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Prospective Cardiovascular Surveillance of Immune Checkpoint Inhibitor–Based Combination Therapy in Patients With Advanced Renal Cell Cancer: Data From the Phase III JAVELIN Renal 101 Trial

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abstract

PURPOSE Both immune checkpoint inhibitors (ICIs) and vascular endothelial growth factor receptor (VEGFR) inhibitors are approved for advanced renal cell carcinoma treatment and can cause cardiovascular events (CVs); thus, combination therapy could lead to major adverse CV events (MACE). Cardiac serum biomarker assessment and imaging, including left ventricular ejection fraction (LVEF) monitoring, can be used to evaluate MACE.

METHODS To our knowledge, the JAVELIN Renal 101 trial, assessing avelumab plus axitinib versus sunitinib in patients with advanced renal cell carcinoma, is the first randomized study of ICI plus VEGFR inhibitor treatment to include prospective serial cardiac monitoring of LVEF and serum cardiac biomarkers.

RESULTS MACE (defined as grade ≥ 3 CV AEs) occurred in 31 patients (7.1%) in the combination arm and 17 patients (3.9%) in the sunitinib arm. Patients in the combination arm who had high baseline troponin T values were at higher risk of MACE versus patients with low values (MACE in 6/35 *v* 7/135, respectively; relative risk, 3.31; 95% CI, 1.19 to 9.22). This association was not observed in patients treated with sunitinib. Other CV baseline risk factors and serum cardiac biomarkers were not significantly predictive for MACE, although a trend toward an association with dyslipidemia was seen in the combination arm. No clinical value of on-treatment routine monitoring of LVEF in relation to MACE was observed. Although LVEF decline was significantly more frequent in the combination arm, most patients recovered, and decline was not associated with other significant cardiac events or symptoms.

CONCLUSION Patients with high baseline troponin T levels receiving ICI and VEGFR combinations may need to be monitored more closely for MACE. Routine monitoring of LVEF in asymptomatic patients is not recommended.

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INTRODUCTION

Combination therapy with immune checkpoint inhibitors (ICIs; anti–programmed death ligand 1 or anti–programmed death 1) and vascular endothelial growth factor (VEGF) pathway inhibitors is an effective treatment for several tumor types, including advanced renal cell carcinoma (aRCC).[1-6] Cardiovascular (CV) adverse events (AEs), including hypertension, cardiomyopathy, cardiac failure, and thromboembolic events, are a well-characterized occurrence with VEGF receptor (VEGFR) inhibitor monotherapy.[7-9] ICIs can cause inflammatory CV AEs, including myocarditis, pericarditis, vasculitis, and arrhythmias.[10-12] Although ICI-related myocarditis occurs in only approximately 1% of ICI-treated patients,[13] it has a high fatality rate (46%) and almost 80% of events occur within six weeks of treatment initiation,[14] highlighting a need for early detection.[15] ICI combination therapy involving an anticytotoxic T-cell lymphocyte-4 antibody and an anti–programmed death 1/programmed death ligand 1 antibody is associated with a higher risk of myocarditis compared with monotherapy.[10] Whether the risk of CV AEs is increased when ICIs are combined with VEGFR inhibitors is unknown. The role of serum cardiac biomarkers in patients receiving potentially cardiotoxic anticancer treatments, including ICIs, has been explored.[16,17] However, the impact of comorbidities, complete clinical features and characteristics, timing, and outcomes of immune-mediated CV AEs remain unclear.[14,15,18]

In the JAVELIN Renal 101 phase III trial, avelumab plus axitinib significantly improved progression-free survival and the objective response rate versus

ASSOCIATED CONTENT

Data Supplement

Protocol

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

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CONTEXT

Key Objective

Are left ventricular ejection fraction decline or serum cardiac biomarker levels predictive for major adverse cardiovascular events (MACE) in patients with advanced renal cell carcinoma receiving immune checkpoint inhibitor plus vascular endothelial growth factor receptor inhibitor combination therapy?

Knowledge Generated

Routine cardiac monitoring showed that patients with high baseline levels of troponin T in their blood were at higher risk of MACE when treated with avelumab plus axitinib versus patients with low levels of troponin T. Left ventricular ejection fraction decline was not associated with MACE.

