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Mechanisms and Clinical Manifestations of Cardiovascular Toxicities Associated with Immune Checkpoint Inhibitors

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Abstract

Immunotherapies have greatly expanded the armamentarium of cancer-directed therapies in the past decade, allowing the immune system to recognize and fight cancer. Immune checkpoint inhibitors, in particular, have revolutionized cancer treatment and have demonstrated survival benefit in numerous types of cancer. These monoclonal antibodies increase anti-cancer immunity by blocking down-regulators of adaptive immunity, including CTLA-4, PD-1, and PD-L1, resulting in anti-tumor activity. As immune checkpoint inhibitors increase immune system activation, they can cause a wide range of inflammatory side effects, termed immune-released adverse events. Though these toxicities can affect nearly any organ, the most fatal toxicity is myocarditis. Here, we discuss the diverse spectrum of cardiovascular toxicities associated with ICI use. In addition, we provide insight and future directions on mechanisms and treatments for immune-related adverse events involving the myocardium, pericardium, vasculature, and conduction system.

Keywords

Cardio-oncology; immune checkpoint inhibitors; cardio-immunology; immunotherapy; immune-related adverse events; myocarditis; pericarditis; vasculitis

Overview of Immune Responses and Immune Checkpoints

Adaptive immune responses are key contributors to both anti-tumor and autoimmune immune responses that are triggered by cancer immunotherapy. The cellular arm of the adaptive immune response involves T cells, which each bear a unique T cell receptor (TCR) generated by random somatic recombination to endow each T cell with a specificity for its cognate antigen. T cells are classified by their surface expression of specific co-receptors.

CD8+ T cells act as cytotoxic effectors that kill target cells by triggering cell death, and recognize intracellular antigens presented by major histocompatibility complex (MHC) class I molecules on the surface of all nucleated cells in the body. Conversely, CD4+ T cells classically recognize antigens processed from the extracellular environment that are presented by distinct MHC class II molecules, which are typically only expressed on professional antigen-presenting cells (APCs) that prime or initiate immune responses. CD4+ T cells are functionally diverse, and encompass multiple populations that can enhance immune responses (via helper T cells that produce proinflammatory cytokines, enhance the cytotoxic activity of CD8+ T cells, or provide stimuli to B lymphocytes through CD40/CD40 ligand interactions which lead to antibody production and isotype class switching for T cell-dependent antigens). In addition, key CD4+ T cell populations also inhibit immune responses, notably regulatory T cells which dampen responses through multiple mechanisms.

The activation of naïve T cells begins with priming, which involves cell-cell interactions with surface receptors on APCs in specialized secondary lymphoid organs. Priming is controlled at several levels to ensure controlled activation and to minimize autoimmunity. First, in addition to TCR recognition of antigen presented by MHC, a second signal is required to activate naïve T cells. This is provided by engagement of the co-receptor CD28 on T cells by the ligands B7–1 (CD80) and B7–2 (CD86) on APCs, in a process termed co-stimulation (Figure 1). Following priming, activated T cells are then able to execute their specific effector functions upon engagement of their cognate antigen presented by MHC in specific tissues, whether tumors or other end organs involved in autoimmune toxicity [1], [2].

Additional regulation of immune activation is provided at the level of specific inhibitory immune receptors, termed immune checkpoints, which dampen both priming and subsequent effector functions within tissues to help maintain a balance between immune activation and self-tolerance. CTLA-4 (CD152) is an inhibitory T cell receptor which is upregulated upon T cell priming, and actually binds to CD80/86 with higher affinity than CD28. This allows for immediate counter-regulation of T cell activation through competitive inhibition of costimulatory ligand binding as well as inhibitory signals such as phosphatase activation that are transduced intracellularly upon engagement [3]. Of note, CTLA-4 is constitutively expressed at high levels on regulatory T cells where it is critical to their suppressive function. An additional inhibitory receptor, PD-1 (CD279), is also inducibly expressed on T cells as well as other immune lineages such as B cells, monocytes, and natural killer T cells upon activation. PD-1 is engaged by 2 known ligands which inhibit T cell effector function, PD-L1 (CD274), which is broadly expressed by both immune cells and non-hematopoietic tissues including many tumors, and PD-L2 (CD273), which is more narrowly and inducibly expressed on macrophages, dendritic cells, and certain populations of B cells and mast cells [4]. PD-1 engagement is thought to inhibit T cell activation through membrane-proximal signaling such as tyrosine phosphatase recruitment, which blocks downstream induction of PI3K/Akt signaling.

Mechanisms of Immune Checkpoint Inhibitors

Immunotherapy enhances the immune system's ability to recognize and fight cancer. Many immunotherapeutic strategies have been shown to augment cancer immunosurveillance, with general approaches including interferon and interleukin therapy (e.g., interferon alpha, IL-2), and more specific approaches including immune checkpoint inhibitors, oncolytic virus therapy, cancer vaccines, and T-cell based therapies (e.g., chimeric antigen receptor (CAR) T cells, bispecific T-cell engagers). Immune checkpoint inhibitors (ICI), in particular, have shown significant benefit in the treatment of a wide range of cancer types, and will be the focus of this review.

Immune checkpoint inhibitors (ICI) are monoclonal antibodies that increase anti-cancer immunity by blocking down-regulators of immunity, such as CTLA-4 and PD-1 or its ligand, PD-L1. As discussed above, inhibition of these immune checkpoints blocks the physiologic "brakes" of the immune system, thus unleashing effector T-cell activity and promoting anti-tumor activity (Figure 1) [5]. At present, several ICI are FDA approved for use in many cancer types, as summarized in Table 1: ipilimumab (anti-CTLA-4); pembrolizumab, nivolumab, cemiplimab (anti-PD-1); atezolizumab, avelumab, durvalumab (anti-PD-L1). While in principle, anti-PD-1 agents may block both PD-L1 and PD-L2 interactions, and some differences in autoimmune toxicity have been seen between specific anti-PD-1 and anti-PD-L1 agents, the anti-tumor efficacy of PD-1 versus PD-L1 blockade has been shown to be largely similar in multiple studies to date.

While these drugs have successfully increased overall survival for patients with many cancers, primary and acquired resistance to anti-PD-1/-L1 therapies remains a concern, as do potential toxicities of therapy. As such, other immune checkpoints remain of interest as possible therapeutic targets and many remain in various stage of clinical development. These novel immune checkpoint inhibitors are targeted against T cell immunoglobulin and mucin domain-containing protein 3 (TIM3), V-domain Ig Suppressor of T cell Activation (VISTA), and T cell immunoreceptor with Ig and ITIM domains (TIGIT), among others. Recently, the anti-TIGIT molecule, tiragolumab, was granted Breakthrough Therapy Designation by the FDA in combination with atezolizumab for patients with metastatic non-small cell lung cancer, based on a phase II trial (CITYSCAPE) that demonstrated that dual therapy improved overall response rates and median survival compared to atezolizumab monotherapy [6]. Another anti-TIGIT monoclonal antibody, vibostolimab, has shown promising results as monotherapy and in combination with pembrolizumab in early clinical trials [7].

In addition, there are emerging immune checkpoint inhibitors that do not target T cells. One example includes a macrophage immune checkpoint, CD47, which is an antiphagocytic signal that is over-expressed by numerous types of cancer cells, allowing malignant cells to evade macrophage-driven immune responses. Anti-CD47 antibodies block CD47 and its ligand SIRP-alpha, leading to phagocytosis of tumor cells and induction of anti-tumor T cell responses. Early clinical trials have shown clinical effectiveness of CD47 blockade by Hu5F9-G4 in combination with rituximab [8] [9] [10]. Further investigation with these and additional non-T cell-based immunotherapies are under active investigation.

Indications for Immune Checkpoint Inhibitors

ICI first emerged for general use in 2011, when ipilimumab (CTLA-4 inhibitor) was approved by the US Food and Drug Administration (FDA) for the treatment of unresectable/ metastatic melanoma [11]. Pembrolizumab and nivolumab were subsequently approved for the treatment of unresectable/metastatic melanoma in 2014, and have become the preferred backbone of immunotherapy regimens due to increased efficacy and decreased toxicity compared to ipilimumab [12]. Since that time, ICI has dramatically shifted the landscape of available systemic therapies for numerous solid and hematologic cancer types. Indeed, it is estimated that approximately 36% of cancer patients are eligible for ICI therapy [13]. Anti-PD-1/PD-L1-based therapies are now approved for use, either as monotherapy or in combination with ipilimumab or with other agents (e.g., chemotherapy, small molecular inhibitors), due to demonstrated survival benefit in a multitude of cancers (Table 1). The contexts in which ICI can be applied also continues to expand, with pembrolizumab and nivolumab approved for the adjuvant therapy of high-risk, resected melanoma in 2017 and 2019, respectively, and ongoing trials in the neoadjuvant space. As indications for therapy continue to expand in the coming years, toxicities associated with independent and combined use will need to be carefully monitored and studied.

ICI-Associated Immune-Related Adverse Effects

Given that ICI use will only become increasingly widespread in coming years, it is crucial for all medical care providers to become familiar with basic concepts regarding ICI mechanisms of action and toxicities. As ICI increase immune system activation, they can cause a wide range of inflammatory side effects, termed immune-related adverse events (irAE) [14]. irAE arise due to the suppression of immune regulatory inhibitory functions and resulting immune system and T cell activation. These toxicities can affect nearly any organ system and include, but are not limited to, colitis, hepatitis, dermatitis, encephalitis, hypophysitis, thyroiditis, radiculoneuropathy, myositis (acute or subacute myalgias, limb-girdle, axial, and oculomotor weakness), and myocarditis (Figure 2) [15]. ICI use is still in its relative infancy compared to decades-long experience with traditional cytotoxic chemotherapy. As such, the medical community continues to learn more about the efficacy of these drugs in certain populations, as well as subtleties in the presentation and treatment of irAE. irAE can vary in severity, from subclinical to life-threatening. Myocarditis, pneumonitis, hepatitis, and myositis are most likely to have fatal complications, while colitis and adrenal insufficiency have the lowest reported fatality rates [14].

Though initially thought to be rare (affecting less than 1% of patients treated with ICI), ICI-associated cardiovascular toxicities are estimated to affect up to 7–9% of patients [16]. ICI-associated cardiovascular toxicities, which can have a fulminant and potentially fatal course, are increasingly being recognized with expanding use of ICI therapy [17]. However, the full spectrum of cardiovascular side effects remains to be defined. In this review, we discuss the diverse spectrum of cardiovascular toxicities associated with ICI use, including involvement of the myocardium, pericardium, vasculature, and conduction system (Figure 2).

