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Major Adverse Cardiac Events With Immune Checkpoint Inhibitors: A Pooled Analysis of Trials Sponsored by the National Cancer Institute—Cancer Therapy Evaluation Program

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abstract

PURPOSE Major adverse cardiac events (MACEs) because of immune checkpoint inhibitors (ICIs) are infrequent immune-related adverse events (irAEs) that comprise a spectrum of cardiac toxicities with variable manifestations. ICI-related MACEs can lead to significant morbidity and mortality, hence the need to better define presentations of MACEs and their association with noncardiac irAEs in ICI-treated patients.

METHODS We conducted a retrospective pooled analysis of MACE captured in the serious adverse events reporting database of the National Cancer Institute–Cancer Therapy Evaluation Program for National Cancer Institute–sponsored investigational clinical trials between June 2015 and December 2019. Patients were eligible if they had been treated with anti–programmed cell death protein-1 (anti–PD-1)/programmed cell death-ligand 1 (anti–PD-L1) alone or with additional anticancer therapies.

RESULTS A total of 6,925 participants received anti–PD-(L)1-based therapies; 48% (n = 3,354) were treated with single-agent anti–PD-(L)1 therapy. Of 6,925 patients, 0.6% (n = 40) qualified as ICI-related MACE, with 77.5% (n = 31 of 40) being ≥ grade 3. Myocarditis accounted for 45% (n = 18 of 40) of total ICI-MACEs. Concurrent multisystem involvement with other noncardiac irAEs was seen in 65% (n = 26 of 40). Most patients with myocarditis (83%, n = 15 of 18) had one or more noncardiac irAEs associated. Incidence of MACE was higher with anti–PD-(L)1 + targeted therapies compared with anti–PD-(L)1 + anti–cytotoxic T-cell lymphocyte-4 combinations (2.1% *v* 0.9%, *P* = .08). There was a higher incidence of myocarditis with anti–PD-(L)1-based combination therapies versus single-agent anti–PD-(L)1 therapies (0.36%, n = 13 of 3,571 *v* 0.15%, n = 5 of 3,354, *P* = .08). Deaths related to myocarditis were identified in 22.5% (n = 4 of 18). All four patients who died had concurrent myositis.

CONCLUSION Increasing patient and prescriber awareness in understanding patterns of ICI-MACE and associated noncardiac irAEs should be emphasized. Better characterization of the risk of MACE with the concurrent use of non–ICI-based anticancer therapies with anti–PD-(L)1 treatments is needed.

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INTRODUCTION

Immune checkpoint inhibitors (ICIs), such as anti–programmed cell death protein-1/programmed cell death-ligand 1 (anti–PD-1/PD-L1), can elicit immune-related adverse events (irAEs) that can occasionally lead to fatal outcomes.[1] ICI-related major adverse cardiac events (ICI-MACEs), although rare (< 1%), involve the cardiovascular system on multiple levels.[2] ICI-MACE primarily includes myocarditis, acute coronary syndromes (ACSs; including non–ST-segment elevation and ST-segment elevation myocardial infarction), congestive heart failure, nonmalignant pericardial disorders, dysrhythmias, and cardiac arrest. ICI-MACE can be potentially life-threatening. This is especially true in the case of fulminant myocarditis, which can have a median time to onset of 30 days from ICI initiation and can potentially be fatal in 25%-50% of the cases.[3] Most of the current understanding of ICI-MACE is based on retrospective multi-/single-institutional case series and postmarketing pharmacovigilance studies.[2,4,5] To our knowledge, for the first time, we herein report on ICI-MACE from a pooled analysis of individual patient reports from the National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP)–sponsored ICI-based interventional clinical trials in the United States and Canada using the centralized CTEP Serious Adverse Event Reporting System (CTEP-SAERS) data capture.

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

To understand the spectrum and clinical outcomes of major adverse cardiac events (MACEs) in immune checkpoint inhibitor (ICI)–based clinical trials sponsored by the National Cancer Institute.

Knowledge Generated

Among 6,925 patients treated in National Cancer Institute–sponsored trials, we identified 40 distinct cases (0.6%) having MACE, with myocarditis being the most common (45%) subtype of MACE. A majority (65%) of patients with MACE had other concurrent noncardiac immune-related adverse events. Myocarditis was mainly associated with dual ICI use, whereas ICIs with targeted therapy or chemotherapy were more commonly associated with nonmyocarditis MACE. MACE led to hospitalizations and treatment discontinuations in a majority of patients. Concurrent myositis was commonly associated with myocarditis and led to poor outcomes.

Relevance

ICI-related MACE, although rare, can significantly affect outcomes and warrant high patient and prescriber awareness, especially with ICI combinations such as dual ICI or ICI with targeted agents.

METHODS

Suspected adverse cardiac events in ICI-based trials (June 2015-December 2019) were extracted from the CTEP-SAERS. We included trials where ICIs were given alone as monotherapy, eg, anti–PD-(L)1, and as dual ICI therapy (eg, PD-(L)1 inhibitors with anti–cytotoxic T-cell lymphocyte-4 [anti–CTLA-4] inhibitors or with other anticancer therapies). Among the filed adverse cardiac event reports, cases were filtered to include only ICI-MACE cases (n = 40) when two independent adjudicators (A.R.N. and M.Y.Y.M.) agreed on their attribution to be at least possibly related to ICI on the basis of predefined criteria and excluding underlying confounders. ICIs included were anti–PD-(L)1 alone or anti–PD-(L)1 with either (1) chemotherapies; (2) anti–CTLA-4; targeted therapies that included (3) tyrosine kinase inhibitors or (4) anti-VEGF agents; and (5) other immunotherapeutic agents, antibody-drug conjugates or epigenetic anticancer agents. Some studies also included three or more concurrent treatment modalities that included anti–PD-(L)1 with chemoradiotherapy or anti–PD-(L)1 with targeted therapies and other immunotherapies or immunomodulatory therapies. ICI-MACE was categorized as (1) ACS (including both non–ST-elevation myocardial infarction and ST-elevation myocardial infarction), (2) myocarditis, (3) congestive heart failure, (4) nonmalignant pericardial disorders, (5) dysrhythmias, and (6) cardiac arrest. These AE reports included unrelated (unlikely or unrelated) and related (likely, probable, or possible) events as categorized by the NCI-CTEP drug monitor or the respective reporting site investigators from the clinical trial study team. Each of the four independent study adjudicators from our group reviewed 25% of the filed adverse cardiac event reports. This first screen assessed the likelihood of any cardiac event related to an ICI regardless of its attribution (related or unrelated) by the primary investigators or CTEP (n = 117). In the second screen, reports of MACE were excluded if there were secondary or confounding medical problems (Fig 1) and when both adjudicators (A.R.N. and M.Y.Y.M.) independently agreed upon an unlikely association between the MACE and the ICI-based treatment. Myocarditis was defined on the basis of the European Society of Cardiology (ESC) consensus statement[6] and as suggested by Bonaca et al.[7] Individual records from patients, including admission notes, discharge notes, or any consult notes from cardiology evaluations, were reviewed. The Common Terminology for Clinical Adverse Events (CTCAE version 5.0) was used to grade MACE severity. Concurrent noncardiac irAEs were defined as irAEs with documented clinical, radiologic, or laboratory evidence occurring 4 weeks before or 4 weeks after an ICI-MACE. Chi-square tests were used to determine associations using SPSS version 22.

