Reviewer's report

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

Version: 1 Date: 17 August 2011

Reviewer: Tyler Curiel

Reviewer's report:

1. Is the question posed by the authors well defined? YES

2. Are the methods appropriate and well described? Yes

3. Are the data sound? YES

4. Does the manuscript adhere to the relevant standards for reporting and data deposition? YES

5. Are the discussion and conclusions well balanced and adequately supported by the data? YES

6. Are limitations of the work clearly stated? No. See comment below about including immune data.

7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished? YES

8. Do the title and abstract accurately convey what has been found? YES

9. Is the writing acceptable? YES, with minor edits as noted below.

Please make your review as constructive and detailed as possible in your comments so that authors have the opportunity to overcome any serious deficiencies that you find and please also divide your comments into the following categories:

- Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)

Some spelling issues and some facts need checking. As examples:

On page 4, interferon, interleukin and ipilimumab should not be capitalized.

Discussion. Paragraph 1: dacarbazine and ipilimumab should not be capitalized

Page 12, second paragraph: granulocyte macrophage colony stimulating factor and ipilimumab should not be capitalized.

- Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct) On page 4 it is stated that Tregs inhibit in a contact-dependent manner, but this inhibition can also be contact independent, particularly in cancer. Further on it states that denileukin diftitox selectively binds to CD25+ cells, but actually it binds to IL-2R cells, including CD25- cells.

Isn't DAB/IL2 now known as denileukin diftitox?

Page 12, second paragraph, the sentence that starts "the failure...". Should
include an exculpatory statement at the end such as "among other factors", as it is likely that additional factors aside from those mentioned also contribute.

- Major Compulsory Revisions (which the author must respond to before a decision on publication can be reached)

This manuscript by Telang, et al., is an interesting addition to the tumor immunotherapy literature. The trial design is well-described, the clinical outcomes are well-defined and survival estimates and statistical methods are appropriate and sound.

The trial design and clinical data are well-presented. However, it would be useful to present the immune data here that correlate with clinical outcomes, as the purported mechanism is immune-based. Where are these data?

The survival relation to season is interesting. Was sun exposure adjusted for? Were there seasonal changes in immune outcomes?