Exhibit D

Declaration of Dr. Richard Pazdur

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

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

DECLARATION OF DR. RICHARD PAZDUR

1. I am a Supervisory Medical Officer in the Office of Oncology, Center for Drug Evaluation and Research ("CDER"), United States Food and Drug Administration ("FDA"), located in Silver Spring, Maryland. My duties include supervision of the Office of Oncology Drug Products, leading the FDA-wide oncology program, and coordinating oncology-related activities and the discussion of reviews of oncology products conducted in other Centers. The purpose of this program is to provide consistency and uniformity in the regulation of oncology-related products throughout the FDA.

2. 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 CDER's control.

3. I submit this declaration in support of the government's Motion for Summary Judgment in the above-captioned case. The purpose of this declaration is to explain why I could not produce any documents in response to the FOIA request that is the subject of the Complaint

in this case.

4. Plaintiff's request asks for, in part, "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." See Attachment 1.

5. I am an addressee of Dr. Maha Hussain's April 27, 2007 letter to numerous FDA employees. See Attachment 2. I am also listed as a "cc" recipient on the April 5, 2007 letters from Dr. Howard Scher to Dr. Janet Woodcock, Director of CDER, to Dr. Celia Witten, Director of the Center for Biologics Evaluation and Research ("CBER"), and Andrew von Eschenbach, Commissioner of FDA. See Attachments 3, 4, and 5.

6. At the request of CDER's Division of Information Disclosure Policy ("DIDP"), I searched both my paper and computer files, and I was unable to locate any documents that were responsive to Plaintiff's request.

7. I recall receiving both hard copies and electronic copies of these letters in April 2007. However, as these letters related to a specific regulatory application conducted by a different FDA Center (CBER), did not fall under my direct regulatory supervision, and did not require a response from me, I shredded my hard copies of these letters and deleted any electronic copies. The documents were shredded and deleted within a month of receipt.

8. I do not keep personal copies of any regulatory communications. Official copies of regulatory correspondence are kept in the official regulatory document room

of the specific center assigned to an application.

9. I did not disclose Dr. Scher's or Dr. Hussain's letters to "a individuals outside of the FDA, or any media outlet, including a publication called 'The Cancer Letter.'" See Attachment 1.

10. I did not write any portion of the letters that Drs. Scher, Hussain, or Fleming sent to the FDA.

11. I never received a copy of a letter from Dr. Thomas Fleming to the FDA regarding Provenge.

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

Executed on 15 day of May, 2009.

Richard Pazdur

Dr. Richard Pazdur
Supervisory Medical Officer
Office of Oncology, CDER

Scott P. Bellinger
Kerry M. Donahue*
*Also admitted in Florida

BELLINGER & DONAHUE
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August 15, 2007

RE: CareToLive v. FDA, Southern District of Ohio, case no. 2:07 CV 729

Brenda S. Zimmer
FDA
6751 Steger Dr.
Cincinnati, Ohio 45237-3097

2007-8316
RECEIVED
SEP 11 2007
FDA DFOI (HFI-35)

Dear Brenda S. Zimmer,

Please consider this a request under the Freedom of Information Act.

We request the following:

1) 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.

We are willing to pay the cost.

Attachment
1

Please call if you have questions about this request. Thank you.

Sincerely,

Kerry Donahue

University of Michigan
Health System
Comprehensive Cancer Center

Maha Hussain, M.D., F.A.C.P.
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April 23, 2007

Andrew C. von Eschenbach
Commissioner
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PKLN RM 1471 HF-1
Rockville, MD 20857

Janet Woodcock, MD
Deputy Commission for OPE
5600 Fishers Lane
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Celia Witten, MD, PhD
Director
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Richard Pazdur, MD
Director
Office of Oncology Drug Products
Center for Drug Eval & Res
WO22, Room 2212
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear Drs:

It is with concern and professional obligation that I write to you as a member of the FDA's Advisory Committee that recently reviewed Sipuleucel-T on March 29, 2007. My concerns relate to medical, scientific and procedural aspects of the meeting and the precedence that will be set for future reviews.

