

PROVENGE SCIENCE OVERVIEW

All trials show that Provenge is efficacious by extending survival (D9901 and D9902a). Triple the survival after 3 years. All six clinical studies following PC patients after Provenge treatment have all demonstrated the effectiveness of Provenge. The Provenge arm had a *median* survival advantage of 4.5 months vs. the control arm. The *median* survival is calculated from each arm by taking the survival time of the person in each arm *at the 50th percentile*. It does not reflect the true long term benefit of a treatment. Numerous Provenge patients are doing well on an ongoing basis at 5, 6 and even 7 years since receiving Provenge, whereupon the men who were randomized to placebo in these trials are nearly all deceased.

The stunning figure is the 34% survival after three years in the Provenge arm, vs 11% in the control arm. This is a disease stage where the typical survival was 16-19 months, so a 34% three-year survival is very impressive. Also, we knew that in March 2007, only 8 of the 28 three-year survivors in the 9901 trial had died (the calculations for the trial ended in Sept 2004). Therefore, this means that as of 3/07, 20 out of 82 men survived between 5.5 and 7.1 years (the enrollment period for 9901 was 1/00 to 9/01). It has been found that Provenge has a delayed effect so that later the results are expected to yield even better data.

Time to Progression (TTP). When the trial began nearly 10 years ago the FDA suggested this TTP endpoint, which has since been determined by the FDA, *to be less important than survival*, which is an endpoint that cannot be faked or manipulated. What is meant when the FDA says "it missed its primary endpoint" is that it did not slow selected symptoms of disease progression to an *extremely statistically significant level*. The p value, as calculated by the study investigators, was 0.052, meaning that it barely missed being "stat sig" to the arbitrarily high level of 0.05. It is not as if the results show that the treatment "failed to slow progression." The results do show that the treatment slowed progression of symptoms of the disease. *Most biostatisticians* would call a $p=0.052$

level of significance “nominally statistically significant.” Why the FDA did not think so in this case is unknown.

Unfortunately the FDA forced clerical errors to be counted in the final analysis, which meant that the FDA-calculated p value was 0.085. This still means that the slower progression seen in the Provenge arm was 91.5%-94.8% due to the Provenge, and not due to random chance. Therefore, combined with the 0.01 survival p value (99% due to the Provenge), you have a pretty strong correlation. So, should a correlation of 91.5% (low end of ttp) and 99% be thrown completely out? Not when, in the real world, you are talking about people's lives. Not when the FDA hasn't believed since at least 2005 that TTP is not an appropriate endpoint.

Fundamentally, the FDA denied Provenge because it did not meet an endpoint the FDA has already said is unacceptable. Provenge met the survival endpoint, *the only endpoint the FDA has accepted for approval since 2005*, at the p=0.01 threshold of significance. There is no defensible, real-world reason (as opposed to biostatistical mathematical abstractions) why the data on survival is less accurate simply because it was not listed as a “primary” endpoint. People die when they die, and whether that death is counted first or second on a piece of paper makes no difference as to whether the person is dead or alive.

Importantly the FDA knew full well that Provenge had missed on the inappropriate FDA advised endpoint of TTP *when it accepted the BLA submission*. The later proclamation that more data were needed because Provenge missed on TTP was therefore post ad hoc contrived. This was completely understood and accepted by the FDA and was not supposed to be a barrier to approval. The scientific community has changed its thinking on TTP and determined along with the FDA that TTP is a chemotherapy evaluation technique that does not translate to evaluation of the efficacy of an immunotherapy like Provenge. The FDA's Oncologic Drugs Advisory Committee (ODAC) determined in 2005 that *survival was the only acceptable endpoint for prostate cancer*. Every pivotal trial for AIPC since then has been advised by the FDA to make survival as a primary endpoint. The

FDA has, to the Appellant's knowledge, never agreed to a Special Protocol Assessment for an AIPC trial with any primary endpoint but survival.

Now, take Provenge's negligible side effects when compared to the only currently approved treatment for late stage prostate cancer, a Chemotherapy treatment called Taxotere. Taxotere kills 2% of its advanced PC patients outright according to published data, not to mention its other severe and debilitating side effects. Despite the severe side effects, Taxotere extends life on average by only 2.5 months. Compared to Provenge, which has occasional side effects of mild flu like symptoms for a few days after treatment (6-9 days total for the entire course of treatment), the current approved treatment is *less* safe and *less* effective. What the antiquated FDA has done is to evaluate new therapies, like Provenge, the same way it has evaluated chemotherapy treatments through the years. The FDA, by virtue of its own revised trial design guidance, has demoted the importance of traditional markers such as TTP, subordinating them to overall survival. The FDA continues to trot out TTP like a champion mare when it suits them, while telling anyone else designing a trial that it is an unacceptable endpoint for making an approval decision. The 9902a study was terminated early because the applicant, prior to the FDA arriving at the same conclusion, determined that survival *should* be the endpoint rather than TTP, and *not* because TTP would be missed.

This begs the question to the FDA: "Which is it?" Your guidance since 2005 has been that TTP is not a suitable endpoint for an approval decision in AIPC, only survival. Yet in the situation with Provenge, TTP was *supposedly* the driver for the decision and the FDA said the survival benefit was insufficient for approval.

The safety profile of Provenge was never really an issue, until Howard Scher (the FDA special employee, who according to newly established guidelines implemented right after the Provenge AC, would not have been eligible to participate in the process, *even* if just only his disclosed conflicts were considered) *after voting with all other AC members that Provenge was safe*, improperly implied in a post AC letter that there may be a safety issues. The FDA post hoc seek to

use it again now as a second red herring to try to justify the non-approval decision. There has been a false concern voiced regarding incidents of cerebral vascular accident (“CVA”) events (strokes) but the CVA’s were not statistically significant as, in this older patient population, small numbers of CVA events are normal. The risk of CVA’s 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 CVA’s. If one estimates that the average survival of this group for the three-year study period was ~26 months, this data would be consistent with the expected risk of CVAs. The Provenge AC voted *unanimously positive on the safety question*, a vote which occurred after the AC discussion of the issue, and members were informed that the FDA and Dendreon have planned to subsequently monitor 3000 Provenge patients for CVAs and any other identified safety issues, in a post approval follow up study. Provenge is considered to have very minimal side effects, in stark contrast to chemotherapy treatments. *Handpicked FDA experts voted 17-0 that Provenge is safe.*

Importantly, the FDA statistician himself said that the chance that the survival data were in error was 1 in 40. Yet the FDA, at the urging of a few employees with their own agenda, delayed approval, with a request that rings hollow; “for more data”. At the three year measuring point, 27% of high grade Gleason grade patients (the sickest to begin with) were alive vs 0% for placebo.

Patients and their advocates are not asking the FDA for any special treatment regarding the rigorous scientific license requirements. Provenge has met each and every Congressional statutory requirement as the submitted BLA data proves. It has also met the endpoint guidance the FDA put in place beginning in 2005. Only the FDA appears to be ignoring its own licensing requirements and guidance. The failure to approve Provenge was all about money, greed and politics. Lost in this, is the patients best interests.