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Research Article

Major Adverse Cardiovascular Events in Patients with Melanoma Receiving Immune Checkpoint Inhibitors

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ABSTRACT

Introduction: Immune checkpoint inhibitors (ICIs) might increase the risk of major adverse cardiovascular events (MACEs). This study aimed to evaluate the risk of MACE in patients with melanoma after ICI initiation. **Methods:** We conducted a before-after cohort study using claims data from Optum's deidentified Clinformatics Data Mart Database. We included adult patients with melanoma who received any approved ICI between 2011 and 2021 with a minimum of 12 months of observable data before ICI. The main outcome was time to first MACE (myocardial infarction, coronary revascularization, stroke, heart failure hospitalization) and rate of MACE before and after ICI, ascertained using *International Classification of Diseases*, 9th/10th Revision diagnostic codes. Hazard ratio (HR) and incidence rate ratio (IRR) were calculated. **Results:** We identified 4024 patients with ICI-treated melanoma. Mean age was 67.4 years (SD 14.1), 36% were women; 3066 (76.2%) received monotherapy and 958 (23.8%) combination immunotherapy. A total of 160 (4%) patients had a MACE before ICI and 224 (5.6%) after ICI (HR, 1.76; 95% CI, 1.47–2.12). MACE rate in the year before ICI was 56.16 per 1000 person-years compared with 80.91 per 1000 person-years the year after ICI (IRR, 1.44; 95% CI, 1.21–1.72). Ten cases of myocarditis were observed after ICI, 50% of them had a MACE. Risk factors associated with MACE after ICI were prior MACE, other cardiovascular conditions, hypertension, and older age. Glucocorticoid use was not associated with MACE. **Conclusion:** Our results suggest that ICI might increase the risk of MACE in patients with melanoma during the first year after ICI.

Keywords: immune checkpoint inhibitors, melanoma, cardiovascular disease, cardiotoxicity

INTRODUCTION

Cancer immunotherapy has dramatically changed the prognosis of patients with cancer over the past decade, including in those with melanoma.[1] Immune checkpoint inhibitors (ICIs) were first approved in melanoma in 2011 (anti-cytotoxic T-lymphocyte-associated protein 4 [CTLA4]) with anti-programmed cell death protein 1 (PD-1) agents approved in 2014 followed by combination ICI therapies. Since that time, they have significantly improved overall survival for patients with melanoma and have also been approved in more than 17 cancers.[2] It was estimated that

more than 40% of US patients with cancer might be eligible for ICI therapy.[3] ICIs work by blocking the negative regulation of patients' immune systems, thus potentially unleashing an antitumoral immune response. However, this immune activation can persistently augment immune and inflammatory pathways and lead to immune-related adverse events (irAEs) that can affect any organ.[4] Acute myocarditis is well described, but fortunately rare, occurring in less than 1% of patients.[5,6] Less is known about other potential cardiovascular effects of ICIs. A previous retrospective pooled analysis of clinical trials showed an increase in cardiovascular events in treated patients; however, 45% of the events were related to myocarditis.[7] Given the association between inflammation and atherosclerosis, it is plausible that ICIs may increase the risk of cardiovascular events.[8–10] Major adverse cardiovascular events (MACEs) refer to a composite clinical endpoint that includes serious cardiovascular outcomes such as myocardial infarction, coronary revascularization, stroke, heart failure with hospitalization, and cardiovascular death. As cardiovascular disease is an important determinant of morbidity and mortality, it is crucial to understand whether ICI can increase MACE in cancer survivors.

Our objective was to evaluate the risk of MACEs in patients with melanoma in the year after initiation of ICI.

METHODS

This study involved human participants but was deemed to be exempt by the institutional review board at the University of Texas MD Anderson Cancer Center, as it only included deidentified claims data (protocol PA14-0949), and individual patient consent was waived.

Data Source and Study Cohort

We conducted a before-after secondary data analysis of patients identified in the Optum's deidentified Clinformatics Data Mart Database (CDM), between January 1, 2011, and June 30, 2021. CMD includes deidentified administrative health claims on more than 77 million patients from the United States.[11]

We identified patients 18 years of age or older who received at least one dose of any of the Food and Drug Administration (FDA)-approved ICIs (Supplemental Table S1, available online) and had *International Classification of Diseases* (ICD), 9th/10th Revision claims diagnoses to identify melanoma (ICD-9 172 and ICD-10 C43) as the primary cancer diagnosis within 60 days before and after the index date (ICI initiation). We required that patients in the cohort have a minimum of 12 months of observable data before receiving ICI therapy. All the criteria for the final cohort selection are shown in Figure 1.

