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July 19, 2007

Dr. Mary Sue Coleman
University of Michigan
Office of the President
503 Thompson Street
2074 Fleming Administration Building
Ann Arbor, MI 48109-1340

Dear Dr. Coleman:

It is with regret that I am compelled to write this letter to you regarding the possible inappropriate actions of a faculty member of your university, Dr. Maha Hussain of the College of Medicine regarding the Dendreon Corporation's immunotherapy known as Provenge. Although I have no professional standing with the University of Michigan, I am an alumnus of the University of Florida (my credentials are enclosed as Attachment 1). I would make the same request regarding a faculty member of my own University under similar circumstances. A University's reputation, in my opinion, is a product of the actions of its faculty, staff, and alumni, and should be guarded at all cost.

First, I must say that I wish no physical harm to Dr. Hussain or her family and friends and personally do not know of any others that do. I understand from reading the press that she is in fear for her life and has been physically threatened. I am an investor (small one at that) in the Dendreon Corporation and also have a dying uncle that has AIPC who would most likely benefit from use of the Provenge immunotherapy were it available now.

I am requesting that the University of Michigan undertake an inquiry under your University's conflict of interest guidelines and other appropriate rules to determine if Dr. Hussain has acted improperly in her role as a representative of the University and as a voting member of a recent U.S. Food and Drug Administration's (FDA's) Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC) which held its meeting on March 29, 2007 regarding the Dendreon Corporation's Biologics License Application (BLA) for the prostate cancer immunotherapy, PROVENGE (sipuleucel-T). I would expect that any investigation regarding Dr. Hussain's role as a member of CTGTAC would require your coordination with the Inspector General of the Department of Health and Human Services which I believe is responsible for assuring the integrity of FDA's activities.

In anticipation of the CTGTAC meeting on Provenge, the FDA produced an excellent "Statistical Briefing Document," which can be found at tinyurl.com/29t5xn. By a unanimous 17-0 vote, the committee's

members found the BLA data established that Provenge is reasonably safe. By an overwhelming 13-4 vote, they also found the BLA data provide substantial evidence that Provenge is efficacious.

Dr. Hussain was one of the four members voting “no” regarding efficacy. As Dr. Hussain was not accepting of the committee’s finding, she prepared a letter purportedly to the FDA putting forth her objections to the CTGTAC committee’s finding of efficacy. Somehow that letter and one written by Dr. Howard Scher, another CTGTAC committee member who voted also voted “no” on the efficacy question, found their way to a non peer reviewed journal called “The Cancer Letter, April 13, 2007, Vol. 33 No. 14”. In addition another biostatistician, Dr. Fleming made comments to “The Cancer Letter”.

It is interesting that Dr. Hussain’s letter outlines her qualifications. If her letter were intended only for the FDA, such elaboration would have not been required and raises the question whether she knowingly acted to make the letter more widely available to the public in an effort to sway public opinion or for other purposes.

Dr. Hussain’s letter that I obtained from other sources is contained in Attachment 2. I’m sure you will want to obtain a certifiable, authentic copy of the material for your review as well as the letters from Dr.’s Scher and Fleming.

It is interesting that Dr. Hussain makes a big point of the Provenge trial not having pre specified survival endpoints and other supposed reasons to keep dying prostate cancer patients from using this immunotherapy now. In addition, it is widely known that the use of study endpoints such as TTP with an immunological agent is not as appropriate in that the effect takes more time to ramp up as compared to use of a drug such as a chemotherapy agent.

Also, previously, she opined in the opposite regarding another trial. A few years back while judging whether a drug for pancreatic cancer should be approved (one that was not as safe as Provenge) Dr. Hussain said in response to Dr.Cheson the following:

“One of the three-panel members who voted against Tarceva, Bruce Cheson, M.D., of Georgetown University said after the vote that the Tarceva benefit did not outweigh its risks. But other panelists, including Maha Hussain, M.D., of the University of Michigan in Ann Arbor said that even slight benefits are significant in “a tough disease.””

http://www.nci.nih.gov/ncicancerbulletin/NCI_Cancer_Bulletin_092005/page5

This is contradictory with regard to her position on Provenge and also raises issues regarding Dr. Hussain’s letter’s objectivity in Attachment 2. She also raises issues regarding whether or not CTGTAC is as qualified as the Oncology Drugs Advisory Committee (ODAC) to review cancer therapies. If she were so concerned, why would she have agreed to sit on this advisory committee? What appears to be here is her unprofessional participation as a willing participant in an unseemly dispute within the FDA regarding drug approvals undertaken by Dr. Richard Padzur, head of FDA’s ODAC.

In addition to Dr. Hussain’s letter, Dr. Scher, another CTGTAG member who voted “no” on the efficacy question regarding Provenge also prepared a letter that appeared in “The Cancer Letter”. It is included in Attachment 3. Attachment 5 contains the “letter” of Dr. Fleming, a biostatistician, that also appeared in “The Cancer Letter”. The Cancer Letter seems to be a very popular place for dissidents who otherwise cannot get their positions heard.

An analysis prepared by knowledgeable followers of Dendreon’s BLA and AC Meeting is presented in

Attachments 4 and 6 and give pause for thought about what Dr.'s Hussain, Scher, and Fleming are trying to do in opposing this innovative therapy.

The next issue regards Dr. Hussain's "Conflict of Interest" (COI) waiver to participate on the Provenge Advisory Committee Panel. The following is Dr. Hussain's filed COI statement.

<http://www.fda.gov/ohrms/dockets/ac/07/waivers/2007-4301-w1-07-Hussain-ACK.pdf>

As shown in the document below, Dr. Hussain and her husband are reported to have significant stock ownership in companies developing drugs and therapies for prostate cancer and other diseases. Of particular note is Dr. Hussain's participation on the Advisory Committee for Novacea, its development of a competing prostate cancer drug, and its recent partnership agreement with Schering Plough soon after Dendreon received an approvable letter for its therapy resulting in delaying its use by dying prostate cancer victims.

