Sipuleucel-T (Provenge®, Dendreon Corp.) is a new class of therapeutic agent used in the treatment of asymptomatic or minimally symptomatic, androgen-independent (hormone-refractory), metastatic prostate cancer. The agent comprises specially treated dendritic cells obtained from the patient through leukapheresis. The cells are then exposed in vitro to proteins that contain prostate antigens and immunologic-stimulating factors and are then reinfused back into the patient. The proposed mechanism of action is that treatment stimulates the patient’s own immune system to resist cancer spread.

Related Policies

- Gene Based Tests for Screening, Detection and Management of Prostate Cancer

Policy

Sipuleucel-T (Provenge®) therapy may be considered medically necessary in the treatment of asymptomatic or minimally symptomatic, androgen-independent (hormone-refractory) metastatic prostate cancer.

Sipuleucel-T therapy (Provenge®) is considered investigational for the treatment of prostate cancer in all other situations, including but not limited to:

- Hormone-responsive prostate cancer
- Moderate to severe symptomatic metastatic prostate cancer
- Visceral (liver, lung, or brain) metastases

Policy Guidelines

Coding

There is a specific HCPCS code for this product:

- Q2043: Sipuleucel-T, minimum of 50 million autologous CD54+ cells activated with PAP-GM-CSF, including leukapheresis and all other preparatory procedures, per infusion

Benefit Application

Benefit determinations should be based on the applicable contract language. To the extent there are any conflicts between these guidelines and the...
contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program (FEP)) prohibit Plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

**Rationale**

**Background**

Prostate cancer is the second leading cause of cancer-related deaths among American men, with an estimated incidence of 218,890 cases and an estimated number of 27,050 deaths in 2007. In most cases, prostate cancer is diagnosed at a localized stage and is treated with prostatectomy or radiotherapy. However, some patients are diagnosed with metastatic disease or recurrent disease after treatment of localized disease. Androgen ablation is the standard treatment for metastatic or recurrent disease. However, most patients who survive long enough eventually develop androgen-independent prostate cancer. At this stage of metastatic disease, docetaxel, a chemotherapeutic agent, has been demonstrated to confer a survival benefit of 1.9 to 2.4 months in randomized clinical trials. Chemotherapy with docetaxel causes adverse effects in large proportions of patients, including alopecia, fatigue, neutropenia, neuropathy, and other symptoms. Trials evaluating docetaxel included both asymptomatic and symptomatic patients, and results suggested a survival benefit for both groups. Because of the burden of treatment and its adverse effects, most patients therefore defer docetaxel treatment until cancer recurrence is symptomatic.

Cancer immunotherapy has been investigated as a treatment which could potentially be instituted at the point of detection of androgen-independent metastatic disease before significant symptomatic manifestations have occurred. The quantity of cancer cells in the patient during this time interval is thought to be relatively low, and it is thought that an effective immune response against the cancer during this time period could effectively delay or prevent progression. Such a delay could allow a course of effective chemotherapy, such as docetaxel, to be deferred or delayed until necessary, thus providing an overall survival benefit.

Sipuleucel-T (Provenge®, Dendreon Corp.) is a new class of therapeutic agent used in the treatment of asymptomatic or minimally symptomatic, androgen-independent (hormone-refractory), metastatic prostate cancer. The agent comprises specially treated dendritic cells obtained from the patient through leukapheresis. The cells are then exposed in vitro to proteins that contain prostate antigens and immunologic-stimulating factors and are then reinfused back into the patient. At reinfusion, the cells are administered as 3 intravenous infusions given approximately 2 weeks apart. The proposed mechanism of action is that the treatment stimulates the patient's own immune system to resist cancer spread.

**FDA Status**

On April 29, 2010, the U.S. Food and Drug Administration (FDA) approved Provenge® (sipuleucel-T; Dendreon Corp., Seattle, WA) via a Biologics Licensing Application for “the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer (for autologous use only).” Approval was
contingent on agreement of the manufacturer to conduct a postmarketing study, based on a registry design, to assess the risk of cerebrovascular events in 1500 men with prostate cancer who receive sipuleucel-T.

