

ImproveHealthCare.org

Drug Development and Regulation: The Case of Provenge

Case Author

Akash Chandawarkar,
Harvard Medical School, MS II

Mentor

Arthur Daemrich
Assistant Professor, Harvard Business School

November 2010



Part I: From Bench to Bedside

In 2009, 27,360 patients died due to prostate cancer in the United States.¹ Additionally, a staggering 192,280 new cases of prostate cancer were diagnosed in the US that year. Surgery or radiation therapy is commonly used to cure localized prostate cancer. However, this disease recurs in 20%–30% of patients, who will then require hormone (androgen deprivation) therapy. Most of these patients have metastases to distant sites.² The goal of androgen deprivation therapy, either by surgical castration or administration of anti-androgenic hormones, is to reduce the level of male androgens. Androgens are normally produced in the testicles and stimulate prostate cancer cells to grow. Lowering the androgen levels can make these cancers shrink or grow more slowly but does not cure prostate cancer.³ Eventually, the disease progresses and androgen deprivation therapy fails; patients at this stage are termed castration-resistant.

Men with metastatic castration-resistant prostate cancer have a median survival between 12.2 and 21.7 months.⁴ Therapies for these patients are largely limited to cytotoxic chemotherapy, secondary androgen deprivation therapy, and palliative radiation therapy. The only of these treatments to improve patient survival is docetaxel, a cytotoxic therapy approved in 2004.^{5,6}

In the face of the devastating prognosis for patients with castration-resistant prostate cancer, novel approaches to extend survival were needed. Immunotherapy was able to enter this void in prostate cancer treatment strategies based on early studies from 1997 in which Stanford researchers were able to induce a cellular immune response against human prostatic acid phosphatase (PAP) in male rats.⁷ Because PAP is uniquely expressed in prostatic tissue, this basic science advancement provided the seeds for specific immunotherapy against prostate cancer.

Dendreon Corporation submitted a biologics license application (BLA) to the FDA in 2006 after creating sipuleucel-T, an autologous cellular immunotherapy based on the original findings almost a decade prior.⁸ Sipuleucel-T first involves harvesting a patient's peripheral blood. Mononuclear cells are extracted and cultured with a chimeric protein that consists of granulocyte-macrophage colony-stimulating factor (GM-CSF) and PAP. The GM-CSF component activates antigen presentation, while the PAP serves as the tumor-associated antigen. The resulting antigen-pulsed antigen-presenting cells (APCs) are infused back into the patient. Patients are treated these infusions three times—once every two weeks—for complete treatment.⁹

A randomized, double-blind, placebo-controlled, Phase 3 clinical trial (D9902B) completed in 2009 that eventually led to FDA approval reported a median survival of 25.8 months in the sipuleucel-T group as compared to 21.7 months in the placebo group.¹⁰ The control group received infusions of autologous mononuclear cells retrieved from the patient's peripheral blood that were not cultured with the chimeric protein. The researchers found that the survival improvement came without antitumor effect, measured by the level of prostate-specific antigen (PSA), computed tomography, and bone scans.¹¹

The 4.1-month survival improvement, along with previously reported Phase III studies presented by Dendreon Corporation, led to FDA approval of sipuleucel-T under the proprietary name of Provenge on April 29, 2010. The approval indicated Provenge “for the

treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer.”¹²

Discussion Questions

- How does a finding go from publication to clinical trial to marketed drug?
- What type of placebo group should be used in human clinical trials?
- How long should it take from preclinical discovery to having widespread clinical impact? How do you weigh patient safety with clinical urgency?

Part II: FDA Approval Delays

Despite the landmark scientific advancement in 1997, it took 13 years for FDA approval of Provenge. Why was this delay so long?

Shortly after the initial scientific findings, Dendreon Corporation began developing sipuleucel-T and ran a Phase III study (D9901) starting in November 1999.¹³ This was a three-year study of 127 men with androgen-independent prostate cancer. The company first submitted preliminary evidence to the FDA in 2002 with the hope of receiving a BLA to sell the treatment. The vaccine did not meet statistical significance for the initial endpoint of time-to-disease progression; however, it did for overall survival.¹⁴ Because overall survival was not a pre-specified endpoint and was discovered during retrospective analyses, the FDA deemed the results as insufficient proof of effectiveness.¹⁵ Therefore, Dendreon was asked to complete a new trial.

