ORIGINAL RESEARCH

Clinical Outcomes Among Immunotherapy-Treated Patients With Primary Cardiac Soft Tissue Sarcomas

A Multicenter Retrospective Study

Amin H. Nassar, MD,[a,*] Edward El-Am, MD,[b,*] Ryan Denu, MD,[c] Sarah Abou Alaiwi, MD,[d] Talal El Zarif, MD,[d]
Walid Macaron, MD,[c] Noha Abdel-Wahab, MD, PHD,[c] Aakash Desai, MD,[e] Caleb Smith, MD,[e] Kaushal Parikh, MD,[e]
Muhannad Abbasi, MD,[b] Elias Bou Farhat, MD,[d] James M. Williams, MD,[f] Jeremy D. Collins, MD,[f]
Ahmad Al-Hader, MD,[g] Rana R. McKay, MD,[h] Carmel Malvar, MD,[h] Mohamad Sabra, MD,[g] Caiwei Zhong, MS,[d]
Raquelle El Alam, MD,[d] Omar Chehab, MD, MSc,[i] Joao Lima, MD, MBA,[i] Minh Phan, MD,[j]
Hanna Ferreira Dalla Pria, MD,[k] Alexandra Trevino, MD,[l] Tomas G. Neilan, MD, MPH,[m] Jennifer M. Kwan, MD, PHD,[a]
Vinod Ravi, MD,[c] Hari Deshpande, MD,[a] George Demetri, MD,[d] Toni K. Choueiri, MD,[d,†] Abdul Rafeh Naqash, MD[j,†]

ABSTRACT

BACKGROUND Primary cardiac soft tissue sarcomas (CSTS) affect young adults, with dismal outcomes.

OBJECTIVES The aim of this study was to investigate the clinical outcomes of patients with CSTS receiving immune checkpoint inhibitors (ICIs).

METHODS A retrospective, multi-institutional cohort study was conducted among patients with CSTS between 2015 and 2022. The patients were treated with ICI-based regimens. The Kaplan-Meier method was used to estimate overall survival (OS) and progression-free survival (PFS). Objective response rates were determined according to Response Evaluation Criteria in Solid Tumors version 1.1. Treatment-related adverse events were graded per the Common Terminology Criteria for Adverse Events version 5.0.

RESULTS Among 24 patients with CSTS, 17 (70.8%) were White, and 13 (54.2%) were male. Eight patients (33.3%) had angiosarcoma. At the time of ICI treatment, 18 patients (75.0%) had metastatic CSTS, and 4 (16.7%) had locally advanced disease. ICIs were administered as the first-line therapy in 6 patients (25.0%) and as the second-line therapy or beyond in 18 patients (75.0%). For the 18 patients with available response data, objective response rate was 11.1% (n = 2 of 18). The median PFS and median OS in advanced and metastatic CSTS (n = 22) were 5.7 months (95% CI: 2.8-13.3 months) and 14.9 months (95% CI: 5.7-23.7 months), respectively. The median PFS and OS were significantly shorter in patients with cardiac angiosarcomas than in those with nonangiosarcoma CSTS: median PFS was 1.7 vs 11 months, respectively (P < 0.0001), and median OS was 3.0 vs 24.0 months, respectively (P = 0.008). Any grade treatment-related adverse events occurred exclusively in the 15 patients with nonangiosarcoma CSTS (n = 7 [46.7%]), of which 6 (40.0%) were grade ≥3.

CONCLUSIONS Although ICIs demonstrate modest activity in CSTS, durable benefit was observed in a subset of patients with nonangiosarcoma, albeit with higher toxicity. (J Am Coll Cardiol CardioOnc 2024;6:71–79)
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ABBREVIATIONS AND ACRONYMS

CSTS = cardiac soft tissue sarcoma(s)

CTLA-4 = cytotoxic T lymphocyte-associated antigen-4

ICI = immune checkpoint inhibitor

ORR = objective response rate

OS = overall survival

PD-1 = programmed cell death protein-1

PD-L1 = programmed cell death ligand-1

PFS = progression-free survival

PR = partial response

trAE = treatment-related adverse event

Primary tumors of the heart are rare.[1-3] Approximately 75% of primary cardiac tumors take the form of benign mesenchymal tumors.[1] Although uncommon, primary cardiac soft tissue sarcomas (CSTS) rank as the second most common type of primary cardiac neoplasm and account for the majority of malignant primary cardiac tumors.[1,3] CSTS may occur at any age but tend to affect individuals in the third to fifth decades of life.[1] The clinical presentation of patients with CSTS varies on the basis of tumor size and location, typically involving symptoms such as dyspnea and secondary symptoms such as embolic phenomena, conduction abnormalities, pericardial effusion, and occasional metastases to other sites such as bone, brain, and colon.[1] Limited small-scale data exist to guide CSTS management. Although complete tumor excision is the preferred treatment strategy in most cases, depending on the tumor location in the heart, the infiltrative nature of these tumors and the extent of local invasion and metastases can make this approach unfeasible.

