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Safety and efficacy of immune checkpoint therapy for the treatment of patients with cardiac metastasis: a multicenter international retrospective study

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ABSTRACT

Background Data on the safety profiles and clinical outcomes of patients with solid tumors and cardiac metastasis treated with immune checkpoint inhibitors (ICIs) are limited.

Methods This is an international multicenter retrospective study of patients with cancer and cardiac metastasis at baseline. Patients who had received ≥1 dose of ICI were included. Treatment-related adverse events (trAEs) were graded per Common Terminology Criteria for Adverse Event V.5.0. Objective response rates (ORR) were evaluated by Response Evaluation Criteria in Solid Tumors V.1.1 when available. Overall survival (OS) and progression-free survival (PFS) were estimated by the Kaplan-Meier method.

Results Among 110 pts, median age at ICI initiation was 65 (IQR: 59–75). Median follow-up time since ICI initiation was 36 (95% CI: 26 to 51) months. Melanoma (38%, n=42) and non-small cell lung cancer (24%, n=26) were the most common. 68 (62%) patients received ICIs as first-line, and 29 (26%) patients were treated with combination anti-programmed death-1 and anti-cytotoxic T-lymphocyte antigen 4. The most common location of cardiac metastasis was in the atria (37%, n=41) and ventricles (35%, n=39). 15 patients (13.6%) had bilateral cardiac/pericardial metastasis, 44 (40%) had left-sided, and 43 (39.8%) had right-sided. At ICI initiation, 21% (n=23) had a cardiac thrombus. Cardiology referrals and cardiac MRIs

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Cardiac metastases are common but often diagnosed post-mortem. Limited data exist on the safety and efficacy of immune checkpoint inhibitors (ICIs) in patients with cardiac metastases.

WHAT THIS STUDY ADDS

⇒ This study shows that ICIs can be safely administered to patients with cardiac metastases, with no increased rates of myocarditis or pericarditis. ICIs demonstrated efficacy, particularly in melanoma and non-small cell lung cancer, with responses observed in both cardiac masses and overall tumor burden. Right-sided cardiac metastases were associated with better survival compared with bilateral involvement.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings support the safe use of ICIs in patients with cardiac metastases and emphasize the need for multidisciplinary management.

at the time of cancer diagnosis were completed on 58 (53%) and 52 (47%) patients, respectively. Cardiac events occurred in 40 (36%) patients, including arrhythmias (n=14, 13%), arterial/venous emboli (n=4, 3.6%), and cardiac tamponade (n=3, 2.7%). 53 (47%) patients developed trAEs; most common were colitis/diarrhea (n=16, 15%), dermatitis (n=13, 12%), and hepatitis (n=9, 8.2%). ICI-related major cardiac trAEs occurred in 2 (1.8%) patients. 22 patients (20%) developed grade ≥3 trAE. Patients with multiple cardiac metastases had significantly lower responses to ICI-based regimens compared with patients with single cardiac metastasis (11% vs 63%, p=0.02). For melanoma, ORR, median PFS, and median OS were 38%, 9.0 months, and 28.9 months, respectively. 83% of patients with melanoma had concordant responses in overall disease burden and cardiac disease. 91 patients discontinued ICIs, and the main reason was progression or death in 55 (49%) patients.

Conclusions Among patients with pre-existing cardiac metastasis, ICIs demonstrated meaningful clinical efficacy with no increase in safety signals. Most patients had concordant responses in the overall disease burden and cardiac mass. Multidisciplinary teams are crucial for the appropriate management of patients with cardiac metastasis.

INTRODUCTION

Cardiac metastasis is an umbrella term that describes the distant spread of a tumor to any of the structures of the heart (pericardium, epicardium, myocardium, endocardium, great vessels, and coronary arteries, heart cavities).[1] Among cardiac tumors, metastases from distant primary tumors are at least 100-fold more common than primary malignant tumors originating from the heart.[2] Most cases of cardiac metastases tend to have a silent clinical presentation and are typically diagnosed post-mortem.[3] Routes of cardiac metastases include direct infiltration from nearby structures, or hematogenous, lymphatic, or venous spread.[4] The most common cancer types associated with cardiac metastases are lung cancer, breast cancer, and hematologic malignancies.[4]