Relevance

Patients with high levels of troponin T at baseline before immune checkpoint inhibitor plus vascular endothelial growth factor receptor inhibitor combination treatment may need to be monitored more closely for MACE.

sunitinib in previously untreated patients with aRCC.[3,5] Unlike other phase III trials of ICI plus VEGFR inhibitor treatment, left ventricular ejection fraction (LVEF) and serum cardiac biomarkers were assessed prospectively. Here, we analyzed the incidence of major adverse CV events (MACE) in patients with aRCC receiving avelumab plus axitinib versus sunitinib in this trial, including the association between MACE and changes in LVEF or baseline levels of serum cardiac biomarkers.

METHODS

Study Design and Participants

The design of the JAVELIN Renal 101 trial has been reported in detail previously.[3] Patients with aRCC were randomly assigned to receive avelumab (10 mg/kg) intravenously every 2 weeks plus axitinib (5 mg) orally twice daily or sunitinib (50 mg) orally once daily for 4 weeks (6-week cycle). Random assignment was stratified according to Eastern Cooperative Oncology Group performance status (0 *v* 1) and geographic region (United States *v* Canada and Western Europe *v* the rest of the world). Inclusion and exclusion criteria have been reported previously.[3,5] CV exclusion criteria included LVEF below the lower limit of normal (LLN) for the institution as assessed by either multigated acquisition (MUGA) scan or echocardiogram (ECHO). Full CV exclusion criteria are provided in the Data Supplement (online only).

An external data monitoring committee reviewed efficacy and safety. An independent cardiac events adjudication committee (CAC) reviewed CV AEs to confirm the diagnosis and relationship to study treatment (detailed in the Data Supplement). Schedules for MUGA scan or ECHO assessments and cardiac biomarker investigation are provided in the Data Supplement. Grade ≥ 3 CV AEs (MACE), including myocarditis, LVEF change from baseline, and cardiac serum biomarker analysis at baseline and the first 16 weeks on treatment, were assessed as AEs of specific interest.

This trial was conducted in accordance with the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines defined by the International Council for Harmonisation. All patients provided written, informed consent before enrollment. The Protocol (online only) was approved by the institutional review board or independent ethics committee at each participating center.

MACE and Baseline CV Risk Factors

MACE were defined according to NCI CTCAE version 4.3 and, consistent with US Food and Drug Administration guidance, included grade ≥ 3 CV AEs of cardiac deaths, fatal stroke, nonfatal myocardial infarction, nonfatal congestive heart failure, nonfatal myocarditis, nonfatal arrhythmia, and nonfatal stroke. Myocarditis was diagnosed by investigators on the basis of new onset of cardiac signs or symptoms, new laboratory cardiac biomarker elevations, and cardiac imaging abnormalities suggestive of myocarditis. Suspected myocarditis events were reviewed by CAC and categorized as definite, probable, and possible per a consensus statement (Data Supplement).[19] The relative risk of MACE was correlated with a prespecified list of baseline CV risk factors, which included age, sex, smoking status, body mass index, and medical history of hypertension, dyslipidemia, diabetes mellitus, and CNS vascular conditions.

LVEF

LVEF was assessed at baseline and day 1 of every two cycles using either MUGA scan or ECHO, per local site practice/preference. LVEF decline was defined as a ≥ 10-point reduction from baseline to a value below the LLN.

Serum Cardiac Biomarkers

After consultation with the US Food and Drug Administration, serum cardiac biomarker monitoring in the first 16 weeks of treatment was added to the protocol while the study was ongoing to assess whether routine monitoring would improve early detection of myocarditis. Cardiac biomarkers (troponin [I or T], B-type natriuretic peptide