Treatment options for recurrent or metastatic CSTS are limited, and responses to anthracycline-based chemotherapy are short lived, with a median progression-free survival (PFS) of 4.4 months in patients treated with first-line palliative chemotherapy.[4] Eventually, most patients succumb to metastatic disease,[4] and the prognosis of patients with CSTS remains poor, characterized by a median overall survival (OS) of <1 year.[1,5]

The introduction of immune checkpoint inhibitors (ICIs) has successfully shifted the treatment paradigm in oncology, and these agents have received regulatory approval for a broad spectrum of tumor types.[6-9] In noncardiac sarcomas, clinical trials of ICIs have shown promising results, with response rates ranging between 5% and 37%.[10,11] To date, however, there are no reports that examine clinical outcomes and side-effect profiles of patients with primary malignant cardiac tumors treated with ICIs. In this collective effort across multiple institutions, we present an exploration of the outcomes and side-effect profiles of patients with CSTS receiving ICIs.

METHODS

PATIENT POPULATION. This study was based on an analysis of a retrospective, multicenter database. Data from 8 participating institutions in the United States (Supplemental Table 1) were obtained and are currently housed at the Dana-Farber Cancer Institute. According to the Declaration of Helsinki, this retrospective study was covered by the Institutional Review Board review at the Dana-Farber Cancer Institute (protocol 21-329) and local Institutional Review Boards at participating sites.

Patients included: 1) had cardiac masses identified by transthoracic echocardiography or cardiac magnetic resonance imaging; 2) had histologic diagnoses of CSTS; and 3) had received any line of ICI therapy (≥1 dose), defined as anti–programmed cell death protein-1 (PD-1) or anti–programmed cell death-ligand 1 (PD-L1) alone or in combination with anti–cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) or other anticancer therapies (ie, chemotherapy or targeted agents) between 2015 and 2022. Patients were excluded if the primary site of origin was noncardiac and the pathology was not a sarcoma. CSTS were classified into 1 of 2 histologic cohorts: angiosarcoma and nonangiosarcoma.

CLINICAL OUTCOMES AND TOXICITY PROFILES. The primary endpoint of this study was OS, defined as the date of ICI initiation to death or censoring at the date of the last follow-up. The secondary endpoints were PFS, objective response rates (ORRs), and treatment-related adverse events (trAEs). PFS

From the aYale University School of Medicine, New Haven, Connecticut, USA; bDepartment of Cardiovascular Medicine, Mayo Clinic, Rochester, Minnesota, USA; cUniversity of Texas MD Anderson Cancer Center, Houston, Texas, USA; dDana-Farber Cancer Institute, Boston, Massachusetts, USA; eDivision of Medical Oncology, Mayo Clinic, Rochester, Minnesota, USA; fDepartment of Radiology, Mayo Clinic, Rochester, Minnesota, USA; gDepartment of Internal Medicine, Indiana University School of Medicine, Indianapolis, Indiana, USA; hMoores Cancer Center, University of California-San Diego, La Jolla, California, USA; iDivision of Cardiology, Department of Medicine, Johns Hopkins University, Baltimore Maryland, USA; jStephenson Cancer Center, University of Oklahoma, Oklahoma City, Oklahoma, USA; kDivision of Diagnostic Imaging, MD Anderson Cancer Center, Houston, Texas, USA; lDepartment of Internal Medicine, Northwestern University, Chicago, Illinois, USA; and the mCardio-Oncology Program, Division of Cardiology, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts, USA. *Drs Nassar and El-Am contributed equally to this work. †Drs Choueiri and Naqash contributed equally to this work.

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FIGURE 1 Response to Immune Checkpoint Inhibitors Among Patients With Cardiac Soft Tissue Sarcoma

(A) Waterfall plot of best percentage change from baseline in the size of target lesions (sum of diameters). (B) Spider plots of percentage of baseline tumor size (sum of target lesion diameters) at each Response Evaluation Criteria in Solid Tumors version 1.1 assessment of cardiac soft tissue sarcoma. Black-colored dashed lines over −30% and 20% represent partial response (PR) and disease progression thresholds, respectively. A = angiosarcoma; NA = nonangiosarcoma; PD = progressive disease; SD = stable disease.

measured the time from ICI initiation to radiologic or clinical disease progression, death, or censoring at the date of the last follow-up. ORRs were assessed by board-certified radiologists at respective centers. Radiologists were blinded to clinical data, and RECIST (Response Evaluation Criteria in Solid Tumors) version 1.1 was used for ORR determination whenever possible. For 4 patients, serial images were not available for RECIST version 1.1 measurements, and instead, response data from radiology reports were used (**Figure 1**). For the remaining 4 patients with response data, serial images were unavailable for radiology review, as they were obtained at outside institutions. trAEs were graded per the Common Terminology Criteria for Adverse Events version 5.0.

