



DEPARTMENT OF HEALTH & HUMAN SERVICES

National Institutes of Health
National Cancer Institute
Freedom of Information / Privacy Act Office
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October 18, 2007

Kelly Donahue
Bellinger & Donahue Attorneys at Law
6295 Emerald Parkway
Dublin, OH 43016

Re: NCI 07-101, FOIA Case No. 34163

Dear Mr. Donahue:

This is a final response to your August 15, 2007 Freedom of Information Act (FOIA) request. You requested copies of all documents, letters, emails and/or correspondence from the National Cancer Institute to the Food and Drug Administration (FDA) or those acting as advisors to the FDA, concerning the BLA filed by the Dendreon Corporation for the fast track approval of Sipuleucil-T, known under its marketing name of Provenge, between January 1, 2007 and May 30, 2007.

We have located 5 pages responsive to your request. These records have been released to you in full. Provisions of the Department of Health and Human Services FOIA Regulations allow us to recover part of the cost of responding to your request. Because the cost is below the Department of Health and Human Services waiver of \$25.00, there is no charge. Thank you for your interest in the National Cancer Institute.

Sincerely,

A handwritten signature in black ink, appearing to read "Suzanne Milliard".

Suzanne Milliard
Freedom of Information Coordinator
NCI/FOIA/OPAR

Enclosures: 5 responsive pages

Dr. Andrew von Eschenbach
Dr. Janet Woodcock
Dr. Jessie Goodman

I am writing to express concerns about the recent review of Provenge at the FDA Advisory Meeting on March 30, 2007. It is based on my experience as a voting member on several ODACs representing the Agency, and separately, as a Presenter to ODAC for Industry Sponsors. I have been one of the Academic Leaders of the Prostate Cancer Clinical Trial Endpoints initiative begun under the joint Sponsorship of the FDA, AACR, ASCO and PCF in 2004, the final recommendations for which were presented at the February 2007, Prostate ASCO Meeting in Orlando, and the final manuscript is currently under review at the NCI, FDA and the Group of established Prostate Cancer Clinical Trial experts who together, formulated the recommendations. I am also the PI of the 10 (Is it really called "10 center..."? If not, I would call it Multicenter...no one uses the number of centers and I thought it was a granting mechanism eg P10) Center Prostate Cancer Clinical Trials Consortium funded by the DOD focused on phase 1 and 2 trials in this disease.

Let me state at the outset that I was one of the 4 Committee Members who voted "no" to the question whether the trials presented by the Sponsor established the efficacy or demonstrated substantial evidence of benefit to justify an approval recommendation to the FDA. **My vote was based on the fact that neither of the two trials presented met their primary endpoint, which renders the significance of results from any subsequent analyses as "exploratory" and "hypothesis generating".** As such, the results can not constitute "proof" of benefit or justify a conclusion that they are "reasonably likely" to predict benefit. The trial data were not consistent. Even should one accept the post-hoc survival analysis results of the larger 127 patient trial (82 men treated with Sipuleucel-T and 45 men treated with a "placebo"), the second trial of 98 patients (65 treated with Sipuleucel-T and 33 with placebo) was not confirmatory. Consequently, the only conclusion that can be reached is that the survival difference observed may have occurred by chance alone, and that the results do not support an approval recommendation. (Scientific basis for the legal standard, FDA Guidance for Industry, Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products, May 1998 - I thought it might be a nice touch to quote their own guidance - what do you think?) This, and the Sponsor's recognition that an additional prospective study was needed, mandates deferring any decision on whether an approval should be granted until the results of the ongoing 500 patient phase 3 trial, powered on survival, is accrued and analyzed.

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Concerns about the validity of the findings were reinforced by the absence of any other signals of an antitumor effect (Multiple endpoints involving different events, FDA Guidance for Industry, Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products, May 1998). Specifically there were no data provided of a favorable effect on PSA, regression or stabilization of soft-tissue or boney disease radiographically, quality of life, or that the product delayed the development of pain. Even the time to the administration of chemotherapy, an indication to the treating Physicians that the clinical course had taken a turn for the worse, was similar between the two groups. Worse still, was the fact that even in response to a direct question, none of the Physicians representing the Sponsor at the meeting could articulate how they felt the product had "helped" any individual patient.