<http://caretolive.com/Hussain%20Timeline.pdf>

The issues raised above make one wonder about the motives and benefits to be gained by Dr. Hussain in her vigilant efforts to keep a new, safe treatment from prostate cancer victims. Their only alternative is a chemotherapy treatment so devastating that more than one half of advanced prostate cancer sufferers would rather die than endure the horrible side effects of the treatment which do include possible premature death from the treatment itself.

In addition to Dr. Hussain's potential COI issues, others have made an analysis of Dr. Scher's COI issues which may be more problematic than that of Dr. Hussain and are the subject of other legal activities beyond the subject of this letter.

By Dr. Hussain's actions and that of her colleagues to delay the availability of Provenge, it is estimated that an additional 30,000 to 90,000 men will die needlessly as a result of not being able to receive this breakthrough cancer immunotherapy. Arguments for statistical purity and related matters seem insignificant to those denied this treatment. As Dr. Hussain has said in the past, "slight benefits are significant in a tough disease". This is more than the case here, and one must wonder about Dr. Hussain's ulterior motives regarding her participation in Provenge's approval process with the FDA.

I look forward to hearing of your efforts to get to the bottom of these activities that in my opinion reflect poorly on the reputation of the University of Michigan and its Medical School.

Sincerely yours,

Bruce E. Holmes, PE

CC:

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Department of Health and Human Services
330 Independence Avenue, S.W.
Washington, DC 20201

Enclosures:

- Attachment 1, Credentials of Bruce E. Holmes, PE
- Attachment 2, Letter of Dr. Hussain published in "The Cancer Letter"
- Attachment 3, Letter of Dr. Scher published in "The Cancer Letter"
- Attachment 4, Response to Dr. Scher published in "The Cancer Letter"
- Attachment 5, Letter of Dr. Fleming published in "The Cancer Letter"
- Attachment 6, More on Fleming's letter in "The Cancer Letter"

Attachment 1

BRUCE E. HOLMES, P.E.

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Bachelor of Science, Master of Engineering, Nuclear Engineering Sciences
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Mr. Holmes is an independent business consultant providing management, engineering, due diligence, and market assessment consulting to business and industry in development, construction, and acquisition of infrastructure, HVAC, demand side management/conservation, new technology, and cogeneration. He is a professional member of The National Society of Professional Engineers, The National Academy of Building Inspection Engineers and the International Desalination Association.

Mr. Holmes previously was a general partner with the national management consulting and engineering firm, R. W. Beck. He has developed and directed numerous studies and investigations for business, government, and utilities and consulted with clients in a wide range of planning, operational and financial matters.

His accomplishments include conceptual development and implementation of three regional energy authorities for public utilities in the southeastern United States involving construction, ownership and operating arrangements with private utilities. He was a principal in the negotiation of contractual arrangements, establishing the public authorities, and arranging the financing of their projects totaling in excess of \$11 billion.

He has prepared and supervised a wide range of economic feasibility studies in support of analysis and financing for construction projects. He has also rendered expert testimony before regulatory commissions regarding such programs and in litigation regarding other developments.

He was program director for development of a long-range supply and conservation plan for the Commonwealth of the Bahamas public electric system. He was also Chair of the Orlando Utilities Commission Customer Advisory Committee on Conservation regarding its water and electric system.

His experience includes analysis of construction programs, cogeneration systems, desalination systems, solid waste management, district cooling systems, conservation and demand side management, strategic planning and forecasting, management advisory services, rates and rate practices, regulatory approval of construction programs, and technical consultation in litigation and contractual disputes.

Mr. Holmes began his professional career with Florida Power Corporation (Progress Energy). He was involved in new facilities construction, environmental programs, licensing, design review, siting of generating facilities, and review of legislative and regulatory matters.

Attachment 2

Letter of Dr. Maha Hussain as it appeared in "The Cancer Letter" April 13, 2007, Vol. 33 No. 14.

“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 ad hoc FDA consultant for several years and currently serve as a member of the Oncology Drugs Advisory Committee. I was a member of and chaired the ODAC special session on prostate cancer endpoints, March 3, 2005, and have been actively involved in the development of endpoints for this disease, a summary of which was recently presented at the 2007 Prostate Cancer ASCO meeting.

I was one of the four 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

“est 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 symptomatic patients.

This clearly raises concern regarding the true efficacy of the agent and reproducibility and reliability of the 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 CVAs, 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.

Attachment 2

Letter of Dr. Maha Hussain as it appeared in "The Cancer Letter" April 13, 2007, Vol. 33 No. 14.

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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 “est 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 symptomatic patients.

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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.

Attachment 3

The letter below is reprinted from The Cancer Letter, Vol. 33 No. 14 April 13, 2007

"I am writing to express concerns about the recent review of Sipuleucel-T at the FDA Advisory Meeting on March 29, 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 Multi-center 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 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 posthoc 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 anti-tumor effect. Specifically there were no data provided of a favorable effect on PSA, regression or stabilization of soft-tissue or bony 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 be 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 was 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 there 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."

Attachment 4

On April 13, 2007, in Volume 33, No. 14 of *The Cancer Letter*, a letter was published which the Editor, Paul Goldberg, attributed to Howard Scher, MD, of the Memorial Sloan-Kettering Cancer Center. In this letter, the author warned the FDA about flaws in the Provenge (Sipuleucel-T) trial data (sponsor, Dendreon Corporation ([DNDN](#))); this, while the FDA decision about Provenge approval is pending.

