Provenge PhIII Trials – The Alternative Explanation of Survival Results

One-page Summary

- Placebo patients lost, on average, **73% of their circulating mononuclear cells** through each apheresis/infusion procedure. At least 50% of apheresed cells were lost in purifications steps at Dendreon's manufacturing facilities and a further 2/3 were kept back from patients and frozen.
- Placebo patients lost these 73% of cells **three times at 2 week intervals.**
- The human body has several mechanisms to restore overall T-cell counts, and this lymphocyte removal would have no consequences in healthy individuals through most of their lives. But the dramatic age-related changes in the immune system that occur around the age of 65-70, imply that the replacement T cells in circulation are **not of the same subtype** or **diversity** as the T cells that were removed.
- There is strong evidence to suggest that both t-cell diversity and the t-cell subtype which the elderly are impaired in replacing, play a **central role in tumor suppression.**
- It is therefore unclear whether the 4 month survival difference between the arms in the three Provenge PhIII trials can be attributed to Provenge efficacy or should be attributed to **harm inflicted on the "placebo" patients** by the removal of a vital part of their innate cancer-fighting defenses.

★ If placebo immunodepletion is indeed the intervention responsible for the survival difference between the groups, it would imply that **Provenge treatment itself is harmful to patients** due to the >50% of their cells lost during Provenge manufacture, and is shortening, not extending the lives of prostate cancer patients. There is evidence that this immunodepletion might reduce survival by >5-6 months. Until it can be proven that immunodepletion did not harm placebo patients, there is risk to every prostate cancer patient being exposed to this treatment.

There are many features of the Provenge PhIII trial data that are unexpected/inexplicable if the 4-month survival difference is attributed to Provenge efficacy. All of these features would be expected if the survival difference is attributed to immunodepletion being harmful to cancer patients >65 yrs of age:

- Patients younger than 65 from any arm of the trials had a median survival of 28-29 months, compared to 23.4 months for the Provenge patients over 65, and 17.3 months for the placebo patients over 65. Age is not prognostic for survival in prostate cancer. These data are mystifying if Provenge "works". The dramatic immune changes that occur at age 65-70 suggest that patients <65 could still recover from the 'placebo' immunodepletion without obvious consequence, whereas older patients' immune systems could not recover to their previous state, and with this change lost much of their cancer-fighting ability.
- The absence of survival difference between treatment arms in patients <65 (~one quarter of all patients) is inexplicable if Provenge works by its proposed mechanism (unless they had better prognosis, for which there is no evidence publicly available).
- Comparison of median survivals and baseline prognostic factors in the Provenge asymptomatic and minimally symptomatic mCRPC trials to the 3 most recent major trials in all-stage CRPC, strongly suggests that the placebo arm in particular should have lived longer than they did.
- This same comparison also suggests in particular that the early (<1 year) death rate in placebo patients was much higher than would have been anticipated given the early stage of their disease.
- Provenge has never been shown to have anti-tumor effects either in vivo or in vitro despite a decade of efforts to shed light on how it might be working. Thus to believe Provenge works is to admit that our understanding of the immune system in cancer is extremely limited. But the person making this admission cannot therefore simultaneously claim that immunodepletion did not damage the placebo group. The proposed mechanism by which immunodepletion could result in shortened survival, though by no means 'proven', is at least consistent with our best and most recent scientific research on immune aging and cancer immunology.

Document Overview:

1. Placebo arm Immunodepletion = NO Placebo

All three of the "placebo-controlled" phase III studies for Provenge had the same 'placebo' design. First, patients in both arms underwent 1.5-2 blood volume mononuclear cell leukapheresis[1, 2]. Assuming 5.25L of blood (men in this study were a little above-average of 5L), this equated to 8-10.5 L of blood leukapheresed. For the drug arm Provenge was prepared using all of the cells collected in this manner and infused in its entirety back into the patients. Placebo patients, however, had 2/3 of their leukapheresed cells frozen (in order that they could be offered Provenge manufactured from the thawed cells upon disease progression) and received back only 1/3 of the cells that had been removed by leukapheresis [3, 4]. Trial participants underwent this procedure 3 times at 2-week intervals, each time with the placebo patients receiving only 1/3 of their cells back.

Dendreon has provided cumulative cell product parameters administered in the pooled Phase III trials[5]. As shown in the table, the median TNCs (total nucleated cells) infused into Provenge patients over 3 doses was $9.8x10^9$, whereas for placebo patients it was $3.4x10^9$.

Table 19: Cumulative Cell Product Parameters Administered in Safety Database

	Sipuleucel –T N=601 Median (range)	Placebo N=303 Median (range)
TNC	9.831×10^9 (0.843×10^9 to 35.974×10^9)	3.384×10^9 (0.093×10^9 to 8.626×10^9)
CD54+	1.877×10^9 (0.108×10^9 to 8.600×10^9)	0.879×10^9 (0.003×10^9 to 6.988×10^9)
CD54+ upregulation Ratio	26.959 (2.900 to 69.648)	2.683 (0.063 to 4.060)

As shown in Table 20, subjects in the sipuleucel-T group received infusions with a higher median cumulative TNC, CD54+ cell count, and CD54 upregulation ratio, compared with subjects in the placebo group. These higher values reflect expected differences between the study product, sipuleucel-T, and the placebo.

Approximately 96% of these nucleated cells were shown to be T cells, B cells, monocytes, and natural killer cells (Appendix A). Thus placebo patients were given a median of 6.19×10^9 fewer lymphocytes/monocytes back than Provenge patients.

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[1] Small et al, Placebo-Controlled Phase III Trial of Immunologic Therapy with Sipuleucel-T (APC8015) in Patients with Metastatic, Asymptomatic Hormone Refractory Prostate Cancer. *J Clin Oncol* (2006) http://jco.ascopubs.org/cgi/content/full/24/19/3089

[2] Small et al, Immunotherapy of Hormone-Refractory Prostate Cancer with Antigen-Loaded Dendritic Cells *J Clinical Oncology*, 2000 http://jco.ascopubs.org/cgi/content/full/18/23/3894

[3] March 2007 CTGT Advisory Committee Meeting, Sipuleucel-T Briefing Document http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4291B1_01.pdf

[4] Higano et al, Integrated Data From 2 Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trials of Active Cellular Immunotherapy With Sipuleucel-T in Advanced Prostate Cancer. *Cancer* 2009;115:3670–9

[5] Clinical Review, Sipuleucel-T, Review Completion Date 04/28/2010, p56: http://www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM214540.pdf

Further, as detailed in Appendix B, over 65% of nucleated cells were lost in the two buoyant density centrifugation steps that transform the raw apheresis product received at the Provenge manufacturing facility into the finished product that is re-infused into patients (this loss of cells applies to both Provenge and placebo patients).

This loss, added to the 2/3 of their cells that are frozen, mean that the median placebo patient is in fact losing $7.8x10^9$ lymphocytes/monocytes 3 times at 2-week intervals.

Mononuclear cell leukapheresis procedure spins blood at just such a speed as to preferentially precipitate the desired lymphocyte and monocyte fraction, leaving most of the neutrophils and other granulocytes in the blood re-entering the patients. So although Provenge and placebo infusions were 96% pure infusions of lymphocytes and monocytes, these cells only constitute approximately 30-40% of the white blood cells in circulating blood.

Dendreon provided patient baseline white blood cell counts[6]:

Table 8: Summary of Baseline Laboratory Values, Intent-to-Treat Population.

Laboratory Evaluation	Sipuleucel-T (n=341) Median	Placebo (n=171) Median	Normal Range
Alkaline Phosphatase (U/L)	99	109	31-131
Hemoglobin (g/dL)	12.9	12.7	12.5-18.1
Serum LDH (U/L)	194	193	53-234
Serum PSA (ng/mL)	51.71	47.19	≤ 2.7 - ≤ 7.2 (Age-dependent cut-off values)
Serum PAP (U/L)	2.7	3.2	0.1-1.2
White Blood Cell count ($10^3/\mu L$)	6.15	5.98	3.8-10.7
Lymphocyte count ($10^3/\mu L$)	1.44	1.41	0.8-3.0

Using the 5.25 L estimation for the volume of blood in this population, the men in this trial can be calculated to have had an average of $6x10^3$ * $5.25x10^6$ circulating white blood cells at baseline, or $31.5x10^9$. Assuming 66% of these to be granulocytes, patients had an average of $10.7x10^9$ circulating lymphocytes/monocytes at baseline.

Thus, on average, placebo patients had $7.8x10^9$ of their baseline $11x10^9$, or 73%, of their circulating lymphocytes/monocytes removed with each treatment cycle. Thus over 3 such cycles, placebo patients unwittingly underwent the removal of a significant number of the baseline T cells, B cells, natural killers cells and dendritic cells upon which they were singularly dependent to fight their prostate cancer.

n.b. these calculations are based upon medians, and individual patients will have undergone far greater and far less cell removal than this median.

Nobody has questioned the potential impact of this imbalance immunodepletion

It is clear in the 160+ FDA documents relating to the Provenge BLA, from the 2007 panel transcript and from conversations with investigators that the potential impact of this immunodepletion has never been considered. There are many studies speaking to the inability even of young, healthy volunteers to fully recover from repeated immunodepletion:

- Wright et al. ***Lymphocyte depletion and immunosuppression with repeated leukapheresis by continuous flow centrifugation***. Blood 1981;58:451-8.

[6] Clinical Review, Sipuleucel-T, Review Completion Date 04/28/2010, p28: http://www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM214540.pdf

- Kolf et al. ***Sustained decreases in lymphocyte counts in serial long-term leukapheresis donors***. Transfusion 2003;43:S28A-9A.
- Koepke et al. ***The safety of weekly plateletpheresis: effect on the donors' lymphocyte population***. Transfusion 1981;21:59-63.
- Senhauser, et al. ***Immune system changes in cytapheresis donors***. Transfusion 1982;22:302-4.
- Strauss et al. ***Effects on donors of repeated leucocytes losses during plateletpheresis***. J Clin Apheresis 1994;9:130-4.
- Heal, et al. ***Long-term follow-up of donors cytoapheresed more than 50 times***. Vox Sanguinis 1983;45:14-24.
- Wolf et al, ***Leukapheresis for the extraction of monocytes and various lymphocyte subpopulations from peripheral blood***. Vox Sanguinis, 2005
- Strasser et al, ***Mononuclear cell variability and recruitment in non-cytokine-stimulated donors after serial 10-liter leukapheresis procedures***. Transfusion, 2005

In the most recent of these studies by Strasser et al, using leukapheresis machines such as those in use in the Provenge trials and still today, 13 young, healthy men underwent four 10L leukapheresis procedures at 2-week intervals. The average 10^{10} MNCs dispensed from these individuals matched exactly the $9.9x10^{9}$ MNCs in the apheresis product dispensed from patients to make Provenge (see Appendix B for details).

2 weeks after the last LP procedure, the men in the trial had statistically significantly lower MNC counts:

- CD3+ T cells ($x10^{9}$/L) 1.29 (before) 1.00 (after) -22.5% (p=0.006)
- CD3+4+ T cells ($x10^{9}$/L) 8.20 (before) 6.66 (after) -18.8% (p=0.03)
- CD3+8+ T cells ($x10^{9}$/L) 3.89 (before) 3.21 (after) -17.5% (p=0.04)
- CD19+ B cells ($x10^{9}$/L) 2.74 (before) 2.27 (after) -17.2% (p=0.24, NS)

Only 5 of the 13 donors (in either case) were available for 2- and 3- year MNC counts (n.b. not the same 5 donors in each comparison to baseline). Compared to the first predonation count of the study, they found:

- CD3+ T cells diminished by 25% at 2 years (p=0.05) 20% at 3 years (p=0.31)
- CD3+4+ T cells diminished by 18% at 2 years (p=0.08)
- CD3+8+ T cells diminished by 35% at 2 years (p=0.07)
- CD19+ B cells were only lessened by 3% at 2 years and 12% at 3 years.

Although the "placebo" patients in the Provenge studies received 28% of these cells back 3 days after each removal, and underwent one fewer such procedure than the men in the Strasser trial, it is clear that we do not know the potential impact of this intervention on overall survival.

