



DEPARTMENT OF HEALTH AND HUMAN SERVICES

TELECONFERENCE MEMORANDUM

Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Date\Time: May 19, 2007, 2-2:30 pm

CBER Representatives: Peter Bross, Ke Liu, Boguang Zhen; Lydia Martynec

Sponsor's Representative: Liz Smith, Mark Frohlich, Lianng Yuh

STN : 125197/0

Subject: FDA informal discussion points re: Sipuleucel-T clinical development plan

Discussion:

Liz Smith and Mark Frohlich from Dendreon requested FDA to provide informal telephone advice to Dendreon regarding the content of a meeting package to be submitted in order to address deficiencies noted in the FDA's Complete Response letter. FDA suggested the following as potential topics for informal discussion; however this does not represent the Agency official advice. FDA noted that a formal meeting is scheduled on May 29, 2007.

In the last SPA submitted on October 11, 2005, the primary analysis for survival is Cox proportional hazards model containing 9 factors/covariates (weight, PSA, age, LDH, ALK/Pho, Hemoglobin, Gleason grade, #bone mets, bisphosphonate use). This proposal seemed reasonable at that time since the final survival analysis results were not available from studies D9901 and D9902A.

1. After review of D9901 and D9902A data, FDA would like to discuss several concerns about using Cox proportional hazards model as the primary analysis approach for the primary survival endpoint in D9902B.
 - a. Missing data on the factors/covariates could lead to difficulties in interpreting the Cox proportional hazards D9902B results. Do you have any information on the amount of missing data collected so far in D9902B?
 - b. There were 9 factors/covariates proposed in the original plan. Too many factors/covariates may have an adverse impact on the fitting of the model.
 - c. Based on the survival results from D9901 and D9902A, the hazards ratio between the two arms over time appeared to be non-proportional. The proportional hazards assumption for Cox model used in D9902B may be violated.

- d. If the delayed effect observed from D9901 and D9902A were observed again in 9902B, you may want to consider modifying your primary analysis method to account for delayed effects.
- e. You could also consider taking the delayed effect into consideration if you want to re-estimate the power for detecting a statistically significant difference in your interim and final analyses.

Regarding the information for missing data (1a), the sponsor did not have the exact number, but stated that the number of patients with missing factors/covariates data in D9902B should be less than those in the previous two studies. The sponsor also acknowledged all the other issues and stated that they would like to have more internal discussions on these issues prior to discussions with FDA later.

- 2. In addition, FDA noted in Section 4.1.1 (Primary Efficacy Variable) that the Cox model was described for the analysis of primary efficacy variable. However, it was not clearly stated as the **primary analysis method** for the primary survival endpoint. If you choose to use Cox regression model or other alternative method as the primary analysis approach for the survival primary endpoint, please state so in this section.

The sponsor agreed.

- 3. FDA would also like to discuss ways in which to optimize the analysis of information that secondary endpoints and other scientific data from D9902B could provide in support of the efficacy of Sipuleucel-T. This could be the topic of an additional meeting.

The sponsor would like to have more detailed discussion during the formal meeting.

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