Dr. Scher served as a member of the Cellular, Tissue and Gene Therapy Advisory Committee (CTG-TAC), which, on March 29, 2007, voted positively on the FDA questions placed before it. The Advisory Committee efficacy vote was 13-4 in favor of Sipuleucel-T; Dr. Scher was among the four committee members who voted in disapproval on that point. The Advisory Committee safety vote was a unanimous 17-0.

In Dr. Scher's letter, there were a number of questionable, or debatable, assertions, and a number of seeming logical flaws and contradictions, to the extent that it seems possible that he was not the actual author of this letter. However, for the sake of discussion, the authorship attribution by *The Cancer Letter* is considered to be factual. This response to Dr. Scher's purported letter is an attempt to address some of those items, both to clarify the issues, and to encourage debate about them.

In addressing his efficacy concerns, Dr. Scher reportedly stated:

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 do not constitute "proof" of benefit or justify a conclusion that they are "reasonably likely" to predict benefit.

This is, of course, in reference to the time to disease progression [TTP] (11.7 weeks Provenge vs. 10.0 weeks placebo) endpoint pre-specified in the primary trial (D9901). Depending on the 2002 unblinding or the 2003 unblinding of the TTP data, the p value was either 0.085 (91.5% chance that the 1.7-week benefit was due to Provenge), or it is 0.052 (94.8% chance that the benefit was due to Provenge).

In other words, Dr. Scher's argument is that because the probability of the 1.7-week benefit being due to Provenge treatment was not 95.0% ($p=0.050$), then the reported survival benefit of $p=0.01$ (99.0% probability that survival benefit was due to Provenge) must be disregarded as an "exploratory" statistic. Provenge supporters contend that the correlation between time to progression (91.5%-94.8%) and survival (99.0%) is so strong that the FDA should approve Provenge as soon as possible, especially considering its much milder side effect profile when compared to the treatment alternatives.

It should be noted that the TTP endpoint is only a surrogate endpoint to survival, often used because it could be measured faster than survival. It is somewhat disheartening to see Dr. Scher make the above argument. He is undoubtedly familiar with "A Clinical Development Paradigm for Cancer Vaccines and Related Biologics", to which the reader is [referred](#) (.pdf).

Dr. Scher is surely aware of the new guideline on "Other Time-to-event Endpoints" on page 6 of the Clinical Development Paradigm ("Therapeutic cancer vaccines pose the possibility of a delayed onset of activity....based on the time required to mount an effective immune response and the time for that response to be translated into an observable clinical effect", with discussion of TTP measurement issues) developed after extensive debate among the FDA, the NCI and outside experts, including Paul B. Chapman, M.D. and James Allison, M.D. from his own institution, Sloan-Kettering. There were no objections to the presentation of this paradigm during the second day of the FDA/NCI Workshop on Bringing Therapeutic Cancer Vaccines and Immunotherapies through Development to Licensure

(February, 2007) and during the panel discussion on the second day, at which the FDA was represented by two physicians. A videocast may be seen [here](#).

Also, see [Slide 7 \(.pdf\)](#), a copy of which was also shown at the Advisory Meeting. A cursory view of Slide 7 of Dr. Small's presentation of Provenge data would indicate that, using this new experience driven change in the way immunotherapies impact TTP and allowing for a three-month ramp up of the immune response, TTP would clearly achieve statistical significance. Of course, if TTP is accepted as significant, it would provide support to the survival benefit finding which, as noted, achieved p-value of .01, highly statistically significant.

Dr. Scher stated, "Another concern is that the requirements for regulatory approval appear to differ between the ODAC and CBER Advisory Committee." His discussion of the work at ODAC on clinical trial endpoints is somewhat stunning in regard to omission, especially with respect to the ODAC meeting on the afternoon of March 3, 2005 which he attended, when that Committee unanimously recommended that survival should be the only endpoint in AIPC / HRPC trials. It is incongruous that Dr. Scher now dismisses the survival finding in the D9901 trial just because the trial slightly missed the TTP endpoint which the FDA, NCI, and experts from around the world decided was inapplicable to immunotherapies.

As an aside, regarding Provenge survival data, the reader is referred to the presentation of Dr. Daniel Petrylak at the Chemotherapy Foundation in New York in November 2006, neglected by Dr. Scher, but accessible [here](#).

Although this presentation was indeed a retrospective analysis of 9901/9902a Provenge data, Dr. Petrylak reported that patients who received Taxotere 4 to 6 months after Provenge, when compared to that predicted by the Halabi nomogram (with which Dr. Scher is familiar), showed an astonishing increase in median survival of some 14 months (as compared to the 2.4 month increase demonstrated in the Taxotere TAX327 pivotal trial and the 4.5 months increase of Provenge as a standalone therapy).

Dr. Petrylak's presentation anticipated follow-up clinical trials in which the sequencing of Provenge, followed by some Taxotere, followed by a Provenge booster can be explored to further extend survival, perhaps in the absence of any prolonged chemotherapy. Surely, Dr. Scher and every oncologist hope that this will be the beginning of unprecedented management of this deadly disease. This further supports the comments of NCI's Dr. Niederhuber at the outset of the second day of the FDA / NCI Workshop, that chemotherapies may be the first combinations used and approved to further improve cancer vaccines.

The FDA will look forward to receiving the confirmatory data and analysis from Provenge's third 9902b trial in 2010. Until then, Dr. Petrylak's future Provenge sequencing trials of Provenge followed by a taxane and perhaps followed by a Provenge booster present reason for real, enduring hope by prostate cancer patients. Such additional studies will, of course, be greatly facilitated by FDA approval of Provenge.

Among his efficacy objections, Dr. Scher found,

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.

None of the cited imbalances was statistically significant. However, Dr. Scher did not mention the most important imbalance, the number of bone metastases [BM] > 10, which heavily favored the placebo arm: 40.2% treatment with #BM>10 compared to 26.7% placebo. This prognostic factor was highly predictive of survival in both D9901 and D9902a trials. It also makes clinical sense, as advanced prostate cancer has a tendency to metastasize to bone, the higher the number of bone metastases, the more severe the disease. AC members thoroughly reviewed issues of imbalances between experimental and control arms. Dr. Scher also stated, “Specifically there were no data provided of a favorable effect on PSA...”

