

Clarifying the Issues Surrounding Dendreon's Provenge
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Wall Diver & Co submit Rebuttal to Scher's "Leaked" Cancer Letter

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 (NasdaqGM: 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 (CTGTAC), 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, 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 ASCEN T1 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.

Disclosure: Author is long DNDN