TABLE 1. Patient Demographics at Baseline

Characteristic	Avelumab Plus Axitinib (n = 442)	Sunitinib (n = 444)
Age, years, median (range)	62.0 (29.0-83.0)	61.0 (27.0-88.0)
Sex, No. (%)		
Male	316 (71.5)	344 (77.5)
Female	126 (28.5)	100 (22.5)
Geographic region, No. (%)		
United States	128 (29.0)	130 (29.3)
Canada and Western Europe	128 (29.0)	128 (28.8)
Rest of the world	186 (42.1)	186 (41.9)
Smoking history, No. (%)		
Never	220 (49.8)	213 (48.0)
Current	43 (9.7)	49 (11.0)
Former	176 (39.8)	181 (40.8)
Not reported	3 (0.7)	1 (0.2)
BMI, kg/m^2, median (range)	27.45 (15.5-52.6)	27.36 (15.5-53.2)
Select medical history, ongoing, No. (%)		
Hypertension	269 (60.9)	242 (54.5)
Dyslipidemia	19 (4.3)	10 (2.3)
Diabetes mellitus	42 (9.5)	34 (7.7)
CNS vascular conditions	14 (3.2)	7 (1.6)
Baseline cardiac biomarker levels, No. (%)[a]		
Troponin T	n = 162	n = 186
Low	0	1 (0.5)
Normal	129 (79.6)	149 (80.1)
High	33 (20.4)	36 (19.4)
Troponin I	n = 209	n = 186
Low	32 (15.3)	22 (11.8)
Normal	173 (82.8)	162 (87.1)
High	4 (1.9)	2 (1.1)
BNP	n = 169	n = 139
Low	0	0
Normal	152 (89.9)	116 (83.5)
High	17 (10.1)	23 (16.5)
NT-proBNP	n = 131	n = 168
Low	1 (0.8)	1 (0.6)
Normal	83 (63.4)	116 (69.0)
High	47 (35.9)	51 (30.4)
CK-MB	n = 258	n = 266
Low	5 (1.9)	5 (1.9)
Normal	244 (94.6)	246 (92.5)
High	9 (3.5)	15 (5.6)

Abbreviations: BMI, body mass index; BNP, B-type natriuretic peptide; CK-MB, creatine kinase MB; NT-proBNP, N-terminal proB-type natriuretic peptide.

[a]The denominator used to calculate percentages for baseline cardiac biomarker levels (shown in each cell) is the number of patients with a baseline assessment and ≥ 1 postbaseline assessment for each parameter in each treatment arm. Low = below lower limit of normal range; normal = within the normal range; high = above the upper limit of normal range.

[BNP], N-terminal proBNP [NT-proBNP], and creatine kinase MB [CK-MB]) were measured at baseline on cycles 1, 2, and 3, on days 1, 15, and 29 of all three cycles, and when clinically indicated (Data Supplement). Cardiac biomarker data were assessed locally, and sites could monitor either troponin T or troponin I and BNP or NT-proBNP on the basis of site practice/preference. Low or high levels of biomarkers were defined as those below the investigator-defined LLN or upper limit of normal ranges, respectively. Normal levels of biomarkers were those within the normal range.

Statistical Analysis

The LVEF percentage was summarized using descriptive statistics of actual values and changes from baseline for each visit over time, and was summarized as frequency of patients with ≥ 10-point decline from baseline to a value below the LLN during treatment. The *P* value was calculated using the two-proportions *Z*-test. MACE were tabulated using descriptive statistics. MACE during the on-treatment period and with onset on or after LVEF decline were summarized. Cardiac biomarkers were summarized descriptively. Shift summaries of cardiac biomarker test results by baseline and worst on-treatment assessment were provided. Associations between baseline risk factors or cardiac biomarkers with MACE were described using relative risk and 95% CIs. Risk difference for MACE between study arms was computed. CIs were based on the unconditional exact method by Santner and Snell and were not adjusted for multiplicity, and the *P* value was calculated using asymptotic chi-square distribution.

RESULTS

Baseline Demographics

Between March 29, 2016, and December 19, 2017, 886 patients were assigned to avelumab plus axitinib (n = 442) or sunitinib (n = 444) arms; 873 patients received study treatment (434 and 439, respectively) and were evaluated for safety. At the data cutoff (June 20, 2018 [first interim analysis]; minimum follow-up of 6 months in all patients), median exposure to avelumab, axitinib, and sunitinib was 37.2 weeks (range, 2.0-110.0 weeks), 39.2 weeks (range, 0.1-108.3 weeks), and 31.7 weeks (range, 0.9-99.9 weeks), respectively. Approximately 60% of patients in each arm had a history of hypertension; other cardiac risk factors were not prevalent (Table 1).

MACE

MACE were reported in 31 patients (7.1%) in the avelumab plus axitinib arm and 17 patients (3.9%) in the sunitinib arm (Table 2). After adjusting for exposure to study treatment, the difference between arms was smaller than in the comparison of nonadjusted data (Data Supplement). Median time to first onset of MACE was 7.7 weeks (range, 0.1-73.3 weeks) in the combination arm and 17.6 weeks (range, 2.0-44.0 weeks) in the sunitinib arm (Data Supplement). Six patients (1.4%) in

TABLE 2. Summary of MACE During the On-Treatment Period (safety analysis set)

