CLINICAL BRIEFS

Immunotherapy for Advanced Prostate Cancer: A Novel Treatment Option to Improve Survival

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With a commentary for managed care decision makers by
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Immunotherapy for Advanced Prostate Cancer: A Novel Treatment Option to Improve Survival

Prostate cancer is the second leading cause of cancer death in men in the United States. Novel immunotherapies are being investigated to improve survival in patients with advanced disease. Sipuleucel-T (PROVENGE®), the first autologous cellular immunotherapy approved by the U. S. Food and Drug Administration, improves survival in men with asymptomatic or minimally symptomatic metastatic castration-resistant (hormone refractory) prostate cancer.

The high probability of progression to fatal metastasis in men with advanced prostate cancer treated with androgen deprivation therapy (ADT) has generated extensive research to identify novel therapies that can induce an antitumor response in castration-resistant patients (Alam 2010, Basler 2007, Drake 2010, Higano 2009, Sowery 2007, Vieweg 2007). In April 2010, the U.S. Food and Drug Administration approved sipuleucel-T (PROVENGE®) — the first autologous cellular immunotherapy for patients with asymptomatic or minimally symptomatic metastatic castration-resistant (hormone refractory) prostate cancer (CRPC) (FDA 2010) — thus opening the way for a breakthrough treatment approach to improve survival in men with this disease.

Epidemiology

In the United States, prostate cancer is the most common type of cancer among men and the second leading cause of cancer death in men (Jemal 2009). According to the American Cancer Society, an estimated 240,890 new cases of prostate cancer will be diagnosed in 2011, and 33,720 men will die from the disease (ACS 2011a). The National Cancer Institute's SEER data from 1975 to 2008 indicate that approximately 1 in 6 men alive today will be diagnosed with prostate cancer during their lifetime (ACS 2011b, NCI 2011), and more than 2 million men with a history of prostate cancer are still alive (Howlader 2011, Skolarus 2010). Between 1999 and 2006, the 5-year survival rate for men with localized prostate cancer was 100 percent, whereas the survival rate for men with advanced (metastatic) disease was only 28.8 percent (Howlader 2011).

Prostate cancer is associated with significant economic and societal burdens, accounting for almost $10 billion in total medical expenditures, and costs are expected to rise with the aging population and more advanced treatment modalities and technologies (Figure 1, page 4). Because prostate cancer has a longer survival compared with other types of cancers, expenditures are greatest during the continuing phase of care (period between the initial phase and last year-of-life phase)(Figure 1). Approximately 60 percent of total prostate cancer cost consists of out-of-pocket costs and the indirect costs of lost productivity, time and resources spent by caregivers, and premature death (Jayadevappa 2010).

The incidence of prostate cancer and the proportion of men under 70 years of age diagnosed with this disease have also increased, due in part to earlier screening with the prostate-specific antigen (PSA) assay now widely used in clinical practice (Damber 2008, Patel 2008, Penson 2008). Before the era of PSA testing, approximately 1 percent of men with newly diagnosed prostate cancer were under age 50 (Ward 2005). Today, 1.8 percent of newly diagnosed men are between the ages of 45 and 54 years (Howlader 2011), which increases the potential for disease recurrence (Ward 2005).

Patients with prostate cancer are always at risk of recurrence following definitive therapy, and there is no point at which they may be considered "cured." Life-long follow-up, therefore, is an important part of disease management.

Risk factors

The exact cause of prostate cancer is unknown. Researchers, however, have found several risk factors for the development of this disease. Advanced age is the strongest risk factor, with 2 out of 3 prostate cancers occurring in men over 65 years old (ACS 2011a, Shen 2010). African-American men have a higher incidence and mortality rate compared with Caucasian and Hispanic men, and African-American men are more likely to be diagnosed at an advanced stage of prostate cancer compared with other ethnic groups (ACS 2011a, ACS 2011b, Howlader 2011). Other risk factors include genetics, diet, obesity, inflammation, and infection, although none of these factors has been confirmed by research studies. A recent study of Vietnam War veterans exposed to Agent Orange has shown a twofold increased risk of developing prostate cancer (Chamie 2008).

Natural history

Most prostate cancers grow very slowly (Kawachi 2010). More than 99 percent of prostate cancers develop from the gland cells; hence, prostate cancer is primarily an adenocarcinoma (ACS 2011b, Shen 2010). Prostatic intraepithelial neoplasia (PIN), characterized by a reduction in basal cells, is most likely a precursor to prostate cancer in which basal cells are absent (Shen 2010). PIN can appear in men as early as 20 years of age, and almost half of all men have PIN by the time they reach age 50 (ACS 2011b). Proliferative inflammatory atrophy and atypical small acinar proliferation are believed to be two other types of precancerous conditions

(ACS 2011b). Clinical prostate cancer may develop from latent prostate cancer foci with critical activating events, or from lack of active suppression, or from other pathogenic processes (Shen 2010). If prostate cancer metastasizes, it is usually to the bone, and this is largely responsible for the effect on patient morbidity and mortality (Shen 2010); however, the molecular factors that promote metastasis of prostate cancer to bone are not well known (Shen 2010).

Diagnosis and current treatment

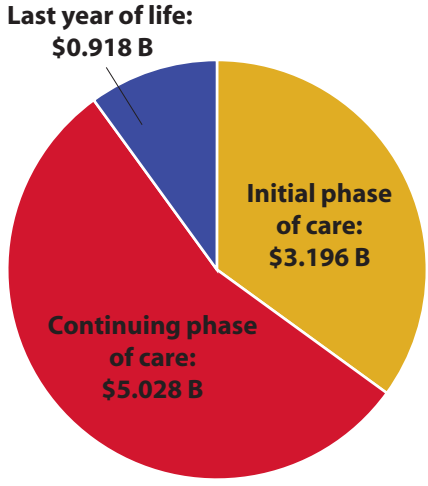
Men with early clinically localized prostate cancer are typically asymptomatic, and their cancer is often discovered by serum PSA testing and/or digital rectal examination. Patients with more advanced prostate cancer may present with symptoms such as urinary obstruction, bleeding, hematospermia, and bone pain (Kawachi 2010). If symptoms or elevated PSA levels suggest prostate cancer, then a biopsy should be performed (Kawachi 2010).

More than 90 percent of new cases of prostate cancer are diagnosed at the local or regional stage and are associated with a 5-year survival rate of 100 percent (Howlader 2011). Deaths due to prostate cancer tend to occur after a period of metastatic disease (Kawachi 2010), and the median survival range is 12.2 to 21.7 months (Carducci 2007, Kantoff 2010, Saad 2002, Sternberg 2009).

Early-stage prostate cancer. Surgery (prostatectomy) is the primary method of treatment for men with early-stage prostate cancer who are in good health (NCI 2005). Radical prostatectomy and radiation therapy (external beam radiation or brachytherapy) are also considered appropriate therapy for localized prostate cancer (Crawford 2010, Mohler 2010) or when surgery is contraindicated because of age, health, or personal choice (Crawford 2010, Mohler 2010, NCI 2005). In early prostate cancer, when the tumor is large, hormone therapy may be used in combination with other treatments, such as radiation therapy, to slow the tumor's growth and is also a viable treatment option after surgery fails (NCI 2005). Some men who undergo radiation treatment will require hormone therapy or prostatectomy within 5 years (NCI 2005).

FIGURE 1
Economic and societal impact of prostate cancer

Total U. S. medical expenditures: **~$10 Billion**



60% of total costs = out-of-pocket costs and costs of caregiving, lost productivity, and premature death

Sources: Jayadevappa 2010, NCI 2010

Metastatic CRPC. Advanced prostate cancer has been traditionally defined as metastasis to bone at presentation. That definition has now been expanded to include biochemical relapse, as indicated by increasing PSA levels, after local therapy has failed (Sowery 2007). About 1 in 5 newly diagnosed men with prostate cancer will move beyond the localized stage (Howlader 2011). The most common treatment for metastatic disease is androgen deprivation therapy (ADT) by either surgical castration (bilateral orchiectomy) or medical castration with a luteinizing hormone-releasing hormone (LHRH) agonist, both of which are equally effective in reducing tumor burden and/or circulating PSA to low or undetectable levels (Mohler 2010, Shen 2010, Sowery 2007). Despite androgen deprivation, however, almost all patients with prostate cancer will develop progressive disease, and their cancer will metastasize to distant sites (Di Lorenzo 2010, Higano 2009, Shen 2010).

Combined androgen blockade (CAB) — the addition of nonsteroidal anti-androgens, such as bicalutamide or flutamide, to surgical castration or medical castration by LHRH agonists — is another treatment option, either as initial therapy or after ADT has failed. CAB, however, offers only a modest survival advantage over castration alone (Sowery 2007). Similarly, secondary hormonal therapies such as adrenal androgen inhibitors, e.g., ketoconazole and hydrocortisone (Kantoff 1999), and other agents, e.g., cyproterone acetate or megestrol (Sowery 2007), have not shown a survival benefit.

Metastatic CRPC is considered incurable, with median survival ranging from 12.2 to 21.7 months in clinical trials (Carducci 2007, Kantoff 2010, Saad 2002, Sternberg 2009). Randomized studies have shown that mitoxantrone-based chemotherapy has a palliative effect but no survival benefit (Kantoff 2010, Tannock 1996). Although cytotoxic chemotherapy was long thought to have little clinical value in men with metastatic CRPC, two clinical trials (Petrylak 2004, Tannock 2004) showed a survival benefit with docetaxel. These studies led the FDA to approve docetaxel plus prednisone for the treatment of metastatic disease (Sowery 2007).