Over the last 30 years, there has been a notable surge in the overall incidence of cardiac metastases, which may be attributed to advances in cancer diagnosis and treatment leading to increased life expectancy in addition to advances in cardiac imaging.[5] Cardiac metastases are discovered at the time of autopsy in up to 9–20% of patients with a cancer diagnosis.[6–8] Cardiac metastases carry a high mortality rate secondary to a heightened susceptibility to arrhythmias and compromised myocardial function. Limited retrospective data suggest that cardiac metastases correlate with poor survival compared with patients with distant metastases but lacking cardiac involvement.[9]

Immune checkpoint inhibitors (ICI) have revolutionized the treatment landscape of cancer, emerging as the standard of care for many malignancies.[10–13] Limited case reports have reported the benefit of ICI in prolonging survival in patients with cardiac metastases.[14 15] However, pharmacovigilance studies have raised some safety concerns regarding patients treated with ICIs who had increased rates of cardiac adverse events (arrhythmias, pericarditis and/or myocarditis, and cardiovascular death) compared with patients not receiving ICIs (HRs ranging between 2.1 and 4.9).[16] While these major adverse cardiovascular events tend to be less than 1% in incidence, they portend high morbidity and mortality, often leading to permanent therapy discontinuation.[17] Consequently, clinicians may be hesitant to administer ICIs in patients with cardiac metastases due to the perceived risk of heightened cardiac adverse events in this unique and understudied population. A recent study showed that patients with metastatic melanoma and cardiac metastasis were significantly less likely to be treated with immunotherapy compared with those without cardiac metastasis (65% vs 80%).[18] This may be particularly relevant for older adults (age >75), in whom clinicians often exhibit a lower threshold for discontinuing therapy, likely owing to the presence of underlying comorbidities and diminished physiological reserve.[19] Thus far, the clinical outcomes, including the safety and efficacy of ICI therapy in patients with cardiac metastases, are not known or documented. In this multi-institutional, large-scale effort, the aim was to determine the safety and efficacy of ICIs among patients with cardiac metastases across all cancer types.

METHODS

Clinical cohort

In a retrospective multicenter study, clinical information was gathered from 20 participating institutions in Australia, Canada, Italy, Israel, Japan, Spain, UK, and the USA (online supplemental table 1). This retrospective study was approved by the institutional review board (IRB) at Dana-Farber Cancer Institute (DFCI) (Protocol #22–337) and local IRBs at participating sites, in accordance with the Declaration of Helsinki. Data were analyzed at DFCI.

Patients with cancer had to meet all the following criteria for inclusion: (1) diagnosed with a cancer with radiographic (including echocardiography, CT and MRI) or pathologic confirmation of distant spread to the heart prior to initiation of ICI. Metastatic involvement of the heart included either involvement of the pericardium, epicardium, myocardium, endocardium, great vessels, coronary arteries, or heart cavities; (2) received at least one dose of ICI therapy, defined as anti-programmed cell death protein 1/ligand 1 (PD-1/L-1) and/or anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) alone or in combination with chemotherapy or tyrosine kinase inhibitors between 2015 and 2022. Patients who did not meet these criteria, including those with pericardial effusions only, were excluded.

Clinical outcomes and toxicity profiles

The primary endpoint of this study was the safety of ICI therapy defined by the number of treatment-related adverse events (trAEs) which were graded per the Common Terminology Criteria for Adverse Events V.5.0. Cardiac events were categorized as dysrhythmias, congestive heart failure, cardiac tamponade, embolic phenomena, pericardial effusion, syncope/obstruction, or valvulopathy. The secondary endpoints were (1) overall survival (OS), defined as the date of ICI initiation to death or censored

at the date of last follow-up (2) real-world progression-free survival (rwPFS): the time from ICI initiation to progression of disease or death, or censored on the date of last follow-up (3) objective response (ORRs) measured either by the clinical investigator or whenever possible per the Response Evaluation Criteria in Solid Tumors (RECIST) V.1.1 criteria for solid tumors. For ORR, responders were defined as patients with partial response (PR) or complete response (CR) at any time after the initiation of ICI and prior to starting another line of therapy. Concordance ORRs were compared between overall disease burden and the cardiac mass.

Statistical analysis

Descriptive statistics were used to characterize the patient demographics and clinical outcomes comprehensively. Multivariable Cox proportional hazards regression models were constructed to analyze rwPFS and OS, adjusting for predefined variables: number of prior systemic treatment lines, laterality of cardiac metastasis (bilateral, left, or right), radiation therapy directed at cardiac metastases, the count of cardiac metastases (single or multiple), and cancer type. Survival distributions for OS and PFS were estimated using the Kaplan-Meier method, and ORRs were quantified as percentages. Statistical analyses were executed using SAS V.9.4. For assessing ORR, we applied multinomial logistic regression to explore the relationships between the ORR and pertinent clinical variables, which included cancer type, the count and laterality of cardiac metastases, exposure to cardiac radiation, and the number of treatment lines. This model was adjusted for confounders selected based on their a priori identified potential impact. We evaluated the models for multicollinearity to ensure the validity of the regression results, presenting findings with ORs and their corresponding 95% CIs.

