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: 1 August 2011

Reviewer: shubhada chiplunkar

Reviewer’s report:

In this single center Phase II trial, in stage IV melanoma patients, (n=60) interleukin 2/diphtheria toxin conjugate (DAB/IL-2, Denileukin Diftitox; ONTAK) was administered to patients to (deplete CD4+CD25hi FOXP3+ regulatory T cells) assess its clinical efficacy. Earlier studies by the investigators had demonstrated the ability of DAB/IL-2 to deplete CD4+ CD25hiFoxP3+ regulatory T cells and expand CD8+ T cells in patients.

The responses were monitored using a combination of 2[18F]-fluoro-2-deoxy-glucose (FDG) positron emission tomography (PET) and Computed tomography (CT) imaging. After DAB/IL-2 administration, partial responses (16.7%), stable disease (5%) and mixed responses (15%) were observed. The important observation was that one year survival was higher in partial responders relative to patients with progressive disease. The chemo/immuno naive patients showed partial responses.

The investigators conclude that DAB/IL-2 has significant clinical activity in unresectable stage IV melanoma patients. This has set the stage for a multi-centric randomized trials of DAB/IL-2 as a monotherapy and in combination with other immunotherapeutic agents for treatment of stage IV melanoma patients.

This is an interesting Phase II study on 60 melanoma patients. However some laboratory data on immunophenotyping of T regs and CD8++ T cells was needed to establish correlation with the clinical responses observed in these patients.

The following points need clarification to appreciate the clinical data.

Major Compulsory Revisions

1) The criteria for defining mixed responses in patients is not clear. How were the cut offs of >30% for tumor regression with simultaneous >20% for tumor growth decided for mixed responses?. Is there a published reference to support this?

2) What is the status of CD4+CD25hi FOXP3+ in patients exhibiting mixed responses compared to stable disease or progressive disease or those showing partial response.

3) The investigators have not reviewed the topic well. There are earlier reports by Attia et al, 2005, J. Immunotherapy. 28(6): 582-592 which does not support the
ability of ONTAK to eliminate regulatory T lymphocytes in melanoma patients. It was important to include this publication and also address the disparity.

4) Some discussion on management of treatment toxicities may be included.

Discretionary Revisions

What were the changes in cytokine scenario in patients before and after receiving Denileukin Difititox? It would be interesting to have some discussion on this point.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

I declare I have no competing interests