Please see safety information on page 7 and accompanying Full Prescribing Information.

Managed Care Considerations

A New Era of Advanced Prostate Cancer Management

By Roger Muller, MD, FACEP, Market Medical Director, Pacific Northwest, UnitedHealth Group

The management of prostate cancer can be thought of as a war on two fronts. The first front is early detection and diagnosis, underscored by the 100 percent 5-year survival rate for men with diagnosed, localized prostate cancer (Howlader 2011). The second front is better management of advanced disease. For men with metastatic prostate cancer, the 5-year survival rate is 28.8 percent (Howlader 2011), and metastatic castration-resistant prostate cancer (CRPC) is ultimately fatal. There are few treatment options and, historically, these have been either toxic, of limited efficacy, or both (Di Lorenzo 2010, Patel 2008).

Roger Muller, MD, FACEP

The emergence of sipuleucel-T (Provenge) is a milestone in the treatment of men with advanced prostate cancer and raises hope for the better care of men with this disease. It offers a novel pathway — immunotherapy (Kantoff 2010). Sipuleucel-T is made from a patient's white blood cells to stimulate the patient's immune system against the cancer and is manufactured for each patient individually.

As with any new treatment modality, identifying appropriate candidates for therapy is vital for developing medical policy.

The National Coverage Determination

On June 30, 2011, the Centers for Medicare and Medicaid Services issued a National Coverage Determination (NCD) for the use of sipuleucel-T in patients with asymptomatic or minimally symptomatic metastatic CRPC (CMS 2011). The NCD clarifies reimbursement for the therapy and states that "sipuleucel-T improves health outcomes" and "thus is reasonable and necessary" for the appropriate patients.

Sipuleucel-T also obtained a new HCPCS code, Q2043, which replaces the old C9273 code. This new Q code allows for electronic claims submission and stronger collection of patient data. In addition, the NCD also provides new ICD-9 codes for filing claims. Please review the ICD-9 codes shown on **page 9** of this brief.

The NCD will help third-party payers develop medical policies that are consistent with the new therapeutic platform that immunotherapy offers.

Moving forward

In managed care, we encourage further development of this platform. Can we get to a point where immunologic response technology improves time to progression, brings even greater survival rates, and reduces cytotoxicity in patients who are treated for metastatic CRPC? New research is continually warranted to address this question.

We must also remain mindful that both the pace of technological advance and our aging population complicate healthcare cost trends. In prostate cancer, 18 percent of tumors are diagnosed when they have spread beyond the local stage (NCI 2011).

Earlier detection reduces the overall cost of treating prostate cancer and allows for the judicious and fair use of emerging technologies, such as immunotherapy, that can improve the lives of men with advanced disease.

References

CMS (Centers for Medicare and Medicaid Services). Decision Memo for Autologous Cellular Immunity Treatment of Metastatic Prostatic Cancer (CAG-00422N). June 30, 2011. http://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=247&ver=12&NcaName=Autologous+Cellular+Immunotherapy+Treatment of Metastatic Prostate Cancer. Accessed Aug. 29, 2011.

Di Lorenzo G, Buonerba C, Autorino R, et al. Castration-resistant prostate cancer: current and emerging treatment strategies. *Drugs*. 2010;70(8):983–1000.

Howlader N, Noone AM, Krapcho M, et al, eds. SEER Cancer Statistics Review, 1975–2008. Bethesda, MD: National Cancer Institute. http://seer.cancer.gov/csr/1975_2008/; based on November 2010 SEER data submission; posted to the SEER Web site in 2011.

Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med*. 2010;363:411–422.

NCI (National Cancer Institute). Surveillance Epidemiology and End Results. SEER stat fact sheets: prostate. http://seer.cancer.gov/statfacts/html/prost.html. Accessed Aug. 29, 2011.

Patel PH, Kockler DR. Sipuleucel-T: a vaccine for metastatic, asymptomatic, androgen-independent prostate cancer. *Ann Pharmacother*. 2008;42(1):91–98.

Note: *This commentary reflects the opinions of the author and not necessarily those of UnitedHealth Group.*

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In the first trial (Tannock 2004), docetaxel given every 3 weeks, 10 cycles of treatment, extended median survival by 2.4 months compared with mitoxantrone plus prednisone, providing median survival of approximately 19 months. Similarly, in the second trial (Petrylak 2004), docetaxel plus estramustine provided a median survival benefit of only 1.9 months over mitoxantrone plus prednisone. Additionally, docetaxel was associated with adverse effects, such as neutropenia, infection, fatigue, anemia, and neuropathy (Patel 2008).

In June 2010, the FDA approved cabazitaxel (Jevtana) in combination with prednisone as second-line therapy for patients with metastatic CRPC who have been treated with a docetaxel-based regimen. After 10 cycles of treatment, cabazitaxel-based therapy showed a median survival benefit of 2.4 months compared with mitoxantrone plus prednisone, providing median survival of approximately 15 months (Jevtana 2010).

Thus, although modest progress has been made in treating metastatic CRPC, more targeted therapies are needed to improve the prognosis in men with this disease. One promising targeted approach is immunotherapy.

Immunotherapy: a novel targeted therapy approach

Immunotherapy is a form of biologic treatment that uses therapeutic vaccines derived from cells in a patient's own immune system to induce an antitumor response (Doehn 2008). This approach delays or stops malignant growth by targeting tumor-associated antigens (TAAs) or by disrupting molecular pathways that promote tumor growth (Drake 2010, Vieweg 2007). With advances in molecular technologies, researchers have been able to identify antibodies and circulating T cells against TAAs. Their findings indicate that tolerance to these antigens can be broken and that an immune response against a tumor can be induced (Alam 2010, Houghton 1994).

Vaccines have been used to prevent infectious diseases, such as smallpox, for more than 200 years. Their clinical efficacy centers on their ability to stimulate a protective immune response against target antigens expressed by the infectious organism while sparing antigens expressed by the host's own cells. In the setting of cancer, this prophylactic approach has been applied successfully against malignancies that are caused by infectious agents, such as hepatocellular carcinoma (associated with hepatitis B infection).

Cancer immunotherapy differs from preventive approaches in that the therapy stimulates a patient's own immune system to rein in or destroy a cancerous tumor and is used primarily in advanced or metastatic malignancies (Vieweg 2007). Several factors make prostate cancer a rational target for immunotherapy:

- Prostate cancer is generally a slowly progressive disease, allowing ample time for an immunotherapy to induce and potentiate T-cell-mediated immunity against the tumor (Sowery 2007).
- Because of their low proliferative index, many prostate cancers are resistant to cytotoxic chemotherapy. Immunotherapy does not depend on high cell proliferation and may be targeted against any gene product expressed by prostate cancer cells (Vieweg 2007).
- The prostate gland is predisposed to various inflammatory conditions that may be related to autoimmunity or that may result from infection. Since the body can produce an immune response when prostate tissue is affected by nonmalignant pathologic conditions, it is reasonable to assume that cell-mediated immune responses also may be mounted to suppress tumor progression in prostate cancer (Sowery 2007).
- The prostate is a relatively nonessential organ; therefore, the development of autoimmunity against prostate-specific TAAs would not be expected to have significant immunologic consequences for the host (Sowery 2007).

The known circulating prostate-specific TAAs offer numerous potential targets for immunotherapy (Vieweg 2007). These antigens include PSA, prostatic acid phosphatase (PAP), and prostate-specific membrane antigen (PSMA) (Drake 2010).

Immunologic data indicate that evolving tumors provoke the proliferation of T cells with anticancer potential; however, these cells remain dormant or nonfunctional in the absence of a triggering intervention (Drake 2010). The primary goal of cancer immunotherapy, therefore, is to activate effector T cells that can then migrate to developing tumors and mediate the destruction of individual cancer cells. One way of doing this is to load a specific antigen onto antigen-presenting cells (APCs) ex vivo (Drake 2010). In the immune system, dendritic cells (DCs), a potent type of APC, prime T cells to attack and destroy invading antigens (Valone 2001).

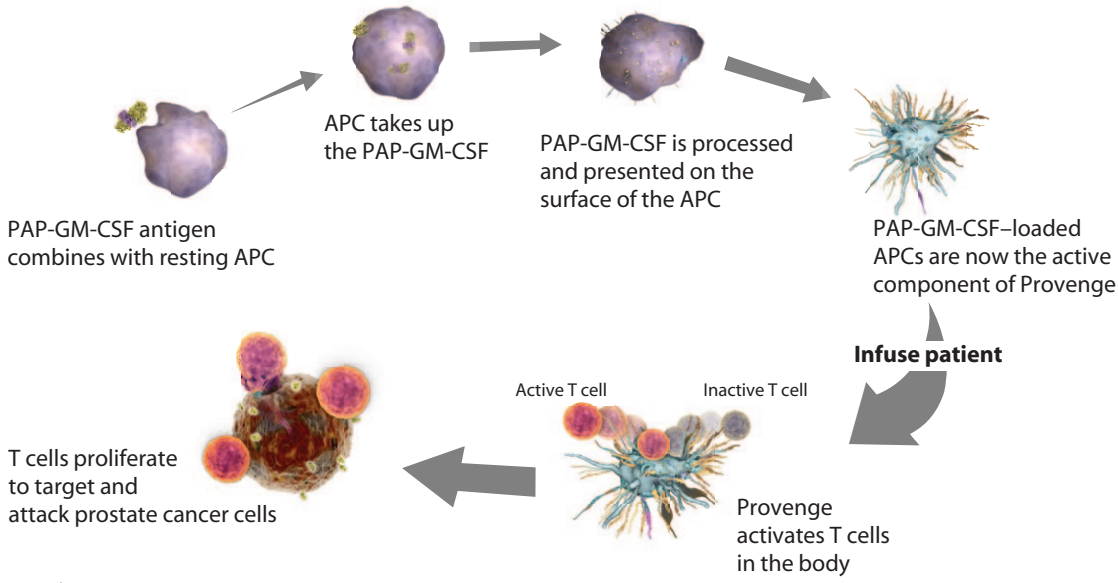
Other immunotherapies are also undergoing clinical trials for the treatment of advanced prostate cancer. These include GVAX, composed of allogeneic prostate tumor cells that have been genetically engineered to secrete granulocyte-macrophage colony-stimulating factor (GM-CSF); DCVax-Prostate, which consists of autologous, monocyte-derived DCs that have been "loaded" with a recombinant form of PSMA; and PROSTVAC-VF, a recombinant vaccinia viral-expression cassette engineered to contain a copy of the human PSA gene as well as several costimulatory molecules (Vieweg 2007).