Clinical Case of Cardiovascular irAE

We present a case of ICI-associated myocarditis to highlight this and other irAE that can arise from ICI therapy. A 76-year-old woman with a history of stage IIIC melanoma of her left leg (dermatopathology notable for microsatellitosis, and micrometastatic lymph node involvement), hypertension, hyperlipidemia, and prior pulmonary embolus on rivaroxaban was started on pembrolizumab given potential for long term immunomodulation and durable response. Two weeks after the first pembrolizumab infusion, she developed abrupt onset bilateral lower extremity myalgias and fatigue. She was prescribed a short course of prednisone by her local outpatient oncologist. Two days later, she developed diplopia and bilateral lower extremity weakness. Due to ongoing myalgias and development of ophthalmoplegia and arm weakness, she presented to the emergency department. Notably, she denied chest pain, dyspnea, orthopnea, or palpitations. ECG showed sinus rhythm with left bundle branch block (LBBB), which was new from a prior ECG. Her cardiac biomarkers were significantly elevated, including cardiac troponin I (cTnI) 23 ug/L (ref: <0.05 ug/L), total creatine kinase 1481 U/L (ref: 37–241 U/L). Her liver function tests were elevated, including ALT 736 U/L (ref: 4–26 U/L), AST 442 U/L (ref: 8–33 U/L). Echocardiogram on admission showed normal left ventricular ejection fraction (LVEF) 70% and no wall motion abnormalities. Coronary angiogram revealed no evidence of coronary artery disease.

Within the first 2 days of admission, she developed worsening ptosis with fixed gaze, binocular diplopia, bilateral lower extremity weakness, and dyspnea. She was noted to have a new erythematous rash on her back. She was intubated due to diaphragmatic weakness. On hospital day #3, she developed complete heart block and intermittent ventricular tachycardia (VT), requiring a temporary transvenous pacer (Figure 3). Repeat echocardiogram showed severely reduced LV systolic function (LVEF 30–35%), focal inferoseptal wall motion abnormality, and LV thrombus. Cardiac magnetic resonance imaging (CMR) showed thinning of the left ventricle with subendocardial and subepicardial late gadolinium enhancement of the septum, as well as LV thrombus (Figure 3).

Additional work up included MRI head and lumbar spine that showed enhancement of paraspinous muscles, suggestive of myositis. Pathology of skin showed bandlike infiltrate of lymphocytes with associated necrotic keratinocytes. Due to myasthenia gravis-like symptoms she underwent nerve electromyography (EMG) that showed evidence for myopathy and a length dependent, sensorimotor axonal polyneuropathy. There was no evidence of a neuromuscular junction disorder. She was treated with high dose solumedrol, intravenous immunoglobulin (IVIg), and mycophenolate. She also received a short course of pyridostigmine without improvement of the myasthenia-like symptoms. She underwent tracheostomy due to ongoing diaphragmatic weakness and was discharged to a long-term acute care facility.

This case highlights that patients can develop irAE with multi-system involvement, including myocarditis, complete heart block, myositis complicated by respiratory failure, myasthenia-like syndrome with opthalmoplegia, hepatitis, dermatitis, and polyneuropathy. Regarding cardiovascular irAE, this patient experienced definite myocarditis with evidence of cardiac injury and newly reduced LV systolic function and hemodynamically significant

complete heart block [18]. Ongoing clinical experience and research continue to define clinical presentations and mechanisms of these and additional cardiovascular toxicities, to be discussed here in further detail.

Myocarditis

Background

Myocarditis is associated with ICI use with a reported incidence of 0.04–1.14%. The time of symptom onset after ICI initiation varies widely, ranging from a median time of 27–65 days [17]. However, 81% present within 3 months of starting therapy, usually within the first three infusions [19]. The median time from treatment initiation to clinical manifestation of irAE is 30 days (IQR: 18–60 days) for myocarditis, 30 days for pericardial disorders (IQR: 8.5–90 days), and 55 days for vasculitis (IQR: 21–98 days) [20]. However, late presentations have also been described [19] [21]. Reporting of myocarditis cases associated with ICI has been rising since 2017, likely due to increased ICI usage, improved recognition of this toxicity, as well as recent consensus of standardized end-point definitions.

Compared to other irAE, myocarditis is associated with significant morbidity and mortality. Myocarditis has the highest fatality rate of estimated to be 39.6%–46% [14], [17], [22]. The different types of ICI have overlapping irAE, though they tend to more severe with anti-CTLA-4 and anti-PD-1/PD-L1 combination use, likely due to the non-redundant mechanisms of these therapies [17]. Indeed, patients who receive combination therapy experience higher incidence of severe myocarditis compared to those who receive nivolumab alone, underlining that combination therapy is an important risk factor for developing irAE [22]. In patients with fatal outcomes associated with combination PD-1/CTLA-4 therapy, 25% of fatalities were due to myocarditis. Up to 40% of patients will need to stop ICI therapy prematurely due to any irAE, thus compromising anti-tumor therapy efficacy.

Several underlying co-morbidities have been associated with increased risk of developing ICI-associated myocarditis. Risk factors associated with irAE include male sex, sleep apnea, higher BMI, and history of radiation [19]. However, the reported male predominance might be due to higher proportion of male patients in earlier ICI therapy trials, as female sex has also been shown to be associated with ICI-associated myocarditis risk in other studies [23] [24]. Patients with underlying autoimmune disease also seem to be at increased risk of irAE, though existing data is inconclusive. In a retrospective study of 137 patients, those with pre-existing antibodies were significantly more likely to experience irAE (odds ratio 3.25; 95% CI: 1.59–6.65) when treated with nivolumab or pembrolizumab monotherapy [25]. Notably, most patients who experience myocarditis do not have a history of underlying cardiovascular disease [26].

Clinical Manifestations of Myocarditis

Patients with ICI-associated myocarditis can present with a wide spectrum of symptoms, ranging from asymptomatic to life-threatening, which can make the diagnosis challenging. A high level of clinical suspicion is required to diagnose myocarditis due to the non-specific symptoms that can be attributed to non-cardiovascular side effects. The most

common symptoms are non-specific and include dyspnea, orthopnea, palpitations, chest pain, and fatigue. Nearly half of patients with ICI-associated myocarditis experience a major adverse cardiovascular event (MACE), including cardiovascular death, cardiogenic shock, heart failure, cardiac arrest, and complete heart block [19], [27] [28]. Patients can be asymptomatic but have elevated cardiac biomarkers or abnormal electrocardiograms on routine surveillance. Arrhythmias, conduction abnormalities, and non-specific ECG changes are frequently observed in ICI-associated myocarditis, including supraventricular arrhythmias, ventricular tachycardia, and atrioventricular block.

Myocarditis is commonly associated with myositis and myasthenia gravis-like symptoms [29]. Specifically, 25–32% of patients with myocarditis have concurrent myositis/rhabdomyolysis, suggesting that autoreactive T cells are targeted towards striated muscle in both the heart and skeletal muscle [30]. It is important to recognize the overlap with myositis due to the severe complications associated with myositis, including prolonged hospitalization and morbidity. Approximately 10–15% of patients with myocarditis also have myasthenia gravis-like symptoms [29]. Myasthenia gravis-like symptoms include ptosis and oculomotor disorders, which could be due to muscle inflammation or neuromuscular junction disorder. It is less common to have concomitant colitis or severe cutaneous events, and 54% have no other immune related side effects [17] [19]. The presence of other irAE, especially myositis and myasthenia gravis-like syndrome, should prompt evaluation for myocarditis due to the frequency of overlap of these clinical manifestations.

Diagnosis of Myocarditis

In order to diagnose ICI-associated myocarditis, other primary causes of cardiac dysfunction and cardiac injury (e.g., elevated cTn) should first be ruled out. The differential diagnosis should include acute coronary syndrome, stress induced cardiomyopathy (e.g., Takotsubo cardiomyopathy), demand ischemia (e.g., secondary to sepsis, anemia), toxins (e.g., chemotherapy, cocaine, alcohol), tachyarrhythmia induced cardiomyopathy, hypertensive cardiomyopathy, and autoimmune disorders. There can be overlap in presentation with coronary artery disease and myocardial infarction, especially due to the high prevalence of coronary artery disease (CAD) risk factors (e.g., older age, hypertension, hyperlipidemia, diabetes) in cancer patients. Acute coronary syndromes should be assessed by coronary angiography, coronary computed tomography angiography, or stress testing with imaging as indicated per ACC/AHA guidelines on an individualized basis.

There is currently no standardized consensus for diagnosing clinically suspected myocarditis, leaving guidelines largely based on expert opinion [18] [31]. History, physical exam findings, biomarkers, electrocardiogram (ECG), echocardiogram and advanced imaging, and ultimately cardiac biopsy can all be helpful in the diagnostic work-up. According to an expert consensus group statement from the European Society of Cardiology, the clinical diagnosis of myocarditis should integrate clinical and diagnostic criteria, while ruling out ischemia, pre-existing cardiovascular disease, and extra-cardiac causes [32]. The NCI Common Terminology Criteria for Adverse Events (CTCAE) provide a framework for categorizing and grading severity of adverse events in the setting of cancer therapies

in clinical trials. However, the most recent criteria from 2017 do not fully capture the full spectrum of ICI-associated myocarditis, lacking asymptomatic or mildly symptomatic patients with elevated biomarkers or abnormal imaging studies.

A recent hierarchical classification system incorporates symptoms and stepwise diagnostic work-up to classify cases as possible, probable, or definite myocarditis. [18]. Definite myocarditis can be diagnosed with tissue pathology that is consistent with myocarditis, CMR diagnostic of myocarditis coupled with elevated cardiac biomarkers or ECG evidence of myo-pericarditis, and new wall motion abnormality on echocardiogram that is not explained by another diagnosis. CMR, echocardiogram, or other nuclear-based cardiac imaging modalities (MUGA and FDG-PET) in combination with symptoms and abnormal biomarkers can be used to support the diagnosis of probable or possible myocarditis.

