

David Miller of BioTech Stock Research, LLC has written a response to the comments that Dr. Sher has published about Provenge. It makes great reading.

On March 29, 2007, the FDA's Cellular Therapy and Gene Therapy (CTGT) Advisory Committee voted 17-0 in favor of the safety and 13-4 in favor of a finding of substantial efficacy for a prostate cancer drug called Provenge. Since that meeting, questions have been raised as to whether that decision was correct. Others have wondered whether the decision perhaps broke new ground for the FDA.

Dr. Howard Scher, a prostate cancer researcher and one of the CTGT panel members who voted no on the efficacy question, wrote a letter to the FDA urging them not to approve Provenge. Dr. Scher's letter serves as a convenient starting point to address whether the decision by the panel matched the data on Provenge as well as addressing whether an approval of Provenge breaks new ground for the Agency.

Dr. Scher's letter is reproduced in its entirety below, with the exception of his introductory paragraph. Dark text indicates Dr. Scher's points.

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."

Dr. Scher is expressing an opinion here not shared by 13 of his fellow panel members. It should be pointed out the 9901 Phase III trial had a p-value of $p=0.052$ when a p-value of $p=0.05$ is considered statistically significant. Biostatisticians would call that "nominally statistically significant." Laypeople would call it "close enough."

The FDA did opine that the correct p-value was $p=0.08$ and that adjustments made to bring the p-value to nominal statistical significance were done after the data were unblinded. This is an important point. There have been instances when unblinded analyses of data start to make the data look better. This phenomenon is a function of human nature where we are more apt to see successes than failures.

The sponsor did not do any unblinded analysis of the TTP data. The scans were not re-read to generate a different answer. The pain questionnaires were not "corrected" to get a different answer. The sponsor, in the process of checking paperwork for the BLA filing, discovered clerical errors. Correcting these errors made the results of the primary endpoint in the 9901 trial statistically significant.

It is important to note the FDA did not argue the corrections themselves were inaccurate. They simply chose to go with the original p-value. The sponsor did not argue the point in

the panel meeting because the focus was correctly on the survival advantage demonstrated in the trial.

The FDA often accepts unblinded data as supportive for approval. The most germane example is that the primary trial leading to approval for Taxotere in prostate cancer was a completely unblinded trial and the FDA had no problem approving that drug for use in this patient population.

As such, the results do not constitute “proof” of benefit or justify a conclusion that they are “reasonably likely” to predict benefit. The trial data were not consistent. Even if one accepts the posthoc survival analysis results of the larger 127 patient trial (82 men treated with Sipuleucel-T and 45 men treated with a “placebo”), the second trial of 98 patients (65 treated with Sipuleucel-T and 33 with placebo) was not confirmatory.

The FDA has accepted a variety of data as confirmatory for the purposes of approval, ranging from single-arm Phase II trials with no p-values to trials that have demonstrated only a statistical trend. With this in mind, it is incorrect to say the second trial (9902a) was not confirmatory. It would certainly not break new ground at the FDA if the second trial was seen as confirmatory, particularly if one looks more closely at the facts.

When a prespecified biostatistical technique called a Cox regression analysis was applied to the second trial, it was indeed statistically significant ($p=0.023$). Cox regression analyses are regularly done in all divisions of the FDA to make sure a claimed efficacy benefit is not the result of some imbalance between the arms of a study. In the case of the second Provenge trial, the Cox analysis corrected for an imbalance that was in favor of the control arm. In other words, the sponsor was unlucky in that patients in the control arm had baseline characteristics that would have made them live longer regardless of the treatment they received. The Cox analysis can correct for such imbalances, and that correction resulted in the second trial also being statistically significant for survival. With this information, the second trial can be seen as confirmatory.

The two Provenge trials were designed to be pooled together. When pooled for survival, there was a statistically-significant survival benefit for Provenge over the control arm ($p=0.011$). When the Cox analysis was applied to the pooled data to correct for imbalances, the result was highly statistically significant at $p=0.0006$ (remember, $p=0.05$ is the accepted threshold for significance).

