Binkley, Joanne

From: Goodman, Jesse
Sent: Thursday, August 16, 2007 9:17 PM
To: Binkley, Joanne
Subject: FW: CBER Advisory Meeting on Provenge
Attachments: GoodmanFDASipuleucel.doc

From: scherh@MSKCC.ORG [mailto:scherh@MSKCC.ORG]
Sent: Friday, April 06, 2007 5:23 PM
To: Goodman, Jesse
Cc: scherh@mskcc.org
Subject: CBER Advisory Meeting on Provenge

Attached please find concerns raised at the Provenge Advisory Committee meeting on which I was a voting member. Your review and comment would be most appreciated. Thank you for your time and consideration.

<<GoodmanFDASipuleucel.doc>>
A hard copy will follow.

Howard I. Scher, M.D.
D. Wayne Calloway Chair in Urologic Oncology
Chief, Genitourinary Oncology Service
Memorial Sloan-Kettering Cancer Center
1275 York Ave.
New York, N.Y. 10021
TEL: Administrative: 646-422-4323
Clinical: 646-422-4330
FAX: 212-988-0851
E-mail: Scherh@mskcc.org

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

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

Binkley, Joanne

From: Goodman, Jesse
Sent: Thursday, August 16, 2007 9:17 PM
To: Binkley, Joanne
Subject: FW: CBER Advisory Meeting on Provenge

From: scherh@MSKCC.ORG [mailto:scherh@MSKCC.ORG]
Sent: Monday, April 09, 2007 10:49 AM
To: Goodman, Jesse
Cc: scherh@mskcc.org
Subject: RE: CBER Advisory Meeting on Provenge

Thank you for your comments. There is no no doubt there is a "diversity" of opinion which was clearly apparent at the meeting. But without preaching to the Choir, the key is to focus on the scientific evidence which I fear got a little lost in the discussion with all the emotional overtones.

Again, appreciate your note and consideration.

One last thing, I noticed an error in the letter on page 4 of my letter with regard to the change in the question which I will correct in the hard copy that is being forwarded.

From: Goodman, Jesse [mailto:jesse.goodman@fda.hhs.gov]
Sent: Monday, April 09, 2007 10:15 AM
To: Scher, Howard I./Medicine
Subject: RE: CBER Advisory Meeting on Provenge

Dear Dr. Scher:

Thanks very much for your input and your participation in the recent Advisory Committee. I assure you that we respect and are considering the full diversity of scientific opinion and input in this ongoing evaluation.

Jesse

Jesse L. Goodman, MD, MPH
Director, Center for Biologics Evaluation and Research (CBER)
US Food and Drug Administration
tel: 301-827-0372
fax:301-827-0440
email: jesse.goodman@fda.hhs.gov

From: scherh@MSKCC.ORG [mailto:scherh@MSKCC.ORG]
Sent: Friday, April 06, 2007 5:23 PM
To: Goodman, Jesse
Cc: scherh@mskcc.org
Subject: CBER Advisory Meeting on Provenge

Attached please find concerns raised at the Provenge Advisory Committee meeting on which I was a voting member. Your review and comment would be most appreciated. Thank you for your time and consideration.

<<GoodmanFDASipuleucel.doc>>
A hard copy will follow.

Howard I. Scher, M.D.
D. Wayne Calloway Chair in Urologic Oncology
Chief, Genitourinary Oncology Service
Memorial Sloan-Kettering Cancer Center
1275 York Ave.
New York, N.Y. 10021
TEL: Administrative: 646-422-4323
Clinical: 646-422-4330
FAX: 212-988-0851
E-mail: Scherh@mskcc.org

Binkley, Joanne

From: Goodman, Jesse
Sent: Thursday, August 16, 2007 9:25 PM
To: Binkley, Joanne
Subject: FW: CBER Advisory Meeting on Provenge

From: Goodman, Jesse
Sent: Monday, April 09, 2007 10:15 AM
To: 'scherh@MSKCC.ORG'
Subject: RE: CBER Advisory Meeting on Provenge

Dear Dr. Scher:

Thanks very much for your input and your participation in the recent Advisory Committee. I assure you that we respect and are considering the full diversity of scientific opinion and input in this ongoing evaluation.