The gold standard for diagnosis of myocarditis is endomyocardial biopsy (EMB) or autopsy that is consistent with the pathologic definition of myocarditis according to the Dallas criteria, defined as the presence of inflammatory cell infiltrates with associated myocyte degeneration or necrosis not due to an ischemic event (Figure 3) [33]. The majority of pathology-proven ICI-associated myocarditis cases have a lymphocytic infiltration. Infiltration of mononuclear cells into the myocardium has been detected in post-mortem autopsy even in the absence of clinically overt myocarditis [34]. When feasible, EMB should be considered if there is clinical suspicion for myocarditis to definitely diagnose myocarditis due to the implications in management and prognosis. Though specific, sensitivity can be reduced due to patchy inflammation or sampling error. However, EMB is underutilized due to its invasive nature and potentially life-threatening complications. In the absence of a histopathologic diagnosis, myocarditis can be diagnosed clinically based on symptoms and additional diagnostic work-up.

Elevated cardiac biomarkers, including serum cardiac troponin (cTn), creatine kinase-myocardial band (CK-MB), total CK, and natriuretic peptide levels are frequently elevated in myocarditis and can be used to support the diagnosis of irAE-associated myocarditis. Elevated troponin is found in 94% of myocarditis cases, at times discovered on surveillance testing in the absence of symptoms [35] [36] [37]. Cardiac troponin, including troponin I, troponin T, and high sensitivity troponin, is the most specific biomarker for detecting myocardial injury. Elevated troponin could also have prognostic information - Troponin T >= 1.5 ng/mL associated with worse prognosis and 4-fold increased risk of MACE [19]. Natriuretic peptides (BNP, NT-pro-BNP) are biomarkers that can support the diagnosis of heart failure from ICI-associated myocarditis and cardiomyopathy, though can be elevated for various reasons even with normal filling pressures and can be chronically elevated in cancer patients [38]. In addition, a reduction in absolute lymphocyte count and elevation in the neutrophil/lymphocyte ratio compared to baseline levels have been associated with ICI myocarditis in a case control study of 55 patients [39]. However, while accessible and convenient, these abnormal biomarkers and laboratory values in ICI myocarditis are non-specific and insufficient. Therefore, cardiac imaging is often required to detect and risk stratify irAE-associated myocarditis.

Transthoracic echocardiogram (TTE) is considered to be the first line noninvasive imaging test in the evaluation of suspected myocarditis. Myocarditis can be associated with abnormalities on echocardiogram, including LV dysfunction and regional wall motion abnormalities. Myocarditis can present with reduced or preserved ejection fraction. Importantly, preserved EF does not portend a more favorable prognosis compared to patients presenting with reduced LV function [19]. Up to 38% patients with normal LVEF can develop major adverse cardiovascular events in the setting of ICI-associated myocarditis, including cardiac arrest, cardiogenic shock, and hemodynamically unstable complete heart block [28]. Most patients that have a baseline TTE performed and have a normal baseline LVEF can subsequently develop LV dysfunction, segmental wall motion abnormalities, and dilatation in the setting of ICI-associated myocarditis. In addition, echocardiographic global longitudinal strain (GLS) by speckle tracking is abnormally low in patients presenting with myocarditis based on retrospective data. Lower GLS is associated with a higher risk of MACE in patients with both reduced and preserved EF [27]. TTE can also detect other cardiac manifestations of irAE, including pericardial effusion or pericardial thickening and intra-cardiac thrombi. Serial TTE can be used to monitor response to therapy in cases of reduced ejection fraction, though frequency of monitoring is based on expert opinion.

Cardiac magnetic resonance imaging is a powerful imaging modality that can detect myocardial edema and late gadolinium enhancement (LGE) related to myocarditis and is one of the most specific non-invasive tests to confirm myocarditis. Severe edema and myocardial necrosis likely contribute to LGE in cases of myocarditis [40]. In a retrospective study of ICI-associated myocarditis patients (n=103) in an international, multi-center registry, LGE was present in 48% of patients and qualitative myocardial edema by T2-weighted short tau inversion recovery (STIR) was present in less than one-third of patients with a normal LVEF. The patterns of LGE were diverse, including diffuse, subendocardial, transmural, and sub-epicardial enhancement (Figure 3). The presence of LGE was positively correlated to higher initial troponin T levels, and was more common when CMR was performed on or after day 4 of admission, suggesting that MRI evidence of myocardial inflammation might not develop immediately at time of symptom onset or detection of biomarker abnormality. Of note, 61% of patients had an EF of >=50% [41]. Though more robust studies are needed, the absence of LGE cannot conclusively exclude the diagnosis of ICI-associated myocarditis. Ongoing studies are assessing the use of cardiac fluorodeoxyglucose positron emission tomography (FDG-PET) in assessing inflammation in patients with myocardial inflammation.

Mechanisms of Myocarditis

The mechanisms of ICI-associated myocarditis are incompletely understood. Myocarditis is associated with extensive lymphocytic infiltration into the myocardium with associated myocyte injury and myonecrosis, suggesting that immune cell infiltration is the pathophysiological driver of myocarditis (Figure 4). The infiltrating immune cells include CD4+ T cells, CD8+ T cells, and CD68+ macrophages, reminiscent of acute cellular rejection following cardiac transplantation and giant cell myocarditis (Figure 4) [19] [42] [43]. There is an absence of other immune cells, such as B cells. Interestingly, there is selective clonal T cell population infiltration into the myocardium, skeletal muscle, and

tumor, suggesting that the antigens present in these different tissues are recognized by the same T cell clone [22]. In the skeletal muscle, T cell infiltration is also associated with skeletal muscle injury, consistent with myositis. However, it remains unclear how T cell infiltration into the myocardium mediates cardiac injury. It is especially important to understand the damage caused by effector T cells due to extremely limited regenerative capacity of adult cardiomyocytes.

There are additional proposed mechanisms of ICI-associated cardiovascular toxicities. These include increased auto-antibodies that target self-antigens (e.g., cardiac troponin, myosin, cardiac β1 adrenergic receptors) and upregulation of T cells that react with shared antigens between cancer and normal cells (for example, surface antigens expressed by cardiomyocytes or skeletal muscle). Furthermore, increased PD-L1 expression on cardiomyocytes could potentially lead to T-cell mediated cardiomyocyte cell death in the setting of anti-PD-1 ICI use (Figure 4). Though PD-L1 is normally expressed on cardiomyocytes at low levels, likely providing protection from auto-immune damage, PD-L1 expression can be up-regulated by cardiomyocytes and endothelial cells following ischemic-reperfusion injury and other stressors [21].

Cytokine release syndrome (CRS), characterized by excess pro-inflammatory cytokine release and immune dysregulation, is rarely associated with ICI-associated irAE [44]. CRS is much more common in the setting of chimeric antigen receptor (CAR) T cell therapy, which can also lead to numerous cardiovascular toxicities related to activation of cytokine signaling cascades [45]. Several pro-inflammatory cytokines, including TNF-a, IL-6, and IL-12, can lead to cardiotoxicity through various mechanisms including dysregulated B-adrenergic signaling and increased cytotoxicity.

Treatment and Management Considerations:

Following the diagnosis of ICI-associated myocarditis, ICI therapy should be discontinued. The first-line therapy for myocarditis is high dose corticosteroids, typically intravenous methylprednisolone 1000 mg IV daily for 3 days followed by oral prednisone 1–2mg/kg daily. This is followed by a prolonged steroid taper, typically over a course of 4–6 weeks [46]. Corticosteroids have been shown to increase the probability of LV function recovery [19] [28]. The duration of the taper depends on the severity of presentation, improvement of cardiac function and serial biomarkers, and should also take into consideration irAE involvement of other organs. Notably, myocarditis is less responsive to corticosteroids than other irAE and might require intensified immunosuppressive therapy.

In cases of steroid-refractory myocarditis, second-line agents such as anti-thymocyte globulin (lymphocyte-depleting antibodies), mycophenolate mofetil, and tacrolimus can be considered to reduce the risk of MACE, cardiac failure, and death (Table 2). These agents are typically used in the management of acute cellular rejection following orthotopic heart transplantation, which is also characterized by focal or diffuse lymphocytic infiltration, cytotoxic injury, myocyte damage, and edema [47]. Given the overlap in immune-mediated toxicity, these medications have been used in the management of ICI-associated myocarditis. Other agents that have been utilized for ICI-associated myocarditis on a case-by-case basis (Table 2): for example, abatacept, which is a fusion protein that binds to CD80/CD86 and

prevents the second co-stimulatory signal of T cell activation, has been used successfully to treat patients with corticosteroid-refractory myocarditis and myositis [48]; the IL-6R inhibitor, tocilizumab, can be considered in the management of severe myocarditis with elevated inflammatory markers (Table 2) [49] [50]. Based on retrospective data from 60 patients that included 36 patients who required intensified immunosuppressive therapy, features that are associated with escalation of immunosuppression include combination ICI therapy, sustained ventricular tachycardia, complete AV block, cardiogenic shock, and concomitant myositis and myasthenia gravis [51].

Patients with ICI-associated myocarditis should be followed closely by oncology and cardiology to guide management of immunosuppression and to monitor cardiovascular sequelae from myocarditis. In general, ICI is permanently discontinued following myocarditis, especially due to the risk of recurrence following repeat ICI administration and the mortality associated with a cardiac event [52]. However, therapy should be individualized according to cancer status and the overall severity of irAE.

Pre-clinical models of myocarditis

PD-1 and PD-L1/2 Deficiency

Pre-clinical models have provided tremendous insight into the roles of the immune response in the pathogenesis of immune-mediated toxicities, including myocarditis. PD-1, PD-L1/2, and CTLA-4 deficient mice have revealed mechanistic roles of these immune checkpoints in preventing autoimmunity. These models have shown that PD-1 has a critical role in myocardial immune responses and protects against myocyte damage in models of T cell mediated myocarditis. PD-1 −/− and PD-L1 −/− mice develop myocarditis and dilated cardiomyopathy only in mouse strains that have a propensity of developing autoimmune disease, including BALB/c and MRL backgrounds [53]. Notably, the PD-1 pathway alone is not sufficient to trigger myocarditis [54]. Indeed, in C57Bl/6 background, PD-1 mice exhibit minimal lymphoproliferation and no evidence of myocarditis [55]. This underlines that specific autoimmune-like phenotypes are dependent on genetic factors in mouse models.

Pdcl1−/− (PD-1 deficient) mice on the BALB/c background, but not BALB/c *Rag2* −/− mice, develop severe biventricular dilated cardiomyopathy with reduced LVEF. *Rag2* −/− mice contain a disruption of the recombination activating gene 2, resulting in the inability to generate mature T and B lymphocytes. PD-1 deficient mice on the BALB/c background experience early mortality, as early as 5 weeks of age, due to congestive heart failure and cardiac injury, as evidenced by a high titer of a cardiac specific 33-kD auto-antigen. Affected hearts show diffuse deposition of IgG on surface of cardiomyocyte [56]. The myocarditis is at least partially caused by autoantibodies against cardiac troponin I, which induced dilation and dysfunction of hearts in WT mice, thought to be from Ca2+ influx into cardiomyocytes [57]. Interestingly, the cardiac phenotype could be recapitulated in *Rag2*−/− mice when splenic or bone marrow cells are transferred from diseased mice, underlining that cardiac dysfunction is due to PD-1 deficiency of lymphocytes [56].

