Peer Review File

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Reviewer A

This phase I/IIb study investigated the safety and efficacy of ONC201, a first-in-class small molecule that activates the integrated stress response (ISR), in combination with nivolumab in MSS treatment-refractory mCRC. Although the study was closed due to lack of efficacy, the combination was found to be safe and tolerable. It is still worthwhile to publish such negative studies as they are informative to the field. However, the Discussion section is rather brief and despite the lack of efficacy seen with this combination, the authors would better serve to inform the reader if they provide some commentary as to why they believed this combination to have failed. Placing the mechanism of action of the novel agent in the context of what is known with CRC would be recommended as well as future directions with agents of this MOA class.
Reply: The discussion section was expanded. Unfortunately given the lack of PK/PD data, we will not be able to have a concise conclusion

Reviewer B

I congratulate the authors on their attempt at evaluating this combination in a phase 1 trial. Comments are included below to help improve the quality of the manuscript.

Page 4, Line 13-15: Please include appropriate reference for pembrolizumab approval in dMMR metastatic CRC
Reply: Reference was added
Page 5, line 3-5: Please mention briefly the recent AtezoTRIBE (PMID: 35636444) study findings.
Reply: The trial was added and reference was provided
Page 5, line 5-7: Please include relevant reference for this sentence
"One of the possible explanation of failure with 6 PD-1 blockade for pMMR CRC is immune suppression through other immune checkpoints or 7 pathways that regulate lymphocyte activation"
Reply: Reference was added
Page 6, line 1-3: Please rephrase this sentence for clarity. Please specify what dose intensification you are referring to.
"With ONC201 dose intensification, it was noted a potent anti-metastasis effect and inhibition of cancer cell migration and invasion leading to a change in ONC201 dosing in all open clinical trials"
Reply: this was part of not published pre-clinical work. It lead to changing the dose in clinical trials using ONC 201 to once a week or once every 3 weeks.
Page 6, line 5-7: Please specify if the combination of Onc 201+ anti PD1 study was in-vitro, in vivo in animal models, or in humans.
"The 5 combination of anti–PD-1 therapy with ONC201 showed increased efficacy in comparison to 6 anti–PD-1 monotherapy in tumors treated with high doses of ONC201, indicating that alleviating 7 T cells of PD-1 expression may enhance ONC201's potency in vivo"
Reply: the combination was evaluated in vitro and in vivo animal models
Page 6, line 10: This should be proficient MMR metastatic colorectal cancer. Please correct.
Reply: statement was corrected
Page 6, line 15: Suggest to be consistent in the use of terms. Authors can choose either proficient MMR or microsatellite stable for the rest of manuscript.
Reply: microsatellite stable was used throughout the manuscript
Page 6, line 18; page 6, line 21; page 7, line 5; page 7, line 11; page 7, line 14: Please pay attention to the use of upper and lower case letters.
Reply: words were corrected
Page 8 line 6-7: Please specify the precise dosing schedule of ONC201 after the day -7 dose.
Reply: Dosing was specified. Single dose was given on day -7 then weekly
Page 8 line 9: Suggest to delete the text included in parenthesis as it is confusing
Reply: could not locate the text in parenthesis. Delete the parenthesis on page 10

Page 9 line 19: ORR not previously defined. Please define acronyms at first mention in the manuscript
Reply: ORR was defined
Page 9 line 21: DCR not previously defined. Please define acronyms at first mention in the manuscript
Reply: DCR was defined

Table 1 and page 11 line 12-13: Please provide tumor mutational burden (TMB) for all patients
Reply: Data on TMB were available on a very limited number of patients.
Page 11 line 14: Please specify if any immune-related adverse events were observed. These immune adverse events are of interest since nivolumab was included in the combination.
Reply: a statement was added. No IR-AE were observed
Page 11 line 16, 17: Please specify the frequency of dosing of Onc 201
Reply: Frequency was specified
Page 12 line 1: EOT not previously defined. Please define acronyms at first mention in the manuscript
Reply: EOT was defined
Page 12 line 12: Please include 'severe' in this statement as follows "and no severe events were related to study treatment"
Reply: severe was added
Page 12 line 15: Please indicate how the biopsy samples that were collected from the accrued patients were analyzed. Were there any interesting findings from the biopsies?
Reply: most patients did not agree to biopsy at progression. Because of lack of response and funding the tissue was has not been processed
Page 13 line 7: TMB not previously defined. Please define acronyms at first mention in the manuscript.
Reply: TMB was defined

Tables/Figure: Please consider including a table or figure to show the response data.
Reply: There was no response in any of the treated patients. We do not believe a figure is needed