Exposure

Use of ICI was the exposure of interest. We defined the treatment as monotherapy or combination therapy. Monotherapy was defined as the use of only one ICI (PD-1, programmed death ligand 1 [PD-L1], CTLA-4); combination therapy was defined as receiving ipilimumab (anti-CTLA4) and nivolumab or pembrolizumab (anti-PD1) on the same day.

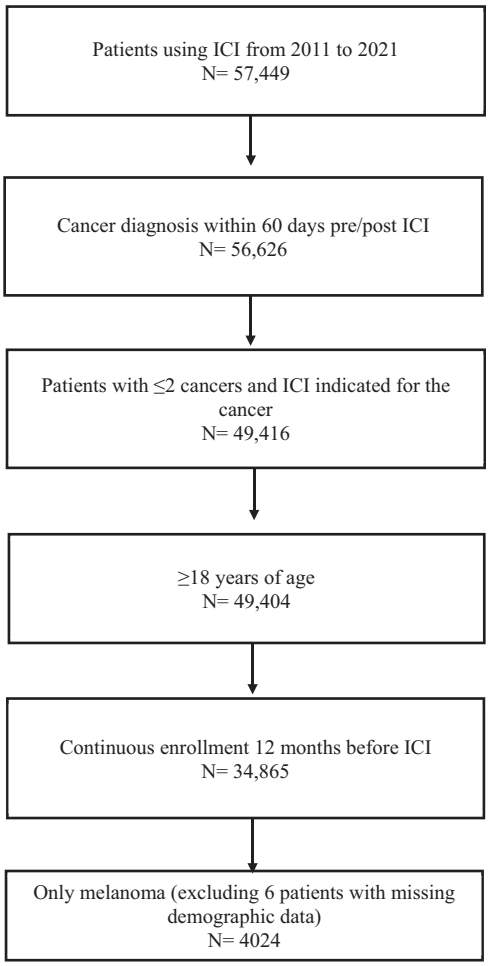

Figure 1. Cohort selection.

Outcomes and covariates

The primary outcome was incident MACE the year before and after ICI initiation. Although many studies have defined MACE as the composite of acute myocardial infarction, stroke, and cardiovascular mortality, others have included hospitalization for unstable angina or revascularization and heart failure in their MACE definition. Variability in MACE use is greater in observational studies of administrative databases.[12] We defined MACE as a composite of myocardial infarction, coronary revascularization, stroke, and heart failure with hospitalization using ICD-9/10 codes. We did not include cardiovascular mortality because CDM does not provide information about disease-specific mortality. The definitions and codes for MACE are shown in Supplemental Table S2, available online. The index date for the year before ICI is 12 months before ICI therapy and the index date for the year after ICI is the date of ICI therapy. We estimated the median time to first MACE before ICI in the interval ranging from 12 months before starting ICI therapy to the day before therapy started.

We evaluated the following covariates: demographic characteristics (i.e., age, sex, race, region), other melanoma treatment (chemotherapy, targeted therapy), comorbidities evaluated by the National Cancer Institute Comorbidity Index algorithm using ICD codes,[13] and cardiovascular risk factors and conditions. We categorized chemotherapeutic and targeted agents as cardiotoxic or non-cardiotoxic. The drugs categorized as cardiotoxic were the mitogen-activated protein kinase (MEK) inhibitors trametinib, cobimetinib, and binimetinib, and the tyrosine kinase inhibitor imatinib. We grouped cardiovascular risk factors and conditions that might be associated with MACE after ICI into four different categories for the purpose of the multivariable adjustment: (1) MACE 12 months before ICI; (2) other cardiovascular conditions defined as any conduction abnormality (includes arrhythmia and atrial fibrillation), chronic heart failure, cardiomyopathy, myocarditis; (3) preexisting atherosclerotic disease: coronary artery disease (CAD), transient ischemic attack (TIA), peripheral artery disease (PAD); and (4) other cardiovascular risk factors: hypertension, diabetes mellitus (insulin-dependent and non–insulin-dependent), dyslipidemia. Supplemental Table S3, available online, shows the definitions and codes for these categories. We identified patients who had myocarditis after ICI initiation using the following codes: ICD-9 422.0, 422.90–422.99; and ICD-10: I40.1, I40.8, I40.9, I41, I51.4. Use of glucocorticoids was assessed using pharmacy claims data. We converted the systemic glucocorticoids to prednisone-equivalent doses (milligrams per day). We calculated the average daily dose, the total dose, and the total days of supply.