	Avelumab Plus Axitinib (n = 434)	Sunitinib (n = 439)	Avelumab Plus Axitinib *v* Sunitinib	
MACE	**No. (%)**	**No. (%)**	**Risk Difference**	**95% CI**
MACE, total	31 (7.1)	17 (3.9)	0.033	–0.034 to 0.099
Cardiac deaths	6 (1.4)	1 (0.2)	0.012	–0.055 to 0.078
Cardiopulmonary failure	0 (0)	1 (0.2)	—	—
Death	4 (0.9)	0 (0)	—	—
Myocarditis	1 (0.2)	0 (0)	—	—
Sudden death	1 (0.2)	0 (0)	—	—
Fatal stroke	1 (0.2)	1 (0.2)	0.000	–0.066 to 0.066
Cerebrovascular accident	1 (0.2)	1 (0.2)	—	—
Nonfatal arrhythmia	4 (0.9)	1 (0.2)	0.007	–0.060 to 0.073
Atrial fibrillation	4 (0.9)	0 (0)	—	—
Electrocardiogram QT prolonged	0 (0)	1 (0.2)	—	—
Nonfatal congestive heart failure	7 (1.6)	3 (0.7)	0.009	–0.057 to 0.076
Cardiac failure	1 (0.2)	0 (0)	—	—
Ejection fraction decreased	6 (1.4)	3 (0.7)	—	—
Nonfatal myocardial infarction	9 (2.1)	3 (0.7)	0.014	–0.053 to 0.080
Acute coronary syndrome	2 (0.5)	0 (0)	—	—
Acute myocardial infarction	3 (0.7)	0 (0)	—	—
Angina pectoris	0 (0)	2 (0.5)	—	—
Coronary artery disease	0 (0)	1 (0.2)	—	—
Coronary artery occlusion	1 (0.2)	0 (0)	—	—
Myocardial ischemia	0 (0)	1 (0.2)	—	—
Troponin I increased	1 (0.2)	0 (0)	—	—
Troponin T increased	1 (0.2)	0 (0)	—	—
Nonfatal myocarditis	1 (0.2)	0 (0)	0.002	–0.064 to 0.069
Myocarditis	1 (0.2)	0 (0)	—	—
Nonfatal stroke	3 (0.7)	8 (1.8)	–0.011	–0.078 to 0.055
Brain hypoxia	0 (0)	1 (0.2)	—	—
Cerebellar hemorrhage	0 (0)	1 (0.2)	—	—
Cerebrovascular accident	2 (0.5)	2 (0.5)	—	—

NOTE. The denominator to calculate percentages is the number of patients in the safety analysis set within each treatment group. CIs for the risk difference were based on the unconditional exact method by Santner and Snell and were not adjusted for multiplicity.

Abbreviations: MACE, major adverse cardiovascular events; QT, interval from beginning of QRS complex to end of T wave.

the avelumab plus axitinib arm and one patient (0.2%) in the sunitinib arm had cardiac death; one patient in each treatment arm had a fatal stroke. More cardiac AEs occurred with avelumab plus axitinib and more nonfatal CNS vascular events occurred with sunitinib.

The difference in MACE rates between study arms could not be attributed to higher hypertension rates with avelumab plus axitinib (52.1%) versus sunitinib (39.0%) because MACE rates were similar in patients with or without hypertension (7.5% *v* 6.8%, respectively; Data Supplement). Within the avelumab plus axitinib arm, most patients with MACE had one or two CV risk factors at baseline (28/31 [90.3%]). No significant correlation was observed between MACE and the baseline risk factors evaluated, except for a trend toward an association with dyslipidemia in the avelumab plus axitinib arm (Table 3).

Seven cases of myocarditis were reported (Data Supplement). Two events in the avelumab plus axitinib arm were assessed as definite myocarditis by the CAC (one fatal). Five events did not meet the criteria for definite myocarditis; two probable and two possible with avelumab plus axitinib, and one possible with sunitinib. The first case of definite myocarditis was a 55-year-old man who experienced a nonfatal event with onset after a single dose of avelumab with symptoms of cardiac failure; troponin levels were normal. The cardiac magnetic resonance imaging was consistent

TABLE 3. Relative Risk of MACE by Baseline Characteristics (safety analysis set)