However, this observation seems disingenuous, and surprising in light of Dr. Scher’s own Slide Presentation at the 3/3/05 ODAC meeting, where a slide was entitled: “Post Therapy Based Outcomes and Survival” states at item 3, “May not apply to non-cytotoxic agents or drugs directed at different aspects of the metastatic process.” Later, under “The Association Between Time Dependent PSA Levels and Relative Risk of Death is Modest”, he indicated that “A large part of the treatment effect is not explained by PSA.”

At page 285 of the Transcript of that meeting, Dr. Scher is quoted as:

So, where does this leave us in terms of PSA change and survival? Trial 9916 showed that there was an association of PSA decline and the treatment effect was eliminated when adjusting for the intermediate, did not see the same effect in both arms of the TAX-327 study. The Q3 week arm was the only arm to show a survival difference.

And, at page 289, “The regulations for accelerated approval are very clear. They require substantial evidence from well-controlled trials regarding a surrogate endpoint.” It is perhaps only slightly gratuitous to note Dr. Scher’s 3/3/05 reference to the term, “substantial evidence”, as opposed to the term, “establish.” This has been the subject of some controversy both during and after the 3/29/07 Advisory Committee meeting. In his letter, Dr. Scher complained,

“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.” Apart from the irony of his own previous statement suggesting general endorsement of the term “substantial evidence” (albeit in regard to accelerated approval), as an Advisory Committee member, Dr. Scher should well understand that this term is specifically cited in the May 1998 FDA Guidance for Industry publication regarding evidence for effectiveness of drugs and biological products regulation (.pdf). The regulatory requirement is that the treatment must find “substantial evidence of efficacy”. There is no deviation between Advisory Committees as long as they conform to clearly articulated regulatory requirements. It is not known why the original wording of the question to AC members was altered from the standard regulatory language, but this alteration created conceptual difficulty, and it was properly corrected.

Despite himself having voted in favor of the Provenge AC safety question, Dr. Scher averred in his letter:

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....Deaths due to CVA’s were recorded in 1.5% of Sipuleucel-T patients and 0.9% of those receiving “placebo.

Readers may recall that the subjects in this trial were elderly men, who, independently of prostate cancer, had an age associated, elevated risk of cerebrovascular accidents (CVAs). The risk of CVAs

of U.S. men older than 65 is anecdotally estimated to be 2-3% per year. For the 147 patients in the 9901/9902A treated group, there were 8 CVAs. If one estimates that the average survival of this group for the three-year study period was ~26 months (median was 23.2 months), this data would be consistent with the expected risk of CVAs.

Dr. Scher further stated:

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).

If true, this absence of CVAs in the TAX-327 trial group would be rather amazing, as these 997, primarily older patients were followed for some 18 months! Instead, it may be that specific CVAs were not reported; e.g. the FDA documents on the trial report only TEAE (Treatment Emergent Adverse Events). How Dr. Scher could confuse the absence of a specific item report with non-occurrence, given generally known incidence, is not readily apparent. Despite being the lead investigator for the ASCENT trial, he seems to not have recalled that, in the 125-patient Taxotere arm, there were 10 (8%) thromboembolic events, of which 2 were CVAs, 1 Myocardial infarction, and 1 arterial thrombosis. [Here](#) is the table from the JCO article on the ASCENT trial and [here](#) is the abstract.

In addition, from five earlier Taxotere studies, 15/149 patients experienced thromboembolic events, including 3 CVAs and 2 arterial embolisms. For example, in [this 2003 Docetaxel citation](#), it is stated,

In the Columbia Presbyterian Phase II trial of docetaxel and estramustine, the occurrence of vascular events, including grade 4 and 5 cerebrovascular accidents (6%) and grade 3 deep vein thrombosis (5%), prompted the initiation of prophylactic anticoagulation.

The above phase II trial tested Taxotere+Estramustine, the same regime tested in the Southwest Oncology Group's phase III counterpart to the TAX-327 phase III trial that Dr. Scher quoted, and 6% of treated patients had CVAs. This data suggests that TAX-327, for whatever reason, simply did not report CVAs. Dr. Scher's suggestion that this proves their absence, and that, in contrast, Provenge is unsafe, seems to represent remarkably flawed reasoning. The Provenge AC voted unanimously positive on the safety question, a vote which occurred after AC discussion of the CVA issue and members being informed that the FDA and Dendreon have planned to subsequently monitor 3000 Provenge patients for CVAs and any other identified safety issues. Provenge is generally considered to have very minimal side effects, in stark contrast to chemotherapy treatments.

Dr. Scher also suggested that the frozen version of Provenge given to placebo crossovers may have harmed them:

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.

However, he did not identify any physiological process to support the assertion, and failed to represent the Dendreon clinical trial evidence that contradicts this assertion. According to the briefing documents posted by Dendreon and FDA, each subject in the Provenge trial underwent apheresis to collect peripheral blood mononuclear cells [PBMC] in certified hemodialysis centers. Subjects in the APC placebo arm underwent the same apheresis procedure as those in APC 8015 arm to harvest PBMCs.

One-third of the total PBMCs were freshly administered to subjects and the other two third were frozen. If a subject in the placebo arm had disease progression, these frozen cells would be thawed and loaded with the therapeutic vaccine- PA2024 (APC8015F) and infused.