Statistical Analysis

For baseline characteristics, we calculated means with SD or median with IQR for quantitative variables and percentages for qualitative variables. We compared these baseline characteristics in patients with and without MACE after ICI.

Our primary analysis was time to first MACE in the year before compared with the year after ICI initiation. Cox proportional hazard models with robust sandwich estimate of the covariance matrix to account for correlated outcomes in the same patient were used to estimate the hazard ratios (HRs) with 95% CIs. Patients were censored at last follow-up or death. We also calculated the incidence rate of MACE before and after ICI initiation per 1000 person-years and the incidence rate ratio (IRR) using exact Poisson distribution regression, 95% CI, and exact mid-P p values.[14] In this analysis, one patient could contribute to more than 1 MACE.

To evaluate the predictors of MACE after ICI initiation, we conducted a Poisson regression model that included prior cardiovascular disease or cardiovascular risk factors (as defined before), age categorized in four groups (18–54, 55–64, 65–74, and 75 and older), sex, type of ICI therapy categorized in three groups (monotherapy PD-1/PD-L1, monotherapy CTLA-4, combination therapy), race (White, Black, or other [due to low cell counts for races other than White or Black]), comorbidity index, income status, melanoma treatment before index date, and melanoma treatment after the index (categorized as cardiotoxic or non-cardiotoxic), glucocorticoids use as average daily dose and total dose, and year of ICI initiation categorized in three groups (2011–2014, 2015–2016, and 2017–2021). This categorization was established based on the year of FDA approval for adjuvant therapy and type of ICI; ipilimumab was approved for adjuvant therapy in 2015[15] and nivolumab was approved for adjuvant therapy in 2017.[16] Therefore, patients treated before 2015 were more likely to have advanced melanoma compared with patients treated after 2015.

The proportional hazards assumption was confirmed in the Cox regression model both graphically and numerically using cumulative sums of martingale-based residuals.[17] Statistical analyses were performed using the SAS software program version 9.4 (SAS Institute, Cary, NC).

This study adhered to the Reporting of Studies Conducted Using Observational Routinely Collected Health Data for Pharmacoepidemiology (RECORD-PE) reporting guidelines for pharmacoepidemiological studies.[18]

RESULTS

Among 49,522 patients with two or fewer cancer diagnoses, 12,130 (24.5%) had two cancers. From a cohort of 34,864 patients who received ICI ($\geq$ 18 years old and 12 months continuously enrolled before ICI), we identified 4024 patients with melanoma. Mean age was 67.4 years (SD 14.1) and 35.8% were women; 2134 (53.03%) received monotherapy PD-1/PD-L1, 932 (23.16%) received monotherapy CTLA-4, and 958 (23.8%) received combination immunotherapy. Overall, 224 (5.6%) patients developed a MACE in the year after ICI initiation. Table 1 shows the characteristics of patients who developed or did not develop MACE. In the unadjusted analysis, patients with MACE were significantly older; more likely to be men; had a higher comorbidity score; had received more often PD-1/PD-L1 monotherapy or combination therapy; had prior MACE, other cardiovascular conditions, atherosclerotic disease (CAD, TIA, PAD), and other cardiovascular risk factors (hypertension, diabetes insulin-dependent, diabetes non–insulin-dependent, dyslipidemia); and used fewer glucocorticoids.

During the period before ICI treatment, 196 (4.87%) patients received cardiotoxic therapy and 387 (9.62%) non-cardiotoxic therapy. In the follow-up period after ICI initiation, 257 (6.37%) patients received cardiotoxic and 405 (10.06%) non-cardiotoxic therapy. No significant differences were observed in these treatments between patients with and without MACE.

