

**MEMORANDUM**

**Subject:** BLA STN 125197 Sipuleucel-T/Provenge®  
OBE/DE review of sponsor's 19 March 2007 draft Pharmacovigilance Plan

**To:** Lori Tull, Regulatory Project Manager OCTGT/CBER  
for Sipuleucel-T review team

**Date:** April 2, 2007

**From:** Kathryn O'Connell M.D. Ph.D.  
Medical Officer, TBSB/DE/OBE/CBER

**Through:** Robert Wise M.D. MPH  
Branch Chief, TBSB/DE/OBE/CBER  
  
M. Miles Braun M.D. MPH  
Division Director, DE/OBE/CBER

---

**Background**

Sipuleucel-T (APC8015) is an autologous active cellular immunotherapy product designed to stimulate an immune response against prostate cancer. The proposed indication for sipuleucel-T is treatment of men with asymptomatic metastatic androgen independent prostate cancer. OBE/DE reviewed the BLA for sipuleucel-T to identify potential safety issues that might need to be addressed in a post-marketing pharmacovigilance plan (PVP) if the product is licensed (Memorandum dated 08 December 2006).

We recommended that the following potential safety issues be addressed in a PVP submitted during the BLA review cycle so that the plan would be ready for implementation if the product is licensed. The rationale for the four issues listed here is explained in our 08 December 2006 Memorandum.

- 1) Outcomes in African American patients
- 2) Secondary hematologic malignancies
- 3) Stroke
- 4) Sepsis

### **Sponsor's Proposed PVP / Reviewer Comments**

The sponsor notes the important PV opportunity afforded by the interactive process for providing sipuleucel-T. Specifically, the sponsor will have complete patient usage data (a denominator), potential for improved reporting and detection of emerging safety signals, and ability to communicate rapidly with all centers about safety “or new treatment recommendations as they evolve”. The draft PVP consists of 3 parts:

- Routine pharmacovigilance in accordance with existing regulations
- Enhanced pharmacovigilance for selected safety issues based on clinical trial adverse events
- A “cohort” study

*Reviewer Comment: The sponsor's mention of “...new treatment recommendations as they evolve” raises concern. If post-marketing information suggests the need for amended treatment recommendations, that data should be submitted to FDA and then reflected in approved labeling.*

### **Routine pharmacovigilance**

*Reviewer Comment: The sponsor has captured in their submission the required elements of routine post-marketing PV and reporting.*

### **Enhanced pharmacovigilance for selected safety issues**

The goal of the proposed enhanced pharmacovigilance is thorough follow-up of spontaneous reports of special interest. These events proposed for such surveillance are:

- Serious infusion-related events
- Potential hypersensitivity
- Serious infections, including those that may be secondary to indwelling infusion catheters
- Potential autoimmune events
- Cerebrovascular accidents
- Secondary malignancies

The sponsor proposes that “questionnaires/case report forms for each category of event will be used at the time these events are first reported spontaneously”...to “provide better understanding of the circumstance and clinical course of each event, its relationship to sipuleucel-T, and provide insight into future prevention strategies”.

*Reviewer Comments:*

- *It is not clear how the proposed “enhanced” data collection for spontaneous reports would differ from thorough sponsor follow-up of spontaneous reports, as required in the*

*Regulations. Asking spontaneous reporters to fill out additional forms largely redundant with MedWatch information is likely to discourage future reporting. Instead, the sponsor should focus efforts on: 1) ensuring that they maintain sufficient clinically trained PV staff to conduct thorough follow-up of AE reports; and, 2) working with prescribers to encourage voluntary reporting.*

- *The identified events are consistent with the clinical trial events, but the number of study subjects was very limited. The plan should include a schedule and methodology for re-evaluation of the “enhanced pharmacovigilance” event list, so that emerging events are included in a timely manner as the exposed population expands.*
- *The event list for “enhanced pharmacovigilance” should include all thromboembolic or hemorrhagic events, not just cerebrovascular accident. The rationale is that if the CVA “signal” in the trials is real, plausible pathophysiologic mechanisms would suggest that other organ system events may emerge as exposures increase.*
- *All of the events on the enhanced reporting list should be submitted to FDA under the Regulations (21CFR 600.80) for expedited reporting, regardless of whether they are unlabeled and serious. Quarterly PSUR submissions should include a cumulative listing of each of these events tallied as unique cases (i.e., not a tally of submissions that would include follow-up reports), along with cumulative usage data expressed as patients treated (i.e., not just the total numbers of infusions).*

