Medical Policy – 8.01.53
Cellular Immunotherapy for Prostate Cancer

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 | Medical Necessity
--- | ---
Sipuleucel-T therapy | Sipuleucel-T therapy may be considered medically necessary in the treatment of asymptomatic or minimally symptomatic, androgen-independent (castration-resistant) metastatic prostate cancer.

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

Therapy | Investigational
--- | ---
Sipuleucel-T therapy | Sipuleucel-T therapy is considered investigational in all other situations, including but not limited to:
- Treatment of hormone-responsive prostate cancer
- Treatment of moderate to severe symptomatic metastatic prostate cancer
- Treatment of visceral (liver, lung, or brain) metastases

Documentation Requirements
The patient’s medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include clinical documentation of all of the following:
- Patient has metastatic prostate cancer that is castrate-resistant (does not respond to hormone treatment)
- Patient is asymptomatic or minimally symptomatic
- Patient has no liver, lung, or brain metastases

Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCPCS</td>
<td></td>
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<tr>
<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 (Provenge®)</td>
</tr>
</tbody>
</table>

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**Description**

Sipuleucel-T (Provenge) is a 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 reinfused into the patient. The proposed mechanism of action is that treatment 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 164,690 cases and an estimated number of 29,430 deaths in 2018.\(^1\) 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 (castration-resistant) prostate cancer. At this stage of metastatic disease, docetaxel, a chemotherapeutic agent, has demonstrated a survival benefit of 1.9 to 2.4 months in randomized clinical trials.\(^2,3\)
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 have 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 that could 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 to 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.

**Summary of Evidence**

For individuals who have asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer who receive sipuleucel-T (Provenge), the evidence includes three randomized controlled trials (RCTs) and a systematic review of these RCTs. The relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related morbidity. The two earlier RCTs of sipuleucel-T were not specifically designed to demonstrate a difference in overall mortality but did show a survival difference. The third RCT, which was designed to demonstrate a mortality difference, showed a similar improvement in overall survival. All three studies were consistent in demonstrating that sipuleucel-T does not delay time to measureable progression of disease. A meta-analysis of the three 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 an RCT. The 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>Ongoing</td>
<td></td>
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<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 2019</td>
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<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 2019</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 2020</td>
</tr>
<tr>
<td>Unpublished</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01306890a</td>
<td>A Registry of Sipuleucel-T Therapy in Men With Advanced Prostate Cancer (PROCEED)</td>
<td>1973</td>
<td>Jan 2017 (completed)</td>
</tr>
</tbody>
</table>

NCT: national clinical trial
a Denotes industry-sponsored or cosponsored trial

Practice Guidelines and Position Statements

American Urological Association

The American Urological Association (2018) amended their 2013 guidelines on castration-resistant prostate cancer.14,15 Table 2 provides the guideline statements on sipuleucel-T.
Table 2. Guidelines on Treatment of Castration-Resistant Prostate Cancer

<table>
<thead>
<tr>
<th>Guideline</th>
<th>SOE</th>
<th>LOE</th>
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</thead>
<tbody>
<tr>
<td>“Clinicians should offer abiraterone plus prednisone, enzalutamide,</td>
<td>Standard</td>
<td>A (abiraterone plus prednisone and enzalutamide)</td>
</tr>
<tr>
<td>docetaxel, or sipuleucel-T to patients with asymptomatic or minimally</td>
<td></td>
<td>B (docetaxel and sipuleucel-T)</td>
</tr>
<tr>
<td>symptomatic mCRPC with good performance status and no prior docetaxel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>chemotherapy.”</td>
<td></td>
<td></td>
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<tr>
<td>“Clinicians should not offer treatment with either estramustine or</td>
<td>Recommendation</td>
<td>C</td>
</tr>
<tr>
<td>sipuleucel-T to patients with symptomatic, mCRPC with good performance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>status and no prior docetaxel chemotherapy.”</td>
<td></td>
<td></td>
</tr>
<tr>
<td>“Clinicians should not offer treatment with either estramustine or</td>
<td>Recommendation</td>
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<tr>
<td>sipuleucel-T to patients with symptomatic, mCRPC with good performance</td>
<td></td>
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<tr>
<td>status and no prior docetaxel chemotherapy.”</td>
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</table>

LOE: level of evidence; mCRPC: metastatic castration-resistant prostate cancer; SOE: strength of evidence.

National Comprehensive Cancer Network (NCCN)

Current National Comprehensive Cancer Network Guidelines (v.2.2019) for prostate cancer 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).

Medicare National Coverage

The Centers for Medicare & Medicaid Services (2011) released a national coverage determination 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 2010, the U.S. Food and Drug Administration approved Provenge® (sipuleucel-T; Dendreon Corp., now Sanpower) under a Biologics Licensing Application for “the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer.” Approval was contingent on 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>
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<tbody>
<tr>
<td>11/09/10</td>
<td>New Policy; add to Therapy section - New policy.</td>
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<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>
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<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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<td>02/15/13</td>
<td>Update Related Policies. Add 8.01.01.</td>
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<td>Replace policy. Policy updated with literature review through May 2013. Reference 10 added. No change to policy statements.</td>
</tr>
<tr>
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<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>
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<tr>
<td>09/08/15</td>
<td>Annual Review. &quot;Hormone-refractory&quot; changed to the current clinically accepted term &quot;castration-resistant&quot; 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 removed; these do not relate to the policy.</td>
</tr>
<tr>
<td>Date</td>
<td>Comments</td>
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<tr>
<td>12/01/16</td>
<td>Annual Review, approved November 8, 2016. No changes to policy statement.</td>
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<tr>
<td>10/10/18</td>
<td>Minor edit, added Documentation Requirements section.</td>
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**Disclaimer:** This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2019 Premera All Rights Reserved.

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  - Qualified interpreters
  - Information written in other languages

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Oromo (Cushite):

Fratçis (French):

Deutsche (German):

Hmoob (Hmong):
Tsab ntawv tshaj xo no muaj cov ntsiab lus tseem ceeb. Tej zaum tsab ntawv tshaj xo no muaj cov ntsiab lus tseem ceeb bokj kaj dawt ntawv thov kev pab los yoj kaj chov kev pab cuam los ntawm Premera Blue Cross. Tej zaum muaj cov hnb tuem tseem ceeb us uas rau hauv daim ntawv no. Tej zaum kaj kaj yuav tau ua qee yam uas peb kaj oj us tis pub dhai cov caj nyong us teev rau hauv daim ntawv no mas kaj thaj yuav tuai bas kev pab cuam kum kho mob los yoj kev pab them tej nqi kho mob ntawv. Kaj muaj cai kom laww muab cov ntsiab lus no uas tau muab sau ua kaj hom lus pub dawb rau kaj. Hu rau 800-722-1471 (TTY: 800-842-5357).

Iliko (Ilocano):
Daytoy a Pakdaara ket naglaon iti Napateg nga Impormasion. Daytoy a pakdaara mabalin nga adda ket naglaon iti napateg nga impormasion maijaanggep iti aplikasyonno yenno coverage babanen Premera Blue Cross. Daytoy ket mabalin dagiti importante a pelsa iti daytoy a pakdaara. Mabalin nga adda rumbeng nga araminredo nga addanga sakkab dagiti particular nga naituding nga adda aldaw tapno mapagtainedeyo ti coverage ti salun-ayno yenno tulung kadagit gastos. Adda karbengano a mangala iti daytoy nga impormasion ken tulung iti bukodyo a pagasaso nga awan ti bayadanyo. Tumawag ti numero nga 800-722-1471 (TTY: 800-842-5357).

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