

Answering Reviewers

1. Comments to the Author: This is an interesting review study by Som and colleagues, examining the widespread and successful use of immune checkpoint inhibitors (ICI) immunotherapies, however, calling the attention for common immune-related adverse events (irAEs). In particular, the authors focus on the ubiquitous development of colitis secondary to the use of ICI for cancer treatment, including pathogenic and clinical aspects, in addition to medical management. Specific comments to Authors: In terms of contents, the approach is interesting and well structured. However, it would be interesting to further discuss differential diagnosis, especially regarding IBD. Which parameters should be used to establish differential diagnosis and to rule out IBD, for example? Another important point emerges from the fact that some patients with irAEs are treated with anti-TNF-alpha agents. Considering that anti-TNF have some relative and absolute contraindications, including some types of cancers, authors should be more specific on that issue.

Revisions: The histology section now describes and answers the above question of how to exclude IBD from ICI colitis.

2. The manuscript is a review of immune checkpoint induced colitis, and includes a mechanistic overview followed by diagnosis, management and the potential for prevention. The topic is novel, under-explored and, as the authors suggest, has the potential to increase in prevalence given the relatively recent use of these drugs and their potential for expansion into widespread use for cancer treatment. The quality is high and there are only minor comments: 1: Mechanism of action section, sentence starting "CTLA-4 is a negative regulator of T-cell-mediated....." There is a grammatical error between 'responses cell' in this sentence. 2: Mechanism of irAEs section, sentence starting 'Consequently, it has been hypothesised that antibody to'. There is a grammatical error also here. 3: Epidemiology section. 2nd paragraph 'Beck et. al.'. The type of cancer(s) treated in the Beck reference should be included.

Revisions: These grammatical errors have been corrected in the revised manuscript.

3. Some minor corrections are suggested. I attach a revised version of the manuscript, showing some of them. In addition, I encourage authors to: 1.- Provide accurate reference for figure 2 2.- Provide accurate reference for table 2 3.- Comment on the assertion, when discussing Mechanism of irAEs that: "Consequently, it has been hypothesized that antibody to CTLA4 might diminish Treg cells and accordingly induce autoimmunity [27]" Is this so now? Reference 27 dates back to 2005. Could authors update this point?

Revisions: The references stated above have been fixed in the revised document.