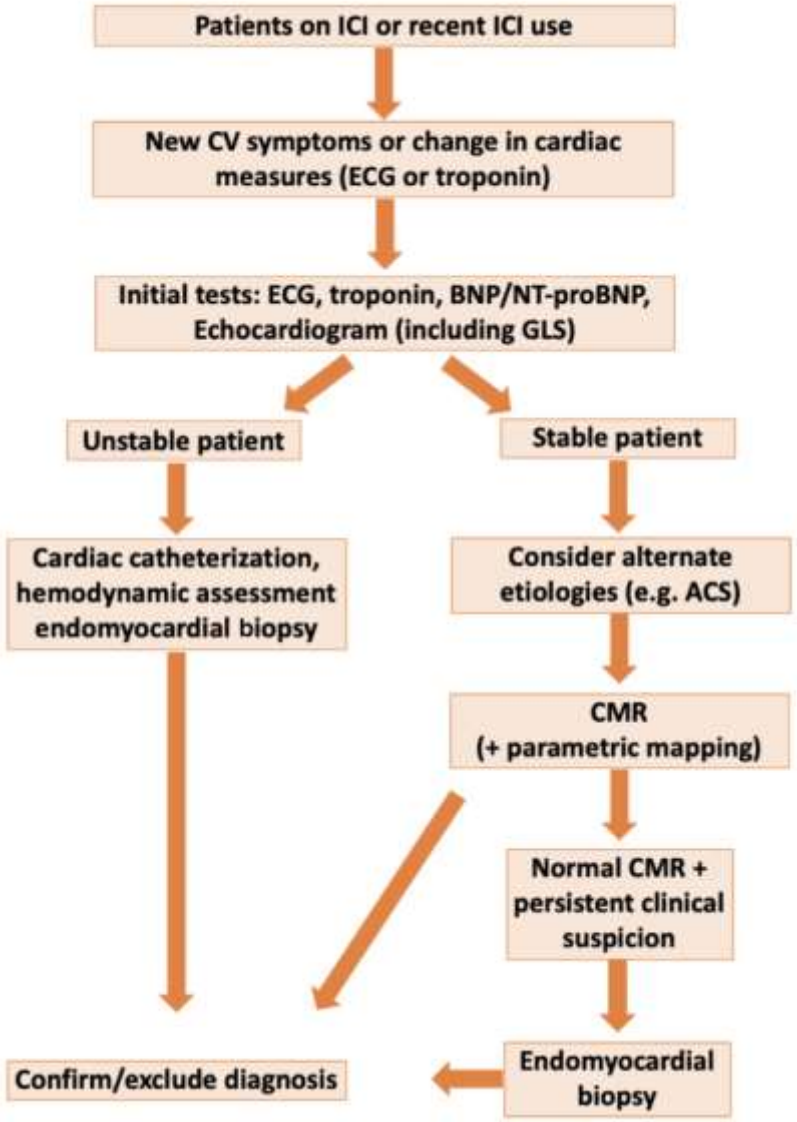




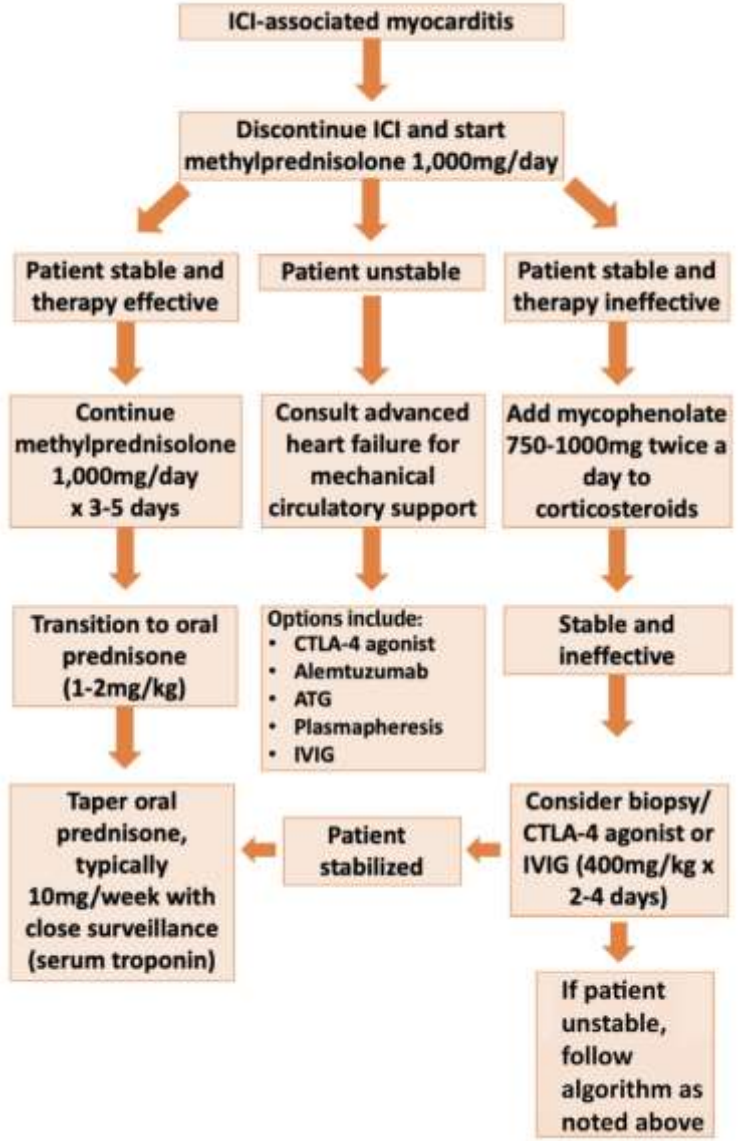


Mahmood, S. et al. J Am Coll Cardiol. 2018 Apr, 71 (16) 1755–1764

