



HAL
open science

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

Franck Thuny, Stéphane Ederhy, Marion Escudier, Nathalie Lalevee, Jennifer Cautela

► To cite this version:

Franck Thuny, Stéphane Ederhy, Marion Escudier, Nathalie Lalevee, Jennifer Cautela. Response by Thuny et al. to Letter Regarding Article, “Clinical Features, Management, and Outcomes of Immune Checkpoint Inhibitor–Related Cardiotoxicity”. 2018, pp.2423 - 2424. 10.1161/CIRCULATIONAHA.118.033783 . hal-01843016

HAL Id: hal-01843016

<https://amu.hal.science/hal-01843016>

Submitted on 24 Jan 2019

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L’archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d’enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution 4.0 International License

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

Franck Thuny, MD, PhD,^{1,2,3,4} Stephane Ederhy, MD,⁵ Marion Escudier, MD,^{1,2,3,4} Nathalie
Lalevee, PhD,² Jennifer Cautela, MD, PhD^{1,2,3,4}

¹ Aix-Marseille Univ, Assistance Publique – Hôpitaux de Marseille, Mediterranean university
Cardio-Oncology center (MEDI-CO center), Unit of Heart Failure and Valvular Heart
Diseases, Department of Cardiology, Hôpital Nord, Marseille, France

² Aix-Marseille Univ, Centre de Recherche Cardiovasculaire et Nutrition (C2VN) -
Inserm 1263, Inra, Marseille, France

³ Groupe Méditerranéen de Cardio-Oncologie (gMEDICO), France

⁴ Aix-Marseille Univ, Assistance Publique – Hôpitaux de Marseille, Oncosaftey Network of
the Early Phases Cancer Trials Center (CLIP²), Marseille, France

⁵ Hôpitaux Universitaires Paris-Est, Hôpital Saint Antoine, Hôpital Tenon. Assistance
Publique – Hôpitaux de Paris, Inserm 856, Université Pierre et Marie Curie (Paris VI), Paris,
France

Total word count: 500

Corresponding Author

Prof. Franck Thuny

Mediterranean University Cardio-Oncology center, Unit of Heart Failure and Valvular Heart
Diseases, Hôpital NORD, Chemin des Bourrely, 13015, Marseille, France

Tel: +33 (0) 491 968 683; Fax: +33 (0) 0491 968 979

e-mail: franck.thuny@gmail.com

We thank Campochoairo 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 of myositis in patients with new cardiovascular event might constitute a criteria to suspect ICI-related cardiotoxicity.

Third, immune therapy was administered 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 them. 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 ».

REFERENCES

1. Escudier M, Cautela J, Malissen N, Ancedy Y, Orabona M, Pinto J, Monestier S, Grob JJ, Scemama U, Jacquier A, Lalevee N, Barraud J, Peyrol M, Laine M, Bonello L, Paganelli F, Cohen A, Barlesi F, Ederhy S and Thuny F. Clinical Features, Management, and Outcomes of Immune Checkpoint Inhibitor-Related Cardiotoxicity. *Circulation*. 2017;136:2085-2087.
2. Johnson DB, Balko JM, Compton ML, Chalkias S, Gorham J, Xu Y, Hicks M, Puzanov I, Alexander MR, Bloomer TL, Becker JR, Slosky DA, Phillips EJ, Pilkinton MA, Craig-Owens L, Kola N, Plautz G, Reshef DS, Deutsch JS, Deering RP, Olenchock BA, Lichtman AH, Roden DM, Seidman CE, Koralknik IJ, Seidman JG, Hoffman RD, Taube JM, Diaz LA, Jr., Anders RA, Sosman JA and Moslehi JJ. Fulminant Myocarditis with Combination Immune Checkpoint Blockade. *N Engl J Med*. 2016;375:1749-1755.
3. Baughman KL. Diagnosis of myocarditis: death of Dallas criteria. *Circulation*. 2006;113:593-5.
4. Friedrich MG, Sechtem U, Schulz-Menger J, Holmvang G, Alakija P, Cooper LT, White JA, Abdel-Aty H, Gutberlet M, Prasad S, Aletras A, Laissy JP, Paterson I, Filipchuk NG, Kumar A, Pauschinger M, Liu P and International Consensus Group on Cardiovascular Magnetic Resonance in M. Cardiovascular magnetic resonance in myocarditis: A JACC White Paper. *J Am Coll Cardiol*. 2009;53:1475-87.
5. Caforio AL, Pankuweit S, Arbustini E, Basso C, Gimeno-Blanes J, Felix SB, Fu M, Helio T, Heymans S, Jahns R, Klingel K, Linhart A, Maisch B, McKenna W, Mogensen J, Pinto YM, Ristic A, Schultheiss HP, Seggewiss H, Tavazzi L, Thiene G, Yilmaz A, Charron P, Elliott PM, European Society of Cardiology Working Group on M and Pericardial D. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J*. 2013;34:2636-48.

DISCLOSURES

Franck Thuny has received modest consultant and lecture fees from Astra-Zeneca, Novartis, Sanofi, Boston Scientific, Bristol-Myers Squibb.

Jennifer Cautela received received modest consultant and lecture fees from MSD, Janssen, Merck, Novartis, Astra-Zeneca.

Stephane Ederhy received modest consultant and lecture fees from Lilly, Daiichy-Sankyo, Celgene, Pfizer, Esperare, Bristol-Myers Squibb, Janssen, Philips Healthcare, Bayer, Novartis, Amgen, Ipsen.