RESULTS

There were 107 anti–PD-(L)1-based clinical trials identified that included both completed and actively accruing trials. Of these, there were one Pilot, 26 phase I, nine phase I/II, 44 phase II, nine phase II/III, and 18 phase III studies. We identified a total of 6,925 distinct participants receiving anti–PD-(L)1-based therapies. About 48% (n = 3,354) of patients were treated with single-agent anti–PD-(L)1 therapy. Anti–PD-(L)1-based combinations were used in 3,571 patients; these included anti–PD-(L)1 + anti–CTLA-4 in 25.5% (n = 1767) of patients, anti–PD-(L)1 + other immunotherapies (non–CTLA-4) in 2.3% (n = 158), anti–PD-(L)1 + targeted therapies in 3.4% (n = 235), anti–PD-(L)1 + antibody drug conjugates or epigenetically targeting agents in 2.8% (n = 191), and anti–PD-(L)1 + chemotherapies in 5.2% (n = 362). Some trials also had more than two concurrent treatment modalities; 6.4% of patients received anti–PD-(L)1 + targeted agents with other ICI or immune modulation therapies (n = 447), and 6% of patients received anti–PD-(L)1 with chemoradiotherapy (n = 411).

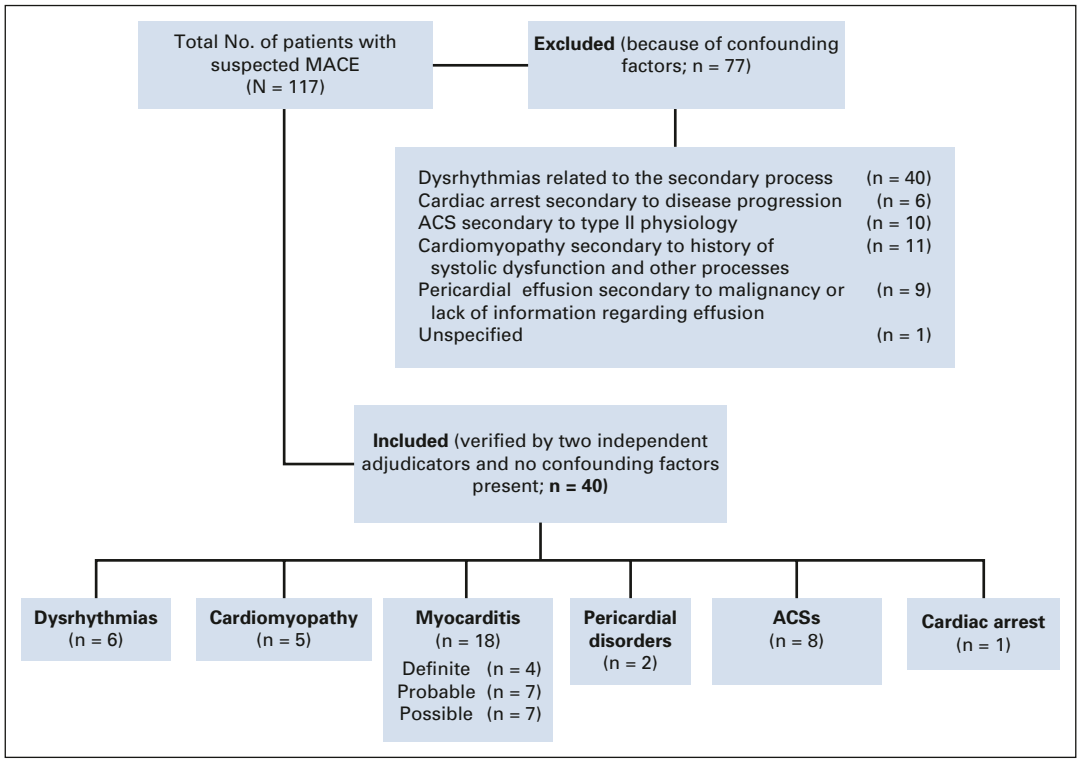

FIG 1. Schema showing inclusion and exclusion criteria for evaluation of ICI-MACE. ACS, acute coronary syndrome; ICI-MACE, immune checkpoint inhibitor-major adverse cardiac event.

Among 6,925 patients receiving anti–PD-(L)1-based therapies, after adjudication, 0.6% (n = 40 of 6,925) of patients qualified as having an ICI-MACE (Fig 1). Among these MACE, 60% (n = 24 of 40) were attributed to anti–PD-(L)1-based combinations (Table 1). Incidence of MACE with single-agent anti–PD-(L)1 was 0.47% (n = 16 of 3,354). For different anti–PD-(L)1-based combinations, the incidence of MACE was 0.90% with anti–PD-(L)1 + anti–CTLA-4 (n = 16 of 1,767), 2.1% with anti–PD-(L)1 + targeted agents (n = 5 of 235), and 0.83% with anti–PD-(L)1 + chemotherapy (n = 3 of 362).

In patients with ICI-MACE, the median age was 68.5 (interquartile range [IQR], 55-74) years; patients were predominantly male (60%, n = 24 of 40) and White (83%, n = 33 of 40; Table 1). The median time to ICI-MACE was 28 (IQR 18-83) days (Fig 2), and 77.5% of ICI-MACEs were ≥ grade 3. A majority of patients (65% n = 26 of 40) demonstrated multisystem organ involvement with other noncardiac irAEs preceding or concurrently with MACE (Table 2). In the entire cohort (n = 40), 7 patients had myositis concurrently with transaminitis, which was the most common pairing of non-MACE adverse events (Fig 2B); most patients with myocarditis (83%, n = 15 of 18) had one or more noncardiac irAEs associated, whereas noncardiac irAEs were observed in 50% (n = 11 of 22) of nonmyocarditis MACE (Figs 2C and 2D). We identified 10 patients with transaminitis (Figs 2C and 2D). Among these patients with both AST and ALT levels available (n = 8), the ratio of AST:ALT was < 1 in five patients and > 1 in three patients. Concurrent myositis was present in all three patients with AST:ALT > 1 and in three of five patients with AST:ALT < 1. Most patients (93%, n = 37 of 40) with MACE underwent hospitalization, with 30% (n = 12 of 40) requiring the intensive care unit. Among those hospitalized with ICI-MACE, myocarditis (46%, n = 17 of 37) was the most common etiology.