Transfusion of leukopheresis product is a safe and widely used clinical option; therefore there is no reason to believe that fresh PBMCs from patients' body would be harmful. On the contrary, data supports that some placebo patients may have benefited from receiving the frozen vaccine. In study 9901, the median overall survival was 21.4 months, contrasted to 19.9 months as predicted by the widely used and validated Halabi nomogram. The 1.5-month benefit showed a trend of some benefit due to frozen Provenge. In addition, placebo patients that received frozen vaccine survived longer than those who did not.

Furthermore, among the placebo patients who received second-line docetaxel therapy, the median survival was 25.7 and 20.2 months for those who received frozen vaccine and those who did not, respectively. In addition, preliminary survival data from the D9901 from an interim unblinding in September 2003, two years after the last patient enrolled, showed a laddered improvement in median survival [MS] from the placebo patients who did not receive salvage Provenge (19.3 months), to the placebo patients who crossed over to receive salvage Provenge after their cancer progressed (23.9 months), to the Provenge trial arm itself (26.3 months). This two-year data strongly indicates that the exact opposite of Dr. Scher's suggestion occurred.

In addition to expressing reservation on efficacy and safety despite votes of majority and unanimity, Dr. Scher was concerned:

that the requirements for regulatory approval appear to differ between the ODAC and CBER Advisory Committees. As an example, ASCENT1 was a prospective randomized phase 2 trial of weekly docetaxel with or without high dose calcitriol (DN-101)... 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 ($P < .16$) ... 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)... 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.

While it can be argued that both DN-101 and Provenge failed to show statistical significance of a primary endpoint analysis, the Provenge study is superior to DN-101 in many aspects:

1. In terms of regulatory preference, time to radiological/clinical progression is preferred to time to PSA response rate. Even if they were the same, study 9901 Provenge prolonged time to progression with a p-value of 0.085, contrasted to 0.16 for the improvement in PSA response rate difference by DN-101. A smaller p-value represents smaller chance error rate. 2. The survival comparison of DN-101 with Provenge is an apple-orange comparison, in that the DN-101 study failed to show statistical significance, while the Provenge study did. The log-rank p-value of the ASCENT1 DN-101 trial was .07, i.e., not statistically significant, while the log-rank p-value of Provenge's D9901 was .01. Even after applying a Cox regression (with some unknown model), the p-value in ASCENT1 was only improved to .035. This should be compared with the Cox p-value of .002 for D9901. In addition, the overall survival benefit in study 9901 for Provenge was supported by study 9902a both alone and integrated, and was extensively examined by the sponsor and confirmed by the FDA reviewers via subgroup analysis, univariable, and multivariable prognostic adjustment and shown to be robust. In contrast, a

second randomized trial had not been conducted for DN-101 when the decision not to file for approval was made.

Since evidence for DN-101 would not be deemed substantial by any division, CBER or CDER, or by any advisory committee, CTGTAC or ODAC, this example would not support Dr. Scher's claim that different regulatory standard exists between CBER CTGTAC and CDER ODAC. On the other hand, the FDA oncology drug division or ODAC have granted approvals that missed statistical significance in overall survival. There are at least two examples: 1. Eli Lilly's Alimta® for NSCLC: The pivotal study failed to show statistically significant non-inferiority with docetaxel but was approved based on superior benefit risk ratio.

2. Guilford's GliadelO` for malignant glioma patients undergoing surgery: The primary analysis of overall survival was not statistically significant. Upon further follow-up, after additional death events were included and the overall survival was re-compared and met the traditional 0.05 level, despite that it should have already been exhausted to 0, the drug was approved.

These examples indicate that, while FDA is aware of the importance of achieving statistical significance, it has displayed flexibility and frequently relies on an assessment overall benefit/risk ratio for otherwise terminal diseases, which is not quantifiable with the usual statistical significance level, when evaluating a drug application. Despite the fact that these two drugs missed statistical significance for overall survival, the benefit/risk ratio was strong enough to warrant approval.

The Provenge situation is similar. The trials did demonstrate a clinically robust and statistically significant overall survival benefit, without risk to patients' safety. Both Dr. Scher and the ODAC have previously acknowledged that overall survival is the most meaningful and reliable clinical trial endpoint. Technically missing the TTP endpoint does not weaken the benefit/risk ratio. To not approve Provenge, despite a substantial benefit/risk ratio favoring Provenge, would seem to create an inconsistency between CBER/CTGTAC and CDER/ODAC.

Presumably, Dr. Scher knows that the FDA regulations retain its authority to withdraw marketing approval should a [post-approval Phase 4 trial fail \(at pages 59 to 65\)](#) (.pdf). Dendreon has indicated that they are in negotiations with the FDA on how to best use their currently ongoing 9902b trial in this regard. The process of obtaining approval for a drug or biological product is extremely complicated, with the potential for a variety of competing interests at any stage of the process. The FDA is currently reviewing regulations regarding AC member conflicts of interest, toward greater safeguards against such conflicts, with [public comments invited](#). It seems very unlikely that Dr. Scher, or other AC members, would allow such conflicts to affect their recommendations.

However, there are other, potential underlying conflicts, such as FDA divisional affiliation, and reasoned but strongly held philosophical positions regarding FDA decision processes and thresholds. Reasonable medical professionals may disagree on such matters. An overwhelming majority of the AC Committee found, with substantial evidence, that Provenge induces survival benefit in use with a terminal disease, with minimal side effects. It is hoped, and expected, that a consensus of medical professionals will emerge in recognition that approval is warranted in such cases. With Provenge, approval will not only advance the science of immunotherapies, but will clearly be of direct benefit to prostate cancer patients.

Attachment 5

“In a letter to FDA published in the April 13, 2007, Cancer Letter, Howard Scher of Memorial Sloan-Kettering Cancer Center presented valid and compelling arguments that FDA await the completion of an ongoing 500 patient (9902B) Phase 3 trial before deciding whether to approve sipuleucel-T in prostate cancer patients. Reportedly, Scher felt motivated to write the letter after being kept awake the night following the March 29, 2007, FDA Cellular, Tissue and Gene Therapies Advisory Committee by the thought that if sipuleucel-T were approved, patients may well forego more effective treatment alternatives. He also struggled with what he might communicate to patients about sipuleucel-T’s safety and efficacy when discussing therapeutic options with them.