In 2005, Dendreon reported the results of another Phase III clinical trial (D9902A) that enrolled an additional 98 patients for three years, with outcome measures of both time to disease progression and overall survival.¹⁶ Additionally, Dendreon followed the time-to-disease progression of patients from D9901 for another 2.5 years. The integrated results of the two trials demonstrated a significant survival benefit of 4.5 months compared to placebo.¹⁷

The patients from the initial D9901 trial did not show significant benefits at first, but a subgroup of them did—those with a less aggressive form of prostate cancer.¹⁸ This likely occurred because patients with further progressed cancer have depleted immune systems. Because Provenge's mechanism of action utilizes the host immune system, a shorter-term trial with these patients would unlikely yield statistically favorable results. However, after following them for a longer period of time, all the patients in the trial showed significantly better time-to-disease progression.¹⁹

With these promising results, the FDA accepted Dendreon's BLA filing for Provenge in January 2007, with an FDA decision due by May 2007.²⁰ Prior to the decision date, on March 29, 2007, the FDA Office of Cellular, Tissue and Gene Therapies Advisory Committee voted 17-0 that Provenge is reasonably safe and 13-4 that the trial data showed substantial evidence that it is effective.²¹

Approval seemed imminent, as the FDA approval committee almost always sides with the recommendations of the advisory committee. However, those in the voting minority launched a campaign against those in the majority accusing them of incompetence regarding statistical matters with these cancer products. According to a May 14, 2007 *Wall Street Journal* article, these prominent members of the oncology community sent strong letters of disapproval to the FDA, which largely overlooked the possibility that the survival data from immunotherapy-based products may need to be judged by different criteria than survival data from standard chemotherapy drugs.²² As a result, on May 9, 2007, the FDA sent Dendreon a euphemistic “approvable” letter, which meant that the product would not be approved at this time and Dendreon would need to complete more testing. Many proponents of immunotherapy and patients diagnosed with hormone refractory prostate cancer labeled this day as “Black Wednesday,” as the promising Provenge vaccine likely

would be delayed for years while testing was completed, and that was only if Dendreon decided not to kill the drug altogether, as they would need to approach investors for another financing round.

Dendreon undertook a third and much larger Phase III trial (D9902B, described in Part I), known as the IMPACT (Immunotherapy for Prostate AdenoCarcinoma Treatment) study,²³ which aimed to include about 500 hormone refractory prostate cancer patients to confirm previous results found in D9901 and D9902A. On April 14, 2009, Dendreon announced that results of the IMPACT study were positive and eventually released the full results at the American Urological Association meeting on April 28, 2009.²⁴

The trial found that, similar to previous studies, patients treated with Provenge lived 4.1 months longer than patients treated with the control, which were infusions of autologous cells without the GM-CSF/PAP chimeric protein.²⁵ This increased survival was statistically significant, and Dendreon submitted an amendment to their BLA in November 2009.²⁶

On April 29, 2010, almost one year after the IMPACT study results were announced and three years after the FDA Advisory Committee voted in favor of Provenge, the FDA approved Provenge for use in the treatment of asymptomatic or minimally symptomatic hormone-resistant metastatic prostate cancer.²⁷

Discussion Questions

- What check points are used in FDA-based drug approval?
- How should retrospective analysis be treated in clinical trials? What biases can enter a study whose endpoints are determined after data analysis?
- How should the FDA balance approval speed and drug safety? Should May 9, 2007 be considered “Black Wednesday”? Could prostate cancer patients have been saved in the three years from Black Wednesday to approval?
- What conflicts of interest exist in the FDA drug-approval process? Which ones were at play in the approval of Provenge?
- How do drug companies get funding for clinical trials?

Part III: Distribution after Approval

Prior to approval, Wall Street analysts predicted that the Provenge price would average around \$62,000 per patient.²⁸ However, Dendreon announced on the day of approval that it would charge significantly more: \$93,000 per patient, which is \$31,000 per infusion.²⁹ Dendreon's chief operating officer (COO), Hans Bishop, explained that their pricing equation assumed that people would be willing to pay about \$23,000 per extra month of life.³⁰ He claimed this was comparable to other cancer therapeutics for terminal patients. Bishop benchmarked Provenge against competitors, such as Sanofi-Aventis's docetaxel (Taxotere), whose treatment costs about \$60,000 per patient when factoring cost of supportive care and hospital expenses. Because Dendreon's drug had been shown to help people live longer and does not have significant associated side effects that traditional chemotherapy does, Bishop claimed that their "price compares favorably to other cancer drugs."³¹ To help patients who cannot afford the drug, Dendreon planned to donate some undisclosed amounts of money to a nonprofit foundation that will help patients make copayments for treatments.³²

The chief executive officer (CEO) of Dendreon, Mitchell Gold, feels optimistic about the future of health insurance reimbursements. Private insurers, such as Aetna, Humana, Kaiser, and a majority of local Medicare contractors said they would pay for Provenge. The Centers for Medicare and Medicaid Services are also reviewing Provenge reimbursements.³³

Additionally, Dendreon is relying solely on one plant in New Jersey that is operating at one-fourth of its full capacity,³⁴ therefore it has been difficult for Dendreon to meet demand for the vaccine. Dendreon will only be able to supply 2,000 patients during Provenge's first 12 months on the market.³⁵ This represents only 2% of the patients who are medically qualified to receive the therapy—the expected demand.³⁶ By August, physicians had already written 500 prescriptions, which left 1,500 prescriptions available until April.³⁷ Dendreon hopes to have two more factories in addition to the New Jersey plant working at full capacity to increase supply, enabling the company to sell between \$1.2–\$2.5 billion worth of Provenge per year.³⁸

Despite Dendreon's plans to ramp up production, patients are anxious to get their hands on the rare supply of treatment, especially because many of them have poor prognoses and short life expectancies. Soon after approval, Dendreon limited Provenge orders to the 50 medical centers in the US that had experience with using it during clinical trials.³⁹ Dendreon will not establish a waiting list for Provenge; they are leaving that decision to the hospitals and doctors. Hospitals are having difficulty figuring out how to ration the drug.⁴⁰ Some hospitals are using similar principles as for high-demand organ transplants, while others are giving priority to those patients that can fully pay for the complete treatment plan. For example, Duke University's Comprehensive Cancer Center and University of Texas's MD Anderson Cancer Center use differing rationing strategies. After severity qualifications are considered, Duke will give the drug in the order in which patients sign up, while MD Anderson will use a random lottery system.⁴¹ However, MD Anderson will give priority to patients who have previously enrolled in clinical trials, while Duke will not. Similarly, other hospitals are trying to develop protocols to fairly, ethically, and efficiently distribute the rare Provenge therapy until production increases in 2011.

Discussion Questions

- Why are the prices for drugs so expensive? What can be done to reduce the costs of drugs? Would drug cost-cutting occur at the expense of patient safety from expensive clinical trials?
- How does Provenge's patient-specific production limit the ability for them to create a sufficient supply to meet their demand?
- What is the best way to ration a rare drug? Whose responsibility should it be to decide who gets the drug and who does not? By what criteria should patients be prioritized to receive Provenge and other rare drugs?
- Are drug companies responsible for producing a sufficient supply of drugs? How can this be regulated by the government/FDA?

¹ Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. *CA Cancer J Clin*. 2009;59:225-249.

² Ward JF, Moul JW. Rising prostate-specific antigen after primary prostate cancer therapy. *Nature Clinical Practice Urology*, 2005;2:174-82.

³ Detailed Guide: Prostate Cancer: Hormone (Androgen Deprivation) Therapy. American Cancer Society, 2010. (Accessed at http://getyourscreentest.com/docroot/CRI/content/CRI_2_4_4X_Androgen_Suppression_Hormone_Therapy_36.asp.)

⁴ Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med* 2010;363:411-22.

⁵ Petrylak DP, Tangen CM, Hussain MH, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N Engl J Med* 2004;351:1513-20.

⁶ Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med* 2004;351:1502-12.

⁷ Fong L, Ruegg CL, Brockstedt D, Engleman EG, Laus R. Induction of tissue-specific autoimmune prostatitis with prostatic acid phosphatase immunization: implications for immunotherapy of prostate cancer. *J Immunol* 1997;159:3113-7.

⁸ Finn T. Summary Basis for Regulatory Action – Provenge. Food and Drug Administration Supporting Documents, 2010.

⁹ Longo DL. New Therapies for Castration-Resistant Prostate Cancer. *N Engl J Med* 2010;363:479-81.

¹⁰ Kantoff, Higano, Shore, et al.

¹¹ Ibid.

¹² Finn.

¹³ National Cancer Institute/Dendreon. Vaccine Therapy in Treating Patients With Metastatic Prostate Cancer That Has Not Responded to Hormone Therapy. NCT00005947. *ClinicalTrials.gov*, 2009. (Accessed at <http://clinicaltrials.gov/ct2/show/NCT00005947?term=D9901&rank=1>.)

