

Exhibit C

Declaration of Nancy B. Sager

UNITED STATES DISTRICT COURT FOR THE
SOUTHERN DISTRICT OF OHIO
EASTERN DIVISION

CARETOLIVE,)	
a not-for-profit corp.,)	
)	Civil No. 2:08-CV-00005
Plaintiff,)	
)	JUDGE FROST
v.)	
)	MAGISTRATE JUDGE KING
U.S. FOOD and DRUG)	
ADMINISTRATION,)	
)	
Defendant.)	

DECLARATION OF NANCY B. SAGER

I, Nancy B. Sager, declare as follows:

1. I am the Director of the Division of Information Disclosure Policy ("DIDP"), Center for Drug Evaluation and Research ("CDER"), United States Food and Drug Administration ("FDA"), in Silver Spring, Maryland.
2. I have supervisory authority over DIDP, which processes and responds to requests made pursuant to the Freedom of Information Act ("FOIA") for documents in the possession of CDER. DIDP is also responsible for proactively reviewing, redacting, and posting on FDA's website, consistent with Executive Order 13392, documents anticipated to be frequently requested, such as drug approval packages and warning letters. In addition, DIDP responds to requests for documents made by the U.S. Congress, foreign, state, and local governments, other federal agencies, and to third-party subpoenas and court orders for CDER documents.
3. At my direction, DIDP personnel search records systems for documents under CDER's control to identify records and other information that may be responsive to particular

requests. DIDP staff gather and review potentially responsive documents to determine whether, before being made available for public disclosure, they should be redacted in part or in their entirety, under any applicable FOIA exemption or other statutory provision.

4. The statements made in this declaration are based upon my personal knowledge and information about which I have become knowledgeable through my review of official agency records within DIDP's control.

5. I submit this declaration in support of the government's Motion for Summary Judgment. The purpose of this declaration is to set forth DIDP's response to the FOIA request that is the subject of the Complaint in this case.

DIDP PROCESSING PROCEDURES

6. DIDP consists of twenty-seven people: a Director, one Special Assistant, three team leaders, thirteen regulatory counsel, two consumer safety officers, five paralegals, and two project specialists. In addition, CDER DIDP currently employs three full-time contractors who assist in reviewing documents and processing FOIA requests.

7. Initially, all FOIA requests for FDA documents are received by FDA's main Freedom of Information office, the Division of Freedom of Information ("DFOI"), Office of Management Programs. DFOI logs in each request, assigns it a reference number, and routes it to the agency component(s) most likely to have records responsive to the request. CDER is the center within FDA that is responsible for the regulation of most human drugs and therapeutic biological products. FOIA requests referred to CDER are sent to DIDP.

8. As discussed in my previous declaration in support of the government's Motion to Stay Proceedings, FOIA requests that are referred to CDER that can be answered quickly with

readily available documents, and that require no redacting, are considered "simple" requests and generally are processed on a fast track (the "Simple Track"), as opposed to "complex" requests, which follow a slower processing track (the "Complex Track"). DIDP staff generally process Simple and Complex Tracks requests in queues, on a first-in, first-out basis.

9. Simple requests do not require DIDP personnel to redact documents, generally because: 1) DIDP has already reviewed and redacted the responsive documents, 2) the documents requested are publicly available, or 3) it is apparent from the face of the request that the documents do not exist in CDER's records.¹

10. For requests in the Complex Track, DIDP may need to search, or contact individuals and direct them to search, numerous agency files. After the search has been carried out and the documents have been sent to DIDP, DIDP conducts a preliminary review of the records collected to verify that they are responsive to the request. DIDP then conducts a page-by-page, line-by-line review of the responsive documents to determine whether any records can be released and whether any FOIA exemptions apply. Any exempt material is redacted. Frequently, a team leader conducts a quality control review to ensure that the responsive documents have been properly prepared for public disclosure. This review ensures that the FOIA exemptions have been properly applied, that no releasable material will be withheld, and that no material meriting protection will be released. Finally, copies of the responsive documents are prepared and delivered to the requester.