Jesse

Jesse L. Goodman, MD, MPH
Director, Center for Biologics Evaluation and Research (CBER)
US Food and Drug Administration
tel: 301-827-0372
fax:301-827-0440
email: jesse.goodman@fda.hhs.gov

From: scherh@MSKCC.ORG [mailto:scherh@MSKCC.ORG]
Sent: Friday, April 06, 2007 5:23 PM
To: Goodman, Jesse
Cc: scherh@mskcc.org
Subject: CBER Advisory Meeting on Provenge

Attached please find concerns raised at the Provenge Advisory Committee meeting on which I was a voting member. Your review and comment would be most appreciated. Thank you for your time and consideration.

<<GoodmanFDASipuleucel.doc>>
A hard copy will follow.

Howard I. Scher, M.D.
D. Wayne Calloway Chair in Urologic Oncology
Chief, Genitourinary Oncology Service
Memorial Sloan-Kettering Cancer Center
1275 York Ave.
New York, N.Y. 10021
TEL: Administrative: 646-422-4323

Clinical: 646-422-4330
FAX: 212-988-0851
E-mail: Scherh@mskcc.org

==========

Binkley, Joanne

From: Goodman, Jesse
Sent: Thursday, August 16, 2007 9:27 PM
To: Binkley, Joanne
Subject: FW: Sipuluecel-T in Prostate Cancer

Attachments: Goodman_.pdf

Goodman_.pdf (258 KB)

-----Original Message-----
From: Fleming, Thomas [mailto:tfleming@u.washington.edu]
Sent: Monday, April 23, 2007 12:56 PM
To: Goodman, Jesse; Woodcock, Janet; Midthun, Karen; Witten, Celia (CBER); Foulkes, Mary
Cc: Fleming, Thomas
Subject: Sipuluecel-T in Prostate Cancer

Dear FDA Colleagues,

The attachment provides a letter addressed to Dr. Jesse Goodman. This letter also was sent by hard copy this morning to Drs. Goodman, Midthun, Witten and Foulkes.

This letter discusses compelling reasons why the FDA should await completion of the ongoing 9902B clinical trial and a careful review of its results before reaching a decision regarding marketing approval for Sipuluecel-T in prostate cancer patients.

It is not my intention for this letter to be only a private conversation. I am willing to have this letter made public. Therefore, if there is a public docket, please feel free to post this letter or please provide an indication to me regarding how I could do so.

I am available for further discussion of these issues if that would be useful.

Thank you,

Thomas R. Fleming, PhD
Professor of Biostatistics
University of Washington

SCHOOL OF PUBLIC HEALTH AND COMMUNITY MEDICINE
DEPARTMENT OF BIOSTATISTICS

UNIVERSITY OF WASHINGTON

April 20, 2006

Jesse L. Goodman, M.D., M.P.H.
Director, Center for Biologics Evaluation and Research
Food and Drug Administration
Building N29B, Room 5NN02
8800 Rockville Pike
Bethesda, MD 20892

Dear Dr. Goodman:

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 Sipuluecel-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 Sipuluecel-T were approved, patients may well forego more effective treatment alternatives. He also struggled with what he might communicate to patients about Sipuluecel-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 Sipuluecel-T in prostate cancer patients.

