We thank the Reviewer for the overall positive evaluation of the manuscript and for the constructive comments. We were happy to read that the manuscript received a very high score, and classified as “Excellent”.
Our responses to the comments are as follows:

Comment 1: “Is ‘Receptors’ in the title required?”
While immune checkpoint-based immunotherapy intends to modulate immune checkpoint-regulated signaling pathways, the current therapies are based on the utilization of antibodies against immune checkpoint surface receptors. Thus, inclusion of the word ‘receptors’ in the title emphasizes the fact that the present review discusses cancer immunotherapy mediated by targeting immune checkpoint receptors, and not other downstream signaling molecules or transcription factors involved in these pathways.

Comment 2: “Page 4, line 16, spelling IL-2-dependent”
The term ‘IL-2’ was mentioned for the first time on page 4, line 16. Therefore, we corrected the text and included the full name of IL-2 (interleukin-2) and the abbreviated name (IL-2).

Comment 3: “Page 5, lines 8-10; requires elaboration on findings, rather then just say altered”
In agreement with the Reviewer’s suggestions, we have included more detailed description of the actual effects of the CTLA-4 knock-down on mice.

Comment 4: “Page 5, lines 11-14; Do cancer cells perturb CTLA4 function or expression as to do with PD-1/PL-L1 pathway?”
The indicated paragraph describe the fact that studies on the biological role of CTLA-4 laid the groundwork for the development of new strategies for cancer immunotherapy. Whether Cancer cells perturb CTLA-4 function or expression depends on the specific type of the cancer and/or its altered/mutated genes and on a specific hematopoietic cell type which might interact with it. Unfortunately, there is no general answer to such a question.

Comment 5: “Page 5, line 27: PD-1. This should be left after the description of the PD-1/PD-L1 pathway below”
In agreement with the Reviewer’s comment, the relevant paragraph was moved to the end of the section describing the utilization of nivolumab, an anti-PD-1 antibody.

Comment 6: “Page 6, line 26-29: Explain how this difference between the 2 subsets achieved”
The actual mechanistic basis for this difference is not known.
However, we have provided one possible explanation for the opposite effects of PD-1-induced signals on the two distinct T cell subtypes. It is based on the role of PKCθ in PD-1-induced signals and the independent findings showing that PKCθ recruits to the center of the immunological synapse of activated effector T-cells but it is sequestered away from the Treg immunological synapse, and concentrates at the opposite pole.

Comment 7: “Page 11, line 9-12; Reference?”
In agreement with the Reviewer’s suggestion, a reference was added at the end of this paragraph.

Comment 8: “What about Th17?”
This is a very good, but also a very general and broad question which can be answered in an independent full-length review manuscript. The aim of the present article is to concentrate on immune checkpoint receptors and their relevance to cancer immunotherapy. We had no intention on focusing on any specific cell type, or writing a thorough and comprehensive review on this topic.

Comment 9: “Page 15, line 1-3; This gives an unnecessary negative impression. Why is this an obstacle to the therapy? Perhaps a better word is needed or rephrase the sentence.”
In agreement with the Reviewer’s suggestion, the relevant sentence has been re-written to reflect a more optimistic view of the current scientific efforts to improve immune checkpoint therapy.