Sipuleucel-T

Sipuleucel-T (Provenge) is the first in a new class of cancer immunotherapeutic agents to be approved by the FDA for the treatment of asymptomatic or minimally symptomatic metastatic CRPC. **Please see important safety infor-**

Please see safety information on page 7 and accompanying Full Prescribing Information.

FIGURE 2
Sipuleucel-T: mechanism of action



Source: Dendreon Corporation

mation on Page 7 and accompanying Full Prescribing Information.

Sipuleucel-T, which is custom manufactured for each patient, consists of the patient's autologous peripheral-blood mononuclear cells (PBMCs), including APCs, that have been activated during a defined culture period with a recombinant human protein, PAP-GM-CSF, consisting of PAP, an antigen expressed in prostate cancer tissue, linked to GM-CSF, an immune-cell activator. PAP is expressed in approximately 95 percent of all prostate cancers and is limited mostly to prostate tissue (Higano 2009, Patel 2008). The patient's PBMCs are obtained via a standard leukapheresis procedure approximately 3 days before the infusion date.

The active components of sipuleucel-T are autologous APCs and PAP-GM-CSF. During ex vivo culture, the recombinant antigen binds to and is processed by APCs into smaller protein fragments, or peptides, which are then displayed on the APCs' surfaces (Figure 2). Because sipuleucel-T is made ex vivo, it offers the potential benefit of enhanced APC activation as a result of removing the cells from the immunosuppressive environment of the patient (Higano 2009, Kalinski 2009). Activating APCs ex vivo facilitates in vivo and ex vivo priming of T cells (Sheikh 2010, Wesley 2010), which is evidenced by increased APC and T-cell activation markers and by ex vivo production of T-cell activation-associated cytokines after the first infusion of sipuleucel-T.

IMPORTANT SAFETY INFORMATION

PROVENGE is intended solely for autologous use and is not routinely tested for transmissible infectious diseases.

In controlled clinical trials, serious adverse events reported in the PROVENGE group include acute infusion reactions (occurring within 1 day of infusion) and cerebrovascular events. Severe (Grade 3) acute infusion reactions were reported in 3.5% of patients in the PROVENGE group. Reactions included chills, fever, fatigue, asthenia, dyspnea, hypoxia, bronchospasm, dizziness, headache, hypertension, muscle ache, nausea, and vomiting. No Grade 4 or 5 acute infusion reactions were reported in patients in the PROVENGE group.

The most common adverse events (incidence ≥15%) reported in the PROVENGE group are chills, fatigue, fever, back pain, nausea, joint ache, and headache.

Please see the accompanying Full Prescribing Information.

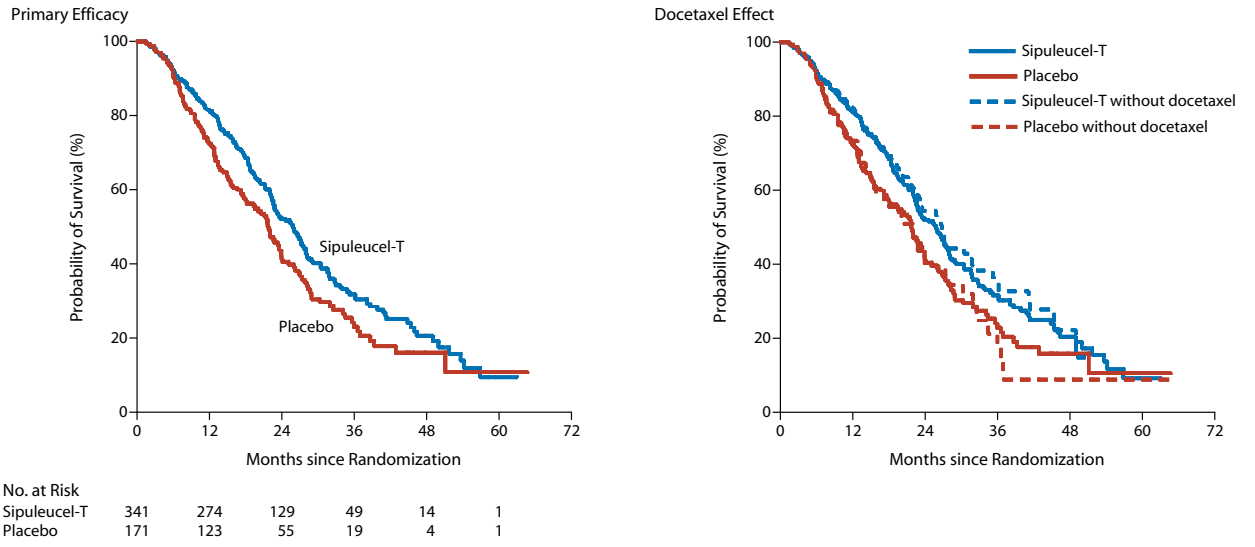
Overall survival: clinical trial data

The FDA considers overall survival to be the gold standard for assessing the clinical benefit of oncology drugs. The pivotal clinical study of sipuleucel-T was the phase 3, multicenter, randomized, double-blind IMmuno-therapy for Prostate AdenoCarcinoma Treatment (IMPACT) trial (Kantoff 2010).

In the IMPACT trial, 512 men with metastatic castration-resistant prostate cancer and an expected survival of at least 6 months were randomized to receive either sipuleucel-T (n=341) or placebo (n=171) administered intravenously every 2 weeks for a total of 3 infusions. The patients'

FIGURE 3

Kaplan-Meier estimates of overall survival (primary efficacy endpoint) with sipuleucel-T versus placebo in the IMPACT trial



No. at Risk

Sipuleucel-T	341	274	129	49	14	1
Placebo	171	123	55	19	4	1

The adjusted hazard ratio for death was 0.78 in the sipuleucel-T group versus the placebo group (P=0.03).
Source: Kantoff 2010. Reproduced with permission.

median age was 71 years. All patients had received previous ADT. The primary endpoint was overall survival, defined as the time from randomization until death from any cause. The median follow-up period was 34.1 months.

The results of the IMPACT trial (Figure 3) indicated that the sipuleucel-T group had a median survival period of 25.8 months vs. 21.7 months in the control group (4.1 months longer). The estimated 36-month survival probability was 31.7 percent for sipuleucel-T compared with 23.0 percent for placebo. The times to objective disease progression were similar in the two groups: 3.7 months for sipuleucel-T vs. 3.6 months for placebo; P=0.63. After treatment, 195 patients (57.2 percent) in the sipuleucel-T group and 86 patients (50.3 percent) in the placebo group received docetaxel. In these patients, the estimated effect of treatment with sipuleucel-T (hazard ratio [HR] for death, 0.78; 95% CI, 0.61 to 0.98; P=0.03) was consistent with the result of the primary efficacy analysis (Kantoff 2010).

Adverse events that were more frequently reported in the sipuleucel-T group by a factor of 2 or more than in the placebo group were chills (54.1 percent vs. 12.5 percent, respectively), fever (29.3 percent vs. 13.7 percent), headache (16.0 percent vs. 4.8 percent), influenza-like illness (9.8 percent vs. 3.6 percent), myalgia (9.8 percent vs. 4.8 percent), hypertension (7.4 percent vs. 3.0 percent), hyperhidrosis (5.3 percent vs. 0.6 percent), and groin pain (5.0 percent vs. 2.4 percent). With the exception of groin pain, most of these events occurred within 1 day after infusion, resolved within 1 to 2 days, and were generally consistent with the release of cytokines (Kantoff 2010). Serious adverse events were reported in 24.0 percent of patients in the sipuleucel-T group and 25.1 percent of patients in the control group. Serious adverse events in the sipuleucel-T group included acute infusion reactions and cerebrovascular events (Provenge 2011).

The investigators concluded that sipuleucel-T provided a significant improvement in overall survival in men with metastatic CRPC (Kantoff 2010). Infusion-related adverse events were mainly Grade 1 or Grade 2 in severity. Treatment with sipuleucel-T had a consistently positive effect on survival across multiple patient subgroups, and the treatment effect remained consistent after adjusting for subsequent docetaxel use and timing (Kantoff 2010).

Although a statistically significant difference in time to progression (TTP) was not demonstrated between the sipuleucel-T group and the control group in the IMPACT study, a statistically significant difference in overall survival — the study's primary endpoint — was evident (Kantoff 2010).