Nonmyocarditis MACE constituted 55% (22 of 40) of total ICI-MACE. ACS was the most common nonmyocarditis MACE (36.3%, n = 8 of 22). Twelve (54.5%) of the 22 patients with nonmyocarditis MACE had received combination anti–PD-(L)1-based therapies, among which anti–PD-(L)1 + anti–CTLA-4 was the most common combination (50%, n = 6). All the patients experiencing dysrhythmia had received combination therapies, whereas four of five patients with congestive heart failure (CHF) had received single-agent anti–PD-(L)-1 therapy. The median time to ACS from ICI initiation was 23.5 (IQR 16-176.50) days. In the five patients who developed de novo systolic dysfunction, the mean ejection fraction at presentation was 28% ± 9.4%, with a median time to onset from ICI initiation being 92 (IQR 17-104) days. An extended description of nonmyocarditis MACE is provided in Table 3.

The overall incidence of myocarditis was 0.26% (n = 18 of 6,925 patients), which accounted for 45% (n = 18 of 40) of total ICI-MACE (Tables 2 and 4). Patients presented with myocarditis after a median of two ICI (IQR 1-3.25) doses

TABLE 1. Baseline Characteristics of Patients From 107 ICI-Based Cancer Therapy Evaluation Program Clinical Trials With Major Adverse Cardiac Events

Characteristic	Total	Single-Agent Anti–PD-(L)1 Therapy	Combination Anti–PD-(L)1-Based Therapy
Total No. of patients	40	16	24
Age, years, median (IQR)	68.5 (58.4-74)	69 (17-83)	68.5 (25-81)
Male, No. (%)	24 (60)	12 (75.0)	12 (50.0)
Ethnicity, No. (%)			
White	33 (82.5)	10 (62.5)	23 (96)
African American	2 (5.0)	2 (12.5)	—
Others	5 (12.5)	4 (25.0)	1 (4.0)
Cancer type			
Melanoma	15 (37.5)	5 (31.0)	10 (42.0)
Genitourinary	4 (10.0)	2 (12.5)	2 (8.0)
GI	5 (12.5)	2 (12.5)	3 (12.5)
Lung	2 (5.0)	2 (12.5)	—
Gynecologic	3 (7.5)	—	3 (12.5)
Lymphoma	2 (5.0)	2 (12.5)	—
Others[a]	9 (22.5)	3 (19.0)	6 (25.0)
ICI treatment type			
Single-agent anti–PD-1/PD-L1	16 (40)	16 (100)	—
Atezolizumab	3 (7.5)	3 (19.0)	—
Nivolumab	6 (15.0)	6 (37.5)	—
Pembrolizumab	7 (17.5)	7 (44.0)	—
Combination of anti–PD-(L)1 with	24 (60)		
Anti–CTLA-4 with or without GM-CSF	16 (40.0)	—	16 (67.0)
Targeted therapies	5 (12.5)		5 (21.0)
Chemotherapy	3 (7.5)		3 (12.5)
Cardiac history, No. (%)			
Cardiac comorbidities			
Hypertension	19 (48.0)	7 (44.0)	12 (50.0)
Hyperlipidemia	12 (30.0)	6 (37.5)	6 (25.0)
Diabetes mellitus	8 (20.0)	5 (31.0)	3 (12.5)
Coronary artery disease	5 (12.5)	3 (19.0)	2 (8.0)
Dysrhythmias	5 (12.5)	2 (12.5)	2 (8.0)
Congestive heart failure	3 (7.5)	2 (12.5)	1 (4.0)
Cerebrovascular disease	1 (2.5)	1 (6.0)	—
Cardiac medications			
Beta blockers	14 (35.0)	9 (56.0)	5 (21.0)
Renin angiotensin aldosterone inhibitors	11 (27.5)	6 (37.5)	5 (21.0)
Statins	11 (27.5)	5 (31.0)	6 (25.0)
Antiplatelet agents	9 (22.5)	4 (25.0)	5 (21.0)
Calcium channel blockers	6 (15.0)	3 (19.0)	3 (12.5)
Antiarrhythmics	5 (12.5)	4 (25.0)	1 (4.0)
Diuretics	5 (12.5)	2 (12.5)	3 (12.5)

Abbreviations: CTLA-4, cytotoxic T-cell lymphocyte-4; GM-CSF, granulocyte-macrophage colony-stimulating factor; ICI, immune checkpoint inhibitor; IQR, interquartile range; PD-1, programmed cell death protein-1; PD-L1, programmed death-ligand 1; RCC, renal cell carcinoma.

[a]Others included adrenal carcinoma = 1, dysembryoplastic neuroepithelial tumor = 1, Merkel cell carcinoma = 1, neuroendocrine = 1, RCC = 2, salivary adenocarcinoma = 1, and thyroid cancer = 1.