A total of 160 (4%) patients had one or more MACE in the year before ICI compared with 224 (5.6%) after ICI initiation. Of the 224 MACEs after ICI, 117 (53.2%) were heart

Table 1. Patient baseline characteristics by occurrence of MACE in the year after ICI treatment initiation

Covariates	Patients with ≥ 1 MACE (*n* = 224)	Patients Without MACE (*n* = 3800)	*p*-value
Age group, years			< 0.001
18–54	11 (4.9)	703 (18.5)	
55–64	23 (10.3)	710 (18.7)	
65–74	65 (29.0)	1110 (29.2)	
75+	125 (55.8)	1277 (33.6)	
Age, years, mean (SD)	74.2 (10.8)	66.9 (14.2)	< 0.001
Sex			0.006
Female	61 (27.2)	1381 (36.3)	
Male	163 (72.8)	2419 (63.7)	
Race			0.155
White	200 (89.3)	3232 (85.1)	
Black	10 (4.5)	183 (4.8)	
Other	14 (6.3)	385 (10.1)	
Low-income subsidy			0.074
Yes	12 (5.4)	116 (3.1)	
No	212 (94.6)	3684 (96.9)	
Region			0.055
Midwest	55 (24.6)	993 (26.1)	
Northeast	31 (13.8)	434 (11.4)	
South	100 (44.6)	1471 (38.7)	
West	38 (17.0)	902 (23.7)	
Comorbidities			< 0.001
0	33 (14.7)	1187 (31.2)	
1	31 (13.8)	1001 (26.3)	
2+	160 (71.4)	1612 (42.4)	
Year of ICI initiation			0.005
2011–2014	18 (8.0)	576 (15.2)	
2015–2016	32 (14.3)	591 (15.6)	
2017–2021	174 (77.7)	2633 (69.3)	
Type of ICI			0.006
Monotherapy PD-1/PD-L1	125 (55.8)	2009 (52.9)	
Monotherapy CTLA-4	34 (15.2)	898 (23.6)	
Combination therapy	65 (29.0)	893 (23.5)	
No. of ICI episodes, mean (SD)	8.9 (12.9)	10.1 (12.3)	0.146
Glucocorticoids, mg, mean (SD)			
Average daily dose	1.7 (5.9)	2.7 (7.9)	0.021
Total dose	13.6 (58.3)	33.8 (205.7)	< 0.001
Total days of supply	0.7 (2.3)	1.6 (6.8)	< 0.001
Cardiac risk factors before ICI			
MACE	36 (16.1)	124 (3.3)	< 0.001
Myocardial infarction	22 (9.8)	64 (1.7)	< 0.001
Ischemic stroke	NR	21 (0.6)	0.047
Hospitalized heart failure	11(4.9)	29 (0.8)	< 0.001
Revascularization	6 (2.7)	20 (0.5)	0.002
Other CV conditions	134 (59.8)	995 (26.2)	< 0.001
Any conduction abnormality	89 (39.7)	677 (17.8)	< 0.001
Heart failure, cardiomyopathy, myocarditis	112 (50.0)	576 (15.2)	< 0.001
Preexisting atherosclerotic disease	104 (46.4)	692 (18.2)	< 0.001
Transient ischemic attack	NR	22 (0.6)	0.053
Peripheral artery disease	23 (10.3)	191 (5.0)	0.002
Coronary artery disease	93 (41.5)	556 (14.6)	< 0.001
Other CV risk factors	181 (80.8)	2550 (67.1)	< 0.001
Hypertension	174 (77.7)	2167(57.0)	< 0.001
Diabetes, insulin-dependent	20 (8.9)	142 (3.7)	< 0.001
Diabetes, non–insulin-dependent	53 (23.7)	487(12.8)	< 0.001
Dyslipidemia	137 (61.2)	1737 (45.7)	< 0.001
Treatment before ICI therapy			
Cardiotoxic	8 (3.6)	188 (4.9)	0.426
Binimetinib	NR	11 (0.3)	≥ 0.99
Cobimetinib	NR	12 (0.3)	≥ 0.99
Imatinib	NR	6 (0.2)	0.331
Trametinib	7 (3.1)	162 (4.3)	0.495

