Peer Review File

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Reviewer Comments: Immune checkpoint inhibitors (ICIs) are immunomodulatory antibodies that intensify the host immune response, thereby leading to cytotoxicity. In the manuscript "Immune Checkpoint Inhibitors in Lymphoma: Challenges and Opportunities", authors outlined the existing and ongoing studies utilizing ICI therapy in various lymphomas, and described the challenges leading to the lack of efficacy with ICI use and discuss potential strategies to overcome those challenges.
Couple questions are required to be answered before it will be accepted.

Comment 1: In the introduction, it was showed that the success with ICIs in hematologic malignancies has been limited. Please provide a supported reference. It is common sense that immunotherapy was more efficacy for hematologic malignancies than solid organ malignancies.
Response 1: We thank the reviewer for this constructive feedback, and we have added reference number 2, by Salik B et al, entitled Targeting immune checkpoints in hematological malignancies.

Comment 2: Under which status, patients with lymphoma should be treated with ICIs?
Response 2: As of now, immune checkpoint inhibitor based therapy is only approved for relapsed/refractory Hodgkin lymphoma and primary mediastinal B-cell lymphoma. We have mentioned these approvals explicitly in the introduction section and are the recommended indications, and also mentioned in the text of individual lymphomas.

Comment 3: In DLBCL, PD-L1 overexpression is observed in about of 20% of DLBCL and occurs primarily on macrophages. Please supplement the analysis about the low frequency of PD-L1 overexpression in DLBCL.
Response 3: Thank you for the feedback. We have now added supplemental data from Kiyasu et. al. who examined over 1250 DLBCL samples using PD-L1 and

PAX5 staining techniques and found that 10.5% of patients expressed PD-L1. This information is presented in the section on diffuse large B-cell lymphoma.

Comment 4: In chronic lymphocytic leukemia/small lymphocytic lymphoma, the PD-L1/PD-1 expression in CLL/SLL can range between 10-90%. The variation of PD-L1/PD-1 expression was so large. Based on what to determine the ICIs were suitable for CLL/SLL.

Response 4: This large variability of PD-L1 expression is likely secondary to differences in antibodies used, methodology employed, and staining specificity. Nevertheless, in aggressive cases of CLL/SLL, there is an expansion of CD8+/PD-1 and T memory cells that subsequently inverts the CD4:CD8 ratio. As presented in the manuscript, ICI therapy has not shown efficacy so far in CLL, but showed some promising activity in Richter transformation, in which the complete responses correlated with PDL1 expression on tumor cells and microenvironment. We have described this in detail in the section on CLL.

Comment 5: How about the expression of PD-1/PD-L1 in Burkitt lymphoma and HIV-associated lymphoma? How about the side effect or adverse events induced by ICIs treatment for lymphoma? Please supplement in the part of Challenges Limiting the Efficacy of ICI Therapy in Lymphoma.

Response 5: Thank you for the feedback. This specific information has been included in the designated sections, pertinent to Burkitt lymphoma and HIV-associated lymphoma. We have also created a separate section discussing about the toxicities of ICI therapy in lymphoma studies, mostly derived from Hodgkin lymphoma.

Comment 6: In cHL, the presence of CD163+/CD68+ macrophages in tumor microenvironment was found to be associated with shorter survival and chemotherapeutic resistance. Why not to move the part of TAMs to the part of TME?

Response 6: Thank you. The following line: “In cHL, the presence of CD163+/CD68+ macrophages in the tumor microenvironment was found to be associated with shorter survival and chemotherapeutic resistance” has been

added to the tumor microenvironment or TME section and the two sections have now been combined in our paper.

Comment 7: Compared to other immunotherapy (such as CAR-T), what are the advantages and disadvantages of ICIs for lymphoma? Please supplement in the discussion.
Response 7: Thank you for this important question. We have updated the discussion to reflect the positive and negatives of ICI therapy in lymphomas in the future directions section. We have highlighted the minimal side effect profile as a strong positive to ICI therapy in lymphomas, with drawbacks being current efficacy is limited depending on what type of lymphoma is being treated.

Comment 8: In these factors limiting the efficacy of ICI therapy in lymphoma, which one was the main causes inhibiting the efficacy of ICI therapy?
Response 8: We thank the reviewer for this question. We have added several factors limiting efficacy of ICI therapy, with the most well documented factor likely dealing with problems in antigen presentation (lines 342-347). We have highlighted this fact in a more obvious way.