For the purpose of multivariable analysis, cancer types were aggregated into broader categories: gynecologic cancers (comprising breast, ovarian, and endometrial cancers), thoracic cancers (including mesothelioma, non-small cell lung cancer (NSCLC), and thymic cancers), sarcomas (encompassing chordoma and other sarcomas), genitourinary cancers (renal cell carcinoma and urothelial carcinoma), skin cancers (melanoma and Merkel cell carcinoma), head and neck cancers and thyroid cancer, and an "other" category for cancers not otherwise classified.

RESULTS

Clinico-pathological characteristics of cardiac metastasis cohort

A total of 110 patients with cardiac metastasis met the eligibility criteria for inclusion in this study. The median age was 65 years (IQR: 16). The most represented cancer types were cutaneous melanoma (n=42, 38%), NSCLC (n=26, 24%), and renal cell carcinoma (n=10, 9.1%, table 1). The majority of patients identified as white

Table 1 Baseline characteristics of patients with cardiac metastasis

	Total (N=110)
	N (%)
Age at ICI start: median (IQR)	65 (59–75)
Sex	
Females	35 (32)
Males	75 (68)
Race	
Asian	10 (9.1)
Black or African American	10 (9.1)
White	90 (82)
Ethnicity	
Hispanic/Latino	2 (2)
Non-Hispanic/non-Latino	105 (95)
Unknown	3 (3)
Region	
USA	93 (84.6)
Europe	3 (2.7)
Asia	7 (6.4)
Australia	7 (6.4)
Smoking	
Never	47 (43)
Former	51 (46)
Current	10 (9)
Unknown	2 (2)
Type of malignancy	
Skin cancer	
Cutaneous melanoma	42 (38)
Merkle cell carcinoma	4 (3.6)
Thoracic cancer	
NSCLC	26 (24)
Thymic carcinoma	1 (0.9)
Mesothelioma	1 (0.9)
Genitourinary cancer	
Renal cell carcinoma	10 (9.1)
Urothelial carcinoma	1 (0.9)
Head and neck squamous cell carcinoma/thyroid cancer	7 (6.3)
Gynecologic cancer	
Breast cancer	1 (0.9)
Endometrial cancer	1 (0.9)
Ovarian cancer	1 (0.9)
Sarcoma/chordoma	5 (4.5)
Others	10 (9.1)
Class of ICI used	
Anti-PD-1	69 (63)

Continued

Table 1 Continued

	Total (N=110)
Anti-PD-L1	6 (5.5)
Anti-PD-1+anti-CTLA-4	29 (26)
Anti-CTLA-4	6 (5.5)
ECOG PS at ICI start	
0	32 (29.1)
1	46 (41.8)
≥2	22 (20)
Unknown	10 (9.1)
Systemic lines prior to ICI	
0	71 (65.7)
1 or 2	32 (29.6)
≥3	5 (4.6)
Radiation to cardiac metastasis	
No	15 (13.9)
Yes	93 (86.1)

ECOG PS:Eastern Cooperative Oncology Group Performance Status
CTLA-4, cytotoxic T-lymphocyte-associated antigen-4; ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1.

(n=90, 83%, table 1). The median follow-up time since ICI initiation was 36 months (95%:CI 26 to 50). The median time of ICI initiation after diagnosis of cardiac metastasis was 0.9 months (IQR: 0.3–2.9). ICIs were administered in the first-line setting in 68 (62%) patients. The most common ICI regimens were chemotherapy-free anti-PD-(L-)1 regimens (n=66, 60%), chemoimmunotherapy (n=9, 8.2%), and dual anti-PD-1+anti-CTLA-4 (n=29, 26%). The majority of patients receiving ICI monotherapy were treated with anti-PD-1 agents (n=69, 63%), while six patients (5.5%) received anti-PD-L1 and anti-CTLA-4 monotherapy, respectively. Of 108 patients with radiation data available, 15 (13.9%) received radiation to the cardiac metastasis. The median dose was 33.4 Gy (IQR: 27.6–49.5). Cardiac MRIs were performed in 52 (n=47%) patients. 18 of 37 (49%) patients had troponin elevations above the upper limit of normal at the time of ICI initiation. Cardiology consultations prior to or at ICI initiation were performed in 58 (53%) patients. Of 91 patients who discontinued ICIs, the main reasons for discontinuation were progression or death in 55 (50%) patients, toxicity in 26 (24%) patients, and completion of therapy in 6 (5.5%) patients.