**Literature Review**

**Metastatic, Androgen-Independent Prostate Cancer**

Sipuleucel-T has been studied most definitively in a series of double-blind, placebo-controlled randomized controlled trials (RCTs). These studies were published by Small et al (2006), Higano et al (2009), and Kantoff et al (2010), and were extensively presented in a briefing document available from the U.S. Food and Drug Administration (FDA). Patients enrolled in these trials all had androgen-independent metastatic prostate cancer, were asymptomatic or mildly symptomatic, in good physical health characterized by Eastern Cooperative Oncology Group (ECOG) Performance Status 0 or 1, and had tumors with positive staining for prostatic acid phosphatase (PAP).

Table 1 describes the 2 early identically designed studies. Patients with asymptomatic metastatic prostate cancer were randomized to receive either sipuleucel-T or a control infusion of untreated dendritic cells. Principal outcome was time to disease progression, defined as the time from randomization to the first observation of disease progression. Disease progression could be defined as radiologic progression (based on several imaging criteria), clinical progression (based on prostate cancer-related clinical events, such as pathologic fracture), or pain progression (based on onset of pain corresponding to anatomic location of disease).

Studies were not designed to establish efficacy based on overall survival. On progression of cancer, patients were allowed to have additional treatment as needed including chemotherapy. Patients originally assigned to placebo were allowed to cross over by receiving their own dendritic cells pulsed with PA2024 antigen (recombinant fusion protein comprising human PAP linked to granulocyte-macrophage colony-stimulating factor [GM-CSF]), but prepared from frozen dendritic cells harvested from their initial leukapheresis procedures.

**Table 1. Description of Randomized Phase 3 Trials of Sipuleucel-T**

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Design</th>
<th>Eligibility</th>
<th>Treatment</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>9901A</td>
<td>Randomized double-blind, placebo-controlled</td>
<td>Metastatic prostate cancer by imaging, asymptomatic and progressing by imaging or rising PSA</td>
<td>Exp: 3 infusions of vaccine Ctl: 3 infusions of placebo dendritic cells</td>
<td>Primary: disease progression (radiologic, clinical, pain) Secondary: time to pain, time to progression</td>
</tr>
<tr>
<td>9902A</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMPACT</td>
<td>Randomized double-blind, placebo-controlled</td>
<td>Metastatic prostate cancer by imaging, asymptomatic or minimally symptomatic and progressing by imaging or rising PSA</td>
<td>Exp: 3 infusions of vaccine Ctl: 3 infusions of placebo dendritic cells</td>
<td>Primary: overall survival Secondary: time to objective disease</td>
</tr>
</tbody>
</table>
As shown in Table 2, results of study 9901A for the principal outcome of time to progression did not show a significant difference between vaccine and control. Median time to progression was 11.7 weeks for the vaccine group and 10.0 weeks for the control group.

Table 2. Results of Randomized, Phase 3 Trials of Sipuleucel-T

<table>
<thead>
<tr>
<th>Study</th>
<th>Vaccine</th>
<th>Control</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study 9901A</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median time to progression, wk</td>
<td>11.7</td>
<td>10.0</td>
<td>0.052</td>
</tr>
<tr>
<td>Median time to clinical progression, wk</td>
<td>10.7</td>
<td>9.1</td>
<td>0.061</td>
</tr>
<tr>
<td>Overall median survival, mo</td>
<td>25.9</td>
<td>21.4</td>
<td>0.01</td>
</tr>
<tr>
<td>Overall survival at 36 mo, %</td>
<td>34</td>
<td>11</td>
<td>0.005 Multivariable adjusted, 0.002</td>
</tr>
<tr>
<td><strong>Study 9902A</strong></td>
<td>n=65</td>
<td>n=33</td>
<td></td>
</tr>
<tr>
<td>Median time to progression, wk</td>
<td>10.9</td>
<td>9.9</td>
<td>0.719</td>
</tr>
<tr>
<td>Overall median survival, mo</td>
<td>19.0</td>
<td>15.7</td>
<td>0.331</td>
</tr>
<tr>
<td><strong>IMPACT Study</strong></td>
<td>n=341</td>
<td>n=171</td>
<td></td>
</tr>
<tr>
<td>Overall median survival, mo</td>
<td>25.8</td>
<td>21.7</td>
<td>0.032</td>
</tr>
<tr>
<td>Overall survival at 36 mo, %</td>
<td>31.7</td>
<td>23.0</td>
<td>0.036</td>
</tr>
<tr>
<td>Time to progression</td>
<td>Not reported</td>
<td>Not reported</td>
<td>HR=0.95, p=0.628</td>
</tr>
</tbody>
</table>

HR: hazard ratio.