Like BALB/c mice, MRL mice are predisposed to systemic autoimmunity, including systemic lupus erythematosus and Sjogren syndrome. MRL-*Pdcl1*−/− mice develop

spontaneous fatal myocarditis characterized by major infiltration of CD4+ and CD8+ T cells in the heart, but sparing the spleen or lymph nodes. This suggests an antigen-specific autoimmune response of the heart. The infiltrated cytotoxic T cells have higher expression of granzyme B and perforin 1, likely contributing to myocyte apoptosis and inflammation. These mice also have experience autoimmune cardiac injury, as evidenced by production of high-titer auto-antibodies against cardiac myosin. The cardiac phenotype is characterized by severe inflammation, ventricular dilatation, intra-cardiac thrombus formation, and severe volume overload (e.g., pleural effusions, ascites, congested hepatopathy). Most mice die from heart failure within 10 weeks. Those that survive longer develop severe glomerulonephritis and autoimmune damage of other tissues. The mechanisms of timing and specificities of organ involvement in strain-specific autoimmune diseases are unknown [55], [57].

MRL-Fas^{lpr} mice are homozygous for the lymphoproliferation spontaneous mutation (Fas^{lpr}) and demonstrate systemic autoimmunity, including aberrant T cell proliferation and severe proliferative glomerulonephritis. These mice develop spontaneous T cell and macrophage-dependent autoimmune disease earlier in life compared to their parent strain (MRL). Due to the role of PD-L1 in downregulating the immune response, it was hypothesized that PD-L1 −/− mice would ameliorate lupus nephritis and systemic illness in MRL-Fas^{lpr} mice. However, PD-L1 −/−;MRL-Fas^{lpr} mice developed severe autoimmune myocarditis, characterized by cardiomegaly, congestive heart failure, and volume overload, as well as early mortality at 2–3 months of age. These mice developed dense PD-1 expressing T cell and macrophage infiltration into the endocardium, myocardium, epicardium of the heart. The infiltrating T cells expressed PD-1 only in the tissues affected by inflammation, suggesting a targeted T cell response in specific tissues. Similar to PD-1 deficiency, these PD-L1 deficient mice also developed anti-cardiac myosin auto-antibodies [58]. Notably, the disease pathology in this model is driven by antibody deposition that is not observed in patients with ICI-associated myocarditis.

The role of PD-1 deficient T cells in regulating pathogenic T cell responses in the heart has been studied by transferring splenic-derived PD-1 deficient T cells to non-deficient host mice. PD-1 deficiency increases CD8+ T-cell mediated cardiac inflammation in a transgenic mouse model where the antigen ovalbumin (OVA) is constitutively expressed as a membrane-bound protein by cardiomyocytes (cMy-mOVA mice). T cells lacking PD-1 proliferated more in the immunized hosts and demonstrated enhanced infiltration of innate immune cells to sites of inflammation. Mice that received PD-1 deficient T cells experienced significantly more myocardial inflammation and myocyte injury (i.e., elevation of circulating cardiac troponin I), possibly due to the enhanced cytotoxic injury produced by PD-1 deficient T cells. In addition, cardiac tissue from cMy-mOVA mice showed enhanced CD8+ T cell response, and increased cytokine levels, including IP-10/CXCL10, IL-10, IFN-γ, and TNF-α. Similarly, adoptive transfer of splenocytes from MRL-$Pdcd1$−/− induced severe myocarditis in sub-lethally irradiated MRL wildtype and MRL-Fas^{lpr} mice [55]. Overall, PD-1 deficient T cells increase cardiac inflammation, neutrophil inflammation, and myocyte death, demonstrating that PD-1 expression on T cells plays an important role in downregulating cytotoxic T cell responses [59].

It remains unknown why the heart is preferentially targeted in PD-1/PD-L1 deficient mice in MRL and BALB/c genetic backgrounds, though could be related to underlying genetic predisposition to autoimmune myocarditis. PD-L1 seems to be critical for limiting cardiac inflammation and injury in mice pre-disposed to autoimmune disease [58]. In addition, injured myocytes and endothelial cells, for example following exposure to IFN-γ, have increased PD-L1 expression. There is also up-regulation of PD-L1 on cardiomyocytes in mice with myocarditis, suggesting that this immune checkpoint helps to limit tissue damage once immune tolerance is broken by suppressing autoreactive T cells that express PD-1.

CTLA-4 Deficiency

The regulatory roles of CTLA-4 in T cell maintenance have been demonstrated by *Ctla4* deficient mice. Unlike PD-1 and PD-L1 deficiency, *Ctla4* deficiency causes massive lymphoproliferation, peripheral T cell activation and proliferation, and tissue destruction even in mice that are not pre-disposed to autoimmune disease (e.g., C57Bl/6 background). In the absence of CTLA-4, mice die prematurely at 3–4 weeks of age. These pre-clinical models demonstrate the important roles of CTLA-4 in downregulating T cell activation and maintaining immunologic homeostasis. Of note, mice heterozygous for the CTLA-4 mutation appear normal and do not have a lymphoproliferative phenotype.

Ctla4 deficiency causes severe non-specific multi-organ (e.g., heart, liver, lung, pancreas, spleen) lymphocytic infiltration, suggesting that the lymphoproliferative immune response is not antigen specific [60]. For example, *Ctla4*–/– mice have severe spleen and lymph node enlargement, with extensive accumulation of lymphocytes in lymph nodes, thymus, and splenic white pulp. The inflammatory infiltrates are a combination of CD4+ and CD8+ cells, F4/80+ macrophages, and few B cells. Peripheral T cells show upregulation of activation markers, including CD44, CD25, and interleukin-2 receptor alpha (IL-2Ra) [61]. These mice develop destructive myocarditis with massive interstitial infiltrate of lymphocytes, macrophages, and neutrophils. Histopathology reveals granular tissue formation in myocardium, suggestive of myocardial infarction. Overall, these models are consistent with non-specific autoimmune tissue destruction, whereby self-reactive T cell clones directly cause widespread tissue inflammation and cell death [62].

Combination Complete PD-1 Loss and CTLA-4 Haploinsufficiency

In order to investigate the higher rates of myocarditis in patients treated with combination therapy with CTLA-4 and PD-1/PD-L1 inhibitors, investigators have recently described a genetic mouse model with genetic absence of *Pdcd1* and haploinsufficiency of *Ctla4*. These *Ctla4*$^{+/-}$ *Pdcd1*$^{-/-}$ mice develop myocarditis, characterized by dense, widespread T cell and macrophage infiltration with associated cardiomyocyte necrosis predominantly involving the epicardium and endocardium. In addition, they experience electrocardiographic instability, including sinus node dysfunction, sinus arrest, bradycardia, and atrioventricular conduction block, similar to patients with ICI-associated myocarditis. Interestingly, treatment with abatacept (recombinant CTLA-4 Ig), which binds to B7 ligands and blocks T cell co-stimulation, reduced mortality of *Ctla4*$^{+/-}$ *Pdcd1*$^{-/-}$ mice and decreased myocardial immune infiltration. Importantly, this mouse model provides a pre-clinical model for studying ICI-

associated myocarditis that recapitulates the clinical syndrome that can potentially be used for studying mechanisms and therapeutic strategies for ICI-associated cardiotoxicity [63].

LAG-3 Deficiency

Lymphocyte activation gene 3 (LAG-3) is a type I transmembrane protein and a critical regulator of autoimmunity. It negatively regulates the function of CD4+ and CD8+ T cells. In non-autoimmune-prone mouse strains, *Lag3* deficiency alone does not induce lethal myocarditis. However, it acts synergistically with PD-1 to prevent autoimmunity in mice. In BALB/c mice, combination LAG-3 and PD-1 deficiency induces lethal myocarditis associated with robust T cell activation. These mice die before 10 weeks of age, thought to be due to loss of the inhibitory function of these immune regulators, resulting in activation of heart-reactive CD4+ T cells [54].

Animal models of ICI-associated immune-mediated adverse events

No significant irAEs have been reported in rodent models following ICI administration alone or in combination due to the overall resistance of mice of developing irAEs compared to humans [64] [65]. However, immune-mediated toxicities have been reported in cynomolgus monkeys given combination nivolumab and ipilimumab. Importantly, the doses in this toxicity study were higher than used clinically over a 4-week period. These monkeys develop immune-mediated toxicities in multiple organs, including the kidney, liver, large intestine, adrenal medulla, and heart, associated with infiltration of lymphocytes and macrophages. The inflammatory myocarditis is characterized by diffuse mononuclear cell infiltration, parenchymal degeneration, and cardiomyocyte necrosis, consistent with the histopathologic diagnostic criteria for myocarditis. In addition, cardiac biomarkers, including NT-pro BNP and cardiac troponin, are also elevated. Interestingly, myocarditis affected 60% (3 out of 5) of the treated monkeys, suggesting that monkeys are more susceptible to immune-related heart inflammation compared to humans, possibly due to underlying low-grade cardiac inflammation [66].

Animal models that recapitulate immune checkpoint-associated irAE are needed to better understand the pathogenesis of cardiovascular toxicities, especially due to the significant morbidity and mortality associated with ICI-associated myocarditis. Importantly, treatment regimens (duration, dose, combination with other ICI or chemotherapies) should mirror those that are clinically relevant in humans. Pre-clinical models could also be helpful in developing specific diagnostic criteria or biomarkers for both predicting and diagnosing ICI-associated cardiovascular irAE.

Pericardial Toxicities

Pericardial disorders related to immune checkpoint inhibitor use include acute pericarditis, pericardial effusion, and tamponade, and can occur in isolation or with myocardial involvement (myopericarditis). Pericardial disorders due to ICI therapy are infrequent [67]. According to a pharmacovigilance study utilizing the WHO VigiBase database, which primarily consists of cases from non-clinical trial settings, pericardial toxicities affect 0.3% of patients receiving immune checkpoint inhibitors [20]. However, due to increased

awareness and recognition of this adverse effect, it is likely that pericardial toxicities due to ICI are currently under-estimated. There has been increased reporting annually of pericardial toxicities since 2012, and this is expected to continue to increase with the expanding use of ICI.

