

MEMORANDUM

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FDA/CBER/OCTGT/DCEPT/CEB**

IND/BLA#125197/1

Submission date	October 30, 2009
Review date	April 28, 2010
Product Reviewers	Thomas Finn, Ph.D., Syed Husain, Ph.D., Malcolm Moos, Ph.D., Steven Oh, Ph.D.
Nonclinical Reviewer	Yongjie Zhou, Ph.D.
Clinical Reviewers	Chaohong Fan, M.D., Ph.D. (safety review) Bindu George, M.D. (efficacy review)
Clinical Team Leader	Peter Bross, M.D.
Biostatistician	Boguang Zhen, Ph.D.
Office Director	Celia M. Witten, Ph.D., M.D.
Pharmacovigilance	Faith Barash, M.D., Craig Zinderman, M.D.
DMPQ Review	Mary Padgett, Gang Wang
Biomonitoring Review	Bhanu Kannan
Advertising and Promotional Labeling Review	Catherine Miller
RPM	Lori Tull, RAC
Consult(s)	Office of Oncology Drug Products (Ning, Ison, Maher)
Sponsor Product(s) Proposed Use	Dendreon Corporation Sipuleucel-T (Provenge®) Treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer
Recommendation	Approval

Dendreon has submitted biologics license application (BLA) 125197 for sipuleucel-T for the treatment of asymptomatic or minimally symptomatic metastatic hormone refractory prostate cancer.

Sipuleucel-T is the first autologous cellular immunotherapy. Sipuleucel-T consists of autologous peripheral blood mononuclear cells (PBMCs), including antigen presenting cells, that have been activated with PAP-GM-CSF, a recombinant human protein. PAP-GM-CSF consists of prostatic acid phosphatase (PAP), an antigen expressed in prostate cancer tissue, linked to granulocyte-macrophage colony-stimulating factor (GM-CSF), an immune cell activator.

Each patient receives three doses of sipuleucel-T, with each dose consisting of the maximum number of cells that can be obtained via a single leukapheresis. The three doses are administered at approximately 2-week intervals, over approximately four weeks. The mechanism of action is uncertain.

Dendreon initially submitted this BLA in 2006, based on the results of Studies D9901 and D9902A. After thorough review, the FDA determined that the available data did not constitute substantial evidence of effectiveness and issued a complete response (CR) letter in 2007. The current BLA amendment contains the results of Study D9902B, a subsequent randomized, double-blind, placebo-controlled, Phase 3 study that was statistically positive on a primary endpoint of overall survival.

The primary reviews of safety and efficacy were conducted by Drs. Chaohong Fan and Bindu George, with Dr. Peter Bross (team leader). The purpose of this memo is to discuss selected review issues.

Efficacy

Regulatory standard for evidence of effectiveness

Study D9902B meets the regulatory requirements for an adequate and well-controlled investigation (21CFR 314.126) that can provide substantial evidence to support an effectiveness claim. However, the FDA Guidance *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* notes that FDA usually requires more than one adequate and well-controlled investigation to support a marketing application. In the current BLA, the primary evidence of effectiveness comes from only one adequate and well-controlled investigation, i.e., Study D9902B. As stated in the effectiveness guidance, “reliance on only a single trial will generally be limited to situations in which a trial has demonstrated a clinically meaningful effect on mortality ... and confirmation of the result in a second trial would be practically or ethically impossible.” As presented in the clinical and statistical reviews of this application, Study D9902B is an adequate and well-controlled investigation in which sipuleucel-T

demonstrates a clinically meaningful effect on survival in patients with metastatic prostate cancer. Because of the effect on survival, a second trial would not be ethical or feasible.

In addition, as stated in the guidance on effectiveness, the assessment of the adequacy of a single trial will consider supportive evidence of efficacy and the characteristics of the single trial.

- 1) In the current BLA, supportive evidence of efficacy comes from two Phase 3 studies, D9901 and D9902B.
 - a) Study D9901 was not statistically positive on its primary endpoint, time to disease progression; therefore, D9901 could not provide primary evidence of effectiveness. Overall survival was not a pre-specified primary or secondary endpoint, and the primary statistical analysis for comparing overall survival in the two arms was not pre-specified. However, a post hoc analysis of overall survival in D9901 provided a p-value of 0.01, a hazard ratio of 0.586 (95%CI: 0.388, 0.884), and a median survival advantage of 4.5 months (25.9 vs. 21.4 months).
 - b) Study D9902A was a Phase 3 study that was stopped early (i.e., before enrolling the planned number of subjects). However, the survival analysis of Study D9902A also trended in favor of sipuleucel-T over placebo ($p = 0.331$), with a median survival advantage of 3.3 months (19.0 vs. 15.7).