Two additional studies have shown an extended overall survival in men with asymptomatic or minimally symptomatic metastatic CRPC. Results of Study D9901, a phase 3, randomized, double-blind, placebo-controlled trial (N=127), indicated a reduction of 41 percent in the risk of death in the sipuleucel-T group compared with the control group (unadjusted HR, 0.586; 95% CI, 0.388 to 0.884; P=0.010) (Provenge 2011). Median survival in the sipuleucel-T group was 4.5 months longer than in the control group (Higano 2009, Small 2006). Moreover, the 36-month survival probability

Please see safety information on page 7 and accompanying Full Prescribing Information.

Listing of ICD-9 codes for the submission of claims relating to the use of sipuleucel-T

Sipuleucel-T is used as an autologous cellular immunotherapy treatment of metastatic prostate cancer in chemotherapy-naïve patients. For claims with dates of service on and after July 1, 2011, for sipuleucel-T (Provenge®), the on-label indication of asymptomatic or minimally symptomatic metastatic, castrate-resistant (hormone refractory) prostate cancer must be billed using ICD-9 code 185 (malignant neoplasm of prostate) and at least one of the ICD-9 codes shown below.

Note: Effective for claims on or after July 1, 2011, all claims must include HCPCS code Q2043 **AND** ICD-9 code 185 **AND** at least one diagnosis code from the ICD-9 listing (BR 7431-04.2).

ICD-9-CM Diagnosis Codes	Description
185	Malignant neoplasm of prostate
196.1	Secondary and unspecified malignant neoplasm of intrathoracic lymph nodes
196.2	Secondary and unspecified malignant neoplasm of intra-abdominal lymph nodes
196.5	Secondary and unspecified malignant neoplasm of lymph nodes of inguinal region and lower limb
196.6	Secondary and unspecified malignant neoplasm of intrapelvic lymph nodes
196.8	Secondary and unspecified malignant neoplasm of lymph nodes of multiple sites
196.9	Secondary and unspecified malignant neoplasm of lymph node site unspecified – The spread of cancer to and establishment in the lymph nodes.
197.0	Secondary malignant neoplasm of lung – Cancer that has spread from the original (primary) tumor to the lung. The spread of cancer to the lung. This may be from a primary lung cancer, or from a cancer at a distant site.
197.7	Malignant neoplasm of liver secondary – Cancer that has spread from the original (primary) tumor to the liver. A malignant neoplasm that has spread to the liver from another (primary) anatomic site. Such malignant neoplasms may be carcinomas (e.g., breast, colon), lymphomas, melanomas, or sarcomas.
198.0	Secondary malignant neoplasm of kidney – The spread of the cancer to the kidney. This may be from a primary kidney cancer involving the opposite kidney, or from a cancer at a distant site.
198.1	Secondary malignant neoplasm of other urinary organs
198.5	Secondary malignant neoplasm of bone and bone marrow – Cancer that has spread from the original (primary) tumor to the bone. The spread of a malignant neoplasm from a primary site to the skeletal system. The majority of metastatic neoplasms to the bone are carcinomas.
198.7	Secondary malignant neoplasm of adrenal gland
198.82	Secondary malignant neoplasm of genital organs

Source: CMS 2011b

was greater in the sipuleucel-T group versus the control group (34 percent vs. 11 percent, respectively) (Small 2006).

In Study D9902A, a phase 3, randomized, double-blind, placebo-controlled, multicenter trial (N=98), patients given sipuleucel-T showed a reduction of 21 percent in the risk of death compared with the control group (unadjusted HR, 0.786; 95% CI, 0.484 to 1.278; *P*=0.33) (Dendreon 2011). Median survival in the sipuleucel-T group was 3.3 months longer than in the control group (Higano 2009). Similarly, the 36-month survival probability was greater for sipuleucel-T than for the control group (31.6 percent vs. 21.2 percent, respectively) (Higano 2010).

Sipuleucel-T and CMS coverage

On June 30, 2011, the Centers for Medicare and Medicaid Services released a National Coverage Determination (NCD) that clarifies the reimbursement of sipuleucel-T for Medicare beneficiaries (CMS 2011a).

The NCD states that the evidence for the administration of sipuleucel-T is "adequate to conclude that the use of autologous cellular immunotherapy treatment — sipuleucel-T; PROVENGE® improves health outcomes for Medicare beneficiaries with asymptomatic or minimally symptomatic metastatic castrate-resistant (hormone refractory) prostate cancer, and thus is reasonable and necessary for that indication under 1862(a)(1)(A) of the Social Security Act." Further, Medicare will fully cover the use of sipuleucel-T at ASP+ 6 percent per course of treatment (CMS 2011a).

CMS also stipulates how claims should be coded. All claims must include the HCPCS code Q2043, the ICD-9 code 185 (malignant neoplasm of prostate), and at least one of the ICD-9 codes in the sequence ICD 196.1 to 198.82 (CMS 2011b). See the complete listing of the ICD-9 codes on this page.

Conclusion

Sipuleucel-T, the first autologous cellular immunotherapy for asymptomatic or minimally symptomatic metastatic CRPC to win FDA approval, is designed to stimulate a

patient's own immune system to target prostate cancer cells. With their ability to target cancer cells, immunotherapies such as sipuleucel-T offer improved survival in men with asymptomatic or minimally symptomatic metastatic CRPC.

Disclosures

Steven R. Peskin, MD, MBA, FACP, reports no financial arrangements or affiliations that may constitute a conflict of interest with respect to companies, organizations, or proprietary products mentioned in this Clinical Brief.

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References

ACS (American Cancer Society). Cancer Facts and Figures 2011. Atlanta: American Cancer Society. http://www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-029771.pdf cancer. Accessed Aug. 29, 2011a.

ACS (American Cancer Society). Prostate cancer. http://www.cancer.org/Cancer/ProstateCancer/DetailedGuide/index. Accessed Aug. 29, 2011b.

Alam S, McNeel DG. DNA vaccines for the treatment of prostate cancer. *Expert Rev Vaccines.* 2010;9:731–745.

Basler M, Groettrup M. Advances in prostate cancer immunotherapies. *Drugs Aging.* 2007;24:197–221.

Carducci MA, Saad F, Abrahamsson PA, et al. A phase 3 randomized controlled trial of the efficacy and safety of atrasentan in men with metastatic hormone-refractory prostate cancer. *Cancer.* 2007;110(9):1959–1966.

Chamie K, DeVere White RW, Lee D, et al. Agent Orange exposure, Vietnam War veterans, and the risk of prostate cancer. *Cancer.* 2008;113:2464–2470.

CMS (Centers for Medicare and Medicaid Services). Decision Memo for Autologous Cellular Immunity Treatment of Metastatic Prostatic Cancer (CAG-00422N). June 30, 2011a. http://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=247&ver=12&NcaName=Autologous+Cellular+Immunotherapy+Treatment of Metastatic Prostate Cancer. Accessed Aug. 29, 2011.

CMS (Centers for Medicare and Medicaid Services). CMS Manual System, Pub 100-04 Medicare Claims Processing. July 8, 2011b. https://www.cms.gov/transmittals/downloads/R2254CP.pdf. Accessed Aug. 29, 2011.

Crawford ED, Black L, Eaddy M, Kruep EJ. A retrospective analysis illustrating the substantial clinical and economic burden of prostate cancer. *Prostate Cancer Prostatic Dis.* 2010;13(2):162–167.

Damber JE, Aus G. Prostate cancer. *Lancet.* 2008;371(9625):1710–1721.

Dendreon Corporation. Data on file. Seattle: Dendreon Corp; 2011.

Di Lorenzo G, Buonerba C, Autorino R, et al. Castration-resistant prostate cancer: current and emerging treatment strategies. *Drugs.* 2010;70(8):983–1000.

Doehn C, Bohmer T, Kausch I, et al. Prostate cancer vaccines: current status and future potential. *BioDrugs.* 2008;22(2):71–84.

Drake CG. Prostate cancer as a model for tumour immunotherapy. *Nature Rev Immunol.* 2010;10:580–593.

FDA (US Food and Drug Administration). FDA Approves a cellular immunotherapy for men with advanced prostate cancer [press release]. Washington, DC: US Food and Drug Admininstration; April 29, 2010. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm210174.html. Accessed Aug. 29, 2011.

Higano CS, Schellhammer PF, Small EJ, 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;115:3670–3679.

Higano CS, Small EJ, Schellhammer PF, et al. Survival consistency in study subpopulations and predictors of outcome from the integrated analysis of sipuleucel-T trials in metastatic castration resistant prostate cancer [poster]. Presented at the 2010 American Society of Clinical Oncology (ASCO) Annual Meeting; June 4–8, 2010; Chicago.

Houghton AN. Cancer antigens: immune recognition of self and altered self. *J Exp Med.* 1994;180:1–4.

Howlader N, Noone AM, Krapcho M, et al, eds. SEER Cancer Statistics Review, 1975–2008. Bethesda, MD: National Cancer Institute. http://seer.cancer.gov/csr/1975_2008/; based on November 2010 SEER data submission; posted to the SEER Web site in 2011.

Jayadevappa R, Schwartz JS, Chatre S, et al. The burden of out-of-pocket and indirect costs of prostate cancer. *Prostate.* 2010;70(11):1255–1264.

Jemal A, Siegel R, Ward E, et al. Cancer statistics 2009. *CA Cancer J Clin.* 2009;59:225–249.

Jevtana (cabazitaxel) Injection [prescribing information]. Bridgewater, NJ: Sanofi-aventis US; June 2010.