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. The 9901 trial also failed to establish benefit on measures of pain or other pre-specified 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

F-600 Health Sciences Center Box 357232 Seattle, Washington 98195-7232
206.543.1044 FAX 206.543.3286

Demonstrate Clear Statistical Significance." *Controlled Clinical Trials* 18: 550-556, 1997). Estimates of effect of Sipuluecel-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 Sipuluecel-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 Sipuluecel-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 Sipuluecel-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 Sipuluecel-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 Sipuluecel-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, Sipuluecel-T may readily provide more harm than benefit. Hence, one should re-examine 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.*"

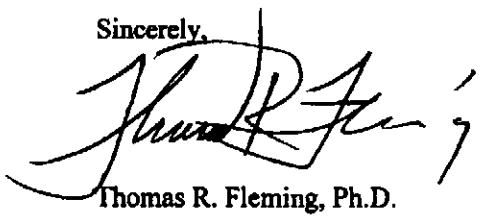
One does not need marketing approval in order to continue clinical research studies evaluating Sipuluecel-T. Marincola's position is tantamount to advocating that regulatory approval be provided for interventions that have not been established to provide a favorable benefit-to-risk profile, in order 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)(2) and (3)).

I do not know whether Sipuluecel-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 Sipuluecel-T by FDA, how would the Agency proceed in the likely scenario that the 9902B trial, when completed, would indicate that Sipuluecel-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 Sipuluecel-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 (Sipuluecel-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 Sipuluecel-T that could diminish the likelihood of obtaining reliable results from the 9902B trial be in the best interests of prostate cancer patients?

Sincerely,



Thomas R. Fleming, Ph.D.
Professor of Biostatistics
University of Washington

Cc: Janet Woodcock, M.D.
Karen Midthun, M.D.
Celia M. Witten, Ph.D., M.D.
Mary A. Foulkes, Ph.D.

Binkley, Joanne

From: Goodman, Jesse
Sent: Thursday, August 16, 2007 9:23 PM
To: Binkley, Joanne
Subject: FW: Letter re- recent advisory com. meeting

Attachments: FDA Mtg Response 4.23.07.pdf

FDA Mtg Response 4.23.07.pdf (...

-----Original Message-----
From: Maha Hussain [mailto:mahahuss@med.umich.edu]
Sent: Monday, April 23, 2007 5:28 PM
To: von Eschenbach, Andrew C.; Witten, Celia (CBER); Woodcock, Janet; Goodman, Jesse; Pazdur, Richard
Cc: Maha Hussain; mulejj@moffitt.usf.edu
Subject: Letter re- recent advisory com. meeting

Dear Drs von Eschenbach,Witten,Goodman, Woodcock, and Pazdur

I am respectfully submitting a letter to you all to share with you some concerns I have regarding the recent advisory committee meeting which reviewed Sipuleucel-T.

Thank you for your consideration

regards

Maha

"Electronic Mail is not secure, may not be read every day, and should not be used for urgent or sensitive issues."

Maha Hussain, M.D., FACP
Professor of Medicine & Urology
7314 CCGC
University of Michigan Comprehensive
Cancer Center
1500 E.Medical Center Dr.
Ann Arbor, MI 48109-0946
tel:734-936-8906
Fax:734-615-2719

Maha Hussain, M.D., F.A.C.P.
University of Michigan
1500 E. Medical Center Drive
7314 CCGC Box 0946
Ann Arbor, Michigan 48109-0946
Tel: 734-936-8906
Fax: 734-615-2719
mahahuss@umich.edu

April 23, 2007

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

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

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

Jesse L. Goodman, MD
Director
Center for Biologics
Eval & Res
8800 Rockville Pike
N29B RM 5NN02 HFM-1
Bethesda, MD 20892