STATISTICAL ANALYSIS. Continuous data are reported as median (Q1-Q3) and categorical data as count (percentage). Kaplan-Meier methods were used to estimate the median OS and PFS using 95% CIs with group comparisons performed using the log-rank test. ORR was defined as the proportion of patients with partial response (PR) or complete response and the percentage reported with exact 95% CI using the exact Clopper-Pearson method. Group comparisons for ORR were performed using the Fisher exact test. Statistical analysis was performed using SAS version 9.4 (SAS Institute), and P values <0.05 were considered to indicate statistical significance.

RESULTS

CSTS COHORT CHARACTERISTICS. Among the 24 patients diagnosed with CSTS, the median age was 45 years (Q1-Q3: 37-54 years), with 13 men (54.2%) and 5 being Asian or Black patients (20.8%) (**Table 1**, Supplemental Table 2). The median follow-up time was 17.9 months (95% CI: 13.3 to not reached). The median cardiac mass diameter was 6 cm (Q1-Q3: 4.2-6.7 cm). The most common histologic subgroup was angiosarcoma (n = 8 [33.3%]). The remaining CSTS cases were grouped into the nonangiosarcoma CSTS cohort (n = 16 [66.7%]) (Supplemental Figure 1). Among the patients, 18 (75.0%) had metastatic CSTS, while 4 (16.7%) had locally advanced disease. Thirteen patients (54.2%) had histories of surgery with curative intent. Complications related to the cardiac mass developed in approximately 16 patients (66.7%), including heart failure (12.5%), valvulopathies (12.5%), and cardiac tamponade (8.3%) (**Table 1**). Baseline cardiac magnetic resonance imaging was performed on 20 patients (83.3%) with CSTS, revealing cardiac thrombi in 7 (29.2%). Cardio-oncology referrals were made for 11 of 24 patients (45.8%). The baseline demographics, clinicopathological characteristics, and treatment plans for each patient are shown in **Table 1** and Supplemental Table 2. Among the 23 patients with available data, 4 had their PD-L1 status assessed, with 2 having tumor proportion scores of 0% and 2 with scores of 1% (Supplemental Table 2).

TABLE 1 Baseline Clinical Characteristics (N = 24)

Age at ICI start, y	45 (37-54)
Female	11 (45.8)
Race	
Asian	3 (12.5)
Black or African American	2 (8.3)
White	17 (70.8)
Other	2 (8.3)
Ethnicity	
Hispanic/Latinx	4 (16.7)
Non-Hispanic/non-Latinx	20 (83.3)
Region of United States	
Northeast	2 (8.3)
Midwest	12 (50.0)
South	9 (37.5)
West Coast	1 (4.2)
Smoking	
Never	16 (66.7)
Former	8 (33.3)
Type of malignancy	
Angiosarcoma	8 (33.3)
Nonangiosarcoma cardiac soft tissue sarcoma[a]	16 (66.7)
Diameter of cardiac mass, cm	6.0 (4.2-6.7)
Complications from cardiac mass	
None	8 (33.3)
Cardiac tamponade	2 (8.3)
Arrhythmia	4 (16.7)
HF	3 (12.5)
Syncope	1 (4.2)
Valvulopathy	3 (12.5)
Dysphagia	1 (4.2)
Pericarditis/pericardial effusion	2 (8.3)
Obstruction-related process[b]	3 (12.5)
Cardiac MRI	20 (83.3)
Cardiac consult at ICI initiation	11 (45.8)
Location of cardiac mass	
Atrial	18 (75.0)
Ventricular	1 (4.2)
Multiple	5 (20.8)
Cardiac thrombus at ICI initiation	7 (29.2)
Number of systemic therapy lines prior to ICI initiation	
0	4 (16.7)
1	12 (50)
≥2	8 (33.3)
Class of ICI used	
Anti-PD-1	17 (70.8)
Anti-PD-1 + anti-CTLA-4	3 (12.5)
Anti-PD-1 + non-ICI-based therapy[c]	4 (16.7)
ECOG status at ICI start	
0	9 (37.5)
1	12 (50)
≥2	2 (8.3)
Unavailable	1

Values are median (Q1-Q3) or n (%). [a]8 pleomorphic cardiac sarcoma, 4 spindle cell sarcoma, 1 liposarcoma, 1 chondroblastic osteosarcoma, 2 intimal sarcoma. [b]Includes mitral valve obstruction and superior vena cava syndrome. [c]1 patient of each: pembrolizumab plus paclitaxel, pembrolizumab plus pazopanib, pembrolizumab + ribociclib, and pembrolizumab + interleukin 2 therapy.