¹ Documents may fall into this category because, for example, they have been assembled and redacted in response to a prior FOIA request or because the request involves a drug approval package that DIDP has already finished processing in preparation for its posting on FDA's website.

PLAINTIFF'S REQUEST

11. On October 15, 2007, DIDP received from DFOI a FOIA request from Bellinger & Donahue, attorneys for Plaintiff, dated August 15, 2007. DFOI forwarded the request to DIDP because, after consultation with CBER, it appeared that CDER was also likely to have records relating to Provenge.

12. DIDP determined that this request did not meet the criteria for the Simple Track, because it requested documents that were not readily available and that would require a search and possible redaction, and therefore, assigned it to the Complex Track.

13. At the time it received Plaintiff's request, DIDP estimated that the request would not rise to the top of the Complex Track for processing until October 2009. Thus, on February 18, 2008, the government filed a Motion to Stay Proceedings (Civil Docket No. 10) in response to Plaintiff's filing of the complaint in this matter on January 2, 2008.

14. This Court granted the government's request on May 22, 2008 (Civil Docket No. 23), ordering DIDP to update the Court on the progress of the FOIA request in the Complex Track queue on December 1, 2008, and to produce all documents responsive to the request no later than May 18, 2009.

15. On December 1, 2008, as required by the Court's order, I estimated in my declaration that the Plaintiff's request was still on track to rise to the top of the queue in October 2009. However, to comply with the Court's order, DIDP stated that it would provide Plaintiff with all responsive documents on or before May 18, 2009.

16. DIDP pulled Plaintiff's request from the Complex Track queue in mid-April 2009.

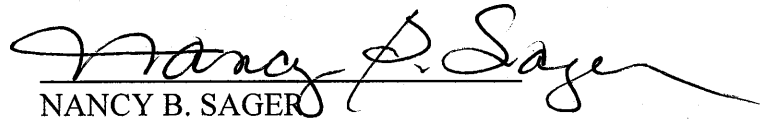
17. A DIDP employee reviewed the documents produced by the Access Litigation and Freedom of Information Branch ("ALFOI"), Center for Biologics Evaluation and Research ("CBER") in response to Plaintiff's request in order to identify individuals in CDER that might have responsive documents. The DIDP employee identified two CDER employees to which the CBER documents had been addressed or copied, and were therefore likely to have responsive documents: Dr. Janet Woodcock, the Director of CDER, and Dr. Richard Pazdur, a Supervisory Medical Officer in CDER's Office of Oncology.

18. Dr. Pazdur did not have any responsive documents. Dr. Woodcock's staff conducted a search of her files, and they were able to locate only one responsive document, a letter dated April 4, 2007 from Dr. Howard Scher to Dr. Andrew von Eschenbach.

19. The DIDP employee determined that the letter did not contain any information that fell within an exemption to the FOIA. The letter, without any redactions, was produced to the Plaintiff on May 18, 2009. See Attachment 1.

20. In an abundance of caution, the DIDP employee also searched: (i) the CDER electronic databases containing application information on drugs and therapeutic biological products; and (ii) CDER's document room, where CDER stores paper application files for drug and therapeutic biological products, even though CDER would not maintain any electronic or paper application files for a vaccine such as Provenge. The DIDP employee did not find any responsive documents in CDER's electronic or paper application archives.

Pursuant to 28 U.S.C. § 1746, I declare under penalty of perjury that the foregoing is true and correct.

A handwritten signature in black ink, reading "Nancy B. Sager". The signature is written in a cursive style with a long horizontal flourish extending to the right.