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Methodologic issues:

Trial 9901 was designed to show an increase in time to disease progression from 16 weeks for placebo to 31 weeks (HR = 1.92, alpha = 0.05, two sided, with 80% power). A total of 127 patients were enrolled using a 2:1 randomization to enhance the power of the experimental arm. The study was blinded

and included an independent review of all imaging results. This estimated time to progression proved to an overestimate, as the actual observed time to progression was 9 to 11 weeks for both arms, a difference that was not statistically significant. Subsequently, a 4.5 month difference in median survival was observed, and while a “p” value for the difference was estimated, the probability of a type 1 error could not. While the 2:1 randomization increased the power was given of experimental arm, it may have inadvertently increased the heterogeneity of the control group and compromised the placebo arm as a representation of patients within the indication. In support of this concern was the treatment group had an inherently better prognosis is supported by the observation that a higher proportion had Gleason 6 disease or less at diagnosis (26.8% vs. 15.6%), while fewer had both bone and soft tissue (52% vs. 69%) at the time therapy was started. Further support that the treatment and control groups may not be comparable was the fact that a post-study change in the progression times of two patients, resulted in a change in the significance estimates.

Some of these issues related to the standards of trial of conduct when the study was designed, that have by necessity been updated. For example, a summary of the progression events showed that 90% (97/114) events were by imaging, 10 were clinical, and 7 were for the new onset of disease related pain. Unrecognized at the time of the design of the trial, was that the eight week interval between disease assessments was too short to observe clinically significant changes, with the result that many of these progressions were more a reflection of the disease worsening that led to trial entry, and not a failure of the treatment. (Scher, Warren and Heller, Clin Cancer Res: xx:xx, 2007) This is similar to what was observed with the endothelin antagonist, atrasentan, in which a 12 week disease assessment interval was used and a large proportion of patients were withdrawn in the absence of clinical worsening of disease (ODAC, September 10, 2005). Recognizing this, the Prostate Cancer Working Group 2 recommendations are to in order to consider a patient to be progressing by bone scan in the absence of symptoms, is to document further progression on confirmatory scan. (Multidisciplinary Prostate Cancer Symposium, (Abstract #221) February 22-24, 2007, Orlando, FL, 2007. A second problem was that serial disease assessments were not performed once a patient was classified as having failed the treatment. The result was that individual sites of disease were no longer being monitored, so that no statements could be made regarding a possible “delayed effect” of the product on disease status.

FDA doesn't accept secondary endpoints unless primary endpoints are met -- is there to be an exception here b/c it is OS? Should be no exception because of the complexities - then can name them e.g., heterogeneity, confounders, 2:1, whatever they were. I change my input here - I see that the 2 trials were not confirmatory so don't need to go down the path of secondary endpoints - the primary contradiction is inconsistent results.

An approval recommendation has far reaching implications that may have the opposite effect than what the well intentioned members of the Committee were hoping to achieve. For one, it provides the Agency's endorsement of Sipuleucel-T as a “standard of care” treatment for an asymptomatic population of men with androgen independent (castration resistant) disease that represents well over 25,000 men in the U.S. The second is that by extension, it elevates Sipuleucel-T to a position of being the new “control” arm for future randomized phase 3 trials of any new experimental agent or approach that are being designed for regulatory approval. Third, it opens the door to premature approval of drugs based on inconclusive data.