While the circulating cell loss might not appear dramatic in the 40-somethings in this study, the age-related changes in the immune system are dramatic (details in next section), and the impact of this immunodepletion on the elderly patients with mCRPC in the Provenge studies could potentially have been catastrophic.

Consequence of placebo being an active intervention

In 1999 when investigators and the FDA agreed upon the trial design, scientists did not yet have much of the understanding that we have gained over the last 10 years on the age-related changes in the immune system. Leukapheresis is performed at blood donation centers on hundreds of volunteers who have agreed to specifically donate white blood cells and, despite the significant cell count declines 2 years later shown in the

study cited, has resulted in no negative consequences sufficiently obvious to have been noticed to date. For most of a person's life, as the body's mechanisms to replace cells of all types are quite robust. But dozens of experiments are now showing the profound changes that occur in the immune system around the age of 65-70, and showing the decline in the body's ability to replace certain cell subtypes after this age. It will be shown, perhaps even in the next few years, if immunodepletion by leukapheresis does indeed, as one might expect, alter the immune systems of the elderly in ways that it does not impact younger people. Any alterations involving the cellular subtypes that are involved in identifying or killing cancer cells have obvious implications for the potential harm that leukapheresis might pose to elderly patients fighting metastatic tumors. Certain studies ongoing today could even be directed to this purpose[7].

While the placebo harm cannot be "***proven***", it would explain (as shown below) all of the unusual features of the PhIII trial results. These self-same features cannot be plausibly explained in the context of Provenge efficacy, and have either been dismissed as extreme chance occurrences, not considered at all, or glossed over as consequences of our poor understanding of cancer immunology. Lacking any other factors that speak to the relative claims of each intervention to have caused the survival difference, **scientific and logical first principles dictate that placebo harm is the more likely intervention to have resulted in this dataset.**

Until it can be proven that placebo patients were not harmed, the studies upon which Provenge was approved are invalid and we have no proof this drug is beneficial. Furthermore, if this immunodepletion is accountable for the shorter survival of placebo patients, it follows that Provenge treatment is also harmful since they lose at least 75% of the number of cells taken from placebo patients due to the large number of cells lost in Provenge's manufacturing process. **There is data to suggest Provenge intervention could shorten life expectancy by greater than 5.5 months.**

The burden of proof lies with the company that designed and ran the trial and the agency that approved the protocol: they must prove that placebo immunodepletion was not harmful before they can justify claims of Provenge efficacy. Until then, treating a single further patient would be unethical and a liability. And until then, taxpayers should not be made to pay for a single Medicare patient undergoing this intervention.

[7] http://clinicaltrials.gov/ct2/show/NCT00104325 , http://clinicaltrials.gov/ct2/show/NCT00073060?term=apheresis&rank=7 , http://clinicaltrials.gov/ct2/show/NCT00067054?term=apheresis&rank=11

2. Immunodepletion in Elderly Cancer Patients

To gain a better understanding of the potential that immunodepletion could have significant consequences in elderly patients with solid tumors, I have drawn upon the thousands of studies in the published literature that form the foremost frontier of our current understanding of the processes in question.

The potential mechanism I shall outline focuses on T-cells. I fully acknowledge the separate roll that each of the cell types lost in immunodepletion might play that could also provide plausible mechanisms, but since T cells are arguably those that have received the most research attention and whose mechanisms in cancer surveillance we understand the best, as well as those with well-defined age-related changes, I believe they are a justifiable focus. I acknowledge that the immune system is highly complex and our understanding of it is very far from complete. Thus, there are many other possible parallel or more important mechanisms in other cell types which could explain the link from lymphocyte depletion to impaired cancer-specific immunity.

With a plausible mechanism described, one can look to the many features of the trial data and see whether these can be more plausibly explained by one explanation for the survival difference than the other (Provenge efficacy or imbalanced cell depletion).

T Cell Populations and Homeostasis

- ***Diversity is the Key to Immune System Strength:*** Generation and maintenance of a massively diverse repertoire of T cell antigen receptors is essential for the immune system to be able to respond to the universe of potential antigens, yet the number of distinct T cell receptors (TCRs) expressed by the estimated 10^{11}-10^{12} T cells in the human body is not known. Using TCR gene amplification Arstila et al[8] have shown that the naïve cells are massively diverse, while the memory subset are orders of magnitude less so.
- ***Activation by its corresponding antigen causes a T cell to proliferate and respond:*** T cells are activated by TCR recognition of a short linear peptide anchored within the peptide-binding groove of a major histocompatibility complex (MHC) molecule present at the surface of an antigen-presenting cell (APC). The best known of these are dendritic cells (DC), although monocytes/macrophages, B cells, and neutrophils are also able to present antigens. Upon activation, naive T cells produce IL-2 and other cytokines, and enter differentiation pathways resulting in the development of various T cell subsets. An effective T cell response requires significant proliferation of the activated cell to accomplish the clonal expansion critical for combatting the source of antigen.
- ***After antigen is destroyed, a few T cells retained as memory T cells:*** At the height of such a response, the antigen-specific T cells may account for 25% of the population in the spleen and even more locally[9]. Although most have a life-span of only a few days, a small pool will survive as long-lived memory cells. Thus, controlled cell death (apoptosis) restores the numerical balance in the immune system, but results in a small shift in the ratio of naïve to memory T cells since the retention of memory T cells allows a more effective response to rechallenge by the same pathogen. Memory T cells possess different stimulatory requirements than naïve T cells, but both naïve and memory cells respond less effectively with age.
- ***New naïve T cells only made in the thymus:*** The generation of T cell receptor diversity depends entirely on the production of new, naive T cells in the thymus[10]. Stem cells seeded into the thymus from the bone marrow perform a random rearrangement of the mini-genes that determine the single specific TCR that that

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[8] Arstila et al. A direct estimate of the human **αβT** cell receptor diversity. Science. 1999

[9] Butz et al, Massive Expansion of Antigen-specific CD8 t cells during an acute virus infection, Immunity (1998) http://jco.ascopubs.org/cgi/content/full/18/23/3894

[10] Nossal et al, Negative Selection of Lymphocytes - Cell (1994)

cell then expresses. After the acquisition of CD4 or CD8 molecules needed for recognition of MHC class 1 and 2 cell surface markers on APCs these cells are then released into pool of circulating naïve cells. From this pool, some cells are selected by antigen to proliferate.

- ***Expansion of Naïve cells in periphery increases to compensate for thymus decline with age:*** After its central importance in establishment of a diverse T cell repertoire, the thymus has been demonstrated to decline in function and output with age. After the ages of 40 to 50 years old, virtually the entire T-cell supply is generated from clonal expansion of existing naïve and memory T cells. The replicative stress associated with repeated clonal expansion can result in shortened telomeres and cellular senescence and lead to phenotypic changes that decrease the functionality of these important cells. Both mechanisms contribute to failure of the elderly to respond to new antigenic challenges such as cancers, poor vaccine responses and increased morbidity with newly arising infections, such as is seen with antigenic shift or drift of the influenza virus.
- ***While absolute T cell numbers are kept constant, relative proportions of subsets change:*** Homeostasis of naïve and memory populations is most probably regulated independently[11,12] coupled with preferred survival of recent thymic emigrants[13]. By maintaining two pools of T cells with a very different repertoire, the immune system combines two conflicting needs: a recognition of a wide array of novel antigens and an efficient and timely response to previously-encountered antigens.
- ***Naïve counts decline and memory counts increase with age:*** Antigenic challenge through life leads to the progressive contraction of the pool of naive T cells. Consequently, the peripheral T cell repertoire of elderly persons (aged 70) consists predominantly of oligoclonal memory cells, and the overall T cell diversity is significantly reduced relative to that seen in younger people. Naïve T cells have a half-life of 6 to 12 months[14 15].
- ***Gradual decline throughout life collapses suddenly around age 65-70:*** Contraction of T cell receptor diversity is not a linear process with age. A diverse naïve CD4+ T cell compartment is maintained for decades by slow naïve cell replication, but this only partly compensates for declining thymic output[16]. This period is followed by a dramatic and sudden collapse of diversity leading to a severely contracted repertoire after the age of 70 years[17].
- ***Most naïve T cells will be found in the blood or lymph, not in tissues populated with memory t cells:*** The extent to which naive T cells migrate through the tissues is quite limited (Mackay, 1991). Their preferred migratory pathway is from the blood back to the lymphatic tissue, where the chance of a rare antigen-specific cell meeting its antigen is optimal. Most of the T cells that do wander into the tissues are memory cells. As their numbers have been considerably increased by prior antigenic activation and clonal expansion, they can afford to patrol the body widely to nip any reinfection in the bud.

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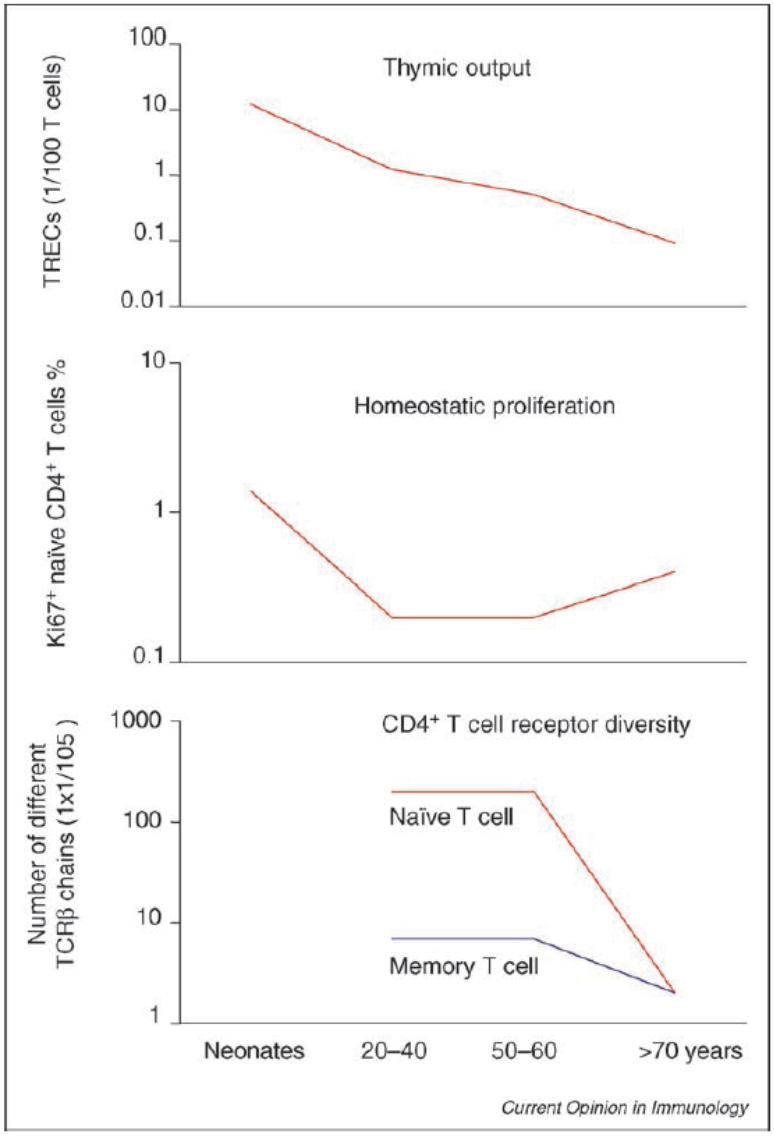
[11] Tanchot et al, Differential Requirements for Survival and Proliferation of CD8 Naïve or Memory T Cells, Science (1997)
[12] Tanchot and Rocha, The organization of mature T-cell pools Immunol. Today (1998) http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1692750/pdf/10794050.pdf
[13] Berzins et al, The Role of the Thymus and Recent Thymic Migrants in the Maintenance of the Adult Peripheral Lymphocyte Pool-J. Exp. Med. (1998) http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2212318/pdf/97-2072.pdf
[14] Hellerstein, Measurement of T-cell kinetics: recent methodologic advances, Immunol. Today 20 (1999) 438–441.
[15] Macallan et al, Rapid turnover of effector-memory CD4(+) T cells in healthy humans, J. Exp. Med. 200 (2004) http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2212011/pdf/20040341.pdf
[16] Wallace et al, Direct measurement of T cell subset kinetics *in vivo* in elderly men and women, *J Immunol* **173** (2004) http://www.jimmunol.org/cgi/content/full/173/3/1787
[17] Naylor et al, The influence of age on T cell generation and T cell receptor diversity, J Immunol 174 (2005) http://www.jimmunol.org/cgi/content/full/174/11/7446



T cell homeostasis and age[18]. The schematic diagram, based on published data, illustrates how parameters of T cell homeostasis change with age. sj TRECs, as a marker of thymic output, show a log linear decline with age. Peripheral turnover is high in the newborn, steady during adulthood, and increases late in life. TCR-b chain diversity in the naive CD4+ compartment is maintained up to the age of 65 to 70 years, after which it collapses. The memory compartment has about tenfold less diversity in TCR-b chains and also contracts at an older age.