Cardiac events and toxicity profiles

Cardiac masses mostly involved the atria (n=41, 37%) or ventricles (n=39, 35%; table 2). The median diameter of the cardiac mass was 3.5 cm (IQR: 3.1). 40 patients (36%) developed adverse events related to the cardiac mass (table 2). Common adverse events included arrhythmias

Table 2 Cardiac features of metastasis to the heart

Diameter of cardiac mass (cm): median (IQR)	3.5 (2.3–5.4)
Cardiac events from cardiac mass	
None	70 (64%)
Cardiac tamponade	3 (2.7%)
CHF	9 (8.2%)
Arrhythmias	14 (13%)
Embolic phenomena	4 (3.6%)
Syncope/obstruction	3 (2.7%)
Valvulopathy	3 (2.7%)
Pericardial effusion	9 (8.2%)
Cardiac MRI	52 (47%)
Cardiac consult at ICI initiation	58 (53%)
Laterality of cardiac mass	
Left	44 (40%)
Right	43 (39.8%)
Bilateral	15 (13.6%)
Location of cardiac mass	
Atrial	41 (37%)
Ventricular	39 (35%)
Pericardial	10 (9.1%)
Multiple	18 (16%)
Cardiac thrombus at ICI initiation	23 (21%)

CHF, Congestive heart failure; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ICI, immune checkpoint inhibitor.

(n=14, 13%), pericardial effusions (n=9, 8.2%), and congestive heart failure (n=9, 8.2%). One patient with an interatrial mass developed complete heart block. Of the entire cohort, 23 (21%) had cardiac thrombi at the time of ICI initiation that were detected radiographically.

Cardiac trAEs occurred in 2 (1.8%) patients. One was sinus tachycardia accompanied by chest pain, and the other was non-ST elevation myocardial infarction, and both cardiac trAEs prompted ICI discontinuation.

There were no cases of ICI-related myocarditis or pericarditis identified in our cohort.

Overall, 53 (48%) patients developed all-grade trAE (figure 1). The most common trAE were colitis/diarrhea (n=16, 15%), dermatitis (n=13, 12%), and hepatitis (n=9, 8.2%). 22 patients (20%) developed grade ≥3 trAE, most commonly colitis/diarrhea (n=8, 7.3%), dermatitis (n=3, 2.7%), pneumonitis (n=3, 2.7%), and hepatitis (n=3, 2.7%, figure 1). There was a significant enrichment for trAEs among patients treated with dual ICIs compared with ICI monotherapy (66% vs 42%, p=0.03). Systemic steroids were used in 35 (32%) patients with 21 patients requiring doses >1 mg/kg prednisone. Two (1.8%) patients required additional immunosuppression (one mycophenolate mofetil and one infliximab).

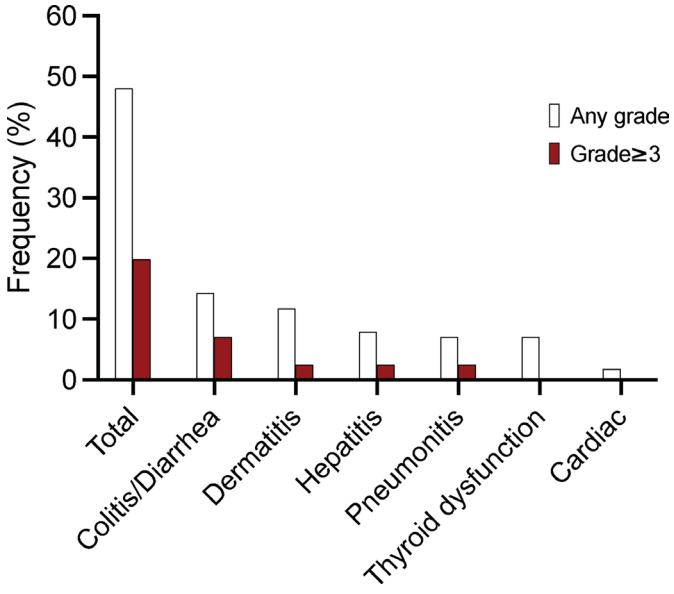

Figure 1 Distribution of trAEs in patients with cardiac metastasis treated with immune checkpoint inhibitor-based regimens. The sum of individual trAEs does not add up to the total as a subset of patients had more than one trAE. trAE, treatment-related adverse event.

