Peer Review File

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Reviewer Comments

Comment 1: What is the difference between this study and published study [Immune checkpoint inhibitors: recent progress and potential biomarkers, Exp Mol Med, PMID: 30546008]? What is the innovation?

Reply 1: The authors agree that the reviewers have cited another well-written review article on this topic [PMID: 30546008]. In the submitted review article, we have provided an approach to organize the currently approved and emerging biomarkers of response into four broad categories of "the inflamed tumor", "tumor antigens", "immune suppression" and "tumor host environment". The authors believe that having this framework for understanding the complex and rapidly evolving field of biomarkers of response to immunotherapy would be extremely beneficial to the clinicians and is a valuable addition to the current literature. Although the organization of the biomarkers may appear to be similar the structure of the discussion, studies covered and the discussion of the biomarkers is different between the our manuscript and the manuscript referenced by the reviewers.

Comment 2: How to provide valuable information about the dynamic nature of the immune response and the regulation of other pathways that need to be targeted by combination therapy?

Reply 2: The authors agree that this is a critical area of current investigation and have included emerging data on combination immunotherapy with HDAC inhibitors, VEGF inhibitors and FGF inhibitors under the section on tumor host environment (the last paragraph).

Comment 3: In the immunotherapy regimen, are there differences in different immune checkpoint inhibitors? Please give a few examples and explain.

Reply 3: Yes, for more established and studied biomarkers like PD-L1, there are differences in predictive value of these biomarkers based on ICPI agents used. This data with examples is listed under "Section IA: PD-L1" as "The predictive value of PD-L1 expression for response to immunotherapy can also vary among the ICPIs agents used or disease setting. For instance, Balar et al demonstrated correlation between increased PD-L1 expression in advanced urothelial cancer with response to first line pembrolizumab in cisplatin-ineligible patients.[25] However, a study by Sharma et al in recurrent, advanced urothelial cancer after platinum-based chemotherapy did not demonstrate a correlation between PD-L1 expression and response to nivolumab.[26]"

Comment 4: The current challenges and future strategies of immune checkpoint inhibitors should be discussed, and how to maximize these challenges and future strategies to maximize the efficacy of immune checkpoint blockade therapy on cancer.

Reply 4: The authors interpret that this comment refers to the challenges and future strategies of developing predictive biomarkers in immune checkpoint inhibitors and have expanded on the current challenges in the conclusion section. The strategies to maximize the utilization of immune checkpoint inhibitors using the current and emerging biomarkers

of response is the focus of this review and has been discussed in the subheadings with focus on each biomarker.

Comment 5: Is there a difference in the efficacy of immune maintenance therapy for patients with different PD-L1 expression levels?
Reply 5: Yes, there is some limited data from Stage III NSCLC post chemoradiation from a post hic analysis of PACIFIC trial that showed that patients with no PD-L1 expression did not have an overall survival benefit with maintenance durvalumab. The authors have included this evidence under the section on PD-L1.

Comment 6: Does immune maintenance therapy have long-term effects on other normal tissues, such as immune interstitial pneumonia?
Reply 6: While long term immune related adverse effects are an important area of investigation, this discussion is not in the scope of this review article focusing on biomarkers of response to immunotherapy.

Comment 7: What is the best time for immune maintenance therapy after radiotherapy and chemotherapy? What is the best time to maintain immunity?
Reply 7: The authors agree that defining the optimal timing of maintenance immunotherapy is an evolving area of investigation but a discussion about this timing is not in the scope of this review.

Comment 8: How to detect adverse reactions in the follow-up course?
Reply 8: At this time, the biomarkers in immunotherapy are not being used in routine clinical practice to predict adverse reactions in the follow up course. Since our review only focuses on biomarkers of therapeutic response to immune checkpoint inhibitors discussion on biomarkers of toxicity was not included as it is not in the scope of this review.