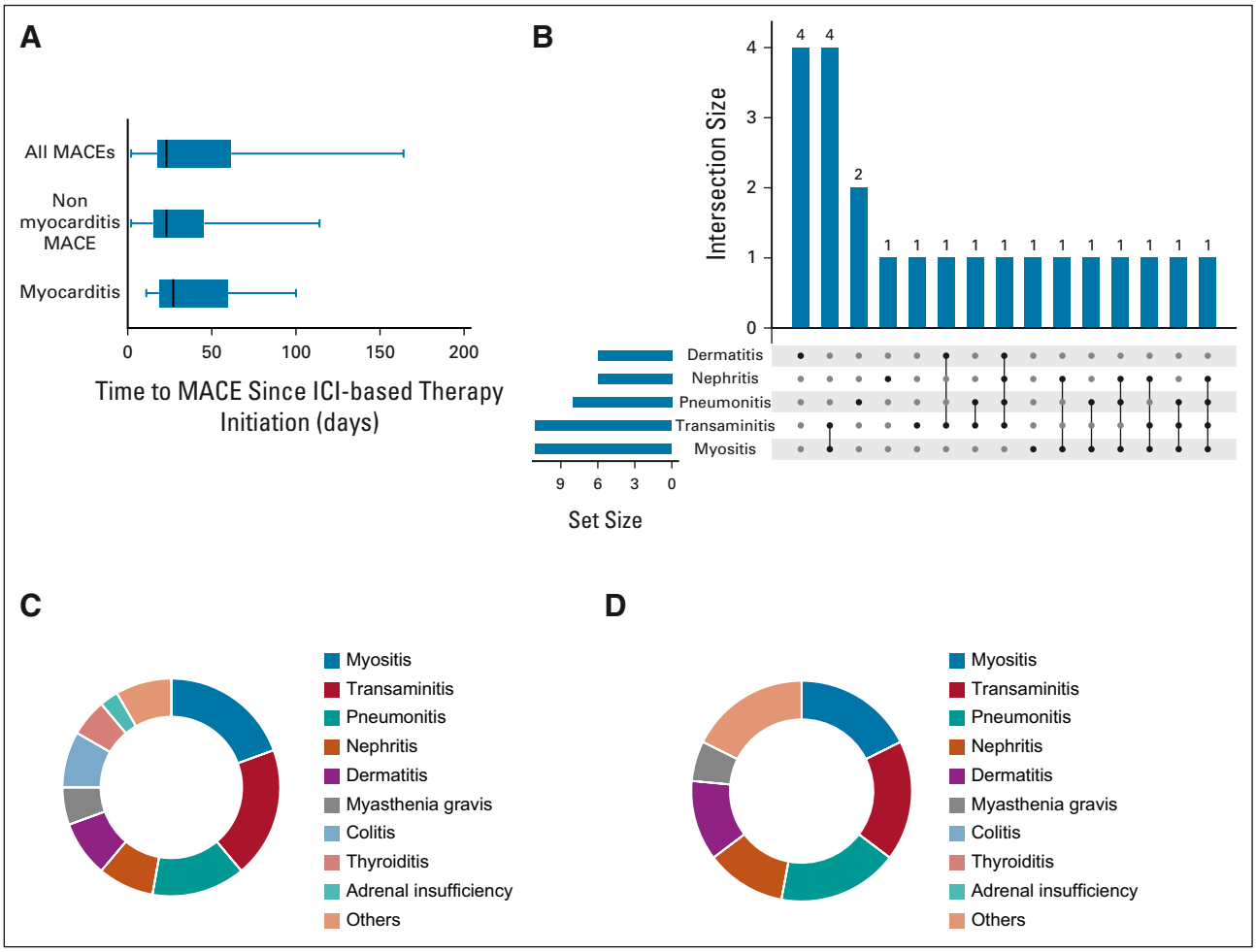

FIG 2. (A) Time to MACE is represented as the median number of days from the first ICI-based therapy infusion. The median time to onset for all MACE was 28 (IQR 18-83) days, myocarditis 35 (IQR 19-80) days, and nonmyocarditis MACE 24 (IQR 17-85.7) days. (B) UpSet[8] plot demonstrating the different interactions for the top five noncardiac irAEs in patients who experienced an ICI-MACE. Myositis was the most common noncardiac irAE that typically occurred concomitantly with transaminitis (n = 7 of 40). Three patients with concurrent myositis/transaminitis are not represented here because of the presence of other less common irAEs that could not be included in the plot. Proportional representation of concurrent noncardiac irAEs associated with (C) myocarditis and (D) nonmyocarditis MACE. In patients with myocarditis experiencing one or more noncardiac irAEs (n = 15), there was a higher proportion of myositis (53%, n = 8 of 15), transaminitis (47%, n = 7 of 15), and pneumonitis (33%, n = 5 of 15) associated with myocarditis. (D) Among patients who experienced nonmyocarditis MACE and noncardiac irAEs (n = 11), myositis, pneumonitis, and transaminitis each occurred in 27% (n = 3 of 11). ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; MACE, major adverse cardiac event.

and after a median of 35 (IQR 19-80) days from initial ICI administration (Fig 2), with 78% of events reported to be ≥ grade 3. There was a higher incidence of myocarditis with the use of combination anti–PD-(L)1-based therapies versus single-agent anti–PD-(L)1 therapy (0.36%, n = 13 of 3,571 *v* 0.15%, n = 5 of 3,354, *P* = .08). Most patients with myocarditis had been treated with anti–PD-1-based combinations (72%, n = 13 of 18), with the most common combination being anti–PD-1 + anti–CTLA-4 (92%, n = 12 of 13; Table 4). One patient with myocarditis had received combination therapy of a tyrosine kinase inhibitor (cabozantinib) with an anti–PD-1 agent for endometrial carcinoma. In patients with myocarditis having one or more irAEs (n = 15), myositis was reported in 53% (n = 8 of 15; Fig 2C), with a median admission creatine phosphokinase (CPK) of 2,002 U/L (range, 267-20,275 U/L). Four of these eight patients had severe fatigue, body aches, and myalgias. Two of the eight patients had worsening shortness of breath and dysphagia to solids. The other two had signs of rhabdomyolysis with acute kidney injury and elevated uric acid, and one of these two had skeletal muscle inflammation demonstrated on autopsy. Among 15 patients with myocarditis who had echocardiograms performed at initial MACE presentation, 26.6% (n = 4 of 15) had an ejection fraction < 50% (Table 4). Cardiac magnetic resonance imaging (cMRI) performed in 39% of patients (n = 7 of 18) showed nonspecific findings (Table 4). Endomyocardial biopsy was obtained in two patients: one showing muscle

TABLE 2. Comparison of Major Adverse Cardiac Events Among 40 Patients From 107 ICI-Based Cancer Therapy Evaluation Program Clinical Trials in Patients Receiving Single and Combination ICI Therapies