# ICI-M Diagnostic Algorithm




# ICI-M Treatment Algorithm

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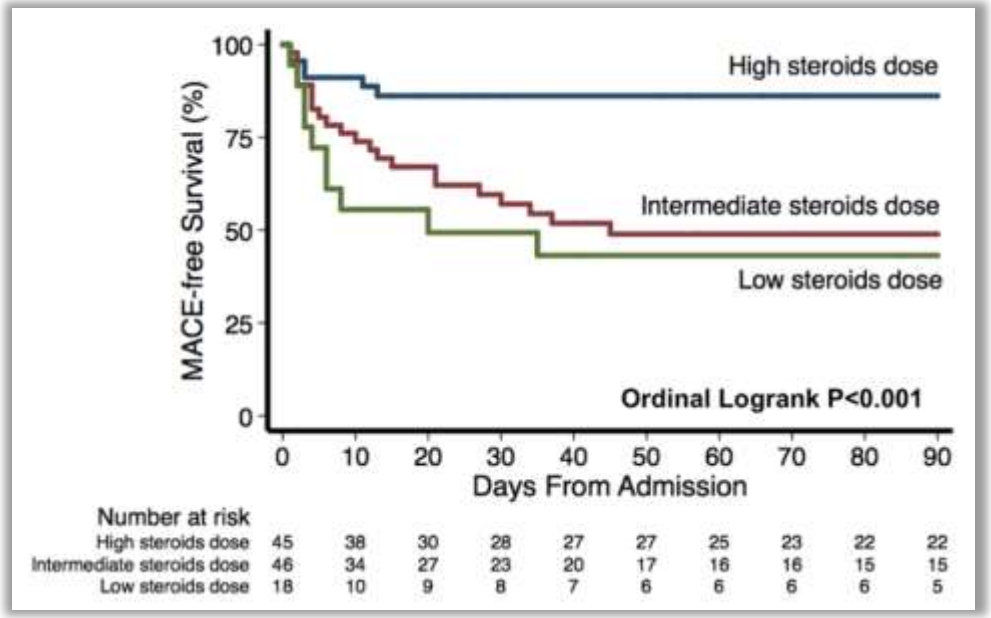
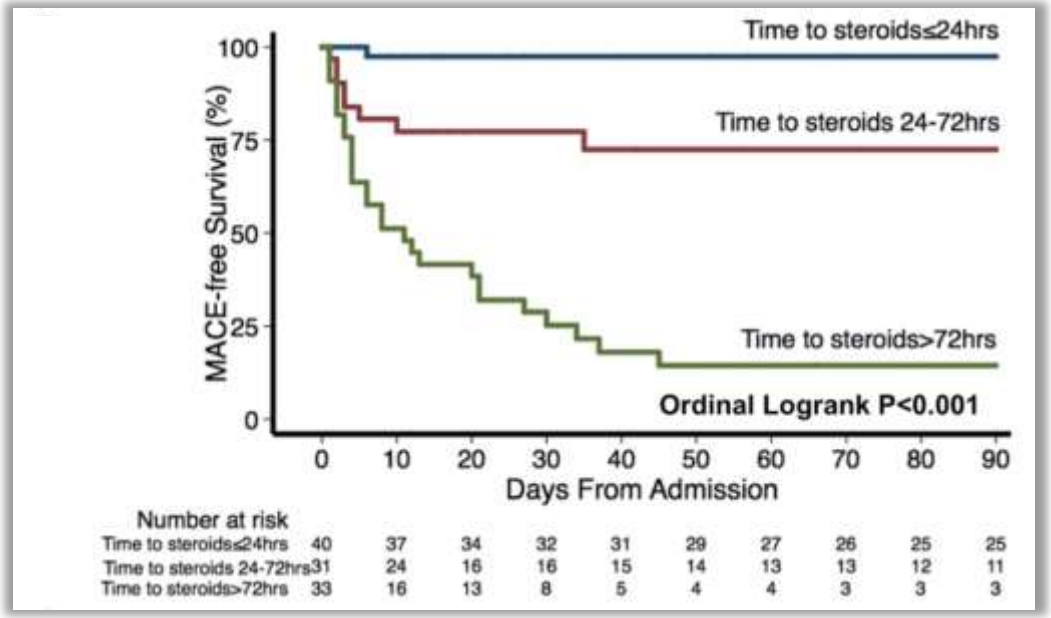
