 DOI: https://doi.org/10.5114/ceji.2025.151335

Deciphering cardiotoxicity in PD-1/PD-L1 inhibitor treatment

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(Cent Eur J Immunol 2025; 50 (1): 2)

Inhibitors targeting the PD-1/PD-L1 immune checkpoint axis have revolutionized cancer treatment, offering unprecedented survival benefits across various malignancies [1]. However, the growing body of evidence linking these therapies to immune-related adverse events (irAEs), particularly cardiotoxicity, demands closer scrutiny [2, 3]. In this issue of the *Central European Journal of Immunology*, Fu *et al.* present compelling experimental findings that shed new light on the mechanisms underpinning PD-1/PD-L1 inhibitor-induced cardiotoxicity [1].

Using a murine model, the authors demonstrate that cardiotoxicity induced by BMS-1, a PD-1/PD-L1 inhibitor, is tightly regulated by macrophage polarisation and the SOCS3/JAK/STAT3 signalling cascade. The study provides critical insights into how innate immune cells, namely M1/M2-polarized macrophages, contribute to myocardial damage under immune checkpoint blockade. Moreover, the identification of the SOCS3 axis as a potential modulator of this process opens new therapeutic avenues for mitigating irAEs without compromising antitumour immunity.

This work complements and extends recent studies in CEJI that highlight the immunological complexity of PD-1/PD-L1-directed therapies. For example, Zhao *et al.* [5] reported heterogeneous patterns of disease progression in hepatocellular carcinoma patients undergoing combination therapies, suggesting that immune modulation in these contexts may not be limited to tumour cells alone. Similarly, Zeng *et al.* [6] demonstrated that PD-L1 expression and tumour-infiltrating lymphocyte profiles differ between primary and metastatic breast tumours, further emphasizing the spatial and temporal diversity of immune responses under checkpoint blockade.

Taken together, these studies underscore a crucial message: while PD-1/PD-L1 inhibitors offer clinical benefit, their broader immunological impact remains under active investigation. The work of Fu *et al.* makes a timely and significant contribution to this dialogue, calling for integrative approaches that couple therapeutic efficacy with immune safety. As the field moves toward increasingly personalised immuno-oncology strategies, mechanistic insights such as those provided here are indispensable in guiding both clinical practice and translational research.

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