HF = congestive heart failure; CTLA-4 = cytotoxic T lymphocyte-associated antigen 4; ECOG = Eastern Cooperative Oncology Group; ICI = immune checkpoint inhibitor; MRI = magnetic resonance imaging; PD-1 = programmed cell death protein 1; trAE = treatment-related adverse event.

CLINICAL OUTCOMES. All patients received anti-PD-1-based therapy, with ICIs administered as the first-line therapy in 4 patients and as the second-line therapy in 20 patients. The median number of treatment doses was 5 (Q1-Q3: 2-7). Supplemental Table 2 provides details on the treatment drug, including dosing, schedule, and the number of treatment cycles. Among the 24 patients, 22 (91.7%) received ICIs in the metastatic or locally advanced setting and were included in the subsequent analyses of clinical outcomes and toxicity (Supplemental Figure 1). For all 7 patients with advanced angiosarcoma, the reason for discontinuation was tumor progression, necessitating subsequent therapy or leading to death. In contrast, only 7 of 15 patients (46.7%) with advanced non-angiosarcoma discontinued ICI because of tumor progression. Among the 18 CSTS with response data, the ORR was 11.1% (2 of 18; 95% CI: 3.1%-33%), with response observed in 1 intimal sarcoma (non-angiosarcoma) and 1 angiosarcoma. Serial imaging-based RECIST version 1.1 measurements were available for 14 patients (Figure 1). For the remaining 4 patients with response data, serial images were unavailable for radiologic review, as they were obtained at outside institutions. When stratifying by administered treatment regimens, 1 of 3 patients with CSTS on nivolumab and ipilimumab achieved a durable PR. Among the 4 patients with CSTS on anti-PD-1 therapy combined with non-ICI regimens, 1 patient on pembrolizumab and paclitaxel achieved a PR. None of the 11 patients with CSTS treated with anti-PD-1 monotherapy responded, with 6 patients achieving stable disease as the best response.

The median time on ICI treatment was longer for nonangiosarcoma CSTS compared with cardiac angiosarcomas (5.5 months [Q1-Q3: 3.3-13.5 months] vs 1.1 months [Q1-Q3: 0.6-3.8 months], respectively). The median PFS and OS in the overall cohort were 5.7 months (95% CI: 2.8-13.3 months) and 14.9 months (95% CI: 5.7-23.7 months), respectively (Figures 2A and 2B, Supplemental Table 3). In an exploratory analysis, median PFS was significantly shorter for cardiac angiosarcoma vs nonangiosarcoma CSTS (1.7 vs 11 months; $P < 0.0001$) (Figure 2C). Similarly, median OS was significantly shorter among patients with cardiac angiosarcomas vs nonangiosarcoma CSTS (3.0 vs 24 months, respectively; $P = 0.008$) (Figure 2D, Central Illustration). To better understand the role of treatment effect vs underlying disease biology, we calculated the PFS of both ICI treatment and the immediate prior systemic line of therapy (prior to ICI) whenever possible (Figure 3). Otherwise, we included the PFS of the subsequent systemic line of therapy after ICI as a comparator if there was no prior line. For