Table 1 continues on next page

Table 1. Continued

Covariates	Patients with ≥ 1 MACE (*n* = 224)	Patients Without MACE (*n* = 3800)	*p*-value
Not cardiotoxic	14 (6.3)	373 (9.8)	0.081
Carboplatin	NR	24 (0.6)	0.654
Cyclophosphamide	NR	5 (0.1)	≥ 0.99
Dabrafenib	8 (3.6)	159 (4.2)	0.862
Dacarbazine	NR	5 (0.1)	0.291
Encorafenib	NR	11 (0.3)	≥ 0.99
Interferon	NR	62 (1.6)	0.582
Interleukin	NR	11 (0.3)	≥ 0.99
Paclitaxel	NR	NR	≥ 0.99
Temozolomide	NR	38 (1.0)	0.271
Vemurafenib	NR	88 (2.3)	0.24
Vincristine	NR	NR	≥ 0.99
Treatment after ICI therapy			
Cardiotoxic	11 (4.9)	246 (6.5)	0.401
Binimetinib	NR	60 (1.6)	0.259
Cobimetinib	NR	9 (0.2)	≥ 0.99
Imatinib	NR	5 (0.1)	0.291
Trametinib	9 (4.0)	188 (4.9)	0.634
Not cardiotoxic	15 (6.7)	390 (10.3)	0.087
Carboplatin	NR	47 (1.2)	0.52
Cyclophosphamide	NR	NR	≥ 0.99
Dabrafenib	9 (4.0)	184 (4.8)	0.747
Dacarbazine	NR	20 (0.5)	0.624
Encorafenib	NR	56 (1.5)	0.074
Interferon	NR	NR	≥ 0.99
Interleukin	NR	NR	≥ 0.99
Paclitaxel	NR	22 (0.6)	≥ 0.99
Temozolomide	NR	56 (1.5)	0.77
Vemurafenib	NR	56 (1.5)	0.77
Vincristine	NR	NR	-

Values are expressed as *n* (%) unless otherwise noted.
CTLA-4: cytotoxic T-lymphocyte-associated antigen 4; CV: cardiovascular; ICI: immune checkpoint inhibitor; MACE: major adverse cardiovascular event; PD-1: programmed cell death 1; PD-L1: programmed death ligand 1; NR: not reportable if *n* is less than 5.

failure, 68 (30.3%) myocardial infarction, 30 (13.4%) ischemic stroke, and 9 (4%) coronary revascularization. The median time to MACE in the 12-month follow-up before ICI was 214.5 days, and median time after ICI initiation was 104 days. The time to first MACE was significantly shorter after ICI treatment compared with the period before ICI with an HR of 1.76, 95% CI 1.47–2.12 ($p < 0.0001$). These results are depicted in Figure 2. The incidence rate of MACE in the year before ICI was 56.16 per 1000 person-years compared with 80.91 per 1000 person-years the year after ICI (IRR, 1.44; 95% CI, 1.21–1.72) (Table 2). Deaths after ICI occurred in 101 (45.1%) of the 224 patients with MACE and in 1015 (26.7%) of the 3800 patients without MACE ($p < 0.0001$).

We identified 10 (0.25%) patients with myocarditis after ICI initiation; 5 (50.0%) of the patients with myocarditis had a MACE claim compared with 219 (5.5%) of 4014 without myocarditis ($p < 0.001$). Most MACE claims in patients with myocarditis were on the same day as a myocarditis claim.

In the multivariable regression model (Table 3) risk factors independently associated with higher risk of MACE after ICI initiation included (1) older age (reference age group 18 to 54; IRR, 3.59; 95% CI, 1.82–7.10 for the age

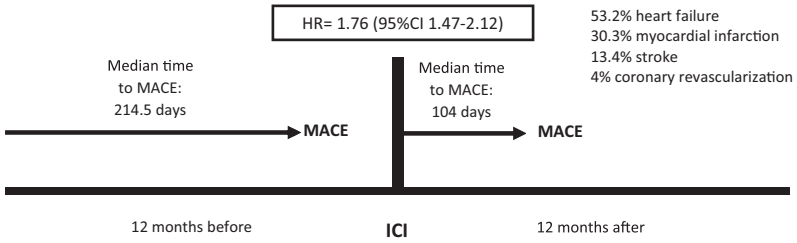

Figure 2. Time to first MACE before and after ICI.

ICI: immune checkpoint inhibitor; MACE: major adverse cardiovascular event.