The predisposing factors of pericardial toxicities from ICI use are not well known. Pericardial disorders are more frequently reported in patients with lung cancer (56.3%), especially those treated with anti-PD1/PD-L1 therapy. A possible explanation is that prior radiation therapy in lung cancer patients primes the immune system, leading to a "double hit" that increases the risk of pericardial toxicities. However, it remains unclear if the higher incidence of pericardial toxicities in lung cancer patients is due to increased immune mediated toxicity or underlying cancer progression into the pericardial space. Patients with baseline pre-existing pericardial disease (e.g., prior pericardial effusion) might be at risk of ICI-associated pericardial toxicity, though more research is needed to further delineate the predisposing factors [68].

Of the pericardial disorders, the most commonly reported manifestation is pericardial effusion. Pericardial effusion typically occurs soon after the first dose of ICI, with a median time of 30 days from initial ICI dose. However, late presentations have also been reported [69]. In some cases, pericardial effusion can be found incidentally on chest imaging or echocardiogram. For example, in patients suspected to have ICI-associated myocarditis, 23.5% had trivial or small pericardial effusions [41]. Patients with ICI-associated pericardial effusions are at risk of recurrent episodes. Like myocarditis, pericarditis and pleural effusions can also have an insidious course and become life-threatening, especially in the setting of hemodynamically significant tamponade [70] [71]. Reported cases of pericardial disorders are associated with a high fatality rate (21.1%), though this is likely over-estimated due to under-representation of asymptomatic or mildly symptomatic cases [20].

There is a broad differential for pericarditis or pericardial effusion that should be considered in cancer patients receiving immune checkpoint inhibitors who are found to have newly diagnosed pericardial effusion or pericarditis. Generally, many cases of pericardial effusion are idiopathic due to non-diagnostic workup [72]. Primary cardiac and pericardial malignancies (e.g., fibrosarcoma, angiosarcoma, mesothelioma) can involve the pericardium, though these are uncommon, and estimated to account for less than 0.01% of cases. Metastatic disease involving the heart and pericardium is more common, and can be due various primary malignancies including lung cancer, breast cancer, melanoma, and lymphoma, among others [73]. Specifically, cancer progression can lead to malignant pericardial effusion, which can resemble ICI-associated pericardial toxicity. Numerous traditional chemotherapies have been associated with pericardial diseases, including cytarabine, busulfan, cyclophosphamide, bleomycin, and anthracycline-based chemotherapies (e.g., doxorubicin, daunorubicin), which should be considered in those receiving concomitant traditional chemotherapy [74]. Prior chest radiation can also cause pericardial disease, such as constrictive pericarditis and pericardial thickening [75].

Additional causes of pericarditis and pericardial effusion should be thoroughly evaluated in patients presenting with new or worsening pericardial effusion while being treated with

ICI. These causes include infection (viral, bacterial, fungal, tuberculosis), autoimmune (e.g., rheumatoid arthritis, SLE), cardiogenic (e.g., post-MI, aortic dissection, cardiomyopathy), metabolic disorders (e.g., renal failure, myxedema), and other causes (e.g., sarcoidosis, chest trauma, prior thoracic surgery). Due to presence of co-morbidities in older cancer patients, these other causes of pericardial effusion should be carefully considered prior to diagnosing ICI-associated pericardial disease.

Diagnostic criteria for pericardial disorders associated with ICI therapy are currently lacking. Therefore, they are usually diagnosed based on pre-existing diagnostic criteria. Acute pericarditis is diagnosed according to the 2015 ESC guidelines for pericardial disease by the presence of at least two of the following four criteria: 1. typical pericarditic chest pain (persistent, retrosternal, pleuritic, positional), 2. pericardial friction rub, 3. new diffuse ST segment elevations or PR depressions on 12-lead ECG, and 4. new or worsening pericardial effusion [76]. Clinical presentations of pericardial toxicity associated with ICI can vary widely from asymptomatic to fatal. Hemodynamically significant pericardial effusion and tamponade physiology can be assessed by vital signs, signs of volume overload (e.g., lower extremity edema, elevated jugular venous pressure), and the presence of pulsus paradoxus [77].

Echocardiogram is the first imaging study recommended by the American Society of Echocardiography in cases of suspected pericardial disease [78]. Echocardiography can characterize the size and appearance of the pericardial effusion, thickness of the pericardium, and echocardiographic signs of hemodynamic significance, including IVC plethora and diastolic collapse of the right-sided chambers and respirophasic variation across the mitral and tricuspid valves (Figure 3) [79]. Additional imaging modalities can be helpful when the diagnosis is uncertain. Contrast CT scan can demonstrate global or localized thickening and contrast-enhancement of the pericardium, suggesting inflammation. Cardiac MR can show pericardial thickening, pericardial late gadolinium enhancement (suggestive of inflammation), pericardial edema (characterized by an increase in T2-weighted short-tau inversion recovery), and concomitant myocardial involvement (Figure 3).

Supporting findings for pericardial toxicities can include elevation of inflammatory markers and evidence of myocardial damage. Laboratory studies, such as inflammatory markers (e.g., ESR, CRP) are non-specific, though can support the diagnosis of inflammatory pericarditis. Troponin elevation can indicate co-existing myocarditis, and should prompt evaluation for myocardial involvement due to the poor outcomes associated with myocarditis and the more aggressive treatment recommendations for myocarditis.

When feasible, histopathology and pericardial fluid analysis should be performed in patients undergoing pericardiocentesis and pericardial window to confirm the diagnosis, though definitive diagnosis might remain elusive, especially due to the possibility of concomitant immune-mediated pericardial toxicity and malignant pericardial effusion [70]. In fatal cases, autopsy can further better characterize the immune-mediated toxicities. Autopsy data of patients with fatal cases of pericarditis show parietal pericardium thickening with fibrinous, hemorrhagic exudate, consistent with fibrinous pericarditis [80].

The mechanisms of pericardial irAE are also not well understood. Pericarditis is characterized by inflammation of the pericardial layers. Based on histopathology from pericardial tissue, there is evidence of inflammatory infiltration, including lymphocytes (mostly CD4+ T cells) and macrophages, as well as reactive mesothelial cells [70]. Immunohistochemistry staining shows inflammatory cell infiltration into the pericardium and epicardium, consisting mostly of CD4+ and CD8+ T cells, in addition to CD68+ macrophages and scattered CD20+ B cells. Pericardial samples also show PD-L1 expression of infiltrating immune cells. Prior chest radiation might prime pericardial tissues to cytotoxic T cell mediated injury through unknown mechanisms, predisposing patients with prior chest radiation to pericardial toxicity. Synergistic effects from radiation therapy could potentially prime the endogenous antigen-specific immune response. Theoretically, there can be cross reactivity of activated T cells, targeting an antigen found both on pericardial tissue and a tumor antigen. In addition, ICI therapy might flare subclinical presentations of pericarditis in patients with subclinical viral infections or autoimmune disease that might predispose them to pericarditis.

There are currently no specific guidelines for medical management of ICI-associated pericardial disorders. In general, management is based on ACC/AHA guidelines of non-ICI-associated pericardial disease and should focus on stabilizing the patient if signs of tamponade, reducing inflammation, and preventing recurrence. Pericardiocentesis or pericardial window should be performed in patients with large pericardial effusions or if there are signs of frank or impending tamponade. Similar to non-ICI-associated pericarditis, medical management of ICI-associated pericarditis includes anti-inflammatory therapy. First-line therapy includes high dose NSAIDs or aspirin in cases of pericarditis without myocarditis. Though steroids are generally not recommended for initial cases of acute pericarditis due to higher risk of recurrence, corticosteroids are indicated in the presence of concomitant myocarditis or other severe immune-related adverse events. High-dose steroids have been used with clinical success in cases of tamponade associated with other irAE effects [69]. In cases of myo-pericarditis, ICI therapy should be discontinued. Colchicine should be considered to prevent recurrent pericarditis.

There is paucity of data regarding re-challenging ICI therapy in patients with a history of pericarditis or pericardial effusion in the absence of myocarditis and no guidelines for long term management of patients with ICI-associated pericardial toxicities. The decision to re-challenge with ICI therapy should be made on a case-by-case basis by oncologists and cardio-oncologists with close monitoring of symptoms. In addition, patients should undergo serial TTE to evaluate for resolution of pericardial effusion and to assess possible sequelae of pericarditis, including pericardial constriction. Future research should aim to develop targeted management and treatment guidelines for ICI-associated pericardial toxicities, including the role of biological agents (e.g., anti-IL-1 agents), human intravenous immunoglobulin (IVIg), or pericardiectomy [81].

Vascular Toxicities

ICI therapy can potentially increase rates of acute coronary syndrome (ACS) and atherosclerosis. Case reports have described coronary artery vasospasm and ACS in the

setting of ICI therapy, though it remains unclear if these are direct immune-mediated adverse events or indirectly related to a chronic pro-inflammatory state [82] [83] [84]. ICI therapy increases local lymphocyte-predominate inflammation (increased CD3+ T cell to CD68+ macrophage ratio) and monocyte recruitment in coronary artery atherosclerotic plaques, which might accelerate plaque progression or pre-dispose certain patients to ACS by promoting fibrous cap breakdown [85]. In addition, activated T cells could produce pro-inflammatory and pro-atherogenic cytokines that might contribute to accelerated progression of atherosclerosis. There is growing evidence that ICI therapy accelerates atherosclerotic vascular events, theoretically due to loss of the negative regulation of atherosclerosis progression provided by immune checkpoints. In a large single center study of 2842 patients treated with ICI and 2842 matched controls, ICI use was associated with a 3-fold higher risk of cardiovascular events, including myocardial infarction, coronary revascularization, and ischemic stroke. In addition, the rate of atherosclerotic plaque progression based on total aortic plaque volume was greater than 3-fold higher in patients treated with ICI compared to controls. This increase in atherosclerosis was mitigated by use of statins or corticosteroids, suggesting that optimization of circulating cholesterol levels and suppression of inflammation could slow progression of atherosclerosis [86]. However, prospective randomized control trials are needed to establish the role of statins and anti-inflammatory medications in reducing progression of atherosclerosis in patients treated with ICI.