Survival outcomes and response rates

Among 110 patients treated with ICIs for advanced cancers, the median OS was 12.2 months (95% CI: 9.1 to 19.6 months), and the median PFS was 5.6 months (95% CI: 4.3 to 9.0 months). ORR were assessed using RECIST V.1.1 criteria in 35 patients (33%) and by investigator assessment in 72 patients (67%). Of 107 patients evaluable for response, ORR was 34% with 6 patients with CR and 31 with PR. Of 98 patients with evaluable response in the cardiac mass, 37 (38%) patients achieved PR or CR in the cardiac mass. The concordance rate between cardiac and overall disease burden response rates was 88%. Of the 110 patients, 15 (13.6%) patients had bilateral cardiac or pericardial metastasis, 44 (40%) had left-sided cardiac or pericardial metastasis, and 43 (39.8%) had right-sided cardiac or pericardial metastasis. On multivariable analysis, there was no statistically significant difference between laterality of cardiac metastasis and PFS. Thoracic cancers and more than two prior lines of systemic therapy were associated with significantly lower PFS compared with skin cancer (thoracic cancers: HR=2.22, 95% CI: 1.17 to 4.2, p=0.014, figure 2). None of the other covariates (methods) were associated with PFS. For OS, head and neck, thyroid cancers, thoracic cancers, and more than two prior lines of systemic therapy were significantly associated with worse OS compared with skin cancers (head and neck, thyroid cancers: HR=9.3, 95% CI: 2.29 to 37.48, p=0.002); thoracic cancers: HR=7.16, 95% CI: 2.23 to 23.06 p<0.001). Right-sided tumors had significantly longer OS compared with bilateral tumors (HR=0.44, 95% CI: 0.2 to 0.98, p=0.04, figure 2). For ORR, the adjusted multinomial logistic regression model showed that patients with "other cancers" were significantly enriched for responders compared with skin cancers (OR=2.2, 95% CI: 1.10 to 4.29, p=0.02). None of the other covariates were associated with ORR.

Out of 42 patients with metastatic cutaneous melanoma, 34 (81%) patients received ICI in the first-line setting and 18 (43%) were on combination ICI. Median OS was 28.9 months (95% CI: 13.5 to 56.8 months, figure 3), and the median PFS was 9.0 months (95% CI: 5.1 to 21.3 months, figure 3). For 39 patients with cutaneous melanoma and evaluable response data, ORR was 38% (n=15) including 3 patients with CR. The concordance rate between cardiac and overall disease burden response rates was 83% (figure 4). Five patients achieved response in their cardiac mass but either had stable disease (n=3) or progressive disease (PD; n=2) in other non-cardiac sites as best response (figure 4). In contrast, one patient achieved PR in other sites but had PD in the cardiac mass.

Out of 26 patients with metastatic NSCLC, median OS was 9.7 months (95% CI: 5.8 to 14.4 months, figure 3), and the median PFS was 4.7 months (95% CI: 3.2 to 11.2 months, figure 3). The ORR for patients with NSCLC was 24% with all six responders achieving PR as best response. The concordance rate between cardiac and overall disease burden response rates was 83% (figure 4). Of four discordant patients, three achieved response in their cardiac mass but had SD (n=3) in other disease, whereas one patient achieved PR in the body but PD in the cardiac mass.

DISCUSSION

With increasing awareness and improvement of the diagnostic accuracy of imaging modalities on one hand, and the broad-scale regulatory approval of ICIs for various cancer types on the other, we are more likely to identify patients with cardiac metastasis who are candidates for ICI treatment. Immunotherapy has been associated with a 1-year absolute risk of cardiac adverse events in close to 7–10% in patients with lung cancer and melanoma.[16] As such, it is vital to better understand and acknowledge both the clinical benefit and the potential cardiac risk inherent to the use of ICIs, particularly in this select patient population. In our cohort, we did not find any additional safety signals with ICI treatment, although the rate of cardiac trAEs was threefold higher than previously reported in a large cohort of 6,925 patients who received anti-PD-(L)1-based therapies (rate of major adverse cardiac events of 0.6%).[17] Moreover, cardiac events from cardiac metastasis occurred in more than one-third of patients consistent with prior retrospective data.[18] Of note, we did not have patients in our cohort who developed ICI-related myocarditis or pericarditis. Finally, among patients with melanoma and NSCLC, ICIs demonstrated consistent clinical responses in the cardiac mass itself and the overall disease burden.