	Avelumab Plus Axitinib (n = 434)			Sunitinib (n = 439)		
Characteristic	**MACE, No.**	**No MACE, No.**	**Relative Risk of MACE (95% CI)**	**MACE, No.**	**No MACE, No.**	**Relative Risk of MACE (95% CI)**
Age, years						
≥ 75	4	29	1.80 (0.67 to 4.84)	0	40	0
< 75	27	374		17	382	
Sex						
Male	21	288	0.85 (0.41 to 1.75)	12	327	0.71 (0.26 to 1.96)
Female	10	115		5	95	
Smoking status						
Smoker	13	200	0.79 (0.39 to 1.58)	9	220	1.03 (0.40 to 2.61)
Nonsmoker	17	202		8	201	
BMI						
≥ 30	11	116	1.31 (0.65 to 2.66)	6	133	1.27 (0.47 to 3.43)
< 30	20	283		10	285	
Blood pressure status						
Hypertension	24	250	2.00 (0.88 to 4.54)	13	240	2.39 (0.79 to 7.21)
No hypertension	7	153		4	182	
Lipid status						
Dyslipidemia	10	72	2.04 (1.00 to 4.17)	3	66	1.15 (0.34 to 3.89)
No dyslipidemia	21	331		14	356	
Blood glucose status						
Diabetes	4	76	0.66 (0.24 to 1.82)	5	72	1.96 (0.71 to 5.40)
No diabetes	27	327		12	350	
CNS vascular/cardiac condition						
Present	7	58	1.66 (0.74 to 3.68)	4	49	2.24 (0.76 to 6.62)
Not present	24	345		13	373	

Abbreviations: BMI, body mass index; MACE, major adverse cardiovascular events.

with myocarditis but the cardiac biopsy was negative. The patient was treated with high-dose steroids but relapsed (both clinically and by imaging) during steroid tapering. The event resolved after a second cycle of high-dose steroids with prolonged tapering. The second case of definite myocarditis was an 80-year-old woman who experienced myocarditis with onset after two doses of avelumab. The patient developed high troponin levels. Although initially asymptomatic, the clinical presentation rapidly evolved with several episodes of ventricular arrhythmia. Cardiac magnetic resonance imaging was not performed. The patient was treated with high-dose steroids from day 9 after clinical onset. The myocarditis was fatal; no autopsy was performed.

LVEF

The maximum LVEF decrease from baseline per patient during treatment and LVEF changes from baseline during the treatment period are shown (Fig 1). In the avelumab plus axitinib and sunitinib arms, 37 patients (8.5%) and seven patients (1.6%), respectively ($P < .0001$), experienced an LVEF decline (as defined in the Methods section) during treatment (Table 4). Decline in LVEF was noted as early as week 6 of treatment and nearly 80% occurred within the first year on treatment (Data Supplement). The median time to onset of LVEF decline was longer with avelumab plus axitinib versus sunitinib (18.1 *v* 7.6 weeks, respectively). At week 14, among the 37 patients who had LVEF decline with avelumab plus axitinib, 22 (59.5%) had recovered to an LVEF value above the LLN and 15 (40.5%) had not recovered. No correlation between LVEF decline and MACE was observed in either arm. Among patients who had an LVEF decline with avelumab plus axitinib, one had cardiac death and one discontinued avelumab only (Data Supplement). No patient in the sunitinib arm had MACE following an LVEF decline. Asymptomatic LVEF decrease was not an indication for treatment modification per study protocol.

Serum Cardiac Biomarker Analysis

Baseline levels of serum cardiac biomarkers and changes from baseline are shown in Table 1 and the Data