Kalinski P, Urban J, Narang R, et al. Dendritic cell-based therapeutic cancer vaccines: what we have and what we need. *Future Oncol.* 2009;5:379–390.

Kantoff PW, Halabi S, Conaway M, et al. Hydrocortisone with or without mitoxantrone in men with hormone-refractory prostate cancer: results of the cancer and leukemia group B 9182 study. *J Clin Oncol.* 1999;17:2506–2513.

Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med.* 2010;363:411–422.

Kawachi MH, Bahnson RR, Barry M, et al. NCCN clinical practice guidelines in oncology: prostate cancer early detection. *J NCCN.* 2010;8:240–262.

Mohler J, Bahnson RR, Boston B, et al. NCCN clinical practice guidelines in oncology: prostate cancer. *J NCCN.* 2010;8:162–200.

NCI (National Cancer Institute). Treatment choices for men with early-stage prostate cancer. Bethesda, MD: National Cancer Institute, National Institutes of Health, US Dept of Health and Human Services; 2005. http://www.cancer.gov/cancertopics/treatment/prostate/understanding-prostate-cancer-treatment/page1. Accessed Aug. 29, 2011.

NCI (National Cancer Institute). Cancer Trends Progress Report – 2009/2010 Update, National Cancer Institute. Bethesda, MD: National Institutes of Health, US Dept of Health and Human Services; April 2010. http://progressreport.cancer.gov. Accessed Aug. 29, 2011.

NCI (National Cancer Institute). Surveillance Epidemiology and End Results. SEER stat fact sheets: prostate. http://seer.cancer.gov/statfacts/html/prost.html. Accessed Aug. 29, 2011.

Patel PH, Kockler DR. Sipuleucel-T: a vaccine for metastatic, asymptomatic, androgen-independent prostate cancer. *Ann Pharmacother.* 2008;42(1):91–98.

Penson DF, Rossignol M, Sartor AO, et al. Prostate cancer: epidemiology and health-related quality of life. *Urology.* 2008;72(6 suppl):S3–11.

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;351:1513–1520.

Provenge (sipuleucel-T) [prescribing information]. Seattle: Dendreon Corporation; April 2011.

Saad F, Gleason DM, Murray R, et al. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. *J Natl Cancer Inst.* 2002;94:1458–1468.

Sheikh NA, dela Rosa C, Stewart FP, et al. Sipuleucel-T treatment results in sequential ex vivo activation of APCs and T cells during the culture step–evidence for in vivo immunological priming [poster]. Presented at the 2010 American Association for Cancer Research (AACR) 101st Annual Meeting; April 17–21, 2010; Washington, DC.

Shen MM, Abate-Shen C. Molecular genetics of prostate cancer: new prospects for old challenges. *Genes Dev.* 2010;24:1967–2000.

Please see safety information on page 7 and accompanying Full Prescribing Information.

Skolarus TA, Zhang Y, Miller DC, et al. The economic burden of prostate cancer survivorship care. *J Urol.* 2010;184:532–538.
Small EJ, Schellhammer 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;24:3089–3094.
Sowery RD, So AL, Gleave ME. Therapeutic options in advanced prostate cancer: present and future. *Curr Urol Rep.* 2007;8:53–59.
Sternberg CN, Petrylak DP, Sartor O, et al. Multinational, double-blind, phase III study of prednisone and either satraplatin or placebo in patients with castrate-refractory prostate cancer progressing after prior chemotherapy: the SPARC trial. *J Clin Oncol.* 2009;27:5431–5438.
Tannock IF, Osoba D, Stockler MR, et al. Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone-resistant prostate cancer: a Canadian randomized trial with palliative end points. *J Clin Oncol.* 1996;14:1756–1764.
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;351:1502–1512.
Valone FH, Small E, MacKenzie M, et al. Dendritic cell-based treatment of cancer: closing in on a cellular therapy. *Cancer J.* 2001;7(suppl 2):S53–S61.
Vieweg J. Immunotherapy for advanced prostate cancer. *Rev Immunol.* 2007;9:1:S29–S38.
Ward JF, Moul JW. Biochemical recurrence after definitive prostate cancer therapy, part I: defining and localizing biochemical recurrence of prostate cancer. *Curr Opin Urol.* 2005;15:181–186.
Wesley JD, Chadwick E, Kuan LY, et al. Characterization of antigen specific T-cell activation and cytokine expression induced by sipuleucel-T [poster]. Presented at the 2010 International Society for Biological Therapy of Cancer (iSBTc) Annual Meeting; Sept. 30–October 4, 2010; Washington, DC.

Dendreon®

P-A-08.11-151.00

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all of the information needed to use PROVENGE® (sipuleucel-T) safely and effectively. See full prescribing information for PROVENGE.

PROVENGE® (sipuleucel-T)
Suspension for Intravenous Infusion
Initial U.S. Approval: 2010

- - - - - - - INDICATIONS AND USAGE - - - - - - -

PROVENGE is an autologous cellular immunotherapy indicated for the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer. (1)

- - - - - DOSAGE AND ADMINISTRATION - - - -

- **For Autologous Use Only**.
- Administer 3 doses at approximately 2-week intervals. (2.1)
- Premedicate patients with oral acetaminophen and an antihistamine such as diphenhydramine. (2.2)
- Before infusion, confirm that the patient's identity matches the patient identifiers on the infusion bag. (2.6)
- **Do not initiate infusion of expired PROVENGE**. (2.7)
- Infuse PROVENGE intravenously over a period of approximately 60 minutes. **Do Not Use a Cell Filter.** (2.7)
- Interrupt or slow infusion for acute infusion reactions, depending on the severity of the reaction. (2.8)

- - - - DOSAGE FORMS AND STRENGTHS - - - -

Each dose of PROVENGE contains a minimum of 50 million autologous $CD54^+$ cells activated with PAP-GM-CSF, suspended in 250 mL of Lactated Ringer's Injection, USP in a sealed, patient-specific infusion bag. (3)

- - - - - - - - - CONTRAINDICATIONS - - - - - - - -

- None. (4)

- - - - - WARNINGS AND PRECAUTIONS - - - - -

- PROVENGE is intended solely for autologous use. (5)
- Acute infusion reactions have been observed in patients treated with PROVENGE. In the event of an acute infusion reaction, the infusion rate may be decreased, or the infusion stopped, depending on the severity of the reaction. Appropriate medical therapy should be administered as needed. Closely monitor patients with cardiac or pulmonary conditions. (2.8, 5.1)
- PROVENGE is **not** routinely tested for transmissible infectious diseases and may transmit diseases to health care professionals handling the product. Universal precautions should be followed. (2.3, 5.2)
- Concomitant use of chemotherapy and immunosuppressive medications with PROVENGE has not been studied. (5.3)

- - - - - - - - - ADVERSE REACTIONS - - - - - - - - -

- The most common adverse reactions (incidence $\geq$ 15%) are chills, fatigue, fever, back pain, nausea, joint ache, and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Dendreon Corporation at 1-877-336-3736 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revision date: June/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

PROVENGE® (sipuleucel-T) is an autologous cellular immunotherapy indicated for the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer.

2 DOSAGE AND ADMINISTRATION

For Autologous Use Only.

For Intravenous Use Only. Do Not Use a Cell Filter.

Do Not Initiate Infusion of Expired Product.

2.1 Dose and Schedule

Each dose of PROVENGE contains a minimum of 50 million autologous $CD54^+$ cells activated with PAP-GM-CSF [*see Description (11)*].

The recommended course of therapy for PROVENGE is 3 complete doses, given at approximately 2-week intervals. In controlled clinical trials, the median dosing interval between infusions was 2 weeks (range 1 to 15 weeks); the maximum dosing interval has not been established.

If, for any reason, the patient is unable to receive a scheduled infusion of PROVENGE, the patient will need to undergo an additional leukapheresis procedure if the course of treatment is to be continued. Patients should be advised of this possibility prior to initiating treatment.

2.2 Premedication

To minimize potential acute infusion reactions such as chills and/or fever, it is recommended that patients be premedicated orally with acetaminophen and an antihistamine such as diphenhydramine approximately 30 minutes prior to administration of PROVENGE [*see Warnings and Precautions (5.1)]*.

2.3 Handling Precautions for Control of Infectious Disease

PROVENGE is **not** routinely tested for transmissible infectious diseases. Therefore, patient leukapheresis material and PROVENGE may carry the risk of transmitting infectious diseases to health care professionals handling the product. Employ universal precautions in handling leukapheresis material or PROVENGE. [*See How Supplied/Storage and Handling (16).*]

2.4 Storage

The PROVENGE infusion bag must remain within the insulated polyurethane container until the time of administration. Do not remove the insulated polyurethane container from the outer cardboard shipping box. [*See How Supplied/Storage and Handling (16).*]

2.5 Confirm Product Release Before Infusion

Do not infuse PROVENGE until confirmation of product release has been received from Dendreon. Dendreon will send a cell product disposition form containing the patient identifiers, expiration date and time, and the disposition status (approved for infusion or rejected), to the infusion site. [*See How Supplied/Storage and Handling (16).*]

2.6 Preparation for Infusion

***See How Supplied/Storage and Handling (16)* for full handling instructions.**

Confirm Patient Identity

PROVENGE is intended solely for autologous use. Confirm the proper product has been received according to the label on the outside of the insulated polyurethane container. Prior to PROVENGE infusion, match the patient's identity with the patient identifiers on the cell product disposition form and the PROVENGE infusion bag.