I also was kept awake the night following the panel. I had been invited by FDA to be screened to serve on the March 29, 2007, FDA Advisory Committee, but declined because I had had limited interactions with the sponsor in the capacity of critiquing available data. Now that the FDA Clinical and Statistical Briefing Documents are in the public domain, I am at liberty to express my own serious concerns about some of the significant flaws and limitations in the 9901 and 9902A clinical trials evaluating Sipuleucel-T in prostate cancer patients.

As noted by Scher, the 9901 and 9902A trials provide evidence that the effect of sipuleucel-T on the pre-specified primary endpoint, progression-free survival, was 1-2 weeks, far less than the 15 week improvement targeted in the 9901 protocol. Therefore, not only did the trials fail to achieve statistically persuasive evidence for benefit, the estimates of effect on that measure indicate that clinically meaningful effects were not achieved. The 9901 trial also failed to establish benefit on measures of pain or other prespecified secondary endpoints.

Major concerns arise when interpreting the survival data from the 9901 and 9902A trials. Overall survival was not a primary or secondary endpoint in 9901 (specifically, only a “descriptive” analysis of overall survival was to be performed), and also was not the pre-specified primary endpoint in 9902A.

The concerns regarding the unreliability of post-hoc analyses are far more profound than that they simply provide a violation of statistical “rules”, as one might believe from comments by the sponsor’s consulting biostatistician, Brent Blumenstein, (see O’Neill RT, “Secondary Endpoints Cannot be Validly Analyzed if the Primary Endpoint Does Not Demonstrate Clear Statistical Significance.” *Controlled Clinical Trials* 18:550-556, 1997). Estimates of effect of sipuleucel-T on overall survival are biased and p-values reported from such analyses convey a false sense of reliability of that evidence. An explanation for this bias was presented in a recent article discussing why proper adjustments must be made when multiple testing arises over the course of the trial, (Fleming et. al., “Maintaining Confidentiality of Interim Data to Enhance Trial Integrity and Credibility.” *Annals of Internal Medicine*, under review). That article states:

“This bias (a form of “regression to the mean” bias) occurs because there is true signal and random noise in every estimate of treatment effect and, when many analyses are conducted, there is a tendency for those results that appear to be most favorable to be, at least in part, due to random overestimates of true effect”.

The risk for “regression to the mean” bias is very substantial in the reported estimates of the survival effect in the Sipuleucel-T trials. A clear illustration of this bias is provided by the recent experiences from the GIPF-001 and the GIPF-007 trials conducted by InterMune to evaluate Actimmune in patients with idiopathic pulmonary fibrosis (IPF). Like Dendreon, InterMune conducted exploratory analyses after their primary analysis of GIPF-001 established Actimmune did not provide a beneficial effect on the primary endpoint (relating to pulmonary function). When a survival advantage (2-sided

p=0.004) was found in patients with mild to moderate impairment in lung function, the sponsor provided a press release indicating “The mortality benefit is very compelling and represents a major breakthrough in this difficult disease.”

Fortunately, the sponsor eventually recognized that their post-hoc analyses of overall survival did not provide reliable evidence of benefit and conducted GIPF-007, a confirmatory trial in 826 IPF patients having mild to moderate impairment in lung function, precisely the same population in which benefit was suggested by the post-hoc survival analysis of the GIPF-001 trial.

The GIPF-007 trial (called INSPIRE) was recently terminated since, according to the sponsor’s March 5, 2007 press release, “the DMC found the overall survival result crossed a predefined stopping boundary for lack of benefit of Actimmune relative to placebo” and where overall mortality was “14.5% in the Actimmune group as compared to 12.7% in the placebo group.” Many parallels between this setting and Dendreon’s evaluation of Sipuleucel-T strongly illustrate the need to await the results of Dendreon’s 9902B trial.

Important concerns with the sponsor’s covariate adjusted survival analyses of the 9902A trial also should be highlighted. The covariate analysis in 9902A that changed the two-sided from $p = 0.33$ to $p < 0.05$ was invalid in that the reported covariate analysis not only provided the intended adjustment for potential confounding, but also inappropriately excluded 10% of study patients, where the patients excluded from the Sipuleucel-T arm had less favorable survival and those excluded from the placebo arm had more favorable survival, as illustrated by the FDA Statistical Briefing Document.

FDA should bring consistent scientific and ethical standards to the oversight and evaluation of clinical research much like a court of law should bring consistent standards to legal justice. FDA approval of Sipuleucel-T would set an unfortunate precedent for accepting lack of rigor, including giving undue credence to post-hoc analyses that very likely reflect misleading estimates of efficacy due to regression to the mean-type bias, and to invalid analyses, such as the covariate adjustment of the 9902A trial that inappropriately excluded many patients who did not have missing outcome data. Furthermore, in light of FDA’s recent consideration of DN101 in prostate cancer that is discussed in Scher’s letter to FDA, how would one defend internal consistency at FDA if Sipuleucel-T were to be approved before availability of the 9902B trial? Like Dendreon, Novacea had obtained a two-sided $p < 0.05$ in supportive analyses of survival in their ASCENT1 trial evaluating DN101 in 250 prostate cancer patients. Extensive available data from ASCENT1 and other investigations of vitamin D also suggest a potential additional beneficial mechanism of DN101 through reduction in the risk of thromboembolic events, (Venner, ASCO, 2006). Nevertheless, ODAC and FDA have recognized the need for Novacea to conduct a 900 patient trial to confirm effects of DN101 on overall survival in prostate cancer patients.