By way of introduction, I am an academic medical oncologist with expertise in GU oncology, extensive clinical trials experience and have been the PI of several NCI sponsored multi-center trials including randomized phase II and III trials. Currently, I am the PI of a Prostate Cancer Clinical Trials grant funded by the Department of Defense that focuses on phase I and II trials in prostate cancer. My experience also includes co-chairing the prostate cancer subcommittee of SWOG overseeing development of national trials for advanced prostate cancer for the past 13 years. I have served as an adhoc FDA consultant for several years and currently serve as a member of the Oncology Drug Advisory Committee. I was a member of and chaired the ODAC special session on prostate cancer endpoints, March 3rd, 2005 and have been actively involved in the development of

Attachment
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endpoints for this disease, a summary of which was recently presented at the 2007 Prostate Cancer ASCO meeting.

I was one of the 4 members who voted "No" to whether the submitted data on Sipuleucel-T established "efficacy" or "demonstrated substantial evidence of benefit" in the intended population at the recent advisory committee meeting.

From the medical and scientific aspects the recommendations for approval that may be inferred from the vote are based on data that can only be characterized at best as "suggestive" of possible benefit. As the discussant for Q5 regarding the persuasiveness of the efficacy evidence my comments are public record but to summarize my conclusion was that the data presented is not conclusive. The context here is not "*is the treatment promising*" or "*does it open the door for more immunotherapy research*", the context here is "*is the treatment effective and are the results solid*" such that this therapy should be offered as "*The Standard of Care*" by physicians to thousands of patients with the confidence that their recommendations truly serves the best interest of the patients. First of all the lead trial (study 1) was a small trial by any standard with 127 patients in total of whom only 82 were treated with Sipuleucel-T. The study was not powered for survival nor was survival an end point. A post hoc analysis indicated a significant survival difference but there were no significant differences between the Sipuleucel-T and placebo group with regard to any of the disease manifestations including PSA, time to disease progression (primary endpoint) or pain. This coupled with a clear imbalance in the arms with the control arm having more patients with bone and soft tissue disease thus potentially bulkier disease, more patients with higher Gleason scores, more % with prior chemotherapy and questions regarding the nature of the agent administered as the control (please see comments below), the small sample size, the fact that survival was not powered for and is a post hoc analysis could lead to a plausible conclusion that the observed survival difference may be related to other factors or chance alone and not to the treatment effect. Please contrast this data with the two phase III trials (TAX-327 with 997 patients, SWOG -9916 with 770 patients) that led to the approval of docetaxel. Both of these trials had very consistent results across them and conclusively demonstrated a survival advantage with notable effects on other disease manifestations.

The sponsor presented a second "supportive trial" which was also a small prematurely terminated trial which showed about a 3 month difference in survival which was not statistically significant. The trial results were especially problematic since both arms had a poorer survival (15.7 and 19.0 months) than expected for asymptomatic patients and worse than the survival observed in study 1. This occurred despite similar eligibility criteria to study 1. Furthermore, even the best arm "Sipuleucel-T treated patients" had a median survival of (19 months) which is comparable to the "asymptomatic" subgroup of men treated on the mitoxantrone arm of the Tax327 trial (19.8 months, Berhold et al, ASCO Prostate Cancer Symposium 2007). Please note that mitoxantrone is not considered the standard first line therapy in general or for asymptomatic patients. This clearly raises concern regarding the true efficacy of the agent and reproducibility and reliability of the

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data hence the application in the intended population at large. Furthermore, considering that the "placebo" treated patients had an unexpected poor survival of 15.7 months which is worse than the median survival of patients on mitoxantrone arm of the TAX-327 of 16.4 months (NEJM 04) which also included symptomatic patients, raising questions regarding a negative effect from the placebo thus leading to an apparent survival benefit. Issues regarding CVA's particularly in the intended population are also of concern without mature toxicity data and in the context of inconclusive efficacy data.