The pooled data and the Cox correction for the survival data on the second trial provide adequate “support” for the first trial, especially given the flexibility the FDA has used in determining what is supportive for other drug approvals.

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.

Both the FDA and the sponsor did an exhaustive set of analyses to determine whether the survival benefit seen in the data set was due to chance. Many of these analyses, particularly those that looked at what treatments patients received after exiting the trial, are rarely required by the FDA for approval. In each case, the trend towards increased survival stayed firmly in Provenge's direction.

Every clinical trial result can be due to chance. Drug approval is not an exact science, and obsessing on p-values (the mathematical representation of how likely a trial is due to chance) is a good way to lose the forest for the trees. Dr. Scher himself recognizes this. At a recent panel discussion sponsored by the biotech company Novacea, which chose Dr. Scher as the primary investigator on the pivotal trial for their prostate cancer drug DN-101, Dr. Scher had this to say:

"It may be time we focus less on statistical significance alone, and more on patient benefit." – MedPage Today, February 26, 2007

This is exactly what the 13 members of the CTGT panel did by voting yes to whether Provenge provided substantial evidence of efficacy.

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.

This is an overstatement. The third clinical trial (IMPACT/9902b) was launched before the three-year survival analysis of either of the first two trials was determined. The trial has since expanded to include mildly symptomatic men, whereas the initial patient population was comprised exclusively of men without symptoms. It is therefore more a label expansion trial than a confirmatory trial.

Many sponsors, particularly large pharmaceutical companies, have other trials underway when they ask for their first approval. The FDA does not consider the existence of these other trials as a reason not to approve a drug. They examine the data in hand to see whether it demonstrates substantial efficacy and safety. On these two points, the CTGT panel voted unanimously that Provenge was safe and 13-4 that it demonstrated substantial efficacy.

Concerns about the validity of the findings were reinforced by the absence of other signals of an anti-tumor effect. Specifically there were no data provided of a favorable effect on PSA, regression or stabilization of soft-tissue or 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.

The difficulty for physicians Dr. Scher describes is not without precedent for oncologists or even in prostate cancer. When treatments are used in the adjuvant setting for cancer, there is no immediately obvious result in most cases. Adjuvant treatments are widely popular because of their long-term benefits, and physicians have adapted to this approach. The delayed benefit apparent with adjuvant treatments is similar to the situation with Provenge, so there is every reason to expect physicians will adapt.

A prostate cancer specific example is the use of bisphosphonates. These drugs are widely prescribed, yet they have no immediate impact on the patient. Prostate cancer doctors know the benefit of these drugs is over the long term. They adapted to not having immediate feedback, indicating prostate cancer doctors should have no problem adapting to the long-term benefits of Provenge.

The scientific community now recognizes active immunotherapies work differently than traditional chemotherapy drugs. The FDA and the National Cancer Institute sponsored a symposium earlier in 2007 focusing on cancer immunotherapies. Speakers from both organizations acknowledged the way clinicians and regulators have traditionally believed a cancer drug “should” work simply does not apply to active immunotherapies like Provenge. The Journal of Immunotherapy recently offered a peer-reviewed assessment of how cancer vaccines and related biologics should be evaluated under a difference clinical development paradigm.

There are many theories as to why this is the case, chief among them that survival is extended because these drugs slow the spread of the disease. Slowing the disease is not a broadly recognized surrogate endpoint for cancer therapy approval. But several classes of new therapies, many of them recently approved by the FDA, slow the growth of tumors far more often than they shrink them.

We first declared war on cancer in the 1970s. We’re making progress, but until the last decade this progress came only at a price of severe side effects. We are now so used to these side effects that when a prostate cancer chemotherapy drug like Taxotere is found by trial investigators to be directly responsible for the death of 1-2% of patients who take it, the side effects are called “acceptable”.

