Name of Policy: Cellular Immunotherapy for Prostate Cancer

Policy #: 432
Category: Medical

Latest Review Date: July 2014
Policy Grade: A

Background/Definitions:
As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. The technology must have final approval from the appropriate government regulatory bodies;
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;
3. The technology must improve the net health outcome;
4. The technology must be as beneficial as any established alternatives;
5. The improvement must be attainable outside the investigational setting.

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. In accordance with generally accepted standards of medical practice; and
2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient’s illness, injury or disease; and
3. Not primarily for the convenience of the patient, physician or other health care provider; and
4. Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient’s illness, injury or disease.
**Description of Procedure or Service:**
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. It consists of specially treated dendritic cells obtained from the patient with leukapheresis. The cells are then exposed in vitro to proteins that contain prostate antigens and immunologic stimulating factors, and then reinfused back into the patient*. The proposed mechanism of action is that the treatment stimulates the patient’s own immune system to resist spread of the cancer.

*A course of treatment is three doses at approximately two week intervals.

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 three intravenous infusions given approximately two weeks apart. The proposed mechanism of action is that the treatment stimulates the patient’s own immune system to resist cancer spread.
Policy:
Sipuleucel-T therapy meets Blue Cross and Blue Shield of Alabama’s medical criteria for coverage for the treatment of asymptomatic or minimally symptomatic, metastatic, androgen-independent (hormone-refractory) prostate cancer for a single course of treatment (three infusions).

Sipuleucel-T therapy does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered investigational in all other situations, including but not limited to treatment of hormone-responsive prostate cancer, treatment of those with moderate to severe symptomatic metastatic prostate cancer, and those with visceral (liver, lung or brain) metastases.

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member’s contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:
The policy is regularly updated with searches of the MEDLINE database. The following is a summary of the key literature to date.

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 two 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>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 progression</td>
</tr>
</tbody>
</table>

Ctl: control arm; Exp: experimental arm; PSA: prostate-specific antigen

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>n=82</th>
<th>n=45</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time to progression, wk</td>
<td>11.7</td>
<td>10.0</td>
<td>0.052</td>
<td></td>
</tr>
<tr>
<td>Median time to clinical progression, wk</td>
<td>10.7</td>
<td>9.1</td>
<td>0.061</td>
<td></td>
</tr>
<tr>
<td>Overall median survival, mo</td>
<td>25.9</td>
<td>21.4</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Overall survival at 36 mo, %</td>
<td>34</td>
<td>11</td>
<td>0.005 Multivariable adjusted, 0.002</td>
<td></td>
</tr>
<tr>
<td>Study 9902A</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median time to progression, wk</td>
<td>10.9</td>
<td>9.9</td>
<td>0.719</td>
<td></td>
</tr>
<tr>
<td>Overall median survival, mo</td>
<td>19.0</td>
<td>15.7</td>
<td>0.331</td>
<td></td>
</tr>
<tr>
<td>IMPACT study</td>
<td>n=341</td>
<td>n=171</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall median survival, mo</td>
<td>25.8</td>
<td>21.7</td>
<td>0.032</td>
<td></td>
</tr>
<tr>
<td>Overall survival at 36 mo, %</td>
<td>31.7</td>
<td>23.0</td>
<td>0.036</td>
<td></td>
</tr>
<tr>
<td>Time to progression</td>
<td>Not reported</td>
<td>Not reported</td>
<td>HR=0.95, p=0.628</td>
<td></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. 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) 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 two studies. 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. 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 three-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. 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, one 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 eight (5%) of 147 vaccine-treated patients experienced cerebrovascular-related adverse events, compared with zero placebo-treated patients in the two early trials. In the latest available report of adverse effects reported in the full prescribing information, 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, three RCTs of sipuleucel-T have been published. The 3 RCTs are consistent in reporting an improvement in overall survival of approximately four 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. Patients with prostate cancer detectable by PSA after radical prostatectomy received three to four 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.

Summary
For patients with metastatic, androgen-independent prostate cancer, three randomized controlled trials of sipuleucel-T reported an improvement in median survival of approximately four months. The two 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 three
studies also were consistent in demonstrating that sipuleucel-T does not delay time to
measureable 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. 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 six 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.

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. 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.
**Key Words:**
Provenge, Sipuleucel-T therapy, Cellular immunotherapy

**Approved by Governing Bodies:**
On April 29, 2010, the U.S. Food and Drug Administration (FDA) approved Provenge® (sipuleucel-T, Dendreon Corp.) via a Biologics Licensing Application (BLA) 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 1,500 patients with prostate cancer who receive sipuleucel-T.

**Benefit Application:**
Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.
ITS: Home Policy provisions apply
FEP: Special benefit consideration may apply. Refer to member’s benefit plan.

**Current Coding:**
HCPCS codes:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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</thead>
<tbody>
<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 <em>(Effective July 1, 2011)</em></td>
</tr>
</tbody>
</table>

**Previous Coding:**
Prior to July 1, 2011, the following codes may be reported:

**CPT Codes:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>36511</td>
<td>Therapeutic apheresis; for white cells</td>
</tr>
<tr>
<td>96365</td>
<td>Intravenous infusion, for therapy, prophylaxis, or diagnosis; initial, up to 1 hour</td>
</tr>
</tbody>
</table>

**HCPCS Codes:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J3590</td>
<td>Unclassified biologics</td>
</tr>
</tbody>
</table>

**References:**
2. Berry DL, Moinpour CM, Jiang CS, et al. Quality of life and pain in advanced stage prostate cancer: Results of a Southwest Oncology Group randomized trial comparing


Policy History:
Medical Policy Panel, May 2010
Medical Policy Group, May 2010 (2)
Medical Policy Administration Committee, June 2010
Available for comment June 18-August 2, 2010
Medical Policy Group, December 2010 (2) 2011 Coding update
Medical Policy Group, May 2011 (1): Coding update
Medical Policy Administration Committee, May 2011
Available for comment May 11 – June 27, 2011
Medical Policy Panel, August 2011
Medical Policy Group, September 2011 (2): Key Points, References updated
Medical Policy Group, August 2012 (2): Key Points, References updated
Medical Policy Group, July 2013 (4): 2013 update to Key Points and References
Medical Policy Panel, July 2014
Medical Policy Group, July 2014 (1): Update to Key Points and References; no change to policy statement

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member’s plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield’s administration of plan contracts.