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EDITORIAL COMMENT

Immune Checkpoint Inhibitors in Cardiac Sarcoma

Reason to Take Heart?*

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Sarcomas are rare connective tissue cancers and include over 70 histologic subtypes with distinct biology, clinical behavior, and therapeutic sensitivity. Chemotherapy remains the standard for most soft tissue sarcomas in the metastatic setting, with response rates of approximately 20% for first-line options and a median survival of 12 to 18 months.[1] Novel approaches to sarcoma treatment are urgently needed.

Antibodies targeting inhibitory receptors on T cells such as PD-1 or CTLA-4 have transformed the therapeutic landscape in oncology, with Food and Drug Administration approvals for an expanding number of cancer types.[2] Experience with immune checkpoint inhibitors (ICIs) in sarcoma is growing, and the emerging picture is one of histology-specific efficacy—most notably in undifferentiated pleomorphic sarcoma, angiosarcoma, and alveolar soft part sarcoma, although responses occur less commonly in other histologies.[3-6] In the SARC028 trial, anti-PD-1 monotherapy with pembrolizumab demonstrated an objective response rate (ORR) of 23% (n = 9 of 40) in undifferentiated pleomorphic sarcoma and 10% (n = 4 of 39) in dedifferentiated liposarcoma cohorts.[3] In the Alliance A091401 trial, combination anti-PD-1/CTLA-4 blockade with ipilimumab/nivolumab yielded an ORR of 16% (n = 6 of 38) in an unselected sarcoma population.[4] In an angiosarcoma substudy of the Dual anti-CTLA-4 and anti-PD-1 Blockade in Rare Tumors (DART) trial, ipilimumab/nivolumab showed an ORR of 25% (n = 4 of 16), with frequent responses in the cutaneous angiosarcoma subset.[5] Finally, the anti-PD-L1 antibody atezolizumab has demonstrated an impressive ORR of 37% (n = 19 of 52) in the ultra-rare subtype alveolar soft part sarcoma[6] and recently garnered Food and Drug Administration approval for this indication.

The efficacy of ICIs has remained largely untested in many other rare sarcoma subtypes, including primary cardiac sarcomas, which are extremely rare but particularly lethal cancers.[7] In this issue of *JACC: CardioOncology*, Nassar et al[8] present the results of a multicenter retrospective study of cardiac sarcoma patients treated with ICIs. Collecting data from 8 institutions within the United States between 2015 and 2022, the investigators report clinical outcomes and safety in 22 patients with advanced cardiac sarcoma receiving anti-PD-1-based therapy. The cohort included various histologic subtypes, of which 7 patients had angiosarcoma, and 15 patients had a mix of other histologies, largely undifferentiated/unclassified soft tissue sarcomas (spindle cell or pleomorphic sarcoma) as well as a few intimal sarcomas, liposarcomas, and a chondroblastic osteosarcoma. Roughly one-half of the patients had a history of prior surgical resection, most had metastatic disease and were receiving ICIs in the second line or later, Eastern Cooperative Oncology Group performance status was 0 to 1 in all but 2 patients, and the median patient age was 45 years. ICI treatment regimens consisted of anti-PD-1 monotherapy (pembrolizumab [n = 14] or nivolumab [n = 1]), combination anti-PD-1/CTLA-4 (ipilimumab/nivolumab [n = 3]), anti-PD-1 + interleukin 2 therapy (ALKS 4230 [n = 1]), and anti-PD-1 + chemotherapy (paclitaxel [n = 1]) or targeted therapy (pazopanib [n = 1] or ribociclib [n = 1]).

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Overall, the efficacy of ICI-based therapy was modest. For the 18 patients evaluable by RECIST (Response Evaluation Criteria in Solid Tumors), the ORR was 11% (2/18 partial responses), with responses in 1 intimal sarcoma patient on ipilimumab/nivolumab and 1 angiosarcoma patient on pembrolizumab + paclitaxel. However, an additional 5 patients, all within the nonangiosarcoma subgroup and treated with anti-PD-1 monotherapy, showed durable stable disease with progression-free survival (PFS) >12 months (3 patients with pleomorphic sarcoma and 2 with spindle cell sarcoma). For the entire cardiac sarcoma cohort, PFS was 5.7 months, and overall survival was 14.9 months. Treatment-related toxicities of any grade occurred in 32% (n = 7 of 22), with grade 3 to 4 events reported in 6 patients and 1 grade 5 pneumonitis in a patient receiving anti-PD-1 therapy. Steroid treatment for the management of immune-related adverse events was required in 5 patients, and ICI discontinued because of toxicity in 23% (n = 5 of 22). Importantly, no immune-related cardiac toxicities were reported.