Prior work suggested that mortality at 2 years was higher for patients with melanoma and cardiac metastasis compared with those without.[18] However, our findings

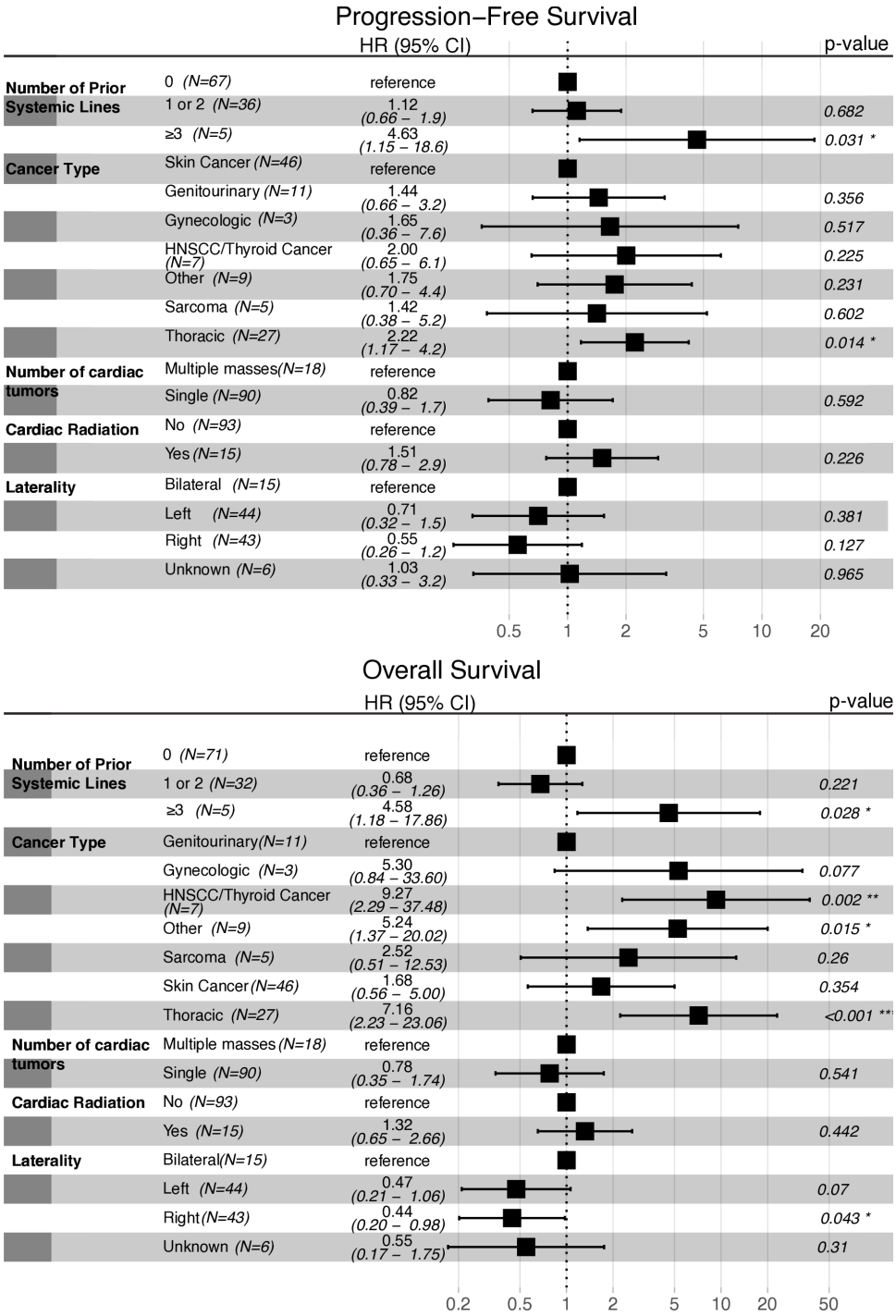

Figure 2 Forest plot for patients with progression-free survival and overall survival data. Covariates are shown. Cox regression p values are indicated on the right. Bars represent the 95% CI. HNSCC, head and neck squamous cell carcinoma.

reveal meaningful clinical benefit in patients with melanoma and NSCLC treated with ICIs, extending responses to cardiac masses. We also noted concordance rates above 80% between responses in the cardiac mass and overall disease burden. This contrasts with our recent study on ICIs among patients with primary cardiac sarcomas, where ORRs were 11%.[20] Moreover, responses in the heart surpassed those observed in the brain, traditionally considered a sanctuary site, where a recent phase II trial of pembrolizumab among patients of different tumor histologies with brain metastasis showed a response rate of 8.8%.[21] This underscores the potential efficacy of immunotherapy in managing secondary cardiac masses. Additionally, our data suggest the need for further exploration to better understand the differences in the cardiac metastasis microenvironment and associated genetic markers compared with the primary tumor.

