# Response by Thuny et al. to Letter Regarding Article, "Clinical Features, Management, and Outcomes of Immune Checkpoint Inhibitor–Related Cardiotoxicity"

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**Response to Letter Regarding Article, « Clinical Features, Management, and Outcomes of Immune Checkpoint Inhibitor–Related Cardiotoxicity »**

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We thank Campochairo et al. for the interesting 3 points they raised in our work.[1]

Firstly, there are no criteria for establishing diagnosis of immune check-point inhibitors (ICIs)-related cardiotoxicity. Thus, the cause-effect relationship is not simple when cardiovascular events occur. As immune-mediated myocarditis is the most widely recognized mechanism for this cardiotoxicity,[2] the evidence of signs of myocarditis under ICIs would make it possible to establish a definite relationship between the cardiovascular event and ICIs. The gold standard for myocarditis diagnosis is based on the endomyocardial biopsy (EMB), which is not always achieved due to its invasive aspect and lack of sensitivity.[3] Cardiac magnetic resonance imaging (CMR) can strongly help in diagnosis but its performance is also not perfect.[4] The European Society of Cardiology has provided simple diagnostic criteria to define suspicion of myocarditis.[5] These are 4 criteria including EKG signs, troponin elevation, cardiac morphological abnormalities and CMR tissue abnormalities. Myocarditis is suspected if ≥1 clinical signs/symptoms and ≥1 diagnostic criteria from different categories, in the absence of: (1) angiographically detectable coronary artery disease; (2) known pre-existing cardiovascular disease or extra-cardiac causes that could explain the syndrome. Suspicion is higher with higher number of fulfilled criteria. In our study, of the 22 patients who did not have EMB or had negative EMB, all had new symptoms, 2 patients fulfilled the 4 diagnostic criteria, 3 had 3 criteria, 9 had 2 criteria, and 8 had 1 criterion. Thus, although some patients had neither EMB nor CMR, the diagnosis of myocarditis could not be ruled out. Furthermore, we cannot exclude as-yet unidentified other mechanisms of cardiotoxicity or a low phenomenon of inflammation that could lead to progressive left ventricular dysfunction without troponin elevation.

Secondly, in our study, 7 patients (23%) showed signs of myositis. Of these, all had EKG abnormalities, 4 had systolic left ventricular dysfunction, and 3 died from cardiovascular

cause. Endomyocardial biopsy was always positive (3/3 patients), as was troponin (6/6 patients). Two patients had CMR, which was positive in only one patient. It seems that signs myositis in patients with new cardiovascular event might constitute a criteria to suspect ICI-related cardiotoxicity.

Third, immune therapy was administrated again in 4 patients after ICI-related cardiotoxicity. Three patients had developed systolic left ventricular dysfunction, with complete improvement after ICIs rechallenging in two of tem. None of the 4 patients had had EMB or CMR before rechallenging and none had received steroids or immune suppressive therapy.

In conclusion, global pathogenesis of ICI-related cardiotoxicity is not well known and diagnostic criteria are lacking. Waiting for future studies and considering the potential severe complications of this adverse event, we believe that a high index of suspicion and low threshold for investigation should be applied in case of cardiovascular signs/symptoms in patients with ICIs. In addition to clinical evaluation, patients should have at least EKG, echocardiography, troponin, and CMR evaluation. Endomyocardial biopsy should be discussed in each difficult case. Guidelines are urgently needed for the management of this novel entity in « the world of the cardio-oncology ».

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## DISCLOSURES

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