Response to: 'Drug-induced lupus erythematosus following immunotherapy with anti-programmed death-(ligand) 1' by Michot *et al* and 'Checkpoint inhibitor-associated immune arthritis' by Arnaud *et al*

We thank Michot *et al* for their comments¹ on our original paper entitled 'Rheumatic disorders associated with immune checkpoint inhibitors in patients with cancer-clinical aspects and relationship with tumour response: a single-centre prospective cohort study'.² We also appreciate the information added in the letter by Arnaud *et al* also reporting data from the WHO database.³

By adding this series of programmed death-(ligand) 1 (PD-(L)1)-induced lupus erythematosus, the authors contribute to our better knowledge of the wide spectrum of immune-related adverse events (irAEs).

Indeed, since PD-1-deficient mice spontaneously developed lupus-like autoimmune diseases with arthritis and glomerulonephritis,⁴ such clinical phenotypes could be expected in patients treated with anti PD-(L)1 agents. However, only a few cases of lupus-like cutaneous reaction have yet been reported with anti-PD-1 agents and, more surprisingly, one lupus-like nephritis has been attributed to anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) treatment.⁵ While the role of immune checkpoints is actively being investigated in murine lupus models,^{6,7} there is still a long road ahead to understand why some patients will experience lupus-like irAE with cancer immunotherapy. We must keep in mind that PD-1 knockout models do not reproduce an anti-PD-1 treatment as PD-1 knockout mice performed their thymic selection without PD-1 expression while patients receive anti-PD-1 treatment many years later, a long time after the major period of thymic selection. This reinforced the hypothesis of a possible genetic background (PD-1 gene polymorphisms) highlighted by Michot *et al*, to be investigated in patients presenting with irAEs in order to elucidate whether checkpoint inhibitors trigger specific disease on host genetic susceptibility or not. Furthermore, it would be worthwhile to know the baseline status for the two patients with antinuclear antibodies as the presence of anti-cyclic citrullinated peptide antibodies has been detected before immunotherapy in some patients experiencing PD-1-induced rheumatoid arthritis.⁸ Another hot research area concerns the role of commensal gut microbiota on the outcome of cancer immunotherapies, focusing mainly on efficacy. The concept that gut microbiota may modulate systemic autoimmunity is not new, and there is emerging evidence that dysbiosis participates in the complex pathogenesis of lupus.⁹ Thus, if microbiota can shape tumour response, its involvement (including viruses) in the pathogenesis of irAEs should be further investigated, as suggested by Chaput *et al* for colitis.¹⁰

PD-(L)1-induced autoimmune diseases have strongly renewed interest in assessing the role of immune checkpoints in classical autoimmune diseases, although we observed some differences in terms of demographics and an autoimmune biology often negative. Co-stimulatory molecules have been tested in the treatment of systemic lupus erythematosus (SLE) such as CD154 and CTLA-4 Ig but trials failed to achieve their primary outcome.¹¹ Despite disappointing results, the central role of co-stimulation between antigen-presenting cells

and T cells in the pathogenesis of lupus, as well as efficacy data of abatacept on articular and cutaneous manifestations,¹² called for further evaluation. Recently, a fully human antibody directed against the inducible T-cell co-stimulator ligand showed safety and potential efficacy in patients with SLE with arthritis.¹³

The next wave of immuno-oncology will include agonists of co-stimulatory signals, such as OX40 antibodies already being tested in clinical trials, which might also trigger lupus-like disease and other autoimmune conditions. As highlighted by Arnaud *et al*, the expanding use of cancer immunotherapies and the better recognition of irAEs result in higher reporting incidence of irAEs. Registers remain the best way to collect more accurate data on characteristics, management and outcomes of irAEs. Such as the European League Against Rheumatism study group for Registers and Observational Drug Studies on bDMARDs,¹⁴ European-wide collaboration across several local/nationwide registers will likely help to improve our management of rheumatic irAEs.

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Contributors MK, CR and TS: conception. MK drafted the manuscript. CR and TS critically reviewed and approved the final version of the manuscript.

Competing interests None declared.

Patient consent Not required.

Provenance and peer review Commissioned; internally peer reviewed.

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To cite Kostine M, Richez C, Schaevebeke T, *et al*. *Ann Rheum Dis* 2019;**78**:e69.

Received 26 May 2018

Accepted 29 May 2018

Published Online First 22 June 2018

► <http://dx.doi.org/10.1136/annrheumdis-2018-213470>

► <http://dx.doi.org/10.1136/annrheumdis-2018-213677>

Ann Rheum Dis 2019;**78**:e69. doi:10.1136/annrheumdis-2018-213691

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