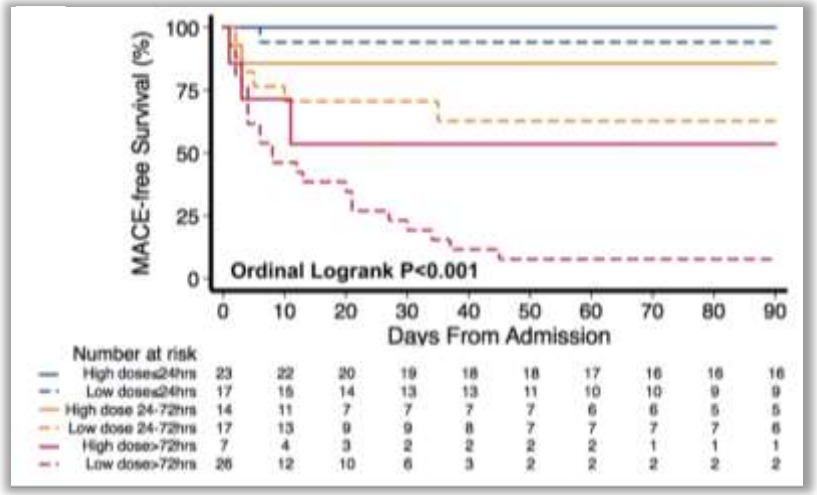
# Higher initial dose and earlier initiation of corticosteroids have been associated with improved cardiac outcomes in ICI-associated myocarditis