### **“Cohort” Study**

The sponsor has proposed a 3000 patient post-approval observational “cohort study” that would follow patients for 3 years. The registry proposal includes gathering of baseline characteristics and adverse events, but curiously states “data on all hospitalizations for reasons other than progression of prostate cancer will be requested”. Embedded within this study is a targeted effort to enroll a larger number of African Americans (AA) than the 10 patients exposed in the clinical trials. Specifically, they propose to enroll 150-300 AA patients. The comparator group for the AA patient portion of the study would be chart review of AA prostate cancer patients within the 2 years preceding sipuleucel-T availability at participating sites.

#### *Reviewer Comments:*

- *The 3000 patient study, as described in the submission, is essentially a registry, not a cohort study. The proposed registry can be the basis for a full cohort study, but the sponsor needs to include details for a comparative analytic approach. They should develop historical controls from the same institutions, matched for age and disease stage, or, preferably, a prospective concurrent cohort, matching otherwise similar patients who select other treatments.*
- *The smaller embedded AA “cohort” study proposes comparator data derived from chart review, but does not address whether charts would be chosen based on baseline disease characteristics. Although an observational study cannot prove efficacy for the AA population, it might generate a clinically important lack-of-efficacy signal if the product does not work in AA patients. For this reason, we strongly recommend that comparator*

*charts be selected randomly from among patients with baseline characteristics similar to the registry patients (which will hopefully be consistent with product labeling).*

- *The proposal is internally inconsistent regarding the number of AA patients to be enrolled (300 vs. 150-300). While neither number is likely to provide a reliable signal for rare adverse events, the lower end of the proposed range should be abandoned as a goal. The latest figures available from NCI's Cancer Statistics Review (2003) indicate that AA men have a higher annual incidence rate of invasive prostate cancer than Caucasian patients (247 vs. 160 per 100,000). The product is designed to elicit an immune response to the tumor cells and it is critically important to gather efficacy data for AA patients, an under-represented population in the clinical trials. In addition, the REasons for Geographic And Racial Differences in Stroke (REGARDS) Study, a national population-based, longitudinal study of 30,000 African-American and white adults aged 45 or greater, has recently reported that blacks continue to have higher stroke incidence (ref: [Stroke](#) 2006 Oct;37(10):2473-8). For these reasons, we recommend that the cohort study goal be at least 500 AA patients in each arm, rather than the 300 proposed. The PV plan should include arrangements for assessing early-on whether affordability is a barrier to AA enrollment, and if so, provisions to mitigate the problem.*
- *It is not clear why the sponsor proposes that "data on all hospitalizations for reasons other than progression of prostate cancer will be requested". The registry design must not preclude possible lack-of-efficacy detection. The sponsor does plan to link all patients lost to follow-up or still alive at the last follow-up assessment to the National Death Index (NDI) to ascertain any deaths not reported in the study. Thus, the apparent exclusion of prostate cancer progression probably represents a need for clarification in the final protocol, rather than an intended design feature.*
- *Given the life-threatening nature of the intended indication, consideration should be given to follow-up evaluations more frequent than every 6 months to avoid loss of important information if the patient dies.*
- *The proposal should include tracking/testing of product parameters that might correlate with individual patient outcomes.*
- *The PV plan should include a commitment to submit all data to FDA in computerized, analyzable format and in a timely manner. This includes outcome/effectiveness data unrelated to product safety. There should be a clear understanding that PV for this product includes not only risk assessment, but risk communication. As such, it is expected that relevant information will be shared with prescribers via labeling, peer-reviewed publication, and/or other formats as needed.*

**DRAFT Pharmacovigilance Plan (PVP) comments to be shared with Dendreon**

NOTE TO DENDREON: *All comments here are relevant only if FDA approves the product. These are draft comments intended to facilitate upcoming PVP discussions.*