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

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

University of Michigan
Health System
Comprehensive Cancer Center

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,

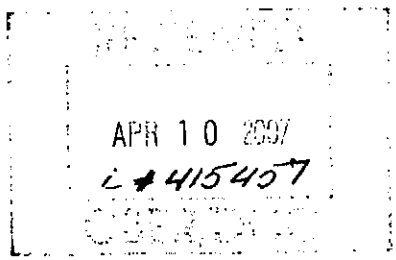
Maha

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

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

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

NCI-designated Comprehensive Cancer Center

results do not constitute "proof" of benefit or justify a conclusion that they are "reasonably likely" to predict benefit. The trial data were not consistent. Even if one accepts the post-hoc survival analysis results of the larger 127 patient trial (82 men treated with Sipuleucel-T and 45 men treated with a "placebo"), the second trial of 98 patients (65 treated with Sipuleucel-T and 33 with placebo) was not confirmatory. Consequently, the only conclusion that can be reached is that the survival difference observed may have occurred by chance alone, and that the results do not support an approval recommendation. This, and the Sponsor's recognition that an additional prospective study was needed, mandates deferring any decision on whether an approval should be granted until the results of the ongoing 500 patient phase 3 trial that is powered on a primary endpoint of survival, is accrued and analyzed.

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

There were also methodologic concerns. Trial 9901 was designed to show an increase in time to disease progression from 16 weeks for placebo treated to 31 weeks for 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

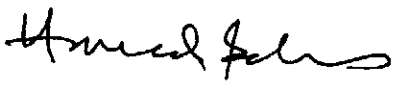
Sipuleucel-T as a "standard of care" treatment for an asymptomatic population of men with androgen independent (castration resistant) disease that represents upwards of 45,000 men in the U.S. The second is that by extension, it elevates Sipuleucel-T to a position of being the new "control" arm for future 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 was: "Does the submitted data establish the efficacy of Sipuleucel-T (APC-8015) in the intended population?" The first 4 respondees on the Committee voted "no". The question was then changed to: Do the data show "substantial evidence". A series of "yes" votes followed.

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

Thank you for your time and consideration.

Yours sincerely,



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

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

CC: Andrew von Eschenbach, MD, Commissioner
Dr. Janet Woodcock, MD, Deputy Commission for OPE
Jessie Goodman, MD, Director, Center for Biologics Evaluation & Research
Richard Pazdur, MD, Director, Office of Oncology Drug Products, Center for Drug Evaluation & Research
James J. Mule, PhD

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. von Eschenbach:

I am writing to express concerns about the recent review of Sipuleucel-T at the FDA Advisory Meeting on March 30, 2007. These concerns are: a recommendation for approval based on data that fall short of the regulatory requirements; an inadequate statistical construct to determine definitive benefit; incomplete data on product safety; and what appear to be different criteria for approval by two Advisory Committees to the Agency. All but the latter were discussed in the open meeting, but warrant further consideration given the outcome. The concerns are based on my experience as a voting member on several ODACs representing the Agency, and separately, as a Presenter to ODAC for Industry Sponsors. I have been one of the Academic Leaders of the Prostate Cancer Clinical Trial Endpoints initiative begun under the joint Sponsorship of the FDA, AACR, ASCO and PCF in 2004, which were presented at the February 2007, Prostate ASCO Meeting in Orlando. The final manuscript is currently under review at the NCI, FDA and the Group of established Prostate Cancer Clinical Trial experts who together, formulated the recommendations. I am also the Principal Investigator of a Multicenter Prostate Cancer Clinical Trials Consortium funded by the Department of Defense that focuses on phase 1 and 2 trials in this disease.

Let me state at the outset that I was one of the four Committee Members who voted "no" to the question whether the trials presented by the Sponsor established the efficacy or demonstrated substantial evidence of benefit to justify an approval recommendation to the FDA. **My vote was based on the fact that neither of the two trials presented met their primary endpoint, which renders the significance of results from any subsequent analyses as "exploratory" and "hypothesis generating".** As such, the

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

NCI-designated Comprehensive Cancer Center

results do not constitute "proof" of benefit or justify a conclusion that they are "reasonably likely" to predict benefit. The trial data were not consistent. Even if one accepts the post-hoc survival analysis results of the larger 127 patient trial (82 men treated with Sipuleucel-T and 45 men treated with a "placebo"), the second trial of 98 patients (65 treated with Sipuleucel-T and 33 with placebo) was not confirmatory. Consequently, the only conclusion that can be reached is that the survival difference observed may have occurred by chance alone, and that the results do not support an approval recommendation. This, and the Sponsor's recognition that an additional prospective study was needed, mandates deferring any decision on whether an approval should be granted until the results of the ongoing 500 patient phase 3 trial that is powered on a primary endpoint of survival, is accrued and analyzed.