A survival analysis of study 9901A was presented in the FDA briefing document, with caveats that the study was not powered to show a survival effect and that a primary method of survival analysis was not prespecified in the protocol. Using a log-rank test, median survival times were 25.9 months for vaccine-treated patients and 21.4 months for placebo-treated patients, a statistically significant difference (p=0.011). At 36 months, survival rate was 34% for vaccine-treated patients and 11% for placebo-treated patients.

The FDA briefing document shows analyses of possible confounders regarding the survival analysis.(7) After disease progression, patients in both groups received chemotherapy, but the rate of chemotherapy was slightly higher in the placebo group (48% vs. 36%, respectively). Examination of the causes of death did not reveal any obvious spurious elevation of noncancer deaths in the placebo group. The published version of study 9901A by Small et al (2006)(4) analyzed the survival data after adjusting for prognostic factors and found a significant association of sipuleucel-T treatment and survival (hazard ratio [HR], 2.12; 95% confidence interval [CI], 1.31 to 3.44).

Because study 9901A did not meet its principal outcome end point for efficacy, enrollment for its partner study 9902A was suspended. Its sample size was therefore smaller, and the study subsequently had lower statistical power. As shown in Table 1, results for study 9902A showed a median time to progression of 10.9 weeks in the vaccine group versus 9.9 weeks in the placebo group, which was not statistically significant. A survival analysis of study 9902A showed that median survival was 19 months in vaccine-treated patients and 15.7 months in control, which also was not statistically significant.
Higano et al (2009) pooled survival data from the 2 studies. (5) Pooled analysis showed a 33% reduction in the risk of death (HR=1.50; 95% CI: 1.10 to 2.05; p=0.011). The association was robust to adjustments in imbalances in baseline prognostic factors and postprogression chemotherapy use.

Because these earlier studies did not meet criteria for success for their principal end points, FDA did not approve sipuleucel-T in 2007. A larger phase 3 trial of similar design called IMPACT enrolling 512 patients was designed with a principal end point of overall survival. (6) Analyses used to support FDA approval reported a 22% reduction in overall mortality in patients treated with sipuleucel-T. Treatment extended median survival by 4.1 months, compared with placebo (25.8 months vs. 21.7 months, respectively) and improved 3-year survival by a relative 38%, compared with placebo (31.7% vs. 23.0%, respectively). Results adjusted for subsequent docetaxel use and timing, as well as analyses examining prostate cancer-specific survival showed similar magnitude and statistical significance of the survival benefit. Of note, 14% of enrolled subjects in this trial had received prior docetaxel. In retrospective, prespecified, multivariate subgroup analysis, several baseline factors were associated with overall survival: prostate-specific antigen (PSA), lactate dehydrogenase, hemoglobin, ECOG Performance Status, alkaline phosphatase, and Gleason score. (8) Analysis of PSA by quartiles showed that men in the lowest quartile had the greatest survival benefit with sipuleucel-T: 49% reduced mortality compared with 26% reduced mortality in the second quartile, 19% in the third quartile, and 16% in the highest quartile.

Regarding the safety of sipuleucel-T, most adverse effects were grade 1 and 2 and resolved within 48 hours. The rate of serious adverse events was not statistically different between vaccine- and placebo-treated patients. However, 1 difficulty in assessing potential adverse effects by comparing sipuleucel-T with placebo is that placebo comprised infusion of untreated dendritic cells, which may cause adverse effects. FDA reviewers expressed concern regarding a possible association of sipuleucel-T with cerebrovascular events, as 8 (5%) of 147 vaccine-treated patients experienced cerebrovascular-related adverse events, compared with zero placebo-treated patients in the 2 early trials. (7) In the latest available report of adverse effects reported in the full prescribing information, (3) incidence of stroke was 3.5% in the sipuleucel-T group and 2.6% in the control group, but these figures appear to include data from trials evaluating a different indication. In the FDA review summarizing cerebrovascular event rates from studies 9901A, 9902A, and interim data from IMPACT, incidence of stroke was 4.9% (17/345) in sipuleucel-T-treated patients and 1.7% (3/172) in placebo-treated patients (p=0.092). FDA review called the cerebrovascular event rate a “potential safety signal” and included as part of the approval a postmarketing study, based on a registry design, to assess the risk of cerebrovascular events in 1500 patients with prostate cancer who receive sipuleucel-T.