FIGURE 2 Survival Outcomes of Patients With CSTS Treated With Immune Checkpoint Inhibitors
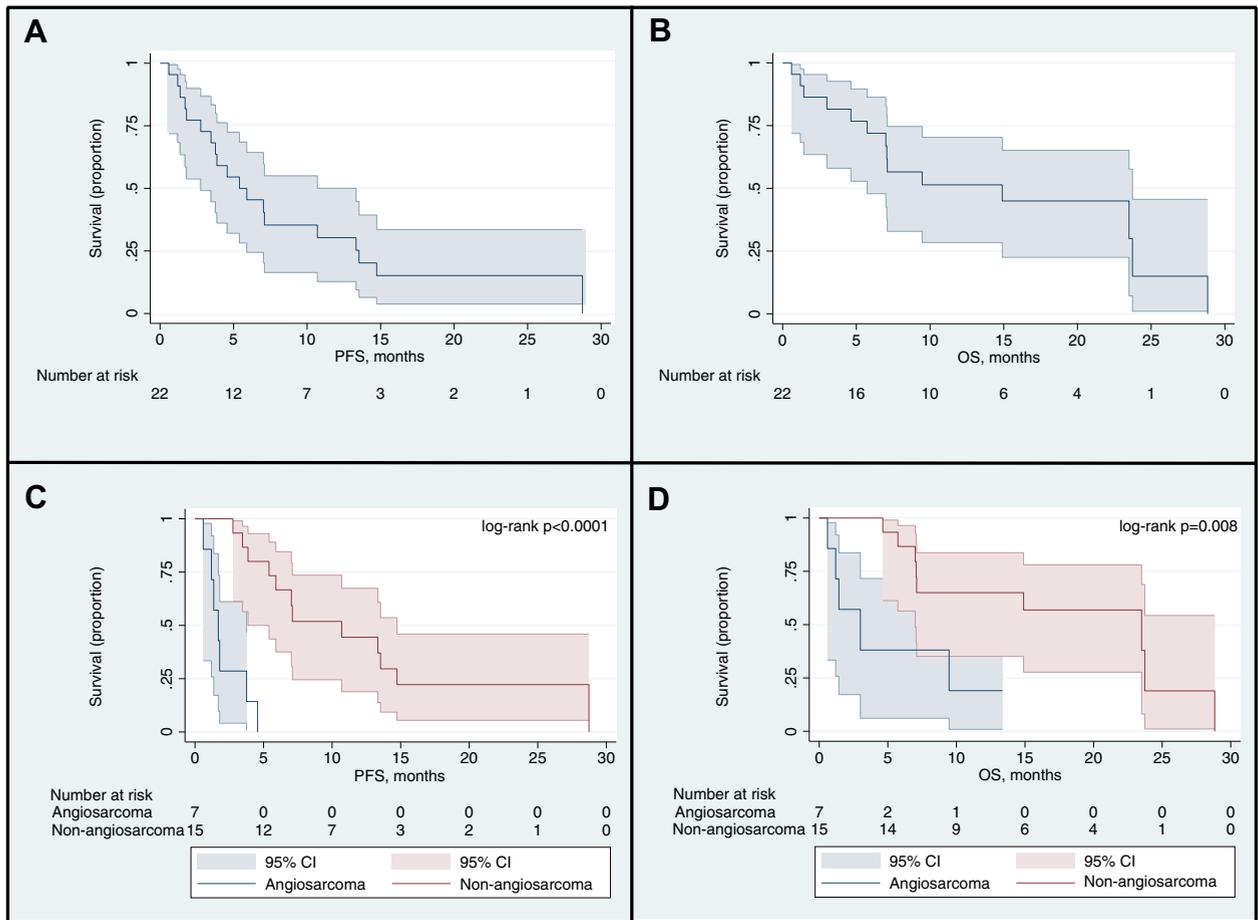
(A) Progression-free survival (PFS) of patients with advanced or metastatic cardiac soft tissue sarcoma (CSTS). (B) Overall survival (OS) of patients with advanced and metastatic CSTS. (C) Progression-free survival of patients with advanced and metastatic CSTS by histology. (D) Overall survival of patients with advanced and metastatic CSTS by histology.

the nonangiosarcoma histology, treatment with ICIs, on average, led to similar PFS compared with the prior systemic or subsequent lines of therapy. In contrast, all patients with angiosarcoma histology derived more benefit from the prior systemic line compared with ICI therapy, as shown by the PFS treatment intervals (**Figure 3**).

TOXICITY PROFILES. trAEs occurred only in patients with nonangiosarcoma CSTS. trAEs of any grade occurred in 7 of 22 patients (31.8%) (Supplemental Table 4). Grade 3 and 4 trAEs were reported in 6 patients (27.3%), and 1 grade 5 pneumonitis was reported, leading to death. None had cardiac trAEs. Five patients (23%) required steroids to manage trAEs. ICIs were discontinued because of trAEs in 5 of 22 patients (22.7%). Six patients were hospitalized because of

trAEs. The distributions of trAEs by histology, use of steroids, and discontinuation because of toxicity are shown in Supplemental Tables 2 and 4.

