

OBR CORPORATE PROFILE:

# Dendreon

## STEPS UP TO THE PLATE

And Cancer Immunotherapy Companies Watch from the Sidelines



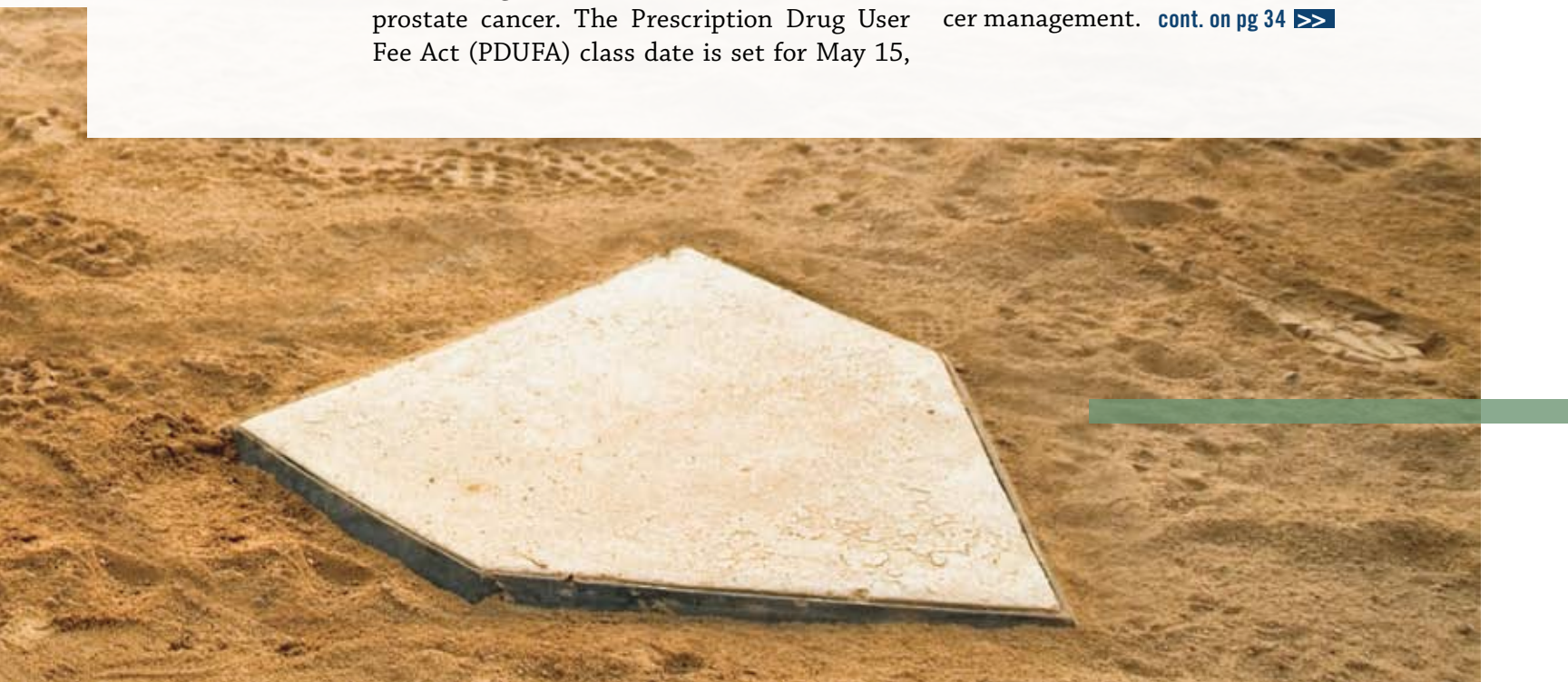
MANY ANALYSTS BELIEVE THAT DENDREON IS POISED TO BE THE FIRST-TO-MARKET WITH A CANCER IMMUNOTHERAPY PRODUCT. WE TOOK A LOOK INSIDE THIS SMALL BIOTECH THAT IS POISED TO STAND AMONG THE GIANTS.