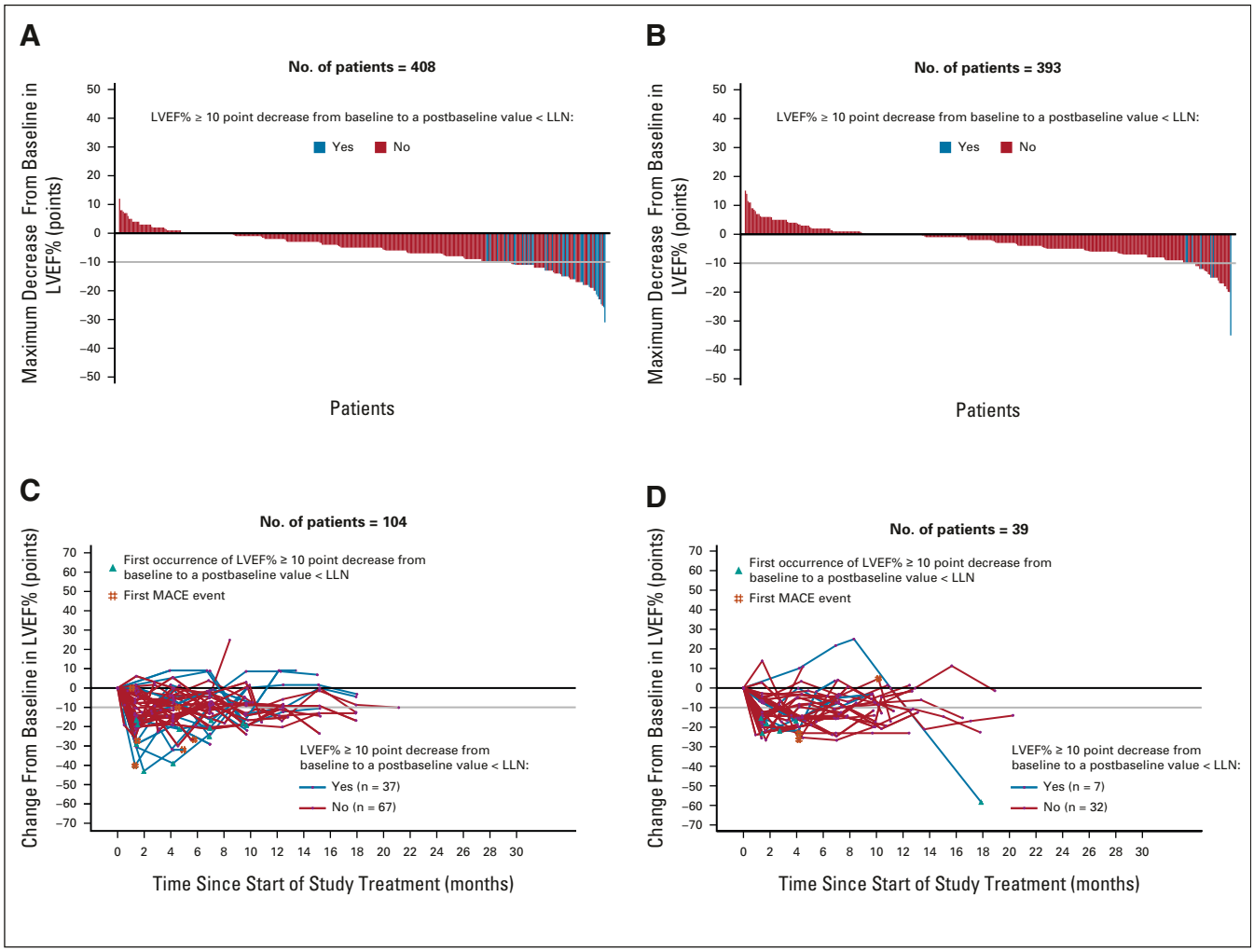

FIG 1. Waterfall plot of maximum decrease in LVEF from baseline during therapy and change from baseline in LVEF during the on-treatment period (patient with LVEF% decrease ≥ 10 points from baseline) with (A, C) avelumab plus axitinib or (B, D) sunitinib. LLN, lower limit of normal; LVEF, left ventricular ejection fraction; MACE, major adverse cardiovascular events.

Supplement, respectively. In both arms, similar proportions of patients had high (above the upper limit of normal range) troponin T levels at baseline (20.4% with avelumab plus axitinib *v* 19.4% with sunitinib). In the sunitinib arm versus the avelumab plus axitinib arm, a higher proportion had normal baseline troponin T and at least one high troponin T value on treatment (22.0% *v* 13.0%, respectively). Baseline troponin I levels were high in 1.9% in the avelumab plus axitinib arm versus 1.1% in the sunitinib arm. In both arms, a similar proportion had low or normal baseline troponin I and developed at least one high value on treatment (8.6% with avelumab plus axitinib *v* 8.1% with sunitinib). The median time to onset of high troponin levels (combined troponin I and T analysis) was 4.1 weeks in both arms.

In the avelumab plus axitinib arm, a higher proportion of patients with high baseline troponin T developed MACE versus patients without high baseline troponin T (6/35 [17.1%] *v* 7/135 [5.2%]; relative risk, 3.31; 95% CI, 1.19 to 9.22; Table 5). This difference was statistically significant at the 0.05 level ($P = .022$). In the sunitinib arm, occurrence of MACE was not significantly different between patients with or without high baseline troponin T levels. Occurrence of MACE did not correlate with baseline levels of other cardiac biomarkers in either arm (Table 5). Baseline cardiac biomarkers were not predictive of myocarditis, potentially because of its rarity in the study population. Of the seven patients with myocarditis, troponin levels were measured at baseline in six patients (troponin T in three patients and troponin I in four patients), and troponin T was high in one patient.