Vasculitis is a rare immune-mediated complication from ICI therapy based on case reports and case series. It can occur following treatment with anti-CTLA-4 and anti-PD-1/PD-L1 immune checkpoint inhibitors, though seems to be more common with anti-PD-1 ICI. Vasculitis and myocarditis are rarely overlapping. It is most commonly reported with melanoma, which could be due to the proportionally large number of clinical trials in patients with melanoma. The median duration from the initiation of ICI to onset of vasculitis is 3 months (1.2–6 months), though late-onset cases (>6 months from treatment initiation) have been reported. Based on a systematic review, there are no sex differences in the incidence of ICI-associated vasculitis [87]. Fatality directly related to ICI-associated vasculitis seems to be rare.

Though vasculitis can be heterogenous, ICI-associated vasculitis tends to affect medium and large vessels with associated end-organ damage. The most common reports are of large vessel vasculitis, including giant cell arteritis (temporal arteritis), isolated aortitis, and vasculitis of the nervous system (e.g., primary angiitis of the CNS, asymmetric vasculitic neuropathy). Others include primary central nervous system vasculitis (PACNS), digital vasculitis, cryoglobulinemic vasculitis, and retinal vasculitis.

Giant cell arteritis is a large vessel granulomatous vasculitis that affects the aorta and its medium to large branches, including branches of the internal and external carotid arteries. It is the most common primary vasculitis of the elderly and can cause significant complications including permanent vision loss, stroke, and aortic arch syndrome. It is usually associated with systemic inflammation. Histopathologically, it is defined by infiltration of CD4+ T cells, activated macrophages, and multinucleated giant cells into arterial walls, leading to destruction of the tunica media, intimal hyperplasia, and neo-angiogenesis [88]. T cell

infiltration is associated with increased pro-inflammatory cytokines, including IFN-γ, IL-17 and IL-21, which could also contribute to vascular inflammation and injury.

The mechanisms of ICI-associated vasculitis are incompletely understood. Biopsy of affected arteries can show perivascular lymphocytic infiltration and necrotizing vasculitis (Figure 3). The role of PD-1/PD-L1 in medium and large vessel vasculitis provides biological plausibility for anti-PD-1 associated vasculitis. GCA-affected temporal arteries from patients have spontaneous loss of PD-L1 and are enriched for PD-1+ T cells. Due to the loss of this immunoinhibitory molecule, there is infiltration of vasculitogenic CD4+ T cells and unopposed T cell activation, predisposing patients to inflammation reactions involving arteries. In a mouse pre-clinical model, higher levels of PD-1+ T cells in vasculitis lesions lead to the formation of microvessels, endothelial activation, and hyperplasia of the intimal layer [89]. In addition, single-nucleotide polymorphisms in genes PD-1 and CTLA-4 have been associated with T cell hyperactivity in the vasculature of patients with vasculitis, suggesting that these genetic polymorphisms can increase genetic susceptibility to vasculitis [90] [91].

There is currently no standardized work up for ICI-associated vasculitis. Patients presenting with vision loss or stroke should undergo prompt evaluation for GCA due to the permanent complications associated with GCA. According to the 2010 American College of Rheumatology classification criteria, GCA can be distinguished from other forms of vasculitis if at least three of these five criteria are present: 1. Age of onset >= 50 years, 2. New headache, 3. Temporal artery abnormality (tenderness to palpation or decreased pulsation), 4. Elevated ESR (>=50 mm/h by the Westergren method), and 5. Abnormal artery biopsy characterized by mononuclear cell infiltration or granulocyte inflammation [92]. Additional studies that can support the diagnosis of medium-large vessel vasculitis include ultrasound, CTA, MRI, and FDG-PET [93] [94]. Specifically, FDG-PET imaging can quantify large arterial inflammation and calcifications in atherosclerotic lesions, which demonstrate increased 2-[^{18}F] fluorodeoxyglucose uptake. Increased ^{18}F-FDG uptake in major arteries in cancer patients has been associated with increased risk of vascular events, including ischemic stroke and MI [95] [96].

Besides discontinuing immunotherapy, there are no specific therapy recommendations for ICI-mediated vasculitis and should be managed in accordance with pre-existing guidelines for vasculitis [93]. For example, GCA is treated with high dose corticosteroids, which can prevent GCA-related ischemic events, including blindness and stroke. High dose steroid therapy is typically followed by a prolonged steroid taper, lasting up to 18–24 months, though risk of relapse is high. The IL-6R inhibitor, tocilizumab was FDA approved in 2017 to treat patients with GCA and has been shown to achieve sustained remission and lower cumulative prednisone doses [97]. In addition, abatacept has been shown to improve relapse-free survival and median remission durations in patients with newly diagnosed or relapsing GCA – abatacept should be considered for patients treated with anti-CTLA-4 antibodies who develop vasculitis [98]. These agents have been used in steroid refractory cases of ICI-associated myocarditis. Patients with steroid-refractory vasculitis should be followed by rheumatology to guide management with biological agents and other steroid-sparing immunosuppressive agents.

Conduction System Toxicities

Several rhythm abnormalities can be seen in patients with cancer being treated with immune checkpoint inhibitors though these can be clinically non-significant. In general, immunotherapy induced arrhythmias can be broadly differentiated into bradycardia and tachycardia, with atrial fibrillation being an important complication. The true incidence of immunotherapy related arrhythmias is likely to be underestimated because routine cardiac monitoring is often not performed or only includes non-continuous 12-lead ECGs. ECG changes are often non-specific, and include ST changes, T wave abnormalities, conduction abnormalities (e.g., QRS prolongation), supraventricular arrhythmia, and ventricular arrhythmias [99] [100]. These changes are common, affecting up to 89% of patients [19]. ECG changes alone cannot diagnose myocarditis, though can be used to support the diagnosis of myocarditis. ECG changes can be dynamic, so important to monitor on telemetry while hospitalized. Changes in rhythm or conduction should be followed up with a 12-lead ECG to fully capture conduction abnormalities. If symptoms and signs of ischemia (ST segment elevation or depressions), coronary artery ischemia should be evaluated.

In an observational, retrospective analysis of the WHO pharmacovigilance study, ICI therapy was associated with increased reporting of supraventricular arrhythmias. However, supraventricular arrhythmias reported in the ICI population were commonly associated with other concurrent irAEs. Thus, it is unclear whether the increased reporting of supraventricular arrhythmias following ICI therapy was due to concurrent irAE complications versus due to ICI treatment itself [20].

Bradycardias can develop in patients in the setting of high degree of AV block. This AV block is likely secondary to inflammatory infiltration of the myocardium (myocarditis), which can include the AV nodal area and the conduction system in the septum, though other mechanisms are still unknown. The extent of AV block can warrant pacemaker implantation, even permanent devices if no resolution occurs due to evolving fibrosis. Based on a 2018 review, 10% of cardiotoxicity events associated with ICI were AV block or conduction disease which led to death in 50% of these patients [101]. Prospective observational studies are needed to accurately assess the risk and significant of cardiac arrhythmias in the setting of ICI use.

The mechanisms of ICI-associated injury of the conduction system are poorly understood. Cardiac histopathology in patients with myocarditis also reveals lymphocytic infiltration involving the sinus and AV nodes, suggesting that T cell infiltration into the conduction system leads to arrhythmias and conduction abnormalities. As described above, a recent pre-clinical mouse model of combination complete PD-1 loss and CTLA-4 haploinsufficiency recapitulates some features of conduction abnormalities related to ICI therapy, though more in-depth studies are needed [63].

There are currently no guidelines regarding management of conduction system dysfunction in the setting of irAE. All patients presenting with signs and symptoms concerning for myocarditis should have a 12-lead ECG to assess for arrhythmias and conduction

abnormalities. Due to the possibility of dynamic and potentially serious arrhythmias, admitted patients should be monitored on telemetry and 12-lead ECG should be performed to detect evolving arrhythmia. Tachy-arrhythmia management should follow usual guidelines. Transvenous pacemaker should be considered in patients with symptomatic brady-arrhythmias or complete heart block while being treated for irAE. With control of inflammation, it is expected that rhythm disorders will improve. However, cases of permanent pacemaker, ICD, or long term anti-arrhythmic therapy should be determined on a case-by-case basis.

Conclusion and Outstanding Questions:

Since the discovery and expanding use of ICI therapy, much has been learned about immune regulation in the heart and the various immune-related adverse events that can affect the cardiovascular system. As these therapies continue to revolutionize cancer treatment, there is a significant need for ongoing basic, translational and clinical research to improve the care of patients receiving these drugs. Pre-clinical animal models are needed to gain mechanistic insight into irAE and to develop targeted treatments to mitigate these potentially life-threatening toxicities. These animal models may also help our understanding of, and develop predictive biomarkers for, the pathogenesis of cardiovascular toxicities. Clinical research should focus on the prospective characterization of toxicities throughout the cardiovascular system, accounting for the spectrum of disease from sub-clinical injury and atypical presentations to fulminant disease. In addition, large retrospective cohort analyses are essential to better define the pre-disposing factors that lead to the development of ICI-associated myocarditis, vasculitis, and pericardial toxicities. We need to develop consensus guidelines for monitoring of cardiovascular toxicities during therapy, and understand when it is safe to re-challenge with life-saving ICI therapy while minimizing future cardiovascular events. The long-term cardiovascular sequelae of patients with a history of cardiovascular irAEs are still unknown, and future work should aim towards a better understanding of long-term care of these patients.

