Author’s response to reviews

Title: A phase II trial of recombinant MAGE-A3 protein with immunostimulant AS15 in combination with high-dose Interleukin-2 (HDIL2) induction therapy in metastatic melanoma

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Author’s response to reviews:

Thank you very much for the opportunity to improve our manuscript. We have addressed each concern as listed below.

Editorial Comments:

1. The reviewers are concerned about overstating the conclusions based on the small sample size analysed. Could you please revise the manuscript to re-draw the conclusions based on the samples analysed and clearly outline the limitations of the study when the manuscript is revised.

RESPONSE: We have revised the discussion on page 13, line 1-10 to avoid overstating conclusions based on the small sample size. Limitations are noted on page 13, line 15-16.
Reviewer 1 Comments: The authors need to update their comparison of the combination of IL2 and MAGE-A3 vaccine to IL2 alone. They reference Atkins 1999. However, more recent data suggest higher response rates. Consider Sullivan, et al, SITC 2016. this is a report of 170 patients with response rate of 18%.

RESPONSE: We have updated the references to include both the Joseph/Sullivan 2012 published report from which the SITC abstract cohort is derived and the Davar 2017 report and noted response rate of 10-19% with HDIL-2. This manuscript describes only 16 patients evaluable for response - therefore a comparison of response rate is of concern, given the wide margin of confidence intervals.

RESPONSE: We have revised the discussion on page 13, line 1-10 to avoid direct comparisons of response rates across these studies and noted limitations with small sample size. The data presented are entirely consistent with data from treatment with IL2 alone - including the response rate and the time to CR - clearly with IL2 alone this can be delayed over time. also the duration of CR. The authors cannot claim that this is an effect of the vaccine maintenance.

RESPONSE: We have revised the discussion on page 13, line 1-10 updating the response rates for HDIL-2 monotherapy alone as per comment 1. We also did add information on the CR rate which is 19% in the present study and 6-8% in HD-IL2 studies though we have again been careful not to overstate the significance of this. We have also noted that responses with HDIL-2 monotherapy can be delayed. The potential data of interest is the immune monitoring over the course of the treatment, but difficult to attribute, since this has not been done long-term following IL2 treatment.

RESPONSE: Thank you. We agree that the immune monitoring data is of interest and that longitudinal immune monitoring with IL2 monotherapy would be of interest.

5. It is of concern that the vaccine is no longer being developed - concern that the authors are over-stating the contribution of the vaccine.

RESPONSE: We have noted that the vaccine is no longer being developed and have revised the manuscript to avoid over-stating conclusions and vaccine contribution as per above.

Reviewer 2 Comments: The figures are not optimally presented. All figures need improvement. As presented, the font size is very small and figure legends need better description.

RESPONSE: We have revised the figures to increase font size and revised the legends.