- ***There is much evidence that Immune aging is related to increased incidence of cancer:*** A direct effect of immunosenescence on cancers can be easily conceptualized and many experimental data seem to support this contention. In cases of failure to clear tumors, it is hypothesized that one reason may be decreased immunosurveillance. This idea is derived from the findings that tumor regression was observed in immunocompetent hosts while cancer incidence increased in immunocompromised hosts.
- ***T cells central to recognising and killing cancer cells:*** It is now established that the immune system has cells, particularly $CD8^+$ cytotoxic T lymphocytes (CTLs), that can recognize tumor antigens and kill tumors[19, 20]. Nevertheless, a major problem is that these T cells are either not induced or only weakly

[18] Goronzy, T Cell development and receptor diversity during aging, Current Opinion in Immunology, 2005
[19] Schreiber, H (1999) in Fundamental Immunology, Tumor Immunology, ed W.E.Paul (Lippincott-Raven Publishers, Philadelphia), pp 1237–1270.

induced, i.e., the T cells are not evident in the systemic circulation. One possibility is that there is inadequate tumor antigen presentation by dendritic cells for eliciting T cell immunity[21]. Another is that tumor-reactive T cells are tolerized by the tumors[19, 22].

- ***Evidence that Cancer mutation allows it to escape T cells that have recognised it:*** Cancer cells are genetically unstable. This often leads to the selection of tumor variants that can escape the destruction by CTL. Thus, a large established tumor may contain cells with various genetic alterations. When CTL are applied to tumors, tumor variants that can not be recognized by CTL will prosper. Another related mechanism by which the tumor can evade recognition is the loss of the tumor antigen recognized by CTL [23] [24]. A third evasion mechanism has also been demonstrated.

  Bai et al [25] have seen evidence for this phenomenon in mice. They frequently observed recurrences of tumors in mice that had initially responded to therapy with high numbers of transgenic Tcells. Analysis of the P1A antigen on the recurrent tumors revealed a variety of mutations in the P1A epitope. These mutations abolished T cell recognition of the tumor cells, demonstrating antigenic drift of tumor antigens as a mechanism for tumor evasion of T-cells in vivo.

- ***New naïve T cells required if tumor has evaded prior T cell responses:*** A least in mice, T cell response to a the first antigenic epitope encountered can be rendered ineffective by selection of tumor antigenic variants, which would require activation of a new naïve t cell to combat it. The iterative nature of this recognition and evasion puts a singular emphasis on the naïve T cell pool in mounting an effective cancer response.

- ***Hypothesis of T Cell destruction of cancer also central to proposed mechanism for Provenge*** Several novel strategies are being explored to induce tumor-specific T cell immunity. DC vaccination, as being pursued by Dendreon, is one of these. The results of many of these studies speak to the importance of T cells, and in particular naïve T cells, to mount an effective CTL-mediated tumor response. Immature DCs capture antigens but lack full T cell–stimulatory activity[26]. In the presence of appropriate stimuli, such as inflammatory cytokines, the DCs mature. DCs upregulate T cell adhesion and costimulatory molecules as well as select chemokine receptors that guide DC migration into lymphoid organs for priming of antigen-specific T cells. The use of DCs as adjuvants is supported by many animal experiments with primarily mature DCs[27]. These studies have shown that the injection of tumor antigen–loaded DCs reliably induces tumor-specific CTL responses, tumor resistance, and in some cases, regression of metastases[27].

- ***Experimental evidence for proposed mechanism:*** Using a defined DC vaccine combined with detailed immunomonitoring, Thurner et al[28], provided proof that vaccination with mature DCs expa nds tumor-specific T cells in advanced melanoma patients. In addition, they found some evidence for the direct interaction between $CD8^+$ CTLs and tumor cells as well as for escape of antigen-negative metastases.

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[20] Van den Eynde, B.J., (1997) T cell defined tumor antigens. Curr. Opin. Immunol. 9:684–693, pmid:9368778
[21] Schuler, G., R.M.Steinman(1997) Dendritic cells as adjuvants for immune-mediated resistance to tumors. J. Exp. Med http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2199101
[22] Pardoll Cancer vaccines - Nat Med. 1998 May;4(5 Suppl):525-31.
[23] Yee el at, Adoptive T cell therapy using antigen-specific CD8+ T cell clones for the treatment of patients with metastatic melanoma: in vivo persistence, migration, and antitumor effect of transferred T cells. *Proc Natl Acad Sci* U S A. 2002 http://www.pnas.org/content/99/25/16168.full
[24] Uyttenhove et al, Escape of mouse mastocytoma P815 after nearly complete rejection is due to antigen-loss variants rather than immunosuppression. J Exp Med. 1983 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2186952/pdf/je15731040.pdf
[25] Bai et al - Antigenic drift as a mechanism for tumor evasion of destruction by cytolytic T lymphocytes, *J Clin Invest,* 2003, 111, 1487-96. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC155049/pdf/JCI0317656.pdf
[26] Banchereau, J., (1998) Dendritic cells and the control of immunity. Nature. 393:245–252, pmid:9521319. http://www.rockefeller.edu/labheads/steinman/pdfs/1998-nature.pdf
[27] Lotze, M.T., (1999) in Dendritic CellsBiology and Clinical Applications, Dendritic cell therapy of cancer and HIV infection, eds M.T.Lotze, A.Thomson (Academic Press, San Diego, CA), pp 459–485.
[28] Thurner et al, Vaccination with mage-3A1 peptide-pulsed mature, monocyte-derived dendritic cells expands specific cytotoxic T cells and induces regression of some metastases in advanced stage IV melanoma, J Exp Med. 1999 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2195739

3. Provenge Trial data explained by Immunodepletion

1. Exceptional Survival of all patients <65 is unprecedented

Table 10 Subgroup Analysis of Overall Survival by Age and Race

	Sipuleucel-T N	Sipuleucel-T Median Survival (95% CI)[1]	Placebo N	Placebo Median Survival (95% CI)[1]	Sipuleucel-T vs. placebo Hazard Ratio (95% CI)[2]
Age					
< 65	106	29.0 (22.8, 34.2)	66	28.2 (23.4, 32.5)	0.919 (0.618, 1.366)
≥ 65	382	23.4 (22.0, 27.1)	183	17.3 (13.5, 21.4)	0.661 (0.538, 0.813)

Patients <65 in the pooled data had median survivals of 28-29 months, compared to 23.4 and 17.3 months for the Provenge and placebo groups in the >65 population. In no other mCRPC trial has age been shown to be a prognostic factor, let alone one of the magnitude implied by these data.

In TAX327 (as shown in subset survival charts in bullet #3 below), the 504 men aged ≤68 had 17.6months median survival and the 502 men aged ≥69 had 18.1 months median survival. Younger age clearly did not confer a survival benefit to these patients. Halabi et al also did not find age to be a prognostic factor in their analysis of many large mCRPC trials.

Since we have no evidence of anti-tumor effects of Provenge, these data could be looked at differently:

	Removal of 54% of circulating T cells (x3 at 2 week intervals)		**Removal of 67% of circulating T cells (x3 at 2 week intervals)**	
	n	**Survival**	**N**	**Survival**
<65	106	29.0 months	66	28.2 months
≥65	382	23.4 months	183	17.3 months

This inexplicably long survival in patients younger than 65 in both arms, several months longer than the survival of the Provenge arm, truly demands plausible mechanistic explanation. No such explanation can be given accompanied by the proposition that Provenge is efficacious. [it has never been disclosed that the <65s enrolled had better prognosis than the >65s, which would be highly improbable since these are 25% of the patients enrolled and age is not correlated with prognosis].

This is exactly what would have been anticipated if the proposed mechanism for immunodepletion harm in patients over 65 was in effect during the trial:

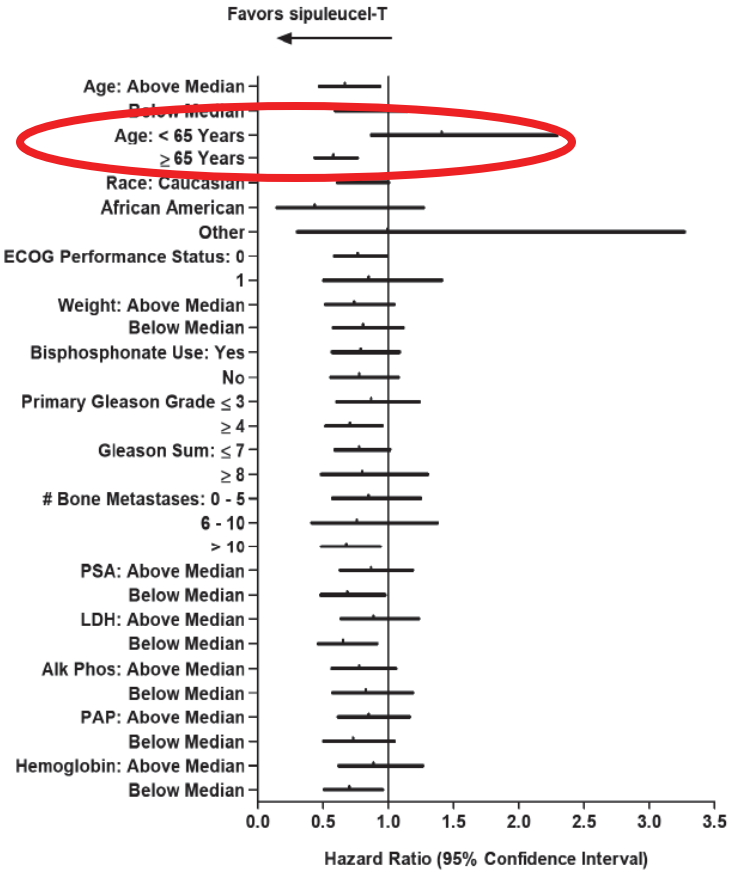
- The patients under 65 whose immune systems could recover from immunodepletion (whether the larger # of cells lost by the placebo patients or the smaller number of cells lost by the Provenge patients) without harm, lived out the relatively long 28-29 months that reflected the good their early, asymptomatic baseline disease characteristic. Patients younger than 65 still could have enough diversity in both t-cell compartments, and sufficient residual ability to replace lost naïve t-cells that they are able to recover to a state of reasonable immune competence after their immunodepletion.
- The patients over 65 that lost ~54% of their circulating T cells in each of 3 Provenge interventions, lived 23.4 months.
- The patients over 65 that lost ~67% of their circulating T cells in each of 3 placebo interventions, lived 17.3 months.

In the older population that have undergone the dramatic immune deterioration which occurs at 65-70 years of age, it could be proposed that the loss of lymphocytes in the immunodepletion harmed their immune systems in a way from which they could not restore their t-cells anywhere close to where they would need to be to mount any meaningful anti-tumor response.
More specifically, as proposed, the few naïve t-cells remaining in the elderly appear to reside preferentially in the circulation & lymph. With thymic output at its nadir, and clonal expansion of the few remaining t-cells both slow and impaired, the greatest impact of the immunodepletion from which they cannot recover could well be the particular loss of naïve number and diversity. As described above, there are several known mechanisms of tumor immune evasion that necessitate the recognition by repeated new naïve T cells to mount an effective response.