Acknowledgements:

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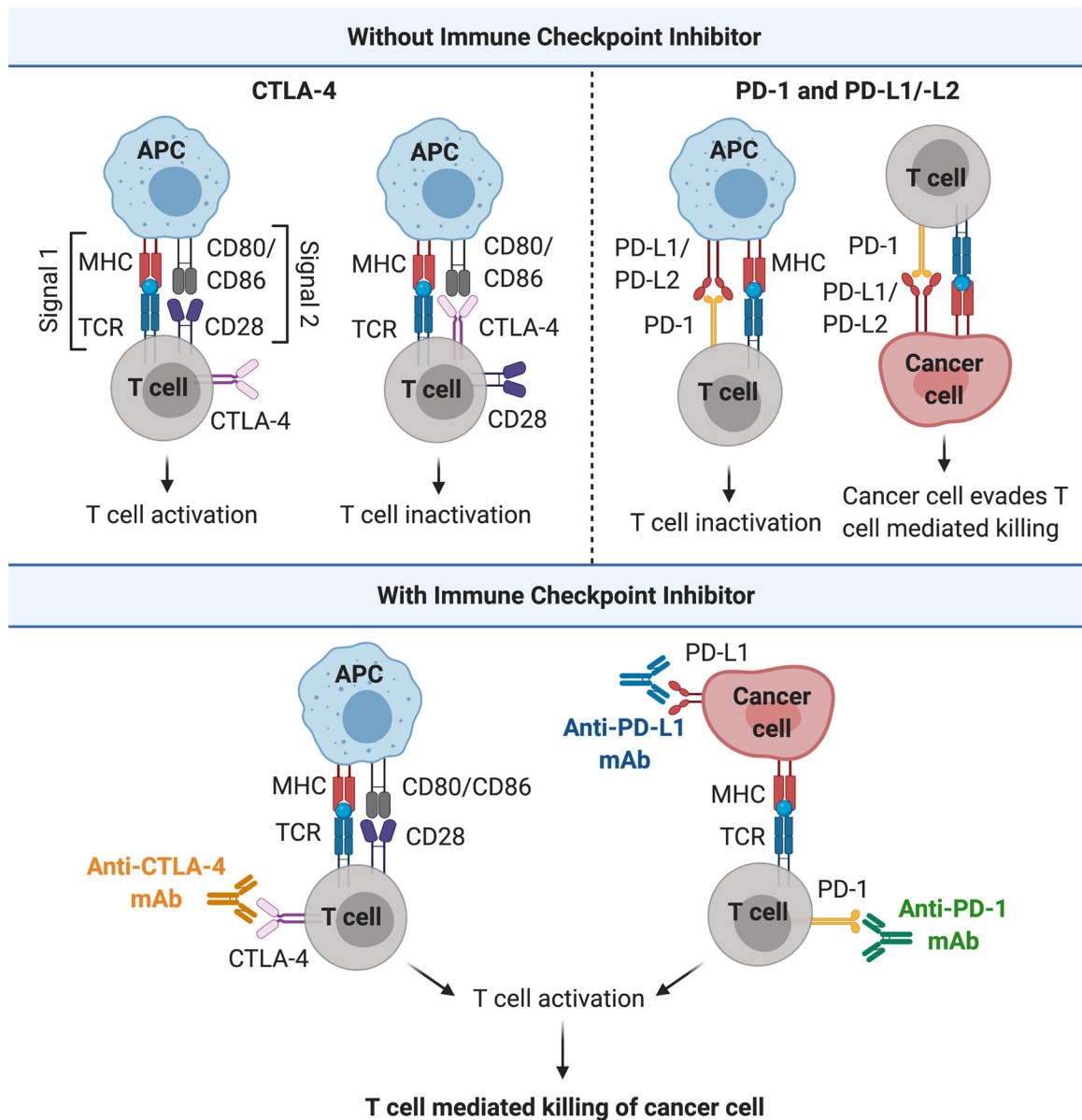
Figure 1:
Immune checkpoints and immune checkpoint inhibitors. CTLA-4 and PD-1/PD-L1/2 signaling dampen T cell activation to maintain a balance between immune activation and self-tolerance. Immune checkpoint inhibitors block CTLA-4 and PD-1/PD-L1 signaling, leading to T cell activation and T cell-mediated killing of cancer cells. Abbreviations: APC, antigen presenting cell; CD, cluster of differentiation; CTLA-4, cytotoxic T lymphocyte-associated protein 4; MHC, major histocompatibility complex; PD-1, programmed cell death protein 1; TCR, T cell receptor
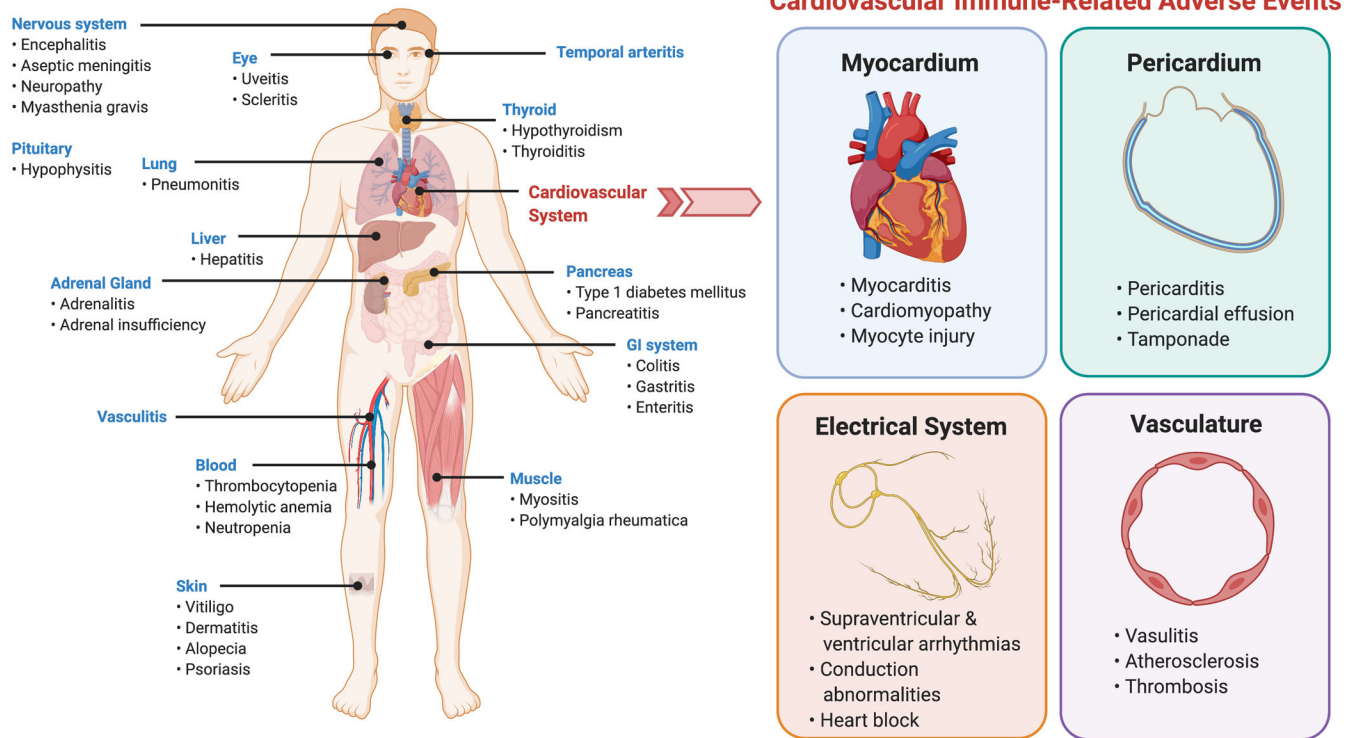
Figure 2:
Types of immune checkpoint inhibitor-associated immune-related adverse events. Immune checkpoint inhibitors can cause a wide range of inflammatory side effects called immune-related adverse events (irAEs). These toxicities can affect nearly every organ system. Cardiovascular system irAE can involve the myocardium, pericardium, vasculature, and conduction system.

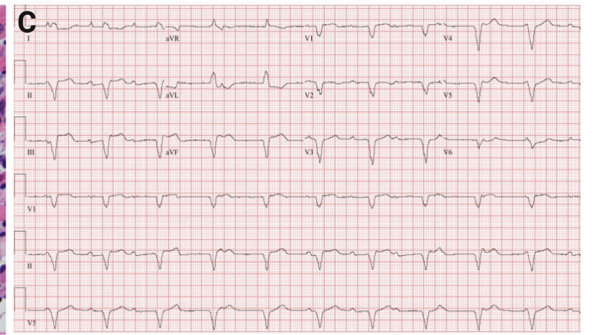## Clinical Images of Cardiovascular Immune-Mediated Adverse Events from Immune Checkpoint Inhibitors

Myocarditis
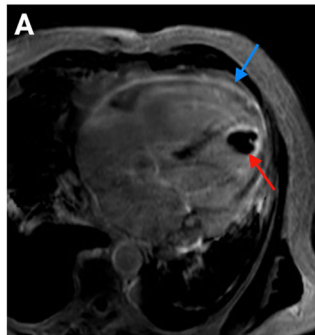
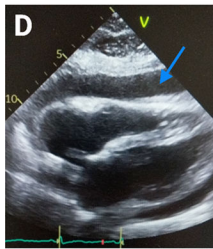
Cardiac MR with contrast, 4-chamber view
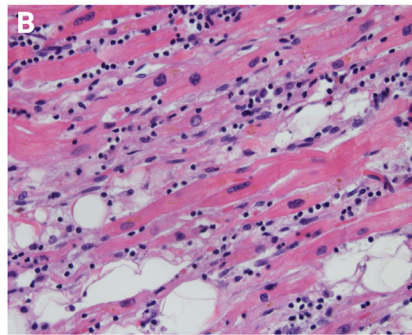
Myocardial biopsy, H&E stain

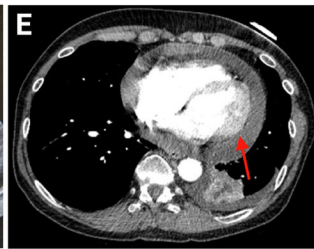**Arrhythmias & Conduction Abnormalities**
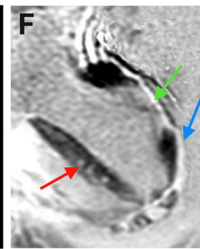
12 lead electrocardiogram (ECG)

Pericarditis/pericardial effusion
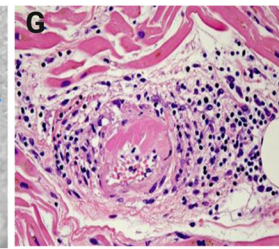
Transthoracic echocardiogram