In the overall cohort, right-sided cardiac metastases were associated with significantly longer OS compared with bilateral cardiac metastases. A plausible explanation

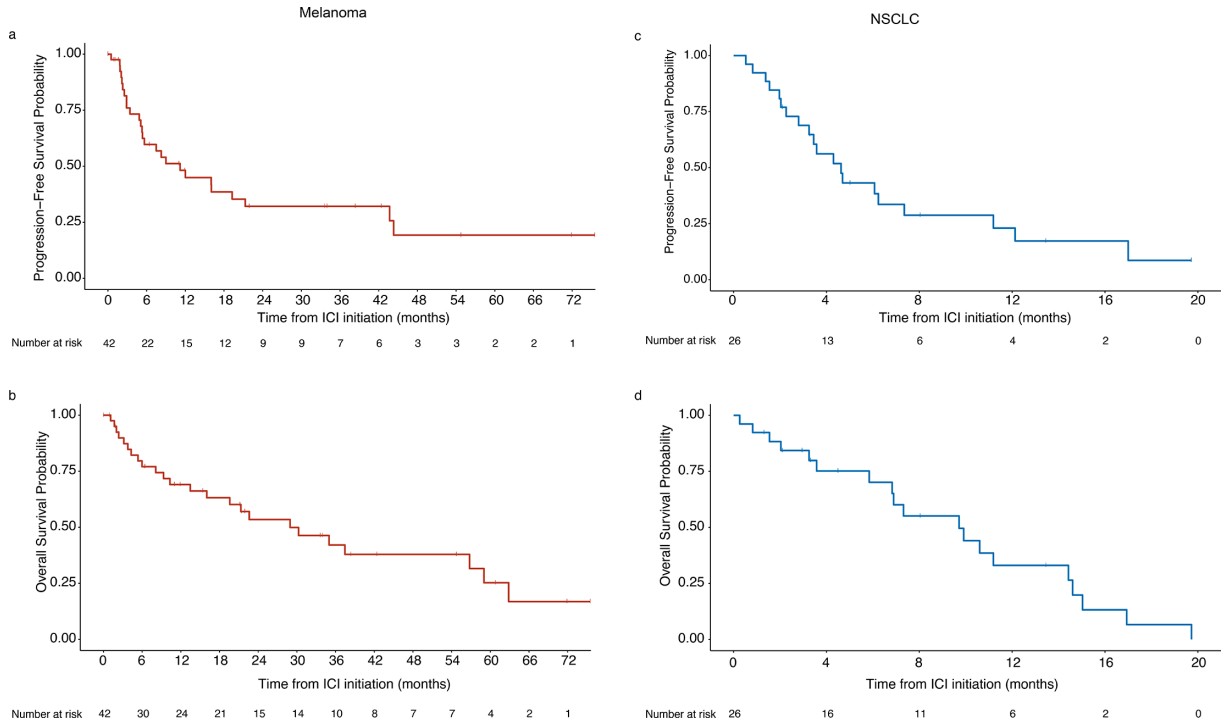

Figure 3 Survival outcomes for patients with cardiac metastasis among common tumor types. Progression-free survival (a) and overall survival (b) of 42 patients with cutaneous melanoma treated with immune checkpoint inhibitor (ICI)-based regimens. Progression-free survival (c) and overall survival (d) of 26 patients with NSCLC treated with ICI-based regimens. NSCLC, non-small cell lung cancer.

is that bilateral cardiac involvement may exacerbate the risk of tumor embolization into both the pulmonary and systemic circulations. This heightened embolic risk could accelerate clinical deterioration and reduce survival. In contrast, right-sided tumors, confined to the pulmonary circuit, may present a lower embolic burden, allowing for more effective management and potentially contributing to the observed survival benefit.[2]