Since age is not prognostic for survival in prostate cancer, in the absence of any other prognostic data to explain why these younger patients had a better survival[1], the simplest implication of these data taken at face value would be that **lymphocyte depletion shortened survival in the placebo group by ~11-12 months, and the less dramatic, yet still significant lymphocyte loss from the Provenge group shortened their survival by 5-6 months.**

2. Provenge did not show benefit in patients younger than 65

Figure 3: Applicant's Analyses of Subgroups Based on Baseline Covariates.



FDA Reviewer's comments*:"In Study D9902B, there were a total of 126 subjects in the ITT population who were <65 years of age; of these subjects, 77/341(23%) were in the sipuleucel-T arm and 49/171 (29%) in*

the placebo arm. In the subgroup of subjects who were less than 65 years of age, the observed hazard ratio of 1.411 (95% CI: 0.869, 2.290) suggests a trend in survival in favor of the control group, compared to the sipuleucel-T group."
The reviewer then proceeds to an exploratory analysis of the pooled data from all 3 trials as shown below.

Table 13: FDA Statistical Reviewer's Analysis of Survival in Subjects < 65 years old

Studies	Sipuleucel-T		Control		Hazard Ratio (Sipuleucel-T vs Placebo)
	N	Median survival in months	N	Median survival in months	
Studies D9901, D9902A and D9902B	*106*	*29 (22.8, 34.2)*	*66*	*28.2 (23.4, 32.5)*	*0.919 (0.618, 1.366)*
D9901	*13*	*35.2 (29.7,...)*	*9*	*28.2 (23.9, 35.7)*	*0.445 (0.148, 1.336)*

The reviewer draws this conclusion "*The above analyses of the data from all three studies (D9901, D9902A, and D9902B) support the hypothesis that the subgroup of subjects who were less than 65 years of age also benefit from treatment with sipuleucel-T.".*

The pooled analysis does not, however, support this assertion. 29 vs 28.2 months survival does not indicate benefit. It is clearly anomalous that no survival-benefit was seen in these patients, and cannot be explained by any known mechanism associated with Provenge's proposed efficacy. It would be an extreme statistical aberration if this was the result of chance in these 172 patients (23% of all patients).

The potential mechanism by which the differential immunodepletion between treatment arms might not affect those patients under 65 is explained above.

3. Should patients have lived longer?

Direct comparison of all available patient baseline prognostic factors and their associated survival to these same data from other CRPC trials should give an indication as to whether the placebo patients lived less long, or the Provenge patients lived longer than would have been anticipated. This would speak directly to the relative likelihood of each intervention as being more probably responsible for the survival difference.

Provenge study participants, defined as having "minimally symptomatic" or "asymptomatic" CRPC, were specifically recruited to represent a patient population prior to the point in progression at which chemotherapy would generally be initiated and has demonstrated survival benefit. The first 3 listed trials in which this comparison was made were all testing chemotherapy regimens and enrolled CRPC patients with all levels of symptoms. Thus by intent enrolled a population with more advanced disease and worse prognosis than the Provenge studies.

For each of the 4 trials I have provided all the data on known prognostic factors that were available for both populations.

TAX327

The TAX 327 study, compared docetaxel Q3w, docetaxel Q1w and mitoxantrone (all with prednisone) in men with metastatic CRPC and demonstrated a median survival of 19.2 months for docetaxel q3w vs. 17.8 months for docetaxel q1w vs 16.3 months for mitoxantrone. [29]

Study enrolled March 2000 to June 2002, and involved centers in 24 countries. IMPACT enrolled from July 2003-October 2007. Stage migration would therefore favor IMPACT patient survival.

	TAX327 Taxotere Q3W n=335	**IMPACT control arm** Doc discretion/tax + pred[30] n=171
Enrollment Criteria		
Pain	all	Absent or minimal pain[31]
Opioids	all	No opioids allowed
Metastases	Excl: brain mets	Excl: lung, liver and brain mets
Life expectancy	all	At least 16 weeks
Baseline Characteristics		
Age (median) yrs	68	70
Serum PSA (median) ng/ml	114	42
Gleason Score ≤ 7	42% [57%]	76%
8-10	31% [42%]	24%
n/a	26%	-
'Substantial pain' *	45%	0%
Bone mets	90%	91.8%
Lung/liver mets	22%	0%
Survival Results		
Overall Survival	19.2 months	21.7 months

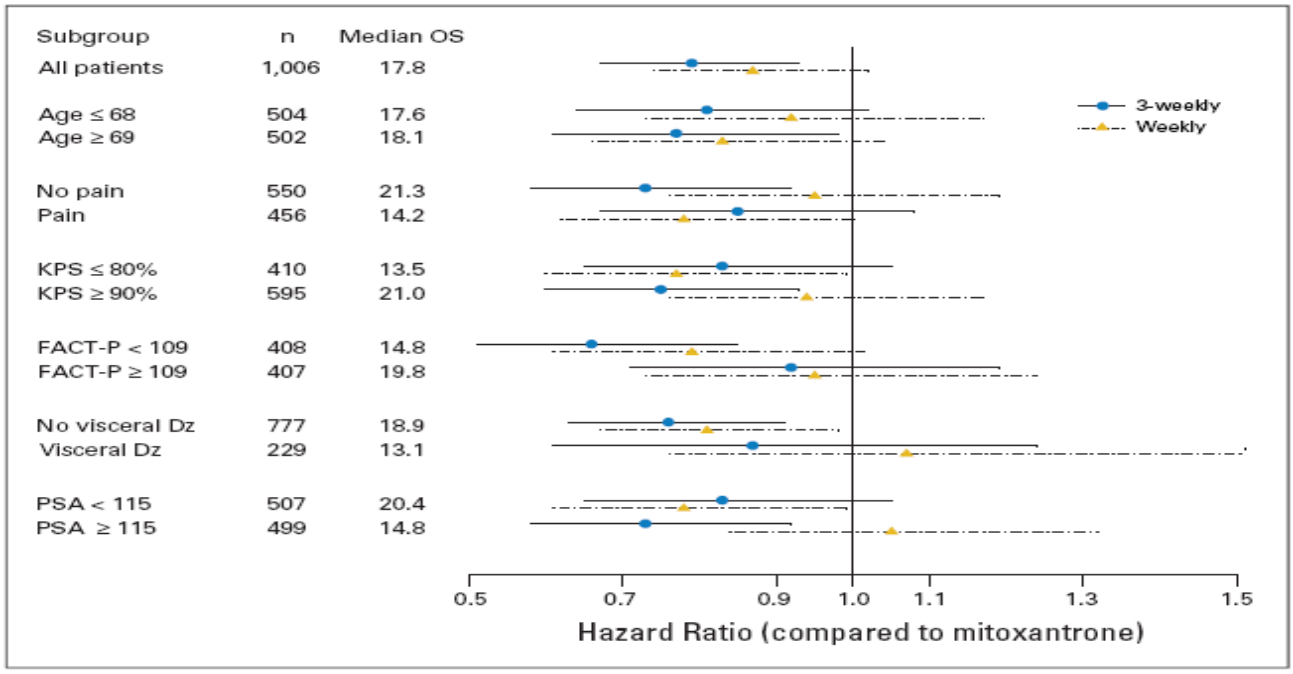
***** Pain PPI ≥ 2 or analgesic score >10

It is clear from the enrollment criteria and baseline characteristics that IMPACT's minimally-symptomatic patients with very little pain, no visceral mets and low serum PSAs represent a far less advanced population than TAX327 in which 45% of patients had substantial pain at baseline, 22% of patients had visceral disease and baseline serum PSA levels and Gleason Scores were also higher.

[29] Tannock et al: Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 351:1502-1512, 2004

[30] Clinical Review, Sipuleucel-T, Review Completion Date 04/28/2010, p27: http://www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM214540.pdf

[31] http://www.clinicaltrials.gov/ct2/show/NCT00065442?term=provenge&rank=1

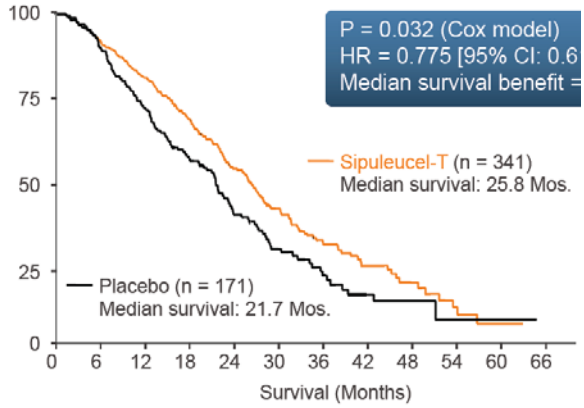


This figure shows survival among various subgroups treated on the TAX 327 trial. At left are the subgroups defined in this exploratory analysis the number of patients in each subgroup, and their median survival time in months, independent of treatment. At right is a Forrest plot showing the median hazard ratios and their 95% CIs for survival on the docetaxel arms compared with the mitoxantrone arm.

Across treatment groups:

- Patients with pain died on average 7 months earlier than those without. (45% vs 0%)
- Patients with visceral disease died on average 6 months earlier than those without. (22% vs 0%)
- Patients with PSA ≥ 115 died 5.6 months earlier than those with PSA below that level. (114 vs 42)

Taken together with the patient baseline characteristics (TAX327 vs IMPACT) repeated above in parentheses and potentially favorable stage migration, one could find it surprising that IMPACT placebo patients lived a mere 2.5 months longer than their far sicker counterparts in TAX327.



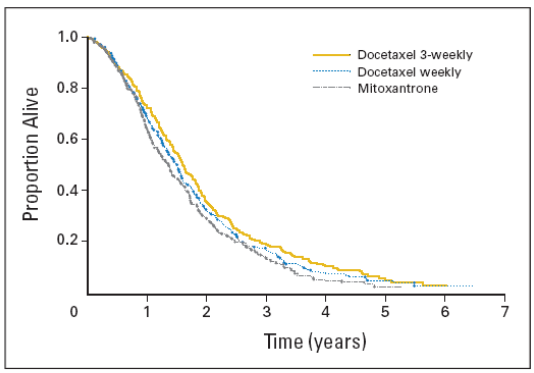


Fig 1. Overall survival data from March 2007, with 867 deaths among 1,006 randomly assigned patients.

Above are the survival curves from the two trials (IMPACT on left): It is also unexpected, given their explicitly earlier stage in disease progression and far better baseline prognostic factors, that as many patients (28%) had died at one year in the IMPACT placebo group as had amongst the taxq3w patients (27%). Could this suggest that there is an unusual early death rate in the IMPACT placebo arm?

CALGB 90401

The CALGB 90401 study comparing docetaxel + Avastin to docetaxel alone presented results at ASCO in June and showed 22.6 and 21.5 months survival in the two arms, respectively (not significant).

	CALGB90401 control arm Docetaxel + prednisone[32] n=525	**IMPACT control arm** Doc discretion / Docetaxel + pred[33] n=171
Enrollment Criteria		
	Progression since last intervention	Progression after hormonal therapy
Pain	all	Absent or minimal pain[34]
Opioids	all	No opioids allowed
Metastases	No known brain mets	Lung, liver and brain mets excluded
Cytologically-positive effusions	all	Pleural effusions or ascites excluded
Life expectancy	all	At least 16 weeks
Baseline Characteristics		
ECOG status 0	55 %[35]	81.3 %
ECOG status 1	41 %	18.7 %
ECOG status 2	5 %	0%
PSA (ng/dl)	85	42
Percent on opioid pain medication	35%	0%
No pain at baseline	Data not public	52.6%
Lung/liver mets	(~19%[§])	0%
Survival Results		
Overall Survival	21.5 months	21.7 months
PS 0 median survival	23.8	
PS 1 median survival	17.2	
PS 2 median survival	<17.2	
PSA ≤ 85	24.5	
PSA > 85	18.4	

[§] In similar populations in TAX327, MSKCC and SWOG9916, 22%, 16% and 19% of patients, respectively, had lung and liver mets at baseline, so these likely indicate an approximate representation in the CALGB population.