Issues of safety and ethics also deserve further discussion. In clinical trials, sipuleucel-T has nearly three-fold higher rate of cerebrovascular events (17/345 on sipuleucel-T versus only 3/172 on placebo patients).

Furthermore, sample sizes in the completed trials are too small to rule out that other important risks exist. In the absence of established benefit, sipuleucel-T may readily provide more harm than benefit. Hence, one should reexamine the reasoning by FDA Advisory Committee member, Francesco Marincola. He supported approval of Sipuleucel-T by stating:

“Even if we make a mistake, even if the [therapy] is not this effective, there is so much to learn by starting to see patients being treated with this and see what else can be added. We should not underestimate the importance of this decision. I don’t think it’s just about the drug and what the drug does, but it’s about opening a field, and the investigation on that field.”

One does not need marketing approval in order to continue clinical research studies evaluating sipuleucel-T. Marincola's position is tantamount to advocating that regulatory approval be provided for interventions that have not been established to provide a favorable benefit-to-risk profile, in order to enable a sponsor to market potentially ineffective and even harmful products to patients, without a requirement for obtaining informed consent, in order to further investigation in the field.

Such use of patients for research purposes without obtaining full informed consent is illegal as well as unethical. Such practice would be in direct violation of federal law, (45 CFR 46.116 and 21 CFR 601.25(d)(2) and (3)).

I do not know whether sipuleucel-T in truth has a favorable benefit-to-risk profile. The current data are inadequate to make a reliable assessment. The 9901 and 9902A trials do not provide "substantial evidence of efficacy." Rather, at best, these trials provide plausibility of efficacy that would justify the conduct of a confirmatory survival trial. That trial (9902B) is well underway. If there is a pre-mature approval of Sipuleucel-T by FDA, how would the Agency proceed in the likely scenario that the 9902B trial, when completed, would indicate that sipuleucel-T does not provide survival benefit, as recently happened in the similar situation with Actimmune in the IPF setting? Or what if a pre-mature approval of sipuleucel-T by FDA compromises the ability or commitment of the sponsor to successfully complete the 9902B trial? The patient advocate on the Advisory Committee, Robert Samuels, stated;

"I look upon (sipuleucel-T) as an opportunity for me to make a choice. That's all the patients want: an opportunity to make a choice."

As a fellow person living with prostate cancer, I strongly disagree with his statement that all patients want is a "choice." Patients want an "informed choice." How then would pre-mature approval of sipuleucel-T that could diminish the likelihood of obtaining reliable results from the 9902B trial be in the best interests of prostate cancer patients?"

Attachment 6

More on Fleming's letter in The Cancer Letter weekly

1. Anyone who did not see the March 29th Advisory Committee Meeting and has become increasingly concerned about the published letters in of Dr,s Scher, Hussein and Fleming in the most recent issue of The Cancer Letter should take some time to look at the DNDN Slide Presentation at the meeting and read the Transcript. Their letters add little or nothing of substance to the issues discussed at the meeting. FDA Advisory Committee, March 29, 2007, DBDB Slide Presentation Slides. See, in particular: Slide 18 (TTP Plots), Slide 19 Secondary Endpoints, Slide 25 Treatment Effective Across Subpopulations. Slide 29 Prostate Cancer Specific Survival. Slide 38 Summary of Survival Benefit

http://www.fda.gov/ohrms/dockets/ac/07/slides/2007-4291S1_1.pdf and the Transcript at:

<http://www.fda.gov/ohrms/dockets/ac/07/transcripts/2007-4291T1.pdf>

2. Fleming: "I also was kept awake the night following the panel. I had been invited by FDA to be screened to serve on the March 29, 2007, FDA Advisory Committee, but declined because I had had limited interactions with the sponsor in the capacity of critiquing available data. Now that the FDA Clinical and Statistical Briefing Documents are in the public domain, I am at liberty to express my own serious concerns about some of the significant flaws and limitations in the 9901 and 9902A clinical trials evaluating Sipuluecel-T in prostate cancer patients on the March 29, 2007, FDA Advisory Committee, but declined because I had had limited interactions with the sponsor in the capacity of critiquing available data. Now that the FDA Clinical and Statistical Briefing Documents are in the public domain, I am at liberty to express my own serious concerns about some of the significant flaws and limitations in the 9901 and 9902A clinical trials evaluating Sipuluecel-T in prostate cancer patients." The much maligned legal profession should take note that if an attorney were to follow this course of action, he or she would be risking censure or disbarment. It would make little difference whether the material provided by a client was in the public domain, the attorney client privilege would bar such discussion, and the seriousness of the breach of the Canon of Ethics would be heightened especially if it occurred while a final decision was pending and in a publication largely designed to reach the decision makers. Are consultants so different? The public could reasonably perceive that, since a client presumably shared confidential information with them, they would have greater access to "hidden", non-disclosed information. If the basis of Fleming's entire letter are facts now public, as he claims, disclosure of his prior relationship reasonably implies that his opposition is, in fact, based on more than he discusses. Does Fleming now believe that the public should value his judgment on what is public and what is not when, for some reason, he turns his back on a former client and chooses to go into public opposition to the interests of his former client? Is Fleming's opposition based on his concern for the public good or on the fact that another statistician was retained by DNDN to present the statistical package to the Advisory Committee? He alleges no improper withholding of relevant data or submission of fraudulent data. So, in effect what he is saying is that the FDA statisticians and Dr. Chappell, the statistician on the Advisory Committee, were not as capable as he would have been in presenting opposing viewpoints. We should all be thankful that the Canon of Ethics requires attorneys to have higher ethical standards than Fleming.