**Section Summary**

For patients with metastatic, androgen-independent prostate cancer, 3 RCTs of sipuleucel-T have been published. The 3 RCTs are consistent in reporting an improvement in overall survival of approximately 4 months compared with placebo. Two trials also reported that 36-month survival was significantly improved for patients receiving sipuleucel-T, with absolute improvements in survival of 9% and 23%. Time to progression was slightly longer in the sipuleucel-T groups, but this difference was not statistically significant. Serious adverse events were not increased in the sipuleucel-T group. There has been concern raised about a possible increase in stroke risk, but the available trials do not show a significantly increased incidence of stroke.
Other Indications

A phase 3 trial of sipuleucel-T in the setting of androgen-dependent, nonmetastatic prostate cancer was published in 2011.(9) Patients with prostate cancer detectable by PSA after radical prostatectomy received 3 to 4 months of androgen suppression therapy and were then randomized (2:1) to receive sipuleucel-T (n=117) or control (n=59). The primary end point was time to biochemical failure. There was no difference in this end point between groups; median time to biochemical failure was 18.0 months for sipuleucel-T and 15.4 months for control (HR=0.936; p=0.737). Sipuleucel-T patients had a 48% increase in PSA doubling time after testosterone recovery (155 vs. 105 days; p=0.038). Sixteen percent of patients developed distant failure. The treatment effect favored sipuleucel-T but was not statistically significant (HR=0.728; p=0.421).

Section Summary

A single RCT has been performed in patients with nonmetastatic prostate cancer, and this trial did not show any benefit for sipuleucel-T compared with control. Therefore, evidence on treatment of nonmetastatic prostate cancer is not sufficient to determine that health outcomes are improved.

Ongoing Trials

Other indications are currently being investigated in clinical trials in progress. A trial to determine whether sipuleucel-T and androgen deprivation therapy augment each other in patients with recurrent but nonmetastatic prostate cancer is currently in progress (NCT01431391). Sipuleucel-T as neoadjuvant therapy for patients with localized prostate cancer undergoing prostatectomy is being investigated (NCT00715104). In men with metastatic, hormone-resistant prostate cancer, concurrent versus sequential sipuleucel-T plus abiraterone is under study (NCT01487863), as is sipuleucel-T in combination with enzalutamide (NCT01981122), radiotherapy (NCT01807065, NCT01818986, NCT01833208), the chemotherapeutic agents indoximod (NCT01560923) and cyclophosphamide (NCT01420965), the investigational agent tasquinimod (NCT02159950), and recombinant interleukin-7 (NCT01881867).

Summary

For patients with metastatic, androgen-independent prostate cancer, 3 randomized controlled trials of sipuleucel-T reported an improvement in median survival of approximately 4 months. The 2 early studies of sipuleucel-T were not specifically designed to demonstrate a difference in overall mortality but did show a survival difference. The third study, which was designed to demonstrate a mortality difference, showed a similar improvement in overall survival. All 3 studies also were consistent in demonstrating that sipuleucel-T does not delay time to measurable progression of disease. In all studies, many patients had further chemotherapy treatment at the discretion of the treating physician; thus, the survival benefit accrues in the context of additional treatment as needed for symptomatic recurrence. This evidence is sufficient to conclude that sipuleucel-T is medically necessary for patients with androgen-independent, asymptomatic or minimally symptomatic, metastatic prostate cancer.

For patients who do not meet the above criteria, evidence does not demonstrate an improvement in health outcomes. One RCT of patients with androgen-dependent, nonmetastatic prostate cancer showed no statistical difference between sipuleucel-T and control in time to biochemical failure or PSA doubling time. This evidence does not support the use of sipuleucel-T for these patients, and therefore sipuleucel-T is considered investigational for all other indications, including but not limited to hormone-responsive
prostate cancer, treatment of moderate to severe symptomatic metastatic prostate cancer, and treatment of visceral (liver, lung, or brain) metastases.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network (NCCN)