CALGB 90401 enrolled from April 2005 to Dec 2007. IMPACT enrolled over a similar timeframe from July 2003 to Oct 2007 (60% of patients enrolled after Nov 2005), so stage migration is not a confounder in this comparison.

Investigators noted that OS with docetaxel/prednisone in this trial was longer than previously reported (21.5m vs 19.2m in TAX327) and proposed it may be due to "stage migration or a good risk population (47% of patients had 24 month predicted survival of >30%)" [32].

As healthy as these patients may have appeared to the investigators in comparison to the TAX327 patients, the IMPACT "placebo" patients had undeniably better prognostic factors:

- ECOG 0 in 81% vs 55%. [amongst the CALGB patients, patients with ECOG 0 lived 6.6 months longer than those with ECOG 1]

[32] ASCO slides obtained from Roche/Genentech "CALGB 90401: A randomized double-blind placebo controlled phase III trial comparing docetaxel, prednisone and placebo with docetaxel, prednisone and bevacizumab in men with metastatic castrate resistant prostate cancer (mCRPC)"

[33] Clinical Review, Sipuleucel-T, Review Completion Date 04/28/2010, p27: http://www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM214540.pdf

[34] http://www.clinicaltrials.gov/ct2/show/NCT00065442?term=provenge&rank=1

[35] Break-down of ECOG 0,1 group as communicated at ASCO oral presentation

- PSA 42 vs 85 [CALGB patients below this median lived 6.1 months longer than those above it]
- Zero vs 35% of patients at baseline on opioid pain medications – cancer-related pain is considered a powerful prognostic factor in metastatic prostate cancer: Halabi et al showed in a multivariable analysis that pain interference predicted OS. In their study population, compared with men with lower pain interference scores, the adjusted hazard ratio (HR) for death of men with high pain scores was 1.43 (95% CI, 1.17 to 1.74; *P* .001 – a 7.4month median OS difference)[36]
- And IMPACT had no patients with visceral metastases, versus an estimated 19% for the CALGB population, a prognostic factor which lead to a 6 month survival disadvantage for patients with liver/lung metastases in TAX327.

Given the earlier disease stage and far better prognosis for IMPACT patients, why did they only live the same length of time (21.7 vs 21.5 months) as the more advanced and sicker CALGB tax-only arm?

SWOG 9916

The SWOG 9916 study randomized 770 patients with progressive mCRPC in the United States to taxotere + estramustine or mitoxantrone + prednisone daily. Taxotere demonstrated a 1.9 month survival benefit over mitoxantrone (17.5 months vs. 15.6 months, P=0.02)

SWOG9916 enrolled patients from Oct 1999 to Jan 2003, while IMPACT enrolled from July 2003 to Oct 2007 (60% of patients enrolled after Nov 2005). Stage migration would favor IMPACT survival.

	SWOG 9916 control arm Docetaxel + estramustine[37] n=338	**IMPACT control arm** Doc discretion / Docetaxel + pred[38] n=171
Enrollment Criteria		
Pain	all	Absent or minimal pain[39]
Opioids	all	No opioids allowed
Metastases	Excl brain mets	Lung, liver and brain mets excluded
Life expectancy	all	At least 16 weeks
Baseline Characteristics		
Age (yrs)	70	70
PSA (ng/dl)	84	42
Bone pain > grade 2	36%	0%
Bone mets	84%	91.8%
Lung/liver mets	18%	0%
Survival Results		
Overall Survival	17.5 months	21.7 months

The prognostic factors of pain, PSA and visceral metastases again favor IMPACT patient prognosis, and this is borne out in their longer OS (a little spurious to claim with any conviction this should be even longer).

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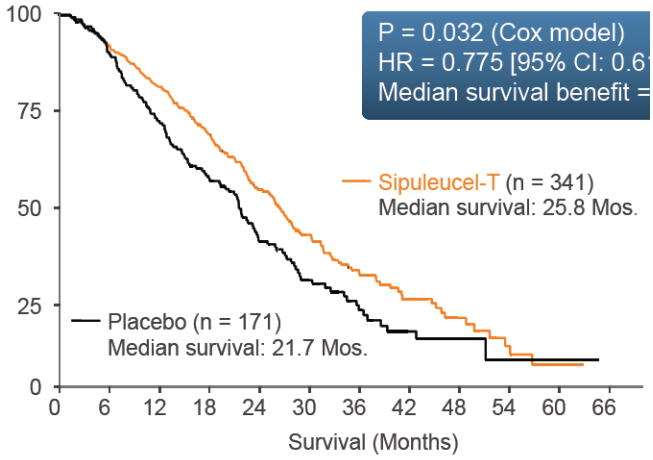
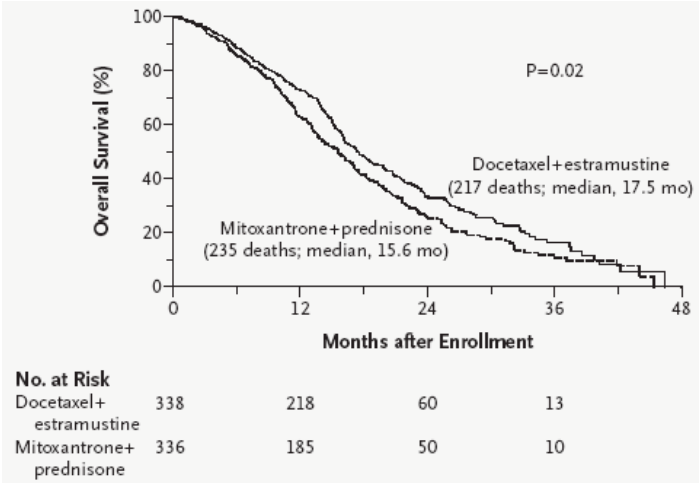
[36] Halabi et al, Pain Predicts Overall Survival in Men With Metastatic Castration-Refractory Prostate Cancer, *J Clin Onc*, 2008 http://jco.ascopubs.org/cgi/content/full/26/15/2544

[37] ASCO slides obtained from Roche/Genentech "CALGB 90401: A randomized double-blind placebo controlled phase III trial comparing docetaxel, prednisone and placebo with docetaxel, prednisone and bevacizumab in men with metastatic castrate resistant prostate cancer (mCRPC)"

[38] Clinical Review, Sipuleucel-T, Review Completion Date 04/28/2010, p27: http://www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM214540.pdf

[39] http://www.clinicaltrials.gov/ct2/show/NCT00065442?term=provenge&rank=1





Yet given their vastly better survival prospects, along with the tailwind of stage migration, why have almost the same proportion of patients (28%) died within one year as in the SWOG 9916 cohort (27%)? Asymptomatic patients ought, intuitively, to outlive symptomatic patients quite decisively in the first 6-12 months as they must spend some months progressing to the stage at which symptomatic patients enrolled.

Berry et al – Mitoxantrone in asymptomatic CRPC

Wanting to have at least one other trial in asymptomatic CRPC for comparison, below are the data from a Phase III study of mitoxantrone + low dose prednisone vs low dose prednisone alone[40]. This study recruited from March 1997 to Jan 1999, which makes D9901 (recruited Jan 2000 to Oct 2001) the most appropriate of the Provenge PhIII trials to compare it to. Though numbers are small, in the absence of any better asymptomatic data, they are noteworthy.

	Mitoxantrone + prednisone n=56	**D9901 Control Arm** Doc discretion (50% Docetaxel) n=45	**IMPACT control arm** Doc discretion / Docetaxel + prednisone[41] n=171
Enrollment Criteria	Asymptomatic HRPC	Asymptomatic HRPC	minimally or asymptomatic HRPC
Baseline Characteristics			
Median Age	70	71	70
PSA (ng/dl)	56	47.9	42
ECOG status 0	75%	82%	81.3 %
ECOG status 1	23%	18%	18.7 %
ECOG status 2	2%	-	0%
Bone mets	86%	91%	91.8%
Soft tissue mets	18% (lymph nodes only)	73%	49%
Lung/liver mets	6%	0%	0%
Survival Results			
Overall Survival	23 months	21.4 months	21.7 months
12-month survival	82%	67%	72%

[40] Berry et al. Phase III study of mitoxantrone plus low dose prednisone versus low dose prednisone alone in patients with asymptomatic hormone refractory prostate cancer. J Urol 2002;168:2439-43.
[41] Clinical Review, Sipuleucel-T, Review Completion Date 04/28/2010, p27: http://www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM214540.pdf

In the D9901 'placebo' arm 50% of patients received Docetaxel, and 63% of patients received any chemotherapy. D9901 patients had a slight edge over the mitoxantrone arm from all prognostic factors: lower PSA, lower ECOG scores, absence of visceral mets, and a 3 year stage migration advantage. Combining this prognosis with the fact that 50% of these patients received the only chemotherapy known to confer a survival benefit, whilst none of the mitoxantrone patients did, it is quite unexpected to find that D9901 "placebo" patients had a worse survival: 21.4 vs 23 months.

Given the above, the <12-month survival of 18% in these asymptomatic patients on mitoxantrone (and the slower decline of their survival curves), makes the D9901 "placebo" patients appear as though they must be harboring some exceptional ill-health that cannot be seen in their baseline characteristics, which would lead to the demise of 33% within one year.

If those mitoxantrone patients in the 90s had the 2.9 month survival benefit of Docetaxel, might they have lived at least to 25.9 months, and hint at the minimal level of survival we ought to be expecting from the unusually healthy asymptomatic patients in our placebo arm?

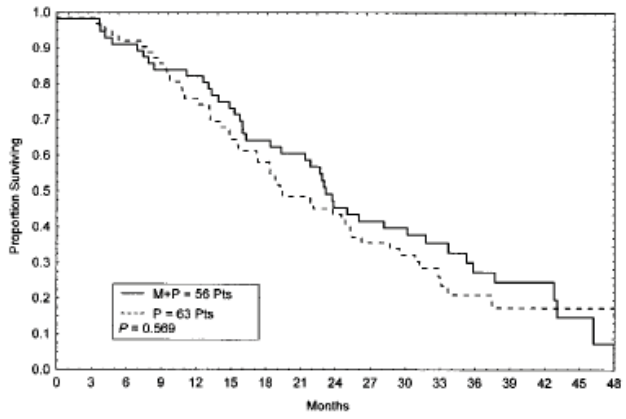
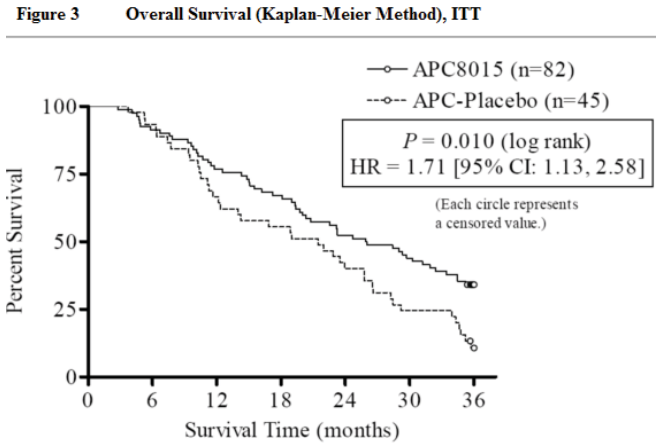


FIG. 2. Estimated survival for patients who received mitoxantrone and prednisone ($M + P$) versus prednisone (P) alone.



Halabi Predicted Survival

Dendreon has presented the IMPACT survival data at ASCO, to FDA, to investors, and elsewhere directly accompanied by the Halabi predicted survival for the two arms.

Survival (months)	Halabi Predicted	Actual
Provenge (n=341)	21.2	25.8
Placebo (n=171)	20.3	21.7

These data have been used to illustrate the fact that Provenge patients lived longer than their predicted survival, whereas placebo patients did not.

However, it has been shown in the original Halabi paper [42] that when testing the model in a validation population, a ***predicted*** survival of 22.8 months corresponded with an ***actual*** survival of 27.2 months. The model is admitted and demonstrated to increasingly underestimate survival of patients as they live beyond 14-15 months.

