FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

MEMORANDUM

Date: June 26, 2007

From: Lori Tull, Regulatory Management Staff, OCTGT, HFM – 705

To: The file, Dendreon STN 125197/0

Subject: BLA teleconference summary

Teleconference Date: May 29, 2007 **Time:** 1-2:30

Location: Woodmont Office Complex 1/ Conference Room 400S

Meeting Requestor/Sponsor: Dendreon Corporation

Product: Sipuleucel-T

Proposed Use: treatment of prostate cancer

Type of meeting: Other BLA

Date draft Faxed to Sponsor: May 25, 2007

Meeting Objectives: This meeting was requested to discuss in detail the deficiencies noted in the May 8, 2007 Complete Response Letter.

Sponsor questions and FDA response:

Clinical

1. Would FDA consider a Subpart E approval for sipuleucel- T based upon a significant finding in time to progression from Study D9901?

CBER - We do not consider that this TTP data could provide sufficient evidence of efficacy for licensure under 21CFR601.41 Subpart E. The progression data had a number of issues which confounded interpretation:

- Small sample size.
- Progressions occurred much earlier than anticipated, median was prior to scheduled second assessment thus making precise measurement of progression very difficult.
- Missing CT scans in some patients which could have missed soft tissue progressions.
- Some progression dates were un-interpretable due to protocol violations.

- Baseline imbalances in bone and soft tissue
- Because the protocol was amended not to require follow-up CT scans for subjects with bone-only disease, asymmetric assessments compounded the difficulty caused by the baseline differences in interpreting the study results.
- Lack of support by D9902A progression data; D9901 findings in Gleason $\leq$7 patients were not replicated in D9902A.

We are willing to discuss our D9901 TTP review findings for the purposes of clarifying why we would not consider this to be supportive and also to optimize analysis of D9902B data, however we do not encourage re-analysis and re-submission of the D9901 TTP data.

During the meeting, Dendreon made several proposals regarding the current on-going trial D9902B:1) analyze D9902B TTP data after 350 progression events; 2) propose to use D9902B TTP data for accelerated approval; 3) Eliminate the interim analysis and perform a final survival analysis after 250 death events occur.

FDA responded that we would consider these proposals, but emphasized the limitations of TTP data as stated above. In addition the integrity of D9902B must be maintained with any proposed plan. We encourage Dendreon to request a meeting with FDA in order to discuss any proposed changes to the D9902B protocol, especially attendant statistical analytic plan.

2. Is the proposed plan in Section 4.0, for providing additional analyses and data to support the efficacy claim earlier than that currently prescribed in Study D9902B, acceptable?

CBER - No, resubmission of TTP data from D9901 would not be recommended (see #1).

3. a) If the additional data from this proposed plan provide further evidence of sipuleucel- T efficacy, will this, in combination with the clinical data already submitted in the BLA, be sufficient for accelerated approval?

CBER – No (see responses to #1-2 above).

3. b) Does FDA agree that the current interim analysis plan for overall survival described under the D9902B Special Protocol Assessment (SPA) agreement, if positive, would be sufficient for licensure when combined with the data already submitted in the Biologics License Application (BLA)?

CBER - Yes, assuming the overall type I error rate is controlled under the level of 0.05 for the final analysis and that positive results are confirmed by FDA's review. However, we encourage you to consider if non proportionality and delayed effect might affect the power of this analysis to detect a difference, as discussed in Dr Blumenstein's lecture at the February 2007 FDA/NCI

Cancer Vaccine workshop. Also please consider the potential impact of any missing covariate data on your primary analysis.

3. c) If the results of the interim analysis are not sufficient for licensure, does the FDA agree that the final analysis plan under the D9902B SPA agreement, if positive, would be sufficient for licensure when combined with the data already submitted in the Biologics License Application (BLA)?

CBER – see response to 3 b above.
Additional comment: we remind you that any modifications to the D9902B clinical protocol and especially to the statistical analysis plan should be clearly identified as a submission for review under a Special Protocol Assessment request. If you modify the clinical protocol, in order to retain the Special Protocol Assessment concurrence, the protocol revision must be submitted to FDA for review under a Special Protocol Assessment request. We encourage you to discuss any proposed modification of the protocol prior to submission in order to expedite review.

Chemistry, Manufacturing, and Controls (CMC)

4. Does FDA agree to accept amendments to the BLA that address the CMC deficiencies prior to the receipt of the additional clinical data?

CBER - We agree that you may submit amendments to the BLA to address CMC deficiencies prior to the submission of additional clinical data. We will review any amendments received as they are submitted and will work with you to resolve any outstanding deficiencies. Please be aware that this review process will be based on the assumption that you will not make any substantial CMC changes. Also be aware that a final review decision cannot be made until your response to our CR letter is complete.

Dendreon - We would not be making any major changes to CMC.

CBER - Since this would be an incomplete response, we would not give a formal written response. There would be an official review memo of the amendment included in the BLA file. Dendreon should note that things could change, but CBER will continue to communicate with Dendreon if any CMC issues arise.

Dendreon - We plan on requesting a telecon to go over the CMC deficiencies in detail. Can we get a draft of the EIR?

CBER - We will check on obtaining a copy of the draft EIR.

Please submit all submissions, in triplicate, to:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center, HFM-99, Suite 200N
1401 Rockville Pike
Rockville, MD 20852-1448
Attn: OCTGT/RMS

If you have any questions, please contact the Regulatory Project Manager, Lori Tull, at (301) 827-5102.

Attachments/Handouts:

FDA Attendees:

Celia Witten, Ph.D., M.D.
Stephanie Simek, Ph.D.
Raj Puri, M.D., Ph.D.
Kimberly Benton, Ph.D.
Ghanshyam Gupta, Ph.D.
Peter Bross, M.D.
Ke Liu, M.D., PhD
Tom Finn, Ph.D.
Malcolm Moos, MD, Ph.D.
Bo Zhen, Ph.D.
Syed Husain, Ph.D.
Deborah Lavoie, JD, RAC
Lori Tull, RAC

Sponsor Attendees:

Elizabeth Smith
Nicole Provost
David Urdal
Mitchell Gould
Mark Frohlich
Lianng Yuh
Brent Blumentstein

OCTGT/IOD/L. Tull:6/5/07
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