Introduction

Immunotherapy is a way to fight disease, even cancer, by using a person’s own immune system. Dendritic cells are part of the immune system. They help the immune system spot cancer cells. When the dendritic cells find and start to break down cancer cells, other immune cells are activated to also attack the cancer cells. In some cases of advanced prostate cancer, a vaccine can be made using a person’s own immune cells. Certain immune cells are removed, treated in a lab to create dendritic cells, and then given back to the person. This very specialized vaccine then helps the body fight prostate cancer. This policy describes when this type of immunotherapy may be approved for prostate cancer.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.
### Therapy

<table>
<thead>
<tr>
<th>Medical Necessity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sipuleucel-T therapy may be considered medically necessary in the treatment of asymptomatic or minimally symptomatic, androgen-independent (castration-resistant) metastatic prostate cancer.</td>
</tr>
</tbody>
</table>

**Note:** Provenge® is the brand or trade name for Sipuleucel-T.

### Therapy

<table>
<thead>
<tr>
<th>Investigational</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sipuleucel-T therapy is considered investigational in all other situations, including but not limited to:</td>
</tr>
<tr>
<td>- Treatment of hormone-responsive prostate cancer</td>
</tr>
<tr>
<td>- Treatment of moderate to severe symptomatic metastatic prostate cancer</td>
</tr>
<tr>
<td>- Treatment of visceral (liver, lung, or brain) metastases</td>
</tr>
</tbody>
</table>

### Coding

#### Code | Description
--- | ---
**HCPCS**
Q2043 | Sipuleucel-T, minimum of 50 million autologous CD54+ cells activated with PAP-GM-CSF, including leukapheresis and all other preparatory procedures, per infusion (Provenge®)

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### Related Information

N/A
Description

Sipuleucel-T (Provenge®; Dendreon Corp.) is a new class of therapeutic agent used to treat asymptomatic or minimally symptomatic, castration-resistant, 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 the infusion of the treated immune cells stimulates the patient’s own immune system to resist cancer spread.

Background

Prostate Cancer

Prostate cancer is the second leading cause of cancer-related deaths among American men, with an estimated incidence of 220,800 cases and an estimated number of 27,540 deaths in 2015.¹ 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.

Treatment

Androgen ablation is the standard treatment for metastatic or recurrent disease. 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.²³ 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 suggest 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 is thought to be relatively low, and it is thought that an effective immune response against the cancer during this interval 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 to treat asymptomatic or minimally symptomatic, androgen-independent (castration-resistant), 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 reinfused back into the patient. 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.

Summary of Evidence

For individuals who have asymptomatic or minimally symptomatic, metastatic, castration-resistant prostate cancer who receive sipuleucel-T (Provenge), the evidence includes 3 randomized controlled trials (RCTs) and a systematic review of these RCTs. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related morbidity. The 2 earlier RCTs 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. A meta-analysis of the 3 RCTs found significantly improved overall survival, but not time to progression, with sipuleucel-T compared with placebo. Serious adverse events did not increase in the sipuleucel-T group. However, the available data suggested, but did not confirm, an increase in stroke risk; this risk is being evaluated in a postmarketing study. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have nonmetastatic, androgen-dependent prostate cancer who receive sipuleucel-T (Provenge), the evidence includes a RCT. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related morbidity. The RCT did not find a statistically significant difference between sipuleucel-T and a control in time to
biochemical failure. The RCT was not designed to evaluate the impact of sipuleucel-T on mortality. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Ongoing and Unpublished Clinical Trials**

Some currently unpublished trials that might influence this policy are listed in Table 1.

### Table 1. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ongoing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01487863a</td>
<td>A Randomized, Open-label, Phase II Trial of Sipuleucel-T With Concurrent Versus Sequential Administration of Abiraterone Acetate Plus Prednisone in Men With Metastatic Castrate Resistant Prostate Cancer (mCRPC)</td>
<td>69</td>
<td>Jun 2016 (ongoing)</td>
</tr>
<tr>
<td>NCT01981122a</td>
<td>A Randomized, Open-label, Phase II Study of Sipuleucel-T With Concurrent Versus Sequential Administration of Enzalutamide in Men With Metastatic Castrate-Resistant Prostate Cancer</td>
<td>52</td>
<td>Jul 2017 (ongoing)</td>
</tr>
<tr>
<td>NCT01807065</td>
<td>Randomized Phase II Trial of Sipuleucel T Immunotherapy Preceded by Sensitizing Radiation Therapy and Sipuleucel-T Alone in Patients With Castrate Resistant Metastatic Prostate Cancer</td>
<td>50</td>
<td>Jan 2018</td>
</tr>
<tr>
<td>NCT03024216</td>
<td>Clinical Study of Atezolizumab (Anti-PD-L1) and Sipuleucel-T in Patients Who Have Asymptomatic or Minimally Symptomatic Metastatic Castrate Resistant Prostate Cancer</td>
<td>34</td>
<td>Jan 2019</td>
</tr>
<tr>
<td>NCT01804465a</td>
<td>A Randomized Phase 2 Trial of Combining Sipuleucel-T With Immediate vs. Delayed CTLA-4 Blockade for Prostate Cancer</td>
<td>54</td>
<td>Dec 2018</td>
</tr>
<tr>
<td>NCT01560923</td>
<td>A Randomized, Double-Blind Phase II Study of Sipuleucel-T (Provenge®) Followed by Indoximod or Placebo in the Treatment of Patients With Asymptomatic or Minimally Symptomatic Metastatic Castration Resistant Prostate Cancer</td>
<td>47</td>
<td>Nov 2017</td>
</tr>
</tbody>
</table>
NCT No. | Trial Name | Planned Enrollment | Completion Date
--- | --- | --- | ---
**Unpublished**
NCT02159950 | A Phase II Randomized Open Label Study of Sipuleucel-T vs. Sipuleucel-T and Tasquinimod in Patients With Metastatic Castrate-Resistant Prostate Cancer (CRPC) | 2 | Apr 2015 (completed)
NCT01306890* | A Registry of Sipuleucel-T Therapy in Men With Advanced Prostate Cancer (PROCEED) | 1973 | Jan 2017 (completed)

NCT: national clinical trial.

* Denotes industry-sponsored or cosponsored trial.

**Practice Guidelines and Position Statements**

*European Association of Urology et al*

In 2016, the European Association of Urology, the European Society for Radiotherapy & Oncology, and the International Society of Geriatric Oncology published joint guidelines on the treatment of relapsing, metastatic, castration-resistant prostate cancer. The guidelines stated that the choice of first-line treatment should be based on factors including performance status, symptoms, comorbidities, and the extent of disease, and that recommended treatment options are, in alphabetic order: abiraterone, cabazitaxel docetaxel, enzalutamide, Ra 223 and sipuleucel-T.”

*American Urological Association*

In 2013 (amended 2015), the American Urological Association published guidelines on castration-resistant prostate cancer. The guidelines included the following statements on sipuleucel-T:

Clinicians should offer abiraterone + prednisone, enzalutamide, docetaxel, or sipuleucel-T to patients with asymptomatic or minimally symptomatic mCRPC [metastatic castration-resistant prostate cancer] with good performance status and no prior docetaxel chemotherapy. [Standard; Evidence Level Grade A (abiraterone + prednisone and enzalutamide)/B (docetaxel and sipuleucel-T)]
Clinicians should not offer treatment with either estramustine or sipuleucel-T to patients with symptomatic, mCRPC with poor performance status and no prior docetaxel chemotherapy. (Recommendation; Evidence Level Grade C)

**National Comprehensive Cancer Network (NCCN)**

Current NCCN Guidelines for Prostate Cancer (v.1.2017) recommend sipuleucel-T as a category 1 treatment for patients with metastatic castration-recurrent prostate cancer, symptomatic or minimally symptomatic; Eastern Cooperative Oncology Group performance status 0 or 1; no liver metastasis; and life expectancy greater 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).

**American Society of Clinical Oncology-Cancer Care Ontario**

In 2014, the American Society of Clinical Oncology and Cancer Care Ontario issued a joint, evidence-based clinical practice guideline on systemic therapy in men with metastatic castration-resistant prostate cancer. The guidelines includes a weak recommendation that “sipuleucel-T may be offered to men who are asymptomatic or minimally symptomatic (benefit: moderate; harm: low; evidence strength: moderate).”

**Medicare National Coverage**

In 2011 a national coverage determination was released by Centers for Medicare & Medicaid Services (CMS) approving sipuleucel-T for treatment of asymptomatic or minimally symptomatic castrate-resistant prostate cancer. Coverage for off-label indications was left to the discretion of local Medicare administrative contractors.

**Regulatory Status**

In April, 2010, the U.S. Food and Drug Administration (FDA) approved Provenge® (sipuleucel-T; Dendreon Corp., now Sanpower, Jiangsu, China) via a Biologics Licensing Application for “the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone
refractory) prostate cancer. Approval was contingent on agreement of the manufacturer conducting 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.

References


## History

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>11/09/10</td>
<td>New Policy; add to Therapy section - New policy.</td>
</tr>
<tr>
<td>05/13/11</td>
<td>Code Update - C9273 added to policy.</td>
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<tr>
<td>11/17/11</td>
<td>Reviewed and recommended by OAP on November 17, 2011.</td>
</tr>
<tr>
<td>10/26/12</td>
<td>Replace Policy. Policy updated with literature review. Reference 10 added. No change to policy statements.</td>
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<tr>
<td>02/15/13</td>
<td>Update Related Policies. Add 8.01.01.</td>
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<tr>
<td>09/27/13</td>
<td>Replace policy. Policy updated with literature review through May 2013. Reference 10 added. No change to policy statements.</td>
</tr>
<tr>
<td>09/23/14</td>
<td>Annual Review. Policy updated with literature review through June 20, 2014. References 6, 8, and 12 added; references 3, 7, 10, and 13 updated; others renumbered/removed. Policy statements unchanged. CPT code 96365 removed from policy; this code is not managed in relationship to this policy.</td>
</tr>
<tr>
<td>09/08/15</td>
<td>Annual Review. “Hormone-refractory” changed to the current clinically accepted term “castration-resistant” prostate cancer in the medically necessary policy statement and throughout the policy. Added brand name Provenge® to the policy section. Policy updated with literature review through June 27, 2015; references 1, 10, and 14 added. Policy statements wording revised as noted. CPT code 36511 and HCPCS code J3590</td>
</tr>
<tr>
<td>Date</td>
<td>Comments</td>
</tr>
<tr>
<td>-----------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>12/01/16</td>
<td>Annual Review, approved November 8, 2016. No changes to policy statement.</td>
</tr>
</tbody>
</table>

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Email AppealsDepartmentInquiries@Premera.com

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U.S. Department of Health and Human Services
200 Independence Avenue SW, Room S09F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)
Complaint forms are available at

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