NANCY B. SAGER
Director
Division of Information Disclosure Policy
Center for Drug Evaluation and Research
Food and Drug Administration
U.S. Department of Health and Human Services

Executed on May 18, 2009 in Silver Spring, Maryland



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

*Food and Drug Administration
Division of Freedom of Information
5600 Fishers Lane, HFI-35
Rockville, MD 20857*

May 18, 2009

File: 07-8316

Kerry M. Donahue, Esq.
BELLINGER & DONAHUE
6295 Emerald Parkway
Dublin, OH 43016

Dear Mr. Donahue:

This is in response to your letter dated August 15, 2007, in which you requested the following:

[A] copy of all letters written to the FDA (or prepared by the FDA) and purported to be from Dr. Scher, Dr. Hussain and Doctor Fleming in between March 29th 2007 and April 30th of 2007, regarding the BLA submitted for Provenge also known as Sipuleucel-T including the envelope or other means of communication whereby the FDA received such letters and a copy of any record of those letters then being disclosed to any media or other persons or specifically a publication called "The Cancer Letter", including the means of communication to the Cancer Letter of the Scher, Hussain and Fleming letters from the FDA or its employees to outside persons, publications or companies.

Your request was received in the Center for Drug Evaluation and Research (CDER) on October 15, 2007.

The records located in CDER's search are enclosed. The following charges may be included in a monthly invoice:

Search: \$0 Review: \$0 Reproduction: \$0.40 TOTAL: \$0.40

The above total may not reflect final charges for this request.

PLEASE DO NOT SEND PAYMENT UNLESS YOU RECEIVE AN INVOICE FOR THE TOTAL MONTHLY FEE.

This concludes CDER's response to your request.

Sincerely,

A handwritten signature in black ink that reads "Howard R. Philips".

Howard R. Philips
FDA/CDER/Division of Information Disclosure Policy

Enclosure: 4 pages

Attachment

1



Howard I. Scher, MD
D. Wayne Calloway Chair in Urologic Oncology
Chief, Genitourinary Oncology Service
Sidney Kimmel Center for Prostate and Urologic Cancers

April 5, 2007

Andrew von Eschenbach, MD
Commissioner
5600 Fishers Lane
PKLN RM 1471 HF-1
Rockville, MD 20857

RE: CBER Advisory Committee for Sipuleucel-T
March 30, 2007

Dear Dr. ^{Andrew} von Eschenbach:

I am writing to express concerns about the recent review of Sipuleucel-T at the FDA Advisory Meeting on March 30, 2007. These concerns are: a recommendation for approval based on data that fall short of the regulatory requirements; an inadequate statistical construct to determine definitive benefit; incomplete data on product safety; and what appear to be different criteria for approval by two Advisory Committees to the Agency. All but the latter were discussed in the open meeting, but warrant further consideration given the outcome. The concerns are 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, which were presented at the February 2007, Prostate ASCO Meeting in Orlando. 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 Principal Investigator of a Multicenter Prostate Cancer Clinical Trials Consortium funded by the Department of Defense that focuses on phase 1 and 2 trials in this disease.

Let me state at the outset that I was one of the four 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

Memorial Sloan - Kettering Cancer Center
1275 York Avenue, New York, New York 10021
Telephone 646.422.4323 • FAX 212.988.0851
E-mail: scherh@mskcc.org

NCI-designated Comprehensive Cancer Center

results do not constitute “proof” of benefit or justify a conclusion that they are “reasonably likely” to predict benefit. The trial data were not consistent. Even if one accepts 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. 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 that is powered on a primary endpoint of survival, is accrued and analyzed.

Concerns about the validity of the findings were reinforced by the absence of other signals of an antitumor effect. Specifically there were no data provided of a favorable effect on PSA, regression or stabilization of soft-tissue or boney disease radiographically, health related quality of life, or that administration of 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 worsened, was similar between the two groups. Reinforcing the uncertainty was the fact that in response to a direct question at the meeting, none of the Physicians representing the Sponsor could articulate how treatment with the product had “helped” any individual patient.