The survival analyses from Studies D9901 and D9902A provide supportive evidence of the effect of sipuleucel-T on survival.

- 2) Characteristics of a single trial that support its use as the only primary evidence of effectiveness include that the study was large and multicenter, with consistent results across study subsets, and a statistically very persuasive finding.
 - a) Study D9902B was a relatively large (512 subjects), multicenter (75 centers) study.
 - b) Study D9902B was statistically positive ($p = 0.032$, with a pre-specified significance threshold of 0.043); this level of statistical significance does not, by itself, rise to the level of very persuasive. However, as described in Dr. Zhen's statistical review, the p-values from multiple sensitivity analyses "ranged from 0.009 to 0.052 ... [with most] below 0.043, the nominal significance level for the final analysis." This consistency across multiple sensitivity analyses makes the primary efficacy result statistically very persuasive.

- c) The sponsor assessed the effect of sipuleucel-T, compared to placebo, in 59 subgroups, based on 27 baseline covariates. As presented in the clinical and statistical reviews, the treatment effect favored sipuleucel-T (i.e., point estimate of hazard ratio was <1) in almost all subgroups.

Therefore, Study D9902B is a large, multicenter study that is statistically very persuasive, with the efficacy result consistent across numerous subgroup analyses. Study D9902B has sufficient characteristics necessary for a single trial to support a license application.

In summary, D9902B, supported by the results of D9901 and D9902B, meets the regulatory standard for a single trial to provide the substantial evidence of effectiveness necessary for marketing approval.

Safety

Sipuleucel-T was generally well-tolerated. Most common adverse events were mild or moderate in severity. The frequency of severe adverse events and serious adverse events were similar in the sipuleucel-T and control groups.

Labeling (directions for use)

Indication statement

For a variety of reasons, the study population (i.e., patients who meet the eligibility criteria) for a clinical trial is almost always a limited subset of the disease population (i.e., everyone who has the disease). However, when a product is approved for marketing, and there is neither evidence nor a strong rationale for believing that the product would be unsafe or ineffective in the disease population, the indication can be generalized from the study population to more closely approximate the disease population. In the current application, the Phase 3 studies of sipuleucel-T excluded patients with more than minimally symptomatic disease. Patients with more symptomatic disease were not adequately studied during drug development. However, in the absence of a good understanding of sipuleucel-T's mechanism of action, there is not a strong scientific basis for believing that the benefit of sipuleucel-T would not occur in patients with more symptomatic disease.

Docetaxel is the only product with a proven effect on survival in patients with metastatic prostate cancer. However, docetaxel is associated with substantial side effects, such that some patients with symptomatic, metastatic prostate cancer may reasonably choose to not take docetaxel. For these patients, sipuleucel-T might be a reasonable alternative. A broader indication statement would make patients with metastatic prostate cancer, and their physicians, aware that sipuleucel-T may be a treatment alternative to improve survival. Then each

physician could weigh the evidence, and patients could make their own risk-benefit assessments. A broader indication statement would empower physicians and patients to make their own decisions regarding whether sipuleucel-T is appropriate in each specific clinical situation.

The clinical review team has thoroughly considered the wording of the label indication statement. The team decision to limit the indication to patients with minimally symptomatic or asymptomatic disease is based on reasonable concerns regarding whether sipuleucel-T is appropriate for the broader population. However, for the reasons stated above, I favor a label indication statement that sipuleucel-T is approved for the treatment of metastatic hormone refractory prostate cancer, omitting the phrase *asymptomatic or minimally symptomatic*. The *Clinical Trials* section of the label could then note that the subjects studied in the pivotal and supportive efficacy studies were asymptomatic or minimally symptomatic.

Dose and regimen

During clinical development of a product, exploration of dose and regimen are essential to determine the optimal dose and regimen. Clinical development of sipuleucel-T included a total of 14 clinical trials. The dose administered in the pivotal study (D9902B) was determined more by manufacturing limitations than by safety and efficacy data. There has been insufficient dose-exploration to determine the optimal dose. Similarly, during clinical development, most studies administered 2-4 doses of sipuleucel-T, in 2-4 week intervals, sometimes with a “booster” dose several months after the initial doses. There has been insufficient regimen-exploration to determine the optimal regimen.

The label-recommended dose and regimen have been proven safe and effective. However, in the absence of extensive clinical exploration, it is unlikely that the recommended dose and regimen are optimal. Postmarketing experience may permit further definition of the optimal dose and regimen.

Conclusion: Sipuleucel-T is effective for the treatment of metastatic hormone refractory prostate cancer. Sipuleucel-T provides an important survival benefit in these patients. The overall risk-benefit assessment is highly favorable.

Recommendation: Approval