Current NCCN Guidelines for prostate cancer (version 2.2014) recommend sipuleucel-T as a category 1 treatment for patients with metastatic castration-recurrent prostate cancer.(10) A note states that sipuleucel-T is appropriate for asymptomatic or minimally symptomatic patients with ECOG Performance Status 0-1; and it is not indicated in patients with liver metastasis or life expectancy less than 6 months. Sipuleucel-T also is recommended for second-line treatment of symptomatic patients with metastatic castration-recurrent prostate cancer who fail chemotherapy and otherwise meet criteria for treatment with sipuleucel-T (category 2A recommendation). This recommendation was based on further analysis of the previously reviewed clinical trials, which showed similar benefit in both those who had and had not received prior chemotherapy.(11)

European Consensus Panel

On September 7, 2013, 21 experts in the field of prostate cancer met in France to “evaluate current opinion regarding the most appropriate sequencing of available therapies for metastatic castration-resistant prostate cancer,” among other objectives.(12) The panel used a modified Delphi method to obtain consensus, based on the biannual St. Gallen Early Breast Cancer Consensus Conference. The panel agreed (≥70% consensus) that sipuleucel-T is a reasonable option for patients with asymptomatic or minimally symptomatic metastatic hormone-refractory prostate cancer and should be considered before docetaxel, abiraterone, and enzalutamide. The panel considered sipuleucel-T a new treatment option “during the time period between development of hormone-refractory disease and becoming a candidate for chemotherapy.”

U.S. Preventive Services Task Force

The use of sipuleucel-T for prostate cancer is not a preventive service.

Medicare National Coverage

On June 30, 2011 a national coverage determination was released by CMS approving sipuleucel-T for treatment of asymptomatic or minimally symptomatic castrate-resistant prostate cancer.(13) Coverage for off-label indications was left to the discretion of local Medicare administrative contractors.

References


**Documentation Required for Clinical Review**

- History and physical
- Previous treatment and response

**Post Service**

- Procedure report

**Coding**

This Policy relates only to the services or supplies described herein. Benefits may vary according to benefit design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of a procedure, diagnosis or
The following service/procedure may be considered medically necessary in certain instances and investigational in others. Services may be medically necessary when policy criteria are met. Services are considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>CPT®</td>
<td>36511</td>
<td>Therapeutic apheresis for white blood cells</td>
</tr>
<tr>
<td></td>
<td>96365</td>
<td>Intravenous infusion for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour</td>
</tr>
<tr>
<td>HCPC</td>
<td>Q2043</td>
<td>Sipuleucel-t, minimum of 50 million autologous cd54+ cells activated with pap-gm-csf, including leukapheresis and all other preparatory procedures, per infusion</td>
</tr>
</tbody>
</table>

ICD-10 Procedure

For dates of service on or after 10/01/2015

- 6A550Z1, 6A551Z1 Extracorporeal therapies, physiological systems, pheresis, circulatory, leukocytes, code by duration (single or multiple)
- 30233Q0, 30243Q0 Administration, circulatory, transfusion, percutaneous, white cells, autologous, code by body part (peripheral vein or central vein)

ICD-9 Procedure

None

ICD-9 Diagnosis

All Diagnoses

ICD-10 Diagnosis

For dates of service on or after 10/01/2015

All Diagnoses

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
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<tbody>
<tr>
<td>1/7/2011</td>
<td>BCBSA Medical Policy adoption</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>4/5/2011</td>
<td>Administrative Review</td>
<td>Administrative Review</td>
</tr>
<tr>
<td>9/30/2014</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
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</table>

Definitions of Decision Determinations

Medically Necessary: A treatment, procedure or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.
Investigational/Experimental: A treatment, procedure or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California / Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a Split Evaluation, where a treatment, procedure or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements

This service (or procedure) is considered medically necessary in certain instances and investigational in others (refer to policy for details).

For instances when the indication is medically necessary, clinical evidence is required to determine medical necessity. For instances when the indication is investigational, you may submit additional information to the Prior Authorization Department.

Within five days before the actual date of service, the Provider MUST confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should also be directed to the Prior Authorization Department. Please call 1-800-541-6652 or visit the Provider Portal www.blueshieldca.com/provider.

The materials provided to you are guidelines used by this plan to authorize, modify, or deny care for persons with similar illness or conditions. Specific care and treatment may vary depending on individual need and the benefits covered under your contract. These Policies are subject to change as new information becomes available.