- 1) It is not clear how the proposed “enhanced” data collection for spontaneous reports would differ from thorough sponsor follow-up of spontaneous reports, as required in the Regulations (21 CFR 314.80 and 21CFR 600.80). Asking spontaneous reporters to fill out additional forms largely redundant with MedWatch information could discourage future reporting. Instead, please focus efforts on: 1) ensuring sufficient clinically trained PV staff to conduct thorough follow-up of AE reports; and, 2) working with prescribers to encourage voluntary reporting.
- 2) The plan for “enhanced pharmacovigilance” should include a schedule and methodology for re-evaluation of the “enhanced pharmacovigilance” event list, so that emerging events are included in a timely manner as the exposed population expands.
- 3) The event list for “enhanced pharmacovigilance” should include all thromboembolic or hemorrhagic events, not just cerebrovascular accident. The rationale is that if the CVA “signal” in the trials is real, plausible pathophysiologic mechanisms would suggest that other organ system events may emerge as exposures increase.
- 4) All of the events on the “enhanced” reporting list should be submitted to FDA as expedited reports, regardless of whether they are unlabeled and serious. We ask that quarterly PSUR submissions include a cumulative listing of each of these events tallied as unique cases (i.e., not a tally of submissions that would include follow-up reports), along with cumulative usage data expressed as patients treated (i.e., not just total numbers of infusions).
- 5) The 3000 patient study, as described in the submission, is essentially a registry, not a cohort study. Please use your proposed registry as the basis for a full cohort study, including details for a comparative analytic approach. Please develop historical controls from the same institutions, matched for age and disease stage as suggested for the African American sub-cohort (see next comment), as well as a prospective concurrent cohort, matching on otherwise similar patients who select other treatments.
- 6) The embedded African American patient (AA) cohort study proposes comparator data derived from chart review, but does not address whether charts would be chosen based on baseline disease characteristics. Although an observational study cannot prove efficacy for this population, it might generate a clinically important lack-of-efficacy signal if the product does not work in AA patients. For this reason, we strongly recommend that comparator charts be prospectively selected randomly *from among patients with baseline characteristics similar to the registry patients*.
- 7) The proposal is internally inconsistent regarding the number of AA patients to be enrolled (300 vs. 150-300). While neither number is likely to provide a reliable signal for rare adverse events, the lower end of the proposed range should be abandoned as a goal. The latest figures available from NCI’s Cancer Statistics Review (2003) indicate that AA men have a higher annual incidence rate of invasive prostate cancer than Caucasian patients (247 vs. 160 per

100,000). The product is designed to elicit an immune response to the patient's tumor cells and it is critically important to gather efficacy data for AA patients, an under-represented population in the clinical trials. In addition, the REasons for Geographic And Racial Differences in Stroke (REGARDS) Study, a national population-based, longitudinal study of 30,000 African-American and white adults aged 45 or greater, has recently reported that blacks continue to have higher stroke incidence (ref: Stroke 2006 Oct;37(10):2473-8). For these reasons, we recommend that the cohort study goal be at least 500 AA patients, rather than the 150-300 proposed. The PV plan should include arrangements for assessing early-on whether affordability is a barrier to AA enrollment, and if so, provisions to mitigate the problem.

- 8) Please clarify why the proposal states that data on all hospitalizations for reasons *other than progression of prostate cancer* will be requested.
- 9) Given the life-threatening nature of the intended indication, consideration should be given to follow-up evaluations more frequent than every 6 months to avoid loss of important information if the patient dies.
- 10) As part of your 3000 patient cohort study, please propose tracking/testing of product parameters that might correlate with individual patient outcomes.
- 11) All data collected under the PVP should be submitted to FDA in computerized, analyzable format and in a timely manner. This includes outcome/effectiveness data unrelated to product safety. The protocol should state that PV for this product includes not only risk assessment, but risk communication. As such, it is expected that relevant information will be shared with prescribers via labeling, peer-reviewed publication, and/or other formats as needed. All information gleaned from pharmacovigilance that could affect patient care should be promptly submitted to FDA for review of revised labeling.