Parameter	Total	Single-Agent Anti–PD-(L)1	Combination Anti–PD-(L)1-Based Therapy
ICI-MACE on presentation, No. (%)	40	16	24
Myocarditis	18 (45)	6 (37.5)	12 (50.0)
ACS	8 (20)	6 (37.5)	2 (8.3)
Dysrhythmias	6 (15)	—	6 (25.0)
Atrial fibrillation or flutter	2 (5.0)	—	2 (8.3)
Atrioventricular block	3 (8.0)	—	3 (12.5)
Ventricular tachycardia or ventricular fibrillation	1 (3.0)	—	1 (4.2)
Congestive heart failure	5 (13)	4 (25.0)	1 (4.0)
Pericardial disorders	2 (5.0)	—	2 (8.0)
Cardiac arrest[a]	1 (2.5)	—	1(4.0)
CTCAE grade on initial or subsequent presentation, No. (%)			
1	4 (10)	3 (19)	1 (4.0)
2	5 (13)	3 (19)	2 (8.0)
3	20 (50)	10 (62.5)	10 (42)
4	8 (20)	3 (19)	5 (21)
5[b]	3 (7.5)	2 (12.5)	1 (4.0)
Symptoms at time of MACE, No. (%)			
Dyspnea/orthopnea/PND	14 (35)	11 (69)	3 (12.5)
Flu-like symptoms	9 (23)	5 (31)	4 (17)
GI	7 (18)	3 (19)	4 (17)
Others	5 (12.5)	3 (19)	2 (8.0)
Chest pain	3 (7.5)	1 (6.0)	2 (8.0)
Lower extremity swelling/anasarca	3 (7.5)	2 (12.5)	1 (4.0)
Palpitations	1 (2.5)	1 (4.0)	0 (0.0)
Time to MACE			
No. of doses	2	2.5	2
No. of days from initial ICI	28	29	25
Other irAEs, No. (%)			
None	14 (35)	6 (37.5)	8 (33.3)
1-2	16 (40)	4 (25)	12 (50)
> 2	10 (25)	6 (37.5)	4 (17)
Type of other irAEs (> 10% of total), No. (%)			
Myositis	11 (27.5)	5 (31)	6 (25)
Transaminitis	10 (25.0)	5 (31)	5 (21)
Pneumonitis	8 (20)	4 (25)	4 (17)
Nephritis	6 (15)	3 (19)	3 (12.5)
Dermatitis	6 (15)	1 (4.0)	5 (21)
Myasthenia symptoms	4 (10)	3 (19)	1 (4.0)
Outcomes, No. (%)			
Hospitalization	37 (92.5)	13 (81)	24 (100)
Need for ICU	12 (30)	6 (37.5)	6 (25)
Death[c]	9 (22.5)	4 (25)	5 (21)
Rechallenged with ICI therapy, No. (%)			
Yes	3 (7.5)	—	3 (12.5)
No	37 (92.5)	16 (100)	21 (87.5)

NOTE. Percentage (%) for each variable is based on the total for the respective column and rounded to the nearest integer for some variables.

Abbreviations: ACS, acute coronary syndrome; CTCAE, Common Terminology Criteria for Adverse Events; ICI, immune checkpoint inhibitor; ICU, intensive care unit; irAE, immune-related adverse event; MACE, major adverse cardiac event; PD-L1, programmed death-ligand 1; PND, paroxysmal nocturnal dyspnea.

[a]One patient presented with pulseless electrical activity and arrest. The patient could not be resuscitated by emergency medical services at home.

[b]MACE labeled CTCAE grade 5 by the primary clinical trial team or study adjudicators was based on patients found to be dead on arrival to the hospital or dead at home after ICI. Of the three patients who had CTCAE grade 5, one patient had ACS and died a week after hospital discharge, the second patient was suspected to have underlying myocarditis, and the third patient presented with pulseless electrical activity arrest.

[c]Cause of death was at least likely related to MACE in seven of nine patients. Because of limited documentation, the cause of death in relation to MACE was unclear in two patients.

necrosis without inflammatory infiltrate and the other with trace focal granular staining for immunoglobulin M and complement. In 78% (n = 14 of 18) of patients with myocarditis having available documentation for MACE management, immunosuppression with steroids was initiated promptly. Among these, two patients received methylprednisolone 1 g once per day for 3-5 days followed by a slow taper. The other 12 patients received methylprednisolone 1-2 mg/kg once daily for 3-5 days before transitioning to oral prednisone taper. As far as additional immunosuppression is concerned, one patient with grade 3 and another with grade 4 myocarditis received one dose of infliximab. These two patients had evidence of other concurrent multisystem irAEs that included nephritis, myositis, pneumonitis, and transaminitis. Another patient with grade 1 myocarditis, concomitant nephritis, and myasthenia gravis received mycophenolate 1 g orally twice daily and two courses of intravenous immunoglobulin. Each course was administered for 5 days. All patients experiencing myocarditis had ICIs permanently discontinued, including patients with grade 1 or 2 events. Death attributed to myocarditis was 22.2% (n = 4 of 18) with a median time of 23 (IQR 17-34) days from ICI initiation. Three of these four patients had been treated with dual ICIs (ie, anti–PD-1 with anti–CTLA-4; Table 4). All four patients who died had concurrent myositis, with three of these patients having concurrent transaminitis.

DISCUSSION

To our knowledge, our results represent the first report of a comprehensive pooled analysis of ICI-MACE obtained from NCI CTEP–sponsored investigational clinical trials. We also report on ICI-MACE incidence with various anti–PD-(L)1-based combination therapies that have not been reported previously to the best of our knowledge. We observed a highly variable spectrum of presentations for ICI-MACE and associated noncardiac irAEs, emphasizing the need to have a high index of suspicion to facilitate timely capture and appropriate management. Interestingly, we observed that the incidence of ICI-MACE with anti–PD-(L)1 with targeted therapies was more than twice that of anti–PD-(L)1 with anti–CTLA-4 therapies, with most of these being non-myocarditis MACE, suggesting the need for added vigilance as more novel agents are being combined with anti–PD-(L)1 therapies for various indications.

In our study, among five patients who presented with CHF, four had received single-agent anti–PD-1 therapy, whereas one patient had chemotherapy with anti–PD-1 therapy. These patients developed a de novo systolic dysfunction after ICI. Nevertheless, as more combination anticancer therapies using ICI and multityrosine kinase targeted therapies or chemotherapies are used, it is essential to highlight the potential synergistic effect of some of these combinations. A recently published analysis from the JAVELIN Renal 101 trial identified a higher incidence of LVEF reduction in patients treated with avelumab and axitinib as compared with sunitinib alone (8.5 *v* 1.6%), suggesting a more pronounced overlapping effect in the combination group.[9] These data support the inclusion of CHF within the composite spectrum of MACE with the potential need for baseline and serial monitoring of cardiac-specific parameters in patients initiated on such combination regimens.

In our study, the median time to ACS was approximately 3 weeks after the initiation of ICI therapy, suggesting that these events are likely related to ICI therapy and are part of the ICI-MACE spectrum. In patients with ACS in the context of ICIs, the underlying pathophysiology has been linked to a proinflammatory process. In a recent study of > 2,000 patients with cancer, patients who received ICIs had a three-fold higher risk of atherosclerotic events than patients who did not receive an ICI.[10] The investigators also observed a nearly five-fold more increased rate of myocardial infarction 2 years after ICI initiation.

