Reply to 'Personalized treatment of immune-related adverse events — balance is required'

Kashayar Esfahani and Leonard Calabrese

We wish to respond to the letter on our Review (Moving towards personalized treatments of immune-related adverse events. *Nat. Rev. Clin. Oncol.* https://doi.org/10.1038/s41571-020-0352-8 (2020))[1] from Martins and Obeid (Personalized treatment of immune-related adverse events — balance is required. *Nat. Rev. Clin. Oncol.* https://doi.org/10.1038/s41571-020-0400-4 (2020))[2]. The study of immune-related adverse events (irAEs) in patients receiving immune-checkpoint inhibitors (ICIs) is incredibly complex and fast moving. While we acknowledge the contribution of Martins et al.[3] in this field, many groups (including ours) have collaboratively worked and reported on fine-tuning the personalized treatments of irAEs by dissecting the drivers of toxicities[4–6]. In their Review and letter, the proposed algorithm is reliant on findings of light microscopy from affected organs, which is both practical and easily feasible. However, we posit that irAEs provide us with a unique window of opportunity for studying autoimmunity, and advanced immunophenotyping techniques (including flow cytometry, multiplex cytokine analysis or advanced immunohistochemistry, among others) should be leveraged to better understand the drivers of toxicities, especially in immunosuppression-refractory cases or those involving critical organs such as in the cases we cite above[4–6]. With this motivation in mind, we have provided a much-needed update to this field by critically appraising the complex immunohistopathological mechanisms by which irAEs are induced in patients receiving ICIs, as well as covering emerging fields such as those of innate immunity and the microbiome[1].

The assertion of Martins and Obeid[2] regarding the dangers of antagonizing cytokines associated with innate immunity (such as IL-5), which might not effectively suppress T cell function, seems to be based on the assumption that all irAEs are T cell mediated and are the result of a breach of self-tolerance. The current evidence points towards an important role of innate immune cells in potentially driving both antitumour responses and irAEs in patients receiving ICIs, as highlighted in our Review[1]. As such, some irAEs are possibly the result of activation of innate immune responses, leading to an autoinflammatory phenotype, with limited or no contribution of self-directed T cell processes. In these situations, we consider that not exposing patients to the deleterious adverse effects of additional immunosuppression might be an important future approach, where "balance is required"[2]. Discriminating between potential causes for irAEs requires leveraging advanced immunophenotyping techniques beyond light microscopy, which is the approach we encourage.

We further agree with Martins and Obeid[2] with regard to the clinical implications of targeted treatments on antitumour responses, another area that has remarkably expanded in the past few months. As an example, Martins and Obeid report their personal use of a B cell-targeted therapy in the setting of irAEs[7]. However, we now have deeper insights into the role of B cells as drivers of antitumour responses in patients receiving ICIs[8]. The potential antagonistic effects of rituximab on cancer immunosurveillance would thus be an interesting topic to further explore. It is under this light that they also rightfully question our proposal of using JAK inhibitors in the setting of irAEs, given that *JAK1/2* mutations are a known resistance mechanism to anti-PD-1 therapy. Since the publication of our Review[1], we have reported that the careful and limited use of the JAK inhibitor tofacitinib can induce remission of immune-related colitis refractory to corticosteroids, infliximab and vedolizumab, without impairing antitumour immune surveillance[9]. This case report provides yet another demonstration of the practical real-life application of the "balance is required" axiom in the management of challenging irAEs. Although novel and promising, such single-case studies reported by our group and Martins et al. require validation in randomized clinical trials.

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Competing interests
The authors declare no competing interests.