The Agency asked the Committee whether the product is “reasonably safe” for the intended population. While the vote was yes, the issue of cardiovascular events as a potential safety signal was raised. The concern was based on the finding that for patients within the indication enrolled on randomized studies, 4.9% (17/345) of the sipuleucel-T and 1.7% (3/172) of the “control” treated patients experienced a cardiovascular event (p=0.092). The odds ratio for developing a stroke was 2.92, with wide confidence intervals (0.82 up to as high as 10 fold). There were also 9 deaths attributable to CVA's among the 406 (2.0%) patients enrolled on randomized trials in the proposed indication (7 of 234 (2.0%) and 2 of 172

(1.2%)). While these differences were not statistically significant, but more important is the recognition that the "placebo" used in this trial is a portion of the isolated mononuclear cell fraction that is culture without the immunizing antigen, and may not be "inert". Given that the product is released for administration based on the increase in the proportion of CD54+ cells, that these cells actually represent on 20% of the final product, it is not clear that product administration results in an immune response in the patient. The contribution of the other cell populations, and cytokines that may be present in the administered product is not know. In this regard, a review of TAX-327 (NEJM 351:1052, 2004) showed no CVA's in the 997 patients enrolled, while ASCENT1 had no CVA in any of 251 patients enrolled (docetaxel plus or minus, DN-101 (JCO 25:669, 2007). It is also curious that the reported publication of the study (JCO 24:3089, 2006) did not list CVA amongst the AE. Thus, on the surface, while the product may be reasonably safe, if approved now, how many additional strokes who justify removal or hold?

A final concern is that paths for regulatory approval appear to differ between ODAC and CBER. ASCENT1 was a prospective randomized phase 2 trial of weekly docetaxel plus or minus high dose calcitriol (DN-101). The trial was powered to detect a 20% difference in the PSA response rate between the two groups as the primary endpoint, with a prespecified survival analysis, similar to that included in the Provenge 9901 as secondary. A total of 252 patients, 125 and 127 per arm were enrolled and followed. The 13% difference observed was not statistically significant, yet here too, a survival difference was observed, HR favoring DN-101 of 0.70 (CI) (JCO 25:669-74, 2007). To ODAC, the results were not considered definitive, no approval filing was made using the 252 randomized survival outcomes, and a separate 900 patient phase 3 trial was designed, initiated and continues to accrue. This contrasts with the regulatory filing history of Provenge, for which an approval recommendation has been made based on a similar post-hoc analysis with roughly half the patients. Why is the first suitable for consideration, and the second not?

Given the eight week interval between disease assessments, many of these progressions were "pseudoprogessions" and not a true failure of the treatment (CCR 13:1488, 2007), this is similar to what was observed with atrasentan using a 12 week interval (ODAC, September 10, 2005). Recognizing this, the Prostate Cancer Working Group 2, has advised that an apparent confirmation of bone scans on a three month assessment, be confirmed by documenting further progression on a subsequent scan. ASCO multidisciplinary Prostate Cancer Symposium, (Abstract #221) February 22-24, 2007, Orlando, FL, 2007.

The conclusion of the manuscript describing the results of trial 9901, published in the Journal of Clinical Oncology in Volume 24, page 3093, in 2006 (JCO 24:3089, 2006) states "that while sipuleucel-T fell short of demonstrating a statically significant difference in TTP, it *MAY* provide a survival advantage to asymptomatic HRPC patients. Supportive studies are underway to confirm this effect." The difficulties cited above, and the Investigator's own conclusions, show how there are simply too many alternative explanations for the observed survival difference in 9901. This coupled with that fact that were no secondary signals of an antitumor effect, and no confirmatory trial, however flawed, mandates that no approval decision be rendered until the phase 3 study, currently underway has been completed and analyzed.

Clin Cancer Res. 2007 Mar 1;13(5):1488-92.

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designed and reached 50% of planned accrual. Why is the first suitable for consideration, and the second not?

To blind the experimental agent, the "placebo" used was an infusion of mononuclear cells that were cultured without the experimental immunogen. This compromised the ability to assess the effect of the vehicle itself, and raises a question regarding the manufacturing and culturing process itself. Questions were raised at the meeting by Dr. Hussain as to why the control group appeared to have an inferior survival to that observed in recently reported randomized comparisons. The "alleged placebo" was actually harmful and resulted in an inferior survival for the "control" group.