There were also methodologic concerns. Trial 9901 was designed to show an increase in time to disease progression from 16 weeks for placebo treated to 31 weeks for Sipuleucel-T treated patients (HR = 1.92, alpha = 0.05, two sided, with 80% power). A total of 127 patients were enrolled using a 2:1 randomization in favor of the experimental therapy. The study was double blind and included an independent review of all imaging results. The estimated time to progression on which the trial was powered proved to an overestimate, as the actual observed median time to progression was 9 to 11 weeks for both arms: a difference that was not statistically significant. A summary of the progression events showed that 90% (97/114) 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 by bone scan, and that in many cases, apparent “progressions” eight weeks after the start of a therapy are more a reflection of disease worsening that led to trial entry, and not a failure of the treatment. (CCR 13:1488, 2007) This is similar to what was observed in the trial with the endothelin antagonist, atrasentan, in which a 12 week disease assessment interval was used and a large proportion of patients were withdrawn at the time of scheduled scans in the absence of clinical worsening of disease (ODAC, September 13, 2005). Recognizing this, the Prostate Cancer Working Group 2 has advised that an apparent progression on bone scan at a three month assessment, be confirmed by documenting further progression on a subsequent scan six or more weeks later before considering a patient to have failed the treatment. (ASCO Multidisciplinary Prostate Cancer Symposium, (Abstract #221) February 22-24, 2007, Orlando, FL, 2007). Although the Sponsor suggested that the effect of the product was delayed, this hypothesis could not be explored because serial imaging to assess disease at defined intervals were not performed once a patient was considered to have “progressed” and taken off study. As a result, 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.

At 3-years, a prespecified survival analysis was performed which showed a 4.5 month difference in median survival favoring Sipuleucel-T, and while a significant p-value for the difference was determined, the type 1 error rate is surely inflated by this additional analysis. Imbalances in disease aggressiveness and disease extent were noted between the Sipuleucel-T and “control” groups including a higher proportion with Gleason 6 disease or less at diagnosis (26.8% vs. 15.6%), and a lower proportion with both bone and soft tissue disease (52% vs. 69%) at the time therapy was started. Both factors favored the Sipuleucel-T arm, predicting a longer survival for the “treated” patients independent of therapy. The 2:1 randomization increased the power of the experimental arm, but it may have

inadvertently made the small 43 patient control group more heterogeneous and less representative of the global population of men for whom the indication was proposed. The potential impact of heterogeneity in small patient cohorts was shown when a post-study change in the progression times of two patients (a change not accepted by the Agency), resulted in a change in the significance estimates.

The first question the Agency posed to the Committee was whether the product was "reasonably safe" for the intended population. While the vote was yes, the issue of cerebrovascular events as a potential safety signal was raised. This concern was based on the finding that 4.9% (17/345) of the Sipuleucel-T and 1.7% (3/172) of "placebo" treated patients who were enrolled on randomized trials for the indication, experienced a cerebrovascular event ($p=0.092$). The odds ratio for developing a cerebrovascular event was 2.92, with wide confidence intervals (0.82 to as high as 10 fold). Deaths due to CVA's were recorded in 1.5% of Sipuleucel-T patients and 0.9% of those receiving "placebo". Unclear is why there is no mention of CVA's in the published report of the study in the Journal of Clinical Oncology (JCO 24:3089, 2006). Given that the product is released for administration based on the increase in the proportion of CD54+ cells and not the absolute number of any particular cell type and that CD54+ cells actually represent only 20% of the final product, the contribution of the other cell populations and cytokines that may be present in the administered product on the development of a cerebrovascular event is not known. More important, and perhaps underappreciated during the discussion, is the recognition that the "placebo" used in this trial, a portion of the leukopheresis product that is cultured without the immunizing antigen and reinfused, may not be inert and in itself contributed to a relative worsening of survival for the control group in this trial. To place the frequency of the neurologic events in perspective, no cerebrovascular events were observed in TAX-327, a 997 patient three arm randomized trial that evaluated two different dose schedules of docetaxel in comparison to mitoxantrone, (NEJM 351:1052, 2004) or ASCENT1, a 251 patient randomized comparison of docetaxel weekly with or without high dose calcitriol (DN-101) (JCO 25:669, 2007). Neurologic events that were not detailed further were observed in 7% of the 338 patients who received estramustine which is known to be thrombogenic, in combination with docetaxel on the SWOG 99-16 trial (NEJM 351:1513, 2004).