It was a great shame that the lead investigator for the first Provenge pivotal trial, Dr. Eric Small, had his flight cancelled by his airline so he was not able to join the panel in time. Dr. David Penson, however, has been an investigator on all three clinical trials for Provenge. During the public commentary section, he clearly articulated how his patients benefited. Dr. Penson came to the CTGT public commentary meeting of his own accord and did not discuss his testimony with the sponsor.

Perhaps more importantly, the administration of Provenge does not interfere with further treatment. This is not typical for other treatments for this patient population. Treatment

with Taxotere extracts a significant cost, weakening many men so much they are not willing or able to take a second type of treatment. While Taxotere claims a benefit to quality of life as one of its advantages, that is only in comparison to another toxic chemotherapy drug.

Dr. Daniel Petrylak looked at the patients who did choose Taxotere after receiving Provenge comparing them to men in the control arm of the two trials who got placebo then took Taxotere. The survival difference was remarkable, 34.5 months compared to 25.4 months for patients randomized to receive placebo who went on to receive Taxotere, a difference of 9.1 months (HR = 1.90; p-value = 0.023). These data were presented by Dr. Petrylak at the 2006 Chemotherapy Symposium of New York.

There were also methodologic concerns. Trial 9901 was designed to show an increase in time to disease progression from 16 weeks for placebo treated to 31 weeks for Sipuleucel-T treated patients (HR = 1.92, alpha =0.05, two sided, with 80% power). A total of 127 patients were enrolled using a 2:1 randomization in favor of the experimental therapy. The study was double blind and included an independent review of all imaging results. The estimated time to progression on which the trial was powered proved to an overestimate, as the actual observed median time to progression was 9 to 11 weeks for both arms: a difference that was not statistically significant. A summary of the progression events showed that 90% (97/114) were by imaging, 10 were clinical, and 7 were for the new onset of disease related pain. Unrecognized at the time of the design of the trial, was that the eight week interval between disease assessments was too short to observe clinically significant changes by bone scan, and that in many cases, apparent “progressions” eight weeks after the start of a therapy are more a reflection of disease worsening that led to trial entry, and not a failure of the treatment.(CCR 13:1488, 2007)

This is similar to what was observed in the trial with the endothelin antagonist, atrasentan, in which a 12 week disease assessment interval was used and a large proportion of patients were withdrawn at the time of scheduled scans in the absence of clinical worsening of disease (ODAC, September 13, 2005). Recognizing this, the Prostate Cancer Working Group 2 has advised that an apparent progression on bone scan at a three month assessment, be confirmed by documenting further progression on a subsequent scan six or more weeks later before considering a patient to have failed the treatment.(ASCO Multidisciplinary Prostate Cancer Symposium, (Abstract #221) February 22-24, 2007, Orlando, FL, 2007). Although the Sponsor suggested that the effect of the product was delayed, this hypothesis could not be explored because serial imaging to assess disease at defined intervals were not performed once a patient was considered to have “progressed” and taken off study. As a result, individual sites of disease were no longer being monitored, so that no statements could be made regarding a possible “delayed effect” of the product on disease status.

We applaud Dr. Scher for including this passage in his letter. It confirms what the scientific community has determined: Progression is a poor endpoint for cancer immunotherapies. In 2005, the FDA's Oncologic Drugs Advisory Committee (ODAC) decided the only proper endpoint for oncology trials was survival. Dr. Scher was on that panel and agreed with the committee's findings. Despite this, Provenge demonstrated a nominally statistically significant result in time to progression in its first trial.

Trial 9901 was designed in 1999. Since then, as Dr. Scher acknowledges, the scientific community has learned a few things. The broader question here is whether we should use that knowledge to penalize prostate cancer patients or help them. 13 members of the CTGT panel chose to apply the knowledge the medical community has gained over the last eight years to help prostate cancer patients by focusing on the survival benefit demonstrated by Provenge.

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.