Previous data from pharmacovigilance databases and multicenter registries have reported a wide incidence range of myocarditis between 0.04% and 1.14% and mortality rates between 25% and 50%.[11] In our study, the overall incidence of myocarditis was 0.26%. However, these cases comprised nearly half of all MACE events, with approximately a quarter of these cases of grade 4 severity and a third requiring intensive care unit admission. In our study, mortality from ICI-related myocarditis was lower than that previously reported in pharmacovigilance studies and other real-world data sets. This is likely due to multiple factors. Our patients were enrolled in regulated clinical trials with closer monitoring, frequent routine follow-up, and management in a tertiary care setting with better access to therapies and perhaps multidisciplinary care. In addition, as it has been widely acknowledged, patients enrolling in clinical trials are, on average, healthier with better performance status because of inherent trial eligibility criteria[12] and of a higher socioeconomic status than the general patient population.[13] This can also affect morbidity and mortality from adverse events occurring on trial.

Similar to other reports,[2,4,11] we observed that most of the suspected myocarditis cases occurred after one to two doses or within 1-2 months of ICI initiation. Most of the patients with myocarditis had received dual ICIs (ie, anti–PD-(L)1 with anti–CTLA-4 therapies). Notably, we observed a 22% mortality attributed to myocarditis, and all patients with fatal outcomes had concurrent or preceding myositis. These features suggest a high-risk population where myositis might indicate a poor prognosis. Early use of alternative strategies such as anti–interleukin-6 or CTLA-4 agonists (eg, abatacept) in addition to steroids may be considered to help improve outcomes in these patients.[14,15] We have previously reported the strong association of concurrent myositis in patients with ICI-related myocarditis.[2,16] These findings have been linked to cross reactive T cells with identical T-cell receptor sequences against shared or homologous antigens on the tumor,

TABLE 3. ICI-Related Nonmyocarditis MACE Detailed Case Description

Patient	Cardiac History	MACE Presentation	Time to MACE From First ICI Dose (days)	Cardiac Diagnostic Workup	Other iRAEs	Death
ACS/myocardial infarction (n = 8)						
61 WF Neuroendocrine cancer (anti–PD-1 + anti–CTLA-4)	—	Chest pain	22	+TnI and BNP ECG: ST depressions and T wave inversion TTE: normal EF, mild/moderate AR	—	Yes
81 Asian M Cholangiocarcinoma (anti–PD-L1)	—	Fever	14	+TnI	Infusion reaction	No
73 WM RCC (anti–PD-1)	HLD	Vertigo Visual changes	23	+TnI ECG: new LBBB, Q waves in V3-V4 TTE: EF 40%, multiple hypokinetic WMA Cath: 80% stenosis in proximal LAD s/p PCI	Myositis Hepatitis Myasthenia gravis Nephritis	Yes
83 WM Bladder adenocarcinoma (anti–PD-L1)	HTN HLD T2DM CHF	Fatigue Flu-like symptoms	13	+TnI ECG: Q waves in inferior leads	Pneumonitis	No
47 WM Melanoma (anti–PD-1)	HTN T2DM	Chest pain	342	+TnI TTE: EF 45%-50% Cath: multivessel CAD	—	No
79 WM Melanoma (anti–PD-1)	CAD	Dyspnea	67	+TnI ECG: atrial flutter TTE: EF 25%, diffuse hypokinesis	—	No
74 WM NSCLC (anti–PD-1)	HTN HLD CAD	Dyspnea Orthopnea	24	+TnI TTE: normal EF ECG: RBBB, AF Cath: severe LM disease s/p PCI	Pneumonitis Myositis Nephritis	Yes
79 WF Melanoma (TKI + anti–PD-1 + anti–CTLA-4)	HTN CAD CHF CVA CKD	Syncope	213	+TnI ECG: AF Cath: mild nonobstructive CAD	Pneumonitis	No
Dysrhythmias (n = 6)						
66 WM Melanoma (anti–PD-1 + anti–CTLA-4)	T2DM	—	14	+TnI ECG: AF with RVR TTE: EF 62%	Myositis	Yes
72 WM Melanoma (anti–PD-1 + anti–CTLA-4)	HTN HLD	Dizziness Fatigue Nausea/vomiting	28	+TnI ECG: 2:1 AVB TTE: EF 55%	—	No
77 WM Cholangiocarcinoma (TKI + anti–PD-L1)	HTN	Fever	16	ECG: AF TTE: 57% cMRI: evidence of myocarditis Cardiac biopsy: negative	Dermatitis	No
69 WF Transitional cell cancer (TKI + anti–PD-1)	HTN CKD	Nausea/vomiting	168	ECG: AVB	—	No
35 WM Colon cancer (chemotherapy + anti–PD-L1)	—	Dyspnea	2	ECG: VF	Hepatitis Encephalitis	No
81 WM Salivary adenocarcinoma (anti–PD-1 + anti–CTLA-4)	—	—	35	ECG: AVB	—	No

(continued on following page)

TABLE 3. ICI-Related Nonmyocarditis MACE Detailed Case Description (continued)

Patient	Cardiac History	MACE Presentation	Time to MACE From First ICI Dose (days)	Cardiac Diagnostic Workup	Other iRAEs	Death
Congestive heart failure (n = 5)						
74 WF Ovarian cancer (chemotherapy + anti–PD-L1)	HTN	Dyspnea LE edema	114	+ TnI ECG: AF with RVR TTE: EF 25%	Nephritis	No
54 American Indian/Alaska Native F Breast cancer (anti–PD-1)	—	Cough Dyspnea Fever	94	TTE: EF 15% Cardiac biopsy: negative	—	No
64 AAM NSCLC (anti–PD-1)	HTN HLD T2DM	Asymptomatic	92	ICD: NSVT TTE: 30%, grade 3 diastolic dysfunction, mild MR	—	No
76 WM Follicular lymphoma (anti–PD-1)	T2DM CAD	PND LE edema	11	ECG: AF TTE: EF 41%	Encephalitis	Yes
46 AAF Breast cancer (anti–PD-1)	HTN HF	Cough Dyspnea	23	+BNP ECG: sinus tachycardia, old LBBB TTE: 30%	—	No
Pericardial disorders (n = 2)						
68 WM Melanoma (anti–PD-1 + anti–CTLA-4)	HTN	Anasarca Dyspnea	56	+TnI and BNP TTE: EF 45%	Dermatitis	No
45 WM Sarcoma (anti–PD-1 + IFN-G)	—	—	19	TTE: pericardial effusion	—	No
Sudden cardiac death (n = 1)						
70 WM Colon adenocarcinoma (chemotherapy + anti–PD-1)	HTN	Dyspnea	18	—	—	Yes

NOTE. Among 40 ICI-MACEs, there were 22 patients with ICI-related nonmyocarditis MACE, which includes ACS/myocardial infarction (n = 8), dysrhythmias (n = 6), CHF (n = 5), pericardial disorders (n = 2), and sudden cardiac death (n = 1).

