Reviewer's report

Title: Phase II Trial of the Regulatory T Cell-Depleting Agent, Denileukin Diftitox, in Patients with Unresectable Stage IV Melanoma

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Reviewer: Claudia M Palena

Reviewer's report:

The goal of this study was to evaluate the clinical efficacy of an interleukin2/diphteria toxin conjugate (DAB/IL2) as a monotherapy in a cohort of 60 patients with unresectable stage IV melanoma. The authors reported here that DAB/IL2 has significant clinical activity in this population of patients, and that lack of prior exposure to chemo/immunotherapy is associated with an increase response rate.

Major Revisions

1. The authors have concluded that DAB/IL2 therapy is more efficient in chemo/immuno naïve patients. In Figure 3, however, it is shown that patients with M1A disease had the highest response rates, and that the response rate in this population of patients was also high in the context of prior treatment(s). In light of the significant impact of tumor subclass (and prior treatments) in the response to DAB/IL2, it will be important to include a Table indicating, for each of the responder patients: the tumor subclass, number of cycles of DAB/IL2, type of response (including PR, SD, or MR), duration of response, and previous treatment(s) received.

2. The authors have indicated that no difference in response rate was observed in patients pre-treated with IL-2. Was there any difference in response rate observed in patients previously treated with any other treatment modality or combination treatment?

3. The analysis conducted in a subpopulation of long-term survivors with regard to the number of deaths by month of the year is not clear. The title of the section indicates analysis in "all patients and long-term survivors", but only long-term survivors data is described. The results, as presented, do not seem to contribute to the general conclusions of the study and should be excluded from this manuscript.

4. How the overall survival achieved in this study (for all patients and each subclass) compares with historical controls or use of other agents in a similar patient population?

Minor Revisions:

In Table 1, there is a typo error in the percentage of chemo-naive patients: indicated as 17 instead of 18%.
Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests.