

PROVENGE®



Approved in the U.S.A.

for Metastatic, Castrate Resistant Prostate Cancer

by Jan Manarite, PCRI Florida Educational Facilitator

A New Option

After many years of research by Dendreon, and waiting by prostate cancer patients, PROVENGE® (sipuleucel-T) has been approved by the FDA for use in the US. **Its approval is for treatment of PC patients who are both metastatic, and castrate resistant.** These patients, according to the FDA labeling, should also have very few cancer symptoms (**minimally symptomatic**), or no cancer symptoms (**asymptomatic**). The most common cancer symptom is pain.

It is also important to note that “castrate resistant” is another way of saying “hormone refractory”, or “androgen independent”. In fact all 3 of these terms have been used interchangeably over the years in sipuleucel-T (PROVENGE) clinical trials and published studies.

Since it is always challenging to make sense of the headlines, this article is intended to help PC patients understand what this FDA approval means for them.

Availability

One of the first big challenges for prostate cancer patients will be when and where they can receive PROVENGE treatment. It is important to understand that PROVENGE is not a prescription, so it will not come from your local pharmacy (see “Apheresis” below). In addition, it will not be found in every city initially, and Dendreon will not have the processing capability to meet 100% of the need right away.¹ Dendreon’s current estimate is to reach full capacity by mid-2011. Still, this availability information will need to be communicated and updated regularly by Dendreon, and can be found through their call center at **1-877-336-3736** (1-877-DENDREON), or on their website at www.PROVENGE.com.

What is PROVENGE®?

There are plenty of online articles about PROVENGE in general, or in scientific terms, including in previous issues of *PCRI Insights*. This article, however, is intended to help men and their families understand what it means to prostate cancer patients today, just after FDA approval. In simple terms, PROVENGE is a new type of treatment option, administered through a new process, with a new way of monitoring cancer response. *(Continued on page 4)*

In clinical trials, PROVENGE® has also been called sipuleucel-T and APC8015



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[For more on the science behind PROVENGE® (sipuleucel-T), see Oct 2001 *PCRI Insights, Dendritic Cells Proving the Key to Prostate Cancer Immunotherapy*, and Feb 2008 *PCRI Insights, Immunotherapy and Advanced Prostate Cancer* available at www.pcri.org.]

PROVENGE® will be new or different for prostate cancer patients in several ways:

- ◆ *Immunotherapy* – PROVENGE does not kill cancer cells. It does, however, trigger, or restart the patient’s own immune system to fight the cancer itself.⁴ Killing cancer is one of the primary tasks of the immune system, and for many reasons (some unknown), a person’s immune system can lose its ability to destroy cancer cells.
- ◆ *Apheresis (also called pheresis)* – PROVENGE will be administered to patients using a 2-part process. First, the patient’s white blood cells are drawn from him in a painless procedure called apheresis, (see figure 2) which usually takes between 2 and 4 hours. Two or three days later, the patient returns to the clinic, where he receives a re-infusion of his own blood cells, but with PROVENGE merged into those cells. This 2nd visit is shorter, and usually takes about 45 - 60 minutes. **Because PROVENGE’s apheresis process extracts white blood cells (leukocytes) from the patient, it is called Leukapheresis.**
- ◆ *3 treatments* – PROVENGE will be given in a series of 3 treatment cycles, approximately 2 weeks apart. Each treatment cycle is the 2 part procedure described above. This entire process usually takes about one month. This is unlike most other cancer treatments which can continue for months, or even indefinitely. It should be noted that although the treatment plan is to administer each pheresis process 2 weeks apart, the science behind PROVENGE suggests that spacing treatments out at longer intervals may not decrease effectiveness. What this means for patients and physicians is that having a treatment delayed for short periods of time, because of unforeseen reasons, is not likely to risk the effectiveness of PROVENGE⁹.
- ◆ *Side effects* – The reported side effects from years of studying PROVENGE are possible flu-like symptoms for a day or two. A recent release by Dendreon stated, “...the most commonly reported adverse events seen in sipuleucel-T treated patients were chills, fever, and headache.” It is also interesting that most side effects were grade 1 or 2, and no patient discontinued PROVENGE because of the side effects.² Of the three PROVENGE treatments, it is more likely that side effects will occur on the last treatment, and least likely that side effects will occur on the first treatment. This is a common principle in most medications – as the dosage increases in the body over time, so can the side effects. Patients in PROVENGE studies were pretreated with Tylenol® and Benadryl® to help relieve these effects.² Still, among the systemic therapies for men with hormone refractory prostate cancer, this remains one of the least difficult treatments to tolerate. Safety information can be found at: www.PROVENGE.com
- ◆ *Response* – Since Immunotherapy takes some time to work⁴ an immediate PSA response will probably not be seen in most men. Earlier PROVENGE trials showed PSA declines of more than 50% in approximately 10% of patients. Another 10% showed PSA declines between 25% and 49%². Even though immediate PSA responses are not commonplace, immune responses in the patients own blood cells are. In fact, virtually every patient sample has demonstrated some type of immune response before it is returned to the patient in the second part of the 2 step treatment process. Dendreon recently published additional data from their phase 3 trials, which showed no immune responses in the placebo group, but documented multiple types of immune responses in the sipuleucel-T group, including PAP (prostatic acid phosphatase) specific responses, T-cell responses, and evidence of a “memory” in the immunologic response. They also reported that immune response was



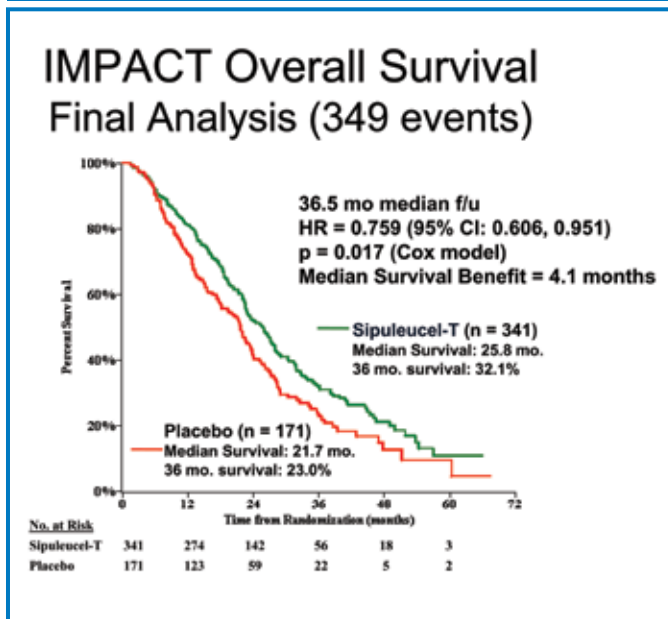
PROVENGE IS NOT A PILL



PROVENGE IS NOT A SHOT

Provenge will be given by leukapheresis.
See figure 2, page 6.

FIGURE 1. Survival Benefit



seen at 6 weeks post treatment, and persisted to 6 months post treatment. Learning to understand and measure immune responses will be a learning process for most patients, many physicians, even science in general. It will be meaningful to watch how this research develops further.

Understanding the Survival Data Discussion

The press is full of articles quoting the 4.1 month survival benefit of PROVENGE over placebo found in Dendreon’s IMPACT trial (Figure 1). However, this survival benefit can sound insignificant to many, and can leave men wondering – *“If Provenge only provided an extra 4 months of survival – why should I be excited?”*

The truth is – it can be difficult at best to turn raw statistical data into understanding of personal benefit. The median survival data usually underestimates the benefit to the actual cancer patient who is considering treatment after a trial drug is approved. PCRI’s late Brad Guess wrote about this in 2006 when Taxotere® was FDA approved for prostate cancer based on a smaller median survival benefit – about 2.5 months. Here are 3 key quotes from this article, titled, *Chemotherapy – Why Bother?*

1. “...survival analysis is very easily misinterpreted, often in the direction of underestimating hope.”
2. Studies which allow placebo patients to “**cross over**” into the drug arm [like Provenge’s study] “... **skewed the differences in survival** between the two treatment groups by improving the survival...” in men in the other [placebo] arm.

3. “...median survival analysis says little about patients on the right side of the survival curve (the men who respond to treatment, despite a poor prognosis)...**The existence of a small group of survivors far past the ‘median’ point, even in cancers with a dire prognosis such as advanced PC, should provide real hope** even when the prognosis is bleak.”

This full article can be found in May 2006 *PCRI Insights*, or online at www.pcri.org.

I would also point out that it is impossible to estimate the additional survival benefit (in the real world) from having access to new treatments as they develop over time, and the benefits of continuing to make well researched, well thought out treatment decisions, which is the essence of the empowered patient.

Patient experiences – in their own words:

Since this treatment will be so different as compared to other HRPC treatments, here are a few patient experiences, in their own words, from men who received PROVENGE in one of the various clinical trials:

1. Patient JW, metastatic HRPC trial in 2009: “He was able to stay on the Provenge for the length of the trial (that concluded in December). He had only one mild, flu-like reaction, which occurred the second time he got the infusion.”
2. Patient CF – hormone sensitive PC trial in 2000: “The only side effects were mild flu-like symptoms following the second and third of three infusions...”

The apheresis procedure is painless but somewhat uncomfortable since the patient is pretty immobile for several hours (better use the facilities before since once it starts, it’s bed pans or ...) ... PSA measured every two or three months. Mine continued to rise... No evidence of metastasis until 2004-05 when several suspicious sites appeared...Once the trial ended, I returned to Pittsburgh for treatment... have never suffered bone pain of any kind. In fact some of my “suspicious” areas have resolved. There was no immediate impact on PSA growth. Though there is no proof, I believe it has been a factor in the long term slow progression of my disease.”

3. Anonymous patient, metastatic HRPC trial in 2010, age 79 – Had no side effects at all, from any of the 3 treatment cycles, except a little tired after first treatment. Process was a bit long, but not difficult. Is currently planning next treatment choice.

(Continued on page 6)

FIGURE 2. PROVENGE ADMINISTRATION – A complete course of Provenge is 3 infusions, typically administered approximately 2 weeks apart. The dosing interval ranged from 1 to 15 weeks in controlled clinical trials.



4. Patient DB - metastatic HRPC trial in 2010, age 54 – Had 2 PROVENGE samples rejected in a row because of unknown “quality control” issue. Proceeded to finish trial with no known side effects. Next CT scan surprisingly stable, after several previous CT scans consistently showed disease progression. Has CT scans every 3-4 months.

of this analysis suggest that the use of PROVENGE as a first-line treatment followed by the chemotherapy docetaxel upon disease progression may provide patients with a substantially prolonged survival benefit.”

This finding creates important questions for researchers, and probable direction for patients and clinicians. It will be of great interest to see how this research continues to develop.

QUESTIONS REMAINING

In the absence of proof, or “level one evidence” (see *Levels of Evidence*, Aug. 2009 Insights), it is important not to ignore lesser evidence. In other words, when we don’t have scientific proof, it is important that we do not default to “do nothing”. And, when we don’t have the answers yet, it is important that we don’t discard the questions. This is especially true when there is a lack of protocol and consensus between physicians, as is often true in hormone refractory prostate cancer.

So, in the absence of what might be considered proof, here are some very important questions regarding using PROVENGE for men with metastatic, hormone refractory prostate cancer.

Does PROVENGE (or immunotherapy in general) help increase the effectiveness of later treatments?

Probably the most interesting analysis on this topic comes from a study presented in 2006 by Dr. Dan Petrylak from Columbia University Medical Center⁵. In this investigation, 82 patients were divided into two groups. Approximately half of the men received PROVENGE BEFORE Taxotere (docetaxel). The other half received only Taxotere. The group that received PROVENGE before Taxotere showed a significant survival advantage, leading Dr. Petrylak to comment that, “*The results*

Were all castrate resistant, metastatic men studied with PROVENGE treatment?

All trials have criteria in the trial design, having to do with the data necessary to achieve statistical results. That being said, it may be important to note that **men with the following conditions were NOT studied** in the metastatic, hormone refractory PROVENGE trials:

- ◆ Cancer pain requiring opioid medications
- ◆ Other significant cancer symptoms
- ◆ Prostate cancer metastases to liver, lung, or brain
- ◆ Hepatitis B or Hepatitis C
- ◆ AIDS/HIV positive

Will PROVENGE be even more effective in early stage prostate cancer?

We know that smaller clinical trials have been conducted in men with hormone-sensitive prostate cancer, and in men who are newly diagnosed, receiving PROVENGE just before prostatectomy. In January 2010, Reuters published this statement – “The CEO also said Dendreon is “looking at” the use of Provenge in earlier-stage prostate cancer as well as other cancer types.”⁸ So it certainly makes sense

to watch for new trials that may develop in earlier stage prostate cancer. These new trials involving PROVENGE (sipuleucel-T) should appear on www.DENDREON.com and on www.clinicaltrials.gov.

Does PROVENGE increase the risk of stroke?

There was a small, statistically insignificant increase in “cerebrovascular events” in the PROVENGE arm of the phase 3 studies, as opposed to the placebo arm. “Cerebrovascular events, including hemorrhagic and ischemic strokes, were observed in 3.5% of patients in the sipuleucel-T group, compared with 2.6% of patients in the placebo control group.”¹² This small increase was not enough to warrant high risk in FDA ruling or labeling, but was enough to warrant a suggestion by Dendreon that patients discuss risk of stroke with their physicians before undergoing treatment with PROVENGE. See Safety Information at www.PROVENGE.com.

Although the definitions can vary slightly, in PROVENGE studies, these 3 terms have meant the same thing:

- *Castrate Resistant*
- *Hormone Refractory*
- *Androgen Independent.*

Does PROVENGE interact with my other medications?

Although it is not expected that PROVENGE will interact with most oral medications, this has not been studied thoroughly. It is suggested that men who are on immunosuppressive therapies, such as steroid medication, discuss this with their physicians before undergoing PROVENGE immunotherapy¹³. See Prescribing Information at www.PROVENGE.com.

STAYING OBJECTIVE

Cancer is emotional. It is likely that you will find information somewhere that overstates what PROVENGE can do. It is possible you will find someone who says it’s a cure. PROVENGE is not a cure for advanced metastatic CRPC, although some men may benefit from long term responses. But somewhere between cure of cancer, and losing your life to cancer – there is a middle road. Do we call it remission? It’s not the exact definition. Can we call it cancer control? Cancer suppression? These terms seem fair. At the very least, this middle road is not the end – it is a road.

Most hormone refractory patients have evolved into very good researchers. This article is designed for you. Try to continually evaluate two things in every treatment – Risk and Benefit. It is a slightly more scientific way of saying Pros and Cons.

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