Inspect the Infusion Bag

Remove the infusion bag from the insulated polyurethane container and inspect the bag for signs of leakage. Do not administer if the bag leaks.

Contents of the bag will be slightly cloudy, with a cream-to-pink color. Gently mix and re-suspend the contents of the bag, inspecting for clumps and clots. Small clumps of cellular material should disperse with gentle manual mixing. Do not administer if the bag leaks during handling or if clumps remain in the bag.

2.7 Administration

Infusion must begin prior to the expiration date and time indicated on the cell product disposition form and Product Label. **Do not initiate infusion of expired PROVENGE**.

Administer PROVENGE via intravenous infusion over a period of approximately 60 minutes. **Do not use a cell filter.** PROVENGE is supplied in a sealed, patient-specific infusion bag; the entire volume of the bag should be infused.

Observe the patient for at least 30 minutes following each infusion.

2.8 Administration Modification for Infusion Reactions

Acute infusion reactions such as chills, fatigue, fever, nausea, and joint ache were frequently observed in studies of PROVENGE. To mitigate such reactions, premedication, consisting

of acetaminophen and an antihistamine such as diphenhydramine, was administered in clinical studies prior to infusion.

In the event of an acute infusion reaction, the infusion may be interrupted or slowed, depending on the severity of the reaction. Appropriate medical therapy should be administered as needed. In controlled clinical trials, symptoms of acute infusion reactions were treated with acetaminophen, intravenous H1 and/or H2 blockers, and low dose intravenous meperidine.

If the infusion of PROVENGE must be interrupted, the infusion should not be resumed if the PROVENGE infusion bag will be held at room temperature for more than 3 hours. **[***See How Supplied/Storage and Handling (16).*]

3 Dosage Forms and Strengths

Each dose of PROVENGE contains a minimum of 50 million autologous $CD54^+$ cells activated with PAP-GM-CSF, suspended in 250 mL of Lactated Ringer's Injection, USP in a sealed, patient-specific infusion bag.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

PROVENGE is intended solely for autologous use.

5.1 Acute Infusion Reactions

Acute infusion reactions (reported within 1 day of infusion) included, but were not limited to, fever, chills, respiratory events (dyspnea, hypoxia, and bronchospasm), nausea, vomiting, fatigue, hypertension, and tachycardia. In controlled clinical trials, 71.2% of patients in the PROVENGE group developed an acute infusion reaction. The most common events ($\geq$ 20%) were chills, fever, and fatigue. In 95.1% of patients reporting acute infusion reactions, the events were mild or moderate. Fevers and chills generally resolved within 2 days (71.9% and 89.0%, respectively).

In controlled clinical trials, severe (Grade 3) acute infusion reactions were reported in 3.5% of patients in the PROVENGE group. Reactions included chills, fever, fatigue, asthenia, dyspnea, hypoxia, bronchospasm, dizziness, headache, hypertension, muscle ache, nausea, and vomiting. The incidence of severe events was greater following the second infusion (2.1% vs. 0.8% following the first infusion), and decreased to 1.3% following the third infusion. Some (1.2%) patients in the PROVENGE group were hospitalized within 1 day of infusion for management of acute infusion reactions. No Grade 4 or 5 acute infusion reactions were reported in patients in the PROVENGE group.

Closely monitor patients with cardiac or pulmonary conditions. In the event of an acute infusion reaction, the infusion rate may be decreased, or the infusion stopped, depending on the severity of the reaction. Appropriate medical therapy should be administered as needed. [*See Administration Modification for Infusion Reactions (2.8) and How Supplied/Storage and Handling (16).*]

5.2 Handling Precautions for Control of Infectious Disease

PROVENGE is **not** routinely tested for transmissible infectious diseases. Therefore, patient leukapheresis material and PROVENGE may carry the risk of transmitting infectious diseases to health care professionals handling the product. Accordingly, health care professionals should employ universal precautions when handling leukapheresis material or PROVENGE. **[***See How Supplied/Storage and Handling (16).*]

5.3 Concomitant Chemotherapy or Immunosuppressive Therapy

Use of either chemotherapy or immunosuppressive agents (such as systemic corticosteroids) given concurrently with the leukapheresis procedure or PROVENGE has not been studied. PROVENGE is designed to stimulate the immune system, and concurrent use of immunosuppressive agents may alter the efficacy and/or safety of PROVENGE. Therefore, patients should be carefully evaluated to determine whether it is medically appropriate to reduce or discontinue immunosuppressive agents prior to treatment with PROVENGE.

5.4 Product Safety Testing

PROVENGE is released for infusion based on the microbial and sterility results from several tests: microbial contamination determination by Gram stain, endotoxin content, and in-process sterility with a 2-day incubation to determine absence of microbial growth. The final (7-day incubation) sterility test results are not available at the time of infusion. If the sterility results become positive for microbial contamination after PROVENGE has been approved for infusion, Dendreon will notify the treating physician. Dendreon will attempt to identify the microorganism, perform antibiotic sensitivity testing on recovered microorganisms, and communicate the results to the treating physician. Dendreon may request additional information from the physician in order to determine the source of contamination.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety evaluation of PROVENGE is based on 601 prostate cancer patients in the PROVENGE group who underwent at least 1 leukapheresis procedure in four randomized, controlled clinical trials. The control was non-activated autologous peripheral blood mononuclear cells.

Almost all (98.3%) patients in the PROVENGE group and 96.0% in the control group reported an adverse event. The most common adverse events, reported in patients in the PROVENGE group at a rate ≥ 15%, were chills, fatigue, fever, back pain, nausea, joint ache, and headache. In 67.4% of patients in the PROVENGE group, these adverse events were mild or moderate in severity. Severe (Grade 3) and life-threatening (Grade 4) adverse events were reported in 23.6% and 4.0% of patients in the PROVENGE group compared with 25.1% and 3.3% of patients in the control group. Fatal (Grade 5) adverse events were reported in 3.3% of patients in the PROVENGE group compared with 3.6% of patients in the control group. The most common (≥ 2%) Grade 3-5 adverse events reported in the PROVENGE group were back pain and chills.

Serious adverse events were reported in 24.0% of patients in the PROVENGE group and 25.1% of patients in the control group. Serious adverse events in the PROVENGE group included acute infusion reactions [*see Warnings and Precautions (5.1)*], cerebrovascular events, and single case reports of eosinophilia, rhabdomyolysis, myasthenia gravis, myositis, and tumor flare.

PROVENGE was discontinued in 1.5% of patients in Study 1 due to adverse events. Some patients who required central venous catheters for treatment with PROVENGE developed infections, including sepsis. A small number of these patients discontinued treatment as a result. Monitoring for infectious sequelae in patients with central venous catheters is recommended.

Each dose of PROVENGE requires a standard leukapheresis procedure approximately 3 days prior to the infusion. Adverse events that were reported ≤ 1 day following a leukapheresis procedure in ≥ 5% of patients in controlled clinical trials included citrate toxicity (14.2%), oral paresthesia (12.6%), paresthesia (11.4%), and fatigue (8.3%).

Table 1 provides the frequency and severity of adverse events reported in ≥ 5% of patients in the PROVENGE group of randomized, controlled trials of men with prostate cancer. The population included 485 patients with metastatic castrate resistant prostate cancer and 116 patients with non-metastatic androgen dependent prostate cancer who were scheduled to receive 3 infusions of PROVENGE at approximately 2-week intervals. The population was age 40 to 91 years (median 70 years), and 90.6% of patients were Caucasian.

Table 1 Incidence of Adverse Events Occurring in ≥ 5% of Patients Randomized to PROVENGE

	PROVENGE (N = 601)		Control* (N = 303)	
	All Grades n (%)	Grade 3-5 n (%)	All Grades n (%)	Grade 3-5 n (%)
Any Adverse Event	591 (98.3)	186 (30.9)	291 (96.0)	97 (32.0)
Chills	319 (53.1)	13 (2.2)	33 (10.9)	0 (0.0)
Fatigue	247 (41.1)	6 (1.0)	105 (34.7)	4 (1.3)
Fever	188 (31.3)	6 (1.0)	29 (9.6)	3 (1.0)
Back pain	178 (29.6)	18 (3.0)	87 (28.7)	9 (3.0)
Nausea	129 (21.5)	3 (0.5)	45 (14.9)	0 (0.0)
Joint ache	118 (19.6)	11 (1.8)	62 (20.5)	5 (1.7)
Headache	109 (18.1)	4 (0.7)	20 (6.6)	0 (0.0)
Citrate toxicity	89 (14.8)	0 (0.0)	43 (14.2)	0 (0.0)
Paresthesia	85 (14.1)	1 (0.2)	43 (14.2)	0 (0.0)
Vomiting	80 (13.3)	2 (0.3)	23 (7.6)	0 (0.0)
Anemia	75 (12.5)	11 (1.8)	34 (11.2)	7 (2.3)
Constipation	74 (12.3)	1 (0.2)	40 (13.2)	3 (1.0)
Pain	74 (12.3)	7 (1.2)	20 (6.6)	3 (1.0)
Paresthesia oral	74 (12.3)	0 (0.0)	43 (14.2)	0 (0.0)
Pain in extremity	73 (12.1)	5 (0.8)	40 (13.2)	1 (0.3)
Dizziness	71 (11.8)	2 (0.3)	34 (11.2)	0 (0.0)
Muscle ache	71 (11.8)	3 (0.5)	17 (5.6)	0 (0.0)
Asthenia	65 (10.8)	6 (1.0)	20 (6.6)	2 (0.7)
Diarrhea	60 (10.0)	1 (0.2)	34 (11.2)	3 (1.0)
Influenza-like illness	58 (9.7)	0 (0.0)	11 (3.6)	0 (0.0)
Musculoskeletal pain	54 (9.0)	3 (0.5)	31 (10.2)	3 (1.0)
Dyspnea	52 (8.7)	11 (1.8)	14 (4.6)	3 (1.0)
Edema peripheral	50 (8.3)	1 (0.2)	31 (10.2)	1 (0.3)
Hot flush	49 (8.2)	2 (0.3)	29 (9.6)	1 (0.3)
Hematuria	46 (7.7)	6 (1.0)	18 (5.9)	3 (1.0)
Muscle spasms	46 (7.7)	2 (0.3)	17 (5.6)	0 (0.0)

	PROVENGE (N = 601)		Control* (N = 303)	
	All Grades n (%)	Grade 3-5 n (%)	All Grades n (%)	Grade 3-5 n (%)
Any Adverse Event	591 (98.3)	186 (30.9)	291 (96.0)	97 (32.0)
Hypertension	45 (7.5)	3 (0.5)	14 (4.6)	0 (0.0)
Anorexia	39 (6.5)	1 (0.2)	33 (10.9)	3 (1.0)
Bone pain	38 (6.3)	4 (0.7)	22 (7.3)	3 (1.0)
Upper respiratory tract infection	38 (6.3)	0 (0.0)	18 (5.9)	0 (0.0)
Insomnia	37 (6.2)	0 (0.0)	22 (7.3)	1 (0.3)
Musculoskeletal chest pain	36 (6.0)	2 (0.3)	23 (7.6)	2 (0.7)
Cough	35 (5.8)	0 (0.0)	17 (5.6)	0 (0.0)
Neck pain	34 (5.7)	3 (0.5)	14 (4.6)	2 (0.7)
Weight decreased	34 (5.7)	2 (0.3)	24 (7.9)	1 (0.3)
Urinary tract infection	33 (5.5)	1 (0.2)	18 (5.9)	2 (0.7)
Rash	31 (5.2)	0 (0.0)	10 (3.3)	0 (0.0)
Sweating	30 (5.0)	1 (0.2)	3 (1.0)	0 (0.0)
Tremor	30 (5.0)	0 (0.0)	9 (3.0)	0 (0.0)

* Control was non-activated autologous peripheral blood mononuclear cells.

Cerebrovascular Events

In controlled clinical trials, cerebrovascular events, including hemorrhagic and ischemic strokes, were observed in 3.5% of patients in the PROVENGE group compared with 2.6% of patients in the control group.

7 DRUG INTERACTIONS

No studies of drug interactions have been performed with PROVENGE.

8 USE IN SPECIFIC POPULATIONS

8.5 Geriatric

In controlled clinical trials, 72.9% of patients (438 of 601) in the PROVENGE group were ≥ 65 years of age. There were no apparent differences in the safety of PROVENGE between patients ≥ 65 years of age and younger patients.

In a survival analysis of the controlled clinical trials of PROVENGE in metastatic castrate resistant prostate cancer, 78.3% of randomized patients (382 of 488) were ≥ 65 years of age. The median survival of patients in the PROVENGE group ≥ 65 years of age was 23.4 months (95% confidence interval 22.0, 27.1), compared with 17.3 months in the control group (95% confidence interval: 13.5, 21.5).

8.6 Race

In controlled clinical trials, 90.6% of patients were Caucasian, 5.8% were African American, and 3.7% were "Other". Due to the low numbers of non-Caucasian patients in the trials, no conclusions can be made regarding the safety or efficacy of PROVENGE by race.

10 OVERDOSAGE

Each PROVENGE infusion comprises the maximum number of cells that can be manufactured from a single leukapheresis procedure. The number of cells in PROVENGE does not exceed the number of cells collected from the leukapheresis. There are no known instances of overdosage from either a single infusion or a full course of therapy with PROVENGE.

11 DESCRIPTION

PROVENGE consists of autologous peripheral blood mononuclear cells, including antigen presenting cells (APCs), that have been activated during a defined culture period with a recombinant human protein, PAP-GM-CSF, consisting of prostatic acid phosphatase (PAP), an antigen expressed in prostate cancer tissue, linked to granulocyte-macrophage colony-stimulating factor (GM-CSF), an immune cell activator. The patient's peripheral blood mononuclear cells are obtained via a standard leukapheresis procedure approximately 3 days prior to the infusion date. Due to the autologous nature of PROVENGE, it is important that the patient and physician adhere to the personalized leukapheresis and infusion schedules.

The active components of PROVENGE are autologous APCs and PAP-GM-CSF. During culture, the recombinant antigen can bind to and be processed by APCs into smaller protein fragments. The recombinant antigen is designed to target APCs, and may help direct the immune response to PAP. Minimal residual levels of the intact PAP-GM-CSF are detectable in the final PROVENGE product.

The cellular composition of PROVENGE is dependent on the composition of cells obtained from the patient's leukapheresis. In addition to APCs, the final product contains T cells, B cells, natural killer (NK) cells, and other cells. The number of cells present and the cellular composition of each PROVENGE dose will vary. Each dose of PROVENGE contains a minimum of 50 million autologous $CD54^+$ cells activated with PAP-GM-CSF, suspended in 250 mL of Lactated Ringer's Injection, USP.

The potency of PROVENGE is in part determined by measuring the increased expression of the CD54 molecule, also known as ICAM-1, on the surface of APCs after culture with PAP-GM-CSF. CD54 is a cell surface molecule that plays a role in the immunologic interactions between APCs and T cells, and is considered a marker of immune cell activation.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

PROVENGE is classified as an autologous cellular immunotherapy. While the precise mechanism of action is unknown, PROVENGE is designed to induce an immune response targeted against PAP, an antigen expressed in most prostate cancers. During ex vivo culture with PAP-GM-CSF, APCs take up and process the recombinant target antigen into small peptides that are then displayed on the APC surface.

In Study 1, 237 out of the 512 patients randomized were evaluated for the development of humoral and T cell immune responses (proliferative and gamma-interferon (γIFN) ELISPOT) to the target antigens at Baseline, and at Weeks 6, 14, and 26. Antibody (IgM and IgG) responses against PAP-GM-CSF and PAP antigen alone were observed through the follow-up period in the PROVENGE group. Neutralizing antibody responses to GM-CSF were transient. T cell proliferative and γIFN ELISPOT responses to PAP-GM-CSF fusion protein were observed in cells collected from peripheral blood of patients through the follow-up period in the PROVENGE treatment group but not in controls. In some patients a response to PAP antigen alone was observed. No conclusions could be made regarding the clinical significance of the observed immune responses.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity or mutagenicity studies of PROVENGE in animals were conducted. No studies on the effects of PROVENGE on fertility have been conducted.

14 CLINICAL STUDIES

The effect of PROVENGE on patients with metastatic castrate resistant (hormone refractory) prostate cancer was studied in three similar randomized, double-blind, placebo-controlled, multicenter trials. Following randomization, patients from both treatment groups underwent a series of 3 leukapheresis procedures (at approximately Weeks 0, 2, and 4). Each leukapheresis was followed approximately 3 days later by infusion of PROVENGE or control. The control was autologous peripheral blood mononuclear cells that had not been activated [*see Description (11*)]. Following disease progression, patients were treated at the physician's discretion with other anti-cancer interventions.

Study 1

Study 1 was a randomized, double-blind, placebo-controlled, multicenter trial in patients with asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer. Eligible patients had metastatic disease in the soft tissue and/or bone with evidence of progression either at these sites or by serial Prostate Specific Antigen (PSA) measurements. Exclusion criteria included visceral (liver, lung, or brain) metastases, moderate to severe prostate cancer-related pain, and use of narcotics for cancer-related pain.

A total of 512 patients were randomized in a 2:1 ratio to receive PROVENGE (n=341) or control (n=171). The median age was 71, and 90% of the patients were Caucasian. Thirty-five percent of patients had undergone radical prostatectomy, 54% had received local radiotherapy, and 82% had received combined androgen blockade. All patients had baseline testosterone levels < 50 ng/mL. Forty-eight percent of patients were receiving bisphosphonates and 18% had received prior chemotherapy, including docetaxel. Eighty-two percent of patients had an ECOG performance status of 0; 58% had primary Gleason scores of four or more; 44% had bone and soft tissue disease; 48% had bone-only disease; 7% had soft tissue-only disease; and 43% had greater than ten bony metastases.

Supportive Studies

Study 2 was a randomized, double-blind, placebo-controlled, multicenter trial in patients with metastatic castrate resistant prostate cancer and no cancer-related pain. The primary endpoint was time to disease progression; analysis of the primary endpoint did not reach statistical significance. All patients were to be followed for survival; however, the survival analysis was not pre-specified. A third study, similar in design to Study 2, was terminated prior to completion of planned accrual.

Summary of Study Results

Figure 1 and Table 2 present overall survival results observed in two randomized, Phase 3 studies of PROVENGE in men with metastatic castrate resistant prostate cancer. The survival findings were consistent across multiple subgroups. Analyses of time to disease progression did not meet statistical significance in any Phase 3 study of PROVENGE.