Dr. Scher's admonition to audience members at that February 2007 panel is applicable here. He said, "It may be time we focus less on statistical significance alone, and more on patient benefit."

Biostatisticians are masters of a very arcane art of interpreting streams of data. Biostatisticians are most concerned with making sure a treatment benefit in a trial is not due to chance. They have set up a dizzying array of rules to prevent people from cheating and changing the rules on interpreting the data of a trial simply because they don't like the outcome. These protections serve us well, as long as they are not taken to the extreme.

Both the first (9901) trial and the pooled data demonstrated a p-value of $p=0.01$. This means that there is only a 1% chance the result is due to chance. Biostatisticians and regulators have arbitrarily chosen 5% ($p=0.05$) as the odds of a result being due to chance are too high for drug approval.

In order to prevent people from switching things up to get results they like better, biostatisticians force trial sponsors to choose in advance which single item they will measure to prove a clinical trial is successful. This is a very good rule, as long as it is not taken to extremes.

Eight years ago, the sponsors of the Provenge trial didn't know any better and chose time to progression as that single item – the primary endpoint. They nominally hit it for one trial and missed it with another. If they instead had chosen survival as that single item, then Dr. Scher would not likely have written his letter and Provenge would likely already be on the market.

Nearly all of the time, when a sponsor switches endpoints around it is a problem. They often dredge data and choose some narrow portion of patients – a subgroup – and claim victory for the trial when that subgroup shows a benefit. This is quite common, and the FDA rightfully rejects these arguments for a whole host of reasons not particularly germane to this discussion.

It is important to realize that's not what is going on here. Provenge demonstrated a survival advantage in all patients in the first trial and when all patients from both trials are combined into one analysis. All patients in the second trial saw a similar survival advantage once that trial was statistically corrected for imbalances.

Should prostate cancer patients be penalized for an eight-year old decision to make progression the primary endpoint? As Dr. Scher himself implies, sometimes you have to look beyond strict biostatistical rules and do what is right for patients. 13 panel members agreed with this point of view, and voted their belief that Provenge demonstrates substantial evidence of efficacy.

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.

Dr. Scher picks only two of many baseline criteria. The sponsor tracked over 20 in this trial. When all the criteria were taken into consideration, it turns out the factors actually were in favor of the control group, predicting a longer survival for “untreated” patients independent of therapy. The FDA concluded this analysis was accurate.

The sponsor went an extra step and ran all patients in the trial through something called a predictive nomogram. A nomogram is a tool doctors can use to predict survival of patients in order to assist the patient in deciding the proper course of treatment. The nomogram bases its prediction on certain baseline diagnostic data.

The appropriate nomogram for this patient population is called the “Halabi nomogram” after one of the doctors who invented and validated it. When the sponsor applied this nomogram to the patients in the clinical trial, there was a 0.2 month (6 day) difference in predicted survival between the Provenge and control arms. This is further proof the arms in the first trial were balanced. These data, incidentally, were presented at the panel meeting. Dr. Scher himself is a big fan of nomograms, having developed and published a number of them himself.

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 19.9-month nomogram-predicted survival advantage for the control arm in the Provenge trial matches nicely with the 19.8 months survival benefit in asymptomatic patients in the control arm of the clinical trial responsible for the approval of Taxotere. Consistency with other reported survival data in similar patient populations makes it unlikely the control group is appreciably different.

The more important point to emphasize is there were no imbalances between the two arms for the first trial than can explain away the benefit of Provenge.

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... 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).

It should be noted the panel voted unanimously that Provenge is reasonably safe. In addition to the vote that Provenge was safe, the FDA asked the panel members to discuss whether the cerebrovascular accidents (CVAs) were a potential safety signal. Dr. Scher led off this discussion with some prepared comments. He concluded his remarks by

noting it is an open question that should be addressed by the sponsor's 3,000-patient "pharmacovigilance" program where patients receiving Provenge will be tracked for a number of years to determine more precisely the risk of CVAs. Everyone agrees the successful completion of this 3,000 patient monitoring program should be a condition of approval. All the panel members voted that the minimal side effects demonstrated by Provenge should not be a barrier to approval.