This study represents the first data reported on ICIs in cardiac sarcomas and highlights the importance of collaborative efforts across many institutions for the study of ultra-rare cancers. Several notable findings emerged from this data set. Importantly, a subset of cardiac sarcoma patients may derive some clinical benefit from ICI-based therapy; however, sensitivity was histology specific, as noted with noncardiac soft tissue sarcomas. Unfortunately, clinical outcomes with ICIs in cardiac angiosarcomas, the most common subtype of primary cardiac sarcoma,[7] were dismal. In an exploratory analysis comparing angiosarcoma and nonangiosarcoma subgroups, the authors showed a significantly shorter PFS (1.7 vs 11 months) and overall survival (3.0 vs 24 months) in angiosarcoma patients.[8] In addition, the 1 angiosarcoma patient who achieved a partial response (with PFS of 3.8 months) received ICI + paclitaxel, so the specific contribution of immunotherapy remains unclear.

Although poor ICI efficacy in cardiac angiosarcomas may reflect a more aggressive tumor biology, visceral angiosarcomas arising at other noncardiac sites were also reported to be less responsive to ICIs than cutaneous angiosarcomas of the head and neck.[5,9] Correlative studies have shown high tumor mutational burden and ultraviolet radiation mutational signatures in the cutaneous subset,[10] suggesting an increase in antigenic targets may contribute to this differential sensitivity, although additional work is needed to test this hypothesis.

Limitations of the present study, some of which seem unavoidable with such a rare cancer, include the retrospective design, small patient numbers (particularly within the nonangiosarcoma subgroup), and heterogeneity in ICI-based treatment regimens (including non-ICI combinations), although most patients received anti-PD-1 or anti-PD-1/CTLA-4. Finally, as pointed out by the authors, a potential selection bias in initiating immunotherapy may have resulted in a healthier patient cohort or perhaps one with more indolent disease.

Given the relatively small subset of sarcoma patients who benefit from current ICI therapies, critical areas of ongoing work include identifying predictive biomarkers of response, understanding the array of tumor immune microenvironments at higher resolution, and determining the relevant mechanisms of immune evasion. Ongoing work to define the full spectrum of ICI activity in sarcoma, even among rare subtypes, will aid in these endeavors, hopefully culminating in a more rational design of effective ICI-based combination approaches.

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REFERENCES

1. Pang A, Carbini M, Maki RG. Contemporary therapy for advanced soft-tissue sarcomas in adults: a review. *JAMA Oncol*. 2016;2(7):941–947.

2. Ribas A, Wolchok JD. Cancer immunotherapy using checkpoint blockade. *Science*. 2018;359(6382):1350–1355.

3. Tawbi HA, Burgess M, Bolejack V, et al. Pembrolizumab in advanced soft-tissue sarcoma and bone sarcoma (SARC028): a multicentre, two-cohort, single-arm, open-label, phase 2 trial. *Lancet Oncol*. 2017;18(11):1493–1501.

4. D'Angelo SP, Mahoney MR, Van Tine BA, et al. Nivolumab with or without ipilimumab treatment for metastatic sarcoma (Alliance A091401): two open-label, non-comparative, randomised, phase 2 trials. *Lancet Oncol*. 2018;19(3):416–426.

5. Wagner MJ, Othus M, Patel SP, et al. Multicenter phase II trial (SWOG S1609, cohort 51) of ipilimumab and nivolumab in metastatic or unresectable angiosarcoma: a substudy of dual anti-CTLA-4 and anti-PD-1 blockade in rare tumors (DART). *J Immunother Cancer*. 2021;9(8):e002990.

6. Chen AP, Sharon E, O'Sullivan-Coyne G, et al. Atezolizumab for advanced alveolar soft part sarcoma. *N Engl J Med*. 2023;389(10):911–921.

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7. Tyebally S, Chen D, Bhattacharyya S, et al. Cardiac tumors: *JACC CardioOncology* State-of-the-Art Review. *J Am Coll Cardiol CardioOnc*. 2020;2(2):293–311.

8. Nassar AH, El-Am E, Denu R, et al. Clinical outcomes among immunotherapy-treated patients with primary cardiac soft tissue sarcomas: a multicenter retrospective study. *J Am Coll Cardiol CardioOncol*. 2024;6(1):71–79.

9. Florou V, Rosenberg AE, Wieder E, et al. Angiosarcoma patients treated with immune checkpoint inhibitors: a case series of seven patients from a single institution. *J Immunother Cancer*. 2019;7(1):213.

10. Painter CA, Jain E, Tomson BN, et al. The Angiosarcoma Project: enabling genomic and clinical discoveries in a rare cancer through patient-partnered research. *Nat Med*. 2020;26(2):181–187.

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