

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 ≥ 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: Month/Year

**FULL PRESCRIBING INFORMATION:
CONTENTS***

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

- 2.1 Dose and Schedule
- 2.2 Premedication
- 2.3 Handling Precautions for Control of Infectious Disease
- 2.4 Storage
- 2.5 Confirm Product Release Before Infusion
- 2.6 Preparation for Infusion
- 2.7 Administration
- 2.8 Administration Modification for Infusion Reactions

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Acute Infusion Reactions
- 5.2 Handling Precautions for Control of Infectious Disease
- 5.3 Concomitant Chemotherapy or Immunosuppressive Therapy
- 5.4 Product Safety Testing

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

- 8.5 Geriatric
- 8.6 Race

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* 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 $\geq 15\%$, 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 ($\geq 2\%$) 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 $\geq 5\%$ 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 $\geq 5\%$ 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 $\geq 5\%$ 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 (γ IFN) 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 γ IFN 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

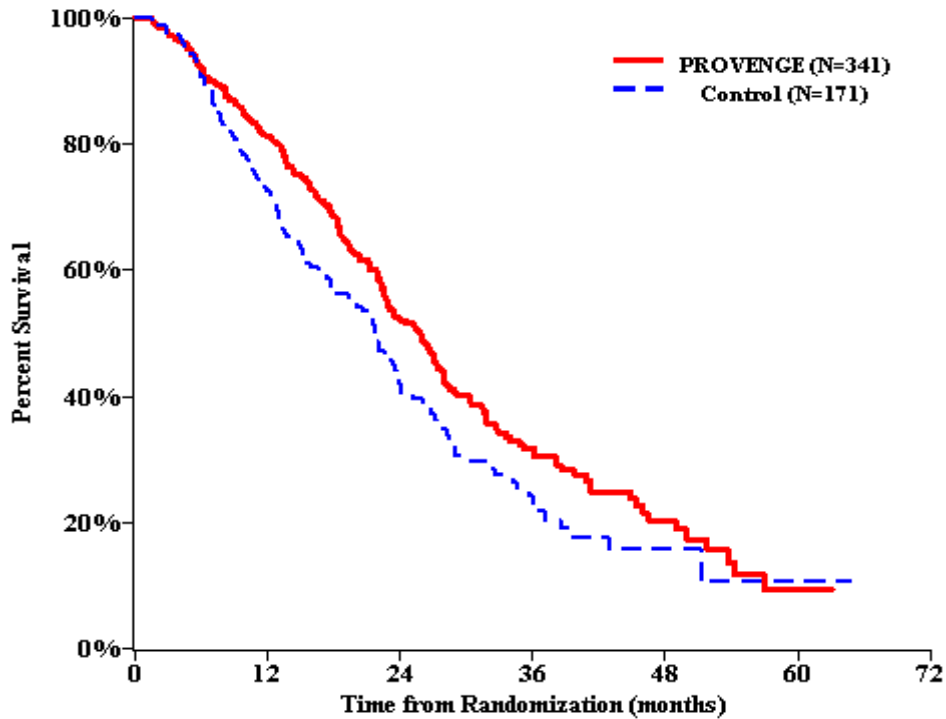


Table 2 Summary of Overall Survival (All Patients as Randomized)

	Study 1		Study 2	
	PROVENGE (N=341)	Control (N=171)	PROVENGE (N=82)	Control (N=45)
Overall Survival				
Median, months	25.8	21.7	25.9	21.4
(95% CI)	(22.8, 27.7)	(17.7, 23.8)	(20.0, 32.4)	(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. 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 PROVENCE infusion, match the patient's identity with the patient identifiers on the Cell Product Disposition Form and the PROVENCE infusion bag.

17 PATIENT COUNSELING INFORMATION

Inform the patient or caregiver about the following:

- The recommended course of therapy for PROVENCE is 3 complete doses. Each infusion of PROVENCE 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 PROVENCE expiration time must not be exceeded.
- If the patient is unable to receive an infusion of PROVENCE, 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 PROVENCE, 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.

Dendreon toll-free number: 1-877-336-3736

Dendreon Corporation
3005 First Avenue
Seattle, Washington
98121

TRN-80010.01
LBS-76022.01

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 special 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 100°F, 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.

Dendreon toll-free number: 1-877-336-3736

Dendreon Corporation
3005 First Avenue
Seattle, Washington
98121

TRN-80011.01
LBS-76022.01
Issue Date (Mo/Year)