BY MICHELLE NOLIN FLEWELL

**T**he Seattle-based Dendreon Corporation has reached a historic milestone with the recent news that they will get an expedited review by the FDA for their active cellular immunotherapy (ACI) product Provenge® (sipuleucel-T) for patients with prostate cancer. The Prescription Drug User Fee Act (PDUFA) class date is set for May 15,

and if approved this year, Provenge stands to be the first commercially available ACI product. For the burgeoning cancer immunotherapy market, this news has intensified interest in—and speculation about—the many challenges and victories of this emerging approach to cancer management. [cont. on pg 34](#) ➡➡



# Dendreon

## STEPS UP TO THE PLATE

### Dendreon's Evolution and Path to Approval

On January 16, 2007, Dendreon announced that the FDA had accepted the company's Biologics License Application (BLA) for Provenge, and granted the agent priority review status. "This is the first active cellular immunotherapy product to have its license application accepted for review by the FDA," said Mitchell H. Gold, MD, President and CEO of Dendreon.



Mitchell H. Gold, MD

In the next year or two, as approval nears, Dr. Gold noted that the company is actively transitioning from R&D to becoming a fully-integrated commercial company. For Dendreon, a company that did not start out in the therapeutic product arena, this marks yet another turn in its natural evolution.

In its early days, the company's co-founders and investigators were focused on their DACS<sup>®</sup>SC stem cell enrichment device, which isolates hematopoietic stem cells from blood for use in patients with cancer who require transplantation following high-dose chemotherapy or radiation.

Dendreon soon shifted its focus from medical devices to developing therapeutic products that fight cancer by manipulating aspects of the immune system, specifically, by stimulating a patient's immune system to mount a cell-mediated response.

In the late 1990s, Dendreon reported that they were investigating therapeutic cancer vaccines through the use of antigen discovery, antigen engineering, and dendritic cell technologies. An IND was filed for Provenge in 1996, and the classification of the product has evolved overtime from a therapeutic cancer vaccine to an investigational ACI for prostate cancer.

As proof of concept, in 2000, Burch et al reported (*Clin Cancer Res.* 2000 Jun;6(6):2175-82) that exposing dendritic cells to antigen induced an antigen-specific cellular immu-

nity in patients with prostate cancer. Also that year, Small et al (*J Clin Oncol.* 2000 Dec 1;18(23):3894-903) reported preliminary clinical efficacy with Provenge. These indicators led the company to construct a clinical development program for Provenge.

### The Role of Technology in Dendreon's Pipeline

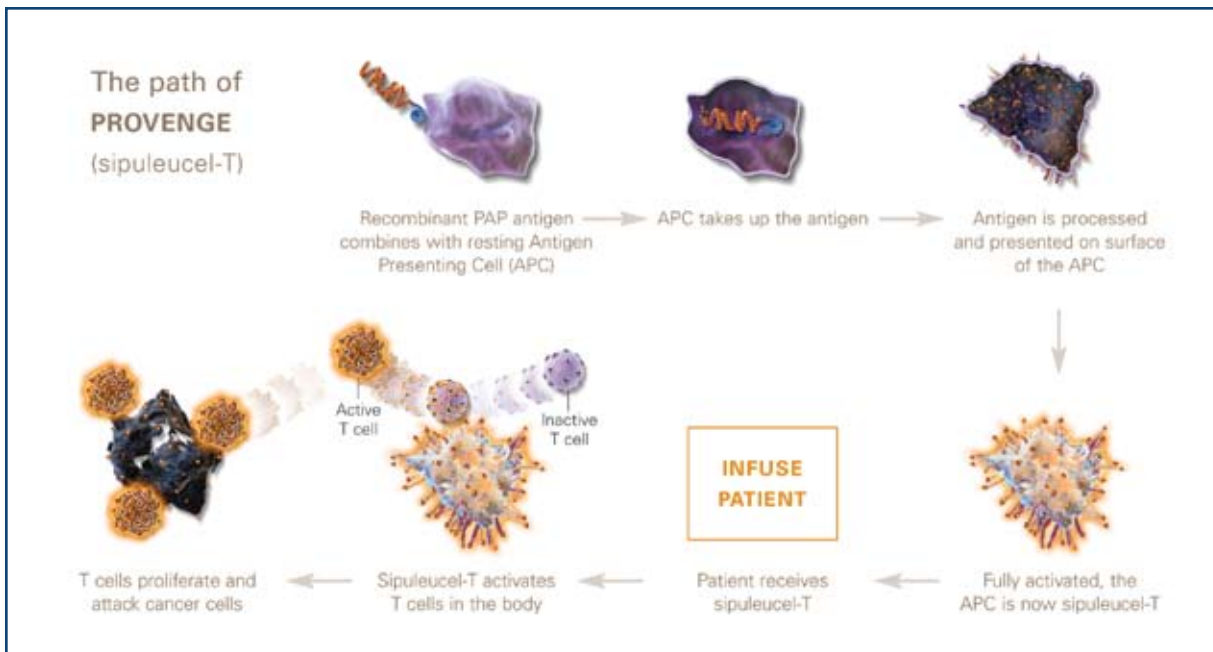
Provenge is composed of dendritic cells derived from a patient's antigen presenting cells (APCs). Patient cells are extracted via a standard blood collection procedure and loaded ex vivo into Dendreon's proprietary *Antigen Delivery Cassette*<sup>™</sup> with a recombinant form of prostatic acid phosphatase (PAP), an antigen found in approximately 95 percent of prostate cancers, and GM-CSF.

"The Antigen Delivery Cassette is a fusion protein with two key components—a target antigen (i.e. PAP), and GM-CSF. The fusion protein allows the immune system to recognize the antigen about a thousand times more efficiently than if it was the naked antigen by itself," said Dr. Gold.

The *Antigen Delivery Cassette*<sup>™</sup> is combined with the patient's own dendritic cells to generate an immune response against the antigen (see Figure 1).

Proprietary technology continues to be central to the development and, importantly, the commercial-scale manufacturing of cancer immunotherapies. Dendreon's R&D efforts and product pipeline currently utilizes three technology platforms: ACI, monoclonal antibodies, and small molecules (see Figure 2).

Dendreon's business philosophy is to leverage the immune system to treat patients with cancer, said Dr. Gold. "Our Antigen Delivery Cassette allows us to plug in a variety of different antigens. For Provenge, it's PAP. We use the same technology platform for our investigational product Neuvenge (lapuleucel-T) which targets HER2/neu-positive cancers." Overexpression of HER2/neu is associated with breast, ovarian, colon, lung and other cancers.



Provenge is composed of dendritic cells...

FIGURE 1. Source: Dendreon Corporation

Dendreon has acquired rights to carcinoembryonic antigen (CEA), a possible target for colorectal, lung, and breast cancers, as well as carbonic anhydrase 9 (CA-9), a possible target for renal, cervical, and renal cancers. “We have developed a technology platform on which to build products, and Provenge happens to be the first candidate to use the platform,” he said.

Dendreon has completed two Phase III trials (D9901; D9902A) with Provenge in the setting of asymptomatic, metastatic, androgen-independent prostate cancer. Although survival benefit and other positive findings have been reported, the results, overall, have been mixed—the two initial Phase III studies showed improved survival, however, the analysis of D9901 showed no statistically significant benefit in time-to-disease progression. The company is currently enrolling a larger trial (called IMPACT) to further study Provenge in the advanced-stage prostate cancer setting.

### Where Provenge Might Fit in the Current Treatment Paradigm

The indication Dendreon is currently seeking for Provenge is prostate cancer that has recurred after some form of primary therapy, and for use in men who have also failed secondary manipulation with hormonal therapy. Dendreon plans to position the product as front-line therapy for asymptomatic, metastatic, androgen-independent (hormone-refractory) prostate cancer. Currently, in the US, approximately 100,000 men fall into that disease-state category.

Most clinicians would agree there is an unmet clinical need in this setting. The only other product approved in this disease-state category is Taxotere (docetaxel), which has shown a survival benefit of 2.4 months and is associated with significant toxicities. The median survival benefit of Provenge is approximately 4.5 months, and it’s generally well tolerated. Data also indicate that one of the key factors that determine the cost of cancer care is time spent receiving infusions. The average time patients [cont. on pg 36 >>](#)





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# Dendreon

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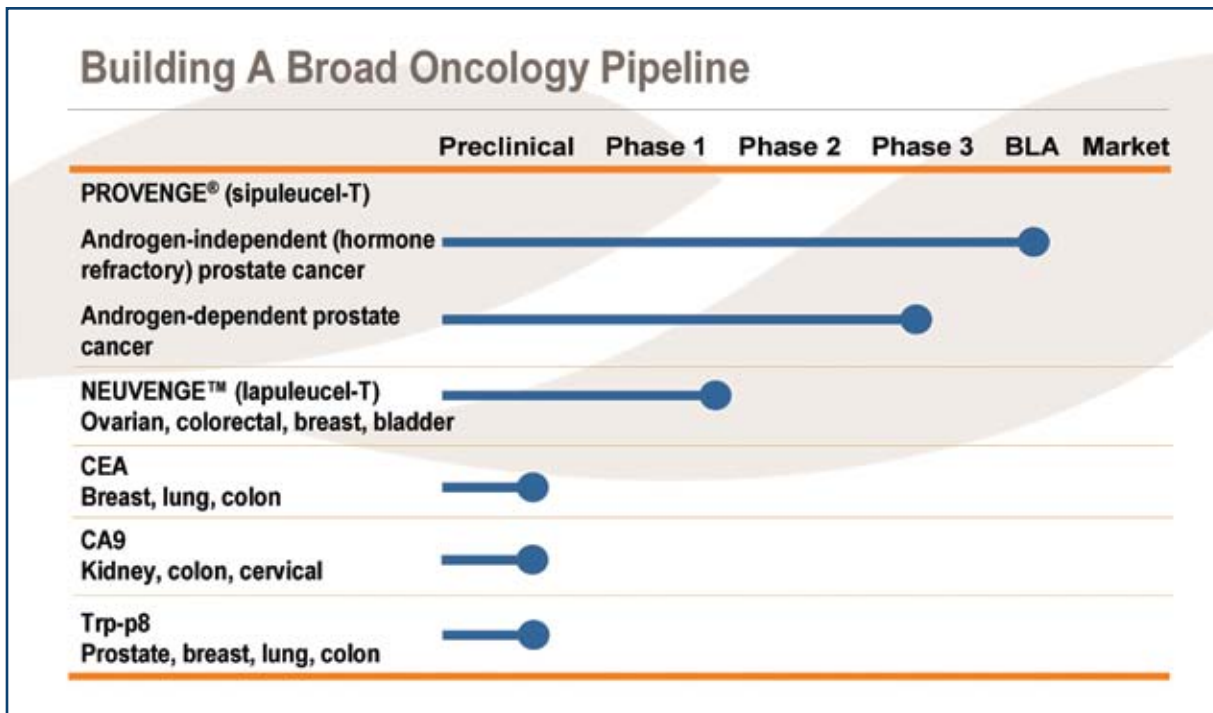


FIGURE 2. Source: Dendreon Corporation

are on Taxotere is 7 months; the course of therapy with Provenge is anticipated to be a 1-month period with 3 infusions delivered, each infusion expected to be 30-60 minutes in duration which would reduce the burden on the health-care system.

Nicholas J. Vogelzang, MD, Director of the Nevada Cancer Institute speculated that good candidates for treatment with Provenge include patients who are asymptomatic but whose PSA levels have started to rise following hormone therapy.

“Provenge represents an exciting potential option for a whole population of men whose PSA is starting to go up, and it could potentially postpone the need for chemotherapy,” he said. Dr. Vogelzang notes that many men are daunted by the prospect of chemotherapy. “Most immunotherapies are relatively non-toxic; therefore, Provenge would be a welcome and appealing option.”

E. David Crawford, MD, Professor and Head of Urologic Oncology at the University of Colorado at Denver and

Health Sciences Center, envisions that for patients with advanced prostate cancer, Provenge may be appropriate before chemotherapy, thereby increasing the window of time before chemotherapy is needed. Both Drs. Vogelzang and Crawford indicated that prolonging the time to chemotherapy for patients in this setting would be a welcome option for clinicians and patients alike.

If approved, the initial indication for Provenge would be to follow chemotherapy. But Provenge is also being investigated for early-stage prostate cancer with different endpoints than those used for late-stage disease. Phase II studies indicate that Provenge may lead to improved PSA doubling time, which may predict a progression to metastatic disease and time-to-death among men with early disease.

Dr. Vogelzang said, “Provenge may fit even better into earlier stage prostate cancer, perhaps in men who have had surgery and radiotherapy, to delay the need for hormone



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therapy if the clinical data demonstrates prolongation of life and no detriment to delaying hormone therapy.” He acknowledges challenges to studying Provenge and other agents in the early prostate cancer setting, including the need for longer studies to demonstrate survival benefit.

With regard to the use of Provenge in earlier stage prostate cancer, Dr. Crawford believes that immunotherapy works best when the tumor burden is low. “There is optimism that Provenge and other active immunotherapies will perform well in these patients.” He added that if the data support its use in early-stage patients, Provenge could compete heavily with hormone therapy.

As hormone therapy use has become more widespread and is used earlier in the treatment paradigm, data have accrued documenting associated risks, including impotence and weight gain, both of which are anticipated effects with anti-androgen therapy, as well as effects that were not expected, such as diabetes and heart problems. As a result, he said, “hormone therapy has lost some of its luster, and the opportunity exists for newer therapies to enter the armamentarium.”

#### **Hurdles to Commercialization and Adoption**

Manufacturing and production of active immunotherapies, especially personalized products like Provenge, have represented a significant hurdle to its commercialization in the past. Dendreon reports that its proprietary technology platform has allowed the company to move past these challenges and is prepared for the commercial-scale production of Provenge. **cont. on pg 38 >>**

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“Because we are currently building up commercial and manufacturing infrastructure for the technology platform used for Provenge, it gives us scalability to invest in other targets that use the same platform, such as with Neuvence. The approval of Provenge will also give us the necessary cash flow to invest in our pipeline,” said Dr. Gold.

According to Dr. Vogelzang, it appears that Dendreon has been able to successfully streamline the production process. He does not anticipate that the time required for leukapheresis and production of patient-specific immunotherapy will be a barrier to acceptance among his peers. “Adoption will depend on the familiarity of the treating physician as well as the patient’s own desire to avoid chemotherapy,” he said.

One issue that might arise, however, is which member of the healthcare team might prescribe and administer the product, as patients transition from a radiation oncologist or urologist to a medical oncologist for chemotherapy over the course of their treatment.

In the coming years, another prostate cancer immunotherapy product could enter the market, albeit one with a different mechanism of action. Cell Genesys reports that they intend to develop and manufacture GVAX®, a non-patient-specific product made from genetically-modified prostate cancer cell lines, as an “off-the-shelf product” to be used after hormonal therapy in the advanced prostate cancer setting. Phase I and II trials have been completed.

Dr. Vogelzang said that if GVAX and Provenge are approved, the two products would not necessarily compete with one another as they have complementary mechanisms of action—GVAX is broadly antigenic, while Provenge is specific to PAP.

Both Drs. Vogelzang and Crawford said they were encouraged by the potential for two immunotherapies with potentially complementary mechanisms of action, and that the two investigational products may not be mutually exclusive in their use. They both commented that immunotherapy products in this setting may ultimately be considered “disease stabilizers” that can extend survival and offer patients and clinicians more options.

Dendreon does not foresee a problem with reimbursement once Provenge is approved; however, there is some speculation that due to its anticipated cost, third-party payers may require use strictly according to its labeled indication.

### The Investment Perspective

Dendreon’s stock, which has been an up and down story since the company went public several years ago, rose nearly 5 percent on the positive regulatory news in January (see Figure 3).

“Products such as Provenge could bring about a paradigm shift in how we treat cancer,” said Charles C. Duncan, PhD, Managing Director and Senior Analyst, Biotechnology, for JMP Securities.

“I used to be a bear on Dendreon, however, now I am a bull...Dendreon was able to demonstrate something that had previously never been shown in hormone-refractory prostate cancer patients, which is a survival benefit of 4-6 months,” he said.

Another reason Dr. Duncan remains bullish on Dendreon is in part because the stock is cheap. At press time, Dendreon was trading in the low \$4 range. “Dendreon’s stock price is low which makes it more attractive. While the risk is big, I believe that the upside is worth it,” he said, admitting that it is possible that the FDA ultimately may produce an analysis which discredits the conclusions of the current Phase III studies.

Looking to the PDUFA in May, Dr. Duncan speculates that the most likely outcome is an approvable letter from the FDA, while full approval or outright rejection are clearly less likely outcomes, but they’re possible.