DISCUSSION

Given the extent of potential person-years lost to related deaths, CSTS can have a considerable societal impact.[12] Because of the rarity of CSTS, no randomized clinical trials have been performed to identify an optimal systemic treatment regimen, and chemotherapy protocols are extrapolated from extracardiac soft tissue sarcoma counterpart data. Additionally, no case reports or other low-evidence data are available regarding patients with CSTS treated with ICIs. For the first time, our data suggest that a subset of

CENTRAL ILLUSTRATION Survival Outcomes and Safety Profiles With Cardiac Soft Tissue Sarcoma Treated With Immunotherapy
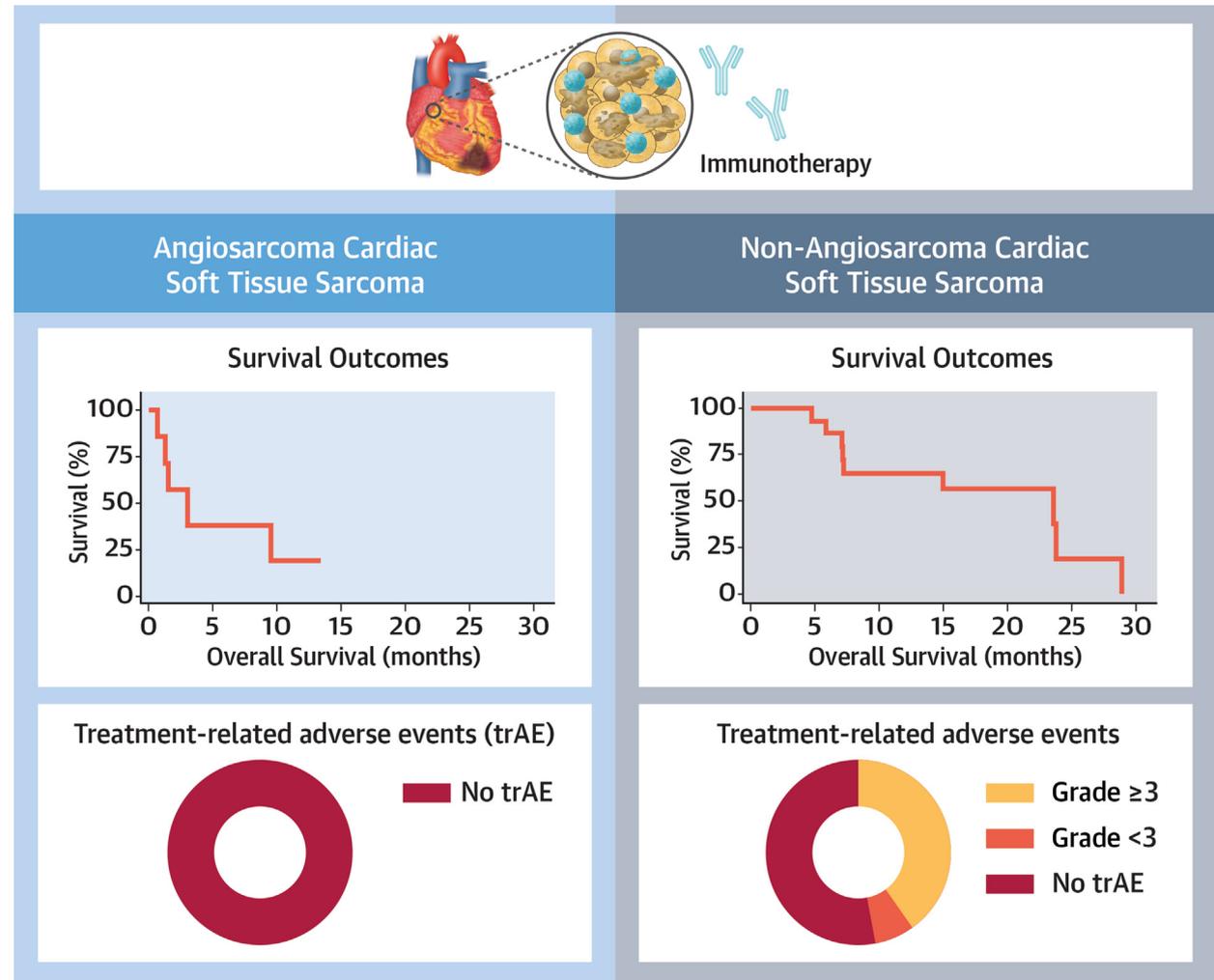
Nassar AH, et al. J Am Coll Cardiol CardioOnc. 2024;6(1):71–79.

The illustration presents the 2 broad histologic categories (angiosarcoma and nonangiosarcoma). The Kaplan-Meier method was used to estimate the median overall survival (OS) using the log-rank test. Treatment-related adverse events (trAEs) were categorized as grade <3, grade ≥3, or none.

patients with primary CSTS can achieve clinical benefit from ICI therapy. Both patients with CSTS whose tumors responded were treated with anti-PD-1-based combinations. Our exploratory analysis revealed that clinical benefit among patients with CSTS treated with ICIs is histology specific, whereas cardiac angiosarcomas showed dismal outcomes compared with patients with nonangiosarcoma CSTS. The swimmer plot analysis of ICI and non-ICI PFS outcomes suggests that anti-PD-1 and anti-PD-L1 ICIs are not as effective for patients with angiosarcoma

but likely have a role as a combination approach with anti-CTLA-4 or chemotherapy in the treatment of patients with nonangiosarcoma CSTS histologies. Moreover, most patients with nonangiosarcoma histologies achieved durable benefit (12-month stable disease or complete response or PR as the best response) when treated with ICIs (1 of 2 intimal, 3 of 7 pleomorphic, and 2 of 4 spindle cell sarcoma).