Table 2. Incidence rate of MACE before and after ICI therapy initiation

Period	*N* total	*N* person-years	*N* MACE	IRR per 1000 Person-Years (95% CI)	IRR (95% CI)
1 year before ICI initiation	4024	4024	226	56.16 (49.98–63.98)	Reference
1 year after ICI initiation	4024	3880	314	80.91 (72.21–90.37)	1.44 (1.21–1.72)

ICI: immune checkpoint inhibitor; IRR: incidence rate ratio; MACE: major adverse cardiovascular events.

group 75 or older; IRR, 2.77; 95% CI, 1.41–5.42 for the age group 65 to 74; and IRR, 2.47; 95% CI, 1.16–5.23 for the age group 55 to 64); (2) MACE before ICI therapy, IRR, 2.21; 95% CI, 1.37 to 3.57; (3) other cardiovascular conditions (any conduction abnormality, heart failure, cardiomyopathy, myocarditis), IRR, 2.08; 95% CI, 1.38–3.15; and (4) hypertension (IRR, 1.62; 95% CI, 1.09–2.40). Table 3 shows all the variables included in the model.

DISCUSSION

We evaluated the risk of MACE after ICI therapy in patients with melanoma. Our results suggest that ICI may increase the risk of MACE in patients with melanoma during the first year after ICI, independently of whether patients had myocarditis as an irAE. These findings are consistent with our hypothesis that the increased inflammation produced by ICI might lead to higher rates of cardiovascular events.

One explanation could be that the increase in cardiovascular events may occur in association with ICI-associated myocarditis, a well-known irAE. Although it is a rare adverse event (overall incidence approximately 1% in patients receiving ICI), the mortality is high, ranging between 25 and 50%.[5] It was previously observed that up to 50% of the patients with ICI-related myocarditis experience an MACE, including heart failure, cardiac arrest, cardiogenic shock, and complete heart block and other arrythmias in a study in which 35 ICI-related myocarditis patients were compared with 105 patients treated with ICI who did not develop myocarditis.[19] In our study, 10 patients had myocarditis (0.25%) after ICI initiation and half of them also had an MACE claim. The incidence of ICI-associated myocarditis was also similar to that reported in the literature (0.09–2.4%).[20,21]

We also hypothesized that treatment with ICI might directly increase the risk of atherosclerotic events, and thus MACE events. There is a crucial role of inflammation in the progression and clinical manifestation of atherosclerosis given that most of the cardiovascular risk factors associated with atherosclerosis are part of the activation of inflammatory pathways.[22] About 10% of all the cells in the atherosclerotic plaque are T cells.[23] Among CD4+ T cells, Th1 cells are predominant and are most closely linked to atherogenesis because they produce inflammatory cytokines; PD-1 expression suppresses Th1 cytokine production, which might confer protection against atherosclerosis.[24] CTLA-4 might also have an immunoregulatory effect providing a protective role on atherogenesis. PD-1 inhibitors may reinvigorate exhausted T cells expressing PD-1 present in atherosclerotic plaques.[25] Calabretta et al[10] measured atherosclerotic activity with positron emission tomography (PET) in 12 patients with lymphoma pre and post therapy with ICI. They measured the 2-[18F] fluorodeoxyglucose (FDG) uptake values in 117 arterial segments and found that ICI resulted in a significant increase in inflammatory activity in the evaluated lesions in arterial segments without previous inflammation.[10] Similarly, a significant increase in the inflammatory activity in large arteries was observed in another study that included patients with melanoma treated with ICI.[26] A recently published study by Drobni et al[27] showed a seven times increase in aortic noncalcified plaque progression of patients with lung cancer on ICI compared with controls.