According to Dr. Duncan, many analysts believe that Provenge won’t be approved until 2010. This is based on projections that the FDA will wait for the outcome of a recently begun 3-year trial (for which Dendreon has a Special Protocols Assessment [SPA]). If the interim analy-

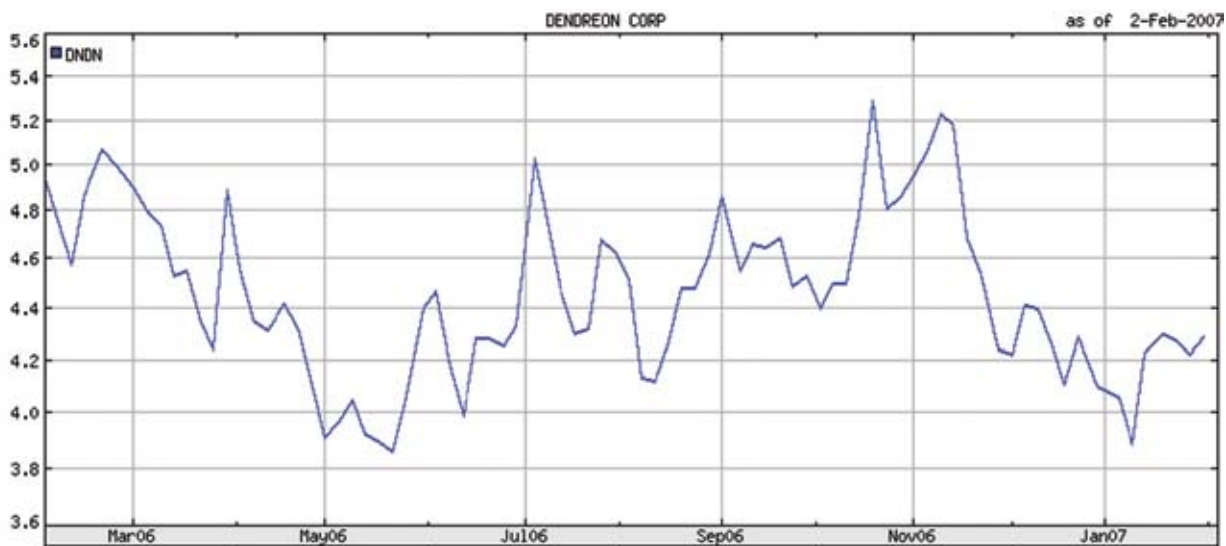


FIGURE 3. Source: www.finance.yahoo.com

“I used to be a bear on Dendreon, however, now I am a bull...”

sis of this trial shows a positive trend, it might be enough for approval in 2008. However, the stock is currently priced as if the product will be approved in 2010, not 2008; therefore, the stock is worth double where it currently is. “The data set currently reported by Dendreon requires the imagination and optimism of the investor,” said Dr. Duncan.

At present, Dr. Duncan says the more optimistic bears in the market say they believe that Provenge will be approved eventually, but not until completion of the Phase III trials, while the pessimists say Provenge is an active immunotherapy and it will never work. “Both of these investor segments are delaying the time for revenues which is holding down the stock price,” he said. He also postulated that the reason the stock price has not moved is in part due to external factors and the widespread evaporation of the tolerance of risk in the biotech market as a whole.

He anticipates market challenges consistent with any newly-launched drug class or new product; however, he is quick to note that oncologists tend to be more experimental and ultimately interested in providing the best care possible for their patients. “If the clinical studies hold up, this product offers 4 months of survival in a late-stage population and it could confer even longer sur-

vival benefit in an earlier stage population. With that in mind, what is the downside risk for the oncologist?” he asked.

### Concluding Thoughts

The next 2 years are expected to be crucial to the development and commercial viability, of active cancer immunotherapies. Dendreon’s approval for Provenge could come this year, although it’s important to note that an expedited review does not guarantee a rapid approval and their product will face the same scrutiny of any seeking clearance to market. Dendreon’s success, or failure, will have considerable implications in the broader immunotherapy market and could help determine the fate of a whole host of other biotech companies with cancer immunotherapies in development. **MNF**