Of 65 patients in the avelumab plus axitinib or sunitinib arm who had a normal baseline troponin T and at least one high troponin T value on treatment (n = 21 and n = 41, respectively), one patient in each arm developed MACE (myocarditis and nonfatal stroke, respectively). Of 31 patients who had a normal baseline troponin I and at least one high troponin I value while on treatment (avelumab plus axitinib, n = 16; sunitinib, n = 15), MACE occurred in four patients

TABLE 4. Summary of Patients With LVEF% Decrease of at Least 10 Points From Baseline to a Postbaseline Value Below the LLN During On-Treatment Period—Safety Analysis Set

Left Ventricular Ejection Fraction Characteristic	Avelumab Plus Axitinib (n = 434)	Sunitinib (n = 439)
Patients with LVEF% ≥ 10-point decrease from baseline to a postbaseline value < LLN, No. (%)[a]	37 (8.5)	7 (1.6)
Time to onset of LVEF% ≥ 10-point decrease from baseline to postbaseline value < LLN, median, weeks[b]	18.1	7.6
Recovery		
Time to LVEF recovery, median, weeks	12.1	12.2
Recovered, No. (%)[c]	22 (59.5)	4 (57.1)
Ongoing, No. (%)[d]	15 (40.5)	3 (42.9)

Abbreviations: LLN, lower limit of normal; LVEF, left ventricular ejection fraction.

[a]The denominator to calculate percentages is the number of patients in the safety analysis set within each treatment group.

[b]Time to first onset of LVEF% decrease of at least 10 points from baseline to a postbaseline value below the LLN (weeks) = (earliest onset date of LVEF% ≥ 10-point decrease from baseline to postbaseline value < LLN during the on-treatment period – date of first dose of study treatment + 1)/7.

[c]The denominator to calculate percentages is the number of patients in the safety analysis set with LVEF% decrease of at least 10 points from baseline to a postbaseline value below the LLN.

[d]LVEF recovery is defined as LVEF% decrease that has recovered to a value of at least the LLN after an at least 10-point decrease from baseline to a postbaseline value below the LLN during the on-treatment period.

(avelumab plus axitinib: nonfatal congestive heart failure [n = 2], nonfatal myocardial infarction; sunitinib: fatal stroke).

DISCUSSION

Both ICIs and VEGFR inhibitors have been associated with CV AEs of different types, creating a theoretical potential for an increased incidence of MACE with combination treatment. To our knowledge, JAVELIN Renal 101 is the first trial where LVEF and serum cardiac biomarkers were assessed prospectively in patients treated with an ICI plus VEGFR inhibitor. Serial cardiac imaging (ECHO or MUGA to measure LVEF changes) and measurement of serum biomarker (troponin T and I, BNP, NT-proBNP, and CK-MB) levels were evaluated per institutional standard practice, and their predictive correlation with MACE was assessed. Of particular interest were troponin T and I, which are biomarkers of myocardial inflammation and damage from myocarditis.[20,21] One study found that troponin T was elevated in 94% of ICI-associated myocarditis cases, and the degree of elevation was a predictor of MACE.[13]

Although MACE were more frequent with avelumab plus axitinib versus sunitinib, the difference was not statistically significant, and the difference between arms was reduced in exposure-adjusted analyses. Although most patients with MACE had at least one baseline CV risk factor, no statistically significant associations with MACE were observed, except for a trend toward an association with dyslipidemia with avelumab plus axitinib. One patient in each treatment arm had a fatal stroke, and six patients (1.4%) and one patient (0.2%) had cardiac death in the avelumab plus axitinib and sunitinib arms, respectively.

Consistent with studies of ICI monotherapy, definite myocarditis with avelumab plus axitinib was rare (< 1%).[10,14,22] Routine monitoring of baseline serum cardiac biomarkers in asymptomatic patients was not found to be useful for early identification of myocarditis in this study. For patients with suspected immune-related myocarditis receiving combination ICI/VEGFR inhibitor therapy, aggressive management including high-dose prednisolone (1-2 mg/kg) has been recommended.[23]

LVEF decline was more frequent with avelumab plus axitinib versus sunitinib. The timing of LVEF assessment (on day 1 of treatment cycles, ie, during daily axitinib treatment in the combination arm but after 2 weeks off treatment in the sunitinib arm) may explain the increased occurrence of LVEF decline in the avelumab plus axitinib arm; this limitation was also highlighted in the ASSURE cardiac substudy of sunitinib and sorafenib.[24] In the combination arm, most patients with an LVEF decline recovered with or without dose modification of study drugs, and the decline was not associated with significant cardiac events or symptoms. On the basis of these findings, routine monitoring of LVEF in asymptomatic patients treated with an ICI plus VEGFR inhibitor or VEGFR inhibitor monotherapy is not recommended.