> Furthermore, patients were grouped into quartiles on the basis of the median of the predicted survival duration. Figure 5 presents the observed survival curves for the four risk groups. The four risk groups have different observed survival probability ($P < .001$). The observed median survival durations were 7.5 months (95% CI, 6.2 to 10.9 months), 13.4 months (95% CI, 9.7 to 26.3 months), 18.9 months (95% CI, 16.2 to 26.3 months), and 27.2 months (95% CI, 21.9 to 42.8 months) for the first, second, third, and fourth risk groups, respectively. The corresponding median predicted survival times were 8.8, 13.4, 17.4, and 22.8 months for the four risk groups.

One could extrapolate from this, therefore, that the observed 25.8 month survival in the Provenge group vs 20.3 month predicted survival cannot be cited in support of the notion that Provenge extended life.

Furthermore, the Halabi model was developed to predict survival in a mixed group of CRPC patients, and cannot therefore be validly applied to an exclusively asymptomatic and minimally symptomatic population. Given that the Halabi model uses neither pain, nor location of metastases as predictive factors, yet both are known as highly correlated with survival, and the IMPACT population excluded both of these patient groups, it is furthermore likely the Halabi model would systematically underestimate the survival of an asymptomatic population excluding these negative prognostic factors.

4. The 4-month apparent "survival benefit" in PhIII trials is the only evidence of Provenge efficacy

Provenge has never shown anti-tumour effects either in vivo or in vitro (see excerpts from FDA review below). Provenge has shown no efficacy in animal models. The **only** piece of evidence that Provenge prolongs survival is the 4.2 month "survival benefit" vs the more immunodepleted arm in its PhIII trials.

Thus, invalidating the PhIII "survival benefit" invalidates the basis upon which the drug was approved and is currently being used.

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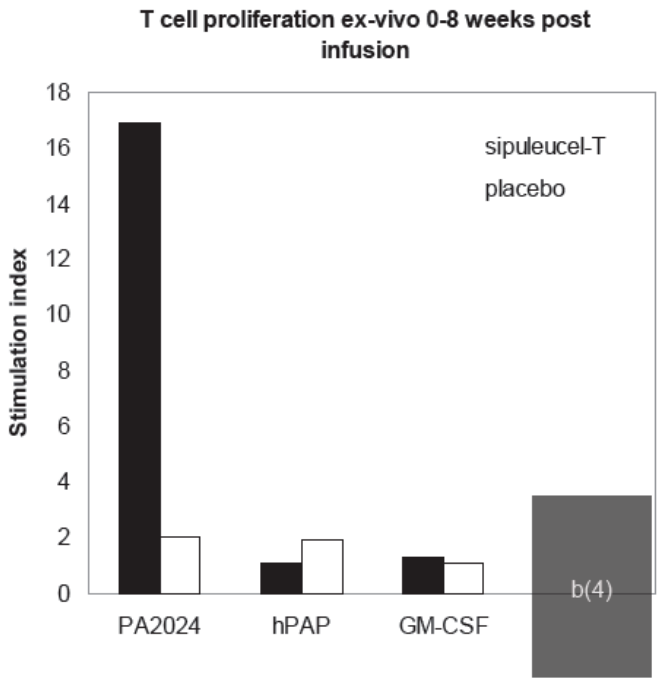
[42] Halabi S, et al. Prognostic Model for Predicting Survival in Men With Hormone-Refractory Metastatic Prostate Cancer. J Clin Oncol. 2003 Apr 1;21(7):1232-7. http://jco.ascopubs.org/cgi/content/full/21/7/1232



To quote the FDA reviewer[43]: "The fact that they are able to get a response to PA2024, but consistently not to PAP tumor antigen is troubling"

"**Summary of immune monitoring.** It is difficult to draw conclusions from the immune monitoring data for several reasons. For some assays only a few patients were examined, and in cases where a reasonable number of patients was examined, no response against PAP was seen. Only PA2024 seems to consistently generate an antigen specific response. It is puzzling how the stimulation index data is presented. If the peripheral blood T cell response is really as high as they are suggesting in some of their graphs, then that would represent a very strong response to PA2024. It is not clear why if they can get that level of response why they do not see much more of a response to PAP. Dendreon intends to perform some --b(4)---------- assays and maybe --b(4)---------- for the ongoing D9902B study, but as yet have not performed any of the assays. Hopefully, the results will be clearer in those studies. During a telecon with Dendreon to discuss some of these figures that were included in Dendreon's advisory committee briefing package it was asked if they had any evidence of a specific response to human PAP. They stated that, no, they do not yet have any evidence."

To quote the CMC reviewer: "Dendreon performed a limited evaluation of the immune response to sipuleucel-T. Immune monitoring was not performed in all trials. For example, no studies were done in D9902A, and so far it does not appear that any analysis has been performed in D9902B, --b(4)---------- Dendreon has stated that one limitation is in getting patient samples sent back to them for analysis. Another problem has been in consistency in the T cell assays. The thought is that if more samples could be assayed at the same time, then consistency may improve.

Even when immune monitoring was performed in a trial, it was not routinely performed and the number of patients examined is somewhat small. Also, some assays appear to have only been done once. It is not clear that Dendreon has put a high priority on measuring the immune response in patients in their trials. Considering that there appears to be very little tumor antigen-specific immune response in the vaccinated patients, one would think that this would be a high priority. Finally, it is difficult to fully interpret the data presented because few details were included on how the studies were performed and figure legends were not provided."[44]

[43] CMC Review p74-75 http://www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM214565.pdf

[44] P 74 http://www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM214287.pdf

4. Summary and Conclusion

Each trial arm received a different active intervention, neither of which can be proven to have had no effect, but one of which is likely to have had a greater role in determining the 4 month survival difference. The large amount of data from the trials speaks to the greater likelihood of one intervention being the primary driver.

Provenge Intervention: Provenge confers a 4.2 month survival advantage in minimally symptomatic mCRPC
Immunodepletion Intervention: Placebo patients were immunodepleted by the repeated removal of 73% of their lymphocytes & monocytes. Provenge patients were also immunodepleted, yet to a lesser degree, due to the loss of >50% of their leukapheresed cells during Provenge manufacture. Immunodepletion of this magnitude in patients >65 cannot be recovered from, causing in rapid tumor progression and death.

Observation from Trial and Experimental Data	**Provenge Hypothesis –** Provenge extends life	**Immunodepletion Hypothesis –** placebo (and to a lesser extent Provenge) patients were harmed
Patients <65 in both arms lived far longer than even the Provenge group	✗✗✗	✓
Provenge appears to confer no survival benefit to patients <65 (marked cliff in T cell diversity and naïve cell populations at 65)	✗✗	✓
Median survival of the placebo group was less than would have been predicted by comparing to other mCRPC studies, such as TAX327, SWOG9916 and CALGB 90401	✗	✓
Early deaths at ≤12 months in the placebo arm in particular appear worse than extrapolation from these other trials would predict	✗	✓
Provenge shows no in vitro or in vivo anti-tumor effects, and showed no benefit in disease progression	✗	✓

The balance of the data would appear to weigh in favor of differential immunodepletion as the cause for the survival observed in this trial. There is no plausible explanation for trial data from reasonable hypotheses regarding how Provenge might be working.

No future studies should be run with imbalanced immunodepletion of this nature. Efforts should be made to reduce the number of cells lost during manufacturing processes similar to this one.

Appendix A

92% of Final Product Cells were lymphocytes and monocytes

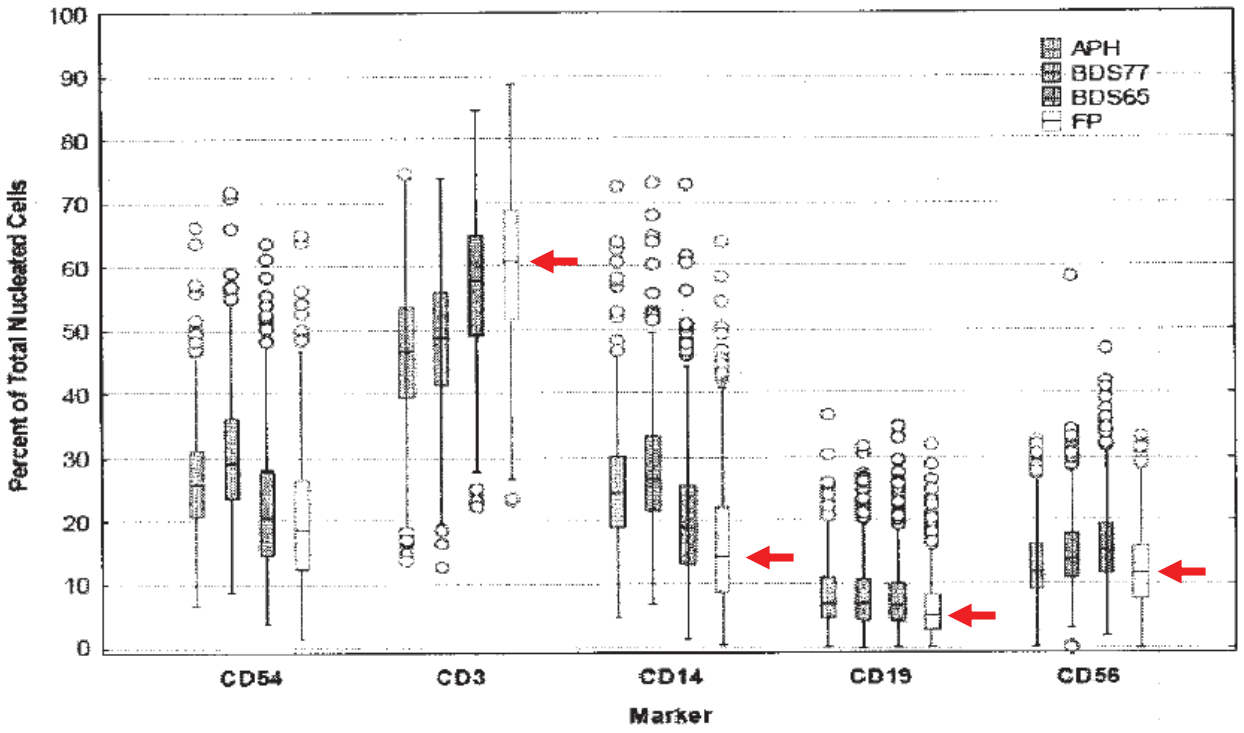


Figure 4. Percentage of leukocyte populations at various manufacturing stages of sipuleucel-T.
Numbers are calculated based on the total nucleated cell counts. Whereas all cell populations decreased when measured by total nucleated cell count, when assessed by percentage of total cell, CD3 positive cells increased. APH = leukapheresis, BDS77 = post first buoyant density centrifugation, BDS65 = post second buoyant density centrifugation just before incubation, FP = final product.

Marker	Cell Type	% of Final Product [45]
CD3	T-Cells	63 %
CD19	B-Cells	6 %
CD56	Natural killer cells	12 %
CD14	Monocytes	15 %
? Other ?	? granulocytes?	4%
TNC		100%

[45] March 2007 CTGT Advisory Committee Meeting CMC Briefing Document, p9
http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4291B1_04a.pdf

Appendix B

Cells Lost During Provenge Manufacture

These steps are performed to remove stray neutrophils and red blood cells that are extracted from patients despite the leukapheresis centrifuge having been set at such a speed as to spin down primarily the desired mononuclear cell fraction (these unwanted cells will contribute to the incoming leukapheresis TNC count, yet are likely only a few percent of the final product TNC count – data redacted from public document[46]).