As you know a definitive trial is in progress and is within 100 patients of achieving target accrual. This trial will lead to definitive answers as to the true efficacy and safety of this agent. These questions will never be answered if the decision regarding this agent is not deferred at this time until all patients are accrued and data are mature, for obvious reasons.

From the scientific and procedural aspects, in general, it would seem that at the end of the day what should determine a positive verdict in any therapeutic trial is the strength of the evidence as critically reviewed by an Advisory Committee with the proper expertise in the context at hand (ODAC in the case of a therapeutic cancer trial), with clear guidance on the questions posed to the committee within the framework of the regulatory guidelines and requirements of the FDA for approval. This needs to be coupled with an atmosphere that is conducive to an objective discussion and vote.

Another concern, based on this case, is the appearance of discordance in the burden of proof required for regulatory approval between CBER and CDER. In the meeting regarding endpoints in 2005 ODAC reaffirmed the importance of powering trials for endpoints that measure true clinical benefit. But fundamentally here this particular agent did not even meet criteria for its primary endpoint.

In conclusion, as physicians we owe it to our patients to maintain the highest scientific standards and rigor. We owe them our objectivity and the assurance that when we make recommendations for treatment that we are basing our decisions on strong conclusive data. We need your help to ensure maintaining this high standard.

Sincerely,

Maha

Maha Hussain, MD
Professor of Medicine & Urology

cc. James Mule PhD
Moffitt Cancer Center
12902 Magnolia Drive SRB-2
Tampa FL 33612
mulejj@moffitt.usf.edu

April 5, 2007

Dr. Janet Woodcock, MD
Deputy Commission for OPE
5600 fishers Lane
PKLN RM 1471 HF-2
Rockville, MD 20857

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

Dear Dr. Woodcock:

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

Attachment
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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 Sipleucel-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: "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 significant benefit. 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

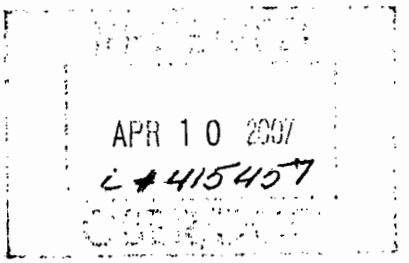
CC: Jesse L. Goodman, MD, Director, Center for Biologics Evaluation & Research
Richard Pazdur, MD, Director, Office of Oncology Drug Products, Center for Drug Evaluation & Research
Celia Witten, MD, PhD, Director, Office of Cellular Tissues & Gene Therapy, Center for Biologics Evaluation & Research
Andrew von Eschenbach, MD, Commissioner
James J. Mule, PhD

Multiple endpoints involving different events, FDA Guidance for Industry, Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products, May 1998

Scientific basis for the legal standard, FDA Guidance for Industry, Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products, May 1998

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



Celia Witten, MD, PhD
Director
Office of Cellular Tissues & Gene Therapy
Center for Biologics Evaluation & Research
1401 Rockville Pike
200N HFM-700
Rockville, MD 20852

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

Dear Dr. Witten:

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

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Attachment
4

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 Sipleucel-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.

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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.

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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

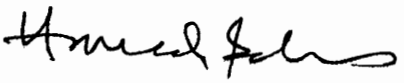
Sipuleucel-T as a "standard of care" treatment for an asymptomatic population of men with androgen independent (castration resistant) disease that represents upwards of 45,000 men in the U.S. The second is that by extension, it elevates Sipuleucel-T to a position of being the new "control" arm for future 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,



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CC: Andrew von Eschenbach, MD, Commissioner
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HFm- A.O 7-2569

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

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Attachment
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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 Sipleucel-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.

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