Another concern is that the requirements for regulatory approval appear to differ between the ODAC and CBER Advisory Committee. As an example, ASCENT1 was a prospective randomized phase 2 trial of weekly docetaxel with or without high dose calcitriol (DN-101). The trial was powered to detect a 20% difference in the PSA response rate at six months between the two groups as the primary endpoint, but also included a pre-specified survival analysis, similar to that included in the Sipuleucel-T 9901 trial as one of the secondary endpoints. PSA response was defined as a 50% or greater decline from baseline according to Consensus Criteria (JCO 17:3461, 1999). A total of 250 patients, 125 per arm were enrolled and followed. The 9% difference in the PSA response rate observed at six months was not statistically significant ($P<.16$), yet here too, the pre-specified survival analysis showed a difference for docetaxel plus DN-101 vs. docetaxel plus placebo: median not reached but estimated to be 24.5 months vs. 16.4 months respectively with a hazard ratio for death of 0.67 ($p=0.04$) (JCO 25:669-74, 2007). The safety of the combination was no worse and perhaps better than docetaxel alone. Appropriately in my view, the results were not considered definitive by ODAC, no approval filing was made, and a new 900 patient phase 3 trial powered to test the hypothesis whether the combination of docetaxel in combination with DN-101 conferred a survival advantage relative to docetaxel alone was designed, initiated and continues to accrue. I am the International Principal Investigator on this trial. Contrast this with the regulatory filing history of Sipuleucel-T where the primary endpoint of the registration trial was also not met, yet, it is being considered for approval based on a similar post-hoc analysis with roughly half the total number of patients, and a control arm that is roughly one third the size. Why do the Sipuleucel-T results establish efficacy, while the DN-101 results do not?

An approval recommendation has far reaching implications beyond making the product available that the data simply do not support or justify. 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 upwards of 45,000 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 that are being designed for the regulatory approval of any new experimental agent or approach. It also opens the door to the premature approval of drugs based on inconclusive data.

Finally, the original question posed by the Agency to the Advisory Committee at the meeting was: "Does the submitted data establish the efficacy of Sipuleucel-T (APC-8015) in the intended population?" The first 4 respondees on the Committee voted "no". The question was then changed to: Do the data show "substantial evidence". A series of "yes" votes followed.

Consider the conclusion in 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) In it, the Investigators state **"that while sipuleucel-T fell short of demonstrating a statistically significant difference in TTP, it MAY provide a survival advantage to asymptomatic HRPC patients. Supportive studies are underway to confirm this effect."** All of the difficulties cited, and the Investigator's own conclusions, show how there are simply too many alternative explanations for the observed survival difference beyond treatment with Sipuleucel-T. Couple this with that fact that were no secondary signals of an antitumor effect and no confirmatory trial however flawed, mandates that any decision for approval be deferred until the phase 3 study, currently underway, has been completed and analyzed.

Thank you for your time and consideration.

Yours sincerely,



Howard I. Scher, M.D.
Member and Attending Physician

Professor of Medicine
Joan and Sanford Weill College of Medicine of Cornell University

CC: Janet Woodcock, MD, Deputy Commission of OPE
Jesse L. Goodman, MD, Director, Center for Biologics Evaluation & Research
Richard Pazdur, MD, Director, Office of Oncology Drug Products, Center for Drug Evaluation & Research
Celia Witten, MD, PhD, Director, Office of Cellular Tissues & Gene Therapy, Center for Biologics Evaluation & Research
James J. Mule, PhD