Prior studies have demonstrated remarkable responses to ICIs in patients with cutaneous angiosarcomas.[13] Although the UV mutation signature may

FIGURE 3 Swimmer Plot: 15 Patients With Nonangiosarcoma and 7 Patients With Angiosarcoma
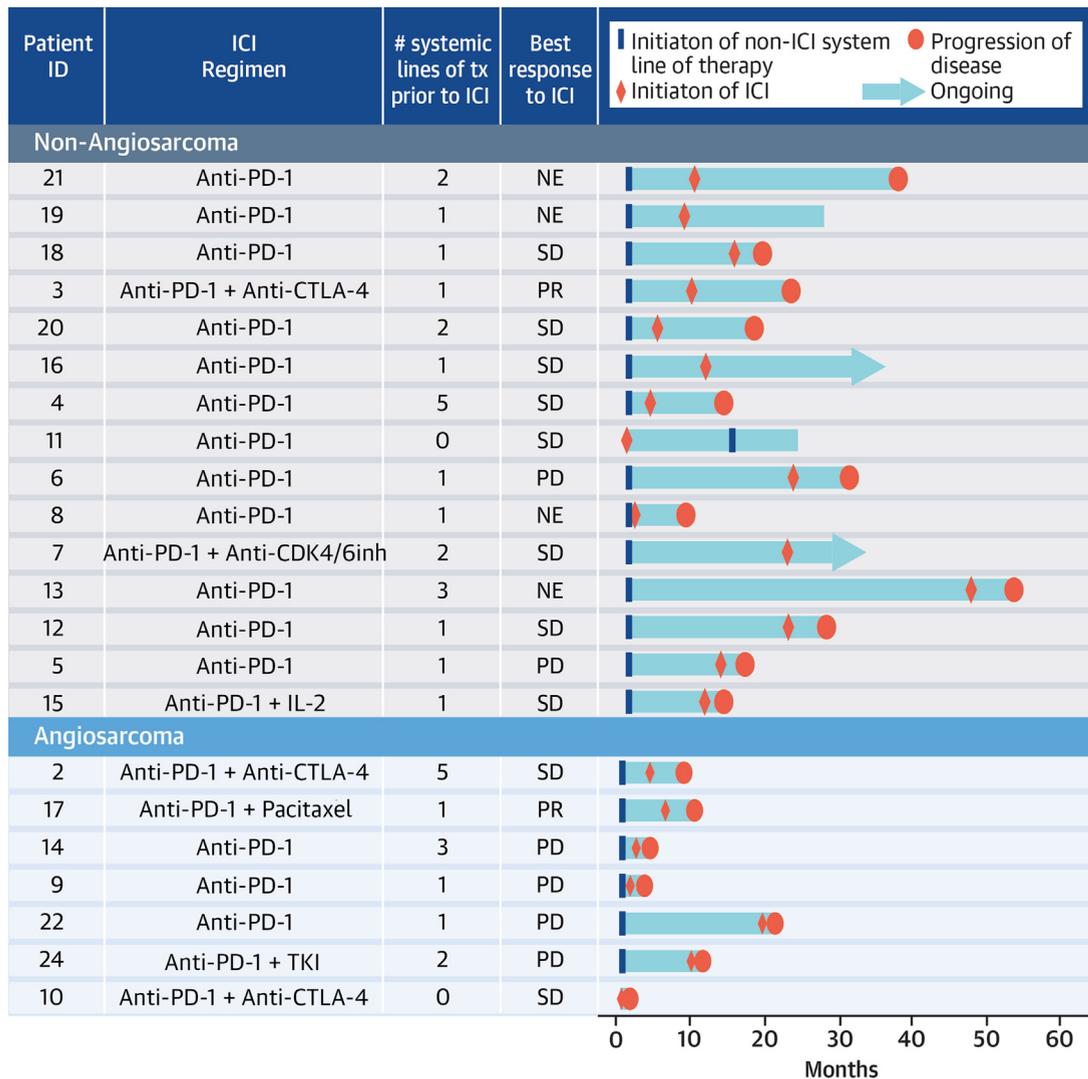
Comparison of progression-free survival between 1) an intrapatient control group, defined as the immediate prior non–immune checkpoint inhibitor (ICI) systemic therapy (if available) or post-ICI therapy if prior non-ICI systemic therapy was not available; and 2) the treatment group of interest (ie, ICI therapy). The goal of this swimmer plot is to characterize whether the treatment effect is due to the underlying behavior of the tumor compared with true treatment-specific efficacy. CDK4/6inh = cyclin-dependent kinase 4/6 inhibitor; CTLA-4 = cytotoxic T lymphocyte–associated antigen 4; IL = interleukin; NE = not evaluable; PD-1 = programmed cell death protein 1; PR = partial response; TKI = tyrosine kinase inhibitor; tx = therapy; other abbreviations as in **Figure 1**.