The Journal of Clinical Oncology article Dr. Scher cites was accepted for publication prior to the sponsor's detailed analysis of cause of death. CVAs were not included in the manuscript because this issue was not yet known.

This side effect should be put into some context. In the SWOG-9906 study that formed the basis for approval for Taxotere, eight men (2%) died directly from side effects of Taxotere. Despite this information, the authors in the publication of these two trials concluded Taxotere was safe.

As men get older, the risk for CVAs rises quickly. The average age of men entering the first clinical trial for Provenge was 73 in the Provenge arm and 71 in the placebo arm. The American Heart Association tells us that the risk of stroke doubles every decade after age 50, or about 12% increased risk each year. The two-year difference in age between the two arms in the first clinical trial could, therefore, explain the difference in CVAs.

It is unknown whether the increased risk of CVAs seen in patients who took Provenge are the result of the drug or the result of the drug making men live longer. The sponsor is being more than reasonable in committing to examine 3,000 Provenge patients to make sure there is no additional CVA risk.

There is little question, given all this, why the panel members – including Dr. Scher – voted unanimously that Provenge was reasonably safe.

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.

We separated this sentence out of its original place in the discussion on CVAs because Dr. Scher suggests men in the placebo arm may have fared worse because 75% of them chose to crossover to an alternate version of Provenge. This view is definitively contradicted by publicly available data, including data presented to the advisory panel.

The Halabi nomogram discussed above predicted men in the placebo arm of the first trial should have lived 19.9 months. They instead lived 21.4 months, or 1.5 months better than expected. These data were presented at the advisory panel meeting. Given this, it is hard to imagine the placebo used in the trial worsened survival in the control group.

A second piece of data refuting Dr. Scher's assertion can be found in the 36-month landmark survival analysis. When examining the pooled data for the first two trials, 49 (33%) men in the Provenge arm lived three years and beyond compared with 12 (15%) of the men in the control arm. Of those 12 men in the control arm, only 2 did not receive the frozen form of Provenge on crossover. If this form of Provenge was harmful, as Dr. Scher suggests, one would expect those numbers to be reversed.

The third item refuting Dr. Scher's assertion is data on the relative median survival of patients who declined to cross over to Provenge. In September of 2003, the sponsor released preliminary survival data from the first trial that broke out median survival results for patients who were randomized to receive Provenge, patients who were randomized to control and then received frozen Provenge, and patients who were randomized to control and did not choose crossover. Men in the Provenge arm had a median survival of 26.3 months. Men who were randomized to control but crossed over to receive frozen Provenge had a median survival of 23.9 months. Men who were randomized to control who never received any form of Provenge had a median survival of 19.3 months. While the data splitting out the control group is not statistically significant, it is one more piece that refutes Dr. Scher's argument that the control group was somehow harmed by the crossover trial design.

The fourth data point here comes from the look at the pooled Provenge data done by Dr. Petrylak. Recall he looked at how Provenge may have boosted the benefit seen by patients who later took Taxotere. His data mirrored those above. For men in the control arm who did not elect to cross over, and were then treated with Taxotere, median survival was 20.2 months. Men in the control arm who chose to cross over, and then received Taxotere, had a higher median survival of 25.7 months. Men who were in the Provenge arm who eventually received Taxotere had the highest median survival of 34.5 months.

Finally, the 19.5-month median survival of the no-crossover patients listed in the sponsor's 2003 data is very close to the 19.9 months predicted for them by the Halabi nomogram. There is simply no evidence men who crossed over to frozen Provenge were harmed. To the contrary, the fact these men appeared to do better than men who did not crossover further supports the fact Provenge demonstrated substantial evidence of a survival benefit.

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?