In our cohort, cardiology specialists were involved in just over 50% of patients with cardiac metastasis. Our study underscores the importance of involving a multidisciplinary team, especially including cardiologists and cardio-oncologists, in the evaluation and management of patients with cardiac metastasis. Cardio-oncology consultation, in particular, can lead to more integrated decision-making that encompasses various aspects of the patient's disease, including cancer, cancer treatment, and cardiovascular comorbidities (eg, cardiac imaging features relevant to risk of adverse events associated with the metastasis). Overall, early collaboration is crucial to safeguard patients' cardiac health, enhance their quality of life, and manage any ensuing cardiac events or cardiotoxicity.[22 23]

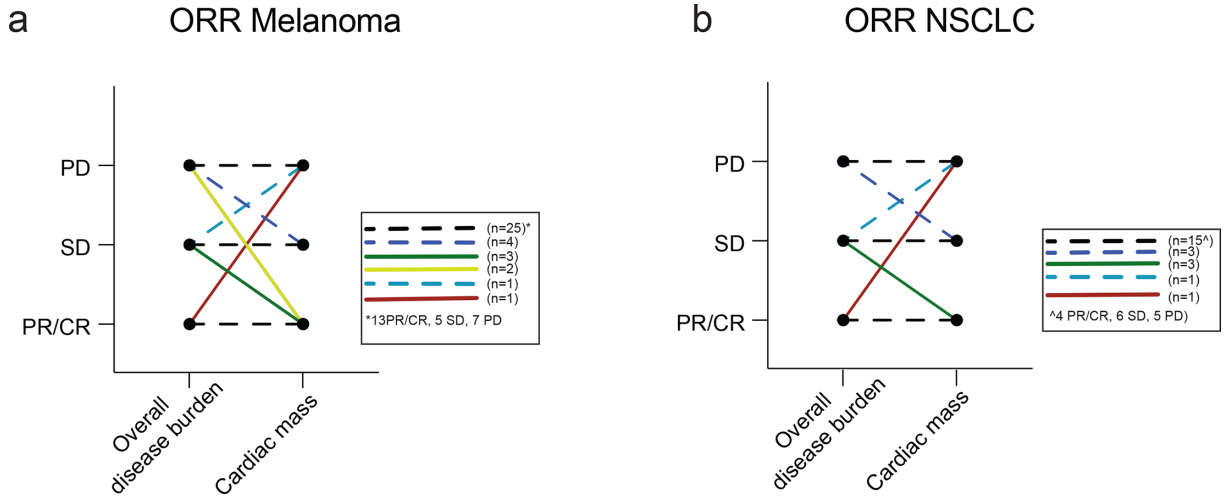

Figure 4 Concordance rates in overall response rate (ORR) between overall disease burden and cardiac mass. Solid lines refer to discordant ORRs. Dashed lines refer to concordant ORRs. (a) cutaneous melanoma (b) NSCLC. CR, complete response; NSCLC, non-small cell lung cancer; PR, partial response; SD: Stable disease; PD: Progressive disease.

Our work has several limitations. First, our study was retrospective and prone to potential selection bias, as patients were mostly treated at academic centers and in countries where ICIs and advanced imaging modalities such as cardiac MRI are available. Moreover, given the lack of autopsy data, the numbers we report are likely an underestimation and involve selection bias against patients with asymptomatic cardiac involvement. Second, response evaluations were a mix of objective response assessments by RECIST V.1.1 (when available from the radiologist) and investigator-based evaluations. Third, the incidence of trAEs is lower than expected based on publicly reported trAE rates. This may be because patients were treated outside of clinical trials and thus subject to suboptimal capture of events. However, the rate of higher grade trAEs (grade ≥3) is less likely to be burdened by under-reporting. It can also be challenging to differentiate between trAEs and cardiac events as a result of the cardiac mass itself. Another limitation is that most cardiac masses were diagnosed radiographically rather than pathologically. However, this is in line with clinical practice, as we seldom perform additional tissue sampling due to the high-risk nature of cardiac biopsies, especially if metastatic involvement has been confirmed at another anatomic location. To circumvent this, all cases were adjudicated by radiology experts as having a malignant appearance. Finally, the heterogeneous mix of cancer types in the cohort may have influenced the frequency and distribution of cardiac events and trAEs.

In conclusion, this retrospective study demonstrated that ICIs can be safely administered to patients with cardiac metastasis and have meaningful clinical efficacy both in the cardiac mass itself and the overall tumor burden. Cardiac metastases can still be associated with cardiac events, and hence a multidisciplinary team including oncologists, cardiologists, hematologists, cardiac rehabilitation professionals, primary care providers, and others is essential in both routine clinical practice and clinical trials.

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