Abbreviations: AAF, African American female; AAM, African American male; ACS, acute coronary syndrome; AF, atrial fibrillation; AR, aortic regurgitation; AVB, AV block; BNP, brain natriuretic peptide; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; cMRI, cardiac magnetic resonance imaging; CTLA-4, cytotoxic T-cell lymphocyte-4; CVA, cerebrovascular accident; EF, ejection fraction; HLD, hyperlipidemia; HTN, hypertension; ICD, intracardiac defibrillator; ICI, immune checkpoint inhibitor; IFN, interferon; irAE, immune-related adverse event; LAD, left anterior descending artery; LBBB, left bundle branch block; LE, lower extremity; LM, left main coronary artery; MACE, major adverse cardiac event; MR, mitral regurgitation; NSCLC, non–small-cell lung cancer; NSVT, nonsustained ventricular tachycardia; PCI, percutaneous coronary intervention; PD-1, programmed cell death protein-1; PD-L1, programmed death-ligand 1; PND, paroxysmal nocturnal dyspnea; RBBB, right bundle branch block; RCC, renal cell carcinoma; RVR, rapid ventricular rate; T2DM, type 2 diabetes mellitus; TKI, tyrosine kinase inhibitor; TnI, troponin I; TTE, transthoracic echocardiogram; VF, ventricular fibrillation; WF, White female; WM, White male; WMA, wall motion abnormality.

TABLE 4. ICI-Related Myocarditis Detailed Case Description

Patient	Cardiac History	Presentation at MACE	Other irAEs	Associated Arrhythmias	Troponin (ng/L)	TTE	cMRI	Biopsy
Death from ICI myocarditis								
63 WM Melanoma (anti–PD-1+ anti–CTLA-4)	HTN	Fatigue DOE	Myositis Nephritis Transaminitis Pneumonitis	CHB VT	A: 47.23 P: 52.6	EF 40%-45% Grade I diastolic dysfunction	—	Insufficient for diagnosis. Immunofluorescence showed trace focal granular staining for IgM and complement in 10% of perimyocyte capillaries
71 WM Melanoma (anti–PD-1)	HTN HLD CAD	Fatigue	Myositis Transaminitis	—	—	—	—	Cardiomegaly Lymphocytic infiltration
72 WM Thyroid carcinoma (anti–PD-1+ anti–CTLA-4)	—	Dyspnea Malaise	Myositis	—	—	—	—	—
72 WF Vulvar carcinoma (anti–PD-1 + anti–CTLA-4)	HLD	Flu-like symptoms	Myositis Transaminitis Hypophysitis Pneumonitis	CHB	A: 4.23 P: 7.63	EF 50%-55% Hypokinetic inferior septum and basal anteroseptum, severely hypokinetic mid anteroseptum	—	—
Recovery from ICI myocarditis								
73 WF Melanoma (anti–PD-1 + anti–CTLA-4)	HLD	Cough	Transaminitis Diplopia	—	A: 0.69 P: 1.48	EF 60%-65%	No LGE EF 55%	—
68 WF Endometrial (TKI + anti–PD-1)	HTN	Epigastric discomfort	Colitis Thyroiditis	—	A: 12 P: 15	EF 65%	—	—
67 WM Merkel cell (anti–PD-1)	—	Fatigue	Myasthenia Myositis Transaminitis	AF VT	A: 2.4 P: 2.7	EF 25%	—	Muscle necrosis
41 WF Melanoma (anti–PD-1 + anti–CTLA-4)	HTN	DOE Orthopnea Cough	Myositis Pneumonitis	—	A: 0.31 P: 0.31	—	—	—
74 WM Melanoma (anti–PD-1 + anti–CTLA-4)	HTN T2DM CAD CKD	Dyspnea Fatigue Orthopnea LE edema Chest pain	Pneumonitis Colitis	Atrial flutter	A: 0.05 P: 0.07	EF 55%	Patchy areas of LGE in the basal to apical inferior wall can be consistent with myocarditis	—
61 WM Melanoma (anti–PD-1)	HTN	Dyspnea Orthopnea	Myasthenia Pneumonitis Transaminitis Nephritis Dermatitis	—	NA	EF 67% Mild diastolic dysfunction	—	—

(continued on following page)

TABLE 4. ICI-Related Myocarditis Detailed Case Description (continued)

Patient	Cardiac History	Presentation at MACE	Other irAEs	Associated Arrhythmias	Troponin (ng/L)	TTE	cMRI	Biopsy
49 WF Melanoma (anti–PD-1 + anti–CTLA-4)	HLD	Nausea Vomiting	None	—	A: 0.15 P: 0.44	EF 55%	—	—
17 HF HL (anti–PD-1)	—	DOE Palpitations	Thyroiditis Myositis Nephritis Transaminitis	—	A: 0.12 P: 0.12	EF 65%	—	—
78 WF Melanoma (anti–PD-1 + anti–CTLA-4)	HLD	Blurry vision	Diplopia Myositis Transaminitis	—	A: 1.97 P: 47.62	EF 47% Diastolic dysfunction	Mild septal fibrosis in a pattern not consistent with myocarditis. Normal RV and LV function. Normal T2 that does not suggest an inflammatory process	—
60 WM RCC (TKI + anti–PD-1 + anti–CTLA-4+)	HTN HLD T2DM CKD	Musculoskeletal chest pain	Dermatitis	—	A: 0.01 P: 0.01	EF 40%-45% Basal anterolateral, basal inferolateral, basal inferoseptal, mid anterolateral, mid inferolateral, inferoseptal, apical septal, apical anterior, lateral, and inferior hypokinesis	Transmural basal lateral wall scar with moderate to severe LV systolic dysfunction, EF 26% T2 elevation suggests the inflammatory mechanism of myocardial damage	—
52 HF Cholangiocarcinoma (anti–PD-L1)	—	Fatigue Dyspnea Palpitations	None	—	A: 6.46 P: —	EF 55%-60%	—	—
67 WM Adrenal carcinoma (anti–PD-1 + anti–CTLA-4)	HTN T2DM HLD CAD	Nausea Vomiting	AI	—	A: 0.08 P: 0.47	—	Mild globally decreased EF (50%) with delayed patchy contrast enhancement in a nonvascular distribution in keeping with a process such as myocarditis	—
25 AF Dysembryoplastic neuroepithelial (anti–PD-1 + anti–CTLA-4)	—	Dyspnea Chest pain Cough	None	—	A: 0.05 P: 0.12	EF 62%	—	—
64 WF Melanoma (anti–PD-1 + anti–CTLA-4)	AF	Chest pain Epigastric pain Nausea Vomiting Diarrhea	Colitis Dermatitis	—	A: 0.04 P: 0.06	EF > 70%	—	—

NOTE. Among 40 ICI-MACEs, there were 18 patients with ICI-related myocarditis. Four patients experienced death, whereas 14 patients recovered from ICI-related myocarditis.