3. Fleming: "As noted by Scher, the 9901 and 9902A trials provide evidence that the effect of Sipuluecel-T on the pre-specified primary endpoint, progression-free survival, was 1-2 weeks, far less than the 15 week improvement targeted in the 9901 protocol. Therefore, not only did the trials fail to achieve statistically persuasive evidence for benefit, the estimates of effect on that measure indicate that clinically meaningful effects were not achieved." Superficially, as an abstraction, this could make some sense, but in reality becomes patently absurd when the TTP plot (Slide 19 in DNDNs presenta-

tion) is viewed: (a) in the context of the immunotherapy “ramp up” time or the Delayed Effect recognized by the FDA and NCI before separation of TTP effects on the ITT and placebo groups, and, (b) in the context of Dr. Scher’s own words that measurement of progression should be continued and not stopped after first assessment that it has occurred, since a finding of progression is often made on improper conclusions based on metastases existing at randomization.

4. Fleming: “In the absence of established benefit, Sipuluecel-T may readily provide more harm than benefit. Hence, one should reexamine the reasoning by FDA Advisory Committee member, Francesco Marincola. He supported approval of Sipuluecel-T by stating:

“Even if we make a mistake, even if the [therapy] is not this effective, there is so much to learn by starting to see patients being treated with this and see what else can be added. We should not underestimate the importance of this decision. I don’t think it’s just about the drug and what the drug does, but it’s about opening a field, and the investigation on that field.”

Fleming continues: “One does not need marketing approval in order to continue clinical research studies evaluating Sipuluecel-T. Marincola’s position is tantamount to advocating that regulatory approval be provided for interventions that have not been established to provide a favorable benefit-to-risk profile, in order to enable a sponsor to market potentially ineffective and even harmful products to patients, without a requirement for obtaining informed consent, in order to further investigation in the field. Such use of patients for research purposes without obtaining full informed consent is illegal as well as unethical. Such practice would be in direct violation of federal law, (45 CFR 46.116 and 21 CFR 601.25(d) (and (3))).” Is that really an accurate representation of what Dr. Marincola said?

4a. From the Transcript: “DR. MARINCOLA: Yes, I’d like to make another comment which is a little broader. Historically, we’re in a very special moment of tumor immunology. This is a very rapidly evolving field, and in some ways this product was designed years ago, and so it’s, you know it’s just showing now some - it is providing one of the best outcomes so far in immunotherapy, yet probably is not perfect because it’s delivered as a single agent, and there is so much more that can be done to understand the biology of this and make it better. And I think it’s true that maybe the information has been provided, but the study is not conclusive, but definitely it is intriguing enough to believe that it’s worth pursuing it, and definitely - let’s put it another way. If I had prostate cancer, I’d like to try this before chemotherapy, no matter - maybe not as a scientist, but as somebody who has prostate cancer.”

4b. When explaining his vote on efficacy: “DR. MARINCOLA: Well, I think that, based on the facts and on the information that we have so far, I think there is substantial evidence, and I think that not only about this particular treatment, but in general in the field, and I do believe that this is just the beginning of an era where there is going to be so much more that can be done to improve these kind of therapies.”

So Dr. Marincola, a renowned immunologist, said that he found that there was substantial evidence of Provenge efficacy (the statutory standard, also spelled out in FDA guidelines) and that given his experience and knowledge that he would take Provenge if he had AIPC/HRPC. That is substantially different than Fleming’s accusation that Dr. Marincola was advocating the use of patients for research purposes without obtaining full informed consent.

5. Fleming: “The patient advocate on the Advisory Committee, Robert Samuels, stated;

“I look upon (Sipuluecel-T) as an opportunity for me to make a choice. That’s all the patients want: an opportunity to make a choice.”

Continuing: “As a fellow person living with prostate cancer, I strongly disagree with his statement that all patients want is a “choice.” Patients want an “informed choice.” How then would pre-mature approval of Sipuluecel-T that could diminish the likelihood of obtaining reliable results from the 9902B trial be in the best interests of prostate cancer patients?”

5a. For a reply, consider the following:

“DR. GUNTER: I appreciate the chance to comment, and I think I already stuck my neck out on this one. I do think it both meets the measure of substantial evidence, and I also believe that it’s pretty definitive. I think that, in this day and age, in the treatment of patients, you know, like Dr. Alexander said, you don’t have to look them in the eye and say, this is good for you. You need to be able to look them in the eye and discuss their treatment options, and present them in a way that they can understand. And I think that these data, even though they’re complex, can be presented by oncologists to patients in a way that they can understand and make reasonable choices. So I definitely support that this is an effective therapy.”

5b. “DR. MULÉ: When I look at the field in general, immunotherapy field, and given the question as it’s restated substantial evidence, I vote yes, with the proviso, however, that the definitive Study 3 is completed, and there’s a commitment for doing so. And wrapped into that is the concern raised by Mr. Samuels with respect to recruitment of minority population.”

5c. The Advisory Committee voted 17 to 0 that Provenge was safe, and 13 to 4 that there was substantial evidence of Provenge efficacy. The SEER and NODB databases show that some 48,000 men in the United States have AIPC / HRPC, and this figure probably substantially understates actual numbers due to what many doctors and patients consider the absence of acceptable treatments, especially for the asymptomatic stage of the disease. Fleming’s concept of informed choice is what he claims his choice will be, not to take Provenge, but would also deny Provenge to all but a handful of men who might be lucky enough to fill out the remaining enrollment slots in the 9902b trial. Does it really make any sense at all that Fleming and the 4 members of the Advisory Committee who voted no on the “substantial evidence” of Provenge efficacy question should be allowed to persuade the FDA to rule out the possibility that many, if not most, of these 48,000 men and others who will join them, of choosing to take Provenge with the likelihood of doubling or tripling their chance of survival three years hence when the 9901 trial data suggests that 89% of this group of men with asymptomatic disease, if left untreated, will otherwise not survive? Where do men like Fleming develop such monumental egos that they would presume to make such a decision for tens of thousands of other men tragically dying from a terrible disease?