In our cohort, we observed a significantly increased risk of MACE within 1 year after ICI initiation compared with the year before ICI, in most cases unrelated to myocarditis. In a systematic review that included randomized controlled trials, there was not a statistically significant association of ICI with increased risk of cardiotoxicity.[28] However, there was a trend toward an increased risk of myocarditis (relative risk [RR], 1.11; 95% CI, 0.64–1.92), myocardial infarction (RR, 1.19; 95% CI, 0.63–2.23), and cardiac arrest (RR, 1.23; 95% CI, 0.61–2.47) in the group treated with ICI. Real-world studies have reported an increase in MACE after ICI[29–32]; however, our study is larger, including more than 4000 patients and we evaluated other important predictors of MACE. A single institutional study that included 2842 patients with cancer treated with ICI reported an increased risk of cardiovascular events within 3 years (composite of myocardial infarction, coronary revascularization, and ischemic stroke) compared with controls (HR, 3.3; 95% CI, 2.0–5.5).[29] In an additional case-crossover analysis, Drobni et al reported an increased risk of cardiovascular events after ICI initiation (IRR, 1.8; 95% CI, 1.4–2.4). This effect is larger than that estimated in our study. This difference may be related to differences in the study population, including the fact that they included other types of cancer and not only melanoma. Further, their controls were historical controls between 2008 and 2012 only, whereas the ICI patients received therapy up to 2019, and differences in diagnostic considerations for MACE events may have changed over time. In another retrospective study published in 2022 from a single tertiary center, the authors included 289 patients with melanoma treated with ICI and compared them with 357 patients with melanoma not treated with ICI and found a higher risk of MACE in the

Table 3. Risk factors associated with MACE after ICI: multivariable regression analysis

Covariates	IRR	Lower CI	Upper CI	*p*
Age group, years				
18–54 (Ref)				
55–64	2.47	1.16	5.23	0.019
65–74	2.77	1.41	5.42	0.003
75+	3.59	1.82	7.10	< 0.001
Sex				
Female (Ref)				
Male	1.13	0.77	1.66	0.526
Race				
White (Ref)				
Black	0.90	0.44	1.86	0.786
Other	0.64	0.34	1.18	0.152
Low-income subsidy				
Yes	1.08	0.58	2.01	0.814
No (Ref)				
Region				
Midwest (Ref)				
Northeast	1.07	0.64	1.78	0.797
South	1.14	0.76	1.70	0.522
West	0.94	0.57	1.54	0.806
Comorbidities				
0 (Ref)				
1	0.76	0.43	1.37	0.369
2+	1.22	0.70	2.14	0.485
Year of ICI initiation				
2011 to 2014 (Ref)				
2015 to 2016	0.81	0.36	1.79	0.598
2017 to 2021	0.85	0.41	1.79	0.675
Type of ICI				
Monotherapy (Ref)				
Combonation therapy	1.28	0.89	1.83	0.183
Glucocorticoids, mg				
Average daily dose	1.05	0.99	1.11	0.114
Total dose	0.99	0.99	1.00	0.08
Cardiac risk factors before ICI therapy				
MACE	2.21	1.37	3.57	0.001
Other CV conditions[a]	2.08	1.38	3.15	< 0.001
Preexisting atherosclerotic disease	1.31	0.85	2.03	0.226
Hypertension	1.62	1.09	2.40	0.016
Diabetes, insulin-dependent	1.82	0.96	3.44	0.066
Diabetes, non–insulin-dependent	1.20	0.82	1.75	0.356
Dyslipidemia	0.72	0.49	1.06	0.092
Treatment before ICI therapy				
Cardiotoxic	1.20	0.33	4.41	0.785
Not cardiotoxic	0.50	0.17	1.41	0.189
Treatment after ICI therapy				
Cardiotoxic	1.30	0.54	3.12	0.556
Not cardiotoxic	0.59	0.28	1.26	0.173

[a]Any conduction abnormality (includes arrhythmia and atrial fibrillation), chronic heart failure, cardiomyopathy, myocarditis.
CTLA-4: cytotoxic T-lymphocyte-associated antigen 4; CV: cardiovascular; ICI: immune checkpoint inhibitor; MACE: major adverse cardiovascular event; PD-1: programmed cell death 1; PD-L1: programmed death ligand 1; Ref: reference.

ICI group (adjusted HR, 2.8; 95% CI, 1.1–6.9).[30] The point estimate is higher than ours (HR, 1.76); however, in that smaller study, the CI is wider, and the real effect might be lower and closer to that observed in our study. Jain et al[31] conducted a retrospective cohort study that used a different database that demonstrated higher incidences of cardiovascular events related to ICI than those reported in the literature previously given their inclusion of various other cardiovascular events in addition to MACE (e.g., arrhythmias and pericarditis).[32] They observed that the median time to the first cardiovascular adverse event was significantly shorter in patients who received ICI (about 3 months) compared with those who did not receive ICI (about 8 months).

