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## REPLY: Cardiotoxicity of BRAF/MEK Inhibitors According to HFA/ICOS Cardiotoxicity Risk Category

We are grateful to Dr Courand and colleagues for their interest in our recent study[1] characterizing the incidence, time course, and risk factors for cancer therapy-related cardiac dysfunction (CTRCD) in patients with melanoma treated with BRAF and MEK inhibitors. We were interested to read their analysis of the incidence of CTRCD in their own cohort using contemporary definitions of CTRCD[2] and risk stratification scores recommended by the Heart Failure Association and International Cardio-Oncology Society.[3] In their analysis of 88 patients, they found that "severe" and "moderate" CTRCD occurred in <1% and 7%, respectively, and that moderate CTRCD was observed mainly in patients in the low and medium baseline risk category. Given that 10% of patients at our own center developed moderate CTRCD, these findings from France are in reasonable agreement with our own and lend support to the validity of findings from both our groups. Furthermore, we concur that CTRCD in these patients does appear to be reversible in the context of treatment with angiotensin-converting enzyme inhibitors and/or beta-blockers. However, the long-term consequences of unrecognized asymptomatic CTRCD remain poorly understood, including the potential for attenuated reversibility of CTRCD and progression to the clinical syndrome of heart failure if unrecognized. Therefore, we agree that current cardiac imaging surveillance strategies remain appropriate for the time being. Importantly, better baseline risk stratification and longitudinal biomarkers of CTRCD are needed for patients treated with BRAF and MEK inhibitors, as the currently recommended risk stratification tool appears to have limited discriminatory potential. We believe that both retrospective analyses reinforce the need for larger, prospective studies to define risk factors for the development and progression of BRAF and MEK inhibitor-associated cardiotoxicity. We are actively working on this. We aim to fill important evidence gaps so that patients can benefit from the important anticancer effects of these drugs while minimizing adverse cardiovascular effects, including via the use of appropriately stratified and targeted cardiovascular surveillance.

**Claire Glen, MBChB**
**Sarah Adam, BSc**
**Caroline J. Coats, MBChB, PhD**
***Ninian N. Lang, MBChB, PhD**

*BHF Glasgow Cardiovascular Research Centre
School of Cardiovascular and Metabolic Health
University of Glasgow
Glasgow G12 8TA, United Kingdom
E-mail: ninian.lang@glasgow.ac.uk
@ninianlang

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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