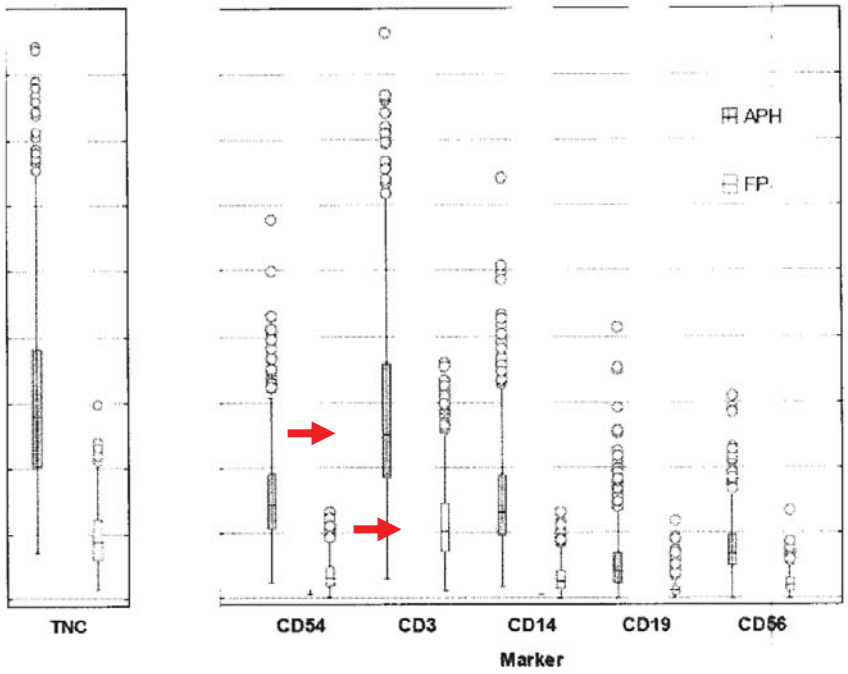


Figure 5. Leukocyte total cell numbers present within the starting leukapheresis material, processed cells, and the final product for autologous vaccination into patie
These plots show the total cell counts for the several cell types at various manufacturing stages. APH = leukapheresis,
FP = final product. Data is based on 526 lots.

"to help describe and visualize the level of variation between individual patient leukapheresis units and between different lots of the final product, the applicant presented the data in the form of box and whisker plots. Data plotted in this way is described in terms of the median, quartiles of the meida, and minimum and maximum quartile extremes, with outliers plotted individually"

[46] March 2007 CTGT Advisory Committee Meeting CMC Briefing Document, p5 & p9-10. http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4291B1_04a.pdf

Dendreon redacted all the data on cell counts from the 2007 CTGT Advisory Committee Meeting CMC Briefing Document. This is the only publicly-available source for this information. The redacted data approximated below was be reverse-engineered from the two cell count charts in Figures 4 and 5 (reproduced above) of the CMC briefing document. Despite the poor quality of the scan and the redaction of the left-hand scale of Figure 5, by extrapolation from the known median cumulative CD54+ cell number in 3 doses of Provenge ($1.877x10^9$), it can be deduced that the baseline is zero and the horizontal lines represent $2x10^9$ increments.

	Apheresis Product		Provenge dose		% loss to Manufacturing APH to FP
	Cell count Ω ($x10^9$) **A**	% of TNC Ψ	Cell count Ω ($x10^9$) **B**	% of TNC Ψ	
T-Cells - CD3	5.0	46 %	2.1	63%	58%
B-Cells - CD19	0.8	7%	0.2	6%	75%
NK cells - CD56	1.4	13%	0.4	12%	69%
Monocytes - CD14	2.7	25%	0.5	15%	81%
Other (calculated)	1.0	9%	0.15	4%	80%
TNC	10.9	100%	3.4*	100%	69%

	Baseline WBCs		Cells lost per intervention Provenge Patients		Cells lost per intervention Placebo Patients		% difference Provenge vs. placebo
	% (approx)	# in 5.25 L man ($x10^9$)	Cell number ($x10^9$) **C**	% of Baseline	Cell number ($x10^9$) **D**	% of Baseline	
T-Cells - CD3	17.0%**	5.36	2.9	54%	3.6	67%	24%
B-Cells - CD19	2.5%**	0.79	0.6	76%	0.67	85%	11%
NK cells - CD56	4.5%**	1.42	0.9	71%	1.03	80%	13%
Monocytes - CD14	10.0%	3.15	2.2	70%	2.37	75%	8%
other			0.8		0.87		
TNC			7.4		8.53		

Ω from Figure 4, above Ψ from figure 5, above

C = A – B , D = C + (2/3 * B)

* This TNC # triangulates with the number in Table 19 on 2nd page of this write-up for TNC in product parameters administered in safety database ($9.831x10^9$ in 3 doses). Small difference due to different data sets.

** lymphocytes total 24% of baseline WBC; triangulates with # in Table 8 on p3 of this write-up showing patient baseline characteristics (1.425/6 cells per µl)

The only source for leukocyte counts during manufacture is the redacted 2007 CMC document. After these data were submitted Dendreon ceased the monitoring of these parameters. The 2010 CMC Review has been redacted to such an extent, it is not clear whether these data were re-examined during the final FDA review prior to approval.

On p31 of the Briefing Document supplied by Dendreon to the 2007 review committee[47] the volume of blood undergoing leukapheresis is stated as "a standard 1.5 to 2.0 L blood volume leukapheresis procedure to collect PBMCs". This is incorrect. The "L" should not be there. The actual volume of blood was 1.5-2 times the entire

[47] March 2007 CTGT Advisory Committee Meeting, Sipuleucel-T Briefing Document
http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4291B1_01.pdf

body blood volume, equating to 8-10.5 L for these patients. This has been confirmed with investigators and is correctly written without the "L" in the Journal of Clinical Oncology paper on the first PhIII study (9901) by Small et al.[48]

These two features of the 2007 briefing documents made it very difficult to see in publicly-available information the magnitude of the cell numbers being lost from Provenge and, to an even larger magnitude, placebo patients.

Data on patient cell counts through the course of treatment were also not made publicly available, so no assessment can be made of the ability of these elderly cancer patients to replace the lost cells. There were no cases of leucopenia or lymphocytopenia reported in AE tables, suggesting that shifts in relative subtypes of leukocytes (e.g. naïve vs memory T cells, T-cell receptor diversity, APC diversity, etc), and their potency/competency, rather than absolute number, would be needed to see which of these might account for a survival impact due to cell loss.

[48]Small et al, Placebo-Controlled Phase III Trial of Immunologic Therapy with Sipuleucel-T (APC8015) in Patients with Metastatic, Asymptomatic Hormone Refractory Prostate Cancer. *J Clin Oncol* (2006) 24:3089-3094

Appendix C

Summary of Phase 3 Clinical Studies

Study #	Year of Patient enrollment	Primary Study Endpoints	Study Design	Population	Product, Dosage, Route of Administration, and Schedule	# of Subjects
D9901	Jan 2000 - ~Oct 2001	**TTP** OS was not a pre-specified endpoint	Placebo-controlled, double-blind, multi-center, randomized (2:1)	**Asymptomatic** metastatic CRPC All Gleason scores no cancer pain	Sipuleucel-T or placebo, with a minimum of 3x106 CD54+ cells/ dose, i.v. at Weeks 0, 2, & 4	127 (82 Sipuleucel-T: 45 Placebo) 19 clinical study centers
D9902A	May 2000 - ~Apr 2002 (completion May 2005 – 3 yr survival announced July 2005)	**TTP** (OS revised secondary endpoint following analysis of D9901)	Placebo-controlled, double-blind, multi-center, randomized (2:1)	**Asymptomatic** metastatic CRPC All Gleason scores No cancer pain	Sipuleucel-T or placebo, with a minimum of 3x106 CD54+ cells/ dose, i.v. at Weeks 0, 2, & 4	98 (65 Sipuleucel-T: 33 Placebo)
D9902B IMPACT	July 2003 40% enrolled by Nov 2005 Gleason removed and minimal pain allowed Oct 2007	**OS** Elevated to primary endpoint in Nov 2005	Placebo-controlled, double-blind, multi-center, randomized (2:1)	**Asymptomatic or minimally symptomatic** metastatic CRPC Minimum 40% Gleason ≤7 Absence/minimal cancer pain	Sipuleucel-T or placebo, with a minimum of 20x106 CD54+ cells/ dose, i.v. at Weeks 0, 2, & 4	512 (341 Sipuleucel-T: 171 Placebo) 71 study locations

- May 2005 first time DNDN announced survival benefit (that would be presented at ASCO)
- August 2003 docetaxel demonstrated survival advantage

Appendix D –Q&A

How could Immunodepletion not cause an increase in infections?

(1) these people have cancer already, and die before infection gets them (2) innate immune system is the body's first line of defense in defense against other organisms. The cells most involved in innate immunity (and those first recruited to sites of infection), namely mast cells, eosinophils, basophils and the phagocytic cells including macrophages and neutrophils are barely affected by the leukapheresis. Although dendritic cells are also involved in innate immunity and through the process of antigen presentation they serve as a link between the innate and adaptive immune systems.

Pathogens that evade the innate immune response are generally rare (often due to successful vaccination programs that make use of the adaptive immune response memory), such as tuberculosis, salmonella typhi (typoid), polio, smallpox, measeles, mumps, rubella and Bacillus anthracis (anthrax). Others, such as staphylococcus and streptococcus are likely to have been encountered previously and be represented in the memory T cell compartment. It seems unlikely if these pathogens had not been encountered previously that these would be encountered for the first time by a study subject during the 6-18 month timeframe of the trial).

I heard leukapheresis is a treatment for cancer, why would they do this if it is bad for cancer patients?

Leukapheresis is only a treatment in cancers of the blood cells, never solid tumors. In the case of hematological malignancies such as acute leukemias, there are white blood cell counts high enough to cause hemostasis and "sludging" in the capillaries. This can effect retinal vasculature leading to vision changes, pulmonary vasculature leading to shortness of breath from decreased efficiency in oxygen exchange, as well as other organ systems such as the brain which would become clinically apparent with neurological deterioration of a patient from cerebrovascular compromise. Leukapheresis aids in reducing WBC numbers and reducing this risk.

Attachment E.

View Public Comments for Autologous Cellular Immunotherapy Treatment of Metastatic Prostate Cancer (CAG-00422N)

Commenter:

Gallagher LLP, Willkie Farr &

Title:
Partner

Organization:
Willkie Farr & Gallagher LLP

Date:
07/30/2010

Comment:

This comment is submitted by the law firm of Willkie Farr & Gallagher LLP on behalf of a client, who wishes to remain anonymous at this time. The purpose of this comment is elaborate on the analysis in “Provenge PhIII Trials – An Alternative Explanation of Survival Results,” which was previously submitted as a comment to CMS by our firm on behalf of the same client by email on July 15, 2010 in response to CMS’s request for public comment on the NCA for Provenge.

The original July 15 submission is available to download in pdf from https://files.me.com/edonaldelliott/ivfyo4

The current July 30 submission is available to download in pdf from https://files.me.com/edonaldelliott/y28re6

Dear CMS reviewer,
We previously filed a working copy of our whitepaper analysis of Provenge through our attorney, Willkie Farr &

Gallagher LLP, by email to the docket on July 15 in order to identify ourselves as investment advisors when we became aware of its unauthorized distribution as an 'anonymous' paper. At that time we had not yet finished validating our hypothesis with recognized experts from the specialized areas of research from which it draws its central tenets. We now elaborate on the July 15 submission by providing additional support for our hypothesis from such experts. One or more of the experts whom we reference in support of our opinions will, we have been told, be submitting separately to you letters conveying, in their own words, their understanding of the relevant facts and research from their area of expertise. Because of the public vilification of anyone that questions Provenge (one need look no further than this NCA comment site), these letters will be anonymous. If a channel is created whereby CMS can promise these experts public anonymity, they may be willing to disclose their identities and credentials which will lend further credibility to the opinions they submit.