CT Chest with contrast

Cardiac MR with contrast
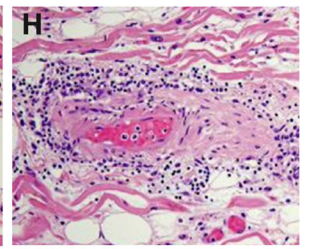
Vasculitis

Arterial biopsy, H&E stain

Figure 3: Clinical images of ICI-associated cardiovascular toxicities.
Myocarditis. A) Cardiac MR with contrast 4-chamber view, showing thinning of left ventricle with subendocardial and subepicardial/pericardial late gadolinium enhancement (blue arrow) and thrombus in the left ventricle (red arrow). B) Photomicrograph of endomyocardial biopsy (H&E staining) demonstrating prominent lymphocytic interstitial inflammation, interstitial edema, and severe injured myocytes with pyknotic nuclei and hyper-eosinophilic cytoplasm (400x). **Arrhythmias and Conduction Abnormalities.** C) Electrocardiogram showing left bundle branch block and third-degree heart block. **Pericardial Toxicities**. D) Transthoracic echocardiogram, subcostal view, showing large, circumferential pericardial effusion (blue arrow). E) CT chest showing large pericardial effusion with pericardial enhancement suggestive of pericarditis (red arrow). F) Cardiac MR with contrast, 4-chamber view showing diffuse pericardial enhancement (blue arrow), transmural late gadolinium enhancement in mid-lateral wall (green arrow) and patchy mid-septal wall enhancement (red arrow). **Vasculitis**. G, H) Photomicrographs of artery biopsy (H&E staining) demonstrating necrotizing vasculitis and perivascular lymphocytic infiltration. Myocarditis H&E image courtesy of Dr. Javid Moslehi, Vanderbilt University. Vasculitis H&E images courtesy of Dr. Robert Padera, Harvard Medical School.
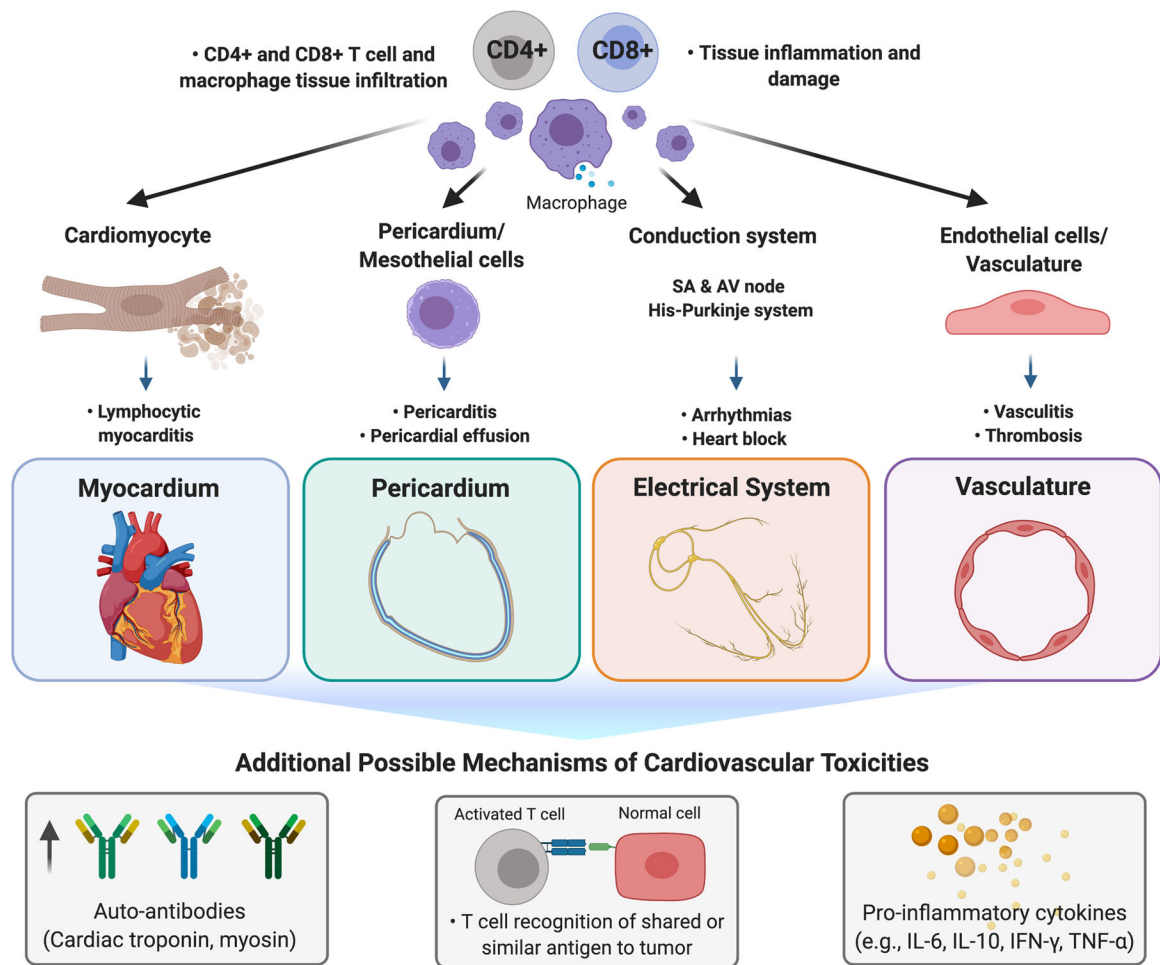
Figure 4:
Mechanisms of immune checkpoint inhibitor associated cardiovascular toxicity. ICI-associated myocarditis is characterized by extensive lymphocytic infiltration (CD4+ T cells, CD8+ T cells, CD68+ macrophages) into the myocardium, myocyte injury, and myonecrosis. Hypothetical mechanisms include increased auto-antibodies that target self-antigens (e.g., cardiac troponin, myosin), T cell recognition of a shared or similar antigen between the tumor and normal cells, and elevation of pro-inflammatory cytokines.

TABLE 1:

FDA-Approved Immune Checkpoint Inhibitors

Drug	Brand Name	Mechanism	Typical Dosing	Initial FDA Approval	Current Indications
ipilimumab	Yervoy®	anti-CTLA-4	• 3 mg/kg Q3W	2011	melanoma (in combination with nivolumab: RCC, MSI-H/dMMR CRC, HCC)
pembrolizumab	Keytruda®	anti-PD-1	• 200 mg Q3W • 400 mg Q6W	2014	melanoma, MCC, NSCLC, SCLC, RCC, urothelial carcinoma, HNSCC, gastric cancer, esophageal cancer, HCC, cervical cancer, any MSI-H/dMMR solid tumor, classical HL, PMBCL, endometrial carcinoma (in combination with lenvatinib), cSCC
nivolumab	Opdivo®	anti-PD-1	• 240 mg Q2W • 480 mg Q4W	2014	melanoma, NSCLC, SCLC, RCC, urothelial carcinoma, HNSCC, HCC, MSI-H/dMMR CRC, classical HL
atezolizumab	Tecentriq®	anti-PD-L1	• 1200 mg Q3W	2016	NSCLC, urothelial carcinoma, TNBC (in combination with paclitaxel)
avelumab	Bavencio®	anti-PD-L1	• 800 mg Q2W	2017	MCC, urothelial carcinoma, RCC (in combination with axitinib)
durvalumab	Imfinzi®	anti-PD-L1	• 10 mg/kg Q2W	2017	NSCLC, SCLC, urothelial carcinoma
cemiplimab	Libtayo®	anti-PD-1	• 350 mg Q3W	2018	cSCC

CRC, colorectal cancer; cSCC, cutaneous squamous cell carcinoma; dMMR, mismatch repair deficient; HCC, hepatocellular carcinoma; HL, Hodgkin's lymphoma; HNSCC, head and neck squamous cell carcinoma; MCC, Merkel cell carcinoma; MSI-H, microsatellite-high; NSCLC, non-small cell lung cancer; PMBCL, primary mediastinal large B-cell lymphoma; RCC, renal cell carcinoma; SCLC, small cell lung cancer; TNBC, triple-negative breast cancer

Table 2:

Therapies for Immune Checkpoint Inhibitor Associated Immune-Mediated Adverse Effects

	Mechanism	Result	Side Effects	Recommendation
High-dose steroids (e.g., intravenous methylprednisolone)	Intracellular glucocorticoid receptor	Multiple immunosuppressive and anti-inflammatory effects	Hypertension Fluid retention Easy bruising Insomnia Altered mental status Weight gain Abdominal discomfort	First line therapy. For myocarditis, consider methylprednisolone 1 gram IV daily × 3 days. IV therapy followed by oral prednisone taper, typically over 4–6 weeks.
Tacrolimus (Prograf)	Binds to immunophilin FKBP12, forming FKBP12-FK506 complex that inhibits calcineurin. Inhibits T-cell signal transduction and IL-2 transcription.	T cell suppression and impairment of T cell-mediated cytotoxicity	Nephrotoxicity Hypertension Hyperlipidemia Tremors Paresthesias Seizures Altered mental status Insomnia	Consider in the management of steroid refractory irAE
Mycophenolate mofetil	Reversible, non-competitive inhibitor of inosine-5'-monophosphate dehydrogenase (IMPDH). Depletion of guanosine nucleotides preferentially in T and B lymphocytes.	Inhibition of T and B cell proliferation, thereby suppressing cell-mediated immune responses and antibody formation.	Myelosuppression GI intolerance (nausea, abdominal pain, diarrhea)	Consider in the management of steroid refractory irAE
Anti-thymocyte globulins (ATG)	Polyclonal antibodies against human T cells. Depletion of T lymphocytes through completement-dependent lysis or activation associated apoptosis	Depletion of T cell lymphocytes	Gastrointestinal intolerance (nausea, vomiting, diarrhea) Dizziness Headache	Consider in the management of steroid refractory irAE
Intravenous immunoglobulin (IVIg)	Blood product composed of immunoglobulins from pooled donors [102]	Suppresses inflammation	Headache Flushing Chills Myalgias Nausea Hypotension Arrhythmia Thrombosis Hemolytic anemia Renal injury Aseptic meningitis	Consider in management of steroid refractory irAE
Infliximab	Chimeric monoclonal antibody against TNF-a	Suppression of TNF-a mediated inflammation	Rash Myalgias Fever Headache Heart failure Stroke Lupus-like syndrome Psoriasis	Consider in management of steroid refractory irAE (case reports of use in GI irAE)
Tocilizumab	IL-6 receptor inhibitor	Reduces IL-6 mediated autoimmune inflammation	Headache Hypertension GI symptoms Myalgias Hepatotoxicity Cytopenias	Consider in management of steroid refractory irAE
Abatacept [48]	CTLA-4-Ig fusion protein that selectively modulates T-cell activation by the CD28/CD80–86 costimulatory pathway	Rapid global T-cell anergy, inactivates the immune response	Headache GI symptoms Nasopharyngitis Hypertension	Consider as second line in the management of steroid refractory irAE
Alemtuzumab [103]	Monoclonal antibody that binds CD52	Complement-mediated destruction of peripheral immune cells.	Headache GI symptoms Cytopenias	Investigational

	Mechanism	Result	Side Effects	Recommendation
			Myalgias Arrhythmia Thyroid dysfunction Kidney injury	
Tofacitinib	Janus kinase (JAK) 1/JAK 3 inhibitor	Interferes with JAK-STAT signaling pathway	Headache GI symptoms Thrombosis Cytopenias	Investigational