¹⁴ Small EJ, Schelhammer PF, Higano CS, 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;24:3089-94.

¹⁵ Finn.

¹⁶ National Cancer Institute/Dendreon. Immunotherapy With APC8015 (Sipuleucel-T, Provenge) for Asymptomatic, Metastatic, Hormone-Refractory Prostate Cancer. NCT01133704. *ClinicalTrials.gov*, 2010. (Accessed at <http://clinicaltrials.gov/ct2/show/NCT01133704?term=D9902A&rank=1>.)

-
- ¹⁷ Higano CS, Schellhammer PF, Small EJ, Burch PA, Nemunaitis J, Yuh L, Provost N, Frohlich MW. 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.
- ¹⁸ Small, Schellhammer, Higano, et al.
- ¹⁹ Gottlieb S. Prostate Drug Promise vs. FDA Rigidity. *Forbes.com*, Feb 18, 2005. (Accessed at http://www.forbes.com/2005/02/18/cz_sg_0218soapbox_inl.html.)
- ²⁰ Feuerstein, A. Dendreon's Date With Destiny. *TheStreet.com*, Mar 15, 2007. (Accessed at <http://www.thestreet.com/newsanalysis/biotech/10343101.html>.)
- ²¹ US Panel: Dendreon cancer therapy appears to work. *Reuters*, March 29, 2007. (Accessed at <http://www.reuters.com/article/idUSN2723384020070329>.)
- ²² Thornton, M. Black Wednesday at the FDA. *The Wall Street Journal*, May 14, 2007; p A16. (Accessed at <http://www.zerocancer.org/site/News2?page=NewsArticle&id=7867>.)
- ²³ Kantoff, Higano, Shore, et al.
- ²⁴ Summary of Phase 3 IMPACT Trial Results Presented at AUA Meeting. Webcast Conference Call. Dendreon, 2009. (Accessed at <http://phx.corporate-ir.net/External.File?item=UGFyZW50SUQ9MjE5NzgxMHx0aGlsZElEPTM3NzI4NnxUeXBIPTI=&t=1>.)
- ²⁵ Kantoff, et al.
- ²⁶ Dendreon Reports PROVENGE Regulatory and Commercialization Progress and Future Pipeline Plans at Analyst Event. Dendreon, 2009. (Accessed at <http://investor.dendreon.com/phoenix.zhtml?c=120739&p=iro-newsArticle&ID=1368891&highlight> .)
- ²⁷ Finn.
- ²⁸ Timmerman L. Dendreon's Big Question: How Much Will People Pay for Provenge. *Xconomy Seattle*, Apr 14, 2010. (Accessed at <http://www.xconomy.com/seattle/2010/04/14/dendreons-big-question-how-much-will-people-pay-for-provenge/>.)
- ²⁹ Timmerman L. Dendreon Sets Provenge Price at \$93,000, Says Only 2,000 People Will Get it in First Year. *Xconomy Seattle*, Apr 29, 2010. (Accessed at <http://www.xconomy.com/seattle/2010/04/29/dendreon-sets-provenge-price-at-93000-says-only-2000-people-will-get-it-in-first-year/>.)
- ³⁰ Timmerman. Dendreon Sets Provenge Price at \$93,000.
- ³¹ Ibid.
- ³² Ibid.
- ³³ Staton, T. Provenge scrips hit 500 as payers agree to pay. *FiercePharma*, Aug 4, 2010. (Accessed at <http://www.fiercepharma.com/story/provenge-scrips-hit-500-payers-agree-pay/2010-08-04>.)
- ³⁴ Timmerman. Dendreon Sets Provenge Price at \$93,000.
- ³⁵ Staton.
- ³⁶ Hobson K. The Provenge Dilemma: Who Gets Dendreon's New Therapy? *Wall Street Journal Health Blog*, Jun 28, 2010. (Accessed at <http://blogs.wsj.com/health/2010/06/28/the-provenge-dilemma-who-gets-dendreons-new-therapy/>.)
- ³⁷ Staton.
- ³⁸ Timmerman L. Dendreon Sets Provenge Price at \$93,000.
- ³⁹ Ibid.
- ⁴⁰ Randall T. Prostate Cancer Patients Face Yearlong Rationing of Provenge. *Bloomberg News*, Jun 28, 2010 Jun 28. (Accessed at <http://www.bloomberg.com/news/2010-06-28/prostate-cancer-patients-face-year-of-rationing-for-dendreon-s-new-vaccine.html>.)
- ⁴¹ Ibid.