explain responses to cutaneous angiosarcoma,[13] this phenomenon likely does not apply to angiosarcomas of visceral organs, such as the heart. Moreover, the aggressive clinical course of visceral angiosarcoma

compared with cutaneous angiosarcoma probably makes it less suitable for ICI treatment. In the SARC028 phase 2 study of the anti-PD-1 antibody pembrolizumab, ORRs of 18% (soft tissue) and 5%

(bone) were observed among 84 patients with advanced or metastatic soft tissue and bone sarcoma.[10] Although monotherapy with the anti-CTLA-4 inhibitor ipilimumab in patients with synovial sarcoma was disappointing, with no responses observed in 6 patients, leading to study closure,[14] ipilimumab in combination with nivolumab resulted in an ORR of 16%, compared with 5% with nivolumab monotherapy.[13,15] The ICI combination led to a median PFS of 4.1 months and OS of 14.3 months.

trAE rates were higher in patients with nonangiosarcoma CSTS compared with those with angiosarcoma. This may be related to a significantly longer time on ICI treatment in the nonangiosarcoma group. Importantly, none of the patients experienced major adverse cardiac events such as myocarditis. In our study, two-thirds of patients had complications related to their cardiac masses, with nearly 30% having cardiac thrombi. In addition, referrals to cardio-oncology were <50%, thus highlighting the critical need for multidisciplinary care in patients with CSTS.

STUDY LIMITATIONS. Our study was limited by its retrospective nature and potential selection bias from large academic centers. Our cohort of patients receiving ICI constituted only a small fraction of those receiving other systemic therapies for cardiac sarcomas, likely representing a relatively healthier population. Moreover, the majority of patients in our study received ICIs as the second-line therapy or beyond for metastatic CSTS, for which clinical outcomes may be dismal. Therefore, the results of our study should be interpreted cautiously in this context. It is worth mentioning that we lacked biomarker data, and only a limited number of patients underwent next-generation sequencing because, in the current landscape, no known biomarkers have been associated with therapeutic implications in soft tissue sarcoma in general. For example, more than 80% of the patients who received immunotherapy did not have tumors testing for PD-1 or PD-L1 status. Only 3 patients had available genomic data; therefore, we excluded the genomic data from the present study.

trAEs were common among patients with nonangiosarcoma histology, but this may be confounded by the longer duration of treatment. A competing risk analysis (considering ICI discontinuation because of progression or other reasons) would account for this but could not be performed because of limited data on the time of occurrence of trAEs. Nevertheless,

given the lack of treatment options and limitations to clinical trials specifically for this rare tumor patient population, we hope our work further augments the evaluation of anti-PD-1-based combination approaches that could benefit patients with CSTS.

CONCLUSIONS

In this first ever report of ICIs in patients with CSTS, a subset of patients with nonangiosarcoma histology treated with anti-PD-1-based combinations derived clinical benefit, compounded by higher trAEs. The high rate of cardiac mass-related complications highlights the need for multidisciplinary interventions to support patients as they receive cancer-directed therapy.

ADDRESSES FOR CORRESPONDENCE: Dr Abdul Rafeh Naqash, Stephenson Cancer Center, University of Oklahoma, Oklahoma City, Oklahoma 73104, USA. E-mail: abdulrafeh-naqash@ouhsc.edu. OR Dr Toni K. Choueiri, Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, 450 Brookline Avenue, Boston, Massachusetts 02215, USA. E-mail: toni_choueiri@dfci.harvard.edu.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: ICIs are associated with durable clinical benefit in a subset of patients with CSTS of nonangiosarcoma histology.

TRANSLATIONAL OUTLOOK: Future research is warranted to determine genomic and clinical biomarkers that can predict response to ICIs among patients with CSTS.

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KEY WORDS cardiac sarcomas, cardiac tumors, immune checkpoint inhibitors, treatment-related adverse events

APPENDIX For a supplemental figure and tables, please see the online version of this paper.