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

There were also methodologic concerns. Trial 9901 was designed to show an increase in time to disease progression from 16 weeks for placebo treated to 31 weeks for 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

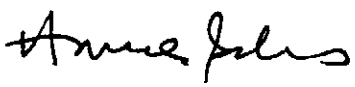
Sipuleucel-T as a "standard of care" treatment for an asymptomatic population of men with androgen independent (castration resistant) disease that represents upwards of 45,000 men in the U.S. The second is that by extension, it elevates Sipuleucel-T to a position of being the new "control" arm for future 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 was: "Does the submitted data establish the efficacy of Sipuleucel-T (APC-8015) in the intended population?" The first 4 respondees on the Committee voted "no". The question was then changed to: Do the data show "substantial evidence". A series of "yes" votes followed.

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

Thank you for your time and consideration.

Yours sincerely,



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

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

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

SCHOOL OF PUBLIC HEALTH AND COMMUNITY MEDICINE
DEPARTMENT OF BIOSTATISTICS

April 20, 2006

Jesse L. Goodman, M.D., M.P.H.
Director, Center for Biologics Evaluation and Research
Food and Drug Administration
Building N29B, Room 5NN02
8800 Rockville Pike
Bethesda, MD 20892

Dear Dr. Goodman:

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 Sipuluecel-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 Sipuluecel-T were approved, patients may well forego more effective treatment alternatives. He also struggled with what he might communicate to patients about Sipuluecel-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 Sipuluecel-T in prostate cancer patients.

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. The 9901 trial also failed to establish benefit on measures of pain or other pre-specified 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

F-600 Health Sciences Center Box 357232 Seattle, Washington 98195-7232
206.543.1044 FAX 206.543.3286

Demonstrate Clear Statistical Significance." *Controlled Clinical Trials* 18: 550-556, 1997). Estimates of effect of Sipuluecel-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 Sipuluecel-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 Sipuluecel-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 Sipuluecel-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 Sipuluecel-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 Sipuluecel-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, Sipuluecel-T may readily provide more harm than benefit. Hence, one should re-examine 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."*

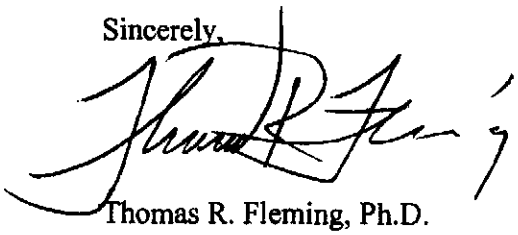
One does not need marketing approval in order to continue clinical research studies evaluating Sipuluecel-T. Marincola's position is tantamount to advocating that regulatory approval be provided for interventions that have not been established to provide a favorable benefit-to-risk profile, in order 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)(2) and (3)).

I do not know whether Sipuluecel-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 Sipuluecel-T by FDA, how would the Agency proceed in the likely scenario that the 9902B trial, when completed, would indicate that Sipuluecel-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 Sipuluecel-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 (Sipuluecel-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 Sipuluecel-T that could diminish the likelihood of obtaining reliable results from the 9902B trial be in the best interests of prostate cancer patients?

Sincerely,



Thomas R. Fleming, Ph.D.
Professor of Biostatistics
University of Washington

Cc: Janet Woodcock, M.D.
Karen Midthun, M.D.
Celia M.Witten, Ph.D., M.D.
Mary A. Foulkes, Ph.D.