Figure 1 Kaplan-Meier Overall Survival Curve for Study 1

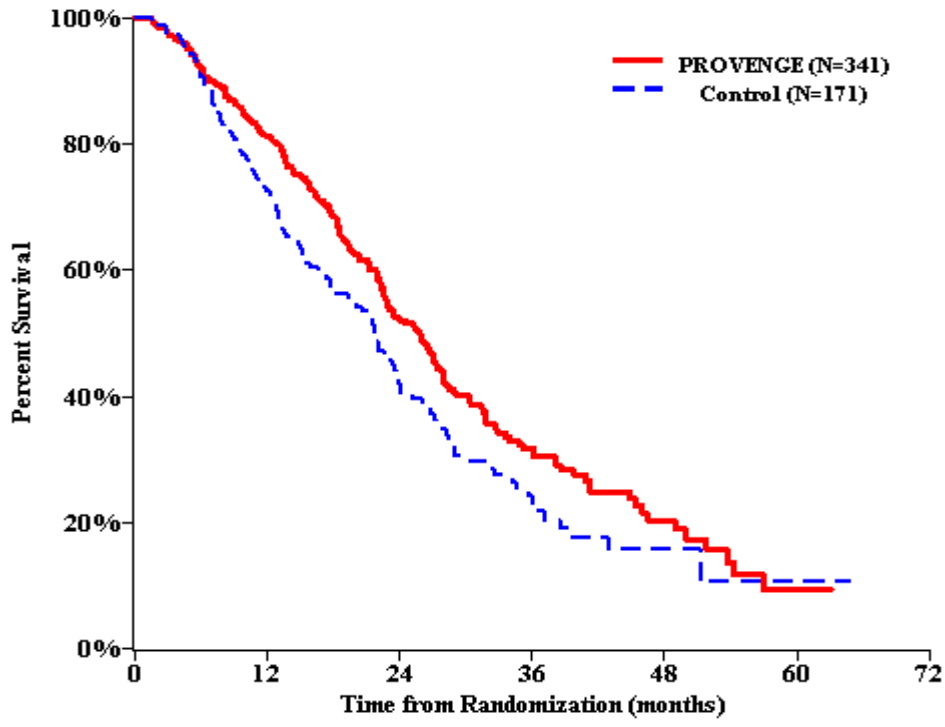

Table 2 Summary of Overall Survival (All Patients as Randomized)

	Study 1		Study 2	
	PROVENGE (N=341)	Control (N=171)	PROVENGE (N=82)	Control (N=45)
Overall Survival				
Median, months (95% CI)	25.8 (22.8, 27.7)	21.7 (17.7, 23.8)	25.9 (20.0, 32.4)	21.4 (12.3, 25.8)
Hazard Ratio (95% CI)	0.775[a] (0.614, 0.979)		0.586[b] (0.388, 0.884)	
p-value	0.032[a]		0.010[c]	

[a] Hazard ratio and p-value based on the Cox Model adjusted for PSA (ln) and LDH (ln) and stratified by bisphosphonate use, number of bone metastases, and primary Gleason grade.
[b] Hazard ratio based on the unadjusted Cox Model (not pre-specified).
[c] p-value based on a log-rank test (not pre-specified).
Abbreviations: CI = confidence interval.

16 HOW SUPPLIED/STORAGE AND HANDLING

PROVENGE IS INTENDED SOLELY FOR AUTOLOGOUS USE. PROVENGE is a 250 mL suspension containing a minimum of 50 million autologous $CD54^+$ cells activated with PAP-GM-CSF in Lactated Ringer's Injection, USP, and supplied in an infusion bag labeled for the specific recipient.

NDC 30237-8900-6: one bag individually packed in a carton.

The identity of the patient must be matched with the patient identifiers on the infusion bag and the cell product disposition form prior to infusion. PROVENGE is **not** routinely tested for transmissible infectious diseases. Therefore, patient leukapheresis material and PROVENGE may carry the risk of transmitting infectious diseases to health care professionals handling the product. Accordingly, health care professionals should employ universal precautions when handling leukapheresis material or PROVENGE.

Handling Instructions:

1. PROVENGE is shipped directly to the infusing provider.
2. PROVENGE will arrive in a cardboard shipping box with a special insulated polyurethane container inside. The insulated container and gel packs within the container are designed to maintain the appropriate transportation and storage temperature of PROVENGE until infusion.
3. Upon receipt, the outer cardboard shipping box should be opened to verify the product and patient-specific labels located on the top of the insulated container. Do **not** remove this insulated container from the shipping box, or open the lid of the insulated container, until the patient is ready for infusion.
4. Do not infuse PROVENGE until confirmation of product release has been received from Dendreon. Dendreon will send a cell product disposition form containing the patient identifiers, expiration date and time, and the disposition status (approved for infusion or rejected), to the infusion site.
5. Infusion must begin prior to the expiration date and time indicated on the cell product disposition form and Product Label. **Do not initiate infusion of expired PROVENGE**. Once the PROVENGE infusion bag is removed from the insulated container, it should remain at room temperature for no more than 3 hours. PROVENGE should **not** be returned to the shipping container**.**
6. Once the patient is prepared for infusion and the cell product disposition form has been received, remove the PROVENGE infusion bag from the insulated container and inspect the bag for signs of leakage. Contents of the bag will be slightly cloudy, with a cream-to-pink color. Gently mix and re-suspend the contents of the bag, inspecting

for clumps and clots. Small clumps of cellular material should disperse with gentle manual mixing. Do **not** administer if the bag leaks or if clumps remain in the bag.

7. Prior to PROVENGE infusion, match the patient's identity with the patient identifiers on the cell product disposition form and the PROVENGE infusion bag.

17 PATIENT COUNSELING INFORMATION

Inform the patient or caregiver about the following:

- The recommended course of therapy for PROVENGE is 3 complete doses. Each infusion of PROVENGE is preceded by a leukapheresis procedure approximately 3 days prior. It is important to maintain all scheduled appointments and arrive at each appointment on time because the leukapheresis and infusions must be appropriately spaced and the PROVENGE expiration time must not be exceeded.
- If the patient is unable to receive an infusion of PROVENGE, the patient will need to undergo an additional leukapheresis procedure if the treatment is to be continued.
- Counsel the patient on the importance of adhering to preparation instructions for the leukapheresis procedure, the possible side effects of leukapheresis, and post-procedure care.
- If the patient does not have adequate peripheral venous access to accommodate the leukapheresis procedure and infusion of PROVENGE, inform the patient about the need for a central venous catheter. Counsel the patient on the importance of catheter care. Instruct the patient to tell their doctor if they are experiencing fevers or any swelling or redness around the catheter site, because these symptoms could be signs of an infected catheter.
- Report signs and symptoms of acute infusion reactions such as fever, chills, fatigue, breathing problems, dizziness, high blood pressure, nausea, vomiting, headache, or muscle aches.
- Report any symptoms suggestive of a cardiac arrhythmia.
- Inform their doctor if they are taking immunosuppressive agents.

For more information, please call the toll-free number: 1-877-336-3736.

Dendreon Corporation
Seattle, Washington 98101

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PATIENT LABELING

Patient Information about PROVENGE® (sipuleucel-T)

This leaflet is designed to help you understand treatment with PROVENGE (pronounced PROH-venj). The more you understand your treatment, the better you will be able to participate in your care. This leaflet does not take the place of talking with your doctor or healthcare professional about your medical condition or your treatment. If you have any questions, speak with your doctor.

What is PROVENGE?

PROVENGE is a prescription medicine that is used to treat certain patients with advanced prostate cancer. PROVENGE is made from your own immune cells.

What should I tell my doctor before getting PROVENGE?

Tell your doctor about all your medical problems, including:

- heart problems
- lung problems
- history of stroke

Tell your doctor about all the medicines you take, including prescription and nonprescription drugs, vitamins, and dietary supplements.

How will I get PROVENGE?

Since PROVENGE is made from your own immune cells, your cells will be collected approximately 3 days before each scheduled infusion of PROVENGE. You will need to go to a cell collection center for this collection. The collection is called “leukapheresis” (pronounced loo-kuh-fuh-REE-sis). Your collected cells are sent to a manufacturing center where they are mixed with a protein to make them ready for your infusion.

You will get PROVENGE in 3 intravenous infusions (put into your veins), about 2 weeks apart. Each infusion takes about 60 minutes. Following each infusion, you will be monitored for at least 30 minutes.

Your doctor will give you a schedule for your cell collection and infusion appointments. It is very important that you arrive on time for your appointments. If you miss an appointment and cannot be infused, your PROVENGE dose will not be usable. Your doctor will work with you to schedule a new appointment at the cell collection center. You may also get a new infusion appointment.

What are the possible or reasonably likely side effects of PROVENGE?

The most common side effects of PROVENGE include:

- chills
- fatigue
- fever
- back pain
- nausea
- joint ache
- headache

PROVENGE infusion can cause serious reactions. Tell your doctor right away if you have breathing problems, chest pains, racing heart or irregular heartbeats, dizziness, nausea, or vomiting after getting PROVENGE because any of these may be signs of heart or lung problems.

Tell your doctor right away if you get a fever over 100ºF, or redness or pain at the infusion or collection sites, because any of these may be signs of infection.

Tell your doctor about any side effect that concerns you or does not go away.

These are not all the possible side effects of PROVENGE treatment. For more information, talk with your doctor.

What are the ingredients in PROVENGE?

The active components of PROVENGE are your own immune cells mixed with the other active component, a protein designed to produce an immune response to prostate cancer. The product is suspended in an infusion solution called Lactated Ringer's Injection, USP, an inactive ingredient.

If you would like more information about PROVENGE, talk with your doctor. You can also call toll-free 1-877-336-3736 or visit www.PROVENGE.com.

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