With regard to the predictors of MACE after ICI, we observed that older age, history of MACE before ICI, other cardiovascular conditions (any conduction abnormality, heart failure, cardiomyopathy, myocarditis), and

hypertension were significantly associated with higher risk of MACE within the first year after initiation of ICI. Jain et al[31] also observed a higher risk of cardiovascular events associated with advanced age and treatment with a CTLA-4 inhibitor. That is different from our results in which we did not find that the type of ICI was associated with higher risk of MACE. Similar to their findings, we did not observe any association of MACE with prior treatment with cardiotoxic therapy, which provides more evidence that prior cardiotoxic therapy does not increase risk of MACE with ICI. Among the prior cardiovascular risk factors associated with an increased risk of MACE, we observed that prior MACE, other cardiovascular conditions, and hypertension were all independently associated with increased risk of MACE after ICI. Wang et al[30] also observed a higher risk of MACE after ICI in patients with a past history of MACE.irAEs are often treated with glucocorticoids. A retrospective study showed that 38% of the patients with melanoma treated with ICI received glucocorticoids.[33] Glucocorticoids are associated with cardiovascular risk factors, atherosclerosis, and cardiovascular events.[34,35] However, in our study, in the multivariable model, glucocorticoid therapy was not associated with an increased risk of MACE after ICI, which could be related to the anti-inflammatory properties of steroids suppressing some of the immune-related increase in inflammation in patients receiving ICI, at least in the short term.

As cancer screening and treatment improve, the number of cancer survivors increases with an estimation of more than 16 million cancer survivors in the United States in 2019 and a projection to reach more than 22 million in 2030.[36] Because there are several cancer treatments that increase the risk of cardiovascular complications, monitoring the cardiovascular health of cancer survivors is essential. Most of the clinical practice guidelines did not include specific recommendations regarding the screening, monitoring, or surveillance of cardiovascular health in patients receiving ICI.[37] Therefore, the results of the present study contribute to the body of evidence showing that ICIs are associated with increased risk of MACE. Furthermore, MACE is associated with a 3-fold increase in healthcare costs.[38] Therefore, preventive strategies such as optimizing the control of hyperlipidemia and hypertension may need to be emphasized concurrent to the receipt of ICI therapy for cancer.

This study has several strengths. To the best of our knowledge, this study analyzed the largest cohort of patients with melanoma treated with ICI to evaluate the risk of MACE after ICI therapy. We used two different approaches to evaluate the risk of MACE after ICI therapy; first we calculated the time to first MACE before and after ICI, and then, because one patient could contribute to more than one event, we also calculated the incidence rate pre- and post-ICI per 1000 person-years. We also evaluated the predictors of MACE after ICI therapy, and we included several covariates including prior cardiovascular disease and atherosclerotic disease, the use of melanoma cardiotoxic drugs, and the use of glucocorticoids, which can also contribute to the risk for cardiovascular events.

The findings of our study should be examined in the context of limitations. First, the inherent risk of bias of retrospective cohort studies, especially related to the adjustment for other known and unknown confounders, cannot be excluded. Among other known confounders, we were not able to adjust for the stage of the disease. Second, we were not able to adjust for cancer stage, although given the period of the study, given FDA approvals, most patients were likely to have metastatic grade IV melanoma. Finally, we cannot ascertain the impact of advanced cancer per se on the development of MACE. However, important factors that might contribute to cardiovascular morbidity, such as the use of glucocorticoids or the treatment with cardiotoxic drugs, were not associated with increased risk of MACE after ICI. Second, the follow-up period after ICI was only for 1 year, whereas the inflammatory state and its effects on atherosclerotic progression initiated by ICI therapy may continue for a longer period. It is therefore plausible that the risk of MACE may increase over time with longer follow-up. Third, although we evaluated the incidence of myocarditis and its potential association with MACE, we did not evaluate other irAEs with potential association with higher risk of MACE, such as pneumonitis. We are also unable to ascertain if some myocarditis events are undiagnosed and reported as MACE events only. Finally, sudden death due to acute myocardial infarction may not be included given we do not have causes of death for the cohort.

CONCLUSION

In patients with melanoma, ICI treatment might be associated with increased risk of MACE during the first year of therapy. Additional studies are needed to evaluate the long-term effects of ICI on cardiovascular outcomes and the potential impact of other risk factors including other irAEs.

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