Novacea is the biotech company sponsoring DN-101 in clinical trials. They also sponsored the panel in February 2007 where Dr. Scher discussed how slavish attention to p-values might not be the best for patients. There are a number of items here Dr. Scher leaves out about the DN-101 trial that shed light on some of his arguments.

The ASCENT-1 trial used a weekly dose of Taxotere in both the treatment and comparison arms. The trial was designed and enrolled before the TAX-327 data demonstrated weekly Taxotere is inferior to Taxotere given every three weeks. There is simply no way for the FDA to resolve this complication in terms of describing how to use DN-101 on the product label. The use of weekly Taxotere, and not p-values or endpoint choices, required Novacea to launch ASCENT-2 – this time using the approved Taxotere every three week schedule.

One other item that is interesting about Dr. Scher's example of DN-101 and his involvement as lead investigator of that trial has to do with the endpoints chosen for the trial. In the design of the ASCENT-2 pivotal study of DN-101, Novacea did not choose to include PSA response, time to progression, progression free survival, or overall response rates as endpoints. Recall Dr. Scher's argument against Provenge above in terms of it having no effect on intermediate disease markers? It seems there is something of a double standard here since Dr. Scher's ASCENT-2 trial doesn't even bother to include these items as endpoints.

It is important to note the ASCENT-2 trial was granted a Special Protocol Assessment (SPA) by the FDA. An SPA is a written agreement between the Agency and the trial sponsor that the endpoints and conduct of the trial are acceptable. In this case, the FDA agreed in writing that a prostate cancer trial looking at no intermediate disease markers and survival only could present sufficient evidence for approval.

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.

Dr. Scher knows decisions about standard of care do not come from the Agency but from organizations like the American Urological Association, the American Society of Clinical Oncologists, and others. The FDA has approved many drugs that are not currently components of the standard of care as specified by various medical and scientific communities.

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.

Despite the fact recognized treatments existed for renal cell carcinoma, the FDA allowed the sponsors of both Nexavar and Sutent to conduct trials using an inert placebo as the control arm. Not to pick on Nexavar, but the FDA offered a Special Protocol Assessment to investigate the drug in melanoma comparing the treatment of melanoma with and without carboplatin and paclitaxel. Neither chemotherapy drug is approved by the FDA for melanoma.

In sum, the FDA has broad latitude on what to require as control arms for future trials. Whether Provenge should be considered as the standard of care for doctors and/or as a control arm for future trials is a separate discussion from whether the drug should be approved.

It also opens the door to the premature approval of drugs based on inconclusive data.

This is based upon his flawed argument above that the data supporting the approval of Provenge is somehow flawed.

More than that, it denigrates the FDA's ability to make seemingly fine distinctions between data that untraditionally proves substantial efficacy and data that is simply inconclusive. The FDA made a couple of approvals in the early part of this decade where many people made precisely the same argument. In May 2004, the FDA had no problem aggressively arguing against approval of a melanoma drug and a breast cancer drug in front of an ODAC panel. To suggest the FDA can't tell the difference between Provenge and inconclusive data does not give the FDA staffers and the regulatory process enough credit.

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.

The Federal Food Drug and Cosmetic Act passed by Congress in 1962 included a provision requiring manufacturers to establish a drug’s effectiveness by “substantial evidence.” A review of the panel meeting clearly indicates panelists were having a hard time trying to determine what level of proof was required for “establish”. The FDA correctly changed the question to reflect Congressionally-mandated approval standards.

During the panel meeting, Dr. Jesse Goodman, the Director of CBER, suggested the question change to Dr. Celia Witten, head of the FDA’s CTGT. Some accounts of the meeting inaccurately report the question was changed by Dr. James Mule, the Chairman of the CTGT Advisory Panel. The top two FDA personnel at the meeting changed the question to match the FA’s own regulations, not the panel itself.

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.”