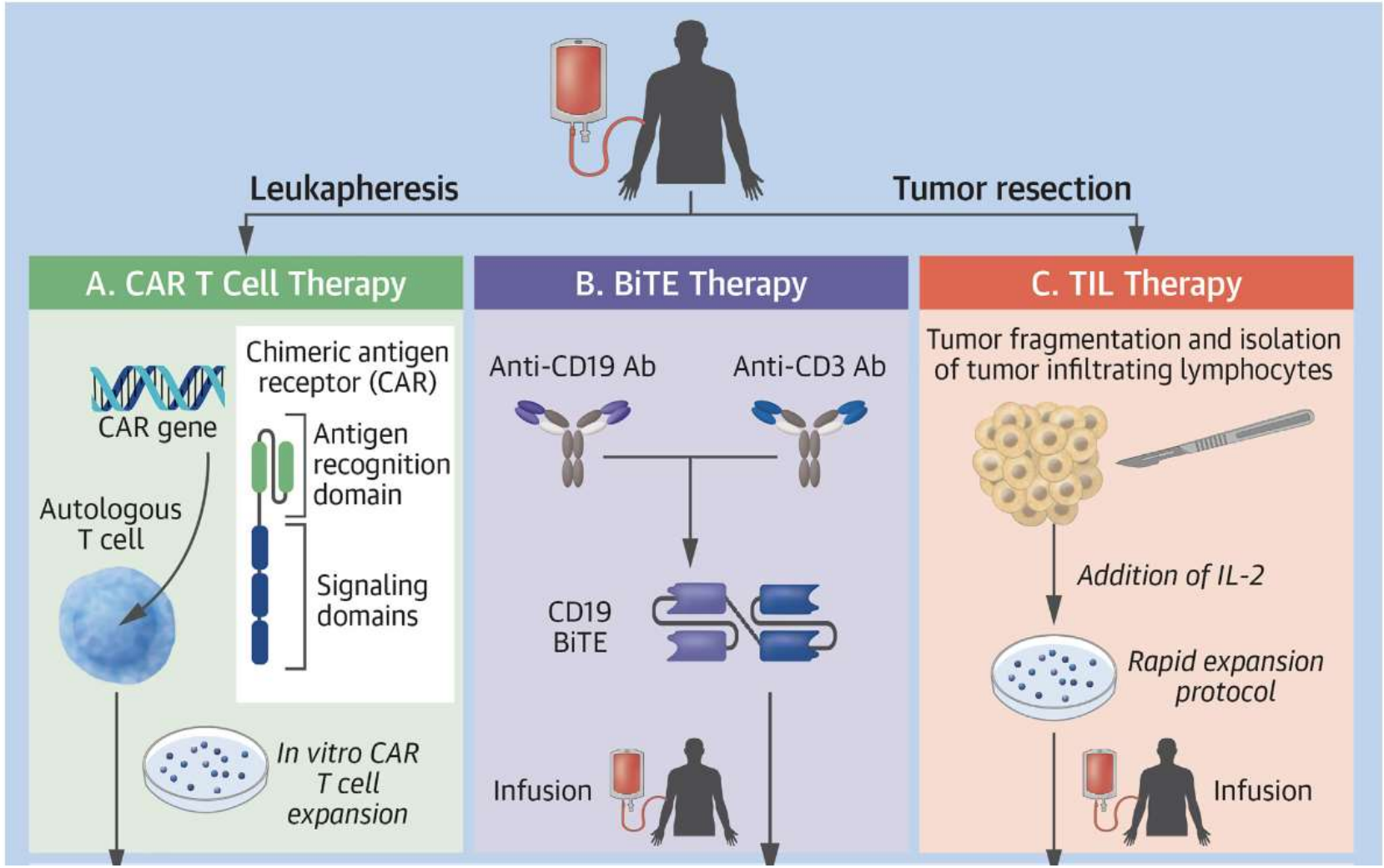


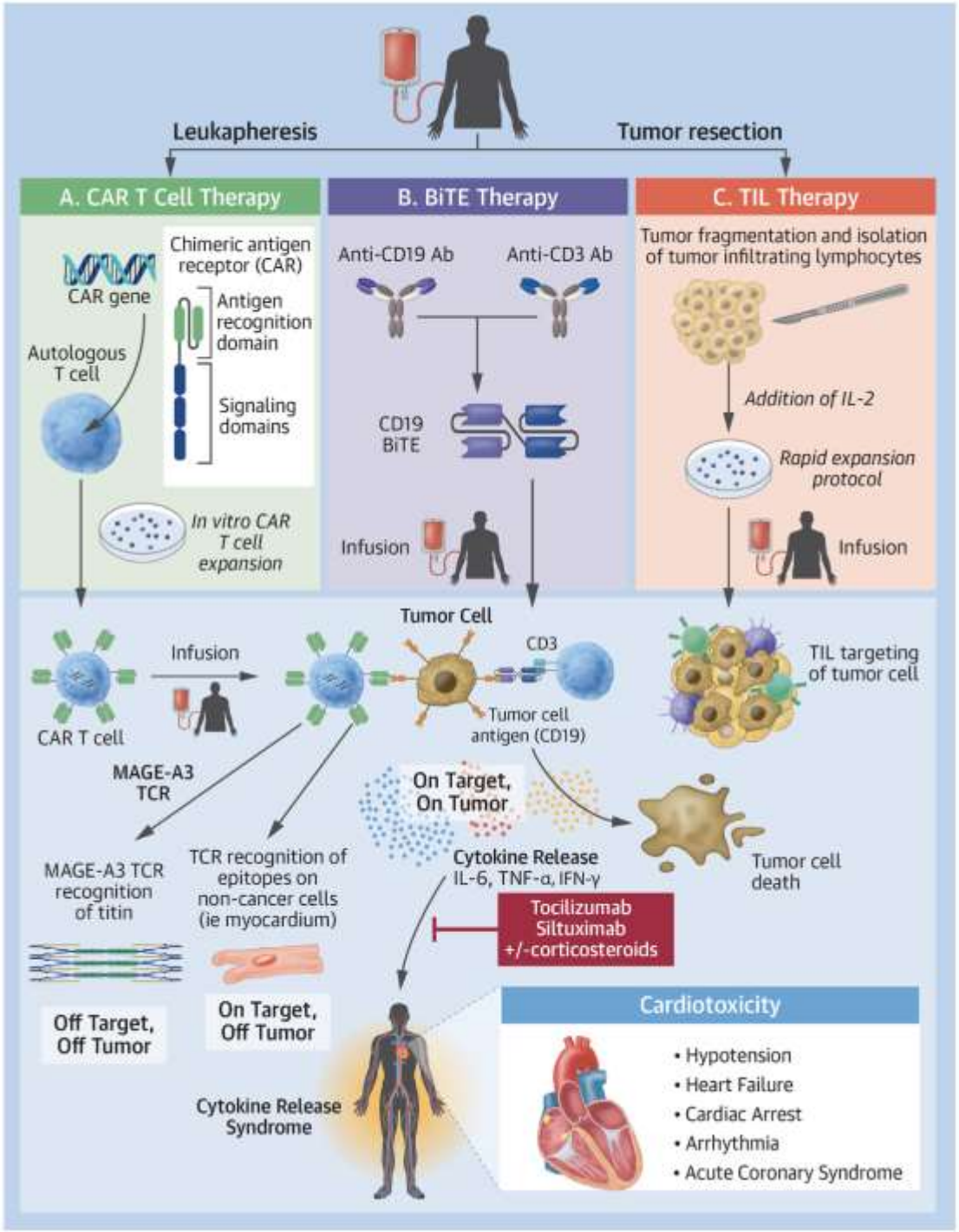

Zhang et al. Circulation. 2020; 141:2031-2034.

# T-cell therapies, including chimeric antigen receptor (CAR) T-cell, bispecific T-cell engager (BiTE), and tumor-infiltrating lymphocyte (TIL) therapies, fight cancer cells harboring specific tumor antigens




Ganatra, S. et al. J Am Coll Cardiol CardioOnc. 2022 Dec, 4 (5) 616–623

# Information regarding T-cell therapy–associated cardiotoxicity is based primarily on experience with CAR T-cell therapy




Activation of the immune response can lead to a systemic inflammatory response, i.e., **cytokine release syndrome (CRS)**, that can result in cardiotoxicity

Retrospective cohort studies have noted MACE in **10-20% of patients** who received CAR T-cell therapy

Ganatra, S. et al. J Am Coll Cardiol CardioOnc. 2022 Dec, 4 (5) 616–623

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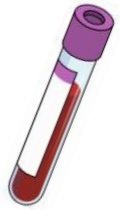
# 70-year-old man with metastatic renal cell carcinoma

Methylprednisolone 1 mg/kg x 5 days



Cardiac biomarkers and myositis improved

Transitioned to prednisone 60 mg daily

# Take Home Points

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Initial treatment of ICI-M includes discontinuation of ICI and early administration of high-dose corticosteroids

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Initial treatment of ICI-M includes discontinuation of ICI and early administration of high-dose corticosteroids

Cytokine release syndrome is a recognized adverse cardiovascular effect of CAR T-cell therapy and needs further study

# Thank you!

AMERICAN COLLEGE of CARDIOLOGY


**Nosheen Reza, MD, FACC, FHFSA**

Assistant Professor of Medicine

Penn Center for Inherited Cardiovascular Disease

Section for Advanced Heart Failure, Transplantation, and Mechanical Support

@noshreza

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