Summary of Provenge Trial Concerns (detailed in whitepaper)

• The 11 month survival difference between placebo patients over and under 65 years of age (p=0.0004) is unanticipated and highly problematic, and implied that the "placebo" intervention may have actually been an active intervention with an age-dependent impact on survival

• Leukapheresis of study participants removed 109 circulating mononuclear cells (>90% of baseline)

• Provenge patients received ~42% of these back as drug infusion, whereas placebo patients had only 14% returned. This leukapheresis and imbalanced return of immune cells was repeated 3 times over a month

• There is strong rationale to believe that in patients >65 the cells replacing those lost are neither of the same competency, nor of the same subtype as before leukapheresis. The competencies lost are required for tumor suppression

• Since immunodepletion appears to be the only identifiable intervention that might have caused the older placebo patients to live 11 months shorter than the younger patients, and since immune aging research supports plausibility of such a causative association, harm inflicted by the greater immunodepletion of placebo patients, and not the efficacy of Provenge, could account for the study results

• Due to the 58% cell loss during Provenge manufacture, this causes us great concern that Provenge treatment itself is harmful to older patients, specifically the Medicare population. This would be suggested by the unexpected 5.5 month shorter survival of patients >65

receiving Provenge (and no benefit in patients <65)

Imperative Requirement for Immune Aging Expertise
Immunologists without expertise in immune aging have opined that the number of immune cells lost in the PhIII trials was too small (0.5 % of total body stores) to have been significant. Provenge's sponsor stated precisely this when asked for comment.
As stated in the Paper, we agree that for most of adulthood there would be no apparent consequences to this cell loss (although our experts believe the adult body has 3*1011 T cells, with demonstrably lower numbers in older individuals, making the median # removed greater than 3%). However, the experts, familiar with the dozens of experiments demonstrating this, believe that what is true of the robustness of the immune system of a healthy adult cannot be said of the immune system of an 80-year-old with metastatic cancer. Since this is an emerging field, immunologists that are not specialists in the aging of the immune system might not have the necessary expertise to opine upon the efficacy and safety of immunotherapies, or the validity of trial designs. In particular this expertise is needed for the unique safety and efficacy considerations of immune-modulating therapies in the Medicare population for whom you bear responsibility. Since it appears that the FDA did not engage experts in immune aging during the review of the Provenge BLA, this would explain why they did not consider this potential flaw in the trial design, nor this potential explanation for the lack of efficacy in patients <65 and lack of demonstrable anti-tumor activity which the reviewers noted as confounding. Much of our understanding of immune decline beyond the age of 65 has been discovered in the last decade, and would not have been known to the sponsor and FDA when agreeing to the phIII trial design in 1999.
We have sought the expert opinion of two of the nation's leading authorities in immune aging, both of whom support our contention that immunodepletion of the magnitude observed in these trials is likely to have harmed the aged immune system in a way from which it cannot recover. In particular, the additional 2/3 of cells removed from placebo patients, but not Provenge patients, unquestionably represents an active intervention and renders this arm an unusable comparator for the survival of patients in the Provenge arm. They further believe, as does an additional expert on cancer immunology, that this cell loss has the potential to impair the ability of older patients to effectively suppress a metastatic solid tumor, with clear survival consequences. Also, reduced lymphocyte counts were found to be an independent mortality risk factor in healthy older persons (Leiden 85-

plus study).
These experts share our concern that the cell loss during Provenge manufacture could result in the shortened survival of patients over 65 (median survival 23.4 months), while the drug confers no benefit to those under 65 (median survival 28.2-29 months in placebo and Provenge patients). It would be a tragedy indeed if this intervention in which so many have placed great hope is, in fact, shortening, not prolonging the lives of patients.
As a result of the utmost importance of understanding these questions, and the strength of their own beliefs and concerns, some of the experts cited have informed us that they will now be pursuing research in their own laboratories and clinical trials to shed further light on the mechanisms by which leukapheresis and immunodepletion might be harmful to elderly patients. We have much to learn.

Extreme Statistical Improbability of Age Stratification of Provenge Trial Results
Very few data are available regarding the age-related performance of patients in the Provenge PhIII trials. Only in the FDA's 2010 review (released in June 2010) was a pooled analysis first made public. In light of the question of whether immunodepletion was benign or harmful to elderly placebo patients, the profound 11-month survival difference between patients above and below 65 years of age is particularly troubling. Age has not been prognostic for survival in any other major mCRPC trial (TAX327, CALGB90401, SWOG9916 or the trials that informed the creation of the Halabi model), and the sponsors have provided no information to lead one to believe that the patients enrolled in this trial were differently skewed with respect to their baseline prognostic characteristics.
While this is a retrospective analysis (conducted by the FDA who chose to pool the PhIII trials, not by someone data-mining for a confounding variable), the fact that age is of central importance to immune functionality and the extremity of the p value obtained render this an insufficient basis on which to ignore the profound facts i.e. the probability that the older placebo patients died 11 months earlier than the younger patients by chance alone is 0.0004 (0.04%) according to an expert in statistical analysis. One must thus consider the possibility that the active intervention of immunodepletion in the placebo arm might have resulted in this shortened survival of the patients >65.

Summary of Statistician Analysis
• Survival by age from FDA 2010 review. FDA analysis of pooled data from D9901, D9902A, D9902B.
Age Provenge

N Median Survival (95% CI) Placebo
N Median Survival (95% CI) Provenge vs Placebo
Hazard Ratio (95% CI)
< 65 106 29.0 (22.8, 34.2) 66 28.2 (23.4, 32.5)
0.919 (0.618, 1.366)
≥ 65 382 23.4 (22.0, 27.1) 106 17.3 (13.5, 21.4)
0.661 (0.538, 0.813)
• Assuming normal distributions for median survival times, the 95% confidence intervals translate into +/- 1.96 standard deviation intervals. i.e, the difference of upper and lower limits is 3.92 standard deviations. We can therefore back out estimates of the standard deviations in question as:
Age Treated (T) Placebo (P)
< 65 (Y) 29 +/- 2.91 28.2 +/- 2.32
≥ 65 (O) 23.4 +/- 1.30 17.3 +/- 2.02
* The exact CI of an exponential would use percentiles of a chi-squared distribution with 2n degrees of freedom. Here n is large enough that those values chi-sqs would be very close to the normal ones, even in the tails. All p-values are for two-sided tests, but the rankings and relative values for one-sided tests would also be almost identical.
• As usual for normals, the standard deviation of a difference is the Pythagorean diagonal of the two component standard deviations. Below are the differences sorted by statistical significance:
Comparison rawDiff Sigmas P-value (2-sided)
PY-PO 10.9 3.54 0.00040
TY-PO 11.7 3.30 0.00097
TO-PO 6.1 2.54 0.011
PY-TO 4.8 1.80 0.072
TY-TO 5.6 1.76 0.078
TY-PY 0.8 0.21 0.83
All three prominent differences in the table involve the older group in the placebo arm, the single largest being the placebo arm “young vs old” difference. Indeed, out of context the most obvious conclusion from this table is that the major effect found by the study is age dependence in the placebo arm. Since the placebo arm age difference is expected to be insignificant, the cause of this “age effect” cannot be separated from the alleged treatment effect. The placebo arm age difference is twice as large as the treatment effect in the older population and drastically less likely.

Post-marketing Studies : Does Provenge extend or shorten survival?
It thus appears mechanistically plausible and statistically undeniable that immunodepletion represented an active intervention in the “placebo” patients, moreover one which probably resulted in the 11-month shortened survival of

the older patients. Thus with no placebo group to which to compare the survival of the Provenge patients, we have no measure of how long they would have lived in the absence of Provenge intervention. One could suggest that the patients <65 from the placebo arm might represent the true “placebo” group in this trial, as their immune systems were still robust enough that the immunodepletion was indeed insignificant. This comparison shows a shorter survival with Provenge - 25.8 months vs placebo 28.2 months - but without detailed baseline characteristics for the “young” placebo subgroup and only 66 patients in this group it is clear that more robust methods must be employed to truly assess Provenge safety and efficacy. When the FDA approved Provenge they did not have the benefit of insights from immune aging experts as we have provided in support of our concerns. CMS most certainly has access to similar experts of your own. We strongly recommend that CMS, as the final gatekeeper with the authority to mandate post-marketing studies, call for further study of this matter before it is too late to conduct these, and protect elderly patients from being subject to this risk until it is resolved.

We hereby strongly urge CMS to commission further study of Provenge while these studies are still feasible. Some studies which might be pursued:

1. Epidemiological study. The sponsor would need to provide individual baseline characteristics and respective survival data for the patients that received Provenge in its Phase 3 clinical program. Using an accepted, pre-determined and peer-reviewed methodology, mCRPC patients with matching baseline characteristics would be drawn from the extensive data sets generated by other trials. This would enable comparison of Provenge survival with a synthetic placebo group with the same baseline prognostic outlook and receiving similar additional therapies/chemo. Suitable patient sets to draw from would be those receiving comparable chemotherapies and standard-of-care from recent mCRPC trials e.g. CALGB 90401 placebo arm (n=525), TAX327 docetaxel q3w arm (n=335), SWOG9916 docetaxel arm (n=338). Additionally or alternatively, more inclusive and appropriate control data set(s) could be drawn directly from Medicare mCRPC patient records from the last few years. This comparative analysis would be the most expedient approach to confirming Provenge efficacy. Although the retrospective analysis would be exploratory and as such imperfect, it would be a vast improvement over the analysis incorporating an immunodepleted placebo group. This suggested study offers multiple additional advantages: (1) it is inexpensive to conduct, (2) it can be initiated immediately, (3) it can be completed within a 1-2 month time frame, (4) it does not require IRB approval, (5) it does

not preclude any other parallel studies, (6) it does not expose new patients to a potentially harmful intervention for study purposes, and (7) it does not prevent patients who seek Provenge in the interim from receiving it.
2. Prospective, randomized, placebo-controlled study. Once a drug is approved for survival benefit, it becomes unethical to withhold this drug from patients in a placebo group, making it impossible to ever again assess its true efficacy, and necessitating this drug as standard-of-care in all future trials of other drugs in the same indication. However, the limited supply of Provenge that the sponsor is currently able to manufacture means that hundreds of would-be recipients of Provenge are already being denied access to this intervention. Many urologist and oncologist offices are currently allocating the 1 or 2 “slots” for Provenge that they have each month by a lottery amongst the 30+ eligible patients that wish to get them. Thus, while the drug is in finite supply, the ethics of randomized allocation of a patient to Provenge vs placebo are very similar to the ethics of prescribing Provenge by lottery. Such a study could be mandated, and would easily enroll numbers of patients greater than in IMPACT before the supply constraints lifted. Within a few years we would have results from a prospective, randomized, placebo controlled study with a VALID placebo comparator for survival. Interim analyses could yield results earlier (particularly if supported by the epidemiological study described above). There are scores of additional laboratory and clinical studies that will be conducted in the next years to shed light on the impacts of leukapheresis and cell loss on immune parameters such as naïve T-cell counts and T-cell receptor diversity, functionality of immune reconstitution in elderly patients, etc. These may shed further light on the mechanisms by which immunodepletion may shorten survival in elderly cancer patients and provide experimental evidence for the alternative hypothesis in the Paper.

Advocating for Patient Protection
Because of the real potential risks that we perceive with Provenge intervention, we are advocating for these further trials for the protection of prostate cancer patients. If CMS shares our trial design concerns, it appears evident from the NCA that, even if it is not harmful, you would wish to confirm the drug’s efficacy, having no desire to spend dollars from an increasingly finite pool on a wasteful and expensive placebo.
Those supporters of Provenge that are also advocates for prostate cancer patients should welcome any or all further studies. If Provenge is effective, we only stand to deepen our understanding of its immunosupportive mechanism (about which we are currently able to demonstrate

nothing) by conducting further trials. Those that wish to silence this scientific discussion and prevent these further analyses CANNOT have cancer patients' best interests at heart.

Since the potential of immune-modulation to yield effective therapies has a solid foundation in our basic understanding of immune cell functions and interactions, and have shown promising in-vitro and in-vivo activity guiding us towards the better approaches, we are enthusiastic supporters of, and sincere believers in the promise of immunotherapies to yield great leaps in cancer treatment, longevity and many other aspects of human health. Those that share this enthusiasm should welcome, as we do, a fuller understanding of the Provenge trials, as this will greatly advance our understanding, not set it back. To turn a blind eye to the unexplored flaw in the Provenge trials does a great disservice to the field of immunotherapy; if it is not effective (or worse, harmful), by "occupying" the asymptomatic window, Provenge effectively blocks the development of any other truly safe and efficacious therapies for this precious window of relative health. Any future immunotherapies showing promise in mCRPC would have their trials undeniably complicated, and potentially confounded by having to test such a therapy on top of the Provenge standard-of-care. To reiterate, we are advocating on behalf of PC patients and the CMS budget that Provenge be proven safe and effective. If the PhIII trials were flawed, the sooner we find out, the better.

www