The role of serum cardiac biomarkers in assessing patients before ICI treatment is unknown. In this study, baseline levels of troponin T were high in approximately 20% of patients in both treatment arms. In the avelumab plus axitinib arm, MACE were more common in patients with high troponin T levels at baseline. Previous studies have reported that elevated troponin T levels are more likely in patients with renal impairment.[25,26] In the JAVELIN Renal 101 trial, 80% of patients had undergone a prior nephrectomy,[3] which might have influenced the observed correlation between MACE and a high baseline troponin T level in this analysis. We suggest that baseline assessment of troponin T levels may be considered when starting treatment with an ICI plus a VEGFR inhibitor, particularly in patients with CV risk factors. Patients with high troponin T levels should be monitored closely for cardiac symptoms during treatment, potentially including ECG monitoring, and a cardiologist should be involved in patient management from the outset of treatment. However, because of the small number of patients with MACE in our study, the predictive value of serum biomarkers other than troponin T cannot be ruled out. In addition, variability in the sensitivity of troponin T and I assays have been reported, which may

TABLE 5. Relative Risk of MACE by Serum Cardiac Biomarker Levels at Baseline

	Avelumab Plus Axitinib (n = 434)			Sunitinib (n = 439)		
Cardiac Serum Biomarker	MACE, No.	No MACE, No.	Relative Risk of MACE (95% CI)	MACE, No.	No MACE, No.	Relative Risk of MACE (95% CI)
Troponin T						
High	6	29	3.31 (1.19 to 9.22)	2	39	0.89 (0.2 to 3.98)
Not high	7	128		9	156	
Troponin I						
High	0	4	0	0	2	0
Not high	15	206		6	203	
BNP						
High	2	15	2.04 (0.48 to 8.68)	0	25	0
Not high	9	147		2	125	
NT-proBNP						
High	7	45	2.34 (0.78 to 7)	1	53	0.29 (0.04 to 2.28)
Not high	5	82		8	118	
CK-MB						
High	2	8	2.68 (0.72 to 9.98)	0	16	0
Not high	19	236		11	256	

Abbreviations: BNP, B-type natriuretic peptide; CK-MB, creatine kinase MB; MACE, major adverse cardiovascular events; NT-proBNP, N-terminal proBNP.

affect analyses of correlation with MACE.[27,28] Larger studies are needed to confirm the findings in this study.

Our study has several potential limitations. Biomarker assays were not standardized between study sites, potentially causing variation in sensitivity limits.[16] Additionally, clinicians were permitted to monitor the biomarkers that were convenient and feasible at each study site; thus, all biomarkers were not monitored at all study sites and some biomarkers had a small sample size. On-treatment electrocardiogram measurements were not reported in this study; this measurement was only performed at baseline, and serial monitoring was not required if there were no signs of arrhythmias at baseline. It was also not possible to separate cardiotoxicity associated with ICI versus VEGFR inhibitor treatment in the avelumab plus axitinib arm; hence, the drug causing MACE could not be distinguished. Finally, the study provided data only for avelumab plus axitinib treatment; similar prospective studies of other ICI-based combinations are needed to confirm findings and enable broader recommendations to be established.

In conclusion, the cardiac safety profile of avelumab plus axitinib did not show any new safety concerns compared with the known safety profiles seen in previous monotherapy studies. Although MACE were more frequently observed with avelumab plus axitinib versus sunitinib, the overall incidence of MACE was low in both arms. Routine cardiac investigations in asymptomatic patients were not useful for early detection of CV AEs, including myocarditis. MACE were not associated with LVEF decline or with hypertension or most other baseline risk factors. However, high baseline troponin T levels were predictive of MACE with avelumab plus axitinib, suggesting that patients found to have high troponin T levels may require additional cardiac monitoring. Cardiac history should not exclude patients from receiving ICI plus VEGFR combination therapy.

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CLINICAL TRIAL INFORMATION

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DATA SHARING STATEMENT

Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual deidentified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Prospective Cardiovascular Surveillance of Immune Checkpoint Inhibitor–Based Combination Therapy in Patients With Advanced Renal Cell Cancer: Data From the Phase III JAVELIN Renal 101 Trial

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