Abbreviations: A, admission (troponin) level; AF, atrial fibrillation; CAD, coronary artery disease; CHB, complete heart block; CKD, chronic kidney disease; cMRI, cardiac magnetic resonance imaging; CTLA-4, cytotoxic T-cell lymphocyte-4; DOE, dyspnea on exertion; EF, ejection fraction; HF, Hispanic female; HL, Hodgkins Lymphoma; HLD, hyperlipidemia; HTN, hypertension; ICI, immune checkpoint inhibitor; IgM, immunoglobulin M; irAEs, ICI-related adverse events; LGE, late gadolinium enhancement; LV, left ventricle; MACE, major adverse cardiac event; P, peak (troponin) level; PD-1; programmed cell death protein-1; PD-L1, programmed death-ligand 1; RCC, renal cell carcinoma; RV, right ventricle; T2DM, type 2 diabetes mellitus; TKI, tyrosine kinase inhibitor; TTE, transthoracic echocardiogram; VT, ventricular tachycardia; WF, White female; WM, White male.

cardiomyocytes, and the skeletal muscle. Transaminitis with concurrent myositis seen in our cohort is unlikely from ICI-induced direct liver damage and more likely from muscle origin of transaminases because of the previously known strong correlation between CPK and AST/ALT.[17]

To date, standardized guidelines for medical management of ICI-MACE, especially in glucocorticoid-refractory patients, are lacking. There is anecdotal evidence of the benefit of intensified immunosuppressive therapies, such as intravenous immunoglobulins, infliximab, mycophenolate, and other therapeutic options.[11,18] Of note, the use of infliximab warrants extra caution in the setting of decompensated heart failure.[19] Depending on the spectrum of the ICI-MACE clinical presentations, as per guidelines from the American College of Cardiology/American Heart Association, initiating appropriate cardiac therapy with diuretics and inotropes in addition to immunosuppression should be considered.[11] Given the paucity of data elucidating the biologic underpinnings of irAEs in general, ongoing multicenter cooperative group–based efforts such as the NCI-Alliance irAE Biorepository study (Alliance 151804)[20] or the South Western Oncology Group (SWOG) S2013: Immune Checkpoint Inhibitor Toxicity (I-CHECKIT) study[21] will be vital in establishing a translational research effort to understand better the mechanisms of cardiac injury and routes for potential prevention, risk mitigation, and treatment.

Although current algorithms have proposed obtaining cMRI and endomyocardial biopsy in cases of suspected ICI-related myocarditis,[11] these may not be readily performed at all centers or, in some cases, even these may miss a potential diagnosis, despite a high clinical suspicion. A hierarchal definition for myocarditis has thus recently been proposed by Bonaca et al,[7] accounting for the heterogeneous presentation and diagnostic workup of patients with cancer with suspected chemotherapy- or immunotherapy-related myocarditis. This new proposed definition categorizes patients as having definite, probable, or possible myocarditis on the basis of a combination of symptoms and pathology, imaging (cMRI or echocardiogram), biomarkers, and electrocardiographic changes.[7] In our study, using combined ESC criteria and the proposed definition of myocarditis, we observed that only a limited number of patients with suspected myocarditis underwent diagnostic cMRIs. This highlights the need to harmonize approaches to aid in the appropriate diagnosis, monitoring, and treatment of ICI-MACE for patients in clinical trials to generate prospective data. Moreover, as we encounter complex irAE scenarios, such as ICI-MACE with accompanying multisystem noncardiac irAEs in the real-world setting, the establishment of multidisciplinary irAE toxicity teams[22] involving oncologists, cardiologists, internists, and members of other disciplines to help guide appropriate and timely management of patients' needs has to be emphasized.

In the context of our findings and the data from the JAVELIN Renal 101 study, one can argue that in the case of ICI with targeted therapy or dual ICI, consisting of anti–PD-(L)1 and anti–CTLA-4-targeting therapies, obtaining baseline echocardiograms and troponin levels may be of value to aid in identifying high-risk patients, requiring better treatment vigilance. Monitoring serial CPK levels starting at baseline to identify early syndromic presentations for myocarditis with concurrent myositis could be considered with anti–PD-(L)1 and anti–CTLA-4 combination therapies given poor prognosis in these patients where early incorporation of additional immune-suppressive therapies may be warranted.[18] We observed that patients with nonmyocarditis MACE had been treated with both single-agent and combination anti–PD-(L)1-based therapy, roughly in an equal distribution, whereas anti–PD-(L)1 with anti–CTLA-4 was the most common combination in patients with myocarditis. However, given the limited number of patients experiencing ICI-MACE, inferring causation and association can be challenging. Again, since we did not have access to baseline data on prior therapies among our 40 cases with MACE and the comorbidities for patients who did not experience any MACE in the 107 interventional trials that we evaluated, we are not able to generate meaningful inferences on baseline risk factors.

In conclusion, our study provides novel and hypothesis-generating data that could have management implications as increasing numbers of patients are treated with either anti–PD-(L)1 as monotherapy or in combination with other novel therapies. We acknowledge that our overall incidence of MACE is not as high as that of other common irAEs involving other organ systems and is consistent with published literature for MACE. However, on the basis of our findings of MACE and associated mortality and morbidity identified among a denominator of close to 7,000 patients, it is imperative to increase patient and prescriber awareness about these unique events and their variable presentations, especially in the context of defining specific MACE risk with various anti–PD-(L)1-based combinations.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Major Adverse Cardiac Events With Immune Checkpoint Inhibitors: A Pooled Analysis of Trials Sponsored by the National Cancer Institute—Cancer Therapy Evaluation Program

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