This article dealt with only one aspect of the data set presented to the panel members. The second clinical trial and the pooled data were not part of the analysis presented by the authors. Data on cause-specific survival, which was incredibly favorable towards the Provenge arm, was not presented. In sum, there was a great deal of supportive data not presented in this JCO article that was available to the panelists, 13 of whom voted that Provenge demonstrated substantial evidence of efficacy.

All of the difficulties cited, and the Investigator’s own conclusions, show how there are simply too many alternative explanations for the observed survival difference beyond treatment with Sipuleucel-T. Couple this with that fact that there were no secondary signals of an antitumor effect and no confirmatory trial however flawed, mandates that any decision for approval be deferred until the phase 3 study, currently underway, has been completed and analyzed.

In reality, there are no alternative explanations for the observed survival difference. The Cox analysis the FDA regularly uses to determine if such explanations exist only decrease the odds the survival benefit demonstrated was due to chance.

The scientific community understands active immunotherapies like Provenge work differently than traditional chemotherapy and other drugs. One common conclusion expressed by presenters at a recent FDA/NCI conference on this class of drugs is that doctors and regulators need to understand these differences. Dr. Scher seems to have

some understanding of this given the DN-101 trial he is heading up for Novacea has none of these secondary signals tracked as endpoints.

Both the second trial, corrected for imbalances between the two arms, and the pooled data provide plenty of “support” as the FDA defines that term. The FDA can be, and often is flexible as to what constitutes “supportive data”. The data presented to support the primary Provenge trial clearly meets these standards.

Dr. Scher himself voted that Provenge is a safe drug. While the data package for Provenge is not perfect, 13 of the panel members voted that the data provided substantial evidence of efficacy. Waiting for data from the IMPACT (9902b) study would delay approval and broad access to Provenge until the middle of 2009 at the earliest. Since the median survival of men with prostate cancer matching those in the Provenge trial is about 20 months, this means another “generation” of prostate cancer patients will die without the chance to have Provenge extend their lives.

“It may be time we focus less on statistical significance alone, and more on patient benefit.” Dr. Scher had it exactly right in February of 2007 when he uttered this line at a panel sponsored by Novacea. There is no patient benefit of higher value than more time with loved ones. Provenge has provided substantial evidence it can do just that, and it is time to make it available to asymptomatic men with metastatic, hormone-refractory prostate cancer without further delay.

About the Author

David Miller is the President and CEO of Biotech Stock Research, LLC (BSR). BSR publishes research on publicly-traded biotechnology companies for investors, physicians, patients, and company executives.

Mr. Miller has been following the Dendreon, the sponsor of Provenge, for almost seven years. He is broadly quoted as an expert on Dendreon. He has been quoted in nearly all of America’s major newspapers as well as appearing multiple times on television. He has attended nearly every major oncology conference since 2003, including all of ASCO’s Prostate Cancer Symposia.

BSR prides itself on its independence. The firm does not run a hedge fund, it does not investment banking, does not run a trading desk, and accepts no compensation from the companies it covers. The firm is 100% supported by subscriptions. BSR allows its staff to

own shares in the companies it covers, subject to an industry-best disclosure and restricted trading policy. Mr. Miller does own shares in Dendreon.

BSR has published the facts collected in this document to its Subscribers previously, but has not published this document previously. This document was created because men with prostate cancer need better treatment options than what is currently available. David's father, Jack, was diagnosed with prostate cancer only after the disease had spread to his bones and affected him to the point he was confined to a motorized wheelchair. His urologist did not administer a PSA test, despite treating Jack for all the classic symptoms of prostate cancer for almost three years, because he believed there were no treatments suitable for someone in his otherwise poor health (COPD, heart disease). While Jack's disease state does not match Provenge's initial label, his story is illustrative of how men with this disease need more options.

Mr. Miller is more than happy to answer questions about this document, or to share his knowledge about Provenge and prostate cancer with patient groups. He may be contacted in Seattle at XXX-XXX-XXXX or via e-mail at david.miller@biotechstockresearch.com.

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